

Targeted radiotherapy with Sm-153-EDTMP in nine cases of canine primary bone tumours

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ABSTRACT

Nine dogs with primary bone tumours were treated with Samarium-153-EDTMP (Sm-153-EDTMP). Conventional treatment protocols were precluded by the size of the dogs and the owners' refusal of limb amputation. All the tumours were of the appendicular skeleton; 4 were confirmed osteosarcomas. The other 5 tumours were radiologically suspect for osteosarcoma. Bone scans were performed on all dogs using Technetium-99m-methylene diphosphonate (Tc-99m-MDP) before administration of Sm-153-EDTMP. Regions of interest were identified over the contralateral limb at the same site as the tumour and counts per pixel were recorded for the tumour and contralateral limb and expressed as a ratio. The dogs were given 1 injection of 37 MBq/kg (1 mCi/kg) of Sm-153-EDTMP intravenously. Thoracic and primary tumour site radiographs were taken at monthly or 2-monthly intervals to monitor progression of the primary tumour and search for evidence of metastasis. Two dogs showed no response to treatment, with an increase in bone pain, and were euthanased within 1 month. In 1 dog, a tumour of the scapula underwent complete involution and the dog is considered free of disease at 20 months post Sm-153-EDTMP treatment. The overall tumouricidal effect of a single dose of Sm-153-EDTMP on primary bone tumours was difficult to evaluate in this group of dogs, as, with one exception, all the primary tumours progressed over time and the dogs were euthanased. Pain control, for which Sm-155-EDTMP is used in man, was not evident, except in the dog that responded completely to treatment.

Key words: canine, osteosarcoma, radiotherapy, Sm-153-EDTMP.

Milner R J, Dormehl I, Louw W K A, Croft S **Targeted radiotherapy with Sm-153-EDTMP in nine cases of canine primary bone tumours.** *Journal of the South African Veterinary Association* (1998) 69(1): 12–17 (En.). Department of Medicine, Faculty of Veterinary Science, University of Pretoria, Private Bag X04, Onderstepoort, 0110 South Africa.

INTRODUCTION

Neoplasia of the skeleton occurs in numerous vertebrate species, although the dog has a higher incidence (6.5 in 100 000) than other domestic species and man^{20,23}. Primary skeletal neoplasia accounts for 80 % of these cases²⁵. Biphasic incidence of osteosarcoma occurs in large breeds of dogs, with a peak at 18–24 months and, in older dogs, a median of 7 years^{11,20,25}. Osteosarcoma in the dog has a predilection for the appendicular skeleton with the majority of tumours occurring in the metaphyseal area (75 %)^{11,25}.

Treatment of osteosarcoma in the dog involves a multi-modality approach. Amputation of the effected limb has been

reported to give a mean survival time of 19.8 weeks with 11.5 % alive at 1 year and 2 % at 2 years²¹. Currently the 'gold standard' appears to be amputation combined with cisplatin chemotherapy, resulting in a median survival rate of 46.4 weeks and a 1 or 2 year survival rate of 45.5 % and 20.9 % respectively². A recent article has reported similar survival rates using doxorubicin and surgery³.

There are, however, a large number of dogs in which amputation is precluded by various factors, for example the size of animal. Heidner *et al.*⁹ explored the use of cobalt 60 radiation and intra-arterial cisplatin without amputation. They reported a median survival time of 34.3 weeks, which rose to 46.9 weeks when dogs with metastases were excluded. Unfortunately this treatment option is not always available. Other treatment options include beta-emitting radio-isotopes coupled to bone-localising pharmaceuticals. To be effective, these isotopes and pharmaceuticals must fulfil certain requirements: minimum chemical

toxicity; half-life of medium duration (approximately 2–8 days) so as to provide optimum radio-biological effect; the radio pharmaceutical must have a high affinity for diseased bone in relation to normal bone; minimal deposition outside the skeleton and within bone marrow; and the mode of radioactive decay should be principally beta-particle emission so that the deposition of energy is concentrated in the immediate vicinity of a lesion¹³. Samarium-153-ethylenediaminetetramethylene phosphonic acid (Sm-153-EDTMP) fulfils these criteria. Samarium-153 is a medium-energy beta-emitting radio-isotope ($E_{\beta\text{max}} = 0.80$ MeV, $T = 46.8$ h) with a gamma photon (abundance 28 %, KeV 103) coupled to the diphosphonate EDTMP^{13,14}. Lattimer *et al.*¹² reported the use of Sm-153-EDTMP in canine bone tumours. Forty dogs were treated with a single intravenous dose of 37 MBq/kg (1 mCi/kg); 20 dogs received an additional intravenous dose 1 week later. The single dose was calculated to expose the neoplasm to approximately 40 Gy of radiation. The results were variable. Seven dogs were regarded as disease-free^d, 25 responded partially, and 8 did not respond. Those with a complete or prolonged response belonged to the single-dose group. The best response was noted in small lesions with minimal lysis, metastatic lesions and axial skeletal neoplasia. It is worth noting that Sm-153-EDTMP was not the only treatment administered in these cases.

Moe *et al.*¹⁹ described treatment of an osteosarcoma of the maxilla with Sm-153-EDTMP combined with surgical debulking of the mass. No local recurrence or metastases were evident 21 months post-surgery. Straw *et al.*²² reported the use of Sm-153-EDTMP in 2 dogs with mandibular osteosarcoma. One dog was lost to follow-up at 41 months. The other dog died of renal failure at 6.9 months, with recurrence of the tumour at the primary local site.

In humans, Sm-153-EDTMP is used

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Received: June 1997. Accepted: November 1997.

^dDogs surviving more than 11 months post-treatment and, at the time of the report, alive or dead from other causes, with no evidence of necropsy.

Table 1: Summary of 9 cases with naturally occurring canine osteosarcomas following treatment with Sm-153-EDTMP.

Case and breed	Age (yrs)	Mass (kg)	Sex	Site	TNM staging ^a	Primary tumour size ^b at Day 0 (cm)	Histopathology/Radiological appearance	T	NTC	T/NTC	Survival (months). Outcome
1 Rottweiler	8	44.4	F	Left proximal humerus	T ₂ M ₀	5 × 4 × 4	Not done / Limited to proximal metaphyseal region, increased opacity with mottled appearance, caudal thin brush-like periosteal reaction.	484	62	7.8	1 m. Euthanased, poor pain control.
2 Great Dane	7	57	F	Right distal radius	T ₂ M ₀	7 × 4 × 4.5	Not done / Metaphyseal region moth-eaten to permeative lysis, endosteal scalloping, destruction of cranial cortex, Codman's triangle.	2911	222	13.1	1 m. Euthanased, poor pain control.
3 Cross-breed	8	34	F	Right proximal humerus	T ₂ M ₀	5 × 3.5 × 3	Fibroblastic osteosarcoma / Destruction of cranial and caudal cortices metaphyseal region, proximal area sclerotic, distal area permeative lysis, periosteal reaction.	NR ^c	NR	NR	3 m. Euthanased, tumour progression, pathological fracture evident.
4 Rottweiler	6	51.55	M	Left distal radius	T ₂ M ₀	5 × 3 × 3	Fibroblastic osteosarcoma / Metaphysis geographic and moth-eaten lysis, Codman's triangle, endosteal scalloping, cortical destruction.	564	83	6.8	4 m. Euthanased, <i>post mortem</i> : multiple lung and spleen metastases.
5 Ridgeback	5	42	F	Left distal radius	T ₂ M ₀	5 × 2.5 × 2.5	Not done / Metaphysis geographic and moth-eaten lysis, Codman's triangle, endosteal scalloping, cortical destruction.	648	221	2.9	4 m. Euthanased, tumour progression.
6 Bull mastiff	5	42	F	Left proximal humerus	T ₂ M ₀	7 × 5 × 4	Fibroblastic osteosarcoma / Sclerotic changes in medullary cavity, destruction of proximal cortices, palisade periosteal reaction.	593	177	3.4	3 m. Euthanased, tumour progression, <i>post mortem</i> : no evidence of metastasis micro- and macroscopically.
7 Rottweiler cross	2	38.3	F	Right distal femur	T ₂ M ₀	7 × 3 × 3.5	Osteoblastic osteosarcoma / Metaphyseal region sclerotic changes, destruction of caudal cortices, solid periosteal reaction.	153	89	1.7	6 m. Amputation at 4 months due to tumour progression, euthanased at 6 months, multiple metastases present in lungs, heart, liver, kidneys, GIT, neck muscles.
8 Boxer	7.5	41	M	Right proximal humerus	T ₁ M ₀	7 × 3 × 3	Not done / Sclerosis in metaphysis with small areas of moth-eaten lysis.	618	219	2.8	7 m. Euthanased, tumour progression, metastasis evident in lungs and other body parts, as reported by private veterinarian.
9 Dalmatian	1.5	22.4	M	Right scapula	T ₂ M ₀	95 % scapula involvement	See Figs 1, 2.	1852	124	14.9	20 m. Alive, no evidence of metastases.

^aT₀ = no evidence of primary tumour; T₁ = tumour confined to within bone medulla/cortex; T₂ = tumour extending beyond periosteum; M₀ = no evidence of metastases; M₁ = distant metastases present.

^bThe sizes of primary tumours were taken from radiographs with the 1st measurement being the length of the tumour along the long axis of the bone followed at the maximum measurement in a cranio-caudal orientation followed by the lateral to medial (maximum) measurement (always at 90° to each other).

^cNR = not recorded.

extensively for palliation of bone pain caused by metastatic bone cancer¹. Bruland *et al.*⁴ recently reported good transient response to treatment of a human vertebral primary osteosarcoma with Sm-153-EDTMP.

Complications of Sm-153-EDTMP treatment are myelotoxicity^{1,12,13} and, in some cases, an increase in bone pain following treatment (flare response)^{1,14}. Myelotoxicity occurs 1 week after treatment and remains haematologically evident for 2–3 weeks^{12,13}. Renal toxicity does not appear to be significant, although Sm-153-EDTMP, like other diphosphonates, is cleared by the kidneys⁷. Acute radiation nephritis is considered to occur only after exposure to radiation of more than 10 Gy¹⁷. Lattimer *et al.*¹² did not report renal toxicity.

On the basis of the above reports, we

concluded that Sm-153-EDTMP might be of some benefit (pain control, tumourcidal effect) in dogs that could not undergo conventional therapies for bone tumours. The results of targeted radiotherapy in 9 dogs are reported.

MATERIALS AND METHODS

All dogs considered to be possible candidates underwent full clinical examinations. Radiographs were taken of the primary tumour site, as well as the following thoracic radiographs: left and right lateral, dorsoventral and ventrodorsal views. Only dogs free of radiological evidence of lung metastases and with signed consent of their owners were selected for treatment (*n* = 9). The mean age of the dogs was 5.56 years (SD ± 2.44) and mean weight 41.4 kg (SD ± 9.88). There was a bias towards heavier animals, as these dogs could not undergo amputa-

tion. The size of primary tumours were recorded from radiographs. The measurements were made sequentially as follows: length of the tumour along the long axis of the bone, maximum measurement in a cranio-caudal orientation, lateral to medial (maximum) measurement (always at 90° to the former measurement). The margins were defined as those areas showing abnormal bone changes associated with bone tumours. The cases were then staged using the TNM method for bone tumours¹⁰, where T₀ = no evidence of a primary tumour, T₁ = tumour confined to within bone medulla/cortex, T₂ = tumour extending beyond periosteum, M₀ = no evidence of metastases and M₁ = distant metastases present.

In all the dogs, the affected limb was lame and non-weight-bearing. Four dogs (see Table 1; Cases 3, 4, 6, 7) had osteosarcomas confirmed by biopsy or at

necropsy. The other 5 dogs had tumours considered to be radiographically typical for appendicular osteosarcoma (site, radiographical appearance, progression with metastases obvious at euthanasia) except case 9, which had a neoplasm of the scapula that was classified as an aggressive primary bone tumour involving the entire wing of the scapula. All dogs underwent an initial bone scan using technetium-99m-methylene diphosphonate (Tc-99m-MDP) (Atomic Energy Corporation of South Africa) as an indicator of tumour uptake by Sm-153-EDTMP to predict the likelihood of successful treatment¹². The intravenous dose of Tc-99m-MDP varied between 185 and 592 MBq depending on body weight. Three hours post-injection, light sedation was achieved using metomidine HCl (Domitor 1 mg/ml, Ciba) at 0.1 ml/10 kg and thiopentone sodium. Scanning was then immediately performed using a Siemens Orbital gamma camera (low energy collimator) (energy peak 140 keV, window 15 %). Two-minute acquisition times were used and the data captured in 64 × 64 word mode. For comparative purposes, a reference region of interest (ROI) was identified at the tumour site and at the same location on the contralateral limb. Counts per pixel were recorded for the tumour (T) and contralateral ROI (NTC = non-tumour counts) and calculated as a ratio (T/NTC) in Table 1. Results of Case 3's Tc-99m-MDP scan were not recorded, as these were lost.

Sm-153-EDTMP (Atomic Energy Corporation of South Africa) was administered to all 9 dogs 7 days later (for logistical reasons) at a dosage rate of 37 MBq/kg intravenously over a 30-second period via an indwelling catheter. The catheter was flushed after administration of Sm-153-EDTMP with 5 ml sterile saline solution to ensure complete administration of the calculated dose. All cases returned monthly or bimonthly for follow-up radiographs of the thorax and primary tumour site. The size of the primary tumour and evidence of metastases were recorded. Blood samples were collected from the cephalic vein in EDTA tubes (Becton Dickinson, Vacutainer Systems, Europe) for haematology after treatment with Sm-153-EDTMP in 2 dogs (Cases 6, 8) at 2 and 4 weeks post-treatment. Blood samples of the other 7 dogs were not taken for various reasons such as owner non-compliance, distance from the academic hospital, and cost of tests.

For ethical reasons all the dogs were dosed with 0.3 mg/kg of a non-steroidal anti-inflammatory substance, piroxicam (Feldene, Pfizer Laboratories), once every

2nd day, for pain control, and 2–5 µg/kg of misoprostil (Cytotec, G D Searle) twice a day to prevent gastric ulceration. These medications were administered for at least 14 days before radio-isotope treatment, to distinguish between pain control by piroxicam and by Sm-153-EDTMP. The owners were requested to monitor improvement in limb function over time, and to note other signs associated with pain, such as loss of appetite.

RESULTS

The results of the Tc-99m-MDP bone scan and other data are presented in Table 1. Clinical staging in all dogs except Case 8 identified single primary tumours not confined to the medulla and cortex with no evidence of metastasis, which were thus staged as T₂M₀. Case 8 was staged as T₁M₀, as the tumour was still confined to the medulla and cortex. All cases except 1, 2 and 9, which were euthanased within 1 month (1, 2), or underwent involution of the tumour (9), developed progressive enlargement of the primary tumour with time. However, in the tumours in Cases 7 and 8 more sclerotic bone was evident radiographically, and these tumours seemed to progress more slowly. Case 7, a female Rottweiler, underwent amputation (no chemotherapy) of the affected limb 4 months after treatment, owing to progressive enlargement of the tumour. At the time when surgery was performed no evidence of metastasis was present. Two months later she was admitted with widely disseminated metastases in most organs, including muscle tissue, and was euthanased. All other cases except Case 9 were eventually euthanased. Necropsies were performed on 3 dogs (Cases 4, 6, 7). Only Case 6 had no evidence of macro- or microscopic metastases.

Pain control was difficult to evaluate, since all dogs had advanced tumours of weight-bearing limbs and were lame. Case 9, which is considered to be disease-free at this stage¹², was the only exception. This dog responded rapidly to treatment, with good control of pain, within a 2-week period post-treatment.

Figures 1 and 2 are radiographs of the scapular tumour (Case 9) on initial presentation and 13 months post-treatment respectively. Figure 3 is a dorsoventral view of the Tc-99m-MDP study illustrating the extensive involvement of the right scapula. Figure 4 is a follow-up Tc-99m-MDP bone scan 13 months post-treatment.

Haematological findings in Cases 6 and 8 included leukopaenia and thrombocytopaenia at 2 weeks, with a return to

normal within 4 weeks. These findings are in agreement with reports in the literature on the effects of Sm-153-EDTMP on blood parameters^{12,13,19}.

DISCUSSION

All the dogs except Case 8 (Table 1) had tumours extending beyond the periosteum, which according to the report by Lattimer *et al.*¹² should be associated with a poor response to Sm-153-EDTMP treatment. Our findings, with the exception of 1 dog (Case 9), support this, as all these tumours progressed, resulting in euthanasia of the dog. After the Sm-153-EDTMP injection, the tumour of the scapula (Case 9) underwent rapid involution that was radiologically evident within 3 months. The right forelimb is fully functional and no metastatic lesions are evident to date (20 months post-treatment) in thoracic radiographs or whole body bone scan. Lattimer *et al.*¹² reported one case that also responded rapidly, with complete involution of the tumour. The tumour was reported to be a chondrosarcoma of the humerus. In a recent report of osteosarcomas of the scapula, high prevalence of metastasis was found, with a short overall survival time (17 weeks)⁸. Partial scapulectomy combined with cisplatin therapy of primary bone neoplasia involving the proximal half of the scapula has also been reported; most cases developed metastatic lesions²⁴. Case 9 is therefore unique, as the tumour involved the whole scapula (Fig. 1), and to date there is no evidence of primary tumour recurrence or metastases.

A relationship between radiographical appearance and uptake of Sm-153-EDTMP as reflected by the T/NTC ratio seems to suggest a higher ratio in tumours with more lytic (radiographic) lesions (Cases 1, 2, 3, 4, 5) than those with sclerotic changes (6, 7, 8). This might be explained by the fact that bone lysis is more indicative of an aggressive lesion that may have more reactive tissue and a greater blood supply and therefore accumulate more isotope^{6,18}. However, Lewington¹⁴ suggested that therapy will be more effective in predominantly sclerotic lesions with a brisk osteoblastic reaction than in more destructive lytic lesions. It is interesting to note that the 3 dogs (6, 7, 8) with radiological evidence of sclerosis had lower T/NTC ratios, but survived longer. Forrest *et al.*⁶ reported that a high pre-treatment count per pixel signifies an aggressive tumour subject to early metastasis, which may explain the poorer response in Cases 1, 2 and 3. The exception was the scapular tumour in Case 9, which showed the highest T/NTC ratio,

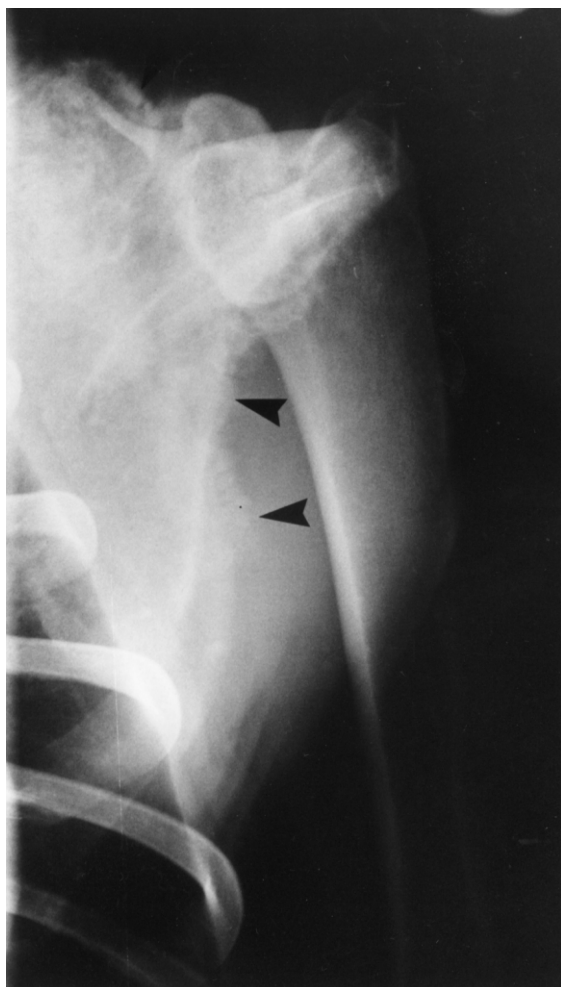


Fig. 1: Caudo-cranial oblique view of the right scapula of Case 9 at presentation. Standard view not possible. The arrows mark the thick brushlike periosteal reaction, with 90 % of the scapula showing extensive permeative lysis and multiple doughnut circles.



Fig. 2: Caudo-cranial view of the right scapula of Case 9, 13 months post-treatment. The radiograph shows a marked improvement with a radiologically virtually normal scapula.

but which underwent complete involution post-treatment.

Some dogs (Cases 1 and 2) experienced an increase in bone pain following injection of Sm-153-EDTMP. This is known in man as a flare response and is seen soon after administration of the radio-pharmaceutical (3 days)¹⁴. The response is thought to be due to radiation-induced endosseous oedema and is, ironically, regarded as a good prognostic sign since these patients reported dramatic pain relief subsequently¹⁴. Lewington¹⁴ reported that pain relief is independent of tumour radiosensitivity, and therefore one should be wary of interpreting control of pain as a reflection of the radio-isotope's tumouricidal effect.

The exact dose received by each tumour in this study is not known, but Lattimer *et al.*¹³ reported that when the lesion to normal bone ratio was 16:1, as determined by acute drill hole model, the dose delivered to the lesion was approximately

40 Gy (skeletal weight of the dog taken as 100 g/kg, where <1 % of the skeleton is involved). This is similar to the total dose used in external beam radiation of appendicular osteosarcoma; however, the dose was delivered in 10 fractions using a Monday, Wednesday and Friday protocol⁹. Only 2 of our dogs (Cases 2, 9) had T:NCT ratios approximating the reported ratio, 13.1 and 14.9 respectively, one of which (Case 9) is regarded as cured.

It is obvious that where the tumour is susceptible to the radiotherapy, as in Case 9, a single dose of 37 MBq/kg Sm-153-EDTMP was adequate to achieve remission of the tumour. However, in the other 8 dogs the results were poor.

It also appears that the diphosphonate, EDTMP, has pharmacological activity that may influence radio-pharmaceutical localisation in neoplastic tissue^{14,15}. Dormehl *et al.*⁵ found that repeated doses of Sm-153-EDTMP in the baboon led to progressively decreased uptake in normal

bone, and this is thought to be due to the blocking effect of the diphosphonate EDTMP.

CONCLUSION

While in this study the results obtained with Sm-153-EDTMP in spontaneously occurring canine osteosarcomas of the appendicular skeleton to control bone pain and/or tumour growth were spectacular in 1 dog, the overall results for the other 8 dogs were inconclusive, and further investigation is required. Evaluation of Sm-153-EDTMP combined with other treatment modalities, as reported by Moe *et al.*¹⁹, may hold more promise, as well as investigation into other beta-emitting radio-pharmaceuticals^{14,16}.

ACKNOWLEDGEMENTS

We thank the radiology section of the Onderstepoort Veterinary Academic Hospital for taking and processing the radiographs and dedicate this article to

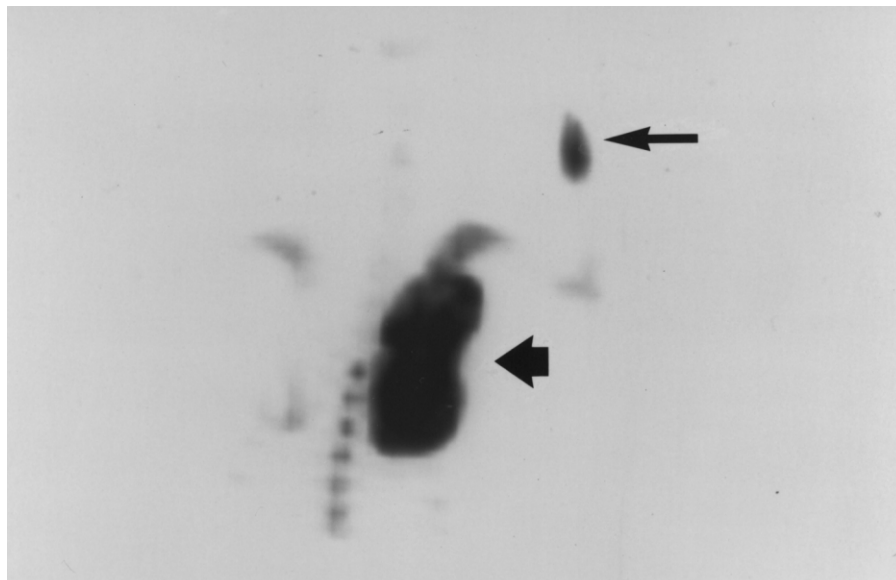


Fig. 3: Dorsoventral Tc-99m-MDP bone scan of Case 9 at presentation. The large arrow indicates very high up-take of the tracer by the tumour in the right scapula. The smaller arrow indicates skin contamination by the tracer at the intravenous injection site. The apparent difference in skeletal uptake between Figs 3 and 4 is due to the gamma camera computer display software, Sophi (Sophar, Meditech), normalising to the point of highest intensity.

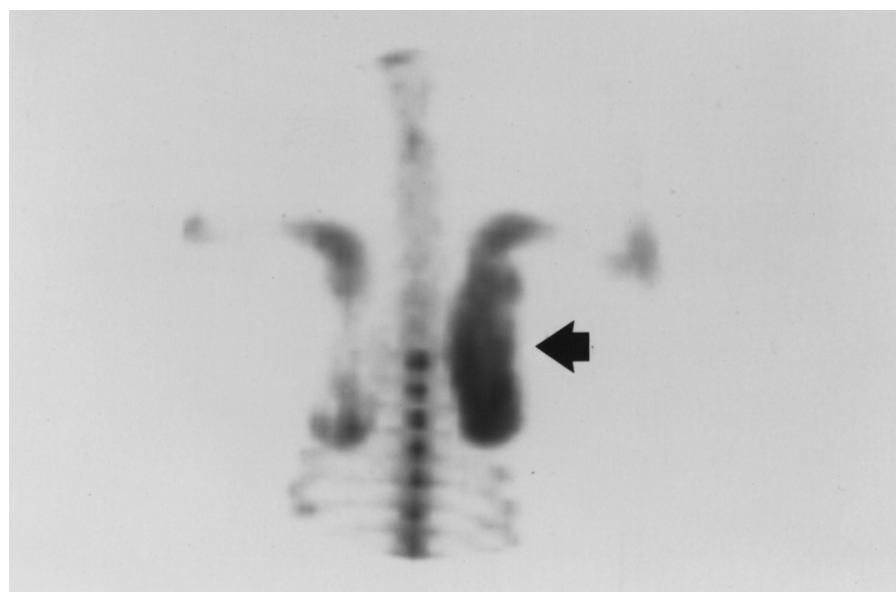


Fig. 4: Dorsoventral Tc-99m-MDP bone scan of Case 9, 13 months post-treatment. The arrow indicates reduced tracer uptake by the right scapula. The T/NTC ratio was 3.0:1 for the right scapula, which is almost a 5-fold decrease in uptake compared to the 1st scan. The right scapula nevertheless showed more up-take than the opposite scapula. This is a common finding in bone scans of old injuries.

the memory of Maria Jimenez who was part of that department. A special word of thanks is due to the following owners and their special dogs: N J Liebenberg (Jessica), E E K Jarvis (Zeus), L Lemmer (Umfubu), T L Pretorius (Chica), E Mobbs (Ascombe), H J du Plessis (Max), I van den Ende (Zack), A D Argyle (Cambel) and A W Hancock (Sheba).

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