

Role of Palliative Radiotherapy for Bone Metastasis

Takeo Takahashi^{1*}, Keiichiro Nishimura¹, Takafumi Yamano¹ and Masatoshi Gika²

¹Department of Radiation Oncology, Saitama Medical Center, Saitama Medical University, Japan

²Palliative Care Team, Saitama Medical Center, Saitama Medical University, Japan

Introduction

With approximately 50-70% of patients with advanced cancer developing bone metastases during the course of their disease, treatment of bone metastases depends on many factors including performance status, pathology, site of disease, and neurologic status [1]. Radiotherapy has become highly precise, improving local control and facilitating minimally invasive treatment, and has attracted attention as a curative treatment method comparable to surgery. On the other hand, radiotherapy also plays an extremely important role in palliative treatment for advanced cancer patients [2]. Palliative care and treatment is aimed at providing relief from pain and other symptoms. Curative and palliative radiotherapies differ in the radiation field size, dose fraction, and treatment schedule. We review the role of radiotherapy in palliative treatment for patients with symptomatic bone metastases.

Characteristics of Palliative Radiotherapy

Palliative radiotherapy usually reduces pain symptoms caused by bone metastases after a short treatment schedule. Since palliative radiotherapy is localized to the tumor lesion in most cases, adverse effects are generally mild, and this therapy is indicated even in patients with a poor general condition. After radiotherapy, improvement in not only tumor related symptoms but also the patient's quality of life (QOL) is expected [3,4]. Bone metastases represent the most common indication for palliative radiotherapy. Radiotherapy, whose treatment method is different from analgesic or bisphosphonate administration, is localized to the lesion responsible for pain, and can also provide tumor reduction and local tumor control.

Radiotherapy for Painful Bone Metastasis

Bone metastasis is a common and severe complication in advanced cancer. The major complications associated with bone metastases are severe pain, spinal cord compression, and pathological fracture. These complications restrict mobility and greatly reduce patient's activity of daily living and QOL. Radiotherapy for bone metastasis is classified into external beam radiotherapy as a local treatment and radionuclide therapy as a systemic therapy. Radiotherapy has been established as an effective treatment for symptomatic bone metastases. Treatment of bone metastasis is mainly palliative and the aims of palliative radiotherapy for bone metastasis are: 1) pain relief, 2) improvement in symptoms due to metastatic spinal cord compression, and 3) prevention of imminent fractures.

Pain-relief effects of external beam radiotherapy (EBRT)

Although various fractionation schedule of EBRT may provide good rates of palliation, common fractionation schedules include 8-Gy single fraction, 20 Gy in five fractions, and 30 Gy in 10 fractions [1,5,6]. Single and multifractions regimen provided equal pain relief [7], and 8-Gy single fraction is a standard treatment [1,5]. A clinical trial (RTOG 7402) performed in the U.S. in the 1970s showed the effectiveness of palliative radiotherapy [8]: Overall, 89% experienced at least minimal relief of pain, with 83% obtaining partial relief and 53% obtaining complete pain relief. In this clinical trial, pain-relieving effects did not differ among dose fraction schedules, showing no dose-dependence

of the pain-relieving effects. A randomized phase III controlled study (RTOG 97-14) showed similar pain-relieving effects between 30 Gy in 10 fractions and 8 Gy in a single fraction [9]. However, the single-fraction group more frequently required re-irradiation. Many subsequent randomized clinical trials comparing multiple fractions and a single fraction of 8 Gy have shown similar pain-relieving effects on painful bone metastasis [9-14] (Table 1). A recent meta-analysis reported that single fraction and multiple fractions provided overall pain response for 60% and 61% of patients respectively [7].

EBRT produces significant reduction of pain caused by bone metastases in 60-90%, with complete pain relief in 30 to 50% of patients, although the effects differ according to the primary lesion and severity of pain when treatment is initiated [9,15] (Figure 1). In particular, relief of pain is observed in about 80% of patients with breast cancer or prostatic cancer. However, in patients with neuropathic pain, the pain-relieving effects of opioids are slight, and those of radiotherapy are observed only in 40-60% [11,16]. The Dutch Bone Metastases Study Group presented that re-irradiation of painful bone metastasis was effective and retreatment response was 63%. Of patients in whom re-irradiation can be performed, 50-70% show pain-relieving effects [17]. The indications for re-irradiation are determined based on the previously applied dose and interval following prior radiotherapy. Re-irradiation is performed so that the total dose will not exceed that tolerated by organs at risk, such as the spinal cord and brainstem. Stereotactic body radiotherapy (SBRT) is expected to be useful for cases with vertebral metastasis because SBRT allows the shaped

Study	Primary Site	RT Schedule	N	Pain Relief
Bone Pain Trail	Breast, Prostate	8 Gy/F	383	78%
Working Party Study [10]	Lung	20 Gy/ 5F, 30 Gy/10F	378	78%
Trans-Tasman	Breast, lung	8 Gy/F	272	53%
Radiation Oncology Group [11]	Prostate	20 Gy/ 5F	272	61%
Dutch Bone Metastasis Study [12]	Breast, Prostate	8 Gy/F	579	71%
	Lung, Other	24 Gy/6F	578	73%
Radiation Therapy Oncology Group 97-14 [9]	Breast, prostate	8 Gy/F	455	65%
		30 Gy/10F	443	66%
Norway and Sweden [13]	Breast, prostate	8 Gy/F	186	No difference
	Lung, other	30 Gy/10F	190	(QOL)

Table 1: Randomized trial for painful bone metastasis.

*Corresponding author: Takeo Takahashi, Department of Radiation Oncology, Saitama Medical Center, Saitama Medical University, Japan, Tel: +81-49-228-3441; Fax: +81-49-228-3753; E-mail: taketaka@saitama-med.ac.jp

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- **Pain relief rate: 60~90%**
 - depends on primary site, initial pain severity, etc.
 - breast cancer, prostate cancer : response rate ↑ 80%
 - neuropathic pain : pain relief 40~60%
- # Pain reduction is clearly shown in the first 4-6 weeks.
- **Complete response: 30~50%**
 - # appropriate analgesic usage

Figure 1: Current clinical results for Painful bone metastasis treated with RT.

dose distribution sparing the spinal cord from high irradiation dose. Especially, SBRT might also be used when re-irradiation is required in previously irradiated sites.

In the presence of single bone metastasis, when the primary lesion is controlled, and the prognosis is favorable, treatment aiming at long-term symptom control is also considered [18-20]. Randomized controlled clinical trials have shown no dose dependence of pain-relieving effects but higher incidences of re-irradiation rate after single-fraction than after multiple-fraction radiotherapy. The Dutch trial presented the rate of retreatment and fracture was higher in the 8-Gy single fraction group compared than in 30 Gy multifraction group. A systematic review showed that the risk of pathological fracture was not significantly different between single fraction and multiple fraction arms [7]. The local recurrence rate was reported to be low in a long-course radiotherapy group [20].

Radiotherapy for metastatic spinal cord compression

In the presence of spinal cord metastasis, an increase in the tumor size causes spinal cord compression, and the resulting paraplegia markedly decreases the patient's QOL. When symptoms of paraplegia develop, appropriate management within 48 hours is necessary. After radiotherapy, the motor function improves in about 40%. When treatment can be initiated while patients can still walk, 80% of them can maintain walking. In patients with paraplegia due to spinal cord compression, the paraplegia improvement rate after radiotherapy is only 7% [21]. Local control is more favorable after long-course than short-course radiotherapy [22]. The prognosis (local control) depends on the location of the primary lesion, presence or absence of visceral metastasis, and the radiotherapy schedule (dose fraction schedule) [22]. Prognostic factors were favorable histology, absence of other bone metastases, absence of visceral metastases, being ambulatory before radiotherapy, a slower development of motor deficits before radiotherapy, and a longer interval between tumor diagnosis and MSCC [22]. For spinal cord compression due to oligometastasis, the local control rates were reported to be 92, 88, and 78% after 1, 2, and 3 years, respectively, showing favorable outcomes [23]. In particular, the prognosis is more favorable when the progression of paraplegia is slower, and the symptoms of paraplegia are milder. Therefore, for metastatic spinal cord compression, the standard treatment may be long-course radiotherapy (30 Gy/10 fractions or 40 Gy/20 fractions) combined with steroid therapy. In particular, in patients in whom survival for at least 6 months is expected, long-course radiotherapy is recommended [6]. A recent matched pair analysis showed no difference in treatment results between the two methods. However, the only randomized clinical trial that compared the effects on spinal cord compression due to spinal cord metastasis between surgery combined with postoperative radiotherapy and radiotherapy alone showed the effectiveness of surgery [24,25]. A systematic review demonstrated that

surgery should be considered for operable MSCC patients with a good prognosis [26]. Radiotherapy should be performed for nonsurgical MSCC patients; For those with a poor prognosis, 8 Gy in single fraction should be given, and for those with a good prognosis, 30 Gy in 10 fractions could be considered [26].

Prevention of imminent fractures

In general, bone metastasis is frequently osteolytic, and its progression causes pathological fracture. After radiotherapy for osteolytic bone metastasis, recalcification is observed in 65-85%. After radiotherapy combined with bisphosphonate administration, recalcification is observed in more than 80%. However, there is no definite evidence that pathological fracture can be prevented by recalcification after radiotherapy. On the other hand, although stereotactic body radiotherapy precisely delivers high dose to the tumor volume, it has a risk of long term vertebral compression fracture.

Relationship Between Prognostic Factors and Radiotherapy Schedule

To estimate the survival of patients with bone metastasis, some scoring systems for survival have been used, and their usefulness has been reported for predicting prognosis of patients with bone metastasis. It is important to select appropriate treatment methods and radiotherapy dose fraction schedules according to the prognosis of patients with bone metastasis [27]. Single-fraction radiotherapy is advantageous for bone metastases patients with a short life expectancy. Fractionated regimen, such as 30 Gy in 10 fractions, 35 Gy in 14 fractions, or 40 Gy in 20 fractions, are favoured for patients with long life expectancy [1].

Radiopharmaceutical Therapy

Radiopharmaceutical therapies are utilized in palliation of painful bone metastases, and recommended for multiple osteoblastic skeletal metastases with pain symptoms [5,28]. Single intravenous administration of β -emitting agents including strontium-89 and samarium-153 can relieve pain in widespread bone metastases. The following conditions should be fulfilled for the use of strontium-89 therapy: (1) Bone scintigraphy shows accumulation at the site of metastasis. (2) The bone marrow function is maintained. (3) The life expectancy is at least 1 month. Pain relief is obtained due to the cytotoxic effects of β -rays emitted by strontium (^{89}Sr). Basically, the main effect of this agent is the alleviation of symptoms, and improvement in pain and a reduction in the analgesic dose are achieved in about 50% of patients. Its adverse effects are myelosuppression and the flare phenomenon. Sr-89 therapy can also be combined with bisphosphonate administration or radiotherapy. Radium-223 is a bone-seeking alpha emitter, and a new agent for bone metastases from prostate cancer. A phase III trial has showed that Radium-223 improved overall survival significantly for patients with metastatic prostate cancer [29]. It is a promising candidate for managing bone metastases of castration-resistant prostate cancer.

Role of Highly Precise Radiotherapy for Bone Metastasis

Intensity-modulated radiotherapy (IMRT) has facilitated highly precise irradiation localized to the tumor, and favorable treatment results have been reported for prostatic and lung cancer. SBRT implies one to hypo fractionated radiotherapy, and delivers high biological effectiveness doses to metastatic spine disease with a steep dose gradient, thereby sparing adjacent critical organs. The role of SBRT in the management of spinal oligometastasis, radioresistant spinal

metastasis, and previously irradiated but progressive spinal metastasis are emerging [1]. The usefulness of highly precise radiotherapy for bone metastasis is also expected in terms of local control [30]. Re-irradiation is possible in most of cases with bone metastasis due to these modern irradiation technique. However, target delineation, total dose, and fractionation schedule have not to be fully defined. These highly precise radiotherapies for bone metastases are still under clinical trials.

Conclusion

Palliative radiotherapy for bone metastases is of significant benefit to patients with painful bone metastasis and metastatic spinal cord compression. Radiotherapy plays an important role in palliative care and treatment for patients with symptomatic bone metastases.

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