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Research Article

The failures and challenges of bone metastases research in radiation oncology

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ABSTRACT

Bone metastases affect a large portion of the cancer population. As treatment options continue to evolve, many added failures and challenges arise. This narrative review details such in palliative radiation therapy for bone metastases. We begin by describing the incidence rates of bone metastases in the cancer population, the current standards of practice in recent literature and clinical trial data. Inconsistencies in end point definitions along with difficulties in measuring response to treatment and controversial areas are outlined. Current literature suggests that there is a discrepancy in physician and patient perspective on treatment options as well as quality of life. The added challenges of treatment side effects are addressed and a review of recent trials is given. Stereotactic radiation therapy is a relatively new treatment option for patients with bone metastases. Therefore, a review of the safety and efficacy of this treatment is provided. Other new areas of bone metastases treatment and research such as high intensity focused ultrasound and nanoparticles are discussed. Physicians need to prevent unwanted side effects of treatment in addition to determining how to integrate many new upcoming treatment options for patients with bone metastases. A continued reluctance to practice evidence based medicine needs to be addressed.

1. Introduction

Bone metastases are a common complication of cancer, with breast and prostate cancers being the most common types to metastasize to bone [1]. 70–85% of cancer patients are diagnosed as having bone metastases at the time of autopsy [2,3]. These bone metastases and the primary cancer itself can cause patients great pain and functional interference. Radiation therapy has been well established for the treatment of symptomatic bone metastases [4].

Although radiation therapy is one of the most common treatments for pain palliation in patients with bone metastases, a number of issues exist. As the radiation oncology field has evolved, a number of added failures and challenges to bone metastases research in radiation oncology have been presented. Radiation oncologists have worked towards establishing evidence-based treatment guidelines; however whether or not these guidelines are followed is one area in which improvement is required. The purpose of this review is to outline the failures and challenges associated with bone metastases research in radiation oncology. As new treatment options become available, radiation oncologist need to work collaboratively with other health care professionals in order to deliver the most current treatments to their patients.

2. Failures

2.1. Different endpoints and controversial conclusions

Many bone metastases trials have been conducted in order to determine efficacy of radiation treatment; however each trial appears to have slightly different endpoints. With these differing endpoints, a number of different conclusions have been drawn. This is a major failure of bone metastases research, as results from trials are often times contradictory.

2.1.1. Inconsistency in endpoints

A number of radiation therapy trials have been conducted over the past few decades to determine the efficacy of the palliation of bone pain due to bone metastases. Although these studies have been greatly beneficial and influential to the radiation oncology field, their inconsistency in endpoint definitions has left radiation oncologists and researchers unable to effectively compare the results of these trials.

Even within the same patient population, endpoints have differed. In a study by Tong et al. with the RTOG, the three

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endpoints of complete relief, partial relief and minimal relief were utilized [5]. Complete relief was defined as the pain score dropping to zero, partial relief defined as pain score dropping below four points and minimal relief defined as pain score dropping below the initial pain score. Whereas in a re-analysis by Blitzer et al. in the same patient population, four endpoints were utilized: complete pain relief (pain score falls to zero), complete pain relief prior to retreatment (pain score falls to zero before retreatment), retreatment (freedom from retreatment), and complete combined relief (pain score and narcotic score fell to zero) [6]. Although both of these studies included the same patient population, the conclusions drawn were different due to the differing endpoint definitions. The study by Tong et al. concluded that low dose, short course schedules are as effective as high dose protracted programs [5], whereas Blitzer et al. concluded that there was an improved complete response with protracted fractionation schedules [6].

In a Canadian trial by Kirkbride et al., yet another definition of response rates was utilized. This trial randomized patients between a single 8 Gy treatment and 20 Gy in 5 fractions for the palliation of painful bone metastases. The endpoint of this trial was the clinically significant pain relief, as defined by a reduction in pain score at the treated site with reduced analgesics or a pain score of zero at the treated site with no increase in analgesics at 3 months post treatment [7]. This trial was closed early; as it was determined that 20 Gy in 5 fractions was superior for pain control when compared to 8 Gy in 1 fraction. However, when pain score was assessed at 3 months independent of analgesic score, the two arms were almost identical.

The observed treatment response is also influenced by the type of pain scale employed, the inclusion of quality of life as an endpoint and the duration of follow-up. If very stringent criteria are utilized, response rates reported may be lower than traditionally accepted rates.

2.1.2. Difficulty in measuring response

An example of the differing response rates when different pain scales are employed is observed in the Danish Bone Pain Trial. Pain relief was assessed utilizing a categorical scale and a visual analog scale. Using the categorical scale, an improvement of at least one category on the 5-point scale was seen in 62% of patients at 4 weeks, whereas a 50% reduction in pain was only seen in 49% of patients at 4 weeks using the analog scale [8]. A difference in response rates was also seen in the timing of follow-up. Fifteen percent of patients had a complete response at 4 weeks post treatment, while 25% of patients had a complete response at any time during the entire 20 week follow-up period. In this same population, complete response dropped to 12% when “no use of morphine” was added to the definition, and complete response rates dropped to 4% when “complete well-being” was included in the definition [8].

It is evident through the Danish trial and other key bone metastases trials that there is a large inconsistency in the definition of response, therefore a number of different conclusions have been reached, many of which contradict each other. Other difficulties in measuring response rate include the fact that radiation therapy is a local treatment, and cancer pain can originate from multiple sites. Other systemic treatments such as analgesics, chemotherapy, hormonal therapy and bisphosphonates also work at the treatment site and can contribute to the response rates seen from radiation therapy.

2.1.3. Controversial areas

Currently, many controversial areas exist, such as the role of analgesic use in assessing treatment response, the definition of “partial response” and the interpretation of retreatment. Wu et al. addressed the end point inconsistency in their review of 12 randomized control trials for palliative radiotherapy. They concluded that although pain relief is a consistent primary outcome, a consensus on the features of treatment endpoints is needed to establish common grounds for future trials [9].

In response to these inconsistencies, Chow et al. surveyed a number of radiation oncologists and established an international consensus on palliative radiotherapy endpoints [10]. Experts were in agreement that pain assessment at the treatment site should be on a scale of 0 (no pain) to 10 (maximal pain). Incorporation of quality of life questionnaires such as the EORTC QLQ-BM22 and/or the QLQ-C15 was recommended for all clinical trials. A period of 1 week between analgesic dosing adjustment and start of radiation was also recommended to minimize risk of analgesic effects confounding radiation treatment effects [10]. It was also recommended that re-irradiation only be considered at least 4 weeks after the radiation treatment. A consensus on response rate definitions was also reached. A complete response was defined as a pain score of 0 at the treated site with no increase in analgesics, while a partial response was defined as a pain score reduction of 2 or more at the treated site without an analgesic increase, or an analgesic reduction of 25% without an increase in pain. Pain progression was defined as an increase in pain score of 2 or more above baseline at the treated site with stable analgesics, or an analgesic increase of 25% above baseline. Lastly, an indeterminate response was defined as any response that does not fit into any of the other three categories [10]. It was concluded that these recommendations should be taken into consideration for all future bone metastases trials.

In order to determine the optimal treatment schedule, Chow et al. have recently published an update on the systematic review of palliative radiotherapy [11]. In their meta-analysis, they compared single and multiple fraction treatment and determined that there is no difference between the response rates of single fraction (60% overall response, 23% complete response), and multiple fraction treatments (61% overall response, and 24% complete response). Pathological fracture and spinal cord compression rates were not statistically different between either arm; however, the likelihood of requiring retreatment was 2.6 times higher in the single fraction arm [11]. Thus, it was recommended that a single 8 Gy fraction be used to treat all patients with uncomplicated bone metastases.

2.2. Reluctance to practice evidence-based medicine

There have been a number of systematic reviews and meta-analyses to determine which treatment is more beneficial for patients with painful uncomplicated bone metastases [10–12]. Of which, it has been determined that there is no difference between single and multiple fractions in terms of pain response. Thus, it has been recommended that physicians prescribe single fraction treatment to patients with uncomplicated bone metastases where possible. However, a reluctance to practice evidenced based medicine still exists [13,14].

2.2.1. Which regimen?

Although it has been recommended that a single 8 Gy fraction be employed for patients with painful uncomplicated bone metastases, the majority of radiation oncologists are still treating patients with multiple fraction regimens [14]. In Canada, the most common fractionation delivered to patients is 20 Gy in 5 fractions, and among American radiation oncologists it is 30 Gy in 10 fractions [14]. Another study on the international patterns of practice has globally demonstrated that despite the abundance of evidence, radiation oncologists still prescribe multi-fractionated