NHS England

Evidence Review:

Palliative radiotherapy for bone pain

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Contents

1. Introduction

Radiotherapy is a highly effective palliative treatment to control pain due to secondary bone disease from a wide range of cancers. A significant number of patients require this type of palliation for secondary bone disease from the more common cancers, such as from prostate, breast, and lung. It may be given combined with other types of treatment, depending on the type of cancer.

NICE has published guidelines for the treatment of pain associated with bone metastases secondary to breast cancer (NICE clinical guideline CG81: http://www.nice.org.uk/guidance/CG81) and lung cancer (NICE clinical guideline CG121: http://www.nice.org.uk/guidance/cg121). In these indications a single fraction of radiotherapy is recommended.

Single fraction radiotherapy is recommended as the standard treatment for the majority of patients with symptomatic bone metastases, both for the above indications and other metastatic bone radiotherapy episodes. Delivering the radiation dose in one fraction and one visit, rather than multiple fractions and multiple visits, will prevent unnecessary travel, discomfort and inconvenience for many patients with no compromise to clinical effectiveness.

2. Summary of results

Summary:
This review set out to answer the following research question regarding palliative radiotherapy for bone pain:
Is there evidence for the use of single fraction of radiotherapy compared to other fractional schedules for the treatment of painful or symptomatic bone metastasis in patients with cancer? This review looks at both primary and re-irradiation treatment for bone metastasis.

Palliative radiotherapy for bone pain is delivered as single or multiple fractions. Overall there is good evidence for the use of single fraction (SF) radiotherapy, compared to multiple fraction (MF) radiotherapy, for the palliative treatment of painful or symptomatic bone metastasis, in patients with cancer. There is level 1 evidence that both treatments deliver the same levels of pain relief and SF therapies have lower levels of acute toxicities. There is also evidence that SF therapies have higher retreatment rates. However, there is level 1 evidence that the response rates of these retreatments are comparable to those of initial treatments.

Detailed summary:

The goal of palliative care includes pain relief, improved quality of life, prevention of further complications and minimisation of hospitalisation, hence there are a large number of outcomes that can be used in order to test the efficacy of palliative treatments. For primary outcomes that the majority of studies have used are complete response rate defined as the decrease in pain score to zero without increased analgesics use, the partial response rate defined as a decrease of at least 2 points in the pain score and overall response rate (OR). Secondary outcomes can include retreatment rates, spinal cord compression rates, pathological fracture rates, acute toxicities and survival time. There is also some variety in the studied dose schedules, although the most common single fraction (SF) intervention was 8 Gy, while multiple fractions (MF) typically range from 20 - 30 Gy over 5 - 10 fractions. Currently there is insufficient evidence to guide optimal dose schedules (see Lohre et al. 2012).

Pain relief outcomes:

The strength of the evidence for the equivalence of SF and MF treatments, in terms of pain relief, has come from the large number of RCTs that have been combined in a number of meta-analyses and systematic reviews (Chow et al. 2012, Chow et al. 2007, Bedard et al. 2014). It should be noted that these are non-blinded RCTs, leading to potential risk of bias, particularly considering the potential for non-optimal use of analgesics in end of life patients. Nonetheless, the number and agreement of the RCTs has led to the conclusion that there is strong evidence for the equivalence in the efficacy of the two fractional regimes. In particular:
- A meta-analysis based on 17 RCTs found complete response rates of 23% of 2641 patients for SF vs 24% of 2622 patients for MF (p=0.97) (Chow et al. 2012)
- The same analysis, based on 25 RCTs found overall response rates of 60% of 2818 patients for SF vs 61% of 2799 patients for MF (p=0.98).
- Numerous studies have reported statistically similar partial response rates including (Howell et al. 2013, Arnalot et

al. 2008, Chow et al. 2014), although these have not been combined in a meta-analysis.
There is strong evidence that SF treatments have higher retreatment rates. A combination of 12 RCTs found retreatment rates of 20% of 2323 patients for SF vs. 8% of 2309 patients for MF ($p<0.00001$).

Pain relief outcomes in re-treatments:
There is level 1 evidence for the efficacy of retreatment coming primarily from two systematic reviews and meta-analyses (Huisman et al., 2012; Wong et al. 2014), including 15 studies with 5 RCTs, that found:
- Overall response rates for retreatment of 58- 68% in 645 patients
- Partial response rates for retreatment of 50% in 355 patients.
- Complete response rates of 20% in 355 patients.

Majority of the analyses involved in these studies did not distinguish between SF or MF re-treatment. Overall response rate of combined primary and retreatment therapy for SF and MF was reported as not significantly different in a meta-analysis of 850 patients. (Bedard et al. 2014).

Safety outcomes:

There is level 1 evidence that SF treatments have lower toxicity levels than MF treatments. A meta-analysis (Yoon & Morton, 2014) found acute grade 2-4 toxicities rates of 20% for MF verses 10% for SF. This difference is primarily due to gastrointestinal and skin toxicities. In particular:
- differences in rates of skin reddening (24% for MF vs 14% for SF, $p=0.002$). (Chow et al. 2014)
- acute toxicity rates of 18% for MF vs 12% for SF. (Arnalot et al. 2008, Howell et al. 2013)
- 15% for MF vs 6% SF gastrointestinal toxicities. (Howell et al. 2013)

There were no differences found in the study of other complications (Chow et al. 2012):
- No difference were found in pathological fracture rates (3.3% of 2120 SF patients vs. 3.0% of 2159 MF patients, $p=0.75$) based on 10 studies.
- No differences were found in spinal compression rates (2.8% of 1443 SF patients vs. 1.9% of 1443 patients, $p=0.13$) based on 6 studies.

It should also be noted that the above studies focused on uncomplicated bone metastases. There is some expert opinion that MF radiotherapies may be more suitable for impending pathological fractures and impending spinal cord compression (Fairchild 2014).

Safety outcomes in re-treatments:
The evidence for the toxicity rates in retreatment is limited and unable to distinguish between the toxicity rates of SF and MF re-treatments (Jeremic et al., 1999; van der Linden et al., 2004; Roszkowski et al, 2005 included in the systematic review by Wong et al. 2014). The studies report similar toxicity rates to those found in the initial treatment, in particular:
- Grade 1 or 2 nausea and vomiting (12%-19%)
- Grade 1 or 2 diarrhea (2%-12%)
- 3 out of 135 patients (2%) had pathological fractures and spinal compressions.

Cost effectiveness:

The cost effectiveness of SF vs MF radiotherapy has been examined in a number of studies (Konski et al. 2009, van der Hout et al. 2003, Pollicino et al. 2005, Steenland et al. 1999, quoted in Chow et al. 2012). The studies find that, after taking into account increased retreatment rates and increased quality adjusted life years, SF radiotherapies are 26%-66% lower cost than MF radiotherapies. Clearly, these figures are sensitive to assumptions in the analysis.

3. Research questions

Is there evidence for the use of single fraction of radiotherapy compared to other fractionation schedules for the treatment of painful or symptomatic bone metastasis in patients with cancer?

4. Methodology

A review of published, peer reviewed literature has been undertaken based on the research questions set out in Section 3 and a search strategy agreed with the lead clinician and public health lead for this policy area. This has involved a PubMed search and search of the Cochrane database for systematic reviews, in addition to review of any existing NICE or SIGN guidance. The evidence review has been independently quality assured.

An audit trail has been maintained of papers excluded from the review on the basis of the inclusion and exclusion criteria agreed within the search strategy. The full list has been made available to the clinicians developing the policy where requested.

5. Results

A detailed breakdown of the evidence is included in the Appendix.

Appendix One

Grade	Study design and intervention			Outcomes					Reference	Other		
Grade of evidence	Study design	Study size	Intervention	Category	Primary Outcome	Primary Result	Secondary Outcome	Secondary Result	Reference	Complications noted	Benefits noted	Comments
1+	Systematic	645 patients	4-8 Gy where applicable in SF	Clinical effectiveness of the intervention compared to existing interventions	Complete response rates (CR), Overall response rate(OR) and Partial Response rates (PR).	CR: 20% of 355 PR: 50% of 355 OR: 68% of 645 No distinction between fractional regimes	Overall survival Toxicity	Overall survival: average 25 weeks, no difference between partial and complete response. Jeremic et al. reported spinal cord compression rates at 2.2%, 18.5% grade 1 or 2 nausea/ vommiting, 11.9% grade 1 or 2 diarrhea and no grade 3- 4 toxicities.	Wong, Erin; Hoskin, Peter; Bedard, Gillian; Poon, Michael; Zeng, Liang; Lam, Henry; Vulpe, Horia; Tsao, May; Pulenzas, Natalie; Chow, Edward. Re-irradiation for painful bone metastases - a systematic review. Radiother Oncol 2014;110(1):61-70.	-	-	This systematic review is concerned with the efficacy and safety of re-irradiation. Re-irradiation can be prescribed if there is no pain relief after first treatment, partial response to first treatment or pain relapse. While it is often, but not always, the case that re-irradiation is a single fraction (SF) treatment and this study did consider a wide range SF and multi fraction (MF) treatments. Meta-analysis found the partial response rates, complete response rates and overal response rates of 50% of 355, 20% of 355 and 68% of 645 patients. Not much distinction between SF and MF, except quote Sayed et al. that found no significant difference in the response rates of SF and MF. Also (Jeremic et al., 1999 and Mithal et al., 1994) considered second re-irradiation and found OR rates of 4 of 6 and 7 of 8.

4	Systematic	Not stated	Between 5 - 15 Gy SF, but mainly 8 Gy.	Clinical effectiveness of the intervention compared to existing interventions	Guidelines following consultation with experts.	-	-	-	Lutz, Stephen; Berk, Lawrence; Chang, Eric; Chow, Edward; Hahn, Carol; Hoskin, Peter; Howell, David; Konski, Andre; Kachnic, Lisa; Lo, Simon; Sahgal, Arjun; Silverman, Larry; von Gunten, Charles; Mendel, Ehud; Vassil, Andrew; Bruner, Deborah Watkins; Hartsell, William; American Society for Radiation Oncology (ASTRO). Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline. Int. J. Radiat. Oncol. Biol. Phys. 2011;79(4):965-976.	-	-	This is not a new study or a systematic review, but rather the guidelines issued on behalf of ASTRO, following an extensive literature review and consultation with many experts in palliative radiotherapy. The study refers to 25 RCTs. Therefore it cannot add further evidence to the research question, but is still of relevance. It's principle results are that multiple trials have demonstrated equivalence in pain relief of SF vs. MF, although SF has higher re-treatment rates. Most studies do not de-lineate treatment relied by spinal vs non-spinal metastases. Numerous studies have shown no significant difference in long term side effects, but is unclear on the definition of long term. Recommendation in 2011 is for patients be entered into randomised trials.

1+	Systematic	303 patients and 276 patients for RCTs	8 Gy x1, 8 Gy x2	Clinical effectiveness of the intervention compared to existing interventions	response rates. duration of response survival rates toxicity	(Maranzano et al. 2009) RCT, 8Gy x 2 vs 8Gy x 1: Equal response, duration of response, survival and toxicity rates. (Maranzano et al. 2005) RCT, 8Gy x 2 vs 5Gy x 3 vs 3Gy x 5: Similar response, duration of response, survival and toxicity rates.	Motor functions ambulatory status	No difference in motor functions in Rades et al. 2009 (8Gy x 1 vs 4Gy x 5 vs 3Gy x 10 vs 2.5 Gy x 15 vs 2Gy x 20), Rades et al. 2004 (3Gy x10 vs 2Gy x 20), Kim et al. (3Gy x10 vs 4 Gy x3 vs 3Gy x 6) No difference in ambulatory status in Rades et al. 2004 (3Gy x10 vs 2Gy x 20), Kim et al, 1993 (2.5 gy x 16 vs 3 Gy x 10 vs 4 Gy x 5	Løhre, Erik Torbjørn; Lund, Jo-Åsmund; Kaasa, Stein. Radiation therapy in malignant spinal cord compression: what is the current knowledge on fractionation schedules? A systematic literature review. BMJ Support Palliat Care 2012;2(1):51-56.	-	-	This systematic review focused on comparing different fractional schedules in patients with Malignant spinal cord compression. After comparing 2 RCT's and 5 prospective non-randomised studies and 17 retrospective studies, the review found no difference in symptom control, duration of response or survival rates. The review also found no difference in post-treatment motor functions, but this was based on just 4 non-randomised trials and retrospective studies, hence considered evidence C at best. The study also points to a retrospective study (Rades et al. 2005), that demonstrates the decline in recurrence rates, with increasing fractions i.e. 8Gy x1: 24%, 4 Gy x 5: 26%, 3 Gy x 10:14%, 2.5 Gy x 15:9% and 2 Gy x 20: 20: 7%.
1-	Systematic	850	8 Gy in Single Fractional	Clinical effectiveness of the intervention compared to existing interventions	Quality of Life questionnaire, core 30 (QLQ-C30)	Statistitically different scores ($p<0.05$), between responders and non responders, in Role functioning, social functioning and constipation	Brief Pain inventory score	Statistically significant lower scores in all domains, between responders and non responders.	Yoon, Frederick; Morton, Gerard C.. Single fraction radiotherapy versus multiple fraction radiotherapy for bone metastases in prostate cancer patients: comparative effectiveness. Cancer Manag Res 2014;6(0):451-457.	-	-	This study is a reanalysis of the RCT discussed in (Chow 14). It's focus was to study the impact of palliative treatment on patients overall quality of life. It does not distinguish between treatment and hence it is not directly relevant to the research questions. The study divided the patients into those responding to palliative treatment and to those not responding. This is defined by the response to re-treatment protocol after 3 months. The study found that patients responding to reirradiation experience superior scores on a range of quality of life criteria. Principle concerns with this study are that it was non-blinded, to both practioners and patients and hence this could introduce a risk of bias.

1++	Systematic	2513 SF vs. 2487 MF	Between 5 - 15 Gy SF, but mainly 8 Gy.	Clinical effectiveness of the intervention compared to existing interventions	Complete response rates (CR) and Overall Response rates (OR)	OR rates were 58% SF vs 59% MF based on 16 trials CR rates were 23% SF vs 24 % MF based on 13 trials	Compare retreatment rates, pathological fracture rates and spinal cord compression rates.	Retreatment rates: 20% of 2,053 SF vs. 8% of 2,032 MF p<0.00001 based on 9 studies. Pathological fracture rate: 3.2% of 2018 SF vs. 2.8% of 2032 p=0.75 based on 8 studies. Spinal compression rates: 2.8% of 1443 SF vs. 1.9% of 1443 based on 5 studies.	Chow, Edward; Harris, Kristin; Fan, Grace; Tsao, May; Sze, Wai M.. Palliative radiotherapy trials for bone metastases: a systematic review. J. Clin. Oncol. 2007;25(11):1423-1436.	-	-	This systematic review combines the results of 16 randomised trials. A comprehensive review of the literature between 1982 and 2006 is completed and trial prone to bias are excluded. The evidence concerning the equivalence of complete and overal response rates is compelling, not one of the 16 trials indicate a statistically significant difference. The secondary outcomes are less clear cut due to reduced statistics. Nonetheless there is a statisitically significant increase in Re-treatment rates in SF 20% vs 8% for MF.

1++	Systematic	2818 for SF vs. 2799 for MF	Between 1 - 15 Gy SF, but mainly 8 Gy.	Clinical effectiveness of the intervention compared to existing interventions	To compare complete response rates (CR) and Overall Response rates (OR)	OR rates were 60% SF vs 61% MF based on 25 trials CR rates were 23% SF vs 24 % MF based on 17 trials	Compare retreatment rates, pathological fracture rates, spinal cord compression rates and acute toxicities.	Retreatment rates: 20% of 2,323 SF vs. 8% of 2,302 MF p<0.00001 based on 12 studies. Pathological fracture rate: 3.3% of 2120 SF vs. 3% of 2159 p=0.75 based on 10 studies. Spinal compression rates: 2.8% of 1443 SF vs. 1.9% of 1443 based on 6 studies.	Chow, E.; Zeng, L.; Salvo, N.; Dennis, K.; Tsao, M.; Lutz, S.. Update on the systematic review of palliative radiotherapy trials for bone metastases. Clin Oncol (R Coll Radiol) 2012;24(2):112-124.	-	-	This systematic review is an update of an earlier review (Chow 07), with the inclusion of a further 9 RCTs such that it is based on 25 RCTs. The average rates have not changed significantly with the addition of the additional trials. In particular the study finds: - No difference in the overall response rates with 60% of 2818 patients for SF vs 61% of 2799 patients for MF (p=0.98) based on 25 RCTs. - No difference in the complete response rates with 23% of 2641 patients for SF vs 24% of 2622 patients for MF (p=0.97) based on 17 RCTs. - A greater retreatment rate for SF therapy with 20% of 2323 patients vs. 8% of 2309 patients for MF (p<0.00001) based on 12 RCTs. -No difference in the pathological fracture rates with 3.3% of 2120 patients for SF vs 3.0% of 2159 patients for MF (p=0.72) based on 10 RCTs. -No difference in spinal cord compression rates with 2.8% of 1443 patients for SF vs 1.9% of 1443 patients for MF (p=0.13) based on 6 RCTs. In addition to these meta analyses, the review also discusses a number of further points. Firstly, the paper suggests that MF treatments may be more suitable for patients with complicated bone metastatses, such as pending spinal cord compression or cauda equine syndrome. Secondly, the paper discusses the suggestion that MF treatment provides better long term pallation. The paper points to (van der Linden et al., 2006) that found equivalent response rates for patients surviving >52 weeks. Thirdly, the review discusses the reduced costs of SF treatment. Fourthly, the review highlight the patients preference for SF treatment. The review also finds four studies making a comparison of acute toxicities between the two treatments. It finds no significant difference in nausea / vomiting and lethargy / tiredness. However, it finds one study (Arnalot et al., 2008) that finds that SF therapy has a lower level of skin reactions than MF.
1+	Systematic	-	Between 5 - 15 Gy SF, but mainly 8 Gy.	Other	Response rates.	15-57%, no clear comparisson with different fractional regimes.	-	-	Bedard, Gillian; Hoskin, Peter; Chow, Edward. Overall response rates to radiation therapy for patients with painful uncomplicated bone metastases undergoing initial treatment and retreatment. Radiother Oncol 2014;112(1):125-127.	-	-	This is another systematic review of the literature. Although the study does not conduct a meta-analysis, it does offer an opinion that is independent of the Chow et al. collaboration. The findings for uncomplicated bone metastases is the same as (Chow et al. 12). However, the study does point to some studies focused on complicated bone metastases. In particular, there is some grade 4 evidence (Agarawal 06) that for impending pathological fractures and impending spinal cord compression (Harada 10). There was no statistically significant differences, in pain response rates, between SF and MF therapy in patients with neuropathic pain.

1+	Systematic	527 patients	Between 4-10 Gy, pedominantly 8 Gy SF, occasional MF	Clinical effectiveness of the intervention	Partial response (PR), complete response rates (CR) and Overall Response rates (OR)	CR 16-28% PR 28 - 45% OR 58% (95% CL : 0.49 - 0.67)	Toxicity	Only reported in 3 studies: In van der Linden et al. 31% of patients report a score of 4 (very bad) consisting mostly of nausea/vommiting 30% report a mild toxicity (1 or 2), again mostly nausea and vommiting	Huisman M., van den Bosch MA, Wijlemans JW, van Vulpen M, van der Linden YM, Verkooijen HM.. Effectiveness of Reirradiation for Painful Bone Metastases: A Systematic Review and Meta-Analysis . Int. J. Radiat. Oncol. Biol. Phys. 2012;84(1):8-14.	-	-	This systematic review and meta analysis reviews the pre 2011 literature on reirradiation. It finds 10 relevant studies of which 7 are combined into a meta analysis. There is good agreement in the reported overall, complete and partial response rates (OR, CR and PR). The only meta-analysis is on the OR which find 58% (95% CL : 0.49 - 0.67). The PR are in the range 28 - 45% and the CR are in 16-28%. The review does not distinguish between SF and MF reirradiations, but the majority are 8Gy SF. Toxicity rates are quoted from a single study (van der Linden et al., 2004) and indicate 31% of patients scored grade 4 (very bad), predominantly for vommiting, nausea and severe fatigue. 30% reported grade 1 or 2, predominantly nausea/vommiting and diarrhea.
1-	RCT	NA	8 Gy over a single fraction	Clinical effectiveness of the intervention compared to existing interventions	Complete response rates (CR) and Overall Response rates (OR).	OR: 77% of 124 patients for MF and 78% of 121 patients for SF CR: 44% of 125 patients for MF and 38% of 122 patients for for SF Based on Dutch bone metastasis study (Steenland et al. 1999), others results quoted, no meta analysis.	Retreatment rates Toxicity Cost effectiveness	Retreatment rates: 33% of 27 patients (SF) vs. 12% of 26 patients (MF) (Sande et al., 2009) Toxicity: acute grade 2-4 toxicityc 20% (MF) vs 10% (SF) (RTOG 9714 trial) Cost effectiveness: $2438 (SF) vs. $3311 (MF) (Steenland et al. 1999), $998 (SF) vs $2316 (MF) (Konski et al, 2009)	Fairchild, Alysa. Palliative radiotherapy for bone metastases from lung cancer: Evidence-based medicine?. World J Clin Oncol 2014;5(5):845-857.	-	-	This systematic review looks to examine response rates of single fraction (SF) and multiple fraction (MF) radiotherapies for different primary tumours. The study consisting of searching the literature for studies which distinguish between primary tumour. It was found that the number of reviews that distinguish between primary tumours is limited and hence the number of patients involved in any meta-analysis is reduced relative to similar systematic reviews. In particular the study finds statistically similar overall response rates, for prostate cancer rates, with 78% of 121 patients for SF vs. 77% of 124 patients for MF. While, again for prostate cancer, the complete response rates 44% of 125 patients for SF and 38% of 122 for MF. This is based on one study (Steenland 99). Other RCT's are considered, but there is no attempt to combine the results in a meta-analysis. Retreatment rates are also considered but the sample sizes were too small for any meaningful comparison. The study also considers response duration and toxicity with similar problems of sample sizes.

1+	RCT	320	8 Gy in Single Fractional	Clinical effectiveness of the intervention compared to existing interventions	Complete response rates (CR) and Overall Response rates (OR).	CR: 62% (SF) vs 48% (MF) p=0.07 OR: 87%(SF) vs 85% (MF) p=0.54	Response rate by primary tumour. Overall Survival	OR by tumour: Breast - 90% (SF) vs 89% (MF) p=0.58 Prostate - 85% (SF) vs 90 % (MF) p=0.11 Lung - 77% (SF) vs 43% (MF) p=0.38 Median survival time (months): 7.6 (SF) vs. 6.5 (MF) p=0.27	van der Linden, Yvette M.; Steenland, Elsbeth; van Houwelingen, Hans C.; Post, Wendy J.; Oei, Bing; Marijnen, Corrie A. M.; Leer, Jan Willem H.; Dutch Bone Metastasis Study Group. Patients with a favourable prognosis are equally palliated with single and multiple fraction radiotherapy: results on survival in the Dutch Bone Metastasis Study. Radiother Oncol 2006;78(3):245-253.	-	-	This RCT study compared single fraction (SF) vs multi - fractional (MF) radiotherapy and found no statistically relevant differences in the responses to the two treatments. Of the 1157 patients, 320 survived for >52 weeks and these were used for statistical analysis. Overall response rates were 87% for SF and 85% for MF, or 80% (for SF) and 85 % (for MF) after excluding retreatment effects. The study raises concerns over the need to distinguish between patients with single or multiple bone metastasis, which was not addressed in this study. Also while the random allocation of patients to trials is sufficient, the method of concealment of treatment is not described. The objectives of the study are more diluted than analalogous studies.
1+	RCT	376	8 Gy in Single Fractional	Clinical effectiveness of the intervention compared to existing interventions	Re-irradiation rates	27% (SF) vs 9% (MF) p=0.002.	Pathological fractures (PF) Spinal Cord Compression (SCC) Skeletal related events (SRE) Survival time	PF: 5% (SF) vs 5% (MF) p=1.00 SCC: 1% (SF) vs 4% (MF) p=0.37 SRE: 33% (SF) vs 19%(MF) p=0.011 Median survival time: 7 months (SF) vs 6 months (MF)	Sande, Tonje Anette; Ruenes, Randi; Lund, Jo Asmund; Bruland, Oyvind S.; Hornslien, Kjersti; Bremnes, Roy; Kaasa, Stein. Long-term follow-up of cancer patients receiving radiotherapy for bone metastases: results from a randomised multicentre trial. Radiother Oncol 2009;91(2):261-266.	-	-	This study did not focus on pain relief of single fraction (SF) vs multiple fraction (MF) treatments, but rather the re-irradiation rates, rates of pathological fractures and spinal cord fractures. The study concludes that there is no difference between SF and MF treatments, but I can only partially agree since the difference in re-irradiation rates of 27% (SF) vs 9% (MF), based on 180 patients, is statistically relevant. It was a RCT and the randomisation of the assignments of treatments is satisfactory, but again the concealment method is not disclosed.

3	RCT	38 centres	Single fraction treatments	Other	Prescription of single fraction treatments	76% offered SF vs 24% MF	-	-	Chow, Edward; Meyer, Ralph M.; Chen, Bingshu E.; van der Linden, Yvette M.; Roos, Daniel; Hartsell, William F.; Hoskin, Peter; Wu, Jackson S. Y.; Nabid, Abdenour; Tissing-Tan, Caroline J. A.; Oei, Bing; Babington, Scott; Demas, William F.; Wilson, Carolyn F.; Wong, Rebecca K. S.; Brundage, Michael. Impact of reirradiation of painful osseous metastases on quality of life and function: a secondary analysis of the NCIC CTG SC.20 randomized trial. J. Clin. Oncol. 2014;32(34):3867-3873.	-	-	This study attempts to determine how often single fraction (SF) therapy is offered in veteran healthcare administration centres. It also looks for possible factors as to why multiple fraction (MF) therapy is still the preferred treatment. It offers no evidence to either support or reject the question of the equivalence of the two treatments.
1+	RCT	1157 patients	8 Gy over a single fraction	Clinical effectiveness of the intervention compared to existing interventions	Pain intensity score by week after randomisation	MF lower score than SF in 6-12 week period, but not statistically significant. See figure 2 for details.	survival time pain response rates	Median survival after randomisation (weeks) 6.5 (MF) vs 7.1 (SF) Pain response rate: 44% (MF) vs 47% (SF)	Meeuse, Jan J.; van der Linden, Yvette M.; van Tienhoven, Geertjan; Gans, Rijk O. B.; Leer, Jan Willem H.; Reyners, An K. L.; Dutch Bone Metastasis Study Group. Efficacy of radiotherapy for painful bone metastases during the last 12 weeks of life: results from the Dutch Bone Metastasis Study. Cancer 2010;116(11):2716-2725.	-	-	This study uses data obtained during an earlier RCT (van der Linden 06), but studies the pain response in the time before death, rather than time after randomisation, in particular the last 12 weeks. Of patients who died with 12 weeks of treatment, there was no significant difference in the pain response between treatments (47% for SF of 134 patients and 44% for MF of 135 patients). The main finding of the paper is that the pain response rate increase with survival time cohort, with 1-4 weeks being 18%, 5-8 weeks 48%, 9-12 weeks 60% and >12 weeks 78%, although this is independent of treatment.

1-	RCT	SF (222 M + 233 F) vs MF (223 M vs 220 F)	8 Gy Single fraction	Clinical effectiveness of the intervention compared to existing interventions	Retreatment rates by gender	Female partner: 7% (MF) vs 16% (SF) p=0.0052 Female no partner: 1% (MF) vs 15% (SF) p=0.0009 Male partner: 8% (MF) vs 18% (SF) p=0.0067 Male no partner 9% (MF) vs 6% (SF) p=0.5551	Survival time (months)	Female partner: 12.6 (MF) vs 8.4 (SF) p=0.14 Female no partner: 10.1 (MF) vs 14.7 (SF) p=0.57 Male partner: 7.7 (MF) vs 8.2 (SF) p=0.78 Male no partner 7.2 (MF) vs 8.3 (SF) p=0.93	Konski, Andre; Desilvio, Michelle; Hartsell, William; Watkins-Bruner, Deborah; Coyne, James; Scarantino, Charles; Janjan, Nora. Continuing evidence for poorer treatment outcomes for single male patients: retreatment data from RTOG 97-14. Int. J. Radiat. Oncol. Biol. Phys. 2006;66(1):229-233.	-	-	This retrospective RCT is designed to examine if there is any gender difference in the response to SF vs. MF radiotherapy. The study found no statistically significant difference in complete and partial response rates. However it found differences in the retreatment rates. In particular it found married men and women and single women, receiving MF therapy, had significantly lower retreatment rates. It also found that although survival rates were similar between SF and MF, the median survival time was lower for men. The principle objection to this study, is that it is not clearly stated how the study accounts for the gender differences in the rates of the primary tumour. To be explict, the study does include prostate and breast cancers, which will have gender differences in the rates. Previous studies have indicated that both pain levels and survival rates are dependant on primary tumour and if this is not accounted for, this could introduce a significant bias.
1-	RCT	376	8 Gy Single Fractional	Clinical effectiveness of the intervention compared to existing interventions	pain score	mean QLQ-c30 pain score 67 (MF) vs 69 (SF) No pain 1% (MF) vs 2% (SF) Moderate 52% (MF) vs 42% (SF) Very strong pain 8% (MF) vs 11% (SF) see table 3 for full results.	survival rates	Median survival times (months): 9.6 (SF) vs 7.9 (MF)	Kaasa, Stein; Brenne, Elisabeth; Lund, Jo-Asmund; Fayers, Peter; Falkmer, Ursula; Holmberg, Matts; Lagerlund, Magnus; Bruland, Oivind. Prospective randomised multicenter trial on single fraction radiotherapy (8 Gy x 1) versus multiple fractions (3 Gy x 10) in the treatment of painful bone metastases. Radiother Oncol 2006;79(3):278-284.	-	-	This RCT study compared single (SF) and multi-fractional (MF) radiotherapy treatments in 376 patients and found no difference in survival probabilities and perceived benefits to pain relief. Survival probabilities are found to be similar for the two treatments, with a median survival time of 9.6 months for SF and 7.9 months for MF. The main concerns are that concealment methods were not disclosed and that the pain responses were not measured using a standard method. Partial, complete or overall response rates are not calculated and so it is difficult to compare to other studies. They also use health related quality of life questionaires and not the Karnofsky performance score. Assessment appears largely qualitative.

1+	RCT	909 patients of which 235 had painful vertibal metastases.	8 Gy over a single fraction	Clinical effectiveness of the intervention compared to existing interventions	Complete (CR), partial (PR), stable (SR) and progressive (ProgR) pain response at 3 months,	CR: 19% (SF) vs 17% (MF) PR: 51% (SF) vs 45% (MF) SR: 18% (SF) vs 28% (MF) ProgR: 12% (SF) vs 10% (MF) see table 4 for full results.	Narcotic Use Survival rates Retreatment Rates Toxicity rates	See paper for full results, but no statistically significant difference in response rates, narcotics use and survival rates. Differences in acute grade 2 toxicity, 20% (MF) vs 10% (SF), in particular with gastrointestinal toxicity, 14% (MF) vs 6% (SF). Higher retreatment rates in SF, 15% vs 5% for MF.	Howell, David D.; James, Jennifer L.; Hartsell, William F.; Suntharalingam, Mohan; Machtay, Mitchell; Suh, John H.; Demas, William F.; Sandler, Howard M.; Kachnic, Lisa A.; Berk, Lawrence B.. Single-fraction radiotherapy versus multifraction radiotherapy for palliation of painful vertebral bone metastases-equivalent efficacy, less toxicity, more convenient: a subset analysis of Radiation Therapy Oncology Group trial 97-14. Cancer 2013;119(4):888-896.	-	-	This RCT is a reanalysis of the RTOG 97-14 study (Hartsell et al., 2005) which involved studying 909 patients, of which 235 had painful vertebral bone metastases and randomly treated with either 8 Gy Single fraction (SF) radiotherapy or 30 Gy over 10 fractions (MF) radiotherapy. The study differs from other similar RCTs in that is distinguishes the patients by spinal location of the metastases (cervical, thoraic, lumber and multiple sites). There was no statistically significant difference between overal response rates (after 3 months), 70% for SF vs. 68% for MF. There was also no significant difference in the different levels of analgesic and narcotic use. SF treatments had a higher overall retreatment rates (15% vs 5% for MF). SF treatment had lower levels of gastrointestinal intoxicity (e.g. esophagitis, nausea or vomitting), 6% vs 14% for MF p=0.01 and overall toxicity (10% for SF vs. 20% for MF). There was no statistically significant difference, in response rates between SF and MF, for different spinal regions.

1+	RCT	160	8 Gy Single Fractional	Clinical effectiveness of the intervention compared to existing interventions	Complete response rates (CR), Overall response rate(OR) and Partial Response rates (PR).	CR: 11% (MF) vs 13% (SF) at 12 weeks OR: 62% (MF) vs 65% (SF) at 12 weeks PR: 51% (MF) vs 52% (SF) at 12 weeks	Acute toxicity Retreatment rate	Acute toxicity: 18% in MF vs 12% in SF Retreatment rate 28% in SF vs 2% in MF	Foro Arnalot, Palmira; Fontanals, Agustí Valls; Galcerán, Joan Carles; Lynd, Frances; Latiesas, Xavier Sanz; de Dios, Nuria Rodríguez; Castillejo, Anna Reig; Bassols, Marti Lacruz; Galán, Joan Lozano; Conejo, Ismael Membrive; López, Manuel Algara. Randomized clinical trial with two palliative radiotherapy regimens in painful bone metastases: 30 Gy in 10 fractions compared with 8 Gy in single fraction. Radiother Oncol 2008;89(2):150-155.	-	-	This RCT has assessed the effectiveness of two radiotherapy treatments, a single 8 Gy fraction verses 30 Gy over 10 fractions. The study found that both treatments had statistically similar complete and partial response rates, assessed over a 3 to 48 week period. Overall response rates were 75% for single fraction therapy and 86% for multi-fractional therapy. The study considered a sample of 160 patients, in similar conditions, who were assigned to treatments using a computerized randomisation table. The main source of concern was that the concealment method was not disclosed. This led to concern about a secondary outcome, notably the claim of higher retreatment rates for multi-fraction treatments. Long term (> 150 days) survival probabilities appear statistically higher for 30-Gy than 10-Gy, but it is believed that this is not statistically robust since survival probabilities are dependant on primary tumour which has not been accounted for.

1+	RCT	850	8 Gy in Single Fractional	Clinical effectiveness of the intervention compared to existing interventions	Complete response rates (CR), Overall response rate(OR) and Partial Response rates (PR).	OR: 28% (SF) vs 32% (MF) CR: 8%(SF) vs 7% (MF) PR: 19% (SF) vs 25% (MF)	Acute toxicity rates Quality of life QLQ-C30	More skin reddening in MF (24% vs 14% for SF p=0.0020) Lack of appetite: 56% (SF) vs 66% (MF) p=0.011 diarrhoea: 23% (SF) vs 31% (MF) p=0.018 Pathological fractures: 7% (SF) vs 5% (MF) p=0.15 Spinal cord compressions: 2% (SF) vs <1% (MF) p=0.094 See table 3 and 4 for additional results.	Chow, Edward; van der Linden, Yvette M.; Roos, Daniel; Hartsell, William F.; Hoskin, Peter; Wu, Jackson S. Y.; Brundage, Michael D.; Nabid, Abdenour; Tissing-Tan, Caroline J. A.; Oei, Bing; Babington, Scott; Demas, William F.; Wilson, Carolyn F.; Meyer, Ralph M.; Chen, Bingshu E.; Wong, Rebecca K. S.. Single versus multiple fractions of repeat radiation for painful bone metastases: a randomised, controlled, non-inferiority trial. Lancet Oncol. 2014;15(2):164-171.	-	-	This study is one of the larger and more thorough RCT, although it is still non-blinded. The study found no statistical differences in the efficacy of pain relief of the two treatments (34% SF to 32% MF), no difference in recurrent pain pain (73% SF vs 72% MF in reasons for re-irradiation, which is not an objective study of relapse pain). The study also finds that MF has higher levels of vommiting (23% vs 13% p=0.001), diarrhoea (31% MF vs 23% SF p=0.018), loss of appetite (66% MF vs 56% SF p=0.011 and skin reddening (24% MF vs 14% SF p=0.002). The study found no difference in survival probabilities. The study lists it's major limitation being the lack of concurrence between intention to treat and per protocol analyses. There are also challenges in seperating optimal analgesic medication from the need for radiation therapy.

Appendix Two

Literature search terms

Assumptions / limits applied to search:	
Original search terms:	n/a
Updated search terms - Population	Population part 1: bone pain OR painful bone OR secondary bone disease OR Population part 2: bone OR bony AND metastases OR metastasis OR metastatic OR symptomatic
Updated search terms - Intervention	Intervention part 1: radiotherapy OR radiation OR re-irradiation OR reirradiation OR EBRT OR external beam AND Intervention part 2: single fraction OR single fractions OR single-fraction OR single-fractions OR fraction*
Updated search terms - Comparator	n/a
Updated search terms - Outcome	n/a

Inclusion criteria	**General inclusion criteria**
	In order of decreasing priority, the following are included: 1. All relevant systematic reviews and meta-analysis in the last 5 years and those in 5-10 years period which are still relevant (e.g. no further updated systematic review available) 2. All relevant RCTs and those in the 5-10 years period which are still relevant (e.g. not superseded by a next phase of the trial/ the RCT is one of the few or only high quality clinical trials available) >>>> If studies included reach 30, inclusion stops here 3. All relevant case control and cohort studies, that qualify after exclusion criteria >>>> If studies included reach 30, inclusion stops here 4. All relevant non analytical studies (case series/ reports etc.) that qualify after exclusion criteria >>>> If studies included reach 30, inclusion stops here 5. Expert opinion
	Specific inclusion criteria
	Clinical Trials Meta-analysis NICE guidance National guidelines and professional consensus guidance e.g. ASTRO
Exclusion criteria	**General exclusion criteria**
	Studies with the following characteristics will be excluded: 1. Do not answer a PICO research question 2. Comparator differs from the PICO 3. < 50 subjects (except where there are fewer than 10 studies overall) 4. No relevant outcomes 5. Incorrect study type 6. Inclusion of outcomes for only one surgeon/doctor or only one clinical site
	Specific exclusion criteria
	n/a