Palliative radiotherapy for painful bone metastases: Short-course or long-course?

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ABSTRACT For patients of bony metastases, the survival time becomes much longer as the anti-tumor strategies developed. External beam radiotherapy is effective for pain-relieving. The appropriate fractionation scheme for the most effective regimen of palliative radiotherapy to treat bone metastases is still in debate. This article reviews the prospective randomized trials comparing short-course or long-course regimens of palliative radiotherapy for painful bone metastases.

KEY WORDS Bony metastases; external beam radiotherapy; short course; long course

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Bone metastases are common in patients with advanced cancers, particularly solid malignancies such as breast cancer, prostate cancer, and lung cancer (1). More than half of women presenting with metastatic breast cancer develop bone metastases (2). Metastases occur most commonly in the axial skeleton (spine, pelvis, or skull). Pain is one of the most obvious symptoms of bone metastases. Nowadays, patients usually have a long survival time after their bone metastases are confirmed. Patients with breast or prostate cancers can survive for years (3). Therefore, efforts should be made to control pain and maintain the quality of life among these patients. The palliative treatment for bone metastases are intended to relieve pain, preserve functions, and maintain skeletal integrity. The currently available pain-relieving strategies include radiotherapy (RT), opioid-based analgesia, bisphosphonates, acupuncture, among others (4). Radiotherapy (e.g., external beam radiotherapy, EBRT) and radiopharmaceutical agents provide successful palliation of painful bone metastasis with very few side effects. EBRT can provide significant palliation of painful bone metastases in 50-80% of patients, with up to one-third of patients achieving complete pain relief at the treated site (5).

There is continued debate over the appropriate fractionation scheme for the most effective regimen of palliative radiation therapy to treat bone metastases (6). The common schemes can be divided as short-course and long-course. Jeremic *et al.* investigated the efficacies of three short-course RT regimens (4 Gy *vs.* 6 Gy *vs.* 8 Gy) in the treatment of painful bone metastasis (7) and confirmed that 8 Gy might be the "lowest" optimal single fraction. The long-course regimens usually include 30 Gy in 10 fractions, 20 Gy in 5 fractions, 24 Gy in 6 fractions, etc. It has been reported that 30 Gy in 10 fractions is the most common scheme in the United States, 20 Gy in 5 fractions is the most common scheme in Canada, and a short-course scheme of 8 Gy in a single fraction remains most common in some European countries (8-10). In this article, we will review the findings of some prospective randomized trials that had compared the short-course or long-course regimens of palliative radiotherapy for painful bone metastases.

In 1982, the Radiation Therapy Oncology Group (RTOG) for the first time reported that short-course RT schedules were as effective as longer-treatment programs in achieving pain relief from bone metastases in their trial RTOG 7402 (11). However, their trial was criticized for many of its shortcomings such as the inclusion of a heterogeneous group of primary cancer sites, the use of physician assessment of pain, and the fact that narcotic relief and the incidence of radiation therapy re-treatment were not taken into consideration. In 2005, Hartsell *et al.* reported the results of RTOG trial 9714, which compared the efficacy of 8 Gy

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in a single fraction with 30 Gy in 10 fractions in the treatment of painful bone metastases in 898 patients (12). In this trial, arcotic relief and the incidence of radiation therapy re-treatment were taken into consideration. Grade 2-4 acute toxicities were more frequent in the 30-Gy arm than in the 8-Gy arm (17% *vs.* 10%, P=0.002). Late toxicity was rare (4%) in both arms. Complete and partial response rates were 15% and 50%, respectively, in the 8-Gy arm compared with 18% and 48% in the 30-Gy arm (P=0.6). The incidence of subsequent pathologic fracture was 5% for the 8-Gy arm and 4% for the 30-Gy arm. Both regimens were equivalent in terms of pain and narcotic relief at 3 months and were well tolerated with few adverse effects. However, the re-treatment rate was significantly higher in the 8-Gy arm than in the 30-Gy arm (18% *vs.* 9%, P<0.001).

The Bone Trial Working Party Study (BTWPG) reported another large scale trial, which compared 8 Gy in a single fraction versus 20 Gy in 5 fractions or 30 Gy in 10 fractions in 765 patients (13). There were no significant differences in the time to first improvement in pain, time to complete pain relief, or time to the first increase in pain at any time up to 12 months from randomisation; furthermore, the class of analgesic used and the adverse events also showed no significant differences. According to the authors, a single fraction of 8 Gy was as safe and effective as a multi-fraction regimen for the palliation of metastatic bone pain for at least 12 months. Furthermore, the greater convenience and lower cost made 8 Gy single fraction the treatment of choice for the majority of patients. However, similar with the RTOG9714 trial, retreatment was twice as common after 8 Gy than after multi-fraction radiotherapy.

Trans-Tasman Radiation Oncology Group (TROG) reported the results of TROG 9,605 study in 2004 (14), which showed that 8 Gy in 1 fraction was not as effective as 20 Gy in 5 fractions for neuropathic pain due to bone metastases. In their study, 272 patients were recruited (8/1:20/5=137:135) from 15 centers (Australia 11, New Zealand 3, UK 1). The intention-to-treat (ITT) overall response rates for 8/1 *vs.* 20/5 were 53% *vs.* 61% (P=0.18). Corresponding figures for the complete response were 26% *vs.* 27% (P=0.89). The estimated median TTFs were 2.4 *vs.* 3.7 months respectively. Outcomes were generally poorer for 8/1, although the quantitative differences were relatively small. There were no significant differences in the rates of cord compression or pathological fracture by arm. Unlike the RTOG9714 trial or BTWPG trial, there were no statistically significant differences in the rates of re-treatment between the two arms.

There were abundant prospective randomized trials from the Europe. In 1999, the Dutch Bone Metastasis Study group evaluated 8 Gy in 1 fraction versus 24 Gy in 6 fractions in 1,171 patients with bone metastases (15). No statistically significant differences were found in pain response, treatment side effects, and quality of life between these two schedules. Several years later, in a Norway prospective randomized multicenter trial (16), 376 patients were randomized to single-fraction (8 Gy x 1) or multiple-fraction (3 Gy × 10) radiotherapy. Both groups experienced similar pain relief within the first 4 months, and this was maintained throughout the 28-week follow-up. No differences were found for fatigue and global quality of life. Survival was similar in both groups, with median survival of 8-9 months. In another European randomized clinical trial comparing these two palliative radiotherapy regimens in painful bone metastases (17), a total of 160 patients were assigned to receive a single 8-Gy fraction or 30 Gy in 10 fractions. This trial also showed that a single-fraction regimen of 8 Gy was as safe and effective as a multi-fraction regimen of 30 Gy for painful bone metastases in terms of pain relief. However, the authors also found that the re-treatment rate of 8-Gy arm was much higher than that of 30-Gy arm (28% *vs.* 2%). A fourth European study compared the efficacies of 8 Gy in 1 and 5 Gy in 4 in a total of 241 patients (18). The two groups did not differ with respect to age, sex, primary tumor, metastasis localization, analgesic consumption (type and dose), performance status, prior systemic treatment, degree of pain, and quality of life. The degree of pain relief did not differ between the two treatment groups. Neither was there any significant difference in the duration of pain relief, the number of new painful sites, and the need for re-irradiation; the toxicity was minor.

Fewer literatures have been published from areas other than Europe and North America. In Iran, the most common clinical RT fractionation schedule for bone metastases is 30 Gy in 10 fractions, which is quite similar with that in the United States. In 2008, Amouzegar–Hashemi *et al.* performed a randomized clinical trial to compare responses to 8 Gy in a single fraction or 30 Gy in 10 fractions among Iranian patients (19), in which 58 patients were enrolled for the evaluation of pain one month after treatment. The results showed that these two schemes showed no significant difference in pain relief. The overall response rate was 71%, similar to results obtained from western countries.

Obviously, most of these prospective randomized trials showed no significant difference between the short-course or long-course schemes in terms of pain control and adverse effects. Some of the trials showed that 8 Gy in one fraction scheme had a higher retreatment rate than the multi-fraction schemes. To compare the need for re-irradiation in patients randomised to single-fraction radiotherapy (8 Gy × 1) or multiple-fraction therapy (3 Gy × 10), Sande *et al.* (20) conducted a long-term follow-up in cancer patients receiving radiotherapy for bone

metastases. Patients in this study were followed up until death, and the result showed that patients in the single-fraction arm received significantly more re-irradiations as compared to the multiple-fraction arm (27% *vs.* 9%, P=0.002).

The Dutch Bone Metastasis Study Group did a societal cost – utility analysis on their randomized, controlled trial (21) and found that, compared with the multiple-fraction radiotherapy, single-fraction radiotherapy provides equal palliation and quality of life and has much lower medical and societal costs.

In conclusion, randomized trials from different areas in the world have demonstrated that single-fraction radiation therapy is sufficient to achieve palliation of painful bone metastases with optimized convenience for both patients and caregivers. A single dose of 8 Gy seems to become the standard treatment. It is also notable, however, patients receiving short-course radiotherapy may receive remarkably more re-irradiations. Therefore, the RT scheme should be tailored for each patient after cautious considerations.

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