ONCOLOGY

Intercalary diaphyseal endoprosthetic reconstruction for malignant tibial bone tumours


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The best method of reconstruction after resection of malignant tumours of the tibial diaphysis is unknown. In the absence of any long-term studies analysing the results of intercalary endoprosthetic replacement, we present a retrospective review of 18 patients who underwent limb salvage using a tibial diaphyseal endoprosthetic replacement following excision of a malignant bone tumour. There were ten men and eight women with a mean age of 42.5 years (16 to 76). Mean follow-up was 58.5 months (20 to 141) for all patients and 69.3 months (20 to 141) for the 12 patients still alive. Cumulative patient survival was 59% (95% confidence interval (CI) 32 to 84) at five years. Implant survival was 63% (95% CI 35 to 90) at ten years. Four patients required revision to a proximal tibial replacement at a mean follow-up of 29 months (10 to 54). Complications included metastases in five patients, aseptic loosening in four, peri-prosthetic fracture in two, infection in one and local recurrence in one. The mean Musculoskeletal Tumor Society score and the mean Toronto Extremity Salvage Score were 23 (17 to 28) and 74% (53 to 91), respectively.

Although rates of complication and revision were high, custom-made tibial diaphyseal replacement following resection of malignant bone tumours enables early return to function and provides an attractive alternative to other surgical options, without apparent compromise of patient survival.

Primary sarcoma of bone occurs more commonly in the metaphysis of long bones than in the diaphysis. In young patients a malignant diaphyseal lesion is most likely to be Ewing's sarcoma, osteosarcoma or adamantinoma, while in older patients metastatic lesions, myeloma and lymphoma are more common. Limb salvage has replaced amputation as the primary local treatment for these lesions, owing largely to improvements in chemotheraphy, imaging and reconstructive techniques which have made this possible without adversely affecting survival. Although rates of complication and revision were high, custom-made tibial diaphyseal replacement following resection of malignant bone tumours enables early return to function and provides an attractive alternative to other surgical options, without apparent compromise of patient survival.

Autografts provide a biological means of reconstruction for short-segment defects. Their use is limited by graft availability, donor site morbidity and difficulty in matching the size of the graft to the defect. Allografts can be used to reconstruct both small and large defects by more accurately matching the size of the graft to the defect. Their use is associated with high rates of fracture (19% to 42%), nonunion (30% to 63%) and infection (18.5% to 30%) following intercalary replacement.

Femoral diaphyseal replacements have demonstrated acceptable long-term survival and functional outcome following resection of malignant bone tumours, but many consider allografts to be the preferred reconstructive option in the tibia. Endoprostheses avoid the risk of disease transmission and allow early weight-bearing. Fixation is not affected by adjuvant chemotherapy and radiotherapy, which have an inhibitory affect on bone healing.

The aim of this study was to evaluate the functional and oncological outcome of tibial reconstruction using a custom-made intercalary
diaphyseal endoprosthesis after primary excision of a malignant bone tumour, and to compare the results with those reported in the literature following allograft reconstruction.

Patients and Methods
All the patients in this study had been referred to a specialist bone tumour unit between May 1998 and November 2008, and were operated on by the senior authors (TWRB, SRC, RCP, JAS). There were 19 patients with malignant tumours of the tibial diaphysis who were treated by excision and endoprosthetic reconstruction using a custom-made intercalary tibial diaphyseal replacement. One patient was lost to follow-up; the remaining 18 were reviewed retrospectively. There were ten men and eight women, with a mean age of 42.5 years (16 to 76). Ethical approval was not required for this retrospective audit.

Indications for implantation included a diaphyseal tumour to be managed by limb salvage, allowing normal joint function above and below the lesion. Contraindications included active sepsis; the presence of metaphyseal or joint involvement that would compromise excision margins; invasion of the neurovascular bundle; or when resection of the tumour would leave inadequate muscle to allow function. Data were collected from case notes, hospital databases, clinic reviews, imaging studies and functional questionnaires. Histological confirmation of the diagnosis was obtained by 11 percutaneous and seven open biopsies. Osteosarcoma was identified in five patients, malignant fibrous histiocytoma in four, Ewing's sarcoma in two, adamantinoma in two, spindle cell sarcoma in two, chondrosarcoma in one, pathological fracture through aggressive osseous fibrous dysplasia in one, and a solitary metastatic deposit from renal cell carcinoma in one (Table I). Preoperative staging included plain radiographs and MRI of the limb, technetium (99Tc) body scintigraphy and chest CT. Chemo- and radiotherapy were administered according to nationally agreed protocols.

Prosthesis. All patients received a custom-made prosthesis (Stanmore Implants Worldwide Ltd, Stanmore, United Kingdom) made of titanium alloy (Ti6Al4V). The implant is manufactured using special software employing computer-aided design and manufacturing technology (CAD-CAM) (Fig. 1). The shaft is made of two parts, which are connected together intra-operatively using two bolts (Fig. 2).

### Table I. Demographics and outcome of the 18 patients treated with tibial diaphyseal endoprosthetic replacement

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age (yrs)</th>
<th>Diagnosis*</th>
<th>Radiotherapy</th>
<th>Chemotherapy</th>
<th>Pre-op metastases</th>
<th>Patient status</th>
<th>Complications†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>39</td>
<td>MFH</td>
<td>Y</td>
<td>Y</td>
<td>Y - lung</td>
<td>Dead</td>
<td>Deep infection: implant revised to PTR</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>33</td>
<td>Recurrent adamantinoma</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Alive</td>
<td>Revision of fibular hardware</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>32</td>
<td>Osteosarcoma, pathological fracture</td>
<td>N</td>
<td>Y</td>
<td>Y - lung</td>
<td>Alive</td>
<td>ASL proximal stem: implant revised to PTR</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>75</td>
<td>MFH</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Dead</td>
<td>ASL proximal stem: implant recemented</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>24</td>
<td>MFH</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Alive</td>
<td>Metastases: capitate</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>49</td>
<td>Solitary renal cell carcinoma metastasis</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Alive</td>
<td>Metastases: scapula</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>70</td>
<td>Spindle-cell sarcoma</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Alive</td>
<td>Local recurrence: AKA</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>76</td>
<td>Spindle-cell sarcoma</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Dead</td>
<td>Metastases: lung</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>49</td>
<td>Recurrent osteosarcoma</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Dead</td>
<td>Peri-prosthetic fracture: implant revised to PTR</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>34</td>
<td>Ewing's sarcoma</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Alive</td>
<td>Metastases: lung</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>18</td>
<td>Osteosarcoma</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Alive</td>
<td>Ankle pain: required diastasis screw</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>36</td>
<td>MFH</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Alive</td>
<td>Common peroneal nerve sacrifice with tumour resection</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>16</td>
<td>Osteosarcoma</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Dead</td>
<td>Metastases: lung</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>48</td>
<td>Osteosarcoma</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Alive</td>
<td>Peri-prosthetic fracture: implant revised to PTR</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>62</td>
<td>OFD, pathological fracture</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Alive</td>
<td>Metastases: lung</td>
</tr>
<tr>
<td>16</td>
<td>F</td>
<td>39</td>
<td>Adamantinoma, pathological fracture</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Alive</td>
<td>Metastases: lung</td>
</tr>
<tr>
<td>17</td>
<td>M</td>
<td>42</td>
<td>Recurrent chondrosarcoma</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Alive</td>
<td>ASL proximal stem: implant recemented</td>
</tr>
<tr>
<td>18</td>
<td>M</td>
<td>23</td>
<td>Ewing's sarcoma</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Alive</td>
<td>Knee pain</td>
</tr>
</tbody>
</table>

* MFH, malignant fibrous histiocytoma; OFD, osteofibrous dysplasia
† PTR, proximal tibial replacement; CRPS, chronic regional pain syndrome; OA, osteoarthritis; ASL, aseptic loosening; AKA, above-knee amputation
Each end has a fluted intramedullary stem, which is cemented into the corresponding canal. The diameter of the stem varies depending on the segment of bone into which the prosthesis is implanted. Wider stems are used for implantation into metaphyseal bone (>10 mm) than for diaphyseal bone (<10 mm). All prostheses in the study, apart from the first one, incorporated a hydroxyapatite (HA) collar. This allows bony ingrowth and osseointegration at the bone-prosthesis junction to enhance fixation. Fixation may be further enhanced by the use of extracortical plates when short-segment intramedullary fixation is <4 cm. There is also the option of incorporating an extendible mechanism into the prosthesis to enable leg-length equality to be restored post-operatively.

Surgical technique. Anaesthesia varied with the medical status of the patient. With the patient supine, an anteromedial tibial incision is made from the tibial tubercle proximally to the medial malleolus distally, incorporating the biopsy tract. Tumour resection is carried out according to the principles defined by Enneking, Spanier and Goodman, endeavouring to achieve wide excision without violating the tumour. Proximal and distal imprints are taken and the specimen is sent for histological examination. The proximal and distal tibial intramedullary canals are reamed, and after adjusting for alignment and rotation the proximal and distal stems are cemented in (the cement used varied with the date of the operation). The aim is to achieve a 2 mm cement mantle around the stem in the metaphysis, which is not possible in the diaphysis owing to the narrowness of the canal relative to the width of the stem. Proximal and distal segments are reduced in situ and connected together using two locking bolts. A medial gastrocnemius muscle flap was required in six patients to cover the anterior surface of the prosthesis. In situations where tumour resection requires sacrifice of the tibial tubercle or the distal patellar tendon, a medial gastrocnemius flap is used to reconstruct the extensor mechanism, with the patellar tendon sutured to it. Intravenous cefuroxime was given on induction and continued for three days. Active physiotherapy and full weight-bearing are commenced on day one. A locked extension brace is used for six weeks if the extensor mechanism has been reconstructed. Patients were reviewed at three-monthly intervals for the first two years, then six-monthly until five years, and annually thereafter (Figs 3 and 4).

Functional outcome. Patients were functionally assessed using the Musculoskeletal Tumor Society (MSTS) scoring system, which is a clinician-based assessment out of 30, and the Toronto Extremity Salvage Score (TESS), which is a patient-reported outcome, calculated as a percentage.

Statistical analysis. Kaplan–Meier survival curves with 95% confidence intervals (CI) for both implant and patient survival were used to compare rates of survival. Implant survival was analysed with amputation or exchange of all or part of the prosthesis for any reason as the endpoint.

Results
The mean follow-up was 58.5 months (20 to 141) for all patients and 69.3 months (20 to 141) for the 12 patients who were still living. A total of six patients died of their disease at a mean of 36.8 months (24 to 59) post-operatively. Cumulative patient survival was 59% (95% CI 32 to 84) at five years (Fig. 5).
Oncological outcome. A total of seven patients developed new metastases post-operatively (Table I), five of whom died at a mean of 38.2 months (24 to 59) after the operation. New metastases to the lung occurred in five patients; two were managed palliatively, one received combined chemo- and radiotherapy, one received chemotherapy alone, and one underwent surgical excision followed by chemotherapy. One of the palliatively managed patients with lung metastases also developed brain and liver metastases; the brain metastases were managed by palliative radiotherapy. New metastases to bone occurred in three patients; two received radiotherapy, and one with a large metastatic deposit in the scapula underwent scapulectomy, followed by radiotherapy at 78 months. There has so far been no further recurrence in this patient.

In one patient local recurrence developed in the anterior tibial compartment and in the fibula, which was treated by above-knee amputation at 23 months; lung metastases also developed, and the patient died at 40 months.

Functional outcome. The mean MSTS score in patients with a functional diaphyseal replacement at the time of this review was 23 (17 to 28). The mean TESS was 74% (53% to 91%). All patients could walk and participate in social activities with friends and family, but all found kneeling and rising from a kneeling position difficult. Two patients required a walking aid for long distances and one developed symptomatic osteoarthritis of the ankle. All patients preferred the option of limb salvage to amputation, and stated that they would have the same procedure done again under similar circumstances.

Implant survival and complications. Implant survival, with amputation or exchange of all or part of the prosthesis for any reason as the endpoint, was 63% (95% CI 35 to 90) at ten years (Fig. 5) with four patients having required revision to a proximal tibial replacement (PTR) at a mean time of 29 months (10 to 54). There was one above-knee amputation for local recurrence.

Aseptic loosening around the proximal stem occurred in four patients after a mean of 23.5 months (8 to 54). The mean length of the proximal stem in these patients was 39.5 mm (28 to 60) and the mean length of defect replaced was 181.5 mm (111 to 212). In three patients the prosthesis was disconnected intra-operatively and the loose proximal segment removed. The distal stems were well fixed in all these cases. Proximal tibial bone stock was adequate to allow for the proximal tibial component to be re-cemented and bone grafted, and for the original proximal segment of the diaphyseal replacement to be re-implanted and bolted to the well-fixed distal segment. In the remaining patient the proximal tibial bone stock was deficient, necessitating revision to a PTR, which was custom-made to articulate with the femoral condyles and bolt into the well-fixed distal segment of the original diaphyseal replacement.

One patient developed deep infection at ten months and underwent radical debridement and single-stage revision to a PTR. This eradicated the infection and restored pain-free mobility, but the patient died of metastatic disease at 37 months after the original operation.

Peri-prosthetic fractures occurred in two patients around the proximal tibial stem following a fall, and required revision to a PTR at 19 months and 32 months, respectively. The mean length of the proximal prosthetic stem in patients with peri-prosthetic fracture was 29 mm (28 to 30) and the mean length of defect replaced was 109 mm (108 to 110).
One patient developed ankle pain at 36 months, secondary to instability of the distal tibiofibular syndesmosis, which was successfully treated by the insertion of a single diastasis screw. None of the implants fractured.

**Discussion**

Factors that affect the choice between different types of local treatment of tibial diaphyseal tumours include tumour type, grade and size; life expectancy; comorbidities and the patient’s personal choice; the incidence of complications; and the durability of the reconstruction. Fibular autografts and distraction osteogenesis provide a biological means of reconstruction, but are not suitable for large defects (< 15 cm) and may result in the formation of new bone that lacks sufficient mechanical strength to withstand physiological loading. Such patients require prolonged rehabilitation and the incidence of complications is high; they may experience donor site morbidity and union may be impaired by the catabolic effects of adjuvant chemo- and radiotherapy on bone repair.8,9,16,22,34

The two most common reconstructive methods following segmental resection of malignant tumours are allograft or endoprosthetic reconstruction. Femoral diaphyseal replacements have demonstrated acceptable long-term results, with a survival rate of 68% at ten years.23 However, many consider allografts to be a superior method in the tibia, as large-segment allografts allow accurate matching of the graft to the defect, permit ligamentous reconstruction, and provide an osteoconductive scaffold into which new bone may grow. At cortical junctions union occurs by the formation of external callus originating from the host bone; at cancellous junctions fibrovascular tissue grows into the allograft, providing a source of osteoblasts for appositional union.35 Host bone has been shown to grow up to 25 mm into the donor allograft, but complete endosteal revascularisation has not been demonstrated.35-37

There are, however, disadvantages with allograft reconstruction, including difficulty in obtaining appropriately sized allografts from bone banks and the risk of disease transmission, although with modern-day screening and irradiation these risks are low. Prolonged immobilisation is required for graft union, and there are high rates of failure after intercalary replacement (as noted in the introduction), which makes their use less favourable for elderly patients and those receiving palliative treatment.

Endoprostheses, on the other hand, are not associated with these problems, as they allow patients to bear weight early, with comparable functional results, and fixation is not affected by adjuvant chemotherapy. Complications include infection, loosening, local recurrence, mechanical failure and fracture, either of the prosthesis or of bone. There are few reports in the literature on the use of intercalary tibial diaphyseal replacements for bone tumours.26 Ahlmann and Menendez26 reported no complications and good functional outcome in two patients with primary diagnosis of adamantinoma and malignant fibrous histiocytoma at a mean follow-up of 17.5 months. Aldlyami et al25 reported a 63% rate of prosthesis survival at ten years for 29 femoral, three tibial and three humeral diaphyseal endoprosthetic replacements. Specific subgroup analyses were not performed; however, they noted poor results following tibial diaphyseal replacements and could not recommend their use except in a palliative setting.

The main cause of revision in our series reported here was aseptic loosening of the proximal stem in four patients. Higher rotational stresses and difficulty in securing interdigitation of the cement into the wider metaphyseal bone may be contributory factors. Three patients underwent re-cementation of the proximal stem following intra-operative dismantling of the modular prosthesis. This allowed good access to proximal bone for debridement and re-cementation. These patients had no further problems with proximal tibial pain. The patient who required revision had a custom-made PTR inserted which bolted into the well-fixed distal component and articulated with the femoral condyles. The mean proximal stem length of the prosthesis in these patients was 39.5 mm (28 to 60). We now advocate the use of extracortical plates to enhance fixation when short-segment intramedullary fixation is < 4 cm. New bone did form on the HA coating of the prosthesis, but this did
not eliminate aseptic loosening in this study. Peri-prosthetic fracture around the proximal stem occurred in two patients. This again may be related to the length of short-segment intramedullary fixation. The use of additional HA-coated extracortical plates may reduce this problem in the future. 28, 29

Infection remains a major problem and is related to difficulties in achieving adequate soft-tissue cover, and to the use of immunosuppressive chemotherapy and radiotherapy. We did not observe a difference in infection rates between types of endoprosthetic replacement, and less than that following allograft reconstruction. 28, 29 This patient was being managed palliatively, and so underwent radical debridement and single-stage revision to a PTR, in preference to amputation. We recommend two-stage revision with insertion of an antibiotic-loaded spacer for patients with a greater life expectancy. We have a low threshold for performing a gastrocnemius muscle flap in the revision setting to ensure adequate soft tissue cover. The choice between revision to a diaphyseal replacement or a PTR is determined by the extent of bone loss, joint function, and the functional demands of the patient.

Implant survival was 63% at ten years (95% CI 35 to 90), with no breakages, which is comparable with diaphyseal replacements performed in the femur. 23, 25 Two patients were alive at 10 years, one of whom had been revised to a proximal Tibial replacement at 54 months for aseptic loosening of the proximal stem. The other patient still had their original prosthesis in situ. There are no comparable studies for survival of the prostheses in the tibia. Patient survival was 59% (95% CI 32 to 84) at five years, at which point seven patients were alive. One of these patients had undergone a revision to a proximal tibial replacement and one had undergone resection of the proximal stem for aseptic loosening of the proximal stem. A heterogeneous group of patients was included in the study: some displayed a poor prognosis (metastatic disease and recurrent osteosarcoma), whereas others had a more favourable one (adamantinoma, aggressive osteofibrous dysplasia). Patient survival is affected by several factors, including delays in diagnosis, the size, grade and location of the primary tumour, the response to chemotherapy and the presence of metastases. Post-operative lung metastases carried an especially bad prognosis. The mean MSTS and TESS scores were 23 points and 74%, respectively, representing a satisfactory functional outcome. All patients preferred the procedure to the thought of amputation. One patient who developed local recurrence requiring above-knee amputation. If this patient had undergone primary below-knee amputation, which has a lower risk of recurrence than limb salvage, their long-term functional outcome may have been better. This and the other risks should be discussed with patients when consent is being obtained.

Limitations to this study include the retrospective design, the low patient numbers, the long study period and the variable length of follow-up. This makes the results prone to bias and confounding from temporal effects. However, it should be recognised that this is an infrequently performed procedure in patients with a reduced life expectancy, and this is the only study in the literature to report long-term outcomes following this type of reconstruction. The study could be improved by multicentre involvement, although a randomised trial comparing allograft and below-knee amputation with endoprosthetic reconstruction is difficult due to the rarity of these patients.

We conclude that tibial diaphyseal endoprosthetic replacement is a viable option for reconstruction following segmental resection for malignant bone tumours of the tibia, with results similar to or better than those reported for allograft reconstruction. There is a high rate of revision for aseptic loosening and peri-prosthetic fracture, and these risks are greater when the length of the short-segment intramedullary stem is < 4 cm.

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References


