Role of Palliative Radiotherapy for Bone Metastasis

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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 is 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 great reducing 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 schedules 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Primary Site</th>
<th>RT Schedule</th>
<th>N</th>
<th>Pain Relief</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone Pain Trail</td>
<td>Breast, Prostate</td>
<td>8 Gy/F</td>
<td>383</td>
<td>78%</td>
</tr>
<tr>
<td>Working Party Study [10]</td>
<td>Lung</td>
<td>20 Gy/5F, 30 Gy/10F</td>
<td>378</td>
<td>78%</td>
</tr>
<tr>
<td>Trans-Taarman</td>
<td>Breast, lung</td>
<td>8 Gy/F</td>
<td>272</td>
<td>53%</td>
</tr>
<tr>
<td>Radiation Oncology Group [11]</td>
<td>Prostate</td>
<td>20 Gy/5F</td>
<td>272</td>
<td>61%</td>
</tr>
<tr>
<td>Dutch Bone</td>
<td>Breast, Prostate</td>
<td>8 Gy/F</td>
<td>579</td>
<td>71%</td>
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<tr>
<td>Metastasis Study [12]</td>
<td>Lung, Other</td>
<td>24 Gy/6F</td>
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<td>73%</td>
</tr>
<tr>
<td>Radiation Therapy</td>
<td>Breast, prostate</td>
<td>8 Gy/F</td>
<td>455</td>
<td>65%</td>
</tr>
<tr>
<td>Oncology Group 97-14 [9]</td>
<td>30 Gy/10F</td>
<td>443</td>
<td>86%</td>
<td></td>
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<tr>
<td>Norway and Sweden [13]</td>
<td>Breast, prostate</td>
<td>8 Gy/F</td>
<td>186</td>
<td>No difference</td>
</tr>
<tr>
<td>Lung, other</td>
<td>30 Gy/10F</td>
<td>190</td>
<td>(QOL)</td>
<td></td>
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Table 1: Randomized trial for painful bone metastasis.

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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 (*89Sr). 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 an alpha emitter, and a new agent for bone metastases from prostate cancer. A phase III trial has shown 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 prostate 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.

References


