Technetium-99m-MDP Scintigraphy and Long-Term Follow-Up of Treated Primary Malignant Bone Tumors

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Local malignant bone tumor excision followed by high-dose extracorporeal irradiation (300 Gy) and subsequent reimplantation is a unique technique for treatment of primary bone and cartilage tumors. The long-term scintigraphic findings of irradiated bone autografts in relation to clinical patient data were reviewed retrospectively. **Methods:** Thirty-seven patients (12 women, 25 men; age range 13.0–66.7 yr; average age 29.1 yr) were studied. Postsurgical anatomopathological diagnoses included osteosarcoma, 20 patients; chondrosarcoma, 7 patients; and other less-frequent primary osteogenic tumors, 10 patients. Three hundred ninety ^{99m}Tc-methylene diphosphonate (MDP) whole-body scans performed between 3 mo and 18.3 yr (mean 6.5 yr) after treatment were reviewed. **Results:** The 10-yr actuarial survival rate was 78%. After a mean period of 19.4 mo, 6 patients developed a local recurrence, and MDP scintigraphy detected the recurrence in 4. Distant metastases developed in 11 patients (30%), of which 10 were nonosseous. Initially, all autografts appeared as photon-deficient areas. Diffusely increased bone uptake was present at osteotomy sites and at articulating surfaces contiguous with autografts within the first few months after surgery. Of all 25 patients with adequate follow-up, 7 showed persistent decreased uptake up to 129 mo after surgery. The other patients developed partial tracer uptake after 19.6 mo, on average. In 6 patients, scintigraphic images consistent with complete revascularisation were noted later (mean 31.5 mo). Local, sometimes multiple, complications were noted in 22 patients, mainly mechanical graft-related (15) or infections (11). Scintigraphic sensitivity for mechanical complications was 100%. Significantly more fractures and collapses were seen when partial tracer uptake suggestive of revascularisation occurred. Altered bone stress gave rise to focal and diffuse scintigraphic abnormalities, often in the spine and lower extremities. In recent literature, similar clinical complication patterns are found for massive allografts. **Conclusion:** Skeletal scintigraphy is a sensitive technique for evaluating long-term follow-up of massive grafts to treat primary malignant bone tumors. Revascularisation and partial bone ingrowth are not sufficient conditions for a lower complication rate.

Key Words: primary bone tumors; extracorporeal irradiation; skeletal scintigraphy; complications

J Nucl Med 1998; 39:1563–1569

The development of adjuvant chemotherapy, preoperative radiation therapy and modern orthopedic appliances has reduced dramatically the use of primary amputation to treat malignant bone and cartilage tumors (*1,2,3*). Radical ablative surgery largely has been abandoned in favor of the limb-saving reconstructive techniques of an endoprosthesis, allograft or bridging (*1,2,3*). The Department of Orthopedic Surgery in Gent has opted for an alternative procedure, namely a wide en-bloc tumor excision, extracorporeal irradiation of the resected specimen with a uniform photon dose of 300 Gy in a short time interval of minutes and reimplantation of the autogeneic bone after removal of the soft tissues and the bulk of the tumor (*5*). This technique enables a biological reconstruction with a precise anatomical fit, avoids long-term endoprosthetic replacement problems such as fracture and loosening, shows distinct advantages over other autograft sterilization techniques, such as autoclaving, and avoids rejection and the need for organization and maintenance of an extensive bone bank for allografts (*5,6*).

As was shown by cell survival studies, this procedure kills all osteogenic and cancer cells (Uyttendaele D, personal communication, 1997). The autograft serves as a devitalized scaffold that is invaded by viable bone tissue with progressive substitution from peripheral adjacent bone. This creeping substitution involves neovascularisation of the graft, resorption and removal of the graft bone and deposition of new host bone on the graft matrix (*7*). It must take place from the ends to the center and inward from the cortical edge for long bones (*8*).

Technetium-99m bone scintigraphy is dependent on both the vascular supply and a living network of osteocytes. For malignant bone tumors, it has proven a useful method for assessing the primary lesion, although MRI provides more detailed local anatomical information (*9*). Bone scintigraphy is well recognized for detecting osseous recurrences and metastases at an early stage (*10*).

Bone scintigraphy was used originally for evaluating new bone growth after surgical implantation of bone grafts because of the considerable time delay required after the surgery before radiographs could provide useful information. For small vascularized grafts, it provides a means of predicting graft failure before radiographic or clinical changes become apparent, and it helps avoid loss of surrounding tissues from graft necrosis and infection (*11*). It is more sensitive than radiographs, CT or MRI in monitoring the revascularization process, and it can be used when MRI cannot be used due to ferromagnetic effects in composite implants (*12*). Data on the long-term aspects and scintigraphic appearance of massive nonviable grafts are scarce and only few studies with a limited number of patients have been published on this subject (*7,13*).

Although the results of both allo- and autografting have been encouraging, recent literature reports that mechanical and infectious complications remain common (*1,2,14*). These complications may have repercussions on the follow-up scintigraphic image, which is important in the differential diagnosis between recurrences and normal graft incorporation.

We have tried to characterize the long-term scintigraphic findings of a series of irradiated bone autografts for malignant bone tumor treatment in the context of clinical patient data. This

Received Aug. 29, 1997; revision accepted Dec. 24, 1997.
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TABLE 1
Tumor Classification by Anatomopathological Diagnosis

Type	Number of patients	%
Osteosarcoma	20	54.1
Chondrosarcoma	7	18.9
Ewing's sarcoma	2	5.4
Fibrosarcoma	2	5.4
Histiocytoma	2	5.4
Hemangioendothelioma	1	2.7
Osteoclastoma	1	2.7
Recurrent chondroblastoma	1	2.7
Non-Hodgkin's lymphoma	1	2.7
Total	37	100

TABLE 2
Anatomical Location of Studied Tumors

Location	Number of patients	%
Femur (proximal and distal)	17	45.9
Pelvic rim	8	21.6
Tibia (proximal)	4	10.8
Humerus	3	8.1
Fibula	2	5.4
Radius	1	2.7
Ulna	1	2.7
Scapula	1	2.7
Total	37	100

combined information should be helpful for determining the role of nuclear medicine bone scintigraphy in monitoring patients for local tumor recurrence, predicting graft outcome and evaluating mechanical and infectious complications related to limb-salvage procedures.

MATERIALS AND METHODS

Patients

Forty-nine patients with bone and cartilage tumors were treated by en-bloc resection, extracorporeal irradiation and reimplantation of the irradiated bone from January 1979 to December 1996. The scintigraphic follow-up was reviewed retrospectively for 37 patients (12 women, 25 men; age range 13.0–66.7 yr; average age 29.1 yr) who underwent the procedures at our department.

Operative Procedure and Postoperative Management

Preoperatively, imaging modalities available at the time of surgery (including radiography, CT, MRI and skeletal scintigraphy) were used to determine the anatomical tumor extension and staging. No patient with evidence of metastatic disease was electable for treatment.

The tumor was either resected marginally or with wide margins and removed from the patient en-bloc (*5*). The extracorporeal irradiation was performed at the nearby high-intensity linear electron accelerator of the Department for Subatomic and Radiation Physics of Gent University. The autografts were transported and irradiated to 300 Gy with a flattened 10-MeV bremsstrahlung photon beam at a dose rate of 1 Gy/s uniform within 10% in a 25 × 25 cm^2 field (*15*). The grafts were transported back to the surgery ward in less than 1 hr and reimplanted in loco. A composite prosthesis consisting of the autograft together with an artificial endoprosthesis was placed in five patients because of the tumor location and extent. In some cases, autologous cancellous bone from the iliac crest was used to fill remaining defects after tumor excision.

All patients with preoperatively suspected osteosarcoma, Ewing's sarcoma or other soft-tissue sarcoma received both pre- and postoperative high-dose chemotherapy.

Postoperatively, immobilization in plaster or in an orthosis device was continued until there was radiographic evidence of bony union. For tumors of the lower limb, weight bearing was prohibited for 1 yr.

Postsurgical Anatomopathological Diagnoses

For all patients with scintigraphic follow-up, the postsurgical anatomopathological diagnoses are summarized in Table 1. Osteosarcoma and chondrosarcoma made up the majority (73%) of the tumors present. One patient with postoperative histological diagnosis of non-Hodgkin's lymphoma was treated by this technique even though he had been diagnosed preoperatively with liposarcoma.

Anatomical Tumor Localization

The anatomical localization of the grafted bones is shown in Table 2. This frequency distribution reflects the fact that the knee (distal femur/proximal tibia) is the major predestination site for osteosarcoma. For extremity bone grafts, in almost all cases, large autografts at least 5 cm in length had to be used.

Technetium-99m-MDP Imaging

A total of 390 postoperative whole-body ^{99m}Tc-methylene diphosponate (MDP) scans were reviewed that were acquired 3 mo–18.6 yr after surgery (average follow-up time 6.5 yr). The number of follow-up scans ranged between 1 and 27 (average 11). During the first year after surgery, bone scintigraphy was performed every few months for most patients and at prolonged intervals afterward. The injected dose of ^{99m}Tc-MDP (depending on the scan year, manufactured by Medgenix Diagnostics, Fleurus, Belgium; Mallinckrodt, Petten, The Netherlands or Salco Basel, Birsfelden, Switzerland) remained constant to 11.1 MBq/kg. Standard whole-body scans and local relevant images were obtained 3–6 hr postinjection with a single- or dual-head gamma camera and a low-energy, all-purpose collimator.

Data Analysis

The postoperative scintigraphic appearance of the autograft, contiguous native bone (osteotomy sites, articulating surfaces), orthopedic artificial materials and other skeletal structures apart from the autograft were analyzed. Clinical and other radiological data were compared to confirm observations of suspected recurrences, metastases and mechanical or infectious complications.

To evaluate new bone cell incorporation in the autograft, uptake pattern versus the contralateral side was noted. Scoring of autograft incorporation was done according to the following four-step ranking: decreased uptake, when the autograft remained relatively photon deficient; partial uptake, when focal or localized diffuse tracer uptake took place; and global diffuse graft uptake, different from and comparable to the contralateral side. Patients were reviewed only until a local recurrence took place or until local complications occurred for which renewed major orthopedic surgery resulted, which altered graft appearance or existence. Three independent investigators, by consensus, reviewed the full range of images.

Descriptive statistics and frequency-distribution tables were applied to analyze the data using SPSS Version 7.0 (SPSS, Inc., Heverlee, Belgium). Where appropriate, Fisher's exact test and the chi-square test were used to evaluate the significance of differences. The Mann-Whitney test was used to relate lesion grading and age-groups to other parameters. Differences between groups were regarded as significant for $p < 0.05$.

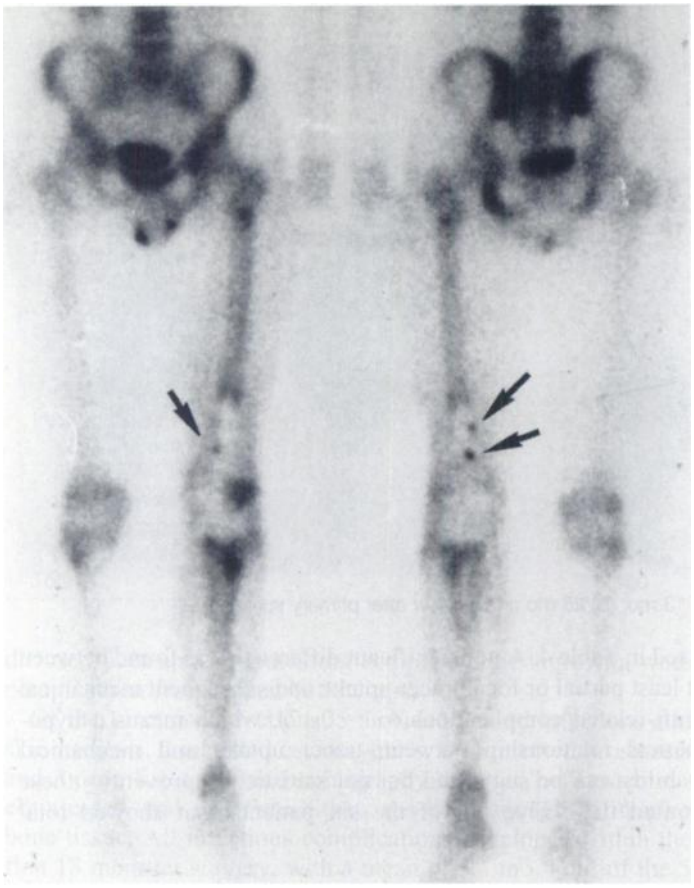

FIGURE 1. Scintigraphic image consistent with multiple recurrence foci (arrows) of osteosarcoma of distal femur.

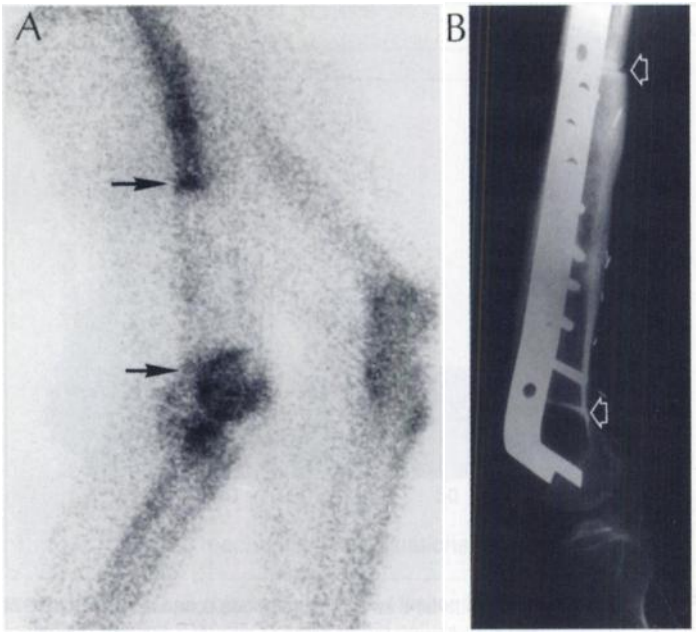

FIGURE 2. (A) Focal hyperactivity at osteotomy sites remaining 1 yr after operation as viewed by lateral scintigrams (closed arrows). (B) Corresponding radiographic image shown for comparison (open arrows indicate osteotomy sites).

RESULTS

Oncological Results

The average age of patients suffering from osteosarcoma was significantly lower than in the other groups ($p = 0.001$) at 20.5 yr for the osteosarcoma group, versus 45.4 yr for chondrosarcoma group and 34.7 yr for the patients with other tumors.

During the reviewed period, four patients (11%) failed to complete follow-up. Seven other patients (19%) died during follow-up after a mean period of 28.9 mo (range 7.1–57 mo). The estimated survival rate after 10 yr for this patient group was 78%.

Local recurrence was seen in six patients (16%) after an average period of 19.4 mo (range 3.2–47 mo). No significant relationship was found between the existence of recurrence and age ($p = 0.88$), major anatomopathological division ($p = 0.23$) or anatomical tumor site ($p = 0.71$). Four recurrences were detected on the bone scan and showed marked focal hyperactivity. Another recurrence involved a nonosseous extension to the ipsilateral psoas muscle and, in the sixth patient, bladder activity interfered with the site of the lesion at the symphysis. Four of these recurrences resulted in subsequent surgery with amputation, and one patient was referred to radiotherapy while the other one was treated palliatively as concurrent metastases were found. An example of the scintigraphic appearance of a recurrence is shown in Figure 1.

Distant metastasis occurred in 11 (30%) patients. Most of them were nonosseous [including the lung in 6 patients (16%)]. One involved the calvary and was detected by bone scintigraphy. None of the lung metastases from these osteogenic tumors was detectable by MDP scintigraphy in our series. Metastases were related to previous or concurrent tumor recurrence ($p = 0.03$). No significant correlation was found between metastasis and tumor type ($p = 0.99$) or age ($p = 0.26$).

Scintigraphic Data

In 18 patients, a bone scan was available within the first 4 mo. In this initial follow-up phase, all of these showed a clear decreased uptake of the large autograft. During these first months, a focal hyperactivity at the osteotomy sites developed in all extremity bones but not in the pelvic bones.

After the initial ingrowth at the proximal and distal osteotomy site, gradually a surface rim delineating the cortex of the autograft became apparent in 14 (61%) of the 23 patients for whom scans were available and interpretable (e.g., graft size large enough) within the first 6 mo after surgery. This rim appeared after an average of 5.6 mo (range 0.4–17 mo).

Figure 2 shows an example of prolonged hyperactivity at the osteotomy sites of a femoral graft. There is a gradually appearing rim present, while corresponding radiographs show signs of union.

To determine further ingrowth in the graft, only those patients with available follow-up scans over 1 yr before their case history terminated (e.g., due to loss of follow-up or death) or before a major graft complication altering the anatomical constitution took place (e.g., reoperation with prosthesis implant due to mechanical complications) were considered. Patients with combined prosthesis implants that made further ingrowth evaluation impossible to interpret were excluded also. Such follow-up scans were accessible for 25 patients.

Over time, a partial tracer uptake was observed, focal or diffuse, reflecting active bone metabolism in subsegments of the graft. Partial uptake was seen in 18 (72%) of the 25 patients and occurred after an average of 19.6 mo (range 1.7–62 mo).

Of these patients with a partial uptake, only six (24%) developed a global diffuse uptake at a later stage indicating a completely revascularized graft (three upper and three lower limb locations). The average period, therefore, was 31.4 mo (range 16–65 mo). Diffuse homogeneous uptake did not always have the same intensity as the contralateral side possibly due to perfusion differences and asymmetrical metabolic activity. Bilateral visually identical intensity occurred in only three

malignant bone lesions and muskuloskeletal tumors has been the possibility of predicting multidrug resistance (*19*).

Local recurrence is an important consideration when comparing this operative technique with radical desarticulation or amputation. The risk of local recurrence can be minimized by careful preoperative planning and staging of the disease, as well as by the use of intensive chemotherapy. Local recurrence rates after amputation and limb-sparing surgery are comparable, ranging between 5% for osteosarcoma of the extremities up to 17% for pelvic tumors, with higher recurrence rates in patients with positive microscopic resection margins (*20*). These recent numbers correspond well to the 16% local recurrences found in our series. Recent data also affirm that the majority of recurrences take place within 24 mo of attempted tumor excision (*20*).

Although bone scintigraphy is a sensitive means for detecting local recurrence of malignant tumors after amputation or resection (*10*), other causes of focally increased tracer uptake should be differentiated such as normal bone ingrowth or mechanical complications. In tumors of the pelvic rim, bladder activity may cause false results. SPECT and special planar incidences such as the tail-on-detector (TOD) view allow visualization of bone structures without overlapping bladder activity. This can improve the detection efficiency of recurrences, although intrinsic bladder artifacts still are to be taken into consideration (*21,22*).

Long-term monitoring of bone grafts used in reconstructive surgery can be a problem. For massive allografts used in tumor limb-salvage surgery, radiographic signs of new bone formation begin to appear at the osteosynthesis site 3–4 mo after transplantation. In most cases for comparable allograft localization and massive sizes, the average time for radiographic union was 6–24 mo (range up to 3 yr) (*3,23*), comparable to 6–12 mo for our autografts reported earlier (*14*). Scintigraphic findings are known to occur 3–6 wk before skeletal radiography and reliably indicate incorporation and/or remodeling at the osteotomy sites (*24*). Focally well-defined activity at the osteotomy junction of a large graft and normal bone most often represents normal healing or normal stress remodeling changes and not recurrent tumor or loosening. This increased uptake can subsist for years after surgery, as is also the case for allografts (*6,7*).

Concerning the scintigraphic appearance of bone incorporation, our findings are in disagreement with earlier short reports on allograft scintigraphy by Smith et al. (*7*) and Bar-Sever et al. (*13*) who both stated that large allograft reconstruction scintigraphic findings in the absence of complications are stable over time. Their results were based on 6 and 20 patients, respectively, with limited follow-up (average 2.2 yr and maximum 5.7 yr, respectively). Recent orthopedic reviews for allografts show proof of normalization after many years (*25*) and, thus, support an evolution like we describe.

The fact that evolution to diffuse and homogeneous radiotracer uptake is not the common feature for all patients in our study is in accordance also with reports of combined allograft radiological and nuclear medicine imaging studies with histological biopsies indicating that the incorporation, perfusion and replacement with new bone is only partial and of a low degree (*3*). Histological samples of bone taken at reoperation 1 yr or later in our hospital also have shown that there is partial replacement by new bone and fresh fibrous tissue but that a framework of dead bone is present also (*5*).

Resorption-apposition activity takes place predominantly in the subperiostal areas. The absence of periostal growth stimulus may be a contributing factor for why some autografts showed a permanent hypoactivity in our study. Part of this discrepancy also may be accounted for by a difference in follow-up time in this subpopulation (average 43 mo versus 107 mo in the other group; $p = 0.009$).

It has been postulated that graft ingrowth by normal bone tissue might weaken the graft's functionality (*3,25*). A low-degree metabolism might result in a high risk of structural complications such as fatigue fractures or collapse (*3*). Although there is no demonstrable change in the initial mechanical properties of dead bone, outer and inner graft resorption increases the porosity and impairs its mechanical properties (*26*). This finding may explain our observations of a relatively larger mechanical complication rate for grafts showing scintigraphic signs of revascularization compared to grafts showing either none or a decreased tracer uptake. Fractures thus may be related to rapid revascularization in the subchondral bone with resultant resorption leading to weakness.

A 300-Gy dose is sufficient to destroy all osteogenic and tumor cells, but it is unlikely to cause deterioration in the biological osteoinductive and osteoconductive properties of the autologous matrix. In laboratory experiments with radiation-sterilized allografts, a delay in healing and a reduction in breaking strength was found only from 25 kGy onward (*6*). Recent clinical data even suggest that such high-dose allograft irradiation is unlikely to jeopardize the clinical outcome (*27*).

In assessing the long-term orthopedic results and the ultimate limb function years after surgery, graft complications remained a major problem. The overall complication rate in our study (59%) is comparable to recent literature on large nonvascularized allografts where frequencies ranging from 42% to 70% are reported (*1,6,23*). Even vascularized grafting shows a complication rate of 48% (*28*). In massive arthroplasty, loosening and material breakage become more likely in the longer term, while also the main complications for allografting are seen in the first few years after surgery (*29*), which confirms our findings.

Fractures and collapses are likely to occur in the lower extremities at hardware insertions that act as stress risers (*23*). These tend to occur 18–36 mo after implantation (*25*). Fracture incidences between 11% and 45% have been reported for allografts (*3,23*) comparable to 21% for fractures or collapses that occurred in this study.

Also for allografts, a significant majority (82%) of fractures and hardware problems occur in young male patients (*23*) compared to 91% for this study. Their activities probably should be abridged for longer periods or large customized implants with strong intramedullary stems should be used. Although children and adolescents could have greater potential for repair and complete incorporation (*7*), we did not find any significant relationship between the time at which partial or diffuse uptake took place and the patient's age at the time of the operation.

Due to the relatively high complication rate for knee and hip autografts, such extracorporeal irradiation autografting largely has been abandoned in favor of immediate replacement with an endoprosthesis. The technique remains useful, however, for other localizations since standardized prostheses are not available always and, in the long-term, prostheses show a higher and increasing complication rate.

Infections were relatively frequent in our series (30%), but this can be expected in these long, and sometimes difficult interventions. Overall infection rates vary between 7% and 30% for comparable allografts (*1,3,23*). The temporal course of such infections also agrees with a previous article (*30*), where values up to 70% during the first month after initial surgery were reported. Both infection and recurrence are known to have a negative effect on outcome in terms of limb survival (*1*).

From the scintigraphic point of view, interpretation problems can arise in cases where sudden focal uptake is seen. Whereas both diffuse normometabolic status and persistent hypoactivity are associated with a low complication probability, intermediary focal or partial uptake may indicate both physiological and pathological effects such as the ingrowth of adjacent bone, a pending fracture, collapse or recurrence. Additional clinical investigation and radiological imaging remain necessary once suspicious unexpectedly intense lesions have been found on a bone scan.

The nuclear medicine physician should be aware of several other pitfalls in the scintigraphic evaluation of large bone grafts such as the autologous graft from the iliac crest that is used to fill up small defects (*31*). Graft fixation, achieved mainly by a combination of an intramedullary rod or nail with a plate and screws, complicates bone scan readings in the absence of radiographic comparison. Also in the case of complex grafting, image fusion modalities might allow better decision making.

Increased bone metabolism distant from the original tumor site frequently occurs, but it is not always clinically significant. Primarily, in the absence of arguments for metastatic disease, such scintigraphic findings can be attributed to altered and increased mechanical stress with possible overuse of the contralateral limb. This again should alert the clinician, at an early stage, to investigate closely these cases of associated symptoms.

CONCLUSION

The improved efficiency of therapy for malignant primary bone tumors has elevated survival rates and has enabled routine serial bone scintigraphy to become an important tool for evaluating disease follow-up. We have shown that for patient monitoring, bone scintigraphy remains a valuable aid. Apart from local recurrence and a major role in detecting metastasis, we have shown that, for limb salvage surgery, the ingrowth of autografts (and by consequence also allografts) can be reliably monitored to indicate mechanical complications at an early stage. More fractures and collapses are seen when revascularization occurs, indicating revascularization is not a good prognostic factor for clinical outcome. Patients who show increased focal tracer uptake at the localization of their graft may be a subgroup prone to complications or may undergo inward remodeling. Any new foci of activity that develop, especially when associated with pain or other clinical symptoms, should prompt further evaluation and more frequent temporal follow-ups.

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