

Radiotherapy for bone pain

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Summary

Painful bone metastases are a common problem for cancer patients. Although current evidence supports the use of a single fraction of radiotherapy as the treatment of choice, many radiotherapists, for a variety of reasons, continue to use fractionated regimens. Over one six month period 105 patients received external beam irradiation for painful bone metastases at the Royal London Hospital (RLH). Thirty-one per cent of the patients were aged 70 or over. The treatment of 97 of these patients was assessed. They had a total of 280 sites treated over the course of their disease. Fifty-nine per cent of sites treated received a fractionated course of radiotherapy. Site significantly influenced fractionation. Overall response rates of 82% were achieved. Fractionation did not appear to influence this. Ten patients received large field irradiation. Fifteen patients had five or more sites irradiated, of whom only one received hemibody irradiation.

Introduction

Painful bone metastases are a frequent cause of morbidity in patients with malignancy. External beam irradiation provides the most effective form of treatment for these patients, who account for about 20% of the workload of a radiotherapy department¹.

Controversy exists over whether single fractions should be used as opposed to the more traditional fractionated regimens. Many radiotherapists remain reluctant to use single fractions. This appears to be due to several reasons^{2,3}.

With fractionation a greater tumour cell kill can be obtained, theoretically giving rise to a better response rate and duration of response. It is, however, debatable whether the relief of pain is related to tumour cell killing or whether it is, in fact, due to modulation of prostaglandin and other cytokinin production locally^{4,5}. Most studies have not found any difference in response rates, speed of response, or duration of response between groups treated with varying radiation doses⁶⁻¹⁵.

Fears also exist of greater long term morbidity with high single doses, and of toxicity when retreating the same site, although no such long-term morbidity has been reported.

Some radiotherapists would prefer to treat bone metastases from relatively radioresistant tumours, such as renal cell carcinomas and melanomas, with fractionated high total dose regimens. Published data shows no relation between histology and response. Fractionated regimens have been advocated in the case of lytic metastases or spinal metastases to promote recalcification and bone healing, although again, this theoretical benefit is not proven. Indeed a higher rate of pathological fractures was reported in those patients who received the highest total dose regimens in a randomized study of the Radiation Therapy Oncology Group (RTOG)¹¹.

Method

Between 1 January 1991 and 1 August 1991, 105 patients received radiotherapy at the RLH for painful bone metastases, excluding those receiving radiotherapy for spinal cord compression or following surgical procedures.

The unit, staffed by three consultant radiotherapists, did not have a departmental policy for the management of painful bony metastases at the time of the study.

The notes of each of these patients have been reviewed, looking at regimens used and response rates in relationship to primary tumour, site treated, and other documented treatment modifications. Complete data was available on a total of 97 patients.

A complete response was recorded when the patient was pain free and off all analgesics at 1 month following irradiation. A partial response was attributed to those pain free, but who remained on analgesics and those with improved but persisting pain. The number of sites which relapsed were also recorded. Statistical analysis was performed using the χ^2 test for association.

Results

Ninety-seven patients were available for analysis, of whom 61 (58%) were women. The median age was

Table 1. The number of patients with primary tumour and sites irradiated

	No. of patients	(%)	No. of sites	(%)
Breast	46	(47)	166	(59)
Prostate	20	(21)	50	(18)
Lung	8	(8)	8	(3)
Unknown	5	(5)	6	(2)
Myeloma	4	(4)	14	(5)
Renal	3	(3)	5	(2)
Other	11	(11)	31	(11)
Total	97		280	

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Table 2. Fractionation related to site treated

Site*	No. of fractions			Total
	1	2-5	>5	
Spine	20 (18%)	3 (3%)	86 (79%)	109
Pelvis/hip(s)	14 (28%)	3 (6%)	33 (66%)	50
Ribs	37 (95%)		2 (5%)	39
Long bones	22 (54%)	3 (7%)	16 (39%)	41
Other	16 (42%)	2 (5%)	20 (53%)	38

*Seven sites are included in two categories

63 years (range 29-87). A total of 280 individual sites of bone pain were irradiated in these 97 patients, the details of which for primary tumour type and irradiation site are shown in Table 1. Sixty-six patients had only one site treated, and in 31 several sites received treatment, and some were retreated. A detailed analysis of these results is published elsewhere¹².

Fractionated radiotherapy was delivered to 59% of the treated sites, the remainder receiving a single dose of radiation alone. No significant relation between number of treatment fractions and primary tumour was observed, but a significant relationship with site of irradiation is seen, spine and pelvis being preferentially treated with multiple fractions, whilst ribs and long bones more often received single fractions. There was particular reluctance to treat the cervical spine with single doses of irradiation, this being the case in only 11% of cervical spine metastases treated. This data is shown in Table 2. There was some suggestion that younger patients (under 50 years) were also more likely to be treated with multiple fractions with only 38% of these patients receiving a single treatment, compared to 51% of those aged 70 and over. No statistically significant correlation with age, however, was seen.

Response was ascertained for 249 sites. Fourteen patients, representing 17 individual treatment sites, died within a month of irradiation, and were therefore unassessable. The other remaining unevaluable patients were not seen at the RLH following treatment due to the distance and difficulties involved in travelling. An overall response rate of 82% was seen, with 20% of patients achieving complete response.

No significant relation between age, sex, fractionation or total dose and response was seen, nor was this influenced by primary tumour type or anatomical site treated.

In 65 patients who had more than one site treated, 59 had an evaluable response in two or more sites. In all but eight of these patients, response at one site predicted for response at other sites, with patients either responding at all sites or failing to respond at all sites.

Details of changes in analgesic medicine were recorded. These were seen in similar proportions of both patients who responded and those who did not respond to local radiotherapy. There was, however, a higher proportion of responding patients who had documented changes in hormone therapy at the time of referral for radiotherapy. This was recorded in 33% of responders, compared to only 15% of non-responders, although this difference is not statistically significant. Conversely 1% of responders and 25% of non-responders were receiving chemotherapy at the time of referral for radiotherapy.

Duration of pain relief varied from 1 month to 8 years. When the single site which had been treated 8 years previously is excluded, the average duration of response was 8 months, with a range from 1-37 months. The incidence of documented relapse defined by recurring or worsening pain was 30%. This was seen in 16% of those receiving a single dose, compared to 33% of those receiving five or more fractions. This is a statistically significant difference ($P < 0.05$).

There is not complete follow-up until death, and therefore overall survival data is not available from this group of patients. Mean survival from time of first radiotherapy for bone metastases for 57 patients known to have died since treatment was 15 months (range 4 days to 10 years).

Discussion

Only 41% of treated sites received a single fraction of radiotherapy in this review. This confirms that many patients continue to receive fractionated courses of radiotherapy for bone metastases, despite current evidence showing that a single fraction is equally effective and less burdensome to the patient.

These figures are in keeping with a previously published survey of British radiotherapists² in which only 36% of 42 responding to a questionnaire about

Table 3. Response rates from the published prospective randomized trials

Reference	No. of treatments	Total dose	No. of fractions	Overall response (complete response)
Tong <i>et al.</i> [Ref 11]	759	15-40.5	5-15	90 (54)
Blitzer reanalysis of RTOG trial [Ref 17]	759	30 & 40.5	10 & 15	48
		15-25	5	35
Madsen <i>et al.</i> [Ref 19]	57	24	6	47
		20	2	48
Price <i>et al.</i> [Ref 13]	288	8	1	82 (45)
		30	10	71 (28)
Okawa <i>et al.</i> [Ref 20]	92	30	15	76
		22.5	5	75
		20	10 (x2 per day)	78
Cole <i>et al.</i> [Ref 15]	29	24	6	100
		8	1	100
Hoskin <i>et al.</i> [Ref 16]	270	4	1	44 (36)
		8	1	69 (39)

the management of a 64-year-old patient with breast cancer and painful uncomplicated dorsal spine metastases, would have used a single fraction. In another survey³, only 25% of responding British radiotherapists would have used a single fraction for the treatment of an uncomplicated painful lumbar spine metastasis in a similar patient.

In the former survey all those using a fractionated regimen would have used a single fraction for rib metastases, and 74% would have done so if the patient was over 70. In our study, site significantly influenced fractionation but, although those aged 70 or over, representing 31% of patients treated, were more likely to receive a single fraction this did not reach statistical significance.

Wide field or hemibody irradiation may be underutilized. Although it is associated with a greater degree of acute toxicity, it can avoid repeated trips to hospital for courses of local treatment when, as they often are, bony metastases are widespread. In the 6 month period we considered, three patients received large field irradiation, but 15 had five or more individual sites irradiated.

Although limited by the problems inherent in any retrospective study based on physician assessments of pain, the overall response rate in this series is 82%, in keeping with those from published randomized prospective studies shown in Table 3.

As with the majority of these studies no relationship between response rates and fractionation, total dose received or sites treated was seen. Only two studies to date have shown any relationship between an increased number of fractions and improved response rates. One was a reanalysis of the RTOG prospective study, initially reported as showing no link between fractionation and response¹⁷. The other was a retrospective study¹⁸.

This latter study found a lower response rate in limb bones, not borne out in our study or those of others. They also found a lower complete response for adenocarcinoma of the kidney and non-small cell lung cancer. Only two other studies have found any relationship between response and primary tumour. Tong *et al.*¹¹ found prostatic and breast bone metastases to be more responsive than lung or other primary metastases. Hendrickson *et al.*⁸ found that prostatic bone metastases were slower to respond, but had a similar response rate to other tumour types by 3 months. In our study response rates for the three major groups, prostate, breast and lung, were 84%, 87% and 63%, respectively.

We would recommend that further prospective studies with long-term follow-up are needed which specifically address the issues of relapse, retreatment and late toxicity with single fraction regimens. In the meantime from the available evidence, more patients should be offered single doses of radiation for the treatment of painful bone metastases, especially those with a poor prognosis and those who are elderly. Hemibody irradiation should also be considered for multiple sites of bone pain as a valuable alternative to repeated local treatments.

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