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Review Article

International patterns of practice in radiotherapy for bone metastases:
A review of the literature

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ABSTRACT

Purpose: Radiation therapy is the standard treatment for symptomatic bone metastases. Several randomized control trials and meta-analyses have concluded a similar efficacy in pain relief when comparing single versus multiple fraction regimes. However, there continues to be reluctance to conform to published guidelines that recommend a single treatment for the palliation of painful bone metastases. The purpose of this literature review is to summarize international patterns of practice, and to determine if guidelines recommending single fraction treatment have been implemented in clinical care. **Methods:** A literature search was conducted in Ovid Medline, Embase, and Cochrane Central. Search words included, 'bone metastases', 'radiation therapy', 'radiotherapy', 'patterns of practice', and 'dose fractionation'. Both prospective and retrospective studies that investigated the prescription of radiotherapy to bone metastases using actual patient databases were included. Articles were excluded if they investigated hypothetical scenarios. **Results:** Six hundred and thirteen results were generated from the literature search. Twenty-six articles met the inclusion criteria. Of these, 11 were Canadian, 8 were European, 6 were American, and 1 was Australian. The use of single fraction radiotherapy (SFRT) ranged from 3% to 75%, but was generally lower in American studies. Choice of fractionation depended on a variety of factors, including patient age, prognosis, site of irradiation, and physician experience. **Conclusion:** Despite the publication of robust randomized control trials, meta-analyses, and clinical practice guidelines recommending the use of a single treatment to palliate uncomplicated bone metastasis, SFRT is internationally underutilized.

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1. Introduction

Bone metastases are a common event in metastatic cancer and are a significant cause of morbidity that can lead to pain, hypercalcaemia, pathologic fracture, spinal cord compression, and reduction in quality of life (QOL) [1]. The prevalence in metastatic breast and prostate cancer patients is as high as 70–90% at autopsy [1,2]. In patients with bone metastases, goals of care often surround pain management and maintenance or improvement of QOL [3]. A variety of treatment modalities are utilized in a multidisciplinary fashion in order to achieve this goal. This includes analgesia, bone modifying agents such as bisphosphonates, and radiation therapy (RT) [3,4]. Where analgesic medications frequently result in side effects like constipation and dry mouth, radiation therapy is well tolerated with fewer side effects and provides significant pain relief in approximately 70% of

patients [5]. Furthermore, RT has been shown to help prevent subsequent skeletal related events associated with bone metastases and improve overall QOL [6].

Many dose fractionation options exist in the palliation of symptomatic bone metastases, with the most common fractionation schedules being a single 8 Gy in one fraction, 20 Gy in five fractions, and 30 Gy in ten fractions [7]. Numerous randomized control trials (RCTs) have concluded that both single fraction radiation therapy (SFRT) and multiple fraction radiation therapy (MFRT) are efficacious in providing pain relief caused by uncomplicated bone metastases [4,7]. MFRT may be indicated in the treatment of complicated bone metastases, such as those causing neuropathic pain, pathologic fractures, or spinal cord compression [8,9]. As such, guidelines from the American Society for Radiation Oncology (ASTRO) and the American College of Radiology (ACR) recommend SFRT as the preferred treatment for uncomplicated bone metastases [10,11].

Despite these evidence based guidelines, studies have shown that there is a reluctance to implement them into current practice [7,12]. Many of these studies are survey-based asking physicians

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about fractionation schedules of choice regarding hypothetical scenarios [12,13]. Conclusions from these studies may overestimate the prevalence of SFRT due to their survey based methodologies. Our review focussed on studies that have investigated actual patient databases with the goal being to present a more accurate assessment of international patterns of practice over the past twenty years, particularly with respect to the use of SFRT.

2. Methods

A literature search was conducted using OvidSP Medline (1946 – Week 4 2014), Embase (1947 – Week 5 2014), and the Cochrane Central Register of Controlled Trials (Dec 2013) databases. A search was also conducted in the bibliographies of chosen articles as well as in the ASTRO 2014 book of published abstracts. The search was limited to English and restricted to those published after 1994. Subject headings and keywords used included ‘bone metastases’, ‘radiation therapy’, ‘radiotherapy’, ‘patterns of practice’, and ‘dose fractionation’. Titles and abstracts were screened independently by two authors (RM, LR) to determine relevant articles to be obtained for full-text review.

Articles met inclusion criteria if they were primary research studies with either a primary or secondary goal of investigating different palliative radiation therapy dose fractionation schedules for treatment courses to bone metastases. The data must have been collected from verified patient databases. Abstracts were also included if they were deemed relevant and provided sufficient information regarding RT regime. Although the focus was patterns of practice in the past twenty years (1994–2014), articles that analyzed data beginning before this time period but continuing past 1994 were included. Exclusion criteria were articles that investigated patient preference or those that surveyed physicians using hypothetical scenarios. Full text articles were again screened independently by two authors (RM, LR). If disagreement existed, a discussion ensued until a consensus was obtained.

The prevalence of various fractionation schedules was extracted from each of the final articles included in the review. Other relevant information, such as significant predictive factors for the use of single fraction radiation therapy, changes in the prevalence of fractionation schedules over time, and types of bone metastases irradiated, was also included. The flow chart describing the inclusion process for the articles can be found in Fig. 1.

3. Results

Of a total of 613 articles generated by the search, 26 met the inclusion criteria. The articles were published from 2003 to 2014:

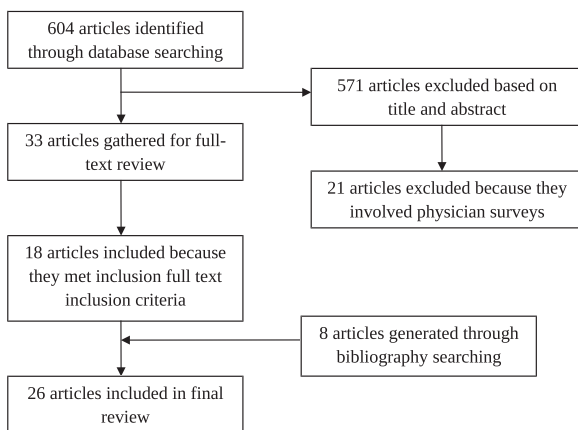


Fig. 1. Flow of article inclusion and exclusion process.

11 were Canadian [14–24], 8 were European [25–32], 6 were American [33–38], and 1 was Australian [39]. The use of SFRT to treat bone metastases was widely variable among the studies examined, ranging from as low as 3.3% to as high as 75% [36,39]. Table 1 features the dose fractionation schedules prescribed in all studies, arranged by region and study period.

3.1. Canada

Eleven Canadian studies that reported on dose fractionation in the treatment of bone metastases were published between 1994 and 2014, with data ranging from 1984 to 2011. The study with the earliest cohort included 44,223 irradiated bone metastases treated between 1984 and 2001 [14]. Thirty four percent of the RT courses were SFRT. The authors also reported a general increase in the prescription of SFRT over time, with 27.2% of patients treated with SFRT in 1984–1986 increasing to 35.4% of patients treated with SFRT from 1999 to 2001 [14]. A Canadian study published by Sutton et al. [15] investigated a similar cohort of irradiated bone metastases (1984–2004), but rather looked at RT schedules prescribed within the last two years of life. Of the 236,078 bone metastases irradiated, 30% were treated with SFRT. The authors did not report on specific changes in SFRT, but did mention that it was more frequently prescribed in the latter half of the time period [15]. Another recent abstract was published by Ashworth et al. [24], which updated the previous cohorts to include 97,150 patients who received 186,694 palliative RT courses to bone from 1984 to 2012. Over the total study period, SFRT was prescribed for 41.3% of RT courses. The prevalence of SFRT was found to increase from 39% in 1999–2003 to 58% in 2006, then decrease to 42% in 2009–2012.

Danjoux et al. [16] investigated a cohort of patients treated between 1996 and 2003. Of a total 2989 RT courses to bone, 45% were treated with SFRT. These authors did not comment on any change in prescription over time. Similar cohorts were investigated by Haddad et al. [17] and Bradley et al. [18], who investigated RT courses to bone delivered from 1998 to 2002 and 1999 to 2005, respectively. Haddad et al. [17] reported that an average 32% of 882 RT courses to bone were prescribed SFRT over the study period. The authors also reported a general decrease in the prescription of SFRT over time, from 37% in 1998 to 28% in 2002. A much higher rate was prescribed to patients included in the study by Bradley et al. [18], with 65% of 965 RT courses to bone treated with SFRT. Contrary to Haddad et al., Bradley et al. [18] found an increase in the prescription of SFRT, from 51% in 1999 to 66% in 2005. Of note, these authors specified that the cohort only included uncomplicated bone metastases, whereas Haddad et al. [17] did not specify the type of bone metastases treated. Wu et al. [20] investigated 1354 bone metastases irradiated between 2003 and 2005. Single fraction radiation therapy was prescribed in 57% and 33% of patients who were treated in rapid access clinics and regular clinics, respectively. These authors did not report on a change in SFRT prescription over time.

Naidoo et al. [19] investigated a group of 7426 patients referred for RT to bone metastases from 2000 to 2010. Of these patients, 35% were prescribed SFRT. Again, these authors did not specify whether there was any change in the prescription over time. Potter et al. [22] conducted a study with 422 RT to bone metastases treated from 2007 to 2008. The authors differentiated intent to treat and reported that, of 137 patients with uncomplicated bone pain, 48.9% were treated with SFRT.

The most recent cohorts investigated were those by Thavarajah et al. [21] and Olson et al. [23], from 2005 to 2012 and 2007 to 2011, respectively. Thavarajah et al. [21] included 2549 RT to bone metastases, of which 65% were prescribed SFRT. These authors stated that there was no significant change in the prescription of

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