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Biology and technology in the surgical treatment of malignant bone tumours in children and adolescents, with a special note on the very young

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Abstract

Purpose: The main challenge in reconstruction after malignant bone tumour resection in young children remains how and when growth-plates can be preserved and which options remain if impossible.

Methods: We describe different strategies to assure best possible long-term function for young children undergoing resection of malignant bone tumours.

Results: Different resources are available to treat children with malignant bones tumours: a) preoperative planning simulates scenarios for tumour resection and limb reconstruction, facilitating decision-making for surgical and reconstructive techniques in individual patients; b) allograft reconstruction offers bone-stock preservation for future needs. Most allografts are intact at long-term follow-up, but limb-length inequalities and corrective/revision surgery are common in young patients; c) free vascularized fibula can be used as stand-alone reconstruction, vascularized augmentation of structural allograft or devitalized autograft. Longitudinal

growth and joint remodelling potential can be preserved, if transferred with vascularized proximal physis; d) epiphysioly-sis before resection with continuous physeal distraction provides safe resection margins and maintains growth-plate and epiphysis; e) 3D printing may facilitate joint salvage by reconstruction with patient-specific instruments. Very short stems can be created for fixation in (epi-)metaphysis, preserving native joints; f) growing endoprosthesis can provide for remaining growth after resection of epi-metaphyseal tumours. At ten-year follow-up, limb survival was 89%, but multiple surgeries are often required; g) rotationplasty and amputation should be considered if limb salvage is impossible and/or would result in decreased function and quality of life.

Conclusion: Several biological and technological reconstruction options must be merged and used to yield best outcomes when treating young children with malignant bone tumours.

Level of Evidence: Level V Expert opinion

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Introduction

Most common malignant paediatric bone tumours are osteosarcoma and Ewing's sarcoma, with age-adjusted estimated incidences of 4.5 and three per million, respectively.¹⁻³ Peak incidence for both is the second decade of life, with around 30% of all Ewing's sarcomas occurring before the age of ten years.³ For high-grade osteosarcoma, a recent survival analysis in a single centre cohort of 402 patients demonstrated a five-year overall survival for age below 16 years of 78.5% without and 21.7% with distant metastases.⁴ The authors demonstrated that overall survival worsened with increasing age and is better in very young patients. For Ewing's sarcoma, a survival estimation tool was recently developed classifying patients into dif-

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ferent risk categories (based on age, volume, localization and disease extent) with corresponding five-year overall survival ranging from 88% to 28%.⁵ For non-metastasized Ewing's sarcoma of the extremity, age below 16 years resulted in better survival: two-, three- and five-year overall survival were 93%, 90% and 88%, respectively.⁵

Important difficulties after tumour resection in very young children are caused by large bone and soft-tissue resections leaving only limited opportunities for reconstruction and remaining growth potential, especially around the knee.^{6,7} The anatomical extent of the tumour determines resection size, which becomes larger in case of pathological fracture with possible haematoma contamination. Several problems arise that are specific to very young children and that should be addressed regarding choice of reconstruction. Involvement of the growth plate will result in growth disturbance that requires further management. With extension to the articular surface, joint replacement is commonly necessary. If obtaining safe margins require large soft-tissue resections, local flaps may be indicated. Also, conventional tumour prostheses are difficult to use in very young children because of mismatch with small medullary cavities, remodelling bone and expected limb-length discrepancy. Furthermore, children have a higher functional demand and lifetime risk for revision surgery is very high. Therefore, in very young patients, biology is often preferred over technology.

The main question regarding reconstruction technique after malignant bone tumour resection in very young children remains how and when the growth plate can or should be saved; and which options remain if this is deemed impossible. Options for limb and/or joint salvage include use of allografts, free vascularized fibula, physeal distraction (epiphysiodesis before resection), growing endoprostheses and patient specific implants. Remaining options if limb salvage is not feasible include rotation-plasty and amputation (5% to 10%).⁷⁻¹¹ If limb salvage is aimed for, functional outcome should be better or in any case not worse compared with amputation. In this review article, we present an update of biological and technological reconstruction options for young children with an extremity malignant bone tumour.

Preoperative planning

For tumour resections performed in paediatric patients the main objective is to remove the tumour with clear margins. Nonetheless, preserving important anatomical structures such as growth plates is important whenever possible.⁸ Preoperative planning is essential to achieve this goal. As a general rule of thumb, one could keep in mind that limb-length discrepancies up to 2 cm in general do

not need further treatment, 2 cm to 4cm may be addressed with acute lengthening or contralateral epiphysiodesis, with expected 6 cm to 10cm a non-invasive grower should be considered when possible, and with > 10 cm rotation-plasty or amputation is commonly indicated.

With preoperative virtual planning, a simulation scenario is created in which it is possible to merge digital imaging modalities. This way, decision-making for different surgical techniques in the individual patients is facilitated.¹²⁻¹⁴

For the creation of optimal 3D images, image acquisition protocols (CT and MRI) are used with cuts of 1 mm to 2mm.^{12,15} Obtained CT and MRI images are merged through image fusion and oncological margins are defined within this virtual scenario using Mimics software (Materialise, Leuven, Belgium).¹² Oncological margins are calculated depending on tumour histology. In tumours such as low-grade chondrosarcoma (without bone marrow oedema), oncological margins between healthy and pathological bone tissue are easy to define. However, in other histological types such as Ewing's sarcoma, oncological margins are more difficult to establish and, therefore, a wider planned margin is often required.^{13,14}

Surgical approach needs to be in concordance with the proposed reconstruction, making it possible to perform a virtual resection before the real intervention.¹² Finally, after virtually resecting the tumour with its planned margins, physicians can foresee different reconstructive alternatives. Having access to a virtual library of banked allografts allows surgeons to practice numerous reconstructions using structural allografts (Fig. 1).¹⁶

Allograft reconstruction

Allografts are a good reconstructive option for paediatric patients. The main advantage is based on the possibility of restoring bone stock in this specific group of patients, for future needs. Another benefit is that – if not affected – the growth plate and thus growth potential of the child can be preserved after tumour resection, contrary to endoprosthetic reconstruction. Another advantage is that in patients with limb-length discrepancy due to resection of the growth plate, elongation of the affected limb can be performed during subsequent surgery.¹⁷

Different techniques of allograft use exist, of which the most commonly used techniques in children are hemicortical resections with inlay allografts and segmental whole-circumference resections with intercalary allografts. An update with long-term results was published for different types of allograft reconstruction in children younger than ten years old, analyzing late complications and limb-length discrepancy at skeletal maturity.^{8,17} Limb-length inequalities and subsequent corrective procedures

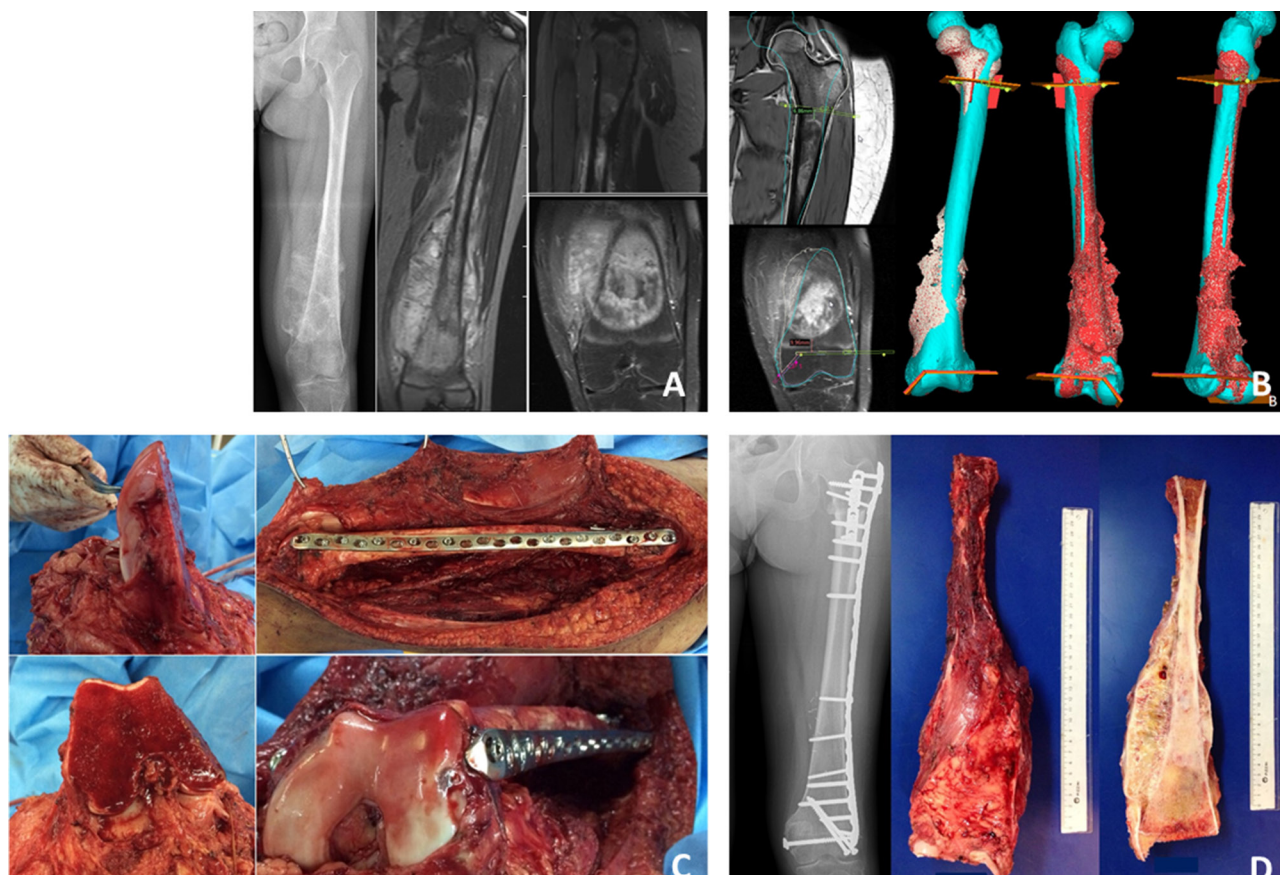


Fig. 1 a) 14-year-old patient with a high-grade femoral osteosarcoma; b) 3D virtual reconstruction of the affected femur followed by planning of resection osteotomies and subsequent reconstruction with intercalary allograft: in this virtual model, we overlap the patient's femur (red femur) with the femoral allograft (blue femur); in this way, not only tumour resection is planned, but also the most similar allograft is selected; c) intraoperative tumour resection followed by reconstruction with intercalary allograft; d) postoperative radiograph of the femoral allograft reconstruction and tumour specimen, showing how preoperative planning could be reproduced.

were common in this small series of very young patients, as were complications resulting in revision operations. Complications included limb-length discrepancy requiring lengthening (38%), fracture (30%), nonunion (6%) and infection (6%).¹⁷ But overall, most allografts remained intact at long-term follow-up.

For low-grade tumours such as adamantinoma and parosteal osteosarcoma, hemicortical resection and inlay allograft reconstruction results in excellent survival; the most common complication is host bone fracture, but generally not necessitating allograft removal.¹⁸ An update with long-term results was recently published for intercalary allograft reconstruction, an acceptable reconstructive option but with a considerable mechanical complication risk.^{19,20} Complications included nonunion and allograft fracture, and to reduce risk of failure, bridging plate fixation is advised. With use of virtual planning and 3D-printed saw jigs, customized structural allografts can also be used for correction of alignment after growth disturbance in for example Ollier's disease. Osteoarticular allograft reconstructions demonstrated high complication

and failure rates at long-term follow-up and routine use is no longer advocated.²¹

Allograft reconstruction after sarcoma resection is considered an appropriate reconstructive procedure in selected skeletally immature children, and it may be a reasonable option to consider as alternative to rotationplasty or endoprosthesis in some patients.¹⁷

Free vascularized fibula

Free vascularized fibular graft (FVFG) can be used in different reconstructive options: single FVFG; vascularized double-barrelled fibula; in combination with structural allograft or devitalized autograft; on-lay graft (fibula osteotomized longitudinally for reconstruction of partial cortical defects); or composite tissue transfer (skin, fascia and muscle harvested concomitantly with the fibula and used for complex reconstructions) (Fig. 2).²²⁻²⁹ The fibula can also be transferred along with its vascularized proximal growth plate, preserving longitudinal growth and provid-

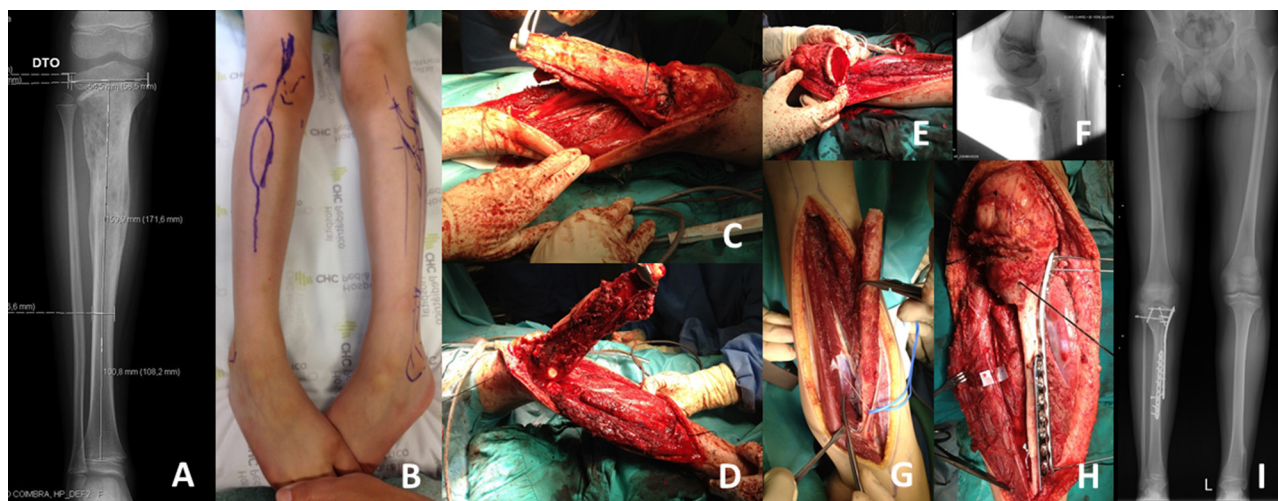


Fig. 2 Radiograph and clinical images of a nine-year-old boy with Ewing's sarcoma (a, b); en bloc intra-epiphyseal resection was performed (c-f); followed by reconstruction with a vascularized fibular graft, combined with an allograft shell (g, h); and radiograph at nine years of follow-up without any evidence of disease (i). The boy has excellent function.

ing remodelling potential to the joint surface. This option is useful for humerus and distal radius reconstructions and has been used with limited success in the proximal femur in young patients.³⁰⁻³² Hybrid reconstructions combining allograft shell and FVFG are indicated for larger defects (> 10 cm). In the largest multicentre study on the use of FVFG after bone tumour resection in 74 patients, including 39 patients < 18 years, limb salvage was achieved in 93% and graft hypertrophy in 88% of patients after a mean follow-up of 6.5 years.²⁹

The allograft provides adequate bone stock and early stability, while FVFG facilitates host-allograft union.^{22,23,27} The vascularized fibula is assembled with the allograft using either an intramedullary or on-lay technique.²⁶⁻²⁸ Damage to the vascular pedicle should be avoided during fitting of the fibula into the allograft. Stabilization is performed with rigid plate fixation, crossing both osteotomies.^{26,31} In case of intra-epiphyseal resection (Fig. 2), where a thin portion of the articular surface is spared, minimal juxta-articular osteosynthesis is performed, by passing Kirschner wires through the epiphysis and plate fixation at the other end of the combined graft.³³

Some authors found no difference in survival of reconstructions between patients treated with massive bone allograft and FVFG and patients with massive bone allograft alone. Femoral intercalary defects may thus be reconstructed with an allograft alone, reserving the vascularized fibula to salvage the allograft only if a fracture or nonunion occurs.³⁴

Possible complications of FVFG include nonunion (19%), fracture (15%), infection (4%), donor site complications (valgus ankle deformity, ankle instability) (3%), peroneal nerve palsy and skin graft failure or hallux flexion impairment.^{28,29,31}

Epiphysiolsis before resection

In metaphyseal paediatric bone sarcomas, Cañadell's technique of controlled epiphysiolsis with continuous physal distraction of 1 mm/day for ten to 15 days before resection preserves as much as possible (mostly the whole epiphysis) in selected cases, while providing a safe resection margin (i.e. thin layer of growth plate cells; Fig. 3).^{35,36} Indications are metaphyseal tumour localization, open growth plate and no tumour involvement of growth plate nor epiphysis. This should be confirmed by MRI preoperatively. The technique has been used in distal femur, proximal tibia, distal tibia, distal fibula, proximal humerus and distal radius. Contraindications are tumours crossing the growth plate and involving the epiphysis, tumours with involvement of the entire growth plate surface, nearly closed growth plates and pathological fracture (unless healed during neoadjuvant chemotherapy).

On the femoral side, the technique of physal distraction maintains the integrity of trochlea and ligament insertions, as well as most of the growth plate. On the tibial side, this technique maintains the insertion of the patellar tendon and ligament insertions, the whole epiphysis and most of the growth plate cartilage.

In a single sarcoma centre, between March 1980 and December 2014, intercalary reconstructions were carried out in 168 patients by means of epiphysiolsis before resection.³⁵ Mean age was 9.4 years. No local recurrences occurred at the preserved epiphysis. Functional results were excellent in most cases (Fig. 4). Complication rate was similar to other limb salvage procedures in paediatric bone sarcomas. This technique is now used worldwide, and other series have confirmed these mid- to long-term results. No local recurrences have been reported. Compli-

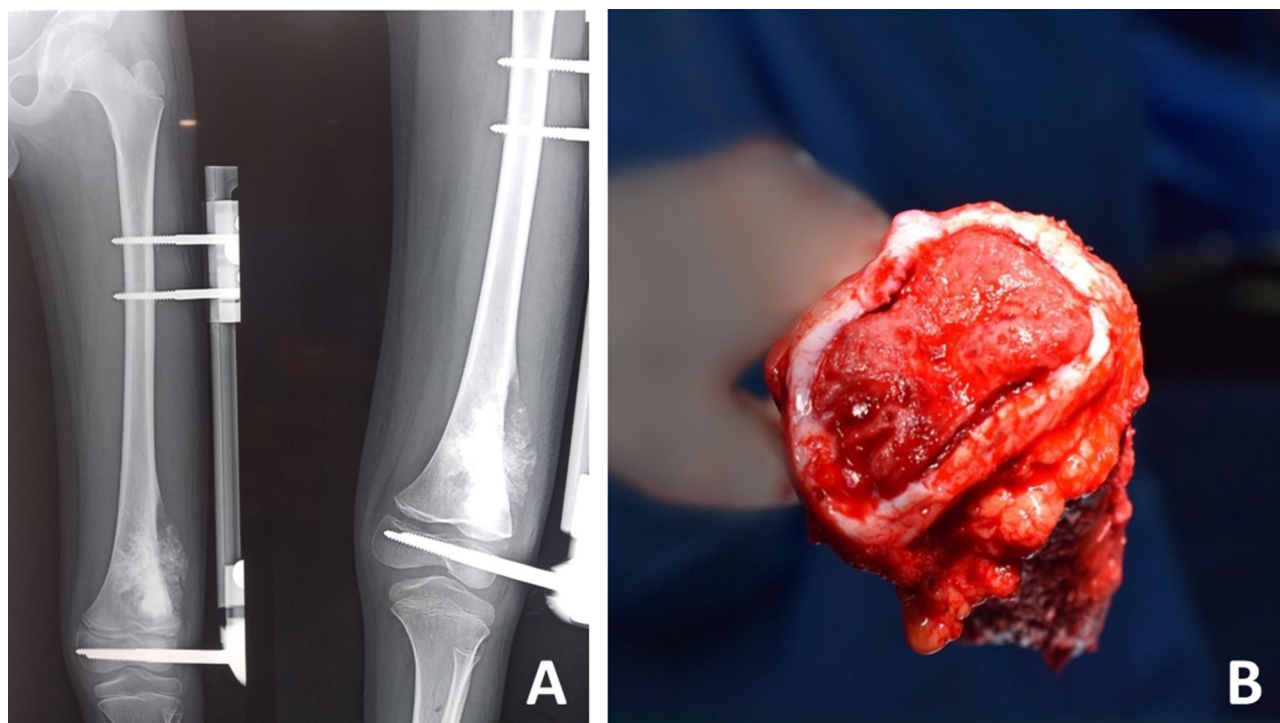


Fig. 3 a) Epiphysiolysis before resection of a distal femur osteosarcoma in a nine-year-old boy; b) thin layer of growth plate covers the metaphysis, providing a safe margin of healthy tissue. Most of the growth plate remains inside the patient, together with the whole epiphysis (reproduced courtesy of Dr. Navaneeth Kamath, Indiana Hospital & Heart Institute, India).

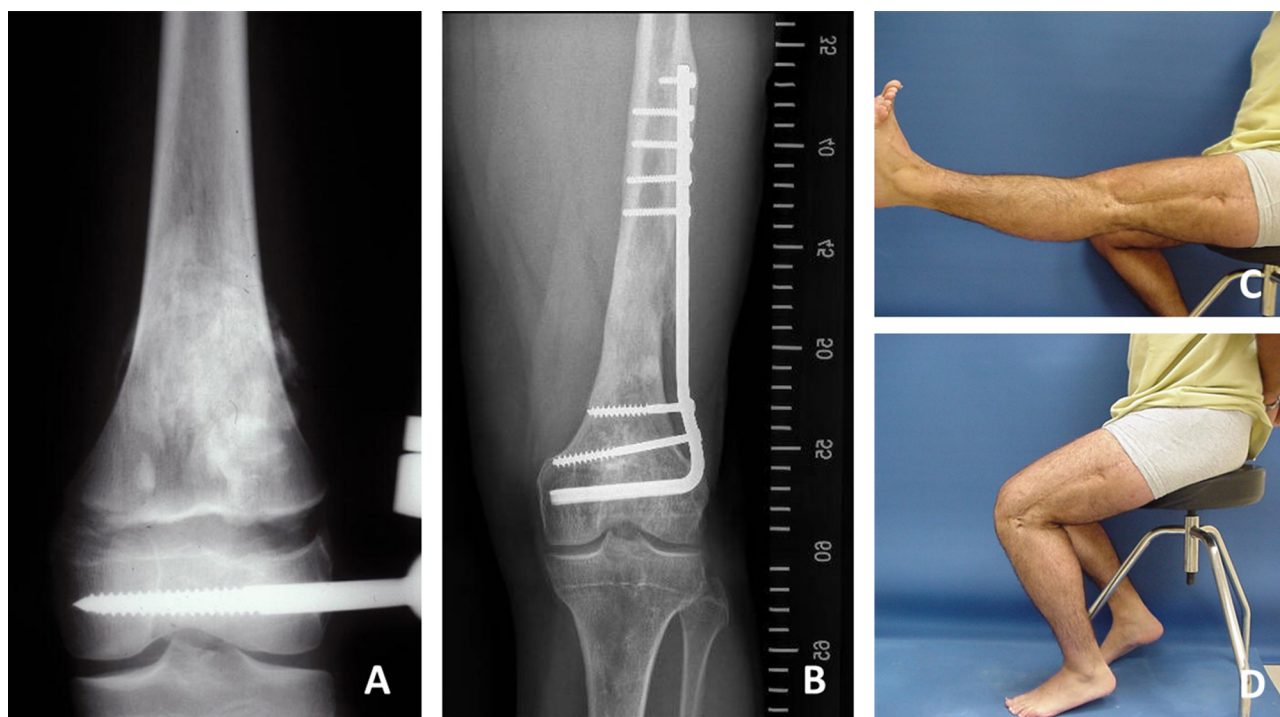


Fig. 4 a) Patient with distal femur osteosarcoma treated with epiphysiolysis before resection in 1986; b) follow-up radiograph 35 years after treatment, no further surgeries were required and there are no degenerative joint changes; c) and d) functional outcome at latest follow-up, with small scars from the fixator pins still visible.

cations include impaired range of movement of the knee, anterior bowing of femur, valgus deformity of tibia and fracture. Postoperative function, measured with MusculoSkeletal Tumour Society (MSTS) and Toronto Extremity Salvage Score (TESS), has been rated good to excellent.^{37,38}

3D printing and patient-specific instruments (PSIs)

With unaffected epiphysis and an intact growth plate, the joint and physis adjacent to the bone tumour may be saved, resulting in preservation of remaining growth. However, malignant bone tumours often reach or are in very close relation with the growth plate, impairing reconstruction with conventional implants. In these cases, joint salvage may be achieved by reconstruction with 3D-printed implants and PSI.³⁹ Advantages are preservation of articular cartilage, soft tissues and ligaments, maintaining natural stability and normal range of movement. Also, there is no need for another implant component at the opposite side of the joint, preventing artificial joint liner wear.

With 3D printing and PSI, a very short stem can be created for fixation in the remaining (epi-)metaphyseal area after tumour resection. Short porous stems may facilitate bone ingrowth and can be fixated through extra-cortical plates, internal fins and pre-routed cancellous screws (Fig. 5). This technique requires deliberate preoperative planning and is facilitated by computer-assisted navigation. However, to date no long-term results are available.

Growing endoprosthesis

Non-invasive growing endoprostheses can be an option to provide for remaining growth after resection of growth plates. This may be a valuable option in older children, but is not always feasible in children under the age of six years, as their medullar cavity is too small to fit regular stems and remaining length of bone-stock and soft-tissue coverage may be insufficient for robust fixation and functional soft-tissue coverage.⁴⁰

Potential problems with lengthening may be the length of the neurovascular bundle, quality and strength of remaining quadriceps muscle and possible extension deficit. Therefore, the advice is not to lengthen > 50% of the estimated final length, and to consider the possibility of inducing growth arrest of the contralateral growth plates through epiphysiodesis.

Open lengthening results in high surgical morbidity because of intended multiple operations including a high infection rate (> 30%), nerve palsy and contracture; and only a limited number of lengthenings can be performed.^{41,42} Non-invasive growing endoprostheses result in less surgical morbidity because of multiple small lengthenings, but require revision to an adult endoprosthesis at the end of lengthening.^{42,43} Complication rate is around 40% and includes soft-tissue complications, aseptic loosening through stress shielding and bone loss at the implant site, structural failure (e.g. broken motor) and infection. Reported survival of growing endoprostheses below the age of ten years is worse compared with older age.⁴⁴

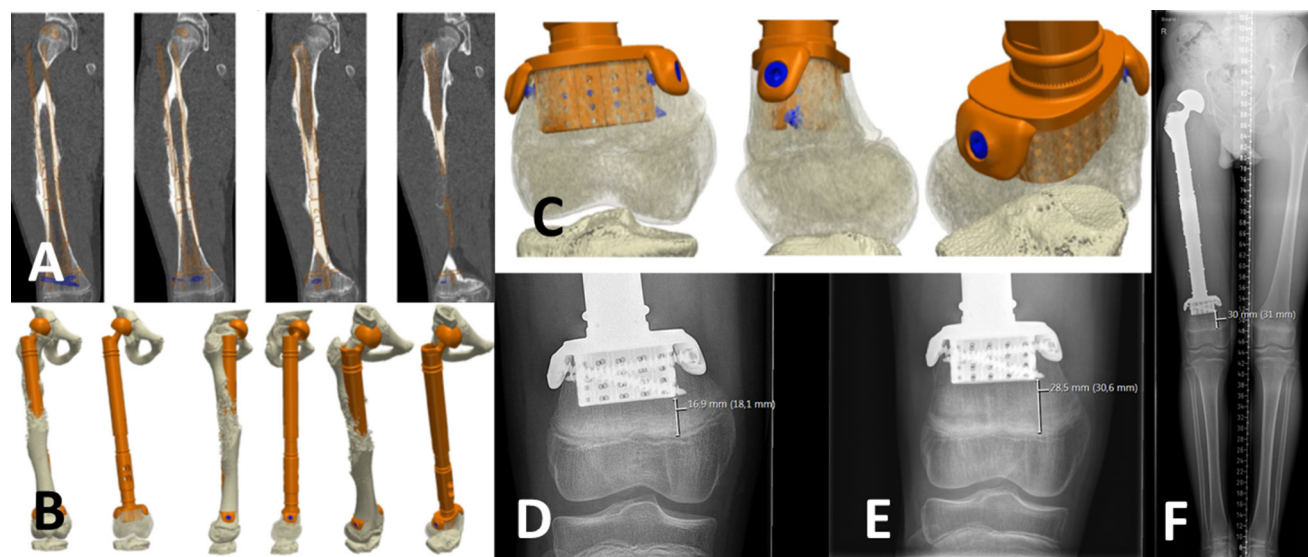


Fig. 5 a) and b) Preoperative virtual planning of proximal femoral resection and reconstruction with 3D-printed custom short osseointegration stem; c) details of custom short osseointegration stem with planned screw fixation; d) and e) growth plate remained intact with continuous growth over time at three and six months postoperative; f) postoperative radiograph at 12 months demonstrating length growth and no clinically relevant leg-length discrepancy.

With growing endoprosthesis, limb survival at ten years was 89%.⁴³ Frequent reoperations are reported (0 to 12), and patients and their parents should be counselled regarding potential future operations at the time of diagnosis. Costs of growing endoprosthesis and multiple surgeries are high, and this option may not be ideal in developing countries.

Rotationplasty and amputation

When safe resection margins cannot be achieved and limb salvage techniques will not result in superior functional or aesthetic results, rotationplasty (Fig. 6) or amputation may be indicated. In very young children with lower limb malignancies with large remaining growth, it is impossible to perform rescue techniques that offer good functional and aesthetic results at the end of growth. Therefore, rotationplasty or amputation may be more suitable.⁴⁵ Although local recurrence rate appears to be somewhat lower with ablative surgery, survival outcomes are similar between limb salvage and ablative surgery.⁴⁶⁻⁴⁸

Advantages of rotationplasty and amputation are that they are both usually a single intervention, providing the widest possible resection margins and with hardly any complications compared with other reconstructive techniques and without requiring new interventions during growth. A low complication rate is important in not dilating the time without chemotherapeutic treatment, especially in aggressive malignancies. Advances in external

prostheses design result in excellent function, even for sports activities.^{46,47} Disadvantages are a lifelong need for external prostheses, and being an amputee with all the social connotations implicated, especially rotationplasty, may not be culturally accepted everywhere. Rotationplasty is an acceptable alternative to amputation as it results in better functional outcome, no phantom pain and finally low costs which makes it ideal in developing countries.

Many studies have compared the functional and social impact of amputee patients with those who have undergone limb salvage techniques, with similar results between groups. Although a difficult comparison because of disparity of cases and functional and quality of life scales used, neither limb salvage nor ablative surgery including amputation and rotationplasty is deemed superior.⁴⁸⁻⁵⁰ Although some authors reported better functional results in patients with limb salvage, quality of life was not affected, except for cosmetic outcomes.^{51,52}

Only a few studies focus on paediatric and adolescent populations, where growth potential is an added difficulty. Longest reported follow-up is around ten to 15 years, possibly underestimating long-term complications of limb salvage including revision arthroplasty or the need for late amputations.⁴⁹

Other authors studied the impact of amputations on level of education, employment, health insurance and marital status, without finding differences between amputation and limb salvage surgery compared with the healthy population.⁵³

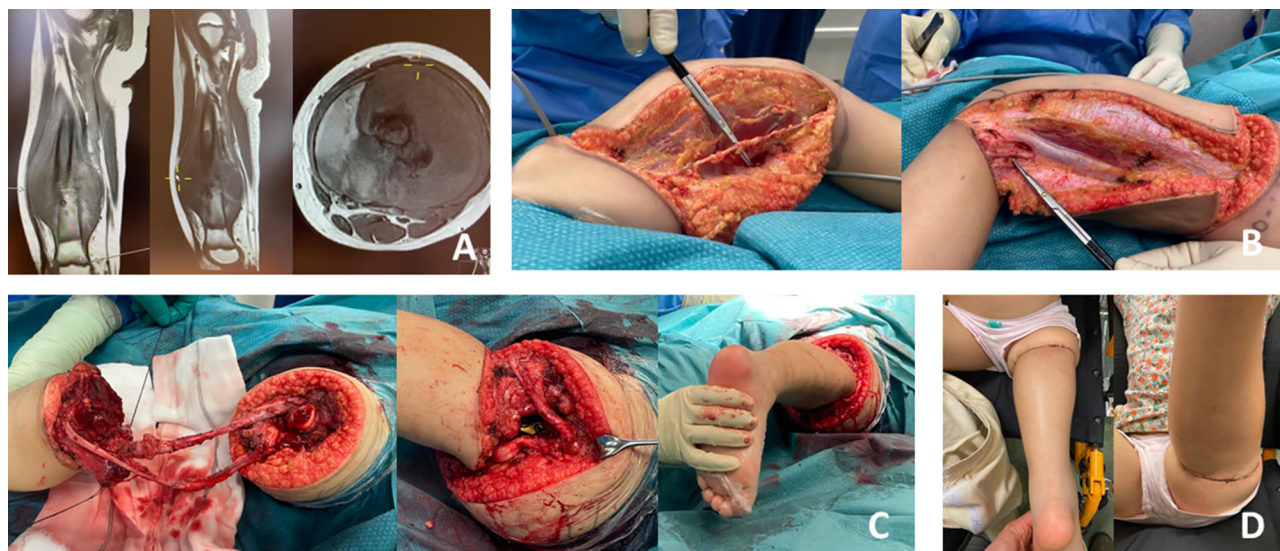


Fig. 6 a) High-grade osteosarcoma in a six-year-old girl with involvement of growth plate and quadriceps muscle, treated with distal femoral resection and rotationplasty; b) intraoperative images of the medial and lateral sides demonstrating femoral vessels and sciatic nerve; c) it is key to save the sciatic nerve and in small children the femoral vessels are also saved and secured in the recess made in the adductor canal, as they are too small to safely create an anastomosis; discrepancy in soft-tissue size is usually overcome by a wavelike incision in the lower leg that normally fits onto the circular incision around the upper leg; d) good functional results after two weeks, without any wound healing or other soft-tissue problems.

Conclusion

The main question regarding reconstruction technique after malignant bone tumour resection in very young children remains how and when the growth plate can or should be saved; and which options remain if this is deemed impossible. Options for limb and/or joint salvage include use of allografts, free vascularized fibula, epiphysi-olysis before resection, growing endoprotheses and PSIs. If limb salvage is impossible, remaining options include rotationplasty and amputation, and both should be considered and discussed with the child and their parents if limb and/or joint salvage would result in lesser function and quality of life. In this review article, we present an update on several biological and technological reconstruction options that must be merged and used to yield best outcomes when treating young children with malignant bone tumours of the extremity.

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COMPLIANCE WITH ETHICAL STANDARDS

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ETHICAL STATEMENT

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Informed consent: As there were no human participants involved in this review article, gathering informed consent was not required.

ICMJE CONFLICT OF INTEREST STATEMENT

All authors declare that they have no conflicts of interest related to this work.

AUTHOR CONTRIBUTIONS

LvdH: Design of manuscript content/outline, Manuscript writing, Final manuscript approval.

GLF: Manuscript writing, Final manuscript approval.

IB: Manuscript writing, Final manuscript approval.

CA: Manuscript writing, Final manuscript approval.

MS: Manuscript writing, Final manuscript approval.

JML-E: Manuscript writing, Final manuscript approval.

MAJvdS: Manuscript writing, Final manuscript approval.

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