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*ORIGINAL STUDY*

# Custom endoprosthetic reconstruction for malignant bone disease in the humeral diaphysis

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**The optimal reconstructive method following segmental resection of malignant tumours in the humeral diaphysis is unknown as there are no prospective long-term studies comparing biologic with endoprosthetic reconstruction. This is a retrospective review of 13 patients who, between 1995 and 2010, had undergone limb salvage at our institution using a custom-made humeral diaphyseal endoprosthetic replacement following excision of malignant bone disease. There were 9 males and 4 females with a mean age of 35 years at the time of surgery (range : 10 to 78). Mean follow-up was 56.8 months (range : 5 to 148). Cumulative patient survival was 75% at 10 years. Implant survival, with removal of the endoprosthesis or part of it for any reason as an end point, was 47% at 10 years. Seven patients required revision (54%). Complications included metastases in four, aseptic loosening in four, peri-prosthetic fracture in two and local recurrence in two. Mean MSTS and TESS scores were 23 (18 to 27) and 67% (52-80) respectively. Custom-made humeral diaphyseal replacement following resection of malignant bone tumours provided functional results superior to amputation, without an obvious compromise in patient survival. There was a relatively high revision rate for aseptic loosening and peri-prosthetic fracture and patients should be counselled about this preoperatively.**

**Keywords** : custom-made ; endoprosthetic ; limb salvage ; MSTS ; humerus ; diaphysis.

## INTRODUCTION

Limb salvage has replaced amputation as the primary treatment for malignant bone tumours of the humerus, largely due to improvements in chemotherapy, radiotherapy, imaging and surgical technique which have made this possible without adversely affecting survival (*32,34*). Limb salvage has been shown to be more cost effective than amputation and can offer improved functional out-

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come although, with the exception of physical functioning, there is no significant difference in quality of life (*3,24,31*).

Diaphyseal resection leaving the adjacent joints intact has several advantages including preservation of the physes in children, juxta-articular bone conservation and preservation of joint function with the prospect of better function and less long-term mechanical complications. Reconstructive options to address segmental diaphyseal resections include autografts which may be vascularised (*11,12,38*) or extracorporeally irradiated (*6,13,28*), allografts (*5,8, 10,16,18,29,30,31*) with may be combined with autogenous fibula grafts, segmental bone transport (*19,38*), or endoprostheses (*1,2,4,25*).

Autografts are useful for short segment reconstruction but graft availability, donor site morbidity and difficulty in matching the size and shape of the graft to the defect limit use (*11*). Allograft reconstruction enables accurate matching of graft to defect, allows ligament reconstruction and results in bone formation at the graft-host junction. However, following intercalary replacement allografts are associated with high rates of fracture (19% to 42%) (*29,37*), non-union (30% to 63%) (*10,17*) and infection (18.5% to 30%) (*17,23*). Endoprostheses have the advantage of allowing early mobilisation with shorter operative times, do not pose a risk with disease transmission and allow immediate commencement of adjuvant chemotherapy which has adverse effect on bone healing (*30*). Disadvantages include infection, loosening and breakage. Functional and oncological outcome, patient survival and prosthesis survivorship for humeral diaphyseal endoprosthetic replacements following bone tumour resections is unknown. The aim of this study was to evaluate these outcome measures following custom-made intercalary humeral endoprosthetic reconstruction after primary excision of malignant bone tumours and compare these results to other types of reconstruction.

## PATIENTS AND METHODS

Between 1995 and 2010, 13 consecutive patients with malignant tumours of the humeral diaphysis were treated by excision and endoprosthetic reconstruction with a custom-made intercalary diaphyseal replacement at our institution. No patients were lost to follow-up. Data was collected from the case notes, hospital databases, clinic reviews, imaging studies and functional questionnaires. There were 9 males and 4 females with a mean age of 35 years (10 to 78). Seven open and six needle biopsies confirmed the diagnoses in all cases. Histological examination showed Ewing's sarcoma in three, osteosarcoma in three, chondrosarcoma in two, metastasis from renal cell carcinoma in two, malignant fibrous histiocytoma in one, myeloma in one and pleomorphic sarcoma in one (Table I). All patients had been referred to our supra-regional sarcoma unit for multi-disciplinary team assessment and underwent preoperative staging which included plain radiographs and MRI of the limb, technetium ($Tc^{99}$) body scintigraphy and chest CT. MRI is mandatory to define the extent of the lesion, involvement of neurovascular bundle and define transection points. Humeral diaphyseal endoprosthetic reconstruction was not considered in the presence of metaphyseal or joint involvement, invasion of the neurovascular bundle or when tumour resection would leave inadequate muscle to allow function. Neo-adjuvant and adjuvant chemo- and radiotherapy were administered according to nationally agreed protocols.

### Functional outcome

Patients were functionally assessed using the Musculoskeletal Tumour Society (MSTS) scoring system (*29*) and Toronto Extremity Salvage Score (*30*) (TESS). The MSTS is a clinician-based assessment and the TESS is a patient-reported outcome measure. The TESS consists of 31 questions on everyday activities such as dressing, working, mobility and leisure. A percentage score is calculated.

### Statistical Analysis

Kaplan-Meier survival curves with 95% confidence intervals (CI) for both implant and patient were used to compare rates of survivorship. Implant survival was analysed with amputation or exchange of all or part of the prosthesis for any reason as the end point. Patients were censored for statistical analysis (observation stopped before the event occurred) if the measured event of failure had not occurred at the time the patient was last assessed.

### The Prosthesis

The custom-made prosthesis is made of titanium alloy (Ti 6Al 4V) and manufactured using special software

Table I. — Demographics and patient survival

| Patient Number | Gender | Age (yrs) | Diagnosis* | Radio-therapy | Chemo-therapy | Pre-op metastases | Patient survival (mths) |
|---|---|---|---|---|---|---|---|
| 1 | F | 64 | MFH | N | N | Y | DOD at 5 |
| 2 | M | 21 | Ewing's sarcoma | Y | Y | N | DOD at 5 |
| 3 | F | 53 | Chondrosarcoma | N | N | N | Alive at 148 |
| 4 | F | 33 | Chondrosarcoma | N | N | N | Alive at 85 |
| 5 | F | 55 | Solitary renal cell carcinoma metastasis pathological fracture | N | Y | Y | Alive at 41 |
| 6 | M | 35 | Osteosarcoma post radiotherapy for synovial sarcoma | Y | Y | N | Alive at 67 |
| 7 | M | 78 | Myeloma | Y | Y | N | DOD at 13 |
| 8 | M | 12 | Ewing's sarcoma | Y | Y | Y | Alive at 112 |
| 9 | M | 22 | Osteosarcoma | Y | Y | N | Alive at 132 |
| 10 | M | 22 | Pleomorphic sarcoma pathological fracture had ORIF and bone graft | Y | Y | Y | Alive at 59 |
| 11 | M | 10 | Osteosarcoma | N | Y | N | Alive at 26 |
| 12 | M | 39 | Metastatic renal cell carcinoma pathological fracture | Y | N | Y | Alive at 35 |
| 13 | M | 11 | Ewing's sarcoma pathological fracture | N | Y | Y | Alive at 10 |

*MFH, Malignant fibrous histiocytoma, ORIF, open reduction and internal fixation, DOD, died of disease.

employing computer-aided design and computer-aided manufacturing technologies (CAD-CAM) (Stanmore Implants Worldwide Ltd, Stanmore, UK). The shaft is made of two parts, which are connected together intra-operatively using two bolts (Fig. 1). Each end has an intramedullary stem, which is cemented into the corresponding canal. Both stems are fluted to provide rotational stability. The use of extra-cortical plates in selected cases provides further rotational stability. The use of a hydroxyapatite (HA) collar at the bone-prosthesis junction allows for osseointegration with reactive new bone forming a bony bridge. This is believed to reduce loosening by acting as a 'purse string' that seals the bone implant interface, preventing the migration of wear particles (*7*). There is also the option of incorporating a non-invasive growing mechanism into the prosthesis to enable limb-length inequality to be restored gradually in the post-operative period without further open procedures (*34*).

**Surgical Technique**

The procedure was carried out with the patient in the supine position. After preparing the skin with antiseptics and appropriate draping, an anterolateral or posterior humeral approach taking a skin ellipse with the biopsy track was used to expose the tumour, which was identified and bony transection points, as identified on pre-operative imaging, accurately marked. Careful tumour resection was carried out according to the principles

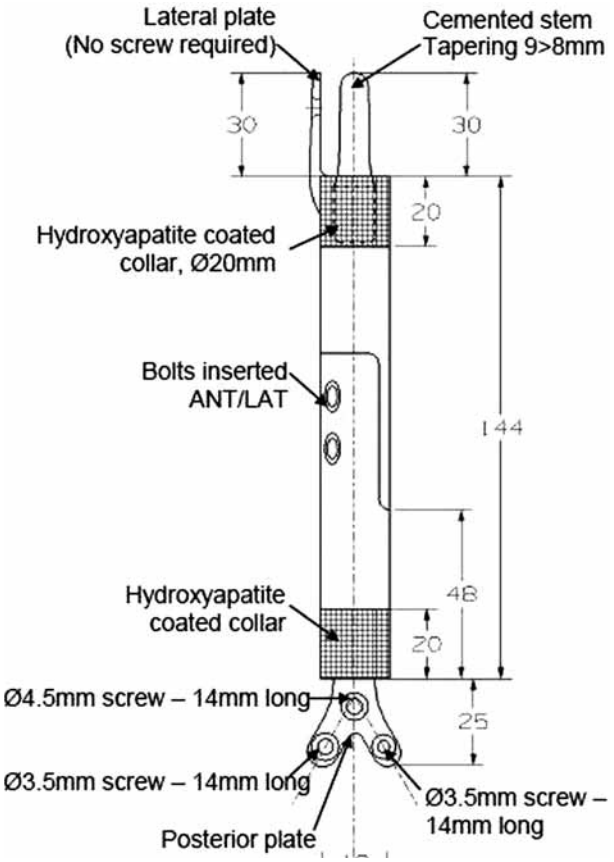


***Fig. 1.*** — Pre-operative schematic of a CAD-CAM humeral diaphyseal replacement for the patient in figure 2 demonstrating the sites for bone cuts. Extra-cortical HA-coated plates may augment fixation when the stem lengths are < 3 cm. The two components are cemented into the bone canals, reduced and connected together by a bolt mechanism.

defined by Enneking (*22*), endeavouring to achieve *en bloc* excision with a surrounding cuff of normal tissue without violating the tumour. The specimen was then sent to histology following which proximal and distal imprints were taken. The intramedullary canals were reamed and after careful adjustment for alignment and rotation, the proximal and distal stems were cemented with a 2 mm cement mantle. Proximal and distal segments of the endoprosthesis were reduced *in situ* and connected using two locking bolts. Soft tissues were closed and a drain inserted. Post-operatively intravenous antibiotics were continued for three days. A humeral brace was used for 2 weeks and gentle physiotherapy commenced day one. Patients were followed up at three-monthly intervals for the first two years, then six-monthly to five years, and annually thereafter (Fig. 2 & 3).

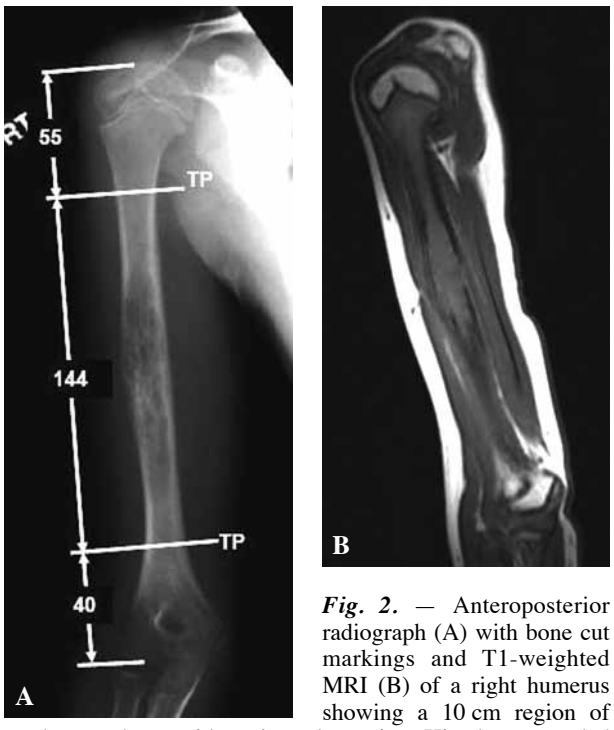


***Fig. 2.*** — Anteroposterior radiograph (A) with bone cut markings and T1-weighted MRI (B) of a right humerus showing a 10 cm region of moth-eaten bone with periosteal reaction. Histology revealed high-grade osteosarcoma.

## RESULTS

Mean follow-up was 56.8 months (5 to 148) for all patients and 71 months (10 to 148) for the 10 patients who were still living at the time of this review. Three patients died of their disease at a mean time of 8 months (5 to 13). Cumulative patient survival was 75% at 10 years (Fig. 4).

### Oncological outcome

Four patients developed new metastases postoperatively, three of whom have died. Three of these patients had known metastatic disease at presentation. New metastases to the lungs occurred in two patients ; one was managed with chemotherapy, the other palliatively. New metastases to bone occurred in two patients ; both received radiotherapy.

Two patients (15%) developed local recurrence at a mean time of 14.5 months (6 to 23). One patient with radiation-induced high grade osteosarcoma as a late complication of previous radiotherapy for a

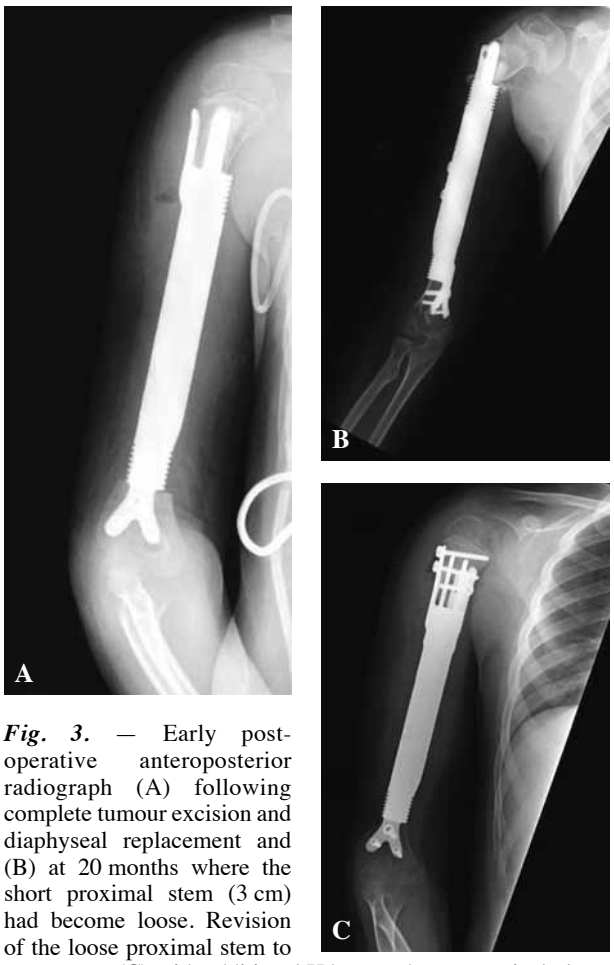


*Fig. 3.* — Early post-operative anteroposterior radiograph (A) following complete tumour excision and diaphyseal replacement and (B) at 20 months where the short proximal stem (3 cm) had become loose. Revision of the loose proximal stem to component (C) with additional HA-coated extra-cortical plates restored stability. The patient remains alive at 26 months with an MSTS of 26 and TESS of 78.

synovial sarcoma, developed proximal recurrence necessitating radical excision and revision to a custom-made proximal humeral replacement (PHR). The other patient developed proximal recurrence following revision to a PHR for aseptic loosening. This patient required shoulder disarticulation with adjuvant chemo- and radiotherapy for disease control. Both patients remain disease free to date.

## Functional outcome

Mean MSTS in the seven patients with a functional humeral diaphyseal replacement was 23 (18 to 27). Mean TESS was 67% (52 to 80). All patients reported an improvement in pain, could place their

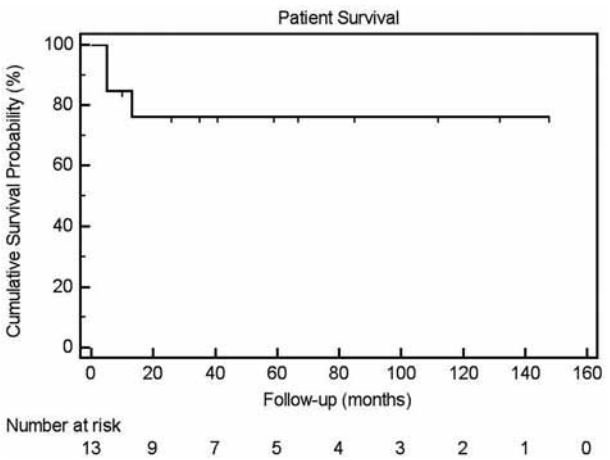


*Fig. 4.* — Kaplan-Meier survival curve for patients

hands behind their head and participate in social activities with friends and family. They universally found tasks involving overhead activities difficult and noted a reduction in strength.

## Complications and survivorship

Implant survival, with amputation or exchange of all or part of the prosthesis for any reason as the end point, was 47% at 10 years (Fig. 5). Seven patients required revision surgery. Four patients were revised for aseptic loosening at a mean time of 29 months (17 to 51). This affected the proximal stem in three patients and distal stem in one. In all patients, the prosthesis was dismantled intra-operatively by removing the two connecting bolts and the loose component removed. One patient required revision of the proximal component to a diaphyseal replacement with extra-cortical plate. One patient with deficient proximal bone stock required revision to a PHR. Two patients had the original loose component re-cemented. One of these patients subsequently required further revision of the distal component to a diaphyseal replacement with extra-cortical plate.

Two patients sustained distal peri-prosthetic fractures following falls at a mean time of 11.5 months (3 to 20). One patient with insufficient distal bone to allow further fixation was revised to a distal humeral replacement (DHR). The DHR was

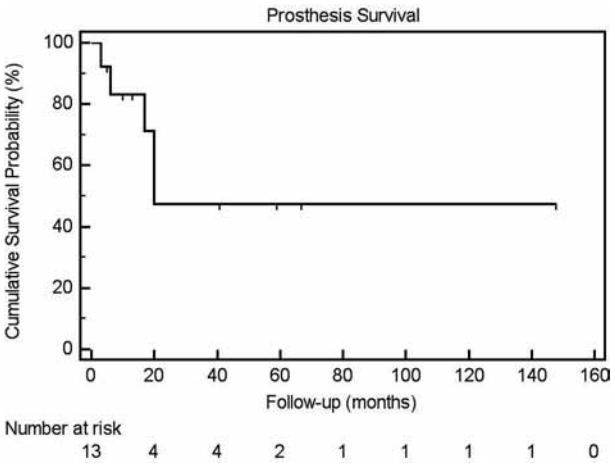


***Fig. 5.*** — Kaplan-Meier survival curve for implants

custom-made to interlock with the well fixed proximal segment of the original diaphyseal replacement. The other patient had a custom-made distal component manufactured with two holes in the stem to allow insertion of locking screws for enhanced prosthetic stability.

Two patients developed nerve injury. One patient developed ulnar nerve axonotmesis which improved. The other patient required radial nerve sacrifice as a consequence of tumour involvement. This patient subsequently underwent radial nerve tendon transfer at 12 months. There were no infections or fractured implants.

## DISCUSSION

Advances in chemotherapy, radiotherapy, reconstructive techniques and MRI have allowed limb salvage to replace amputation as the mainstay of surgical treatment for malignant bone tumours of the upper limb. Although there may be a higher incidence of local recurrence, patient survival is not compromised (*32,34*).

Important factors that influence the method of reconstruction include tumour type, grade and size, co-morbidities, life expectancy and functional demands of the patient, incidence of complications and longevity of reconstruction. Reconstructive options following humeral diaphyseal excision include autografts, allografts or endoprostheses. Fibula autografts hypertrophy under mechanical load, but are not suitable for large defects, do not allow early weight bearing and result in frequent complications and donor site morbidity (*12,38*). Distraction osteogenesis may provide bone with adequate biomechanical strength but is time-consuming, associated with a high incidence of complications, limited by the large defects often created (< 15 cm) and potentially inhibited by the catabolic effects of adjuvant chemo and radiotherapy on bone repair (*26,30,38*).

Allografts provide a biological means of reconstruction, allow ligament reconstruction and accurate matching of graft to defect, however devoid of vascular supply complications are frequent, prolonged immobilisation is required to allow graft union and there is a risk of disease transmission. Following intercalary replacement, high rates of fracture (19% to 42%) (*29,37*), non-union (30% to 63%) (*17,31*) and infection (18.5% to 30%) (*17,23*) have been reported. Bone formation by creeping substitution occurs at the allograft-host junction providing a biological means of reconstruction, however histological examination has shown this not to exceed > 2 cm at the allograft-host osteotomy, and not more than 3 mm at the ends of the graft (*9,21*). No study has ever demonstrated endosteal revascularisation in massive allografts (*27*). Availability of allograft from bone banks is a further problem encountered in many countries. Extra-corporally irradiated bone has overcome this to some extent, however the high complication rates and prolonged immobilisation times remain a problem (*6,13,28*), rendering these techniques unsuitable for elderly patients with medical co-morbidities and those being treated palliatively.

Endoprostheses generally show improved functional outcome, allow patients to weight bear early, enable immediate commencement of adjuvant chemotherapy and in the skeletally immature patient there is now the option of lengthening, using a minimally or non-invasive growing mechanism (*34*). There are very few reports in the literature on the use of humeral diaphyseal replacements for bone tumours (*4,37*). Aldlyami *et al* (*4*) reported a 63% prosthetic survival for 35 diaphyseal endoprosthetic

replacements (3 humeral, 3 tibial, 29 femoral) at 10 years. They did not perform subgroup analyses. Damron *et al* (*14*) reviewed the results of 17 patients who had a humeral intercalary spacer performed palliatively for metastatic bone disease. They reported an overall complication rate of 41% with 4 failures (2 peri-prosthetic fracture, 2 implant disengagement) at mean follow-up of 16 months (2 to 105). They used a cemented conical-coupled device and noted 2 implants disengaged at the couple junction. We did not experience this complication with the prosthesis. However the limited follow-up and different indications makes comparison with the present study difficult as we would ordinarily recommend intramedullary stabilisation for palliative management of diaphyseal bone metastases.

In this series aseptic loosening was the main cause of revision. As the endoprosthesis is made of two parts, revision surgery is facilitated by requiring exchange only of the loose component. The well fixed component may be left *in situ* as a new component can be manufactured that bolts into the well fixed component, which preserves bone stock. Where cortical bone around the site of loosening is adequate we would recommend intra-operative dismantling of the modular prosthesis, debridement and re-cementation of the loose component. If there is concern regarding stability of fixation, we would advocate exchange of the loose component to a custom-made diaphyseal replacement with HA-coated extra-cortical plate (*36*). Where bone is inadequate for further fixation we would recommend joint replacement. The other major cause of revision was peri-prosthetic fracture around the distal stem which occurred in two patients following falls. This complication will remain a problem in young and active patients. The choice between revision to a diaphyseal replacement or distal humeral replacement (DHR) is determined by the extent of bone loss, joint function and functional demands of the patient.

Implant survival was 47% at 10 years. Survival is worse than diaphyseal replacements performed in the femur but similar to that for the tibia (*4*). The length of the short segment fixation and narrower diameter of the humerus compared to the femur for cement interdigitation, combined with higher rotational stresses may explain this. In situations where prosthesis stem length is < 3 cm, we would now advocate replacement of the joint. Metaphyseal involvement is a contraindication to implantation. Patient survival was 75% at 10 years which compares favourably to other studies of limb salvage in malignant bone disease (*4,25*). Presence of metastases, size, grade, location of primary tumour and response to chemotherapy are the most important factors affecting survival. Mean MSTS and TESS scores were 23 and 67% respectively demonstrating satisfactory functional outcome. These scores are comparable to other studies on intercalary replacements (*2,25*).

There are limitations to this study. It is a retrospective design with small patient numbers, long study period and variable length of follow-up. The results may be affected by confounding and bias. Interviewer and measurement bias may affect functional outcome and survivorship analyses, and selection bias makes comparison with other studies difficult. It is however important to note that humeral diaphyseal tumours are rare and patients with bone sarcoma have a relatively poor survival. This means prospective randomised controlled trials are not feasible.

This is the first study analysing the outcome of humeral diaphyseal replacements for primary malignant bone tumours. Principles of limb salvage require adequate excision of tumour without compromise of patient survival, restoration of pain and early return to function. This reconstruction method alleviated pain and enabled early return to function with no apparent compromise in patient survival. Patients should be aware of the need for possible revision, but in our experience, this is usually uncomplicated and allows early return to function. Aseptic loosening was the main cause of failure. The use of HA-coated extra-cortical plates may reduce this problem in the future. Large segment humeral diaphyseal bone defects pose a challenging reconstructive problem with high complication rates with all types of reconstruction. An observational study of fibula autograft versus allograft versus endoprothetic reconstruction is needed to evaluate which is the optimal method for the humerus.

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*Author contributions*

SRC and TWRB designed the study. The remaining authors (AM, MDS, SAH, RP and JAS) contributed equally to data collection, analysis, interpretation and formulating and the final manuscript.

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