Pol J Med Phys Eng 2009;15(1):33-45.
PL ISSN 1425-4689
doi: 10.2478/v10013-009-0004-x
website: http://www.pjmpe.waw.pl

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External beam radiotherapy for palliation of painful bone metastases: pooled data bioeffect dose response analysis of dose fractionation

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Bone metastases develop in up to 70% of newly diagnosed cancer patients and result in immobility, anxiety, and depression, severely diminishing the patients quality of life. Radiotherapy is a frequently used modality for bone metastasis and has been shown to be effective in reducing metastatic bone pain and in some instances, causing tumor shrinkage or growth inhibition. There is controversy surrounding the optimal fractionation schedule and total dose of external beam radiotherapy, despite many randomized trials and overviews addressing the issue. This study was undertaken to apply BED to clinical fractionation data of radiotherapeutic management of bone metastases in order to arrive at optimum BED values for acceptable level of response rate.

A computerised literature search was conducted to identify all prospective clinical studies that addressed the issue of fractionation for the treatment of bone metastasis. The results of these studies were pooled together to form the database for the analysis. A total of 4111 number of patients received radiation dose ranging from 4 to 40.5 Gy in 1 to 15 fractions with dose per fraction ranging from 2 to 10 Gy. Single fraction treatments were delivered in 2013 patients and the dose varied from 4 to 10 Gy. Multifraction treatments were delivered in 2098 patients and the dose varied from 15 to 40.5 Gy. The biological effective dose (BED) was evaluated for each fractionation schedule using the linear quadratic model and an α/β value of 10 Gy. Response rate increased significantly beyond a BED value of 14.4 Gy ($p < 0.01$). Based on our analysis and indications from the literature about higher retreatment and fracture rate of single fraction treatments, minimum BED value of 14.4 Gy is recommended.

Key words: palliative radiotherapy, painful bone metastases.

Introduction

Nearly 50% of the practice of radiotherapy is on palliation of which the management of bone metastases constitutes the most common palliative work load [1-22]. Although they may arise from any primary malignant tumor, certain tumors, such as breast, prostate, lung, thyroid, kidney and myeloma, have a predilection for spread to bone. Although some bone metastases are painless, many frequently cause significant and debilitating pain. Besides bone pain, bone metastases can also give rise to pathological fracture and spinal cord compression, which are two important complications that result in significant morbidities. Treatment of bone metastasis often requires a multimodality approach, the main aims of which are to alleviate pain and prevent future complications.

Bone metastases develop in up to 70% of newly diagnosed cancer patients and result in immobility, anxiety, and depression, severely diminishing the patients quality of life [1-22]. Despite a variety of treatment options, cancer pain remains inadequately managed for most patients. Pain secondary to osseous metastases can be managed by analgesics, cytotoxic chemotherapy, hormonal therapy, phosphonates, and radiotherapy. Radiotherapy is a frequently used modality for bone metastasis and has been shown to be effective in reducing metastatic bone pain and in some instances, causing tumor shrinkage or growth inhibition [1-22]. Patients who require palliative radiotherapy for painful bone metastases are often entering the end stages of their life, when quality of life is an important goal. Durable pain control is an important aspect of quality of life. Local field beam irradiation has been the mainstay of treatment, as it is effective in 70% of patients. Alternative radiotherapeutic approaches include the use of hemibody irradiation and systemic radionuclide therapy.

There is controversy surrounding the optimal fractionation schedule and total dose of external beam radiotherapy, despite many randomized trials and overviews addressing the issue [1-22]. Most of these studies demonstrate that lower doses of radiotherapy are equivalent to higher doses for the end point of pain relief, quality of life and survival response rates. However, several studies demonstrate higher re-treatment and fracture rates in arms using shorter, low dose schedules. Despite these potential differences, many overviews, authors, national guidelines, and institutional protocols recommended the use of 8 Gy single fraction radiotherapy for the majority of patients with painful bone metastases. This ‘evidence-based’ approach is rationalized by arguing that any potential benefit of longer schedules of higher dose, in terms of re-treatment

and fracture rates, is far outweighed by the cheaper cost and convenience for patients using a single fraction.

The bioeffect of a physical dose depends on the nature of the tissue, fractionation scheme, dose rate and treatment time. The absorbed dose need to be translated in to a bioeffect dose, which takes into account treatment variables and the radiobiological characteristics of the relevant tissue. Various bioeffect models have been proposed to predict the biological effect of radiotherapy treatments. From time to time, various concepts like Nominal Standard Dose (NSD) [23], Cumulative Radiation Effect (CRE) [24, 25] and Time dose Fractionation (TDF) factors [26, 27] were put forward to test the equivalence of treatment schedules. The NSD formula, despite of its limitations provided radiotherapists with an important initial step in understanding the effects of fractionation on the tolerance of skin and connective tissue. The TDF formula allowed addition of the TDF values for different portions of a course of radiation treatment. These concepts were widely accepted in spite of their empirical nature. However doubts have been raised periodically as to the accuracy of prediction of early and late effects of normal tissues. Now linear quadratic (LQ) model is being used increasingly to predict the biological effect of fractionated radiotherapy using different parameters for a particular tissue like α/β, μ, K and Td [28-34]. Dale [29] have proposed Extrapolated Response Dose (ERD) equations for external beam therapy, intracavitary brachytherapy and interstitial brachytherapy. Within the context of the LQ model the parameter which quantifies the overall biological effect on a given tissue is the biologically effective dose (BED) which is obtained by applying repopulation correction to ERD [33]. This study was undertaken to apply BED to clinical fractionation data of radiotherapeutic management of bone metastases in order to arrive at optimum BED values for acceptable level of response rate.

Materials and methods

A computerised literature search was conducted to identify all prospective clinical studies that addressed the issue of fractionation for the treatment of bone metastasis. The results of these studies were pooled together to form the database for the analysis (Table 1). The endpioint selected for analysis was complete response. It was felt that this endpoint was most likely to be evaluated in a consistent fashion by different investigators. To allow comparison of the different study arms, the biological effective

Table 1. Radiotherapy treatment details of various studies of management of bone metastasis

Reference	Number of patients	Dose [Gy]	Number of fractions	Complete response rate [%]	BED [Gy]
Tong [21]	74	40.5	15	61	51.4
	72	20	5	53	28.0
	167	30	10	57	39.0
	143	15	5	49	19.5
	155	20	5	56	28.0
	148	25	5	49	37.5
Price [13]	140	8	1	35	14.4
	148	30	10	27	39.0
Hoskin [4]	137	4	1	36	5.6
	133	8	1	39	14.4
Rasmusen [14]	100	30	10	40	39.0
	100	15	3	41	22.5
Niewald [12]	51	20	5	33	28.0
	49	30	15	31	36.0
Gaze [3]	134	10	1	39	20.0
	131	22.5	5	42	32.6
Jeremic [6]	109	4	1	21	5.6
	108	6	1	27	9.6
	110	8	1	32	14.4
Nielsen [11]	122	8	1	25	14.4
	119	20	4	25	30.0
Bone pain trial working party [1]	383	8	1	57	14.4
Koswig [10]	55	30	10	33	39.0
	52	8	1	31	14.4
Steenland [18]	585	8	1	37	14.4
	586	24	6	33	33.6

dose (BED) was evaluated for each fractionation schedule using the linear quadratic model and an α/β value of 10 Gy [29, 33, 34].

Results

The data regarding BED values for each of the individual fractionation schedule along with treatment details are given Table 1. A total of 4111 number of patients received radiation dose ranging from 4 to 40.5 Gy in 1 to 15 fractions with dose per fraction ranging from 2 to 10 Gy. Single fraction treatments were delivered in 2013 patients and the dose varied from 4 to 10 Gy. Multifraction treatments were delivered in 2098 patients and the dose varied from 15 to 40.5 Gy.

Figure 1 shows the relationship between BED and complete response rate for all the investigators. The data in the figure shows scatter of the BED vs complete response points. A trend line for the data is also shown in the figure. Table 2 shows the correlation of BED with complete response rate. Response rate increased significantly beyond a BED value of 14.4 Gy ($p<0.01$).

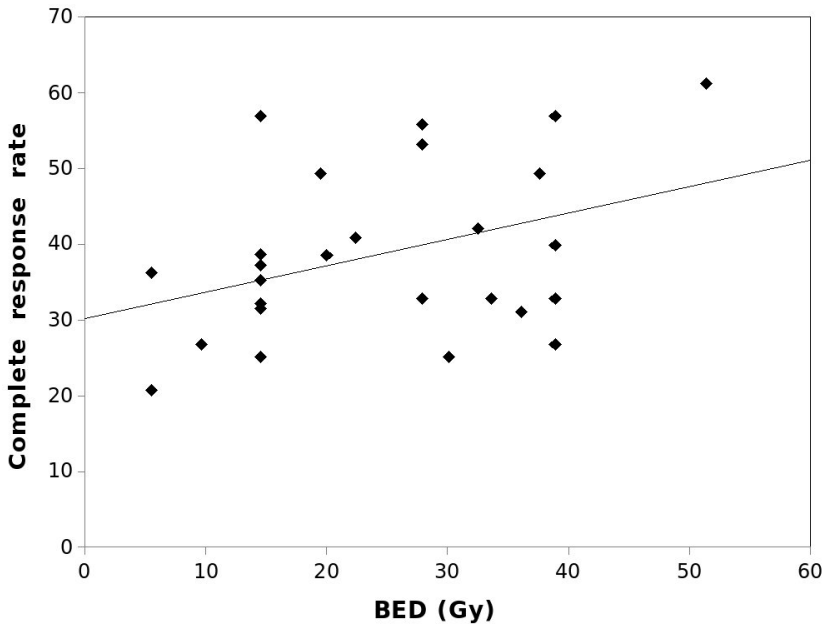

Figure 1. Relationship between BED and complete response rate for all the investigators

Table 2. Correlation of BED with complete response rate

BED [Gy]	No./Total	Response rate [%]
5.6-9.6	101/354	28.5
14.4-22.5	781/1902	41.1
28-40.5	746/1855	40.0

Discussion

Josef et al. [8] conducted a survey to study the current approaches to the clinical problem of the management of painful osseous metastases in the radiotherapy community. A questionnaire was sent to 2500 members of the American Society for Therapeutic Radiology and Oncology. It consisted of 30 multiple-choice questions regarding four hypothetical clinical scenarios likely to be encountered in daily practice. Questions related to the technique of choice (local field (LF) vs. hemibody radiotherapy (HBI), the use of systemic radionuclides (SR), fractionation schemes, dose, the integration of modalities, and the follow-up of these patients. The analysis is based on 817 (33%) responses received regarding 3268 cases. Local field is the most common form of therapy. Overall, LF was used, alone or in combination with other forms of therapy, in 54% and 75% of patients, respectively. LF was used more frequently in patients with breast cancer than in patients with prostate cancer (79% vs 45%; $p=0.0001$) long fractionation schemes were used by 90% of physicians in 96% of cases. Short fractionation schemes were used by 7% of physicians in 4% of cases. This tendency was more pronounced in private practice than in the university or government / multidisciplinary settings ($p = 0.008$) and in physicians starting their practice before 1982 ($p = 0.05$). The most common schedule was 30 Gy in 10 fractions, used by 77% of physicians in 64% of cases. HBI was used, alone or in combination with other forms of therapy, in 1% and 2% of patients, respectively. Treatments in patients with prostate cancer than in patients with breast cancer (1-2% vs 0.1% respectively). SR were used alone or in combination with local field irradiation in 21% and 40% of cases, respectively. SR were used more frequently in patients with prostate cancer than in those with breat cancer (28% vs 0.2%, respectively; $p<0.00001$). The most common radionuclide in ues is Sr-89 (99) at a dose of 4 mCi(73%) or 10.8 mCi (26%).

Chow et al. [2] determined the current pattern of practice of oncologists in Canada for the palliation of bone metastases. A survey was sent to 300 practicing radiation oncologists in Canada. Five case scenarios were presented. The first three were patients with a single symptomatic site: breast cancer patient with pelvic metastasis, lung cancer male with metastasis to L3 and L1, respectively. The last two were breast and prostate cancer patients with multiple symptomatic bone metastases. A total of 172 questionnaires were returned (57%) for a total of 860 responses. For the three cases with a single painful bone metastasis, over 98% would prescribe radiotherapy. The doses ranges from a single 8 to 30 Gy in ten fractions. Of the 172 responds, 117%) would use the same dose fractionation for all three cases, suggesting that they had a standard dose fractionation for palliative radio therapy. The most common dose fractionation was 20 Gy in five fractions used by 84/117 (72%), and 8 Gy in one fraction by 84/117 (16%). In all five case scenarios, 81% would use a short course of radiotherapy (single 8 Gy, 17%; 20 Gy in five fractions, 64%), and 10% would prescribe 30 Gy in ten fractions. For the two cases with diffuse symptomatic bone metastates, half body irradiation (HBI) and radionuclides were recommended more frequently in prostate cancer than in breast cancer (46/172 vs. 4/172, $P < 0.0001$; and 93/172 vs. 9/172, $P < 0.0001$, respectively). Strontium was the most commonly recommended radionuclide (98/103 = 95%). Since systemic radionuclides are not readily available in our health care system, 41/98 (42%) of radiation oncologists who would recommend strontium were not familiar with the dose. Bisphosphonates were recommended more frequently in breast cancer than in prostate cancer 13/172 (8%) vs. 1/172 (0.6%, $p = 0.001$).

Roos [15] surveyed Australian and New Zeland (ANZ) radiation oncologist on their preferred fractionation regimens for pain due to bonemetastases, in the context of similar overseas surveys and the large body of evidence from randomized trials. Delegates to the October 1998 Royal ANZ college of radiologists annual scientific meeting were asked to state their fractionation for four hypothetical cases viz. local bone pain from metastatic breast, Prostate and lung cancer and neuropathic (radicular) from metastatic lung cancer. In addition to demographic data, respondents were asked to select reasons for their choices and indicate what factors would influence a change in their recommended fractionation. Twelve of 32 trainees and 41 of 82 specialists completed the survey, giving overall response rate of 46%. There was decreasing use of shorter fractionation schedules from lung through prostate to breast cancer with, in particular, single fractions recommended by, respectively 42, 28 and 15% of respondents

for local bone pain ($p = 0.013$). However the presence of neuropathic pain from metastatic lung cancer led to lower use of single fractions (15%, $p = 0.0046$). There were no statistically significant differences in preferred fractionation with respect to other variables assessed in this survey. The commonest reasons cited for fractionating were desire to minimize recurrent pain and the influence of training, with desire to minimize the risk of neurological progression and optimize tumour regression also important for sympathic pain. By contrast, use of single fractions was most commonly based upon literature results and patient convenience. Changing from multiple to single fractions was most influenced by poor performance status, while the presence of neurological signs/symptoms had the worse effect.

Steenland et al. [18] conducted a global analysis of the Dutch bone metastsis study to answer the question whether a single fraction of radiotherapy that is considered more convenient to the patient is as effective as a dose of multiple fractions for palliation of painful bone metastases. 1171 patients were randomized to receive either 8 Gy × 1 (n= 585) or 4 Gy × 6 (n = 586). The primary tumour was breast in 39% of the patients, prostate in 23%, using in 25% and in other locations in 13%. Bone metastases were located in the spine (30%), pelvis (36%), femur (10%), ribs (81%), humerous (6%) and other sites (10%). Questionnaires were mailed to collect information on pain, analgesics consumption, quality of life and side effects during treatment. The main endpoint was pain measured on a pain scale from 0 (no pain at all) to 10 (worst imaginable pain). Costs per treatment schedule were estimated. On average patient participated in th study for 4 months. Median survival was 7 months. Response was defined as a decrease of at least two points as compared to the initial pain score. The difference in response between the two treatment groups proved not significant and stayed well within the margin of 10%. Overall, 71% experienced a response at some time during the first year. An analysis of repeated measures confirmed that the two treatment schedules were equivalent in terms of palliation. With regard to pain medication, quality of life and side effects no differences between the two treatment groups were found. The total number of retreatments was 188 (16%). This number was 147 (25%) in the 8 Gy × 1 irradiation group and 41 (7%) in the 4 Gy × 6 group. It was shown that the level of pain was an important reason to retreat. There were also indications that doctors were more willing to retreat patients in the single fraction group because time to retreatment was substantially shorter in this group and the preceeding pain score was lower, unexpected observed in the single fraction group, but the absolute percentage was low. In a more pathological fractures

were cost analysis, the costs of the 4 Gy × 6 and the 8 Gy × 1 treatment schedules were calculated at 2305 and 1734 Euro respectively. Including the costs of retreatment reduced this 25% cost difference to only 8%. The saving of radiotherapy capacity, however, was considered the major economic advantage of the single dose schedule.

Josef et al [9] conducted a pooled dose response analysis using data from published Phase III clinical trials. Complete response (CR) was used as an endpoint because it was felt to be least susceptible to inconsistencies in assessment. The biological effective dose (BED) was calculated for each schedule using the linear quadratic model and an α/β of 10. BED was categorized, and odds ratios for each level were calculated. CR was assessed early and late in 383 and 1,007 patients, respectively. Linear regression on the early response data yielded a poor fit and a poor at and nonsignificant dose coefficient. With the late response data there was an excellent fit (R square = 0.842) and a higher significant dose coefficient. ($p=0.0002$). Fitting early CR to a logistic model, we could not establish a significant dose response relationship. However, with the late response data there was an excellent fit and the dose coefficient was significant different from zero (0.017 ± 0.00524; $p = 0.0012$). Using BED of < 14.4 Gy as a reference level, the odds ratios for late CR were 2.29-3.32 (BED of 19.5-51.4 Gy, respectively).

Sze et al [19] a systematic review of randomized studies, examining the effectiveness of single fraction radiotherapy versus multiple fraction radiotherapy for metastatic bone pain relief and prevention of bone complication. Randomized studies comparing single fraction radio therapy with multi fraction radiotherapy on metastatic bone pain. The analysis were performed using intension to treat principle. The results were pooled using meta-analysis to estimate the effect of treatment on pain response, re-treatment rate, pathological fracture rate and spinal cord compression rate. Twelve trials involving 3261 sites were included in the meta analysis. The overall pain-response rates for single fraction radiotherapy and multifraction radiotherapy were 60% (1080/1814) and 59% (1060/1807), respectively, giving an odds ratio (OR) of 1.03 (95% confidence interval [CI] 0.90-1.19), indicating no difference between the two radiotherapy schedules. There was also no difference in complete pain response rates for single fraction radiotherapy (34% [508/1476]) and multifraction radiotherapy (32% [475/1473]), with an OR of 1.10 (95% CI 0.94-1.30). Patients treated by single fraction radiotherapy had a higher re-treatment rate, with 21.5% (267/1240) requiring re-treatment compared with 7.4% (91/1236) of patients in multifraction radiotherapy arm (OR 3.44 [95% CI 2.67-4.43]). The pathological fracture rate was also higher in

single fraction radiotherapy arm patients. Three per cent (37/1240) of patients treated by single fraction radiotherapy developed pathological fracture compared with 1.6% (20/1236) for those treated by multifraction radiotherapy (OR 1.82 [95% CI 1.06-3.11)]. The spinal cord compression rates were similar for both arms (OR 1.41 [95% CI 0.72-2.75]). Single fraction radiotherapy was as effective as multifraction radiotherapy in relieving metastatic bone pain. However, the re-treatment rate and pathological fracture rate were higher after single fraction radiotherapy. Studies with quality of life and health economic end points are warranted to find out the optimal treatment option.

Wu et al. [22] compared pain relief among various dose fractionation schedules of localized radiotherapy (RT) in the treatment of painful bone metastases. A systematic search for randomized trials of localized RT on bone metastases using different dose fractionations was performed using Medline (1966 to February 2001) and other sources. The primary outcomes of interest were complete and overall pain relief. The studies were divided into three groups: comparisons of doses given as a single fraction, single vs multiple fractions, and comparisons of doses given as multiple fractions. The complete and overall pain responses for studies comparing single vs. multiple fractions were pooled. Exploratory analysis of the dose-response relationship, using the biologic dose ($\alpha/\beta = 10$), were performed using results from all three groups of trials. Two trials comparing single vs. single, eight trails comparing single vs. multiple, and six trails comparing multiple vs multiple fractions were included. The complete and overall response rates from studies comparing single fraction RT (median 8 Gy, range 8-10 Gy) against multifraction RT (median 20Gy in 5 fractions, range 20 Gy in 5 fractions to 30 Gy in 10 fractions) were homogeneous and allowed pooling of data. Of 3260 randomized patient in seven studies, 539 (33.4%) of 1613 and 523 (32.3%) of 1618 patients achieved a complete response after single and multifraction RT, respectively giving a risk ratio of 1.03 (95% confidence interval 0.94–1.14; $p = 0.5$). The overall response rate was in favor of single fraction RT (1011 [62.1%] of 1629) compared with multifraction (958 [58.7%] of 1631; risk ratio 1.05, 95% confidence interval 1.00-1.11, $p = 0.04$), reaching statistical significance. However, when the analysis was restricted to evaluated patients alone, the overall response rates were similar for single fraction and multifraction RT, at 1011 (72.7%) of 1391 and 958 (72.5%) of 1321, respectively (risk ratio 1.00; $p = 0.9$). Exploratory analysis by biologic effective dose did not reveal any dose response relationship among the fractionation schedules used (single 8 Gy to 40 Gy in 15 fractions). Of the other results and observations reported in the trails, only the

re-irradiation rates were consistently different between the treatment arms (more frequent re-irradiation in lower dose arms among trails reporting re-irradiation rates).

We analysed the pooled clinical fractionation data of radiotherapeutic management of painful bone metastases. BED had a strong relationship with complete response data. Response rate increased beyond a BED value of 14.4 Gy which falls into multifractionation data. Based on our analysis and indications from the literature about higher retreatment and fracture rate of single fraction treatments, minimum BED value of 14.4 Gy is recommended.

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