

Executive summary

The aims of radiation therapy (RT) are either curative or palliative. According to the American statistics, about 45% of all cancer patients received RT during their course of illness from diagnosis to death, among which 25–30% received RT for the purpose of symptomatic relief. Bone metastasis is one of the major causes of cancer pain, which has been known to be effectively alleviated by RT. Palliative RT for pain relief has been applied with various doses and treatment schedules, from single fraction to multiple fractions over 2 weeks or longer.

Prospective randomized clinical trials have been performed since late 90's to compare palliative effects and adverse side effects by single fraction and multiple fractions in the palliative RT for bone metastasis, which showed that the single fraction had the equivalent palliative results when compared to multiple fractions. In particular, it is found in the literatures that the single fraction can be preferred in patients with short life expectancy of less than a few months. On the other hand, schedules of multiple fractions are preferred even in patients with bad prognosis, supported by the argument that the previous studies are not reliable because of high drop-out rates in the analysis.

Since no systematic studies on standard RT for patients with bone metastasis have been performed in Korea, the necessity has arisen for a study on the optimal palliative RT schedule in patients with short life expectancy, fully considering the adequacy of treatment effect, the accessibility to treatment, and the expenses. Therefore, this study was

intended to find the evidence and the differences in the patterns of RT practice in patients with bone metastasis in Korea, and to find the clues to overcome those differences.

First of all, a systematic review was performed to confirm the evidence whether a single fraction in the palliative RT of cancer patients with bone metastasis is equivalent to multiple fractions. Among the randomized clinical trials comparing single fraction and multiple fractions in palliative RT, a total of 16 articles were included in the final evaluation after excluding the studies with less than 6 Gy for a single fraction and the studies that were not original articles. The quality evaluation was performed for these literatures using a tool recommended by the SIGN (Scottish Intercollegiate Guidelines Networks), which resulted in 7 studies with 1++, 6 studies with 1+, and 3 studies with 1-. Evaluation categories were divided into effectiveness aspects (complete or partial response, re-treatment, pathologic fracture, and spinal cord compression) and safety aspects (nausea/vomiting, fatigue, and skin reaction). The evaluation results for effectiveness aspects showed no significant difference in overall response, pathologic fracture, and spinal cord compression between single fraction and multiple fractions, but the re-treatment rate was 2.5 times higher in patients with single fraction method. These results were similar in the sub-group analysis according to the quality evaluation, and thus it was analyzed as having no difference in all categories except re-treatment rate between two treatment groups. In the safety aspect, which was stated as a form of description in all studies, no difference in nausea/vomiting, fatigue, and skin reaction was observed between two treatment groups. This study was the 7th systematic review following the previous systematic literature reviews, and the results were comparable with the those of the previous studies, confirming that either fraction schedule could lead to similar

results in the palliative RT for patients with bone metastasis.

Two additional studies were designed. First, a survey was performed to understand the practice patterns of palliative RT for bone metastasis in Korea and to find out the decision factors that affected the prescription of RT fractionation. The survey questionnaire included general information of subjects, 3 types of scenario depending on the life expectancy of patients, and the decision factors affecting the RT prescription. The questionnaire was presented with the following three case scenarios according to the state of life expectancy of patients: good prognosis (case 1: breast cancer), a good performance status with the diagnosis of localized spine metastasis after 3 years of treatment; intermediate prognosis (case 2: small cell lung cancer), a good performance status with the diagnosis of liver and intra-abdominal lymph node metastasis and localized spine metastasis after 1 year of treatment; poor prognosis (case 3: non-small cell lung cancer), a poor performance state with the diagnosis of multiple bone metastasis while being treated for mediastinal lymph node metastasis and liver metastasis after 1 year and 8 months of treatment. And the fraction dose and fraction number of RT for each case were replied. A web survey was performed from October 5 to October 23, 2009 among 177 regular members of The Korean Society for Therapeutic Radiology and Oncology (KOSTRO) and 88 members returned their answers (response rate 49.71%). In responses, 86 (97.7%) answered to prescribe RT for case 1, 80 members (90.9%) for case 2, and 84 members (95.5%) for case 3, respectively. For cases 1 and 2, the prescription of 30 Gy/10 fractions was answered by 42 members (48%) and 61 members (76.3%), respectively. On the other hand, for case 3, the prescription of 20 Gy/5 fractions was answered by 29 (34.5%) and the prescription of 30 Gy/10 fractions was answered by 31 members (36.9%). For case 1,

two members prescribed a single fraction of high dose stereotactic body RT of 18 Gy and 16 Gy, respectively. There was no prescription of single fraction for case 2, and only 1 member prescribed 8 Gy of single fraction for case 3. In the analysis of decision factors for the prescription for case 3 in two groups of less than 10 fractions of treatments (40, 47.6%) and over 10 fractions (44, 52.4%), RT with less than 10 fractions was preferred as the daily average number of patients planned for treatment increased in a respondent's hospital. The number of prescriptions of less than 10 treatments was 9 (29%), 16 (48.5%), and 15 (75%) in cases when the daily average number of patients for treatment was less than 50, 50~150, and more than 150, respectively. As for the important decision factors affecting the RT schedule, the answers with the most frequency were the general performance of patients (72.7%) and the prognosis of patients (69.3%). In addition, expectation for the efficacy (23.9%) and the complications of RT (18.2%) were followed, while the departmental policy (including financial consideration) (6.8%), training habits (4.5%), convenience (3.4%), and the age of patients (1.1%) were low. It was found that the prescription of single fraction has been seldom made customarily in Korea. Increased number of prescribing less than 10 fractions was observed as the life expectancy shortened, however, the prescription rate of single fraction is still low. The general performance (and/or accompanying diseases) of patients and the life expectancy were the mostly considered factors in deciding the prescription of RT, and the RT of 10 or more fractions was mostly prescribed if the life expectancy was not too short, which seems the general pattern of practice in the country for palliative RT for bone metastasis.

The second method performed to evaluate the clinical patterns of practice and treatment results of palliative RT in Korea was a retrospective study in lung cancer patients with multiple bone

metastasis and bad prognosis. The target populations were the patients diagnosed with lung cancer and had multiple bone metastasis with relatively poor general performance (ECOG performance status of over 2 or higher), and received RT for symptomatic areas of bone metastasis. Among patients who met the above criteria, 192 patients (a total of 268 areas) were selected who received RT between January 1, 2008 and December 31, 2008 at Samsung Medical Center (Sungkyunkwan University), Seoul National University Hospital, Asan Medical Center (Ulsan University), and Yonsei University Health System. Evaluation categories included the numeric rating scale (NRS) for pain and WHO analgesic ladder, RT fractionation, and treatment response rate, treatment failure rate, treatment response duration, and survival rate after treatment. The median age was 64 (21-86) years, and 120 (62.5%) were male. About 70% of patients were diagnosed as lung cancer with other organ metastasis with bone metastasis, and 103 patients (53.6%) were diagnosed with synchronous bone metastasis. The sites for RT were vertebra in 51.9%, pelvic bone in 17.9%, and the extremities in 19.4%. The prescribed doses for palliative RT varied, among which the dose of 30 Gy/10 fractions was 47.4% with the highest frequency, and 20 Gy/5 fractions was 21.6%. The prescription of single 8 Gy fraction accounted for only 5.2%. The patients who completed the planned course of treatment were 93.2% of all patients and the patients seldom gave up the treatment half way although multiple fractions were applied. In the analysis of patients with good follow-up observations, the treatment response was observed in about 65% of patients and the average treatment response period was about 3 months, and the treatment failure was observed in 58.5% of patients. The median survival time of all patients was 6.3 months, and the 1-year survival rate was 35.5%. When these patients were divided into two groups of patients who were diagnosed as

synchronous and metachronous bone metastasis, the median survival of each group was 9.7 months and 3.4 months, respectively, which was significantly different ($p < 0.001$). Additional analysis on the factors that might affect the treatment response and treatment failure did not demonstrate any specific factors. Although there were some difficulties in obtaining clear conclusions, because accurate information on treatment response and treatment failure in all patients were not available due to the retrospective nature the study, it was found that the multiple fractionated scheme of RT was preferred for palliative RT in patients with short life expectancy in major Korean hospitals.

It was confirmed that the single fraction method for palliative treatment of patients with bone metastasis had the similar effect to multiple fractions in pain relief through the systematic literature review. However, through the questionnaire survey and retrospective study, it was found that the multiple fractions were more preferred to the single fraction in Korea, which was contrary to the evidence from the systematic review. As the first step to narrow the difference between the evidence and the practice pattern, we organized a panel discussion to share the study results and to exchange expert opinions in various specialties on Nov. 27, 2009, as a part of this study. Various opinions on the reasons for the differences, and the ideas to narrow these differences were widely discussed. The necessity to conduct a prospective randomized clinical trial and to prepare a practice guideline considering various clinical settings were also raised.