KCE REPORT 211S

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

SUPPORTIVE TREATMENT FOR CANCER – PART 3: TREATMENT OF CANCER PAIN: MOST COMMON PRACTICES

APPENDIX





KCE REPORT 211S
GOOD CLINICAL PRACTICE

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

SUPPORTIVE TREATMENT FOR CANCER – PART 3: TREATMENT OF CANCER PAIN: MOST COMMON PRACTICES

APPENDIX

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Disclaimer:	• **The external experts were consulted about a (preliminary) version of the scientific report. Their comments were discussed during meetings. They did not co-author the scientific report and did not necessarily agree with its content.** • **Subsequently, a (final) version was submitted to the validators. The validation of the report results from a consensus or a voting process between the validators. The validators did not co-author the scientific report and did not necessarily all three agree with its content.** • **Finally, this report has been approved by common assent by the Executive Board.** • **Only the KCE is responsible for errors or omissions that could persist. The policy recommendations are also under the full responsibility of the KCE**
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APPENDIX I

1. SELECTION OF RELEVANT TOPICS BY EXTERNAL EXPERT PANEL

1.1. Accompanying letter

Table of possible topics

Dear Expert,

In order to help us select the most relevant topics to deal with in the guideline we are currently developing on “treatment of pain in cancer”, please make your choice at the Table below (see 1.2):

1. First, make a choice of the most relevant topics, by putting a cross in the yellow blocks at row g (maximum of 8 yellow blocks). For some of the yellow blocks, there is a subdivision of light blue blocks (at row h). If you choose this yellow block, please indicate in the light blue blocks which subtopics should be addressed (indicate 1) or not (indicate 0).
2. Now look at the dark blue blocks (lines 61-69, row g), that address “Outcomes”. Please put numbers from 1 (most important) to 9 (least important), according to the importance you give to this outcome parameter. Should anything be unclear, please do not hesitate to contact us. Thank you for your time!

1.2. Table of possible topics and result of selection by experts

Table 1 – Table of possible topics and result of selection by experts

	a	b	c	d	e	f	g	h	Results: Number of experts that crossed the topic (Total of 8 experts) Grey: items included in report (score >4)
1	A.Treatment								
2		*Disease-Modifying*							
3			Radiotherapy						7
4				Bone-lesions					7
5				Other (please					3 (nerve or spinal cord compression; soft tissue

	a	b	c	d	e	f	g	h	Results: Number of experts that crossed the topic (Total of 8 experts) Grey: items included in report (score >4)
				specify)					masses)
6			Chemotherapy						1
7		*Symptomatic*							
8			Pharmacotherapy						
9				Paracetamol and NSAIDs					**7**
10				Opoids					**8**
11				Other-multipurpose					
12					Anti-depressants				**6**
13					Corticosteroids				**5**
14					Topical agents				1
15						lidocaine			1
16						capsaicin			1
17						Other (please specify)			
18					Other				1
19						clonidine			1
20						Other (please specify)			
21				Other-neuropathic					
22					Anticonvulsants				**7**
23						gabapentin			**6**

	a	b	c	d	e	f	g	h	Results: Number of experts that crossed the topic (Total of 8 experts) Grey: items included in report (score >4)
24						pregabalin			5
25						Other (please specify)			2 (carbamazepine, valproate)
26					Other				
27						Sodium-channel drug e.g. intravenous lidocain			1
28						GABA antagonist e.g. Baclofen, clonazepam			1
29						N-methyl-D-aspartate inhib e.g. ketamine			2
30						Other (please specify)			
31				Other-bone pain					5
32					Biphosphonates				7
33					Radionuclides				5
34					Calcitonine				1
35				Other- bowel obstrucion					2
36					Anticholinergic				2

	a	b	c	d	e	f	g	h	Results: Number of experts that crossed the topic (Total of 8 experts) Grey: items included in report (score >4)
					drugs				
37					Somatostatine analogue				2
38			Interventional						
39				Epidural/ Intrathecal					3 (*included in other KCE report in preparation)
40					Opoids				4
41					Local anaesthetics				4
42					Clonidine				3
43					Other (please specify)				
44				Neuroablative					
45					Peripheral nerves				2
46						peripheral nerve block			2
47						plexus neurolysis			
48						intercostal neurolysis			1
49					Visceral plexus block				**5**
50						plexus coeliacus			**5**

	a	b	c	d	e	f	g	h	Results: Number of experts that crossed the topic (Total of 8 experts) Grey: items included in report (score >4)
51						plexus hypogastricus			3
52					Other				1
53						chordotomy			1
54						lower end block			1
55						Other (please specify)			
56				Neurostimulation					2
57					Peripheral nerve (TENS)				3
58					Spinal cord stimulation				
59					Deep brain stimulation				1
60				Other (radiofrequency ablation or laser or cryoablative techniques for metastases, …)(please specify)					3 (not specified by experts)
61	B.Outcomes								**Results: Total of scores (ranking) (Grey: included in report)**
62		Pain intensity (scale), pain reduction, pain relief							**9 (1)**

	a	b	c	d	e	f	g	h	Results: Number of experts that crossed the topic (Total of 8 experts) Grey: items included in report (score >4)
63		Quality of life, psychological well-being (measured by validated scale)							**21 (2)**
64		Side-effects							**30 (4)**
65		Reduction of other associated pain medication							47 (6)
66		Functional impairment due to pain							**27 (3)**
67		Duration of effects							35 (5)
68		Drop-outs							54+ (one expert no number)
69		Anxiety, depression, measured by validated scale							48 (7)
70		Other (please specify)							one expert (compliance)

1.3. Definitions of palliative care and terminal care

During the course of their disease, patients can go through several phases: the phase of active curative cancer treatment, the phase after a patient has been cured of cancer, the phase of living with cancer as a chronic illness, the palliative phase etc. All phases of the disease are within the scope of this report, although most cancer guidelines developed by the KCE focus on the active curative treatment period only.

The World Health Organisation (WHO) definition of 2002 clarifies when pain treatment can be considered to be palliative care: "Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.

Palliative care is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy." (Portenoy 2011; WHO 2007)[1, 2]. Hence, palliative care can be provided during the period of active curative cancer treatment. It can also be provided when treatment does not aim to cure the cancer anymore but aims to improve quality of life. Both these phases will be included in the current report.

However, the phase of "terminal care" (the very last phase of palliative care) is excluded from this report. Terminal care aims to provide assistance and comfort during the process of dying; different definitions exist for the length of this period but mostly it varies from days to a few weeks before death (Dutch guideline on cancer pain 2008)[3].

2. QUALITY APPRAISAL INSTRUMENTS

2.1. AMSTAR

Table 2 – AMSTAR

Question	Answer
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable

Question	Answer
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable

Question	Answer
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable

2.2. Cochrane Collaboration's tool for assessing risk of bias

Table 3 – Cochrane Collaboration's tool for assessing risk of biais

Domain	Support for judgement	Review authors' judgement
Selection bias		
Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment
Performance bias		
Blinding of participants and personnel **Assessments should be made for each main outcome (or class of outcomes)**	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study
Detection bias		
Blinding of outcome assessment **Assessments should be made for each main outcome (or class of outcomes)**	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Detection bias due to knowledge of the allocated interventions by outcome assessors

Domain	Support for judgement	Review authors' judgement
Attrition bias		
Incomplete outcome data **Assessments should be made for each main outcome (or class of outcomes)**	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any reinclusions in analyses performed by the review authors	Attrition bias due to amount, nature or handling of incomplete outcome data
Reporting bias		
Selective reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found	Reporting bias due to selective outcome reporting
Other bias		
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool If particular questions/entries were prespecified in the review's protocol, responses should be provided for each question/entry	Bias due to problems not covered elsewhere in the table

3. SEARCH SYNTAX BY DATABASE

3.1. Systematic reviews

3.1.1. OVID Medline

Search date: 20-07-2012

1 exp Neoplasms/ (2364463)
2 Neoplasm Staging/ (106878)
3 tumor$.ab,ti. (838376)
4 cancer$.ti,ab. (891443)
5 tumour$.ab,ti. (181026)
6 carcinoma$.ab,ti. (415894)
7 neoplasm$.ab,ti. (87168)
8 lymphoma.ab,ti. (98633)
9 melanoma$.ab,ti. (71101)
10 Staging.ab,ti. (43075)
11 metastas$.ab,ti. (188271)
12 metastatic.ab,ti. (120748)
13 exp Neoplasm Metastasis/ (143186)
14 exp Neoplastic Processes/ (304429)
15 neoplastic process$.ab,ti. (2142)
16 non small cell.ab,ti. (25168)
17 adenocarcinoma$.ab,ti. (83504)
18 squamous cell.ab,ti. (56938)
19 nsclc.ab,ti. (13999)
20 osteosarcoma$.ab,ti. (13286)
21 phyllodes.ab,ti. (1159)
22 cystosarcoma$.ab,ti. (540)
23 fibroadenoma$.ab,ti. (2744)
24 (non adj small adj cell).ab,ti. (25168)
25 (non adj2 small adj2 cell).ab,ti. (25367)
26 (nonsmall adj2 cell).ab,ti. (1555)
27 plasmacytoma$.ab,ti. (4961)
28 myeloma.ab,ti. (32458)
29 multiple myeloma.ab,ti. (20518)
30 lymphoblastoma$.ab,ti. (257)
31 lymphocytoma$.ab,ti. (252)
32 lymphosarcoma$.ab,ti. (3581)
33 immunocytoma.ab,ti. (397)
34 sarcoma$.ab,ti. (66039)
35 hodgkin$.ab,ti. (47865)
36 (nonhodgkin$ or non hodgkin$).ab,ti. (27355)
37 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 31 or 32 or 33 or 34 or 35 or 36 (2715502)
38 pain.mp. or exp Pain/ (470036)
39 Radiotherapy/ (33327)
40 radiothera$.tw. (98642)
41 39 or 40 (119538)
42 exp Radioisotopes/ or exp Radiopharmaceuticals/ (268186)
43 (radiopharmaceutical$ or radioactive isotope$ or radioisotope$ or radionuclide$).mp. (231598)
44 42 or 43 (312770)
45 paracetamol.mp. or exp Acetaminophen/ (14948)
46 exp *Anti-Inflammatory Agents, Non-Steroidal/ (85994)
47 ((non-steroidal and anti-inflammatory) or nsai$).mp. (56396)
48 45 or 46 or 47 (118134)
49 exp *Analgesics, Opioid/ (58094)
50 (opioid$ or morphine).mp. (98269)
51 49 or 50 (115589)

52 exp Antidepressive Agents/ (114258)

53 (antidepressant$ or antidepressive agent$ or antidepressive drug$).mp. (59678)

54 52 or 53 (125388)

55 exp Glucocorticoids/ (153182)

56 (gl?cocortico$ or corticosteroid$).mp. (134114)

57 55 or 56 (220583)

58 gabapentin.mp. (3673)

59 pregabalin.mp. (1128)

60 anticonvulsant$.mp. or exp Anticonvulsants/ (117675)

61 antiepileptic$.mp. (14159)

62 58 or 59 or 60 or 61 (123069)

63 exp Diphosphonates/ or (diphosphon$ or bi?phosphon$).mp. (22348)

64 exp Celiac Plexus/ or (celiac plexus or plexus coeliacus or visceral plexus or solar plexus).mp. (1060)

65 exp Nerve Block/ or (chemical neurolysis or chemodenervation or block or blockade).mp. (236401)

66 64 and 65 (468)

67 41 or 44 or 48 or 51 or 54 or 57 or 62 or 63 or 66 (1098652)

68 meta-analysis.mp,pt. or review.pt. or search:.tw. (1857981)

69 37 and 38 and 67 and 68 (3140)

70 limit 69 to yr="2001 - 2012" (2026)

3.1.2. OVID PreMedline

Search date: 20-07-2012

1 exp Neoplasms/ (5)

2 Neoplasm Staging/ (0)

3 tumor$.ab,ti. (34249)

4 cancer$.ti,ab. (46805)

5 tumour$.ab,ti. (8005)

6 carcinoma$.ab,ti. (16842)

7 neoplasm$.ab,ti. (3448)

8 lymphoma.ab,ti. (3527)

9 melanoma$.ab,ti. (2400)

10 Staging.ab,ti. (2027)

11 metastas$.ab,ti. (9031)

12 metastatic.ab,ti. (6085)

13 exp Neoplasm Metastasis/ (1)

14 exp Neoplastic Processes/ (1)

15 neoplastic process$.ab,ti. (62)

16 non small cell.ab,ti. (1819)

17 adenocarcinoma$.ab,ti. (3521)

18 squamous cell.ab,ti. (2637)

19 nsclc.ab,ti. (1211)

20 osteosarcoma$.ab,ti. (497)

21 phyllodes.ab,ti. (53)

22 cystosarcoma$.ab,ti. (11)

23 fibroadenoma$.ab,ti. (94)

24 (non adj small adj cell).ab,ti. (1819)

25 (non adj2 small adj2 cell).ab,ti. (1825)

26 (nonsmall adj2 cell).ab,ti. (97)

27 plasmacytoma$.ab,ti. (119)

28 myeloma.ab,ti. (1089)

29 multiple myeloma.ab,ti. (841)

30 lymphoblastoma$.ab,ti. (10)

31 lymphocytoma$.ab,ti. (7)

32 lymphosarcoma$.ab,ti. (83)

33 immunocytoma.ab,ti. (2)

34 sarcoma$.ab,ti. (2832)

35 hodgkin$.ab,ti. (1409)

36 (nonhodgkin$ or non hodgkin$).ab,ti. (882)

37 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 (85982)

38 pain.mp. or exp Pain/ (20790)

39 Radiotherapy/ (0)

40 radiothera$.tw. (4255)

41 39 or 40 (4255)

42 exp Radioisotopes/ or exp Radiopharmaceuticals/ (0)

43 (radiopharmaceutical$ or radioactive isotope$ or radioisotope$ or radionuclide$).mp. (1418)

44 42 or 43 (1418)

45 paracetamol.mp. or exp Acetaminophen/ (435)

46 exp *Anti-Inflammatory Agents, Non-Steroidal/ (3)

47 ((non-steroidal and anti-inflammatory) or nsai$).mp. (1185)

48 45 or 46 or 47 (1561)

49 exp *Analgesics, Opioid/ (1)

50 (opioid$ or morphine).mp. (2877)

51 49 or 50 (2877)

52 exp Antidepressive Agents/ (0)

53 (antidepressant$ or antidepressive agent$ or antidepressive drug$).mp. (2222)

54 52 or 53 (2222)

55 exp Glucocorticoids/ (0)

56 (gl?cocortico$ or corticosteroid$).mp. (4159)

57 55 or 56 (4159)

58 gabapentin.mp. (240)

59 pregabalin.mp. (166)

60 anticonvulsant$.mp. or exp Anticonvulsants/ (571)

61 antiepileptic$.mp. (735)

62 58 or 59 or 60 or 61 (1502)

63 exp Diphosphonates/ or (diphosphon$ or bi?phosphon$).mp. (827)

64 exp Celiac Plexus/ or (celiac plexus or plexus coeliacus or visceral plexus or solar plexus).mp. (28)

65 exp Nerve Block/ or (chemical neurolysis or chemodenervation or block or blockade).mp. (11025)

66 64 and 65 (18)

67 41 or 44 or 48 or 51 or 54 or 57 or 62 or 63 or 66 (17962)

68 meta-analysis.mp,pt. or review.pt. or search:.tw. (18244)

69 37 and 38 and 67 and 68 (24)

70 limit 69 to yr="2001 - 2012" (19)

3.1.3. EMBASE

Search date: 20-07-2012

'neoplasm'/exp OR 'cancer staging'/exp OR 'metastasis'/exp OR 'oncogenesis and malignant transformation'/exp OR cancer*:ab,ti OR tumor*:ab,ti OR tumour*:ab,ti OR carcinoma*:ab,ti OR neoplasm*:ab,ti OR lymphoma:ab,ti OR melanoma:ab,ti OR staging:ab,ti OR metastas*:ab,ti OR metastatic:ab,ti OR (neoplastic:ab,ti AND process*:ab,ti) OR (non:ab,ti AND small:ab,ti AND cell:ab,ti) OR adenocarcinoma*:ab,ti OR (squamous:ab,ti AND cell:ab,ti) OR nsclc:ab,ti OR osteosarcoma*:ab,ti OR phyllodes:ab,ti OR cystosarcoma*:ab,ti OR fibroadenoma*:ab,ti OR (non:ab,ti AND small:ab,ti AND next:ab,ti AND cell:ab,ti) OR (small NEAR/2 cell):ab,ti OR (nonsmall NEAR/2 cell):ab,ti OR plasmacytoma*:ab,ti OR myeloma:ab,ti OR (multiple:ab,ti AND myeloma:ab,ti) OR lymphoblastoma*:ab,ti OR lymphocytoma*:ab,ti OR lymphosarcoma*:ab,ti OR immunocytoma:ab,ti OR sarcoma*:ab,ti OR hodgkin*:ab,ti OR nonhodgkin*:ab,ti OR (non:ab,ti AND hodgkin*:ab,ti) AND ('pain'/exp OR pain:ab,ti) AND ('radiotherapy'/exp OR radiothera*:ab,ti OR 'radioisotope'/exp OR 'radiopharmaceutical agent'/exp OR 'paracetamol'/exp OR 'nonsteroid antiinflammatory agent'/exp OR 'pregabalin'/de OR 'gabapentin enacarbil'/de OR 'anticonvulsive agent'/de OR 'opiate receptor agonist'/exp OR opioid* OR morphine OR 'antidepressant agent'/exp OR 'corticosteroid'/exp OR 'bisphosphonic acid derivative'/exp OR ('celiac plexus'/exp AND 'nerve block'/exp)) AND ([cochrane review]/lim OR [meta analysis]/lim OR [systematic review]/lim) AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND [embase]/lim AND [2001-2012]/py (Results 1,017)

3.1.4. Cochrane Library

Search date: 23-07-2012

#1 MeSH descriptor Neoplasms explode all trees
#2 MeSH descriptor Neoplasm Staging, this term only
#3 cancer*:ti,ab
#4 tumor*:ti,ab
#5 tumour*:ti,ab
#6 carcinoma*:ti,ab
#7 neoplasm*:ti,ab
#8 lymphoma:ti,ab
#9 melanoma:ti,ab
#10 staging:ti,ab
#11 metasta*:ti,ab
#12 MeSH descriptor Neoplasm Metastasis explode tree 1
#13 MeSH descriptor Neoplastic Processes explode tree 1
#14 neoplastic process*:ti,ab
#15 non small cell:ti,ab
#16 adenocarcinoma*:ti,ab
#17 squamous cell:ti,ab
#18 nsclc:ti,ab
#19 osteosarcoma*:ti,ab
#20 phyllodes:ti,ab
#21 cystosarcoma*:ti,ab
#22 fibroadenoma*:ti,ab
#23 (non NEXT small NEXT cell):ti,ab
#24 (nonsmall NEAR/2 cell):ti,ab
#25 plasmacytoma*:ti,ab
#26 myeloma:ti,ab
#27 lymphoblastoma*:ti,ab
#28 lymphocytoma*:ti,ab
#29 lymphosarcoma*:ti,ab
#30 immunocytoma:ti,ab
#31 sarcoma*:ti,ab
#32 hodgkin*:ti,ab
#33 nonhodgkin*:ti,ab
#34 non hodgkin*:ti,ab
#35 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34)
#36 MeSH descriptor Pain explode tree 1
#37 pain:ti,ab
#38 (#36 OR #37)
#39 MeSH descriptor Radiotherapy explode all trees
#40 radiothera*:ti,ab
#41 (#39 OR #40)
#42 MeSH descriptor Radioisotopes explode all trees
#43 MeSH descriptor Radiopharmaceuticals explode all trees
#44 (radiopharmaceutical* OR radioactive isotope* OR radioisotope* OR radionuclide*):ti,ab
#45 (#42 OR #43 OR #44)
#46 MeSH descriptor Acetaminophen explode tree 1
#47 paracetamol:ti,ab
#48 MeSH descriptor Anti-Inflammatory Agents, Non-Steroidal explode tree 1
#49 ((non-steroidal AND anti-inflammatory) OR nsai*):ti,ab
#50 (#46 OR #47 OR #48 OR #49)
#51 MeSH descriptor Analgesics, Opioid explode tree 1
#52 (opioid* OR morphine):ti,ab
#53 (#51 OR #52)
#54 MeSH descriptor Antidepressive Agents explode all trees

#55 (antidepressant* OR antidepressive agent* OR antidepressive drug*):ti,ab
#56 (#54 OR #55)
#57 MeSH descriptor Glucocorticoids explode tree 1
#58 (glucocortico* OR glycocortico* OR corticosteroid*):ti,ab
#59 (#57 OR #58)
#60 MeSH descriptor Anticonvulsants explode all trees
#61 (gabapentin OR pregabalin OR anticonvulsant* OR antiepileptic*):ti,ab
#62 (#60 OR #61)
#63 MeSH descriptor Diphosphonates explode tree 1
#64 (diphosphon* OR biphosphon* OR bisphosphon*):ti,ab
#65 (#63 OR #64)
#66 MeSH descriptor Celiac Plexus explode tree 1
#67 MeSH descriptor Nerve Block explode tree 1
#68 (celiac plexus OR plexus coeliacus OR visceral plexus OR solar plexus):ti,ab
#69 (chemical neurolysis OR chemodenervation OR block OR blockade):ti,ab
#70 (#66 OR #68)
#71 (#67 OR #69)
#72 (#70 AND #71)
#73 (#41 OR 45 OR #50 OR #53 OR #56 OR #59 OR #62 OR #65 OR #72)
#74 (#35 AND #38 AND #73)
#75 (#74), from 2001 to 2012

3.2. Randomized controlled trials

3.2.1. OVID Medline

Search date: 13-11-2012
1 exp Neoplasms/ (2408989)
2 Neoplasm Staging/ (109806)
3 tumor$.ab,ti. (858149)
4 cancer$.ti,ab. (918960)
5 tumour$.ab,ti. (184552)
6 carcinoma$.ab,ti. (423729)
7 neoplasm$.ab,ti. (88668)
8 lymphoma.ab,ti. (100533)
9 melanoma$.ab,ti. (72654)
10 Staging.ab,ti. (44153)
11 metastas$.ab,ti. (193036)
12 metastatic.ab,ti. (124043)
13 exp Neoplasm Metastasis/ (145973)
14 exp Neoplastic Processes/ (310824)
15 neoplastic process$.ab,ti. (2175)
16 non small cell.ab,ti. (26133)
17 adenocarcinoma$.ab,ti. (85398)
18 squamous cell.ab,ti. (58426)
19 nsclc.ab,ti. (14672)
20 osteosarcoma$.ab,ti. (13560)
21 phyllodes.ab,ti. (1181)
22 cystosarcoma$.ab,ti. (542)
23 fibroadenoma$.ab,ti. (2777)
24 (non adj small adj cell).ab,ti. (26133)
25 (non adj2 small adj2 cell).ab,ti. (26335)
26 (nonsmall adj2 cell).ab,ti. (1601)
27 plasmacytoma$.ab,ti. (5014)

28 myeloma.ab,ti. (33057)

29 multiple myeloma.ab,ti. (21010)

30 lymphoblastoma$.ab,ti. (260)

31 lymphocytoma$.ab,ti. (254)

32 lymphosarcoma$.ab,ti. (3596)

33 immunocytoma.ab,ti. (399)

34 sarcoma$.ab,ti. (67018)

35 hodgkin$.ab,ti. (48502)

36 (nonhodgkin$ or non hodgkin$).ab,ti. (27748)

37 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 (2769885)

38 pain.mp. or exp Pain/ (482411)

39 Radiotherapy/ (33734)

40 radiothera$.tw. (100789)

41 39 or 40 (121895)

42 exp Radioisotopes/ or exp Radiopharmaceuticals/ (270711)

43 (radiopharmaceutical$ or radioactive isotope$ or radioisotope$ or radionuclide$).mp. (233994)

44 42 or 43 (315635)

45 paracetamol.mp. or exp Acetaminophen/ (15283)

46 exp *Anti-Inflammatory Agents, Non-Steroidal/ (87462)

47 ((non-steroidal and anti-inflammatory) or nsai$).mp. (57638)

48 45 or 46 or 47 (120366)

49 exp *Analgesics, Opioid/ (59253)

50 (opioid$ or morphine).mp. (100333)

51 49 or 50 (117777)

52 exp Antidepressive Agents/ (115784)

53 (antidepressant$ or antidepressive agent$ or antidepressive drug$).mp.(60897)

54 52 or 53 (127257)

55 exp Glucocorticoids/ (155208)

56 (gl?cocortico$ or corticosteroid$).mp. (136625)

57 55 or 56 (223996)

58 gabapentin.mp. (3789)

59 pregabalin.mp. (1216)

60 anticonvulsant$.mp. or exp Anticonvulsants/ (118991)

61 antiepileptic$.mp. (14492)

62 58 or 59 or 60 or 61 (124574)

63 exp Diphosphonates/ or (diphosphon$ or bi?phosphon$).mp. (22870)

64 exp Celiac Plexus/ or (celiac plexus or plexus coeliacus or visceral plexus or solar plexus).mp. (1073)

65 exp Nerve Block/ or (chemical neurolysis or chemodenervation or block or blockade).mp. (240957)

66 64 and 65 (473)

67 41 or 44 or 48 or 51 or 54 or 57 or 62 or 63 or 66 (1114669)

68 randomized controlled trial.pt. (341521)

69 controlled clinical trial.pt. (85628)

70 randomized.ab. (244176)

71 placebo.ab. (136288)

72 clinical trials as topic.sh. (163570)

73 randomly.ab. (174754)

74 trial.ti. (105518)

75 68 or 69 or 70 or 71 or 72 or 73 or 74 (789737)

76 exp animals/ not humans.sh. (3807580)

77 75 not 76 (727544)

78 37 and 38 and 67 and 77 (2151)

79 limit 78 to yr="2001 - 2012" (1374)

3.2.2. OVID PreMedline

Search date: 13-11-2012

1 exp Neoplasms/ (9)
2 Neoplasm Staging/ (0)
3 tumor$.ab,ti. (37261)
4 cancer$.ti,ab. (51173)
5 tumour$.ab,ti. (8689)
6 carcinoma$.ab,ti. (18252)
7 neoplasm$.ab,ti. (3895)
8 lymphoma.ab,ti. (3970)
9 melanoma$.ab,ti. (2685)
10 Staging.ab,ti. (2326)
11 metastas$.ab,ti. (10211)
12 metastatic.ab,ti. (6743)
13 exp Neoplasm Metastasis/ (1)
14 exp Neoplastic Processes/ (1)
15 neoplastic process$.ab,ti. (65)
16 non small cell.ab,ti. (2190)
17 adenocarcinoma$.ab,ti. (3982)
18 squamous cell.ab,ti. (2936)
19 nsclc.ab,ti. (1498)
20 osteosarcoma$.ab,ti. (573)
21 phyllodes.ab,ti. (59)
22 cystosarcoma$.ab,ti. (12)
23 fibroadenoma$.ab,ti. (109)
24 (non adj small adj cell).ab,ti. (2190)
25 (non adj2 small adj2 cell).ab,ti. (2193)
26 (nonsmall adj2 cell).ab,ti. (111)
27 plasmacytoma$.ab,ti. (128)
28 myeloma.ab,ti. (1234)
29 multiple myeloma.ab,ti. (957)
30 lymphoblastoma$.ab,ti. (12)
31 lymphocytoma$.ab,ti. (10)
32 lymphosarcoma$.ab,ti. (85)
33 immunocytoma.ab,ti. (1)
34 sarcoma$.ab,ti. (3057)
35 hodgkin$.ab,ti. (1533)
36 (nonhodgkin$ or non hodgkin$).ab,ti. (983)
37 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or
31 or 32 or 33 or 34 or 35 or 36 (93575)
38 pain.mp. or exp Pain/ (22362)
39 Radiotherapy/ (0)
40 radiothera$.tw. (4574)
41 39 or 40 (4574)
42 exp Radioisotopes/ or exp Radiopharmaceuticals/ (0)
43 (radiopharmaceutical$ or radioactive isotope$ or radioisotope$ or radionuclide$).mp. (1528)
44 42 or 43 (1528)
45 paracetamol.mp. or exp Acetaminophen/ (434)
46 exp *Anti-Inflammatory Agents, Non-Steroidal/ (3)
47 ((non-steroidal and anti-inflammatory) or nsai$).mp. (1271)
48 45 or 46 or 47 (1646)
49 exp *Analgesics, Opioid/ (1)
50 (opioid$ or morphine).mp. (2974)
51 49 or 50 (2974)
52 exp Antidepressive Agents/ (0)

53 (antidepressant$ or antidepressive agent$ or antidepressive drug$).mp. (2290)

54 52 or 53 (2290)

55 exp Glucocorticoids/ (0)

56 (gl?cocortico$ or corticosteroid$).mp. (4506)

57 55 or 56 (4506)

58 gabapentin.mp. (265)

59 pregabalin.mp. (170)

60 anticonvulsant$.mp. or exp Anticonvulsants/ (603)

61 antiepileptic$.mp. (838)

62 58 or 59 or 60 or 61 (1657)

63 exp Diphosphonates/ or (diphosphon$ or bi?phosphon$).mp. (901)

64 exp Celiac Plexus/ or (celiac plexus or plexus coeliacus or visceral plexus or

solar plexus).mp. (28)

65 exp Nerve Block/ or (chemical neurolysis or chemodenervation or block or

blockade).mp. (11665)

66 64 and 65 (18)

67 41 or 44 or 48 or 51 or 54 or 57 or 62 or 63 or 66 (19190)

68 randomized controlled trial.pt. (462)

69 controlled clinical trial.pt. (22)

70 randomized.ab. (13341)

71 placebo.ab. (5136)

72 clinical trials as topic.sh. (1)

73 randomly.ab. (13022)

74 trial.ti. (5292)

75 68 or 69 or 70 or 71 or 72 or 73 or 74 (30196)

76 exp animals/ not humans.sh. (3)

77 75 not 76 (30196)

78 37 and 38 and 67 and 77 (75)

79 limit 78 to yr="2001 - 2012" (67)

3.2.3. EMBASE

Search date: 13-11-2012

('neoplasm'/exp OR 'cancer staging'/exp OR 'metastasis'/exp OR 'oncogenesis and malignant transformation'/exp OR cancer*:ab,ti OR tumor*:ab,ti OR tumour*:ab,ti OR carcinoma*:ab,ti OR neoplasm*:ab,ti OR lymphoma:ab,ti OR melanoma:ab,ti OR staging:ab,ti OR metastas*:ab,ti OR metastatic:ab,ti OR (neoplastic:ab,ti AND process*:ab,ti) OR (non:ab,ti AND small:ab,ti AND cell:ab,ti) OR adenocarcinoma*:ab,ti OR (squamous:ab,ti AND cell:ab,ti) OR nsclc:ab,ti OR osteosarcoma*:ab,ti OR phyllodes:ab,ti OR cystosarcoma*:ab,ti OR fibroadenoma*:ab,ti OR (non:ab,ti AND small:ab,ti AND next:ab,ti AND cell:ab,ti) OR (small NEAR/2 cell):ab,ti OR (nonsmall NEAR/2 cell):ab,ti OR plasmacytoma*:ab,ti OR myeloma:ab,ti OR (multiple:ab,ti AND myeloma:ab,ti) OR lymphoblastoma*:ab,ti OR lymphocytoma*:ab,ti OR lymphosarcoma*:ab,ti OR immunocytoma:ab,ti OR sarcoma*:ab,ti OR hodgkin*:ab,ti OR nonhodgkin*:ab,ti OR (non:ab,ti AND hodgkin*:ab,ti)) AND ('pain'/exp OR pain:ab,ti) AND ('radiotherapy'/exp OR radiothera*:ab,ti OR 'radioisotope'/exp OR 'radiopharmaceutical agent'/exp OR 'paracetamol'/exp OR 'nonsteroid antiinflammatory agent'/exp OR 'pregabalin'/de OR 'gabapentin enacarbil'/de OR 'anticonvulsive agent'/de OR 'opiate receptor agonist'/exp OR opioid* OR morphine OR 'antidepressant agent'/exp OR 'corticosteroid'/exp OR 'bisphosphonic acid derivative'/exp OR ('celiac plexus'/exp AND 'nerve block'/exp)) AND [randomized controlled trial]/lim AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND [embase]/lim AND [2001-2012]/py (Results 2171)

3.2.4. CENTRAL

Search date: 13-11-2012

#1 MeSH descriptor Neoplasms explode all trees

#2 MeSH descriptor Neoplasm Staging, this term only

#3 cancer*:ti,ab

#4 tumor*:ti,ab

#5 tumour*:ti,ab

#6 carcinoma*:ti,ab
#7 neoplasm*:ti,ab
#8 lymphoma:ti,ab
#9 melanoma:ti,ab
#10 staging:ti,ab
#11 metasta*:ti,ab
#12 MeSH descriptor Neoplasm Metastasis explode tree 1
#13 MeSH descriptor Neoplastic Processes explode tree 1
#14 neoplastic process*:ti,ab
#15 non small cell:ti,ab
#16 adenocarcinoma*:ti,ab
#17 squamous cell:ti,ab
#18 nsclc:ti,ab
#19 osteosarcoma*:ti,ab
#20 phyllodes:ti,ab
#21 cystosarcoma*:ti,ab
#22 fibroadenoma*:ti,ab
#23 (non NEXT small NEXT cell):ti,ab
#24 (nonsmall NEAR/2 cell):ti,ab
#25 plasmacytoma*:ti,ab
#26 myeloma:ti,ab
#27 lymphoblastoma*:ti,ab
#28 lymphocytoma*:ti,ab
#29 lymphosarcoma*:ti,ab
#30 immunocytoma:ti,ab
#31 sarcoma*:ti,ab
#32 hodgkin*:ti,ab
#33 nonhodgkin*:ti,ab
#34 non hodgkin*:ti,ab
#35 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34)
#36 MeSH descriptor Pain explode tree 1
#37 pain:ti,ab
#38 (#36 OR #37)
#39 MeSH descriptor Radiotherapy explode all trees
#40 radiothera*:ti,ab
#41 (#39 OR #40)
#42 MeSH descriptor Radioisotopes explode all trees
#43 MeSH descriptor Radiopharmaceuticals explode all trees
#44 (radiopharmaceutical* OR radioactive isotope* OR radioisotope* OR radionuclide*):ti,ab
#45 (#42 OR #43 OR #44)
#46 MeSH descriptor Acetaminophen explode tree 1
#47 paracetamol:ti,ab
#48 MeSH descriptor Anti-Inflammatory Agents, Non-Steroidal explode tree 1
#49 ((non-steroidal AND anti-inflammatory) OR nsai*):ti,ab
#50 (#46 OR #47 OR #48 OR #49)
#51 MeSH descriptor Analgesics, Opioid explode tree 1
#52 (opioid* OR morphine):ti,ab
#53 (#51 OR #52)
#54 MeSH descriptor Antidepressive Agents explode all trees
#55 (antidepressant* OR antidepressive agent* OR antidepressive drug*):ti,ab
#56 (#54 OR #55)
#57 MeSH descriptor Glucocorticoids explode tree 1
#58 (glucocortico* OR glycocortico* OR corticosteroid*):ti,ab
#59 (#57 OR #58)

#60 MeSH descriptor Anticonvulsants explode all trees

#61 (gabapentin OR pregabalin OR anticonvulsant* OR antiepileptic*):ti,ab

#62 (#60 OR #61)

#63 MeSH descriptor Diphosphonates explode tree 1

#64 (diphosphon* OR biphosphon* OR bisphosphon*):ti,ab

#65 (#63 OR #64)

#66 MeSH descriptor Celiac Plexus explode tree 1

#67 MeSH descriptor Nerve Block explode tree 1

#68 (celiac plexus OR plexus coeliacus OR visceral plexus OR solar plexus):ti,ab

#69 (chemical neurolysis OR chemodenervation OR block OR blockade):ti,ab

#70 (#66 OR #68)

#71 (#67 OR #69)

#72 (#70 AND #71)

#73 (#41 OR 45 OR #50 OR #53 OR #56 OR #59 OR #62 OR #65 OR #72)

#74 (#35 AND #38 AND #73)

#75 (#74), from 2001 to 2012

4. SELECTION PROCESS

4.1. Results of selection process

4.1.1. Guideline websites and websites of organisations in oncology

Table 4 – Guideline websites and websites of organisations in oncology

Search terms: "cancer pain", "neoplasm pain", "guideline", "evidence"; selection on Title and Summary, duplicates removed. Search date: August 2nd 2012.

Alberta Heritage Foundation For Medical Research (AHFMR)	http://www.ahfmr.ab.ca/ via http://www.ihe.ca/ 0 relevant
American Society of Clinical Oncology (ASCO)	http://www.asco.org/ 1 relevant
American College of Surgeons (ACS)	http://www.facs.org/cancer/coc/ 0 relevant
Cancer Care Ontario	http://www.cancercare.on.ca/english/home/ 2 relevant
CMA Infobase	http://mdm.ca/cpgsnew/cpgs/index.asp 1 relevant
Guidelines International Network (GIN)	http://www.g-i-n.net/ 2 relevant
National Comprehensive Cancer Network (NCCN)	http://www.nccn.org/ 1 relevant
National Guideline Clearinghouse	http://www.guideline.gov/ 7 relevant
National Cancer Institute	http://www.cancer.gov/ 0 relevant
Haute Autorité de Santé	http://bfes.has-

(HAS)	sante.fr/HTML/indexBFES_HAS.html 0 relevant
BC Cancer Agency	http://www.bccancer.bc.ca/default.htm 0 relevant
Institute for Clinical Systems Improvement (ICSI)	http://www.icsi.org/index.asp 0 relevant
National Health and Medical Research Council (NHMRC)	http://www.nhmrc.gov.au/ 0 relevant
Scottish Intercollegiate Guidelines Network (SIGN)	http://www.sign.ac.uk/ 1 relevant
New Zealand Guidelines Group (NZGG)	http://www.nzgg.org.nz/ 0 relevant
Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC)	http://www.fnclcc.fr/sor/structure/index-sorspecialistes.html; http://www.unicancer.fr/ 0 relevant
National Institute for Health and Clinical Excellence (NICE)	http://www.nice.org.uk/ 4 relevant

4.2. Specific selection criteria

4.2.1. Bisphosphonates

The 59 RCTs obtained from all the SRs and the 3 RCTs from the RCT update (see report chapter 4.4.2), were ranked according to the different bisphosphonate molecules and the comparators in the control group. The full text of the RCTs was further evaluated according to the following parameters:

- use of a standardized pain scale (e.g. reporting of “mild or severe pain” without the use of a scale is excluded);
- use of a composite pain score including also e.g. performance status; in this case the results of the pain score have to be mentioned separately;
- reporting of the quantitative data (e.g. reporting of p-value only, or reporting of the results in a figure without reporting the data, is excluded).

The results of this selection process are presented below.

After this selection process, of the 62 RCTs from SRs and from the RCT update, 22 RCTs were definitively included in the literature overview.

Pamidronate

- Pamidronate-placebo

Ten RCTs were retrieved; 4 were included (Hortobagyi 1996, Hultborn 1999, Small 2003 and Theriault 1999)[4-7]. The reasons for exclusion are the following: no pain related outcome (Musto 2003)[8], quantitative results not provided (Berenson 1996, Brinker 1988)[9, 10], duplicate because the sample is described in other papers (Berenson 1998, Hortobagyi 1998)[11, 12] and no separate pain related outcome because of the use of a composite pain score including performance status and number of days off (Vinholes 1997)[13].

- Pamidronate-control condition

Seven RCTs were retrieved; only one RCT was included (Conte 1996)[14]. The reasons for exclusion are the following: no pain related outcome (Attal 2006, Van Holten-Verzantvoort 1993)[15, 16], duplicate because the sample is described in other papers (Conte 1994)[17], composite pain score including

number of days off and number of hospitalization days (Terpos 2000)[18]; pain score methodology not provided (Van Holten-Verzantvoort 1987)[19], population (no bone metastases) (Van Holten-Verzantvoort 1996)[20].

- Pamidronate-pamidronate

Four RCTs were retrieved (Glover 1994, Cascinu 1998, Colemen 1998, Koeberle 1999)[21-24]; none was included because comparing different doses of pamidronate and/or different routes of administration was considered to be out of scope.

- Pamidronate-zoledronate

Two RCTs were retrieved; 1 was included (Berenson 2001)[25]**.** The other RCT was excluded because no quantitative results were provided (Rosen 2001)[26].

- Pamidronate-clodronate

One RTC was retrieved (Jagdev 2001)[27] but was not included because pain score included performance status.

Clodronate

- Clodronate-placebo

Twenty RTCs were retrieved; 10 RCTs were included (Tubiana-Hulin 2001, Robertson 1995, Piga 1998, O'Rourke 1995, Lahtinen 1992, Kylmälä 1997, Ernst 2003, Dearnaley 2003, Ernst 1992, Ernst 1997)[28-37].

The reasons for exclusion are the following: no pain related outcome (Elomaa 1983, Siris 1980)[38, 39], sample size of 12 patients only (Delmas 1982)[40], pain evaluation methodology not provided (Siris 1983; Elomaa 1992, McCloskey 2001),[41-43] quantitative results not provided (Adami 1989, Ernst 1992, Ernst 1997, Martoni 1991, Strang 1997)[29, 30, 44-46] and duplicate because the sample is described in other papers (McCloskey 1998)[47].

- Clodronate-control

Three RTCs were retrieved; none was included. Two publications (Kristensen 1999, Kulmälä 1993)[48, 49] were excluded because no quantitative values were provided: the results were presented in graphs. One publication (Arican 1999)[50] was excluded because comparing different doses of clodronate was considered to be out of scope.

Ibandronate

- Ibandronate–placebo

Five RCTs were retrieved; 2 were included (Diel 2004, Tripathy D 2004)[51, 52]. The three others were excluded because no quantitative data are provided (Body 2003, Menssen 2002)[53, 54] and pain was not measured by a scale (Body 2004)[55].

- Ibandronate-zoledronic acid

One RCT was retrieved (Body 2007)[56] and included.

Zoledronate

- Zoledronate-placebo

Two RCTs were retieved; one was included (Saad 2002)[57]. The other one (Kohno 2005)[58] was excluded because no quantitative data are provided.

The sample of Saad 2002 was the subject of multiple publications[57]. Two of these papers (Saad 2004, Weinfurt 2006)[59, 60] were included and are reported here as one publication with Saad 2002. Saad 2005 and Saad 2010 were excluded because no additional data on pain relief and QoL are provided[61, 62]. Maung 2002 was excluded because pain was not reported on a validated scale[63]. Weinfurt 2005 was excluded because pain and QoL were not analyzed in relation to a specific intervention[64].

- Zoledronate-control condition

One RCT was retrieved (Musto 2008)[65] but was excluded because no pain outcome presented in the results section.

- Zoledronate-denosumab

Two RTCs were retrieved ; none was included. The 2 RCTs (Fizazi 2011, Stopeck 2010)[66, 67] were excluded because pain was not measured by a scale.

- Zoledronate–pamidronate

See pamidronate

- Zoledronate-ibrandronate

See ibandronate

Etidronate

Three RCTs compare etidronate to placebo. One RCT was included (Daragon 1993)[68]. Belch 1991 was excluded because no pain related outcome were presented[69]. Smith 1989 was excluded because the pain scale used was not defined[70].

Residronate

One RCT (Meulenbeld 2012)[71] was retrieved and included.

List of 22 included RCTs specified by molecule and by tumour type

Breast cancer: B ; Prostate cancer: P ; Multiple myeloma: MM ; mixed cancer types: mixed.

(All RCTs compare intervention against placebo, except: Against control: Conte 1996B; Meulenbeld 2012P. Against other biphosph: Berenson 2001 B&MM; Body 2007B)

- **Pamidronate**
  Hortobagyi 1996B
  Hultborn 1999B
  Theriault 1999B
  Small 2003P
  Conte 1996B
- **Pamidronate versus zoledronate**
  Berenson 2001 B&MM
- **Ibandronate**
  Diel 2004B
  Tripathy 2004B
- **Ibandranote versus zoledronate**
  Body 2007B
- **Clodronate**
  Dearnaly 2003P
  Ernst 2003P
  Kylmala 1997P
  Lahtinen 1992MM
  O'Rourke 1995mixed
  Piga 1998mixed
  Robertson 1995mixed
  Tubiana-Hulin 2001B
  Ernst 1992mixed
  Ernst 1997mixed
- **Zoledronate**
  Saad 2002P
- **Etidronate**
  Daragon 1993MM
- **Residronate**
  Meulenbeld 2012P

5. MEASUREMENT INSTRUMENTS

5.1. Pain scales

Pain measurement is challenging. Indeed, pain is a blend of the strength of the underlying stimulus and of the patient's emotional response to it. The patient's response is influenced by biological factors but also by both social and psychological factors[72].

The most common strategies to measure pain intensity are verbal rating scales, numerical rating scales, visual analog scales. Some authors (i.e. Kalso 1996)[73] used several scales together to measure pain intensity. Pain assessment is often self-reported and daily recorded in a diary.

Verbal rating scales (VRS)

The verbal rating method consists in asking patients to chose among main descriptors (e.g. mild, moderate, severe)[74]. Results can be presented as wording or score. In that case, points are attributed to each descriptors. Verbal rating scale can be used to assess pain intensity or pain relief.

List of VRS used in this report:

- For pain intensity
  - 4 levels pain scale (none, mild, moderate, severe)
  - 5-point pain scale (0=none, 1=mild, 2=moderate, 3=severe or 4=intolerable)
  - 6-point pain scale (0=none, 1=mild, 2=moderate, 3=severe, 4=very severe or 5=unbearable)
  - 8-point verbal rating scale based on Turket's Pain Perception Profile (see below)
- For pain relief
  - 5-point verbal rating scale based on Turket's Pain Perception Profile (see below)

Numerical rating scales (NRS)

This pain measurement approach involves asking the patient to pick a number that represents their pain level (e.g. 0-10)[74].

List of NRS used in this report:

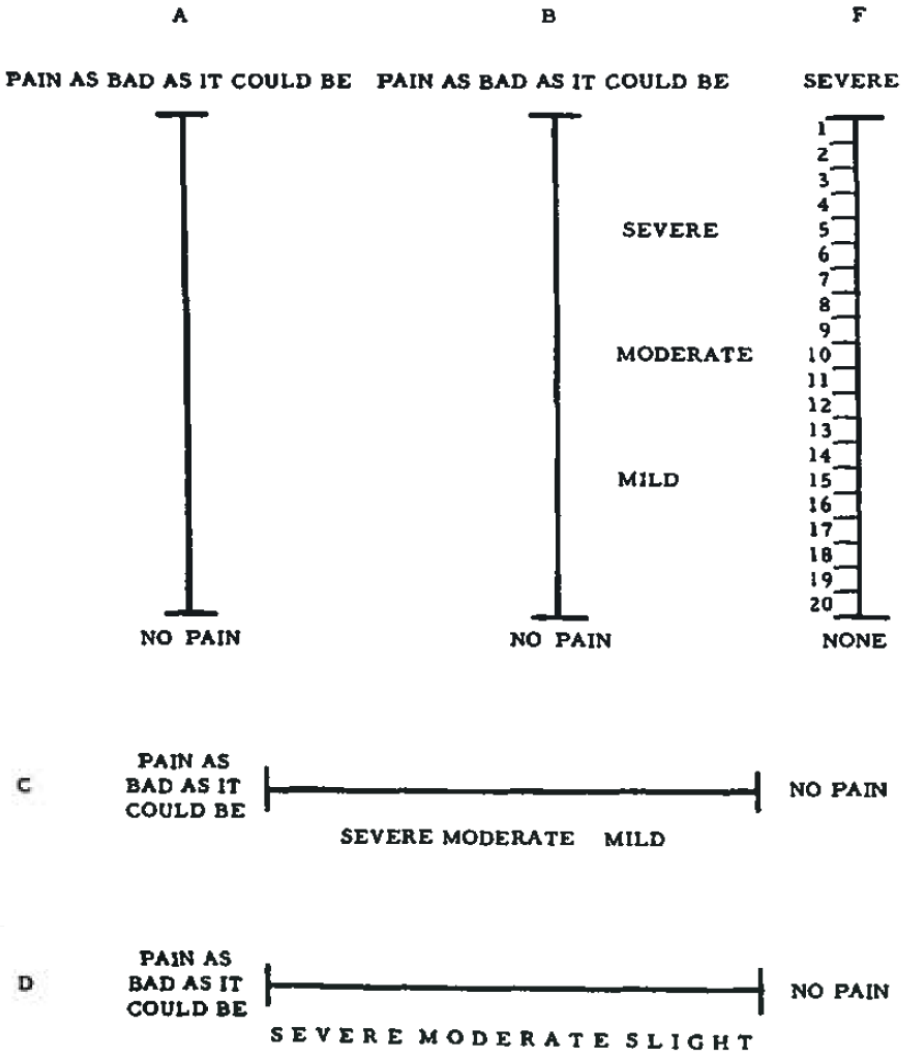
- Numerical scale from 0 to 10 for pain intensity

Visual analogue pain rating scales (VAS)

The visual analogue rating methods lies in placing a mark at a certain distant along a line to represent the intensity of a stimulus. Huskisson popularized the application of VAS to measuring pain during the 1970's. By convention, the line is 10 cm but variations may be encountered (i.e. 150 mm,…). It is now widely used in the assessment of cancer-related pain.

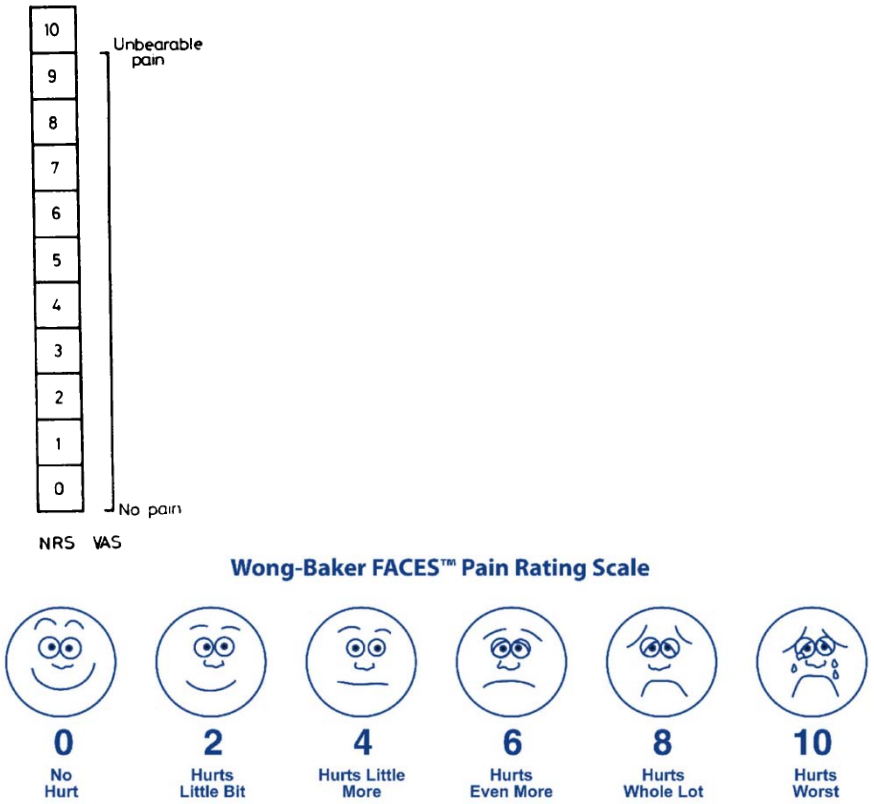
The VAS tool consists in line with labels at extremity (i.e. 'pain as bad as it could be' and 'no pain or') as shown in Figure 1[72].

Figure 1 – Examples of visual analogue pain rating scales (A to D) and numerical scale (F)[75]



Many variants of this scale exist. Labels at extremity can have different wording (i.e. no pain' to 'worst possible pain') or descriptive terms may be placed along the plain line (i.e. 'severe', 'moderate' or 'mild' or 'none', 'mild', 'moderate', 'severe'). VAS can also take the form of a numerical rating scale (see F in the previous figure). The Likert scales on 5, 7 or 10 points are example of this type of assessment.

Figure 2 – Examples of numerical scale



Sources: up Downie 1978 [76], down in Savino F, Vagliano L, Ceratto S, Viviani F, Miniero R et al. (2013) Pain assessment in children undergoing venipuncture: the Wong–Baker faces scale versus skin conductance fluctuations. PeerJ 1:e37

List of VAS used in this report:

- Huskisson VAS
- 10-point Scott-Huskisson scale
- Present Pain Intensity - VAS: 10 cm horizontal line marked 'no pain' to 'worst possible pain'
- VAS 150 mm
- VAS pain score (from 0-10)
- 7-point Likert scale

Alternative forms of tool to assess pain can be found (15 cm plastic slider moved by patient and revealing the perceived pain intensity, scales presented as thermometers, scales with pictures of faces expressing pain). VAS is often preferred to verbal or numerical scales because of its greater sensibility and therefore, the smaller sample size required. However, VAS may give rise to difficulties for some target patients populations (i.e. elderly, less-educated respondents,…).

In estimating **pain relief**, other scales are undertaken as descriptive scale (as 'none', 'slight', 'moderate' or 'complete relief') or VAS running from no relief to complete relief of pain. The pain relief scale presents the advantage of measuring the potential response whatever the initial pain level.

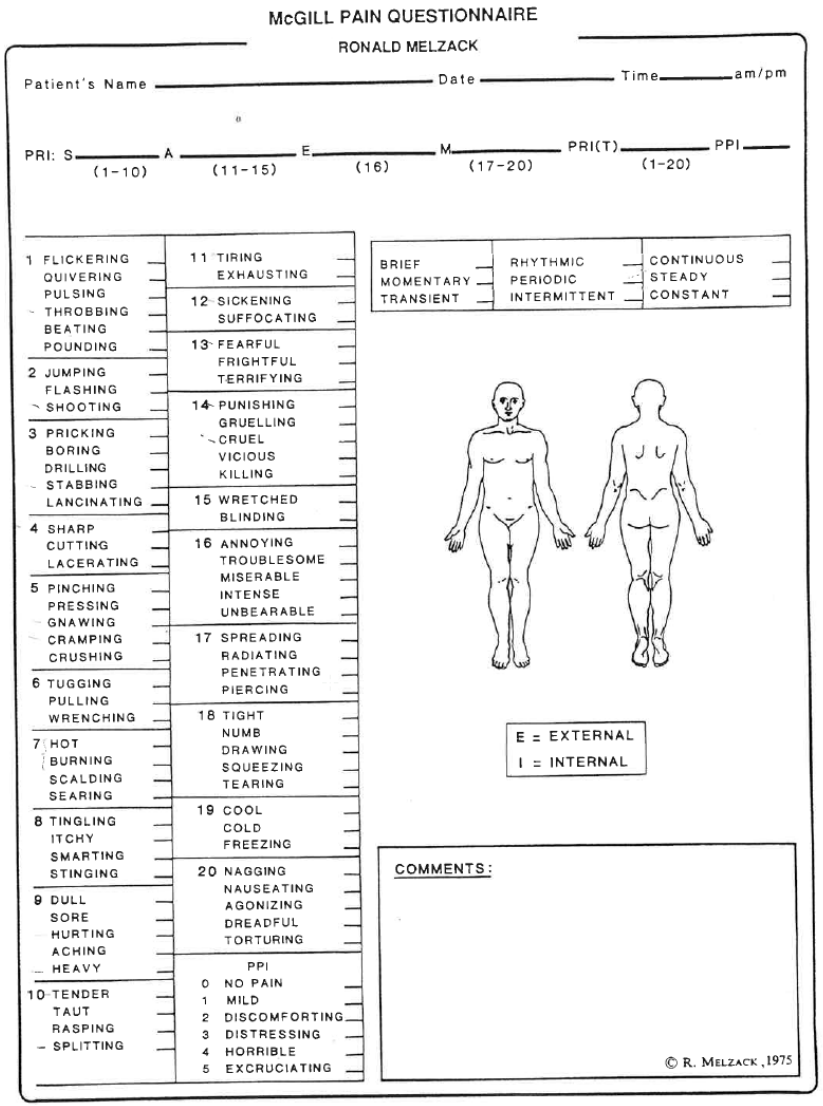
List of VAS for pain relief used in this report:

- Pain relief: Scale from 0 to 3 (not at all, slight, a lot, awful)
- Pain relief VAS: 0 inefficient, 1 mild response 2 effective 3 excellent pain relief 4 pain frequency

McGill Pain Questionnaire[72]

This pain evaluation method was developed in 1975 by Ronald Melzack. With the McGill Pain Questionnaire, Melzack wanted to assess the different psychological dimensions of pain: sensory-discriminative ("S", sensory), motivational-affective ("A", affective) and cognitive-evaluative ("E", evaluative)[77]. Descriptors are grouped in 20 groups. These groups are in turn classified in the dimensions; besides the S, A and E dimension, there is also a "miscellaneous (M)" dimension.

Figure 3 – McGill Pain Questionnaire[77]



McGILL PAIN QUESTIONNAIRE

RONALD MELZACK

Patient's Name _____ Date _____ Time _____ am/pm

PRI: S _____ A _____ E _____ M _____ PRI(T) _____ PPI _____
(1–10) (11–15) (16) (17–20) (1–20)

1 FLICKERING	11 TIRING	BRIEF	RHYTHMIC	CONTINUOUS
QUIVERING	EXHAUSTING	MOMENTARY	PERIODIC	STEADY
PULSING	12 SICKENING	TRANSIENT	INTERMITTENT	CONSTANT
THROBBING	SUFFOCATING			
BEATING	13 FEARFUL			
POUNDING	FRIGHTFUL			
2 JUMPING	TERRIFYING			
FLASHING	14 PUNISHING			
SHOOTING	GRUELLING			
3 PRICKING	CRUEL			
BORING	VICIOUS			
DRILLING	KILLING			
STABBING	15 WRETCHED			
LANCINATING	BLINDING			
4 SHARP	16 ANNOYING			
CUTTING	TROUBLESOME			
LACERATING	MISERABLE			
5 PINCHING	INTENSE			
PRESSING	UNBEARABLE			
GNAWING	17 SPREADING			
CRAMPING	RADIATING			
CRUSHING	PENETRATING			
6 TUGGING	PIERCING			
PULLING	18 TIGHT			
WRENCHING	NUMB			
7 HOT	DRAWING			
BURNING	SQUEEZING			
SCALDING	TEARING			
SEARING	19 COOL			
8 TINGLING	COLD			
ITCHY	FREEZING			
SMARTING	20 NAGGING			
STINGING	NAUSEATING			
9 DULL	AGONIZING			
SORE	DREADFUL			
HURTING	TORTURING			
ACHING				
HEAVY	PPI			
10 TENDER	0 NO PAIN			
TAUT	1 MILD			
RASPING	2 DISCOMFORTING			
SPLITTING	3 DISTRESSING			
	4 HORRIBLE			
	5 EXCRUCIATING			

E = EXTERNAL
I = INTERNAL

COMMENTS:

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Before using the questionnaire, words can be read to the patient by an interviewer to ensure the comprehension of each ones. The respondent is then asked to select the one word in each subclass that most accurately describes the pain at that time.

Four rating procedures can be used: the number of words chosen (NWC), the present pain intensity (PPI), the rank value system (PRI(R)), the weighted-rank system (see Figure 4 below)



Figure 4 – Scoring the McGill Pain Questionnaire

SCORING:

Number of Words Chosen (NWC)
The NWC score is obtained by counting the number of words selected by the respondent in part 2 and will range from 0 to 78.

Present Pain Intensity (PPI)
The PPI score is obtained by scoring the response to question "Which word describes your pain right now?" and this therefore ranges from 1 (mild) to 5 (excruciating).

Scoring of dimensions - Pain Rating Index (PRI):

Item scaling	2- to 6-point Likert scales
Weighting of items	**Weighted-Rank system**: Each word chosen in a subclass is given a *weighted-rank score* obtained by multiplying the rank value of the word by the weighted score of its subclass (see Appendix)
Extension of the Scoring Scale	Not needed according to the author
Scoring Procedure	**Rank value method - PRI(R)**: Each word within each subclass is given a value based on its rank, e.g. the first word in each subclass is given the value 1, the next word is given the value 2, and so on. A Pain Rating Index (PRI) for each dimension as well as a total score can be obtained by adding the rank values of the words chosen by the respondent. **Weighted-Rank system**: All the *weighted-rank scores* can be combined to

Scaling and Scoring version 1.0: June 2010

	give separate dimension and total scores.
Interpretation and Analysis of missing data	If a word is not checked it means that quality is not felt and no value is calculated
Interpretation of multiple answers for one item	All descriptors are useful. If checked, a word applies
Interpretation and Analysis of 'non-concerned' answers	Not applicable

Appendix

Weightings for the subclasses:

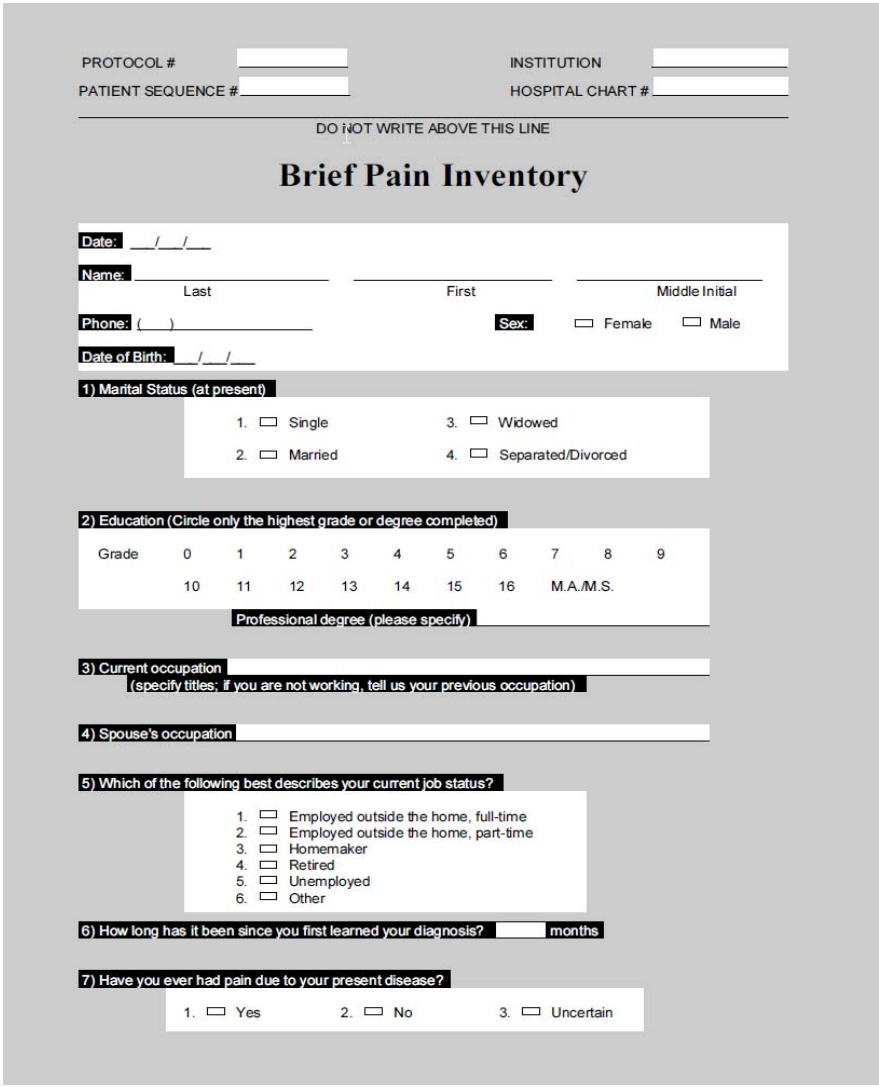
(1) 0.69	(6) 1.19	(11) 1.74	(16) 1.01
(2) 1.38	(7) 1.28	(12) 2.22	(17) 1.22
(3) 0.93	(8) 0.70	(13) 1.87	(18) 0.82
(4) 1.59	(9) 0.72	(14) 1.32	(19) 1.00
(5) 0.81	(10) 0.95	(15) 2.33	(20) 1.15

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Brief Pain Inventory Pain Score[72] (BPI)

This scale was originally designed for the evaluation of cancer-related pain but can also be used for other diseases. Brief Pain Inventory (BPI) includes 4 ratings of the intensity of pain (item 12- 15) and 7 ratings for the impact of pain (item 23 A-G). Pain intensity is recorded on a visual analogue scale running from 0 (no pain) to 10 ('pain as bad as you can imagine'). The intensity can be rated in the time of completing the questionnaire, or at worst, least or average pain over the past day or week. The impact of the pain is rated on a 0-to-10 scale running from 'no interference' to 'interferes completely'. The BPI allows the record of pain localization on a diagram. It contains descriptors to indicate the extent and duration of pain relief obtained from analgesics.

Figure 5 – Brief Pain Inventory[78] – reprint with permission of Dr CS Cleeland (MD Anderson Cancer Center)



PROTOCOL # _____ INSTITUTION _____

PATIENT SEQUENCE # _____ HOSPITAL CHART # _____

DO NOT WRITE ABOVE THIS LINE

Brief Pain Inventory

Date: ___/___/___

Name: _____ _____ _____

Last First Middle Initial

Phone: (___) _____ Sex: ☐ Female ☐ Male

Date of Birth: ___/___/___

1) Marital Status (at present)

1. ☐ Single 3. ☐ Widowed
2. ☐ Married 4. ☐ Separated/Divorced

2) Education (Circle only the highest grade or degree completed)

Grade 0 1 2 3 4 5 6 7 8 9

10 11 12 13 14 15 16 M.A./M.S.

Professional degree (please specify) _____

3) Current occupation _____

(specify titles; if you are not working, tell us your previous occupation)

4) Spouse's occupation _____

5) Which of the following best describes your current job status?

1. ☐ Employed outside the home, full-time
2. ☐ Employed outside the home, part-time
3. ☐ Homemaker
4. ☐ Retired
5. ☐ Unemployed
6. ☐ Other

6) How long has it been since you first learned your diagnosis? _____ months

7) Have you ever had pain due to your present disease?

1. ☐ Yes 2. ☐ No 3. ☐ Uncertain

8) When you first received your diagnosis, was pain one of your symptoms?

1. ☐ Yes 2. ☐ No 3. ☐ Uncertain

9) Have you had surgery in the past month? 1. ☐ Yes 2. ☐ No

If YES, what kind? _____

10) Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, toothaches). Have you had pain other than these everyday kinds of pain during the last week?

1. ☐ Yes 2. ☐ No

10a) Did you take pain medications in the last 7 days?

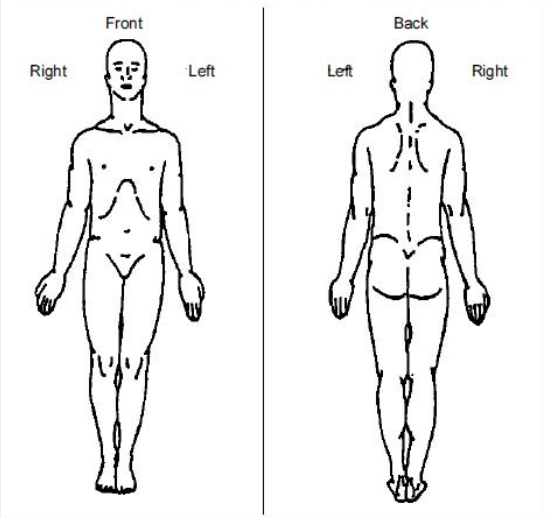
1. ☐ Yes 2. ☐ No

10b) I feel I have some form of pain now that requires medication each and every day.

1. ☐ Yes 2. ☐ No

IF YOUR ANSWERS TO 10, 10a, AND 10b WERE ALL NO, PLEASE STOP HERE AND GO TO THE LAST PAGE OF THE QUESTIONNAIRE AND SIGN WHERE INDICATED ON THE BOTTOM OF THE PAGE.
IF ANY OF YOUR ANSWERS TO 10, 10a, AND 10b WERE YES, PLEASE CONTINUE.

11) On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



12) Please rate your pain by circling the one number that best describes your pain at its worst in the last week.

0 No Pain 1 2 3 4 5 6 7 8 9 10 Pain as bad as you can imagine

13) Please rate your pain by circling the one number that best describes your pain at its least in the last week.

0 No Pain 1 2 3 4 5 6 7 8 9 10 Pain as bad as you can imagine

14) Please rate your pain by circling the one number that best describes your pain on the average.

0 No Pain 1 2 3 4 5 6 7 8 9 10 Pain as bad as you can imagine

15) Please rate your pain by circling the one number that tells how much pain you have right now.

0 No Pain 1 2 3 4 5 6 7 8 9 10 Pain as bad as you can imagine

16) What kinds of things make your pain feel better (for example, heat, medicine, rest)?

_____

_____

17) What kinds of things make your pain worse (for example, walking, standing, lifting)?

_____

_____

18) What treatments or medications are you receiving for pain?

_____

_____

19) In the last week, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0% No Relief 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% Complete Relief

20) If you take pain medication, how many hours does it take before the pain returns?

1. ☐ Pain medication doesn't help at all	5. ☐ Four hours
2. ☐ One hour	6. ☐ Five to twelve hours
3. ☐ Two hours	7. ☐ More than twelve hours
4. ☐ Three hours	8. ☐ I do not take pain medication

21) Check the appropriate answer for each item.
I believe my pain is due to:

☐ Yes ☐ No 1. The effects of treatment (for example, medication, surgery, radiation, prosthetic device).
☐ Yes ☐ No 2. My primary disease (meaning the disease currently being treated and evaluated).
☐ Yes ☐ No 3. A medical condition unrelated to my primary disease (for example, arthritis).
Please describe condition: _____

22) For each of the following words, check Yes or No if that adjective applies to your pain.

Aching	☐ Yes	☐ No
Throbbing	☐ Yes	☐ No
Shooting	☐ Yes	☐ No
Stabbing	☐ Yes	☐ No
Gnawing	☐ Yes	☐ No
Sharp	☐ Yes	☐ No
Tender	☐ Yes	☐ No
Burning	☐ Yes	☐ No
Exhausting	☐ Yes	☐ No
Tiring	☐ Yes	☐ No
Penetrating	☐ Yes	☐ No
Nagging	☐ Yes	☐ No
Numb	☐ Yes	☐ No
Miserable	☐ Yes	☐ No
Unbearable	☐ Yes	☐ No

23) Circle the one number that describes how, during the past week, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

24) I prefer to take my pain medicine:

1. ☐ On a regular basis
2. ☐ Only when necessary
3. ☐ Do not take pain medicine

25) I take my pain medicine (in a 24 hour period):

1. ☐ Not every day
2. ☐ 1 to 2 times per day
3. ☐ 3 to 4 times per day
4. ☐ 5 to 6 times per day
5. ☐ More than 6 times per day

26) Do you feel you need a stronger type of pain medication?

1. ☐ Yes 2. ☐ No 3. ☐ Uncertain

27) Do you feel you need to take more of the pain medication than your doctor has prescribed?

1. ☐ Yes 2. ☐ No 3. ☐ Uncertain

28) Are you concerned that you use too much pain medication?

1. ☐ Yes 2. ☐ No 3. ☐ Uncertain

If Yes, why? _____

29) Are you having problems with side effects from your pain medication?

1. ☐ Yes 2. ☐ No

Which side effects? _____

30) Do you feel you need to receive further information about your pain medication?

1. ☐ Yes 2. ☐ No

31) Other methods I use to relieve my pain include: (Please check all that apply)

Warm compresses ☐ Cold compresses ☐ Relaxation techniques ☐

Distraction ☐ Biofeedback ☐ Hypnosis ☐

Other ☐ Please specify _____

32) Medications not prescribed by my doctor that I take for pain are:

_____

_____

Please sign the back of this questionnaire.

Patient's Signature _____

Thank you for your participation.

Remark: A short form of the questionnaire is also available

Other scales

Composite pain measurement tool including intensity of pain and its frequency

Scale used in this report:

- Bone pain scores were calculated by multiplying the score for pain severity (graded from 0 to 3) by the score for pain frequency (graded from 0 to 3). A score of 0 indicates no bone pain, and a score of 9 indicates constant, severe bone pain (Theriault 99, Hortobayi 1996).

5.2. Analgesic use measurement

The scales used in this indirect measurement of pain intensity are not standardized or validated. The scales used in this report are the following:

- Daily oral morphine equivalent
- 2-point scale score (0=none, 1=NSAID, 2=opiates)
- 3-point scale for analgesic requirement (0=no analgesic, 1=non-opioids, 2=weak opioids, 3=strong opioids)
- 5-point scale for analgesic (0: none, 1: simple analgesic [paracetamol] or NSAID, 2:mild analgesic + NSAID, 3: moderate analgesic (e.g. codeine), 4:opiates <40 mg morphine daily, 5: opiates ≥40 mg, daily).
- 6-point scale (0:none, 1: mild analgesic [aspirin or paracetamol/acetaminophen] or NSAID, 2: mild analgesic + NSAID, 3: moderate analgesic, 4: opiates <40 mg morphine [or equivalent] daily, 5: opiates ≥40 mg, but <100 mg morphine [or equivalent] daily, or 6: opiates ≥100 mg morphine [or equivalent] daily).
- Class1: paracetamol; Class2 codeine, dextropropoxyphene; Class3 (morphine)

5.3. Performance status scales

Karnofsky Performance Index (KPI)

This scale was designed by Karnofsky in 1940's for measurement of performance status in lung cancer patients. This 11-point rating scale goes from normal functioning (100) to dead (0). The KPI is used in the majority of clinical trials related to cancer patients measuring the performance status[79].

Table 5 – Karnofsky Performance Status Index[80]

General category	Index	Specific criteria
Able to carry on normal activity; no special care needed	100	Normal, no complaints, no evidence of disease
	90	Able to carry on normal activity, minor signs or symptoms of disease
	80	Normal activity with effort, some signs or symptoms of disease
Unable to work, able to live at home and care for most personal needs, varying amount of assistance needed	70	Cares for self, unable to carry on normal activity or to do work
	60	Requires occasional assistance from others but able to care for most needs
	50	Requires considerable assistance from others and frequent medical care
Unable to care for self, requires institutional or hospital care or equivalent, disease may be rapidly progressing	40	Disabled, requires special care and assistance
	30	Severely disabled, hospitalization indicated, death not imminent
	20	Very sick, hospitalization necessary, active supportive treatment necessary
	10	Moribound
	0	Dead

ECOG performance status

Eastern Cooperative Oncology Group (ECOG) is a cooperative group performing multi-centre cancer trials in US, Canada and South Africa. The ECOG performance status scale is graduated from 0 (fully active) to 5 (dead). This 6-point scale was published first by Oken (1982)[81] and belongs to the public domain. The scale is also called ***WHO performance status scale***.

Table 6 – Eastern Cooperation Oncology Group performance status scale[81]

ECOG PERFORMANCE STATUS*

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

5.4. Quality of life scales

EORTC QLQ-C30[72]

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) was design by EORTC and is regularly revised. Several versions were developed in different languages. The measurement system compromise a generic core questionnaire (QLQ-C30) plus disease- and treatment-specific modules. The generic core questionnaire is often used in clinical trial and covers several dimensions of function, symptoms and possible side-effects of treatment. The dimensions assessed by QLQ-C30 are listed in the following table.

Table 7 – Dimensions assessed by EORTC QLQ-C30

Dimensions assessed	N° of item(s)
Physical function	1 to 5
Role function	6 and 7
Cognitive function	20 and 25
Emotional function	21 to 24
Social function	26 and 27
Fatigue	10, 12 and 18
Nausea	14 and 15
Pain	9 and 19
Global Quality of Live	29 and 30
Dyspnea	8
Sleep disturbance	11
Appetite loss	13
Constipation	16
Diarrhea	17
Financial impact of cancer	28

Figure 6 – EORTC QLQ–C30



EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

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The QLQ-C30 does not provide a overall score but evaluates multidimensional character of quality of life. The method of rating items is provided online (http://groups.eortc.be/qol/manuals).

Spitzer's quality of live index[72]

The quality of life index aims to measure the general well-being of patients with terminal illness. The scale rates 5 dimensions from 0 to 2: activity level, activities of daily living, feeling of healthiness, quality of social support and psychosocial outlook). A total score on 10 is obtained by adding scores for each dimension without any weighting. A self-administrated version of the questionnaire exists but is not shown here.

Figure 7 – Spitzer's Quality of Live Index[82]

QUALITY OF LIFE INDEX

SCORING FORM

Study No. _____/_____

Age _____ ☐☐

Sex M_1 F_2 (Ring appropriate letter) _____ ☐

Primary Problem or Diagnosis _____

_____ ☐☐☐

Secondary Problem or Diagnosis, or complication (if appropriate) _____ ☐☐☐

Scorer's Specialty _____ ☐☐☐

Score each heading 2, 1 or 0 according to your most recent assessment of the patient.

ACTIVITY

During the last week, the patient

- has been working or studying full-time, or nearly so, in usual occupation; or managing own household; or participating in unpaid or voluntary activities, whether retired or not . . . 2
- has been working or studying in usual occupation or managing own household or participating in unpaid or voluntary activities; but requiring major assistance or a significant reduction in hours worked or a sheltered situation or was on sick leave . . . 1
- has not been working or studying in any capacity and not managing own household . . . 0

☐

DAILY LIVING

During the last week, the patient

- has been self-reliant in eating, washing, toiletting and dressing; using public transport or driving own car . . . 2
- has been requiring assistance (another person or special equipment) for daily activities and transport but performing light tasks. . . . 1
- has not been managing personal care nor light tasks and/or not leaving own home or institution at all . . . 0

☐

HEALTH

During the last week, the patient

- has been appearing to feel well or reporting feeling "great" most of the time . . . 2
- has been lacking energy or not feeling entirely "up to par" more than just occasionally . . . 1
- has been feeling very ill or "lousy", seeming weak and washed out most of the time or was unconscious . . . 0

☐

SUPPORT

During the last week

- the patient has been having good relationships with others and receiving strong support from **at least one** family member and/or friend . . . 2
- support received or perceived has been limited from family and friends and/or by the patient's condition . . . 1
- support from family and friends occurred infrequently or only when absolutely necessary or patient was unconscious . . . 0

☐

OUTLOOK

During the past week the patient

- has usually been appearing calm and positive in outlook, accepting and in control of personal circumstances, including surroundings . . . 2
- has sometimes been troubled because not fully in control of personal circumstances or has been having periods of obvious anxiety or depression . . . 1
- has been seriously confused or very frightened or consistently anxious and depressed or unconscious . . . 0

☐

QL INDEX TOTAL ☐☐

How confident are you that your scoring of the preceding dimensions is accurate? Please ring the appropriate category. ☐

Absolutely Confident	Very Confident	Quite Confident	Not Very Confident	Very Doubtful	Not at all Confident
1	2	3	4	5	6

Prostate Cancer-Specific QoL Instrument (PROSQOLI)

There is various of health-related QoL scales(i.e. EQ-5D, SF-36,…). The one used in this report is a disease specific scale: the Prostate cancer-Specific QoL instrument.

This was developed in the 1980's. It consists in a combination of self adminstrated instruments (Stockler 1998[83]):

- 9 linear analog self-assessment scales (pain, physical activity, fatigue, appetite, constipation, family/marriage relationships, mood, passing urine, and overall weel-being). The lines are measured in millimeters (maximum score = 100 mm);
- Scale of present pain intensity from McGill Pain Questionnaire (see above): 0=no pain, 1=mild pain, 2=discomforting pain, 3=distressing pain, 4=horrible pain, 5=excruciating pain;
- Analgesic score calculated by multiplying the average daily intake during the previous week of each drug recorded in a diary by a predetermined score.

Table 8 – PROSQOLI (adapted from Stockler 1998[83])

Pain 0 _____100
Fatigue 0 _____100
Appetiite 0 _____100
Constipation 0 _____100
Physical activity 0 _____100
Mood _____100
Family/marriage relationships 0 _____100
Overall well-being 0 _____100
Passing urine 0 _____100

Present Pain intensity

❑ no pain ❑ mild pain ❑ discomforting pain ❑ distressing pain ❑ horrible pain ❑ excruciating pain

Analgesic score

5.5. Summary table of scales used in this report

The following table summarizes the scales used in cancer patients to measure the pain intensity, the performance status or the quality of life.

Table 9 – Classification of scales used to measure cancer pain

Name of the scale	Dimension(s) measured	Type of scale
Verbal rating scales	Pain intensity Pain relief	Descriptors with(out) score
Numerical rating scales	Pain intensity	Numerical score
Huskisson	Pain intensity	Visual analogue pain rating scale
Scott-Huskisson scale	Pain intensity	Visual analogue pain rating scale
Likert scale	Pain intensity	Visual analogue pain rating scale
Scale from 0 to 3 (not at all, slight, a lot, awful)	Pain relief	Visual analogue pain rating scale
Scale from 0 inefficient, 1 mild response 2 effective 3 excellent pain relief 4 pain frequency	Pain relief	Visual analogue pain rating scale
McGill Pain Questionnaire	Pain intensity	Verbal scale
Brief Pain Inventory Pain Score	Pain intensity and impact of pain	Verbal and numerical scales
Pain Perception Profile	Pain intensity	Verbal scale

Karnofsky Performance Index	Performance status	Verbal and numerical scales
ECOG performance status	Performance status	Score
WHO performance status	Performance status	Score
EORTC QLQ-C30	Quality of Live	Multi-dimensions scores
Spitzer's quality of live index	Quality of Live	Overall score
PROSQOLI	Quality of Live (cancer specific)	Multi-dimensions scores

Reprint permissions were obtained for the McGill Pain questionnaire, the Brief Pain Inventory and EORTOC QLQ-C30. The reference of the specific publication was mentioned for the other scales.

6. COMPOSITION OF GUIDELINE DEVELOPMENT GROUP

6.1. Composition of the panel of external experts

Table 10 – Panel of external experts

Experts	Field of expertise, affiliations
Cécile Avril	representative of the patient organisation « Stichting tegen Kanker-Fondation contre le cancer »
Ahmad Awada	medical oncologist, Institut Jules Bordet Bruxelles
Erik Briers	representative of the patient organisation « Wij Ook »
Tom Boterberg	radiation oncologist, UZ Gent
Annemie Coolbrandt	oncology nurse, UZ Leuven
Mieke Depril	oncology nurse, UZ Leuven
Fréderic Duprez	radiation oncologist, UZ Gent
Marie-Elisabeth Faymonville	pain specialist, CHU de Liège
Chantal Goossens	representative of the patient organisation « Stichting tegen Kanker-Fondation contre le cancer »
Guy Hans	pain specialist, UZ Antwerpen
Lia Le Roy	representative of the patient organisation « Werkgroep Hersentumoren vzw »
Johan Menten	radiation oncologist, palliative care coordinator, UZ Leuven
Marc Peeters	gastroenterologist, UZ Antwerpen; president of the National College of Oncology

6.2. Composition of the stakeholder panel

Table 11 – Panel of stakeholders

Stakeholders	Field of expertise, affiliations
Susan Broekmans	Clinical nurse specialist pain at UZ Leuven, member of NVKVV (Nationaal Verbond van Katholieke Vlaamse Verpleegkundigen en Vroedvrouwen), member of Belgian Pain Society
Marc De Kock	Anaesthesiologist at Cliniques Universitaires UCL Saint-Luc, member of Society for Anesthesia and Resuscitation of Belgium (BVAR-SBAR)
Peter Demeulenaere	GP in “Huisartsengroep Groenenborg”, palliative care specialist at GZA-ziekenhuizen, member of Domus Medica

Alain Dessard	GP, representative of Delta aslb, member of Fédération Wallonne des Soins Palliatifs
Jacques Devulder	Pain specialist at UZ Gent, member of Society for Anesthesia and Resuscitation of Belgium (BVAR-SARB)
Chantal Doyen	Medical oncologist at Cliniques Universitaires UCL Mont-Godinne, member of Fédération Wallonne des Soins Palliatifs
Koen Lauwers	Pain specialist at “Klinieken Noord-Antwerpen”, member Vlaamse Anesthesiologische Vereniging voor Pijnbestrijding (VAVP) and Belgian Pain Society (BPS)
Filomena Mazzeo	Medical oncologist at Cliniques Universitaires UCL Saint-Luc, member of Belgian Society of Medical Oncology (BSMO)
Ivo Nagels	Representative of the patient organisation «Stichting tegen Kanker; Fondation contre le Cancer »
Patrick Paulus	Specialist in Nuclear Medicine at CHR de la Citadelle Liège, member of Belgian Society for Nuclear Medicine (BELNUC)
Barbara Plehiers	Specialist palliative care at CHU Ambroise Paré-Mons, member of Fédération Wallonne des Soins Palliatifs
Jan Poelaert	Anaesthesiologist at UZ Brussel, member of Society for Anesthesia and Resuscitation of Belgium (BVAR-SBAR)
Dirk Schrijvers	Medical oncologist at Ziekenhuis Netwerk Antwerpen-Middelheim, member of Belgian Society of Medical Oncology (BSMO)
Marc Tanghe	Head nurse palliative care unit at CHRPBW (Centre Hospitalier de Réadaptation et de Psychiatrie du Brabant Wallon), Bois de la Pierre, Wavre, member of Federatie Palliatieve Zorg Vlaanderen
Bart Van den Eynde	Palliative care specialist at Gasthuiszusters Antwerpen, member of Domus Medica
1 patient	One patient, contacted through “Werkgroep Hersentumoren vzw”, participated in the expert meetings. For privacy reasons his/her name is not mentioned.

6.3. Composition of the KCE expert team

Table 12 – KCE expert team

KCE member	Specific role
Marijke (Maria) Eyssen	Project leader; scientific research Background: • Medical specialist in Pediatrics, Pediatric Neurology and Rehabilitation Medicine
Nadia Benahmed	Scientific research Background: • Master in Public Health • Master of Advanced Study in Epidemiology and Statistical Methods • Interuniversity Certificate in Health Economics
Anja Desomer	Scientific research Background: • Master in Physiotherapy and Rehabilitation Sciences
Kristel De Gauquier	Program director Background: • Medical Doctor • Postgraduate Course in Tropical Medicine • Master of Health Care Management and Policy • Master of Health Data Management

6.4. Composition of the scientific validation team

Table 13 – Scientific validation team

Validator	Specific role
Hilde Verbeke	President validation meeting Background: • Member of Belgian Centre for Evidence-based Medicine (CEBAM) • Anaesthesiologist at the LAC (Leuvens Algologisch Centrum), UZ Leuven
Paul M.J. Clement	Belgian representative in validation meeting Background: • Medical oncologist at the Department of General Medical Oncology at UZ Leuven • Associate Professor at the Department of Oncology, section Experimental Oncology, KU Leuven
Kris C.P. Vissers	International representative in validation meeting Background: • Anaesthesiologist, Head of department Academic Centre for Pain and Palliative Medicine, Radboud University Nijmegen Medical Center (The Netherlands) • Professor in Pain and Palliative Medicine, Radboud University, Nijmegen (the Netherlands)

APPENDIX II

1. QUALITY APPRAISAL

1.1. Guidelines including multiple topics

Table 14 – Quality appraisal of guidelines including multiple topics

Guideline	A priori study design	Duplicate study selection and data	Comprehensive literature search	Publication status not used as inclusion	List of in- and excluded studies	Characteristics of included studies provided	Study quality assessed and documente	Quality assessment used in conclusion	Appropriate methods to combine findings	Likelihood of publication bias .	Conflict of interest stated
Landelijke richtlijnwerkgroep Pijn bij Kanker (2008)[1]	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No applicable	No applicable	Review Yes Studies No
SIGN (2008)[2] - Control of pain in adults with cancer	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No applicable	No applicable	Review Yes Studies No
Ministry of Health Malaysia (2010)[3] - Clinical Practice Guidelines: Management of Cancer Pain	Yes	Yes	Yes	Yes	No	No	Yes but no method is provided	Yes	No applicable	No applicable	Review Yes Studies No

Agency for Healthcare Research and Quality – Carr (2002)[4] Management of Cancer Symptoms: Pain, Depression, and Fatigue	Yes	Can't answer	Yes	Yes	No	Yes	Yes	Yes	Not applicable	Not applicable	Review No Studies No

1.2. NSAIDs and paracetamol

Table 15 – NSAIDs and paracetamol: Quality appraisal of systematic reviews

	A priori study design	Duplicate study selection and data	Comprehensive literature search	Publication status not used as inclusion	List of in- and excluded studies	Characteristics of included studies provided	Study quality assessed and documented	Quality assessment used in conclusion	Appropriate methods to combine findings	Likelihood of publication bias assessed	Conflict of interest stated
McNicol 2011[5]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Review No Studies No
Nabal 2012[6]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Not applicable	Not applicable	Review: Yes Studies:No
Alkhenizan 2004[7]	Yes	Can't answer	No	No	No	No	Yes	No	Not applicable	No	Review: No Studies: No

Table 16 – NSAIDs and paracetamol: Quality appraisal of randomized controlled trials

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Complete outcome data	All relevant outcomes reported	Absence of other sources of bias	Overall Risk of bias: high-low-unclear
Jameel 1995[8]	Yes	Unclear	Unclear	Unclear	No	Yes	Unclear	High
Rodriguez 2003[9]	Yes	Yes	Yes	Unclear	No	Yes	Unclear	High
Sima 2012[10]	Yes	Yes	Yes	Yes	No	Yes	Unclear	High

1.3. Opioids

Table 17 – Opioids: Quality appraisal of systematic reviews

	A priori study design	Duplicate study selection and data extraction	Comprehensive literature search	Publication status not used as inclusion	List of in- and excluded studies	Characteristics of included studies provided	Study quality assessed and documented	Quality assessment used in conclusion	Appropriate methods to combine findings	Likelihood of publication bias assessed	Conflict of interest stated
Cairns 2001[11]	Yes	Can't answer	Yes	No	No	Yes	Yes	Yes	Not applicable	Not applicable	Review No Studies Yes
Caraceni 2011[12]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Review Yes Studies No

Dale 2011[13]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Not applicable	Yes	Review Yes Studies No
Fallon 2011[14]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Can't answer	Review Yes Studies No
Hansen 2012[15]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Yes	Review Yes Studies No
King 2011[16]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Not applicable	Can't answer	Review Yes Studies Yes
Nicholson 2008[17]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Not applicable	Not applicable	Review Yes Studies No
Pigni 2011[18]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Review Yes Studies No
Quigley 2008[19]	Yes	Can't answer	No	Yes	Yes	Can't answer	Yes	Yes	Not applicable	Not applicable	Review Yes Studies No
Quigley 2009[20]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Review Yes Studies No

Quigley 2010 [21]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Review Yes Studies No
Reid 2006 [22]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Review Yes Studies No
Tassinari 2011a[23]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Not applicable	Not applicable	Review Yes Studies No
Tassinari 2011 b[24]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Not applicable	Not applicable	Review Yes Studies No
Wiffen 2010[25]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Review Yes Studies Yes
Zeppetella 2009 [26]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Review Yes Studies No

Table 18 – Opioids: Quality appraisal of randomized controlled trials

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Complete outcome data	All relevant outcomes reported	Absence of other sources of bias	Overall Risk of bias: high-low-unclear
Ahmedzai 2012[27]	Yes	Yes	Yes	Yes	No	Yes	No	High
Cubero 2010[28]	Yes	Yes	Yes	Yes	No	Yes	Yes	High
Elsner 2005[29]	Unclear	No	No	Yes	Yes	Yes	Yes	High
Johnson 2009[30]	Yes	No	No	No	No	Yes	Yes	High
Kress 2008[31]	Yes	No	No	No	Yes	Yes	No	High
Mercadante 2007[32]	Yes	No	No	No	Yes	Yes	Unclear	High
Mercadante 2009[33]	Unclear	No	No	No	No	Yes	No	High
Mercadante 2010[34]	Yes	No	No	No	No	Yes	Yes	High
Moksnes 2011[35]	Yes	No	No	No	No	Yes	Yes	High
Mystakidou 2005[36]	Unclear	Unclear	Unclear	Unclear	No	Yes	Yes	High
Pistevou-Gompaki 2004[37]	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
Portenoy 2006[38]	Unclear	Unclear	No	No	Unclear	Yes	No	High
Rauck 2009[39]	Unclear	Yes	Yes	Yes	Unclear	Unclear	No	Unclear
Rauck 2010[40]	Yes	Unclear	Yes	Yes	Unclear	Yes	No	Unclear
Rauck 2012[41]	Yes	Yes	Yes	Yes	Unclear	Unclear	No	Unclear
Slatkin 2007[42]	Yes	Yes	Yes	Yes	Yes	Yes	No	Low

1.4. Corticosteroids

No systematic review and no RCT included

2. GRADE PROFILES BY INTERVENTION AND OUTCOME

2.1. NSAIDs and paracetamol

Table 19 – NSAIDS and paracetamol: overview of results and GRADE profiles

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
Different NSAIDs/aspirin versus placebo									
Pain relief (McNicol 2011)[5](n=555)	No pooling, superior pain reduction in single dose NSAID group in all studies	7	0	0	-1	0	0	1. Jadad scores (McNicol 2011): 4 4 3 4 4 3 3 3. heterogeneity in outcome measures	Moderate
Adverse events (McNicol 2011)[5] (n=555)	No pooling, no difference between single dose-placebo (7 studies)	7	0	0	-1	0	0	1. Jadad scores (McNicol 2011): 4 4 3 4 4 3 3 3. heterogeneity in outcome measures.	Moderate
Aspirin versus placebo									
Pain relief (McNicol 2011)[5] (n=194)	No pooling, superior pain reduction in single dose aspirin group (4 studies)	4	0	0	-1	0	0	1. Jadad scores (McNicol 2011): 3 4 4 3 3.heterogeneity in outcome measures, small sample size	Moderate
Paracetamol versus placebo									
Pain relief (McNicol 2011)[5] (n=29)	No difference between single dose-placebo in moderate to severe cancer pain	1	0	-1	-2	0	0	1. Jadad score (McNicol 2011): 3 2. single study 3. small sample size	Very low
Paracetamol + opioid versus placebo									
Pain relief (Sima	Sign lower in	1	-1	-1	-1	0	0	1. high risk of bias	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
2012)[10] (n=126)	placebo							2. single study 3. small sample size	
Different NSAIDs/aspirin/dipyrone versus other NSAIDs/aspirin/dipyrone									
Pain relief (McNicol 2011 + Rodriquez 2003)[5, 9] (n=989)	No pooling, 4/14 studies statistically significant result in favour of one NSAID	14	-1	-1	-2	0	0	1. Jadad score (McNicol 2011): 1 4 3 4 2 2 3 4 2 2 3 2 2; high risk of bias (Rodriguez 2003) 2. heterogeneity in results 3. heterogeneity in outcome measures and study design	Very low
Adverse events (McNicol 2011+ Rodriguez 2003)[5, 9] (n=989)	No pooling, 4/14 studies statistically significant result in favor of one NSAID	14	-1	-1	-2	0	0	1. Jadad score (McNicol 2011): 1 4 3 4 2 2 3 4 2 2 3 2 2; high risk of bias (Rodriguez 2003) 2. heterogeneity in results 3. heterogeneity in outcome measures and study design	Very low
Aspirin versus other NSAIDs									
Pain relief (McNicol 2011)[5] (n=176)	No pooling, no significant difference in 4 studies	4	-1	0	-2	0	0	1. Jadad score (McNicol 2011): 4 2 3 4th study major methodological flaws 3. heterogeneity in outcome measures and study design; small sample size	Very low
Adverse events (McNicol 2011)[5] (n=176)	No pooling, no significant difference in 4 studies	4	-1	0	-2	0	0	1. Jadad score (McNicol 2011): 4 2 3 4th study major methodological flaws 3. heterogeneity in outcome measures and study design; small sample size	Very low
Dipyrone versus other NSAIDs									
Pain relief (McNicol 2011)[5] (n=100)	No pooling, in 2 studies difference statistically in advantage of NSAIDs	2	-1	0	-2	0	0	1. Jadad score (McNicol 2011): 2 2 3. small sample size; heterogeneity in outcome measures and study design (note: difference statistically significant but not clinically meaningful)	Very -low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
Adverse events (McNicol 2011)[5] (n=100)	No pooling, in 2 studies difference statistically in advantage of NSAIDs	2	-1	0	-2	0	0	1. Jadad score (McNicol 2011): 2 2 3. small sample size; heterogeneity in outcome measures and study design (note: difference statistically significant but not clinically meaningful)	Very low
Paracetamol versus other NSAIDs									
Pain relief (McNicol 2011)[5] (n=65)	NS	1	-1	-1	-1	0	0	1. several methodological flaws 2. single study 3. small study sample	Very low
Adverse events (McNicol 2011)[5] (n=65)	NS	1	-1	-1	-1	0	0	1. several methodological flaws 2. single study 3. small study sample	Very low
Different NSAIDs versus different opioids									
Pain relief (McNicol 2011 (n=385)[5]+ Jameel 1995 (n=51)[8])	7 studies (McNicol 2011 (n=385)+ Jameel 1995 (n=51)); in 3/7 studies difference statistically in advantage of NSAIDs	7	0	-1	-2	0	0	1. Jadad score (McNicol 2011): 3 3 3 3 1 3; Jameel 1995 high risk of bias 2. heterogeneity in results 3. heterogeneity in outcome measures and study design (note: difference statistically significant but not clinically meaningful)	Very low
Pain relief (McNicol 2011 (n=385)[5]+ Jameel 1995 (n=51)[8])	Subanalysis of 2 studies (n=96): MD -2.96 (95%CI -14.72 to 8.80), p=0.62 (pain intensity scale 0-100)	2	0	-1	-1	0	0	1. Jadad score (McNicol 2011): 3 3 3. small sample size 2. heterogeneity in results (I^2=72%)	Low
Adverse events	7 studies (McNicol	7	0	-1	-2	0	0	1. Jadad score (McNicol 2011): 3 3 3 3 1 3;	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
(McNicol 2011 (n=385)[5]+ Jameel 1995 (n=51)[8])	2011 (n=385)+ Jameel 1995 (n=51))							Jameel 1995 high risk of bias 2. heterogeneity in results 3. heterogeneity in description of adverse events and study design	
Adverse events (McNicol 2011 (n=385)[5]+ Jameel 1995 (n=51)[8])	Subanalysis of 3 studies (n=161): OR 0.30 (95%CI 0.08 to 1.08), p=0.07 (number of patients reporting adverse events)	3	-1	0	-1	0	0	1. Jadad score (McNicol 2011): 3 1 3 3. small sample size, few events and large CI	Low
Aspirin versus different opioids									
Pain relief (McNicol 2011)[5] (n=136)	No pooling, no significant difference in 2 studies	2	0	0	-2	0	0	1. Jadad score (McNicol 2011): 4 3 3. small sample size, heterogeneity in outcome measures and study design	Low
Dipyrone versus opioids									
Pain relief (McNicol 2011)[5] (n=194)	NS	1	0	-1	-2	0	0	1. Jadad score (McNicol 2011): 3 2. single study 3. small sample size, large CI	Very low
Adverse events (McNicol 2011)[5] (n=194)	NS	1	-1	-1	-1	0	0	1. Jadad score (McNicol 2011): 3; poor data reporting 2. single study 3. small sample size	Very low
Paracetamol versus opioids									
Pain relief (McNicol 2011)[5] (n=29)	NS	1	-1	-1	-1	0	0	1. Jadad score (McNicol 2011): 3; cross-over design, no wash-out period 2. single study	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
								3. small sample size	
Different NSAIDs/aspirin/paracetamol versus NSAID/aspirin/paracetamol+opioids									
Pain relief (McNicol 2011)[5] (n=997)	No pooling, in 4/8 studies difference statistically in advantage of NSAID + opioid as compared to NSAID	8	0	-1	-2	0	0	1. Jadad score (McNicol 2011): 3 3 4 3 3 4 4 3 2. heterogeneity in results 3. heterogeneity in study design, outcome measures	Very low
Adverse events (McNicol 2011)[5] (n=838)	OR 0.77 (95%CI 0.35 to 1.67), p=0.50	8	0	-1	-1	0	0	1. Jadad score (McNicol 2011): 3 3 4 3 3 4 4 3 2. heterogeneity in results (I^2=65%) 3. large CI	Low
Aspirin versus NSAID+opioids									
Pain relief (McNicol 2011)[5] (n=260)	No pooling, no significant difference in 2 studies	2	-1	0	-2	0	0	1. Jadad score (McNicol 2011): 4 3 (latter study 75% drop-out at 10 days) 3. small sample size, heterogeneity in study design and outcome measures	Very low
Paracetamol versus NSAID+opioids									
Pain relief (McNicol 2011)[5] (n=104)	No pooling, no significant difference in 2 studies	2	0	0	-2	0	0	1. Jadad score (McNicol 2011): 4 3 3. small sample size, heterogeneity in study design and outcome measures	Low
Different NSAIDs+opioids versus opioids									
Pain relief (McNicol 2011 + Nabal 2012)[5, 6] (n=162)	No pooling, no significant difference in 2/6 studies	6	0	-1	-2	0	0	1. Jadad score (McNicol 2011): 3 3 3 3 5; 6th study high risk of bias (Nabal 2012) 2. heterogeneity in results 3. small sample size, heterogeneity in study design and outcome measures	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
Adverse events (McNicol 2011 + Nabal 2012)[5, 6] (n=162)	No pooling, no significant difference in 5/6 studies	6	0	-1	-2	0	0	1. Jadad score (McNicol 2011): 3 3 3 3 5; 6th study high risk of bias (Nabal 2012) 2. heterogeneity in results 3. small sample size, heterogeneity in study design and outcome measures	Very low
Dipyrone+opioids versus opioids									
Pain relief (Nabal 2012)[6] (n=34)	No quantitative results	1	0	-1	-2	0	0	1. unclear risk of bias (allocation concealment unclear, Nabal 2012) 2. single study 3. small sample size, no quantitative results	Very low
Paracetamol+opioids versus opioids									
Pain relief (McNicol 2011+ Nabal 2012)[5, 6] (n=224)	No pooling, no significant difference in 5/6 studies	6	-1	0	-2	0	0	1. Jadad score (McNicol 2011): 4; Nabal 2012: one study low RoB, 4 studies high RoB (4 studies no intention-to-treat analysis) 3. small sample size, heterogeneity in study design and outcome measures	Very low
Adverse events (McNicol 2011+ Nabal 2012)[5, 6] (n=224)	No pooling, no significant difference in 5/6 studies	6	-1	0	-2	0	0	1. Jadad score (McNicol 2011): 4; Nabal 2012: one study low RoB, 4 studies high RoB (4 studies no intention-to-treat analysis) 2. heterogeneity in results 3. small sample size, heterogeneity in study design and outcome measures	Very low

2.2. Opioids

Table 20 – Opioids: overview of results and GRADE profiles

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
Morphine modified release versus oxycodone									
Pain intensity (Bruera 1998, Ferrell 1989, Heiskanen 1997, Heikanen 2000, Lauretti 2003, Mucci LoRusso 1998)[43-48]	MO=OXY	6	-1	0	-1	0	0	1. risk of bias low in 3/6 studies but poor reporting of outcomes in some studies, small studies that might not be powered to detect differences 3. heterogeneity among studies e.g. in measurement instruments precluding pooling	Low
Morphine immediate release versus oxycodone immediate release									
Pain intensity (Kalso 1990)[49]	MO=OXY	1	-1	-1	-1	0	0	1. high risk of bias 2. single study 3. small sample size	Very low
Morphine i.m. versus oxycodone i.m.									
Pain relief (Beaver 1978)[50]	MO=OXY	1	-1	-1	-1	0	0	1. high risk of bias 2. single study 3. small sample size	Very low
Morphine sustained release versus oxycodone sustained release									
Pain intensity (Mercadante 2010)[34]	MO=OXY	1	-1	-1	-1	0	0	1. high risk of bias 2. single study 3. small sample size	Very low
Morphine versus hydromorphone									
Pain intensity (Moriarty 1999, Hanna 2008, Houde 1986)[51-53]	MO=HY	4	-1	-1	-1	0	0	1. risk of bias unclear or high in 3 of 4 studies 2. consistency in results of most but not all studies 3. heterogeneity of studies precluded combination of data	Very low
Oral morphine versus oral methadone									
Pain intensity	MO=ME	3	-1	0	-1	0	0	1. 2/3 studies high risk of bias (not blinded) 3.	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
(Bruera 2004, Mercadante 1998, Ventafridda 1986)[54-56]								heterogeneity of studies precluded combination of data; overall data reporting poor	
Morphine i.v. vs methadone i.v.									
Pain intensity (Grochow 1989)[57]	MO=ME	1	-1	-1	-1	0	0	1. only 12 of 23 included patients evaluated 2. single study 3. small sample size	Very low
Morphine i.m. vs methadone i.m.									
Pain intensity (Beaver 1967)[58]	MO=ME	1	-1	-1	-1	0	0	1. dose selection not random 2. single study 3. small sample size, poor data reporting	Very low
Morphine modified release versus tramadol modified release									
Pain intensity (Leppert 2001)[59]	at 1 week (100 mm VAS): 19.25 with morphine versus 57.00 with tramadol, p<0.05; at more than 1 week: MO=TR	1	-1	-1	-1	0	0	1. study with high risk of bias (not blinded) 2. single study 3. small study sample	Very low
Morphine solution 1% versus tramadol solution 5%									
Pain intensity (mean (± SD) score on 5-point verbal rating scale (0 = none, 4 = unbearable) (Wilder-Smith 1994)[60]	at day 1: p<0.01 in favour of morphine (no quantitative data); at day 4: morphine 1.6 ± 1.2, n = 17 and tramadol 1.5 ± 1.3, n = 16 (no	1	-1	-1	-1	0	0	1. cross-over design, no wash-out period 2. single study 3. small study sample, poor data reporting	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
	p-value)								
Oxycodone versus oxymorphone									
Pain intensity (Gabrail 2004)[61]	ns	1	-1	-1	-1	0	0	1. high risk of bias 2. single study 3. small study sample, poor data reporting	Very low
Oxycodone versus hydromorphone									
Pain intensity at 7 days (Hagen 1997)[62]	ns (100 mm VAS; 5-point categorical scale)	1	-1	-1	-1	0	0	1. high risk of bias 2. single study 3. small study sample	Very low
Side effects (Hagen 1997)[62]	OXY = HY	1	-1	-1	-1	0	0	1. high risk of bias 2. single study 3. small study sample	Very low
Oxycodone versus oxycodone + naloxone									
Pain intensity at 4 weeks (BPI-SF scores); Quality of live (EQ-5D) (Ahmedzai 2012)[27]	ns; ns	1	-1	-1	-1	0	0	1. high risk of bias 2. single study 3. small study sample	Very low
Constipation (Mean (SD) PAC-SYM scores) (Ahmedzai 2012)[27]	oxycodone - naloxone: 1.47 ± 1.07 vs oxycodone: 2.03. ± 1.29, p<0.01	1	-1	-1	-1	0	0	1. high risk of bias 2. single study 3. small study sample	Very low
Fentanyl improved transdermal patch (FIT-patch) versus other oral and transdermal opioids									
Pain score (NRS 0 to 10) Mean difference (95% IC) (Kress 2008)[31]	FIT-patch versus oral opioids: -1.1 (-0.92, 7.0), p=0.795	1	-1	-1	-1	0	0	1. RoB high 2. single study 3. small study	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
Pain score (NRS 0 to 10) Mean difference (95% IC) (Kress 2008)[31]	FIT-patch versus standard transdermal opioids: -5.6 (-11.8, 0.5), p=0.072	1	-1	-1	-1	0	0	1. RoB high 2. single study 3. small study	Very low
Adverse events (tolerability score from 0 to 3) (Kress 2008)[31]	FIT-patch = oral opioids = standard transdermal opioids	1	-1	-1	-1	0	0	1. RoB high 2. single study 3. small study	Very low
Transdermal fentanyl versus codeine or paracemol									
Pain relief (Mystakidou 2005, Pistevou-Gompaki 2004)[36, 37]	TDF > CO-PA	2	-1	-1	-1	0	0	1. Rob high, high 2. heterogeneous study results 3. statistical significant but clinically questionable results, poor data reporting	Very low
Adverse events (Mystakidou 2005, Pistevou-Gompaki 2004)[36, 37]	TDF = CO-PA	2	-1	0	-1	0	0	1. Rob high, high 3. heterogeneous data reporting	Low
Switching between morphine and methadone									
Pain intensity (NRS from 0 to 10) Mean (SD) (Cubero 2010)[28]	MO 4.26 (2.33); ME 3.31 (2.71); p=0.03	1	-1	-1	-1	0	0	1. RoB high 2. single study 3. small study sample	Very low
Constipation (0 to 3 scale) Mean (SD); xerostomia (0 to 3 scale) Mean (SD)	MO 1.81 (1.03); ME 0.70 (1.06); p<0.001)/ MO 1.51 (1.12); ME	1	-1	-1	-1	0	0	1. RoB high 2. single study 3. small study sample	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
(Cubero 2010)[28]	0.93 (0.96); p=0.003)								
Pain intensity reduction with addition of acetaminophen (NRS from 0 to 10) Mean (SD) (Cubero 2010)[28]	ME + placebo -0.79 (2.32); ME + acetaminophen -1.09 (3.19); p=0.57	1	-1	-1	-1	0	0	1. RoB high 2. single study 3. small study sample	Very low
Time to reach equianalgesia (pain intensity equal or lower than the baseline) with addition of acetaminophen. Median hours (range) (Cubero 2010)[28]	ME + placebo 24 (24-144); ME + acetaminophen 24 (24-120); p=0.70	1	-1	-1	-1	0	0	1. RoB high 2. single study 3. small study sample	Very low
Switching between morphine or oxycodone to methadone (stop and go versus progressive switching)									
Pain intensity at 3 days/ at 14 days Mean average pain intensity difference between groups (95%IC) (Moksnes 2011)[35]	0.5 (-1.2 – 2.2)/ 2.1 (-0.8 – 5.0)	1	-1	-1	-1	0	0	1. RoB high 2. single study 3. small study sample	Very low
Relative risk dropouts in the 'stop and go' strategy	RR = 3.3 (1.1-8.5)	1	-1	-1	-1	0	0	1. RoB high 2. single study 3. small study sample	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
(95%CI) (Moksnes 2011)[35]									
Opioids versus opioids + celiac plexus block versus Opioids + thoracoscopic splanchnicectomy									
Pain intensity at 2 weeks/ 2 months (Brief Pain Inventory score) Mean ± SD (Jonhson 2009)[30]	O: 4.16±1.78, O_CPB: 4.02±1.40, O_TS: 3.86±2.44; ns/ O: 4.16±1.78, O_CPB: 4.02±1.40, O_TS: 3.86±2.44; ns	1	-1	-1	-1	0	0	1. RoB high 2. single study 3. small study sample	Very low
Morphine in breakthrough pain									
Baseline pain exacerbations that persisted for more than 24h; pain intensity at 4 days (Elsner 2005)[29](VAS-score 0-100±SD)	Intravenous morphine 41 ± 31 vs subcutaneous morphine: 31 ± 16; p= 0.37	1	-1	-1	-1	0	0	1. RoB high 2. single study 3. small study sample	Very low
Baseline pain exacerbations that persisted for more than 24h; mean time to adequate analgesia (Elsner 2005)[29]	53 min (intravenous morphine) and 77 min (subcutaneous morphine) (ns, p=0.051)	1	-1	-1	-1	0	0	1. RoB high 2. single study 3. small study sample	Very low
Oral fentanyl versus placebo									
Weighted sum of	Oral fentanyl >	3	-1	0	-2	0	0	1. RoB high, unclear, unclear 3. heterogeneity in	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
pain intensity differences (PI at time point minus PI at baseline) at 5 10 15 30 min Portenoy (2006)[38] Rauck (2009)[39] Rauck (2010)[40] Rauck (2012)[41]	placebo							outcome measures and study design, small study sample	
Weighted sum of pain intensity differences (PI at time point minus PI at baseline) at 5 10 15 30 45 60 min Rauck (2009)[39] Rauck (2010)[40] Rauck (2012)[41]	Oral fentanyl > placebo	3	0	0	-2	0	0	1. RoB unclear, unclear, low 3. heterogeneity in outcome measures and study design, small study sample	Low
Pain intensity at 10 minutes Rauck (2009)[39] Rauck (2012)[41]	Oral fentanyl > placebo	2	-1	0	-2	0	0	1. RoB unclear, unclear 3. heterogeneity in outcome measures and study design, small study sample, data presented in graph only	Very low
Pain intensity at 30 minutes Farrar 1998[63] Portenoy (2006)[38] Rauck (2009)[39] Rauck (2010)[40] Rauck (2012)[41]	Oral fentanyl > placebo	5	-1	0	-2	0	0	1. RoB Jadad score 4, high, unclear, unclear, unclear 3. heterogeneity in outcome measures and study design, in 4/5 studies data presented in graph only (quantitative results presented in Portenoy 2006 only, study with high risk of bias)	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
Pain intensity at 60 minutes Rauck (2009)[39] Rauck (2010)[40] Rauck (2012)[41]	Oral fentanyl > placebo	3	-1	0	-2	0	0	1. RoB unclear, unclear, unclear 3. heterogeneity in outcome measures and study design, small study sample, data presented in graph only	Very low
Number of episodes with ≥ 33%/≥ 50%/ improvement in pain intensity score at 10 min Slatkin (2007)[42]	FBT: 16% vs placebo 10%, p=0.007/ FBT: 7% vs placebo 4%, p=0.033	1	0	-1	-1	0	0	1. RoB low 2. single study 3. small study sample	Low
Number of episodes with ≥ 33 %/≥ 50%/ improvement in pain intensity score at 15 min Portenoy (2006)[38] Rauck (2010)[40] Slatkin (2007)[42]	Oral fentanyl > placebo/ Oral fentanyl > placebo	3	0	0	-2	0	0	1. RoB high, unclear, low 3. heterogeneity in outcome measures and study design, small study sample	Low
Number of episodes with ≥ 33 %/≥ 50%/ improvement in pain intensity score at 30 min Portenoy (2006)[38] Rauck (2010)[40] Slatkin (2007)[42]	Oral fentanyl > placebo/ Oral fentanyl > placebo	3	0	0	-2	0	0	1. RoB high, unclear, low 3. heterogeneity in outcome measures and study design, small study sample	Low
Number of episodes with ≥ 33 %/≥ 50%/	Oral fentanyl > placebo/ Oral	3	0	0	-2	0	0	1. RoB high, unclear, low 3. heterogeneity in outcome measures and study design, small	Low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
improvement in pain intensity score at 60 min Portenoy (2006)[38] Rauck (2010)[40] Slatkin (2007)[42]	fentanyl > placebo							study sample	
Pain relief (5-point NRS) at 10 min Rauck (2009)[39] Slatkin (2007)[42]	Oral fentanyl > placebo	2	0	0	-2	0	0	1. RoB unclear, low 3. heterogeneity in outcome measures and study design, small study sample	Low
Pain relief (5-point NRS) at 30 min/60 min Portenoy (2006)[38] Rauck (200)9[39] Rauck (2010)[40] Rauck (2012)[41] Slatkin (2007)[42]	Oral fentanyl > placebo/ Oral fentanyl > placebo	5	0	0	-2	0	0	1. RoB high, unclear, unclear, unclear, low 3. heterogeneity in outcome measures and study design, results presented in graphs only for 4/5 studies	Low
Intranasal fentanyl versus placebo									
Pain intensity from 5 to 60 minutes (11-point NRS) (Portenoy 2010)[64]	Intranasal fentanyl < placebo	1	0	-1	-1	0	0	1. RoB low 2. single study 3. small study	Low
Pain intensity difference (PID) at 5 minutes (Portenoy 2010)[64]	Intranasal fentanyl > placebo, p=0.07	1	0	-1	-1	0	0	1. RoB low 2. single study 3. small study	Low
PID at 10 minutes	Intranasal	2	0	0	-2	0	0	1. RoB low, low 3. heterogeneity in outcome	Low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
(Portenoy 2010, Kress 2009)[65]	fentanyl > placebo							measures and study design	
Mean sum of pain intensity difference (PID) at 30 minutes ($SPID_{30}$ (± SD))/ SPID from 10 to 60 minutes (Portenoy 2010)[64]	Intranasal fentanyl 6.57±4.99 versus placebo 4.45±5.51/ Intranasal fentanyl > placebo	1	0	-1	-1	0	0	1. RoB low 2. single study 3. small study	Low
SPID at 60 minutes ($SPID_{60}$) Mean $SPID_{60}$ (± SD) (Portenoy 2010, Kress 2009)[64, 65]	Intranasal fentanyl > placebo	2	0	-1	-1	0	0	1. RoB low, low 3. heterogeneity in outcome measures and study design	Low
Reduction in pain intensity by more than 33 % at 10 min (Kress 2009)[65]	Intranasal fentanyl 380/659 episodes vs placebo 62/219 episodes (p<0.001)	1	0	-1	-1	0	0	1. RoB low 2. single study 3. small study	Low
Oral transmucosal fentanyl citrate (OTFC) versus intranasal fentanyl spray (INFS)									
Mean pain intensity difference (11-point categorical rating scale) at 10 minutes/ 30 minutes (Mercadante 2009)[33]	INFS 2.27 (1.98-2.56) vs OTFC 1.08 (0.79-1.36), p<0.001/ INFS 4.15 (3.82-4.48) vs OTFC 3.39 (3.06-3.72), p<0.001	1	-1	-1	-1	0	0	1. RoB high 2. single study 3. small study sample	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
Sum of pain intensity difference at 15 minutes/60 minutes (Median (range)) (Mercadante 2009)[33]	INFS 1.66 (1.46-1.87) vs OTFC 0.85 (0.64-1.05), p<0.001/ INFS 3.52 (3.26-3.79) vs OTFC 2.83 (2.56-3.09), p<0.001	1	-1	-1	-1	0	0	1. RoB high 2. single study 3. small study sample	Very low
Proportion of episodes with pain intensity reduction ≥33% at 5 minutes/ 30 minutes (Mercadante 2009)[33]	INFS 25.3% vs OTFC 6.8%, p<0.001/ INFS 51.0% vs OTFC 23.6%, p<0.001	1	-1	-1	-1	0	0	1. RoB high 2. single study 3. small study sample	Very low
Proportion of episodes with pain intensity reduction ≥50% at 5 minutes/ 30 minutes (Mercadante 2009)[33]	INFS 12.8% vs OTFC 2.1%, p<0.001/ INFS 36.9% vs OTFC 9.7%, p<0.001	1	-1	-1	-1	0	0	1. RoB high 2. single study 3. small study sample	Very low
Fentanyl versus morphine									
Percentage of episodes with ≥ 2-point reduction in pain intensity at 10 and 15 minutes/ at 5, 30, 45 and 60 minutes (Davies 2011)[66]	FPNS > IRMS (p<0.05)/ FPNS=IRMS	1	0	-1	-1	0	0	1. RoB: Jadad score 3 2. single study 3. small study sample	Low
Percentage of	FPNS=IRMS	1	0	-1	-1	0	0	1. RoB: Jadad score 3	Low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
episodes requiring rescue medication (Davies 2011)[66]								2. single study 3. small study sample	
Treatment-emergent adverse events (Davies 2011)[66]	FPNS > IRMS (related to higher doses of FPNS)	1	0	-1	-1	0	0	1. RoB: Jadad score 3 2. single study 3. small study sample	Low
Mean pain intensity difference (15, 30, 45, 60 min) (Coluzzi 2001)[67]	OTFC>IRMS (p<0.008)	1	0	-1	-1	0	0	1. RoB: Jadad score 5 2. single study 3. small study sample	Low
Percentage of episodes needed rescue medication (Coluzzi 2001)[67]	OTFC 2% vs IRMS 1% (ns)	1	0	-1	-1	0	0	1. RoB: Jadad score 5 2. single study 3. small study sample	Low
Mean pain intensity scores at 15 minutes/ at 30 minutes (Mercadante 2007)[32]	IV-MO better than OTFC (p=0.013)/ IV-MO=OTFC	1	-1	-1	-1	0	0	1. RoB high 2. single study 3. small study sample	Very low
Porportion of patients with > 33 % pain reduction/ > 50 % pain reduction (Mercadante 2007)[32]	IV-MO=OTFC/ IV-MO=OTFC	1	-1	-1	-1	0	0	1. RoB high 2. single study 3. small study sample	Very low
Oral transmucosal fentanyl citrate (OTFC) versus regular rescue medications (oxycodone, hydromorphone, hydrocodone and propoxyphene)									
Pain intensity (11-point categorical rating scale) at 15, 30, 60 minutes	OTFC>regular rescue medications	1	-1	-1	-1	0	0	1. RoB high 2. single study 3. small study	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
(Christie 1998)[68]									
Pain relief (5-point categorical rating scale) at 15, 30, 60 minutes (Christie 1998)[68]	OTFC>regular rescue medications	1	-1	-1	-1	0	0	1. RoB high 2. single study 3. small study	Very low

2.3. Corticosteroids

No systematic review and no RCT included

3. FOREST PLOTS

3.1. NSAIDs and paracetamol

Figure 8 – Pain intensity post-intervention: NSAIDS versus opioids (pain intensity scale 0-100)

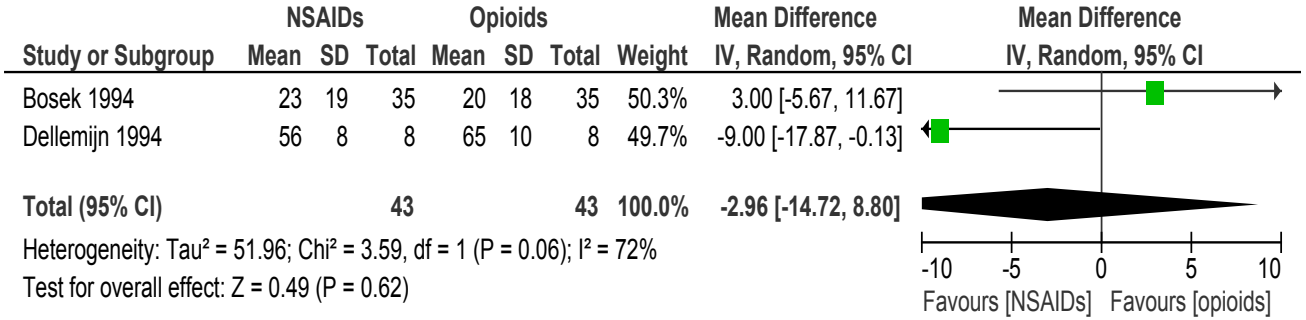
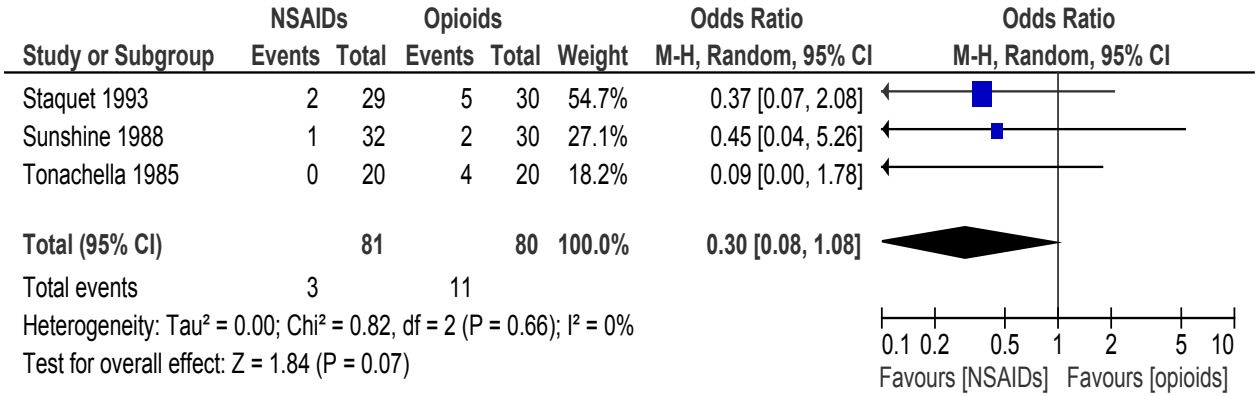


Figure 9 – Incidence of adverse events (number of patients reporting adverse events)



3.2. Opioids

No pooling

3.3. Corticosteroids

No pooling

4. EVIDENCE TABLES

4.1. NSAIDs and paracetamol

Table 21 – NSAIDs and paracetomal: evidence table of systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
McNicol (2011)[5]	• Design: SR • Sources of funding: Richard Saltonstall Charitable Foundation (USA), the Evenor Armington Fund (USA), Agency for Healthcare Research and Quality Contract No 290-97-0019 (USA) • Search date: from each database set-up date to 2002 (CENTRAL), 2003 (Medline), 2001 (EMBASE and LILACS) • Searched databases: MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL),	• Eligibility criteria: o Males and females of all ages and ethnicities o Patn with all types of cancer and concurrent pain (i.e. pain from cancer itself, as side-effect of therapy or procedures or unrelated to cancer) o Cancer-related oral mucositis is excluded o Only RCTs and CCTs • Patient characteristics: o 3084patn in total o 16 different	• Comparisons o NSAID vs placebo o NSAID vs NSAID o NSAID vs opioid o NSAID vs NSAID+ opioid o Opioid vs opioid+ NSAID o NSAID/opioid vs NSAID/opioid o Dose-range comparisons	***Pain*** • NSAID vs placebo (8 trials, no MA): 7/8 superior pain reduction in NSAID arm, 1/8 trend towards superiority of NSAID arm • NSAID vs NSAID (13 trials, no MA): 4/13 sign pain reduction (in ketoprofen 400mg, ketorolac 30mg (2trials), diflunisal 500mg), 1/8 sign diff after ≥7days • NSAID vs opioids (10 trials, no MA): 4/10 pain reduction but low clinical sign or not quantified, 2/10	***Adverse events*** • NSAID vs placebo (8 trials, no MA): no diff between groups • NSAID vs NSAID: not adequately described • NSAID vs opioid: o 6/10 reduction in NSAID group, 2/10 no diff between groups o MA: OR 0.38 (95%CI 0.15 to 0.97) ➔ sign lower proportion of patn in NSAID group (p=0.043) • NSAID vs NSAID+ opioid: o MA on number	• AMSTAR evaluation: Y, Y, Y, Y, Y, Y, Y, Y, Y, N, Y • Authors' conclusions: Based on limited data, NSAIDs appear to be more effective than placebo for cancer pain, clear evidence to support superior safety or efficacy of one NSAID over another is lacking and trials of combinations of an NSAID with an opioid have disclosed either no difference, a statistically insignificant trend towards superiority or at most a slight but statistically significant advantage compared with either single entity. The short duration of studies undermines generalization of their findings on efficacy and safety of NSAIDs for

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
	LILACS, reference lists • Included study designs: RCTs and CCTs • Number of included: 42 Bjorkman 1993 Bosek 1994 Carlson 1990 Chary 1994 Corli 1993 Danninger 1993 Dellemijn 1994 Estape 1990 Ferrer-Brechner 1984 Frankendal 1973 Gallucci 1992 Johnson 1994 Levick 1988 Lomen 1986 Martino 1976 Minotti 1989 Minotti 1998a Minotti 1998b Moertel 1971 Moertel 1974	NSAIDs o No studies on the use of COX-2 inhibitors o Median quality score (Jadad): 3 (range 1-5)		no diff • NSAID vs NSAID+ opioid (8 trials, no MA): 4/8 superior pain reduction in NSAID +opioid but clinical diff >25% of outcome measure • Opioid vs opioid+ NSAID (6 trials, no MA): 5/6 superior pain reduction in opioid+NSAID • NSAID/opioid vs NSAID/opioid (3 trials, no MA): 2/3 no sign diff • Dose-range comparisons (9 trials): o 4/9 superior pain reduction with increased dose o MA (3trials): OR -0.69 (95%CI -0.96	of patn withdrawing due to adverse events OR 0.45 (95% CI 0.06 to 3.57) o no sign diff between groups (p=0.45) o MA on number of patn with adverse events OR 0.77 (95% CI 0.35 to 1.67) o No sign diff between groups (p=0.50) o o NSAID vs NSAID+ opioid: o MA on number of patn withdrawing due to adverse events OR 0.80 (95% CI 0.06 to 10.56) ➔ No sign diff between groups	cancer pain. • Notes: Quality and heterogeneity of the studies precluded any combination of data and results by meta-analysis for the outcome of pain relief. Longer-term efficacy of NSAID may be over-or underestimated and the potential for serious side-effects may be underestimated. Barriers to draw conclusions are heterogeneity of study designs and length of study.

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
	Panutti 1999 Rodriguez 1994 Sacchetti 1984 Saxena 1994 Stambaugh 1980b Stambaugh 1982b Stambaugh 1988a Stambaugh 1988b Staquet 1989 Staquet 1993 Strobel 1992 Sunshine 1988 Tonachella 1985 Toscani 1994 Turnbull 1986 Ventafridda 1975 Ventafridda 1990a Ventafridda 1990b Weingart 1985 Wool 1991 Yalcin 1997 Yalcin 1998			to -0.43) Sign reduction for high vs low-dose NSAIDs (p<0.00001)	(p=0.87) • NSAID/opioid vs NSAID/opioid: not reported • Dose-range comparisons: MA (6trials) OR 1.58 (95%CI 0.88 to 2.83) ➔ No sign diff between doses (p=0.12)	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
Nabal (2012)[6]	• Design: SR • Sources of funding: European Palliative Research Collaborative (EPCRC) through the European Union Sixth Framework Programme (contract no 037777), the Floriani Foundation of Milan, the Italian Association for Cancer Research (grant IG 9347) • Search date: from 2002 to 2010 • Searched databases: MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL), LILACS, reference lists • Included study designs: RCTs and CCTs • Number of	• Eligibility criteria: o Human, adult patients with chronic cancer pain o Only MA, RCTs and CCTs containing data on patient-reported efficacy and/or side effects • Patient characteristics: o 7 trials on NSAIDs/opioid combination with opioid alone and 5 trials on paracetamol/opioid combinations. o Quality of studies: small sample sizes, large loss to follow-up, no ITT analysis, heterogeneity between studies	• Comparisons o NSAID in addition to opiods o Paracetamol in addition to opioids	***Pain*** • NSAID in addition to opioids (7trials, no MA): 3/7 superior reduction in NSAIDs, 2/7 no sign diff between groups • Paracetamol in addition to opioids (5trials, no MA): 4/5 no sign diff between groups, 1/5 slight mean diff in favour of paracetamol combination	***Adverse events*** • NSAID in addition to opioids (7 trials, no MA): 2/7 reduction of opioid consumption in NSAIDs, 6/7 no sign diff between groups, 1/7 sign more constipation in opioids (p=0.006) and sign more gastric discomfort in NSAIDs (p<0.0005) • Paracetamol in addition to opioids: o Opioid consumption: 4/5 not reported, 1/5 no sign diff between groups o Number of mediactions for breakthrough pain: 2/5 no sign diff	• AMSTAR evaluation: Y, Y, Y, Y, Y, N, Y, Y, NA, NA, Y • Authors' conclusions: There is weak evidence that NSAIDs can imrporve analgesia or reduce the opioid dose requirements for patients with cancer pain on a WHO step III opioid regimen. The available evidence is also too weak to support the use of paracetamol in this indication. The clinical practice implications of these results are limited by the lack of more direct evidence. • Notes: Quality and heterogeneity of the studies precluded any combination of data and results by meta-analysis for the outcome of pain relief.

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
	included: 12 Duarte-Souza 2007 Mercadante 2002 Bjorkman 1993 Johnson 1994 Lomen 1986 Weingart 1985 Ferrer-Brechner 1984 Israel 2010 Cubero 2010 Tasmacioglu 2009 Stockler 2004 Axelsson 2003				o Side effects: 4/5 no sign diff, 1/5 more somnolence in NSAID+ opioids	

Table 22 – NSAIDs and paracetomal: evidence table of randomized controlled trials

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
Rodriguez (2003)[9]	• Design: multicenter, double-blind randomized, parallel group trial • Sources of funding: Menarini Research Florence, Italy and Barcelona, Spain	Eligibility criteria: Patients of both sexes with disseminated malignancies presenting with metastatic bone pain ate the units of pain management of the participating hospitals, age over 18years, a diagnosis of malignancy and bone metastases,	Intervention: Dexketoprofen trometamol (25mg q.i.d.), every 6 hours during 7+1 days, along with meals (n=57) vs. Control: Ketorolac (10mg q.i.d.), every 6 hours	**Pain score** (VAS, mm, mean±SD) • At baseline dexketoprofen: 69±15 ketorolac: 75±16 ➔ Non sign diff between groups • At day 3 Dexketoprofen: 37±22 Ketorolac: 43±28 ➔ No sign diff between groups	**Functional performance** (Karnofski score, mean±SD) • At baseline dexketoprofen: 69±11 ketorolac: 72±11 ➔ No sign diff between groups • At day 7 dexketoprofen: 71±16 ketorolac: 74±12 ➔ No sign diff	Risk of bias: unclear Author's conclusion: Dexketoprofen trometamol is a good analgesic therapy in the early treatment of bone cancer pain, comparable to ketorolac, with a good tolerability profile. Remarks: no longterm follow-up

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
	• Setting: Spain • Sample size: n=115 • Duration: 7days	bone cancer pain lasting for more than 10 days, mental status sufficient to complete efficacy and tolerance tests, and Karnofsky performance >40%, level of >40mm on the VAS and a pain rating index of >10 required for inclusion Exclusion criteria: visceral or neuropathic pain, patn undergoing adjuvant therapy at time of entering study or who had completed radiotherapy or chemotherapy within 15days before start of study, or had undergone diagnostic or therapeutic invasive interventions within last 15 days, clinical evidence of brain or liver metastases, treated with continuous and scheduled regimen or	during 7+1 days, along with meals (n=58) Main outcomes (at baseline, day 3 and on day 7): intensity of pain (VAS and pain rating index), % of patn reaching a pain intensity difference from baseline >20mm and absolute level of pain <30mm on VAS, QoL (Karnofsky performance) (only at baseline and at final visit), overall assessment of analgesic efficacy (4-point verbal scale), requirements of rescue medication, adverse events	• At day 7 Dexketoprofen: 32±24 Ketorolac: 40±30 ➔ No sign diff between groups	**Adverse effects:** dexketoprofen: 16% ketorolac: 24% ➔ Mostly mild to moderate (gastrointestinal complaints)	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
		opioids or NSAIDs in 15days before start, etc. Patient characteristics: Age (years) [mean (range)]: dexketoprofen 72±7 (50-89), ketorolac 68±10 (39-89); Gender (M/W): dexketoprofen 42/14, ketorolac 44/13. Both groups were comparable except for age (sign older patn in dexketoprofen group).				
Jameel (1995)[8]	• Design: randomised, double-blind, cross-over trial • Sources of funding: Syntex pharmaceuticals • Setting: UK • Sample size: n=51 • Duration:	Eligibility criteria: Patients with proven diagnosis of cancer resulting in moderate to severe pain which was inadequately controlled with existing analgesia Exclusion criteria: patients receiving opiates or other NSAIDs, patients whose pain was considered unlikely to	Intervention: Ketorolac tromethamine, IM 10mg 6-hourly (n=27) vs. Control: Morphine, IM 10mg 6-hourly (n=24) Main outcomes (at day 3): intensity of pain (5-point rating	**Pain score** (5-point categorical scale) • At baseline ketorolac: very severe: 0 severe: 7 (26.9%) moderate: 16 (61.5%) mild: 3 (11.5%) Morphine very severe: 4 (16.7%) severe: 5 (20.8% moderate: 14 (58.3%) mild: 1 (4.2%)	**Adverse effects:** • ketorolac: 7/18 (38.9%) nausea and/or vomiting: 3 (16.7%) drowsiness: 1 (5.6%) • morphine: 7/11 (63.6%) nausea and/or vomiting: 5 (45.5%) drowsiness: 1 (9.1%) ➔ sign more in the morphine group (P<0.05)	Risk of bias: high Author's conclusion: Ketorolac appears to be a well tolerated and effective analgesic in patients suffering from cancer pain when administered IM. With a comparable efficacy to that of morphine, it is a potentially valuable additional analgesic without opiate toxicity for

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
	3days	be controlled with the permitted dose of morphine and patients who required analgesia within 6 hours of the initial dose of study medication, patients who had received radiotherapy to the site of pain and patients with neuropathi pain, a history of asthma, gastrointestinal disease and diabetes or other metabolic disease Patient characteristics: Age (years) [median (range)]: ketorolac 63 (36-82), morphine 66 (44-84); Gender (M/W): ketorolac 7/20, morphine 2/22. Both groups were comparable at baseline.	scale), adverse events	➔ No sign diff between groups • At day 3 (max overall pain) ketorolac: very severe: 3 (7.1%) severe: 13 (31.0%) moderate: 18 (42.9%) mild: 7 (16.7%) none: 1 (2.4%) Morphine very severe: 3 (9.7%) severe: 3 (9.7%) moderate: 13 (41.9%) mild: 8 (25.8%) none: 4 (12.9%) ➔ No sign diff between groups		cancer patients. Remarks: no longterm follow-up, small sample size, non-completion of study
Sima (2012)[10]	• Design: randomised placebo-controlled trial	Eligibility criteria: Pathologic diagnosis of malignant solid tumours with bone	Intervention: oxycodone/paracetamol, 1-3 tablets, 4x/day, during 3 days (n=126)	**Pain relief** (mean pain intensity difference, NRS scores) • At baseline	**Breakthrough pain:** • At baseline oxycodone/paracetamol 70(55.6%)	Risk of bias: unclear Author's conclusion: Our results show that oxycodone/paraceta

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
	• Sources of funding: not mentioned • Setting: China • Sample size: n=246 • Duration: 3days	metastasis confirmed by imaging, bone-metastasis-related pain rated ≥4 on an 11-point numeric rating scale, having undergone titration and receiving treatment with controlled-release morphine or transdermal fentanyl patches for ≥1 week, conscious mental status and ability to take oral tablets and at least 18years of age. Exclusion criteria: having received chemotherapy, radiotherapy or endocrine or mono-amine oxidase-inhibitor therapy within 30days before the beginning of the study or during the study period, alcohol abuse or severe hepatic disease, having received NSA-Ids or paracetamol combinations	vs. Control: placebo, 1-3 tablets, 4x/day, during 3 days (n=120) Main outcomes (at day 3): mean pain intensity difference, number of patn experiencing breakthrough pain, number of patn who used IR morphine	oxycodone/paracetamol 5.2 (95% CI 5.1-5.4) Placebo: 5.3 (95% CI 5.2-5.5) ➔ No sign diff between groups (p=0.410) • At day 1: oxycodone/paracetamol 0.9 (95% CI 0.7-1.1) Placebo: 0.3 (95% CI 0.2-0.5) ➔ PID sign higher in oxycodone/paracetamol group (p<0.001) • At day 3: oxycodone/paracetamol 1.5 (95% CI 1.2-1.7) Placebo: 0.3 (95% CI 0.2-0.5) ➔ PID sign higher in oxycodone/paracetamol group (p<0.001)	placebo: 61(50.8%) ➔ No sign diff between groups (p=0.270) • At day 3 oxycodone/paracetamol 38 (30.2%) placebo: 58 (48.3%) ➔ sign diff between groups (p<0.001) ➔ need for rescure morphine decreased from 63(50%) to 35 (27.8%) in oxycodone/paracetamol and from 56(46.7%) to 52 (43.3%) in placebo (p=0.008) **Adverse effects:** Total of 5 patn moderate to severe treatment-related adverse events (2 asthenia, 2 dizziness, 1 nausea), 1 withdrew	mol relieves this type of pain in bone as shown by a reduction in pain score, a lowered incidence of breakthrough pain and reduced necessity for rescue morphine. Patients with bone-cancer pain, who are already on opioids, obtain clinically important, further pain-control with regular oxycodone/paracetamol dosing. Remarks: no longterm follow-up

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
		Patient characteristics: Age (years) [mean, SD (range)]: placebo 62.4±8.4 (28-81), oxycodone/paracetamol 61.8±9.1 (33-84); Gender (M/W): placebo 62/58, oxycodone/paracetamol 60/66. Both groups were comparable at baseline.				

4.2. Opioids

Table 23 – Opioids: evidence table of systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
Caraceni (2011)[12]	• Design: SR • Sources of funding: EU Sixth Framework Programme, Floriani Foundation of Milan • Search date: from 2007 and 2009 • Searched databases: MedLine, EMBASE and Cochrane Central Register of Controlled Trials databases. • Included study designs:. RCT or MA • Number of included:17 + 1 unpublished study Pace 2007 Van Seventer 2003 Lauretti 2003 Bruera 2004 Ventafridda 1986 Mercadane 2008 Heiskanen 1997 Mucci LoRusso 1998 Moriarty 1999 Ahmedzai 1997 Wong 1997 Kalso 1990 Hanna 2008	• Eligibility criteria: o . Chronic cancer pain (breakthrough pain excluded) • Patient characteristics: o .adult patients	• Intervention:... Oral morphine • Control:.placebo or others opioids	**Morphine vs transdermal buprenorphine** **(1 study)** Better efficacy and side effects profile fir buprenorphine **Morphine vs other opioids** **(14 studies)** No difference with diamorphine, methadone, oxycodone, transdermal fentanyl, hydromorphone, **(1 unpublished study)** Better analgesia with morphine than with hydromorphone	***Adverse events***: Less constipation with transdermal opioids	• AMSTAR evaluation: Yes, Yes, Yes, Yes, Yes, Yes, Yes, Yes, Not applicable, Not applicable, Yes • Authors' conclusions: No added information to Wiffen 2007 (see updated version above). Morphine, oxycodone and hydromorphone haave similar efficacy and toxicity in cancer patients • Notes: 8/17 studies received some kind of sponsorship from pharmaceutical industry Quality of the large number of studies are low with low statistical power

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
	Napp Laboratoires 2000 (unpublished)					
Hansen (2012)[15]	• Design: SR • Sources of funding: Falck A/S, Denmark • Search date: 3 march 2011 • Searched databases: PubMed database, Embase, Google scholar, Cochrane database, and the Cumulative Index to Nursing and Allied Health Literature • Included study designs:. RCTs • Number of included: 3 Portenoy 2010 Kress 2009 Davies 2011	• Eligibility criteria: • Patient characteristics:	• Intervention: Intranasal fentanyl • Control:. Placebo or immediate-release morphine	***Pain*** • Portenoy 2010 PI: 11-point numeric scale (0 = no pain to 10 = worst possible pain). PR: 5-point numeric scale (0 = none to 4 = complete). Compared with placebo, Fentanyl Pectin Nasal Spray significantly improved PI and PR scores • Kress 2009 Significant higher pain intensity difference with IN fentanyl compared with placebo • Davies 2011 Significant higher PID at 10 and 15 min after administration of IN fentanyl but	***Adverse events (3 studies)***: No majoar side effects	• AMSTAR evaluation: Yes, Yes, Yes, Yes, Yes, Yes, Yes, Yes, Not applicable, Yes, Yes • Authors' conclusions: The trials of breakthrough cancer pain demonstrated a significant analgesic effect of IN fentanyl compared with Placebo and oral morphine but considerable placebo effect observed and low quality study for morphine • Notes:

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
				no differences in supplemental analgesics		
King (2011)[16]	• Design: SR • Sources of funding:.EC 6th Framework Programme, University of Bristol • Search date: 31 July 2009 • Searched databases:.CENTRAL E, MedLine, EMBASE, CINAHL • Included study designs:. MA, RCTs • Number of included: 3 **MA**: Ried 2006 **RCTs**: Gabrail 2004 Lauretti 2003	• Eligibility criteria: o . use of oxycodone • Patient characteristics: o .adult patients with moderate to severe cancer-related pain o Patients without previous switching	• Intervention:... Any formulation, any route of oxycodone • Control:.other drugs	**MA** Mean pain scores Oxycone vs morphine or hydromorphone Mean difference: 0.04 (95% CI 0.29 to 0.36; p=0.8) Heterogeneity:, I^2=62% Oxycone vs morphine 0.2 (95% CI 0.04 to 0.44) Oxycone vs hydromorphone -0.36 (95% CI 0.71 to 0.00) -> no clinically significant **RCTs** *Controlled release oxycodone vs oxymorphine (1 study)* Mean pain		• AMSTAR evaluation: Yes, Yes, Yes, Yes, No, Yes, Yes, Yes, Not applicable, Can't answer, Yes • Authors' conclusions: In patient with moderate to severe cancer-related pain, there is no significant difference between tolerability and efficacy of oxycodone and morphine or hydromorphone (step III opioids) • Notes: studies reported in English only • The review of Fallon 2011 included one RCT (Lauretti 2003) and concluded that only a weak recommendation can support combination opioid therapy due to the paucity of evidence. The authors warned on the balance of desirable effects and

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
				intensity scores and side effects are similar *Sustained release oxycodone (SR) vs controlled release (CR) morphine* Weekly immediate release morphine consumption is 38 % higher in the CR morphine than in SR oxycodone		disadvantages of the combination. • Reid 2006 and Cairns 2001 are two other reviews that all RCTs are included in King 2011. Cairns concluded that morphine remain the drug of first choice but oxycodone could be considered as switching when side-effects related to morphine appear. Reid recommended morphine as first choice for the management of moderate to severe cancer pain because oxycodone is almost 4 times more expensive than morphine (in England) and do not provide more pain relief. • Another review by Wang 2012 including only Chinese observational studies concluded that the efficacy and the tolerability of oxycodone are superior to other strong opioids (morphine, codeine and

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
						tramadol). The utilization is therefore recommended in cancer-related pain in China.
Nicholson (2008)[17]	• Design: SR • Sources of funding: not mentioned • Search date: august 2002 • Searched databases: Cochrane Pain, Palliative & Supportive Care Trials Register, CENTRAL/CCTR, MEDLINE, EMBASE, CINAHL, CancerLit • Included study designs:. RCTs • Number of included: 9 *Oral methadone vs oral morphine* Bruera 2004 Mercadente 1998 Ventafridda 1986 *Oral methadone vs oral methadone + ibuprofen* Ferrer-Brechner 1984	• Eligibility criteria: o Patients with any cancer pain of any age, any gender, any malignant aetiology, any pain intensity and in any setting (home, outpatient setting or inpatient unit • Patient characteristics: o .	• Intervention:... Methadone • Control:. Placebo or other opioids or antidepressants or anticonvulsants	***Reduction in pain intensity*** • Oral methadone vs oral morphine (4 studies) Similar efficacy for both groups • Parenteral methadone vs parenteral morphine (3 studies) Similar size of effect in each case • Methadone vs Methadone + ibuprofen (1 study) Addition of ibuprofen to methadone resulted in improved analgesic	***Adverse effects*** Similar in nature and in intensity between groups of patients taking methadone, morphine	• AMSTAR evaluation: Yes, Yes, Yes, Yes, Yes, Yes, Yes, No, Not applicable, Not applicable, Yes • Authors' conclusions: From the available evidence, methadone appears to be an effective analgesic in patients with cancer pain. The adverse effect profile for methadone appears similar to morphine, but clinicians should be aware of the increased side effects and mortality in case of methadone accumulation. These findings do not support a more superior role for methadone for neuropathic pain. • Notes: No meta-analysis has been conducted because of the quality

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
	Oral methadone vs dextromoramide or pethidine Matts 1964 *Oral methadone vs diamorphine + cocaine* Twycross 1977 *i.v. methadone vs i.v morphine and I;m; methadone vs oral methadone* Beaver 1967 *Methadone i.m. vs oral or i.m. morphine* Gourlay 1986 *Parenteral methadone vs morphine i.v. or orally* Grochow 1989			efficacy • Methadone vs dextromoramide or pethidine (1 study) Similar pain relief • Response rate (4 studies)		and the heterogeneity of studies included
Pigni (2011)[18]	• Design: SR • Sources of funding: European Palliative Research Collaborative – FP6 – contract n° 037777 • Search date: from each database set-up	• Eligibility criteria: o. human adult patients with chronic cancer pain • Patient characteristics: o.	• Intervention:... Hydromorphone • Control:. Morphine or Morphine + oxycodone	***Pain*** No difference excepted in one unpublished RCT (Napp Laboratories 2000) in favour of morphine		• AMSTAR evaluation: Yes, Yes, Yes, Yes, Yes, Yes, Yes, Yes, Not applicable, Not applicable, Yes • Authors' conclusions: Hydromorphone can give similar analgesic results

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
	date to 31 July 2009 • Searched databases: MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials Databases.. • Included study designs:. 9 RCTs, 2 non-randomized controlled studies, 2 uncontrolled prospective studies • Number of included: *5 RCTs for efficacy of hydromorphone*: Hanna 2008 Napp Laboratories 2000 Moriarty 1999 Houde 1986 Hagen 1997 *4 RCTs for route of administration (excluded topic):* Moulin 1991 Houde 1986 Hays 1994 Bruera 1996			(p<0.004) ***Side effects*** No difference excepted in one unpublished RCT (Napp Laboratories 2000) in favour of morphine		in comparison with morphine or oxycodone. In one unpublished trial, morphine was superior to hydromorphone. • Notes: only the results of 5 RCTs challenging the efficacy of hydromorphone are reported here. Quality and heterogeneity of the studies precluded any combination of data and results by meta-analysis
Quigley (2008)[19]	• Design: SR • Sources of funding: not mentioned • Search date: from inception to July 2007	• Eligibility criteria: o SR and RCT in any language, containing more than 20	• Comparisons o Morphine vs placebo fentanyl	**<u>Morphine</u>** 6 SR, 12 RCTs • *Pain control*: Compared with	**<u>Morphine</u>** 6 SR, 12 RCTs • Adverse effects Compared with	• AMSTAR evaluation: Yes, can't answer, no, yes, yes, can't answer, yes, yes, not applicable, not applicable, yes

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
	• Searched databases: MEDLINE, EMBASE, Cochrane Database of Systematic Review, Cochrane Central Register of Controlled Trials (CENTRAL), NHS Centre of reviews and dissemination (CRD), NICE • Included study designs: SR and RCTs • Number of included: 7 SR and 15 RCT <u>SR</u> Wiffen 2002 Clark 2004 Quigley 2007 Nicholson 2007 Reid 2006 Rischitelli 2002 <u>RCT</u> *Morphine* Beaver 1967 Bruera 2004 Grochow 1989 Kalso 1990 Leppart 2001 Mercadante 1998	individuals of whom than 50% were follow up • Patient characteristics: o Cancer patients	trasndermal hydromorphone oral methadone parenteral methadone oxycodone tramadol o Codeine vs placebo o Fentanyl vs placebo morphine hydromorphone oral methadone parenteral methadone oxycodone tramadol o Oxycodone vs hydromorphone o Tramadol vs placebo codeine dihydrocodeine	fentanyl transdermal, oral methadone, parenteral or oral methadone, oxycodone or tramadol No evidence whether morphine is more effective (very low-quality evidence) • *Need for rescue analgesia* Compared with fentanyl No evidence whether morphine is more effective in breakthrough pain (very low-quality evidence) Compared with hydromorphone No evidence whether morphine is more effective (very low-quality evidence) **<u>Codeine</u>** 1 RCT • *Pain control:*	fentanyl (transdermal), more adverse effect with morphine and more withdrawals from treatment (low-quality evidence) **<u>Fentanyl</u>** 4 RCTs • Adverse effects See morphine **<u>Tramadol</u>** 3 RCTs • Quality of live compared with placebo, more effective (low-quality evidence)	• Authors' conclusions: Morphine is the standard of moderate to severe cancer pain. Insufficient evidence is available to judge how to compare morphine with other opioids • Notes:

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
	Moriarty 1999 Napp Laboratories 2000 Ventafridda 1986 Wilder-Smith 1994 *Oxycodone* Hagen 1997 *Tramadol* Arbaiza 2007 *Codeine* Dhaliwal 1995 *Transdermal opioids* Kongsgraad 1998 van Seventer 2003			compared with placebo, codeine is more effective (low-quality evidence). Compared with tramadol, no evidence on superiority of codeine (very low-quality evidence) • *Need for rescue analgesia* Compared with placebo, codeine is more effective (low-quality evidence). **<u>Fentanyl</u>** 4 RCTs • *Pain control:* compared with placebo, no more effective (very low-quality evidence) Compared to morphine, see morphine • *Need for rescue analgesia*		

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
				See morphine **Hydromorphone** 2 RCTs • *Pain control*: compared with oxycodone no evidence whether hydromorphone is more effective (low-quality evidence) • *Need for rescue analgesia* See morphine **Methadone** 3 RCTs See morphine **Oxycodone** 1 RCT • *Pain control*: Compared with hydromorphone see hydromorphone Compared with morphine, see morphine **Tramadol** 3 RCTs		

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
				• Pain control: compared with placebo, more effective (low-quality evidence) Compared to morphine, see morphine Compared to codeine, see codeine Compared to dihydrocodeine, no evidence whether tramadol is more effective (very low-quality evidence) • *Need for rescue analgesia* Compared with placebo, more effective (low-quality evidence)		
Quigley (2009)[20]	• Design: SR • Sources of funding: non mentioned • Search date: November 2006 • Searched databases: MEDLINE, EMBASE and Cochrane Central Register of Controlled	• Eligibility criteria: o Adults and children suffering from any illness with either acute pain or chronic pain including cancer pain and	• Intervention:... Hydromorphone • Control:. Morphine or oxycodone	***Hydromorphone vs morphine*** Moriarty 1999 No significant difference in pain intensity and adverse events		• AMSTAR evaluation: Yes, No, Yes, Yes, Yes, Yes, Yes, Yes, Not applicable, Not applicable, Yes • Authors' conclusions: The evidence available does not demonstrate clinical superiority of

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
	Trials Database, CINAHL, the Oxford Pain relief Database.. • Included study designs:. 61 RCTs with 10 RCTs for cancer patients and only 3 RCTs on efficacy • Number of included: 3 Napp Laboratories 2000 Moriarty 1999 Hagen 1997	post-operative pain (only cancer pain are reported here)		Napp 2000 Significant higher pain scores with hydromorphone and significant more dose of rescue analgesia ***Hydromorphone versus oxycodone*** Hagen 1997 • Overall pain VAS score Oxycodone: 28 mm vs hydromorphone 30.6 mm, ns • Rescue analgesia ns • Adverse effect Vas score Sedation Oxycodone: 23.6 mm vs hydromorphone 18.2 mm, ns Nausea Oxycodone: 15.5		hydromorphone over other strong opioid analgesics. At present morphine remains the 'gold standard' for the management of moderate to severe cancer pain. • Notes:

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
				mm vs hydromorphone 13.1 mm, ns		
Tassinari (2011a)[23]	• Design: SR • Sources of funding: not granted. • Search date: December 2009 • Searched databases: Medline, EMBASE, CINAHL, CRISP and Cochrane systematic Reviews databases • Included study designs:. RCTs • Number of included: 7 Arbaiza 2007 Brema 1996 Leppert 2001 Rodriguez 2008 Rodriguez 2007 Tawfik 1990 Wilder-smith 1994	• Eligibility criteria: o . Adult pain in cancer patients • Patient characteristics: o .patients pre-treated with NSAID and never treated with opioids for chronic pain	• Intervention:... Tramadol • Control:. placebo or other opioids	Tramadol vs placebo **Tramadol vs other opioids** Tramadol is well-tolerated but no definitive data for his superiority in comparison with codeine/paracetamol or other opioids		• AMSTAR evaluation: Yes, Yes, Yes, Yes, No, Yes, Yes, Yes, Not applicable, Yes, Yes • Authors' conclusions: Tramadol is an effective drug but the evidence supporting its front-line use is quite weak • Notes:
Tassinari (2011b)[24]	• Design: SR • Sources of funding:.not granted • Search date: Decembre 2009 • Searched databases:.Medline, Embase, CINAHL,	• Eligibility criteria: o . Adult patients with moderate to severe cancer pain • Patient characteristics: o .Patients never	• Intervention:... Transdermal opioids • Control:. Placebo or other opioids	**Transdermal buprenorphine (TB) vs placebo** **(3 studies)** TB is superieur than placebo **Transdermal fentanyl (TF) vs**		• AMSTAR evaluation: Yes, Yes, Yes, Yes, No, Yes, Yes, Yes, Not applicable, Not applicable, Yes • Authors' conclusions: There is a low level of evidence to support that transdermal opioids

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
	CRISP and Cochrane Systematic Reviews Databases. • Included study designs:. MA and RCTs • Number of included:7 Ahmedzai 1997 Hunt 1999 Mercadante 2008 Pace 2007 Poulain 2008 Kongsgaard 1998 Sittl 2003 Sorge 2004 Tassinari 2008 Tassinari 2009 Van Seventer 2003 Wirtz 2009 Wong 1997	treated with strong opioids for chronic pain and requiring stable doses of opioids		**placebo** **(1 study)** TF is not superior than placebo **Transdermal opioids (TO) vs oral morphine** **(5 RCTs + 2 MA)** • No analgesic difference • Lower constipation rate in TO group **TO (TB or TF) vs slow release oral morphine** **(13 studies)** • Low evidence to spport TO in front-line • Uncertain risk/beneift • Uncertain trade-oof recommandation to the use of TO		(fentanyl or buprenorphine) are better than oral morphine in treatment of moderate to severe cancer pain. The risk/benefit ratio and the trade-off use is uncertain. • Notes: Grading evaluation: Low level = 4 studies; very low level = 9 studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
Wiffen (2010)[25]	• Design: SR • Sources of funding: Oxford Pain Research funds, UK. Department of Health, UK. • Search date: January 1966) to December 2006 • Searched databases: CENTRAL, Medline, Embase, Oxford Pain Relief database, Cochrane Pain, Palliative and Supportive Care Group Trials Register • Included study designs: RCT • Number of included studies: 21 • Included studies: Ahmedzai 1997 Bruera 1998 Bruera 2004 Coluzzi 2001 Dellemijn 1994 Ferrell 1989 Heiskanen 1997 Heiskanen 2000 Kalso 1990 Lauretti 2003 Leppart 2001	• Eligibility criteria: cancer pain requiring treatment with opioids • Patient: adults and children	• Intervention: Oral morphine • Control: other opioids or non-opioids	**Morphine modified release vs** • Oxycodone (13 studies) Adequate analgesia with both agents when doses were titrated. No hallucination with oxycodone • Hydromophone (1 study) No difference in pain control • Transdermal fentanyl (3 studies) No difference in pain control but less constipation with fentanyl • Dextropropoxyphene (1 study) Pain relief was achieved with lower doses on dextropropoxyphe		• AMSTAR evaluation: Yes, Yes, Yes, Yes, Yes, Yes, Yes, Yes, Not applicable, Not applicable, Yes • Authors' conclusions: oral morphine is an effective analgesic in patients with cancer pain. It remains the gold standard for moderate to severe pain. Limited evidence suggests that transmucosal fentanyl may be superior for breakthrough pain. Small number of patients do not benefit from morphine or develop intolerable side effects. • Notes: Meta-analysis of the RCTs was not possible

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
	Melzack 1979 Mercadante 1998 Moriarty 1999 Mucci LoRusso 1998 Rodriguez 1994 Twycross 1977 van Seventer 2003 Ventafridda 1986 Wilder-Smith1994 Wong 1997			ne but only 16 patients/group • Tramadol (1 study) Morphine was more effective at treating neuropathic pain • Methadone (1 study) At 8 days, 37/49 methadone and 42/54 morphine patients had > 20 % reduction in pain intensity (ns) but more adverse events in methadone group • Naproxen (1 study) Pain assessed by 101-point numerical rating scale. Small trial (16 patients). Paracetamol as rescue medication was greater in morphine group		

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
				Morphine immediate release vs • Brompton Cocktail (2 studies) No difference between Brompton Cocktails (no more used nowedays) Cocaïne did not enhance analgesia. • Methadone (1 study) Methadone has value in cancer pain but needs to be mamanged differently from morphine • Tramadol (1 study) Similar pain intensity at 8 days		

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
				• Oxycodone (1 study) Signficantly less nausea and no hallucination with oxycodone • Transmucosal fentanyl citrate (1 study) Pain intensity score was lower with fentanyl • Dipyrone (1 study) Dipyrone 2 g and morphine 10 mg showed benefits over dipyrone 1g		
Zeppetella (2009)[26]	• Design: MA • Sources of funding: not mentioned. • Search date: January 2005 • Searched databases:. MEDLINE, EMBASE, CancerLit, CINAHL	• Eligibility criteria: o. Patients with cancer and breakthrough pain in any setting • Patient characteristics: o.Both male and	• Intervention: Opioids analgesics • Control:.placebo or other opioids or other active control group for relief of	***Pain intensity (4 studies)*** 11-point numerical rating scale • At 15 min Mean difference: -0.68 (95% CI		• AMSTAR evaluation: Yes, Yes, Yes, Yes, Yes, Yes, Yes, Yes, No, Yes • Authors' conclusions: The practice of delivering a fixed proportion of the around

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
	and Cochrane databases • Included study designs:. RTCs • Number of included: 4 Christie 1998 Coluzzi 2001 Farrar 1998 Portenoy 1999a	female o All ages	breakthrough pain	-1.03, - 0.34; p=0.56) Heterogeneity: χ^2=2.06, df=3, p=0.00011, I^2=0.0% • At 30 min Mean difference: -0.91 (95% CI -1.23, - 0.59; p=0.09) Heterogeneity: χ^2=6.39, df=3, p<0.00001, I^2=53% ***Pain relief (4 studies)*** 5-point visual rating scale • At 15 min Mean difference: 0.54 (95% CI 0.40, 0.69; p=0.004) Heterogeneity: χ^2=13.16, df=3, p<0.00001, I^2=77%		the clock rescue medication is not supported by this review • Notes:

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
				• At 30 min Mean difference: 0.61 (95% CI 0.47, 0.75; p=0.01) Heterogeneity: χ^2=10.66, df=3, p<0.00001, I^2=72%		

Table 24 – Opioids: list of randomized controlled trials included in the chapter

Reference	Design	Intervention	Comparison	n patients	mentionned in systematic review
A. Morphine					
Beaver (1967)[58]	crossover study	Different dosage scheme of morphine followed by methadone	Different dosage scheme of morphine followed by methadone	43	Nicholson 2008, Quigley 2008
Beaver (1978)[50]	crossover study	Morphine i.m. + codeine phosphate	oxycodone i.m.	32	King 2011, Reid 2006
Bruera (1998)[43]	crossover study	Morphine modified release	Oxycodone immediate release	32	Cairns 2001,King 2011,Reid 2006,Wiffen 2010
Bruera (2004)[54]	crossover study	Morphine modified release	Methadone	103	Caraceni 2011,Nicholson 2008, Quigley 2008,Wiffen 2010
Ferrell (1989)[44]	RCT	Morphine modified release	Pxycodone	83	Wiffen 2010
Grochow (1989)[57]	RCT	Morphine i.v.	Methadone i.v.	23	Nicholson 2008,Quigley 2008
Hanna (2008)[51]	RCT	Morphine modified release	Hydromorphone	200	Caraceni 2011,Pigni 2011

Reference	Design	Intervention	Comparison	n patients	mentionned in systematic review
Heiskanen (1997)[45]	crossover study	Morphine modified release	Oxycodone sutained release	45	Cairns 2001,Caraceni 2011,King 2011,Reid 2006,Wiffen 2010
Heiskanen (2000)[46]	crossover study	Morphine modified release	Oxycodone modified release	45	Wiffen 2010
Houde (1986)[52]	crossover study	Morphine	Hydromorphone	48	Pigni 2011
Kalso (1990)[49]	crossover study	Morfine immediate release	Oxycodone immediate release	20	Caraceni 2011,King 2011,Quigley 2008,Reid 2006,Wiffen 2010
Lauretti (2003)[47]	crossover study	Morphine modified release	Oxycodone modified release	26	Caraceni 2011,Fallon 2011,King 2011,Wiffen 2010
Leppert (2001)[59]	RCT	Morfine immediate release	Tramadol immediate release	40	Quigley 2008,Tassinari 2011a
Melzack (1979)[69]	crossover study	Morphine	Brompton cocktail	44	Wiffen 2010
Mercadante (1998a)[55]	RCT	Oral morphine	Oral methadone	40	Nicholson 2008,Quigley 2008
Mercadante (2010)[34]	RCT	Sustained release oral morphine	Sustained release oral oxycodone	60	Update
Moriarty (1999)[53]	crossover study	Morphine modified release	Hydromorphone	100	Caraceni 2011,Pigni 2011,Quigley 2008,Quigley 2009,Wiffen 2010
Mucci LoRusso (1998)[48]	RCT	Morphine modified release	Oxycodonemodified release	100	Cairns 2001,Caraceni 2011,King 2011,Reid 2006,Wiffen 2010
Napp Laboratories (2000)[70]	crossover study	Oral controlled release morphine	Oral controlled release hydomorphone	87	Caraceni 2011,Pigni 2011,Quigley 2008,Quigley 2009
Twycross (1977)[71]	crossover study	Morphine + cocaine	Dimorphine + cocaine (Brompton coktail)	699	Nicholson 2008,Wiffen 2010
Ventafridda (1986)[56]	RCT	Morphine (oral)	Methadone (oral)	66	Caraceni 2011,Nicholson 2008,Quigley 2008,Wiffen 2010
Wilder-smith (1994)[60]	crossover study	Morphine immediate release	Tramadol sol 5 %	20	Quigley 2008,Tassinari 2011a,Wiffen 2010
B. Oxycodone					

Reference	Design	Intervention	Comparison	n patients	mentionned in systematic review
Ahmedzai (2012)[27]	RCT	Oxycodone + naloxone	Oxycodone	185	Update
Gabrail (2004)[61]	crossover study	Oxycodone controlled release	Oxymorphone controlled release	44	King 2011
Hagen (1997)[62]	crossover study	Oxycodone sustained release	Hydromorphone sustained release	44	King 2011,Pigni 2011,Quigley 2008,Quigley 2009,Reid 2006
C. Tramadol					
Arbaiza(2007)[72]	RCT	Oral tramadol	Placebo	36	Quigley 2008,Tassinari 2011a
Brema (1996)[73]	RCT	Oral tramadol	Oral buprenorphine	131	Tassinari 2011a
Rodriguez (2007)[74]	RCT	Oral tramadol	Hydrocodone or paracetamol/codeine	117	Tassinari 2011a
Rodriguez (2008)[75]	RCT	Oral tramadol	Hydrocodone/ paracetamol	118	Tassinari 2011a
D. Codeine					
Dhaliwal (1995)[76]	crossover study	codeine	placebo	35	Quigley 2008
E. Breakthrough					
Christie (1998)[68]	RCT	Fentanyl-TTS	OTFC	62	Zeppetella 2009
Coluzzi (2001)[67]	crossover study	Oral transmucosal fentanyl citrate	Morphine immediate release	134	Wiffen 2010,Zeppetella 2009
Davies (2011)[66]	RCT	Fentanyl pectin nasal spray	Morphine immediate release	79	Hansen 2012
Elsner (2005)[29]	RCT	Morphine i.v.	Subcutaneous morphine	39	Update
Farrar (1998)[63]	RCT	Oral transmucosal fentanyl citrate	Placebo	130	Zeppetella 2009
Kress (2009)[65]	RCT	Intranasal fentanyl spray	Placebo	110	Hansen 2012
Mercadante (2007)[32]	RCT	Oral transmucosal fentanyl citrate	iv-morphine 4mg	25	Update

Reference	Design	Intervention	Comparison	n patients	mentionned in systematic review
Mercadante (2009)[33]	RCT	Intranasal fentanyl spray	Oral transmucosal fentanyl	139	Update
Portenoy (2006)[38]	RCT	Fentanyl buccal tablet	Placebo	701	Update
Portenoy (2010)[64]	RCT	Fentanyl Intranasal	Placebo	73	Hansen 2012
Rauck (2009)[39]	RCT	Sublingual fentanyl orally disintegrating	Placebo	66	Update
Rauck (2010)[40]	RCT	Fentanyl buccal soluble film	Placebo	82	Update
Rauck (2012)[41]	crossover study	Fentanyl sublingual spray	Placebo	98	Update
Slatkin (2007)[42]	RCT	Fentanyl buccal tablet	Placebo	87	Update
Kongsgaard (1998)[77]	RCT	Transdermal fentanyl	Placebo	138	Quigley 2008,Tassinari 2011b
Kress (2008)[31]	RCT	Fentanyl Improved Transdermal patch	Standard oral or standard transdermal opioids	220	Update
Mercadante (2008)[78]	RCT	Transdermal fentanyl	Sustained release oral morphine	108	Caraceni 2011,Tassinari 2011b
Mystakidou (2005)[36]	RCT	Radiotherapy + transdermal therapeutic fentanyl system patch	Radiotherapy + codeine or paracetamol	422	Update
Pace (2007)[79]	RCT	Transdermal bupremorphine	Sustained release oral morphine	52	Caraceni 2011
Pistevou-Gompaki (2004)[37]	RCT	Radiotherapy + transdermal therapeutic fentanyl system patch	Radiotherapy + codeine or paracetamol	26	Update
Poulain (2008)[80]	RCT	Transdermal bupremorphine	Placebo	289	Tassinari 2011b

Reference	Design	Intervention	Comparison	n patients	mentionned in systematic review
Van Seventer (2003)[81]	RCT	Transdermal fentanyl	Morphine modified release	131	Caraceni 2011,Quigley 2008,Tassinari 2011b,Wiffen 2010
Wirtz (2009)[82]	RCT	Transdermal opioids	Sustained release hydromorphone	174	Tassinari 2011b
G. Celiac Plexus Block					
Johnson (2009)[30]	RCT	opoids analgesia + Celiac Plexus Block	Opioid analgesia + Thoracoscopic splanchnicectomy	65	Update
H. Opioids switching					
Cubero (2010)[28]	RCT	Switching morphine to methadone + acetaminophen	Switching morphine to methadone + placebo	50	Update
Moksnes (2011)[83]	RCT	progresive swithching	stop and go	42	Update

Table 25 – Opioids: evidence table of randomized controlled trials

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
Ahmedzai (2012)[27]	• Design: international, multicenter, randomized, double-blind, active-controlled, double-dummy, parallel-group, phase II study • Sources of funding: Mundipharma	Eligibility criteria: Patients over 18 year old with a diagnosis of cancer and moderate/severe, chronic cancer pain, requiring round-the-clock opioid therapy Patient characteristics: Age (years) [median (range)]: intervention 62.0	Intervention: Oxycodone/naloxone prolonged-release tablets (OXN PR) vs. Control: Oxycodone prolonged-	*Results are not in ITT* **Pain score at 4 weeks** *Mean (SD) BPI-SF scores* OXN PR: 3.50 ± 1.88 vs OxyPR: 3.52 ± 1.80, ns **Quality of live** • **EQ-5D**	**Side effects:** *Number of patients* • Gastrointestinal disorders OXN PR 77/92 vs OxyPR 62/92 • Nausea OXN PR 7/92 vs OxyPR 12/92 • Vomiting	Risk of bias: High Author's conclusion: The patients with opioid-induced constipation and moderate/severe cancer pain who were switched directly from others

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
	Research GmbH & Co. KG • Setting: Australia, Czech Republic, France, Germany, Hungary, Israel, Netherlands, Poland, UK • Sample size: n=92 (control); n=92 (intervention) • Duration: 4 weeks	(36-84), control 66.0 (42-82); Gender (M/F): intervention 48/44, control 46/46; The treatment groups were balanced with respect to demographics and all baseline disease characteristics but higher percentage of patients aged ≤65 years in intervention group	release tablets (OxyPR)	*Mean (SD) index scores* OXN PR: 0.55 ± 0.33 vs OxyPR: 0.49 ± 0.38, ns • **QLQ-C30 score** ns	OXN PR 6/92 vs OxyPR 5/92 • Diarrhea OXN PR 4/92 vs OxyPR 4/92 • Worsened constipation OXN PR 6/92 vs OxyPR 6/92 • Patient assessement of constipation symptoms *Mean (SD)* OXN PR: 1.47 ± 1.07 vs OxyPR: 2.03. ± 1.29, p<0.01 **SOWS (subjective opiate withdrawal scale)** *Mean (SD) SOWS scores* OXN PR: 8.10 ± 7.76 vs OxyPR: 8.90 ± 7.81, ns	opioids to a combination of oxycodone and naloxone prolonged-release, experienced a similar analgesic effect compared with those switched to Oxycodone prolonged-release Remarks:
Cubero 2010[28]	• Design: 2-arm, randomized, control trial	Eligibility criteria: Patients over 18 year old using morphine due to	Intervention: Switching morphine to	*Morphine (baseline) vs Methadone* **Pain improvement**	**Time to reach equianalgesia** Interval between	Risk of bias: High

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
	• Sources of funding: not mentioned • Setting: Brazil • Sample size: n=25 (control); n=25 (intervention) • Duration: 7 days	oncologic pain Patient characteristics: Age (years) [median (range)]: intervention 58.1 (19-81), control 59 (25-76); Gender (M/F): intervention 13/11, control 13/12; Pain score in the numerical scale [median (range)]: intervention 5 (0-8), control 3.5 (0-10); Pain score in the face scale [median (range)]: intervention 6 (0-8), control 4 (0-10); The treatment groups were balanced with respect to demographics and all baseline disease characteristics	methadone + acetaminophen vs. Control: Switching morphine to methadone + placebo	**from baseline to 7 days** • Faces rating scale [FS] (expression of faces from happiness (without pain) to weeping (intense pain)) Mean (SD) Morphine 4.49 (2.23) vs Methadone 3.31 (2.79); p=0.05 • Numerical rating scale (from 0 to 10) [NRS] Mean (SD) Morphine 4.26 (2.33) vs Methadone 3.31 (2.71); p=0.03 **Quality of live (QLQ-C30 score)** • Global health (mean) Morphine 52.27 vs Methadone 58.54 p=0.11 • Functional health (mean) Morphine 50.17 vs Methadone 57.00 p=0.011	the switching and the first time NRS and FS were equal or lower than baseline Most patients reached the equianalgesic dose in 24h *Morphine (baseline) vs Methadone* **Side effects (0 to 3 degrees):** • Constipation Mean (SD) Morphine 1.81 1.03) vs Methadone 0.70 (1.06); p<0.001 • Xerostomia Mean (SD) Morphine 1.51 1.12) vs Methadone 0.93 (0.96); p=0.003 • Nausea, Vomiting, Somnolence: ns *Methadone + acetaminophen*	Author's conclusion: Methadone should be considered a therapeutic option for oncologic patients and presents evident economic Remarks:

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				• Symptoms (mean) Morphine 49.05 vs Methadone 37.46 p<0.11 *Methadone + acetaminophen (MA) vs Methadone + placebo (MP)* • Reduction in points in NRS [mean (SD)] MA -1.09 ± 3.19 vs MP -0.79 ± 2.32; p=0.57 • Reduction in FS MA -0.91 ± 2.60 vs MP -0.74 ± 2.68; p=0.71	*(MA) vs Methadone + placebo (MP)* • Worse somnolence MA 10/25 vs MP 2/25; p=0.037 Constipation, Xerostomia, Nausea, Vomoniting: ns	
Elsner 2005[29]	• Design: open randomized, control trial • Sources of funding: not mentioned • Setting: 1 centre in Germany • Sample size: n=21 (iv); n=18 (sc); • Duration: 4 days •	Eligibility criteria: Cancer patients ≥ 18 years with persisting pain exacerbations for > 24 hours and sufficiently treated with immediate-release morphine (iv or sc). Patient characteristics: Age (years) [median (range)]: iv 60 (27-76), sc 58 (27-76); Gender (M/F): iv 12/6, sc 9/9; Pain diagnoses (nociceptive/neuropathic)	Intervention: Intravenous morphine (iv) every 5 minutes vs. Control: Subcutaneous morphine every 30 minutes Bolus doses were calculated according to the	**Pain intensity** VAS 100mm Mean ± SD • At inclusion iv: 83±17, sc: 68±24; p=0.03 • At 4 days iv: 41±31, sc: 31±16; p=0.37 **Percentage of theorical maximum of total pain relief (% TOTPAR)** AUC = area under the		Risk of bias: High Author's conclusion: Intravenous and subcutaneous-morphine titration are adequate to treat breakthrough cancer pain

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
		iv 16/5, sc 16/3;	background treatment of the patient	curve of residual pain against time TMT=theorical maximum of total pain relief = VAS(start)*t_{end} TOTPART=TMT-AUC %TOTPART= TOTPAR/TMT*100 iv: 31 %, sc=15%; p=0.005 **Proportion of patients with ≥ 50% pain reduction at the end of the titration** iv: 14/21, sc: 7/18 **Proportion of patients with ≥ 30% pain reduction at the end of the titration** iv: 18/21, sc: 10/18		
Johnson 2009[30]	• Design: randomized, control trial • Sources of funding: Health Technology Assessment Programme • Setting: 4 centres in UK	Eligibility criteria: Patients with irresectable malignancy in upper abdominal viscera and with pain requiring any opioid medication at least once per day Patient characteristics: Age (years) [median	Intervention: Opioid analgesia + Celiac Plexus Block (CPB) vs. Opioid analgesia + Thoracoscopic splanchnicectomy (TS)	**Effective Pain relief** (not reported, composite scale) **Mean Pain score** Brief Pain Inventory Mean ± SD • At 2 weeks MM: 4.16±1.78, CPB: 4.02±1.40, TS:	**Side effects:** Constipation was the most reported side effect **Opioids use:** The rate of opioids cessation was similar in all groups	Risk of bias: High Author's conclusion: There is no evidence to support the systematic use of intervention (CPB or TS) for effective pain relief in

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
	• Sample size: n=24 (opioids); n=20 (CPB); n=21 (TS); • Duration: 7 days	(SD)]: MM 65.5 (9.13), CPB 60.5 (9.22), TS 60.2 (9.31); Gender (M/F): MM 16/8, CPB 10/10, TS 6/15; Pancreas cancer MM 17/24, CPB 19/20, TS 18/21; Opioids naïve MM 7/24, CPB 4/20, TS 5/21;	Vs Control: Opioid analgesia (MM)	3.86±2.44; ns • At 2 month MM: 4.00±1.17, CPB: 2.46±1.75, TS: 3.46±2.43; ns		patients with upper abdominal viscera cancer. Remarks:
Kress 2008[31]	• Design: randomized, open, parallel group, multinational, multicenter trial • Sources of funding: Nycomed Group • Setting: Norway, Sweden, Finland, Denmark, Germany, Austria, Russia • Sample size: n=103 (control); n=117 (intervention) • Duration: 30 days	Eligibility criteria: Patients (>18 years) with chronic cancer-related pain requiring long-term use (≥30 days) Step 3 WHO Ladder opioid treatment and with Karnofsky score >50 at Patient characteristics: Age (years) [mean]: intervention 63.1, control 61.9; Gender (M/F): intervention 68/49, control 64/39; Mean baseline pain intensity: intervention 5.0, control 5.0; Mean baseline Karnofsky: intervention 77.1, control 77.0	Intervention: Fentanyl Improved Transdermal patch (FIT-patch) vs. Control: Standard oral (Oral) or standard transdermal opioid treatment (MF)	**Pain intensity** Score rating on 0-10 point Numerical rating (NRS) Mean (least square means from analysis of variance models adjusting for center, baseline and baseline pain intensity) (SE) and difference (95% IC) FIT-patch vs Oral: 32.0 (2.27) vs 33.0 (3.82); p=0.795 Difference -1.1 (-0.92, 7.0) FIT-patch vs MF: 32.0 (2.27) vs 37.6 (2.99); p=0.072 Difference -5.6 (-11.8,	**Side effects:** Tolerability scores: 0= none, 1=mild, 2=moderate, 3=severe • Number of patients with adverse: events: 72/117 (FIT-patch) vs 58/103 (Oral+MF) • Number of patients with seriouse adverse events: 26/117 (FIT-patch) vs 27/103 (Oral+MF) • Nausea Number of patients:	Risk of bias: High Author's conclusion: FIT-patch is as efficiency and as safe as standard treatment (oral or other transdermal opioids) Remarks:

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				0.5)	16/117 (FIT-patch) vs 15/103 (Oral+MF) Mean score 0.5 (FIT-patch) vs 0.7 (Oral) vs 0.6 (MF), ns • vomiting Number of patients 4/117 (FIT-patch) vs 13/103 (Oral+MF) • Constipation Number of patients 7/117 (FIT-patch) vs 5/103 (Oral+MF) Mean score 0.7 (FIT-patch) vs 0.8 (Oral) vs 0.8 (MF), ns • Anxiety Number of patients with 7/117 (FIT-patch) vs 2/103 (Oral+MF) • Insomnia	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
					Number of patient 0/117 (FIT-patch) vs 4/103 (Oral+MF) Mean score 0.7 (FIT-patch) vs 0.6 (Oral) vs 0.7 (MF), ns	
Mercadante 2007[32]	• Design: randomized, crossover, controlled study • Sources of funding: not mentioned • Setting: 1 centre in Italy • Sample size: n=25 • Duration: not clear	Eligibility criteria: Adult patients (from 18 to 80) with cancer-related pain using opioids doses ≥ 60 mg of oral morphine equivalents Patient characteristics: Patient characteristics: Age (years) [mean (95%CI)]: 59 (55-63); Gender (M/F): 12/13	Intervention: Oral transmucosal fentanyl citrate (OTFC) vs. Control: iv-morphine 4mg (IV-MO)	**Pain intensity** Numerical scale from 0 to 3 Mean (95% CI) • At 15 min OTFC: 4.1 (3.5-4.7) vs IV-MO: 3.3 (2.7-3.8), p=0.013 • At 30 min OTFC: 2.4 (1.8-2.9) vs IV-MO: 1.7 (1.2-2.3), p=0.059 **Porportion of patients with > 33 % pain reduction** • At 15 min OTFC: 30 (57%) vs IV-MO: 39 (74%), p=0.066	**Side effects:** Scale from 0 to 3 (absent, slight, moderate, severe) Adverse effects with an intensity of 2/3 on the scale used (moderate intensity) in episode treated with OTFC and IV-MO • Nausea OTFC: 4 (7.5%) vs IV-MO: 2 (3.7%) • Drowsiness OTFC: 7 (13.2%) vs IV-MO: 10 (18.8%)	Risk of bias: High Author's conclusion: IV-MO and OTFC were as effective to treat breakthrough pain episodes. The effect of IV-MO is faster. Adverse effects were compatible and not troublesome. The treatment with OTFC could be feasible for outpatients or home patients without requiring complex titration procedures. Remarks:

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				• At 30 min OTFC: 45 (85%) vs IV-MO: 46 (87%) p=0.23 **Porportion of patients with > 50 % pain reduction** • At 15 min OTFC: 20 (38%) vs IV-MO: 29 (55%), p=0.39 • At 30 min OTFC: 29 (55%) vs IV-MO: 40 (75%), p=0.20	• Confusion OTFC: 1 (1.8%) vs IV-MO: 3 (5.6%)	Wash-out period of 6 hours
Mercadante 2009[33]	• Design: open-label crossover trial • Sources of funding: not mentioned • Setting: 44 centres in Austria, France, Germany, Italy, Poland, Spain, UK • Sample size: n=139 • Duration: up to 2 weeks	Eligibility criteria: In- and outpatients with cancer (> 18 years) with life expectancy of ≥ 3 months, who were experiencing ≥ 3 BTP episodes/week but ≤ 4 BTP episodes per day, background pain at baseline (none or mild) Patient characteristics: Age (years) [mean ± SE]: 62.0 ± 11.6; Gender (M/F): 79/60	Intervention: Intranasal fentanyl spray (INFS) vs. Control: Oral transmucosal fentanyl (OTFC)	**Time to onset 'meaningful' pain relief** Assessed by patients Proportion of patients with a faster onset of 'meaningful' pain relief with INFS compared to OTFC: 65,7 %, p<0.001 *Following results are no intention-to-treat* **Pain intensity difference** Assessed on a standard 11-point	*Results are no intention-to-treat* **Side effects:** • Number of patients experienced adverse events related to treatment: 15/122 (INFS) vs 22/118 (OTFC) • Number of paitents experienced severe adverses	Risk of bias: High Author's conclusion: Intranasal fentanyl spray produice a greater pain intensity difference from 5 minutes post-dosing than Oral transmucosal fentanyl. Remarks:

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				numerical rating scale (from 0 to 10) Mean (95% CI) • At 10 minutes INFS: 2.27 (1.98-2.56) vs OTFC: 1.08 (0.79-1.36), p<0.001 • At 30 minutes INFS: 4.15 (3.82-4.48) vs OTFC: 3.39 (3.06-3.72), p<0.001 **Sum of pain intensity difference (SPID)** Area under the curve for PID/time interval in minutes • At 15 minutes INFS: 1.66 (1.46-1.87) vs OTFC: 0.85 (0.64-1.05), p<0.001 • At 60 minutes INFS: 3.52 (3.26-3.79) vs OTFC: 2.83 (2.56-3.09), p<0.001 **Proportion of episodes pain intensity reduction ≥33% (clinical important level of**	events: 16/122 (INFS) vs 9/118 (OTFC) • Number of paitents experienced serious adverses events: 13/122 (INFS) vs 6/118 (OTFC) • Number of patients with adver events leading to trial withdrawal: 10/122 (INFS) vs 8/118 (OTFC)	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				pain relief) • At 5 minutes INFS: 25.3% vs OTFC: 6.8%, p<0.001 • At 30 minutes INFS: 51.0% vs OTFC: 23.6%, p<0.001 **Proportion of episodes pain intensity reduction ≥50%** • At 5 minutes INFS: 12.8% vs OTFC: 2.1, p<0.001 • At 30 minutes INFS: 36.9% vs OTFC: 9.7%, p<0.001		
Mercadante 2010[34]	• Design: randomized control trial • Sources of funding: not mentioned • Setting: one centre in Italy • Sample size: n=30 (control); n=30	Eligibility criteria: Pancreatic cancer patients with local disease, abdominal pain intensity ≥ 4/10 and no longer responsive to nonopioid analgesics Patient characteristics: Age (years) [mean ± SE]: 63.2 ± 9.48; Gender	Intervention: Sustained release oral oxycodone (OX) vs. Control: Sustained release oral morphine (MO)	*Results are no intention-to-treat* **Pain intensity** Average pain intensity in the last 24 hours (numerical rating scale 0 to 10) Mean (±SD) • At 1 week OX: 2.09 (±2.07) vs MO: 1.41 (±1.81),	*Results are no intention-to-treat* **Adverse effects:** Results are presented in the paper at 1, 2, 4 and 8 weeks. Only results at 4 weeks are reported here. Mean score on a	Risk of bias: High Author's conclusion: Oxycodone and morphine provided similar analgesisia and adverse effects in patients with pancreatic cancer pain

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
	(intervention) • Duration: 8 weeks	(M/F): 19/27		p=0.232 • At 2 weeks OX: 1.8 (±1.76) vs MO: 1.62 (±2.04), p=0.528 • At 3 weeks OX: 2.79 (±2.04) vs MO: 2.17 (±2.14), p=0.297 • At 4 weeks OX: 3.15 (±3.0) vs MO: 2.35 (±2.36), p=0.492 • At 8 weeks OX: 2.0 (±1.2) vs MO: 1.2 (±1.03), p=0.189	scale from 0 to 3 (absent, slight, moderate, and severe) • Nausea OX: 0.84 (±0.90) vs MO: 0.60 (±0.75), p=0.400 • Drowsiness OX: 0.37 (±0.60) vs MO: 0.35 (±0.59), p=0.917 • Confusion OX: 0.37 (±0.49) vs MO: 0.25 (±0.44), p=0.429 • Dry mouth OX: 0.63 (±0.68) vs MO: 0.60 (±0.68), p=0.876 • Constipation Scale: 0=one passage/1 to 2 days, 1=one passage/3 to 4 days, 2=one passage/more than 4 days, and 3=only by enema OX: 0.63 (±0.68) vs	Remarks:

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
					MO: 0.70 (±0.92), p=0.926	
Moksnes 2011[35]	• Design: prospective, open, parallel group, multicentre randomised controlled phase II trial • Sources of funding: Norwegian Cancer Society and the Norwegian Research Council • Setting: 4 hospitals in Norway • Sample size: n=21 (control); n=21 (intervention) • Duration: 14 days	Eligibility criteria: Patients over 18 year old using morphine due to oncologic pain Patient characteristics: Age (years) [mean (95%CI)]: SAG 61 (58-65) vs 3DS 58 (54-63); Gender (M/F): SAG 12/9 vs 3DS 10/10; Pain intensity [mean (95%CI)]: SAG 5.4 (4.1-6.6) vs 3DS 5.5 (4.4-6.5), Karnofsky performance status [mean (95%CI)]: SAG 59 (53-65) vs 3DS 60 (52-67) The two groups are similar except time on WHO step 3 opioids:mean difference (%95 CI): -14.4 (-26.6 to -2.3)	Intervention: '3-days switch' (3DS) where the dose of current opioids is reduced stepwise by 1/3 every day and substituted with 1/3 of the equianalgesic dose of methadone over three days vs. Control: Stop and go where the current opioid is immediately replaced by methadone (SAG)	*Results are no intention-to-treat* **Pain relief** Brief pain inventory (BPI) based on a 0 to 10 numerical rating scale Mean (95% CI) • Average pain intensity o Day 3 SAG: 4.1 (2.3-5.9) vs 3DS: 3.6 (2.9-4.3), mean difference 0.5 (-1.2-2.2) o Day 14 SAG: 4.9 (2.1-7.7) vs 3DS: 2.8 (1.8-3.9), mean difference 2.1 (-0.8-5.0) • Pain intensity now (before 12 am) o Day 3 SAG: 3.3 (1.6-5.0) vs 3DS: 2.8 (1.7-3.9), mean difference 0.5 (-	*Results are no intention-to-treat* **Side effects:** 0 to 10 numerical rating scale before 12 am using a Norwegian version of the Edmonton Symptom Assessment system • Drowsiness o Day 3 SAG: 2.7 (1.5-3.9) vs 3DS: 2.7 (1.7-3.6), mean difference 0.0 (-1.3-1.6) o Day 14 SAG: 2.9 (0.9-4.8) vs 3DS: 2.9 (1.8-4.0), mean difference 0.0 (-2.0-1.9) • Nausea o Day 3 SAG: 1.0 (0.3-1.7)	Risk of bias: High Author's conclusion: The SAG patients reported a trend of more pain, had significantly more dropouts and adverse events. SAG strategy should not replace the 3DS when switching from high doses of morphine or oxycodone to methadone. Remarks:

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				1.4-2.3) o Day 14 SAG: 3.3 (1.9-4.7) vs 3DS: 2.6 (1.6-3.7), mean difference 0.7 (-1.0-2.3)	vs 3DS: 0.9 (0.3-1.7), mean difference 0.1 (-1.0-1.0) o Day 14 SAG: 1.3 (0.8-3.3) vs 3DS: 0.7 (0.1-1.5), mean difference 0.6 (-1.1-2.1) • Loss of appetite o Day 3 SAG: 3.9 (1.7-6.0) vs 3DS: 2.7 (0.3-1.7), mean difference 1.2 (-1.1-3.5) o Day 14 SAG: 2.9 (0.4-6.1) vs 3DS: 2.7 (1.4-4.1), mean difference 0.2 (-2.6-2.8) • Dry mouth o Day 3 SAG: 3.0 (1.5-4.5) vs 3DS: 2.4 (1.7-3.7), mean difference 0.6 (-1.2-3.5)	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
					o Day 14 SAG: 1.6 (-0.2-3.3) vs 3DS: 2.0 (1.2-2.8), mean difference -0.4 (-1.9-1.1)	
Mystakidou 2005[36]	• Design: randomized, control trial • Sources of funding: not mentioned • Setting: Greece • Sample size: n=221 (control); n=201 (intervention) • Duration: 2 months	Eligibility criteria: Cancer patients with bone metastases and moderate to severe pain refractory to common analgesic. Patients were naïve to mild or strong opioids Patient characteristics: Age (years) [mean (95%CI)]: TTS-F 60.7 ± 13.23 vs CP 60.9 ± 12.1 ; Gender (M/F): TTS-F 95/106 vs CP 124/97	Intervention: Radiotherapy + transdermal therapeutic fentanyl system (TTS-F) – 25 µg per hours patch applied every 72 hours vs. Control: Radiotherapy + codeine or paracetamol (CP) – total dose per day 120 mg	*Results are no intention-to-treat* **Number of patients increasing baseline dose** TTS-F: 206/215 vs CP 4/201 **Quality of live** Assessed by a visual analog scale from 0 to 10 at 28 days (other timeframes reported in graph) Mean ± SD TTS-F: 4.23 ± 1.31 vs CP: 4.43 ± 1.35 **Pain intensity** Greek Brief Pain Inventory (question 5, 9i, 9ii) Mean difference from baseline ± SD	**Side effects:** • **Constipation** o At 72 hours TTS-F: 37/215 vs CP 66/201 o At 7 days TTS-F: 37/215 vs CP 63/201 o At 14 days TTS-F: 36/215 vs CP 54/201 o At 28 days TTS-F: 29/215 vs CP 46/201 o At 2 months TTS-F: 30/215 vs CP 43/201 • **Nausea** o At 72 hours TTS-F: 16/215 vs CP 22/201 o At 7 days	Risk of bias: High Author's conclusion: TTS-F offers more effective pain relief than CP, in combinaison with radiotherapy in patients with metastatic bone pain obtaining improvement in their quality of live. Remarks:

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				5: TTS-F 5.39 ± 1.54 vs CP 5.26 ± 1.46 9i: TTS-F 5.38 ± 1.65 vs CP 5.22 ± 1.40 9ii: TTS-F 5.60 ± 1.87 vs CP 5.33 ± 1.63	TTS-F: 20/215 vs CP 19/201 o At 14 days TTS-F: 19/215 vs CP 16/201 o At 28 days TTS-F: 11/215 vs CP 11/201 o At 2 months TTS-F: 12/215 vs CP 6/201 • **Sleep disturbance** o At 72 hours TTS-F: 37/215 vs CP 40/201 o At 7 days TTS-F: 37/215 vs CP 45/201 o At 14 days TTS-F: 31/215 vs CP 37/201 o At 28 days TTS-F: 17/215 vs CP 16/201 o At 2 months TTS-F: 5/215 vs CP 5/201	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
					• **Vomiting** o At 72 hours TTS-F: 13/215 vs CP 3/201 o At 7 days TTS-F: 11/215 vs CP 3/201 o At 14 days TTS-F: 6/215 vs CP 1/201 o At 28 days TTS-F: 2/215 vs CP 2/201 o At 2 months TTS-F: 2/215 vs CP 1/201	
Pistevou-Gompaki 2004[37]	• Design: 2-arm, randomized, control trial • Sources of funding: not mentioned • Setting: Greece • Sample size: n=13 (control); n=13 (intervention) • Duration: 3 months	Eligibility criteria: Patients with moderate to severe bone metastatic pain naïve to strong opioids Patient characteristics: Age (years) [range]: TTS-F 58-82 vs CP 54-78 ; Gender (M/F): TTS-F 9/4 vs CP 10/3	Intervention: Radiotherapy + transdermal therapeutic fentanyl system (TTS-F) – 25 µg per hours patch applied every 72 hours vs. Control:	*Results are no intention-to-treat* **Pain intensity** 10 cm visual Analogue Scale Difference (Mean ± SD) between baseline at 3 months TTS-F: 7.0±2 to 1.1±1 vs CP 8.3±0.4 to 4.3±2	**Side effects:** Mild nausea and vomiting TTS-F: 3/13 vs CP 3/13	Risk of bias: Unclear Author's conclusion: Transdermal fentanyl combined with radiotherapy was more effective in reducing metastatic bone pain and resulted in greater improvements in

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
			Radiotherapy + four times daily: codeine (30 mg) + oral paracetamol (500 mg)(CP) All patients received palliative radiotherapy at the site of painful bony metastases in ten daily fractions (total dose of 30 Gy, 3 Gy per fraction, 5 days a week)	Mean ± SD at 1 month TTS-F: 2.0±1.2 vs CP 4.7±1.8, p<0.01 **Quality of live** Greek Brief Pain Inventory (all items are rated on a scale ranging from 0 to 10) Physical functioning TTS-F: 7.7±1.3 to 0.8±1.3 vs CP 8.6±1.0 to 4.5±1.5, p=0.001 Global QoL score TTS-F: 22/100 to 96/100 vs CP 22/100 to 51/100, p<0.001		quality of live than paracetamol and codeine Remarks:
Portenoy 2006[38]	• Design: randomized, double-blind, placebo controlled study • Sources of funding: Cephalon, CIMA labs • Setting: 32 outpatients sites in Israël	Eligibility criteria: Opioid-treated adult patients (≥18 years old) with chronic cancer pain who experienced 1-4 Breakthrough Pain episodes / day, lifeexpectancy ≥ 3 months, ECOG performance status rating ≤ 2	Intervention: Fentanyl buccal tablet (FBT) vs. Control: Placebo	*Results are presented in breakthrough pain episodes* **Pain intensity** 11-point numeric scale, from 0 to 10 Decrease mean pain score at 30 minutes (± SE) FBT: 2.3±0.2 vs	*Results are no intention-to-treat* **Side effects:** Reported in more than 5 % of the population Nausea: 27/123 Dizziness 27/123 Headache 18/123 Fatigue 15/123 Vomiting 13/123	Risk of bias: High Author's conclusion: FBT provides rapid-onset analgesia and is effective and safe as a treatment for cancer-related breakthrough pain

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
	• Sample size: n=208 breakthrough pain episodes (control); n=493 breakthrough pain episodes (intervention) • Duration: 21 days	Patient characteristics: Age (years) [mean (±SD)]: 57.5 (±13.6); Gender (M/F): 42/35		placebo 1.4±0.2; p≤0.0001 **Summed pain intensity difference (SPID)** LSM ± SEM • At 30 minutes FBT: 3.0±0.12 vs placebo: 1.8±0.18; p<0.0001 **Number of episodes with ≥ 33 % improvement in pain intensity score** • At 15 minutes FBT: 69/493 vs placebo 20/208, p<0.05 • At 30 minutes FBT: 240/493 vs placebo 61/208, p<0.0001 • At 45 minutes FBT: 352/493 vs placebo 93/208, p<0. 0001 • At 60 minutes FBT: 373/493 vs	Somnolence 12/123 Constipation 10/123 Asthenia 9/123	Remarks: Global medication performance assessed by patients is not reported

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				placebo 100/208, p<0.0001 **Number of patients with ≥ 50 % improvement in pain intensity score** • At 15 minutes FBT: 44/493 vs placebo 13/208, ns • At 30 minutes FBT: 122/493 vs placebo 34/208, p<0.05 • At 45 minutes FBT: 253/493 vs placebo 52/208, p<0.0001 • At 60 minutes FBT: 319/493 vs placebo 74/208, p<0.0001 **Pain relief** 5-point numeric scale, where 0=none and 4=complete Results are presented in graph and not reported		

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				At each time point, pain relief were significantly higher for FBT than for placebo (p<0.003)		
Rauck 2009[39]	• Design: randomized placebo-controlled multi-dose phase III study • Sources ProStrakan Group • Setting: 36 centres in USA • Sample size: n=66 • Duration: 2 weeks (efficacy) 12 months (safety)	Eligibility criteria: Patients (≥ 17 years) with stable cancer related pain with regularly experiencing 1 to 4 epiosodes of breakthrough pain per day and receiving a fixed-schedule oral opioids regimen Patient characteristics: Age (years) [mean (±SD)]: 53.3 (±11.3); Gender (M/F): 31/35	Intervention: Sublingual fentanyl orally disintegrating tablet (SFODT) vs. Control: Placebo	*Results are in number of episodes* **Pain intensity** 11-point scale (0 = no pain and 10 = worst pain) Mean pain intensity difference (results reported in graph) From 10 to 60 minutes, p≤0.0055 in favor of SFODT **Sum of pain intensity difference (SPID)** Area under the curve of PID against time • At 60 min post-dose SFODT: 143.0 vs placebo 104.5, p=0.0002 **Pain relief** 5-point scale (0 = no relief to 4 = complete	*Results are presented for patients of titration phase* **Side effects:** Gastrointestinal disorders: 22/131 Nausea: 16/131 Vomiting: 7/131 Nervous system disorders: 15/131 Headache: 5/131 Somnolence: 6/131	Risk of bias: Unclear Author's conclusion: SFODT is an efficacious, weel-tolerated treatment option for opioid-tolerant patients suffering cancer related breakthrough pain Remarks:

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				relief). Mean pain relief score (results reported in graph) From 10 to 60 minutes, p≤0.049 in favor of SFODT **Responders** Patients with pain reduction of ≥ 30 % between baseline and 30 minutes SFODT:53/61 vs placebo 37/57 **Use of rescue medication** SFODT: 44/393 vs placebo 46/168		
Rauck 2010[40]	• Design: multicenter, randomized, double-blind, placebo-controlled, crossover study • Sources of funding: BioDelivery	Eligibility criteria: Men or nonpregnant nonlactating women (≥18 years) with cancer or cancer treatment related pain required (stable) opioid therapy and experiencing 1 to 4 episodes of breakthrough pain daily, at least	Intervention: Fentanyl buccal soluble film (FBSF) vs. Control: Placebo	**Pain intensity** 11-point scale (0 = no pain and 10 = worst pain) Mean pain intensity difference from the baseline to time points FBSF is statistically significant superior to placebo at 30 min	**Side effects:** Nausea: 9.9 % Vomiting 9.9 % Headache 1.2 %	Risk of bias: Unclear Author's conclusion: FBSF is an effective and well tolerated option for control of breakthrough pain

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
	Sciences International • Setting: 30 clinical sites in USA • Sample size: n=82 • Duration: 14 days	partially relief with opioids. Patient characteristics: Age (years) [mean (±SD)]: 56.8 (±13.0); Gender (M/F): 36/44		(p<0.05), at 45 min (p<0.01) and at 60 min (p<0.001) (data presented in graph only). **Number of episodes with ≥ 33 % improvement in pain intensity score** Percentage of episodes with decreases in pain scores (mean±SEM) • At 15 minutes FBSF: 26.4 (3.55) vs placebo 21.3 (3.66), p=0.100 • At 30 minutes FBSF: 47.3 (4.05) vs placebo 38.2 (4.45), p=0.009 • At 45 minutes FBSF: 57.5 (3.93) vs placebo 46.5 (4.50), p=0.004 • At 60 minutes FBSF: 64.3 (3.72) vs placebo 48.2 (4.51), p<0.001		in patients receiving ongoing opioid therapy. Remarks: Global satisfaction assessed by patients is not reported

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				Number of episodes with ≥ 50 % improvement in pain intensity score Percentage of episodes with decreases in pain scores (mean±SEM) • At 15 minutes FBSF: 14.9 (2.81) vs placebo 14.7 (3.35), p=0.963 • At 30 minutes FBSF: 32.8 (3.78) vs placebo 24.1 (3.87), p=0.002 • At 45 minutes FBSF: 41.1 (4.11) vs placebo 30.5 (4.10), p=0.008 • At 60 minutes FBSF: 46.3 (4.17) vs placebo 34.0 (4.30), p<0.001 **Weighted sum over the first 30 min post dose (SPID30)** LSM±SEM FBSF: 47.6±3.9 vs placebo 38.1±4.3,		

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				p=0.004 Statistically significant separation from placebo starting at 15 min post dose (P < 0.05) through 60 min post dose (P < 0.001) **Pain relief** 5-point scale (0 = no relief to 4 = complete relief). FBSF is superior to placebo from 30 min to 60 min (p< 0.01)(no further information) **Number of episodes needed rescue medication** Mean (±SEM) FBSF: 30.0%±3.5% vs placebo 44.6%±4.4%, p=0.002		
Rauck 2012[41]	• Design: multicenter, randomized, double-blind, placebo-controlled, crossover study	Eligibility criteria: Men or nonpregnant nonlactating women (≥18 years) with cancer or cancer treatment related pain of no more than moderate intensy and	Intervention: Fentanyl sublingual spray (FSS) vs.	*Results are no intention-to-treat-number of episodes in each group not mentioned* **Pain intensity**	**Side effects:** Any adverse events: 47/98 Nausea 7/98 Somnolence 2/98 Vomiting 4/98	Risk of bias: Unclear Author's conclusion: FSS is effective

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
	• Sources of funding: Insys Therapeutics • Setting: 24 centres in USA • Sample size: n=98 • Duration: 30 days	experiencing 1 to 4 episodes of breakthrough pain daily. Patient characteristics: Mean baseline pain intensity (SD): FSS 63.0 ± 20.1 vs placebo 62.5 ± 20.5	Control: Placebo	100 mm visual analog scale from 0 (no pain) to 100 (worst possible pain) Mean pain intensity difference (results reported in graph) At 5 minutes p<0.05 From 10 to 60 minutes; p<0.0001 **Pain relief** 5-point scale (0 = no relief to 4 = complete relief). Mean ± SE • At 30 minutes FSS 2.8±0.08 vs placebo 2.0±0.08, mean difference: 0.8±0.09, p<0.0001 • At 60 mimutes FSS 3.1±0.08 vs placebo 2.2±0.08, mean difference: 0.9±0.1, p<0.0001 **Cumulative sum across time (SPID)** Mean SPID±SD	Dizziness 2/98 Pyrexia 1/98 Peripheral edema 5/98 Diarrhea 3/98 Hyperhidrosis 5/98	and well tolerated in opioids-tolerant cancer patients with breakthrough pain Remarks:

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				• At 5 min FSS 40.3±6.0 vs placebo 32.0±5.4, mean difference 8.3±3.6, p=0.0219 • At 10 min FSS 115.0±13.6 vs placebo 81.1±11.3, mean difference 34.0±8.5, p=0.0002 • At 15 min FSS 220.6±21.9 vs placebo 150.3±18.0, mean difference 70.3±14.6, p<0.0001 • At 30 min FSS 640.3±47.8 vs placebo 399.6±40.8, mean difference 240.7±37.8, p<0.0001 • At 45 min FSS 1122.0±76.3 vs placebo 667.0±64.1, mean difference 454.9±65.4, p<0.0001 • At 60 min FSS 1679.0±105.9 vs placebo 965.7±89.9, mean difference 683.3±94.4, p<0.0001		

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				Use of rescue medication within 60 minutes of treatment FSS 10 % vs placebo 28%, p<0.0001		
Slatkin 2007[42]	• Design: Multicenter, randomized, double blind, placebo-controlled study • Sources of funding: Cephalon • Setting: 30 centres in USA • Sample size: n=87 • Duration: 3 weeks	Eligibility criteria: Patients (18 to 80 years) with malignant solid tumor or hematologic malignancy causing cancer-related pain, life expectancy ≥ 2 years, using a fixed-dose of opioid regimen for persistent pain, pain intensity <7 and experiencing 1 to 4 breakthrough pain episodes per day Patient characteristics: Age (years) [mean (±SD)]: 53.9 (±11.3); Gender (M/F): 33/53 Mean pain intensity (±SD) during breakthrough pain was similar in the 2 group before starting the trial (FBT: 6.4±1.8 vs placebo 6.4±1.7)	Intervention: Fentanyl buccal tablet (FBT) vs. Control: Placebo	*Results are in number of episodes (n FBT: 493, n placebo = 223)* **Pain intensity** 11-point scale (0 = no pain and 10 = worst pain) Mean pain intensity difference from the baseline to time points • At 10 minutes FBT: 0.9 vs placebo 0.5, p<0.0001 • Other time points Differencial between FBT and placebo increased up to 90 minutes and then was maintained through 2 hours (results presented in graph), p<0.0001 **Sum of pain intensity**		Risk of bias: Low Author's conclusion: Fentanyl buccal tablet was an efficient and well tolerated treatment for breakthrough pain episodes in cancer-related chronic pain

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				difference at 60 min (SPID) $SPID_{60}$ = (1/3 x PID_5) + (1/3 X PID_{10}) + (1/3 x PID_{15}) + PID_{30} + PID_{60} Mean ±SE FBT 9.7±0.63 vs 4.9±0.50, p<0.0001 **Proportion of breakthrough pain episodes with ≥ 33% improvement in pain intensity score** • At 10 minutes FBT: 16% vs placebo 10%, p=0.007 • At 15 minutes FBT: 29% vs placebo 14%, p<0.0001 • At 30 minutes FBT: 51% vs placebo 26%, p<0.0001 • Other time points (through 60 minutes to 120 minutes) Differencial between FBT and placebo increased up to 60 minutes and then was		

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				maintained through 2 hours (results presented in graph), p<0.0001 **Proportion of breakthrough pain episodes with ≥ 50% improvement in pain intensity score** • At 10 minutes FBT: 7% vs placebo 4%, p=0.033 • At 15 minutes FBT: 18% vs placebo 8%, p<0.0001 • At 30 minutes FBT: 38% vs placebo 15%, p<0.0001 • Other time points (through 60 minutes to 120 minutes) Differencial between FBT and placebo increased up to 60 minutes and then was maintained through 2 hours (results presented in graph),		

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				p<0.0001 **Pain relief** 5-point Likert scale (0 = no relief to 4 = complete relief). • At 10 minutes FBT: 0.815 vs placebo 0.606, p<0.0001 • Other time points Differential between FBT and placebo increased up to 90 minutes and then was maintained through 2 hors (results presented in graph), p<0.0001 **Number of episodes needed rescue medication** FBT 53/493 vs placebo 67/223		

4.3. Corticosteroids

No systematic review and no RCT included

5. OVERVIEW OF INCLUDED AND EXCLUDED STUDIES

5.1. Overview of included SRs

The table below presents an overview of the finally included SRs retrieved from the literature search or from the guideline search, for the topics corticosteroids, NSAIDs and opioids.

Table 26 – Included SRs per topic

Topic	References
Corticosteroids	/
NSAIDs	Alkhenizan 2004, Nabal 2012, McNicol 2011
Opioids	Cairns 2001, Caraceni 2011, Fallon 2011, Hansen 2012, King 2011, Nicholson 2008, Pigni 2011, Quigley 2008, Quigley 2009, Reid 2006, Wiffen 2010, Zeppetella 2009,
Several topics	Dutch Guideline on cancer pain 2008, Guideline of the MoH Malaysia 2008, SIGN 2008

5.2. Overview of included SRs found by handsearch

The table below presents an overview of the finally included SRs found by handsearch, for the topics corticosteroids, NSAIDs and opioids.

Table 27 – Included SRs per topic

Topic	References
Corticosteroids	/
NSAIDs	/
Opioids	Tassinari 2011a, Tassinari 2011b
Several topics	Carr 2002

5.3. Overview of excluded SRs

Persons who are interested in the detailed list of excluded studies per study topic, can contact the authors of this report (see colophon).

5.4. Overview of included RCTs

This table presents a list of all RCTs that have been included per topic. These RCTs were retrieved through the update search for RCTs or extracted from included SRs or guidelines.

Table 28 – Included RCTs per topic

Topic	References
Corticosteroids	/
NSAIDs	Axelsson 2003, Bjorkman 1993, Bosek 1994, Carlsson 1990, Chary 1994, Corli 1993, Cubero 2010, Dellemijn 1994, Duarte-Souza 2007, Estape 1990, Ferrer-Brechner 1984, Frankendal 1973, Gallucci 1992, Israel 2010, Jameel 1995, Johnson 1994, Lomen 1986, Martino 1976, Mercadante 2002, Minotti 1998a, Minotti 1998b, Moertel 1971, Moertel 1974, Panutti 1999, Portenoy 2010, Rodriguez 1994, Rodriguez 2003, Sacchetti 1984, Saxena 1994, Sima 2012, Stambaugh 1980b, Stambaugh 1982b, Stambaugh 1988a, Stambaugh 1988b, Staquet 1989, Staquet 1993, Stockler 2004, Strobel 1992, Sunshine 1988, Tasmacioglu 2009, Tonachella 1985, Toscani 1994, Turnbull 1986, Ventafridda 1975, Ventafridda 1990a, Ventafridda 1990b, Weingart 1985, Wool 1991, Yalcin 1980, Yalcin 1997:
Opioids	Ahmedzai 2012, Arbaiza 2007, Beaver 1967, Beaver 1978, Brema 1996, Bruera 1998, Bruera 2004, Christie 1998, Coluzzi 2001, Cubero 2010, Davies 2011, Dhaliwal 1995, Elsner 2005, Farrar

	1998, Ferrell 1989, Gabrail 2004, Grochow 1989, Hagen 1997, Hanna 2008, Heiskanen 1997, Heikanen 2000, Houde 1986, Johnson 2009, Kalso 1990, Kongsgaard 1998, Kress 2008, Kress 2009, Lauretti 2003, Leppert 2001, Melzack 1979, Mercadante 1998a, Mercadante 2007, Mercandante 2008, Mercadante 2009, Mercadante 2010, Moksnes 2011, Moriarty 1999, Mucci LoRusso 1998, Mystakidou 2005, Napp Laboratories 2000, Pace 2007, Pistevou-Gompaki 2004, Portenoy 2006, Portenoy 2010, Poulain 2008, Rauck 2009, Rauck 2010, Rauck 2012, Rodriguez 2007, Rodriguez 2008, Slatkin 2007, Twycross 1977, Van Seventer 2003, Ventafridda 1986, Wilder-Smith 1994, Wirtz 2009

5.5. Overview of excluded RCTs

This table presents the number of RCTs that have been excluded from the update search for RCTs. In the table only the reasons for exclusion on full text are mentioned, without differentiation per topic (corticosteroids, NSAIDs or opioids) or without listing all references. Persons who are interested in the detailed list of excluded studies, can contact the authors of this report (see colophon).

Reason for exclusion	Number of RCTs
Population	11
Intervention	37
Outcome	12
Design	35
Language	5
Duplicate	42
Not retrieved	3

6. EXAMPLE OF OPIOID EQUIANALGESIC TABLE

Morphine		Fentanyl	Oxycodone		Hydromorphone	Tramadol	Buprenorphine
oral	**s.c/i.v.**	**patch**	**oral**	**s.c/i.v.**	**oral**	**oral**	**patch**
mg/24 hours	*mg/24 hours*	*µg/hour*	*mg/24 hours*	*mg/24 hours*	*mg/24 hours*	*mg/24 hours*	*µg/hour*
30	10	12	15	7.5	4	150	17.5
60	20	25	30	15	8	300	35
120	40	50	60	30	16	-	70
180	60	75	90	45	24	-	105
240	80	100	120	60	32	-	140
360	120	150	180	90	48	-	-
480	160	200	240	120	64	-	-

Source: adapted from www.pallialine.nl

For rotation from one opioids to another, it is advised to give from $^{2}/_{3}$ to $^{3}/_{4}$ of the equianalgesic dose, because of incomplete cross-tolerance. For further information, the reader is invited to consult the scientific report (see 4.3.1.1.3.).

APPENDIX III

1. QUALITY APPRAISAL

1.1. Guidelines including multiple topics

Table 29 – Quality appraisal of guidelines including multiple topics

Guideline	A priori study design	Duplicate study selection and data extraction	Comprehensive literature search	Publication status not used as inclusion	List of in- and excluded studies	Characteristics of included studies provided	Study quality assessed and documented	Quality assessment used in conclusion	Appropriate methods to combine findings	Likelihood of publication bias assessed	Conflict of interest stated
Landelijke richtlijnwerkgroep Pijn bij Kanker (2008)[1]	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No applicable	No applicable	Review Yes Studies No
SIGN (2008)[2] - Control of pain in adults with cancer	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No applicable	No applicable	Review Yes Studies No
Ministry of Health Malaysia (2010)[3] - Clinical Practice Guidelines: Management of Cancer Pain	Yes	Yes	Yes	Yes	No	No	Yes but no method is provided	Yes	No applicable	No applicable	Review Yes Studies No

Agency for Healthcare Research and Quality – Carr (2002)[4] Management of Cancer Symptoms: Pain, Depression, and Fatigue	Yes	Can't answer	Yes	Yes	No	Yes	Yes	Yes	Not applicable	Not applicable	Review No Studies No

1.2. Antidepressants

Table 30 – Antidepressants: Quality appraisal of systematic reviews and guidelines including systematic reviews

Systematic review	A priori study design	Duplicate study selection and data extraction	Compre-hensive literature search	Publica-tion status not used as inclusion	List of in- and excluded studies	Charac-teristics of included studies provided	Study quality assessed and documented	Quality assess-ment used in conclusion	Appropriate methods to combine findings	Likelihood of publication bias assessed	Conflict of interest stated
Librach (2006)[5]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Review Yes Studies No
Bennett (2011)[6]	Yes	Yes	No	Yes	No	Yes	No	No	Can't answer	Can't answer	Review Yes Studies No
Saarto (2012)[7]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Review Yes Studies No

Table 31 – Antidepressants: Quality appraisal of randomized controlled trials

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Complete outcome data	All relevant outcomes reported	Absence of other sources of bias	Overall Risk of bias: high-low-unclear
Kalso (1996)[8]	Unclear	Yes	Yes	Yes	No	Yes	No	High
Mercadante (2002)[9]	Unclear	Yes	Yes	Yes	Unclear	Yes	No	Unclear
Reuben (2004)[10]	Yes	Yes	Yes	Yes	Yes	Yes	No	Low
Tasmuth (2002)[11]	Yes	Yes	Yes	Yes	No	Yes	No	High
Kautio (2008)[12]	Yes	Yes	Yes	Yes	No	Yes	Yes	High
Kautio (2009)[13]	Yes	Yes	Yes	Yes	No	Yes	Yes	High
Amr (2010)[14]	Yes	Yes	Yes	Yes	No	Yes	Unclear	High
Arai (2010)[15]	Yes	Yes	No	No	No	Yes	Unclear	High
Mishra (2012)[16]	Yes	Unclear	Yes	Yes	No	Yes	Unclear	High

1.3. Anticonvulsants

Table 32 – Anticonvulsants: Quality appraisal of systematic reviews and guidelines including systematic reviews

Systematic review	A priori study design	Duplicate study selection and data extraction	Compre-hensive literature search	Publica-tion status not used as inclusion	List of in- and excluded studies	Charac-teristics of included studies provided	Study quality assessed and documented	Quality assess-ment used in conclusion	Appropriate methods to combine findings	Likelihood of publication bias assessed	Conflict of interest stated
Librach (2006)[5]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Review Yes Studies No
Bennett (2011)[6]	Yes	Yes	No	Yes	No	Yes	No	No	Can't answer	Can't answer	Review Yes Studies No
Moore (2011)[17]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Review Yes Studies No

Table 33 – Anticonvulsants: Quality appraisal of randomized controlled trials

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Complete outcome data	All relevant outcomes reported	Absence of other sources of bias	Overall Risk of bias: high-low-unclear
Amr (2010)[14]	Yes	Yes	Yes	Yes	No	Yes	Unclear	High
Arai (2010)[15]	Yes	Yes	No	No	No	Yes	Unclear	High
Caraceni (2004)[18]	Yes	Yes	Yes	Yes	Unclear	No	Unclear	Unclear
Fassoulaki (2002)[19]	Yes	Yes	Yes	Yes	No	Yes	Unclear	High
Keskinbora (2007)[20]	Yes	Unclear	No	No	No	Yes	Unclear	High
Mishra (2012)[16]	Yes	Unclear	Yes	Yes	No	Yes	Unclear	High
Rao (2007)[21]	Yes	Yes	Yes	Yes	Yes	No	Unclear	Low

1.4. Radiotherapy for painful bone metastases

Table 34 – Radiotherapy for painful bone metastases: Quality appraisal of systematic reviews and guidelines including systematic reviews

	A priori study design	Duplicate study selection and data extraction	Comprehensive literature search	Publication status not used as inclusion	List of in- and excluded studies	Characteristics of included studies provided	Study quality assessed and documented	Quality assessment used in conclusion	Appropriate methods to combine findings	Likelihood of publication bias assessed	Conflict of interest stated
Guideline											
Alberta Health Services (2010)[22] - Palliative Radiotherapy	Yes	No	Yes	Yes	No	No	Yes	Yes	Not applicable	Not applicable	Review No Studies No
NICE (2008)[23] - Metastatic spinal cord compression: Diagnosis and management of patients at risk of or with	Yes	No	Can't answer	Yes	No	No	Yes	Yes	Not applicable	Not applicable	Yes

metastatic spinal cord compression (CG 75)											
Systematic review											
Falkmer (2003)[24]	Yes	Can't answer	No	Yes	No	Yes	Yes	Yes	Not applicable	Not applicable	Review No Studies No
McQuay (2008)[25]	Yes	Can't answer	Yes	Yes	Yes	Yes	Yes	No	No	No	Review Yes Studies No
Sze (2003)[26]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Review No Studies No
Sze (2011)[27]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Review Yes Studies No
George (2010)[28]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Review Yes Studies No

Table 35 – Radiotherapy for painful bone metastases: Quality appraisal of randomized controlled trials

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Complete outcome data	All relevant outcomes reported	Absence of other sources of bias	Overall risk of bias: high-low-unclear
Radiotherapy for painful bone metastases								
Amouzegar (2008)[29]	Unclear	Unclear	Unclear	Unclear	Yes	No	No	Unclear
Foro (2008)[30]	Yes	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
Hamouda (2007)[31]	No	Unclear	Unclear	Unclear	Yes	No	Yes	High
Hartsell (2005)[32]	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear
Hoskin (1992)[33]	Yes	Yes	No	No	No	Yes	Unclear	High
Jeremic (1998)[34]	Unclear	Unclear	Unclear	Unclear	No	Yes	Unclear	High

Roos (2005)[35]	Yes	Yes	No	No	Yes	Yes	Yes	High
Sarkar (2002)[36]	Unclear	Unclear	No	No	No	Yes	Unclear	High
Manas (2008)[37]	Yes	Yes	Unclear	Unclear	No	Yes	Unclear	Unclear
Spinal cord compression								
Maranzano (2005)[38]	Yes	Yes	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Maranzano (2009)[39]	Yes	Yes	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Hemibody irradiation								
Salazar (2001)[40]	Yes	Unclear	Unclear	Unclear	No	Yes	Unclear	High

1.5. Radionuclides for painful bone metastases

Table 36 – Radionuclides for painful bone metastases: Quality appraisal of systematic reviews

	A priori study design	Duplicate study	Comprehensive literature	Publication status not	List of in- and excluded	Characteristics of	Study quality assessed and	Quality assessment	Appropriate methods to combine findings	Likelihood of publication bias assessed	Conflict of interest stated
Systematic review											
Roqué (2011)[41]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Review Yes Studies No
Christensen (2012)[42]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	NA	NA	Review Yes Studies No
Alberta Health Services (2010)[22] - Palliative Radiotherapy	Yes	No	Yes	Yes	No	No	Yes	Yes	Not applicable	Not applicable	Review No Studies No

Table 37 – Radionuclides for painful bone metastases: Quality appraisal of randomized controlled trials

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Complete outcome data	All relevant outcomes reported	Absence of other sources of bias	Overall Risk of bias: high-low-unclear
Baczyk (2007)[43]	Unclear	Unclear	Unclear	Unclear	No	Yes	No	High
Buchali (1988)[44]	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Unclear	Unclear
Han (2002)[45]	Yes	Yes	Yes	Yes	No	Yes	Unclear	High
Lewington (1991)[46]	Yes	Yes	Yes	Yes	No	Yes	Unclear	High
Maxon(1991)[47]	Unclear	Unclear	Yes	Unclear	No	Yes	Unclear	High
Nair (1999)[48]	Unclear	Yes	Unclear	Unclear	No	Yes	Unclear	High
Nilsson (2007)[49]	Yes	Yes	Yes	Unclear	No	Unclear	No	High
Porter (1993)[50]	Unclear	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear
Sartor (2004)[51]	Yes	Unclear	Yes	No	Unclear	Yes	Unclear	Unclear
Sciuto (2001)[52]	Unclear	Unclear	No	No	No	Yes	Unclear	High
Serafini (1998)[53]	Unclear	Unclear	Yes	Unclear	No	Yes	Unclear	High
Smeland (2003)[54]	Unclear	Unclear	Yes	Unclear	No	Yes	No	High
Nilsson (2005)[55]	Yes	Unclear	Unclear	Unclear	No	Yes	No	High
Wang (2003)[56]	Yes	Unclear	Unclear	Unclear	No	Yes	Yes	High

1.6. Bisphosphonates for painful bone metastases

Table 38 – Bisphosphonates: Quality appraisal of systematic reviews and guidelines including systematic reviews

	A priori study design	Duplicate study selection and data	Comprehensive literature search	Publication status not used as inclusion	List of in- and excluded studies	Characteristics of included studies provided	Study quality assessed and documented	Quality assessment used in conclusion	Appropriate methods to combine findings	Likelihood of publication bias assessed	Conflict of interest stated
Berry (2006)[283]	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Not applicable	Not applicable	Review Yes Studies No
Mhaskar (2012)[57]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Review Yes Studies No
Wong (2004)[277]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Review Yes Studies No
Wong (2009)[58]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Review Yes Studies No
Wong (2012)[59]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Review Yes Studies No
Yuen (2010)[60]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Review Yes Studies No

Table 39 – Bisphosphonates: Quality appraisal of randomized controlled trials

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Complete outcome data	All relevant outcomes reported	Absence of other sources of bias	Overall Risk of bias: high-low-unclear
Berenson (2001)[61]	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	No	Unclear
Body (2007)[62]	Yes	Unclear	Unclear	Unclear	Yes	Yes	No	Unclear
Conte (1996)[63]	Unclear	Unclear	No	Unclear	No	Yes	No	High
Daragon (1993)[64]	No	No	No	No	Yes	No	No	High
Dearnaley (2003)[65]	Unclear	Unclear	Yes	Yes	Yes	Yes	No	Unclear
Diel (2004)[66]	Unclear	Unclear	Yes	Unclear	Yes	Yes	No	Unclear
Ernst (1992)[67]	Yes	Yes	Yes	Yes	Unclear	Unclear	No	Unclear
Ernst (1997)[68]	Yes	Yes	Yes	Yes	Unclear	Unclear	No	Unclear
Ernst (2003)[69]	Unclear	Unclear	Yes	No	Yes	No	No	Unclear
Hortobagyi (1996)[70]	Yes	Yes	Yes	Yes	Yes	No	No	Low
Hultborn (1999)[71]	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Low
Kylmälä (1997)[72]	Unclear	Unclear	Unclear	Unclear	No	No	No	High
Lahtinen (1992)[73]	No	No	Yes	Yes	Yes	Yes	Yes	High
Meulenbeld (2012)[74]	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	No	Unclear
O'Rourke (1995)[75]	Unclear	Unclear	Yes	Unclear	Yes	No	No	Unclear
Piga (1998)[76]	Unclear	Yes	Yes	Unclear	Yes	No	Yes	Unclear
Robertson (1995)[77]	Unclear	Unclear	Yes	Unclear	Yes	Yes	No	Unclear
Saad (2002)[78]	Yes	Yes	Yes	Unclear	Yes	Yes	No	Low
Small (2003)[79]	Unclear	Unclear	Yes	Unclear	Yes	No	No	Unclear
Theriault (1999)[80]	Yes	Yes	Yes	Yes	Yes	Yes	No	Low
Tripathy (2004)[81]	Unclear	Unclear	Yes	Unclear	Yes	Yes	No	Unclear
Tubiana-Hulin (2001)[82]	Unclear	Unclear	Yes	Unclear	No	Yes	Yes	High

1.7. Celiac Plexus Block

Table 40 – Celiac Plexus Block: Quality appraisal of systematic reviews and guidelines including systematic reviews

Systematic review	A priori study design	Duplicate study selection and data	Compre-hensive literature search	Publica-tion not as used inclusion	List of in- and excluded studies	Charac-teristics of included studies	Study quality assessed and documented	Quality assess-ment in conclusion	Appropriate methods to combine findings	Likelihood of publication bias assessed	Conflict of interest stated
Arcidiacono (2011)[83]	Yes	Can't answer	Yes	Yes	Yes	Yes	Yes	No	Yes	Can't answer	Review Yes Studies No
Yan (2007)[84]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Review Yes Studies No

Table 41 – Celiac Plexus Block s: Quality appraisal of randomized controlled trials

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Complete outcome data	All relevant outcomes reported	Absence of other sources of bias	Overall Risk of bias: high-low-unclear
Kawamata (1996 Cochr)[85]	Unclear	Unclear	No	No	Yes	Yes	Yes	High
Lillemoe (1993 Cochr)[86]	Unclear	Unclear	Yes	Yes	No	Yes	Yes	High
Mercadante (1993 Cochr)[87]	Unclear	Unclear	No	No	Yes	Yes	Yes	High
Polati (1998 Cochr)[88]	Unclear	Unclear	No	Yes	Yes	Yes	No	High
Wong (2004 Cochr)[89]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Zhang (2008 Cochr)[90]	Unclear	Unclear	No	Yes	Unclear	Yes	Yes	High
Wyse (2011)[91]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Ischia (1992)[92]	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Unclear
Süleyman Özylalçin (2004)[93]	Yes	Yes	No	Yes	Yes	Yes	Yes	High

2. GRADE PROFILES BY INTERVENTION AND OUTCOME

2.1. Antidepressants

Table 42 – Antidepressants: overview of results and GRADE profiles

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
Pain intensity **VAS 10 cm** **50 mg** **Short term (up to 4 weeks)** **Median (range)** (Kalso 1996)[8]	Ipsilateral arm AMI 1.9 (0-9.1) vs placebo 2.5 (0-9.2), ns Breast scar area AMI 1.8 (0-5.1) vs placebo 2.6 (0-6.6), ns	1	-2	-1	-2	0	0	1.unclear randomization, no intention-to-treat analysis, selection bias 2. single study 3. outcome only of combined periods of the cross-over design (carry-over effect not analysed), very small sample size, CI not quantified	Very low
Pain intensity **VRS 8-point verbal rating scale** **50 mg** **Short term (up to 4 weeks)** **Median (range)** (Kalso 1996)[8]	Ipsilateral arm AMI 2.6 (1-5) vs placebo 3.1 (1-8), ns Breast scar area AMI 2.2 (1-5) vs placebo 2.3 (1-4), ns	1	-2	-1	-2	0	0	1. unclear randomization, no intention-to-treat analysis, selection bias 2. single study 3. outcome only of combined periods of the cross-over design (carry-over effect not analysed), very small sample size, CI not quantified	Very low
Pain relief **VRS 5-point verbal rating scale** **50 mg** **Short term (up to 4 weeks)** **Median (range)**	Ipsilateral arm VRS: AMI 3 (1-5) vs placebo 1 (1-5), ns Breast scar area VRS: AMI 3 (1-5) vs placebo 1 (1-5),	1	-2	-1	-2	0	0	1. unclear randomization, no intention-to-treat analysis, selection bias 2. single study 3. outcome only of combined periods of the cross-over design (carry-over effect not analysed), very small sample size, CI not quantified	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
(Kalso 1996)[8]	ns								
Pain intensity **VAS 10 cm** **100 mg** **Short term (up to 4 weeks)** **Median (range)** (Kalso 1996)[8]	Ipsilateral arm AMI 0.5 (0-3.0) vs placebo 5.0 (0.-9.4), p<0.05 Breast scar area AMI 0.2 (0-4.3) vs placebo 3.1 (0.7-5.5), ns	1	-2	-1	-2	0	0	1. unclear randomization, no intention-to-treat analysis, selection bias 2. single study 3. outcome only of combined periods of the cross-over design (carry-over effect not analysed), very small sample size, CI not quantified	Very low
Pain intensity **VRS 8-point verbal rating scale** **100 mg** **Short term (up to 4 weeks)** **Median (range)** (Kalso 1996)[8]	Ipsilateral arm AMI 1.8 (1-4) vs placebo 3.0 (1-8), p<0.05 Breast scar area AMI 1.9 (1-5) vs placebo 2.7 (1-6), p<0.05	1	-2	-1	-2	0	0	1. unclear randomization, no intention-to-treat analysis, selection bias 2. single study 3. outcome only of combined periods of the cross-over design (carry-over effect not analysed), very small sample size, CI not quantified	Very low
Pain relief **VRS 5-point verbal rating scale** **100 mg** **Short term (up to 4 weeks)** **Median (range)** (Kalso 1996)[8]	Ipsilateral arm AMI 3 (2-5) vs placebo 2 (1-4), p<0.05 Breast scar area AMI 3 (2-5) vs placebo 1.5 (1-5), p<0.05	1	-2	-1	-2	0	0	1. unclear randomization, no intention-to-treat analysis, selection bias 2. single study 3. outcome only of combined periods of the cross-over design (carry-over effect not analysed), very small sample size, CI not quantified	Very low
Pain intensity at 1 week	AMI 4.7 (3.9-5.6) vs placebo 5.4	1	-1	-1	-2	0	0	1. unclear randomization, unclear intention-to-treat analysis	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
Numerical scale from 0-10 **50 mg** **Mean 95%CI** (Mercadante 2002)[9]	(4.9-6.0), ns							2. single study 3. outcome only of combined periods of the cross-over design (carry-over effect not analysed), very small sample size, CI not quantified	
Pain intensity at 2 weeks **Numerical scale from 0-10** **50 mg** **Mean 95%CI** (Mercadante 2002)[9]	AMI 4.9 (3.9-6.0) vs placebo 6.1 (5.4-6.9), ns	1	-1	-1	-2	0	0	1. unclear randomization, unclear intention-to-treat analysis 2. single study 3. outcome only of combined periods of the cross-over design (carry-over effect not analysed), very small sample size, CI not quantified	Very low
Pain relief (2 weeks) **Scale from 0 to 3** **Mean 95%CI** (Mercadante 2002)[9]	AMI 3.5 (1.7-5.3) vs placebo 2.3 (0.3-4.4), ns	1	-1	-1	-2	0	0	1. unclear randomization, unclear intention-to-treat analysis 2. single study 3. outcome only of combined periods of the cross-over design (carry-over effect not analysed), very small sample size, CI not quantified	Very low
Drowsiness (2 weeks) **Scale from 0 to 3** **Mean 95%CI** (Mercadante 2002)[9]	AMI 1.6 (1.2-2.0) vs placebo 0.8 (0.4-1.4), p=0.036	1	-1	-1	-2	0	0	1. unclear randomization, unclear intention-to-treat analysis 2. single study 3. outcome only of combined periods of the cross-over design (carry-over effect not analysed), very small sample size, CI not quantified	Very low
Confusion (2 weeks)	AMI 0.6 (0.2-1.1) vs placebo 0.06 (0-	1	-1	-1	-2	0	0	1. unclear randomization, unclear intention-to-treat analysis	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
Scale from 0 to 3 **Mean 95%CI** (Mercadante 2002)[9]	0.2), p=0.003							2. single study 3. outcome only of combined periods of the cross-over design (carry-over effect not analysed), very small sample size, CI not quantified	
Dry mouth (2 weeks) **Scale from 0 to 3** **Mean 95%CI** (Mercadante 2002)[9]	AMI 1.8 (1.4-2.3) vs placebo 1.3 (0.9-1.8), p=0.034	1	-1	-1	-2	0	0	1. unclear randomization, unclear intention-to-treat analysis 2. single study 3. outcome only of combined periods of the cross-over design (carry-over effect not analysed), very small sample size, CI not quantified	Very low
Constipation (2 weeks) **Scale from 0 to 3** **Mean 95%CI** (Mercadante 2002)[9]	AMI 2.5 (1.9-3.0) vs placebo 2.5 (2.0-3.0), ns	1	-1	-1	-2	0	0	1. unclear randomization, unclear intention-to-treat analysis 2. single study 3. outcome only of combined periods of the cross-over design (carry-over effect not analysed), very small sample size, CI not quantified	Very low
Number of patients using extra morphine as rescue drug (Mishra 2012) [9]	AMI 17/30 vs placebo 30/30	1	-2	-1	-1	0	0	1. selected reporting outcome, no intention-to-treat analysis, lack of allocation concealment 2. single study 3. small study sample	Very low
Variation in VAS score from baseline to 4 weeks (Mishra 2012)[9]	AMI 7.71 ± 1.1 to 3.23 ± 0.70 vs placebo 7.47 ± 1.0 to 3.4 ± 0.66	1	-2	-1	-1	0	0	1. selected reporting outcome, no intention-to-treat analysis, lack of allocation concealment 2. single study 3.small study sample, unities of VAS were unclear	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
Quality of live EORTC QLQ- C30 (global health score) at 4 weeks (Kautio 2008)[12]	AMI 62 vs placebo 54	1	-1	-1	-1	0	0	1. no intention-to-treat analysis 2. single study 3. trial population (cancer patients with numbness, tingling or pain) differed from population of interest (patients with cancer related pain); small study sample	Very low
Quality of live EORTC QLQ- C30 (global health score) at 8 weeks (Kautio 2008)[12]	AMI 55 vs placebo 49	1	-1	-1	-1	0	0	1. no intention-to-treat analysis 2. single study 3. trial population (cancer patients with numbness, tingling or pain) differed from population of interest (patients with cancer related pain); small study sample	Very low
Severity of sensory neuropathy in National Cancer institute Common Toxicity Criteria (NCI-CTC) at 3 cycles (Kautio 2009)[13]	Amitriptyline 31/54 vs placebo 28/43	1	-1	-1	-1	0	0	1. no intention-to-treat analysis 2. single study 3. small study sample	Very low
Severity of sensory neuropathy in NCI-CTC at 6 cycles (Kautio 2009)[13]	Amitriptyline 24/43 vs placebo 20/36	1	-1	-1	-1	0	0	1. no intention-to-treat analysis 2. single study 3. small study sample	Very low
Severity of sensory	Amitriptyline 14/21 vs placebo 17/20	1	-1	-1	-1	0	0	1. no intention-to-treat analysis 2. single study	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
neuropathy in NCI-CTC at 9 cycles (Kautio 2009)[13]								3. small study sample	
Severity of motor neuropathy in NCI-CTC at 3 cycles (Kautio 2009)[13]	Amitriptyline 12/54 vs placebo 13/43	1	-1	-1	-1	0	0	1. no intention-to-treat analysis 2. single study 3. small study sample	Very low
Severity of motor neuropathy in NCI-CTC at 6 cycles (Kautio 2009)[13]	Amitriptyline 14/44 vs placebo 15/36	1	-1	-1	-1	0	0	1. no intention-to-treat analysis 2. single study 3. small study sample	Very low
Severity of motor neuropathy in NCI-CTC at 9 cycles (Kautio 2009)[13]	Amitriptyline 3/21 vs placebo 6/20	1	-1	-1	-1	0	0	1. no intention-to-treat analysis 2. single study 3. small study sample	Very low
Pain intensity at rest **VAS score (0-10)** **At 1 day** **75 mg venlafaxine** **Pre-emptive** **Mean ± SD** (Reuben 2004)[10]	Venlafaxine: 1.8 ±1.0 vs placebo 2.1 ±1.6, ns	1	0	-1	-1	0	0	2. single study 3. small sample size, CI not quantified	Low
Pain intensity at	Venlafaxine: 2.7 ±1.4 vs placebo	1	0	-1	-1	0	0	2. single study	Low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
movement **VAS score (0-10)** **At 1 day** **75 mg venlafaxine** **Pre-emptive** **Mean ± SD** (Reuben 2004)[10]	3.0 ±1.8, ns							3. small sample size, CI not quantified	
Pain intensity at rest **VAS score (0-10)** **At 1 month** **Pre-emptive** **75 mg venlafaxine** **Mean ± SD** (Reuben 2004)[10]	Venlafaxine: 1.6 ±1.0 vs placebo 1.7 ±1.2, ns	1	0	-1	-1	0	0	2. single study 3. small sample size, CI not quantified	Low
Pain intensity at movement **VAS score (0-10)** **At 1 month** **75 mg venlafaxine** **Pre-emptive** **Mean ± SD** (Reuben 2004)[10]	Venlafaxine: 2.7 ±1.1 vs placebo 2.4 ±1.4, ns	1	0	-1	-1	0	0	2. single study 3. small sample size, CI not quantified	Low
Pain intensity at rest **VAS score (0-10)** **At 6 months**	Venlafaxine: 1.1 ±0.9 vs placebo 1.5 ±1.0, ns	1	0	-1	-1	0	0	2. single study 3. small sample size, CI not quantified	Low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
75 mg venlafaxine Pre-emptive Mean ± SD (Reuben 2004)[10]									
Pain intensity at movement VAS score (0-10) At 6 months 75 mg venlafaxine Pre-emptive Mean ± SD (Reuben 2004)[10]	Venlafaxine: 2.3 ±1.4 vs placebo 3.2 ±1.8, p=0.01 (note: overlap of standard deviations)	1	0	-1	-1	0	0	2. single study 3. small sample size, CI not quantified	Low
Analgesic use mg of morphine At 1 day 75 mg venlafaxine Pre-emptive Mean ± SD (Reuben 2004)[10]	Venlafaxine: 22.8 ±5.8 vs placebo 23.4 ±6.8, ns	1	0	-1	-1	0	0	2. single study 3. small sample size, CI not quantified	Low
Analgesic use Number of patients At 6 months 75 mg venlafaxine Pre-emptive Mean ± SD (Reuben 2004)[10]	Venlafaxine: 8/48 vs placebo 26/47, p=0.002	1	0	-1	-1	0	0	2. single study 3. small sample size, CI not quantified	Low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
Current pain intensity **VAS score (100 mm)** **At 2 weeks** **37.5 mg venlafaxine** **Median (range)** (Tasmuth 2002)[11]	Venlafaxine 13 (0-62) vs placebo 8 (0-67), ns	1	-2	-1	-2	0	0	1. no intention-to-treat analysis, selection bias 2. single study 3. outcome only of combined periods of the cross-over design, very small sample size, CI not quantified	Very low
Current pain intensity **VRS 8-point verbal rating scale** **At 2 weeks** **37.5 mg venlafaxine** **Median (range)** (Tasmuth 2002)[11]	Venlafaxine 0 (0-4) vs placebo 1 (0-4), ns	1	-2	-1	-2	0	0	1. no intention-to-treat analysis, selection bias 2. single study 3. outcome only of combined periods of the cross-over design, very small sample size, CI not quantified	Very low
Current pain intensity **VAS score (100 mm)** **At 2 weeks** **75 mg venlafaxine** **Median (range)** (Tasmuth 2002)[11]	Venlafaxine 0 (0-35) vs placebo 3.1 (0.6-70), ns	1	-2	-1	-2	0	0	1. no intention-to-treat analysis, selection bias 2. single study 3. outcome only of combined periods of the cross-over design, very small sample size, CI not quantified	Very low
Current pain intensity	Venlafaxine 0 (0-4) vs placebo 1 (0-2),	1	-2	-1	-2	0	0	1. no intention-to-treat analysis, selection bias 2. single study	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
VRS 8-point verbal rating scale **At 2 weeks** **75 mg venlafaxine** **Median (range)** (Tasmuth 2002)[11]	ns							3. outcome only of combined periods of the cross-over design, very small sample size, CI not quantified	
Current pain relief **VAS score (100 mm)** **At 2 weeks** **37.5 mg venlafaxine** **Median (range)** (Tasmuth 2002)[11]	Venlafaxine 20 (0-100) vs placebo 0 (0-69), ns	1	-2	-1	-2	0	0	1. no intention-to-treat analysis, selection bias 2. single study 3. outcome only of combined periods of the cross-over design, very small sample size, CI not quantified	Very low
Current pain relief **VRS 5-point verbal rating scale** **At 2 weeks** **37.5 mg venlafaxine** **Median (range)** (Tasmuth 2002)[11]	Venlafaxine 3 (1-5) vs placebo 1 (1-5), ns	1	-2	-1	-2	0	0	1. no intention-to-treat analysis, selection bias 2. single study 3. outcome only of combined periods of the cross-over design, very small sample size, CI not quantified	Very low
Current pain relief **VAS score (100 mm)** **At 2 weeks** **75 mg venlafaxine** **Median (range)**	Venlafaxine 42 (0-100) vs placebo 25 (0-100), ns	1	-2	-1	-2	0	0	1. no intention-to-treat analysis, selection bias 2. single study 3. outcome only of combined periods of the cross-over design, very small sample size, CI not quantified	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
(Tasmuth 2002)[11]									
Current pain relief VRS 5-point verbal rating scale At 2 weeks 75 mg venlafaxine Median (range) (Tasmuth 2002)[11]	Venlafaxine 1.5 (0-4) vs placebo 1 (0-3), ns	1	-2	-1	-2	0	0	1. no intention-to-treat analysis, selection bias 2. single study 3. outcome only of combined periods of the cross-over design, very small sample size, CI not quantified	Very low
Consumption of paracetamol (mg)/ codeine (mg) between 2 and 10 days postmastectomy Mean ± SD (Amr 2010)[14]	Paracetamol: Venlafaxine 3305 ± 2166 vs placebo 5216 ± 2320, p<0.0001; codeine: Venlafaxine 185 ± 54 vs placebo 300 ± 156, p< 0.0001	1	-1	-1	-1	0	0	1. no intention-to-treat analysis 2. single study 3.small study sample	Very low
Number of patients with burning pain at 6 months (Amr 2010)[14]	Venlafaxine 1/50 vs placebo 11/50, p=0.0018	1	-1	-1	-1	0	0	1. no intention-to-treat analysis 2. single study 3.small study sample	Very low
Number of patients with stabbing or pricking pain at 6 months (Amr 2010)[14]	Venlafaxine 7/50 vs placebo 18/50, p=0.05	1	-1	-1	-1	0	0	1. no intention-to-treat analysis 2. single study 3.small study sample	Very low
VAS (100 mm) at 6	Venlafaxine 12 ± 5	1	-1	-1	-1	0	0	1. no intention-to-treat analysis	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
months Mean ± SD (Amr 2010)[14]	vs placebo 22 ± 9, p< 0.0001							2. single study 3.small study sample	
Number of patients using opioids analgesics at 6 months (Amr 2010)[14]	Venlafaxine 8/50 vs placebo 18/50, p=0.02	1	-1	-1	-1	0	0	1. no intention-to-treat analysis 2. single study 3.small study sample	Very low

2.2. Anticonvulsants

Table 43 – Anticonvulsants: overview of results and GRADE profiles

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
Gabapentin versus placebo (in patients who underwent breast surgery)									
Pain relief after movement during first 24h postop (Amr 2010)[14]	No quantitative results, ns	1	-1	-1	-1	0	0	1.high risk of bias 2.single study 3.small study sample, no quantitative results	Very low
Pain relief after movement during first 24h postop (Fassoulaki 2002)[19]	No quantitative results, ns	1	-1	-1	-1	0	0	1.high risk of bias 2.single study 3.small study sample, no quantitative results	Very low
Pain relief at rest	No quantitative	1	-1	-1	-1	0	0	1.high risk of bias	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
during first 24h postop (Amr 2010)[14]	results, ns							2.single study 3.small study sample, no quantitative results	
Pain relief at rest during first 24h postop (Fassoulaki 2002)[19]	No quantitative results, ns	1	-1	-1	-1	0	0	1.high risk of bias 2.single study 3.small study sample, no quantitative results	Very low
Pain relief after movement during next 9 consecutive days (Amr 2010)[14]	No quantitative results, p<0.0001 (sign less in gabapentin group)	1	-1	-1	-1	0	0	1.high risk of bias 2.single study 3.small study sample, no quantitative results	Very low
Pain relief after movement during next 8 consecutive days (Fassoulaki 2002)[19]	No quantitative results, p<0.005 (sign less in gabapentin group)	1	-1	-1	-1	0	0	1.high risk of bias 2.single study 3.small study sample, no quantitative results	Very low
Pain relief at rest during next 9 consecutive days (Amr 2010)[14]	No quantitative results, ns	1	-1	-1	-1	0	0	1.high risk of bias 2.single study 3.small study sample, no quantitative results	Very low
Pain relief at rest during next 8 consecutive days (Fassoulaki 2002)[19]	No quantitative results, p<0.005 (sign less in gabapentin group)	1	-1	-1	-1	0	0	1.high risk of bias 2.single study 3.small study sample, no quantitative results	Very low
Pain relief after movement at 10th day postop (Fassoulaki 2002)[19]	25±20.8mm vs 30±25.7mm, ns	1	-1	-1	-1	0	0	1.high risk of bias 2.single study 3.small study sample	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
Pain relief at rest at 10th day postop (Fassoulaki 2002)[19]	9±12.4mm vs 10±15.7mm, ns	1	-1	-1	-1	0	0	1.high risk of bias 2.single study 3.small study sample	Very low
Pain relief at 3 months (Fassoulaki 2002)[19]	No quantitative results, ns	1	-1	-1	-1	0	0	1.high risk of bias 2.single study 3.small study sample, no quantitative results	Very low
Pain relief at 6 months (Amr 2010)[14]	No quantitative results, ns	1	-1	-1	-1	0	0	1.high risk of bias 2.single study 3.small study sample, no quantitative results	Very low
Analgesic use (morphine) during first 24h (Amr 2010)[14]	13.5±0.5 vs 22±2.1; p<0.0001 (sign less in gabapentin group)	1	-1	-1	-1	0	0	1.high risk of bias 2.single study 3.small study sample	Very low
Analgesic use (propoxyphene IM and paracetamol IM) during first 24h (Fassoulaki 2002)[19]	119±50mg vs 116±58mg (propoxyphene IM), 954±400mg vs 925±467mg (paracetamol IM), ns	1	-1	-1	-1	0	0	1.high risk of bias 2.single study 3.small study sample	Very low
Analgesic use during next 9 consecutive days (codeine and paracetamol) (Amr 2010)[14]	3105±1998mg vs 5216±2320mg (codeine), 180±22mg vs 300±156mg (paracetamol), p<0.0001 (sign lower in gabapentin	1	-1	-1	-1	0	0	1.high risk of bias 2.single study 3.small study sample	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
	group)								
Analgesic use during next 9 consecutive days (codeine and paracetamol) (Fassoulaki 2002)[19]	No quantitative results, p=0.029 (codeine and paracetamol) (sign lower in gabapentin group)	1	-1	-1	-1	0	0	1.high risk of bias 2.single study 3.small study sample, no quantitative results	Very low
Analgesic use at 6 months (Amr 2010)[14]	17 vs 18, ns	1	-1	-1	-1	0	0	1.high risk of bias 2.single study 3.small study sample	Very low
Adverse events (Amr 2010)[14]	No quantitative results, ns	1	-1	-1	-1	0	0	1.high risk of bias 2.single study 3.small study sample, no quantitative results	Very low
Gabapentin versus placebo (in patients with neuropathic pain)									
Pain relief at 4 weeks (Mishra 2012)[16]	No quantitative results, ns	1	-1	-1	-1	0	0	1.high risk of bias 2.single study 3.small study sample, no quantitative results	Very low
Pain relief at 10 days (Caraceni 2004)[18]	4.6 vs 5.4, p=0.025	1	-1	-1	-1	0	0	1.unclear risk of bias 2.single study 3.small study sample	Very low
Pain relief after 6 weeks (Rao 2007)[21]	3.3 (group G/P) vs 3.0 (group P/G) (NRS), p=0.8 1.7 (group G/P) vs 1.8 (group P/G)	1	0	-1	-1	0	0	1.low risk of bias 2.single study 3.small study sample	Low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
	(ENS), p=0.3								
Pain relief after 14 weeks (Rao 2007)[21]	3.1 (group G/P) vs 2.5 (group P/G) (NRS), p=0.2 1.5 (group G/P) vs 1.5 (group P/G) (NRS), p=0.7	1	0	-1	-1	0	0	1.low risk of bias 2.single study 3.small study sample	Low
Analgesic use at 4 weeks (Mishra 2012)[16]	33% vs 100%, p-value not mentioned	1	-1	-1	-1	0	0	1.high risk of bias 2.single study 3.small study sample, no quantitative results	Very low
Analgesic use at 10 days (Caraceni 2004)	47.1% of patn vs 64.7% of patn, p=0.0999	1	-1	-1	-1	0	0	1.unclear risk of bias 2.single study 3.small study sample, no quantitative results	Very low
Analgesic use at 6 weeks (Rao 2007)[21]	14% (group G/P) vs 12% (group P/G), p=0.8	1	0	-1	-1	0	0	1.low risk of bias 2.single study 3.small study sample	Low
Analgesic use at 14 weeks (Rao 2007)[21]	9% (group G/P) vs 12% (group P/G), p=1.0	1	0	-1	-1	0	0	1.low risk of bias 2.single study 3.small study sample	Low
Adverse events (Mishra 2012)[16]	No quantitative results, p-value not mentioned (sign more in control group)	1	-1	-1	-1	0	0	1.high risk of bias 2.single study 3.small study sample, no quantitative results	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
Adverse events (Caraceni 2004)[18]	36.2% of patn vs 17.0% of patn, p-value not mentioned	1	-1	-1	-1	0	0	1.unclear risk of bias 2.single study 3.small study sample, no quantitative results	Very low
Adverse events at 6 weeks (Rao 2007)[21]	44 (group G/P) vs 50 (group P/G), p=0.2	1	0	-1	-1	0	0	1.low risk of bias 2.single study 3.small study sample	Low
Adverse events at 14 weeks (Rao 2007)[21]	29 (group G/P) vs 31 (group P/G), p=0.7	1	0	-1	-1	0	0	1.low risk of bias 2.single study 3.small study sample	Low
Gabapentin versus antidepressants (Imipramine)									
Pain relief at 7 days (Arai 2010)[15]	2 (2-3) group Gab+Imi vs 4.5 (3-6) group Gab200 vs 4 (3-5) group Gab400 vs 5 (3-6.5) group Imi, p=0.005 (sign decreased pain score in group Gab+imi compared to Gab200 (p<0.05) and to group Imi (p<0.05)	1	-1	-1	-1	0	0	1.high risk of bias 2.single study 3.small study sample	Very low
Analgesic use at 7 days (Arai 2010)[15]	8 (0-25) group Gab+Imi vs 30 (25-30) group Gab200 vs 25 (20-40) group	1	-1	-1	-1	0	0	1.high risk of bias 2.single study 3.small study sample	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
	Gab400 vs 25 (15-42.5) group Imi, p=0.008 (sign diff between group Gab+imi and group Gab200 (p<0.05)								
Adverse events (Arai 2010)[15]	5 group Gab+Imi vs 5 group Gab200 vs 7 group Gab400 vs 4 group Imi, p=0.559 (mild drowsiness) 1 group Gab+Imi vs 1 group Gab200 vs 1 group Gab400 vs 1 group Imi, p=0.999 (nausea)	1	-1	-1	-1	0	0	1.high risk of bias 2.single study 3.small study sample	Very low
Gabapentin versus antidepressants (Venlafaxine)									
Pain relief after movement during first 24h postop (Amr 2010)[14]	No quantitative results, ns	1	-1	-1	-1	0	0	1.high risk of bias 2.single study 3.small study sample, no quantitative results	Very low
Pain relief at rest during first 24h postop (Amr 2010)[14]	No quantitative results, ns	1	-1	-1	-1	0	0	1.high risk of bias 2.single study 3.small study sample, no quantitative results	Very low
Pain relief at 6 months (Amr	21±12 (gab) vs12±5 (venl), p<0.0001	1	-1	-1	-1	0	0	1.high risk of bias 2.single study	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
2010)[14]								3.small study sample	
Analgesic use (morphine) during first 24h (Amr 2010)[14]	13.5±0.5 vs 21±1.5, p<0.0001 (sign less in gabapentin group)	1	-1	-1	-1	0	0	1.high risk of bias 2.single study 3.small study sample	Very low
Analgesic use at 6 months (Amr 2010)[14]	17 vs 8, p=0.03	1	-1	-1	-1	0	0	1.high risk of bias 2.single study 3.small study sample	Very low
Adverse events (Amr 2010)[14]	No quantitative results, ns	1	-1	-1	-1	0	0	1.high risk of bias 2.single study 3.small study sample, no quantitative results	Very low
Gabapentin versus other anticonvulsants (Pregabalin)									
Pain relief at 4 weeks (Mishra 2012)[16]	3.07±0.80 vs 2.5±0.70, p=0.042 (sign less in preg)	1	-1	-1	-1	0	0	1.high risk of bias 2.single study 3.small study sample	Very low
Analgesic use at 4 weeks (Mishra 2012)[16]	33% vs 16.7%, p-value not mentioned	1	-1	-1	-1	0	0	1.high risk of bias 2.single study 3.small study sample, no quantitative results	Very low
Adverse events (Mishra 2012)[16]	No quantitative results, p-value not mentioned	1	-1	-1	-1	0	0	1.high risk of bias 2.single study 3.small study sample, no quantitative results	Very low
Gabapentin versus opioids									
Pain relief on 4th day (Keskinbora	No quantitiative results, p=0.0001	1	-1	-1	-1	0	0	1.high risk of bias	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
2007[20])	(mean pain intensity)							2.single study 3.small study sample, no quantitative results on mean pain intensity	
Pain relief on 13th day (Keskinbora 2007)[20]	No quantitiative results, p=0.0001 (mean pain intensity) -7.39±2.86 vs -5.78±2.35, p=0.018 (burning pain); -6.77±3.37 vs -4.66±2.80, p=0.009 (shooting pain)	1	-1	-1	-1	0	0	1.high risk of bias 2.single study 3.small study sample, no quantitative results on mean pain intensity	Very low
Adverse events (Keskinbora 2007)[20]	No quantitative results, p=0.015 (sign lower in gab)	1	-1	-1	-1	0	0	1.high risk of bias 2.single study 3.small study sample, no quantitative results	Very low

2.3. Radiotherapy for painful bone metastases

Table 44 – Radiotherapy single/multiple fractions: overview of results and GRADE profiles

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
Single fraction versus single fraction									
Complete pain response at 2 weeks	RR 0.77 [0.48-1.22], p=0.27	2	-1	0	-1	0	0	1. high risk of bias for included RCTs 3. CI includes both benefit and harm	Low
Complete pain response at 4 weeks	RR 0.71 [0.25-2.06], p=0.53	2	-1	0	-2	0	0	1. high risk of bias for included RCTs 3. CI includes both appreciable benefit and harm	Very low
Complete pain response at 8 weeks	RR 0.97 [0.45-2.06], p=0.93	2	-1	-1	-2	0	0	1. high risk of bias for included RCTs 2. statistical heterogeneity I^2=68% (p=0.08), effects at both sides 3. CI includes both appreciable benefit and harm	Very low
Overall pain response at 2 weeks	RR 0.62 [0.46-0.84], p=0.002	1	-1	-1	-1	0	0	1. high risk of bias for included RCT 2. only one study 3. small study	Very low
Overall pain response at 4 weeks	RR 0.64 [0.51-0.80], p=0.0001	1	-1	-1	-1	0	0	1. high risk of bias for included RCT 2. only one study 3. small study	Very low
Overall pain response at 8 weeks	RR 0.75 [0.62-0.90], p=0.003	1	-1	-1	-1	0	0	1. high risk of bias for included RCT 2. only one study 3. small study	Very low
Retreatment rate	RR 1.50 [0.74-3.07], p=0.26	2	-1	0	-1	0	0	1. high risk of bias for included RCTs 3. CI includes both benefit and harm	Low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
Single fraction versus single fraction (add-on to bisphosphonates)									
Overall pain response at 7 months (mean VAS score) (Manas 2008)[37]	1.04 vs 1.79, p=0.0668 (supine); 0.96 vs 1.67, p=0.1226 (seated); 1.27 vs 2.34, p=0.0058 (standing)	1	-1	-1	-1	0	0	1. unclear risk of bias for included RCT 2. only one study 3. small study	Very low
Adverse events (% of patients with adverse events) (Manas 2008)[37]	21.25% vs 14.04% (p<0.05)	1	-1	-1	-1	0	0	1. unclear risk of bias for included RCT 2. only one study 3. small study	Very low
Single fraction versus multiple fraction									
Overall pain response at 4 weeks	RR 1.02 [0.97-1.07], p=0.44	16	-1	0	0	0	0	1. unclear risk of bias for included RCTs	Moderate
Overall pain response at 8 weeks	RR 0.90 [0.78-1.04], p=0.15	3	-1	0	0	0	0	1. unclear risk of bias for included RCTs 3. CI lower border is 0.78: probably not low enough to recommend in favour of "multiple fractions"	Moderate
Overall pain response at 12 weeks	RR 1.01 [0.85-1.19], p=0.92	2	-1	0	-1	0	0	1. unclear risk of bias for included RCTs 3. small study sample	Low
Complete pain response at 4 weeks	RR 1.05 [0.95-1.15], p=0.35	11	-1	0	0	0	0	1. unclear risk of bias for included RCTs	Moderate
Complete pain response at 8 weeks	RR 0.95 [0.72-1.25], p=0.70	3	-1	0	-1	0	0	1. unclear risk of bias for included RCTs 3. CI includes both appreciable benefit and harm	Low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
Complete pain response at 12 weeks	RR 0.89 [0.67-1.19], p=0.44	3	-1	0	-1	0	0	1. unclear risk of bias for included RCTs 3. CI includes both appreciable benefit and harm	Low
Retreatment rate	RR 2.54 [2.14-3.01], p<0.00001 (Significant more in single fraction)	9	-1	0	0	0	0	1. unclear risk of bias for included RCTs 2. statistical heterogeneity I^2=70% (p=0.0008), but all effects at one side and sufficient overlap between CI	Moderate
Pathological fracture rate	RR 1.67 [1.04-2.69], p=0.04 (Significant more in single fraction)	6	-1	0	-1	0	0	1. unclear risk of bias for included RCTs 3. CI includes both no effect and appreciable harm	Low

Table 45 – Radiotherapy for pain in metastatic spinal cord compression: overview of results and GRADE profiles

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
Short course vs split course radiotherapy in patients with spinal cord compression									
Complete pain response in short course vs. split-course RT (timing of outcome measurement not given) (Maranzano 2005)[38]	Total n= 47/153 (31%) in short-course vs total n= 47/147 (32%) in split-course (not sign different, p-value not given)	1	-1	-1	-1	0	0	1. unclear risk of bias for included RCT 2. only one study 3. no CI given, no p-value	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
Partial pain response in short course vs. split-course RT (timing of outcome measurement not given) (Maranzano 2005)[38]	Total n= 33/153 (22%) in short-course vs total n= 32/147 (22%) (not sign different, p-value not given)	1	-1	-1	-1	0	0	1. unclear risk of bias for included RCT 2. only one study 3. no CI given, no p-value	Very low
No pain relief in short course vs. split-course RT (timing of outcome measurement not given) (Maranzano 2005)[38]	Total n= 62/153 (41%) in short-course vs total n= 55/147 (37%) in split-course (not sign different (p-value not given)	1	-1	-1	-1	0	0	1. unclear risk of bias for included RCT 2. only one study 3. no CI given, no p-value	Very low
Adverse events in short course vs. split-course RT (dysphagia, nausea, vomiting) (Maranzano 2005)[38]	No relationship between RT regimen and acute adverse events (see evidence table for frequencies)	1	-1	-1	0	0	0	1. unclear risk of bias for included RCT 2. only one study 3. low incidence of events	Very low
Complete pain response in single dose vs. short-course RT (timing of outcome measurement not given)	Total n= 35/150 (23%) in short-course vs total n= 42/153 (27%) in single dose (not sign different, p-value	1	-1	-1	-1	0	0	1. unclear risk of bias for included RCT 2. only one study 3. no CI given, no p-value	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
(Maranzano 2009)[39]	not given).								
Partial pain response in single dose vs. short-course RT (timing of outcome measurement not given) (Maranzano 2009)[39]	Total n= 45/150 (30%) in short-course vs total n= 38/153 (25%) in single dose (not sign different, p-value not given)	1	-1	-1	-1	0	0	1. unclear risk of bias for included RCT 2. only one study 3. no CI given, no p-value	Very low
No pain relief in single dose vs. short-course RT (timing of outcome measurement not given) (Maranzano 2009)[39]	Total n= 70/150 (47%) in short-course vs total n= 73/153 (48%) in single dose (not sign different, p-value not given)	1	-1	-1	-1	0	0	1. unclear risk of bias for included RCT 2. only one study 3. no CI given, no p-value	Very low
Adverse events in single dose vs. short-course RT (dysphagia, nausea, vomiting, diarrhoea) (Maranzano 2009)[39]	No relationship between RT regimen and acute adverse events (see evidence table for frequencies)	1	-1	-1	-1	0	0	1. unclear risk of bias for included RCT 2. only one study 3. low incidence of events	Very low

Table 46 – Hemibody irradiation: overview of results and GRADE profiles

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
Short hyperfractionation (2x4Gy) versus control: 15Gy (5x3 Gy in 5 days)									
Complete pain response (Salazar 2001)[40]	32% (I) vs 63% (C) (p=0.016) (signless)	1	-1	-1	-1	-1	0	1.high risk of bias (unclear allocation concealment and blinding, no complete outcome data) 2.only one study 3.CI not quantified, small sample size 4.part of study population in developing countries	Very low
Partial pain response (Salazar 2001)[40]	57%vs 29% (p>0.05)	1	-1	-1	-1	-1	0	1.high risk of bias (unclear allocation concealment and blinding, no complete outcome data) 2.only one study 3.CI not quantified, small sample size 4.part of study population in developing countries	Very low
No pain response (Salazar 2001)[40]	11% vs 8% (p>0.05)	1	-1	-1	-1	-1	0	1.high risk of bias (unclear allocation concealment and blinding, no complete outcome data) 2.only one study 3.CI not quantified, small sample size 4.part of study population in developing countries	Very low
Time to maximum pain relief (Salazar 2001)[40]	8 days vs 9 days (p>0.05)	1	-1	-1	-1	-1	0	1.high risk of bias (unclear allocation concealment and blinding, no complete outcome data) 2.only one study 3.CI not quantified, small sample size 4.part of study population in developing countries	Very low
QoL (Salazar 2001)[40]	65% vs 72% (p>0.05)	1	-1	-1	-1	-1	0	1.high risk of bias (unclear allocation concealment and blinding, no complete outcome data) 2.only one study 3.CI not quantified, small sample size 4.part of study population in developing countries	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
Grade 3-4 toxicities (Salazar 2001)[40]	16% vs 8% (p>0.05)	1	-1	-1	-1	-1	0	1.high risk of bias (unclear allocation concealment and blinding, no complete outcome data) 2.only one study 3.CI not quantified, small sample size 4.part of study population in developing countries	Very low
Accelerated hyperfractionation (2<3Gy over 2 consecutive days) versus control: 15Gy (5x3 Gy in 5 days)									
Complete pain response (Salazar 2001)[40]	43% vs 63% (p>0.05)	1	-1	-1	-1	-1	0	1.high risk of bias (unclear allocation concealment and blinding, no complete outcome data) 2.only one study 3.CI not quantified, small sample size 4.part of study population in developing countries	Very low
Partial pain response (Salazar 2001)[40]	51%vs 29% (p>0.05)	1	-1	-1	-1	-1	0	1.high risk of bias (unclear allocation concealment and blinding, no complete outcome data) 2.only one study 3.CI not quantified, small sample size 4.part of study population in developing countries	Very low
No pain response (Salazar 2001)[40]	6% vs 8% (p>0.05)	1	-1	-1	-1	-1	0	1.high risk of bias (unclear allocation concealment and blinding, no complete outcome data) 2.only one study 3.CI not quantified, small sample size 4.part of study population in developing countries	Very low
Time to maximum pain relief (Salazar 2001)[40]	6 days vs 9 days (p>0.05)	1	-1	-1	-1	-1	0	1.high risk of bias (unclear allocation concealment and blinding, no complete outcome data) 2.only one study 3.CI not quantified, small sample size 4.part of study population in developing countries	Very low
QoL	75% vs 72%	1	-1	-1	-1	-1	0	1.high risk of bias (unclear allocation concealment	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
(Salazar 2001)[40]	(p>0.05)							and blinding, no complete outcome data) 2.only one study 3.CI not quantified, small sample size 4.part of study population in developing countries	
Grade 3-4 toxicities (Salazar 2001)[40]	10% vs 8% (p>0.05)	1	-1	-1	-1	-1	0	1.high risk of bias (unclear allocation concealment and blinding, no complete outcome data) 2.only one study 3.CI not quantified, small sample size 4.part of study population in developing countries	Very low

2.4. Radionuclides for painful bone metastases

Table 47 – Radionuclides: overview of results and GRADE profiles

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
Mix of radionuclides versus placebo (ITT-analysis) (Roqué 2011)									
Complete pain response	RR 2.11 [1.32 to 3.37], p=0.0017	4	-1	0	-1	0	0	1.overall high or unclear risk of bias 3.small study sample, large CI	Low
Partial pain response	RR 1.79 [1.16 to 2.77], p=0.009	3	-1	0	-1	0	0	1.overall high or unclear risk of bias 3.small study sample	Low
Any pain response	RR 1.42 [0.81 to 2.49], p=0.23	5	-1	-1	-1	0	0	1.overall high or unclear risk of bias 2. statistical heterogeneity I^2=68%, p=0.02 3.small study sample, large CI that includes favourable outcome control/favourable outcome intervention	Very low
Analgesic use	No meta-analysis	4	-1	-1	-1	0	0	1.overall high or unclear risk of bias	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
	(Porter 1993, Han 2002, Nilsson 2007, Maxon 1991)							2.heterogeneous outcome measures 3.no CI	
89Sr versus placebo (ITT-analysis)									
Complete pain response	RR 1.87 [0.93 to 3.77], p=0.08	2	-1	0	-1	0	0	1. risk of bias: high or unclear 3.small study sample, large CI	Low
Partial pain response	RR 1.65 [1.02 to 2.68], p=0.04	2	-1	0	-1	0	0	1. risk of bias: high or unclear 3.small study sample, large CI	Low
Any pain response	RR 1.03 [0.60 to 1.79], p=0.90	3	-1	-1	-1	0	0	1. risk of bias: 2x high, 1x unclear 2. statistical heterogeneity: borderline I^2=43%, p=0.17; little overlap CIs 3.small study sample, large CI that includes favourable outcome control/favourable outcome intervention	Very low
Radionuclides adjuvant to radiotherapy (Roqué 2011)									
Complete pain response	RR 2.55 [0.52 to 12.63], p=0.25	2	-1	0	-1	0	0	1. risk of bias: high or unclear 3.small study sample, large CI that includes favourable outcome control/favourable outcome intervention	Low
Partial pain response	RR 1.64 [1.05 to 2.55], p=0.029	2	-1	0	-1	0	0	1. risk of bias: high or unclear 3.small study sample, large CI that includes favourable outcome control/favourable outcome intervention	Low
Any pain response	RR 0.80 [0.50 to 1.27], p=0.34	1	-1	-1	-1	0	0	1. risk of bias: high or unclear 2. single study 3. small study sample	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
Adverse events: results for mix of radionuclides (Roqué 2011)									
Leucocytopenia	Risk difference 0.07 [0.04 to 0.11], p=0.00012	4	-1	0	-1	0	0	1. risk of bias: 3x unclear, 1x high 3. few events	Low
Thrombocytopenia	Risk difference 0.04 [-0.03 to 0.11], p=0.25	4	-1	-1	-1	0	0	1. risk of bias: 2x high, 2x unclear 2. statistical heterogeneity I^2=60%, p=0.06 3.few events	Very low
Anemia	Risk difference 0.03 [-0.04 to 0.09], p=0.44	2	-1	0	-1	0	0	1. risk of bias: high and unclear 3.small study sample	Low
Incidence of pain flares	RR 0.74 [0.27 to 2.06], p=0.57	2	-1	0	-1	0	0	1. risk of bias: high and unclear 3.small study sample; large CI that includes favourable outcome control/favourable outcome intervention	Low
Adverse events: 89Sr									
Leucocytopenia	RR 0.10 [0.03 to 0.26], p=0.006	2	-1	0	-1	0	0	1. risk of bias: 2x unclear 3.small study sample, few events	Low
Thrombocytopenia	RR 0.17 [-0.02 to 0.36], p=0.08	2	-1	0	-1	0	0	1. risk of bias: high and unclear 3.small study sample	Low
Head-to-head comparisons of 89Sr versus 153Sm (Roqué 2011)									
Pain response	RR 0.75 (95%CI 0.44-1.29) (ns)	1	-1	-1	-1	0	0	1. risk of bias: high 2. single study 3.small study sample	Very low
Head-to-head comparisons of 89Sr versus 32P (Roqué 2011)									
Pain response	RR 1.07 (95% CI 0.49-2.32), ns	1	-1	-1	-1	0	0	1. risk of bias: high 2. single study 3.small study sample; large CI	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
Head-to-head comparisons of 89Sr versus 186Re-HEDP (Roqué 2011)									
Pain response	1.00 (95% CI 0.45-2.24), ns	1	-1	-1	-1	0	0	1. risk of bias: high 2. single study 3.small study sample; large CI	Very low
Radionuclides (89Sr) compared to chemotherapy (Nilsson 2005)									
Pain intensity at 3, 6, 9, 12 weeks	At 3 weeks: mean 1.71 (±0.99) in 89Sr and mean 1.53 (±0.92) in FEM (ns); at 6 weeks mean 1.65 (SD 1.17) in 89Sr and mean 1.73 (SD 1.33) in FEM (ns); at 9 weeks mean 2.00 (SD 1.17) in 89Sr and mean 2.07 (SD 1.22) in FEM (ns); at 12 weeks mean of 2.12 (SD 1.67) in 89Sr and mean of 1.93 (SD 1.33) in FEM (ns)	1	-1	-1	-1	0	0	1. risk of bias: high 2. single study 3. small study; CI not reported	Very low
Adverse events	More in FEM, p<0.05 and hospitalization in 2/14 in 89Sr vs 7/16 in FEM (no p-value mentioned)	1	-1	-1	-1	0	0	1. risk of bias: high 2. single study 3. small study; CI not reported	Very low

2.5. Bisphosphonates for painful bone metastases

Table 48 – Bisphosphonates: overview of results and GRADE profiles

* CA: categories of outcomes: 1: pain response [proportion of all patients with a specific pain response]; 2: pain scale [change in mean/median pain score before and after treatment]; 3: analgesic response [proportion of all patients with a specific reduction/increase in analgesics]; 4: analgesic scale [change in mean/median analgesic consumption], 5: performance status [proportion of all patients with improvement, or change in performance scale], 6: different types of comparison not to placebo or control condition but between two different bisphosphonates.

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
Pamidronate versus placebo									
Decreased pain score [pain severity (0-3) x pain intensity (0-3)] at 12 months for patients with pain at baseline (Hortobayi 1996)[70] – CA 1*	44% in placebo group vs 32% in pamidronate i.v. 90 mg group; p=0.03	1	-1	-1	-1	0	0	1. not all outcome measures reported; unclear intention-to-treat 2. only one study 3. CI not quantified	Very low
Proportion (%) of patients using opioids at study start vs. using ever opioids during study (duration: 2 to 2.9 years) (Hultborn 1999)[71] – CA 3*	Intervention group (34% / 37%) vs Control group (36% / 55 %); p=0.14	1	0	-1	-1	0	0	1. no downgrading for unclear intention-to-treat 2. only one study 3. CI not quantified	Low
Increase in mean pain score [pain severity (0-3) x pain intensity (0-3)] at 24 weeks	+1.6 (placebo group) vs 0.5 (pamidronate); p = 0.007	1	0	-1	-2	0	0	2. only one study 3. CI not quantified, small study	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
(Theriault 1999)[80] – CA 2*									
Mean pain change in BPI at week 9 (Small 2003)[79] – CA 2*	-0.61 point in BIP scale (SE 0.17 / n=147) in pamidronate i.v. 90 mg group; -0.44 point in BIP scale (SE 0.16 / n=154) in placebo (p=0.46)/	1	-1	-1	-1	0	0	1. unclear randomisation, no intention-to-treat for this outcome 2. only one study 3. CI not quantified	Very low
Mean pain change in BPI at week 27 (Small 2003)[79] – CA 2*	intervention -0.40 SE 0.25, n=110; control: -0.27 SE 0.24 n=108 (p=0.71)	1	-1	-1	-1	0	0	1. unclear randomisation, no intention-to-treat for this outcome 2. only one study 3. CI not quantified	Very low
Retreatment rate for bone pain at week 9 (Small 2003)[79] – CA 1*	11/169 in pamidronate i.v. 90 mg group 10/181 in placebo group (ns)	1	-1	-1	-1	-1	0	1. unclear randomisation 2. only one study 3. CI not quantified 4. indirect outcome	Very low
Retreatment rate for bone pain at week 27 (Small 2003)[79] – CA 1*	25/169 in pamidronate i.v. 90 mg group 29/181 in placebo group (ns)	1	-1	-1	-1	-1	0	1. unclear randomisation 2. only one study 3. CI not quantified 4. indirect outcome	Very low
Oral morphine equivalent score at week 9 (Small 2003)[79] – CA	+16.6 points in OME score (SE 6.8 / n=147) in pamidronate i.v.	1	-1	-1	-1	0	0	1. unclear randomisation, no intention-to-treat for this outcome 2. only one study 3. CI not quantified	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
4*	90 mg group; +10.2 points in OME score (SE 6.6 / n=154) in placebo (p=0.50)								
Decrease or stable analgesic use at week 27 (Small 2003)[79] – CA 3*	46/110 in in pamidronate i.v. 90 mg group 52/108 in placebo group (ns)	1	-1	-1	-1	0	0	1. unclear randomisation, no intention-to-treat for this outcome 2. only one study 3. CI not quantified	Very low
Pamidronate versus zoledronic acid									
Pain score from 1 to 10 (Brief Pain Inventory BPI) (Berenson 2001)[61] – CA 6*	End-of-study mean pain score (± SD): 0.4 mg zoledronic acid: 3.5 ± 2.55 (n=68)- difference to baseline -0.3 (SD 3.23) 2 mg zoledronic acid: 2.9 ± 2.70 (n=72)- difference to baseline -0.6 (SD 2.19) 4 mg zoledronic acid: 3.0 ± 2.86 (n=63)- difference to baseline -0.7 (SD 3.33) 90 mg pamidronate: 3.1	1	-1	-1	-1	0	0	1. randomisation and blinding unclear, no intention-to-treat for this outcome 2. only one study 3. small study	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
	± 2.82 (n=68)- difference to baseline -0.1 (SD 3.28) (NS for comparison to zoledronic acid)								
Pain score from 1 to 10 (Brief Pain Inventory BPI) - Among patients with pain at study entry, % of decrease in pain score (Berenson 2001)[61] – CA 6*	0.4 mg zolodronic acid:29/57 2 mg zolodronic acid: 30/62 4 mg zolodronic acid: 37/55 90 mg pamidronate: 31/62	1	-1	-1	-1	0	0	1. randomisation and blinding unclear 2. only one study 3. small study	Very low
ECOG Performance status scale - Among patients with score> 0 at study entry, N) of patients with improvement (Berenson 2001)[61] – CA 6*	Among patients with score> 0 at study entry, % of improvement 0.4 mg zoledronic acid:4 /52 2 mg zoledronic acid: 19/54 4 mg zoledronic acid: 12/50 90 mg pamidronate: 7/54: NS as compared to zoledronic acid	1	-1	-1	-1	-1	0	1. randomisation and blinding unclear 2. only one study 3. small study 4. influenced by non-pain related factors	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
Pamidronate + chemotherapy versus chemotherapy									
Six points scale (none, mild, moderate, severe, very severe or unbearable) (Conte 1996)[63] – CA 1*	Some improvement (1 point over 2 consecutive reports or 2 points in 1 report) CP: 29 (21%) vs C: 42 (30%), ns	1	-2	-1	-1	0	0	1. unclear randomisation, no blinding, no complete outcome data 2. only one study 3. small study, CI not quantified	Very low* (*also included in pooled data)
Six points scale (none, mild, moderate, severe, very severe or unbearable) (Conte 1996)[63] – CA 1*	Marked improvement (*2 points over 2 consecutive reports)* CP: 54 (44%) vs C: 38 (30%), p=0.025	1	-2	-1	-1	0	0	1. unclear randomisation, no blinding, no complete outcome data 2. only one study 3. small study, CI not quantified	Very low* (*also included in pooled data)
Ibandronate versus placebo									
Variation in mean pain scores (scale 0-4) between baseline and last assessment (up to 96 weeks) (Diel 2004)[66] – CA 2*	IB6 -0.28±1.11 vs control 0.19±0.11;p<0.001	1	-1	-1	-1	0	0	1. unclear randomisation and treatment allocation 2. only one study 3. CI not quantified	Very low
Analgesic use (6 points scale) ; change in analgesic score between baseline and last assessment (up to	IB6 0.51±1.54 vs control 0.90±1.64;NS	1	-1	-1	-1	0	0	1. unclear randomisation and treatment allocation 2. only one study 3. CI not quantified	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
96 weeks) (Diel 2004)[66] – CA 4*									
Bone pain scale from 0 (none) to 4 (intolerable).Change from baseline to 96 weeks (Tripathy 2004)[81] – CA 2*	IB20: -0.06 vs control 0.21;p=0.071; IB50: 0.03 vs control 0.21;p=0.201	1	-1	-1	-1	0	0	1. unclear randomisation and treatment allocation 2. only one study 3. small study, CI not quantified	Very low
Analgesic use: Scale from 0 to 6 (as described in Diel 2004). Change from baseline to 96 weeks (Tripathy 2004)[81] – CA 4*	IB20 0.43 vs control 0.96;p=0.006 IB50 0.73 vs control 0.96;p=0.074	1	-1	-1	-1	0	0	1. unclear randomisation and treatment allocation 2. only one study 3. small study, CI not quantified	Very low
Ibandronate versus zoledronic acid									
Mean pain score (scale 0-4) (±SD) at 12 weeks (Body 2007)[62] – CA 6*	IB -0.14 ± 0.78 vs ZA -0.21 ± 0.77, p = NS	1	-1	-1	-1	0	0	1. unclear treatment allocation, unclear blinding 2. only one study 3. small study, CI not quantified	Very low
Mean analgesic score (scale 0-5) (±SD) at 12 weeks (Body 2007)[62] – CA 6*	Mean score (±SD) at 12 weeks IB -0.05 ± 0.84 vs ZA -0.11 ± 0.53, p = NS	1	-1	-1	-1	0	0	1. unclear treatment allocation, unclear blinding 2. only one study 3. small study, CI not quantified	Very low
Mean WHO performance status at 12 weeks	IB -0.03 vs ZA -0.02	1	-1	-1	-1	-1	0	1. unclear treatment allocation, unclear blinding 2. only one study 3. small study, CI not quantified	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
(Body 2007)[62] – CA 6*								4. measurement influenced by non-pain related factors	
Ibandronate versus placebo									
Pain response two or more reduction in the Present Pain Intensity (PPI) 0-5 scale in comparison with baseline without increase in analgesic score and maintained on two consecutive evaluations at least 3 weeks apart (Ernst 2003)[69] – CA 1*	Intervention 34/115 control 27/112; p=0.34	1	-1	-1	-1	0	0	1. unclear randomisation and treatment allocation 2. only one study 3. small study, CI not quantified	Very low* (*also included in pooled data)
Analgesic response defined as a 50% decrease in analgesic score from the baseline with no increase in pain and maintained on two consecutive evaluations at least 3 weeks apart (Ernst 2003)[69] – CA 3*	Intervention 34/115 control 32/112 ; p=0.84	1	-1	-1	-1	0	0	1. unclear randomisation and treatment allocation 2. only one study 3. small study, CI not quantified	Very low
Proportion of patients with no pain at 1 month	Intervention 10/28, control 6/29 (ns)	1	-2	-1	-1	0	0	1. unclear randomisation, treatment allocation and blinding, no intention-to-treat outcome analysis	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
(Kylmälä 1997)[72] – CA 1*								2. only one study 3. small study, CI not quantified	
Proportion of patients with no pain at 3 months (Kylmälä 1997)[72] – CA 1*	Intervention 9/28, control 6/29 (ns)	1	-2	-1	-1	0	0	1. unclear randomisation, treatment allocation and blinding, no intention-to-treat outcome analysis 2. only one study 3. small study, CI not quantified	Very low
Proportion of patients with no pain at 6 months (Kylmälä 1997)[72] – CA 1*	Intervention 6/28, control 5/29 (ns)	1	-2	-1	-1	0	0	1. unclear randomisation, treatment allocation and blinding, no intention-to-treat outcome analysis 2. only one study 3. small study, CI not quantified	Very low
Proportion of patients with no pain at 12 months (Kylmälä 1997)[72] – CA 1*	Intervention 4/28, control 4/29 (ns)	1	-2	-1	-1	0	0	1. unclear randomisation, treatment allocation and blinding, no intention-to-treat outcome analysis 2. only one study 3. small study, CI not quantified	Very low* (*also included in pooled data)
Proportion of patients without analgesic at 1 month (Kylmälä 1997)[72] – CA 3*	Intervention 13/28, control 8/29 (ns)	1	-2	-1	-1	0	0	1. unclear randomisation, treatment allocation and blinding, no intention-to-treat outcome analysis 2. only one study 3. small study, CI not quantified	Very low
Proportion of patients without analgesic at 3 months (Kylmälä 1997)[72] – CA 3*	Intervention 8/28, control 5/29 (ns)	1	-2	-1	-1	0	0	1. unclear randomisation, treatment allocation and blinding, no intention-to-treat outcome analysis 2. only one study 3. small study, CI not quantified	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
Proportion of patients without analgesic at 6 months (Kylmälä 1997)[72] – CA 3*	Intervention 6/28, control 5/29 (ns)	1	-2	-1	-1	0	0	1. unclear randomisation, treatment allocation and blinding, no intention-to-treat outcome analysis 2. only one study 3. small study, CI not quantified	Very low
Proportion of patients without analgesic at 12 months (Kylmälä 1997)[72] – CA 2*	Intervention 4/28, control 4/29 (ns)	1	-2	-1	-1	0	0	1. unclear randomisation, treatment allocation and blinding, no intention-to-treat outcome analysis 2. only one study 3. small study, CI not quantified	Very low* (*also included in pooled data)
Proportion of patients with no pain at baseline versus at 12 months (Lahtinen 1992)[73] – CA 1*	Intervention 23.8% vs 52.1 % Control 29.3% vs 45.9% No difference between groups	1	-1	-1	-1	0	0	1. no adequate randomization 2. only one study 3. CI not given	Very low* (*also included in pooled data)
Proportion of patients with no pain at 24 months (Lahtinen 1992)[73] – CA 1*	Intervention 23.8% vs 53.6 % Control 29.3% vs 53.6% No difference between groups	1	-1	-1	-1	0	0	1. no adequate randomization 2. only one study 3. CI not given	Very low
Use of non-narcotic analgesic (Mean daily number of tablets/ capsules) at baseline vs 12	Intervention 1.5 (0.1) vs 0.6 (0.1) Control 1.2 (0.1) vs 0.6 (0.1) No difference	1	-1	-1	-1	0	0	1. no adequate randomization 2. only one study 3. CI not given	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
months (Lahtinen 1992)[73] – CA 4*	between groups								
Use of non-narcotic analgesic (Mean daily number of tablets/ capsules) at baseline vs 24 months (Lahtinen 1992)[73] – CA 4*	Intervention 1.5 (0.1) vs 0.5 (0.1) Control 1.2 (0.1) vs 0.4 (0.1) No difference between groups	1	-1	-1	-1	0	0	1. no adequate randomization 2. only one study 3. CI not given	Very low
Use of narcotic analgesic (Mean daily number of tablets/ capsules) at baseline vs 12 months (Lahtinen 1992)[73] – CA 4*	Intervention 0.4 (0.1) vs 0.3 (0.1) Control 0.5 (0.1) vs 0.3 (0.1) No difference between groups	1	-1	-1	-1	0	0	1. no adequate randomization 2. only one study 3. CI not given	Very low
Use of narcotic analgesic (Mean daily number of tablets/ capsules) at baseline vs 24 months (Lahtinen 1992)[73] – CA 4*	Intervention 0.4 (0.1) vs 0.2 (0.1) Control 0.5 (0.1) vs 0.2 (0.1) No difference between groups	1	-1	-1	-1	0	0	1. no adequate randomization 2. only one study 3. CI not given	Very low
Mean pain score at 4 weeks (VAS 10 cm scale)	control 3.4 ± 0.8 vs 400 mg clodronate 2.7 ±	1	-1	-1	-1	0	0	1. unclear randomisation, treatment allocation 2. only one study 3. small sample size, CI not given	Very low* (*also included in

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
(O'Rourke 1995)[75] – CA 2*	0.7 vs 1600 mg clodronate 2.7 ± 0.6 vs 3200 mg clodronate 3.5 ± 0.8 No difference between groups								pooled data)
Mean pain score baseline vs 3 months (Huskisson VAS 10 cm) (Piga 1998)[76] – CA 2*	Intervention 7.5 ± 5.4 vs 5.1 ± 4.8 Control 6.4 ± 5.4 vs 6.4 ± 5.9 No difference between groups (p=0.424)	1	-1	-1	-1	0	0	1. unclear randomisation 2. only one study 3. small sample size, CI not given	Very low* (*also included in pooled data)
Mean of days on analgesics baseline vs 3 months (Piga 1998)[76] – CA 4*	Intervention 16.3 ± 13.9 vs 18.1 ± 13.6 (p=0.065) Control 10.0 ± 13.1 vs 15.0 ± 13.4 (p=0.0002) No difference between group (p=0.176)	1	-1	-1	-1	0	0	1. unclear randomisation 2. only one study 3. small sample size, CI not given	Very low
Patients increasing analgesic scores at 3 months (analgesic score: O: none, 1: NSAIDS 2: opiates) (Piga 1998)[76] – CA 3*	Intervention 5/27 Control 10/22 p=0.042	1	-1	-1	-1	0	0	1. unclear randomisation 2. only one study 3. small sample size, CI not given	Very low
Patients with	Intervention	1	-1	-1	-1	-1	0	1. unclear randomisation	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
Karnofsky performance status stable or minor change at 3 mo (Piga 1998)[76] – CA 5*	18/24, control 13/21 (ns)							2. only one study 3. small sample size, CI not given 4. measurement influenced by non-pain related factors	
Patients with Karnofsky performance status increased by 20 % at 3 mo (Piga 1998)[76] – CA 5*	Intervention 1/24, control 0/21 (ns)	1	-1	-1	-1	-1	0	1. unclear randomisation 2. only one study 3. small sample size 4. measurement influenced by non-pain related factors	Very low
Patients with Karnofsky performance status decreased by 20 % at 3 mo (Piga 1998)[76] – CA 5*	Intervention 5/24, control 8/21 (ns)	1	-1	-1	-1	-1	0	1. unclear randomisation 2. only one study 3. small sample size, CI not given 4. measurement influenced by non-pain related factors	Very low
Change in median pain from entry to 1 month [VAS(0-10 points)] (Roberson 1995)[77] – CA 2*	Intervention -0.9 (-2.6 — -0.4) vs control +0.4 (-0.1 — +4.0) p=0.03	1	-1	-1	-1	0	0	1. unclear randomisation, allocation concealment 2. only one study 3. small sample size, CI not given	Very low
Increase in analgesic use (not further specified) (1 month) (Robertson 1995)[77] – CA 3*	Intervention 16/27 control 18/28 (difference not significant)	1	-1	-1	-1	0	0	1. unclear randomisation, allocation concealment 2. only one study 3. small sample size, no clear definition of “increase”, CI not given	Very low
Proportion of	Intervention 23/69	3	-1	-1	-1	0	0	1. unclear randomisation, allocation	Very low*

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
patients with no pain at 12 months (Tubiana-Hulin 2001)[82] – CA 1*	vs control 13/68 (ns)							concealment; no complete outcome data 2. only one study 3. small sample size, CI not given	(*also included in pooled data)
Mean difference in VAS (100 mm) between baseline and 12 months evaluation (Tubiana-Hulin 2001)[82] – CA 2*	Intervention -11.8 ± 3.2 vs control 4.5 ± 4.7; p=0.007	1	-1	-1	-1	0	0	1. unclear randomisation, allocation concealment; no complete outcome data 2. only one study 3. small sample size, CI not given	Very low
Use of analgesics (not further defined, study duration 12 months) (Tubiana-Hulin 2001)[82] – CA 3*	Intervention 46/69 vs control 57/68; p=0.02	1	-1	-1	-1	0	0	1. unclear randomisation, allocation concealment; no complete outcome data 2. only one study 3. small sample size, CI not given	Very low* (*also included in pooled data)
Increase in dosage of analgesics (not further defined, study duration 12 months) (Tubiana-Hulin 2001)[82] – CA 3*	Intervention 51.4 % vs control 48.7%; p=0.83	1	-1	-1	-1	0	0	1. unclear randomisation, allocation concealment; no complete outcome data 2. only one study 3. small sample size, CI not given	Very low
Increase in analgesic category (not further specified, study duration 12 months) (Tubiana-Hulin 2001)[82] – CA 3*	Intervention 38/69 vs control 36/68; ns	1	-1	-1	-1	0	0	1. unclear randomisation, allocation concealment; no complete outcome data 2. only one study 3. small sample size, CI not given	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
Average decrease in 10 cm VAS at 7 days (Ernst 1992)[67] – CA 2*	Cl_2MDP vs. placebo – 0.89 (SE = 0.27); 95 % CI -1.43 to -0.35, p=0.004	1	-1	-1	-1	0	0	1. unclear if complete outcome data 2. only one study 3. small sample size, CI not given	Very low
Change in Daily oral morphine equivalent (7 days) (Ernst 1992)[67] – CA 4*	Cl_2MDP: +10 mg (SE = 8.1) vs Placebo +62 mg (SE = 29.6) ; p=0.096	1	-1	-1	-1	0	0	1. unclear if complete outcome data 2. only one study 3. small sample size, CI not given	Very low
Decrease in 150 mm visual analogue scales from baseline to 14 days (Ernst 1997)[68] – CA 2*	C: 22 mm (SE = 7.2) vs P: 13.2 mm (SE=7.5), p=0.51	1	-1	-1	-1	0	0	1. unclear if complete outcome data 2. only one study 3. small sample size, CI not given	Very low
Average change in daily morphine equivalent doses (14 days) (Ernst 1997)[68] – CA 4*	C: -6.4 (SE = 2.9) vs P:+24.6 (SE=14.9), p=0.03	1	-1	-1	-1	0	0	1. unclear if complete outcome data 2. only one study 3. small sample size, CI not given	Very low
Zoledronate versus placebo									
Brief Pain inventory (scale from 1 to 10); mean variation from the baseline at 15 months (ZA 4 mg) (Saad 2002, 2004)[78, 94] – CA 2*	ZA4 0.58 (95 % CI =0.29 to 0.87) vs control 0.88 (95 % CI =0.61 to 1.15);p=0.134	1	0	-1	-1	0	0	2. only one study 3. CI not given	Low
Brief Pain inventory	ZA4 0.58 vs	1	0	-1	-1	0	0	2. only one study	Low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
(scale from 1 to 10); mean least-squares change from baseline at 18 months (ZA 4 mg) (Saad 2002, 2004)[78, 94] – CA 2*	control 0.95; -0.37 (95% CI -0.78 to -0.04); p=0.075							3. CI not given	
Brief Pain inventory (scale from 1 to 10); mean least-squares change from baseline at 21 months (ZA 4 mg) (Saad 2002, 2004)[78, 94] – CA 2*	ZA4 0.56 vs control 1.07; -0.51 (95% CI -0.91 to -0.10); p=0.014	1	0	-1	-1	0	0	2. only one study 3. CI not given	Low
Brief Pain inventory (scale from 1 to 10); mean least-squares change from baseline at 24 months (ZA 4 mg) (Saad 2002, 2004)[78, 94] – CA 2*	ZA4 0.58 vs control 1.05; -0.47 (95% CI -0.88 to -0.06); p=0.024	1	0	-1	-1	0	0	2. only one study 3. CI not given	Low
Analgesic score 0-4: variation in mean from baseline to 24 months (ZA 4 mg) (Saad 2002, 2004)[78, 94] – CA 4*	ZA4 1.04 vs control 1.17 ; p=0.491	1	0	-1	-1	0	0	2. only one study 3. CI not given	Low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
Etidronate versus placebo									
Huskisson (VAS) pain index (cm±SD) at 4 months (Daragon 1993)[64] – CA 2*	Etidronate 1.7 ±2 vs placebo 2±2.3, ns	1	-1	-1	-1	0	0	1. no adequate randomization and allocation concealment, no blinding 2. only one study 3. small sample size, CI not given	Very low* (*also included in pooled data)
Analgesic use (Class1: paracetamol; Class2 codeine, dextropropoxyphene ; Class3 morphine) Analgesic class2+3 at 4 months (Daragon 1993)[64] – CA 4*	Etidronate 7/39 vs placebo 12/39, ns	1	-1	-1	-1	0	0	1. no adequate randomization and allocation concealment, no blinding 2. only one study 3. small sample size, CI not given	Very low
Karnofsky's scale - Performance status at 4 months (Daragon 1993)[64] – CA 5*	Etidronate 85.1 ±10.7 vs placebo 81.8±12.2, ns	1	-1	-1	-1	-1	0	1. no adequate randomization and allocation concealment, no blinding 2. only one study 3. small sample size, CI not given 4. measurement influenced by non-pain related factors	Very low
Residronate + docetaxel + prednisone versus docetaxel + prednisone									
Pain response (≥2 point reduction from baseline median PPI score, without increase in analgesic class, or decrease in	Response rate Control group 27.9% vs intervention group 31.2% (respons not different	1	-1	-1	-1	0	0	1. unclear randomization and allocation concealment, unclear blinding 2. only one study 3. CI not given	Very low* (*also included in pooled data)

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
analgesic class without increase in PPI score, for 2 consecutive evaluations at least 3 weeks apart) (Meulenbeld 2012)[74] – CA 1*	between groups)								
Bisphosphonates versus placebo or control									
Proportion of patients with no pain at 12 months (Kylmälä 1997, Lahtinen 1992, Tubiana-Hulin 2001)[72, 73, 82] – CA 1*	RR[CI95%] 1.21 [0.99-1.49] P=0.07	3	-2	0	0	0	0	1. high risk of bias for 3 RCTs (no adequate randomization in Lahtinen 1992)	Low
Proportion of patients with predefined partial pain relief at some point during study (Conte 1996, Ernst 2003, Meulenbeld 2012)[63, 69, 74] – CA 1*	RR[CI95%] 1.07 [0.92-1.25] P=0.36	3	-2	0	0	0	0	1. 3 studies unclear randomization and allocation concealment; Conte 1996 no blinding	Low
Mean change in VAS score at 1 to 4 months (Daragon 1993, O'Rourke 1995, Piga 1998)[64, 75, 76] – CA 2*	Mean difference [CI95%] -0.63 [-1.02, -0.24] P=0.001	3	-2	0	0	0	0	1. 3 studies unclear or inappropriate randomization; Daragon 1993 no blinding	Low

Results	Effect estimate		N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
Proportion of patients without analgesic at 12 months (Kylmälä 1997, Tubiana-Hulin 2001)[72, 82] – CA 3*	RR[CI95%] [1.02-3.15] favour intervention P=0.04	1.79 in of	2	-1	0	-1	0	0	1. high risk of bias for 2 RCTs 3. small sample size	Low
Withdrawal from therapy due to adverse events (Conte 1996, Dearnaly 2003, Ernst 1992, Hortobagyi 1996, Hultborn 1999, Kylmäla 1997, Saad 2002, Small 2003, Theriault 1999, Tripathy 2004, Tubiana-Hulin 2001)[63, 65, 67, 70-72, 78-82]	RR [1.08,1.85]; p=0.01	1.41	11	-1	0	0	0	0	1. four studies low, 4 studies unclear and 3 studies high risk of bias.	Moderate
Nausea (Kylmäla 1997, Lahtinen 1992, Saad 2002, Small 2003, Tripathy 2004)[72, 73, 78, 79, 81]	RR [0.92,1.32]; p=0.31	1.10	5	-1	0	0	0	0	1. one study low, 2 studies unclear and 2 studies high risk of bias.	Moderate
Nausea and/or vomiting (Ersnt 2003, Kylmäla 1997, Lahtinen 1992,	RR [0.94,1.21]; p=0.33	1.07	8	-1	0	0	0	0	1. one study low, 4 studies unclear and 3 studies high risk of bias.	Moderate

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
O'Rourke 1995, Saad 2002, Small 2003, Tripathy 2004, Tubiana-Hulin 2001)[67, 72, 73, 75, 78, 79, 81, 82]									

2.6. Celiac Plexus Block

Table 49 – Celiac Plexus Block: overview of results and GRADE profiles

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
Posterior percutaneous or surgical Celiac Plexus Block vs Conventional pain management with narcotics alone									
Pain control at 4 weeks (Arcidiacono 2011)[83]	-0.42 point in VAS scale (95% IC -0.71 - -0.14); p=0.004	4	-1	0	-1	0	0	1. overall risk of bias of included studies high 3. small sample size	Low
Pain control at 8 weeks (Arcidiacono 2011)[83]	-0.44 point in VAS scale (95% IC -0.89 - -0.01); p=0.06	5	-1	-1	-1	0	0	1. overall risk of bias of included studies high 2. inconsistent results confirmed by statistical heterogeneity I^2 89% (p=0.00001) 3. small sample size	Very low
Opioid use at 4 weeks (Arcidiacono 2011)[83]	-34.33 mg (95% CI -44.42– -24.24; p<0.000001)	5	-2	0	-1	0	0	1. overall risk of bias of included studies high; results of one low risk RCT (Wong 2004) not in line with pooled results 2. no downgrading for statistical heterogeneity I^2 76% (p=0.002) 3. small sample size	Very low
Adverse event: constipation	Risk ratio: 0.38 (95% CI 0.25–	6	-1	0	-1	0	0	1. overall risk of bias of included studies high 3. small sample size	Low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
(Arcidiacono 2011)[83]	0.59;p=0.00001)								
Adverse event: diarrhea (Arcidiacono 2011)[83]	Risk ratio: 3.25 (95% CI 0.95–11.13;p=0.060)	4	-1	0	-2	0	0	1. overall risk of bias of included studies high 3. small sample size, few events	Very low
Early Endoscopic Ultrasound-guided Celiac Plexus Block vs Conventional pain management with narcotics alone									
Pain control at 1 month (Wyse 2011)[91]	-1.0 point in Likert scale (95% IC -1.7 - -0.1); p=0.01	1	0	-1	-1	0	0	2. single study 3. small sample size	Low
Pain control at 3 months (Wyse 2011)[91]	-2.2 point in Likert scale (95% IC -3.1 - -1.4); p<0.001	1	0	-1	-1	0	0	2. single study 3. small sample size	Low
Change in morphine equivalent (MEQ)consumption at 1 month (Wyse 2011)[91]	-1.0 MEQ (95% CI -47.7– +49.2; p=0.99)	1	0	-1	-2	0	0	2. single study 3. CI includes appreciable harm and benefit	Very low
Change in morphine equivalent (MEQ) consumption at 3 month (Wyse 2011)[91]	-49.5 MEQ (95% CI -127.5– 7.0; p=0.10)	1	0	-1	-1	0	0	2. single study 3. small sample size	Low
QoL (DDQ-15 score (mean percentage change) at 1 month (Wyse 2011)[91]	No significant difference	1	0	-1	-2	0	0	2. single study 3. CI not quantified	Very low
QoL (DDQ-15 score (mean percentage	No significant difference	1	0	-1	-2	0	0	2. single study	Very low

Results	Effect estimate	N studies	1. Risk of bias	2. Inconsistency	3. Imprecision	4. Indirectness	5. Publication bias	Reasons for downgrading	Level of evidence
change) at 3 months (Wyse 2011)[91]								3. CI not quantified	
Comparison of three posterior CPB techniques (celiac plexus retrocrural vs. transaortic vs. bilateral splanchnic nerve block technique)									
Immediate total or partial pain relief (Ischia 1992)[92]	No statistical significant differences among the 3 techniques	1	-1	-1	-2	0	0	1. unclear allocation concealment 2. single study 3. small study, CI not quantified	Very low
Comparison of transaortic celiac plexus (CP) vs. bilateral splanchnic (BS) nerve block technique in patients with pancreatic cancer located in body or tail									
Pain relief at 4 resp. 8 weeks (Süleyman Özyalçin 2004)[93]	Mean difference between interventions for pain rating at 4 resp. 8 weeks significant better for BS (p<0.001)	1	-1	-1	-2	0	0	1. no blinding 2. single study 3. small study, CI not quantified	Very low

3. FOREST PLOTS

3.1. Radiotherapy for painful bone metastases

Figure 10 – Single fraction versus single fraction: complete pain response at 2 weeks

Study or Subgroup	4-Gy Events	4-Gy Total	8-Gy Events	8-Gy Total	Weight	Risk Ratio M-H, Random, 95% CI
Hoskin 1992	15	137	16	133	48.7%	0.91 [0.47, 1.77]
Jeremic 1998	13	109	20	110	51.3%	0.66 [0.34, 1.25]
Total (95% CI)		**246**		**243**	**100.0%**	**0.77 [0.48, 1.22]**
Total events	28		36			

Heterogeneity: Tau² = 0.00; Chi² = 0.48, df = 1 (P = 0.49); I² = 0%

Test for overall effect: Z = 1.11 (P = 0.27)

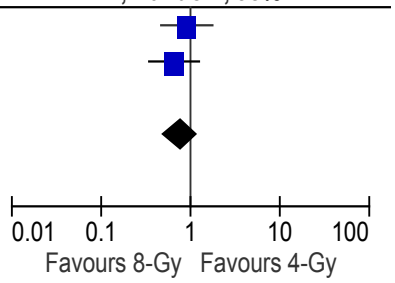


Figure 11 – Single fraction versus single fraction: complete pain response at 4 weeks

Study or Subgroup	4-Gy Events	4-Gy Total	8-Gy Events	8-Gy Total	Weight	Risk Ratio M-H, Random, 95% CI
Hoskin 1992	25	137	22	133	60.3%	1.10 [0.66, 1.86]
Jeremic 1998	4	109	11	110	39.7%	0.37 [0.12, 1.12]
Total (95% CI)		**246**		**243**	**100.0%**	**0.71 [0.25, 2.06]**
Total events	29		33			

Heterogeneity: Tau² = 0.42; Chi² = 3.12, df = 1 (P = 0.08); I² = 68%

Test for overall effect: Z = 0.63 (P = 0.53)

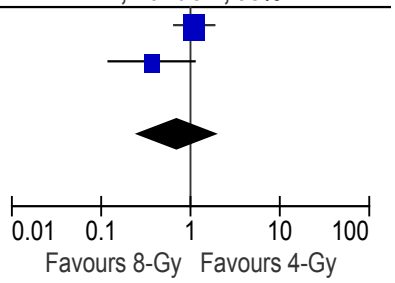


Figure 12 – Single fraction versus single fraction: complete pain response at 8 weeks

Study or Subgroup	4-Gy Events	4-Gy Total	8-Gy Events	8-Gy Total	Weight	Risk Ratio M-H, Random, 95% CI
Hoskin 1992	31	137	21	133	49.1%	1.43 [0.87, 2.36]
Jeremic 1998	23	109	35	110	50.9%	0.66 [0.42, 1.04]
Total (95% CI)		**246**		**243**	**100.0%**	**0.97 [0.45, 2.06]**
Total events	54		56			

Heterogeneity: Tau² = 0.24; Chi² = 5.01, df = 1 (P = 0.03); I² = 80%
Test for overall effect: Z = 0.08 (P = 0.93)

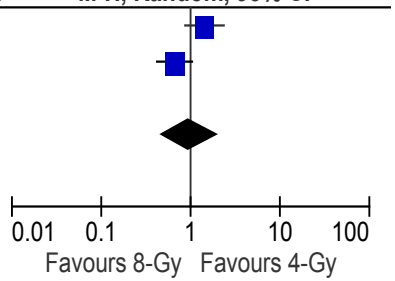


Figure 13 – Single fraction versus single fraction: overall pain response at 2 weeks

Study or Subgroup	4-Gy Events	4-Gy Total	8-Gy Events	8-Gy Total	Weight	Risk Ratio M-H, Random, 95% CI
Jeremic 1998	38	109	62	110	100.0%	0.62 [0.46, 0.84]
Total (95% CI)		**109**		**110**	**100.0%**	**0.62 [0.46, 0.84]**
Total events	38		62			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.09 (P = 0.002)

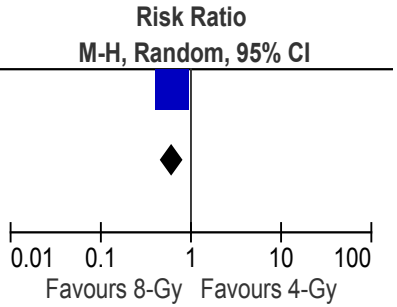


Figure 14 – Single fraction versus single fraction: overall pain response at 4 weeks

Study or Subgroup	4-Gy Events	4-Gy Total	8-Gy Events	8-Gy Total	Weight	Risk Ratio M-H, Random, 95% CI
Jeremic 1998	51	109	81	110	100.0%	0.64 [0.51, 0.80]
Total (95% CI)		**109**		**110**	**100.0%**	**0.64 [0.51, 0.80]**
Total events	51		81			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.88 (P = 0.0001)

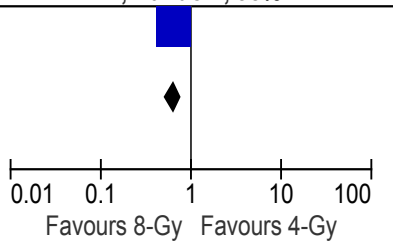


Figure 15 – Single fraction versus single fraction: overall pain response at 8 weeks

Study or Subgroup	4-Gy Events	4-Gy Total	8-Gy Events	8-Gy Total	Weight	Risk Ratio M-H, Random, 95% CI
Jeremic 1998	64	109	86	110	100.0%	0.75 [0.62, 0.90]
Total (95% CI)		**109**		**110**	**100.0%**	**0.75 [0.62, 0.90]**
Total events	64		86			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.02 (P = 0.003)

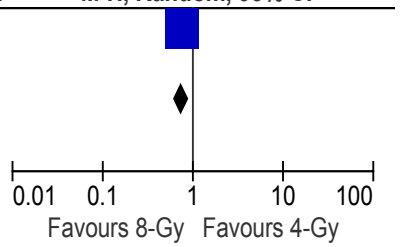


Figure 16 – Single fraction versus single fraction: retreatment rate

Study or Subgroup	4-Gy Events	4-Gy Total	8-Gy Events	8-Gy Total	Weight	Risk Ratio M-H, Random, 95% CI
Hoskin 1992	28	137	12	133	42.9%	2.27 [1.20, 4.26]
Jeremic 1998	46	109	42	110	57.1%	1.11 [0.80, 1.53]
Total (95% CI)		**246**		**243**	**100.0%**	**1.50 [0.74, 3.07]**
Total events	74		54			

Heterogeneity: $Tau^2 = 0.20$; $Chi^2 = 4.10$, df = 1 (P = 0.04); $I^2 = 76\%$

Test for overall effect: Z = 1.12 (P = 0.26)

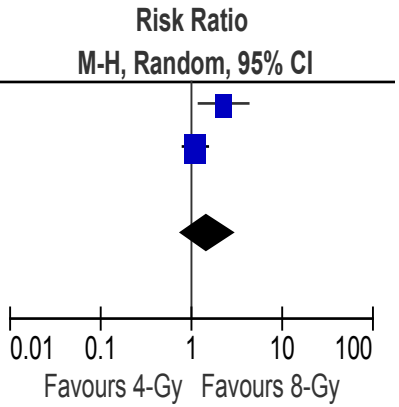
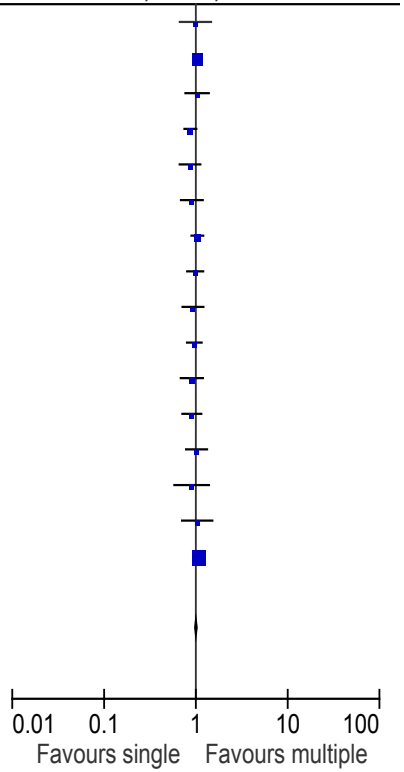


Figure 17 – Single fraction versus multiple fraction: overall pain relief at 4 weeks

Study or Subgroup	single fraction Events	Total	multiple fraction Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Amouzegar-Hasgemi 2008	21	36	20	34	1.8%	0.99 [0.67, 1.47]
BPTWP 1999	274	383	257	378	22.9%	1.05 [0.96, 1.16]
Cole 1989	14	16	11	13	1.1%	1.03 [0.77, 1.39]
Foro 2008	59	78	71	82	6.1%	0.87 [0.75, 1.02]
Forro 1998	19	25	22	25	1.9%	0.86 [0.66, 1.12]
Forro 1998	19	25	21	25	1.9%	0.90 [0.68, 1.20]
Gaze 1997	108	151	99	144	9.0%	1.04 [0.90, 1.21]
Hamouda 2007	40	52	43	55	3.7%	0.98 [0.80, 1.21]
Kagei 1990	12	14	12	13	1.1%	0.93 [0.71, 1.21]
Koswig 1999	41	52	45	55	3.9%	0.96 [0.80, 1.16]
Nielsen 1998	52	122	56	119	5.0%	0.91 [0.68, 1.20]
Ozsaran 2001	27	36	29	35	2.6%	0.91 [0.71, 1.15]
Ozsaran 2001	27	36	28	38	2.4%	1.02 [0.78, 1.33]
Price 1986	29	140	34	148	2.9%	0.90 [0.58, 1.40]
Sarkar 2002	21	35	22	38	1.9%	1.04 [0.71, 1.52]
Steenland 1999	392	579	361	578	31.9%	1.08 [1.00, 1.18]
Total (95% CI)		**1780**		**1780**	**100.0%**	**1.02 [0.97, 1.07]**
Total events	1155		1131			

Heterogeneity: Chi² = 11.57, df = 15 (P = 0.71); I² = 0%

Test for overall effect: Z = 0.78 (P = 0.44)



Remark: Foro 2008 used a time frame of 3 weeks

Figure 18 – Single fraction versus multiple fraction: overall pain relief at 8 weeks

	single fraction		multiple fraction			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Hamouda 2007	42	52	46	55	31.1%	0.97 [0.81, 1.15]	
Roos 2005	73	137	83	135	58.2%	0.87 [0.71, 1.06]	
Sarkar 2002	13	35	16	38	10.7%	0.88 [0.50, 1.56]	
Total (95% CI)		**224**		**228**	**100.0%**	**0.90 [0.78, 1.04]**	
Total events	128		145				

Heterogeneity: Chi² = 0.75, df = 2 (P = 0.69); I² = 0%

Test for overall effect: Z = 1.45 (P = 0.15)

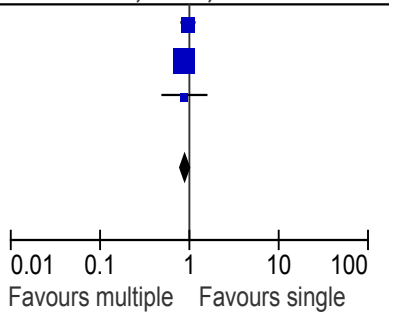


Figure 19 – Single fraction versus multiple fraction: overall pain relief at 12 weeks

	single fraction		multiple fraction			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Foro 2008	51	78	51	82	55.5%	1.05 [0.83, 1.33]	
Hamouda 2007	37	52	41	55	44.5%	0.95 [0.76, 1.20]	
Total (95% CI)		**130**		**137**	**100.0%**	**1.01 [0.85, 1.19]**	
Total events	88		92				

Heterogeneity: Chi² = 0.34, df = 1 (P = 0.56); I² = 0%

Test for overall effect: Z = 0.10 (P = 0.92)

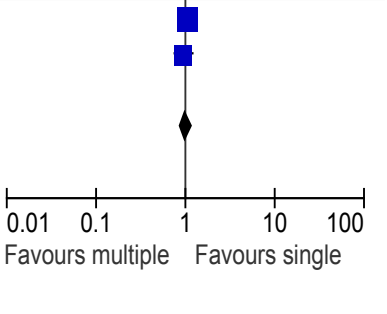


Figure 20 – Single fraction versus multiple fraction: complete pain relief at 4 weeks

Complete pain relief is defined as a pain score = 0.Same authors added the arrest of the reduction of analgesic consumption as a supplementary parameter.

	single fraction		multiple fraction			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Amouzegar-Hasgemi 2008	6	36	11	34	2.2%	0.52 [0.21, 1.24]	
BPTWP 1999	199	383	192	378	37.1%	1.02 [0.89, 1.17]	
Foro 2008	12	78	11	82	2.1%	1.15 [0.54, 2.45]	
Gaze 1997	50	151	47	144	9.2%	1.01 [0.73, 1.41]	
Hamouda 2007	20	52	23	55	4.3%	0.92 [0.58, 1.46]	
Kagei 1990	8	14	4	13	0.8%	1.86 [0.73, 4.72]	
Koswig 1999	16	52	18	55	3.4%	0.94 [0.54, 1.64]	
Nielsen 1998	12	122	14	119	2.7%	0.84 [0.40, 1.73]	
Price 1986	13	140	13	148	2.4%	1.06 [0.51, 2.20]	
Sarkar 2002	11	35	12	38	2.2%	1.00 [0.51, 1.96]	
Steenland 1999	199	579	175	578	33.6%	1.14 [0.96, 1.34]	
Total (95% CI)		**1642**		**1644**	**100.0%**	**1.05 [0.95, 1.15]**	
Total events	546		520				

Heterogeneity: Chi² = 5.89, df = 10 (P = 0.82); I² = 0%

Test for overall effect: Z = 0.93 (P = 0.35)

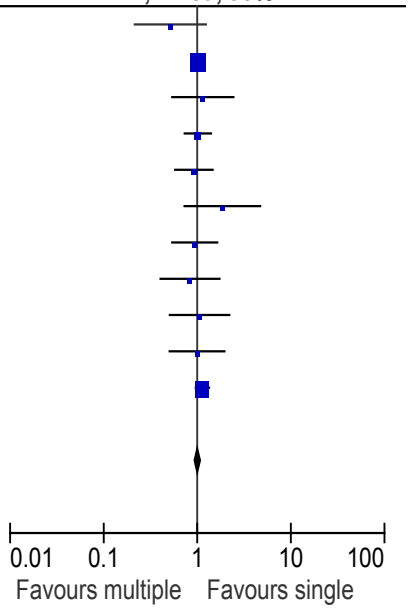


Figure 21 – Single fraction versus multiple fraction: complete pain relief at 8 weeks

	single fraction		multiple fraction			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Hamouda 2007	23	52	25	55	35.6%	0.97 [0.64, 1.48]	
Roos 2005	35	137	36	135	53.1%	0.96 [0.64, 1.43]	
Sarkar 2002	6	35	8	38	11.2%	0.81 [0.31, 2.11]	
Total (95% CI)		**224**		**228**	**100.0%**	**0.95 [0.72, 1.25]**	
Total events	64		69				

Heterogeneity: Chi² = 0.12, df = 2 (P = 0.94); I² = 0%

Test for overall effect: Z = 0.38 (P = 0.70)

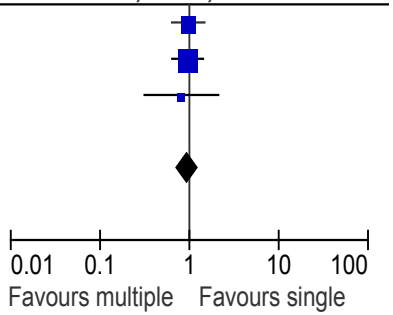


Figure 22 – Single fraction versus multiple fraction: complete pain relief at 12 weeks

	single fraction		multiple fraction			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Foro 2008	10	78	9	82	10.7%	1.17 [0.50, 2.72]	
Hamouda 2007	19	52	22	55	26.1%	0.91 [0.56, 1.48]	
Hartsell 2005	44	455	51	443	63.1%	0.84 [0.57, 1.23]	
Total (95% CI)		**585**		**580**	**100.0%**	**0.89 [0.67, 1.19]**	
Total events	73		82				

Heterogeneity: Chi² = 0.49, df = 2 (P = 0.78); I² = 0%

Test for overall effect: Z = 0.77 (P = 0.44)

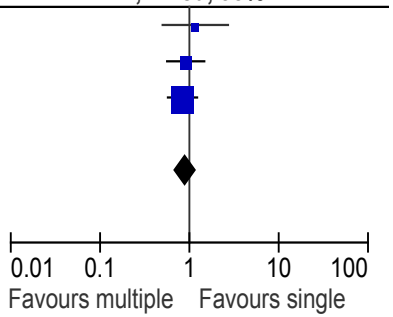


Figure 23 – Single fraction versus multiple fraction: retreatment rate

	single fraction		multiple fraction			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
BPTWP 1999	76	383	32	378	19.9%	2.34 [1.59, 3.45]	
Cole 1989	4	16	0	13	0.3%	7.41 [0.44, 126.20]	
Foro 2008	22	78	2	82	1.2%	11.56 [2.81, 47.55]	
Hamouda 2007	6	52	1	55	0.6%	6.35 [0.79, 50.94]	
Hartsell 2005	76	455	33	443	20.7%	2.24 [1.52, 3.30]	
Nielsen 1998	25	122	14	119	8.8%	1.74 [0.95, 3.19]	
Price 1986	15	140	4	148	2.4%	3.96 [1.35, 11.66]	
Roos 2005	40	137	33	135	20.6%	1.19 [0.80, 1.77]	
Steenland 1999	147	579	41	578	25.4%	3.58 [2.58, 4.96]	
Total (95% CI)		**1962**		**1951**	**100.0%**	**2.54 [2.14, 3.01]**	
Total events	411		160				

Heterogeneity: Chi² = 26.68, df = 8 (P = 0.0008); I² = 70%

Test for overall effect: Z = 10.73 (P < 0.00001)

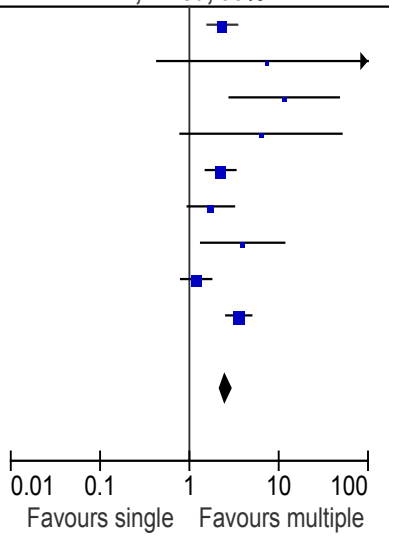
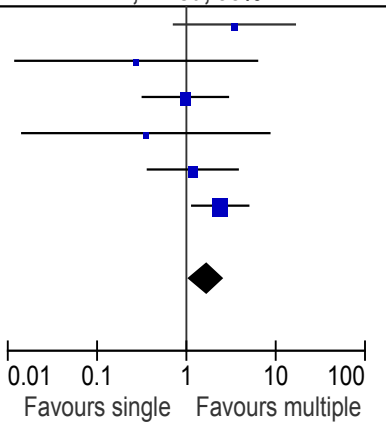


Figure 24 – Single fraction versus multiple fraction: pathological fracture rate

	single fraction		multiple fraction			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
BPTWP 1999	7	383	2	378	7.7%	3.45 [0.72, 16.52]
Cole 1989	0	16	1	13	6.3%	0.27 [0.01, 6.23]
Nielsen 1998	6	122	6	119	23.2%	0.98 [0.32, 2.94]
Price 1986	0	140	1	148	5.6%	0.35 [0.01, 8.58]
Roos 2005	6	137	5	135	19.2%	1.18 [0.37, 3.78]
Steenland 1999	24	579	10	578	38.1%	2.40 [1.16, 4.96]
Total (95% CI)		**1377**		**1371**	**100.0%**	**1.67 [1.04, 2.69]**
Total events	43		25			

Heterogeneity: Chi² = 5.22, df = 5 (P = 0.39); I² = 4%

Test for overall effect: Z = 2.11 (P = 0.04)

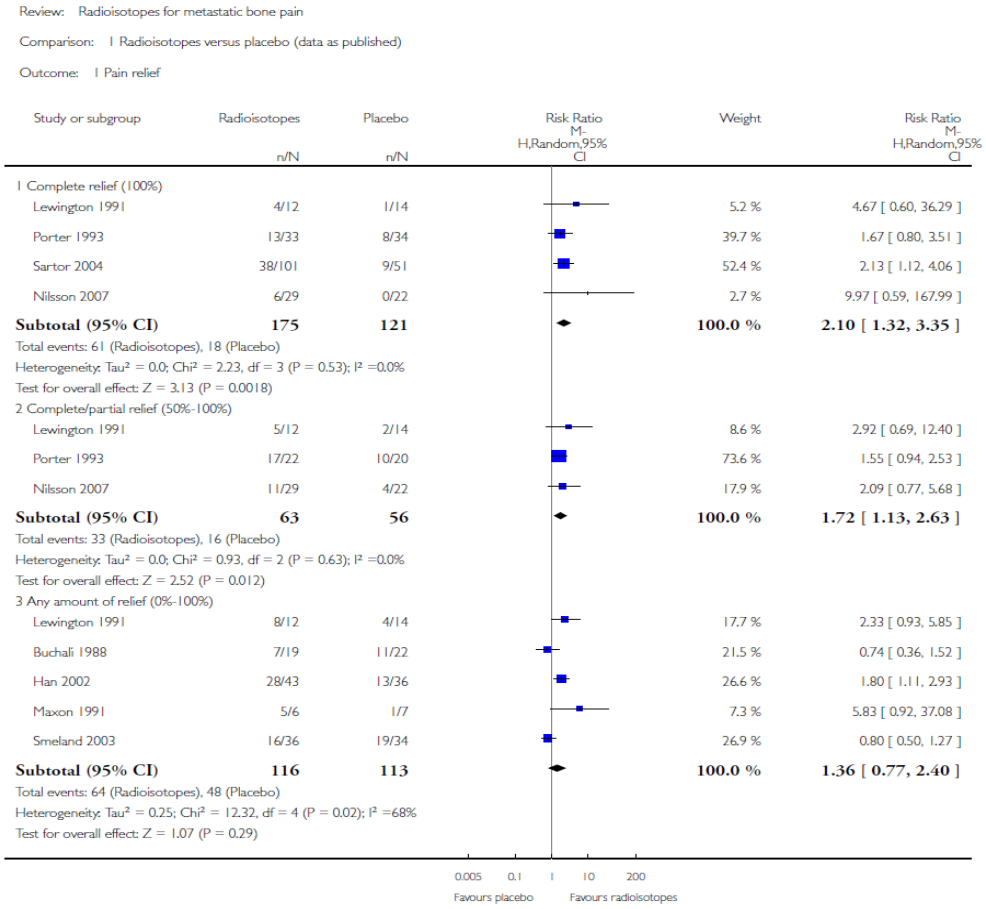


3.2. Radionuclides for painful bone metastases

3.2.1. Radionuclides versus placebo

Pain relief: overall results for complete pain response, partial pain response and any amount of pain response (available data, no ITT-analysis) (extracted from the review of Roqué 2011)

Figure 25 – Radionuclides versus placebo: pain relief



Pain relief: overall results for complete pain response, partial pain response and any amount of pain response (ITT-analysis) (extracted from the review of Roqué 2011)

Figure 26 – Radionuclides versus placebo: pain relief

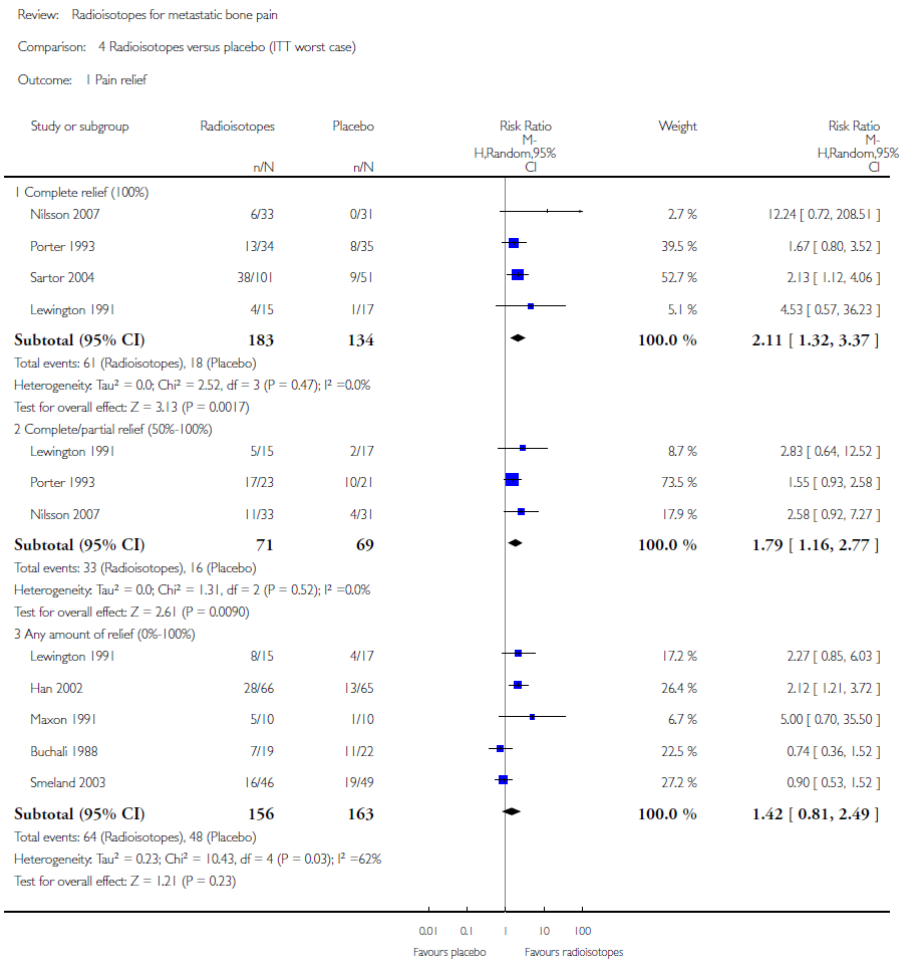


Figure 27 – 89Sr versus placebo: complete pain response (available data, no ITT-analysis)

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Lewington 1991	4	12	1	14	11.5%	4.67 [0.60, 36.29]
Porter 1993	13	33	8	34	88.5%	1.67 [0.80, 3.51]
Total (95% CI)		**45**		**48**	**100.0%**	**1.88 [0.94, 3.78]**
Total events	17		9			

Heterogeneity: Tau² = 0.00; Chi² = 0.87, df = 1 (P = 0.35); I² = 0%
Test for overall effect: Z = 1.78 (P = 0.07)

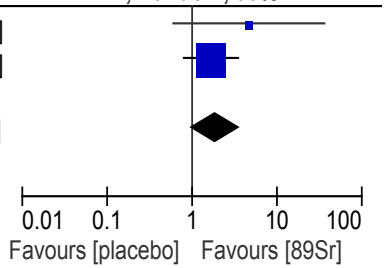


Figure 28 – 89Sr versus placebo: partial pain response

Study or Subgroup	89Sr Events	Total	placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Lewington 1991	5	12	2	14	10.4%	2.92 [0.69, 12.40]
Porter 1993	17	22	10	20	89.6%	1.55 [0.94, 2.53]
Total (95% CI)		**34**		**34**	**100.0%**	**1.65 [1.04, 2.63]**
Total events	22		12			

Heterogeneity: Tau² = 0.00; Chi² = 0.72, df = 1 (P = 0.40); I² = 0%
Test for overall effect: Z = 2.10 (P = 0.04)

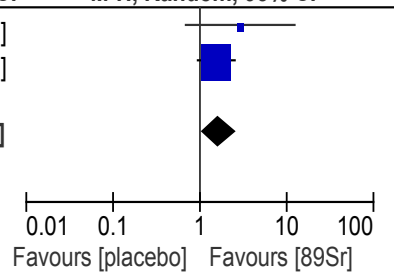


Figure 29 – 89Sr versus placebo: any pain response

Study or Subgroup	89Sr Events	89Sr Total	placebo Events	placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Buchali, 1988	7	19	11	22	31.9%	0.74 [0.36, 1.52]
Lewington 1991	8	12	4	14	24.9%	2.33 [0.93, 5.85]
Smeland 2003	16	36	19	34	43.1%	0.80 [0.50, 1.27]
Total (95% CI)		**67**		**70**	**100.0%**	**1.01 [0.55, 1.86]**
Total events	31		34			

Heterogeneity: Tau² = 0.16; Chi² = 4.68, df = 2 (P = 0.10); I² = 57%
Test for overall effect: Z = 0.05 (P = 0.96)

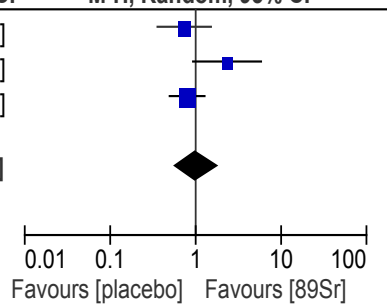


Figure 30 – 89Sr versus placebo: complete pain response (ITT-analysis)

Study or Subgroup	89Sr Events	89Sr Total	placebo Events	placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Lewington 1991	4	15	1	17	11.3%	4.53 [0.57, 36.23]
Porter 1993	13	34	8	35	88.7%	1.67 [0.80, 3.52]
Total (95% CI)		**49**		**52**	**100.0%**	**1.87 [0.93, 3.77]**
Total events	17		9			

Heterogeneity: Tau² = 0.00; Chi² = 0.81, df = 1 (P = 0.37); I² = 0%
Test for overall effect: Z = 1.76 (P = 0.08)

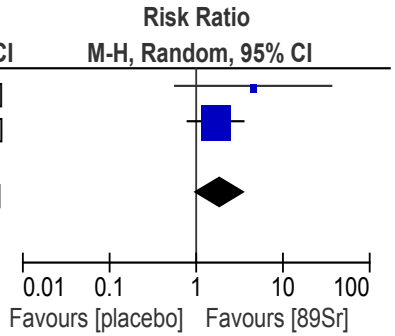


Figure 31 – 89Sr versus placebo: partial pain response

Study or Subgroup	89Sr Events	89Sr Total	placebo Events	placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Lewington 1991	5	15	2	17	10.5%	2.83 [0.64, 12.52]
Porter 1993	17	23	10	21	89.5%	1.55 [0.93, 2.58]
Total (95% CI)		**38**		**38**	**100.0%**	**1.65 [1.02, 2.68]**
Total events	22		12			

Heterogeneity: Tau² = 0.00; Chi² = 0.61, df = 1 (P = 0.43); I² = 0%
Test for overall effect: Z = 2.04 (P = 0.04)

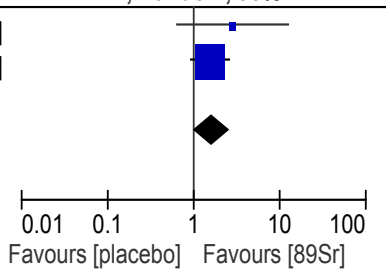
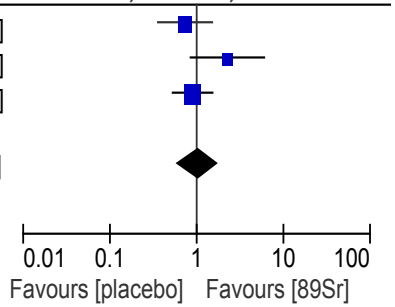


Figure 32 – 89Sr versus placebo: any response

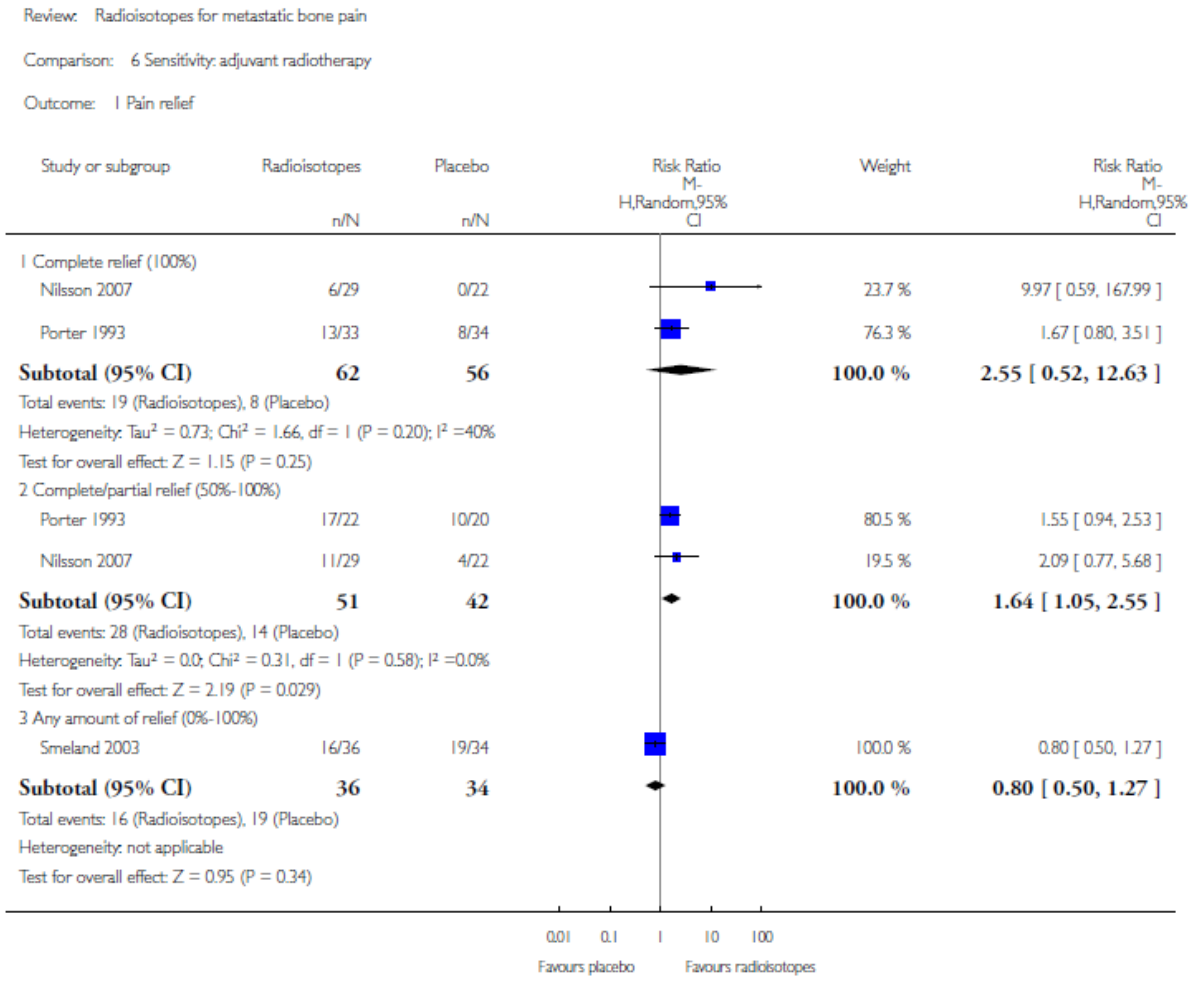
Study or Subgroup	89Sr Events	89Sr Total	placebo Events	placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Buchali, 1988	7	19	11	22	33.0%	0.74 [0.36, 1.52]
Lewington 1991	8	15	4	17	22.4%	2.27 [0.85, 6.03]
Smeland 2003	16	46	19	49	44.7%	0.90 [0.53, 1.52]
Total (95% CI)		**80**		**88**	**100.0%**	**1.03 [0.60, 1.79]**
Total events	31		34			

Heterogeneity: Tau² = 0.10; Chi² = 3.54, df = 2 (P = 0.17); I² = 43%
Test for overall effect: Z = 0.12 (P = 0.90)



Pain relief: radionuclides adjuvant to radiotherapy including complete pain response, partial pain response and any response (available data, no ITT-analysis) (extracted from the review of Roqué 2011)

Figure 33 – Radionuclides adjuvant to radiotherapy: complete pain response (Roqué 2011)



Adverse events: overall results for leucocytopenia, thrombocytopenia and anemia (extracted from the review of Roqué 2011)

Figure 34 – Adverse events: Overall results for leucocytopenia, thrombocytopenia and anemia (Roqué 2011)

Review: Radioisotopes for metastatic bone pain

Comparison: 1 Radioisotopes versus placebo (data as published)

Outcome: 7 Side effects grade III-IV

Study or subgroup	Radioisotopes n/N	Placebo n/N	Risk Difference M-H,Random,95% CI	Weight	Risk Difference M-H,Random,95% CI
1 Leucocytopenia					
Porter 1993	7/67	0/57		9.6 %	0.10 [0.03, 0.18]
Buchali 1988	3/22	1/17		1.9 %	0.08 [-0.10, 0.26]
Sartor 2004	5/93	0/47		18.0 %	0.05 [0.00, 0.11]
Serafini 1998	6/71	0/36		10.1 %	0.08 [0.01, 0.16]
Subtotal (95% CI)	**253**	**157**		**39.5 %**	**0.07 [0.04, 0.11]**
Total events: 21 (Radioisotopes), 1 (Placebo)					
Heterogeneity: Tau² = 0.0; Chi² = 1.26, df = 3 (P = 0.74); I² =0.0%					
Test for overall effect: Z = 3.84 (P = 0.00012)					
2 Thrombocytopenia					
Lewington 1991	2/12	1/15		1.0 %	0.10 [-0.15, 0.35]
Buchali 1988	11/22	4/17		0.7 %	0.26 [-0.03, 0.56]
Sartor 2004	3/93	0/47		23.3 %	0.03 [-0.02, 0.08]
Serafini 1998	1/71	0/36		21.8 %	0.01 [-0.04, 0.06]
Subtotal (95% CI)	**198**	**115**		**46.9 %**	**0.04 [-0.03, 0.11]**
Total events: 17 (Radioisotopes), 5 (Placebo)					
Heterogeneity: Tau² = 0.00; Chi² = 7.42, df = 3 (P = 0.06); I² =60%					
Test for overall effect: Z = 1.15 (P = 0.25)					
3 Anemia					
Sartor 2004	11/93	6/47		4.5 %	-0.01 [-0.13, 0.11]
Serafini 1998	5/71	1/36		9.1 %	0.04 [-0.04, 0.12]
Subtotal (95% CI)	**164**	**83**		**13.6 %**	**0.03 [-0.04, 0.09]**
Total events: 16 (Radioisotopes), 7 (Placebo)					
Heterogeneity: Tau² = 0.0; Chi² = 0.67, df = 1 (P = 0.41); I² =0.0%					
Test for overall effect: Z = 0.77 (P = 0.44)					
Total (95% CI)	**615**	**355**		**100.0 %**	**0.05 [0.02, 0.07]**
Total events: 54 (Radioisotopes), 13 (Placebo)					
Heterogeneity: Tau² = 0.00; Chi² = 9.55, df = 9 (P = 0.39); I² =6%					
Test for overall effect: Z = 3.67 (P = 0.00024)					
Test for subgroup differences: Chi² = 1.82, df = 2 (P = 0.40), I² =0.0%					

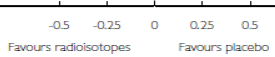


Figure 35 – Adverse events: 89 Sr for leucocytopenia

Study or Subgroup	89Sr Events	89Sr Total	placebo Events	placebo Total	Weight	Risk Difference M-H, Random, 95% CI
Buchali, 1988	3	22	1	17	15.6%	0.08 [-0.10, 0.26]
Porter 1993	7	67	0	57	84.4%	0.10 [0.03, 0.18]
Total (95% CI)		**89**		**74**	**100.0%**	**0.10 [0.03, 0.17]**
Total events	10		1			

Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.78); I² = 0%

Test for overall effect: Z = 2.74 (P = 0.006)

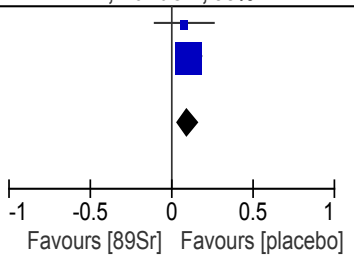


Figure 36 – Adverse events: 89 Sr for thrombocytopenia

Study or Subgroup	89Sr Events	89Sr Total	placebo Events	placebo Total	Weight	Risk Difference M-H, Random, 95% CI
Buchali, 1988	11	22	4	17	41.7%	0.26 [-0.03, 0.56]
Lewington 1991	2	12	1	15	58.3%	0.10 [-0.15, 0.35]
Total (95% CI)		**34**		**32**	**100.0%**	**0.17 [-0.02, 0.36]**
Total events	13		5			

Heterogeneity: Tau² = 0.00; Chi² = 0.81, df = 1 (P = 0.37); I² = 0%

Test for overall effect: Z = 1.76 (P = 0.08)

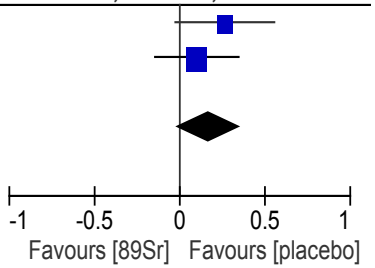
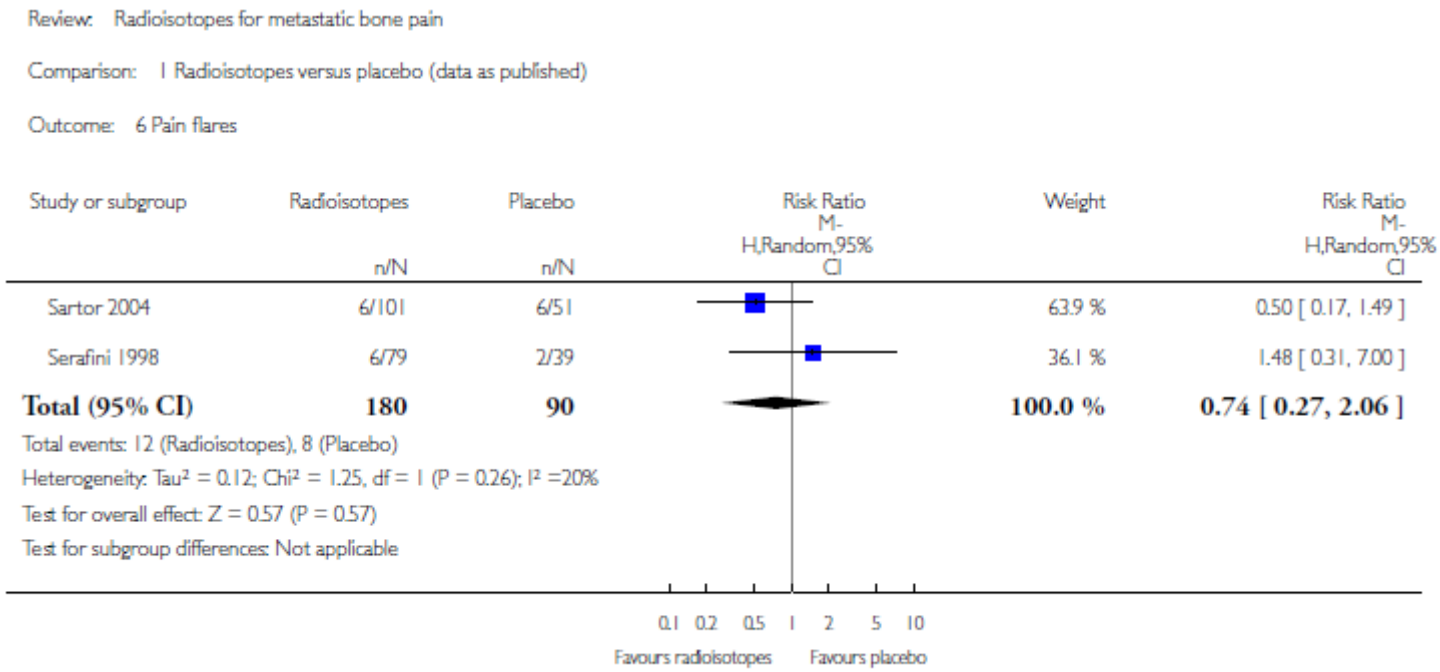


Figure 37 – Incidence of pain flares (Roqué 2011)



3.3. Bisphosphonates for painful bone metastases

Figure 38 – Clodronate versus placebo: patients without pain at 12 months

Study or Subgroup	Treatment Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kylmälä 1997	4	28	4	29	4.2%	1.04 [0.29, 3.74]
Lahtinen 1992	87	168	77	168	81.9%	1.13 [0.91, 1.41]
Tubiana-Hulin 2001	23	69	13	68	13.9%	1.74 [0.96, 3.15]
Total (95% CI)		**265**		**265**	**100.0%**	**1.21 [0.99, 1.49]**
Total events	114		94			

Heterogeneity: Chi² = 1.90, df = 2 (P = 0.39); I² = 0%
Test for overall effect: Z = 1.82 (P = 0.07)

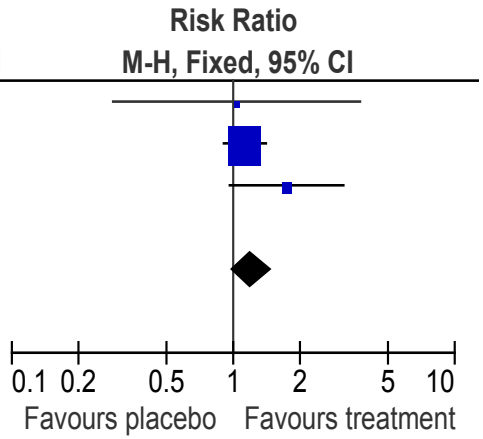


Figure 39 – Clodronate versus placebo: patients without analgesic at 12 months

Study or Subgroup	Treatment Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kylmälä 1997	4	28	4	29	26.2%	1.04 [0.29, 3.74]
Tubiana-Hulin 2001	23	69	11	68	73.8%	2.06 [1.09, 3.89]
Total (95% CI)		**97**		**97**	**100.0%**	**1.79 [1.02, 3.15]**
Total events	27		15			

Heterogeneity: Chi² = 0.88, df = 1 (P = 0.35); I² = 0%
Test for overall effect: Z = 2.03 (P = 0.04)

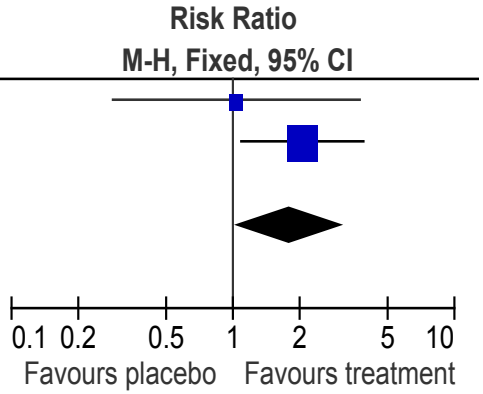


Figure 40 – Bisphosphonates: partial pain relief

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Conte 1996	83	152	80	143	42.9%	0.98 [0.79, 1.20]
Ernst 2003	34	115	27	112	14.2%	1.23 [0.80, 1.89]
Meulenbeld 2012	91	291	84	301	42.9%	1.12 [0.87, 1.44]
Total (95% CI)		**558**		**556**	**100.0%**	**1.07 [0.92, 1.25]**
Total events	208		191			

Heterogeneity: Chi² = 1.30, df = 2 (P = 0.52); I² = 0%
Test for overall effect: Z = 0.91 (P = 0.36)

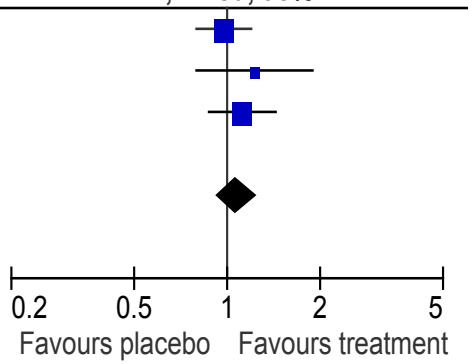


Figure 41 – Bisphosphonates: pain improvement (measured by scales)

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Daragon 1993	1.7	2	49	2	2.3	45	19.6%	-0.30 [-1.17, 0.57]
O'Rourke 1995	2.7	0.6	19	3.4	0.8	21	78.8%	-0.70 [-1.14, -0.26]
Piga 1998	5.1	4.8	27	6.4	5.9	23	1.6%	-1.30 [-4.32, 1.72]
Total (95% CI)			**95**			**89**	**100.0%**	**-0.63 [-1.02, -0.24]**

Heterogeneity: Chi² = 0.84, df = 2 (P = 0.66); I² = 0%
Test for overall effect: Z = 3.20 (P = 0.001)

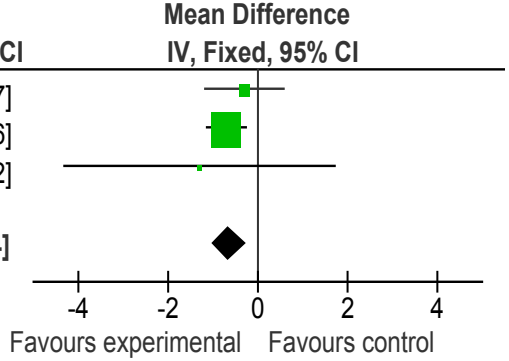


Figure 42 – Bisphosphonates: withdrawal from therapy due to adverse events

Study or Subgroup	Treament Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Conte 1996	1	143	0	152	0.7%	3.19 [0.13, 77.61]
Dearnaly 2003	13	155	2	156	3.3%	6.54 [1.50, 28.51]
Ernst 1992	1	20	0	20	0.7%	3.00 [0.13, 69.52]
Hortobagyi 1996	3	185	0	195	0.8%	7.38 [0.38, 141.84]
Hultborn 1999	9	201	3	203	4.3%	3.03 [0.83, 11.03]
Kylmälä 1997	2	28	1	29	1.3%	2.07 [0.20, 21.58]
Saad 2002	38	214	29	208	36.5%	1.27 [0.82, 1.99]
Small 2003	12	180	13	194	12.5%	0.99 [0.47, 2.12]
Theriault 1999	36	182	30	189	37.2%	1.25 [0.80, 1.93]
Tripathy 2004	3	144	1	143	1.4%	2.98 [0.31, 28.30]
Tubiana-Hulin 2001	2	69	1	68	1.3%	1.97 [0.18, 21.23]
Total (95% CI)		**1521**		**1557**	**100.0%**	**1.41 [1.08, 1.85]**
Total events	120		80			

Heterogeneity: Tau² = 0.00; Chi² = 9.37, df = 10 (P = 0.50); I² = 0%

Test for overall effect: Z = 2.53 (P = 0.01)

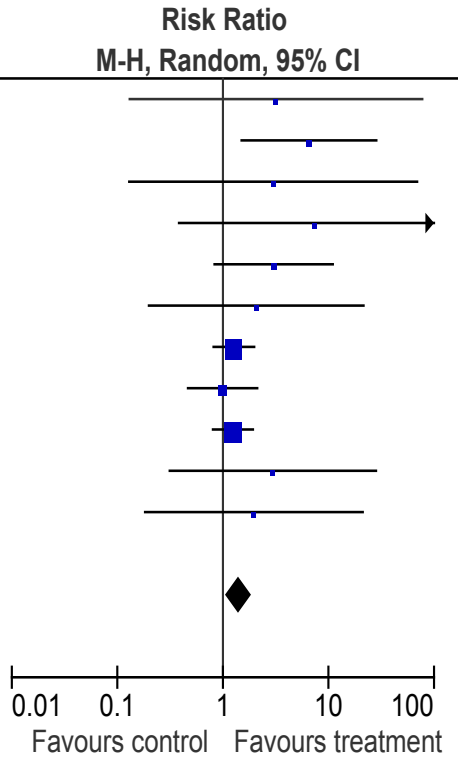


Figure 43 – Bisphosphonates: nausea

Study or Subgroup	Treatment Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kylmälä 1997	9	28	11	29	6.8%	0.85 [0.42, 1.73]
Lahtinen 1992	29	168	25	168	15.8%	1.16 [0.71, 1.89]
Saad 2002	77	214	77	208	49.3%	0.97 [0.76, 1.25]
Small 2003	50	180	43	194	26.1%	1.25 [0.88, 1.78]
Tripathy 2004	8	144	3	143	1.9%	2.65 [0.72, 9.78]
Total (95% CI)		**734**		**742**	**100.0%**	**1.10 [0.92, 1.32]**
Total events	173		159			

Heterogeneity: Chi² = 3.74, df = 4 (P = 0.44); I² = 0%
Test for overall effect: Z = 1.01 (P = 0.31)

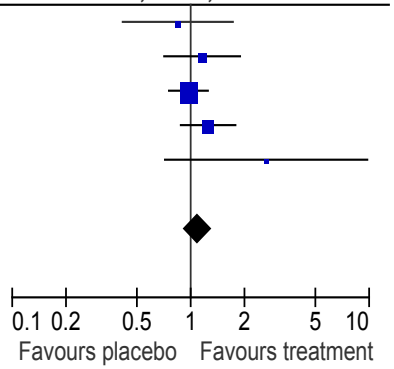
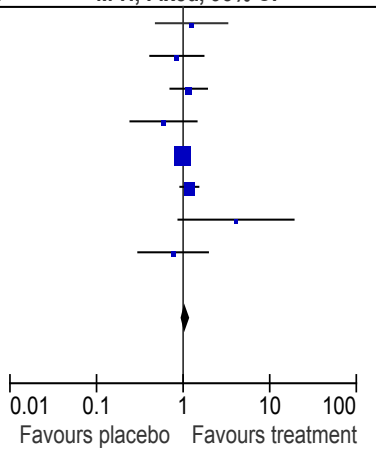


Figure 44 – Bisphosphonates: nausea and/or vomiting

Study or Subgroup	Treatment Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ernst 2003	9	115	7	112	2.8%	1.25 [0.48, 3.25]
Kylmälä 1997	9	28	11	29	4.2%	0.85 [0.42, 1.73]
Lahtinen 1992	29	168	25	168	9.8%	1.16 [0.71, 1.89]
O'Rourke 1995	10	59	6	21	3.5%	0.59 [0.25, 1.43]
Saad 2002	123	214	120	208	47.6%	1.00 [0.85, 1.17]
Small 2003	81	180	74	194	27.9%	1.18 [0.93, 1.50]
Tripathy 2004	8	144	2	147	0.8%	4.08 [0.88, 18.90]
Tubiana-Hulin 2001	7	69	9	68	3.5%	0.77 [0.30, 1.94]
Total (95% CI)		**977**		**947**	**100.0%**	**1.07 [0.94, 1.21]**
Total events	276		254			

Heterogeneity: Chi² = 7.09, df = 7 (P = 0.42); I² = 1%
Test for overall effect: Z = 0.97 (P = 0.33)



4. EVIDENCE TABLES

4.1. Antidepressants

Remark: No systematic review

Table 50 – Antidepressants: evidence table of randomized controlled trials

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
Kalso (1996)[8]	• Design: Double blind placebo controlled crossover design. • Sources of funding: Academy of Finland, Paulo Foundation, Centre of International Mobility • Setting: 1 hospital in Finland • Sample size:.crossover n_{total} = 15 patients.. • Duration:.10 weeks	• Eligibility criteria: o.Patients with moderate to severe neuropathic pain following the treatment for breast cancer and that previously took part in a questionnaire survey • Patient characteristics: o.Age (years) [median (Range)]: 56 (39-72); Time elapse from breast surgery (months) [median (Range)]: 45 (15-79); Type of surgery: 3/15 radical mastectomy, 12/15 breast conserving	• Intervention: Sustained release amitriptyline (AMI) with dose escalation from 25 mg to 100 mg (ceiling dose reach when adverse events appear) • Control: Placebo..	*Cross-over design: only combined results of 2 periods together presented* **Pain intensity** *VAS: 10 cm horizontal line marked 'no pain' to 'worst possible pain'* *VRS: 8-point verbal rating scale* *Median (range)* • At 50 mg vs placebo Ipsilateral arm VAS: AMI 1.9 (0-9.1) vs placebo 2.5 (0-9.2), ns VRS: AMI 2.6 (1-5) vs placebo 3.1 (1-8), ns Breast scar area VAS: AMI 1.8 (0-	**Adverse events** AMI caused significantly more tiredness, dry mouth, constipation and sweating.	• High risk of bias • Pain at breast and arm not reported because presented in graph without quantitative data in the paper

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
		surgery		5.1) vs placebo 2.6 (0-6.6), ns VRS: AMI 2.2 (1-5) vs placebo 2.3 (1-4), ns • At 100 mg vs placebo Ipsilateral arm VAS: AMI 0.5 (0-3.0) vs placebo 5.0 (0.-9.4), p<0.05 VRS: AMI 1.8 (1-4) vs placebo 3.0 (1-8), p<0.05 Breast scar area VAS: AMI 0.2 (0-4.3) vs placebo 3.1 (0.7-5.5), ns VRS: AMI 1.9 (1-5) vs placebo 2.7 (1-6), p<0.05 **Pain relief** *VRS: 5-point verbal rating scale* *Median (range)* • At 50 mg vs placebo Ipsilateral arm VRS: AMI 3 (1-5) vs placebo 1 (1-5), ns		

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
				Breast scar area VRS: AMI 3 (1-5) vs placebo 1 (1-5), ns • At 100 mg vs placebo Ipsilateral arm VRS: AMI 3 (2-5) vs placebo 2 (1-4), p<0.05 Breast scar area VRS: AMI 3 (2-5) vs placebo 1.5 (1-5), p<0.05		
Mercadante (2002)[9]	• Design: randomized, double-blind, placebo controlled, cross over design after 1 week without wash-out period • Sources of funding: not mentioned • Setting: 1 centre in Italy • Sample size: n=16 • Duration: 2.weeks	• Eligibility criteria: o Cancer patients with moderate neuropathic pain on systemic morphine therapy and no longer receiving oncologic treatment. • Patient characteristics: o Age (years) [mediane (range)]: 65.5 (57-80); Sexe (M/F): 10/6; Neuropathy type: sacral 7/16, brachial 4/16,	• Intervention: 3 first days,.25 mg of amitrityline (AMI). Following 4 days, 50 mg AMI • Control: placebo...	**Pain intensity** *Numerical scale from 0 to 10* *Mean 95%CI* • At 1 week AMI 4.7 (3.9-5.6) vs placebo 5.4 (4.9-6.0), ns • At 2 weeks AMI 4.9 (3.9-6.0) vs placebo 6.1 (5.4-6.9), ns **Pain relief** *Scale from 0 to 3 (not at all, slight, a lot, awful)* *Mean 95%CI*	**Adverse events** *Scale from 0 to 3 (not at all, slight, a lot, awful)* *Mean 95%CI* • Drowsiness AMI 1.6 (1.2-2.0) vs placebo 0.8 (0.4-1.4), p=0.036 • Confusion AMI 0.6 (0.2-1.1) vs placebo 0.06 (0-0.2), p=0.003 • Dry mouth AMI 1.8 (1.4-2.3) vs placebo 1.3 (0.9-1.8), p=0.034	• Unclear risk of bias • Include all type of cancer • No wash out period before the cross-over

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
		lumbar 3/16, chest wall 1/16, cervical-brachial 1/16		• At 2 weeks AMI 3.5 (1.7-5.3) vs placebo 2.3 (0.3-4.4), ns **Opioids consumption** In mg (mean 95% CI) AMI 104 (66.3-142.4) vs placebo 109 (75.7-142.3), ns **Quality of live** *Spitzer's quality of live index* No difference	• Constipation AMI 2.5 (1.9-3.0) vs placebo 2.5 (2.0-3.0), ns	
Reuben (2004)[10]	• Design: Double-blind randomized placebo controlled trial • Sources of funding:.Rays of Hope Foundation and Wyeth-Ayerst Laboratories • Setting:.USA • Sample size: intervention (n=48), control (n=47) • Duration:.2 weeks	• Eligibility criteria: o .Adult patients with partial or modified radical mastectomy with axillary lymph node dissection.. • Patient characteristics: o .Age (years) [means ± SD]: Venlafaxine 46 ± 8 vs placebo 45 ± 7; Type of surgery (number of partial mastectomy):.	• Intervention: Extended-release venlafaxine 75 mg during 2 weeks started the night prior surgery • Control:.Placebo..	*Results are not in ITT (reasons for drop-out comparable in 2 groups)* **Pain intensity** *Vas pain score (from 0-10) – mean ± SD* • At day 1 o At rest Venlafaxine: 1.8 ±1.0 vs placebo 2.1 ±1.6, ns	**Chronic pain and symptoms at 6 months** *Number of patients* • Chronic pain Venlafaxine: 14/48 vs placebo 34/47, p=0.0001 • Phantom pain Venlafaxine: 9/48 vs placebo 10/47, ns • Edema Venlafaxine: 19/48	• Low risk of bias

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
		Venlafaxine 25/47 vs placebo 28/48; Chemotherapy:. Venlafaxine 28/47 vs placebo 32/48; Radiation therapy:. Venlafaxine 37/47 vs placebo 39/48; No significant differences between groups with respect to age, height, weight, procedure, procedure time, adjuvant chemotherapy, or radiation treatment		o At movement Venlafaxine: 2.7 ±1.4 vs placebo 3.0 ±1.8, ns • At 1 month o At rest Venlafaxine: 1.6 ±1.0 vs placebo 1.7 ±1.2, ns o At movement Venlafaxine: 2.7 ±1.1 vs placebo 2.4 ±1.4, ns • At 6 months o At rest Venlafaxine: 1.1 ±0.9 vs placebo 1.5 ±1.0, ns o At movement Venlafaxine: 2.3 ±1.4 vs placebo 3.2 ±1.8, p=0.01 (note: overlap of standard deviations) **Analgesic use** • At day 1 *Mg of morphine* Venlafaxine: 22.8 ±5.8 vs placebo	vs placebo 16/47, ns • Decreased sensation Venlafaxine: 31/48 vs placebo 34/47, ns **Side-effects**: not reported	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
				23.4 ±6.8, ns • At 6 months *Number of patient* Venlafaxine: 8/48 vs placebo 26/47, p=0.002		
Tasmuth (2002)[11]	• Design:.randomized, double-blind, cross-over trial.. • Sources of funding:.Helsinki University Central Hospital Research Funds • Setting:.1 centre in Finland.. • Sample size:.n=15 • Duration: starting dose 2 weeks, increased dose 2 weeks, followed by a 2 weeks wash-out period. Same scheme after cross-over.	• Eligibility criteria: o.Patients with moderate to severe neuropathic pain after a modified radical mastectomy or breast-conserving surgery and that previously took part in a questionnaire survey • Patient characteristics: o Age (years) [median (Range)]: 55 (37-72); Time elapse from breast surgery (months) [median (Range)]: 20 (18-26); Type of surgery: 5/15 radical	• Intervention: Sustained release venlafaxine (AMI) with dose escalation from 37.5 mg to 75 mg (ceiling dose reach when adverse events appear) • Control: Placebo..	*Cross-over design: only combined results of 2 periods together presented. Results were collected every two weeks. For retrospective results on pain intensity and pain relief during last 3 days of week preceding evaluation see publication* **Pain intensity** *VAS: 100 mm horizontal line marked 'no pain' to 'worst possible pain'* *VRS: 8-point verbal rating scale* *Median (range)* • At 37.5 mg vs	**Adverse events** Dry mouth is increased in venlafaxine	• High risk of bias

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
		mastectomy, 8/15 breast conserving surgery...		placebo VAS: Venlafaxine 13 (0-62) vs placebo 8 (0-67), ns VRS: Venlafaxine 0 (0-4) vs placebo 1 (0-4), ns • At 75 mg vs placebo VAS: Venlafaxine 0 (0-35) vs placebo 3.1 (0.6-70), ns VRS: Venlafaxine 0 (0-4) vs placebo 1 (0-2), ns **Pain relief** *VAS* *VRS: 5-point verbal rating scale* *Median (range)* • At 37.5 mg vs placebo VAS: Venlafaxine 20 (0-100) vs placebo 0 (0-69), ns VRS: Venlafaxine 3 (1-5) vs placebo 1 (1-5), ns • At 75 mg vs placebo		

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
				VAS: Venlafaxine 42 (0-100) vs placebo 25 (0-100), ns VRS: Venlafaxine 1.5 (0-4) vs placebo 1 (0-3), ns		
Kautio (2008)[12]	• Design:.double-blind, randomized, placebo-controlled parallel group study • Sources of funding: Finnish Cancer Society and research funds of Helsinki University Central hospital • Setting: Departement of Oncology of the Helsinki University Central Hospital • Sample size: intervention (n=22), control (n=22) • Duration: 8 weeks	• Eligibility criteria: Cancer patients aged 20-65 years, with chemotherapy-induced neuropathy manifesting as numbness, tingling, or pain of at least moderate severity (≥ 3/10 on a numeric scale)(58% of patients with pain at baseline) • Patient characteristics: Age (years) [mean (range)]: 54 (35-69); Sexe (M/F): 12/32	• Intervention: Dose elevation from 10 mg amitriptyline up to 50 mg/day (if tolerated) • Control:.. Placebo	**Quality of live** EORTC QLQ-C30 Global health score • At baseline Amitriptyline 48 vs placebo 62 • At 4 weeks Amitriptyline 62 vs placebo 54 • At 8 weeks Amitriptyline 55 vs placebo 49 p=0.038 Results for **numeric scale on pain** not given.	**Global improvement of neuropathic symptoms** Five-point verbal rating scale Mean ± SD At 8 weeks Amitriptyline 3.4±3.6 vs placebo 1.9±3.1 (ns)	• High risk of bias
Kautio (2009)[13]	• Design:.double-blind, randomized, placebo-controlled parallel group study • Sources of funding: Finnish Cancer	• Eligibility criteria: Cancer patients aged 20-75 years without previous neuropathy who were starting their first neurotoxic	• Intervention: Dose elevation from 25 mg/week amitriptyline up to 100 mg/day (if tolerated)	**Severity of sensory neuropathy** *National Cancer institute Common Toxicity Criteria*	**Side effects with stable dose** *Four-point verbal scale (none, mild, moderate, severe*) • Dry mouth	• High risk of bias

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
	Society and research funds of Helsinki University Central hospital • Setting: Departement of Oncology of the Helsinki University Central Hospital • Sample size: intervention (n=58), control (n=56) • Duration: 27 weeks	chemotherapy with vinca alcaloids, platinum derivatives or taxanes • Patient characteristics: Age (years) [mean (range)]: amitriptyline 55 (25-75) vs placebo 57 (26-75); Sexe (M/F): amatriptyline 19/39 vs placebo 13/43	• Control:.. Placebo	*(NCI-CTC)* • At 3 cycles (mean time 9 weeks) Amitriptyline 31/54 vs placebo 28/43 • At 6 cycles (mean time 18 week) Amitriptyline 24/43 vs placebo 20/36 • At 9 cycles (mean time 27 week) Amitriptyline 14/21 vs placebo 17/20 **Severity of motor neuropathy** *NCI-CTC* • At 3 cycles Amitriptyline 12/54 vs placebo 13/43 • At 6 cycles Amitriptyline 14/44 vs placebo 15/36 • At 9 cycles Amitriptyline 3/21 vs placebo 6/20 Rem: no significant difference in NCI-	more severe in the maitriptyline p<0.001 • Tremor more severe in the maitriptyline p=0.034 • Not statistical differences for other sides effects • No statistical association between the severity of the side-effects and the drug concentration	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
				CTC scoring between amitriptyline and placebo. The intensity of neuropathy was mild in the majority of the cases **Quality of live** EORTC QLQ-C30 no significant difference		
Mishra (2012)[16]: see Evidence tables anticonvulsants	cfr	cfr	cfr	cfr	cfr	cfr
Amr (2010)[14]: see Evidence tables anticonvulsants	cfr	cfr	cfr	cfr	cfr	cfr

4.2. Anticonvulsants

Remark: The systematic reviews were only used as a source for primary studies. No separate analyses were performed in these reviews on the effectiveness of anticonvulsants for cancer-related pain.

Table 51 – Anticonvulsants: evidence table of randomized controlled trials

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
Amr	• Design:	• Eligibility criteria:	All drugs were	**Pain relief (after**	**Analgesic use**	• risk of bias:

(2010)[14]	prospective, randomized, double blind design • Sources of funding: not mentioned • Setting: Egypt • Sample size: total n=150 • Duration: up to 6 months after treatment	patients scheduled for partial or radical mastectomy with axillary dissection Exclusion criteria: ASA physical status >2, patn taking antidepressants or anticonvulsants, NSAIDs or opioid analgesics, patn with hepatic or renal impairment, history of diabetes or other neuropathic disease, allergies for any used drugs • Patient characteristics: no sign diff at baseline o Age (mean, SD): group 1 (venl) 45y±6, group 2 (gab) 43y±5y, group 3 (plac) 44y±8 o Patn who had chemotherapy: group 1 (venl) 42/50, group 2 (gab) 34/50, group 3 (plac) 39/50 o Patn who had radiotherapy: group 1 (venl) 17/50, group 2	administered 10 days postoperatively, starting the night before surgery. • Intervention: o Group 1 (n=50): venlafaxine extended release 37.5mg/d, once daily + 1 placebo capsule (identical in appearance with gab) o Group 2 (n=50): gabapentin 300mg/d, once daily+ 1 placebo capsule (identical in appearance with ven) • Control: group 3 placebo (n=50): 2 capsules sugar once daily, during 10 postoperative days • Primary outcomes: pain scores at rest and movement (abduction of the arm by 90 degrees)(VAS) at 4,	**movement)(mean not given):** • during first 24h: overall decrease in pain score but no sign diff between the three groups • group 2 (gab) vs group 3 (plac): sign reduced at day 2 (p=0.0003), 3-10 day (p<0.0001) • group 1 (venl) vs group 3 (plac): sign reduced at day 8 (p=0.0002), day 9-10 (p<0.0001) • at 6 months: o group 1 (venl): 12±5 o group 2 (gab): 21±12 o group 3 (plac): 22±9 ➔ sign more reduced in group 1 (venl) (p<0.0001) **Pain relief (at rest):** no sign diff between groups during first 10days postoperatively	• analgesic requirement (intravenous morphine mean mg±SD) in recovery room: o group 1 (venl): 7±0.5 o group 2 (gab): 4.5±0.5 o group 3 (plac): 7±1.1 ➔ sign decrease in group 2 (gab) (p<0.0001) • time to first analgesic request: o group 1 (venl): 105±15min o group 2 (gab): 155±17min o group 3 (plac): 100±12min ➔ sign delay in group 2 (gab) (p<0.0001) • total morphine consumption in first 24h (mean mg±SD): o group 1 (venl): 21±1.5 o group 2 (gab): 13.5±0.5 o group 3 (plac): 22±2.1 ➔ sign reduced in group 2 (gab) (p<0.0001) • at 6 months: sign more patients use opioid analgesics in group 3 (p=0.02) and group 2 (gab) (p=0.03) vs group 1 (venl) (N= 18,17, 8 resp)	high • Authors' conclusion: Gabapentin decreased pain scores at movement, morphine and analgesic consumption in the acute phase but had no significant effect on the incidence of chronic pain except lower incidence of burning pain sensations 6 months later. Vanlafaxine anf gabapentin have equipotent effects, although gabapentin is more effective in reducing pain after movement. • Notes: no quantitative results of pain scores, small sample sizes

	(gab) 16/50, group 3 (plac) 20/50	12 and 24h postoperatively, daily from 2nd until 10th day postoperatively and at 6 months (via questionnaire) • Secondary outcomes: adverse events, medication use (morphine, codeine, paracetamol)	**Chronic pain (at 6 months)** • incidence of burning pain: ➔ sign decrease in group 1 (venl) vs group 3 (p=0.0018)(1/50 vs 11/50) ➔ no sign diff in group 2 vs group 3 (p=0.143)(6/50 vs 11/50) • stabbing or pricking sign reduced in group 1 (venl) vs group 2 (gab) (p=0.028)(7/50 vs 20/50) and 3 (p=0.003)(16/50 vs 20/50) • no significant differences between groups for throbbing, aching, tender or troublesome chronic pain	• codeine consumption day 2-10 (mean mg±SD): o group 1 (venl): 185mg±54 o group 2 (gab): 180mg±22 o group 3 (plac): 300mg±156 o sign reduced in group 1 (venl) and group 2 (gab) vs group 3 (p<0.0001) o paracetamol consumption day 2-10 (mean mg±SD): o group 1 (venl): 3305mg±2166 o group 2 (gab): 3105mg±1998 o group 3 (plac): 5216mg±2320 ➔ sign reduced in group 1 (venl) and group 2 (gab) vs group 3 (p<0.0001) **Adverse events** • about 50%: nausea, about 1/3: vomiting ➔ no sign diff between group 1 and 2 ➔ drowsiness and dizziness more common in group 1 and 2 vs group 3 (not sign)

Arai (2010)[15]	• Design: RCT • Sources of funding: not mentioned, conflict of interest not mentioned • Setting: Japan • Sample size: total n=52 • Duration: up to 7 days after treatment	• Eligibility criteria: cancer patn with neuropathic pain that was not completely controlled with opioids analgesics and NSAIDs Exclusion criteria: not mentioned • Patient characteristics: no sign diff at baseline o Age (mean, range): group Gab+Imi 65y (58-73), group Gab200 67.5y (64-70), group Gab400 69y (65.5-71.5), group Imi 65y (60.5-79) Daily opioid dose (mg/day)(mean, range): Gab+Imi 45 (30-60), group Gab200 55 (45-60), group Gab400 55 (30-60), group Imi 35 (22.5-120)	• Intervention: o group Imi (n=12): Imipramine 10mg/12h o Group gab200 (n=14): gabapentin 200mg/12h o Group Gab400 (n=12): gabapentin 400mg/12h • Control: Group Gab+Imi (n= 14): 200mg/12h gabapentin and 10mg/12h imipramine • Primary outcomes: average intensity of pain (0-10 numerical scale) at 1st visit and 7days after start medication, • Secondary outcomes: adverse events, medication use, other pain symptoms (shooting/lancinating pain)	**Pain relief (total pain score+ range)** • at baseline: o Group Gab+Imi: 7 (5-8) o group Gab200: 7 (5-8) o group Gab400: 6.5 (6-7) o group Imi: 7 (5-8) ➔ no sign diff between groups at baseline (p=0.970) **Pain relief (total pain score+ range)** • at 7days: o Group Gab+Imi: 2 (2-3) o group Gab200: 4.5 (3-6) o group Gab400: 4 (3-5) o group Imi: 5 (3-6.5) ➔ sign diff	**Analgesic use (opioid rescue dose at 7 days (mg/day))** o Group Gab+Imi: 8 (0-25) o group Gab200: 30 (25-30) o group Gab400: 25 (20-40) o group Imi: 25 (15-42.5) ➔ sign diff between groups at baseline (p=0.008) ➔ sign diff between group Gab+Imi and group Gab200 (p<0.05) **Adverse events:** o in all groups: incidence of mild drowsiness and nauseau but no sign diff between groups (p=0.559 and p=0.999) o in group Gab 400: additional incidence of mild and severe dizziness o 3 patn in group Gab400 discontuned treatment	• risk of bias: high • Authors' conclusion: The combination of low-dose gabapentin and imipramine alleviated more effectively cancer pain than gabapentin or imipramine alone, without severe adverse effects. • Notes: small sample sizes, no p-values on evolution over time

between groups (p=0.005)

➔ sign decreased pain score in group Gab+imi compared to Gab200 (p<0.05) and to group Imi (p<0.05)

Daily paroxysmal pain episodes

- at baseline
  - Group Gab+Imi: 4.5 (3-6)
  - group Gab200: 4 (4-5)
  - group Gab400: 5 (4-5)
  - group Imi: 4 (4-6)
  - ➔ no sign diff between groups at baseline (p=0.749)
- at 7days
  - Group Gab+Imi: 1

				(0-2) o group Gab200: 3 (3-4) o group Gab400: 3.5 (2.5-4.5) o group Imi: 4 (3-6) ➔ sign diff between groups at 7 days (p<0.001) ➔ group gab+imi sign diff from other groups (p<0.05)		
Fassoulaki (2002)[19]	• Design: RCT • Sources of funding: not mentioned, conflict of interest not mentioned • Setting: Greece • Sample size: total n=75 • Duration:	• Eligibility criteria: ASA physical status I or II female patients Exclusion criteria: body weight > 20% of ideal body weight, age > 59y, heart block, preoperative treatment with analgesics other than those determined by the protocol, sedatives, hypnotics, antidepressants, calcium channel blockers, patients who received chemotherapy or	Administration of drugs and placebo started evening before surgery and continued for 10days postoperatively. • Intervention: o Group 1 mexiletine (mex) (anti-arhytmica) (n= 21): 200mg/d, 3x per day+ 1 placebo capsule (identical in appearance with gab) o Group 2	• **Pain relief (after movement)** Mean VAS score during first 24h: o group 1 (mex): 26±24.3mm o group 2 (gab): 20±12.7mm o group 3 (plac): 30±25.7mm ➔ overall decrease in pain score but no sign diff between the	**Analgesic use** • analgesic requirement (intramuscular propoxyphene + paracetamol) during first 24h ➔ no sign diff between groups • time to first analgesic request o group 1 (mex): 22±15min o group 2 (gab): 33±18min o group 3 (plac): 25±19min ➔ no diff between groups	• risk of bias: high • Authors' conclusion: Mex and gab have equipotent effects in reducing analgesic requirement, although gab is more effective in reducing pain after movement. • Notes: no quantitative results of pain

up to 3 months after treatment	radiotherapy before surgery • Patient characteristics: no sign diff at baseline o Age (mean, SD): group mex 46y±5, group gab 42y±7y, group plac 45y±9 o Patn with modified radical mastectomy: group mex 6/20 (30%), group gab 8/22 (36%), group plac 7/24 (29%) o Patn who had chemotherapy: group mex 17/20 (85%), group gab 16/22 (73%), group plac 19/23 (83%) o Patn who had radiotherapy: group mex 7/20 (35%), group gab 5/22 (23%), group plac 10/24 (42%)	gabapentin (gab) (n=22): gabapentin 400mg/d, 3x per day + 1 placebo capsule (identical in appearance with mex) • Control: group 3 placebo (plac) (n=24): capsules identical in appearance of gab and mex, 3x per day • Primary outcomes: pain scores at rest and movement (abduction of the arm by 90 degrees)(VAS) at 0, 3, 6, 9 and 24h postoperatively, daily from 2nd until 10th day postoperatively and at 3 months (via questionnaire) • Secondary outcomes: adverse events, medication use (codeine, paracetamol)	three groups • at 3rd day postop: sign reduced in group 1 (mex) and group 2 (gab) compared to group 3 (plac) (mean not given; both p<0.05) • at 2nd, 4th, 5th day postop: sign reduced in group 2 (gab) compared to group 3 (plac) (mean not given; p<0.05) • no sign diff on other days (mean not given) • mean VAS score at 10th day: o group 1 (mex): 28±16.7mm o group 2 (gab): 25±20.8mm o group 3 (plac): 30±25.7mm ➔ no sign diff between 3 groups **Pain relief (at rest):** • mean VAS score	(p>0.05) • codeine consumption day 2-10: o group 1 (mex): 55mg±54 o group 2 (gab): 65mg±53 o group 3 (plac): 113mg±78 ➔ sign reduced in group 1 (mex) and group 2 (gab) vs group 3 (p=0.029) • paracetamol consumption day 2-10 o group 1 (mex): 2209mg±2178 o group 2 (gab): 2600mg±2130 o group 3 (plac): 4533mg±3120 ➔ sign reduced in group 1 (mex) and group 2 (gab) vs group 3 (p=0.029) • total paracetamol consumption: o group 1 (mex): 2305mg±2176 o group 2 (gab): 2600mg±2130 o group 3 (plac): 4992mg±3317 ➔ sign reduced in group 1 (mex) and group 2 (gab) (p=0.0085)	scores, small sample sizes

during first 24h:
- group 1 (mex): 9mm±12.4
- group 2 (gab): 5mm±8.2
- group 3 (plac): 7mm±8.6

➔ no sign diff between groups

- at day 3 postop: sign decrease in group 1 (mex) and group 2 (gab) compared to group 3 (plac) (both p<0.05)
- no sign diff on other days
- mean VAS score on 10th day postop:
  - group 1 (mex): 6±11.0mm
  - group 2 (gab): 9±12.4mm
  - group 3 (plac): 10±15.7mm

➔ no sign diff between 3

- at 3 months, number of patients requiring analgesics: similar in groups (data not provided):

Adverse events: not clearly reported

Chronic pain

- incidence of chronic pain (total) at 3 months:
  - group 1 (mex): 9/20 (45%)
  - group 2 (gab): 12/22 (54%)
  - group 3 (plac): 14/24 (58%)

➔ no sign diff between groups

- incidence of burning pain at 3 months:
  - group 1 (mex): 1/20
  - group 2 (gab): 1/22
  - group 3 (plac): 7/24

➔ sign increase in group 3 (p=0.033)
(no significant differences between groups for throbbing, aching, tender, stabbing/pricking or troublesome chronic pain)

			groups			
Mishra (2012)[16]	• Design: prospective, double blind, placebo-controlled RCT • Sources of funding: Instituta Research Grant of All India Institute of Medical Sciences, conflict of interest not mentioned • Setting: • Sample size: total n=120 • Duration: up to 4 weeks after treatment	• Eligibility criteria: patn with cancer having neuropathic pain Exclusion criteria: unstable cardiovascular, respiratory hepatic or haematological disease or psychological disorder, drug abuse • Patient characteristics: no results presented on age, sex, cancer treatment, no sign diff on Leeds assessment of Neuropathic Symptoms and Signs (LANSS)	In subsequent visit, irrespective of neuropathic symptoms if the patients had a VAS>3, immediate release morphine was given orally for rescue analgesia. • Intervention: o Group AT (Amitriptyline) (=AD)(n=30): 50mg/d for 1 week, weekly increase as fixed dose schedule 75mg/d (2nd week) and 100mg/d (3rd week), at bedtime o Group GB (gabapentin) (=AC) (n=30): 900mg/d for 1 week, weekly increase as fixed dose schedule 1200mg/d (2nd week), 1800mg/d (3rd	**Pain relief (global intensity of pain)** VAS 10 cm • At baseline o Group AT: mean 7.77 o Group GB: mean 7.5 o Group PG: mean 7.77 o Group PL: mean 7.47 ➔ No sign diff between all groups (p=0.491) • Over time (4weeks vs baseline) (mean, SD) o Group AT: from 7.77±1.0 to 3.23±0.70 o Group GB: from 7.5±1.1 to 3.07±0.80 o Group PG: from 7.77±0.81 to 2.5±0.70 o Group PL:	**Analgesic use (requirement of extra morphine)** • At second visit: o Group AT: 30% of patn required extra morphine o Group PL: 100% of patn required extra morphine o No results presented quantitatively for 2 other groups • In third visit: o Group AT: 46.7% of patn o Group GB: 23.3% of patn o Group PG: 16.7% of patn o Group PL: 100% of patn ➔ Increase in all groups (no p-values mentioned) • In fourth visit: o Group AT: 56.7% of patn o Group GB: 33.3% of patn o Group PG: 16.7% of	• risk of bias:? • Authors' conclusion: All antineuropathic drugs are effective in relieving neuropathic pain in patients with cancer but pregabaline has statistically and clinically significant morphine-sparing effects in relieving neuropathi cancer pain and neuropathic symptoms as compared to other antineuorpathic drugs. • Notes: not all results quantitatively presented, small sample sizes

	week) in 3 divided doses o Group PG (pregabalin) (=AC) (n=30): 150mg/day for one week, weekly increase as fixed dose schedule 300mg/d (2nd week), 600mg/d (3rd week) for one week in 2 divided doses • Control: group PL (placebo) (n=30): placebo capsules of gabapentin, amitryptiline, pregabalin) • Primary outcomes: global intensity of pain (VAS) (daily and averaged over 7 days) during 4 weeks, • Secondary outcomes: analgesic use (requirement of extra morphine), intensity of burning, schooting/lancinating, dysesthesia (numerical scale 0-10), adverse effects (mild, moderate,	from 7.47±1.0 to 3.4±0.66 ➔ Sign decrease over time in all groups ➔ In all 4 groups: VAS was sign less in every visit as compared to previous visit ➔ In 3rd visit: mean VAS in group PG sign lower than in group AT (p=0.003) and group PL (p=0.024) ➔ In 4th visit: mean VAS sign lower in group PG than in group GB (p=0.042)	patn o Group PL: 100% of patn ➔ All study drugs had morphine-sparing effect ➔ Morphine-sparing effect stat and clin sign with pregabalin **Other pain symptoms:** • Lancinating pain (evolution over time) o Group AT: from 73.3% to 56.7% of patn o Group GB: from 66.75% to 26.7% of patn o Group PG: from 70.05% to 3.3% of patn o Group PL: from 70.05% to 43.3% of patn ➔ In 4th visit: sign less patn with lancinating pain in group PG compared to group GB (p=0.026), group PL (p=0.004) and group AT (p=0.009) ➔ In 4th visit: sign less patn with lancinating pain in group GB compared to group AT (p=0.018) and group PL (p=0.095) • Dysesthesia (evolution

		severe), patient functional capacity (Eastern Co-operative Oncology Group ECOG), global satisfaction (Verbal Rating Scale, VRS) (at end of study)	over time): o Group AT: from 93.3% to?% of patn o Group GB: from 93.3% to 33.3% of patn o Group PG: from?% to 6.7% of patn o Group PL: from 66.7% to?% of patn ➔ In 1st visit: sign less patn with dysesthesia in group PL ➔ In 2nd visit: sign decrease in patn in group GB compared to group AT and group PL ➔ In 4th visit: sign less patn in group PG compared to group GB (p=0.021) and compared to group PL (p=0.014). Other group diff were non-sign. • Allodynia (evolution over time) o Group AT: from 2.10% to 1.10% of patn o Group GB: from 2.47% to 0.97% of patn o Group PG: from 2.80% to 1.13% of patn o Group PL: from 2.60% to 1.87% of patn ➔ In 1st visit: no sign diff

between groups (p=0.803)

➔ In 4th visit: decrease in % of patn greatest in group GB

- Burning pain (evolution over time)
  - o Group AT: from 4.7% to 2.74% of patn
  - o Group GB: from 4.0% to 1.47% of patn
  - o Group PG: from 4.87% to 1.37% of patn
  - o Group PL: from 4.17% to 2.87% of patn

  ➔ 1st visit: no sign diff between groups (p=0.756)

  Functional capacity
  - o Group AT: from 2.07% to % of patn
  - o Group GB: from 2.90% to % of patn
  - o Group PG: from 2.77% to % of patn
  - o Group PL: from 2.43% to % of patn

  ➔ In 1st visit: no sign diff between groups (p=0.680)

  ➔ In 4th visit: max improvement found in group PG and sign diff compared to other

					groups (p<0.001) **Adverse events** o Most common: somnolence, dizziness, dryness of mouth, nausea, constipation ➔ Gradual increase in all groups ➔ Group PG max number of patn only mild (score 1) compared to other groups (mild (score 2) or moderate (score3)) ➔ In group PL max number of patn with moderate and sign diff compared to other groups	
Caraceni (2004)[18]	• Design: multicenter, double-blind, placebo-controlled parallel-design RCT • Sources of funding: Pfizer Italy, Pfizer Spain and partially from a	• Eligibility criteria: patn with an active cancer lesion causing pain by infiltration or compression of nervous structures, age>18y, pain intensity>5 on numerical rating scale (0-10) in the 24-h period preceding screening visit, referred to neuropathic pain syndrome, regurlarly scheduled systemic opioid therapy	• Intervention: gabapentin group (n=79) started with two capsules per day (300mg gabapentin every 12 hours), increased to 4 capsules per day r (300mg+300mg+600 mg gabapentin) and subsequently to 6 capsules per day (600mg gabapentin every 8 hours). Dose increase could be on any study day. • Control: placebo group (n=41)	**Pain relief (average global pain intensity) (ITT-analysis)** • Gabapentin group: 4.60 (0.25 SE) • Placebo group: 5.45 (0.32 SE) ➔ Sign lower mean global pain score in gabapentin group (p=0.0250) ➔ Sensitivity analyses did not alter this result	**Other pain symptoms** • Shooting pain o Gabapentin group: 3.76 (0.33SE) o Placebo group: 4.31 (0.41 SE) ➔ No sign diff between both groups (p=0.1988) • Burning pain o Gabapentin group: 2.17 (0.40SE) o Placebo group: 2.32 (0.43 SE) ➔ No sign diff between both groups (p=0.6809) • Dysesthesias	• risk of bias: low • Authors' conclusion: A limited role of gabapentin as adjuvant to opioids for neuropathic cancer pain, although significant benefit could be seen in some patients. The association of 300mg gabapentin to the opioid drug

grant from the Associazione Italiana per la Ricerca sul Cancro, no conflict of interest
- Setting: Italy and Spain
- Sample size: total n=120
- Duration: 10-day trial

without sufficient analgesia with significant opioid-related side-effects, stable dose of opioid medication for at least 24h, life expectancy >30days, Karnofsky performance status>40.

Exclusion criteria: plasma creatinine >1.5mg/mL in association with creatinine clearance<60mL/min, previous or current gabapentin use, chemotherapy from 3 days before screening throughout the study, radiotherapy to the pain-producing lesion from 15days before screening throughout the study, hormone therapy could be started before the study but dose could not be changed afterwards

- Patient characteristics:
  - no sign diff at baseline for

received identical capsules and same treatment plan
- Primary outcomes: average pain intensity (VAS) at baseline and after 10days
- Secondary outcomes: other pain symptoms (shooting/lancinating pain, burning pain, dysesthesias, allodynia), adverse events, use of additional analgesics

  - Gabapentin group: 4.28 (0.26SE)
  - Placebo group: 5.24 (0.32 SE)
  - ➔ Sign diff between both groups: dysesthesias less severe in gabapentin group (p=0.0077)
- Number of episodes of lancinating pain
  - Gabapentin group: 4.91 (0.87SE)
  - Placebo group: 4.92 (1.07 SE)
  - ➔ No sign diff between both groups (p=0.9930)

Analgesic use

- Use of additional analgesic doses
  - Gabapentin group: 47.1%
  - Placebo group: 64.7%
  - ➔ Higher in placebo group but not stat sign (p=0.0999)
- Frequence of use of additional analgesic doses
  - Gabapentin group: 21.6% of follow-p days
  - Placebo group: 35.8% of follow-up days

regimen is usually safe but in frail patients with high opioid doses and complex drug regimens (benzodiazepines) a more cautious titration schedule is recommendable.
- Notes:

			age, sex, KPS, stabilized opioid daily dose but global pain intensity was higher in placebo group o presence of shooting pain, burning pain and dysesthesias similar in both groups, but allodynia and number of episodes more frequent in placebo group
			➔ More frequent in placebo group but not stat sign (p=0.0559) **Time-related pain analyses** • Average % of follow-up days per patient with PID>33% (=pain control) o Gabapentin group: 51.6% of follow-up days (SD 36.5%) o Placebo group: 37.8% of follow-up days (SD 38.8%) ➔ Sign higher in gabapentin group (p=0.039) • Time needed to reach PID>33% (=pain control): results on Kaplan-Meyer curves ➔ Higher number of patn in first days of treatment in gabapentin group (p=0.0048) **Adverse events:** • Treatment discontinuation o Gabapentin group: 6 (7.5%) o Placebo group: 3 (7.3%) • Most frequent side effects: mild to moderate somnolence and dizziness ➔ More common in

					gabapentin group (36.2% vs 17.0%)	
Rao (2007)[21]	• Design: multicenter, double-blind, placebo-controlled, cross-over RCT • Sources of funding: Public Health Services grants, conflict of interest not mentioned • Setting: USA • Sample size: total n=115 • Duration: 14weeks (two 6-week phases seperated by a 2-week "wash-out"	• Eligibility criteria: adult patn with duration >1month symptomatic chemotherapy-induced peripheral neuropathy due to neurotoxic chemotherapy, patn who were receiving chemotherapy or who had completed chemotherapy at start of study, symptom severity either a rating of >4 on Numercial Rating Scale or a score>1 on the Eastern Cooperative Oncology Group neuropathy scale, serum creatinine<1.5times the upper limit of normal and an estimated life expectancy of >6 months Exclusion criteria: patn with pre-existing symptomatic neuropathy due to other causes or were pregnant or lactating,	• Intervention: gabapentin followed by placebo (G/P) (n=57), gabapentin doses (300mg capsules) were increases over 3 weeks to a target dose of 9 capsules a day (2700mg gabapentin) • Control: placebo followed by gabapentin (P/G) (n=58) • Primary outcomes: average pain (NRS and ENS), adverse events (both assessed weekly) • Secondary outcomes: evaluation of CIPN related symptoms (World Health Organization classification for neuropathy related symptoms, the Short Form-McGill Pain Questionnaire, Brief Pain Inventory-Short Form, the Subjective Global Impression of Change, the	**Pain relief (average pain score)** • NRS scores for average daily pain (at baseline) o Group G/P: 4.3 o Group P/G: 3.6 ➔ No sign diff between groups at baseline (p=0.06) • NRS scores for average daily pain (at 6 weeks) o Group G/P: 3.3 o Group P/G: 3.0 ➔ No sign diff between groups at 6 weeks (p=0.8) • NRS scores for average daily pain (at 14 weeks) o Group G/P: 3.1 o Group P/G: 2.5	**Analgesic use** • Use of opioids (at baseline) ➔ No use of opioids at baseline in both groups • Use of opioids (at 6 weeks) o Group G/P: 14% o Group P/G: 12% ➔ No sign diff between groups (p=0.8) • Use of opioids (at 14 weeks) o Group G/P: 9% o Group P/G: 12% ➔ No sign diff between groups (p=1.0) • Use of nonopioid analgesics (at baseline) o Group G/P: 33% o Group P/G: 36% • Use of nonopioid analgesics (at 6weeks) o Group G/P: 33% o Group P/G: 50% • Use of nonopioid analgesics (at 14 weeks) o Group G/P: 23% o Group P/G: 31% **Adverse events (grade >2)** • At baseline ➔ No adverse events at	• risk of bias: low • Authors' conclusion: The findings suggest a lack of benefit to gabapentin use to treat CIPN-related symptoms. A statistically significant and gradual decline in the severity of CIPN-related pain in all patients, irrespective if therapy received. • Notes:

period)	patn who were using antidepressants, opioids, adjuvant analgesic agents, topical analgesics and amifostine • Patient characteristics: o Age: mean 59y (28-84) in group G/P, mean 60y (25-80) in group P/G o Chemotherapy: 47% active and 53% discontinued or completed in group P/G, 53% active and 47% discontinued or completed in group G/P	Symptom Distress Scale, the Profile of Mood States Short Form and a Quality of Life Uniscale), assessed at baseline an at the end of 6, 8 and 14 weeks	➔ No sign diff between groups at baseline (p=0.2) • ENS scores for average daily pain (at baseline) o Group G/P: 1.9 o Group P/G: 2.0 ➔ No sign diff between groups at baseline (p=0.7) • ENS scores for average daily pain (at 6weeks) o Group G/P: 1.7 o Group P/G: 1.8 ➔ No sign diff between groups at 6 weeks (p=0.3) • ENS scores for average daily pain (at 14weeks) o Group G/P: 1.5 o Group P/G:	baseline in both groups • at 6weeks o Group G/P: 44 o Group P/G: 50 • No sign diff between both groups (p=0.2) • at 14 weeks o Group G/P: 29 o Group P/G: 31 ➔ No sign diff between both groups (p=0.7) **Secondary outcomes** ➔ No sign diff between groups at any time point for SDS, McGill Pain Rating Index, BPI, QOL Uniscale, SGI ➔ McGill Pain Rating Index score at 6 weeks was lower in G/P group (17.6 vs 19.9, p=0.03)

		1.5 ➔ No sign diff between groups at 14 weeks (p=0.7) • NRS scores for worst pain (at baseline) o Group G/P: 5.0 o Group P/G: 4.7 ➔ No sign diff between groups at baseline (p=0.5) • NRS scores for worst pain (at 6 weeks) o Group G/P: 4.4 o Group P/G: 4.0 • No sign diff between groups at baseline (p=0.8) • NRS scores for worst pain (at 14 weeks) o Group G/P: 4.2 o Group P/G: 3.2	

				➔ No sign diff between groups at baseline (p=0.05)		
Keskinbora (2007)[20]	• Design: randomised, single center, open trial • Sources of funding: not mentioned, conflict of interest not mentioned • Setting: Turkey • Sample size: total n=75 • Duration: 13 days	• Eligibility criteria: patn having sufficient relief of the nociceptive but not the neuropathic component of cancer pain while receiving ongoing opioid treatment without significant opioid-related side effects, pain intensity ≥4 on a numerical rating scale ranging from 0-10, a Karnofsky score of more than 60 Exclusion criteria: unable to take medication orally, currently receiving oncologic treatment, plasma creatinine >1.5mg/ml or creatinine clearance <60ml/min, patn taking nonopioid analgesics and other adjuvant drugs • Patient	• Intervention: gabapentin as adjuvant to ongoing opioid treatment (n=38), 100mg 3 times daily for patn>60years and 300mg 3 times daily for patients<60years, doses titrated up to 3600mg/day • Control: opioid treatment alone (n=37), doses increased incrementally according to WHO analgesic ladder • Primary outcomes: change in pain intensity measured by a 0-10 numerical scale (at baseline, day 4 and day 13) • Secondary outcomes: presence or absence of allodynia, consumption of study drugs and need for rescue	**Pain relief (change in pain intensity) for burning pain** • at baseline: no diff between groups (p=0.451) • on 4th day: o gabapentin group: sign decrease compared to baseline (p=0.0001) o opioid group: sign decrease compared to baseline (p=0.0001) • on 13th day o gabapentin group: sign decrease compared to baseline (p=0.0001) o opioid group: sign decrease compared to baseline (p=0.0001)	**Other pain symptoms (allodynia)** • at baseline: no sign diff between groups (p=0.26) • on 4th day: o gabapentin group: sign decrease compared to baseline (p=0.002) o opioid group: no sign diff compared to baseline ➔ no sign diff between groups (p=0.08) • on 13th day o gabapentin group: sign decrease compared to baseline (p=0.0001) o opioid group: sign diff compared to baseline (p=0.004) ➔ no sign diff between groups (p=0.16) **Analgesic use** ➔ no reporting per group **Adverse events** ➔ no adverse events requiring discontinuation of	• risk of bias: high • Authors' conclusion: Our results suggest that better results on burning and shooting pain, allodynia can be obtained by gabapentin and an opioid combination in neuropathic cancer pain. • Notes: small sample size, drop-outs, focus on shooting and burning pain

	characteristics: o Age: mean 57.55±14.82y in gabapentin group, mean 52.28±16.27y in opioid group	analgesics, adverse events	➔ no sig diff between 4th and 13th day in gabapentin group (p>0.05) ➔ sign diff between 4th and 13th day in opioid group (p<0.001) ➔ mean pain intensity sign higher on 4th and 13th day in opioid group (both p<0.0001) ➔ absolute decrease in NRS scores sign higher in gabapentin group (-7.39±2.86 vs -5.78±2.35, p=0.018) **Pain relief (change in pain intensity) for shooting pain** • at baseline: no diff between groups (p=0.717) • on 4th day: o gabapentin group: sign decrease	treatment in both groups ➔ sign lower rate of adverse events in gabapentin group (p=0.015)	

			compared to baseline (p=0.0001) o opioid group: sign decrease compared to baseline (p=0.0001) • on 13th day: o gabapentin group: sign decrease compared to baseline (p=0.0001) o opioid group: sign decrease compared to baseline (p=0.0001) ➔ no sig diff between 4th and 13th day in gabapentin group (p>0.05) ➔ sign diff between 4th and 13th day in opioid group (p<0.001) ➔ mean pain intensity sign higher on 4th and 13th day in opioid group	

				(both p<0.0001) ➔ absolute decrease in NRS scores sign higher in gabapentin group (-6.77±3.37 vs -4.66±2.80, p=0.009)		

4.3. Radiotherapy for painful bone metastases

Table 52 – Single fraction versus multiple fraction: evidence table of systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
Sze (2003)[26]	• Design: MA • Sources of funding: not mentioned • Search date: until 2002 • Searched databases: Medline, Embase, CancerLit, Controlled Trials Register on the Cochrane Library • Included study designs: RCTs • Number of included studies: 12 (n=3508) o Bone Pain Trial Working Party, 1999 o Cole, 1989 o Foro, 1998 o Gaze, 1997	• Eligibility criteria: patients having painful bone metastases from any primary tumour • Patient characteristics: o age and sex not mentioned o 3621 painful sites	• Intervention: external irradiation (single fraction, ranging from 8Gy to 10Gy) • Control: external irradiation (multiple fraction, ranging from 5Gy times 3 fractions to 3Gy times 10 fractions)	**Overall pain response (based on 12 trials)** no sign diff between single and multiple fraction: 60%vs 59%, pooled OR 1.03 (95%CI 0.90-1.19)(p=0.7) **Complete pain response (based on 8 trials)** No sign diff between single and multiple fraction: 34% vs 32%,	**Retreatment rate (based on 5 trials)** More re-treatments after single fraction (21.5% vs 7.4%), pooled OR 3.44 (95%CI 2.67-4.43)(p=0.00001) **Adverse events** • Pathological fracture (based on 5 trials) More pathologic fractures after single fraction (3% vs 1.6%), pooled OR 1.82 (95%CI1.06-	• AMSTAR evaluation: Y, Y, Y, Y, Y, Y, Y, Y, Y, N, N • Risk of bias of SR: low • Overall risk of bias of included RCTs: unclear • Authors' conclusion: radiotherapy is effective in relieving metastatic bone pain and the MA demonstrates no difference in the efficacy between single and multifraction radiotherapy, although the re-treatment and pathological fracture rates are higher after single-dose radiotherapy. Complete pain relief was still not achieved in about

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
	o Kagei, 1990 o Koswig, 1999 o Nielsen, 1998 o Ozsaran, 2001 o Price, 1986 o Sarkar, 2002 o Steenland, 1999 o Warde, 2001 (Abstract)			pooled OR 1.10 (95%CI 0.94-1.30)(p=0.2)	3.11)(p=0.03) • Spinal cord compression (based on 3 trials) No sign diff between single and multiple fraction: 1.9% vs 1.4%, pooled OR 1.41 (95%CI 0.72-2.75) (p=0.3) • Side-effects (based on 10 trials) Nausea and vomiting most common: similar in single and multiple fraction	two-thirds of patients. • Notes: o Heterogeneous pain response criteria o Significant amount of data missing (drop-outs 0-69%) o No diff in results after excluding dropout patients

Table 53 – Single fraction versus signle fraction: evidence table of randomized controlled trials

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
Hoskin (1992)[33]	• Design: 2-arm, prospective, randomized, controlled trial • Sources of funding: not mentioned • Setting: Royal Marsden Hospital, UK	Eligibility criteria: adults with clinical diagnosis of local bone pain due to metastases, all histological types of primary tumour were included Exclusion criteria: estimated prognosis of <6weeks, pathological fracture and inability to	4-Gy in a single fraction vs. 8-Gy in a single fraction	*Pain was evaluated in both studies with 4 levels pain scale (none, mild, moderate, severe). Results are recalculated in intention-to-treat* **Overall pain relief** At least 1 category reduction in 4 level	*Results are no intention-to-treat* **Adverse events** not mentioned	Risk of bias: high Author's conclusion: We have observed significantly better pain relief following 8-Gy compared to 4-Gy as a single fraction. The difference was

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
	• Sample size: total n= 270, n in 4-Gy=137, n in 8-Gy= 133; • Duration: 12 weeks after treatment	complete the pain form Patient characteristics: - Age: median 65y - Sex: 58% (n=157) women, 42% (n= 113) men - No sign diff in initial pain scores or analgesic use		graded scale 44% (4-Gy) vs 69% (8-Gy) (ITT-analysis not possible because of poor quality of results reporting) **Complete pain relief** A change in score from severe, moderate or mild to none 1. Complete pain relief at 2 weeks 13% (15/113) (15/137 ITT-analysis) in 4-Gy vs 15% (16/109) (16/133 ITT-analysis) in 8-Gy 2. Complete pain relief at 4 weeks 26% (25/98) (25/137 ITT-analysis) in 4-Gy vs 23% (22/96) (22/133 ITT-analysis) in 8-Gy 3. Complete pain relief at 8 weeks		most marked at 4 weeks when the observed difference was more than 20%. However, a single dose of 4-Gy is effective in a large proportion of patients and can be used in situations where there is judged to be limited tolerance. Remarks: • incomplete data on overall pain response

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				36% (31/86) (31/137 ITT-analysis) in 4-Gy vs 28% (21/75) (21/133 ITT-analysis) in 8-Gy 4. Complete pain relief at 12 weeks 36% (27/75) (27/137 ITT-analysis) in 4-Gy vs 39% (26/66) (26/133 ITT-analysis) in 8-Gy **Retreatment rate** 20% (28/137) in 4-Gy vs 9% (12/133) in 8-Gy		
Jeremic (1998)[34]	• Design: three arms, randomized, controlled trial • Sources of funding: not mentioned • Setting: department of Oncology, University Hospital in Kragujevac, Yugoslavia	Eligibility criteria: adults with metastatic bone pain from histologically or cytologically proven malignant disease, were not treated at the same site with surgery or radiation therapy, evaluable pain history Exclusion criteria: life expectancy of less than 8 weeks, existing pathological bone fracture or metastatic spinal cord compression or metastatic	4-Gy fraction single Vs 6-Gy fraction single Vs 8-Gy fraction single	*Pain was evaluated in both studies with 4 levels pain scale (none, mild, moderate, severe). Results are intention-to-treat* ***Complete pain response (4-point categorical scale)*** A complete disappearance of pain • At 2 weeks 13/109 (4-Gy) vs	*Results are no intention-to-treat* ***Adverse events*** 1. pathological fracture not during 8-weeks post-treatment, but after this period (no sign diff p=0.99): 3/48 (6%)(3/109 ITT-analysis) in 4-Gy, 3/45 (7%)(3/108 ITT-analysis) in 6-Gy, 3/44 (7%)(3/110 ITT-	Risk of bias: high Authors' conclusion: The 8-Gy single fractions achieved better results than the 4-Gy in terms of complete response, and significantly better in terms of overall response rates. No sufficient data to

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
	• Sample size: total n= 327, n= 109 in 4-Gy, n= 108 in 6-Gy, n= 110 in 8-Gy • Duration: 8 weeks post treatment	bone lesion located in superficial bones (ribs, sternum...) due to inavailability of orthovoltage x-ray machine Patient characteristics: o no differences among the three treatment groups regarding initial pain score and use of analgesics o approximately 80% of patients in each group had moderate to severe pain o sex: 41 men and 68 women (n=109) in 4-Gy vs 39 men and 69 women (n=108) in 6-Gy vs 41 men and 69 women (n=110) in 8-Gy o median age: 59y (33-70) in 4-Gy, 58y (35-71) in 6-Gy, 62y (30-71) in 8-Gy		20/110 (8-Gy) p=0.77 • At 4 weeks 16/109 (4-Gy) vs 28/110 (8-Gy) p=0.047 • At 8 weeks 23/109 (4-Gy) vs 35/110 (8-Gy) p=0.072 ***Overall pain response (4-point categorical scale)*** Complete + partial pain response (i.e. an improvement in pain score by at least one category) • At 2 weeks 38/109 (4-Gy) vs 62/110 (8-Gy) p=0.0014 • At 4 weeks 51/109 (4-Gy) vs 81/110 (8-Gy) p=0.000049 • At 8 weeks 64/109 (4-Gy) vs 86/110 (8-Gy) p=0.0019	analysis) in 8-Gy 2. spinal cord compression not during 8-weeks post-treatment, but after this period (no sign diff p=0.91): 4/61 (7%)(4/109 ITT-analysis) in 4-Gy, 5/63 (8%)(5/108 ITT-analysis) in 6-Gy, 4/66 (6%)(4/110 ITT-analysis) in 8-Gy 3. toxicities nausea and vomiting (grade 1 & 2) (chi-square p=0.81): 21/109 (19%) in 4-Gy, 20/108 (18%) in 6-Gy, 24/110 (22%) in 8-Gy diarrhea (grade 1&2)(chi-square p=0.75): 14/109 (13%) in 4-Gy, 12/108 (11%) in 6-Gy, 16/110 (15%) in 8-Gy	support a clear statement concerning dose-response relationship and response duration beyond 3 months Remarks: Jemeric 1998 also compared 6-Gy vs 8-Gy and obtained similar results. The authors suggests that additional studies are needed to determine the minimal single fraction dose

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				Retreatment rate No sign diff between 3 groups (p=0.71): 46/109 (42%) in 4-Gy, 47/108 (44%) in 6-Gy, 42/110 (38%) in 8-Gy		
Manas (2008)[37]	• Design: RCT • Sources of funding: not mentioned, no conflict of interest • Setting: Spain • Sample size: total n=118 • Duration: 7 month	Eligibility criteria: patients with histopathological diagnosis of cancer with bone metastases, cancer spread to the bone, scheduled radiotherapy for at most 2 treatable bone metastases, osteolytic or osteoblastic lesions, single or multiple in the axial skeleton or limbs (demonstrated radiologically), no treatment with biphosphonates during the month prior to inclusion, no previous history of radiotherapy in the same area Patient characteristics: • Age: mean 62.72 in 8Gy vs mean 66.12 in 6Gy • Sex: 47 men, 20 women in 8Gy vs 30men, 21	Intervention: single dose of 8Gy + zoledronic acid (4mg IV) (n=67) Control: single dose of 6Gy + zoledronic acid (4mg IV) (n=51) Follow-up: 7month Primary outcomes: pain (VAS) in supine, seated and standing positions Secondary outcomes: functional status (Karnofsky	***Pain relief at 7 months*** • Supine position: no sign diff between 8Gy and 6Gy (p=0.0668) • Seated position: no sign diff between 8Gy and 6Gy (p=0.1226) • Standing: sign diff between 8Gy and 6Gy (p=0.0058) ➔ Improvement over time in both groups	***Medication use***: 88.98% took some form of analgesic medication (no differentiation between groups) ***Quality of life:*** Sign improvement over time in both groups (p<0.05) ***Adverse events*** • Skeletal event – pathological fracture, reirradiation, compression of the spinal medulla): o 19.40% in 8Gy vs 23.53% in 6Gy ➔ No sign diff	Risk of bias: unclear Author's conclusion: The two groups achieved similar levels of pain control in supine, seated and standing positions. Also QoL improved in both groups. However the higher dose of 8Gy is associated with a longer period without skeletal events. Remarks:

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
		women in 6Gy	scale), QoL (EORTC QLQ C-30), adverse events, medication use		between groups (p=0.5870) o Most frequent: pathological fracture and reirradiation ➔ No sign diff between groups o Median time to onset: sign longer in 8Gy ➔ Sign diff between groups (Log-Rank Test=0.0211) • Adverse reactions: higher incidence in 8Gy 8Gy (21% of patients with adverse events versus 14%; p-value not given) ***Functional performance*** • Sign diff in 8Gy over time (p=0.0052) vs no sign diff in 6Gy (p=0.8403) ➔ No sign diff in	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
					evolution between groups (p=0.1635)	

Table 54 –Single fraction versus multiple fraction: evidence table of randomized controlled trials

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
Amouzegar-Hashemi (2008)[29]	• Design: 2-arm, randomized, control trial • Sources of funding: not mentioned • Setting: Tehran (Iran) • Sample size: 70 patients were randomized (multiple fraction n=34; single fraction n=36) but 5 died and 7 were lost of follow-up; Finally, n=58 (multiple radiotherapy n=31; single radiotherapy n=27)	Eligibility criteria: Adult patients with painful uncomplicated bone metastases requiring palliative radiotherapy. Patients with cord compression or existing or impending pathologic fracture were excluded Patient characteristics: there were no significant differences in terms of sex, mean age, and grade before treatment between the 2 groups	8 Gy in a single fraction vs. 30 Gy in 10 fractions over 2 weeks	*Results are no intention-to-treat* **Overall pain relief** At least 1 grade reduction in 4 level graded scale (at 1 month) 21/27 single fraction (21/36 ITT-analysis) vs 20/31 multiple fraction (20/34 ITT-analysis) p>0.1 **Complete pain relief** At least 2 grades reduction in 4 level graded scale (at 1 month) 6/27 (6/36 ITT-	*Results are no intention-to-treat* **Side effects:** Mild gastro-intestinal disturbances (nausea and diarrhea) • Single fraction 3/27 (3/36 ITT-analysis) • Mult fraction 5/31 (5/34 ITT-analysis) **Effect of age on pain relief** After adjustment for confunding variables (sex, primary tumor, radiotherapy site, or type of treatment (single vs multiple fraction)	Risk of bias: high Author's conclusion: No significant difference in pain relief after palliative radiotherapy with 1 or with 10 fractions. Younger patients experienced better pain relief. Remarks:

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
	• Duration: 1 month			analysis) single fraction Vs 11/31 (11/34 ITT-analysis) multiple fraction Not significant	Younger patients (50 yrs or younger) experienced better pain relief than patients more than 50 yrs of age	
Foro (2008)[30]	• Design: 2-arm, randomized, control trial • Sources of funding: not mentioned • Setting: single institution in Spain • Sample size: n=160 (30-Gy multiple fraction n=82; 8-Gy single fraction n=78) • Duration: 48 weeks	Eligibility criteria: 18 years or older patients with painful multiple bone metastases in only one site of pain, with life expectancy ≥1 month, without pain due to a pathological or impending fracture, without spinal cord compression, without prior radiotherapy at the same site Patient characteristics: Patients performance status<70 KPS*: 14/82 (30-Gy) vs 15/78 (8-Gy) – ns (no significant difference); Men: 47/82 (30-Gy) vs 45/78 (8-Gy) – ns; Mean age: 63.4 ± 11.4 (30-Gy) vs 64.8 ± 10.0 (8-Gy) - ns; Pain severity: 7.0 ± 1.6 (30-Gy) vs 7.1 ± 1.6 (8-Gy) – ns; primary tumor – ns; histology – ns;	8-Gy in a single fraction vs. 30-Gy in 10 fractions over 2 weeks	*Results are intention-to-treat* **Pain relief** 1. Overall response rate • At 3 weeks 71/82 (30-Gy) vs 59/78 (8-Gy) - ns • At 3 months 51/82 (30-Gy) vs 51/78 (8-Gy) - ns 1. Complete response rate (absence of pain without the need to increasing analgesia) • At 3 weeks 11/82 (30-Gy) vs 12/78 (8-Gy) - ns • At 3 months 9/82 (30-Gy) vs 10/78 (8-Gy) - ns		Risk of bias: unclear Author's conclusion: A single fraction of 8 Gy for the treatment of bone metastases is as effective as a 30-Gy regimen in terms of complete, partial and overall response rates. Also, there are no significant differences between the two arms in response duration, pain progression, net pain relief, gain and toxicity. The percentage of re-irradiations is significantly higher

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
		localization of radiation – ns; mean survival - ns Patient characteristics were well balanced between two arms		2. Partial response rate (improvement ≥2 on the 10 points scale with no need for increasing analgesia) • At 3 weeks 60/82 (30-Gy) vs 47/78 (8-Gy) - ns • At 3 months 42/82 (30-Gy) vs 41/78 (8-Gy) - ns **Decrease in pain relief with time between days 21 and 360** No significant difference between 2 arms for overall and complete response rate **Mean of response rate** 1. Overall response rate 23 weeks (30-Gy) vs 23 weeks (8-Gy) - ns 2. Complete		for the single fraction vs the multiple fraction schedules Remarks:

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				response rate 25 weeks (30-Gy) vs 28 weeks (8-Gy) - ns **Net pain relief** (period of pain relief divided by period of survival in days; in percentage) 71% (30-Gy) vs 68% (8-Gy) - ns **Decrease in pain** (subtracting pain severity on the ordinal pain scale (range 0 to 10) following the therapy, from pain prior to radiotherapy) 3.5 (30-Gy) vs 4 (8-Gy) - ns **Adverse events:** 18% (30-Gy) vs 12% (8-Gy) - ns **Re-treatment:** 2% (30-Gy) vs 28% (8-Gy) – p=0.001		
Hamouda (2007)[31]	• Design: Randomized control trial • Sources of	Eligibility criteria: epithelial malignancy with bone metastases and without chemotherapy or hormonal therapy within	8-Gy in a single fraction vs.	*Results are no intention-to-treat* **Pain relief:** 1. Complete		Risk of bias: high Author's conclusion:

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
	funding: not mentioned • Setting: 1 centre in Egypt • Sample size: 107 patients were randomized (multiple fraction n=55; single fraction n=52) but 2 early died in single fraction and 3 early died in multiple fraction • Duration: 24 weeks	30 days, without previous radiotherapy to the treatment area and without pathological fractures. Patient characteristics: Age (mean ±SD): 59 ±13 (40-Gy) vs 62 ±11.1 (8-Gy) - p>0.05; Sex (% of male): 40% (40-Gy) vs 44.2% (8-Gy) - p>0.05;; Pain score (VAS scale - %score<5 / 5-7 / 8-10): 16%/36% /48% (40-Gy) vs 17.3%/38.5%/44.2% (8-Gy) - p>0.05; Primary tumor (% Breast/ Prostate/ Lung/ Other): 50%/16%/20%/14% (40-Gy) vs 46.2%/ 19.2%/21.2%/13.4% (8-Gy) - p>0.05; Metastasis sites (% Spine/ Pelvis/ Limbs/ Other): 42%/30%/20%/8% (40-Gy) vs 42.6%/ 28.8%/23.1%/5.8% (8-Gy) - p>0.05; Patient characteristics were well balanced between two arms	40-Gy in 20 daily fractions, 5 fractions/ weeks	response % of patients with 0 on a 10 point VAS scale • At 2 weeks 26.9% (14/55 ITT-analysis) (40-Gy) vs 28% (14/52 ITT-analysis)(8-Gy) – p>0.05 • At 4 weeks 44.2% (23/55 ITT-analysis)(40-Gy) vs 40% (20/52 ITT-analysis)(8-Gy) – p>0.05 • At 8 weeks 48.1% (25/55 ITT-analysis)(40-Gy) vs 46% (23/52 ITT-analysis)(8-Gy) – p>0.05 • At 12 weeks 44% (22/55 ITT-analysis)(40-Gy) vs 39.6% (19/52 ITT-analysis)(8-Gy) – p>0.05 • At 20 weeks 35.5% (16/55 ITT-analysis)(40-Gy)		A single fractions of 8 Gy is as effective as 40 Gy in 20 fractions in relieving pain from bone metastasis. The use of a single fraction could be of benefit by reducing the treatment burden for both the patient and the hospital staff. Remarks: 7 patients (6 in 8-Gy group and 1 in 40-Gy group) had their bone metastases re-irradiated with 8-Gy single fraction.

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				vs 28.5% (12/52 ITT-analysis)(8-Gy) – p>0.05 • At 24 weeks 30.9% (13/55 ITT-analysis)(40-Gy) vs 23.7% (9/52 ITT-analysis)(8-Gy) – p>0.05 2. Overall Response rate ≥ 50% reduction in pain score • At 2 weeks 73.1% (38/55 ITT-analysis)(40-Gy) vs 68% (34/52 ITT-analysis)(8-Gy) – p>0.05 • At 4 weeks 82.6% (43/55 ITT-analysis)(40-Gy) vs 80% (40/52 IT-analysis)(8-Gy) – p>0.05 • At 8 weeks 88.5% (46/55 ITT-analysis)(40-Gy) vs 84% (42/52 ITT-analysis)(8-Gy) – p>0.05		

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				• At 12 weeks 82% (41/55 ITT-analysis)(40-Gy) vs 77.1% (37/52 ITT-analysis) (8-Gy) – p>0.05 • At 20 weeks 62.2% (28/55 ITT-analysis)(40-Gy) vs 59.5% (25/52 ITT-analysis)(8-Gy) – p>0.05 • At 24 weeks 59.5% (25/55 ITT-analysis)(40-Gy) vs 52.6% (20/52 ITT-analysis)(8-Gy) – p>0.05 *Comments: pain relief did not differ between two group at 8 weeks with respect to the primary tumor, the metastatic sites and the performance status* **Analgesic requirement:** Four-point scale		

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				(o=no analgesic, 1=non-opioids, 2=weak opioids, 3=strong opioids) Significant reduction in analgesic use in both arms after treatment ($p<0.05$); no significant difference between both groups before and after treatment. **Duration of pain relief:** 13.5 weeks (40-Gy) vs 12 weeks (8-Gy)-ns **% of patients with pain relief at 24 weeks:** 59.5% (40-Gy) vs 52.6% (8-Gy) **Toxicity** 6/52 (5/55 ITT-analysis) (40-Gy) vs 3/50 (3/52 ITT-analysis) (8-Gy) **Re-treatment** 1/52 (1/55 ITT-analysis) (40-Gy) vs 6/50 (6/52 ITT-analysis)(8-Gy)		

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
Hartsell (2005)[32]	• Design: prospective, phase III two-arms, randomized study, controlled • Sources of funding: supported by grants from the National Cancer Institute • Setting: USA • Sample size: total n=898, n= 455 in single fraction group (8-Gyx1), n= 443 in multiple fraction (30-Gyx10) at start of trial, • Sample size at 3 months: n= 288 in 8-Gy and n=285 in 30-Gy	Eligibility criteria: Age of 18 years or older, histologically proven primary malignancy of breast or prostate radiographic evidence of bone metastasis, a Karnofsky performance status of at least 40 and an estimated life expectancy of at least 3months Patient characteristics: - Mean age: 65.5y (33-92y) in 8-Gy, 67y (31-91y) in 30-Gy - Sex: 49% (n=222) men and 51% (n=233) women in 8-Gy vs 50% (n=223) men and 50% (n=220) women in 30-Gy - Painful sites: solitary in 271 in 8-Gy, 236 in 30-Gy; multiple in 184 in 8-Gy, 207 in 30-Gy - Patn characteristics are well balanced	Single fraction (8-Gy x1) Vs Multiple fraction (30-Gy x10)	*Results are no intention-to-treat* **Pain relief at 3 months (Brief Pain Inventory):** 1. complete pain relief (pain score of zero with stable or reducing analgesic intake) No sign diff (p=.6): 10% (n=25/256)(45/455 ITT-analysis) in 8-Gy vs 12% (n=31/255) (53/443 ITT-analysis)in 30-Gy 2. Partial pain relief (≥ 2 points lower on a 10 points scale) No sign diff (p=.6): 50% (n=143/288)(227/455 ITT-analysis) in 8-Gy vs 48% (n=137/285)(213/443 ITT-analysis) in 30-Gy 3. Stable pain relief	*Results are no intention-to-treat* **Adverse events:** 1. Toxicities (maximum acute toxicities per patient) G1:43/433 (43/455 ITT-analysis) in 8-Gy vs 65/414 (65/443 ITT-analysis) in 30-Gy G2: 31/433 (31/455 ITT-analysis) in 8-Gy vs 55/414 (55/443 ITT-analysis) in 30-Gy G3: 11/433 (11/455 ITT-analysis) in 8-Gy vs 13/414 (13/443 ITT-analysis) in 30-Gy G4: 0/433 (0/455 ITT-analysis) in 8-Gy vs 2/414 (2/443 ITT-analysis) in 30-Gy 2. Incidence of pathologic fractures: Within treatment field: 5% in 8-Gy vs 4% in 30-Gy	Risk of bias: unclear Authors' conclusion: We found that external beam radiation therapy was effective at palliating pain from bone metastases with complete or partial improvement in pain observed at 3 months after randomization in 66% (n=375) of the 573 patients. At 3 months we found no significant difference between the response in 8-Gy compared to 30-Gy in terms of pain relief, narcotic relief, pathologic fracture incidence. Treatment was well tolerated with few adverse events. The primary difference between

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
		in both groups		(one-point change in 10 points pain score in either direction) No sign diff (p=.6): 26% (n=74) in 8-Gy vs 24% (n=69) in 30-Gy 4. Progressive pain relief (pain score that was at least two points higher than the initial score) No sign diff (p=.6): 9% (n=27) in 8-Gy vs 10% (n=28) in 30-Gy **Medication use at 3 months** 1. None No sign diff (p=.483): 20% (n=65) in 8-Gy vs 22% (n=69) in 30-Gy 2. Nonnarcotic analgesic No sign diff (p=.483): 13% (n=40) in 8-Gy	Adjacent to treatment site: 3-4% (data unclear, not further used for analysis) 3. 30y-retreatment rate Sign diff (p<.001): 18% (n=76 of 449)(76/455 ITT-analysis) in 8-Gy vs 9% (n=33 of 432) (33/443 ITT-analysis) in 30-Gy	the two arms was found was the higher rate of retreatment in 8-Gy arm. Remarks: violations of the protocol: in random sample of 30%, 87.1% were within protocol guidelines or with minor deviations, 7.0% had incomplete treatment or major deviations and 5.9% were not evaluable for compliance because of incomplete data

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				vs 10% (n=30) in 30-Gy 3. Narcotic No sign diff (p=.483): 67% (n=213) in 8-Gy vs 68% (n=211) in 30-Gy **Re-treatment:** 9% (30-Gy) vs 18% (8-Gy) – p<0.001		
Roos (2005)[35]	• Design: multicentre two arm phase III randomized control trial • Sources of funding: Royal Adelaide Hospital Special Purposes Fund Grant-in)Aid and National Health and Medical Research Council (NHMRC) Project Grant 981871	Eligibility criteria: Patients with neuropathic bone pain or dysaesthesia du to bone metastasis pain whose life expectancy is ≥ 6 weeks but without recent or planned change in systemic treatment, without another metastasis within the distribution of neuropathic pain, cord/cauda equine compression, extra-skeletal index site and previous radiotherapy to the index site. Patient characteristics:	8-Gy in a single fraction vs. 20-Gy in, 5 fractions over one week	*Results presented in intention-to-treat* **Overall response rate** Improvement in pain score in a 4 level scale (severe, moderate, mild, none pain) by at least one grade with no increase in analgesia for the index pain at 2 months 1. Number of patients 73/137 (8-Gy) vs 83/135 (20-Gy) 2. % of patients (95% CI)		Risk of bias: unclear Author's conclusion: The authors did not show that that single fraction is as effective as multiple fraction for neuropathologic bone pain; neither did they show 8/1 to be significantly worse. Outcomes were generally poorer for single fraction, although the quantitative

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
	• Setting: 15 centres (Australia 11, New Zealand 3, UK 1) • Sample size: n=272 (20-Gy multiple fraction n=135; 8-Gy single fraction n=137) • Duration: 30 months	Sex (% Male): 71% (20-Gy) vs 73% (8-Gy); Age (means (range)): 68 (32-89) (20 Gy) vs 67 (29-86); Primary tumor (%Lung/ Prostate/Breast/ Other): 29%/30%/10%/30% (20-Gy) vs 33%/28%/7%/33% (8-Gy);Systemic treatment at randomization (% chemotherapy / % hormonal therapy): 7%/31% (20 Gy) vs 2%/25% (8 Gy); Index site (% spine/ % rib/ % other): 85%/12%/2 % (20 Gy) vs 92%/6%/2%; Pre-treatment index pain severity (% none/ % mild/ % moderate/ % severe/ % unknown): 0%/15%/44%/40%/1% (20-Gy) vs 1%/20%/41%/37%/1% (8-Gy); Pre-treatment index pain analgesia (% none/ % non opioids analgesic/ % corticosteroid/ % adjuvant analgesic/ % opiods): 4%/64%/20%/16%/78% (20-Gy) vs 4%/70%/18%/14%/80% (8-Gy); Concurrent pain elsewhere: 34% (20-Gy)		53 (45-62) (8-Gy) vs 61 (53-70) (20-Gy) 3. Difference between % of patient (95% CI) -8% (-20% – 4%) p=0.18 **Complete response** Change in pain score from severe, moderate, or mild to none with no analgesia or adjuvant analgesia for index pain at 2 month 1. Number of patients 35/137 (8-Gy) vs 36/135 (20-Gy 2. % of patients (95% CI) 26 (18-34) (8-Gy) vs 27 (19-35) (20-Gy) 3. Difference between % of patient (95% CI) -1% (-12% – 10%) p=0.89 **Failures**		differences were relatively small. In general, multiple fraction is recommended. However for significant patient sub-sets with short expected survival, such as those with poor performance status and/or primary other than breast/prostate, for whom the added cost and inconvenience of fractionation may not be offset by clinical benefit. In addition, single fraction would not be unreasonable in centres with long waiting times for fractionated treatment Remarks: 1. Patients randomized to multiple fraction waited longer

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
		vs 28% (8-Gy) Patient characteristics were well balanced between two arms (no statistically significant difference between arms)		Worsening in pain score by at least one category and/or significant increase in analgesia (e.g. S50% increase in dose; change from non-opioid to opioid), re-irradiation, progression/development of pathological fracture, or development of clinical cord/cauda equine compression 1. Number of failures at 30 month 82/137 (8-Gy) vs 78/135 (20-Gy) Hazard ratio [8 Gy-20Gy] (IC95%) 1.35 (0.99 – 1.85) p=0.056 2. Number of patients without failure at 1 year 20/137 (8-Gy) vs 32/135 (20-Gy) 3. Percentage of patients without		significantly to commence radiotherapy than patients randomized in single fraction (% of patients waiting >14 days – 8% (8-Gy) vs 14% (20-Gy) p=0.0043) 2. Protocol violations were detected in 21 % of patients but no significant difference between arms (p=0.66 for all violations; p=0.46 for major violations)

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				failure at 1 year (%95 CI) 15 (7-28) (8-Gy) vs 24 (16-36) **Re-treatment** Number of patients 40/137 (8-Gy) vs 33/135 (20-Gy) p=0.41 **Serious complications** 1. Cord/cauda equine compressions 9/137 (8-Gy) vs 8/135 (20-Gy) ns 2. Pathological fractures 6/137 (8-Gy) vs 5/135 (20-Gy) ns **Acute toxicity at 4 weeks** As the worst grade experienced since commencing radiotherapy according to Radiation Therapy Oncology Group (RTOG) criteria 1. 3 patients in each		

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				arm experienced upper GI tract and lung Grade 3 acute toxicities 2. No Grade 4 toxicities recorded **Flare effect** Temporary increase in pain at the index site within a week of commencing radiotherapy graded in 1=mild, 2=moderate, 3= severe increase in pain Number of patients with mild, moderate and severe flare: 2, 5, 7 (8-Gy) vs 2, 2, 2 (20-Gy) p=0.029 comparing trends across grades		

Table 55 – Spinal cord compression: evidence table of randomized controlled trials

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
Maranzano (2005)[38]	• Design: Phase III, randomized multicenter trial • No conflict of interest, sources of funding: not mentioned • Setting: not clearly mentioned • Sample size: n= 142 (short-course) n=134 (split-course) • Duration: short course RT 1 week, split-course RT 2 weeks, analysis of response at 1 month after RT, follow-up once a month for 1y and 4 times per year until death	Eligibility criteria: MSCC (metastatic spinal cord compression) diagnosed by MRI or CT in patients with progressive neoplastic disease, no criteria indicating a primary surgical approach, patients had to have a short life expectancy (<6 months) because of unfavourable histologies or favourable histologies with motor or sphincter dysfunction and/or low performance status Patient characteristics: well balanced for sex, age, performance status, ambulatory status and histology • Sex: n=99 men and n=43 women in short course (total n=142),	Intervention: short course RT (8Gy, 6-day rest and then 8Gy→total dose of 16Gy in 1 week) Control: split-course RT (5Gy x3, 4-day rest and then 3Gyx5→ total dose of 30Gy in 2 weeks) Primary outcomes: pain relief (back pain), motor function (walking capacity), sphincter control Secondary outcomes: adverse events	Outcomes: timing of outcome measurement not given. Complete response= patients who had no pain after radiotherapy (RT) Partial response = patients using narcotics or minor analgesics before RT who had pain requiring minor analgesics after RT. Non-response= patients with no pain before RT who developed pain or those with pain requiring minor analgesics who started taking narcotics after RT **Pain relief (=complete + partial pain response)** • N= 80 (56%) (ITT 80/153) in short course vs n= 79 (59%) (ITT	**Adverse effects:** • Dysphagia: grade 1 to 2 oral or esophageal dysphagia in n=39 (14%), grade 3 esophagitis in n=3 (1%) (2 in split course and 1 in short course), grade 3 pharyngeal dysphagia in n=1 (0.5%) (in split course) • patients taking anti-emetic prophylaxis: occurrence of grade 1 to 2 vomiting in n=22 (13%), grade 3 vomiting in n=5 (3%) (same incidence in both groups) • Nausea: grade	Risk of bias: unclear Author's conclusion: Both RT are effective with no severe adverse effects. However, considering the convenience of the short course regimen in terms of time sparing for patients and the advantage for radiation oncology centers, short course therapy could be the treatment of choice in clinical practice. Remarks: no comparison possible with other studies, no p-values mentioned

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
		n=92 men and n=42 women in split course (total n= 134) • Age: median 66y in short course, median 68y in split-course		79/147) in split course • no significant difference (p-value not given) **Complete pain response (= no pain after RT)**: • Total n= (ITT 47/153, 31%) in short-course vs total n= (ITT 47/147, 32%) in split-course (not sign different (p-value not given) **Partial pain response:** • Total n= (ITT 33/153, 22%) in short-course vs total n= (ITT 32/147, 22%) (not sign different (p-value not given) • In group with no analgesics pretreatment: no appearance of pain in both intervention	1 to 2 in n=16 (9%), grade 3 in n=5 (3%) • No late spinal cord morbidity ➔ No relationship between RT regimen and acute adverse events	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				groups **No pain relief**: • Total n= (ITT 62/153) in short-course vs total n= (ITT 55/147) in split-course (not sign different (p-value not given) **Motor function:** no significant difference between groups: • In group with walking pretreatment: walking in 83/93 (89%) in short course vs 83/91 (91%) in split course • In group with not walking pretreatment: walking regained in 14/49 (29%) in short course vs 12/43 (28%) in split course Total: 63% (ITT 97/153) and 65% (ITT 95/147) were able to walk after RT		

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				• **Sphincter control:** see publication (no significant difference between groups) ➔ No sign diff in response rates between **short and split course** regimens		
Maranzano (2009)[39]	• Design: phase III randomized multicentre Italian trial • Sources of funding: not clearly mentioned, conflict of interest not mentioned • Setting: 13 radiation oncology Italian centres • Sample size: n=150 in short course, n= 153 in single dose • Duration: response at 1 month after	Eligibility criteria: metastatic spinal cord and/or cauda equine compression diagnosed by MRI or CT in patients with progressive neoplastic disease, no criteria indicating a primary surgical approach, patients with a short life expectancy (<6 months) because of presence of unfavourable histologies or favourable ones with motor/sphincter dysfunction and/or low performance status	Intervention: short course radiotherapy (RT) regimen of 8Gyx2 (8Gy, 6-day rest and then 8Gy, total dose of 16 Gy in 1 week) Control: single dose of 8Gy Primary outcomes: pain relief (back pain), sphincter control, motor function Secondary outcomes:	Outcomes: timing of outcome measurement not given. Complete response= patients who had no pain after radiotherapy (RT) Partial response = patients using minor narcotics before RT who had stable pain or pain requiring minor analgesics after RT; or patients using minor analgesics before RT who had stable pain. Non-response=	**Adverse events**: • Dysphagia: grade 1 to 2 oral or esophageal dysphagia in n=20 (7%), grade 3 esophagitis in n=2 (1%) (both in short course) • Diarrhoea: grade 1-2 in n=6 (2%) (all in short course), no grade 3-4 • patient treated	Risk of bias: unclear Author's conclusion: Both RT were equally feasible and effective. So 8Gy single-fraction RT should be considered the schedule of choice in clinical practice for MSCC patients with short life expectancy. Remarks: no comparison possible with other studies, no p-values mentioned for the

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
	treatment, follow-up 1x/month for 1y and 4x/y until death	Patient characteristics: well balanced for sex, age, performance status, ambulatory status and histology in both arms • Sex: n=95 men and n=55 women in short course vs n=102 men and n= 51 women in single dose • Age: median of 67y (range 39-87) in short course vs median of 67y (range 33-87) in single dose	adverse events	patients with no pain before RT who developed pain; or those with pain requiring minor analgesics who started taking narcotics after RT; or those using minor narcotics who passed to major narcotics; or those using major narcotics before and after RT **Complete pain relief**: • Total n= (ITT 35/150, 23%) in short-course vs total n= (ITT 42/153, 27%) in single dose (not sign different (p-value not given). • In half of the patient who had a pain response, complete pain relief was obtained after the radiotherapy intervention (44% in short-course and 53% in	with anti-emetic prophylaxis: (total n=114): grade 1-2 vomiting in n=20 (17.5%)(same incidence in both groups), grade 3 vomiting in n=1 (1%) (in short course) • Nausea: grade 1 to 2 in n=19 (17%), no grade 3-4 • No myelopathy after median follow-up of 31 months ➔ No relationship between RT regimen and acute adverse events	primary outcomes

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				single-dose RT. **Partial pain relief:** • Total n= (ITT 45/150, 30%) in short-course vs total n= (ITT 38/153, 25%) in single dose (not sign different (p-value not given) **No pain response:** • Total n= (ITT 70/150, 47%) in short-course vs total n= (ITT 73/153, 48%) in single dose (not sign different (p-value not given) **Motor function:** no significant difference between groups: • in group with walking pretreatment: walking in 91/101 (90%) in short course vs 86/98 (88%) in single dose • in group with no		

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				walking pretreatment: ambulation regained in 13/49 (26%) in short course vs 9/55 (16%) in single dose • Total ambulatory after RT: 69% in short-course RT and 62% in single-dose RT **Sphincter control:** see publication (no significant difference between groups) ➔ no sign diff in response rates between short course and single dose		

Table 56 – Hemibody irradiation: evidence table of randomized controlled trials

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
Salazar (2001)[40]	• Design: Phase III, randomized multicenter trial • Sources of funding: International Atomic Energy Agency, no conflict of interest • Setting: Brazil, Cameroon, Pakistan, Peru, Spain, United States • Sample size: n= 51 (arm A), n=56 (arm B), n=49 (arm C) • Duration: time point of assessment not clearly	Eligibility criteria: a pain and/or narcotic score of 4 or greater, an age no more than 80years, initial ECOG performance status 1-4, pathologic proof of the primary tumor, life expectancy of at least 2 months, no history of active cardiac or renal diseases, no previous history of radiation to large volumes within the upper part of the body, adequate blood counts (defined as white blood count ≥3000, platelets ≥100 000 and Hg≥10g), adequate renal function and at least 4weeks from previous radiation or chemotherapy. Patient characteristics:	Three different types of HBI: upper half of the body, lower half of the body, midportion of the body Intervention: • short hyperfractionation (Arm B): 2 fractions (6-8h apart) of 4Gy each in a single day (total of 8Gy) • accelerated hyperfractionation (Arm C): 3Gy each, twice daily (6-8h apart) on 2 consecutive days (total of 12Gy) Control: • daily (Arm A), 3Gy for 5 days (total of 15Gy) Primary outcomes: pain response (severity (0-3) x frequency (0-3)) Secondary outcomes:	**Complete pain response:** total of 45% • arm A: 63% • arm B: 32% • arm C: 43% ➔ sign diff between arm A and arm B (p=0.016) ➔ non-sign diff between arm A and arm C (p=0.22) **Partial pain response**: total of 46% • arm A: 29% • arm B: 57% • arm C: 51% ➔ no sign levels mentioned **No pain response:** total of 9% • arm A: 8% • arm B: 11% • arm C: 6% ➔ no sign levels mentioned	**QoL** • net pain relief: average of 71% o arm A: 72% o arm B: 65% o arm C: 75% ➔ no sign diff (p>0.05) • initial performance status: results only on graphs **Adverse events** • RTOG system o No complications: overall 38% (arm A: 43%, arm B: 32%, arm C: 41%) o Mild and moderate: overall 50% (arm A: 49%, arm B: 52%, arm C: 59%) o Grade 3-4 toxicity: overall 12% (arm A: 8%, arm B: 16%,	Risk of bias: high Author's conclusion: Arm B delivered the highest daily dose in the shortest time but more acute toxicities were observed. Delivering 2 daily doses of 3Gy each on 2 consecutive days (arm C) appears to be as effective and efficient as delivering single daily dose of 3Gy on 5 consecutive days (arm A). Developing countries should benefit from this faster HBI schedule to palliate a significant number of symptomatic, wide-spread metastatic bone cancers rapidly

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
	described	• Primary tumour type: breast (46%), prostate (32%), lung (6%), miscellaneous (16%) • Initial performance status: 1-2 (65%), 3-4 (35%) • Type of HBI: mid-body HBI (6%), upper HBI (44%), lower HBI (51%)	QoL (net pain relief (pain-free survival time/overall survivalx100), performance status Adverse events: toxicities (peripheral blood counts), RTOG grading system	**Time to pain relief**: • any type of pain relief: average of 3 days (same in all arms) • maximum pain relief: average of 8 days o arm A: 9 days o arm B: 8 days o arm C: 6 days ➔ no sign diff (p>0.05)	arm C: 10%) ➔ No sign diff between arms (p=0.31) • Hematological toxicities: neutropenia and thrombocytopenia most common and majority in grade 2-4 toxicity	and safely.

4.4. Radionuclides for painful bone metastases

Table 57 – Radionuclides: evidence table of systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
Roqué (2011) [41]	• Design: SR and MA • Sources of funding: not mentioned and no existing conflict of interest • Search date: up to October 2010 • Searched databases: Central, Medline, PaPaS Trials Register and Embase • Included study designs: RCTs • Number of	• Eligibility criteria: Participants of any age with metastatic bone pain caused by any primary tumour and defined by technetium-99m bone scan, MRI or another imaging • Patient characteristics: Adults of either sex, aged 18 years or over.	• Efficacy of radio-isotopes versus placebo (8 studies) • Head-head-comparisons (3studies) • Dose-comparisons (out-of-scope for this report)	**Efficacy of radioisotopes** • Complete pain relief: RR 2.10 (95%CI 1.32 to 3.35), p=0.0018, ITT RR 2.11 (95% CI 1.32 to 3.37), p=0.0017 • Partial pain relief: RR 1.72 (95%CI 1.13 to 2.63), p=0.0012, ITT RR 1.79 (95% CI 1.16 to 2.77), p=0.0090 • Any amount of pain: RR 1.36 (95%CI 0.77 to 2.40), p=0.29, ITT RR 1.42 (95%CI 0.81 to 2.49), p=0.23 • Adverse events: leucocytopenia RR 0.07 (95%CI 0.04 to 0.11), p=0.00012; thrombocytopenia RR 0.04 (95%CI -0.03 to 0.11), p=0.25; anemia RR 0.03 (95%CI -0.04 to 0.09), p=0.44 **Head-to-head comparisons**: no MA • 89SR versus 153Sm: o Pain relief: sign improvements in both groups but no sign diff between groups o Adverse events: (severe) pancytopenia: 5 cases (3 patients in 89-Sr group and	**Efficacy of radioisotopes** • **Medication use:** heterogenous results • **QoL**: poor reporting of results, no MA possible • **Incidence of pain flares:** RR 0.74 (95%CI 0.27 to 2.06), p=0.57 • **Sensitivity analysis adjuvant radiotherapy:** complete pain relief RR 2.55 (95% CI 0.52 to 12.63), p=0.25; partial pain relief RR 1.64 (95%CI 1.05 to 2.55), p=0.029; any amount og relief RR 0.80 (95%CI 0.50 to 1.27), p=0.34 **Head-to-head comparisons** • 89SR versus 153Sm: o Functional performance: sign improvements in both groups but no sign diff between groups o Analgesic use: sign	• AMSTAR evaluation: Yes, Yes, Yes, Yes, Yes, Yes, Yes, Yes, Yes, Yes, can't answer • Quality of SR: low risk of bias • Quality of included RCTs: overall unclear risk of bias • Authors' conclusions: There is moderate quality evidence to support a beneficial effect of radioisotopes over placebo for pain control in the short and

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
	included studies: n=14 (in MA) Included studies: Baczyk 2007 Buchali 1988 Han 2002 Lewington 1991 Maxon 1991 Nair 1999 Nilsson 2007 Palmedo 2003 Porter 1993 Resche 1997 Sartor 2004 Sciuto 2001 Serafini 1998 Smeland 2003			2 patients in 153-Sm=EDTMP-group), (moderate) granulocytopenia and/or thrombocytopenia: 20 cases (8 patients in 89-Sr group and 12 patients in 153-Sm-EDTMP-group), Hypercalcaemia: 10 cases (5 patients in 89-Sr group and 5 patients in 153-Sm-EDTMP-group • 89Sr versus 186Re: o Pain relief: sign improvements in both groups but no sign diff between groups o Adverse events: no sign diff in toxicities between both groups • 89Sr versus 32P: o Pain relief: sign improvements in both groups but no sign diff between groups o Adverse events: no sign diff in toxicities between both groups	improvements in both groups but no sign diff between groups	medium term, with no modification of analgesia use. A higher incidence of severe secondary effects has been observed. This review has identiefied scarce and low quality evidence on the relative effeicacy and safety of different radiopharmaceuticals. • Note: the three RCTS included in the review of Christensen 2011 are also included in this SR.

Table 58 – Radionuclides: evidence table of randomized controlled trials

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
Nilsson (2005)[55]	• Design: Phase III, randomized trial • Sources of funding: not mentioned, conflict of interest not mentioned • Setting: Sweden • Sample size: n= 18 (89Sr), n=17 (chemotherapy) • Duration: 12 weeks	Eligibility criteria: primary or secondary hormone-refractory prostate cancer, skeletal metastases, persisting pain despite analgesic treatment and lif expectancy more than 3 months Exclusion criteria: significantly impaired renal function or previous administration of strontium-89 or chemotherapy Patient characteristics: mean age 68y	Intervention: strontium-89 (89Sr) (n=18) 150 MBq intravenous Control: chemotherapy (FEM) (n=17), 5-fluorouracil (750mg/m2), epirubicin (40mg/m2) and mitomycin-C (0.1mg/kg) Follow-up: every 3 weeks for 12 weeks Primary outcomes: pain intensity (verbal rating scale 0-4), pain frequency (1-4) Secondary outcomes: analgesic	**Pain intensity** • At baseline: o median of 3 (severe) in each group o mean of 2.8 (±0.65) in 89Sr (n=18) and mean of 2.9 (±0.50) in FEM (n=16) ➔ equal in both groups • at 3 weeks: o 89Sr: mean 1.71 (SD 0.99), p=0.004 o FEM: mean 1.53 (SD 0.92), p<0.001 ➔ Sign reduction at three weeks ➔ No sign diff between groups (p=0.645) • at 6 weeks: o 89Sr: mean 1.65 (SD 1.17), p=0.010 o FEM: mean 1.73 (SD 1.33),	**Analgesic consumption:** no diff compared to baseline in both groups **Adverse events:** sign more mild and severe adverse events in FEM compared to 89Sr (p<0.05)	Risk of bias: high Author's conclusion: Side effects and the need for hospitalization were much more frequent in the FEM group than in the 89Sr group. As the effect on pain was comparable, 89Sr treatment is preferable.

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
			consumption, adverse events	p=0.008 ➔ Sign reduction at 6 weeks compared to baseline ➔ No sign diff between groups (p=0.846) • at 9 weeks: o 89Sr: mean 2.00 (SD 1.17), p=0.050 o FEM: mean 2.07 (SD 1.22), p=0.047 ➔ Sign reduction at 9 weeks compared to baseline ➔ No sign diff between groups (p=0.906) • at 12 weeks: o 89Sr: mean 2.12 (SD 1.67), p=0.090 o FEM: mean 1.93 (SD 1.33), p=0.039 ➔ Sign reduction at 12 weeks compared to baseline ➔ No sign diff between groups (p=0.751)		

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				Pain frequency • 89Sr: sign lower at 3 wks (p=0.016), 6 wks (p=0.014) and at 9 wks (p=0.039) • FEM: sign lower at 3 wks (p<0.002), 6 wks (p=0.008) and at 9 wks (p=0.045) ➔ No sign diff between groups (no p-value mentioned)		
Wang (2003)[56]	• Design: RCT • Sources of funding: not mentioned, conflict of interest not mentioned • Setting: Peking, China • Sample size: n= 9 (153Sm-EDTMP), n=9 (biphosphonate) • Duration: 4 months	Eligibility criteria: histologically proven metastatic bone cancer, bone pain, bone metastases intensively positive in a recent bone scan or determined by magnetic resonance imaging and computed tomography scan, pain refractory to analgesics, therapies not changed and/or modified, pain not originating from pathological bone fracture, absence of signs of spinal cord	Intervention: 153Sm-EDTMP (n=9), single dose of 37 MBq/kg, kept in isolation Control: pamidronate (n=9), 30mg/500ml saline Follow-up: weekly interval 1st month, 2-weekly interval 2nd month, 4week interval	**Pain intensity** • At baseline: o 153SM-EDTP: 8.0±3.4 o Pam: 7.7±2.2 • Overall effective rate o 153SM-EDTP: 77.8% (0 inefficient relief, 2 mild response, 7 effective, 0 excellent) ➔ Palliative effect started between 7th and 15th day ➔ Duration: 3.5±2.3 months	**Analgesic consumption:** not reported **Physical performance:** not reported **Acute adverse events:** no acute adverse events in both groups **Pain flare phenomenon**: 3/9 in 153Sm-EDTMP vs 1/9 in pam	Risk of bias: high Author's conclusion: The therapeutic efficacy of 153Sm-EDTMP was greater than that of pamidronate disodium. Hematological toxicities were mainly with 153Sm-EDTMP. The reduced level of myelotoxicity is a major advantage of biphoshonates.

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
		compression, life expectancy >3months, absence of hepatic and renal insufficiency and signs of disseminated intravascular coagulation, white blood cells ≥3.0X10/l, platelets ≥80x10/l and absence of signs of rapid depletion of bone marrow reserve Patient characteristics: • Sex: 6 men, 3 women in 153Sm-EDTMP vs 3 men, 6 women in pamidronate • Age: 52±1 in 153Sm-EDTMP vs 60±21 in pamidronate	for remaining 4 months) Primary outcomes: pain intensity (VAS, 0 (inefficient), 1 (mild response), 2 (effective), 3 (excellent relief), pain frequency (VAS, 1-4), regional pain index (intensity x frequency) Secondary outcomes: medication use, performance status (Karnofsky scale)	o Pam: 44.4% (4 inefficient relief, 1 mild response, 3 effective, 1 excellent) ➔ Palliative effect started between 3rd and 5th day ➔ Duration: 2.5±1.9 months **Pain frequency:** results not reported	Toxicities: • 153Sm-EDTMP: transient bone marrow suppresion (mild and reversible after week 6) • Pam: no hematological toxicities	

4.5. Bisphosphanates for painful bone metastases

Table 59 – Bisphosphonates: evidence table of systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
Mhaskar (2012)[57]	• Design: SR and MA.. • Sources of funding: Leukämie-Initiative Bonn e.v., Germany, Cochrane Haematological Malignancies Group (CHMG), Germany. • Search date:.update octobre 2011.. • Searched databases:. Medline;Central; ClinicalTrials.gov, Embase, Lilacs, American Society of Hematology. • Included study designs:. RCT.. • Number of included studies:.12 RTC • Included studies: o RCTs bisphosphonates vs placebo: - Etidronate	• Eligibility criteria: o. Patients with the diagnosis of Multiple Myeloma.. • Patient characteristics: o Not specified.	• Intervention:. treatment included any bisphosphonate.. • Control:.no therapy, placebo or other bisphosphonates		***Pain*** RR:0.75 (95% CI 0.60 - 0.95; p= 0.01) Heterogeneity: ζ^2=0.04, χ^2=18.93, df=7, p= 0.01, I^2=63% ***Adverse events***: No difference in frequency between intervention and control (Gastrointestinal symptoms, osteonecrosis of the jaw, hypocalcemia, renal dysfunction)	• AMSTAR evaluation: Yes, Yes, Yes, Yes, Yes, Yes, Yes, Yes, Yes, Yes, Yes • Authors' conclusions: Adding bisphosphonates to the treatment of Multiple Myeloma reduces vertebral fractures and probably pain. Zoledronate appears to be superior to etidronate (nonaminobisphosphonate) and placebo. However, whether zoledronate is superior to pamidronate and other aminobisphosphonates remains to be determined • Notes: update of the Wong 2004's SR

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
	Daragon 1993[p g r] - Pamidronate Attal 2006 [oj] Berenson 1998[p g h] Brincker 1998[g] Musto 2003 [h oj] Terpos 2000 [p g] - Clodronate Delmas 1982[p] Heim 1995 [p] Lahtinen 1992 [p g r] McCloskey 2001 [p g h] - Ibandronate Menssen 2002[p] o RCTs bisphosphonates vs no therapy: - Zoldronate Musto 2008 [oj]					

Outcomes: [p] Pain, or adverse effects [g] Gastrointestinal toxicity or [h] Hypocalcaemia or [r] Renal dysfunction or [oj] Osteonecosis of jaw

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
Wong (2009)[58]	• Design: SR MA • Sources of funding: Princess Margaret Hospital, University Heath Network, Canada. Marie Curie Cancer Care, UK. Toronto Sunnybrook Regional Cancer Center, Cancer Care Ontario, Canada. • Search date:.March 2003 • Searched databases: Medline, Embase, Cancerlit, Cochrane library (CCTR), Oxford Pain database • Included study designs:.RCTs • Number of included studies: 30 Arican 1999[BM] Belch 1991[MM*] Berenson 1996 [MM] Brincker 1998[MM*] Cascinu 1998[BM] Coleman 1998[B] Conte 1994[B] Daragon 1993[MM*] Delmas 1982[MM*] Elomaa 1992[P] Ernst 1992[BM]	• Eligibility criteria: o. Patients with bone metastases.from any primary neoplasms. • Patient characteristics: not specified	• Intervention: bisphosphonate agents. • Control:.placebo or open controls	***Proportion of patients with pain relief*** ***4 weeks (6 studies)*** OR:2.21 (95% CI 1.19 - 4.12; p=0.012) Heterogeneity: χ^2=1.87, df=5, p=0.87, I^2=0.0% ***8 weeks (1 study)*** OR: 2.57 (95% CI 0.64 - 10.31; p=0.18) ***12 weeks (5 studies)*** OR: 2.49 (95% CI 1.38 - 4.48; p=0.0024) Heterogeneity: χ^2=5.94, df=4, p=0.20, I^2=33 % ***Pooled results (8 studies):*** OR: 2.37 (95% CI 1.61-3.5; p=0.000014) Heterogeneity: χ^2=7.21, df=7, p=0.41, I^2=3.0 % ***Mean pain score (non standardized)***	***Toxicity*** ***Nausea and vomiting (6 studies)*** OR:1.11 (95% CI 0.79 - 1.58; p=0.55) Heterogeneity: χ^2=3.62, df=5, p=0.61, I^2=0.0%	• AMSTAR evaluation: Yes, Yes, Yes, Yes, Yes, Yes, Yes, Yes, Yes, Yes, Yes • Authors' conclusions: There is insufficient evidence to recommend bisphosphonates: o for first line therapy to manage of painful bony metastases. o to recommend the selection of patients for this treatment strategy based on primary histologies • Notes: Wong 2004 is another SR in the same topic with the same RCTs (plus one additional RCT see Carr 2002). The Wong 2004's

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
	Ernst 1997[BM] Glover 1994[B] Heim 1995[MM*] Hortobagyi 1996[B] Hultborn 1996[B] Koeberle 1999[BM] Kylmala 1997[P] Lahtinen 1992[MM*] Martoni 1991[B] Moiseyenko 1998[BM] O'Rourke 1995[BM] Piga 1998[BM] Robertson 1995 [BM] Siris 1983[B] Smith 1989[P] Strang 1997[P] Theriault 1999[B] Van Holten-Verzantzoort 1993[B] Vinholes 1997[BM]			***4 weeks (2 studies)*** Reduction in the mean pain score: 0.49 (95% CI -0.09 – 1.07; p=0.098) Heterogeneity: χ^2=0.38, df=4, p=0.54, I^2=0.0 % ***8 weeks (1 study), 12 weeks (5 studies):*** no pooling ***Proportion of patients with reduction in analgesic use*** ***4 weeks (3 studies)*** OR:2.81 (95% CI 1.24 - 6.38; p=0.013) Heterogeneity: χ^2=0.93, df=2, p=0.63, I^2=0.0 % ***12 weeks (3 studies)*** OR:2.37 (95% CI 1.10 - 5.12; p=0.028) Heterogeneity: χ^2=0.48, df=2, p=0.79, I^2=0.0 %		meta-analyses is included in the guideline of Ministry of Health Malaysia 2010

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
Wong (2012)[59]	• Design: SR • Sources of funding: National Institute for Health Research/ Department of Health Cochrane Review Incentive Scheme 2010, UK • Search date: update from January 2006 to April 2011 of a previous SR • Searched databases: Cochrane Breast Cancer Group's Specialised Register, Medline, Embase, WHO international Clnical Trials Registry Platform • Included study designs: RCT • Number of included studies:. Bone pain: 14 RCT QoL: 7 RCT.. • Included studies: *Bone Pain*: - Bisphosphonate versus control Kohno 2005 Aredia 2000	• Eligibility criteria: History of Breast Cancer • Patient characteristics: Women with breast cancer bone metastases (BCBM), with advanced breast cancer (ABC) without bone metastases, with early breast cancer (EBC)	• Intervention: o The use of any bisphosphonates, administered orally or intravenously, in any dose and for any duration o The use of other bone-acting agents, administered in any dose and for any duration • Control: oplacebo groups oopen control groups (no treatment)	***Bone pain improvement*** ***Pamidronate*** Improvement with i.v. 90 mg form (1 study) or with oral form (1 study) No improvement with lower dose (2 studies) ***Ibandronate*** Improvement with i.v. 6 mg form (1 study) or with oral 50 mg form (1 study) ***Clodronate*** Improvement with with oral form (1 study) No improvement (2 studies) ***i.v bisphosphonate (clodronate or pamidronate) versus oral clodronate*** Better pain reduction with i.v. form (1	***Quality of live improvement*** ***Ibandronate*** Significant improvement with 60 mg of i.v. form (1 study) and with 50 mg of oral form (1 study) ***Pamidronate*** Trend towards better global QoL with i.v. 90 mg form. No significant change in overall QoL with oral form (2 studies) No difference noticed between i.v. pamidronate and i.v. zoledronic acid (1 study) ***Clodronate*** No significant change in overall QoL with oral form (1 study)	• AMSTAR evaluation: Yes, Yes, Yes, Yes, No, Yes, Yes, Yes, Yes, Yes, Yes. • Authors' conclusions: • Intravenous zoledronic acid (4 mg every three to four weeks), is as effective as i.v. pamidronate (90 mg), with regard to the time to pain and QoL. • Intravenous pamidronate (90 mg every three to four weeks), in addition to chemotherapy or hormone therapy, is effective in reducing bone pain in women with advanced BCBM. • Intravenous ibandronate (6mg every three to four weeks), in addition

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
	Hultborn 1999 Conte 1996 Van Holten 1987 Body 2003 Tripathy 2004 Body 2004 Martoni 1991 Tubiana-Hulin 2001 Kristensen 1999 - Bisphosphonate A versus bisphosphonate B Rosen 2004 Diel 1999 - Denosumab versus bisphosphonate Stopeck 2010 *QoL*: - Bisphosphonate versus control (breast cancer with metastases) Van Holten 1987 Body 2003 Body 2004 Kristensen 1999 - Bisphosphonate A versus bisphosphonate B Rosen 2004			study not yet fully published) ***i.v zoledronic acid (4 mg) versus i.v. pamidronate (90 mg)*** No significant difference in overall pain between the 2 form (1 study)		to chemotherapy or hormone therapy, is effective in reducing bone pain and improving global QoL. • Oral clodronate (1600 mg taken daily, in single or divided doses), in addition to chemotherapy or hormone therapy, may also reduce bone pain in women. • Oral ibandronate (50 mg taken daily), in addition to chemotherapy or hormone therapy, is effective in reducing bone pain, and improving global QoL. • The ideal choice of bisphosphonates and other bone

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
	- Bisphosphonate versus control (breast cancer without metastases) Van Holten 1996					agents may be different from patient to patient. It is likely to depend on the bisphosphonate efficacy versus its toxicity, ease of administration, patient's prior treatment, patient preference, drug availability and local guidelines and legislation.

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
Yuen (2010)[60]	• Design: SR and MA.. • Sources of funding:. Tuen Mun Hospital, Hong Kong, China, Velindre NHS Trust, Cardiff, Wales, UK. • Search date:.May 2005.. • Searched databases:. Medline, Embase, Lilacs, Dare, amed, Central, American Society of Clinical Oncology • Included study designs: RCT... • Number of included studies:.10.. • Included studies: Adami 1989 Dearnaley 2003 Elomaa 1992 Ernst 2003 Kylmala 1993 Kylmala 1997 Saad 2002 Small 2003 Smith 1989 Strang 1997	• Eligibility criteria: o .confirmed bone metastases from prostate cancer • Patient characteristics: o ..no restriction.	• Intervention: Bisphosphonate excepted radioactive bisphosphonates. • Control:.placebo, no bisphosphonate treatment (open control) or another bisphosphonate treatment (active control)	***Proportion of patients with pain response (evaluable patients as defined by original studies)*** OR:1.64 (95% CI 1.02 - 2.61; p=0.04) However, no significant statistical effect when intention-to-treat analysis: OR:1.54 (95% CI 0.97 - 2.44; p=0.07). Heterogeneity: χ^2=1.04, df=3, p=0.79, I^2=0% ***No effect reported on*** o Proportion of patients with decreased analgesic consumption: OR:1.27 (95% CI 0.82 - 1.98; p=0.28). o Proportion of patients having any skeletal events or particular ones[$]	***Adverse events: proportion of patients having nausea*** OR:1.35 (95% CI 1.02 - 1.77; p=0.03) Heterogeneity: χ^2=0.00, df=1, p=0.99, I^2=0% ***No effect reported on*** o Treatment response (death, disease progression and radiological response) o Improvement in performance status o Vomiting and anaemia	• AMSTAR evaluation: Yes, Yes, Yes, Yes, Yes, Yes, Yes, Yes, No, Yes, Yes • Authors' conclusions: Bisphosphonate may have a role in decreasing pain and skeletal complications in patients with metastatic prostate cancer. Statistical analysis is limited by relatively small sample size and heterogeneity in study design. • Note: Berry 2006 is another SR on the same topic; it includes all studies included by Yuen 2010; and the same conclusion. The version 2006 of Yuen 2010's meta-analyses is included in the guideline of Ministry of Health Malaysia 2010

** no significant statistical effect when intention-to-treat analysis*
$ patients having vertebral fractures, non-vertebral fractures, spinal cord compression and patients received bone radiotherapy, bone surgery

Table 60 – Pamidronate: evidence table of randomized controlled trials

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
Berenson (2001)[61] (Wong 2004)	• Design: randomized, double-blind, doubledummy, parallel group multicenter study • Sources of funding: Novartis Pharmaceuticals Corp., East Hanover, NJ • Setting: USA, UK • Sample size: n= 68 (0.4 mg zolodronic acid) n= 73 (2 mg zolodronic acid) n= 66 (4 mg zolodronic acid) n= 73 (90 mg pamidronate) • Duration: ± 1 year	Eligibility criteria: Patients with a histologically confirmed diagnosis of metastatic breast carcinoma or multiple myeloma and with radiologic evidence of at least one osteolytic lesion Patient characteristics: Age (years) (mean±SD): 57.6 ± 12.9 (0.4 mg zolodronic acid) vs 56.5 ± 13.6 (2 mg zolodronic acid) vs 59.9 ± 11.3 (4 mg zolodronic acid) vs 57.7 ± 11.8 (90 mg pamidronate); Gender (M/F): 19/49 (0.4 mg zolodronic acid) 21/51 vs (2 mg zolodronic acid) vs 17/50 (4 mg zolodronic acid) vs 10/63 (90 mg pamidronate); ECOG status=0 (%) 24 (0.4 mg zolodronic acid) vs 25 (2 mg zolodronic acid) vs 25 (4 mg zolodronic acid) vs 26 (90 mg pamidronate); Pain score=0 (%) 16 (0.4 mg zolodronic acid) vs14 (2 mg zolodronic acid) vs 19 (4 mg zolodronic acid) vs 14 (90 mg pamidronate);	Intervention: 90 mg pamidronate Control: Zolodronic acid 0.4 mg, 2 mg and 4 mg	**Pain**: Pain score from 1 to 10 (Brief Pain Inventory BPI) End-of-study mean pain score (± SD): 0.4 mg zolodronic acid: 3.5 ± 2.55 (n=68)- difference to baseline -0.3 (SD 3.23) 2 mg zolodronic acid: 2.9 ± 2.70 (n=72)- difference to baseline -0.6 (SD 2.19) 4 mg zolodronic acid: 3.0 ± 2.86 (n=63)- difference to baseline -0.7 (SD 3.33) 90 mg pamidronate: 3.1 ± 2.82 (n=68)- difference to baseline -0.1 (SD 3.28): NS for comparison to zoledronic acid	**Adverse events**: Skeletal pain 0.4 mg zolodronic acid:31/68 2 mg zolodronic acid: 40/73 4 mg zolodronic acid: 30/66 90 mg pamidronate: 44/73 Nausea 0.4 mg zolodronic acid:30/68 2 mg zolodronic acid: 32/73 4 mg zolodronic acid: 26/66 90 mg pamidronate: 37/73 Vomiting: 0.4 mg zolodronic acid:16/68 2 mg zolodronic acid: 19/73	Risk of bias: unclear Author's conclusion: There was a slight trend for greater improvements in performance status and pain with 4.0 mg zoledronic acid compared with pamidronate. Skeletal pain also was reported as an adverse event less frequently by patients treated with zoledronic acid than patients treated with pamidronate. Remarks:

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				Among patients with pain at study entry, % of decrease in pain score 0.4 mg zolodronic acid:29/57 2 mg zolodronic acid: 30/62 4 mg zolodronic acid: 37/55 90 mg pamidronate: 31/62 NS **Performance status:** Among patients with score> 0 (ECG performance status) at study entry, % of improvement 0.4 mg zolodronic acid:4 /52 2 mg zolodronic acid: 19/54 4 mg zolodronic acid: 12/50	4 mg zolodronic acid: 24/66 90 mg pamidronate: 25/73	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				90 mg pamidronate: 7/54: NS as compared to zoledronic acid		
Conte (1996)[63] (Wong 2012)	• Design: RCT • Sources of funding: Ciba-Geigy • Setting: 43 centers from Argentina, Canada, France, Italy, Spain, Switzerland, United-Kingdom • Sample size: n= 143 (control) n= 152(intervention) • Duration: 3 years	Eligibility criteria: Female breast cancer patients with lytic or mixed lytic/sclerotic bone metastasis No prior bisphosphonate therapy, WHO performance status≤3 Patient characteristics: Age (years) [mean (range)]: CP 58 (30-79) vs C 58 (31-78)	Intervention: Chemotherapy plus pamidronate (CP) Control: Chemotherapy alone (C)	*Some improvement = 1 point reduction in pain for >6 weeks or 2 points reduction for >3 weeks* *Market improvement = 2 points reduction for > 6 weeks* *Results are not in ITT and presented in number of patients* **Pain:** Six points scale (none, mild, moderate, severe, very severe or unbearable) • Some improvement CP: 29 (21%) vs C: 42 (30%), ns • Market		Risk of bias: high Author's conclusion: Pamitronate i.v. hos a significantly greater proportion of patients achived marked reduction of pain. The therapy is remarkably well tolerated Remarks:

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				improvement CP: 54 (44%) vs C: 38 (30%), p=0.025 **Analgesic:** Six points scale: 0, no analgesic; 1, simple analgesic (e.g; paracetamol) or NSAIDs; 2, simple analgesics plus NSAIDs; 3, moderate analgesics (e.g; codeine); 4, opiates to ≤40 mg morphine daily; 5, opiates equivalent to more than ≥40 mg of morphine daily. • Some improvement (no definition given) CP: 23% vs C: 29%, ns • Market improvement CP: 13% vs C: 8%, ns **Performance**		

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				Status: WHO performance status • Some improvement (no definition given) CP: 28% vs C: 24%, ns • Market improvement CP: 14% vs C: 9%, ns		
Hortobagyi (1996)[70] (Wong 2004 / 2012)	• Design: RCT • Sources of funding: Pharmaceuticals Division, Ciba–Geigy, Summit, N.J. • Setting: 97 study sites in United States, Canada, Australia, and New Zealand • Sample size: n= 195 (control) n= 185 (intervention)	Eligibility criteria: Breast cancer Bone metastases required Pain required Co-intervention: chemotherapy as indicated clinically Performance status criteria: life expectancy > 9 months, ECOG PS </ = 3 Other criteria: exclude previous skeletal complications, hypercalcemia, ascites, renal, liver, cardiac dysfunction, bisphosphonate/radiotherapy within 60 days, calcitonin	Intervention: Pamidronate i.v. 90 mg monthly for 1 year Control: Placebo	**Pain:** 0-9 point scale [pain severity (0-3) x pain frequency (0-3)] *At 3, 6 and 9 months* Control group (first decrease, then increase from base line in bone pain) vs Intervention group (decrease from base line in bone pain); p≤ 0.05 (no data given) *At 12 months*	**Adverse effects:** Intervention: (withdrawn from study) Weakness: 1 Fatigue: 1 Hypocalcemia: 1 Control: None described	Risk of bias: low Author's conclusion: There were significant initial decreases in pain and narcotic scores in the pamidronate group, but not in the placebo group. By the final measurement, pain scores increased in both groups, but they increased

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
	• Duration: from January 1991 through March 1994	within 2 weeks Patient characteristics: Age (years) (mean ± SD): pamidronate 57 ± 12 vs placebo 56 ± 12; ECOG<2 (%): pamidronate 65 vs placebo 66 ; Patients with no pain (%) pamidronate 17 vs placebo 14 Patients in both groups were comparable for all above baseline characteristics		Among the patients with pain at base line, % of patients with decreased pain scores: control group (32 %) vs Intervention (44 %); p=0.03 **Analgesic:** similar pattern reported**,** no data given **Performance Status:** ECOG score baseline to 12 months: more worsening in the control group (p=0.03; no data given). **Spitzer quality-of-live:** Baseline to 12 months: NS, no data given		significantly more in the placebo group The effect of pamidronate on bone pain may partly explain the fact that there was significantly less worsening of ECOG performance scores in the pamidronate group. Remarks: Update of these results in Hortobagyi 1998 Withdrawals: Active: 0/185 Control: 2/197 Protocol 19 Aredia Breast Cancer Study Group
Hultborn (1999)[71] (Wong 2012)	• Design: Randomized, double-blind, placebo-controlled, multicenter study	Eligibility criteria: Breast cancer Bone metastases required Pain not required Co-intervention: as clinically indicated Performance status criteria:	Intervention: Pamidronate Intravenous 60 mg every 4 weeks, up to 2 yrs	**Pain:** VAS scale (patient reported) and Performance status: results reported in	**Adverse effects** Withdrawal from therapy Intervention group: 9/201 Control group:	Risk of bias: low Author's conclusion: Pamidronate i.v. 60 mg q ' weeks adds

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
	• Sources of funding: not mentioned • Setting: Sweden (8 oncology centers + 16 surgical units), Norway (4 oncology centers) • Sample size: n= 203 (control) n= 201 (intervention) • Duration: 2 years from inclusion of last patient (from december 1990 to september 1993)	life expectancy >3 months Other criteria: exclude previous bisphosphonates, hypercalcemia Patient characteristics: Age (years) (mean (median)): pamidronate 59.7 (60) vs placebo 58.8 (61); Performance status (WHO grade) <2 (%): pamidronate 80 vs placebo 80 ; Patients with no pain (%) pamidronate 17 vs placebo 14 Patients in both groups were comparable for all above baseline characteristics	Control: Placebo	graph only without presenting numbers: for this reason excluded from further use of these data in this report) Proportion (%) of patients that had ever used Opioids at the entry of the study / at the end of the study Intervention group (34% / 37%) vs Control group (36% / 55 %); p=0.14 NS for other pain drugs	3/203	to the QoL in women with bone metastases from breast cancer. Well-being reflected by performance status and pain scores show a benefit of the pamidronate treatment, also suggested by the absence of escalation in opioid analgesic consumption. However, according more recently published results, a higher dosage (90 mg) may be more effective. Remarks:
Small (2003)[79] (Yuen 2010) Pamidronate versus placebo	• Design: Randomized double-blind, placebo-controlled trial (conducted as two distinct	Eligibility criteria: Prostate cancer (hormone refractory). Bone metastases. Pain required. Life expectancy 6 months or above. RT and radio-isotope allowed.	Intervention: Pamidronate 90mg in 250ml D5 iv infusion over 2h q3w x 27 weeks	**Pain:** Brief Pain Inventory (11 point numeric rating scale 0-10) Pain response = mean change from baseline BPI	**Adverse effects:** bone pain: intervention 77/180, control 75/194 nausea:	Risk of bias: unclear Author's conclusion: Treatment with 90 mg pamidronate

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
	trials; results presented as one). • Sources of funding: Novartis Oncology, East Hanover, NJ • Setting: USA (1 trial) + international trial (other trial) • Sample size: Control $n_{randomized}$= 196 / $n_{analysed}$= 181 Intervention $n_{randomized}$= 182 / $n_{analysed}$= 169 • Duration: 27 weeks	Exclusion: leucopenia, thrombocytopenia, serum Cr 5mg/dL or above, corrected serum Ca 11mg/dL or above or 8. 4mg/dL or below, magnesium 0.8mg/dL or below, or total bilirubin more than 2.5mg/dL. Patient with untreated brain metastases, prior bisphosphonate therapy, abnormal ECG, ascites, impending spinal cord compression or spinal orthosis, or skeletal event within 1 month. Change in chemotherapy or hormone therapy within 6 weeks. Receiving drugs that affected osteoclast activity. Patient characteristics: Age (years) (Median (range)): pamidronate 72 (46-89) vs placebo 71 (42-88); BPI score (mean ± SD): least pamidronate 2.3 ± 1.9 vs placebo 2.4 ± 1.9 / average pamidronate 4.3 ± 2.1 vs placebo 4.5 ± 2.1 /worst pamidronate 6.0 ± 2.5 vs placebo 6.3 ± 2.4 ; OME score (mean ± SD):	Control: Placebo	Mean Pain change (average BPI) at week 9: intervention -0.61 SE 0.17, n=147; control: -0.44 SE 0.16 n=154 (p=0.46)/ At week 27: intervention -0.40 SE 0.25, n=110; control: -0.27 SE 0.24 n=108 (p=0.71) Patients having Radiotherapy for bone pain, week 9: intervention 11/169 control 10/181; week 27: control 25/169 control 29/181 (ns) **Analgesics**: Oral morphine equivalent (OME) Analgesic response = OME scores OME score, week	intervention 50/180, control 43/194 fatigue, anorexia, constipation, vomiting intervention 31/180, control 31/194 anaemia intervention 38/180, control 39/194 fever, weight decrease, asthenia, diarrhoea, dyspnoea, urinary tract infection, dizziness.	disodium did not lower pain scores in the intent-to-treat patient population compared with placebo at either 9 weeks or 27 weeks. First- and second-generation bisphosphonates have limited activity in advanced prostate cancer with painful bone metastases Remarks: Data pooled from two trials Aredia Prostate Cancer Group

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
		pamidronate 58.3 ± 153.5 vs placebo 48.2 ± 101.6		9: intervention +16.6 SE 6.8, n=147; control: +10.2 SE 6.6 n=154 (p=0.50) OME score, week 27: intervention +28.5 SE 8.9, n=110; control: +16.6 SE 68.7 n=108 (p=0.31) Decreasing or stable analgesic use at week 9: intervention 53/147, control 68/154 (ns); week 27: intervention 46/110, control 52/108 (ns).		
Theriault (1999)[80] (Wong 2004)	• Design: double-blind, placebo-controlled trial • Sources of funding: Novartis Pharmaceuticals, East Hanover, NJ. • Setting: USA • Sample size: n=	Eligibility criteria: Breast cancer (on stable hormonal therapy within 3 months) Bone metastases required Pain not required Co-intervention: Hormonal/ chemotherapy as clinically indicated Performance status criteria: life expectancy >/=9 months Other criteria: exclude	Intervention: Pamidronate i.v. 90 mg every 4 weeks x24 cycles Control: Placebo	**Pain:** 0-9 point scale [pain severity (0-3) x pain intensity (0-3)] Difference from in mean values of pain score Intervention group	**Adverse effects:** • Intervention group Allergic reaction: 1/182 Interstitial pneumonia: 1/182 • Control group None	Risk of bias: low Author's conclusion: Patients treated with 90 mg of pamidronate as a 2-hour infusion every 4 weeks as a supplement to hormonal therapy

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
	192 (control) n= 182 (intervention) • Duration: 2 years	patients on chemotherapy, cord compression, calcitonin/ mitramycin within 14 days prior to enrolment, skeletal event within 2 weeks, renal cardiac, liver dysfunction Patient characteristics: Age (years) (mean ± SD): pamidronate 60 ± 12 vs placebo 62 ± 11; ECOG<2 (%): pamidronate 79 vs placebo 73 ; Patients with no bone pain (%) pamidronate 15 vs placebo 20;QoL ≤ 5 (%) pamidronate 5 vs placebo 9 Patients in both groups were comparable for all above baseline characteristics	Hormonal therapy / chemotherapy as was necessary	vs Control group • At 12 month P=0.002 • At 24 month +0.5 vs +1.6; p=0.007 **Analgesic:** Score for the type of medication x frequency Mean analgesic use at 12 month and at the 24 month increased significantly more from baseline in the controle group than in the intervnetion group (P = 0.001 and P < 0.001, respectively). **ECOG performance status and Spizer QoL scores:** worsened from baseline in both treatment groups, with no statistically significant		in women with breast cancer, experienced a decrease in bone pain over the first year of the study. Although an increase in bone pain scores was reported at the second year time point for both groups in this study, the difference from placebo continued to be significant in favor of pamidronate. The performance status and QoL worsened in the 2 groups. This may be attributable to the additional year of follow-up time, during which progression of the underlying disease continued in most patients. Remarks:

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				difference between the two groups		Protocol 18 Aredia Breast Cancer Study Group

Table 61 – Clodronate: evidence table of randomized controlled trials

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
Dearnaley (2003)[65] (Yuen 2010) Clodronate versus placebo	• Design: Randomized double-blind placebo-controlled study • Sources of funding: Medical Research Council + Boehringer Mannheim • Setting: UK, New Zealand • Sample size: n=155 (intervention); n=156 (control) • Duration: 3 years	Eligibility criteria: Prostate cancer bone metastases. Pain not required. Commencing or responding to hormonal therapy; no previous use of long-term hormone therapy; normocalcaemia; WHO performance status 2 or less; bisphosphonates naive; serum creatinine less than 2 x ULN; no other active malignancy; no acute severe bowel inflammatory conditions; no serious concomitant disease; no drug trial within 12 months. Patient characteristics: Age (years) [median	Intervention: Clodronate oral 2080mg/day up to 3 years Control: Placebo up to 3 years	**Performance status:** WHO score • Sustained deterioration of WHO performance status: active 79/155 control 98/156; Hazard ratio (HR) = 0.71, 95%CI = 0.56-0.92, P=0.008, favours active. No data on pain outcome	**Adverse events**: Higher risk of adverse effects in active group, HR = 1.71 (1.21-1.41, P 0.002), Number of adverse events: Total active 123/155, control 82/156: gastrointestinal (active 31/155 control 21/156), cardiovascular, joint pain, dyspnoea, urinary, skin, second primary malignancy, tiredness, central nervous system,	Risk of bias: unclear Author's conclusion: Compared with patients in the control group, patients in the active group had a statistically significant increase in the time to deterioration of their WHO performance status. Drug-related toxicity was tolerable: the most commonly reported toxicities were gastrointestinal

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
		(range)]: intervention 71 (49-88), control 71 (47-88); Performance status (WHO score: %score 0 /%score 1/ %score 2): intervention 65/30/5, control 66/27/7			bone pain/fracture, sweats, dizziness, headaches, abnormal blood counts (active 2/155 control 3/156) or biochemistry, paresthesia, sleep, hepatic, memory, gastrointestinal bleeding, etc.	problems or asymptomatic increases in lactate dehydrogenase Remarks:
Ernst (1992)[67] (Wong 2004)	• Design: randomized controlled cross-over trial • Sources of funding: not mentioned • Setting: Canada • Sample size: n=24, randomized to two groups (intervention-control, no data on number of participants in each group)	Eligibility criteria: Cancer patients with bone metastasis Patient characteristics: Age (years) [median (range)]: 59 (36-82); male:female ratio 1:2	Intervention: Cl_2MDP 600 mg in 500 ml of normal saline followed 500 ml of normal saline alone as placebo Control: 500 ml of normal saline alone as placebo followed Cl_2MDP 600 mg in 500 ml of	**Pain**: VAS 10 cm At 7 days: Average decrease in pain (Cl_2MDP vs. placebo) – 0.89 (SE = 0.27); 95 % CI -1.43 to -0.35, p=0.004 **Analgesic use:** Daily oral morphine equivalent Cl_2MDP: +10 mg (SE = 8.1) vs Placebo +62 mg (SE = 29.6) ;		Risk of bias: unclear Author's conclusion: Cl_2MDP is safe and has analgesic properties that may prove to be useful for metastatic bone pain. Although the findings demonstrate a statistically significant reduction in pain intensity, the magnitude of the

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
	• Duration: 7 days		normal saline	p=0.096		effect may be of limited clinical relevance. Remarks:
Ernst (1997)[68] (Wong 2004)	• Design: Randomized Controlled crossover trial • Sources of funding: not mentioned • Setting: 2 centers in Canada • Sample size: n=60, randomized to two groups (intervention-control); only 46 patients evaluable • Duration: 28 days	Eligibility criteria: Metastatic cancer with refractory bone pain Patient characteristics: Age (years) [median (range)]: 63 (37-85)	Intervention: intravenous infusion of clodronate (600 mg or 1500 mg) followed by placebo (C) Control: placebo followed by clodronate (600 mg or 1500 mg) (P)	**Pain**: 150 mm visual analogue scales that assessed general pain, pain at rest, pain with movement, level of activity, nausea, depression, anxiety, drowsiness, appetite, and general wellbeing. Decrease from the baseline For days 11-14 CI: 22 mm (SE = 7.2) vs P: 13.2 mm (SE=7.5), p=0.51 No significant reduction in pain at rest (p=0.78) and pain with movement (p=0.22) **Analgesic use:**		Risk of bias: unclear Author's conclusion: Clodronate appeared to have an analgesic effect in patients with refractory pain Remarks:

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				Daily morphine equivalent doses Average change CI: -6.4 (SE = 2.9) vs P:+24.6 (SE=14.9), p=0.03		
Ernst (2003)[69] (Yuen 2010)	• Design: Randomized double-blind controlled study • Sources of funding: no mentioned • Setting: Canada (17 sites) • Sample size: n=115 (intervention), n=112 (control); • Duration: 44 months	Eligibility criteria: Prostate cancer. Progressive bone disease. Castration testosterone levels. Hormonal treatment stopped before randomization. Pain required: PPI = 1 or more. Stable analgesic intake required. ECOG performance status < 3, adequate baseline cardiac, haematologic and biochemical function, able to complete pain and QOL scores. Exclusion: prior malignancy, more than one previous chemotherapy regimen or a previous regimen containing mitoxantrone or an anthracycline, precious bisphosphonate therapy, treatment with radiotherapy within the previous 4 weeks or radioisotopes within the previous 8 weeks,	Intervention: clodronate 1500mg i.v. q3w until disease progression in responding patients Control: placebo q3w Cointervention: mitoxantrone 12mg/m2 iv q3w and prednisolone 5mg po bid	**Pain**: six-point PPI scale 0-5 (Present pain intensity scale of the McGill-Melzack Pain Questionnaire) Pain response: (two or more reduction in the PPI score in comparison with baseline, without increase in analgesic score and maintained on two consecutive evaluations at least 3 weeks apart) Intervention 34/115 control 27/112; p=0.34 **Analgesic use:**	**Adverse events**: Adverse effects (grade3/4) (active:control): granulocytopenia 14/115 14/112, anaemia 8/115 5/112, thrombocytopenia 2/115 4/112, cardiovascular 0/115 3/112 nausea/vomiting 9/115 7/112 headache 4/115 1/112 dyspnoea 4/115 7/112 infection 7/115 3/112	Risk of bias: unclear Author's conclusion: Routine use of clodronate cannot be recommended for palliation of symptomatic bone disease in patients with HRPC. A palliative role may exist for patients with moderate to severe pain, but this remains to be confirmed in a prospective clinical trial. Remarks: ineligible: active 11/115, control 7/112; analysed:

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
		radicular or back pain suggestive of epidural metastases, potential spinal cord or nerve root compression, impending pathological fracture, and uncontrolled cardiac failure or active infection Patient characteristics: Age (years) [median (IQR)]: clodronate 70.1 (65.4-76.4) vs placebo 70.6 (64.4-74.6); Daily morphine equivalents mg: clodronate 70 (40-114) vs placebo 57 (28.5-107); PPI %mild (PPI 1-2): clodronate 75 % vs placebo 78 %; ECOG performance status: clodronate 67 % vs placebo 75 %		Analgesic score defined by total number of analgesics units (1 unit = standard doses of nonopioid, 2 units = morphine 10-mg equivalents). • Analgesic response (defined as a 50% decrease in analgesic score from the baseline with no increase in pain and maintained on two consecutive evaluations at least 3 weeks apart) Intervention 34/115 control 32/112 ; p=0.84 • No need for analgesic Intervention 33/115 control 27/112; p=0.42 **Palliative**		active 104, control 105

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				response: defined as either 2-point reduction in PPI (present pain intensity score, six-point, 0-5) without increase in analgesic score; or >50% decrease in analgesic score, without increase on PPI. These criteria had to be maintained on two consecutive evaluations at least 3 weeks apart. Intervention 49/115, control 41/112; p=0.37 **QoL** HRQOL response was defined as a 1-cm improvement from baseline on the 10-cm visual analog scale for overall well-being maintained on two		

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				successive visits no less than 3 weeks apart Intervention 39/115 control 44/112 ; p=0.61		
Kylmälä (1997)[72] (Yuen 2010/Wong 2004)	• Design: Randomized double-blind placebo-controlled study • Sources of funding: Finnish Academy of Sciences, Finnish Cancer Foundation, Finnish Medical Society Duodecim, Reino Lahtikari Foundation and Leiras Clinical Research • Setting: Finland • Sample size: n=28 (intervention); n=29 (control) • Duration: 12	Eligibility criteria: Prostate cancer (failed hormonal therapy). Bone metastases required. No pain required. Life expectancy 6 months or more. Exclusion radiotherapy within 2 weeks. Hormonal/ chemotherapy allowed Patient characteristics: Age (years) [mean (range)]: intervention 72 (52-81) vs control 76 (59-86); Baseline pain (grade 0,1,2,3,4): intervention 6,13,5,3,0/28 control 2,12,12,1,0/29; Performance status (WHO)< 2: 16/28 (intervention) vs 6/29 (control)	Intervention: Clodronate (i.v. 300mg/day x 5days followed by oral 1.6g/day x 12 months) Control: Placebo All received estramustine 280mg twice daily.	**Pain**: Proportion of patient without pain at (assessed by patient): • 1 month Intervention 10/28, control 6/29 (ns). • 3 months Intervention 9/28, control 6/29 (ns). • 6 months Intervention 6/28, control 5/29 (ns). • 12 months Intervention 4/28, control 4/29 (ns). **Analgesic:** Proportion of patient without analgesic: • 1 month	**Adverse events**: Nausea at 1 month: Intervention 33% placebo 40%. No renal failure	Risk of bias: high Author's conclusion: Clodronate i.v. at the start of treatment followed by an oral maintenance dose does not improve the palliation of painful bone metastases due to prostate cancer. Remarks:

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
	months			Intervention 13/28, control 8/29 (ns). • 3 months Intervention 8/28, control 5/29 (ns). • 6 months Intervention 6/28, control 5/29 (ns). • 12 months Intervention 4/28, control 4/29 (ns). **Performance status (WHO):** Five-step grading scale (0, asymptomatic; 1, minor symptoms; 2, less than 50% of the time in bed; 3, more than 50% of the time in bed; 4,totally bedridden): differences between groups in performance changes not significant at 1, 3, 6, 12 months (no numbers given) Rem: at admission		

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				significant difference between groups		
Lahtinen (1992)[73] (Wong 2004 / Mhaskar 2012)	• Design: Double-blind placebo-controlled trial • Sources of funding: Huhtamäki Oy, Leiras, Turku and Finnish Cancer Foundation • Setting: Finland (26 sites) • Sample size: n= 168 (intervention), n=168 (control) • Duration: 24 months	Eligibility criteria: Multiple myeloma Bone lesion not required No pain requirement Co-intervention: chemotherapy Other: exclude patients who are asymptomatic, unable to tolerate chemotherapy, previous bisphosphonates Patient characteristics: Gender (M/F):intervention 84/84 vs control 82/86; Age (years) [% < 65 / % 65-74 / > 75]:intervention 51/35/14 vs control 37/45/18	Intervention: Clodronate Oral 2.4 g/day at 4 weeks post CT, then for 24 months Control: Placebo All patients received mephalan and prednisone	**Pain**: Pain measurement tool: 0-4 pain scale, patient reported % of patient with no pain • Baseline vs 12 months Intervention 23.8% vs 52.1 % (p<0.001) Control 29.3% vs 45.9% (p<0.001) No difference between group • Baseline vs 24 month Intervention 23.8% vs 53.6 % (p<0.01) Control 29.3% vs 53.6% (p<0.001) No difference between group	**Adverse events**: Intervention / Control group: Nausea: 29/25 Diarrhea: 17/15 Constipation: 0/8 Abdominal pain: 18/33 Allergic reaction: 15/3	Risk of bias: high Author's conclusion: There is no difference in pain improvement between clodronate and placebo because of the pain relief in the placebo group induced by chemotherapy alone. The treatment is well tolerated, no more side-effects were reported Remarks: Withdrawals: Intervention arm: 7/175 Control arm: 7/175

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				Analgesic use: Mean daily number of tablets/ capsules Use of non-narcotic analgesic • Baseline vs 12 months Intervention 1.5 (0.1) vs 0.6 (0.1) (p<0.001) Control 1.2 (0.1) vs 0.6 (0.1) (p<0.001) No diference between group • Baseline vs 24 month Intervention 1.5 (0.1) vs 0.5 (0.1) (p<0.001) Control 1.2 (0.1) vs 0.4 (0.1) (p<0.001) No diference between group Use of narcotic analgesic • Baseline vs 12		

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				months Intervention 0.4 (0.1) vs 0.3 (0.1) (p<0.05) Control 0.5 (0.1) vs 0.3 (0.1) (p<0.05) No diference between group • Baseline vs 24 month Intervention 0.4 (0.1) vs 0.2 (0.1) (ns) Control 0.5 (0.1) vs 0.2 (0.1) (ns) No diference between group		
O'Rourke (1995)[75] (Wong 2004)	• Design: double-blinded randomized placebo-controlled trial • Sources of funding: Boehringer Mannheim,Germany	Eligibility criteria: Patients with cancer associated osteolysis Patients were excluded if fasting urinary calcium excretion < 0.175 mmol/mmol creatine, radiotherapy within 1 month hormone treatment, bisphosphonates within 3	Intervention: Oral sodium clodronate 400 mg/d or 1600 mg/d or 3200mg/d	**Pain score**: VAS at 4 weeks control 3.4 ± 0.8 vs 400 mg clodronate 2.7 ± 0.7 vs 1600 mg clodronate 2.7 ± 0.6 vs 3200 mg clodronate 3.5 ± 0.8	**Adverse events**: Nausea or vomiting Clodronate (all doses) 10/59 Placebo 6/21 Diarrhea	Risk of bias: unclear Author's conclusion: After 4 weeks of treatment, the overall analgesic requirement remained the same

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
	• Setting: UK (1 centre) • Sample size: n= 21 (control), n=20 (400 mg clodronate); n=19 (1600 mg clodronate); n=20 (3200 mg clodronate); • Duration: 4 weeks	months before randomization, live expectancy < 1 year, presence of hyperparathyroidism, Paget's disease of bone, vitamin D deficiency, treatment with thiazide diuretics or mithramycin Patient characteristics: Age (years) [median (range): control 57 (34-80) vs 400 mg clodronate 57 (39-78) vs 1600 mg clodronate 54 (41-78) vs 3200 mg clodronate 61 (28-73); Pain score (mean ± SD): control 4.9 ± 0.8 vs 400 mg clodronate 2.6 ± 0.6 vs 1600 mg clodronate 3.4 ± 0.7 vs 3200 mg clodronate 4.0 ± 0.8	Control: Placebo	No difference between groups	Clodronate (all doses) 5/59 Placebo 1/21 Flatulence Clodronate (all doses) 5/59 Placebo 0/21	and there was no discernible change in pain score within or between treatment groups. The failure to detect any change in analgesic requirements or pain scores with clodronate is probably due to the relatively slow onset of the analgesic effect of oral bisphosphonates Remarks:
Piga (1998)[76] (Wong 2004)	• Design: double-blind randomized placebo controlled trial • Sources of funding: not mentioned • Setting: Italy	Eligibility criteria: Any primary (poor prior response to chemotherapy) Bone metastases required No pain requirement Co-intervention: none described Performance status criteria: life expectancy ≥3m, PS	Intervention: Clodronate Oral 1600 mg/day x1 year Control: Placebo	**Pain**: Huskisson VAS Baseline vs 3 months (mean ±SD) Intervention 7.5 ± 5.4 vs 5.1 ± 4.8 Control 6.4 ± 5.4 vs 6.4 ± 5.9	**Adverse events**: Intervention: GI discomfort: 3/27 Control: GI discomfort: 5/23	Risk of bias: unclear Author's conclusion: Patients receiving clodronate had a significant lower

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
	• Sample size: n= 27 (intervention), n = 23 (control) • Duration: 3 months	≥40 Other criteria: exclude hypercalcemia, renal dysfunction Patient characteristics: Age (median): Clodronate 65, Placebo 63		No difference between group (p=0.424) **Analgesics:** Analgesic score: 0: none; 1: NSAIDS; 2: opiates Number of patients increasing analgesic scores at 3 months Intervention 5/27 Control 10/22 p=0.042 Baseline vs 3 month (mean of days on analgesics ±SD) Intervention 16.3 ± 13.9 vs 18.1 ± 13.6 (p=0.065) Control 10.0 ± 13.1 vs 15.0 ± 13.4 (p=0.0002) No difference between group (p=0.176) **Karnofsky Performance status (Ps)**		increase in analgesic use and pain scores were tendentially in favor of clodronate Remarks:

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				baseline vs. 3 months: Patients with Ps stable or minor change: Intervention 18/24, control 13/21; Increase 20 %: Intervention 1/24, control 0/21; Decrease 20 %: Intervention 5/24, control 8/21. No difference between groups (p=0.323)		
Robertson (1995)[77] (Wong 2004)	• Design: double-blind, placebo-controlled randomized study • Sources of funding: Boehringer, Mannheim UK • Setting: UK (1 centre) • Sample size: n=27 (intervention),	Eligibility criteria: Any primary (Resistant to first line chemotherapy) Bone metastases required Pain required Co-intervention: hormonal/chemotherapy as clinically indicated Performance status criteria: life expectancy: >2m Other criteria: exclude renal dysfunction, use of bisphosphonates	Intervention: Clodronate Oral 1600 mg/day Control: Placebo	**Pain**: Pain measurement tool: VAS(0-10 points). patient reported Change from entry to 1 month [Median (range)] Intervention -0.9 (-2.6 ─ -0.4) vs control +0.4 (-0.1 ─ +4.0) p=0.03	**Adverse events**: Intervention: Hypocalcemia: 2/27 Control: Hypocalcemia: 0/28	Risk of bias: unclear Author's conclusion: Patients with bone pain from advanced metastasic disease gain a statistically significant, but clinically modest benefit from supportive

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
	n= 28 (control) • Duration: not mentioned; results at 1 month presented	Patient characteristics: Age (years) [mean ±SEM] : intervention 60 ± 4.6, control 65 ± 3.8, Vas score [Median (range)]: intervention 3.2 (1.6-7.5), control 4.8 (2.1-6.9), Opiate dose (morphine equivalents; mg/d) [mean ±SEM]: intervention 124 ± 39, control 133 ± 72		**Analgesic use:** Increase in analgesic use (not further specified) (1 month) Intervention 16/27 control 18/28 (no significant difference)		clodronate therapy. Before such treatment gains wide spread acceptance, further studies will be required to compare the clodronate response with that of established treatments for bone pain such as radiotherapy, chemotherapy and adjustment of analgesic regimen. Remarks:
Tubiana-Hulin (2001)[82] (Wong 2012)	• Design: Double-blind randomised controlled study • Sources of funding: not mentioned • Setting: France (16 sites) • Sample size: n=69 (intervention), n=68 (control) • Duration: 12	Eligibility criteria: Patients with Breast Cancer and osteolytic bone metastases and live expectancy > 12 months Patient characteristics: Age (years) [median (range)]: intervention 57 (30-74) control 59.5 (30-78); VAS (mm) intervention 38.3 control 37.8; Patients with no pain: intervention 12/69,	Intervention: Oral clodronate 1600 mg/d Control: Placebo	**Pain**: VAS (100 mm) Mean difference between baseline and 12 months evaluation Intervention -11.8 ± 3.2 vs control 4.5 ± 4.7; p=0.007 Patients without pain Intervention 23/69	**Adverse events**: Intervention Nausea/vomitting: 7/69 Diarrhea / constipation: 4/69 Abdominal pain: 2/69 Other GI discomfort: 4/69	Risk of bias: high Author's conclusion: The pain intensity and the analgesic consumption are in favor of clodronate Remarks:

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
	months	control 8/68		control 13/68 (ns) **Analgesics consumption** Use of analgesics (not further defined, study duration 12 months): Intervention 46/69 vs control 57/68; p=0.02 Increase in dosage of analgesic (not further defined, study duration 12 months): Intervention 51.4 % vs control 48.7%; p=0.83 Increase in analgesic category (not further defined, study duration 12 months): Intervention 38/69 vs control 36/68 (ns)	Control Nausea/vomitting: 9/68 Diarrhea / constipation: 0/68 Abdominal pain: 5/68 Other GI discomfort: 4/68	

Table 62 – Ibandronate: evidence table of randomized controlled trials

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
Body (2007)[62] (update)	• Design: multicenter, randomized, open-label trial • Sources of funding: Hoffmann-La Roche • Setting: multi-center study in 7 countries • Sample size: n= 137 (IB), n=137 (ZA) • Duration: 12 weeks	Eligibility criteria: Adult female patients with breast cancer and at least one osteolytic or mixed bone lesion, performance status (WHO) from 0 to 2, life expectancy of ≥ 6 months; adequate renal function at baseline; and stable antineoplastic therapy (including corticosteroids) for at least 4 weeks Patient characteristics: Age (years) [median (range)]: IB 55 (29-85) vs ZA 55 (31-80); WHO performance status =0: IB 31/137 vs ZA 38/137; Pain score: IB 0.92 vs ZA 0.82 The treatment groups were balanced with respect to demographics and all baseline disease characteristics	Intervention: oral ibandronate (50 mg/day) (IB) Control: i.v. zoledronic acid (4 mg every 4 weeks) (ZA)	**Pain**: 5 point scale (where 0 = no pain and 4 = intolerable pain) Mean score (±SD) at 12 weeks IB -0.14 ± 0.78 vs ZA -0.21 ± 0.77, p = NS **Analgesic score:** 0:None,1:Simple analgesic or NSAID, 2:Simple analgesic + NSAID,3: Moderate analgesic (e.g. DFI 18),4: Opiates (< 40 mg morphine daily),5:Opiates (>40mg morphine daily) Mean score (±SD) at 12 weeks IB -0.05 ± 0.84 vs ZA -0.11 ± 0.53, p = NS **Performance status:** Mean WHO performance status at 12 weeks IB -0.03 vs ZA -0.02	**Adverse events**: • Musculoskeletal and connective tissuedisorders IB 15/137 ZA 28/137 • Gastrointestinal disorders IB 15/137 ZA 11/137 • General disorders and administration site conditions IB 5/137 ZA 45/137 • Nervous system disorders IB 3/137 ZA 15/137	Risk of bias: unclear Author's conclusion: Effects of oral IB and i.v. ZA are equivalent. More patients experienced adverse events with i.v. ZA 4 mg than with oral IB 50 mg Remarks:

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
Diel (2004)[66] (update)	• Design: randomised, double-blind, placebo-controlled, parallel group, phase III study • Sources of funding: Roche • Setting: 75 centres in Europe, Kuwait, Russia, South Africa and the United States. • Sample size: n= 158 (control), n=154 (IB2), n=154 (IB6) • Duration: 96 weeks	Eligibility criteria: Patients with breast cancer and bone metastases, WHO performance status ≤2 and aged ≥ 18 years Patient characteristics: Age (years) [median (rage)]: control 53.0 (27-82); IB2 55.5 (32-77), IB6 57.0 (34-97); No bone pain: control 26/158, IB2 30/154, IB6 21/154, WHO performance status=0: control 27/158, IB2 41/154, IB6 32/154	Intervention: 2 mg ibandronate by i.v. bolus injection (IB2) Or 6 mg ibandronate by i.v. infusion (IB6) Control: Placebo	**Pain**: 5 points scale 0:none, 1:mild, 2:moderate, 3:severe or 4:intolerable Variation in mean pain scores between baseline and last assessment IB2 0.21±0.09 vs control 0.19±0.11;NS IB6 -0.28±1.11 vs control 0.19±0.11;p<0.001 **Analgesic use:** 6 points scale 0:none, 1:mild analgesic [aspirin or paracetamol/acetaminophen] or NSAID, 2:mild analgesic + NSAID, 3:moderate analgesic, 4:opiates <40 mg morphine [or equivalent] daily, 5:opiates ≥40 mg, but <100 mg morphine [or equivalent] daily, or 6: opiates ≥100 mg morphine [or equivalent] daily). Change in score between baseline and last assessment (up to 96 weeks): IB2 0.65±1.25 vs control	**Adverse events**: Control 46/158 IB2 41/154 IB6 38/154	Risk of bias: unclear Author's conclusion: Ibandronate treatment significantly improves QoL in patients with metastatic bone disease due to breast cancer, and significantly reduces pain scores. Remarks: Efficacy variables were evaluated using last-observation-carried-forward (LOCF) assessments

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				0.90±1.64;NS IB6 0.51±1.54 vs control 0.90±1.64;NS **QoL:** Quantitative data not reported		
Tripathy (2004)[81] (Wong 2012)	• Design: randomized, double-blind, placebo-controlled trial • Sources of funding: Roche • Setting: 68 centers in the USA, Australia, New Zealand, Bulgaria, Russia and South Africa • Sample size: n= 143 (control), n=144 (IB20), n=148 (IB50) • Duration: 96 weeks	Eligibility criteria: Adult women with breast cancer and bone metastases, WHO performance status of 0–2 Patient characteristics: Age (years) [median (rage)]: control 57.0 (31-83); IB20 56 (30-82), IB50 57 (29-92); Pain score (mean ± SD): control 1.23±0.81, IB20 1.34±0.82, IB50 1.30±0.84, WHO performance status<2: control 122/143, IB20 117/144, IB50 132/148 IB50 group had a lower percentage of patients with a WHO status of 2	Intervention: Oral ibandronate 20 mg (IB20) or Oral ibandronate 50 mg (IB50) once daily for up to 96 weeks Control: Placebo,	**Pain**: Bone pain scale from 0 (none) to 4 (intolerable). Change from baseline to study end point at 96 weeks (LOCF, last outcome carried forward) IB20 -0.06 vs control 0.21;p=0.071 IB50 0.03 vs control 0.21;p=0.201 **Analgesic use:** Scale from 0 to 6 (see Diel 2004) IB20 0.43 vs control 0.96;p=0.006 IB50 0.73 vs control 0.96;p=0.074	**Adverse events**: • Abdominal pain control 2/143, IB20 1/144, IB50 5/147 • Dyspepsia control 11/143, IB20 12/144, IB50 15/147 • Nausea control 3/143, IB20 8/144, IB50 7/147 • Esophagitis control 2/143, IB20 2/144, IB50 4/147 • Nausea and vomiting control 3/143, IB20 0/144, IB50 2/147 • Flatulence control 3/143,	Risk of bias: unclear Author's conclusion: The mean decrease in bone pain scores from baseline to endpoint was highly statistically significant, and was not due to increased analgesic use (this was actually lower with IB50 than with placebo). QoL also significantly improved with oral ibandronate, an effect not reported over 2 years of treatment with

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
		(10.8%) compared with the IB20 (19.4%) and control (15.4%) groups			IB20 0/144, IB50 1/147 • Diarrhea control 2/143, IB20 1/144, IB50 1/147 • Hypocalcemia control 6/143, IB20 9/144, IB50 10/147	other bisphosphonates for metastatic bone disease. In addition to its efficacy benefits, the availability of oral ibandronate would improve treatment compliance and enhance home maintaining. Remarks: Pain scores and analgesic use were assessed using last observation carried forward (LOCF) scores

Table 63 – Zoledronic acid: evidence table of randomized controlled trials

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
Saad (2002)[78] Saad (2004)[94] (Yuen 2010)	• Design: Randomized double blind placebo-controlled study • Sources of funding: Novartis Pharma • Setting: Sample size: n= 214 (ZA4), n=221 (ZA8), n=208 (control) • Duration: 15 months	Eligibility criteria: Prostate cancer (hormone refractory). Bone metastases required. Pain not required. ECOG performance status of 0,1,2. Co-intervention: Antineoplastic therapy allowed. Exclusion: bone pain requiring strong narcotic therapy, chemotherapy (except estramustine), RT within 3 months, previous bisphosphonate treatment, severe heart disease or hypertension, a serum creatinine of more than 3mg/dL or calcium less than 8mg/dL or greater than 11.6mg/dL. Patient characteristics: Age (years) [mean±SD]: ZA4 71.8±7.9 vs ZA8 71.2±8.0 vs control 72.2±7.9; ECOG status<2: ZA4 197/214 vs ZA8 202/221 vs control	Intervention: Zoledronic acid 4mg (ZA4) Or Zoledronic acid 8mg (ZA8) (reduced to 4 mg during the trial because of renal function deterioration. For this reason results of ZA 8 mg not mentioned-see Saad 2004) Control: Placebo q3w Ca supplement and vit D.	Results of ZA8 not mentioned because dose was lowered during trial for reason of renal function deterioration (see Saad 2004) **Pain**: Brief Pain Inventory pain score Variation in mean from baseline to: • 15 months ZA4 0.58 (95 % CI =0.29 to 0.87) vs control 0.88 (95 % CI =0.61 to 1.15); p=0.134 BPI, mean least-squares change from baseline value at: • 18 months ZA4 0.58 vs control 0.95; -0.37 (95% CI -0.78 to -0.04); p=0.075 • 21 months ZA4 0.56 vs control 1.07; -0.51 (95% CI -0.91 to -	**Adverse events**: • Bone pain ZA4 108/214, ZA8 133/218, control 127/208, • Nausea ZA4 77/214, ZA8 115/218, control 77/208 • Anaemia ZA4 57/214, ZA8 60/218, control 37/208 • Vomiting ZA4 46/214, ZA8 115/218 control 43/208,	Risk of bias: low Author's conclusion: Long-term treatment with ZA4 provides durable palliation of bone pain in patients with bone metastases secondary to hormone-refractory prostate cancer. Remarks:

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
		190/208; BPI score [mean±SD]: ZA4 2.0±2.0 vs ZA8 2.5±2.1 vs control 2.1±2.0		0.10); p=0.014 • 24 months ZA4 0.58 vs control 1.05; -0.47 (95% CI -0.88 to -0.06); p=0.024 **Analgesic use:** Analgesic score 0-4 Variation in mean from baseline to 24 months ZA4 1.04 vs control 1.17; p=0.491		

Table 64 – Etidronate: evidence table of randomized controlled trials

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
Daragon (1993)[64] (Mhaskar 2012)	• Design: RCT • Sources of funding: Association pour la recherche contre le cancer, Ligue nationale de lutte contre le cancer	Eligibility criteria: Patients with multiple myeloma Patient characteristics: Age (years) [mean±SD]: etidronate 65.6±9.8 vs placebo 66.9±9; Male/female: etidronate 22/27 vs placebo 22/23; pain index (±SD):	Intervention: Etidronate tablets 10 mg/kg/d Control: Placebo tablets	Measurements at 4 months on 39/39 patients, no intention-to-treat. **Pain**: Huskisson (VAS) index (cm±SD) at 4 months Etidronate 1.7 ±2 vs placebo 2±2.3, ns Pain index to evaluate the severy (severe, moderate,		Risk of bias: high Author's conclusion: Etidronate per os (10 mg/kg/day for 4 month) has no effect on clinical parameters

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
	• Setting: 6 centers in France • Sample size: n= 49 (etidronate); n=45 placebo • Duration: 4 months	etidronate 4.6±5.2 vs placebo 4.9±6.3, analgesic (class 2+3) etidronate 14 vs placebo 17, Karnofsky (±SD): etidronate 77±16 vs placebo 75±16		light), the rhythm (permanent, intermittent) and the number of pain areas at 4 months: Etidronate 2.3 ±3.1 vs placebo 3±4.6, ns **Analgesic use** Class1: paracetamol; Class2 codeine, dextropropoxyphene; Class3 (morphine) Analgesic class2+3 at 4 months: Etidronate 7/39 vs placebo 12/39, ns **Performance status** Karnofsky's scale at 4 months: Etidronate 85.1 ±10.7 vs placebo 81.8±12.2, ns		Remarks:

Table 65 – Residronate: evidence table of randomized controlled trials

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
Meulenbeld (2012)[74] (update)	• Design: randomised, open label, phase II/III trial • Sources of funding: Sanofi-Aventis • Setting: 45 centres in the Netherlands and 1 in Norway • Sample size: n= 301 (D), n=291 (DR) • Duration: treatment every 3 weeks, until tumor progression; maximal treatment duration 30 weeks (10 cycles of intervention), then follow-up	Eligibility criteria: Adult patients histologically proven prostate cancer patient with progression during prior castration and castration levels of testosterone, with bone metastases, with an ECOG performance status ≤2, and adequate haematological, hepatic and renal function Patient characteristics: Age (years) [median (range)]: D 69 (46-84), DR 68 (46-89); WHO performance status <2: D 88%, DR 89 %; Present Pain Inventory PPI<2 D 76 %, DR 76 %	Intervention (until tumor progression): Docetaxel 75 mg/m² i.v., every 3 weeks + prednisone 5 mg bid + risedronate 30 mg oral od (DR) Control (until tumor progression): Docetaxel 75 mg/m² i.v., every 3 weeks + prednisone 5 mg bid (D)	**Pain**: Pain response was defined as ≥2 point reduction from baseline median PPI score, without increase in analgesic class, or a decrease in analgesic class without an increase in PPI score, maintained for 2 consecutive evaluations at least three weeks apart. Pain response was only determined for subjects with baseline measurable disease, PSA>20 ng/ml or median PPI score >2. • Response rate (reported at 24 months) D 27.9% vs DR 31.2% (response not different between groups) • Duration of response (months) D 5.5 vs DR 3.4; HR 1.27 (0.84–1.92) (response not different between groups)	**Adverse events**: • Abdominal pain control 2/143, IB20 1/144, IB50 5/147 • Hypocalcemia control 6/143, IB20 9/144, IB50 10/147	Risk of bias: unclear Author's conclusion: The addition of the third generation risedronate to docetaxel in patients with metastatic Castration Resistant Prostate Cancer, although well tolerated, has no effect on pain response Remarks:

4.6. Celiac Plexus Block

Table 66 – Celiac Plexus Block: evidence table of systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
Arcidiacono (2011) [83]	• Design: SR and MA • Sources of funding: mentioned that no existing conflict of interest • Search date: December 2010 • Searched databases: Central, Medline, Gateway and Embase • Included study designs: RCT with 4 weeks of follow-up • Number of included studies: 6; MA: N=358 Included studies[§§]: Kawamata 1996 Lillemoe 1993 Mercadante 1993 Polati 1998 Wong 2004[§§]	• Eligibility criteria: Abdominal or back pain due to pancreatic cancer at any stage, confirmed by CT* or ultrasound, EUS** and clinical criteria.. • Patient characteristics: Adults of either sex, aged 18 years or over.	• Intervention: percutaneous CPB[$] (posterior approach)(5 studies) or CPB performed during cancer surgery (1 study) • Control: Treatment with NSAIDs and morphine	**Pain control (Absolute mean difference):** • At 4 weeks (4 studies) 10 points VAS scale scores[#]: -0.42 (95% CI -0.71– -0.14; p=0.004) Heterogeneity: χ^2=2.77, df=3, p=0.43, I^2=0% (fixed effect model) • At 8 weeks (5 studies) 10 points VAS scale [#]: -0.44 (95% CI -0.89–0.01;p=0.06) Heterogeneity: tau^2=0.22, χ^2=37.03, df=4, p<0.000001, I^2=89% (random effect model) **Adverse events** • Constipation (4 studies)	**Opioid use*:*** • At 4 weeks (5 studies) mg of opioids: -34.33 (95% CI -44.42– -24.24; p<0.000001) Heterogeneity: χ^2=16.69, df=4, p=0.002, I^2=76% **QoL**: no information provided	• AMSTAR evaluation: Yes, can't answer, Yes, Yes, Yes, Yes, No, Yes, can't answer, Yes • Quality of SR: low risk of bias • Quality of included RCTs: overall high risk of bias • Authors' conclusions: A significant but limited advantage of CPB[$] over standard analgesic therapy; limited side effects and more side effects in control group (higher opioid consumption). Note: Yan 2007 is another SR on the same topic; it

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
	Zhang 2008			Risk ratio: 0.38 (95% CI 0.25–0.59;p=0.00001) Heterogeneity: χ^2=5.34, df=3, p=0.15, I^2=44% (fixed effect model) Significantly more likely in the control group (higher opioid consumption) • Diarrhea (4 studies) Risk ratio: 3.25 (95% CI 0.95– 11.13);p=0.06 Heterogeneity: χ^2=1.53, df=2, p=0.47, I^2=0% (fixed effect model) More frequent in intervention group, not significant.		includes all studies included by Arcidiacono 2011; Yan's conclusion: CPB is a safe procedure associated with a statistically significant (but limited) reduction in pain, opioid consumption, and constipation in patients with unresectable pancreatic cancer. While CPB may be used as an adjunctive therapeutic modality in appropriately selected patients, it does not replace standard pain control measures, nor does it improve QoL or survival.

** CT: computered tomography, ** EUS: endoscopy ultrasonography, $ CPB: Celiac Plexus Block, # VA*
S scores: visual analogue scale (presented here as in favour of CPB), §§ only Wong 2004 had an adequate sequence generation and allocation concealment

Table 67 – Celiac Plexus Block: evidence table of randomized controlled trials

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
Wyse (2011)[91]	• Design: randomized, double-blind, controlled trial • Sources of funding: not mentioned, authors indicated no potential conflicts of interest • Setting: Algology Centre Hospitalier de l'Université de Montréal, Québec, Canada • Sample size: n=49 (control) n=49 (intervention) • Duration: 3 months	Eligibility criteria: Patients with painful, inoperable pancreatic cancer and without allergy to bupivacaine, possible future surgical management of the tumor, expected sur vival less than 3 month, and inability or unwillingness to provide informed consent Patient characteristics: Age (years) (mean ± SD): control 66.5 ± 10.0 vs intervention 66.6 ± 9.32; Gender (Male sex): control 42.9% vs intervention 53.1 %; Pain history, weeks (means ± SD): control (9.6 ± 8.4) vs intervention (8.6 ± 5.4); Narcotic consumption, morphine-equivalent: control (36.8 ± 61.7 vs intervention (41.9 ± 74.1); Abdominal pain	Intervention: early Endoscopic Ultrasound Celiac Plexus Neurolysis at the time of diagnosis Control: conventional pain management with narcotics alone	**Pain relief to baseline:** 7 points Likert scale (Absolute mean change in pain score) • Control group o At 1 month -0.6 (95% IC, -1.1 to -0.09) o At 3 months -0.3 (95% IC, -0.9 to + 0.2) • Intervention group o At 1 month -1.6 (95% IC, -2.1 to -1.0) o At 3 months -2.6 (95% IC, -2.1 to – 1.0) • Control vs intervention o At 1 month -1.0 (95% IC, -1.7 to -0.1) p=0.01 o At 3 months -2.2 (95% IC, -3.1 to - 1.4)	**Morphine use** Change in morphine equivalent (MEQ) consumption compared to patient's baseline morphine equivalent consumption • Control group o At 1 month +54 95%IC: +20 to +96 o At 3 months +100 95%IC +49 to +180 • Intervention group o At 1 month +53 95% IC: +28 to +89 o At 3 months +50 95% IC: +28 to +79 • Control vs intervention	Risk of bias: low Author's conclusion: In patients with painful, Inoperable pancreatic adenocarcinoma, early Endoscopic Ultrasound Celiac Plexus Neurolysis provides better pain relief and may prevent progressive increases in morphine consumption compared with conventional management, particularly in patients who do not receive chemo-XRT Remarks: results at 1 month borderline

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
		intensity (Likert score – means ± SD): control (4.1 ± 1.6) vs intervention (5.2 ± 1.6); QoL (Digestive Disease Questionnaire Score – means ± SD): control (3.1 ± 0.7) vs intervention (3.1 ± 0.7); Constipation: control 40.9% vs intervention 54.3 %; Nausea control 48.9% vs intervention 44.7 %; Patients in both groups were comparable for all above baseline characteristics		p<0.001	o At 1 month -1.0 MEQ 95%IC -47.7–+49.2 p=0.99 o At 3 months -49.5 MEQ 95%IC:-127.5to 7.0 p=0.10 **QoL** Digestive Disease Questionnaire-15 (DDQ-15) score (mean percentage change) • Control group o At 1 month +6 95% IC, 0 to +11 o At 3 months +18 95%IC, +12 to + 26 • Intervention group o At 1 month +14 95%IC, +7 to +19 o At 3 months	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
					+19 95%IC, +10 to +27 • Control vs intervention o At 1 and 3 month Not significant difference	
Ischia (1992)[92]	• Design: 3-arm, single blind, randomised, non controlled trial • Sources of funding: not mentioned • Setting: Pain relief Center in Roma, Italy • Sample size: n=61 (transaortic celiac plexus block n=20, retrocrural block n=20, bilateral chemical splanchnicectomy n=21) • Duration: until death with a duration of 0.5 to 18 month	Eligibility criteria: patients with unresectable pancreatic cancer and pancreatic cancer pain Patient characteristics: Age range 39-73y ; bilateral/unilateral visceral pain: 18/2 vs 17/3 vs 17/21 ; qualitative pain assessment (Scott-Huskisson values > 6 mark): 18/20 vs 18/20 vs 17/21; performance status (Karnofsky and Burchenal index ≥ 50): 14/20 vs 12/20 vs 12/21; Mean time period elapsing between the onset of pain and	Transaortic celiac plexus block vs. Retrocrural block vs. Bilateral chemical splanchnicectomy All patients were placed in prone position (posterior approach). Correct placement of the needle is verified by fluoroscopy	10-point Scott-Huskisson scale: **Immediate total pain relief:** 10/20 vs 8/20 vs 11/21 **Partial pain relief (SH scale 3-7):** 7/20 vs 11/20 vs 9/21 **No pain relief (SH scale 7-9):** 3/20 vs 1/20 vs 1/21 **QoL**: no information provided		

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
		commencement of intervention (in month): 4.8 vs 5.1 vs 4.4. Comparable groups for pain level, although no information provided about the demographic data				
Süleyman Özyalçin (2004)[93]	• Design: prospective, single blind, randomized study • Sources of funding: not mentioned • Setting: Algology Department of Medical Faculty of Istanbul • Sample size: n=39 (Celiac plexus block (GC) n=19, bilateral splanchic nerve block (GS) n=20) • Duration: 18 weeks	Eligibility criteria: Patients with pain due to body and tail located pancreatic cancer Patient characteristics: Age (years) (median, min-max): GC 57.5, 47-69 vs GS 65, 41-69 ; Gender (M/F): GC 14/5 vs GS 12/8 ; Statistical comparable groups for demographic features (age and gender)	Celiac plexus block performed by transaortic technique vs. Bilateral splanchic nerve block All procedures were performed by posterior approach under fluoroscopic guidance.	**Pain relief:** 10 points VAS scale values at the specific controls • At 2 weeks GC 4.8 vs GS 2.3 (p<0.001) • At 4 weeks GC 5.4 vs GS 2.75 (p<0.001) • At 6 weeks GC 5 vs GS 2.5 (p<0.001) • At 8 weeks GC 4.9 vs GS 2.4 (p=0.001) • At 10 weeks GC 5.1 vs GS 2.8 (p=0.001)		

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				• At 12 weeks GC 5.5 vs GS 3 (p=0.002) • At 14 weeks Non significant differences **Total daily codeine consumption:** In mg • At 2 weeks GC 113 vs GS 74 (p=0.003) • At 4 weeks GC 115 vs GS 84 (p=0.041) • At 6 weeks GC 120 vs GS 72 (p=0.005) • At 8 weeks GC 123 vs GS 80 (p=0.021) • At 10 weeks GC 131 vs GS 83 (p=0.028) • At 12 and 14 weeks Non significant differences		

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of study quality
				QoL: Patient satisfaction scale (Kawamata 1996) • At 4 weeks GC 5.3 vs GS 4.35 (p=0.003) • At 2, 6, 8, 10, 12, and 14 weeks Non significant differences **Performance status** (Kawamata scale 1996) • At 6 weeks GC 3 vs GS 2.2 (p=0.032) • At 2, 4, 8, 10, 12, and 14 weeks Non significant differences **Remark:** • At 16 and 18 weeks: no more patients alive in GC group		

5. OVERVIEW OF INCLUDED AND EXCLUDED STUDIES

5.1. Overview of included SRs

The table below presents an overview of the finally included SRs retrieved from the literature search or from the guideline search, for the topics anticonvulsants, antidepressants, bisphosphonates, celiac plexus block, radionuclides, radiotherapy.

Table 68 – Included SRs per topic

Topic	References
Anticonvulsants	Bennett 2011, Librach 2006, Moore 2011
Antidepressants	Bennett 2011, Librach 2006
Bisphosphonates	Berry 2006, Mhaskar 2012, Yuen 2010, Wong 2004, Wong 2009, Wong 2012
Celiac Plexus Block	Arcidiacono 2011, Yan 2007
Radiotherapy	McQuay 2008, Sze 2003, Sze 2011, Falkmer 2003, George 2010, Alberta Health Services 2010, NICE 2008
Radionuclides	Christensen 2012, Roqué 2011, Alberta Health Services 2010
Several topics	Dutch Guideline on cancer pain 2008, Guideline of the MoH Malaysia 2008, SIGN 2008

5.2. Overview of included SRs found by handsearch

The table below presents an overview of the finally included SRs found by handsearch, for the topics anticonvulsants, antidepressants, bisphosphonates, celiac plexus block, radionuclides, radiotherapy.

Table 69 – Included SRs per topic

Topic	References
Anticonvulsants	/
Antidepressants	Saarto 2012
Bisphosphonates	/
Celiac Plexus Block	/
Radionuclides	/
Radiotherapy	Sze 2003
Several topics	Carr 2002

5.3. Overview of excluded SRs

Persons who are interested in the detailed list of excluded studies per study topic, can contact the authors of this report (see colophon).

5.4. Overview of included RCTs

This table presents a list of all RCTs that have been included per topic. These RCTs were retrieved through the update search for RCTs or extracted from included SRs or guidelines.

Table 70 – Included RCTs per topic

Topic	References
Anticonvulsants	Amr 2010, Arai 2010, Caraceni 2004, Fassoulaki 2002, Keskinbora 2007, Mishra 2012, Rao 2007
Antidepressants	Amr 2010, Arai 2010, Kalso 1996, Kautio 2008, Kautio 2009, Mercadante 2002, Mishra 2012, Reuben 2004, Tasmuth 2002
Bisphosphonates	Berenson 2001, Body 2007, Conte 1996, Daragon 1993, Dearnaley 2003, Diel 2004, Ernst 1992, Ernst 1997, Ernst 2003, Hortobagyi 1996, Hultborn 1999, Kylmälä 1997, Lahtinen 1992, Meulenbeld 2012, O'Rourke 1995, Piga 1998, Robertson 1995, Saad 2002, Small 2003, Theriault 1999, Tubiana-Hulin 2001, Tripathy 2004
Celiac Plexus Block	Ischia 1992, Süleyman Özyalçin 2004, Wyse 2011, Kawamata 1996, Lillemoe 1993, Mercadante 1993, Polati 1998, Wong 2004, Zhang 2008
Corticosteroids	/
NSAIDs	Axelsson 2003, Bjorkman 1993, Bosek 1994, Carlsson 1990, Chary 1994, Corli 1993, Cubero 2010, Dellemijn 1994, Duarte-Souza 2007, Estape 1990, Ferrer-Brechner 1984, Frankendal 1973, Gallucci 1992, Israel 2010, Jameel 1995, Johnson 1994, Lomen 1986, Martino 1976, Mercadante 2002, Minotti 1998a, Minotti 1998b, Moertel 1971, Moertel 1974, Panutti 1999, Portenoy 2010, Rodriguez 1994, Rodriguez 2003, Sacchetti 1984, Saxena 1994, Sima 2012, Stambaugh 1980b, Stambaugh 1982b, Stambaugh 1988a, Stambaugh 1988b, Staquet 1989, Staquet 1993, Stockler 2004, Strobel 1992, Sunshine 1988, Tasmacioglu 2009, Tonachella 1985, Toscani 1994, Turnbull 1986, Ventafridda 1975, Ventafridda 1990a, Ventafridda 1990b, Weingart 1985, Wool 1991, Yalcin 1980, Yalcin 1997:
Opioids	Ahmedzai 2012, Arbaiza 2007, Beaver 1967, Beaver 1978, Brema 1996, Bruera 1998, Bruera 2004, Christie 1998, Coluzzi 2001, Cubero 2010, Davies 2011, Dhaliwal 1995, Elsner 2005, Farrar 1998, Ferrell 1989, Gabrail 2004, Grochow 1989, Hagen 1997, Hanna 2008, Heiskanen 1997, Heikanen 2000, Houde 1986, Johnson 2009, Kalso 1990, Kongsgaard 1998, Kress 2008, Kress 2009, Lauretti 2003, Leppert 2001, Melzack 1979, Mercadante 1998a, Mercadante 2007, Mercandante 2008, Mercadante 2009, Mercadante 2010, Moksnes 2011, Moriarty 1999, Mucci-LoRusso 1998, Mystakidou 2005, Napp Laboratories 2000, Pace 2007, Pistevou-Gompaki 2004, Portenoy 2006, Portenoy 2010, Poulain 2008, Rauck 2009, Rauck 2010, Rauck 2012, Rodriguez 2007, Rodriguez 2008, Slatkin 2007,

	Twycross 1977, Van Seventer 2003, Ventafridda 1986, Wilder-Smith 1994, Wirtz 2009
Radionuclides	Baczyk 2007, Buchali 1988, Han 2002, Lewington 1991, Maxon 1991, Nair 1999, Nilsson 2005, Nilsson 2007, Palmedo 2003, Porter 1993, Resche 1997, Sartor 2004, Sciuto 2001, Serafini 1998, Smeland 2003, Wang 2003
Radiotherapy	Amouzegar 2008, BPTWP 1999, Chi 2009, Cole 1989, Foro 1998, Foro 2008, Gaze 2007, Hamouda 2007, Hartsell 2005, Hoskin 1992, Jeremic 1998, Kagei 1990, Koswig 1999, Manas 2008, Maranzano 2005, Maranzano 2009, Nielsen 1998, Ozsaran 2001, Patchell 2005, Price 1986, Roos 2005, Salazar 2001, Sarkar 2002, Steenland 1999

5.5. Overview of excluded RCTs

This table presents the number of RCTs that have been excluded from the update search for RCTs. In the table only the reasons for exclusion on full text are mentioned, without differentiation per topic (antidepressants, anticonvulsants, bisphosphonates, celiac plexus block, radionuclides, radiotherapy) or listing all references. Persons who are interested in the detailed list of excluded studies, can contact the authors of this report (see colophon).

Reason for exclusion	Number of RCTs
Population	4
Intervention	13
Outcome	15
Design	35
Language	8
Duplicate	43
Not retrieved	3

APPENDIX IV

1. CONSULTATION OF EXPERT PANEL

After the consultation of the experts, the recommendations as formulated below (column “Recommendation(s) after experts meeting”) were presented to a panel of stakeholders for further adjustment (See 1 Consultation of stakeholder panel). For further information on the methodology of the recommendations drafting: see scientific report chapters 2.8 to 2.11.

GoR: Grade of Recommendation(s); LoE: Level of Evidence

Table 71 – Reporting of the modifications proposed by the expert panel

Recommendation(s) before experts meeting	GoR	LoE	Recommendation(s) after experts meeting	GoR	LoE	Comments
Radiotherapy for painful bone metastases						
			• Aspects such as life expectancy of the patient and curability of the bone metastases into account when deciding on the preferred radiotherapy scheme for pain relief in bone metastases	strong	very low level	• Decrease in analgesic use= important outcome • Side effects: increase in pain possible after radiotherapy (is even preferred as sign of reaction on radiotherapy). Sometimes increased use of analgesics before radiotherapy • Clincial situation of patients (early, late, palliative stage of disease) is different and differences should be mentioned no differntiation neede between tumour types but focus on multiple bone metastases • More information needed towards the patients concerning the analgesic purpose of the treatment, side effects. Communication needed for therapy adherence

Recommendation(s) before experts meeting	GoR	LoE	Recommendation(s) after experts meeting	GoR	LoE	Comments
Radiotherapy for painful bone metastases						
• It is not yet possible to recommend on whether 4-Gy should be preferred on 8-Gy single fraction radiotherapy for short term (4 to 8 weeks) complete or partial pain relief in patients with bone metastases, regardless the primary tumour site. More research is necessary	strong/weak	very low level	• The use of a 8-Gy single fraction radiotherapy for short term (4 to 8 weeks) complete or partial pain relief in patients with uncomplicated bone metastases is the option of first choice, after aspects such as life expectancy of the patient, curability of the bone metastases and patient preferences have been taken into account (weak recommendation; very low level of evidence)	weak	very low level	• Preference for single fraction of 8Gy, is common practice in Belgian hospitals (expert consensus)

Recommendation(s) before experts meeting	GoR	LoE	Recommendation(s) after experts meeting	GoR	LoE	Comments
Radiotherapy for painful bone metastases						
It is plausible that single and multiple fraction radiotherapy are equally effective for short term (4 to 8 weeks) complete or partial pain relief in patients with bone metastases, regardless the primary tumour site (moderate level of evidence). It is also plausible that radiotherapy by a single fraction is associated with more retreatments (moderate level of evidence) and more pathological fractures (low level of evidence)	strong/weak	from moderate to low	It is plausible that single and multiple fraction radiotherapy are equally effective for short term (4 to 8 weeks) complete or partial pain relief in patients with uncomplicated bone metastases, regardless the primary tumour site (moderate level of evidence). It is also plausible that radiotherapy by a single fraction is associated with more retreatments (moderate level of evidence) and more pathological fractures (low level of evidence), but the overall rate of retreatment and pathological fractures is relatively low. Therefore the use of single fraction radiotherapy for short term complete or partial pain relief in patients with uncomplicated bone metastases is recommended as treatment of first choice. However, the definitive decision on the treatment modality should also take into consideration the preferences of the patient after he/she has been well-informed, and aspects such as life expectancy of the patient and curability of the bone metastases	strong	from moderate to low	• Preference for single fraction of 8Gy for pain relief, despite higher retreatment rate, in order to avoid burden to the patient • Only for complicated metastases, preference for multifractionated schedule (depends also on patients life expectancy) • Side effects ± idem but 8Gy more effective for pain relief preference

Recommendation(s) before experts meeting	GoR	LoE	Recommendation(s) after experts meeting	GoR	LoE	Comments
Radiotherapy for painful bone metastases						
No specific radiation dose can be considered as preferable for the treatment of pain due to metastatic spinal cord compression (strong/weak recommendation; very low level of evidence)	strong/weak	very low level	Decompressive surgical tumor resection with or without stabilization of the spine and followed by radiotherapy is the option of first choice in patients with metastatic spinal cord compression, after aspects such as duration of the spinal cord compression, life expectancy of the patient, and patient preferences have been taken into account	weak	very low level	• Higher dose in multiple fraction needed, except if life expectancy is less than 3 months. Recently more patients seen with spinal cord compression, because they stay longer in systemic treatment. Goal of treatment is regaining the ability to walk again. • If solitary: more aggresive miltimodal apporach needed (e.g. combination with decrompressive surgery)
			There is insufficient evidence to advise on the preferred radiation dose for the treatment of pain due to metastatic spinal cord compression	weak	very low level	
There is insufficient evidence to advise on the preferred schedule for hemibody irradiation in patients with widespread bone metastases	strong/weak	very low level	There is insufficient evidence to advise on the preferred schedule for hemibody irradiation as treatment of pain in patients with widespread bone metastases	Weak	very low level	Hemi-body irradiation with 4Gy more frequently used in the past but can still be useful and is maybe as efficient as radionuclides (that can provide a systemtic toxicity but have good results in terms of survival)

Recommendation(s) before experts meeting	GoR	LoE	Recommendation(s) after experts meeting	GoR	LoE	Comments
Radiotherapy for painful bone metastases						
			Hemibody irradiation can be a treatment option in patients with widespread bone metastases who suffer from pain after all systemic pain treatment options failed, and after life expectancy of the patient and patient preferences have been taken into account	weak	very low level	Not often provided in Belgian practice
			A multimodal pain treatment approach should be considered for uncomplicated or complicated bone metastases. Besides local treatment with single or multiple fraction radiotherapy, systemic therapies should also be considered throughout the treatment course, e.g. NSAIDs, opioids, cytotoxic chemotherapy, anticancer hormone therapy. This is supported by the significant number of patients with uncomplicated bone metastases who don't obtain total pain relief from single or multiple fraction radiotherapy (strong recommendation; very low level of evidence)	strong	very low level	Radiotherapy in combination with systemic therapies: support with systemic therapies needed in anticipation of radiotherapy

Recommendation(s) before experts meeting	GoR	LoE	Recommendation(s) after experts meeting	GoR	LoE	Comments
Radionuclides						
Bone-seeking radio-isotopes can be considered as a secondary option to obtain complete or partial (more than 50%) pain relief in the short and medium term (up to 6 months) for painful bone metastases in cancer patients regardless of the primary tumour site, when conventional treatment failed	strong/weak	low level	Bone-seeking radio-isotopes can be considered as a secondary option to obtain complete or partial (more than 50%) pain relief in the short and medium term (up to 6 months) for widespread painful osteoblastic bone metastases in cancer patients regardless of the primary tumour site, when conventional treatment failed (weak recommendation; low level of evidence)	Weak	low level	In Belgian practice: preference for increase of morphine rather than longer procedure of radionuclides. Radionuclides only effect on longterm with chance of pain flares and incidence of adverse events but increase of morphine often necessary
It is recommended to inform patients that this treatment can be associated with an increased incidence of severe adverse events, such as leucocytopenia	strong/weak	low level	It is recommended to inform patients that this treatment can be associated with an increased incidence of severe adverse events, such as leucocytopenia (strong recommendation; low level of evidence)	strong	low level	Emphasized by experts and patients
The use of radio-isotopes adjuvant to external beam radiotherapy can be considered as an option to obtain partial (more than 50%) pain relief in the short and medium term (up to 6 months), in cancer patients with painful bone metastases	strong/weak	low level				Recommendation deleted: included patients need to be on stable analgetics dose, often reason not to participate in studies

Recommendation(s) before experts meeting	GoR	LoE	Recommendation(s) after experts meeting	GoR	LoE	Comments
Bisphosphonates						
Given the available evidence on efficacy (very low level of evidence), and given the available evidence on possible adverse events (moderate level of evidence), bisphosphonates cannot be considered/ cannot be considered as first line therapy in the treatment of metastatic bone pain in the short, medium or long term. This report does not advise on the usefulness of bisphosphonates for other indications in patients with metastatic bone involvement, e.g. hypercalcemia, pathological fractures, impending fractures, spinal cord compression	strong/weak	from moderate to very low	Given the available evidence on efficacy (very low level of evidence), and given the available evidence on possible adverse events (moderate level of evidence), bisphosphonates cannot be considered as first line, purely analgesic treatment of metastatic bone pain in the short, medium or long term. This report does not deal with the usefulness of bisphosphonates for other indications in patients with metastatic bone involvement, e.g. hypercalcemia, pathological fractures, impending fractures, spinal cord compression	strong	from moderate to very low	• Experts were suprised that so little evidence is available in contrast to the use in clinical practice. • In Belgian practice: biphosphonates are started for bone metastases not as first line therapy for pain. The use of biphosphonates leads to a decrease of bone fractures and has an indirect effect on pain • Agreement on treatment period of 2 years, aftr 2 years biphosphonates are taken once every 3 months in case of absence of pain and urinary markers • Wording of recommendation: preference for 'cannot be considered as first line therapy'; change 'does not advise' in 'does not deal with' • Agreement between experts that biphosphonates can be started in prevention of fractures and spinal cord compression, however cannot be considered as firstline analgesic therapy for pain • Necrosis of the jaw underreported in RCTs

Recommendation(s) before experts meeting	GoR	LoE	Recommendation(s) after experts meeting	GoR	LoE	Comments
Antidepressants						
The available evidence on the use of antidepressants to prevent post-mastectomy pain in breast cancer patients or to prevent chemotherapy-induced neuropathy does not allow to recommend for or against it	strong/weak	low level	The available evidence on the use of antidepressants to prevent post-mastectomy pain in breast cancer patients or to prevent chemotherapy-induced neuropathy does not allow to recommend for or against it	strong	low level	Agreement on recommendation: in thorax region higher chronic pain scores but less effect of antidepressants as pre-operative pain therapy
The available evidence on the use of antidepressants for the treatment of neuropathic pain in cancer patients does not allow to recommend for or against it (very low level of evidence). However, based on expert consensus, as a consequence of the proven benefit of tricyclic antidepressants (e.g. amytriptiline) and venlafaxine as first-line drug to treat neuropathic pain in other diagnostic patient groups, their use as first-line drug in cancer patients with neuropathic pain can be considered, with careful monitoring of side effects	strong/weak	very low level	The available evidence on the use of antidepressants for the treatment of neuropathic pain in cancer patients does not allow to recommend for or against it (very low level of evidence). Individual patient assessment should determine the appropriate treatment option in cancer patients with neuropathic pain or with a mixed type of pain including neuropathic components, and antidepressants can be considered alone, sequentially, or with other analgesic agents, including opioids. Their effectiveness and side-effects should be monitored carefully. This recommendation is based on consensus that the proven benefit of antidepressants (e.g. amytriptiline) as first-line drug to treat neuropathic pain in non-cancer diagnostic patient groups can be extended to patients suffering from neuropathic cancer pain	strong	very low level	• Addition of experts' opinion: proven benefit of antidepressantas first line therapy in non-cancer patients can also be extended to cancer patients • Venlafaxine: not used in Belgian practice in such low doses and for pain treatment • In Belgian practice: often combination therapy • Suggestion of researchers: 1 recommendation of 2nd and 3rd recommendation

Recommendation(s) before experts meeting	GoR	LoE	Recommendation(s) after experts meeting	GoR	LoE	Comments
Antidepressants						
The available evidence on the use of antidepressants for the treatment of neuropathic pain in cancer patients does not allow to recommend for or against it (very low level of evidence). However, based on expert consensus, in cancer patients with a mixed type of pain including neuropathic components, individual patient assessment should determine the appropriate treatment option and antidepressants can be considered alone, sequentially, or with other analgesic agents, including opioids. Their effectiveness and side-effects should be monitored carefully	strong/weak	very low level				

Recommendation(s) before experts meeting	GoR	LoE	Recommendation(s) after experts meeting	GoR	LoE	Comments
Anticonvulsants						
Based on expert consensus extending the demonstrated effectiveness of anticonvulsants in non-cancer neuropathic pain, anticonvulsants including gabapentin (and pregabalin?) can be considered for first-line treatment in neuropathic cancer pain. Side-effects should be monitored carefully	strong/weak	very low level				
OR:						
Based on the available evidence, it is not possible to recommend for or against the use of gabapentin or pregabalin as first-line treatment in neuropathic cancer pain. Based on the available evidence, the use of gabapentin or pregabalin cannot be considered as first-line treatment in neuropathic cancer pain	strong/weak	very low level	Based on the available evidence, it is not possible to recommend for or against the use of gabapentin or pregabalin as treatment to prevent neuropathic cancer pain	strong	very low level	• Choice of experts: 2nd formulation • Anticonvulsants more often used tha antidepressants (less adverse events) in cancer pain treatment

Recommendation(s) before experts meeting	GoR	LoE	Recommendation(s) after experts meeting	GoR	LoE	Comments
Anticonvulsants						
Based on the available evidence, gabapentin can be considered as add-on to opioids in neuropathic cancer pain with careful monitoring of effectiveness and side-effects./ gabapentin is not a treatment option as add-on to opioids in neuropathic cancer pain./ it is not possible to recommend for or against the use of gabapentin or pregabalin as add-on to opioids in neuropathic cancer pain	strong/weak	very low level	The available evidence on the use of gabapentin for the treatment of neuropathic pain in cancer patients does not allow to recommend for or against it (very low level of evidence). Individual patient assessment including sensory symptoms, should determine the appropriate treatment option in cancer patients with neuropathic pain or with a mixed type of pain including neuropathic components, and anticonvulsants, including gabapentin, can be considered alone, sequentially, or with other analgesic agents, including opioids. Their effectiveness and side-effects should be monitored carefully. This recommendation is based on consensus that the proven benefit of anticonvulsants as first-line drug to treat neuropathic pain in non-cancer diagnostic patient groups can be extended to patients suffering from neuropathic cancer pain	strong	very low level	• Belgian practice: gabapentin often used for opioid-sparing effect but doses are higher. Intrathecal procedures can be avoided by use of gabapentin+ often combination of antidepressants and anticonvulsants because clinicians are convinced of effect and morphine-sparing effect • Same wording as antidepressants: gabapentin as add-on

Recommendation(s) before experts meeting	GoR	LoE	Recommendation(s) after experts meeting	GoR	LoE	Comments
Anticonvulsants						
Based on the available evidence, it is not possible to recommend for or against the use of gabapentin or pregabalin as treatment to prevent neuropathic cancer pain	strong/weak	very low level	The available evidence on the use of pregabalin for the treatment of neuropathic pain in cancer patients does not allow to recommend for or against it (very low level of evidence). Individual patient assessment including sensory symptoms, should determine the appropriate treatment option in cancer patients with neuropathic pain or with a mixed type of pain including neuropathic components, and pregabalin can be considered alone, sequentially, or with other analgesic agents, including opioids. Its effectiveness and side-effects should be monitored carefully. This recommendation is based on consensus that the proven benefit of anticonvulsants as first-line drug to treat neuropathic pain in non-cancer diagnostic patient groups can be extended to patients suffering from neuropathic cancer pain	weak	very low level	• Pregabalin not anyway recommended but as treatment option if gabapentin is not efficacious or not supported • Strength of recommendation: weak

Recommendation(s) before experts meeting	GoR	LoE	Recommendation(s) after experts meeting	GoR	LoE	Comments
Anticonvulsants						
Based on expert consensus, in cancer patients with a mixed type of pain including neuropathic components, individual patient assessment should determine the appropriate treatment option. Anticonvulsants can be considered after other analgesic agents, including opioids, failed./ Anticonvulsants can be considered alone, sequentially, or with other analgesic agents, including opioids. Their effectiveness and side-effects should be monitored carefully./ Anticonvulsants are not a treatment option	strong/weak	very low level				Individual pain assessment included in all recommendations
Based on the available evidence, it is not possible to recommend whether anticonvulsants should be preferred or not over antidepressants, in the first-line or add-on treatment of neuropathic cancer pain	strong/weak	very low level	Based on the available evidence, it is not possible to recommend whether anticonvulsants should be preferred or not over antidepressants, in the first-line or add-on treatment of neuropathic cancer pain	strong	very low level	In Belgian practice: no preference for antidepressants or anticonvulsants, is determined by type of pain
Based on the available evidence, it is not possible to recommend for or against the combined use of an anticonvulsant and an antidepressant in the treatment of patients with neuropathic cancer pain	strong/weak	very low level				Included in above-mentioned recommendation
It is recommended to inform patients on the potentially increased incidence of adverse events associated with the use of anticonvulsants. Their preferences should be taken into account when deciding on the treatment	strong/weak	very low level				Included in all recommendations

Recommendation(s) before experts meeting	GoR	LoE	Recommendation(s) after experts meeting	GoR	LoE	Comments
			Carbamazepine can be considered to be the preferred anticonvulsant to treat neuropathic pain resulting from cancerous involvement of the trigeminal nerve. This recommendation is based on consensus that the demonstrated effectiveness of carbamazepine for the treatment of trigeminal neuralgia in non-cancer patients can be extended to cancer patients	strong	very low level	Addition of role of carbamazepine by experts in treatment of pain resulting from trigeminal nerve

Recommendation(s) before experts meeting	GoR	LoE	Recommendation(s) after experts meeting	GoR	LoE	Comments
Celiac plexus Block						
CPB is not recommended as a first line treatment in patients suffering from pancreatic cancer pain. For selected patients, it can be considered as one possible treatment option, after these patients have been well informed on the limited effectiveness on pain, the possible effect on opioid dosing and constipation, the rare adverse events associated with the intervention itself, and the low level of scientific evidence that currently supports these data	strong/weak		Based on the limited short term (4 weeks) effectiveness of celiac plexus block (CPB) on pain as compared to standard analgesic treatment, based on its short term possible positive effect on opioid consumption, based on the need to repeat the procedure and on the rare but important complications that can be associated with the procedure, but taking into account that the life expectancy of patients with pancreatic cancer is mostly limited, CPB can be considered as one treatment option for patients suffering from pancreatic cancer, although CPB should not be the treatment of first choice	weak	very low level	Additions by experts: transitory effect should be mentioned, time-point is immediately after surgery, maximum of 2 repetitions due to complications and complex surgery, in pancreatic cancer seen as first sign but is already stage 4, seen as last treatment option
			It is recommended to inform patients with pancreatic cancer clearly on the limited short term (4 weeks) effectiveness of CPB on pain as compared to standard analgesic treatment, but also on the short term (4 weeks) possible positive effect on opioid dosing. They should also be informed on the need to repeat the procedure over time, and on the possible side-effects and complications of celiac plexus block (CPB) for pain relief in pancreatic cancer	strong	very low level	Patients need to be informed about the risks of narcotics, severe complications and side-effects

Recommendation(s) before experts meeting	GoR	LoE	Recommendation(s) after experts meeting	GoR	LoE	Comments
Celiac plexus Block						
			A multimodal pain treatment approach should be considered for cancer pain. In patients who underwent CPB, other analgesic therapies should still be considered throughout the treatment course, e.g. NSAIDs, opioids	weak	very low level	Emphasis on importance of multimodal approach, e.g. Adjuvantic drugs for neuropathic components and CPB for visceral aspects of pain

Recommendation(s) before experts meeting	GoR	LoE	Recommendation(s) after experts meeting	GoR	LoE	Comments
Glucocorticoids						
Corticosteroids alone or combined with other therapeutic options can be considered in cancer patients for pain related to a mass effect of the tumour, e.g. headache caused by raised intracranial pressure, pain in spinal cord compression, multifocal bone pain, abdominal pain from liver capsule distention, intestinal obstruction, etc. They may be also be used to help manage other symptoms in cancer patients at an advanced or terminal stage of the disease, e.g. anorexia, nausea, fatigue, general weakness or feelings of malaise and depression. Side-effects should be monitored carefully	weak/strong	very low level	Corticosteroids alone or combined with other therapeutic options can be considered in cancer patients for pain related to a mass effect of the tumour, e.g. headache caused by raised intracranial pressure, pain in spinal cord compression, multifocal bone pain, abdominal pain from liver capsule distention, intestinal obstruction, etc. They may be also be used to help manage other symptoms in cancer patients at an advanced or terminal stage of the disease, e.g. anorexia, nausea, fatigue, general weakness or feelings of malaise and depression. Side-effects should be monitored carefully	strong	very low level	• Preference for first wording • Clinical evidence is clear and convincing, often used after radiotherapy • Randomised trials would be unethically
OR:						

Based on the available evidence, it is not possible to recommend for or against the use of corticosteroids in the treatment of cancer pain	weak/strong	very low level

Recommendation(s) before experts meeting	GoR	LoE	Recommendation(s) after experts meeting	GoR	LoE	Comments
NSAIDs						
Monotherapy with paracetamol or an NSAID (including aspirin) is recommended as the first line treatment option for mild to moderate cancer pain (WHO step I). Relative contra-indications such as pre-existing gastro-intestinal, cardiovascular, hematological or renal conditions should be taken into consideration, and side-effects should be carefully monitored, especially with NSAIDs (paracetamol: very low level of evidence, NSAID: moderate level of evidence; strong/weak recommendation)	strong/weak	very low to moderate level				
OR:						

Recommendation(s) before experts meeting	GoR	LoE	Recommendation(s) after experts meeting	GoR	LoE	Comments
NSAIDs						
Paracetamol and/or an NSAID (including aspirin) are recommended as the first line treatment option for mild to moderate cancer pain (WHO step I). Relative contra-indications such as pre-existing gastro-intestinal, cardiovascular, hematological or renal conditions should be taken into consideration, and side-effects should be carefully monitored, especially with NSAIDs	strong/weak	very low to moderate level	Paracetamol at a correct dose (1 gr./dose; up to 4 gr./day for adults) and/or an NSAID (including aspirin) are recommended as the first line treatment option for mild to moderate cancer pain (WHO Step I) (paracetamol: very low level of evidence, NSAID: moderate level of evidence). An NSAID can be preferred for specific indications, such as bone pain or inflammatory conditions (very low level of evidence). Relative contra-indications such as pre-existing gastro-intestinal, cardiovascular, hematological, renal or hepatic conditions should be taken into consideration, and side-effects should be carefully monitored, especially with NSAIDs	strong	moderate to very low level	• Preference for combination therapy • NSAIDs: only used for bone pain due to bone metastases, inflammatory component and combination therapy • Paracetamol: used for mild cancer pain + correct dosage needed (1000mg for adults, not more than 4g per day) • Contra-indications needs to be added
Clear evidence is lacking to support superior efficacy or safety of one NSAID (including aspirin) over another in patients with cancer pain. Therefore it is not possible to recommend for or against one NSAID over another in patients with cancer pain	strong/weak	very low level	Clear evidence is lacking to support superior efficacy or safety of one NSAID (including aspirin) over another in patients with cancer pain. Therefore it is not possible to recommend for or against one NSAID over another in patients with cancer pain, but the individual sensitivity of each patient should be taken into account	weak	very low level	• No preference for a specific NSAID • Preference for first recommendation + taking into account the individual sensitivity of the patient
OR:						

Recommendation(s) before experts meeting	GoR	LoE	Recommendation(s) after experts meeting	GoR	LoE	Comments
NSAIDs						
Clear evidence is lacking to support superior efficay or safety of one NSAID (including aspirin) over another in patients with cancer pain. However, differences in efficacy and side-effects demonstrated in other conditions between individual NSAIDs might inform clinicians in their choice for one over another NSAID.	strong/weak	very low level				
The available evidence does not allow to draw firm conclusions on the comparison of analgesic effect or side-effects between NSAIDs (including aspirin), and WHO step II or step III opioids in the treatment of moderate to severe cancer pain. Therefore it is not possible to recommend on whether an NSAID or a step II or step III opioid should be recommended as first line treatment option for moderate to severe cancer pain.	strong/weak	very low level	The available evidence does not allow to draw firm conclusions on the comparison of analgesic effect or side-effects between NSAIDs (including aspirin), and WHO Step II or Step III opioids in the treatment of moderate to severe cancer pain. Therefore it is not possible to recommend on whether an NSAID or a Step II or Step III opioid should be recommended as first line treatment option for moderate to severe cancer pain.	weak	very low level	No change in wording needed

Recommendation(s) before experts meeting	GoR	LoE	Recommendation(s) after experts meeting	GoR	LoE	Comments
NSAIDs						
If paracetamol (and/)or an NSAID (including aspirin) no longer adequately relieve(s) the pain, an opioid drug should be considered. Based on the available evidence, it is not possible to recommend for or against the Step II WHO recommendation that an NSAID or paracetamol should be combined with a “weak” opioid (e.g. codeine) for the management of moderate cancer pain.	strong/weak	very low level	If paracetamol (and/)or an NSAID (including aspirin) no longer adequately relieve(s) the pain, an opioid drug should be considered. There is conflicting evidence as to the question whether combining an NSAID (including aspirin) or paracetamol with a WHO Step II opioid is superior to an NSAID (including aspirin) or paracetamol alone in patients with cancer pain (very low level of evidence). There are indications that oral codeine and tramadol are effective and well-tolerated drugs as compared to placebo in the management of mild to moderate cancer pain never treated with opioids (low level of evidence). There are indications that initiating strong opioids (Step III) instead of weak opioids (Step II) for mild to moderate cancer pain after conventional treatment with NSAIDs and/or paracetamol failed, leads to better pain control but at the cost of more side effects (very low level of evidence). Therefore weak opioids (Step II) should be considered in the management of mild to moderate cancer pain after conventional treatment with NSAIDs and/or paracetamol failed.	strong	very low level	• Similar to opioids chapter • Reserachers suggest to mention only these two opioids as “Step II” opioids. Tilidine is only availble in Belgium combined with naloxone/ buprenorphine is usually considered a strong opioid/ nefopam has not been included in the systematic review/ dipyrone should not be routine use given its potential side effects • Codeine always in combination with paracetamol in Belgium but not aften used anymore, now use of tramadol • Experts still convinced of importance of step II opioids • Some experts prefer combinations of opioids istead of increasing the dose. Ceiling effect determined by increasing adverse events • Methadone useful for clinical practice but not mentioned in report • In recommendation: codeine should be replaced by tramadol

Recommendation(s) before experts meeting	GoR	LoE	Recommendation(s) after experts meeting	GoR	LoE	Comments
NSAIDs						
There are indications that NSAIDs as add-on to WHO step III opioids in comparison to step III opioids alone for mild or moderate to severe cancer pain show no difference or show a low clinical difference (<25% difference) to the advantage of the combination NSAIDs-opioids. Based on the available evidence, it is not possible to draw firm conclusions on the comparison of adverse events in both groups. Therefore the use of NSAIDs as add-on to a stabilized regimen of WHO step III opioids should not be considered as a route treatment option	strong/weak	very low level	There are indications that NSAIDs as add-on to WHO Step III opioids in comparison to Step III opioids alone for mild or moderate to severe cancer pain show no difference or show a low clinical difference (<25% difference) to the advantage of the combination NSAIDs-opioids. Based on the available evidence, it is not possible to draw firm conclusions on the comparison of adverse events in both groups. Therefore the use of NSAIDs as add-on to a stabilized regimen of WHO Step III opioids should not be considered as a route treatment option	weak	very low level	Overall agreement
There are indications that paracetamol as add-on to a stabilized regimen of WHO step III opioids for mild cancer pain shows no difference in pain relief as compared to the step III opioids alone. Therefore the use of paracetamol as add-on to a stabilized regimen of WHO step III opioids should not be considered	strong/weak	very low level	There are indications that paracetamol as add-on to a stabilized regimen of WHO step III opioids for mild cancer pain shows no difference in pain relief as compared to the step III opioids alone. Therefore the use of paracetamol as add-on to a stabilized regimen of WHO step III opioids should not be considered	strong	very low level	Overall agreement

Recommendation(s) before experts meeting	GoR	LoE	Recommendation(s) after experts meeting	GoR	LoE	Comments
Opioids						
The WHO analgesic ladder prescribes the use of non-opioid analgesics for mild or moderate cancer pain (Step I), and the use of or combination with opioid analgesics if the pain persists or if the patient is in severe pain. Weak opioids should be used for the treatment of persistent mild to moderate pain (Step II), and strong opioids for severe pain or if the pain persists despite the use of weak opioids (Step III). At each step, adjuvant drugs should also be considered. There is evidence that by application of the WHO analgesic ladder pain relief can be achieved in 75-90% of cancer patients (very low level of evidence). It should be considered to follow the principles of treatment outlined in the WHO analgesic ladder Step I (and Step III?) should be followed when treating pain in patients with cancer	strong/weak	very low level	The WHO analgesic ladder prescribes the use of non-opioid analgesics for mild or moderate cancer pain (Step I), and the use of or combination with opioid analgesics if the pain persists or if the patient is in severe pain. Weak opioids should be used for the treatment of persistent mild to moderate pain (Step II), and strong opioids for severe pain or if the pain persists despite the use of weak opioids (Step III). At each step, adjuvant drugs should also be considered. There is evidence that by application of the WHO analgesic ladder pain relief can be achieved in 75-90% of cancer patients (very low level of evidence). It should be considered to follow the principles of treatment outlined in the WHO analgesic ladder when treating pain in patients with cancer	strong	very low level	Opioid-sparing effect if NSAIDs and paracetamol so preference for combination therapy with opioids
Strong interindividual differences in response to opioids are a well-known clinical phenomenon, underpinned by recent scientific insights in genetic variation in opioid metabolism. Therefore, all opioids should be titrated according to individual analgesic response and occurrence of side-effects	strong/weak	very low level	Strong interindividual differences in response to opioids are a well-known clinical phenomenon, underpinned by recent scientific insights in genetic variation in opioid metabolism. Therefore, all opioids should be titrated according to individual analgesic response and occurrence of side-effects	strong	very low level	Overall agreement

Recommendation(s) before experts meeting	GoR	LoE	Recommendation(s) after experts meeting	GoR	LoE	Comments
Opioids						
Based on clinical experience, oral delivery of opioids is effective and simple. Therefore, the oral route should be used for the administartion of opioids, if practical and feasible. In patients with stable pain who are unavailable to swallow oral medication transdermal administration should be considered. Continuous subcutaneous infusion of opioids is simpler to administer and equally as effective as continuous intravenous infusion and should be considered for patienst unable to take opioids orally	strong/weak	very low level	Based on clinical experience, oral delivery of opioids is effective and simple. Therefore, the oral route should be used for the administration of opioids, if practical and feasible. However, depending on the evolution of the patient's condition and taking into account his/her preferences, the route of administration should be adjusted dynamically and transdermal, subcutaneous, or intravenous opioid administration should be considered. Rarely, intrarectal, intramuscular or intraspinal administration can be considered. Sustained release oral opioids cannot be administered by gastic tube since it is not allowed to crush these formulations	strong	very low level	• Added preferences of patients • Sustained release oral opioids cannot be admnistrated by gastric tube • Intrarectal, IM and instraspanial can be considered in rare cases

Recommendation(s) before experts meeting	GoR	LoE	Recommendation(s) after experts meeting	GoR	LoE	Comments
Opioids						
There are indications that the effectiveness of oral morphine in the treatment of cancer pain compares well to other available strong opioids (oxycodone, hydromorphone, methadone) when titration to effect is performed (very low level of evidence; Cairns 2001, Caraceni 2011, Fallon 2011, King 2011, Nicholson 2008, Quigley 2008, Quigley 2009, Reid 2006, Wiffen 2010, Pigni 2011, Mercadante 2010). There are indications that for oral morphine treatment side effects are common, but that intolerable adverse effects occur in a small number of patients only (4%) and that non-respons is infrequent (very low level of evidence; Wiffen 2010). There are indications that modified-released morphine every 12h is as effective and well-tolerated as immediate-release morphine every 4h (very low level of evidence; Wiffen 2010). Therefore oral morphine (immediate-release or modified-released formulation) should be considered as the drug of first choice and the gold standard for moderate to severe cancer pain	strong/weak	very low level	There are indications that the effectiveness of oral morphine in the treatment of cancer pain compares well to other available strong opioids (oxycodone, hydromorphone, methadone) when titration to effect is performed (very low level of evidence). There are indications that for oral morphine treatment side effects are common, but that intolerable adverse effects occur in a small number of patients only (4%) and that non-respons is infrequent (very low level of evidence). Therefore oral morphine should be considered as the drug of first choice and the gold standard for moderate to severe cancer pain	strong	very low level	• Immediate-relase should be deleted • Long-working morphine (oxycodone) and patches more available on the market

Recommendation(s) before experts meeting	GoR	LoE	Recommendation(s) after experts meeting	GoR	LoE	Comments
Opioids						
There are indications that oral oxycodone, hydromorphone and morphine, when titration to effect is performed, have a similar efficacy and toxicity in cancer-related pain. Therefore, depending on the tolerability of each individual patient, oral oxycodone or hydromorphone (immediate-release or modified-released formulation) can be considered as an alternative to oral morphine in the first-line treatment of moderate to severe cancer pain	strong/weak	very low level	There are indications that oral morphine, oral oxycodone, oral hydromorphone and transdermal fentanyl, when titration to effect is performed, have a similar efficacy and toxicity in cancer-related pain (very low level of evidence). Therefore, depending on the tolerability of each individual patient, other oral strong opioids in their equi-analgesic dose can be considered as an alternative to oral morphine in the first-line treatment of moderate to severe cancer pain. Likewise, transdermal fentanyl, in an equi-analgesic dose, can be used as an alternative to oral opioids for moderate to severe cancer pain, after a stable opioid regimen has been established	strong	very low level	• Recommendation on transdermal will be added • Emphasis on skilled professional: dosage needs to be known

Recommendation(s) before experts meeting	GoR	LoE	Recommendation(s) after experts meeting	GoR	LoE	Comments
Opioids						
The pharmacological properties of methadone suggest that it might be useful in the treatment of neuropathic pain. However, based on the available evidence it is not possible to conclude on the superiority of methadone to morphine in patients with neuropathic cancer pain (very low level of evidence; Bruera 2004). Therefore morphine remains the opioid of first choice for the treatment of moderate to severe neuropathic cancer pain	strong/weak	very low level	The pharmacological properties of methadone suggest that it might be useful in the treatment of neuropathic pain. However, based on the available evidence it is not possible to conclude on the superiority of methadone to morphine in patients with neuropathic cancer pain (very low level of evidence). There are indications that oral methadone and morphine have a similar efficacy in the treatment of nociceptive or mixed types of moderate to severe cancer pain (very low level of evidence). Because of its pharmacokinetics and pharmacodynamics, the adverse effects of methadone may become more prominent with repeated dosing. One of its specific although rare adverse effects is prolongation of the QT interval leading to cardiac dysrhythmias, especially at high doses. In Belgium, it should be considered to limit the initiation of a treatment with methadone as add-on to another opioid for analgesic purposes (such as in cancer patients with moderate to severe pain) to medical specialists in pain treatment, or palliative care physicians. Once optimal dosing has been identified, continuation of maintenance treatment can be carried out by another physician	strong	very low level	No comments

Recommendation(s) before experts meeting	GoR	LoE	Recommendation(s) after experts meeting	GoR	LoE	Comments
Opioids						
Individual patient assessment should determine the appropriate treatment option in cancer patients with neuropathic pain or with a mixed type of pain including neuropathic components, and opioids can be considered alone, or combined with adjuvant analgesics (antidepressants, anticonvulsants)	strong/weak	very low level	Individual patient assessment should determine the appropriate treatment option in cancer patients with neuropathic pain or with a mixed type of pain including neuropathic components, and opioids can be considered alone, or combined with adjuvant analgesics (antidepressants, anticonvulsants)	strong	very low level	No comments
Based on the available evidence it is not possible to recommend on the relative efficacy and side-effects of transdermal buprenorphine as compared to oral morphine for moderate to severe cancer pain, nor on the relative efficacy and side-effects of transdermal opioids against other opioids than oral morphine	strong/weak	very low level	Based on the available evidence it is not possible to conclude on the relative efficacy and side-effects of transdermal buprenorphine as compared to oral morphine, to other oral opioids or to transdermal fentanyl for moderate to severe cancer pain. Based on its pharmacological properties and mixed working mechanism, oral or transdermal buprenorphine might be considered as a treatment option for selected cases of neuropathic cancer pain	weak	very low level	• More effect on neuropathic pain • Need to be added: or in selected cases if neuropathic pain

Recommendation(s) before experts meeting	GoR	LoE	Recommendation(s) after experts meeting	GoR	LoE	Comments
Opioids						
There are indications that oral codeine and tramadol are effective and well-tolerated drugs as compared to placebo in the management of mild to moderate cancer pain never treated with opioids (low level of evidence; Tassinari 2011a). There are indications that initiating strong opioids (Step III) instead of weak opioids (Step II) for mild to moderate cancer pain after conventional treatment with NSAIDs and/or paracetamol failed, leads to better pain control but at the cost of more side effects (very low level of evidence; Tassinari 2011a). Therefore weak opioids (Step II) should not be considered (as first choice?) in the management of mild to moderate cancer pain after conventional treatment with NSAIDs and/or paracetamol failed (very low level of evidence; strong/weak recommendation)	Strong/Weak	Very low level of evidence	If paracetamol (and/) or an NSAID (including aspirin) no longer adequately relieve(s) the pain, an opioid drug should be considered. There is conflicting evidence as to the question whether combining an NSAID (including aspirin) or paracetamol with a WHO Step II opioid is superior to an NSAID (including aspirin) or paracetamol alone in patients with cancer pain (very low level of evidence). There are indications that oral codeine and tramadol are effective and well-tolerated drugs as compared to placebo in the management of mild to moderate cancer pain never treated with opioids (low level of evidence). There are indications that initiating strong opioids (Step III) instead of weak opioids (Step II) for mild to moderate cancer pain after conventional treatment with NSAIDs and/or paracetamol failed, leads to better pain control but at the cost of			After general discussion, rewording was proposed
OR						

Therefore weak opioids (Step II) should be considered (as first choice?) in the management of mild to moderate cancer pain after conventional treatment with NSAIDs and/or paracetamol failed (very low level of evidence; strong/weak recommendation)	more side effects (very low level of evidence). Therefore weak opioids (Step II) should be considered in the management of mild to moderate cancer pain after conventional treatment with NSAIDs and/or paracetamol failed	
OR		
Therefore strong opioids (Step III) should be considered as first choice in the management of mild to moderate cancer pain after conventional treatment with NSAIDs and/or paracetamol failed, but for some patients weak opioids (Step II) might be an alternative treatment (very low level of evidence; strong/weak recommendation)		

Recommendation(s) before experts meeting	GoR	LoE	Recommendation(s) after experts meeting	GoR	LoE	Comments
Opioids						
There are indications that there is no difference in efficacy between tramadol, hydrocodone (combined or not with paracetamol) and codeine combined with paracetamol (low level of evidence; Tassinari 2011a). RCTs directly evaluating other combinations of weak opioids against each other are not available for this indication. Therefore, when weak opioids are considered in the management of mild to moderate cancer pain after conventional treatment with NSAIDs and/or paracetamol failed, codeine, tramadol and hydrocodone can be considered as equivalent treatment options, and the choice for one of them should depend on the tolerability of each individual patient.	strong/weak	very low level	There are indications that there is no difference in efficacy between tramadol and codeine combined with paracetamol (low level of evidence). RCTs directly evaluating other combinations of weak opioids against each other are not available for this indication. Therefore, when weak opioids are considered in the management of mild to moderate cancer pain after conventional treatment with NSAIDs and/or paracetamol failed, codeine and tramadol can be considered as equivalent treatment options, and the choice for one of them should depend on the tolerability of each individual patient	weak	very low level	• Hydrocodone not anymore used in Belgium • List of available opioids needs to added in discussion
For cancer patients on a stable around-the-clock (ATC) regimen of opioids, the first approach to breakthrough pain should be to optimize the ATC regimen	strong/weak	very low level	For cancer patients on a stable around-the-clock (ATC) regimen of opioids, the first approach to breakthrough pain should be to optimize the ATC regimen	strong	very low level	• Only apstral available in Belgium

Recommendation(s) before experts meeting	GoR	LoE	Recommendation(s) after experts meeting	GoR	LoE	Comments
Opioids						
For cancer patients on a stable and optimized around-the-clock (ATC) regimen of opioids, different formulations of oral and intranasal fentanyl have been proven to be effective and safe as compared to placebo in the treatment of breakthrough cancer pain (low level of evidence). Publicatons are lacking on the effeciveness and safety of immediate release oral morphine as well as other forms of oral opioids commonly used for breakthrough pain in this indication (oxycodone, hydromorphone, hydrocodone). Based on the available evidence no conclusions can be made on whether one form of oral or intranasal fentanyl, or one of the other oral opioids is superior to another (very low level of evidence). Therefore breakthrough pain in cancer patients on a stable and optimized around-the-clock (ATC) regimen of opioids can be treated by oral or intranasal fentanyl independent from which opioid is used for the maintenance therapy, or these patients can be treated by the short acting form of the opioid of their maintenance therapy (strong/weak recommendation)	strong/weak	very low level				
OR:						
Opioids						

Recommendation(s) before experts meeting	GoR	LoE	Recommendation(s) after experts meeting	GoR	LoE	Comments
For cancer patients on a stable and optimized around-the-clock (ATC) regimen of opioids, different formulations of oral and and intranasal fentanyl have been proven to be effective and safe as compared to placebo in the treatment of breakthrough cancer pain (low level of evidence). Publicatons are lacking on the effeciveness and safety of immediate release oral morphine as well as other forms of oral opioids commonly used for breakthrough pain in this indication (oxycodone, hydromorphone, hydrocodone). Based on the available evidence no conclusions can be made on whether one form of oral or intranasal fentanyl is superior to another (very low level of evidence). Based on the available evidence, there are indications that oral transmucosal fentanyl citrate (OTFC) and fentanyl pectin nasal spray (FPNS) might be superior to immediate release morphine sulfate (IRMS) (low level of evidence). Based on the available evidence no conclusions can be made on whether one of the other oral opioids is superior to another (very low level of evidence). Therefore breakthrough pain in cancer patients on a stable and optimized around-the-clock (ATC) regimen of opioids can be treated by oral or intranasal fentanyl independent from which opioid is used for the maintenance therapy	strong/weak	very low level	For cancer patients on a stable and optimized around-the-clock (ATC) regimen of opioids, different formulations of oral and and intranasal fentanyl have been proven to be effective and safe as compared to placebo in the treatment of breakthrough cancer pain (low level of evidence). Publications are lacking on the effectiveness and safety in this indication of immediate release oral morphine as well as other forms of oral opioids commonly used for breakthrough pain (oxycodone, hydromorphone). Based on the available evidence no conclusions can be made on whether one form of oral or intranasal fentanyl is superior to another (very low level of evidence). Based on the available evidence, there are indications that oral transmucosal fentanyl citrate (OTFC) and fentanyl pectin nasal spray (FPNS) might be superior to immediate release morphine sulfate (IRMS) (low level of evidence). Based on the available evidence no conclusions can be made on whether one of the other oral opioids is superior to another (very low level of evidence). Therefore breakthrough pain in cancer patients on a stable and optimized around-the-clock (ATC) regimen of opioids can be treated by oral or intranasal fentanyl independent from which opioid is used for the maintenance therapy	weak	very low level	Preference for second formulation

Recommendation(s) before experts meeting	GoR	LoE	Recommendation(s) after experts meeting	GoR	LoE	Comments
Opioids						
Based on the available evidence, it should be considered to titrate the dose of rescue opioid medication in the same way that the around-the-clock opioid medication is titrated until a successful dose is found, rather than using a dose proportional to the total around-the-clock (ATC) opioid dose	strong/weak	low level	Based on expert opinion, it should be considered to start the rescue medication at a dose proportional to the total around-the-clock (ATC) opioid dose; and then titrate it in the same way that the around-the-clock opioid medication is titrated	strong	very low level	Starting with a dose that corresponds to around-the-clock medication
Based on the available evidence, it is not possible to recommend on whether intravenous or subcutaneous morphine titration should be preferred for the treatment of patients with persisting exacerbations of cancer pain	strong/weak	very low level				
OR:						
Based on the available evidence, both intravenous and subcutaneous morphine titration are adequate for the treatment of patients with persisting exacerbations of cancer pain	strong/weak	very low level	Based on the available evidence, both intravenous and subcutaneous morphine titration are adequate for the treatment of patients with persisting exacerbations of cancer pain	weak	very low level	Preference for second formulation

Recommendation(s) before experts meeting	GoR	LoE	Recommendation(s) after experts meeting	GoR	LoE	Comments
Opioids						
The available evidence does not allow to conclude on the effectiveness of opioid switching in patients with inadequate pain relief and intolerable opioid-related toxicity or adverse effects. However, opioid switching can be a treatment option in some of these patients, after a thorough reassessment of pain management has been performed	strong/weak	very low level	The available evidence does not allow to conclude on the effectiveness of opioid rotation in patients with inadequate pain relief and intolerable opioid-related toxicity or adverse effects. However, opioid rotation can be a treatment option in some of these patients, after a thorough reassessment of pain management has been performed	strong	very low level	• Wording: change switching in rotation • Few studies in cancer patients but a lot of evidence in non-cancer patients
Based on the limited evidence of two trials, there are indications that transdermal fentanyl and oral sustained-release morphine show comparable efficay for moderate to severe cancer pain, but it is not possible to conclude on their relative profile of adverse effects. Therefore, oral morphine remains the standard treatment of moderate to severe cancer pain. However, the use of transdermal opioids can be reserved to selected patients e.g. in patients with swallowing difficulties or vomiting, after a stable opioid regimen has been established	strong/weak	very low level	see recommendation on oral morphine			• Preference for 3th wording • Dynamic view needed on administration route • Merge this recommendation with that related to oral morphine
OR:						

Recommendation(s) before experts meeting	GoR	LoE	Recommendation(s) after experts meeting	GoR	LoE	Comments
Opioids						
Based on the limited evidence of two trials, there are indications that transdermal fentanyl and oral sustained-release morphine show comparable efficay for moderate to severe cancer pain, but it is not possible to conclude on their relative profile of adverse effects. Therefore, oral morphine remains the standard treatment of moderate to severe cancer pain. However, the use of transdermal opioids can be reserved to selected patients, after a stable opioid regimen has been established	strong/weak	very low level				
OR:						
Based on the limited evidence of two trials, there are indications that transdermal fentanyl and oral sustained-release morphine show comparable efficay for moderate to severe cancer pain, but it is not possible to conclude on their relative profile of adverse effects. Based on expert consensus, transdermal opioids can be used as an alternative to oral morphine for moderate to severe cancer pain, after a stable opioid regimen has been established	strong/weak	very low level				

Recommendation(s) before experts meeting	GoR	LoE	Recommendation(s) after experts meeting	GoR	LoE	Comments
Opioids						
The available evidence does not allow to conclude on the effectiveness of the concurrent use of two strong opioids for background analgesia in cancer patients with inadequate pain relief and/or intolerable opioid-related adverse effects while using a single strong opioid. However, the concurrent use of two carefully selected strong opioids can be a treatment option in some of these patients, after a thorough reassessment of pain management has been performed. Skilled professionals should be preferred to initiate, to adjust and to monitor such treatment. It should be considered to limit the initiation of such treatment to medical specialists in pain treatment, or palliative care physicians. Once optimal dosing has been identified, continuation of maintenance treatment can be carried out by another physician	strong/weak	very low level	The available evidence does not allow to conclude on the effectiveness of the concurrent use of two strong opioids for background analgesia in cancer patients with inadequate pain relief and/or intolerable opioid-related adverse effects while using a single strong opioid. However, the concurrent use of two carefully selected strong opioids can be a treatment option in some of these patients, after a thorough reassessment of pain management has been performed. It should be considered to limit the initiation of such treatment to medical specialists in pain treatment, or palliative care physicians. Once optimal dosing has been identified, continuation of maintenance treatment can be carried out by another physician	weak	very low level	Do not mentioned 'Skilled professionals should be preferred to initiate, to adjust and to monitor such treatment.'

2. CONSULTATION OF STAKEHOLDER PANEL

For information on the methodology of the drafting of recommendations: see scientific report chapters 2.8 to 2.11. The recommendations as formulated after the experts meetings were presented to a panel of stakeholders (see colophon and see Appendix I) for further adjustment. These modifications are documented in the Table 2 below. The formulation of recommendations as proposed by the stakeholder panel is the final formulation.

Only two further adaptations (indicated by * in the table below) were proposed by the validators and accepted by the authors of the report:

1. recommendations on prevention (chapters antidepressants and anticonvulsants) were deleted since prevention was out of scope for this report;
2. in the chapter on NSAIDs and paracetamol, “short term” was added in the following phrase: “The available evidence does not allow to draw firm conclusions on the comparison of analgesic effect or short term side-effects between NSAIDs, and WHO step II or step III opioids in the treatment of moderate to severe cancer pain.”

Finally, after the stakeholder meeting some language adaptations were performed by the authors of the report, in order to improve the wording of the recommendations. These adaptations did not impact the content of the recommandations.

Table 72 – Reporting of the modifications proposed by the stakeholder panel

REC / GCP	Recommendation(s) and Good Clinical Practice Point(s)	Strength of Recom.	GRADE Level of Evidence	$\bar{x}$	Scores included	Nb resp	Comments	Modifications during stakeholdersmeeting	New formulation recommendations
PAIN ASSESSMENT									
GCP	Prior to treatment, an accurate assessment should be performed to determine the cause, type and severity of pain, and its functional and psychosocial impact on the patient. Validated assessment questionnaires should be used as well as clinical evaluation and laboratory tests or medical imaging if necessary. The assessment should be repeated if treatment does not alleviate the pain even after careful adjustment.			4,4	4:8 5:6	14	Most important member in this pain assessment is indeed the patient himself,because he has to give us as much as possible in detail how he experiences his pain	no modification	
GCP	The patient is the most reliable assessor of pain and should, where possible, be the prime assessor of his or her pain.			4,6	4:5 5:9	14		no modification	
GCP	Patients with cancer pain should have treatment outcomes monitored regularly using unidimensional pain instruments such as visual analogue scales (VAS), numerical rating scales (NRS) or verbal rating scales (VRS). Multidimensional pain instruments can be used for complex pain syndromes. Examples are the McGill Pain questionnaire and the Brief Pain Inventory, which incorporate NRS and VRS. Observational pain rating scales should be preferred in patients who cannot complete a self assessment scale.			4,8	2:1 4:5 5:9	14	also cancer pain has biopsychosocial impact. Psychologists can en will sometimes use multidimimensional questionnaires	The psychosocial issue have to be taken into account therefore 'can be' replaced by: should be	Patients with cancer pain should have treatment outcomes monitored regularly using unidimensional pain instruments such as visual analogue scales (VAS), numerical rating scales (NRS) or verbal rating scales (VRS). Multidimensional pain instruments **should** be used for complex pain syndromes. Examples are the McGill Pain questionnaire and the Brief Pain Inventory, which incorporate NRS and VRS. Observational pain rating scales should be preferred in patients who cannot complete a self assessment scale.
GCP	The minimal objective of pain treatment should be a clinically relevant decrease of the pain (2 points on a 0-10 scale and/or a decrease of 30%, and preferentially a pain intensity of <5).			4,1	2:1 4:8 5:3 NA:1	13	The cut off point < 5 is trivial, even in this report there are suggestions for a cut off of 3 / e-mail : zou ik willen verwijzen naar tabel 11 (p28), waar pijn wordt ingedeeld als mild (1-<4) en moderate (4-7). Is het dan niet logischer om ook bij de aanbeveling voor behandeling dezelfde cut- off te gebruiken?	clear arguments should be added : explanation of the cut-off of 5 is due to the emergence of functional impairment	
GCP	Patients should be given information about pain and instruction about pain management; they should be encouraged to take an active role in their pain management.			4,6	4:5 5:9	14		no modification	

REC / GCP	Recommendation(s) and Good Clinical Practice Point(s)	Strength of Recom.	GRADE Level of Evidence	$\bar{x}$	Scores included	Nb resp	Comments	Modifications during stakeholdersmeeting	New formulation recommendations
NSAIDs AND PARACETAMOL									
REC_1	Paracetamol at a correct dose (1 gr./dose; up to 4 gr./day for adults) and/or an NSAID (including aspirin) are recommended as the first line treatment option for mild to moderate cancer pain (WHO step I)	**Strong**	paracetamol: very low , NSAID: moderate	4,0	2:2 4:9 5:4	15	**1.** First line treatment of pain should always be paracetemol due to the safety and side effects in relation to NSAID/ **2.** doubts about "including aspirin". No experience, we never use aspirin in a long term to prevent stomach ulcers.	stakeholders preferred to abandon aspirin as a recommended treatment option, because of its potential side-effects (gastro-intestinal bleeding). NSAIDs are prohibited to patients treated with cis-platine or patients with myeloma. Aspirin is never prescribed by the stakeholders attending the meeting! (agreement by all stakeholders because of side effects) "Including aspirin": should be deleted for geriatric patients: 3gr/day paracetamol	Paracetamol at a correct dose (1 gr./dose; up to 4 gr./day for adults; up to 3gr./day for older patients) and/or an NSAID are recommended as the first line treatment option for mild to moderate cancer pain (WHO step I)
	An NSAID can be preferred for specific indications, such as bone pain or inflammatory conditions . Relative contra-indications such as pre-existing gastro-intestinal, cardiovascular, hematological, renal or hepatic conditions should be taken into consideration, and side-effects should be carefully monitored, especially with NSAIDs .		Very low	4,1	3:1 4:8 5:2	11	**1.** For specific indications an NSAID can be used.The patient should be carefully monitored in relation to the risk of stomach bleeding and cardiovascular problems with NSAIDS **2.** but long term use of NSAID's should be avoided due to side-effects (e.g. gastro-intestinal)	monitored **and instructed to the patient**	An NSAID can be preferred for specific indications, such as bone pain or inflammatory conditions . Relative contra-indications such as pre-existing gastro-intestinal, cardiovascular, hematological, renal or hepatic conditions should be taken into consideration, and side-effects should be carefully monitored **and instructed to the patient**, especially with NSAIDs .
REC_2	Clear evidence is lacking to support superior efficay or safety of one NSAID (including aspirin) over another in patients with cancer pain. Therefore it is not possible to recommend for or against one NSAID over another in patients with cancer pain, but the individual sensitivity of each patient should be taken into account.	**Weak**	Very low	3,5	2:5 4:7 5:3	15	**1.** recent studies are warning for the cardiovascular toxicity and side-effects **2.** NSAID's certainly differ considering effects and side effects **3.** new data on cardiovascular toxicity are available for diclofenac and should be mentionned in the guideline (McGettigan P, Henry D. mc gettigan et al. PloS mED 2013; 10(2)) **4.** I think there must be evidence that cox2 heve less stomach side-effects. But may me not proven in cancer patients ? **5.** Be aware of the cardiovacular problems with diflocenac **6.** but also consider impact on side-effects (e.g. cardiotoxicity) to chose a NSAID	side-effects (cardiovascular toxicity): already mentioned in previous recommendation- no evidence found on COX-2 inhibitors. Some studies report more cardiovascular toxicities, but less gastrointestinal side effects. aspirin: should be deleted no evidence on half-life of NSAIDs diclofenac: recent advise from government against	Clear evidence is lacking to support superior efficay or safety of one NSAID over another in patients with cancer pain. Therefore it is not possible to recommend for or against one NSAID over another in patients with cancer pain, but the individual sensitivity of each patient should be taken into account.

REC / GCP	Recommendation(s) and Good Clinical Practice Point(s)	Strength of Recom.	GRADE Level of Evidence	$\bar{x}$	Scores included	Nb resp	Comments	Modifications during stakeholdersmeeting	New formulation recommendations
NSAIDs AND PARACETAMOL									
REC_3	The available evidence does not allow to draw firm conclusions on the comparison of analgesic effect or side-effects between NSAIDs (including aspirin), and WHO step II or step III opioids in the treatment of moderate to severe cancer pain. Therefore it is not possible to recommend on whether an NSAID or a Step II or Step III opioid should be recommended as first line treatment option for moderate to severe cancer pain.		Very low	3,7	2:2 3:1 4:11 5:1	15	For moderate to severe cancer,I should start conform the pain ladder with a weak opioid	WHO ladder p.25 including aspirin: should be deleted- studies in the present study on synergy between NSAIDs and opioids show no clear evidence confirming a dose-sparing effect of NSAIDs. Maybe evidence about combination in dose-seeking studies, which is not in scope of this report	The available evidence does not allow to draw firm conclusions on the comparison of analgesic effect or **short term*** side-effects between NSAIDs, and WHO step II or step III opioids in the treatment of moderate to severe cancer pain. Therefore it is not possible to recommend on whether an NSAID or a Step II or Step III opioid should be recommended as first line treatment option for moderate to severe cancer pain. * added after validation meeting
REC_4	If paracetamol (and/)or an NSAID (including aspirin) no longer adequately relieve(s) the pain, an opioid drug should be considered. There is conflicting evidence as to the question whether combining an NSAID (including aspirin) or paracetamol with a WHO step II opioid is superior to an NSAID (including aspirin) or paracetamol alone in patients with cancer pain.	**Strong**	Very low	4,1	3:1 4:12 5:2	15		including aspirin: should be deleted- paracetamol is preferred to NSAIDs by the most stakeholders but this is not supported by evidence and both have side-effects. Agreement to mention paracetamol/NSAID	If **paracetamol/NSAID** no longer adequately relieve(s) the pain, an opioid drug should be considered. There is conflicting evidence as to the question whether combining an NSAID or paracetamol with a WHO step II opioid is superior to an NSAID or paracetamol alone in patients with cancer pain.
	There are indications that oral codeine and tramadol are effective and well-tolerated drugs as compared to placebo in the management of mild to moderate cancer pain never treated with opioids.		Low	3,7	2:2 3:1 4:8 5:1	12	pharmacologiquement: la codeine est non transformée chez 10% de la population, tramadol: inhibe recapture serotonine et nordadrenaline + effet agoniste Mu + stimule secretion neuronale serotonine, il faut tenir compte de ces particularités dans le choix de la molécule.	report p 49 (4,3,1,1,7 & 8), monitoring of the patients' outcomes can be added to this recommendation	
	There are indications that initiating strong opioids (Step III) instead of weak opioids (Step II) for mild to moderate cancer pain after conventional treatment with NSAIDs and/or paracetamol failed, leads to better pain control but at the cost of more side effects.		Very low	3,9	3:1 4:12	13	I don't fully agree with "more side-effects". There is too little evidence		
	Therefore weak opioids (Step II) should be considered in the management of mild to moderate cancer pain after conventional treatment with NSAIDs and/or paracetamol failed.		Very low	3,6	2:1 3:3 4:8	12	**1**. most logical way of handling this problem **2.** in my experience, gp's hesitate too much before using strong opioids. Monitoring and treating side effects (if any!)seems a better recommendation	"and patient outcomes should be monitored": will be added to recommendation NSAID is never given as single treatment. Wording: paracetamol put first, before NSAIDs--> paracetamol/NSAIDs	Therefore weak opioids (Step II) should be considered in the management of mild to moderate cancer pain after conventional treatment with **paracetamol/NSAIDs** failed, **and patient outcomes should be monitored.**

REC / GCP	Recommendation(s) and Good Clinical Practice Point(s)	Strength of Recom.	GRADE Level of Evidence	$\bar{x}$	Scores included	Nb resp	Comments	Modifications during stakeholdersmeeting	New formulation recommendations
NSAIDs AND PARACETAMOL									
REC_5	There are indications that NSAIDs as add-on to WHO step III opioids in comparison to step III opioids alone for mild or moderate to severe cancer pain show no difference or show a low clinical difference (<25% difference) to the advantage of the combination NSAIDs-opioids. Based on the available evidence, it is not possible to draw firm conclusions on the comparison of adverse events in both groups. Therefore the use of NSAIDs as add-on to a stabilized regimen of WHO step III opioids should not be considered as a route treatment option .	**Weak**	Very low	3,5	2:5 4:8 5:2	15	**1.** cette remarque ne tient pas compte du type de douleur ni de l'étiologie de la douleur **2.** exception should be made for specific problems as trauma, fracture - here NSAID's migth play a pain-relieving role. **3.** in specific cases 'e.g. trauma, fractures, nsiads may be of value **4.** The available evidence does not allow to recommand for or against it, but use of NSAID or paracetamol as add-on can be considered, giving the opioid sparing effect in other populations (e.g. orthopedic patients) **5.** **-** Nabal et al. (2012) Palliat.Med. Weakly supports the proposal that the addition of NSAID's can improve analgesia or reduce opioid dose requirement in advanced cancer - McDaid et al. (2010) Health Technol. Assess 24h morphine consumption decreased when paracetamol, NSAID or Cox-2 were added to PCA morphine following surgery - Maund et al. (2011) Br.J.Anaesth. Similar findings as McDaid	McDaid 2010 and Maund 2011: following major surgery--> no focus on cancer patients and only 24h postsurgery--> in our report at least 7days postop Comment: the association remains interesting when bone pain occured but in this case, we are not in routine care -> emphasis on 'routine care'	There are indications that NSAIDs as add-on to WHO step III opioids in comparison to step III opioids alone for mild or moderate to severe cancer pain show no difference or show a low clinical difference (<25% difference) to the advantage of the combination NSAIDs-opioids. Based on the available evidence, it is not possible to draw firm conclusions on the comparison of **short term*** adverse events in both groups. Therefore the use of NSAIDs as add-on to a stabilized regimen of WHO step III opioids should not be considered as **a route treatment option** . * added after validation meeting

REC / GCP	Recommendation(s) and Good Clinical Practice Point(s)	Strength of Recom.	GRADE Level of Evidence	x̄	Scores included	Nb resp	Comments	Modifications during stakeholdersmeeting	New formulation recommendations
NSAIDs AND PARACETAMOL									
REC_6	There are indications that paracetamol as add-on to a stabilized regimen of WHO step III opioids for mild cancer pain shows no difference in pain relief as compared to the step III opioids alone. Therefore the use of paracetamol as add-on to a stabilized regimen of WHO step III opioids should not be considered.	**Strong**	Very low	2,9	2:9 4:4 5:2	15	**1.** pourtant la littérature met en évidence une efficacité spécifique de l'association paracetamol+ opioides dans les douleurs oncologiques sur métastases osseusesATS19 - Questions pratiques d'actualité « douleurs des métastases osseuses » Doi : DOU-11-2006-7-HS2-1624-5687-101019-200609298 S. Donnadie **2.** (exception should be made for other or specific pains as headache e.a. **3.** except for new emergent pain (mucositis, headache. **4.** for specific indications (e.g; headache) paracetamol may be used **5.** Acetaminophen (paracetamol) improves pain and well-being in people with advanced cancer already receiving a strong opioid regimen: a randomized, double-blind, placebo-controlled cross-over trial. Stockler M, Vardy J, Pillai A, et al.Journal of Clinical Oncology 2004 22: 3389-3394 **6.** Paracetamol improves pain and well-being in people with advanced cancer already receiving a strong opioid regimen: a randomized, double-blind, placebo-controlled cross-over trial. Stockler M, Vardy J, Pillai A, et al.Journal of Clinical Oncology 2004 22: 3389-3394	ATS19 - Questions pratiques d'actualité « douleurs des métastases osseuses » Doi : DOU-11-2006-7-HS2-1624-5687-101019-200609298 S. Donnadie: not found; Stockler M, Vardy J, Pillai A, et al.Journal of Clinical Oncology 2004 22: 3389-3394: included in report see p 42 par 4,2,3,3,3; however this was the only study out of 5 studies showing an advantage of 0,4 on a VNS of 10 points (as route treatment option) as routine treatment: will be added NSAIDs seen as rescue medication not as routine treatments. In bone pain: association with NSAIDs, but will not be added in the recommendation.	There are indications that paracetamol as add-on to a stabilized regimen of WHO step III opioids for mild cancer pain shows no difference in pain relief as compared to the step III opioids alone. Therefore the use of paracetamol as add-on to a stabilized regimen of WHO step III opioids should not be considered **as routine treatment.**
GCPP								Added according the below remarks	Patients should be informed on the benefits and potential side-effects associated with the use of NSAIDs. Their preferences should be taken into account when deciding on the treatment

REC / GCP	Recommendation(s) and Good Clinical Practice Point(s)	Strength of Recom.	GRADE Level of Evidence	x̄	Scores included	Nb resp	Comments	Modifications during stakeholdersmeeting	New formulation recommendations
	OPIOIDS **General principles**								
REC_1	The WHO analgesic ladder prescribes the use of non-opioid analgesics for mild or moderate cancer pain (Step I), and the use of or combination with opioid analgesics if the pain persists or if the patient is in severe pain. Weak opioids should be used for the treatment of persistent mild to moderate pain (Step II), and strong opioids for severe pain or if the pain persists despite the use of weak opioids (Step III). At each step, adjuvant drugs should also be considered. There is evidence that by application of the WHO analgesic ladder pain relief can be achieved in 75-90% of cancer patients (very low level of evidence). It should be considered to follow the principles of treatment outlined in the WHO analgesic ladder when treating pain in patients with cancer	**Strong**	Very low	4,1	3:1 4:12 5:2	15	there is little evidence to use step II medication before step III medication, there is no evidence that this ladder is the best treatment option in neuropathic cancer pain		
REC_2	Strong interindividual differences in response to opioids are a well-known clinical phenomenon, underpinned by recent scientific insights in genetic variation in opioid metabolism. Therefore, all opioids should be titrated according to individual analgesic response and occurrence of side-effects	**Strong**	Very low	4,5	4:8 5:7	15			
REC_3	Based on clinical experience, oral delivery of opioids is effective and simple. Therefore, the oral route should be used for the administration of opioids, if practical and feasible. However, depending on the evolution of the patient's condition and taking into account his/her preferences, the route of administration should be adjusted dynamically and transdermal, subcutaneous, or intravenous opioid administration should be considered. Rarely, intrarectal, intramuscular or intraspinal administration can be considered. Sustained release oral opioids cannot be administered by gastic tube since it is not allowed to crush these formulations.	**Strong**	Very low	4,2	4:12 5:3	15	**1.** intraspinal might be considered if disadvantages of opiods don't outweigh the pain killing effect **2.** considering the aspect of medication adherence and the more steady blood levels, sustained release should be preferred, in that perspective transdermal patches may be preferred	except for palladone slow release (hydromorphone) (microgranules): added as exception (also added in report)	Based on clinical experience, oral delivery of opioids is effective and simple. Therefore, the oral route should be used for the administration of opioids, if practical and feasible. However, depending on the evolution of the patient's condition and taking into account his/her preferences, the route of administration should be adjusted dynamically and transdermal, subcutaneous, or intravenous opioid administration should be considered. Rarely, intrarectal, intramuscular or intraspinal administration can be considered. Slow release oral opioids cannot be administered by gastic tube since it is not allowed to crush these formulations. However, one slow release oral formulation is an exception and since the capsules have been specifically developed to be opened although they should not be crushed (slow release hydromorphone: Palladone Slow Release®)

REC / GCP	Recommendation(s) and Good Clinical Practice Point(s)	Strength of Recom.	GRADE Level of Evidence	x̄	Scores included	Nb resp	Comments	Modifications during stakeholdersmeeting	New formulation recommendations
OPIOIDS									
	Strong opioids								
REC_4	There are indications that the effectiveness of oral morphine in the treatment of cancer pain compares well to other available strong opioids (oxycodone, hydromorphone, methadone) when titration to effect is performed.	**Strong**	Very low	4,1	4:13 5:2	15			
	There are indications that for oral morphine treatment side effects are common, but that intolerable adverse effects occur in a small number of patients only (4%) and that non-respons is infrequent.		Very low	4,1	3:1 4:10 5:2	13	except fo neuropathic pain ?		
	Therefore oral morphine should be considered as the drug of first choice and the gold standard for moderate to severe cancer pain.		Very low	3,9	2:1 3:1 4:9 5:2	13	morphine or its oral derivatives such as oxycodone; transdermal administration could also be a good alternative.	see row 29 (oral route of administration: see report)	
REC_5	There are indications that oral morphine, oral oxycodone, oral hydromorphone and transdermal fentanyl, when titration to effect is performed, have a similar efficacy and toxicity in cancer-related pain.	**Strong**	Very low	3,7	2:3 4:10 5:2	15	is conflicting with rec 4	no, term "gold standard"	
	Therefore, depending on the tolerability of each individual patient, other oral strong opioids in their equi-analgesic dose can be considered as an alternative to oral morphine in the first-line treatment of moderate to severe cancer pain. Likewise, transdermal fentanyl, in an equi-analgesic dose, can be used as an alternative to oral opioids for moderate to severe cancer pain, after a stable opioid regimen has been established.		Very low	4,1	4:12 5:1	13			
REC_6	Based on the available evidence it is not possible to conclude on the relative efficacy and side-effects of transdermal buprenorphine as compared to oral morphine, to other oral opioids or to transdermal fentanyl for moderate to severe cancer pain. Based on its pharmacological properties and mixed working mechanism, oral or transdermal buprenorphine might be considered as a treatment option for selected cases of neuropathic cancer pain.	**Weak**	Very low	3,5	2:3 3:1 4:11	15	**1.** brupenorphine: effet plafond demontré chez animal et chez homme (mais posologies mal connues). Cf SOR tt antalgiques médicamenteux des douleur cancéreuses par excès de nociception chez l'adulte 2002 **2.**Theoretically buprenorfine can have beneficial effects on neuropathic pain, evidence is completely lacking !	remark 1: cfr report p49 (4,3,1,1,6) preference for this product but not specific for neuropathic pain--> for selected cased of neuropathic cancer pain: deleted less ceiling effect described in theory, but not yet seen in clinical practice- no studies found for sublingual buprenorphine-will be put after recommendation for oral morphine	Based on the available evidence it is not possible to conclude on the relative efficacy and side-effects of transdermal buprenorphine as compared to oral morphine, to other oral opioids or to transdermal fentanyl for moderate to severe cancer pain. Based on its pharmacological properties and mixed working mechanism, oral or transdermal buprenorphine might be considered **as a treatment option**.

REC / GCP	Recommendation(s) and Good Clinical Practice Point(s)	Strength of Recom.	GRADE Level of Evidence	$\bar{x}$	Scores included	Nb resp	Comments	Modifications during stakeholdersmeeting	New formulation recommendations
OPIOIDS									
	Strong opioids								
REC_7	The pharmacological properties of methadone suggest that it might be useful in the treatment of neuropathic pain. However, based on the available evidence it is not possible to conclude on the superiority of methadone to morphine in patients with neuropathic cancer pain.	**Strong**	Very low	4,1	3:1 4:12 5:2	15	other drugs such as antidepressants should be considered in first line		
	There are indications that oral methadone and morphine have a similar efficacy in the treatment of nociceptive or mixed types of moderate to severe cancer pain.		Very low	3,8	2:1 3:1 4:10 NA:1	13			
	Because of its pharmacokinetics and pharmacodynamics, the adverse effects of methadone may become more prominent with repeated dosing. One of its specific although rare adverse effects is prolongation of the QT interval leading to cardiac dysrhythmias, especially at high doses. In Belgium, it should be considered to limit the initiation of a treatment with methadone as add-on to another opioid for analgesic purposes (such as in cancer patients with moderate to severe pain) to medical specialists in pain treatment, or palliative care physicians. Once optimal dosing has been identified, continuation of maintenance treatment can be carried out by another physician.		Very low	4,1	3:2 4:7 5:3 NA:1	13	remarque:l'étude de Suresh Reddy (Journal of palliative medecine 2010) montre qu'il n'y a pas de retentissement clnique a cet espacement qt chez les patients avec cancer avancé sous methadone. A mon sens la recommandation d'expert pour la mise en place methadone se justifie plus par sa pharmacocinétique complexe que par l'espacement qt	experts agree that methadone should be given by specialists, but in Belgium only very low dose available on the market. Add-on: due to QT interval prolongation. In clinical practice: good results with methadone, but stakeholders don't agree with "add-on" formulation. Is also used as firstline treatment (mainly in rotation) by experts--> add-on: deleted. To use methadon under supervision of experts is not unique for Belgium, "In Belgium" should be deleted- Specialists should be replaced by experts because physicians in palliative care don't have the official title of specialist. --> experts in palliative care	Because of its pharmacokinetics and pharmacodynamics, the adverse effects of methadone may become more prominent with repeated dosing. One of its specific although rare adverse effects is prolongation of the QT interval leading to cardiac dysrhythmias, especially at high doses. **It should** be considered to limit the initiation of a treatment with methadone for analgesic purposes (such as in cancer patients with moderate to severe pain) to **medical experts in pain treatment or palliative care.** Once optimal dosing has been identified, continuation of maintenance treatment can be carried out by another physician.
REC_8	Individual patient assessment should determine the appropriate treatment option in cancer patients with neuropathic pain or with a mixed type of pain including neuropathic components, and opioids can be considered alone, or combined with adjuvant analgesics (antidepressants, anticonvulsants).	**Strong**	Very low	4,1	4:12 5:2 NA:1	15		preference for strong	

REC / GCP	Recommendation(s) and Good Clinical Practice Point(s)	Strength of Recom.	GRADE Level of Evidence	$\bar{x}$	Scores included	Nb resp	Comments	Modifications during stakeholdersmeeting	New formulation recommendations
OPIOIDS									
Weak opioids									
REC_9	If paracetamol (and/)or an NSAID (including aspirin) no longer adequately relieve(s) the pain, an opioid drug should be considered. There is conflicting evidence as to the question whether combining an NSAID (including aspirin) or paracetamol with a WHO step II opioid is superior to an NSAID (including aspirin) or paracetamol alone in patients with cancer pain.	**Strong**	Very low	2,1	2:6 3:1 4:7 5:1	15	**1.** à nouveau, cette recommandation ne tient pas compte de l'origine de la douleur (cf metastases osseuses, hepatalgies…) **2.** Conform an article dated September 2008 with subject WHO Analgesic Ladder step2 chronic opioid therapy may have fewer life-threatening risks than long-term daily use of NSAIDS	remark 1: no evidence available on specific subtypes of pathology- same recommendations as row 13 to 16	double: see NSAIDs
	There are indications that oral codeine and tramadol are effective and well-tolerated drugs as compared to placebo in the management of mild to moderate cancer pain never treated with opioids.		Low	4,0	4:13	13			double: see NSAIDs
	There are indications that initiating strong opioids (Step III) instead of weak opioids (Step II) for mild to moderate cancer pain after conventional treatment with NSAIDs and/or paracetamol failed, leads to better pain control but at the cost of more side effects .		Very low	3,8	2:1 4:12	13	There is too little evidence to state that there will be more side-effects		double: see NSAIDs
	Therefore weak opioids (Step II) should be considered in the management of mild to moderate cancer pain after conventional treatment with NSAIDs and/or paracetamol failed.		Very low	3,7	2:2 4:11	13		remark 1: no evidence available on specific subtypes of pathology- same recommendations as row 13 to 16	double: see NSAIDs
REC_10	There are indications that there is no difference in efficacy between tramadol and codeine combined with paracetamol	**Weak**	Low	3,7	2:3 4:10 5:2	15	les acétyleurs lents ne metabolisent pas la codeine.	see also row 14: report p 49 (4,3,1,1,7 & 8)	
	RCTs directly evaluating other combinations of weak opioids against each other are not available for this indication. Therefore, when weak opioids are considered in the management of mild to moderate cancer pain after conventional treatment with NSAIDs and/or paracetamol failed, codeine and tramadol can be considered as equivalent treatment options, and the choice for one of them should depend on the tolerability of each individual patient		Very low	4,2	2:1 4:12	13	le mecanisme d'action de ces molécules doit laisser la place à une spécificité de chacune en fonction dy type de douleur (nociceptive, mixte, neuropathique).	no evidence available on specific subtypes of pathology-	RCTs directly evaluating other combinations of weak opioids against each other are not available for this indication. Therefore, when weak opioids are considered in the management of mild to moderate cancer pain after conventional treatment with **paracetamol/NSAIDs** failed, codeine and tramadol can be considered as equivalent treatment options, and the choice for one of them should depend on the tolerability of each individual patient

REC / GCP	Recommendation(s) and Good Clinical Practice Point(s)	Strength of Recom.	GRADE Level of Evidence	$\bar{x}$	Scores included	Nb resp	Comments	Modifications during stakeholdersmeeting	New formulation recommendations
OPIOIDS									
Breakthrough cancer pain									
REC_11	For cancer patients on a stable around-the-clock (ATC) regimen of opioids, the first approach to breakthrough pain should be to optimize the ATC regimen	**Strong**	Very low	3,8	2:2 4:9 5:2	13	**1.** les btp doivent être traitées de manière spécifique afin d'éviter des surdosages en dehors des épisodes douleureux qui sont bref de par leur définition: breakthrought pain **2.** both issues should be combined: good breakthrough and overall pain control.this is different for end-of dosing pain **3.**with short acting opioids	definition breakthrough pain: p 74 (4,3,3,9) more general recommendation, not completely based on literature should be added: as quick as possible and with breakthrough pain medications incident pain (=bone pain) is not breakthrough pain (day dosis is not suitable) but other stakeholders emphasize the short and heavy presence of breakthrough pain. to optimize: doses optimally divided over the day/moment of administration approach: should be aim	For cancer patients on a stable around-the-clock (ATC) regimen of opioids presenting with breakthrough pain, the first **aim** should be to optimize the ATC regimen **to differentiate between breakthrough pain and end of dose pain.**

REC / GCP	Recommendation(s) and Good Clinical Practice Point(s)	Strength of Recom.	GRADE Level of Evidence	x̄	Scores included	Nb resp	Comments	Modifications during stakeholdersmeeting	New formulation recommendations
OPIOIDS									
Breakthrough cancer pain									
REC_12	For cancer patients on a stable and optimized around-the-clock (ATC) regimen of opioids, different formulations of oral and intranasal fentanyl have been proven to be effective and safe as compared to placebo in the treatment of breakthrough cancer pain.	**Weak**	Low	3,9	2:2 4:11 5:2	15	le fentanyl est la molécule de choix pour ses caractéristiques pharmaceutiques de liposolobilité, la molécule agit plus vite et moins longtemps à la différence de la morphine qui agit pdt 4h !!!		
	Publicatons are lacking on the effectiveness and safety in this indication of immediate release oral morphine as well as other forms of oral opioids commonly used for breakthrough pain (oxycodone, hydromorphone). Based on the available evidence no conclusions can be made on whether one form of oral or intranasal fentanyl is superior to another.		Very low	3,3	2:3 3:2 4:7 NA:1	13	**1.**fentanyl + efficace que morphine DANS CETTE INDICATION PRECISE, non pas au niveau de l'action antalgique mais au niveau de la spécificité du tt au besoin du patient présentant une BTP **2.**randomized trial that the effect is similar to oral morphine **3.**Intranasal fentanyl is superior to another.Reference article PMID:21819159	remark 2: RCT? remark 3: cfr (one study of INFS-transmucosal prepararation)	
	Based on the available evidence, there are indications that oral transmucosal fentanyl citrate (OTFC) and fentanyl pectin nasal spray (FPNS) might be superior to immediate release morphine sulfate (IRMS).		Low	3,6	2:2 3:2 4:7 5:1	12	**1.**in one study the effect was similar **2.**but the cost for the patient should be taken into consideration!!!!	we agree on cost, see report p 92	
	Based on the available evidence no conclusions can be made on whether one of the other oral opioids is superior to another. Therefore breakthrough pain in cancer patients on a stable and optimized around-the-clock (ATC) regimen of opioids can be treated by oral or intranasal fentanyl independent from which opioid is used for the maintenance therapy.		Very low	3,4	2:4 3:1 4:7 5:1	13	**1.**oral morphine can also be used **2.**but the cost for the patient should be taken into consideration!!!!	we agree on cost, see report p 92 aspects of costs only mentioned in "other considerations", not in recommendations- oral morphine can be a cheaper alternative: changed in recommendation . A study of Minnerva showed that oxycodone is superior to INF but not in cancer patients. Subcutaneous morphine is not reimbursed in Belgium. The magistral formulae are very cheap	Based on the available evidence no conclusions can be made on whether one of the other oral opioids is superior to another. Therefore breakthrough pain in cancer patients on a stable and optimized around-the-clock (ATC) regimen of opioids can be treated by oral or intranasal fentanyl independent from which opioid is used for the maintenance therapy. **Although there are indications that oral and intranasal fentanyl might be superior, oral morphine (e.g. as a syrup) can be considered as an effective and cheaper alternative in Belgium.**

REC / GCP	Recommendation(s) and Good Clinical Practice Point(s)	Strength of Recom.	GRADE Level of Evidence	x̄	Scores included	Nb resp	Comments	Modifications during stakeholdersmeeting	New formulation recommendations
OPIOIDS									
Breakthrough cancer pain									
REC_13	Based on expert opinion, it should be considered to start the rescue medication at a dose proportional to the total around-the-clock (ATC) opioid dose; and then titrate it in the same way that the around-the-clock opioid medication is titrated.	**Strong**	Very low	4,1	1:1 4:10 5:4	15	**1.**ce n'est pas ce qui est recommandé par la HAS: on commence par la plus faible dose de fentanyl transmuqueux, puis on adapte par titration **2.**this might be in conflict with REC_11	remark 1: discuss remark 2: wording conclusion: no changes necessary	
REC_14	Based on the available evidence, both intravenous and subcutaneous morphine titration are adequate for the treatment of patients with persisting exacerbations of cancer pain.	**Weak**	Very low	3,4	1:1 2:4 4:8 5:2	15	**1.**pic douleureux et bTP ont des caractéristiques et tt différents. **2.**it's true but oral or intranasal drug are more convenient (eg fentanyl) **3.**first the oral route should be used **4.** First:oral.Reference article PMID:21819159:oral normal-release morphine has long been considered the gold standard for cancer breakthrough pain.	consider adjusting wording after adequate oral opioid treatment has failed: to be added to recommendation	Based on the available evidence, both intravenous and subcutaneous morphine titration are adequate for the treatment of patients with persisting exacerbations of cancer pain, **after adequate oral opioid treatment has failed**.
Opioid rotation									
REC_15	The available evidence does not allow to conclude on the effectiveness of opioid rotation in patients with inadequate pain relief and intolerable opioid-related toxicity or adverse effects. However, opioid rotation can be a treatment option in some of these patients, after a thorough reassessment of pain management has been performed.	**Strong**	Very low	4,1	4:14 5:1	15			
Combination of Opioids									
REC_16	The available evidence does not allow to conclude on the effectiveness of the concurrent use of two strong opioids for background analgesia in cancer patients with inadequate pain relief and/or intolerable opioid-related adverse effects while using a single strong opioid. However, the concurrent use of two carefully selected strong opioids can be a treatment option in some of these patients, after a thorough reassessment of pain management has been performed. It should be considered to limit the initiation of such treatment to medical specialists in pain treatment, or palliative care physicians. Once optimal dosing has been identified, continuation of maintenance treatment can be carried out by another physician.	**Weak**	Very low	4,1	3:1 4:11 5:2	14	There is no recommendation concerning the combination of step II and step III opioids	no modification	
GCPP								Added according the below remarks	Patients should be informed on the benefits and potential side-effects associated with the use of opioids. Their preferences should be taken into account when deciding on the treatment

REC / GCP	Recommendation(s) and Good Clinical Practice Point(s)	Strength of Recom.	GRADE Level of Evidence	$\bar{x}$	Scores included	Nb resp	Comments	Modifications during stakeholdersmeeting	New formulation recommendations
ANTIDEPRESSANTS									
REC_1	The available evidence on the use of antidepressants to prevent post-mastectomy pain in breast cancer patients or to prevent chemotherapy-induced neuropathy does not allow to recommend for or against it.		Low	3,7	2:3 4:11 5:1	15		few studies, but will be kept	Prevention is out-of-scope of the review, this recommendation will be deleted* * added after validation meeting
REC_2	The available evidence on the use of antidepressants for the treatment of neuropathic pain in cancer patients does not allow to recommend for or against it. Individual patient assessment should determine the appropriate treatment option in cancer patients with neuropathic pain or with a mixed type of pain including neuropathic components, and antidepressants can be considered alone, sequentially, or with other analgesic agents, including opioids. Their effectiveness and side-effects should be monitored carefully. This recommendation is based on consensus that the proven benefit of antidepressants (e.g. amytriptiline) as first-line drug to treat neuropathic pain in non-cancer diagnostic patient groups can be extended to patients suffering from neuropathic cancer pain.	**Strong**	Very low	4,1	4:14 5:1	15	Cochrane review Saarto 2009	no modification	
GCPP	Patients should be informed on the potentially increased incidence of adverse events associated with the use of antidepressants. Their preferences should be taken into account when deciding on the treatment.			4,3	4:10 5:4	14	Shouldn't this GCP also be included in the previous medications?	GCP addded to NSAID/paracetamol section and opioid section	
ANTICONVULSANTS									
REC_1	Based on the available evidence, it is not possible to recommend for or against the use of gabapentin or pregabalin as treatment to prevent neuropathic cancer pain.	**Strong**	Very low	3,7	2:2 4:12	14	different reimbursment in belgium. this should be taken into account in the guideline	cfr report p 105 (4,6,1) in general no comments on reimbursement in recommendations, is also already included in strength of recommendation	Prevention is out-of-scope of the review, this recommendation will be deleted* * added after validation meeting

REC / GCP	Recommendation(s) and Good Clinical Practice Point(s)	Strength of Recom.	GRADE Level of Evidence	$\bar{x}$	Scores included	Nb resp	Comments	Modifications during stakeholdersmeeting	New formulation recommendations
ANTICONVULSANTS									
REC_2	The available evidence on the use of gabapentin for the treatment of neuropathic pain in cancer patients does not allow to recommend for or against it.	**Strong**	Very low	3,8	2:2 4:12 5:1	15	**1.**Gabapentine heeft een significant additief analgetisch effect op neuropathische kankerpijn t.o.v. opioïden in monotherapie BENNETT MI; 2011 Eff ectiveness of antiepileptic or antidepressant drugs when added to opioids for cancer pain: systematic review.Palliative Medicine 553 - 559 **2.**Gabapentine + opioids results in better analgesia than opioids in monotherapy. Bennett MI 2011 Eff ectiveness of antiepileptic or antidepressant drugs when added to opioids for cancer pain: systematic review. Palliat Med 25: 553–59.	We did include Bennett 2011 but only the RCTs (Bennett also included non-RCTS: p 105 par 4,6,2); conclusion is not clearly in favor of gabapentine	
	Individual patient assessment including sensory symptoms, should determine the appropriate treatment option in cancer patients with neuropathic pain or with a mixed type of pain including neuropathic components, and anticonvulsants, including gabapentin, can be considered alone, sequentially, or with other analgesic agents, including opioids. Their effectiveness and side-effects should be monitored carefully. This recommendation is based on consensus that the proven benefit of anticonvulsants as first-line drug to treat neuropathic pain in non-cancer diagnostic patient groups can be extended to patients suffering from neuropathic cancer pain.		Very low	4,1	4:11 5:1	12	De combinatie morfine/gabapentine geeft betere analgesie aan lagere dosering van elk geneesmiddel bij neuropathische pijn dan elk product afzonderlijkKeskinbora K, Pekel AF, Aydinli I Gabapentin and an Opioid Combination Versus Opioid Alone for the Management of Neuropathic Cancer Pain: A Randomized Open Trial. Journal of Pain and Symptom Management, 2007, 183-189	cfr report p 110 (par 4,6,3): Keskinbora is open label trial with high risk of bias; for first comparison mean values not given (only p-value); for second comparison values are given but confidence intervals overlap	
REC_3	The available evidence on the use of pregabalin for the treatment of neuropathic pain in cancer patients does not allow to recommend for or against it.	**Weak**	Very low	4,1	4:14 5:1	15		cfr report p 105 (4,6,1) in general no comments on reimbursement in recommendation-included in strength of recommendation	
	Individual patient assessment including sensory symptoms, should determine the appropriate treatment option in cancer patients with neuropathic pain or with a mixed type of pain including neuropathic components, and pregabalin can be considered alone, sequentially, or with other analgesic agents, including opioids. Its effectiveness and side-effects should be monitored carefully. This recommendation is based on consensus that the proven benefit of anticonvulsants as first-line drug to treat neuropathic pain in non-cancer diagnostic patient groups can be extended to patients suffering from neuropathic cancer pain.		Very low	4,1	4:12 5:1	13		no modification	

REC / GCP	Recommendation(s) and Good Clinical Practice Point(s)	Strength of Recom.	GRADE Level of Evidence	$\bar{x}$	Scores included	Nb resp	Comments	Modifications during stakeholdersmeeting	New formulation recommendations
ANTICONVULSANTS									
REC_4	Carbamazepine can be considered to be the preferred anticonvulsant to treat neuropathic pain resulting from cancerous involvement of the trigeminal nerve. This recommendation is based on consensus that the demonstrated effectiveness of carbamazepine for the treatment of trigeminal neuralgia in non-cancer patients can be extended to cancer patients.	**Strong**	Very low	3,9	4:12 5:2	15		no modification	
REC_5	Based on the available evidence, it is not possible to recommend whether anticonvulsants should be preferred or not over antidepressants, in the first-line or add-on treatment of neuropathic cancer pain.		Very low	3,9	4:12 5:2	15		no modification	
GCPP	Patients should be informed on the potentially increased incidence of adverse events associated with the use of anticonvulsants. Their preferences should be taken into account when deciding on the treatment			4,2	4:11 5:3	14		no modification	
RADIOTHERAPY FOR PAINFUL BONE METASTASES									
REC_1	Aspects such as life expectancy of the patient and curability of the bone metastases should be considered when deciding on the preferred radiotherapy scheme for pain relief in bone metastases.	**Strong**	Very low	3,8	2:1 3:2 4:8 5:2 NA:1	14	**1.** phrasing not correct: never a curative therapy in metastastic disease **2.** Only aspect as life expectancy and the widespreadness area of the bone tumors should be considered. **3.** Avec comme commentaires pour les REC 1 à 3; ajout des critères suivants afin de décider du schéma de RTE; - les organes à risque en regard des os à irradier et de leur tolérance (exemple le rectum et la vessie dans les irradiations de bassins,...), tenant compte des alpha-béta (radiobiologiquement donner 30 Gy en # de 2Gy n'engendre pas le même effet que 30 Gy en # de 3Gy par exemple) - le type d'os à irradier; par exemple, le risque fracturaire est supérieur pour les vertèbres porteuses (charnière dosolombaire) => attention aux fractions uniques à ce niveau - l'état de la corticale ossuse et le risque fracturaire en fonction de celui-ci; exemple; humérus et fémur; il vaut mieux parfois enclouer avant la RTE - il faut aussi tenir compte des situations de réirradiation où nous	and clincial condition of the patient: will be added- solitary metastasis: only exceptionally curative aims cfr report p 114 par 4,7,1,1	Aspects such as life expectancy, **clinical condition** of the patient and curability of the bone metastases should be considered when deciding on the preferred radiotherapy scheme for pain relief in bone metastases.

REC / GCP	Recommendation(s) and Good Clinical Practice Point(s)	Strength of Recom.	GRADE Level of Evidence	$\bar{x}$	Scores included	Nb resp	Comments	Modifications during stakeholdersmeeting	New formulation recommendations
RADIOTHERAPY FOR PAINFUL BONE METASTASES									
REC_2	It is plausible that single and multiple fraction radiotherapy are equally effective for short term (4 to 8 weeks) complete or partial pain relief in patients with uncomplicated bone metastases, regardless the primary tumour site.	**Strong**	Moderate	3,6	3:4 4:7 5:2 NA:1	14		no modification	
	It is also plausible that radiotherapy by a single fraction is associated with more retreatments		Moderate	3,5	2:1 3:3 4:6 NA:1	11	this is only of interest if the survival after radiotherapy is long.		
	and more pathological fractures ,		Low	3,0	2:2 3:2 4:2 NA:1	7			
	but the overall rate of retreatment and pathological fractures is relatively low. Therefore the use of single fraction radiotherapy for short term complete or partial pain relief in patients with uncomplicated bone metastases is recommended as treatment of first choice. However, the definitive decision on the treatment modality should also take into consideration the preferences of the patient after he/she has been well-informed, and aspects such as life expectancy of the patient and curability of the bone metastases.			3,8	3:3 4:6 5:1 NA:1	11			but the overall rate of retreatment and pathological fractures is relatively low. Therefore the use of single fraction radiotherapy for short term complete or partial pain relief in patients with uncomplicated bone metastases is recommended as treatment of first choice. However, the definitive decision on the treatment modality should also take into consideration the preferences of the patient after he/she has been well-informed, and aspects such as life expectancy **and clinical condition** of the patient and curability of the bone metastases.
REC_3	The use of a 8-Gy single fraction radiotherapy for short term (4 to 8 weeks) complete or partial pain relief in patients with uncomplicated bone metastases is the option of first choice, after aspects such as life expectancy of the patient, curability of the bone metastases and patient preferences have been taken into account.	**Weak**	Very low	3,7	3:4 4:8 NA:2	14			The use of a 8-Gy single fraction radiotherapy for short term (4 to 8 weeks) complete or partial pain relief in patients with uncomplicated bone metastases is the option of first choice, after aspects such as life expectancy **and clinical condition** of the patient, curability of the bone metastases and patient preferences have been taken into account.
REC-4	A multimodal pain treatment approach should be considered for uncomplicated or complicated bone metastases. Besides local treatment with single or multiple fraction radiotherapy, systemic therapies should also be considered throughout the treatment course, e.g. NSAIDs, opioids, cytotoxic chemotherapy, anticancer hormone therapy etc. This is supported by the significant number of patients with uncomplicated bone metastases who don't obtain total pain relief from single or multiple fraction radiotherapy.	**Strong**	Very low	3,9	3:3 4:8 5:2 NA:1	14		no modification	

REC / GCP	Recommendation(s) and Good Clinical Practice Point(s)	Strength of Recom.	GRADE Level of Evidence	$\bar{x}$	Scores included	Nb resp	Comments	Modifications during stakeholdersmeeting	New formulation recommendations
RADIOTHERAPY FOR PAINFUL BONE METASTASES									
REC-5	Decompressive surgical tumor resection with or without stabilization of the spine and followed by radiotherapy is the option of first choice in patients with metastatic spinal cord compression, after aspects such as duration of the spinal cord compression, status and type of the disease, prior and available anticancer therapies, life expectancy of the patient, and patient preferences have been taken into account.	**Weak**	Very low	3,7	1:1 3:3 4:6 5:2 NA:2	14	**1.** à mon sens si l'on peut éviter un geste chirurgical type décompression de la moelle et administrer la RTE en 1ère intention ce serait plus logique sauf si; il s'agit d'une réirradiation, ou si il est nécessaire d'avoir une histologie, ou si le corps vertébral est tellement atteint qu'il est menaçant et impossible d'envisager une reconstruction osseuse non chirurgicale(naturelle) dans le décours de la RTE, ou si il y a un bloc neurologique complet et d'autrant plus s'il est survenu au-delà de 48 à 72h avant la mise en route de la RTE. **2.** choice for surgery also depends on the radiosensitivity of the tumor (for ex often not necessary in multiple myeloma	1: cfr literature consensus 2, wording of recommendation seems OK: … Status and type of disease to be added: anticancer therapies and corticosteroids	Decompressive surgical tumor resection with or without stabilization of the spine and followed by radiotherapy is the option of first choice in patients with metastatic spinal cord compression, after aspects such as duration of the spinal cord compression, status and type of the disease, prior and available anticancer therapies, **use of corticosteroids**, life expectancy of the patient, and patient preferences have been taken into account.
REC-6	There is insufficient evidence to advise on the preferred radiation dose for the treatment of pain due to metastatic spinal cord compression.		Very low	3,5	2:1 3:5 4:5 5:1 NA:2	14	On sait juste que 10x3 Gy est supérieur à 1x8 Gy en terme de consolidation osseuse et contrôle à plus long terme des douleurs mais ce dernier point dans une moindre mesure. Pour le 5x4 Gy pas assez de recul.	see single versus multiple fractions report p 118 agreement, also rarely done	
REC-7	Hemibody irradiation can be a treatment option in patients with widespread bone metastases who suffer from pain after all systemic pain treatment options failed, and after life expectancy of the patient and patient preferences have been taken into account.	**Weak**	Very low	3,3	2:1 3:6 4:4 NA:3	14	is rarely done	agree	
REC-8	There is insufficient evidence to advise on the preferred schedule for hemibody irradiation as treatment of pain in patients with widespread bone metastases.		Very low	3,3	3:8 4:3 NA:3	14		no modification	
GCPP	Patients should be clearly informed on the benefits and side-effects of the different radiotherapy schemes for pain relief in bone metastases, so that their preferences can be taken into account when deciding on the treatment modality.			4,3	3:1 4:7 5:5	13		no modification	

REC / GCP	Recommendation(s) and Good Clinical Practice Point(s)	Strength of Recom.	GRADE Level of Evidence	x̄	Scores included	Nb resp	Comments	Modifications during stakeholdersmeeting	New formulation recommendations
RADIONUCLIDES									
REC_1	Bone-seeking radio-isotopes can be considered as a secondary option to obtain complete or partial (more than 50%) pain relief in the short and medium term (up to 6 months) for widespread painful osteoblastic bone metastases in cancer patients regardless of the primary tumour site, when conventional treatment failed .	**Weak**	Low	3,7	3:3 4:7 NA:3	13	**1.** For radionuclide therapy the place of Dichlorure of 223-Radium (alpha emittor) is not sufficiently separate in term of low side effects and effectiveness on survival in regard of Beta emittors **2.** It saoule be important to differenciate Ra223 alpha emitter from conventional beta emitters because of lésés or no toxicity and gain in survival	strontium has a cumulative toxic effect, preference for samaritum, but now preference for radium-new study found by stakeholder, can be added to "other considerations" (study from 2013). In the practice, Samarium153 was prefered because of the cremation. The Radium 223 increases the survival at 4 and 6 months and decreases side effects	
REC_2	It is recommended to inform patients that this treatment can be associated with an increased incidence of severe adverse events, such as hematological toxicity and in particular leucocytopenia.	**Strong**	Low	3,0	3:3 4:4 5:1 NA:3	13			
GCPP	Patients should be informed on the benefits and potential side-effects associated with the use of bone-seeking radio-isotopes. Their preferences should be taken into account when deciding on the treatment			4,2	3:1 4:6 5:3 NA:2	12		no modification	
BISPHOSPHONATES									
REC_1	Given the available evidence on efficacy ,	**Strong**	Very low	4,0	3:2 4:7 5:2	11	Radiotherapy is the first line treatment	no modification	
	and given the available evidence on possible adverse events , bisphosphonates cannot be considered as first line, purely analgesic treatment option of metastatic bone pain in the short, medium or long term. This report does not deal with the usefulness of bisphosphonates for other indications in patients with metastatic bone involvement, e.g.hypercalcemia, pathological fractures, impending fractures, spinal cord compression .		Moderate	4,1	3:1 4:6 5:2	9		no modification	
GCPP	Patients should be informed on the benefits and potential side-effects associated with the use of bisphosphonates. Their preferences should be taken into account when deciding on the treatment			1,3	3:1 4:9 5:4	14		no modification	

REC / GCP	Recommendation(s) and Good Clinical Practice Point(s)	Strength of Recom.	GRADE Level of Evidence	$\bar{x}$	Scores included	Nb resp	Comments	Modifications during stakeholdersmeeting	New formulation recommendations
CORTICOSTEROIDS									
REC_1	Corticosteroids alone or combined with other therapeutic options can be considered in cancer patients for pain related to a mass effect of the tumour, e.g. headache caused by raised intracranial pressure, pain in spinal cord compression, multifocal bone pain, abdominal pain from liver capsule distention, intestinal obstruction, etc. They may be also be used to help manage other symptoms in cancer patients at an advanced or terminal stage of the disease, e.g. anorexia, nausea, fatigue, general weakness or feelings of malaise and depression. Side-effects should be monitored carefully.	**Strong**	Very low	4,3	4:11 5:4	15	In cases of headache caused by raisen intracranial pressure and brain oedeema it is only cortisone that can decrease the headache.	no modification	
GCPP	Patients should be informed on the possible benefits and side-effects associated with the use of corticosteroids for the treatment of pain or other symptoms. Their preferences should be taken into account			4,3	4:9 5:4	13		no modification	

REC / GCP	Recommendation(s) and Good Clinical Practice Point(s)	Strength of Recom.	GRADE Level of Evidence	x̄	Scores included	Nb resp	Comments	Modifications during stakeholdersmeeting	New formulation recommendations
CELIAC PLEXUS BLOCK									
REC_1	Based on the limited short term (4 weeks) effectiveness of celiac plexus block (CPB) on pain as compared to standard analgesic treatment, based on its short term possible positive effect on opioid consumption, based on the need to repeat the procedure and on the rare but important complications that can be associated with the procedure, but taking into account that the life expectancy of patients with pancreatic cancer is mostly limited, CPB can be considered as one treatment option for patients suffering from pancreatic cancer, although CPB should not be the treatment of first choice.	**Weak**	Very low	3,7	2:1 3:2 4:11 NA:1	15	it should better to mention 'some' weeks instead of 4 weeks (it can be more than 5 en less than 8 !) ; 'should not be the treatment of first choice but considered quickly if start of opioiduse seems te be unsuccesfull' seems better ; de evidence grading and recommendations contrast strong with 'Evidence based interventional pain medicine according to clinical diagnoses' (Van Zundert et al, 20011), although the references are strongly corresponding ! Also collegue Nagels' review (2013) is added	4 weeks: adjust wording +- 4 weeks (around 4 weeks) Nagels (2013): included RCT as well as observational studies; 9 RCTs included of which 7 are also included in the KCE report (1 is considered out of scope; 1 is not included); meta-analysis of 5 RCTs shows a mean difference of less than 1 point on a 10 point scale (in favor of CPB) which is statistically significant but its clinical relevance can seriously be questioned. We expressed this in the report p 151 par 4,10,4 conclusion 1 Van Zundert 2011 is based on Vissers K 2011; we excluded this SR because of methodological limitations (databases used not mentionned; no search strategy, no quality appraisal)	Based on the limited short term (**around** 4 weeks) effectiveness of celiac plexus block (CPB) on pain as compared to standard analgesic treatment, based on its short term possible positive effect on opioid consumption, based on the need to repeat the procedure and on the rare but important complications that can be associated with the procedure, but taking into account that the life expectancy of patients with pancreatic cancer is mostly limited, CPB can be considered as one treatment option for patient suffering from pancreatic cancer, although CPB should not be the treatment of first choice. **Patients should be timely informed on this treatment option.**
REC_2	It is recommended to inform patients with pancreatic cancer clearly on the limited short term (4 weeks) effectiveness of CPB on pain as compared to standard analgesic treatment, but also on the short term (4 weeks) possible positive effect on opioid dosing. They should also be informed on the need to repeat the procedure over time, and on the possible side-effects and complications of celiac plexus block (CPB) for pain relief in pancreatic cancer.	**Strong**	Very low	3,8	2:1 3:2 4:10 5:1 NA:1	15	the same reason I don't agree : it should be some weeks instead of 4		It is recommended to inform patients with pancreatic cancer clearly on the limited short term (**around** 4 weeks) effectiveness of CPB on pain as compared to standard analgesic treatment, but also on the short term (**around** 4 weeks) possible positive effect on opioid dosing. They should also be informed on the need to repeat the procedure over time, and on the possible side-effects and complications of celiac plexus block (CPB) for pain relief in pancreatic cancer.
REC_3	A multimodal pain treatment approach should be considered for cancer pain. In patients who underwent CPB, other analgesic therapies should still be considered throughout the treatment course, e.g. NSAIDs, opioids, etc.	**Weak**	Very low	4,1	3:2 4:10 5:3	15			
GCPP	Patient preferences should be taken into account when deciding on the use of a celiac plexus block in the treatment of pain related to pancreatic cancer			4,2	3:2 4:8 5:5	15			

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