REVIEW

Single fraction radiotherapy versus multiple fraction radiotherapy for bone metastases in prostate cancer patients: comparative effectiveness

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Abstract: External beam radiotherapy (EBRT) is an effective treatment for symptomatic bone metastases from a variety of primary malignancies. Previous meta-analyses and systematic reviews have reported on the efficacy of EBRT on bone metastases from multiple primaries. This review is focused on the comparative effectiveness of single fraction radiotherapy versus multiple fraction radiotherapy for bone metastases in prostate cancer patients.

Keywords: radiotherapy, bone, metastases, prostate, comparative effectiveness

Introduction

In 2014 there will be an estimated 233,000 new cases of prostate cancer and 29,480 deaths from prostate cancer in the USA.[1] Approximately 50% of advanced prostate cancer patients develop bone metastases.[2,3] Treatment options for prostate cancer-related bone metastases include palliative external beam radiotherapy (EBRT), medical management with analgesics, radionuclides, and systemic treatments such as androgen deprivation therapy, bisphosphonates, and chemotherapy. Palliative EBRT is an effective treatment option for pain control from symptomatic bone metastases. Multiple randomized controlled studies, meta-analyses, and systematic reviews have all shown equivalence in pain response between single fraction (SF) radiotherapy and multiple fraction (MF) radiotherapy in cancer patients with bone metastases from a variety of primary malignancies.[4–8] We conducted a review of the comparative effectiveness of single versus multifractionated radiotherapy for bone metastases from prostate cancer.

Methods

An Internet literature search was conducted using the PubMed online biomedical search engine for literature published between January 2000 and April 2014 using the following search terms: bone, metastasis or metastases, radiation or radiotherapy, prostate, fraction, single, and multiple. The search language was restricted to English. Another Internet search of the Medical Literature Analysis and Retrieval System Online (MEDLINE); the US National Cancer Institute's cancer literature database on PubMed (formerly CancerLit); and the Cochrane Library was conducted to identify randomized controlled trials published during the same time period, using the following Medical Subject Heading (MeSH) terms: Bone Neoplasms/radiotherapy, Bone Neoplasms/secondary, and Dose Fractionation.

Eligible published studies were also identified from reference lists of retrieved papers and review articles. Included were all published randomized controlled trials

comparing SF or MF schedules for the treatment of bone metastases. Only trials using conventional EBRT were included. Trials involving the use of hemi-body radiotherapy and radionuclides were excluded, as were studies involving patients with complicated bone metastases causing spinal cord compression, cauda equina syndrome, or pathological fractures.

Results

A total of seventeen randomized controlled studies were found that fit our inclusion criteria. Table 1 lists these seventeen studies. Only three studies broke down their results by both fractionation arm and primary malignancy. There are no published randomized controlled studies involving prostate cancer patients with sufficient patient numbers to enable a statistically valid comparative effectiveness analysis between SF and MF regimens in prostate cancer patients.

Response rates

In the updated systematic review published in 2012 by Chow et al, the overall response rates for all patients with bone metastases from various primary malignancies were similar, with 1,696 of 2,818 (60%) patients in the SF arm and 1,711 of 2,799 (61%) patients in the MF arm achieving a response.[8] Using an intention-to-treat analysis, 620 of 2,641 (23%) SF patients and 634 of 2,622 (24%) of MF patients reported a complete response. There is little convincing evidence that the pain response rate from prostate metastases differs from that of other primary malignancies. Some evidence suggests a higher response rate from prostate cancer than other primaries,[9–16] with the possible exception of breast cancer, while other studies have not supported this.[2,17–20] In general, however, results from randomized control studies have not been broken down simultaneously by both primary malignancy and fractionation schedules to elucidate if there is a difference in response rates specifically for prostate cancer

Table 1 Randomized controlled studies comparing single versus multiple fractions of radiotherapy in bone metastases

Author (country)	Year	Treatment arms	Number of patients	Number of prostate cancer patients (%)	Breakdown of results for prostate cancer patients
Cole[25] (UK)	1989	8 Gy/1 F versus 24 Gy/6 F	29	4 (14%)	No
Amouzegar-Hashemi et al[34] (Iran)	2008	8 Gy/1 F versus 30 Gy/10 F	70	10 (14%)	No
Foro Arnalot et al[27] (Spain)	2008	8 Gy/1 F versus 30 Gy/10 F	160	40 (25%)	No
Gaze et al[2] (UK)	1997	10 Gy/1 F versus 22.5 Gy/5 F	265	54 (20%)	No
Hartsell et al[21] (RTOG 9714; USA)	2005	8 Gy/1 F versus 30 Gy/10 F	898	445 (50%)[a]	No
Kaasa et al[28] (Norway/Sweden)	2006	8 Gy/1 F versus 30 Gy/10 F	376	139 (37%)	No
Nielsen et al[26] (Denmark)	1998	8 Gy/1 F versus 20 Gy/4 F	241	80 (33%)	No
Steenland et al[10] (The Dutch Bone Metastasis Study; the Netherlands)	1999	8 Gy/1 F versus 24 Gy/6 F	1,171	Absolute number of prostate patients not given (23%)	Yes
Sande et al[22] (Norway)[b]	2009	8 Gy/1 F versus 30 Gy/10 F	180	53 (30%)	Partially[c]
Price et al[13] (UK)	1986	8 Gy/1 F versus 30 Gy/10 F	288	24 (8%)	Partially[d]
Roos et al[18] (TROG 96.05; Australia/New Zealand/UK)	2005	8 Gy/1 F versus 20 Gy/5 F	272	79 (29%)	Partially[e]
Sarkar et al[35] (India)	2002	8 Gy/1 F versus 30 Gy/10 F	73	4 (5%)	No
Bone Pain Trial Working Party[24] (UK/New Zealand)	1999	8 Gy/1 F versus 30 Gy/10 F or 20 Gy/5 F	765	260 (34%)	No
van der Linden[11] (the Netherlands)[f]	2006	8 Gy/1 F versus 24 Gy/6 F	320	74 (23%)	Yes
Safwat et al[36] (Egypt)	2007	8 Gy/1 F versus 30 Gy/10 F versus 20 Gy/5 F	60	4 (7%)	No
Hamouda et al[9] (Egypt)	2007	8 Gy/1 F versus 40 Gy/20 F	102	18 (18%)	Yes
El-Shenshawy et al[23] (Egypt)	2006	8 Gy/1 F versus 30 Gy/10 F or 20 Gy/5 F	150	43 (29%)	Partially[g]

Notes: [a]Hartsell did not report specifically on the number of prostate cancer patients, but only breast and prostate patients were included in this study and 445 patients were male in this study; [b]this study is a long-term follow-up of the subset of Norwegian patients in the larger study by Kaasa et al (2006); [c]Sande et al reported retreatment rates by primary tumor; [d]although no breakdown was given by fractionation and tumor type, the publication stated that "pain relief was independent of the histology of the primary tumour"; [e]exploratory multifactor analyses were carried out, adjusting for primary cancer (lung/prostate/breast/other), with no significant changes in the results and conclusions; [f]this study was a subset of the Dutch Bone Metastasis Study for patients who survived more than 52 weeks; [g]this paper reported the median times to pain progression by primary malignancy.
Abbreviations: Gy, Gray; F, fraction; RTOG, Radiation Therapy Oncology Group; TROG, Trans Tasman Radiation Oncology Group.

patients between single and multifractionated regimens. Exceptions do exist, however. One study from Egypt by Hamouda et al reported a 100% response rate to palliative radiotherapy for prostate patients in both the SF and MF arms.[9] This study had only 18 prostate cancer patients, so no conclusions between SF and MF regimens can be made from this relatively small study, especially with a 100% response rate for both fractionation schemes. There was a significantly lower response rate for lung cancer patients (61.9%) in comparison to patients with breast (91.8%) and prostate (100%) cancer ($P<0.05$ for both comparisons). The Dutch Bone Metastasis Study by Steenland et al also provided results by fractionation arm and primary malignancy, but did not provide statistical analysis by primary tumor type, probably because of small numbers for individual primary tumors.[10] In a subset analysis of patients living more than 1 year in the Dutch Bone Metastasis Study reported by van der Linden et al, results were analyzed by primary malignancy.[11] Seventy-four prostate patients were included in this analysis (34 patients in the 8 Gray [Gy]/1 fraction [F] arm [8 Gy/1 F arm] and 40 patients in the 24 Gy /6 F arm [24 Gy/6 F] arm), and the pain response rates were similar at 85% and 90% (P=0.11) for the 8 Gy/1 F and 24 Gy/6 F arms, respectively. This subset analysis was underpowered to draw any firm conclusions between SF and MF regimens for prostate cancer patients. Price et al did not provide a specific breakdown of results for prostate cancer patients but did state in their paper that "pain relief was independent of the histology of the primary tumour".[13]

Hartsell et al reported the results of Randomized Trial of Palliative Radiation Therapy For Osseous Metastases Study 9714 (RTOG 9714), which randomized 898 patients with bone metastases from breast or prostate cancer to receive either 8 Gy as a SF (8 Gy/1 F) or 30 Gy in ten fractions (30 Gy/10 F).[21] Half of the patients had a primary diagnosis of prostate cancer. A complete response was defined as having no pain at 3 months after radiotherapy, a partial response was defined as a pain score that was at least two points lower than the baseline score, a stable response was defined as a one-point change in pain score (either worse or better), and progression was defined as a pain score that was at least two points higher than the baseline score. The complete and partial response rates at 3 months for the 288 patients in the 8 Gy/1 F arm were 15% (44 patients) and 50% (143 patients), respectively; for the 285 patients in the 30 Gy/10 F arm the complete and partial response rates were 18% (51 patients) and 48% (137 patients), respectively (P=0.6).

The Dutch Bone Metastasis Study, which randomized patients between 8 Gy as a SF (8 Gy/1 F) and 24 Gy in six fractions (24 Gy/6 F), analyzed some of its results by primary tumor site but did not provide statistical analysis by primary tumor, perhaps because of small numbers for individual primary sites. The study did state, however, that there was no indication that the treatment effect of fractionation was dependent on tumor type.[10] The pain response rates in prostate cancer patients were 77% (96/124) for the 24 Gy/6 F arm and 78% (95/121) for the 8 Gy/1 F arm. The complete response rates for prostate cancer patients were 44% (55/125) and 38% (46/122) for the 24 Gy/6 F arm and 8 Gy/1 F arm, respectively. There was a higher rate of response and complete response for breast and prostate patients compared to lung and other primary tumors. The response rates for breast and prostate patients were 76% and 78%, respectively, compared to 60% for lung patients and 62% for all other primary diagnoses analyzed together. The complete response rates for breast and prostate patients were 44% and 41%, respectively, compared to 24% for lung patients and 16% for other primary sites.

Therefore, based on the limited data in the literature, there do not appear to be any apparent differences in response rates to single versus multifractionated radiotherapy for bone metastases from prostate cancer, which is consistent with bone metastases from other primary sites in general.

Bone metastases causing neuropathic pain are considered to be complicated bone metastases, and perhaps require a larger dose of radiation to control them. Trans-Tasman Radiation Oncology Group trial (TROG 96.05) compared 8 Gy/1 F and 20 Gy/5 F in 272 patients with neuropathic pain from bone metastases.[18] Prostate cancer patients represented 29% of the population. The overall response rates for 8 Gy/1 F and 20 Gy/5 F were 53% and 61%, respectively (P=0.18), with complete response rates of 26% and 27%, respectively (P=0.89). The estimated median time to treatment failure (TTF) was 2.4 months (95% confidence interval [CI]: 2.0–3.3 months) and 3.7 months (95% CI: 3.1–5.9 months), respectively, for 8 Gy/1 F and 20 Gy/5 F. There was a trend to shorter TTF in the SF arm with a hazard ratio of 1.35 (P=0.056). There were no significant differences in the rates of retreatment, spinal cord compression, or pathological fracture between the two arms. Exploratory analyses were carried out adjusting for treatment site (spine versus non-spine) and for primary malignancy (lung/prostate/breast/other), with no changes in the conclusions by treatment arm. Therefore, it appears that even for bone metastases causing neuropathic pain, SF regimens are equivalent to MF regimens in overall and complete

response rates. However, there may be a trend toward earlier treatment failure for a SF regimen for neuropathic pain.

Retreatment rates

The meta-analysis by Chow et al reported a significantly higher number of retreatments for SF patients, 473 of 2,323 (20%), compared to MF patients, 178 of 2,309 (8%), (P<0.00001).[8] RTOG 9714 reported a statistically significant difference in retreatment rates between the two arms with 3-year retreatment rates of 18% (76/449 patients) in the 8 Gy/1 F arm and 9% (33/432 patients) in the 30 Gy/10 F arm (P<0.001).[21] Most of the retreatments were given in the first 9 months after the initial radiotherapy, and retreatments were rarely delivered after 1 year of the initial treatment. Sande et al reported retreatment rates by primary tumor and the retreatment rates for prostate cancer patients undergoing 8 Gy/1 F was 33% (9/27 patients) versus 12% (3/26 patients) in those undergoing 30 Gy/10 F.[22] However, the numbers were too small for a valid statistical comparison between the two arms. Furthermore, multiple biases may lead to a higher and earlier retreatment rate following a SF of radiotherapy.

Response duration

There is some evidence to support the belief that prostate patients have a longer time to pain progression than other primaries, with the exception of breast cancer.[11,13–16] El-Shenshawy et al found a median time to progression of 32 weeks, 18 weeks, 9 weeks, and 6 weeks for breast, prostate, lung, and other cancers, respectively (P=0.0001).[23] Pain progression was defined in that study as a return to the initial pain score or higher. However, the study did not analyze time to progression for prostate cancer patients between the different fractionation groups. Gaze et al had 20% of patients in their study with prostate cancer, and reported no difference in duration of pain control between 10 Gy/1 F and 22.5 Gy/5 F (a median of 13.5 weeks and 14 weeks, respectively).[2] Results were not broken down by primary malignancy. Price et al reported no difference in the onset or duration of pain relief between 8 Gy/1 F and 30 Gy/10 F, and pain relief was independent of the histology of the primary malignancy.[13] These results are consistent with other randomized controlled studies that showed no difference in how quickly symptoms resolved or in the duration of pain relief, when a SF regimen was compared to a MF regimen.[3,9–11,24–26]

The Dutch Bone Metastasis Study reported progression rates of 53% (51/96) and 61% (58/95) for the 24 Gy/6 F and 8 Gy/1 F arms, respectively, but no statistical analysis for this difference was provided.[10] A subset analysis of the Dutch Bone Metastasis Study was performed on patients who survived more than 1 year to see if there was an impact on fractionation schedules on pain control in long-term survivors with bone metastases.[11] There were 320 patients who survived more than 1 year, and 74 (23%) of these patients had prostate cancer. For all 320 patients, 87% responded to SF and 85% to MF (P=0.54). Complete response was seen in 62% of SF patients and 48% of MF patients (P=0.07). The mean time to response was 4 weeks in both SF and MF patients. Mean duration of response was 29 weeks for SF patients (median duration 35 weeks) and 30 weeks for MF patients (median duration 42 weeks). Progressive pain was reported in 55% of SF patients who responded and in 53% of MF patients who responded. For patients who experienced progressive pain, the mean time to progression after a response was 17 weeks for SF patients and 18 weeks for MF patients. Therefore, even in patients with a good prognosis, which includes many breast and prostate cancer patients, there does not appear to be any difference in the duration of response after SF and MF regimens.

Sande et al reported that there was no significant difference between 8 Gy/1 F and 30 Gy/10 F in time to re-irradiation.[22] Most of the re-irradiations, 64.5% for the 30 Gy/10 F arm and 63.4% for the 8 Gy/1 F arm, were given within the first 9 months. This suggests that the duration of pain relief was similar for the two treatment regimens, in accordance with other studies.[10,24] Receiving 8 Gy/1 F may not make it more likely that physicians will retreat patients earlier. These findings may indicate that physicians do not use a lower clinical threshold of pain for retreatment after SF radiotherapy compared to MF radiotherapy.

The findings by Sande et al are contrary to those found in the Dutch Bone Metastasis Study.[10] The Sande et al study reported a 25% (147/579) retreatment rate for the 8 Gy/1 F arm and a 7% (41/578) retreatment rate in the 24 Gy/6 F arm. Prostate patients had a retreatment rate of 22% (29/129) in the 8 Gy/1 F arm and an 11% (15/138) retreatment rate in the 24 Gy/6 F arm. Retreatment was demonstrated to occur earlier in pain progression in the 8 Gy/1 F arm (at an average of 14 weeks) compared to 23 weeks in the multifraction group (P<0.0001). The pain score preceding retreatment was higher in the multifraction arms at 7.52/10 compared to 6.82/10 in the SF arm. This difference suggests that physicians may use a higher patient threshold of pain before retreating a patient who initially underwent a MF treatment.

Toxicity

RTOG 9714 reported that more patients had acute grades 2–4 toxicities in the 30 Gy/10 F arm (17%) than in the

8 Gy/1 F arm (10%) (difference =7%; 95% CI =3% to 12%; P=0.002).[21] The most common toxicity was gastrointestinal toxicity and accounted for approximately half of all acute side effects. Two patients, both of whom received 30 Gy/10 F, had grade 4 acute toxicities (one with emesis and one with neutropenia). The incidence of ≥ grade 2 late toxicity was 4% in both arms. Four patients, two in each treatment group, experienced late grade 3 toxicity. In a subset analysis of the RTOG 9714 trial looking at vertebral body metastases, 235 of 909 total patients (26%) had vertebral body metastases. No differences were found in terms of pain relief (62% for 30 Gy/10 F and 70% for 8 Gy/1 F; P=0.59), but significant differences in acute grade 2–4 toxicity (20% and 10% for 30 Gy/10 F and 8 Gy/1 F, respectively; P=0.01) and acute grade 2–4 gastrointestinal toxicity (14% and 6%, respectively; P=0.01) were observed at 3 months, with lower toxicities seen in the patients treated with SF. Late toxicity was rare and no spinal cord myelopathy was recorded.

Foro Arnalot et al and Kaasa et al also reported more cases of acute toxicity in MF patients, but did not provide specific data on prostate cancer patients.[27,28] Acute side effects can include nausea/vomiting, diarrhea, fatigue, and radiation dermatitis. Roos et al reported a worse pain flare in SF patients;[18] however, no other randomized controlled study has reported on pain flares. Acknowledging these exceptions, the meta-analysis by Chow et al did not find any differences in acute toxicities between SF and MF patients in any other study.[8]

The systematic review by Chow et al reported no statistically significant differences in pathological fracture or spinal cord compression rates between SF and MF regimens.[8] The Dutch Bone Metastasis Study provided fracture rates by both primary malignancy and fractionation, and reported the higher fracture rate in prostate cancer patients treated with 8 Gy/1 F of 5% (7/129) compared to 2% (3/138) in patients treated with 24 Gy/6 F, but did not provide a statistical analysis of this.[10]

Cost-effectiveness

Various studies have reported on the economic advantage of SF over MF regimens.[10,29–32] In the Dutch Bone Metastasis Study the estimated cost of radiotherapy, including retreatments and nonmedical costs, was significantly lower for the SF regimen than for the MF regimen ($2,438 [US dollars] versus $3,311, P<0.001).[31] The saving of radiotherapy capacity was considered a major economic advantage of the SF regimen. No differences were found between the SF and MF schedules in life expectancy (43.0 versus 40.4 weeks; P=0.20) or quality-adjusted life expectancy (17.7 versus 16.0

weeks; P=0.21). Another consideration is that the retreatment rate in the Dutch Bone Metastasis Study was four times higher in the SF arm, which is considerably higher than seen in the latest systematic review by Chow et al,[8] which reported a two and six-tenths times higher rate of retreatment for patients treated with a SF compared to MFs. The higher rate of retreatment seen in the Dutch Bone Metastasis Study would tend to decrease the economic advantages of SF radiotherapy in bone metastases. Despite this, an economic advantage was still seen.

Konski et al published an analysis of the RTOG 9714 study using a Markov model to evaluate the cost-effectiveness of 30 Gy/10 F compared with 8 Gy/1 F.[29] The mean cost and quality-adjusted survival in months for the 8 Gy/1 F regimen were $998 (US dollars) and 7.26 months, and $2,316 (US dollars) and 9.53 months for the 30 Gy/10 F regimen. The incremental cost-effectiveness ratio was $6,973 US dollars/ quality-adjusted life year, in favor of the SF regimen. This means that it only costs $6,973 (US dollars) for each quality-adjusted life year using a SF regimen to treat bone metastases compared to using a MF regimen.

A cost-effectiveness analysis of TROG 96.05 showed that the 8 Gy/1 F regimen, including retreatments, costs $222 (Australian dollars) and that the 20 Gy/5 F regimen costs $724 (Australian dollars).[30]

Discussion

Janjan et al generated a therapeutic guideline for the treatment of bone metastases for the American College of Radiology and recommended SF radiotherapy because of its similar pain response, no differences in survival, better cost-effectiveness, and more convenience compared with MFs.[3] A guideline by the American Society for Radiation Oncology similarly recommended a SF for uncomplicated bone metastases.[33] Based on the limited data looking exclusively at prostate cancer patients we would recommend the same, namely that a SF of radiotherapy be the standard treatment for uncomplicated bone metastases from prostate cancer. There is some evidence from TROG 96.05 that bone metastases causing neuropathic pain may have a shorter TTF, but this difference was not statistically significant and there were no differences in the overall and complete response rates between 8 Gy/1 F and 20 Gy/5 F.[18] Prostate cancer patients with bone metastases may have a better prognosis, along with breast cancer patients, compared to patients with bone metastases from other primaries, thus some believe that a MF regimen can produce longer-lasting pain relief in these better prognosis patients. However, the available evidence indicates that the duration of pain relief is

similar between SF and MF regimens, including in patients with a good prognosis who live for more than a year.[11] A SF regimen should be used for all uncomplicated bone metastases from prostate cancer, especially in patients who have a poorer prognosis, poor performance status, reside far from a cancer center, have difficulty traveling to and from treatments, and/or receive treatments in cancer centers with long wait times.

Although the RTOG 9714 study focusing exclusively on breast and prostate patients is one of the few studies that found a difference in radiation-related toxicities between SF and MF regimens, most studies have not found significant differences in toxicity between SF and MF treatments. There is no fundamental reason to expect the radiation-related side effects experienced for prostate cancer patients to be substantially different than those with other primary malignancies. However, even if there were a difference in toxicities, a SF regimen would be preferable due to the lower reported rates of radiotherapy side effects for a SF.

The costs of radiotherapy can differ between jurisdictions, but studies from three countries on three continents have consistently shown a cost-effectiveness advantage to SF regimens.[29–31] Healthcare costs should not play a disproportionate role in treatment decisions, but are still an important consideration, and favor SF regimens.

Conclusion

There are no published randomized controlled studies involving prostate cancer patients with sufficient patient numbers and statistical analyses to draw any firm conclusions on the comparative effectiveness of SF and MF radiotherapy regimens specifically for bone metastases in prostate cancer patients. An individual patient meta-analysis of prostate cancer patients from previously-published randomized controlled studies may help to establish the comparative effectiveness of SF and MF regimens in this population of patients. Despite this, the available evidence supports the use of SF radiotherapy as a standard for all uncomplicated bone metastases from prostate cancer.

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Disclosure

The authors report no conflicts of interest in this work.

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