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The Use of Palliative Radiotherapy in the Management of Breast Cancer

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INTRODUCTION

OVERALL BETWEEN 30 and 50% of radiation treatments in Europe and North America are given with palliative rather than radical intent [1–4]. It has been estimated that palliative radiation therapy consumes approximately $900 million per annum in the United States with the three most common circumstances being treatment of patients with primary non-small cell lung cancer; metastases in bone and metastases in brain [5]. The USA 1984–1985 patterns of care study suggested that 26.5% of palliative treatments were given for patients with breast cancer, generally for brain and bone metastases [1].

Despite the frequency of palliative treatments as part of the routine practice of most radiation therapists there are no universally accepted "palliative" schedules and considerable uncertainties remain. These uncertainties are: relationship between symptom production and cancer growth; relationship between cytotoxicty, symptom relief and radiation dose; risk of normal tissue damage using "palliative" schedules (low total dose, high dose per fraction); reliable prognostic factors for patients with metastatic disease to allow estimation of survival times. Problems in evaluating outcome in studies of palliative radiotherapy are: patients multiple symptoms—one may respond while others do not; patients taking multiple therapies which affect threshold for appreciation of symptom, e.g. analgesia and steroids; patients taking systemic therapy which may affect treatment growth in addition to radiotherapy (RT), e.g. hormones, cytotoxics, biphosphonates.

PALLIATIVE RADIOTHERAPY: DOSE AND DOSE PER FRACTION

Radiotherapy is given with "palliative" intent when a patient is known to have incurable disease but has distressing symptoms related to it. Less than 50% reductions in tumour volume can be associated with symptom relief in palliative situations [6].

The ideal palliative schedule involves a single treatment visit and a dose low enough to avoid acute reactions which are inevitable after total doses of 20–30 Gy. In practice 8–12 Gy is the largest single dose tolerated by an average palliative volume without unacceptable acute effects, e.g. nausea and vomiting. Studies of the response of small subcutaneous metastases from breast cancer suggests that 8–12 Gy can result in a volume reduction of 20–80% with delay of regrowth for at least as long as 3 months [7]. A dose of 8 Gy can be shown to relieve bone pain in the majority of patients with breast cancer for at least 3 months [8]. Similarly doses of 10–20 Gy in a single fraction have been used successfully to treat spinal cord compression by metastatic cancer. In both cases, symptom free survival and incidence of complications appear to be comparable with results of fractionated schedules using higher doses [9]. Symptoms associated with brain metastases can be relieved for a few months using a single dose of 10 Gy or two fractions of 6 Gy without unacceptable acute side effects as long as steroid cover is used to prevent acute oedema [10, 11].

There is, however, a widespread reluctance to use such schedules, both because the total dose is perceived as too low to produce an adequate period of growth delay for those living longer than 6 months and the dose per fraction is perceived as too high to allow safe retreatment if tumour recurs [2–4, 12]. This reluctance is partly related to the uncertainties as to the precise relationships between total radiation dose, dose per fraction and the risk of unacceptable damage to normal tissues when using "non-standard" schedules (>2–3 Gy per fraction).

In the radical dose range (50–70 Gy), the higher the dose delivered, the higher the chance of both erradicating all cancer cells and causing unacceptable damage to normal tissue. This apprently simple equation is complicated by the fact that the reversible normal tissue reactions developing within days or weeks (acute effects), e.g. mucositis are to some extent independent of irreversible changes developing months or years later (late effects), e.g. fibrosis, vascular and neurological damage. Both are dependent on volume included and total dose delivered but late damage is also dependent on the size of dose delivered at each treatment. This implies that if the dose per fraction is too high, normal tissue tolerance can be exceeded, with unexpected damage developing months after treatment, using total doses which are too low to produce the early warning of florid acute reactions.

Dische *et al.* [13] reported the use of a schedule of 35 Gy in six fractions in the treatment of non-small cell lung cancer. The total dose is well within safe limits for spinal cord using standard fraction size of 2–3 Gy, was effective in symptom relief and was initially well tolerated. The majority of patients died before the period when they would be at risk for late tissue damage; however, a significant minority survived for more than 6 months. A small number of these unexpectedly developed radiation myelopathy. Reducing the dose and dose per fraction by a relatively small increment (30 Gy in six fractions) restored safety.

Late complications after cranial radiation can also be severe and debilitating, e.g. brain atrophy, necrosis, leucoencephalopathy and dementia. Even using 3 Gy whole brain irradiation daily for 10 treatments, clinical dementia will occur in 10–15% of the few long term survivors [14].

This type of data contributes to the reluctance of many therapists to use large fractions of radiation to treat patients if a significant minority may live more than 6–12 months.

These points are further illustrated by results of a survey of Scandinavian radiation therapists who were asked why they would not give a single fraction of radiotherapy in the treatment of bone metastases from breast cancer [15]. In this survey only 1/113 therapists would be prepared to do so and preferred to give 10 fractions of 3 Gy. Therapists were less concerned about initial response (30%) than about later effects, in particular the risk of recurrence and associated problems of retreatment and

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*Table 1. Survival predicted for patients with brain and bone metastases by 278 European radiation therapists**

	Brain metastases (small cell lung carcinoma) %	Bone metastases (breast carcinoma) %
<6 months	67.5	1.0
6–12 months	30.0	10.0
1–2 years	1.5	40.0
2–5 years	0.0	35.0
>5 years	0.0	1.0
Don't know	1.0	13.0

*Data taken from Lawton *et al.* [3].

the risk of late damage to normal tissues (70–80%) where the spinal cord is to be included in the irradiated field.

PROGNOSIS OF PATIENTS WITH BONE AND BRAIN METASTASES FROM BREAST CANCER

For all patients with bone metastases a number of factors have been associated with a significant number of survivors for more than 6 months after palliative radiotherapy, including breast as the primary site, one bone metastases only, disease confined to bone, long disease free interval, previous hormone response, good performance status and age less than 60 [2, 16–19]. Evaluation of published series of radiation treatment of bone metastases from breast cancer is complicated by the fact that radiotherapy may be given at different points in the natural history of the disease, depending on a number of factors, including the organisation of cancer services in each country [3, 4]. Patients may not require radiotherapy for pain relief until some months after first diagnosis of bone metastases and have been managed using hormone therapy or chemotherapy alone. Thus, while the median survival of all patients with bone metastases as site of first recurrence is reported to be 20 months or more, [16] the median survival after radiotherapy in reported randomised trials may be as low as 4–6 months with less than 20% surviving more than one year after radiation [8]. This discrepancy reflects both a reluctance to enter "good prognosis" patients into clinical studies involving a low dose hypofractionated radiation treatment arm and a genuine uncertainty as to prognosis in these patients, as illustrated by Table 1. [3, 5] documenting the range of survival times estimated by 278 radiotherapists for the same theoretical patient with metastatic bone cancer presenting two years after resection of a T_2 breast cancer.

A review of survival times for all brain metastases reported in large series over the last 30 years are more consistant and show that approximately 15% of patients survive 1 year, while <10% survive 2 or more years with a median survival of 3–6 months [10, 11, 20–24].

A recent multivariate analysis of a large RTOG study identified four factors associated with improved survival: Karnofsky performance status >70, an absence of controlled primary, age <60 years and a metastatic spread limited to the brain. Patients with all four characteristics constituted approximately 11% of the study population and had a predicted 200 day survival of 53%. In contrast, patients with none of the four favourable characteristics had a median predicted survival time of 1.8 months [24]. While it is widely believed that the prognosis for brain metastases and breast cancer is significantly better than that for metastatic lung cancer, it has not been possible to identify primary site as a significant prognostic variable in large randomised studies so far [11]. Again Table 1 illustrates the variation in predicted prognosis for a patient with brain metastases, in this case from lung cancer [3, 4].

Predicted prognosis is important in selection of an appropriate radiotherapy schedule; however, the criteria for selecting "good" and "bad" prognostic groups for metastatic breast cancer treated with radiotherapy are surprisingly imprecise and require clarification before a high recruitment for palliative trials can be expected.

RANDOMISED STUDIES IN THE FIELD OF PALLIATIVE THERAPY

Brain metastases

Several randomised phase III studies have been conducted by the RTOG to evaluate the effectiveness of different time/dose fractionation schemes in the treatment of patients with brain metastases. The first two studies evaluated five different schedules of cranial irradiation including 20 Gy in 1 week, 30 Gy in 2 weeks and 40 Gy in 4 weeks. All were comparable in terms of frequency of improvement of symptoms and time to progression. In the early studies options of 10 Gy in one fraction and 12 Gy in two fractions were also compared with a more protracted course of radiation, again with comparable improvement in neurological function and survival [10, 11, 23]. The RTOG also evaluated long and short schedules in those thought to have a favourable prognosis and failed to distinguish the outcome for 30 Gy in 10 fractions and 50 Gy in 20 fractions [11, 24].

Bone metastases

A number of retrospective studies have demonstrated comparable pain relief for a wide variety of schedules from 8 Gy in a single fraction to 40 Gy in 20 fractions [18, 19]. The value of randomised clinical trials has been limited either by the use of unreliable measures of response (e.g. physician rather than patient based assessment) or by trials of only a few hundred patients and limited statistical power, particularly when looking for outcome at more than 6 months after irradiation.

While there appears to be an increase in complete pain relief and freedom from recurrence of symptoms for those treated with a single fraction of 8 Gy as compared with those treated with only 4 Gy [25], only two authors have suggested an advantage for doses of radiation higher than 8 Gy. These exceptions are a reanalysis of the RTOG studies by Blitzer *et al.* [26] and a recent non-randomised Italian study [27] where doses greater than 40 Gy were claimed to be more effective both in achieving pain relief and preventing pain recurrence.

There are no randomised studies looking specifically at the effect of different fractionation schedules in maintaining the integrity of bone and/or prevention of complications of bone metastases, e.g. pathological fracture of long bones or spinal cord compression, which may occur in 10–20% of patients with metastatic breast cancer [16, 28].

The published data suggests a trend towards higher doses and more fractions being used where pathological fracture has occurred e.g. a retrospective analysis of treatment of 27 pathological fractures reported pain relief in 67% and remineralisation in 35% after 40–50 Gy in 4–5 weeks [30].

The common perception that high dose radiotherapy is required to restore/maintain structural integrity of bone was not supported in the RTOG trials where an increased risk of

pathological fracture of the long bone was demonstrated in those receiving 40.5 Gy as compared with 25 Gy [17].

Crush fractures of the vertebral column are more frequent than pathological fractures of long bones. Price *et al.* noted 15% in her series with comparable pain relief after both 8 and 30 Gy at 4 weeks and no significant difference in response as compared with those without pathological fracture. Again in those patients surviving more than a year, just over half maintained pain relief with an equal symptom free period in both arms of the study [8].

There is thus rather sparse evidence to support the view that "high" doses of radiation will either extend the symptom free period or preferentially maintain the structural integrity of bone and prevent the development of pathological fracture. Retrospective series suggest that the median time from initial diagnosis of breast cancer to pathological fracture of a long bone is of the order of 50 months (0–216 months); from irradiation to fracture of the order of 10 months (2–18 months) and from fracture to death 9 months (1–39 months) [28]. Similarly spinal cord compression may occur up to 22 months after irradiation of a bone metastases at that site [29]. It may be argued that the median survival of patients entered into randomised clinical trials is too low to allow one to investigate questions of interest, particularly as such complications are both infrequent and tend to occur more than 6 months after irradiation.

MEASUREMENT OF OUTCOME IN PALLIATIVE THERAPY

The most common end point for studies of palliative radiotherapy is symptom relief [3, 4]. Most patients have multiple symptoms, e.g. Twycross *et al.* noted 303 pains in 100 patients with cancer [31]. 80 had at least two sites of pain and 34 had at least four. This complicates evaluation of pain control, e.g. after irradiation of a single bone metastases where pain relief in one site may uncover another less severe pain. Similarly Hoskin *et al.* noted that patients with brain metastases often have at least four symptoms and in a single patient one symptom may respond completely, while another may be less responsive [20]. Patients treated palliatively are usually taking multiple therapies which may affect the threshold for a particular symptom, while not producing tumour cell kill, e.g. analgesia in the case of bone metastases and steroids in the case of brain metastases. In some cases such as bone metastases from breast or prostate cancer, patients may be taking other cytotoxic or cytostatic therapies which may affect tumour growth and cell kill, e.g. hormones, chemotherapy, or more recently, biphosphonates, in addition to localised palliative radiotherapy. In one such study 17% of all patients randomised for treatment for bone metastases had a change in systemic treatment involving hormones or chemotherapy within 1 month of radiation [8]. Finally, the majority of the reports in the literature do not use validated self-rating instruments to evaluate symptoms, but rely on physicians assessment which are associated with significantly higher response rates to palliative radiation [18, 19, 32]. The importance of agreement of measure of outcome is illustrated by the two analyses of the RTOG bone metastases studies. Initially Tong *et al.* reported no difference between two fractionation schedules in the treatment of apparently solitary bone metastases and four schedules in the treatment of multiple metastases [17]. Blitzer reanalysed these results, combining results for single and multiple metastases and including analgesic requirements in the scoring system. This reanalysis then showed a significant difference in complete pain relief between 40.5 Gy in 15 fractions and 25 Gy in five fractions (55% and 28%, respectively) [26].

In the treatment of brain metastases the common measures of outcome have been symptom relief, incidence of brain failure and survival. Attempts have been made to develop quality of life measures, e.g. palliative index used by the RTOG representing the percentage of survival time in an improved or stable function class [10, 18]. Another measure reported by Patchell *et al.* was termed 'functional independence' scale and was measured in terms of the period of time a patient had a Karnofsky score >70 [33].

SYMPTOM PRODUCTION AND TUMOUR GROWTH; SYMPTOM RELIEF AND CYTOTOXICITY

Bone metastases

There is uncertainty as to the pathogenesis of cancer related bone pain. In small metastases the consensus of opinion appears to be that it is the result of stimulation of endostial nerve endings by cytokinins, e.g. bradykinin, prostaglandins, histamine and Substance P either by direct release from tumour cells; or by interaction with normal tissue cells [18, 19]. In larger metastases stretching of the periosteum by tumour bulk; pathological fracture or nerve compression by tumour may be contributory [18, 19]. While bone metastases can be divided into lytic, sclerotic and mixed according to X-ray changes, microscopically there are no qualitative differences between lytic and sclerotic metastases. Bone scan positivity alone with no obvious X-ray change can be associated with severe pain, e.g. in a recent British series 25% of patients requiring radiotherapy for bone pain had no evidence of destruction on X-ray but a positive bone scan only [2]. Conversely, gross destruction may be relatively pain free.

Overall response to radiation of 50–80%, depending on method of assessment, can be expected with a median time to pain relief of about 2 weeks. The majority of those responding have done so by 4 weeks [18, 19]. Wide field or hemibody radiation (6 Gy upper half and 8 Gy lower half) appear to be associated with particularly rapid pain relief, i.e. within 24–48 h [34]. Animal studies of enzyme histochemistry demonstrate cellular damage and release of enzymes from lysosomes 1 h after irradiation with 1 Gy [35]. *In vitro* work suggests substantial tumour cell kill at doses of 2 Gy [36]. Such data supports the hypothesis that immediate pain relief, which can be seen after 24 h, e.g. in hemibody radiation may be related to a modification of chemical mediators as a result of immediate cytotoxic damage [18].

There appears to be no direct relationship between pain relief and the rate of recalcification seen on X-ray [18, 19, 28].

Brain metastases

For brain metastases the majority of symptoms can be related to a mass effect with associated oedema. Volume reduction sufficient to produce improvement of symptoms may be very small and may not always require cell kill, e.g. steroids may reduce capillary permeability to small molecules and reduce tumour related oedema with symptom relief for 2–3 months [11, 20].

The most common presenting symptom is that of headache with behavioural or mental changes seen in as many as 75% [11]. Approximately half of all patients are fully ambulatory at the time of diagnosis but less than 20% are able to work [21]. Nearly one-third of patients present with four or more symptoms and 40% report motor symptoms [20]. Other presenting symp-

*Table 2. RT dose and number of fractions proposed for brain and bone metastases by 278 respondents from 21 European countries**

	Bone metastases	Brain metastases
Total dose (Gy) (median)	30	30
Range	5–50	13–60
No. of fractions (median)	10	10
Range	1–49	2–30

*Data taken from Lawton *et al.* [3].

*Table 3. Aims of RT treatment of brain and bone metastases by 278 respondents from 21 European countries**

	Bone metastases (%)	Brain metastases (%)
Relief symptoms	87	97
Present symptoms	39	35
Give hope	20	12
Extend life	23	5

*Data taken from Lawton *et al.* [3].

toms include ataxia, aphasia, cranial nerve palsy, oedema and vomiting [10, 11, 20, 24].

Overall response rate of symptoms to radiotherapy is 70–90% [11] but symptom relief may be relatively short term with a probability of relapse of 20–30% at 6 months and 30–40% at one year [11, 20].

Once volume reduction sufficient to relieve symptoms has been achieved, further cell kill might be expected to increase symptom free survival by extending the period of growth delay but this will only be the case if a patient lives long enough for tumour regrowth to reach the threshold for symptoms again. As the median survival time is 3–6 months with only 25–30% dying as a direct result of progressive brain metastases [11, 20], it is unlikely that any schedule will demonstrably increase symptom free survival time unless it is possible to identify a favourable subgroup of patients with a longer median survival.

FUTURE STUDIES AND CONCLUSIONS

Clinical trials appear to have less influence on routine practice in the field of palliative radiotherapy than in other areas, e.g. a survey by Priestman *et al.* suggests that fewer than 3% of surveyed radiotherapists were influenced by published literature when treating bone metastases [37].

An appropriate palliative schedule depends on the site and size of disease, the problems it is causing, the normal tissues included and the patients' life expectation. Two further factors will also be influential: what is the acceptable risk of under-treatment of the minority and what resources are available?

A recent survey investigated the variation in palliative radiation schedules used between centres and between countries. A sample of 650 Canadian, American and European radiotherapists responded to a questionnaire asking about management of typical palliative cases including patients with brain and bone metastases [3, 4].

Amongst other questions about management, radiation therapists were asked the dose and number of treatments proposed, the aim of palliative treatment and the estimated survival of the patient. The European sample consisted of 278 respondents from a total of 21 countries [3]. Some of the responses are summarised in Tables 1–3.

The survey revealed variation in the total dose, number of fractions and dose per fraction prescribed for bone and brain metastases. There were differences also in the perceived aims of palliative therapy, i.e. to relieve symptoms only or also to prevent symptoms or, in the case of treatment of brain metastases, to extend life. There were also differences in predicted survival of the patients. These differences in aims and expectations had a marked influence on fractionation proposed in that those predicting longer survival gave higher doses and more treatments; those who aimed to extend life gave higher doses than those who did not and those who aimed to prevent symptoms tended to give higher doses than those who aimed to relieve symptoms only [3, 4].

If clinical trials are to successfully recruit patients and significantly affect routine practice, priorities might therefore include: clarification of prognosis of those patients currently receiving radiotherapy for metastatic disease and identification of reliable prognostic factors to allow appropriate stratification; agreement as to appropriate measures of outcome and use of patient self assessment questionnaires rather than only physician assessment; investigation of biological questions of interest, e.g. the relationship between structural integrity of bone, dose and fraction size; long term follow up of low dose hypofractionated regimens, e.g. 8–12 Gy single fractions to bone metastases to assess the time course of recurrence and the risk of normal tissue damage.

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