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Local Control of Soft Tissue Sarcoma of the Extremity: The Experience of a Multidisciplinary Sarcoma Group With Definitive Surgery and Radiotherapy

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Data gathered on 62 patients with soft tissue sarcoma of an extremity, treated in entirety by an experienced multidisciplinary sarcoma group, were analysed. With a philosophy of emphasising attainment of histologically negative margins at carefully planned limb sparing surgery, combined with either pre-operative or postoperative radiation therapy, a crude local control rate of 95% (59 of 62 patients) at a minimum of 24 months follow-up was obtained. Of 9 patients with microscopically positive margins after definitive surgery, 8 had undergone maximal resection compatible with preservation of function. One of these 9 failed locally, indicating that radiation therapy is effective in eradicating microscopic disease in this tumour. The excellent local control obtained with limb-sparing surgery in this series justifies early referral of patients with these uncommon cancers to an experienced multidisciplinary unit. 26 patients (42%) failed systemically at a minimum of 24 months follow-up, and 19 (30.6%) died of their disease, confirming the need for effective systemic therapy in soft tissue sarcoma. Tumours greater than 10 cm in diameter had a greater risk of systemic relapse.

Key words: sarcoma, extremity, radiotherapy, surgery
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INTRODUCTION

IN THE past two decades, the management of patients with soft tissue sarcoma of the extremity has undergone a considerable evolution. The recognition that sarcoma cells tend to spread widely within the fascial barriers that form the compartments of a limb led to the advocacy of radical resection of the entire involved muscle compartment or, alternatively, amputation [1]. Standard nomenclature was developed that defined wide resection as excision of the tumour in a complete layer of normal tissue, marginal resection as excision of the tumour through its

pseudocapsule, and intralesional resection as one during which the gross mass of the tumour is entered [1].

The rationale for combining irradiation with wide or marginal resection is that subclinical disease, evident at the margin of the soft tissue tumour, can be eliminated by radical external beam irradiation treatment [2]. This permits the surgeon to undertake a less extensive procedure avoiding radical surgery. Clinical studies have demonstrated that wide resection combined with adjuvant radiotherapy can result in rates of local control that are equivalent to the rates obtained with radical resection [2–10]. These studies have reported a probability of local recurrence of about 10% and functional and cosmetic results superior to those obtained by radical resection.

This paper presents an analysis of the experience and results of a multidisciplinary team approach with a consistent philosophy of treatment.

PATIENTS AND METHODS

The prospectively collected database of patients, presenting to the practice of a single orthopaedic surgical oncologist, between 1986 and 1991, was searched for adult patients presenting with a primary sarcoma of an extremity that was treated by limb salvage surgery and adjuvant radiation therapy. All patients had a minimum follow-up of 24 months from the date of surgery. All patients had complete clinical, operative, pathological and radiotherapy data available for review. Patients presenting as a local recurrence, having gross residual disease after surgery or unresectable tumour, requiring amputation, with metastatic disease, or refusing treatment (surgery or radiation) were excluded. 62 patients were found to fulfil these criteria, and are the subject of this review. 52 patients were excluded for the following reasons: 21 presented as local recurrences after previous surgical excision, 13 patients with small superficial tumours excised with greater than 2 cm clear margins were judged not to require radiation, 7 were found to have metastatic disease on workup at presentation, 8 were treated with primary amputation, 1 patient refused surgery after completing pre-operative radiation therapy, 1 patient died on the fifth postoperative day from a pulmonary embolus and 1 patient was lost to follow-up.

Staging investigations

All patients underwent a complete history and physical on initial evaluation, and were assessed for functional status on presentation, according to the guidelines of the Musculoskeletal Tumour Society. The patients were then evaluated for stage of local and systemic disease. All underwent computed tomography (CT) and/or magnetic resonance imaging (MRI) of the local lesion, and CT scanning of the chest. If not biopsied before referral, all patients underwent a small incisional biopsy or needle biopsy prior to treatment. Patients biopsied elsewhere had their specimens reviewed by one experienced sarcoma pathologist. The tumour was categorised as high or low grade, permitting staging of the lesion based on Enneking's staging system [1, 11]. Patients who had undergone a primary procedure performed elsewhere were evaluated to determine what type of surgery had been performed. Following review of the operative and pathology reports, and discussion with the referring surgeon and pathologist, it was determined whether the initial margins of resection were positive or negative for microscopic disease. If negative margins had been achieved, no further surgery was performed and radiation was given, if appropriate. These patients who did not undergo surgery at our centre were not included in this review. If it was determined that the initial gross or microscopic resection margins were positive, both re-excision and radiation were performed. These patients, who had re-excision at our centre following previous, initial inadequate resection done elsewhere, were included in this study.

Before advising the patient as to the treatment options, the probable status of regional nerves and vessels was determined from the local staging studies. If these structures appeared likely to be involved by microscopic disease, the risk of relapse following a positive resection margin was discussed with the patient, and the functional loss that would be evident following neural or vascular resection was also described. By contrast, if neurovascular structures were grossly involved by the tumour on pre-operative staging studies, resection of the involved structure with reconstruction of the vessels if necessary, was invariably advised and undertaken.

Radiation therapy

Pre-operative radiation was based on relatively complex and individualised treatment plans. A 5-cm margin in the longitudinal plane encompassed potential proximal or distal extensions of the tumour. The axial margins included the fascial boundary of the compartment-harbouring tumour, as demonstrated by treatment planning CT. There was free use of compensators, wedge filters and CT planning systems, and a wide range of photon and electron energies, but most were treated with parallel opposing fields, with either telecobalt or 6 MV photon beams. A longitudinal strip of the limb circumference as well as joints and pressure areas were always spared from the high-dose region. All scars and drains were included in the radiation volume. The pre-operative dose was 50 Gy in 25 fractions over 5 weeks, prescribed to the isocentre as laid out in the guidelines of the ICRU Report No. 29. It was intended that all patients would then receive postoperative boost irradiation of 10–16 Gy, depending on tumour grade. The volume of the boost was the same as that used pre-operatively.

Postoperative radiation therapy utilised similar principles, but the longitudinal margins beyond all surgical tissues were 5–7 cm, depending on grade, which also determined the dose of 60–66 Gy. The field outlines were conservative and did not include the donor site of any vascularised myocutaneous flap. Radiation was commenced as soon as wound healing was complete, usually in 3–4 weeks postsurgery.

Surgery

All resections were performed by one surgical oncologist. The resection was planned using pre-operative CT or MRI scans to provide a margin of normal tissue measuring 1–2 cm, or a fascial plane surrounding all of the circumference of the tumour, wherever feasible. Major neurovascular structures were treated as discussed above. All patients underwent detailed intraoperative evaluation of the resected specimen to ensure negative margins.

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Pathology

The pathological examination of the resected specimens was examined according to a strict protocol involving:

(1) Examination of the resected specimen by the pathologist in the operating room for purposes of orientation.
(2) Painting of the resection margins with silver nitrate.
(3) Examination of the serially sectioned specimen by the surgeon and pathologist in the surgical pathology suite. The closest margins to the tumour were recorded. If the margin of resection was <1 cm of normal tissue, orientated frozen sections were obtained to assess the presence of microscopic disease.
(4) Following tissue fixation in formalin, all "close" margins were assessed using orientated sections cut from the margin.

Conduct of retrospective review

In this study, after the list of eligible patients was assembled, the records were reviewed by one investigator. The operative and pathology reports for each patient were reviewed independently by two investigators, without knowledge of the patient's outcome. Each patient was characterised as either having, or not having, histological evidence of disease at the margin of resection. One of the following criteria was used to define histological evidence of disease at that margin: (1) any visualisation of the tumour tissue during the surgical procedure, (2) a description by the pathologist of microscopic foci of tumour at the margins of the resection. If the tumour had been exposed during surgical treatment, and then further normal tissue excised, the margin was designated as positive. After independently characterising the margins, the reviewers compared their results. Only in 1 patient was there disagreement with regard to results, and, after further discussion, this was resolved when it was shown that one observer had misread the operative report. Outcome analysis was conducted by a separate observer.

RESULTS

The mean age of the 62 patients was 49.45 years (range 15–86). 30 patients were male and 32 were female. Forty-six lesions were at or proximal to the knee or elbow, and 16 were distal. Four tumours were superficial to the deep fascia and 58 deep. Thirty-one lesions were extracompartmental and 31 were contained within a fascial compartment. Sixteen tumours were less than 5 cm in size, 25 were 5–10 cm and 21 were greater than 10 cm. The mean size was 8.99 cm (range 3–24) in diameter.

Fifty-five tumours were high grade and 7 were low grade. Distribution of histopathological types of sarcoma in this series is shown in Table 1. 3 patients received chemotherapy concurrent with the radiation therapy. 2 patients received three courses of doxorubicin and ifosfamide, according to EORTC study protocol 62874/SR1, and 1 patient, with a PNET tumour, was treated with a protocol of vinblastine, doxorubicin, cyclophosphamide (VAC), alternating with etoposide and ifosfamide, to a total of five courses.

39 patients received pre-operative radiotherapy and 23 postoperative radiotherapy. Of the pre-operative radiation group, 14 patients did not receive the postoperative boost radiotherapy. The boost was omitted because of a protracted postoperative course due to wound complications in 10 patients, following complete excision of a low-grade tumour in 2 patients, refusal of the boost by 1 patient and in 1 case there was non-compliance, in that the patient did not return for follow-up after surgery for a period in excess of 6 months. All 14 patients did receive 50 Gy in 25 fractions in 5 weeks.

Table 1. Histopathological types of 62 sarcomas of soft tissues of the extremities

	Histology	Number	%
1.	Malignant fibrous histocytoma	20	32.3
2.	Liposarcoma	12	19.4
3.	Synovial sarcoma	9	14.5
4.	Leiomyosarcoma	5	8.1
5.	Fibrosarcoma	3	4.8
6.	Malignant haemangiopericytoma	3	4.8
7.	Rhabdomyosarcoma	2	3.2
8.	Malignant schwannoma	2	3.2
9.	Alveolar soft part sarcoma	1	1.6
10.	Primitive neuroectodermal tumour	1	1.6
11.	Mesenchymal chondrosarcoma	1	1.6
12.	Unclassifiable	3	4.8

25 patients completed both the pre-operative radiotherapy and received a postoperative boost as well. 16 patients were treated to 66 Gy in total, 4 patients to 64 Gy, 1 patient to 62 Gy and 4 patients to 60 Gy. 23 patients received postoperative radiotherapy only. 19 patients received between 60 to 70 Gy in 2-Gy daily fractions. 2 patients, both with large tumours of the shoulder girdle, received 50 Gy because the radiation fields involved a large volume of lung as well as chest wall. In 1 patient, treatment was stopped at 40 Gy in 20 fractions after wound breakdown due to infection occurred. 1 patient received a non-standard regime of 50 Gy in 20 fractions in 4 weeks.

The independent assessment of the adequacy of the resection margins demonstrated interobserver agreement in all cases. 53 (85.5%) patients were judged to have negative margins and 9 (14.5%) patients positive margins. Positive margins were related to the preservation of major neurovascular structures in 5 patients, to very large tumours at the limit of limb sparing surgery in 3 patients and due to surgical error in 1 patient.

With a minimum follow-up time of 24 months (median 48.5, range 24–79), 3 patients had a local recurrence of their sarcoma, giving 95.2% local control in this series of patients, Table 2. The recurrence was within the irradiated field in 2 cases (20 and 33 months from date of surgery), and >10 cm away and outside the radiation field, but within the same limb, in 1 patient (13 months from date of surgery). One of these local failures occurred with simultaneous regional nodal disease. Local control was attempted and obtained in 2 patients (one by amputation of the limb, resection of the regional nodal disease and radiation to the nodal areas, and the other by wide resection and postoperative radiation). All 3 patients developed systemic disease within 4 months of local failure, and all died of the disease. Of the 2 patients who failed within the radiation field, one had received adequate postoperative radiation to a dose of 64 Gy. In the other case, the patient (a paraplegic) only received a pre-operative dose of 40 Gy because of concern about wound healing postoperatively. He did have a protracted postoperative course due to wound complications, and received 26 Gy postoperative radiation 88 days after definitive surgery. Only in 1 of these patients with local failure was the resection margin positive. This positive margin was occasioned by a decision to spare the femoral nerve and vein in a patient with a large tumour of the anterior thigh, and the failure occurred within the irradiated field. This patient was treated with postoperative radiation to a total dose of 64 Gy.

1 further patient developed simultaneous regional nodal failure and distant metastases, but no local failure 61 months after

Table 2. Local failure at minimum of 24 months (median 48.5 months) related to margin status post-definitive surgery and radiation technique

	Pre-operative radiation only		Pre-operative radiation plus postoperative boost		Postoperative radiation	
	Margin positive	Margin negative	Margin positive	Margin negative	Margin positive	Margin negative
Local failure	0/1	0/13	0/3	1/22	1/6	1/17

Numbers refer to actual patient numbers.

surgery. 26 patients (42%) had evidence of systemic disease at the time of writing this paper. Systemic disease occurred between 5 to 60 months from date of surgery. An actuarial analysis of systemic relapse-free survival was carried out for tumours whose maximum diameter was less than 10 cm and tumours greater than 10 cm. The 1 patient who died of intercurrent disease was censored. As shown on Figure 1, logrank regression analysis showed a significant difference between the two groups, suggesting that size of tumour is a predictor of systemic relapse. At a minimum follow-up time of 24 months (median 48.49, range 24–79 months), 35 patients were alive with no evidence of disease, 7 were alive with disease, 19 had died of their disease, and 1 patient had died of another cause.

DISCUSSION

A previous retrospective review of all patients seen at our Radiation Oncology Clinic from 1976 to 1982, analysed 100 patients with soft tissue sarcoma of the extremity treated by a variety of surgeons in different hospitals [12]. We demonstrated local relapse in 50% of patients treated with resection with positive margins, despite aduvant radiotherapy, in contrast to only 8% of patients with negative microscopic margins. Independent review of the operative and pathology reports showed that only 52 of the 100 patients could be said to have negative margins after definitive surgery. The information in that report was relevant since it reflected the reality faced by a sarcoma specialist group when advising patients who had undergone surgical resection at other centres with limited experience in the management of sarcoma. The series reported in the current paper, although a selected series, demonstrates the excellent local control possible in patients undergoing all definitive treatment by an experienced musculoskeletal oncology group, and justifies early referral to such a unit. The local control rate of 95% at a minimum 24-month follow-up matches those of published radical amputation series [6, 13, 14] and fully validates the philosophy of excision of the sarcoma to attain negative margins, with the use of pre- or postoperative radiation to eradicate remaining microscopic disease. The presence of histological evidence of disease at the surgical margin was the only variable that significantly contributed to the risk of local relapse in analysis of the previously reported series [12], and this has led us to emphasise attainment of negative margins at definitive surgery.

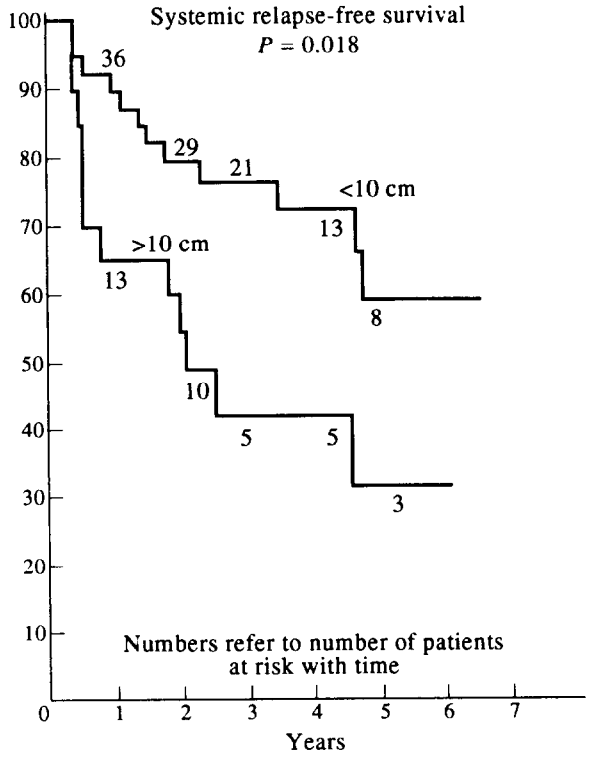

Figure 1. Systemic relapse-free survival.

Besides local control, the other primary aim of limb sparing treatment is to leave the patient with an asymptomatic and functional limb. Hence, while the surgery is planned to provide negative margins, this has to be balanced with the aim of good function. We have shown [15, 16], that functional outcome is affected primarily by tumour size, complications and neural sacrifice. Large tumours require resection of more normal functional tissue, complications hinder rehabilitation potential and neural sacrifice has a direct impact on outcome. Proximal tumours of the upper or lower extremity are associated more frequently with these three important variables. In a recent review of patients treated by our group, we found that large tumour size (>10 cm) and pre-operative radiation are associated with the risk of complications. We have also shown that the risk of complications may be decreased by the use of vascularised tissue transfer [17]. Barwick and colleagues have also reported successful use of vascularised tissue transfer for closure of irradiated wounds after soft tissue sarcoma resection [18]. There is good evidence that radiation can successfully eradicate minimal residual disease at moderate doses [2, 4, 5, 7–10]. In this series, 9 of the 62 patients had positive margins after definitive surgery. In 8 of these, maximal resection compatible with preservation of function was undertaken with the expectation that the surgical margin may well be microscopically positive or, at best, very close. The fact that only 1 of this group of patients failed locally supports the use of radiation as an adjunctive therapy to limb-sparing surgery, allowing limb preservation at a low risk of local recurrence. In the other 53 patients, pathological

assessment in the operating suite demonstrated negative margins in 52 of these patients. Simon and Enneking [1] showed that microscopic extensions of sarcoma perforate the pseudocapsule of the tumour with longitudinal extension along intermuscular and intramuscular fascial planes, and this is the probable explanation for the high recurrence rate following excisional biopsy alone. This series demonstrates that, with carefully planned surgery, negative margins can be achieved in most cases.

It is commonly stated that the volume of normal tissue radiated is less when the radiation is given pre-operatively as opposed to postoperatively. The reason is that, with pre-operative radiation, the field normally only includes the clinically and radiologically demonstrated sarcoma and expected patterns of spread, whereas postoperative radiation normally encompasses all tissues disturbed during surgery, for at least part of the radiation therapy course [2]. The surgical field necessary to excise large sarcomas frequently involves most of the limb circumference, and adequate adjuvant therapy requires that enormous fields are treated to a radical dose since microscopic residual tumour may be present anywhere in the surgical wound. Hence, late radiation damage to normal tissue is theoretically reduced with pre-operative radiation. We have shown quantitative data that confirm that pre-operative radiation therapy volumes are smaller than postoperative volumes [19]. Pre-operative radiation therapy is probably also advantageous since the radiation oncologist can plan the treatment field with the tumour *in situ*, rather than relying on the surgeon's description of what tissue planes were violated at surgery. Another advantage to pre-operative radiation is that the treatment volume prior to surgery is better vascularised and tumour cells better oxygenated than in the postoperative situation. It is a well-established principle of radiation oncology that treatment is less effective in hypoxic tissues. We have, therefore, developed a policy of pre-operative radiation for patients fulfilling the following criteria:

(1) bulky tumour more than 10 cm in diameter;
(2) uncertainty about the presence of a tumour-free plane between sarcoma and major neurovascular structures on staging CT/MRI scan;
(3) tumour location, where large-field postoperative radiation would be anticipated to involve a clinically significantly greater volume of sensitive organs (e.g. bowel).

In this series, local control was equally good for pre-operative and postoperative radiation although, as stated above, the selection criteria for pre-operative radiation means that the two groups are not comparable. Suit and colleagues [2] have reported a similar experience with the use of pre-operative and postoperative radiation at the Massachusetts General Hospital.

There are no clear guidelines as to the optimum dose of radiotherapy for soft tissue sarcoma of the extremity in the adjuvant setting. Suit and colleagues [2] recommended 64–66 Gy in 2-Gy fractions. In contrast, the EORTC Sarcoma Study Group recommend a dose of 50 Gy in 2 Gy fractions (Dr V. Bramwell, London, Ontario, Canada). Eilber treated patients with 3500 cGy in 10 fractions and with intra-arterial doxorubicin [4], and reported a local recurrence rate of 4%, but an unacceptably high complication rate. Reduction of the radiation dose to 1750 cGy did reduce the serious complication rate, but doubled the number of local recurrences [3].

Analysis of the interval between the last day of pre-operative radiation and the first day of the postoperative boost radiation in the 25 patients in our study, who completed both phases, showed a very wide range from 23 to 199 days, with a median of 66 days. Several institutions have reported diminished clinical efficacy with split-course radiation techniques [19, 20, 21]. Overgaard [20] found that an additional 20% total dose was required after a 3-week break in treatment in order to achieve a local control equivalent to that achieved with continuous irradiation in the treatment of squamous cell carcinoma of the larynx. Given the very long gap between the pre- and postoperative radiation in this series, plus the low dose of the boost (10–16 Gy), it can be postulated that this boost radiation may be wasted and contributes little to the overall treatment. Only 1 of these 25 patients failed as described above, and this patient can be said to have had an inadequate pre-operative radiation dose (40 Gy). It is interesting to note that, of the 14 patients in our series who received a total dose of 50–54 Gy, none have failed locally. We are now questioning the need for doses of 64–66 Gy in patients with negative margins. Reduction of the dose would produce less long-term radiation side-effects, and improve the cosmetic and functional results of the therapy [22].

The disappointing feature of the management of soft tissue sarcoma is the high incidence of systemic disease. Our incidence of 42% at 24 months is typical of other published series [3, 4, 5, 7, 8, 10] with similar numbers of large tumours. The risk of distant metastases appears to be correlated to tumour size. Suit [2] reported that size was an important prognostic factor for survival, which is directly related to the appearance of metastatic disease. In their series, patients with tumours less than 25 mm in size had a 92% 5-year survival, whereas those patients with tumours greater than 150 mm had a 26% 5-year survival. We were unable to correlate tumour grade with distant metastases, but the number of low-grade tumours in this series was small. The fact that 19 of the 62 patients died of systemic disease, and all but one with local control of the primary, highlights the great need for an effective systemic therapy for soft tissue sarcoma.

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The Effect of Clodronate on Bone in Metastatic Prostate Cancer. Histomorphometric Report of a Double-blind Randomised Placebo-controlled Study

T. Taube, T. Kylmälä, C. Lamberg-Allardt, T.L.J. Tammela and I. Elomaa

57 patients with advanced prostate cancer and a failure of prior hormonal treatment were selected for a double-blind placebo-controlled trial, in which they were randomly allocated to receive either clodronate (C) or placebo concomitantly with the basic cancer treatment, estramustine phosphate (E) (560 mg daily). The treatment was started intravenously with 300 mg of C or placebo in 5 consecutive days, and thereafter maintained orally with 1600 mg of C or identical placebo daily for 3 months. Bone biopsies were taken at admission and at 3 months. Measurements of serum calcium, phosphate, alkaline phosphatase, prostate-specific antigen and creatinine were made at the time of both bone biopsies and at 1 month. Serum intact parathyroid hormone and vitamin D metabolites were measured at admission and at 3 months. Because of several discontinuations, the study groups at final analysis comprised 20 patients taking E+C and 19 patients taking E and placebo. Bone resorption, as judged by eroded surface and osteoclast number, was markedly increased especially in biopsies taken from tumour-involved bone. Treatments with E+C or E both induced a significant decrease in bone resorption, but were associated with the development of hypocalcaemia, secondary hypoparathyroidism, hypophosphataemia and severe impairment of mineralisation of newly formed bone, i.e. osteomalacia. Since the patients were not vitamin D deficient, we conclude that osteomalacia resulted from a relative deficiency of calcium and phosphate. The transiency of pain relief achieved with anti-resorptive agents in the treatment of bone metastases from prostate cancer may be due to the development of osteomalacia.

Key words: clodronate, estramustine phosphate, bone resorption, osteomalacia, histomorphometry, prostate cancer, bone metastases
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INTRODUCTION

MORE THAN 90% of the skeletal metastases from prostate cancer are osteosclerotic in character [1, 2]. However, a number of histomorphometric studies have indicated that the high rate of osteoblastic bone formation within metastases is accompanied with markedly increased osteoclastic bone resorption, which may also be accelerated at tumour-free sites of the skeleton [3–5]. Bone disease in patients with metastatic prostate cancer is an important cause of morbidity. One of the major features is bone pain, which has recently been associated with increased bone resorption [6, 7].

Basic cancer treatment is directed to reduce tumour growth,