Original Article

Efficacy of single fraction conventional radiation therapy for painful uncomplicated bone metastases: a systematic review and meta-analysis

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Background: Single fraction radiotherapy (SFRT) and multiple fraction radiotherapy (MFRT) are effective for painful uncomplicated bone metastases and have been shown to be of similar efficacy. The optimal conventional external beam SFRT dose for maximum pain relief remains uncertain. The aim of this systematic review was to comprehensively review and synthesize overall pain response rates by dose.

Methods: A literature search was conducted in Ovid MEDLINE(R) (1946 to June 2016 week 3), Embase Classic & Embase (1947 to 2016 week 26) and Cochrane Central Register of Controlled Trials (May 2016) using keywords such as bone metastases, radiotherapy and single fraction (SF).

Results: The 635 results from the search were screened, and ultimately 27 were included for quantitative synthesis. The review indicated that 10 and 6 Gy may produce superior overall response (OR) and complete response (CR) rates compared to 8 Gy, and 6 Gy may result in better partial response (PR) than 8 Gy. However, only a few studies documented doses other than 8 Gy. In trials that directly compared 8 Gy to 4 Gy or 6 Gy, 8 Gy was deemed statistically superior.

Conclusions: 8 Gy SFRT was the most commonly administered dose for palliation of bone metastases supporting its efficacy and safety. Future studies should explore the efficacy of 10 Gy while minimizing its side effects.

Keywords: Palliative radiotherapy; single fraction (SF); bone metastases; pain response

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Introduction

Bone is a common metastatic site accounting for cancer-related pain (1,2). Radiation therapy (RT) is a well-accepted treatment for painful uncomplicated bone metastases (3). Many studies have documented the effect of single fraction (SF) and multiple fraction (MF) regiments, with the majority of them concluding that the SFRT was equally as effective as MFRT for pain relief (4-20). These findings have been reflected in the guidelines from Choosing Wisely Canada and United States, the national Choosing Wisely campaign and the American Society for Therapeutic Radiology and Oncology—they all recommend SFRT for uncomplicated bone metastases (21-23). A recent study by Conway et al demonstrated that SFRT yields similar improvement to

MFRT in patient-reported outcomes for pain, function and symptom frustration in both the complicated and uncomplicated setting of bone metastases (1).

The optimal conventional external beam SFRT dose for maximum pain relief remains unknown. In trials that directly compared 8 and 4 Gy, the larger-dose arm produced statistically superior pain responses (24). Across all trials included, trial doses of 8 Gy or more consistently produced superior response rates when compared to doses less than 8 Gy. Taking into account that 8 Gy has been by far the most commonly administered dose; the final recommendation from a past review was the adoption of 8 Gy as the standard dose to be compared against in future studies due to its reproducible pain response rates (24).

The past review included studies up until September 2012 (24). Since then, several papers have been published documenting the outcome of SFRT (25,26). The aim of this systematic review was to include recently-published papers that detailed SFRT outcomes and to conduct a meta-analysis to portray pain response rates by dose.

Methods

Search strategy

A literature search was conducted in Ovid MEDLINE(R) (1946 to June 2016 week 3), Embase Classic & Embase (1947 to 2016 week 26) and Cochrane Central Register of Controlled Trials (May 2016). Keywords and subject headings such as "bone metastasis", "radiotherapy" and "single fraction" were employed. The search was limited to English-language papers and excluded reviews and re-irradiation studies (*Figure 1*). Titles and abstracts of search results were screened to determine eligibility for full-text article review.

Eligibility for full-text articles review

References were included if they reported outcomes of conventional external beam radiotherapy in a population where SFRT was administered for the first time, in either a prospective or retrospective setting. Articles not clearly identifying patient populations, study designs or dose fractions were conservatively included for review. Studies were excluded if they were duplicates, combined radiotherapy with other concurrent local or systematic treatments, or employed hemi-body-, radiopharmaceutical- or stereotactic radiation therapy.

Articles selected for synthesis

Full-text articles were included in this review if they reported pain response. Reference lists of articles were also reviewed, and full-text articles of relevant papers were obtained and similarly analyzed. Discrepancies for final selections were resolved by authors via consensus.

Data abstraction

The primary endpoints were pain response. When possible, reported pain response was categorized into partial, complete and overall pain response as reported in each study. Pain response assessments closest to 1–2 months following SFRT were recorded, as this is a common time to evaluate response and also a clinically important time frame for assessment of re-treatment (24,27,28).

Partial response (PR) rates were recorded as defined by authors in their studies, and complete response (CR) was generally defined as absence of pain following SFRT; defined criteria for CR and PR, were noted when reported. Overall response (OR) was defined as an improvement in pain after radiotherapy, and usually a summation of PR and CR. When studies did not separately document PR and CR, the response rate was documented as OR. PR, CR and OR were both documented under the analyses of both Intention-To-Treat (ITT) and Evaluable Patients (EP). Response rates when documented using percentages were converted to ratios; when multiple ratios yielded the same percentage, the number with lower patient response was noted. When conflicting number of EP were presented (8), the larger-value of EP was taken into account. Under circumstances where EP was not documented, ITT was recorded as EP.

The secondary endpoints were the rates of re-treatment, spinal cord compression, pathological fracture and acute toxicities such as pain flare, nausea, vomiting and diarrhea. Average duration of pain flare was recorded. Additional information extracted from articles included the type of study, key eligibility criteria, dose, pain assessment tool, and time to pain response.

Results

A total of 635 articles were identified from the database search, and with an additional 39 articles included from reference lists, 674 papers were reduced to 417 records after duplicates (n=257) were removed. Ninety two full-

Database: Ovid MEDLINE(R) <1946 to July Week 1 2016> Search Strategy:

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1 exp Bone neoplasms/sc (22523)
2 (bone adj3 metastas*).mp. (14160)
3 exp neoplasms/rt (153918)
4 exp neoplasms/ (2868811)
5 exp Radiotherapy/ (155769)
6 (1 or 2) and (3 or (4 and 5)) (3697)
7 (single fraction or single dose).mp. (48878)
8 exp Radiotherapy dosage/ (53290)
9 single.mp. (1175441)
10 7 or (8 and 9) (52751)
11 6 and 10 (332)
12 limit 11 to (meta-analysis or "review" or systematic reviews) (70)
13 11 not 12 (262)
14 limit 13 to (english language and humans) (234)

Database: Embase Classic+Embase <1947 to 2016 Week 29> Search Strategy:

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1 exp bone metastasis/ (33823)
2 exp bone cancer/ (79521)
3 exp metastasis/ (502161)
4 1 or (2 and 3) (44910)
5 exp cancer radiotherapy/ (142410)
6 exp neoplasm/ (3935496)
7 exp radiotherapy/ (513958)
8 5 or (6 and 7) (343614)
9 (single fraction or single dose).mp. (74107)
10 exp radiation dose fractionation/ (16079)
11 single.ti,ab. (1561489)
12 9 or (10 and 11) (75773)
13 4 and 8 and 12 (413)
14 limit 13 to (human and english language) (358)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <June 2016> Search Strategy:

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1 exp bone neoplasms/sc (81)
2 (bone adj3 metastas*).mp. (1219)
3 exp neoplasms/rt (2438)
4 exp neoplasms/ or (neoplas* or cancer or tumor ot tumour).mp. (85867)
5 exp radiotherapy/ or (radiotherapy or radiation therapy).mp. (15761)
6 (1 or 2) and (3 or (4 and 5)) (294)
7 (single fraction or single dose).mp. (15195)
8 exp radiotherapy dosage/ or ((radiotherapy or radiation) adj3 (dosage or fraction*)).mp. (3525)
9 single.mp. (91948)
10 7 or (8 and 9) (15520)
11 6 and 10 (53)
12 limit 11 to english language (43)

Figure 1 Database search strategies.

text articles were assessed for eligibility, with 31 identified for potential quantitative synthesis (*Figure 2*). Ultimately 27 studies that reported the appropriate endpoints were included in this review (*Figure 2*). Twenty-three (4-9, 16,25,29-43) and 3 (25,44,45) studies reported about pain response and pain flare, respectively, while one paper (46) documented both. When compared with the last review (24), four published before 2012 (35,39,41,43) and five additional papers published after 2012 (16,25,32,37,40) have been included in the current review. Studies included in the prior review that was written in languages other than English were not included, to be consistent with the search strategy with language-limitation.

There were four studies reporting on 4 Gy from 1988–2015, 3 studies on 6 Gy from 1995–2002, 23 studies on 8 Gy from 1986–2015 and 1 study on 10 Gy published in 1997.

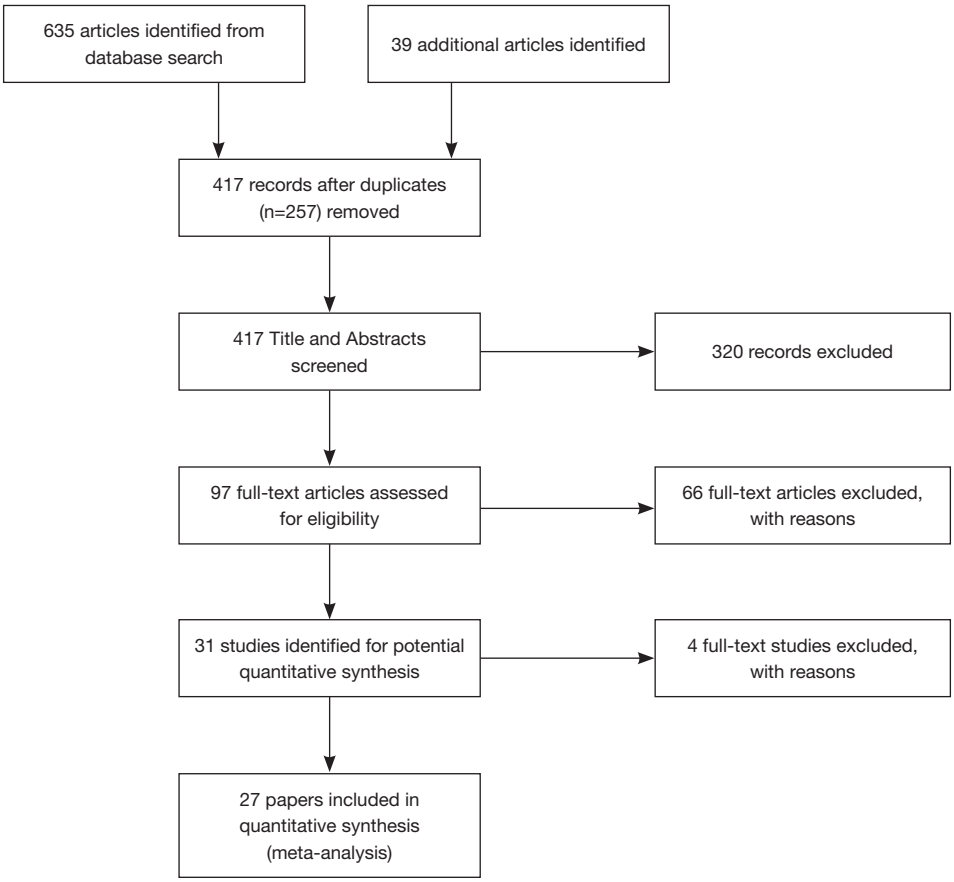

Figure 2 PRISMA flow diagram.

Of the 24 studies that documented pain response, 1 (16) was a retrospective study, 1 (39) was an observational study, and the remaining 22 (4-9,25,29-38,40-43,46) were prospective studies. Only three studies (36-38) compared head-to-head different SFRT doses, while other studies reviewed SFRT *vs.* MFRT (4-9,16,25,29-34,38,41,46) or just SFRT alone (34,39,40,42). Key eligibility criteria varied slightly in each study; in general, enrolled patients were consenting adults with proven malignancy and pain due to metastatic disease (*Table 1*).

Studies differed in their employed assessment tool for pain response—one relied on physician consult and a patient diary (7), while others used numerical point scales (5,6,8,16,29-31,34,36,37,39,41-43,46), Brief Pain Inventory (35,37) or Visual Analog Scale (4,25,32,39,40). The majority of studies measured pain response within 1 month (4-6, 9,16,25,29,31-34,36-40,43,46), with a few studies noting response after 6 weeks (42), 2 months (41), 3 months (35) or 6 months (7). CR and PR was reported in all but three studies (7,42), with study-specific criteria for CR and PR noted in *Table 2*. While some studies contained 10–20 patients (7,16,32,42), others featured a study population in excess of 300 patients (8,9,35,37). PR ranged from 14% (6) to 62% (33), CR from 4% (42) to 39% (45) and OR from 24% (6) to 81% (5,7) (*Table 2*).

ITT analysis

10 Gy had the highest overall OR of 81%. 6, 8 and 4 Gy had 74%, 60% and 54% OR rates respectively. CR was also highest for 10 Gy at 37%. 6 Gy seconded at 30% while 8 and 4 Gy had 22% and 21% respectively. The highest PR rate was 6 Gy (44%), followed by 10 Gy (43%), 8 Gy (38%) and 4 Gy (32%) (*Table 3*).

EP analysis

10 Gy registered the highest overall OR of 84%. 6, 8 and

Table 1 Background information of studies detailing pain

Study	Outcomes of interest	Type of study	Key eligibility criteria
Amouzegar-Hashemia *et al.* 2008 (29)	Pain response	Randomized clinical trial of 8 Gy/1 and 30 Gy/10	Adult patients with multiple painful uncomplicated bone metastases
Anter 2015 (30)	Pain response; acute toxicities	Prospective randomized study comparing 8 Gy/1 and 20 Gy/5	Patients 18 or older, histologically proven primary malignancy, radiographic evidence of bone metastases, KPS equal or greater than 40
Badzio *et al.* 2003 (31)	Pain response	Randomized trial comparing 8 Gy/1 and 20 Gy/5	Cytological or histopathological evidence of malignant disease, painful bone metastases confirmed by X-ray, patient compliance
Gutiérrez Bayard *et al.* 2014 (25)	Pain response; re-treatment; pathological fracture	Randomized trial of 8 Gy/1 and 30 Gy/10	Histologically proven malignant primary tumor (biopsy, cytolo Gy) or radiological confirmation of metastatic bone lesion (verified either by bone X-ray, bone scan, computed tomography, or magnetic resonance imaging)
Berwouts *et al.* 2015 (32)	Pain response; re-treatment; spinal cord compression; pathological fracture	Phase II trial of 8 Gy/1 and 16 Gy/1 with dose-painting numbers, and 8 Gy/1 conventional radiotherapy	Patients 18 or older, histologically proven diagnosis of solid tumor (excluding multiple myeloma), maximum of three painful bone lesions, KPS score equal or greater than 50
Bone Pain Trial Working Party 1999 (9)	Pain response; re-treatment; spinal cord compression; pathological fracture; acute toxicities	Prospective randomized clinical trial comparing 8 Gy/1 with multifraction regimen	Histological or cytological diagnosis of malignant disease, age over 18 years, clinical diagnosis of skeletal pain due to malignant disease, willingness on the part of the patient to complete regular pain questionnaires for 12 months, independently witnessed written informed consent
Cole 1989 (7)	Pain response; re-treatment; acute toxicities	Randomized trial of 8 Gy/1 compared to 24 Gy/6	Metastatic bone pain, life expectancy of at least three months, out-patient
Foro Arnalot *et al.* 2008 (33)	Pain response; re-treatment; toxicities	Randomized clinical trial of 8 Gy/1 and 30 Gy/10	18 years or older, presence of painful bone metastases site, estimated life expectancy of at least 1 month, assigned informed consent
Gaze *et al.* 1997 (5)	Pain response acute toxicities	Randomized trial of 22.5 Gy/5 and 10 Gy/1	Histologically or cytologically proven malignancy of epithelial origin, one or more bone metastases demonstrated by plain radiography or skeletal scintigraphy which were causing sufficient pain
Güden *et al.* 2002 (35)	Pain response	Prospective study analyzing 6 Gy/1	Histolopathologically proven malignancy cases, and developed bone metastases
Hartsell *et al.* 2005 (34)	Pain response; re-treatment; pathological fracture; acute toxicities	Phase III randomized trial, assigning patients to 8 Gy/1 and 30 Gy/10	18 years or older, histologically proven primary malignancy of breast or prostate, radiographic evidence of bone metastases, pain corresponding to area of bone metastases, KPS of at least 40, estimated life expectancy of at least 3 months
Hayashi *et al.* 2014 (16)	Pain response; acute toxicities	Retrospective analysis of 8 Gy/1 to multiple-fraction treatment	Diagnosis of bone metastases on the basis of clinical courses, presence of symptoms, radiological imaging studies

Table 1 (*continued*)

Table 1 (*continued*)

Study	Outcomes of interest	Type of study	Key eligibility criteria
Hoskin *et al.* 1992 (36)	Pain response	Prospective randomized trial of 4 Gy/1 or 8 Gy/1	Proven malignant disease and pain associated with bone metastases
Hoskin *et al.* 2015 (37)	Pain response; re-treatment	Randomized study of 8 Gy/1 or 4 Gy/1	Aged 18 years or more, histological diagnosis of malignancy, radiological evidence of painful bone metastasis, life expectancy of 12 weeks or more
Jeremic *et al.* 1998 (38)	Pain response; re-treatment; spinal cord compression; pathological fracture; acute toxicities	Prospective randomized trial comparing 4 Gy/1, 6 Gy/1 and 8 Gy/1	Metastatic bone pain from histologically or cytologically proven malignant disease, were not treated at the same site with surgery or radiation therapy, had evaluable pain history
Majumder *et al.* 2012 (40)	Pain response; acute toxicities	Randomized study comparing 30 Gy/10 and 8 Gy/1	Not exceeding 75 years with painful uncomplicated radiologically proven bone metastases
Nielsen *et al.* 1998 (4)	Pain response; re-treatment; pathological fracture	Randomized phase III trial between 8 Gy/1 and 20 Gy/4	Malignant disease histologically or cytologically confirmed, metastases radiologically confirmed, life expectancy more than 6 weeks
Nuzzo *et al.* 2015 (39)	Pain response	Observational study of 8 Gy/1	Painful bone metastases of any primary site, ECOG status less than or equal to 4
Price *et al.* 1986 (6)	Pain response; re-treatment; spinal cord compression; pathological fracture	Prospective randomized trial comparing 8 Gy/1 and 30 Gy/10	Cytological or histological evidence of malignant disease, pain associated with bone metastases
Price *et al.* 1988 (41)	Pain response; re-treatment	Pilot study examining efficacy of 4 Gy/1	Cytological or histological proof of malignancy, pain was clinically judged to be related to bone metastases
Roos *et al.* 2005 (46)	Pain response; re-treatment; spinal cord compression; pathological fracture	Phase III randomized trial comparing 8 Gy/1 and 20 Gy/5	Pathologically confirmed malignancy, plain X-ray or bone scan evidence of bone metastasis at the index site, pain or dysaesthesia predominantly of a neuropathic nature, life expectancy of at least 6 weeks, able to complete pain assessments, written informed consent
Safwat *et al.* 2007 (42)	Pain response; re-treatment	Randomized trial of 8 Gy/1, 20 Gy/5 and 30 Gy/10	Known malignancy metastatic to bone causing neuropathic pain, life expectancy of at least 3 months
Steenland *et al.* 1999 (8)	Pain response; re-treatment; spinal cord compression; pathological fracture;	Randomized trial of 8 Gy and 24 Gy/6	At least 2 on an 11-point pain scale, painful bone metastases had to be treatable in one target volume
Uppelschoten *et al.* 1995 (43)	Pain response; spinal cord compression	Prospective study analyzing 6 Gy/1	Histologically or cytologically proven malignancy, metastatic disease, pain due to bone metastases, no previous radiotherapy at the same locus, no previous surgical intervention at the same locus, no symptoms of spinal cord compression, no imminent pathological fracture, evaluable pain history, informed consent

ECOG, Eastern Cooperative Oncology Group; Gy, gray; KPS, Karnofsky Performance Status; N/A, not applicable; not documented in study.

Table 2 Pain response by study

Study	Dose (Gy)	Pain assessment tool	Time to pain response	CR and PR criteria	Pain response rates [%]					
					OR		CR		PR	
					ITT	EP	ITT	EP	ITT	EP
Amouzegar-Hashemia *et al.* 2008 (29)	8	4-point numerical scale	1 month	CR: pain reduction of 2 grades or more; PR: pain reduction of 1 grade or more but less than 2 grades	21/36 [58]	21/27 [78]	6/36 [17]	6/27 [22]	15/36 [42]	15/27 [56]
Anter 2015 (30)	8	Numeric Rating Scale	3 months	CR: no pain 3 months after RT; PR: at least 2 points lower than baseline	33/51 [65]	33/44 [75]	8/51 [16]	8/44 [18]	25/51 [49]	25/44 [57]
Badzio *et al.* 2003 (31)	8	4-point pain intensity scale	4 weeks	CR: complete disappearance of pain and withdrawal of analgesic drugs; PR: decrease in pain score or decrease in dose of analgesic drug	53/72 [74]	53/64 [83]	23/72 [32]	23/64 [36]	30/72 [42]	30/64 [47]
Gutiérrez Bayard *et al.* 2014 (25)	8	Visual Analog Score	1 month	CR: no pain; PR: decrease in pain score	35/45 [78]	35/45 [78]	7/45 [16]	7/45 [16]	28/45 [62]	28/45 [62]
Berwouts *et al.* 2015 (32)	8	Visual Analog Score	1 month	CR: no pain with no increase in daily oral morphine equivalent; PR: score reduction of 2 or more, and no increase in daily oral morphine equivalent	8/15 [53]	8/14 [57]	2/15 [13]	2/14 [14]	6/15 [40]	6/14 [43]
Bone Pain Trial Working Party 1999 (9)	8	Pain Questionnaire	1 month	CR: no pain; PR: lesser degree of pain	282/383 [74]	282/351 [80]	92/383 [24]	92/351 [26]	190/383 [50]	190/351 [54]
Cole 1989 (7)	8	Physician consult and patient diary	6 months	N/A	13/16 [81]	13/14 [93]	N/A	N/A	N/A	N/A
Foro Arnalot *et al.* 2008 (33)	8	Ordinal pain scale	3 weeks	CR: absence of pain without need for increasing analgesia; PR: improvement of equal or greater than 2 on scale with no need for increasing analgesia	59/78 [76]	59/76 [78]	12/78 [15]	12/76 [16]	47/78 [60]	47/76 [62]

Table 2 (*continued*)

Table 2 (*continued*)

Study	Dose (Gy)	Pain assessment tool	Time to pain response	CR and PR criteria	Pain response rates [%]					
					OR		CR		PR	
					ITT	EP	ITT	EP	ITT	EP
Gaze et al. 1997 (5)	10	Five-point categorical scale	1 month	CR: complete pain relief; PR: decrease in pain score	108/134 [81]	108/129 [84]	50/134 [37]	50/129 [39]	58/134 [43]	58/129 [45]
Güden *et al.* 2002 (35)	6	11-point scale	4 weeks	CR: no pain; PR: decrease in pain by at least 4 points	55/62 [89]	55/62 [89]	23/62 [37]	23/62 [37]	32/62 [52]	32/62 [52]
Hartsell *et al.* 2005 (34)	8	Brief Pain Inventory	3 months	CR: no pain; PR: at least 2 points lower than initial response	187/455 [41]	187/288 [65]	44/455 [10]	44/288 [15]	143/455 [31]	143/288 [50]
Hayashi *et al.* 2014 (16)	8	11-point scale	1 month	CR: absence of pain without need for increasing analgesics; PR: improvement of equal or greater than 2 on pain scale without need for increasing analgesia, or decrease in analgesia	9/12 [75]	9/12 [75]	2/12 [17]	2/12 [17]	7/12 [58]	7/12 [58]
Hoskin *et al.* 1992 (36)	4	4-point categorical pain scale	4 weeks	CR: no pain; PR: improvement in pain score by at least one category	75/137 [55]	75/98 [77]	25/137 [18]	25/98 [26]	50/137 [37]	50/98 [51]
	8				94/133 [71]	94/96 [98]	22/133 [17]	22/96 [23]	72/133 [54]	72/96 [75]
Hoskin *et al.* 2015 (37)	4	4-point categorical pain scale	4 weeks	CR: no pain; PR: improvement in pain score by at least one category	186/326 [57]	186/260 [72]	87/326 [27]	87/260 [33]	99/326 [30]	99/260 [38]
	8				227/325 [70]	227/274 [83]	95/325 [29]	95/274 [35]	132/325 [41]	132/274 [48]
Jeremic *et al.* 1998 (38)	4	4-point categorical pain scale	4 weeks	CR: complete disappearance of pain; PR: improvement in pain score by at least one category	51/109 [47]	51/109 [47]	16/109 [15]	16/109 [15]	35/109 [32]	35/109 [32]
	6				70/108 [65]	70/108 [65]	23/108 [21]	23/108 [21]	47/108 [44]	47/108 [44]
	8				81/110 [74]	81/110 [74]	28/110 [25]	28/110 [25]	53/110 [48]	53/110 [48]
Majumder *et al.* 2012 (40)	8	Visual Analog Scale	1 month	CR: no pain; PR: reduction of 2 or more points without analgesic increase	24/31 [77]	24/27 [89]	3/31 [10]	3/27 [11]	21/31 [68]	21/27 [78]
Nielsen *et al.* 1998 (4)	8	Visual Analog Scale	4 weeks	CR: absence of pain; PR: improvement of at least one-category	60/120 [50]	60/106 [57]	11/120 [9]	11/106 [10]	49/120 [41]	49/106 [46]

Table 2 (*continued*)

Table 2 (*continued*)

Study	Dose (Gy)	Pain assessment tool	Time to pain response	CR and PR criteria	Pain response rates [%]					
					OR		CR		PR	
					ITT	EP	ITT	EP	ITT	EP
Nuzzo *et al.* 2015 (39)	8	Visual Analog Scale	3 weeks	CR: no pain with no associated increase in daily oral morphine equivalent; PR: reduction of 2 or more on pain score without change in daily oral morphine, or no change in score and increase in daily oral morphine of at least 25%	109/248 [44]	109/248 [44]	58/248 [23]	58/248 [23]	51/248 [21]	51/248 [21]
Price *et al.* 1986 (6)	8	4-point pain scale	28 days	CR: complete loss of pain; PR: reduced pain	33/140 [24]	33/49 [67]	13/140 [9]	13/49 [27]	20/140 [14]	20/49 [41]
Price *et al.* 1988 (41)	4	4-point pain scale	2 months	CR: no pain; PR: improvement in pain score by at least one category	10/26 [38]	10/21 [48]	1/26 [4]	1/21 [5]	9/26 [35]	9/21 [43]
Roos *et al.* 2005 (46)	8	4-point categorical pain scale	4 weeks	CR: no pain with no analgesia or adjuvant analgesia; PR: improvement in pain score by at least one grade with no increase in analgesia	73/137 [53]	73/119 [61]	35/137 [26]	35/119 [29]	38/137 [28]	38/119 [32]
Safwat *et al.* 2007 (42)	8	5-point categorical scale	6 weeks	N/A	14/20 [70]	14/20 [70]	N/A	N/A	N/A	N/A
Steenland *et al.*1999 (8)	8	11-point scale	N/A	CR: 0 to 1 pain score, independent of analgesics consumption; PR: decrease in initial pains score by at least two points	392/579 [68]	392/545 [72]	199/579 [34]	199/545 [37]	193/579 [33]	193/545 [36]
Uppelschoten *et al.*1995 (43)	6	4-point pain scale	4 weeks	CR: total disappearance of pain; PR: decrease in pain of at least one category	149/199 [75]	149/170 [88]	66/199 [33]	66/170 [39]	83/199 [42]	83/170 [49]

CR, complete response; EP, evaluable patients; Gy, gray; ITT, intention-to-treat; N/A, not applicable; not documented in study; OR, overall response; PR, partial response.

Table 3 Pain response by dose

Dose	Study	Response rate	
		ITT	EP
Overall response			
4 Gy	Hoskin *et al.* 1992 (36)	75/137	75/98
	Hoskin *et al.* 2015 (37)	186/326	186/260
	Jeremic *et al.* 1998 (38)	51/109	51/109
	Price *et al.* 1988 (41)	10/26	10/21
	Overall response rate	322/598 (54%)	322/488 (66%)
6 Gy	Güden *et al.* 2002 (35)	55/62	55/62
	Jeremic *et al.* 1998 (38)	70/108	70/108
	Uppelschoten *et al.* 1995 (43)	149/199	149/170
	Overall response rate	274/369 (74%)	274/340 (81%)
8 Gy	Amouzegar-Hasemia *et al.* 2008 (29)	21/36	21/27
	Anter 2015 (30)	33/51	33/44
	Badzio *et al.* 2003 (31)	53/72	53/64
	Gutiérrez Bayard *et al.* 2014 (25)	35/45	35/45
	Berwouts *et al.* 2015 (32)	8/15	8/14
	Bone Pain Trial Working Party 1999 (9)	282/383	282/351
	Cole 1989 (7)	13/16	13/14
	Foro Arnalot *et al.* 2008 (33)	59/78	59/76
	Hartsell *et al.* 2005 (34)	187/455	187/288
	Hayashi *et al.* 2014 (16)	9/12	9/12
	Hoskin *et al.* 1992 (36)	94/133	94/96
	Hoskin *et al.* 2015 (37)	227/325	227/274
	Jeremic *et al.* 1998 (38)	81/110	81/110
	Majumder *et al.* 2012 (40)	24/31	24/27
	Nielsen *et al.* 1998 (4)	60/120	60/106
	Nuzzo *et al.* 2015 (39)	109/248	109/248
	Price *et al.* 1986 (6)	33/140	33/49
	Roos *et al.* 2005 (46)	73/137	73/119
	Safwat *et al.* 2007 (42)	14/20	14/20
	Steenland *et al.* 1999 (8)	392/579	392/545
	Overall response rate	1,807/3,006 (60%)	1,807/2,500 (72%)
10 Gy	Gaze *et al.* 1997 (5)	108/134	108/129
	Overall response rate	108/134 (81%)	108/129 (84%)

Table 3 (*continued*)

Table 3 (*continued*)

Dose	Study	Response rate	
		ITT	EP
Complete response			
4 Gy	Hoskin *et al.* 1992 (36)	25/137	25/98
	Hoskin *et al.* 2015 (37)	87/326	87/260
	Jeremic *et al.* 1998 (38)	16/109	16/109
	Price *et al.* 1988 (41)	1/26	1/21
	Overall complete response rate	129/598 (21%)	129/488 (26%)
6 Gy	Güden *et al.* 2002 (35)	23/62	23/62
	Jeremic *et al.* 1998 (38)	23/108	23/108
	Uppelschoten *et al.* 1995 (43)	66/199	66/170
	Overall complete response rate	112/369 (30%)	112/340 (33%)
8 Gy	Amouzegar-Hasemia *et al.* 2008 (29)	6/36	6/27
	Anter 2015 (30)	8/51	8/44
	Badzio *et al.* 2003 (31)	23/72	23/64
	Gutiérrez Bayard *et al.* 2014 (25)	7/45	7/45
	Berwouts *et al.* 2015 (32)	2/15	2/14
	Bone Pain Trial Working Party 1999 (9)	92/383	92/351
	Foro Arnalot *et al.* 2008 (33)	12/78	12/76
	Hartsell *et al.* 2005 (34)	44/455	44/288
	Hayashi *et al.* 2014 (16)	2/12	2/12
	Hoskin *et al.* 1992 (36)	22/133	22/96
	Hoskin *et al.* 2015 (37)	95/325	95/274
	Jeremic *et al.* 1998 (38)	28/110	28/110
	Majumder *et al.* 2012 (40)	3/31	3/27
	Nielsen *et al.* 1998 (4)	11/120	11/106
	Nuzzo *et al.* 2015 (39)	58/248	58/248
	Price *et al.* 1986 (6)	13/140	13/49
	Roos *et al.* 2005 (46)	35/137	35/119
	Steenland *et al.* 1999 (8)	199/579	199/545
	Overall complete response rate	659/2,970 (22%)	659/2,433 (27%)
10 Gy	Gaze *et al.* 1997 (5)	50/134	50/129
	Overall complete response rate	50/134 (37%)	50/129 (39%)

Table 3 (*continued*)

Table 3 (*continued*)

Dose	Study	Response rate	
		ITT	EP
Partial response			
4 Gy	Hoskin *et al.* 1992 (36)	50/137	50/98
	Hoskin *et al.* 2015 (37)	99/326	99/260
	Jeremic *et al.* 1998 (38)	35/109	35/109
	Price *et al.* 1988 (41)	9/26	9/21
	Overall partial response rate	193/598 (32%)	193/488 (40%)
6 Gy	Güden *et al.* 2002 (35)	32/62	32/62
	Jeremic *et al.* 1998 (38)	47/108	47/108
	Uppelschoten *et al.* 1995 (43)	83/199	83/170
	Overall partial response rate	162/369 (44%)	162/340 (48%)
8 Gy	Amouzegar-Hasemia *et al.* 2008 (29)	15/36	15/27
	Anter 2015 (30)	25/51	25/44
	Badzio *et al.* 2003 (31)	30/72	30/64
	Gutiérrez Bayard *et al.* 2014 (25)	28/45	28/45
	Berwouts *et al.* 2015 (32)	6/15	6/14
	Bone Pain Trial Working Party 1999 (9)	190/383	190/351
	Foro Arnalot *et al.* 2008 (33)	47/78	47/76
	Hartsell *et al.* 2005 (34)	143/455	143/288
	Hayashi *et al.* 2014 (16)	7/12	7/12
	Hoskin *et al.* 1992 (36)	72/133	72/96
	Hoskin *et al.* 2015 (37)	132/325	132/274
	Jeremic *et al.* 1998 (38)	53/110	53/110
	Majumder *et al.* 2012 (40)	21/31	21/27
	Nielsen *et al.* 1998 (4)	49/120	49/106
	Nuzzo *et al.* 2015 (39)	51/248	51/248
	Price *et al.* 1986 (6)	20/140	20/49
	Roos *et al.* 2005 (46)	38/137	38/119
	Steenland *et al.* 1999 (8)	193/579	193/545
	Overall partial response rate	1,120/2,970 (38%)	1,120/2,466 (45%)
10 Gy	Gaze *et al.* 1997 (5)	58/134	58/129
	Overall partial response rate	58/134 (43%)	58/129 (45%)

Gy, gray; ITT, intention-to-treat; EP, evaluable patients.

4 Gy had 81%, 72% and 66% rates respectively. CR was also highest for 10 Gy at 39%. 6 Gy had 33%, while 8 and 4 Gy had 27% and 26% respectively. 6 Gy had the highest PR rate (48%), with 10, 4 and 8 Gy reported at 45%, 40% and 38% (*Table 3*).

Adverse events

Sixteen studies (4,6-9,25,32-34,36-38,41-43,46) reported the incidence of re-treatment, 7 on the occurrence of spinal cord compression (6,8,9,32,38,43,46), 11 on the frequency of pathological fracture (4,6-9,25,32,35,38,43,46) and 9 on acute toxicities (5,7,9,16,30,33,35,38,39). Re-treatment varied from 9% (36) to 44% (38), while spinal cord compression and pathological fracture spanned 2% (6,8,9) to 8% (38) and 0% (6,7) to 16% (25), respectively. Acute toxicities, when specified, were reported as hematologic (30,35), lung (30,35), central nervous system (CNS) (30,35,39), gastrointestinal (GI) (30,35), nausea (5,7,9,16,38), vomiting (5,7,9,38), diarrhea (7,38) and fatigue/tiredness (5) (*Table 4*).

When analyzed by dosage, 4 Gy had the highest incident of re-treatment (28%), followed by 6 Gy (23%) and 8 Gy (21%). Similarly, 4 Gy had the highest incidence of spinal cord compression and pathological fracture (7% and 6%, respectively) compared to 6 Gy (4% for both) and 8 Gy (3% and 4%, respectively). Nausea and vomiting were reported together in the 4, 6 and 10 Gy setting, with the higher dose of 10 Gy reporting the most incidence at 40%. Nausea and vomiting were separately reported in the 8 Gy setting at 52% and 30%, respectively. Diarrhea occurred more frequently in the 4 Gy (13%) than 6 Gy (11%) (*Table 5*). However, the information of the radiation area was not detailed enough in the publications to allow further analysis of the gastro-intestinal side effects.

Pain flare documented across four studies (26,44-46) pertained to the 8 Gy dosage. Three different pain assessment tools were used—Brief Pain Inventory (26,44), Present Pain Intensity (45) and a 4-point categorical pain scale (46). Pain flare rates ranged from 10% (46) to 57% (45), with the overall combined rate being 25%. Gomez-Iturriaga *et al.* noted a mean pain flare duration of 3 days (26), while Loblaw *et al.* reported a median duration of 3 days (45) (*Table 6*).

Discussion

This systematic review contains nine additional studies when compared with that of Dennis *et al.* (24), and also combined pain response rates reported by studies. Although the combined rates suggest that 10 and 6 Gy may produce superior OR and CR compared to 8 Gy, and 6 Gy may result in better PR than 8 Gy under EP, it is important to note that only a few studies document doses other than 8 Gy. The last study examining 6 Gy was from 2002 (34) and the only study examining 10 Gy was published in 1997 (5). The overall rates for doses other than 8 Gy need to be interpreted with caution especially in non-randomised studies. The three studies that did compare SFRT doses were conducted in 1992 (36), 1998 (38) and recently in 2015 (37). Hoskin *et al.* compared 4 and 8 Gy in 1992 and 2015, and concluded both times that 8 Gy produced superior pain response rates (36,37). Similarly, Jeremic *et al.* reported that 8 Gy had better pain response than 6 and 4 Gy SFRT (38). To date, there have been no trials comparing a single 8 Gy versus a single 10 Gy or higher.

There was a wide range of pain response rates in the heavily-studied 8 Gy arm, likely accounted for by the different criteria for pain response set out by each study. While CR generally had the same criteria (no pain following SFRT), the different parameters for PR may have led to different outcomes. Some studies noted PR as any improvement in pain scale (5,43,46), while others required at least a 2-point improvement on their pain scale and variable use of analgesics (41). Cultural influences could also have impacted the reporting of pain, with studies being conducted in different geographical locations (24).

The considerable amount of studies investigating 8 Gy SFRT and its accompanying overall lower rates of re-treatment, spinal cord compression and pathological fracture verifies the safety of administration. This reproducible data sets a standard for future SFRT doses to be compared against (24). 10 Gy has the highest response rates but with increased side effects in this review. Future efforts can be directed to confirm the efficacy of 10 Gy when compared with a single 8 Gy while minimizing the side effects of nausea and vomiting.

Pain flare was only well-documented in the 8 Gy SFRT setting, making it difficult to be compared to other doses. While Kirkbride and Aslanidis did present an abstract regarding pain flare in the 12 Gy SFRT, their results were never published in a paper (47). Although pharmaceutical responses have been examined to manage pain flare (48-50), clinicians should also examine whether there is a dose response with the occurrence of pain flare.

This review was not without limitations. It only included

Table 4 Prospectively-evaluated rates of re-treatment, spinal cord compression, pathological fractures, and acute toxicities by study

Study	Dose (Gy)	Re-treatment [%]	Spinal cord compression [%]	Pathological fracture [%]	Acute toxicities
Anter 2015 (30)	8	N/A	N/A	N/A	GI: 10/51 (20%); hematologic: 4/51 (8%); lung: 1/51 (2%); CNS: 1/51 (2%)
Gutiérrez Bayard *et al.* 2014 (25)	8	6/45 [13]	N/A	7/45 [16]	N/A
Berwouts *et al.* 2015 (32)	8	2/15 [13]	1/15 [7]	1/15 [7]	N/A
Bone Pain Trial Working Party 1999 (9)	8	76/351 [22]	6/351 [2]	7/351 [2]	Nausea : 34/61 (56%); vomiting: 18/61 (30%)
Cole 1989 (7)	8	4/16 [25]	N/A	0/16 [0]	Nausea: 69%; vomiting: 8%; diarrhea: 30%
Foro Arnalot *et al.* 2008 (33)	8	28/76 [36]	N/A	N/A	Toxicity: 12/76 (16%)
Gaze *et al.* 1997 (5)	10	N/A	N/A	N/A	Nausea and vomiting: 44/110 (40%); tiredness: 32/110 (29%)
Hartsell *et al.* 2005 (34)	8	76/449 [17]	N/A	23/449 [5]	Skin: 16/433 (4%); lung: 2/433 (0.5%); CNS: 4/433 (1%); GI: 53/433 (12%); hematologic: 19/433 (4%)
Hayashi *et al.* 2014 (16)	8	N/A	N/A	N/A	Nausea: 2/8 (25%)
Hoskin *et al.* 1992 (36)	4	28/137 [20]	N/A	N/A	N/A
	8	12/133 [9]			
Hoskin *et al.* 2015 (37)	4	72/274 [26]	N/A	N/A	N/A
	8	45/285 [16]			
Jeremic *et al.* 1998 (38)	4	46/109 [42]	4/61 [7]	3/48 [6]	Nausea and vomiting: 21/109 (19%); diarrhea: 14/109 (13%)
	6	47/108 [44]	5/63 [8]	3/45 [7]	Nausea and vomiting: 20/108 (18%); diarrhea: 12/108 (11%)
	8	42/110 [38]	4/66 [6]	3/44 [7]	Nausea and vomiting: 24/110 (22%); diarrhea: 16/110 (15%)
Majumder *et al.* 2012 (40)	8	N/A	N/A	N/A	GI: 6/27 (22%)
Nielsen *et al.* 1998 (4)	8	25/120 [21]	N/A	6/120 [5]	N/A
Price *et al.* 1986 (6)	8	15/120 [13]	2/120 [2]	0/120 [0]	N/A
Price *et al.* 1988 (41)	4	7/26 [27]	N/A	N/A	N/A
Roos *et al.* 2005 (46)	8	40/137 [29]	9/137 [7]	6/137 [4]	N/A
Safwat *et al.* 2007 (42)	8	7/20 [35]	N/A	N/A	N/A
Steenland *et al.* 1999 (8)	8	147/579 [25]	13/579 [2]	24/579 [4]	N/A
Uppelschoten *et al.* 1995 (43)	6	18/170 [11]	4/170 [2]	6/170 [4]	N/A

CNS, central nervous system; GI, gastrointestinal; Gy, gray; N/A, not applicable; not documented in study.

Table 5 Prospectively-evaluated rates of re-treatment, spinal cord compression, pathological fractures, and acute toxicities (nausea, vomiting, diarrhea) by dose

Study	Re-treatment	Spinal cord compression	Pathological fractures	Acute toxicities
4 Gy				
Hoskin *et al.* 1992 (36)	28/137			
Hoskin *et al.* 2015 (37)	72/274			
Jeremic *et al.* 1998 (38)	46/109	4/61	3/48	Nausea and vomiting: 21/109; diarrhea: 14/109
Price *et al.* 1988 (41)	7/26			
Overall rates	153/546 (28%)	4/61 (7%)	3/48 (6%)	Nausea and vomiting: 21/109 (19%); diarrhea: 14/109 (13%)
6 Gy				
Jeremic *et al.* 1998 (38)	47/108	5/63	3/45	Nausea and vomiting: 20/108; diarrhea: 12/108
Uppelschoten *et al.* 1995 (43)	18/170	4/170	6/170	
Overall rates	65/278 (23%)	9/233 (4%)	9/215 (4%)	Nausea and vomiting: 20/108 (19%); diarrhea: 12/108 (11%)
8 Gy				
Gutiérrez Bayard *et al.* 2014 (25)	6/45		7/45	
Berwouts *et al.* 2015 (32)	2/15	1/15	1/15	
Bone Pain Trial Working Party 1999 (9)	76/351	6/351	7/351	Nausea: 34/61; vomiting: 18/61
Cole 1989 (7)	4/16		0/16	
Foro Arnalot *et al.* 2008 (33)	28/76			
Hartsell *et al.* 2005 (34)	76/449		23/449	
Hayashi *et al.* 2014 (16)				Nausea: 2/8
Hoskin *et al.* 1992 (36)	12/133			
Hoskin *et al.* 2015 (37)	45/285			
Nielsen *et al.* 1998 (4)	25/120		6/120	
Price *et al.* 1986 (6)	15/120	2/120	0/120	
Roos *et al.* 2005 (46)	40/137	9/137	6/137	
Safwat *et al.* 2007 (42)	7/20			
Steenland *et al.* 1999 (8)	147/579	13/579	24/579	
Overall rates	483/2,346 (21%)	31/1,202 (3%)	74/1,832 (4%)	Nausea: 36/69 (52%); vomiting: 18/61 (30%)
10 Gy				
Gaze *et al.* 1997 (5)				Nausea and vomiting: 44/110
Overall rates				Nausea and vomiting: 44/110 (40%)

Gy, gray.

Table 6 Pain flare

Study	Dose (Gy)	Type of study	Pain assessment tool	Patients experiencing pain flare [%]	Average duration of pain flare
Gomez-Iturriaga *et al.* 2015 (26)	8	Prospective observational study of 8 Gy/1 and 20 Gy/5	Brief pain inventory	14/42 [33]	Mean: 3 days
Hird *et al.* 2009 (44)	8	Observational study of 8 Gy/1 and multiple fractions	Brief pain inventory	27/70 [39]	N/A
Loblaw *et al.* 2007 (45)	8	Prospective randomized controlled trial comparing 8 Gy/1 and 20 Gy/5	Present pain intensity	13/23 [57]	Median: 3 days
Roos *et al.* 2005 (46)	8	Phase III randomized trial comparing 8 Gy/1 and 20 Gy/5	4-point categorical pain scale	14/137 [10]	N/A
Combined rate	8	–	–	68/272 [25]	

Gy, gray; N/A, not applicable; not documented in study.

English papers, thereby missing out on other published studies (51,52) that comparably reported OR, CR and PR in a similar setting. Additionally, there was a lack of statistical analysis to determine if certain doses are significantly more efficacious than others. As a result, rankings of response rates based on a few percentage-points should be interpreted with great caution, taking into account heterogeneity of data and also lack of weighting of studies.

8 Gy SFRT was the most commonly administered dose for palliation of bone metastases. While 8 Gy SFRT cannot decisively be determined as the optimal dose for pain relief, studies that did directly compare different doses reported better pain responses for 8 Gy over 4 and 6 Gy (36,39). With extensive data supporting its efficacy and safety, 8 Gy SFRT should be the standard for all future comparable treatments, in an attempt to determine which dose produces the maximum benefit.

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Footnote

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