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THE USE OF EXPANDABLE MEGAPROSTHESES FOR RECONSTRUCTION OF THE DISTAL FEMUR IN PEDIATRIC PATIENTS AFTER BONE TUMOR RESECTION

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Background and outline of this thesis

Expandable prostheses are becoming increasingly popular in the reconstruction of children with bone sarcomas of the lower limb. Since the introduction of effective chemotherapy in the treatment of these pathologies, in the 70s, there has been need for new limb salvage techniques. In children, limb salvage of the lower limbs is particularly challenging, not in the last place, because of the loss of growth potential. Therefore, expandable prostheses have been developed. However, the first experiences with these implants were not very successful. High complication rates and unpredictable outcomes raised major concerns on this innovative type of reconstruction. The rarity of the indication is one of the main reasons why there has been a relatively slow learning curve and implant development regarding this type of prosthesis. This PhD thesis, gives an overview of the introduction, the development, the current standards, and the future perspectives of expandable prostheses for the reconstruction of the distal femur in children.

Chapter 1 is dedicated to the main two pathologies that frequently arise at the distal femur in this age group: osteosarcoma and Ewing sarcoma. Clinical aspects and principles of treatment are presented.

In Chapter 2, the surgical treatments for bone sarcomas at the distal femur are discussed. Specific problems related to limb salvage surgery in children are described in detail. Major issues, like the high functional demands, difficulties in implant fixation, and loss of growth are being addressed. This chapter also contains the reports on three clinical studies that deal with the reconstructive challenges in children. Two studies were dedicated to the problem of prosthetic implant fixation in children. A study was performed to interpret the reactions from pediatric bone to the presence of an endomedullary stem from a megaprosthesis. The remodeling process was described, typical radiographic patterns were recognised and their prognostic significance was determined. A second study describes the use of cylindrical allograft augmentation to increase the length of the proximal femoral stump either in primary surgery or revision surgery with a megaprosthetic distal femoral implant in children. One study in this chapter, looked at implant survival and growth preservation of the tibia, with the use of a special pediatric type tibial component in megaprosthetic distal femoral implants.

Chapter 3 is completely dedicated to expandable endoprostheses. The evolution of these implants is described. Specific problems and concerns are outlined, and two clinical studies on non-invasive growing prostheses are presented. A study on the Repiphysis non-invasive expandable distal femoral prosthesis was performed and published prior to this PhD course and was the main reason to critically look at the evolution and outcome of expandable prostheses during this project. It not only demonstrated the poor quality of that specific implant itself. It also showed how short-term preliminary reports and small case series of innovative techniques, can sometimes blind us with early promising results. Subsequently to that article, a multicenter, international study on the Stanmore JTS implant was performed. The results of this study are also presented in Chapter 3.

Chapter 4 is dedicated to the final project of this PhD thesis: the EMSOS study on expandable prosthesis. This European multicenter study included data from 15 referral centers for orthopedic oncology in 9 different European countries, and represents the largest database on expandable endoprosthesis ever presented, with nearly 300 cases. This unique project, shows how international collaboration is essential for studying rare pathologies and, even rarer surgical reconstruction techniques. The EMSOS study finally gives us detailed insights in the indications, trends, complications, and outcomes of expandable prostheses in sarcoma treatment for children in Europe.

Chapter 5 contains the main conclusions of this thesis with implications to our current practice and future perspectives for further implant development.

INDEX

CHAPTER 1

BONE SARCOMAS IN CHILDREN

1.1 INTRODUCTION

Primary bone malignancies, or sarcomas, are infrequent pathologies. Their incidence in the age group between 0 and 14 years, accounts for approximately 2 to 5% of all pediatric malignant neoplasms. They are less frequent in Asian countries and South America, and have their peak incidence in Europe and North America.
In this age group, almost all primary malignant bone tumors are osteosarcomas and Ewing sarcomas, and there is a clear predominance of boys in the gender distribution.
The worldwide annual incidence of new cases is estimated around 4.5 cases/10^6 persons for osteosarcoma and 3.0 cases/10^6 persons for Ewing sarcoma.
In Italia, in the age group between 0 and 14 years, the incidence of annual new sarcoma cases is estimated around 9 cases/10^6 (95% CI 7.2-11.2) for males, and 7.2 cases/10^6 (95% CI 5.5-9.2) for females. Based on the latest numbers of the overall population (60x10^6 inhabitants) and the estimated percentage of children (17% of total population), according to the 2008 Istat data, this means that between 75 and 80 new sarcoma cases are expected to be diagnosed each year in Italy.
Both osteosarcoma and Ewing sarcoma are particularly rare in the first 5 years of life and have their peak incidence in the age group between 10 and 14 years (Figure 1).

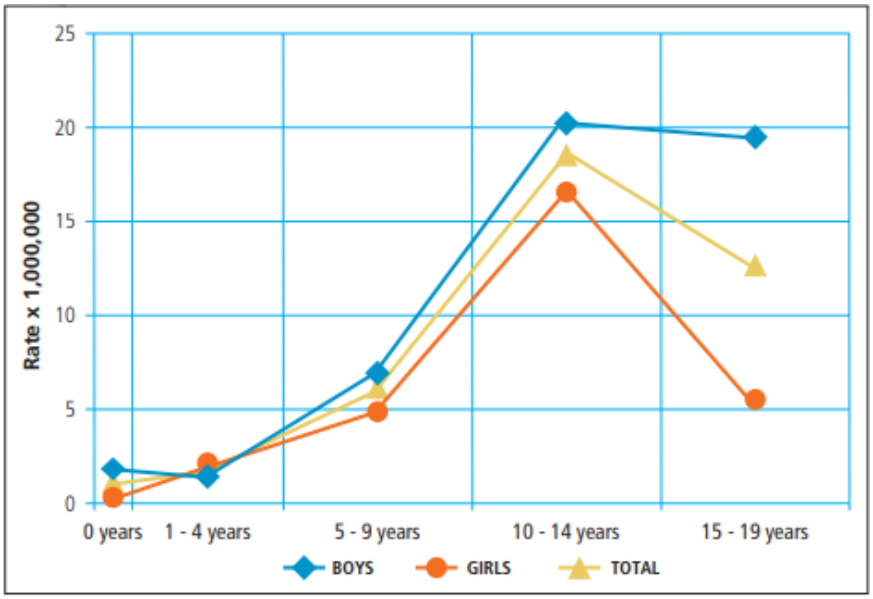


Fig. 1 Age at sarcoma diagnosis (<19 years)

The most frequently involved sites are the femur (42%), tibia (19%) and humerus (10%), and more specifically, the metaphyseal region of these long tubular bones. In approximately 8% the sarcomas arise in the cranio-facial region and in another 8% they involve the pelvis. At diagnosis, between 15% and 20% of patients has metastatic disease. Another 40% develops metastases during the course of the disease.

From an orthopedic point of view, the main difference between the pediatric and the adult skeleton is the growth, which is more pronounced in the metaphyseal regions of the long bones. At least 75% of bone sarcomas arise in the vicinity of growth plates. Therefore, their treatment, which is based on neoadjuvant chemotherapy and wide surgical removal of the tumor, leads to growth loss in skeletally immature patients. For this reason, the skeletal maturation status of the patient, needs to be taken into consideration in the decision-making process, for each individual pediatric case.

1.2 OSTEOSARCOMA

Osteosarcoma is a neoplasm that arises primarily from the bone, made of malignant mesenchymal cells that typically produce osteoid matrix or immature bone tissue. Very rarely this type of tumor can also arise primarily from the soft tissue (extra-skeletal osteosarcoma).
The World Health Organization (WHO) divides osteosarcomas in central and superficial tumors, based on their position of origin, either inside the bone or on the bone surface. Furthermore, there are several histotypes, all with different histopathological appearances, biological aggressiveness, and typical localizations and patient characteristics. The most frequent subtype is the high -rade central osteosarcoma, which accounts for approximately 80% of all osteosarcoma cases.
The pathogenesis of osteosarcoma is still unknown. The only certain agent that is directly related to the development of osteosarcomas, is ionizing irradiation. It is estimated that approximately 2% of all osteosarcomas are, especially in the adult patients, is caused by irradiation. The risk of osteosarcoma after irradiation is directly correlated to the radiation dose. Furthermore, there are several hypotheses on the pathogenesis, like, for example, the viral origin. However, most researchers believe that there is a multifactorial cause for osteosarcoma development. It seems plausible that genetic factors also play an important role in this perspective. There are numerous reports of families in which more than one osteosarcoma patient was present in the same nucleus. A certain predisposition for osteosarcomas has been shown in patients who have had a retinoblastoma and in patients with Li-Fraumeni syndrome.

Epidemiology
Osteosarcoma is the most frequent primary malignant bone tumor. In Italy, there is an estimate of 500 new cases of primary malignant bone tumors every year. Approximately 20-25% of these are osteosarcomas. Of all malignant neoplasms, only 0.2% are osteosarcomas, which makes it a rare tumor type.
The peak incidence is in the second decade of life and approximately 75% of all osteosarcomas occur between 15 and 25 years of age. Very rarely an osteosarcoma arises before 6, or after 60 years of age. For the age distribution, see Figure 2.

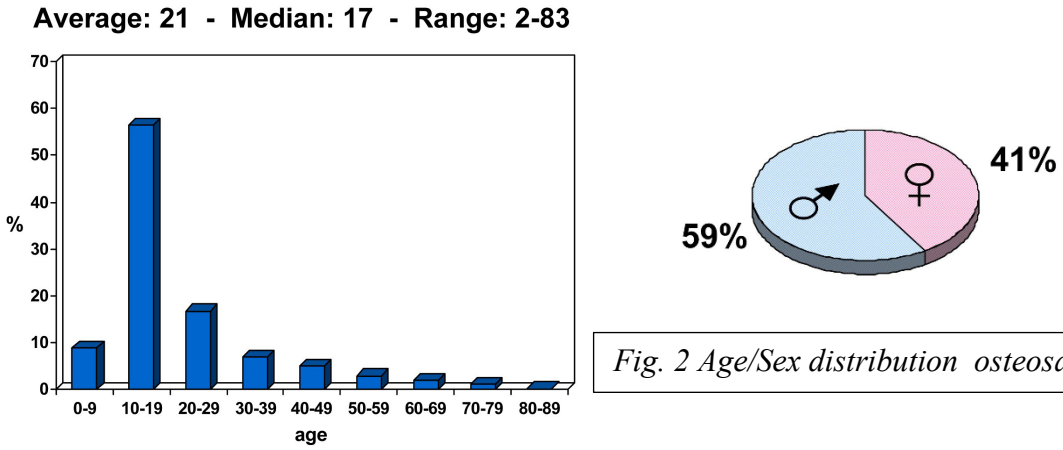


Fig. 2 Age/Sex distribution osteosarcoma

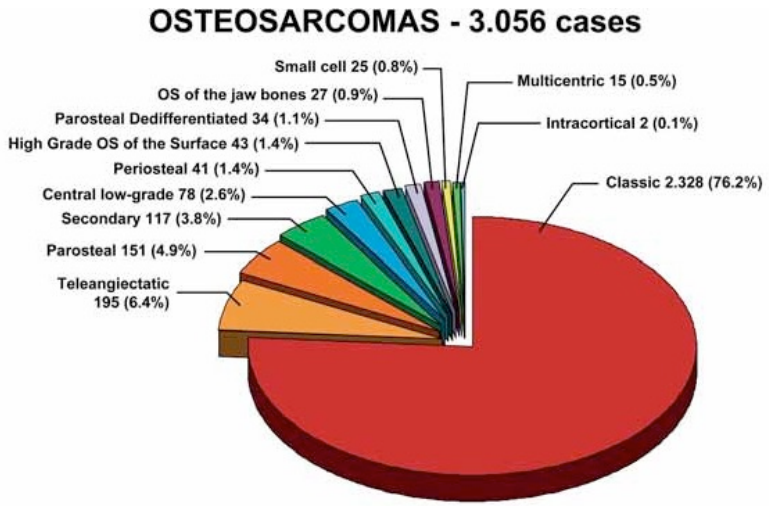
1900-2012 - Istituto Ortopedico Rizzoli - Laboratory of Experimental Oncology - Section of Epidemiology - Bologna - Italy

Genetics and molecular biology

The pathogenesis of osteosarcomas is yet unknown and osteosarcomas have complex and variable karyotypes. For certain, exposure to irradiation is a predisposing factor. There is a direct correlation between the radiation dose and the risk of osteosarcoma. Radiation induced osteosarcomas are rare, accounting for approximately 4% of all osteosarcomas is large series. Alterations in the onco-suppressor gene p53 increase the risk of osteosarcoma. Osteosarcomas are found in approximately 30-50% of patients with a mutation or deletion at the p53 gene. For example, patients with Li-Fraumeni syndrome, characterized by alterations of the p53 gene, have a high risk of developing osteosarcomas during their life, besides many other primary tumors. Another gene with an important role in osteosarcoma pathogenesis is the retinoblastoma gene. It has been demonstrated, that patients with alterations of the retinoblastoma gene have a 500 times higher risk of osteosarcoma formation than the normal population. Also, in 60% of osteosarcomas, there is a partial or complete deletion of the retinoblastoma gene RB1.

Histopathology and imaging

There are several variants of osteosarcoma, all characterized by different histopathological, clinical and radiographic appearances (Figure 3).



Atlas of Musculoskeletal Tumors and Tumorlike Lesions; Rizzoli Syllabus

Fig. 3 Prevalence of osteosarcoma histotypes

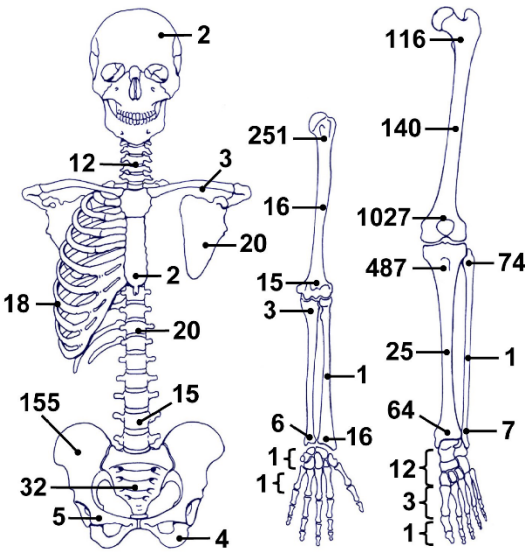


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Fig. 4 Localization of osteosarcomas

The most frequent subtype of osteosarcoma, is the classic high-grade central osteosarcoma, accounting for almost 90% of all osteosarcomas. It is an aggressive, rapidly growing tumor that arises typically in the metaphysis of the long bones in children or young adults (Figure 4).

Atlas of Musculoskeletal Tumors and Tumorlike Lesions; Rizzoli Syllabus

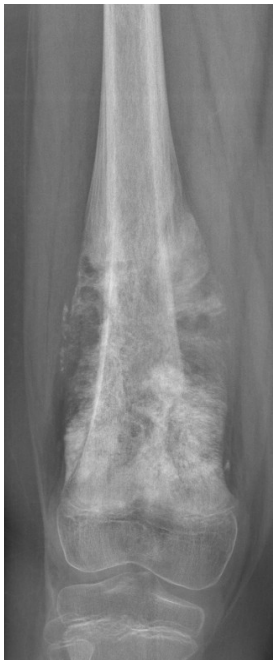


Fig.5 Radiograph of Classic High Grade Central Osteosarcoma

This tumor has a high tendency to metastasize, usually to the lungs, rarely to lymphnodes or bone. On imaging studies, bone destruction is evident, with lytic and sclerotic areas, cortical breakthrough and extraosseous extension, with osteoid matrix in the soft tissues (Figure 5).

Histologically, the tumor is characterized by osteoid formation of the malignant cells. This osteoid matrix has various stages of calcification/ossification,and looks disorganized. When most of the matrix shows ossified differentiation, the osteosarcoma is called osteoblastic. Some osteosarcomas show more chondroid matrix production, and they are called chondroblastic. There is also a fibroblastic type of classic osteosarcoma (Figure 6). The cells are pleomorphic, often spindle shaped, hyperchromatic and show evident atypia. Extensive necrosis and numerous mitotic figures are present.

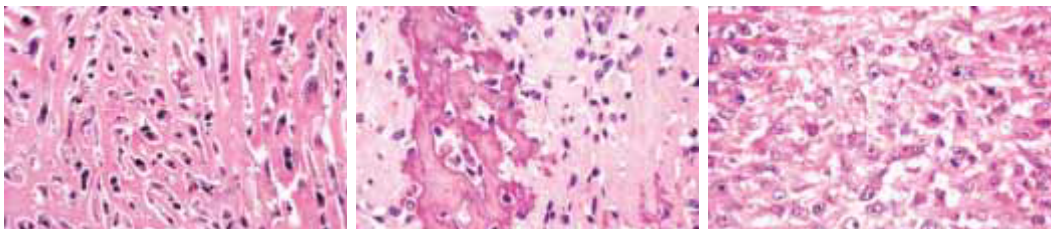
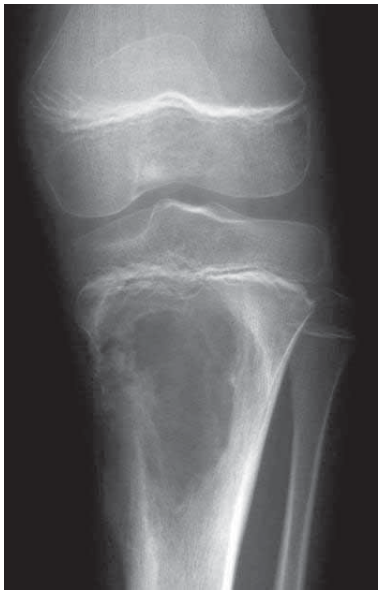


Fig. 6 Histologic variants of classic osteosarcoma

A rare subtype of osteosarcoma is the teleangiectatic osteosarcoma, accounting for 3-5% of all osteosarcomas. This high-grade variant is characterized by the very prominent necrotic and hemorrhagic areas. On radiographs,this type of osteosarcoma presents as a mainly lytic lesion (Figure 7).



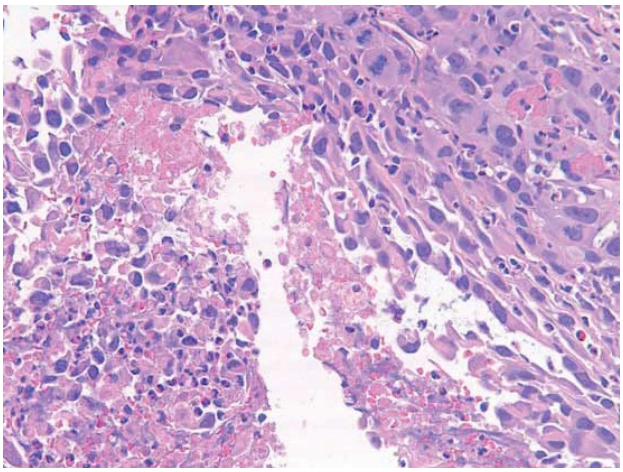


Fig.7 Radiograph (left) and histology (above) of Teleangiectatic Osteosarcoma

Central low-grade osteosarcoma is another rare variant, representing 1-2% of all osteosarcomas. This tumor grows slowly over time and is usually diagnosed in the 2nd or 3rd decade of life. Radiographically they appear as mixed lesions, with lytic and sclerotic areas, and the most frequent site is the distal femur. Patients with a low-grade central osteosarcoma have an excellent prognosis and do not need to undergo chemotherapy.

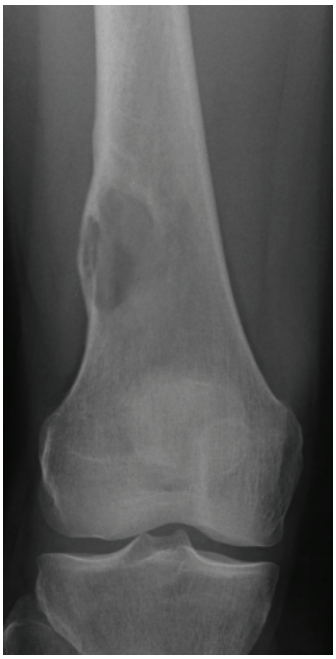


Fig. 8 Radiograph of Low Grade Central Osteosarcoma

There are several subtypes of surface osteosarcomas, together accounting for 5-10% of osteosarcomas. They are characterized by their growth on the surface of the bones. There is a low-grade, very slowly growing variant, called parosteal osteosarcoma. This subtype shows extensive dense and mature osteoid formation, that presents on radiographs as sclerotic tissue on the bone surface (Figure 9).

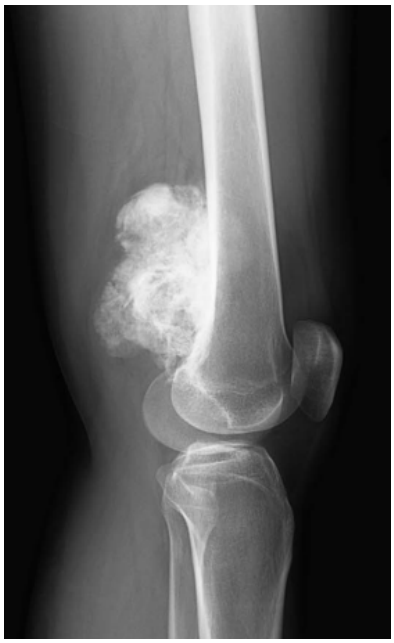


Fig.9 Radiograph of Parosteal Ostesarcoma

The cells show little atypia and only rare mitotic activity. Patients are usually in their 3rd decade of life, and the distal femur and proximal tibia are the most frequent sites. Prognosis is excellent, these low-grade malignant tumors never metastasize, and the treatment is based on only surgical resection. In a third of cases of parosteal osteosarcoma, there are areas of high-grade tumor. This variant is called dedifferentiated parosteal osteosarcoma. If the high-grade areas are frequent, chemotherapy treatment is suggested because of the higher risk of metastatic disease. Another surface variant is the periosteal osteosarcoma. This tumor typically on the surface of the diaphysis of long bones, grows relatively slowly, causing a lytic footprint on the bone from the outside. On radiographs, some subtle osteoid matrix may be seen. Histologically, this variant is characterized by mainly uncalcified chondroid matrix with some central osteoid formation. This tumor is considered intermediate grade. Prognosis is relatively good, with low risk of metastasis. For this reason, chemotherapy is not part of the standard treatment for this rare subtype. The last surface variant is the high-grade surface osteosarcoma. This is an aggressive, rapidly growing malignancy, showing local bony destruction from the outside and soft tissue extension. Metastases are frequent and prognosis is poor. This subtype is requires treatment with chemotherapy and wide surgical resection.

An extremely rare subtype of osteosarcoma is the small cell osteosarcoma. This subtype is characterized by the main tumor cells that appear as small round cell, like in Ewing sarcoma, but there is extensive osteoid matrix and more pleomorphism than in Ewing sarcoma. This tumor has a poor prognosis, and treatment is based on chemotherapy and surgery.

There are rare forms of secondary osteosarcomas that arise in elderly patients. These can arise on benign or pseudotumerous lesions like fibrous dyplasia, Paget's disease or bone infarcts. These tumors are generally highly aggressive and arise around the 6th or 7th decade of life.

Signs and symptoms

Pain is usually the first symptom of osteosarcomas. Although pain may be initially only present on weightbearing, soon the cortical destruction and periosteal stressing will lead to continuous pain, independent from activity or load bearing. Especially in children, if bone or joint pain is not clearly associated with a trauma or injury, and is persistent or progressive, one should investigate further starting with a plain radiograph. Local swelling is another early sign and is usually progressive. This is caused by the soft tissue extension of the pathological tissue, that is typically surrounded by reactive inflammatory tissue giving rise to further swelling and pain. A pathological fracture is caused by weakening of the bone. This happens in approximately 15% of the cases.

Alkaline phosphatase (AF) and lactate dehydrogenase (LDH) and the erythrocyte sedimentation rate (ESR) are usually elevated in the blood tests.

Treatment

The treatment of osteosarcomas is based on a combination of chemotherapy and wide surgical resection. Before the introduction of effective chemotherapy in the 70s, the prognosis for patients with high-grade osteosarcoma was very poor, with a 10-year overall survival between 10 and 20%. The current standard of treatment is represented by preoperative multidrug chemotherapy, wide surgical excision, and postoperative multidrug chemotherapy. Wide surgical excision means that the tumor has to be covered circumferentially by a layer of normal tissue (Figure 10).

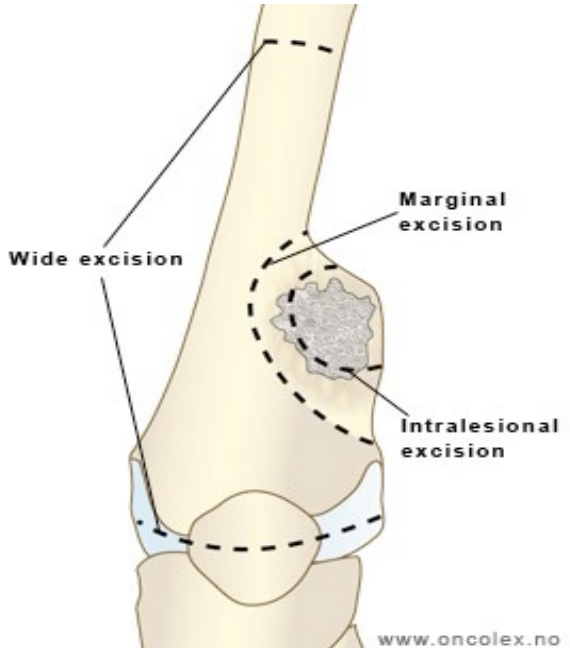


Fig.10 Classification of surgical margins

The amount and quality of normal tissue that is required to obtain wide margins is controversial. However, there is no advantage in terms of local control when radical margins are obtained, for example by amputation. Instead, local recurrence risk is increased when resection is performed through tumor tissue (intralesional excision) or reactive tissue around the tumor (marginal excision). The response to preoperative chemotherapy is essential to determine the treatment strategy in the postoperative period. Response to chemotherapy can be measured clinically, radiographically, and, above all, histologically, by an estimate percentage of necrosis of the tumor cells. Metastatic disease is treated by chemotherapy, and whenever possible, by surgical excision of the metastatic lesions. Osteosarcomas are not particularly sensitive to radiotherapy, which is not part of the standard treatment of these tumors.

Prognosis

With modern multimodal treatments, including multidrug neoadjuvant chemotherapy and wide surgical excision, the overall survival of patients with osteosarcomas is around 65-70%. Patients who are metastatic at diagnosis have a worse prognosis. Also, tumors in the axial skeleton do worse than in the extremities. Tumor size or volume is an important prognostic factor and also age influences survival. Patients younger than 14 and older than 40 years tend to have a worse outcome. LDH and FA in the lab tests have a predictive value for outcome and finally, the response to preoperative chemotherapy is an important prognostic factor. Patients with a good response to induction chemotherapy (more than 90% necrosis of the tumor cells) have a 5-year survival of 80%. Survival is 40% for patients who have a poor response.

Follow-up

Patients with osteosarcomas need follow-up visits for at least ten years after completion of their treatment. Surgical complete remission is essential for survival. Local and distant disease relapse have a negative effect on outcome. Follow-up visits should include a specific examination of the operated area and at least an exam of the thorax, as the lungs represent the most frequent site of metastases. More rarely osteosarcomas can recur in the bones, lymph nodes or soft tissues.

1.3 EWING SARCOMA

This malignant bone tumor was first described in the radius of a 14-year old girl, by Dr. James Ewing, in 1920. This tumor has a neuroectodermal origin and can arise anywhere in the skeleton, both in the long bones and the flat bones (Figure 11). But rarely, it can even arise in the soft tissues. The most frequent sites are the femur, tibia, humerus and fibula in the long bones, pelvis, spine, scapula and ribs in the flat bones.

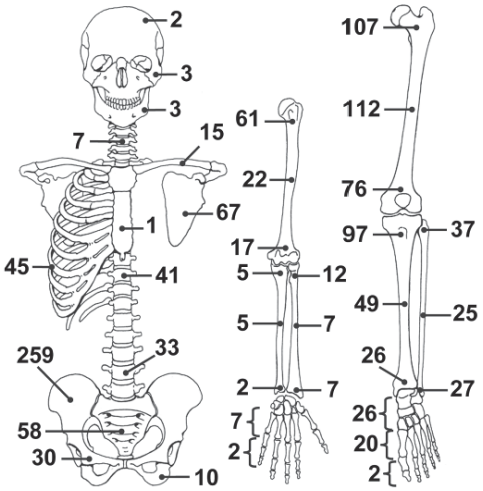


Fig.11 Localization of Ewing Sarcoma

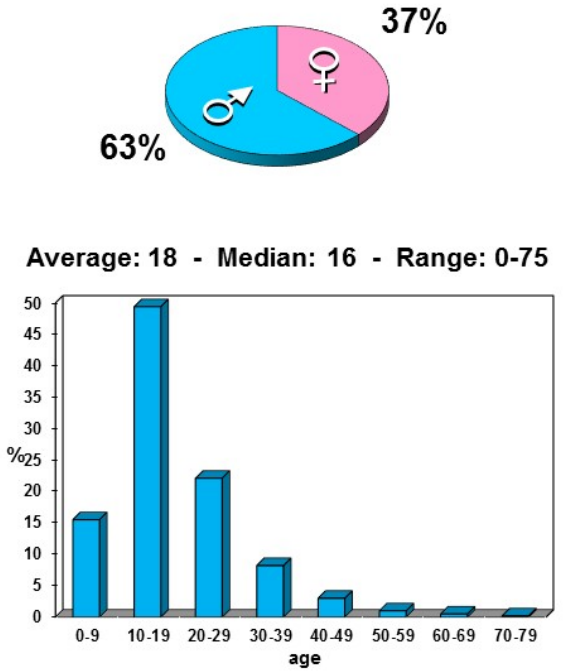


Fig.12 Age/Sex distribution Ewing Sarcoma

Epidemiology

Ewing sarcoma represents 6-8% of all primary malignant bone tumors. In patients below 20 years of age, it is the second most frequent malignant bone tumor, after osteosarcoma. Below age 15, it has an incidence of 2.7 cases per million. Peak incidence is in the second decade of life (Figure 12), and the male-female ratio is 1.5:1.

Genetics and molecular biology

The pathogenesis of this tumor is yet unknown. Molecular analysis has demonstrated common genetic alteration in most Ewing sarcomas. A specific translocation between the EWS and the FLI1 gene, is present in approximately 85% of the cases. Other translocations involving the EWS gene, like t(21;22) t(7;22) and t(17;22) are present in 5-10% of the cases.

Histopathology and imaging

Histologically, this tumor is characterized by monotonous sheets of small round cells, with hyperchromatic nuclei in scarce cytoplasm (Figure 13).

No specific matrix is produced by the tumor cells. Immunohistochemistry shows positivity for CD99, S-100 and vimentin.

Ewing can arise just about anywhere in the skeleton. On radiographs aggressive features are present. Periosteal reactions and reactive bone formation may be seen (Figure 14).

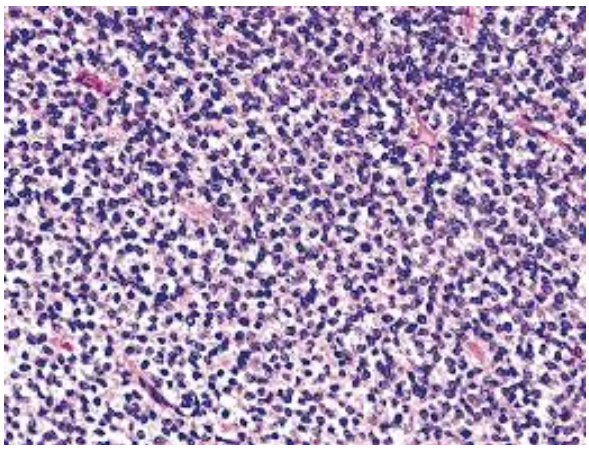


Fig.13 Histopathology of Ewing Sarcoma

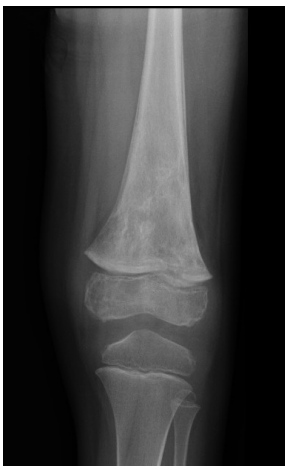


Fig.14 Radiograph of Ewing Sarcoma

The tumor grows rapidly, with an infiltrative pattern, breaking through the cortex and extending into the surrounding soft tissues. Radiographic features might be subtle in the early phase, but CT or MRI scans quickly reveal the aggressive behavior of these tumors.

Signs and symptoms

Like in osteosarcoma, also in Ewing sarcoma, pain is generally the first symptom. The rapid and destructive growth, extending into the soft tissues usually creates a painful swelling. Pathologic fractures may occur, and frequently systemic symptoms like fever and loss of apatite are reported. ESR, CRP and LDH are typically elevated in the blood tests. Sometimes, the differential diagnosis with osteomyelitis can be difficult.

Treatment

Multidrug neoadjuvant chemotherapy is standard practice for Ewing sarcoma. The local treatment can either be wide surgical resection, radiotherapy, or a combination of these. Whenever wide surgical excision is feasible, this is the first choice of treatment. However, in certain difficult to access areas (for example, the sacrum, skull base, spine, pelvis) or in case of metastatic disease, local radiotherapy may become the preferred local treatment. Also, metastatic lesions can either be treated surgically, or by radiotherapy, in combination with systemic treatment. Radiotherapy can have important side effects like radio-induced sarcoma, growth disturbances in children, avascular necrosis, and reduced osteointegration in case of allograft reconstructions.

Prognosis

With modern multimodality treatments, the 5-year survival for patients with Ewing sarcoma is 65%. Stage is the most important prognostic factor. Approximately one third of patients has metastatic disease at presentation. Tumor site, tumor volume, age of patients, response to chemotherapy and LDH, are other prognostic factors.

Follow-up

Patients with Ewing sarcoma require strict follow-up with regular a local examination and chest imaging for at least 10 years, to exclude local recurrence and distant metastases.

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CHAPTER 2

SURGICAL TREATMENT OF BONE SARCOMAS OF THE DISTAL FEMUR IN CHILDREN

2.1 INTRODUCTION

The cornerstone of local treatment for bone sarcomas is wide surgical resection. In the past, this was obtained by very debilitation surgery, like amputations and disarticulations. After the introduction of neoadjuvant chemotherapy in the 70s, the prognosis for patients with bone sarcomas increased from 10% to approximately 65% survival at 5 years. This prognostic improvement has raised the need for limb salvage surgery and long-lasting reconstructions. Nevertheless, demolitive surgery is still required in about 5-10% of patients who present with bone sarcomas of the distal femur. Above-the-knee amputation has a dramatic impact on quality of life, with important loss of function and difficult control of an external prosthesis because of the relatively short stump. Whenever the sciatic nerve can be preserved, a rotationplasty offers the patient a clear functional advantage over an above-the-knee amputation.

Whenever the extensor mechanism, sciatic nerve and main vessels can be preserved or reconstructed, limb salvage is feasible. In this case, several reconstructive options are available for the distal femur: endoprostheses, massive bone allografts or prosthetic allograft composites all may offer good to excellent function, but septic and mechanical failure remain a major concern.

Modular megaprostheses have the advantage that they are widely available, surgery is relatively easy and the functional outcome is overall good and predictable. Massive bone allografts have the advantage that they restore bone stock and allow for better soft tissue reattachment. The disadvantage of these implants is that the joint surface deteriorates quickly, mechanical complications are frequent, and surgery is relatively complex. Furthermore, allografts require high quality bone bank facilities, that are not everywhere available. Because of the high complication rate, nowadays, osteoarticular allografts are hardly ever for reconstruction of the distal femur. Allograft-prosthetic composites join the advantages of good function, bone stock restoration, and possibility soft tissue reattachment. However, the complex surgery and need for bone bank facilities, make this technique unpopular. Currently, endoprosthetic reconstruction is the most frequently used reconstruction method of the distal femur for both adults and children.

There are specific problems associated with the reconstruction of the distal femur in children, that make limb salvage reconstructions in this patient group particularly challenging. The high turnover and elasticity of the bone, anatomical small size, and potential growth loss need to be addressed. Furthermore, young children usually present limited compliance, and require long implant survival, in spite of their high functional demands.

Therefore, for this thesis, a study was performed that looked specifically at the megaprosthetic implant fixation in children. In this age group, due to the high bone turnover, there is generally an evident reaction to the presence of an endomedullary stem inside the host bone. The reaction to this stem and the different fixation methods, can lead to gradual loss of bone stock and implant mobilization. The study describes the radiographic changes that can be seen around the femoral stem of distal femoral replacements in children, and their prognostic importance to implant fixation.

In another study, a surgical technique to overcome the problem of a short residual femoral stump after primary bone tumor resection or after implant revision, was described.

Finally, a study was performed that determines the efficacy of the smooth tibial stem. This endoprosthetic component is designed specifically for reconstruction in children who undergo distal femoral replacements, to allow for continuous growth of the proximal tibia. In this study, different types of tibial components have been studied on both implant survival, and preservation of growth.

2.2 DEMOLITIVE SURGERY

Prior to the introduction of chemotherapy in the 70s, bone sarcomas were routinely treated with radical demolitive surgery. For patients with sarcomas of the distal femur, this meant an above-the-knee amputation or hip disarticulation. In spite of this drastic surgery, the prognosis for these patients was invariably poor. In 1975, Price et al reported on the outcome for 125 children who had been treated with early amputation after the diagnosis of a lower limb osteosarcoma. Only 12% was disease-free at 5 years. In the same period, Campanacci et al presented their experience with the treatment osteosarcoma in 345 patients. Only 11% was still alive at 10 years. Thanks to the introduction of multimodality treatment and intensive chemotherapy, over the following decade the prognosis for sarcoma patients quickly improved. It also became clear, that wide surgical resection was just as effective as a local treatment as radical surgery, and therefore patients could survive even after limb-salvage surgery.
The decision on whether limb salvage surgery is feasible depends mainly on tumor extension, site, involvement of neurovascular structures, joints and surrounding soft tissues. Also, stage of disease, overall prognosis, patient age, general health conditions, and functional expectations are taken into consideration. Whenever the main neurovascular structures are involved and require sacrifice to obtain wide surgical margins, there is an absolute indication for demolitive surgery. The level of amputation is based on tumor extension. As a general rule, the amputation stump should be kept as long as possible, to obtain the best functional result. A long stump has biomechanical advantages over a short stump and allows the patient for better control of an external prosthesis.

2.2.1 Above-the-knee amputation

For sarcomas of the distal femur, an above-the-knee amputation remains a rapid, save, inexpensive and relatively simple operation. Although technically not particularly demanding, there are some specific aspects that require special attention in pediatric patients.
As in any other cortical bone, the proximal and distal epiphyseal growth plates are responsible for growth which takes place mainly at one end of the bone. In the femur, the contribution of the distal growth plate is about 70 per cent whilst only 30 per cent is provided by the proximal plate at the femoral head and the greater trochanter. The loss of the distal epiphyseal plate therefore greatly retards the growth in length of the femur. The younger the child at the time of amputation, the greater will be the disproportion between the length of the remaining femur compared with the amputated side. For example, an amputation between the middle and distal third at the age of 2 years will become a very short stump once the patient has reached maturity. Stump revision due to overgrowth is uncommon in the femur, however the end of the bone can become very sharp because of the lack of growth and it may be necessary to round this edge with a minimum of further shortening.
If the tumor extends to the proximal third of the femur, a hip disarticulation may become necessary (Figure 1). In this case, the absence of a functional amputation stump has dramatic consequences for functional outcome, quality of life, and patient satisfaction.
For very young children, younger than 4-5 years of age, who have a sarcoma of the distal femur, demolitive surgery is generally preferred over limb-salvage surgery, as it offers the patient a

better functional result and quality of life. The limb sparing alternatives in this age group are usually unsuccessful, because of the small size and enormous loss of growth potential.

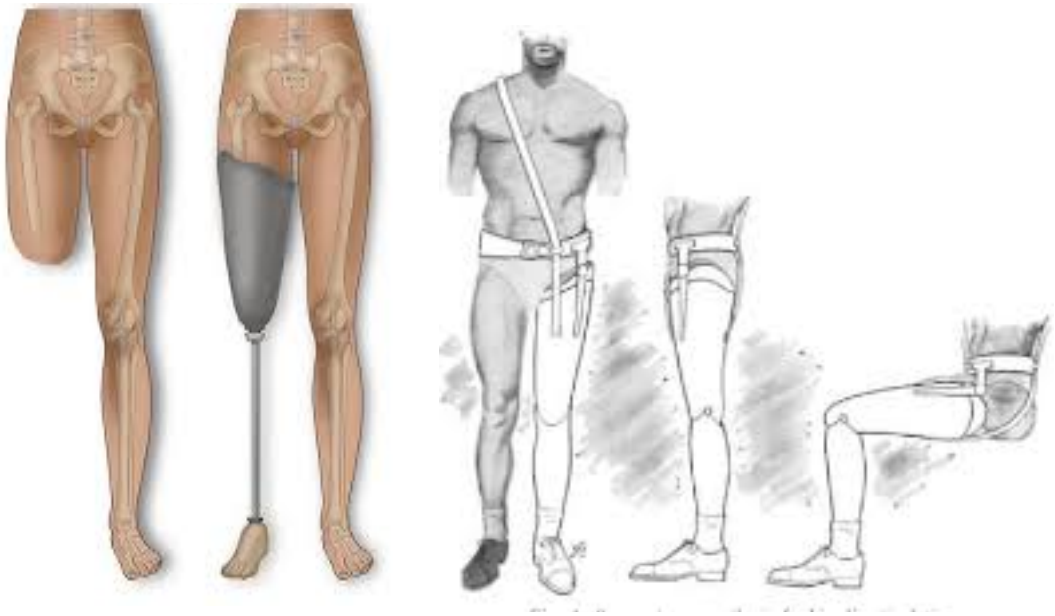


Fig.1 Above-the-knee amputation and hip disarticulation with external prosthesis

Overall, children can more readily adapt to amputation than adults can. In this light, a single amputation surgery, with a reliable and functionally acceptable outcome, may be preferred over a limb-sparing procedure with an uncertain outcome. Especially, considering the fact that limb-sparing reconstructions in children generally have a high complication rate and often require multiple future surgical interventions. The gradual evolution of prosthetic materials and limb-fitting techniques, has led to significant improvements in function with also the possibilities to perform high level sports activities for amputees.

2.2.3 Rotationplasty

A special type of 'partially demolitive reconstruction' is the rotationplasty (Figure 2). In this technique, the original knee, including the distal part of the femur in case of a sarcoma at this site, is excised but the sciatic nerve is preserved, and the vascular structures are spared or reconstructed. Rotating the distal part of the lower leg with a well-functioning ankle and foot, and fusing this segment to the proximal part of the femur, a new 'knee joint' is created, with the ankle fitting into a below-knee prosthesis (Figure 3).

While limb salvage surgery, through the years, has become more popular, the indication for rotationplasty has slowly decreased. However, even today rotationplasty may be indicated in a selected group of patients. Especially in very young children, under the age of 5 years, in cases with substantial vascular involvement, or when the tumor involved the whole anterior compartment of the thigh, this procedure offers functional advantages over an above-the-knee amputation and is more durable than an endoprosthesis.

This technique was first described by Borggreve in a 12-year old boy who had a stiff knee from tuberculosis. Later, this technique was popularized by Van Nes, who used it to improve function and quality of life, in patients with a congenital limb deformities. Winkelmann made a modified classification of rotationplasties based on reconstructions after tumor resections at different levels of the lower limb.

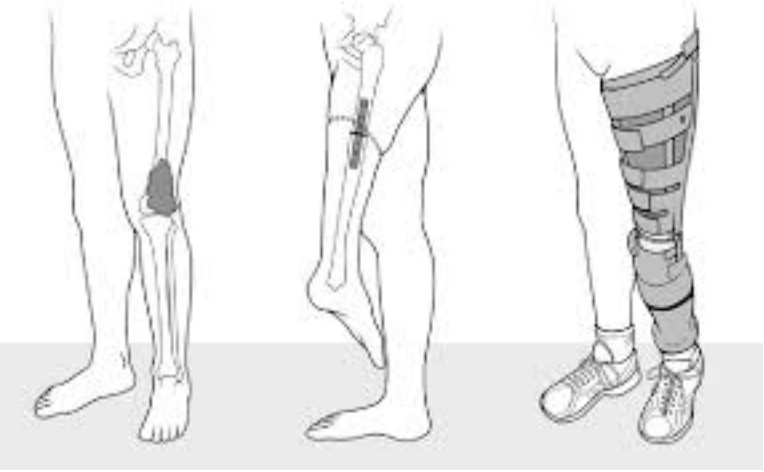
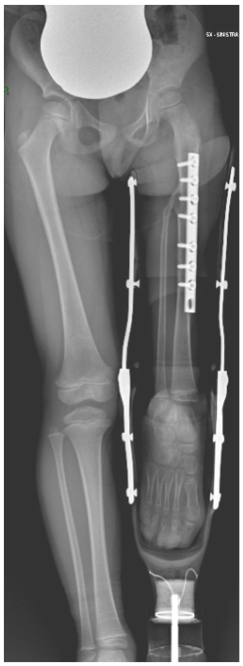


Fig.2 Schematic illustration of a Type A1 rotationplasty. The distal femur is removed, the remaining leg and foot are rotated 180° and reattached to the residual femur. This creates a new knee joint that can be used to control an external prosthesis.



There are well-demonstrated functional advantages of rotationplasty over an above-the-knee amputation. Thanks to the new 'knee joint' the patients can reach very high functional levels, that are similar to those for patients with below-the-knee amputation. Even compared to patients with endoprosthesis, rotationplasty patients have less restrictions in their daily activities and sports exercises. Also, quality of life scales in these patients do not differ significantly from a control population. However, the biggest controversy for this procedure is the cosmetic appearance without a prosthesis which makes this operation not acceptable for every suitable candidate.

Fig.3 Radiograph after rotationplasty for a sarcoma in the distal femur

2.3 LIMB SALVAGE SURGERY

Historically, limb-salvage surgery has been less eagerly adopted for pediatric patients compared to adults. One of the reasons is the superior adaptive potential of children to demolitive surgery. Furthermore, the small sized anatomy of immature patients, creates reconstructive challenges. But the main issue, is the sacrifice of the distal femoral physis and loss of growth potential in children, leading to significant limb length discrepancies at skeletal maturity and important functional limitations in adulthood.
With improved survival prognosis, thanks to multimodality treatments, and improved reconstructive options thanks to bone bank facilities and orthopedic implant development, limb salvage indications have been gradually extended to the pediatric population as well. When limb salvage surgery was compared with demolitive surgery in observational studies, a significant number report better function, lower lifetime costs, and similar oncologic outcomes for patients with limb salvage. Several surgical techniques can be taken into consideration for reconstruction of the distal femur in children. Metallic endoprostheses, massive allografts, and prosthetic allograft composites have been used to recreate this bone segment in patients who underwent tumor resection. However, the evidence available to decide the best limb salvage treatment in children with a distal femur tumor is limited and inconclusive. This is partly due to the rarity of these diseases in children. Most of the literature available on this subject is based on small case series. An additional limitation from these series comes from their heterogeneity in patient age and anatomical sites. Distal femur, proximal tibial and proximal femur reconstructions are often considered included in the same study, but behave differently in terms of outcome, complications and failure.

2.3.1 Allografts

Since the 60s, massive frozen bone allografts, harvested from donor cadavers, have been used for skeletal reconstructions after bone tumor resections. Allografts can be easily adapted to the bone defect, have a high biocompatibility and thanks to a partial osteointegration, they can restore the bone stock. The main advantage of bone allografts though, is the possibility to reattach soft tissues (muscles and tendons) to their anatomic tendon insertions, with significant functional advantages for the patient. Allografts may be used in various patients (Figure 4), with different ages, different disease sites and resection lengths, and can also be used in combination with vascularized autografts and endoprostheses.
Unfortunately, allografts are frequently complicated by infection, fracture and non-union. Due to the cryopreservation process, the chondrocytes in the joint surfaces of allografts have limited viability. For this reason, degenerative changes and subchondral fractures are common problems in osteoarticular allografts. Finally, the surgical procedures are technically demanding and associated with a relatively long learning curve.

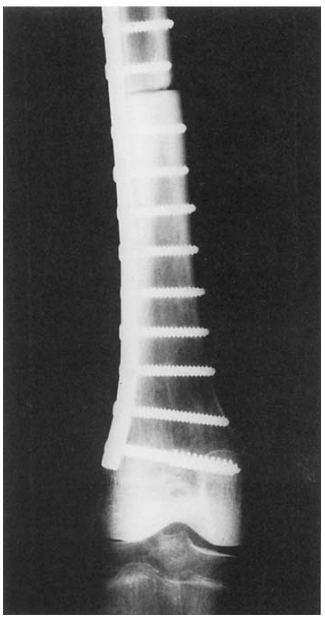
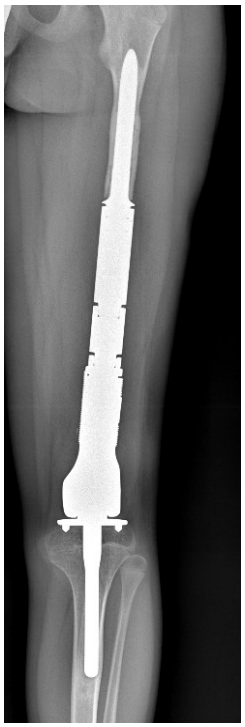


Fig.4 Osteoarticular allograft reconstruction the distal femur.

Several technical modifications have improved the durability of these reconstructions. Filling of the medullary canal with polymethylmetacrylate (cement) and adequate osteosynthesis can reduce the risk of graft fracture. Step-cut osteotomies and autograft from the iliac crests are used to reduce the non-union rate. Navigated surgery and personalized cutting block reduce the operating time and, therefore, the infection risk. However, due to the unpredictable outcome and frequent complications of allograft reconstructions compared to endoprostheses, and the need for bone bank facilities for this demanding technique, nowadays, osteoarticular allografts are hardly ever used after tumor resections of the distal femur.

There is still an indication for intercalary allografts, whenever the distal femoral epiphysis can be spared. In children, physeal distraction has been applied to allow for this type of reconstruction. In long resection segments, intercalary allografts are sometimes combined with a vascularized fibular autograft to reduce the risk of complications.

2.3.2 Endoprostheses



Modular endoprosthetic reconstructive systems (Figure 5) are widely available, off the shelve, for adult patients who undergo distal femoral resection. The high versatility and long durability of these systems make them a popular resource for reconstruction of this segment. There are several modular reconstruction systems on the market. The length of the implant can be adapted during surgery, based on the tumor resection length, by adding cylindrical components of different sizes. Over the years, innovation in implant design has moved from fixed to rotating hinge endoprosthetic replacements, that may be cemented, press-fit or compressed. Wear, loosening, implant breakage and infection are complications that are associated with modular endoprosthetic implants, although they have diminished since the introduction of modern implants. Functional outcome and implant survival have gradually improved through the years. Most patients obtain good to excellent function with implant survival that exceeds 80% at 10 years. The endoprosthetic impant allows them to walk, cycle, drive a car and cyclic sports activity with an overall good quality of life.

Fig.5 Radiograph after endoprosthesis for a distal femoral bone tumor

2.3.3 Allograft-prosthetic composites

The combination of massive allografts and revision-type prosthesis is a reconstruction technique that joins the advantages of an endoprosthetic reconstruction (early rehabilitation, long durability, versatility) with the advantages of allografts (bone stock restoration, soft tissue reattachment, improved outcome). This type of reconstruction has been used frequently in the proximal femur, proximal tibia and proximal humerus, as in these segments there are important muscle and tendon structures that with an anatomical reattachment can improve the final functional result. Less frequently, this technique has been used in the distal femur (Figure 6) where tendon and muscle reattachments are less important for function.

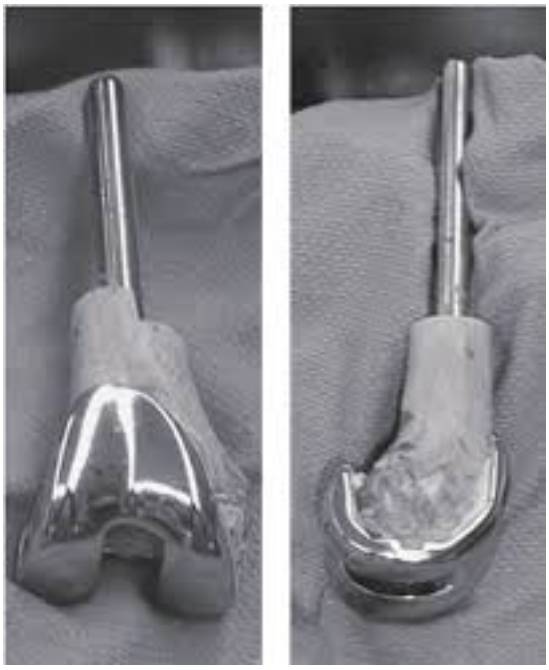


Fig.6 Allograft-Prosthesis composite of the distal femur.

2.4 PROBLEMS OF DISTAL FEMORAL RECONSTRUCTIONS IN CHILDREN

There are several issues that make distal femoral reconstructions in children particularly challenging.

First of all, children have high functional demands and are generally less compliant than adult patients. Because of their young age and a potentially long survival time, it is essential to create a durable reconstruction. As they are likely to need further surgeries in the future, it is preferable to preserve or restore bone stock as much as possible.

The small anatomy of pediatric patients can be a problem in both prosthetic and allograft reconstructions. Standard modular prostheses are available in limited sizes, that are often not compatible with the small size femur and tibia of young children. Allografts are harvested from adults, and therefore difficult to adapt to children, especially osteoarticular allografts that require exact congruency with the opposite joint surface.

Also, endoprosthetic implant fixation can be challenging in children. The high bone turnover in children is the cause of frequent bone remodeling. In case of a well-fixed stem, the load forces by-pass the surrounding bone that gradually disappears according to Wolff's law ('bone remodels in response to forces applied to it'). This phenomenon is known as stress shielding. On the other hand, in case of a loose stem, either septic or aseptic, activated macrophages and osteoclasts will cause osteolysis and bone resorption.

Finally, the loss of growth potential is a major issue in pediatric reconstructions, especially in the distal femur. The distal femoral physis is responsible for 60-70% of growth of the femur,

which accounts for almost 1cm of growth per year. In females, skeletal maturity is reached around 14 years of age, in males around 16 years of age. Loss of growth potential is not easily addressed by standard modular adult-type implant design, which requires revision surgery with partial substitution of the components to be lengthened. At the proximal tibia, an invasive adult type tibial component, requires extensive bone sacrifice causing a fusion of the proximal tibial growth plate. Loss of growth at the proximal tibia, added to the removal of the distal femoral physis in young children, will eventually lead to an important limb length discrepancy at skeletal maturation. Allografts do not address the problem of growth loss at the distal femur, but they do avoid damage to the tibial proximal physis.

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2.5 CLINICAL STUDIES

2.5.1
The clinical importance of different bone remodeling patterns around the femoral stem in pediatric patients with distal femoral megaprostheses

Introduction

Background: Osteosarcoma and Ewing sarcoma are primary malignant bone tumors that typically arise in children or young adults. For both neoplasms, the most frequently involved site is the distal femur, where the standard surgical treatment is wide tumor resection and reconstruction with a megaprosthesis. This implant can be a modular or custom prosthesis, with or without expansion potential, and is fixed to the host bone with either a cemented or uncemented stem.

In the course of their follow-up, patients with megaprosthetic implants of the distal femur often show bone remodeling around the femoral stem. Change in load stresses, foreign body reactions, infection and implant micromovements, can play a role in this process and can lead to changes in shape, diameter, density, and architecture of the surrounding bone. Due to high bone turnover, the remodeling process can be more pronounced in the pediatric skeleton.

Rationale: Bone remodeling and resorption around the stem of a megaprosthesis can potentially reduce the quality of implant fixation and lead to mechanical failure. Due to the changing biological properties of their bone, generally high functional demands, and potentially long survivorship, children are at high risk of mechanical failure and revision surgery over time. In the literature, there is lacking data about how to interpret bone remodeling around femoral stems in megaprosthetic implants in this age group, and about its clinical importance.

Research question: The aim of this study was to provide specific information on the radiographic changes that can be seen around the stem in pediatric patients with megaprostheses of the distal femur, and to try to determine their prognostic impact on implant survival. We therefore asked: What patterns of bone remodeling can we recognize? (1); how often is evident bone remodeling associated with failure of the implant fixation? (2); which factors are associated with failure of stem fixation in this setting? (3). Finally, we describe surgical techniques to prevent and address mechanical complications related to bone resorption in pediatric patients.

Materials and Methods

A retrospective study was performed of all patients, under the age of 13 years, who underwent a distal femoral replacement with a megaprosthesis in our Institute, in the period between 2000 and 2015. Only primary distal femoral replacements, at the time of tumor resection, were included.

Clinical charts and radiographs were reviewed for all cases. The study period started from 2000 in order to include only 'modern design' implants and digitalized imaging studies. Cases with a follow-up of less than one year were excluded.

Clinical data on patient factors (age, gender, weight, height), tumor factors (diagnosis, length of resection, adjuvant treatments), reconstruction factors (type of implant, implant sizes, fixation technique of the femoral stem) and complications, were extracted from the clinical charts. Complications were classified according to the ISOLS classification.

Different types of megaprosthetic designs were used in this time frame, including expandable and non-expandable implants, rotating hinge and fixed hinge prostheses. Different types of femoral stem fixation were used: uncemented or press-fit fixation, classic cementation (≥1mm

thickness of the cement mantle), line-to-line or minimal cementation (<1mm of cement mantle). All implants had a classical endomedullary stem fixation.
Anteroposterior digital radiographs were reviewed for all cases to determine changes in bone shape, presence of osteolytic areas and periosteal reactions. Bone diameter was measured at three different levels of the femoral stem. Level A at the tip of the stem, B halfway the stem and C one centimeter proximal to the bone-prosthetic junction (see Figure 1).

A difference in bone diameter of more than 2mm in adjacent levels at the same radiograph, was considered positive for bone resorption secondary to stress shielding.

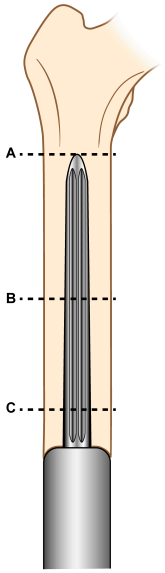

Fig.1 Measurement of femoral diameter was performed at three levels. A: at the apex of the stem; B: halfway the stem; C:at 1cm from the bone-prosthesis junction

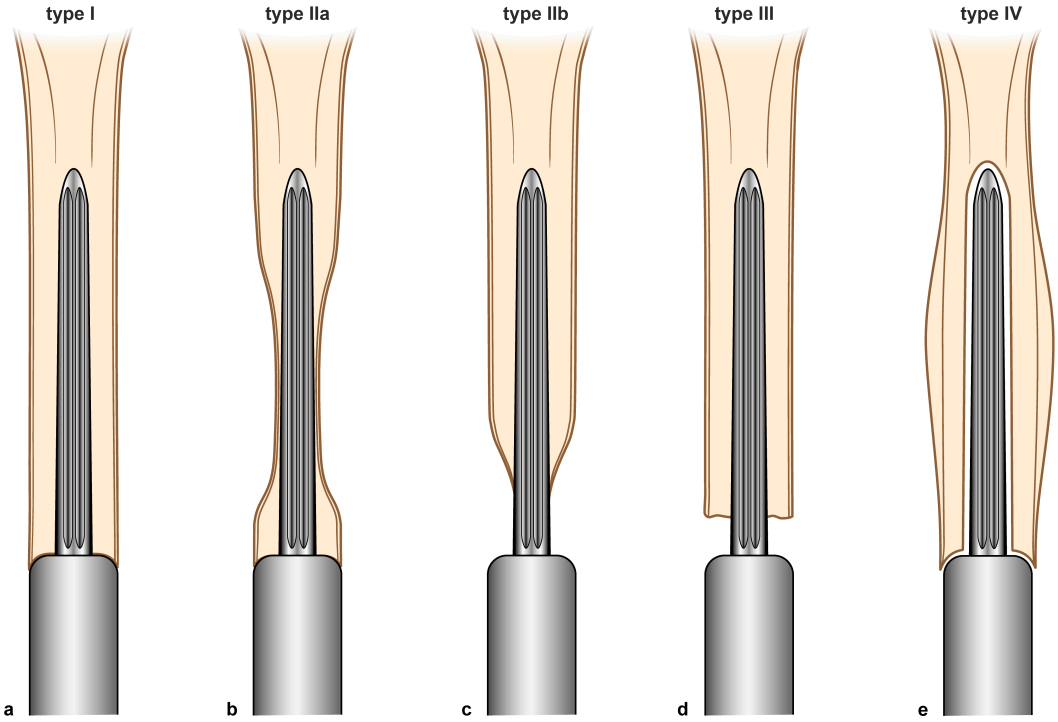

Fig.2 Four remodeling patterns were identified. Type I: symmetrical growth of the femur. Thype IIa: stress shielding halfway the stem. Type IIb:stress shielding near the junction. Type III: debris related osteolysis. Type IV: loosening related changes.

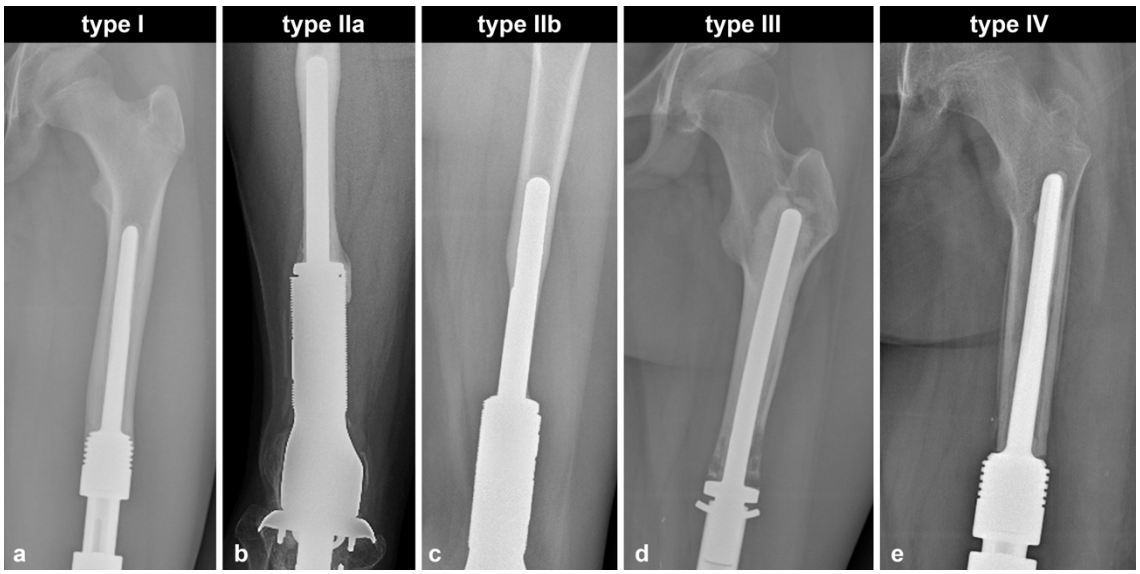

Fig.3 Radiographs of the remodeling patterns

Four different patterns of bone remodeling around the stem were recognized and the cases were classified accordingly (Figure 2 and 3). Type I was considered normal, without changes in bone shape and symmetrical increase of the femoral diameter over the three different levels due to skeletal growth. In Type II remodeling, the femoral bone showed gradual resorption around a well-fixed stem, a process known as 'stress shielding'. This pattern of bone resorption along the shaft was either present halfway the stem (Type IIa), or near the bone-prosthesis junction (Type IIb). In some cases, the remodeling pattern slowly changed over time from Type IIa to a Type IIb. Type III remodeling was an irregular and relatively well described bone resorption near the bone-prosthesis junction, which represents the osteolytic reaction to particle debris. Finally, a longitudinal periosteal reaction or cortical widening, often associated with a radiolucent stem-bone or cement-bone interface was seen in Type IV remodeling, which is secondary to prosthetic micromovements. Both septic and aseptic loosening can cause this type of remodeling. If more than one type was present, the case was classified according to the pattern that was most significant at the last radiograph.
Femoral stem removal was considered the primary end-point of mechanical failure, as some of the reconstruction systems used in this series allow for partial implant revision with retention of a well-fixed femoral stem, in case of failure of the prosthetic body or tibial component.
We evaluated radiographs that were taken immediately post-operatively, at 1 year follow-up, 2 years follow-up, and at the last available follow-up radiograph; either at the most recent outpatient visit or at the time of femoral stem removal.

Results

Patients

Forty-six patients were included in this study. Half were males and half were females. The mean age at the time of resection was 9.4 years (ranging from 5 years and 3 months to 12 years and 11 months). Two patients were diagnosed with a Ewing sarcoma, whereas the remaining patients had an osteosarcoma. Eight patients died of disease, seven had at least one event of disease relapse but were free of disease at final follow-up, and the remaining thirty-one patients were continuously disease free.

Prostheses

Of the different prosthetic designs that were used for reconstruction, 24 were expandable implants (14 Stanmore Juvenile Tumour System, 9 Wright Repiphysis, 1 Stryker custom minimally-invasive expandable prosthesis). The remaining implants where all modular distal femoral replacements with standard available stems (15 Stryker GMRS, 6 Stryker HMRS, 1 Implantcast Mutars). A total of 32 implants had a fixed hinge, whereas 14 implants had a rotating hinge design.

Twenty femoral stem fixations were uncemented and twenty-six were cemented. In six of these, a line-to-line or minimal cementation technique was applied. The mean stem length was 11.7 cm (range 7.5cm - 14.0cm) and the mean diameter was 10.8 mm (range 8 mm - 15 mm).

Bone remodeling

Average follow-up was 66 months and ranged from 16 to 163 months. Bone remodeling was radiographically evident in 29 cases (63%) at final follow-up. In 17 cases no change of bone shape was radiographically evident.

The most frequent type of bone remodeling was Type II stress shielding. In 6 cases this was seen halfway the stem (Type IIa), in 9 cases near the bone-prosthetic junction (Type IIb). Debris related remodeling, with irregular osteolytic areas near the bone-prosthetic junction was present in 7 cases, and in another 7 cases longitudinal periosteal reaction, cortical widening and/or radiolucent lines (Type IV remodeling) were seen.

Stem revision

A total of fifteen patients had their femoral stem revised at an average of 58 months (range 22 to 129 months).

In six cases the femoral stem was revised although it was well-fixed inside the host bone. In all cases a complete revision of a custom implant was necessary because of mechanical failure at the level of the femoral body (breakage) or the tibial component, and it was impossible to keep the well-fixed femoral stem in situ for the revision implant. In four of these six cases, there were initial signs of bone remodeling type Type III (debris related), but this was not the reason for revision. The other two cases showed Type I remodeling (normal shape of bone, no osteolysis).

In three cases the femoral stem was removed, together with the rest of the implant, because of a deep infection. In all three cases a radiolucent line was seen between the cement and the host bone (Type IV remodeling).

In six cases the femoral component was revised due to aseptic loosening. In half of these cases, there were signs of debris-related (Type III) remodeling, whereas in the other half an early periosteal reaction (Type IV) suggested that the loosening was related to primary insufficient stem fixation by inadequate cementation. In all three cases a line-to-line cementation technique had been applied.

Table 1 shows the frequencies of the various remodeling patterns, and the number of stem revisions in each group. Type III and Type IV were clearly associated with mechanical failure, with revision rates of respectively 100% and 86%. None of the cases with Type II remodeling underwent revision of the femoral stem. The average follow-up in this latter group was almost 7 years (mean 81 months, range 16-146 months).

In eight of the fifteen revised stems, a cylindrical allograft was used in the revision, as the residual proximal femur was very short. With the cylindrical allograft extension added to the residual femur, the revision could be performed with a modular distal femoral replacement system, avoiding a total femur replacement or an expensive custom implant.

Table 1

Remodeling Pattern	N°	Stem Revisions	Reason for Revision (ISOLS failure classification)
Type I	17	2	2 Implant breakage (3A)
Type II	15		
Type III	7	7	4 Implant Breakage (3A) 3 Aseptic Loosening (2A)
Type IV	7	6	3 Aseptic Loosening (2A) 3 Infection (4A)

Discussion

Bone remodeling is frequently seen around the endomedullary stem of orthopedic prosthetic implants. The concepts of stress shielding, septic and aseptic loosening, and their radiographic appearance have been described in detail, but mainly in the presence of conventional arthroplasty. Bone remodeling in children is known to be more pronounced, as their immature skeleton shows a higher bone turnover than the adult skeleton. Indeed, children who undergo megaprosthetic replacement after bone tumor resection, often show significant remodeling around the implant stem. As a consequence, extensive bone resorption could lead to insufficient fixation and, thus, mechanical implant failure. The clinical importance and prognostic impact on implant survival of bone remodeling in patients with megaprostheses, has not been addressed in the literature. There is a complete lack of data on this subject, especially for the pediatric population. Therefore, we decided to study the bone reaction and remodeling around femoral stems in megaprosthetic implants in children after bone tumor resection.

The main limitation of this series is its retrospective study design. Also, measurements of bone diameter were performed on anteroposterior plain radiographs. Although, we decided to include only cases with digitalized imaging studies, there might be a certain level of inaccuracy compared to multi-dimensional studies. Furthermore, the remodeling is measured considering shape and diameter of the bone, not density. Although a significant attempt was made to create a homogenous study group, including only distal femoral replacements for patients under 13 years of age, this series includes several types of implants (expandable vs non-expandable, fixed hinge vs rotating hinge) and different types of stem fixation techniques (uncemented, classical cementation, line-to-line cementation). All implants included in this study, had a conventional endomedullary stem design. We have no experience with compression stem fixation techniques in paediatric patients.

With this study we tried to define the clinical significance of visible bone remodeling around the stem in pediatric patients with a distal femoral megaprosthesis. In this series, 63% of the patients showed some degree of change in bone shape of the femoral shaft on serial radiographs.

We were able to recognize different patterns of bone remodeling (question 1), as shown in figure 2, and the cases were classified according to these patterns. Type I represents the preferred situation, in which the femur gradually grows in a symmetrical manner along the stem, without areas of localized bone resorption or loss of bone stock. The Type II pattern is

caused by the lack of load stress along the femoral diaphysis, due to stress shielding of a well-fixed stem. The bone resorption secondary to this process was typically gradual, creating either an hourglass (IIa) or fluted (IIb) shape of the shaft and, although it led to significant bone loss in several cases, it never progressed to insufficient stem fixation (Figure 4). The irregular osteolysis close to the prosthesis-stem junction in pattern III, is typical for particle debris related bone resorption. This was seen in a specific type of expandable prosthesis that we previously related to high mechanical failure rates because of implant breakage and excessive particle debris formation. This type of bone resorption tends to be progressive, leading to loss of bone stock and stem loosening (Figure 5).

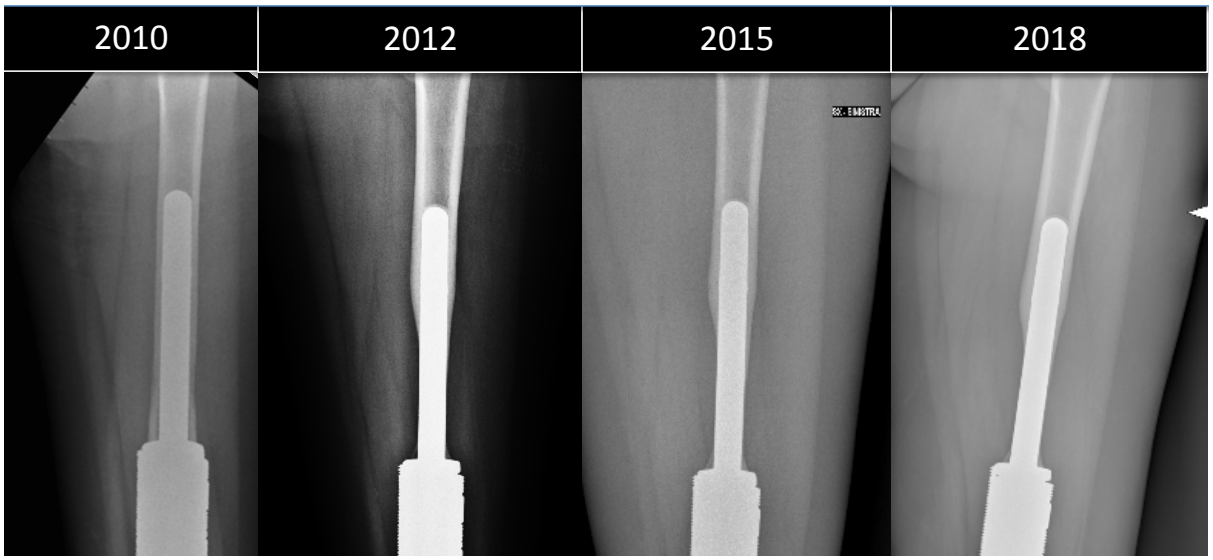

Fig.4 Type IIb (stress-shielding) bone remodeling that remained stable aver time.

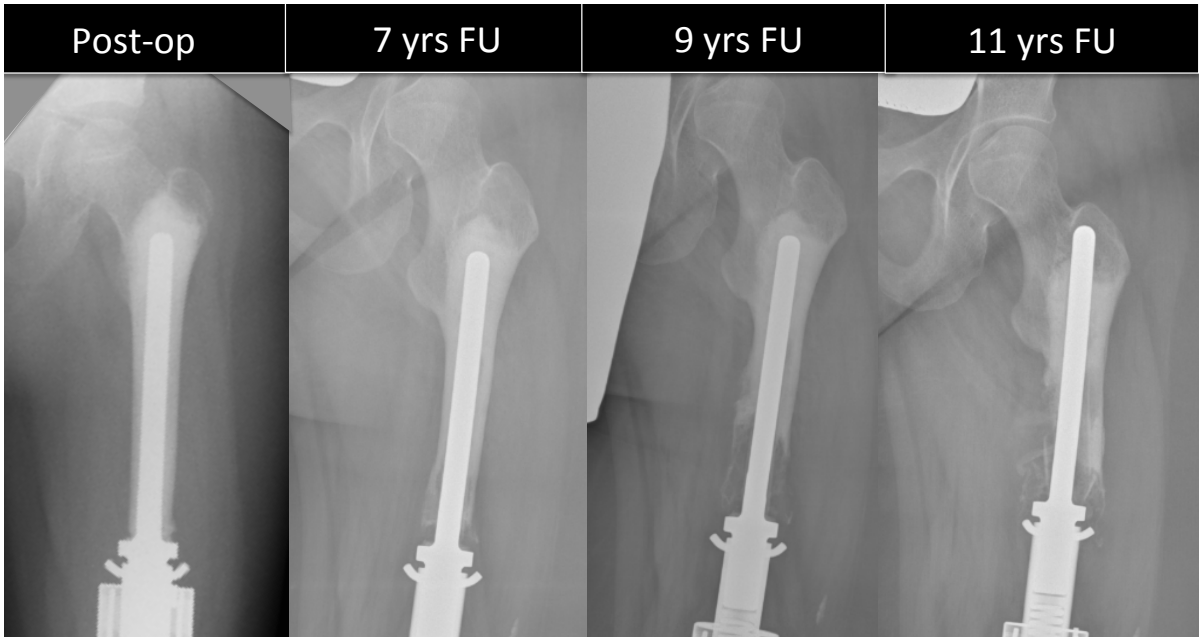

Fig.5 Progressive bone resorption in a Type III (debris-related) bone remodeling, with proximal migration of the stem.

The remodeling associated with longitudinal periosteal reaction, or cortical expansion and radiolucent endosteal lines between the cortex and the stem or cement mantle, is a sign of stem loosening and is always progressive. At the first signs of Type IV remodeling, further investigation to exclude infection is warranted. Both type III and IV remodeling are indications for revision, when symptoms become evident, whereas stress shielding should be kept under observation but does not require stem revision or additional strut grafts, as suggested in previous reports.

Our second question was: how often does evident bone remodeling lead to failure of the implant fixation? Although in this study, Type II remodeling was seen frequently, in 15 of 46 cases, bone resorption secondary to stress shielding never lead to failure of stem fixation and was never a reason for implant revision. On the other hand, type III remodeling, that represents debris-related osteolysis can progress to aseptic loosening. This was the main reason for implant revision in 3 of the 7 cases in which Type III changes could be detected. Finally, Type IV remodeling is clearly associated with stem loosening and was followed by implant revision in 6 of the 7 cases in which this pattern was present. In three of these the implant loosening was associated with a (peri)prosthetic infection. The only patient in which the implant was not removed, in spite of Type IV remodeling, died from metastatic disease at 35 months follow-up.

Based on this study, we could not conclude on which stem fixation technique is most reliable in pediatric patients, comparing cemented and uncemented techniques. However, in three cases in which minimal (line-to-line) cementation had been applied to a smooth stem with an HA-collar, there was early aseptic stem loosening requiring implant revision at 4, 4 and 2 years from index surgery. Therefore, we have abandoned this technique in smooth stems that are designed for conventional cementation.

This study confirmed that the Repiphysis expandable prosthesis was associated with frequent bone resorption due to excessive debris formation. Type III remodeling was present in 7 of 9 cases with this specific prosthesis and all implants eventually failed. Aseptic loosening was the main reason for revision in 3 of these cases. All other Repiphysis prostheses had to be removed because of implant breakage.

In pediatric patients we strongly suggest to preserve bone stock as much as possible, for this may become essential in future revisions. Whenever possible, we cover the prosthesis-stem junction with a short flap of periosteum, which helps to seal of the bone-prosthetic interface by new bone formation. Based on our personal experience, this is particularly efficient in the presence of a hydroxyapatite collar. In order to reduce the phenomenom of stress shielding, we have used a custom designed press-fit uncemented smooth stem with 3 centimeters of hydroxyapatite coverage near the bone-prosthesis junction and antirotation fins, with encouraging results (Figure 6). Finally, in case of a very short residual bone segment of the proximal femur, either at primary or revision surgery, we use a cortical cylindrical allograft to increase femoral bone stock and improve our endomedullary stem fixation.

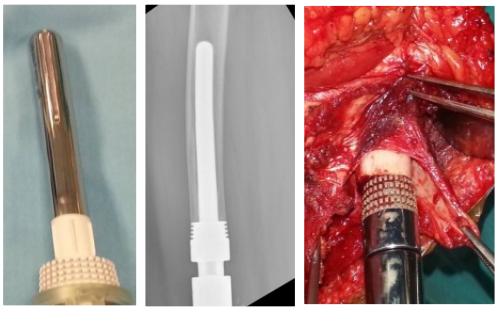

Fig.6 Implantation of a customized uncemented press-fit smooth stem, that has 3cm of hydroxyapatite coverage to engage distally, near the prosthesis-bone junction. One mm thick fins provide rotational stability. With this type of stem, we had no early mobilization, good bone integration, and no signs of stress shielding at four years follow-up.

Conclusion

This study demonstrates that bone remodeling with significant bone resorption is common in pediatric patients who are reconstructed with a distal femoral megaprosthesis. It is important to recognize the pattern of bone remodeling as it has a prognostic significance for the stem fixation. Debris-related osteolysis, and loosening should be detected early to avoid unnecessary loss of bone stock. Stress shielding does not directly lead to mechanical failure and can be kept under observation. However, bone resorption due to stress shielding should be avoided as much as possible, as it creates an unfavorable situation for future implant revisions, that are often required for patients in this age group.

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2.5.2
Use of cylindrical allograft to restore bone stock for femoral stem fixation in pediatric patients

Background
Limb salvage surgery for tumors of the distal femur extending into the proximal part of the femoral diaphysis is challenging. Whenever the residual proximal femur is very short, implant fixation of a distal femoral replacement can become insufficient. In these cases, a total femoral replacement, is often used for reconstruction. However, a total femoral replacement is frequently associated with implant instability and poor functional outcome with a Trendelenburg gait, because of gluteus muscle disruption. In pediatric patients, sacrifice of the proximal femur and hip joint, can also lead to dysplasia of the acetabulum and hip instability, early degenerative changes in case of a hemiarthroplasty of the hip, and increased limb length discrepancy. Therefore, in case of a very short residual femur after distal femoral bone tumor resection of implant revision, we suggest the use of a cylindrical allograft to extend the proximal femoral stump. In this way, stem fixation for a distal femoral replacement can be guaranteed.

Methods
A retrospective review was performed of all pediatric cases in which a cylindrical bone allograft was used to extend a short proximal femur, to improve stem fixation of a distal femoral megaprosthesis. Both primary and revision cases were included. The study period was from 2008 to 2019. A total of 15 pediatric patients underwent reconstruction with a distal femoral megaprosthesis, associated with allograft augmentation of the residual femur. Five reconstructions were performed as primary limb salvage procedures and ten were performed as revision procedures, after failure of a previous megaprosthetic implant. In three cases the distal femoral component was expandable. All other implants were conventional modular megaprostheses. In three of these cases, the reconstruction was slightly overlengthened, to compensate for growth loss. Average age of the patients age 12,5 year (range 7-18 years). Eight males and 7 females comprised the study group (Table 1).
Freeze-dried diaphyseal segmental allografts of the femur were used in fourteen cases. In one case, a diaphysis with metaphyseal segment was used. The allograft was cut to the required length, reamed to appropriate diameter, and manipulated with a high-speed burr as needed to maximize allograft-host bone contact. In all but one case there was an overlap between the allograft and the host bone, in order to increase the graft-host bone contact area. In two cases the allograft had a smaller diameter than the host bone and was placed partially inside the residual femur canal (Figure 1). In twelve cases, the allograft diameter was larger than that of the host bone, and the allograft overlapped the host bone on the outside (Figure 2). In one case, there was no overlap between allograft and host bone, that had similar diameter, and a direct cortical contact was obtained. Cement was used to fix the stem in both the allograft and the host bone in six cases. In three cases, cement was used only inside the allograft augmentation. In the remaining six cases, no cement was used for stem fixation.
A Stryker/Howmedica (Rutherford, USA) implant was used in six cases; Zimmer-Biomet/OSS (Warsaw, USA) in four cases; Stanmore JTS (Middlesex, UK) in three cases and Link Megasystem C silver coated (Hamburg, Germany) in two cases. Two of the Stanmore implants had a lateral extracortical side plate (Figure 3). Additional fixation was obtained by cortical strut grafts in two cases, cerclage wires in two cases, and screws in one case. Postoperative rehabilitation involved early range of motion and touchdown weightbearing until there was radiographic evidence of healing.

Si no	Age (years)	Sex	Indication	Residual femur length (mm)	Length of allograft (mm)	Length of overlap (mm)	Percentage of prosthesis in femur (%)	Contact graft – host bone	Stem length (mm)	Cement used for stem	Time to union (months)	Stem revised	Age at final follow-up (years)	Duration of follow up (months)
1	13.75	M	Revision	110	53	48	57.44	Host bone into allograft	130	No	3	No	19.92	74
2	15.58	F	Revision	118	46	20	59.41	Host bone into allograft	130	In allograft and host bone	11	No	23.33	93
3	18.33	F	Revision	60	108	26	53.07	Host bone into allograft	150	In allograft and host bone	11	No	20.25	22
4	13.67	M	Revision	99	60	31	61.12	Host bone into allograft	130	In allograft and host bone	5	No	18.33	55
5	13.42	F	Revision	129	48	40	57.55	Host bone into allograft	130	No	4	No	19.58	73
6	14.08	M	Revision	167	65	2	49.78	Host bone into allograft	160	In allograft and host bone	10	No	16.50	28
7	13.17	M	Revision	152	43	11	49.35	Allograft into host bone	120	No	4	No	16.50	39
8	15.00	M	Revision	175	60	19	50.53	Host bone into allograft	150	Only in allograft	6	No	17.50	29
9	16.08	M	Revision	180	51	9	50.96	Allograft into host bone	160	No	4	No	17.33	15
10	14.33	M	Revision	116	90	13	50.48	Host bone into allograft	165	In allograft and host bone	4	No	15.67	16
11	10.58	M	Primary	39	96	17	64.94	Host bone into allograft	130	Only in allograft	4	No	14.17	43
12	12.25	M	Primary	87	94	22	58.96	Host bone into allograft	160	In allograft and host bone	3	No	13.50	15
13	7.08	M	Primary	90	24	15	61.22	Host bone into allograft	110	No	4	No	7.50	4
14	9.58	M	Primary	77	71	0	59.78	Allograft on host bone	130	Only in allograft	6	No	20.25	128
15	7.08	F	Primary	71	68	9	59.00	Host bone into allograft	120	No	5	Yes	13.33	74

Table 1. Clinical data of the 15 cases. Case nr.15 is colored red because it was the only failure, due to aseptic loosening. This case was recently revised using the same augmentation technique (see Figure 4).

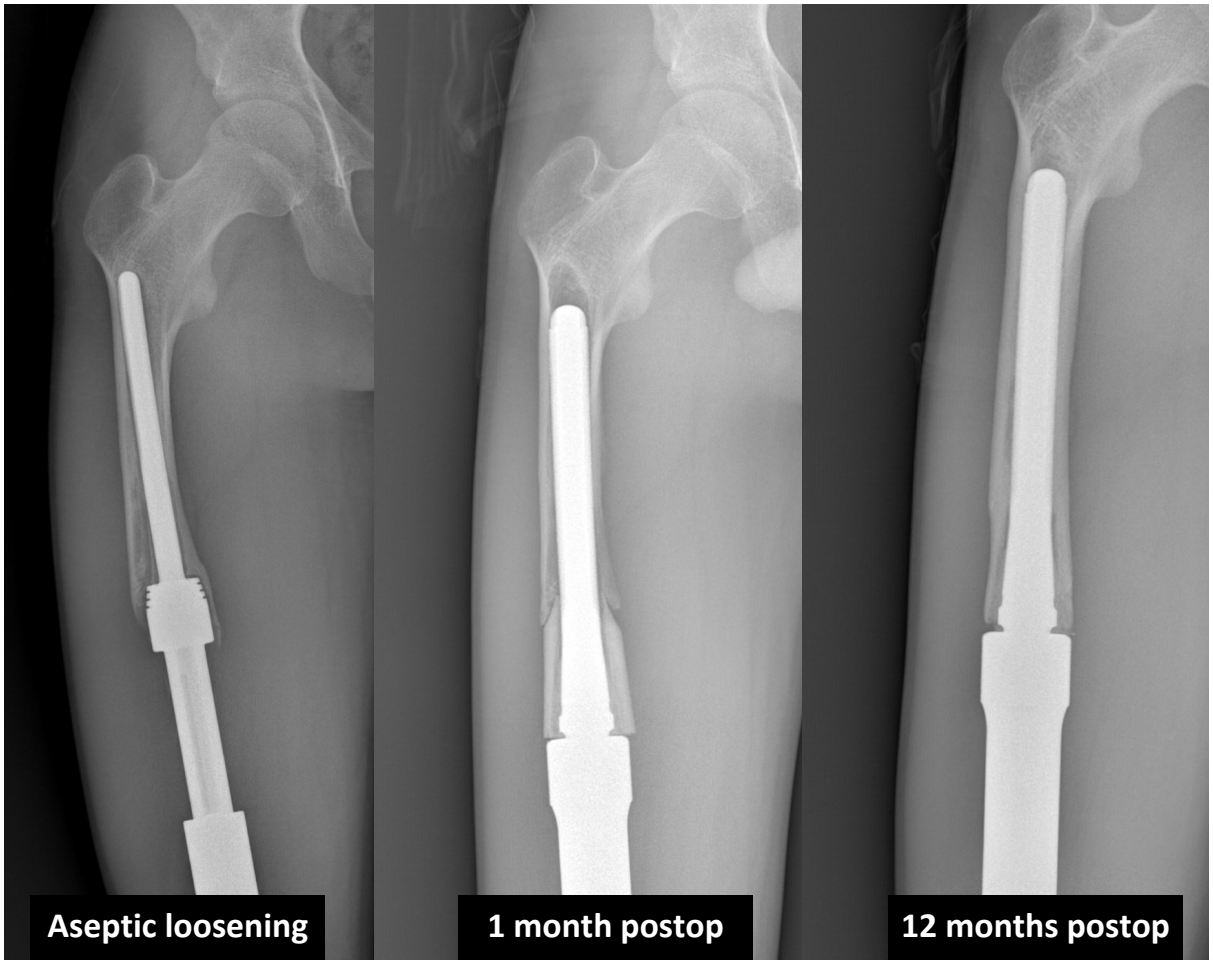

Fig.1 Sixteen-year old male with aseptic loosening of an expandable megaprosthesis. Revision surgery using an uncemented stem and allograft augmentation of the short residual femur with press-fit overlap ***inside*** *the host bone. On the right, 12 months follow-up radiograph.*

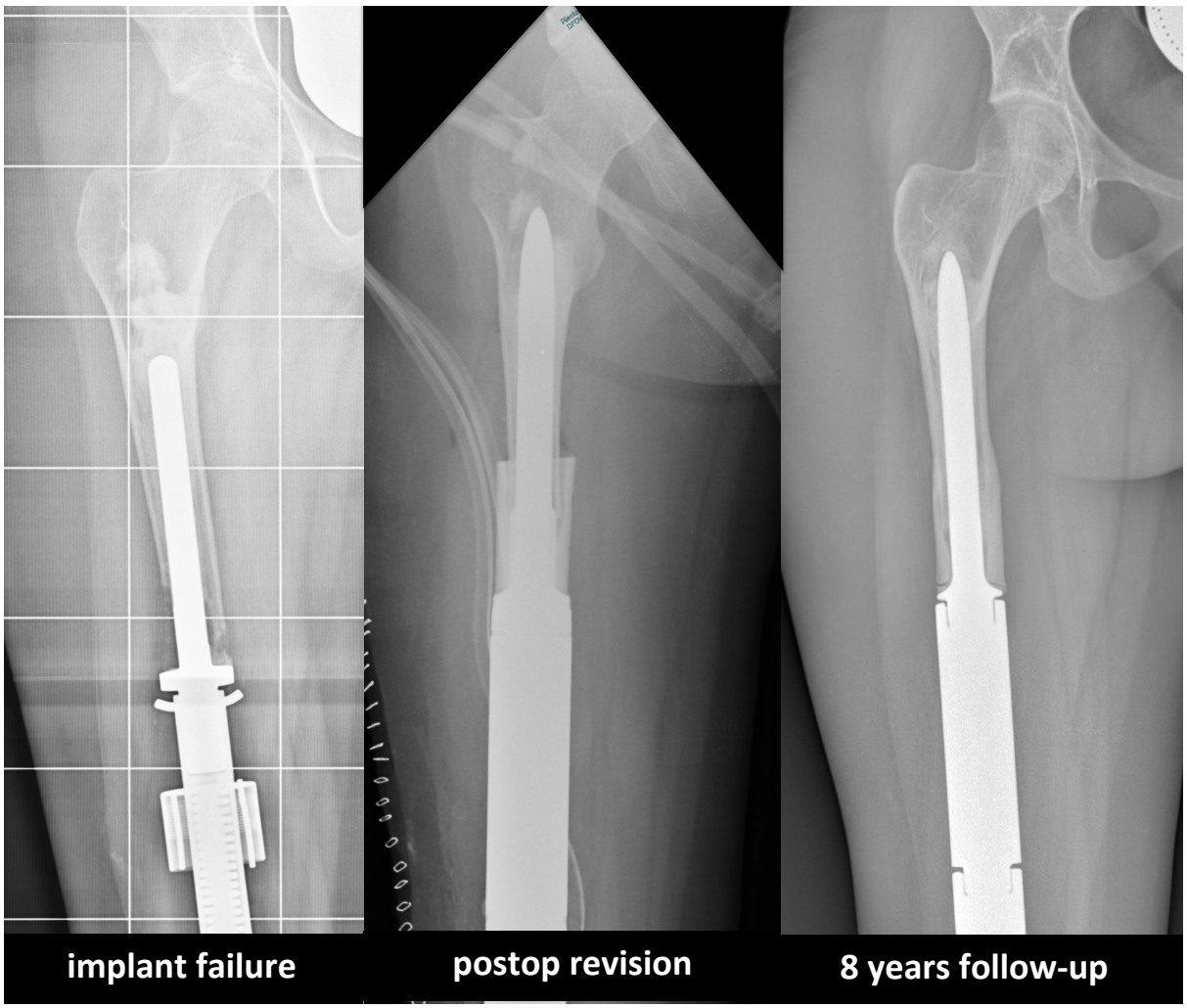

Fig.2 Fifteen-year old female with implant breakage of an expandable megaprosthesis. Revision surgery using an uncemented stem and allograft augmentation of the short residual femur with press-fit overlap ***outside*** *the host bone. On the right, 8 years follow-up radiograph.*

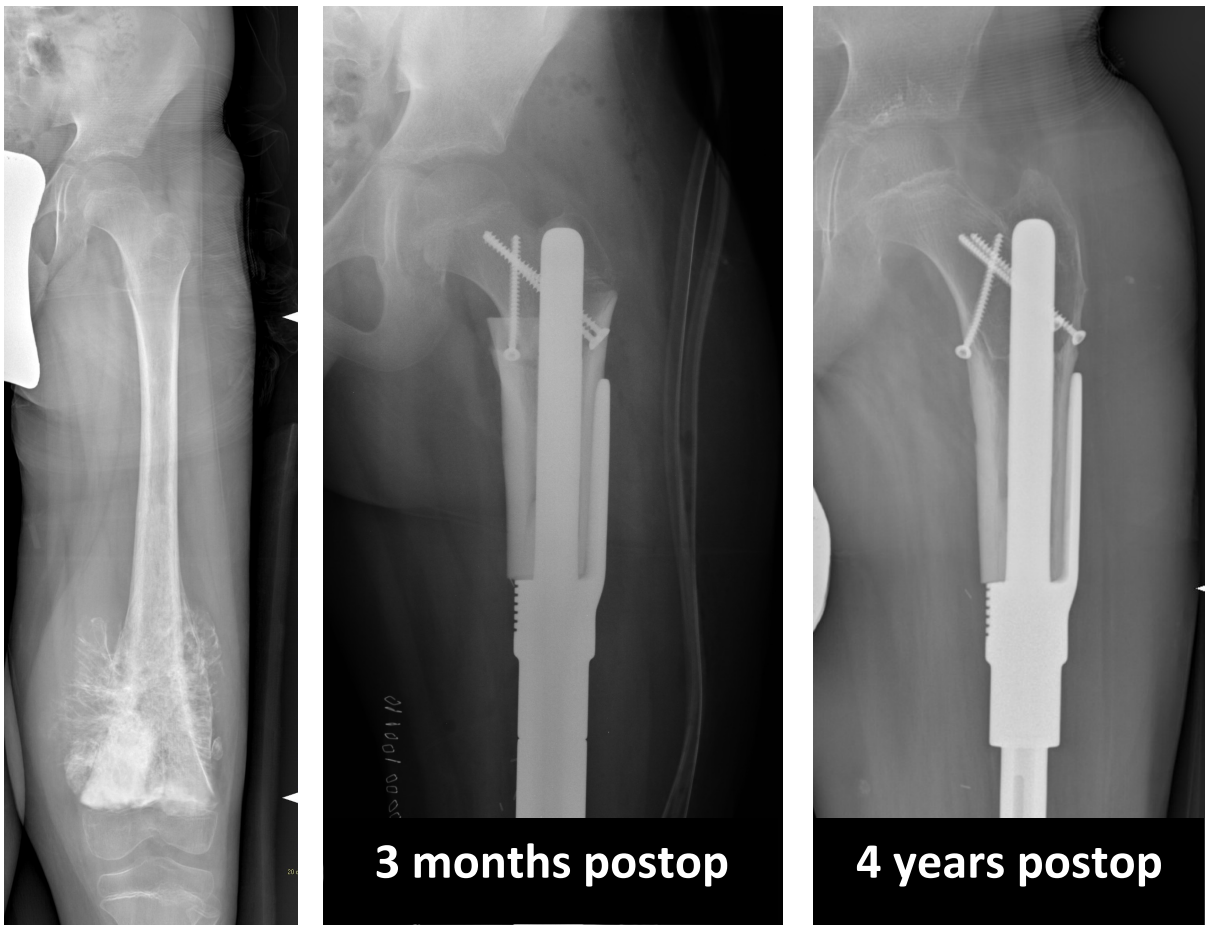

Fig.3 Ten-year old male with distal femoral osteosarcoma extending to the proximal femur. Reconstruction with allograft augmentation overlapping the residual femur on the outside, Stanmore JTS implant with extracortical plate, cemented into the allograft, and screws to fix the allograft to the host bone. Good graft integration and stable fixation at 4 years

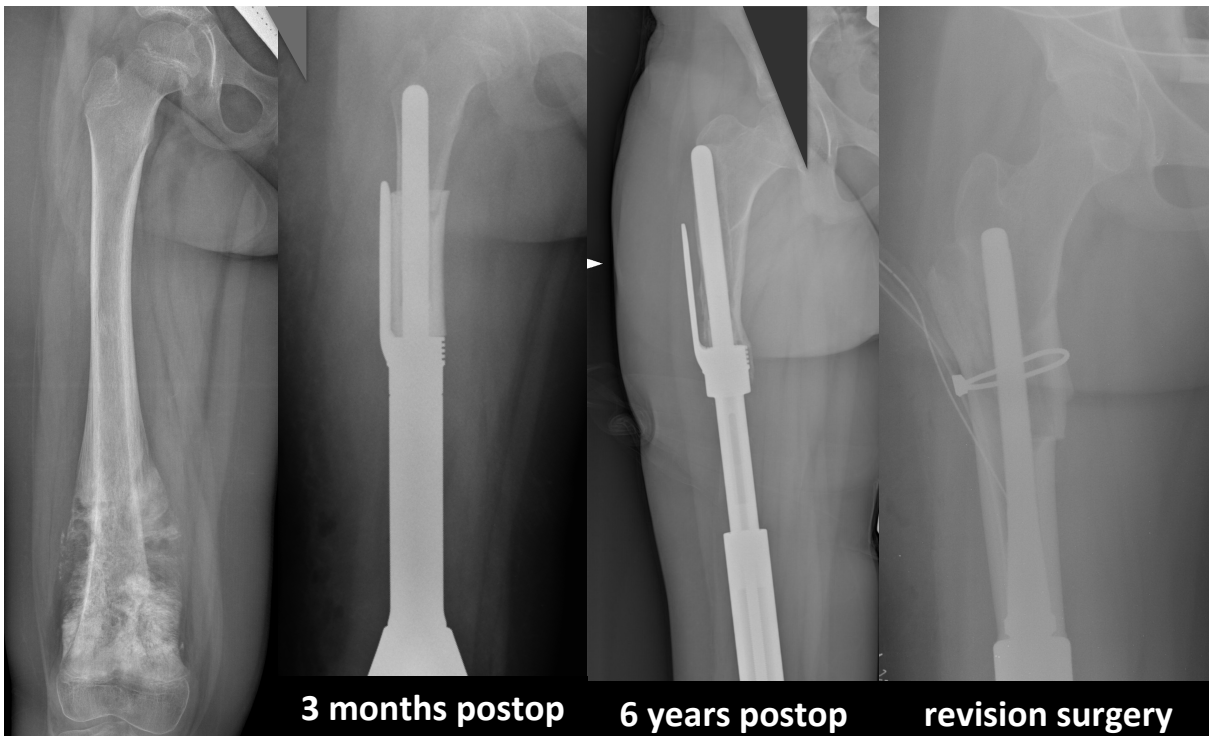

Fig.4 Seven-year old female with an osteosarcoma of the distal femur, extending to the proximal femur. Reconstruction with allograft augmentation of the short residual femur, Stanmore JTS implant with extracortical plate, cemented inside the allograft. Revision surgery with new allograft augmentation for aseptic loosening at 6 years follow-up.

Results

The residual femur measured on average 111mm (range 39-180mm) from the tip of the greater trochanter to the osteotomy site. On average, the length of the cylindrical allograft augmentation was 65mm (range 24-108mm). Prosthetic stem length was 138mm on average (range 110-165mm). Overlap between graft and host bone was on average 19 mm (range 0–48 mm).

Follow-up was on average 40 months (range 4-93 months). One patient died during follow-up, at 43 months from primary surgery with allograft augmentation. All the remaining patients were free of disease at final follow-up. Only one patient underwent revision of the implant, because of aseptic loosening of the femoral stem after 74 months (Figure 4). There were no cases of infection, non-union or graft fracture. Time to union ranged from 3 month to 11 months (mean 5,5 months).

Discussion

Limb salvage surgery with a megaprosthetic implant, either expandable or non-expandable, has become the standard treatment for children with bone tumors of the distal femur. However, these reconstruction remains challenging, due to the high functional demands of children, and their potentially long survival time. Infection, implant breakage, aseptic loosening, soft tissue problems, and limb length discrepancies are complications that have been frequently reported in children, and patients in this age group are likely to require one or more revision surgeries during their lives.

Compared to distal femoral replacements, total femur protheses show higher complication rates and poorer functional outcome. Trendelenburg gait, dislocation, degenerative changes, chondrolysis, and limb length discrepancies are frequent complications that patients with total femoral replacements have to deal with. Preservation of the hip joint can potentially avoid these problems. Therefore, whenever possible, it is preferable to reconstruct with a distal femoral replacement, even in the case of a very short residual proximal femur.

In this study, we describe a surgical technique, that allows for the extension of the proximal femur, in order to improve distal femoral endoprosthetic stem fixation. The advantage of the cylindrical allograft augmentation is that it restores bone stock. This may be useful for future revisions, that are likely for skeletally immature patients. Fixation of the allograft is obtained by press-fit overlap between the graft and host bone. The allograft can be easily adapted to the size of the host bone with a high-speed burr. This technique has shown excellent results, with complete union for all cases in this study. Furthermore, in the current series, there was no infection, no allograft fracture and only one patient had aseptic loosening of the implant, but could be revised with a modular megaprosthesis, using the original allograft that was well-integrated with the host bone. Therefore, in all 15 cases in this series, the hip joint could be preserved and a total femoral replacement could be avoided.

There are several techniques to cope with a very short residual proximal femur after long distal femoral resections or revision surgeries. One alternative, is the Compress implant (Zimmer-Biomet, Warsaw, USA). This technique uses compressive forces to create osteointegration fixation, avoiding stress shielding. The standard intramedullary component is 80mm long, but shorter fixation components, up to 46mm, have been reported. Although the overall results for this fixation technique are promising, with aseptic loosening reported between 3,8% and 14%, it is not clear how well these implants perform in case of a short proximal femur.

Custom made stems have been described for short residual femur fixation. Cannon et al described 135° cross-pin fixation through a cemented stem in 14 cases. One patient had implant loosening.

Diekmann et al described 15 cases of reconstruction with a custom made uncemented short Buxtehude stem (Implantcast, Buxtehude, Germany), that was stabilized with a locked spongiosa screw into the femoral neck. In ten cases, the stem was used for a distal femoral megaprosthesis, in one case for a diaphyseal replacement, and in four cases for lengthening of a short amputation stump. Average patient age was 33 years and only one patient was skeletally immature. A minimal residual femur length of 40mm was required. Revision surgery was necessary in two cases for aseptic loosening. One of these reconstructions had to be converted into a total femoral replacement. In another case, the femoral neck screw broke, but the patient did not undergo further surgery.
Moon et al have described a similar allograft-prosthesis composite as used in our series. They cemented a modular stem inside both allograft and host bone in all 12 cases. In 7 cases additional plate fixation was used. Graft related complications were frequent and included infection, allograft fracture, non-union and stem perforation. Especially non-union was frequent and required surgical revision in 29% of the cases. Half of the patients received the allograft-prosthetic reconstruction for primary surgery. Average patient age was 19 years and mean follow-up was more than 7 years (89 months).
Stevenson et al recently reported on custom-made endoprostheses with short medullary stems and extracortical plates. This study included 13 distal femoral replacements. The authors reported implant survival similar to conventional modular implants, and hypothesized that the lateral extracortical plate could provide extra protection against aseptic loosening, especially for very long distal femoral replacements, in which the offset from the mechanical axis increases.
The technique described in the current study, using a cylindrical allograft with extensive graft-host bone contact, is shown to be a relatively cheap and reliable way to avoid sacrifice of the hip joint in case of a short residual proximal femur after bone tumor resection or megaprosthetic implant revision. Compared to a total femoral replacement, there are obvious functional advantages. Compared to custom-made implants, there are advantages from both an economical and manufacturing time, point-of-view. Also, the possibility to adapt the allograft at time of implantation, to the host bone diameter and length, makes this technique more versatile than customized solutions. Finally, the excellent osteointegration, especially in very young patients, restores useful bone stock for possible future revisions.
The improved results of our series compared to the series by Moon et al, could be the result from a different surgical technique. We adapt the allograft meticulously to the host bone, in order to optimize the contact between graft and host bone. This press-fit overlap was on average almost 2 cm. Also the fact that we used cement inside the host bone in only six cases, against all 12 cases in the series from Moon et al, could explain the major graft union in our series. Cement could interfere with the graft-host bone contact and also cause stress shielding. Finally, the younger age of patients in our series, could have influenced the osteointegration in a positive manner.

Conclusions

Cylindrical allografts are a useful, economic and reliable solution to augment a short residual proximal femur after long bone tumor resections of the distal femur, or long megaprosthetic implant revisions. This study showed excellent osteointegration in a pediatric group of patients, with restoration of bone stock which is useful for likely future revisions. In all cases in this series, a total femoral replacement could be avoided thanks to this technique. During surgery, it is essential to obtain good graft-host bone contact by creating a press-fit overlap between the graft and host bone.

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2.5.3
Tibial growth after distal femoral megaprosthesis in children: the efficacy of pediatric tibial components

Background
Most bone sarcomas occur in the distal femur of children. Wide tumor resection and endoprosthetic replacement represents the standard local treatment for these tumors. Both the removal of the distal femoral physis and the endoprosthetic reconstruction, involving the proximal tibia, can have important consequences for skeletal growth. The younger the child at the time of surgery, the more important the expected limb length discrepancy at skeletal maturity. To overcome the problem of growth loss in children after bone tumor resection, specific implants have been developed. Expandable prostheses compensate for the lost growth potential at the resected segment. For distal femoral replacements, specific pediatric tibial components have been developed to minimize the impact on residual proximal tibial growth. These components are characterized by a relatively thin and smooth stem that penetrates the proximal tibial physis and allows the residual physis to continue its growth. Although several of these components have been developed, not much data is available on their survival and performance in terms of growth preservation. Therefore, we studied cases in which a pediatric tibial component was used at our institution since 1993. We wanted to know specifically: what is the implant survival for these components [1]? What were the reasons for revision [2]? How much does the tibia grow in the presence of these components [3]?

Methods
We identified all cases of pediatric bone sarcomas of the distal femur, in which a specific smooth stemmed pediatric tibial component was used for reconstruction, at our Institute, in the period between 1993 and 2016. Only cases with at least 2 years follow-up were included for tibial growth analysis. Pediatric tibial components from two reconstruction systems were implanted in the study period: HMRS/GMRS *(Stryker/Howmedica Osteonics, Rutherford NJ, USA)* and JTS *(Stanmore Implants Worldwide, Middlesex, UK)*. With each system, two different types of tibial components were used during the study period. Initially, HMRS/GMRS implants had a small uncemented standard fixed hinge (SFH) component. This specific component was used in the period between 1993 and 2001. Since 2002, uncemented custom fixed hinge components (CFH), with larger tibial plates, were used (Figure 1).

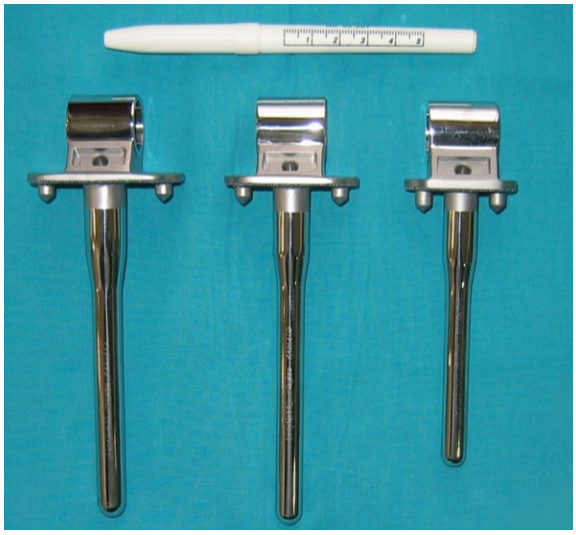

Fig.1 Stryker/Howmedica pediatric tibial components. On the right, the standard fixed hinge component (SFH) that was initially used. From 2002, custom fixed hinge (CFH) components with larger tibial plates were implanted. Two of these are shown on the left.

JTS implants have been used since 2009 in our Institute. Initially, this reconstruction system came with a rotating hinge (RH) component, for which a small polyethylene sleeve was cemented on the proximal tibia, and a smooth stem rotated freely inside the tibial medullary canal. Since 2014, in all cases reconstructed with the JTS, an uncemented fixed hinge (FH) flexion-extension.mechanism was used (Figure 2).

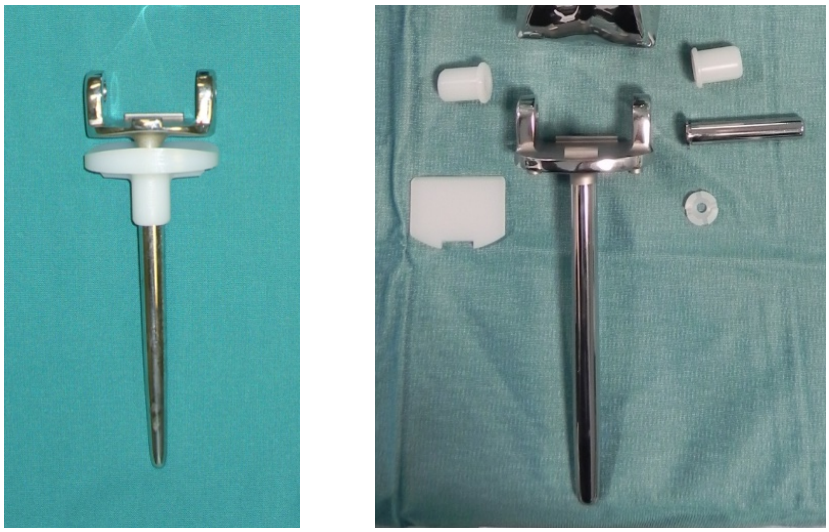

Fig.2 Stanmore JTS compatible pediatric tibial components. On the left, the rotating hinge (RH) component with a polyethylene sleeve that is cemented on the proximal tibia. On the right, the less invasive fixed hinge (FH) component, that has been used at our institute since 2014.

Tibial components survival was calculated using Kaplan-Meier's method. Tibial growth and limb length discrepancy were determined in patients who had calibrated long leg radiographs The growth of the tibia with the prosthetic component was compared to that of the contralateral tibia and reported as a percentage of growth at the non-operated tibia. If epiphysiodesis was performed, growth analysis was performed on the last radiograph before intervention for discrepancy.

Results

Megaprostheses with a pediatric type tibial component were implanted in 70 children. They had a mean age of 10 years (range 5-14 years) at index surgery. Mean follow-up was 82 months (range 5-256 months). In 24 patients an expandable prosthetic body was used.

In 18 cases, the standard (early design) uncemented fixed hinge HMRS stem (HMRS-SFH) was implanted. Because of frequent subsidence of this implant (Figure 3), the manufacturer changed this implant design, and since 2002, offered a component with a larger tibial plate (HMRS-CFH). This component was implanted in 34 cases.

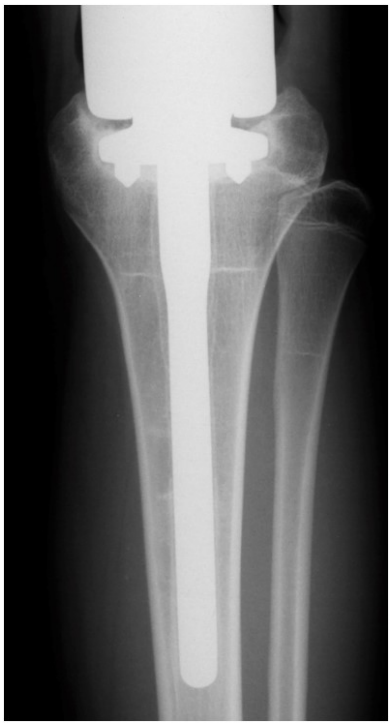

Fig.3 Distal migration into the proximal tibia was a frequent complication of the standard fixed hinge (SFH) with small tibial plate. For this reason, since 2002, custom components with larger plates were used only with the Howmedica/Stryker systems.

The JTS is a non-invasive expandable implant that we implanted using the rotating hinge component with a cemented polyethylene sleeve in the first 14 cases. However, in our series, this component was frequently complicated by an angular varus deformity of the proximal tibia (Figure 4). This complication was seen in as much as 73% of the cases in which the RH component was implanted. For this reason, since 2014 (in the last 4 cases included in this study), we used the JTS prosthesis with an uncemented fixed hinge (FH) component.

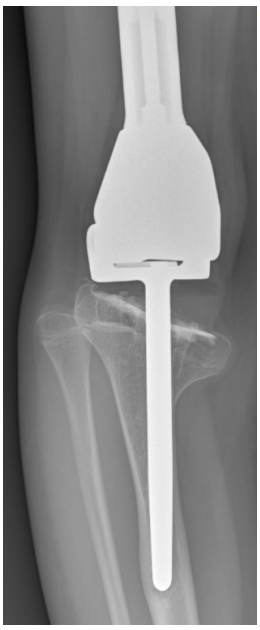

Fig.4 In 73% of the JTS rotating hinge pediatric components, we detected a progressive varus deformity of the proximal tibia.

During follow-up 27 tibial components were removed. In 8 cases revision was not related specifically to the tibial component. In 3 cases the complete implant was revised due to infection; in 2 cases because of local recurrence; in 2 cases the reason was related to hip pathology (instability and wear); in 1 case implant revision was performed because of a rigid knee with very poor function.
A total of 19 (27%) tibial components had to be revised because of mechanical failure of this specific part of the implant. In seven cases there was rotational instability of the tibial component. In six cases there was subsidence of the tibial component into the proximal tibia. In another six cases there was angular deformity, due to asymmetric growth of the proximal tibia.
For the 18 HMRS-SFH components, the 5-year implant survival was 44%. For the 34 HMRS-CFH stems, 5-year survival was 71%. For the 14 JTS-RH components, 5-year survival was 37%. The 4 JTS-FH stems are all in situ, but follow-up is relatively short. For this implant, the 2-year survival was 100% (Figure 5).

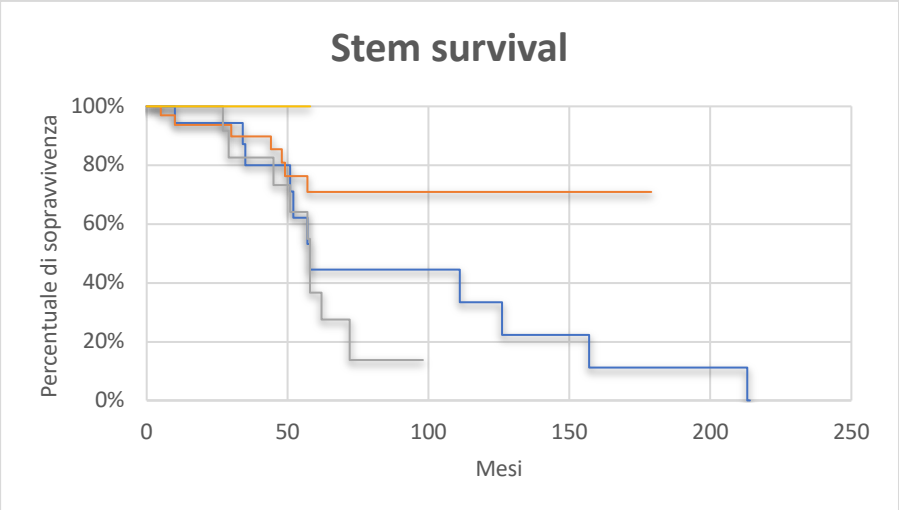

Fig. 5 Stem survival
Blue: HMRS-SFH
Orange: HMRS-CFH
Gray: JTS-RH
Yellow: JTS-FH

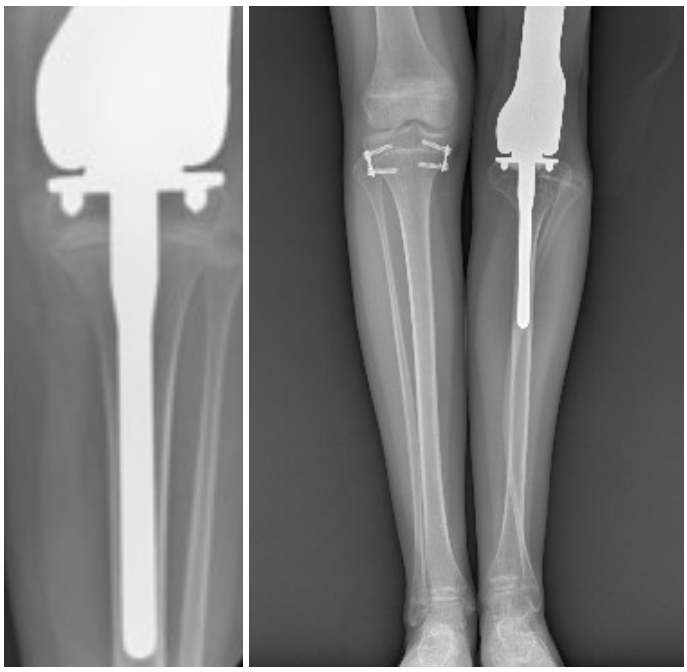

Fig.6 This patient, treated with a HMRS-CFH component, the operated tibia showed reduced growth compared to the non-operated tibia.
For this reason, the patient underwent epiphysiodesis of the

Ten patients underwent contralateral epiphysiodesis (Figure 6). Thirty-six patients had more than 2 years follow-up and adequate radiographies for growth analysis at skeletal maturity. Evaluating the preserved percentage of growth at the operated tibias (Figure 7), the HMRS-CFH stem allowed for 87% (range: 72-105%) of normal growth (total of 526 months follow-up). The more recently implanted JTS-FH components (total of 125 months follow-up), showed 92% of growth (range: 78-100%), as compared to the contralateral tibia.

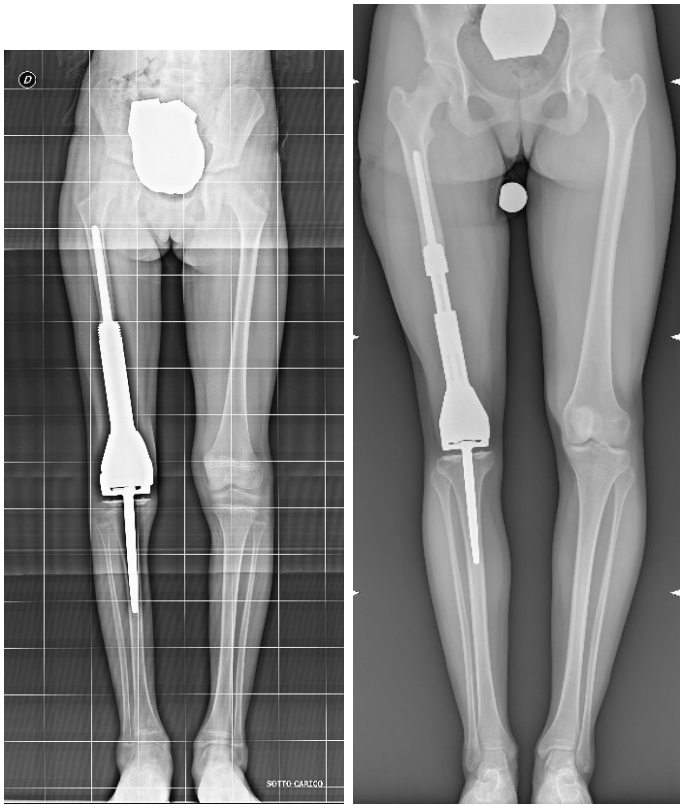

Fig.7 This patient was operated at 8 years of age, with a Stanmore JTS-RH implant. On the right, long leg radiographs at 6 months, on the left at 90 month follow-up, showing lengthening of the femoral component, and continuous growth of the tibia, comparable to that of the non-operated tibia. In this cases, growth was considered 100%..

Discussion

One of the major issues of megaprosthetic reconstructions of the distal femur in children after bone tumor resections is the growth loss due to the removal of the distal femoral physis, and possible damage to the proximal tibial physis. Loss of growth potential can lead to significant limb length discrepancy and loss of function. Specific pediatric tibial components have been developed, to reduce the growth loss at the proximal tibia. These components have a less invasive design with a relatively thin and smooth stem, to reduce damage to the proximal tibial physis, and thus, allow for continuous growth at the proximal tibia. There is lack of scientific evidence of the performance of these components. Their durability and efficacy in maintaining growth have not been studied in detail. Here we present a study of the pediatric tibial components that have been used in a single tertiary orthopaedic oncology center.

In this study, two generations of pediatric tibial components designed for the Stryker/Howmedica reconstruction system, and two different pediatric tibial components designed for the Stanmore Juvenile Tumour System, were included.

Limitations of this study are the retrospective study design, the small patient numbers, and the relatively short follow-up, especially for the JTS-FH component, that we only have used since 2014.

The most recently implanted versions of the pediatric tibial components, the HMRS-CFH and JTS-FH stems, showed good implant survival at short to medium term. However, longer follow-up is required.

The early design of the HMRS/GMRS system (HMRS-SFH) had a very high failure rate because of subsidence. This was probably due to the small tibial base plate that was not large enough to equally distribute the load stresses over the proximal tibia. For this reason, the manufacturer increased the size of the components' tibial plate since 2002 (HMRS-CFH). This design change improved significantly the survival rate of the component from 44% to 71%.

The rotating hinge mechanism of the JTS system (JTS-RH) was frequently associated with aseptic loosening due to severe varus deformity. This complication was not reported in other series on this specific implant. The reason for this progressive deformity could be linked to the invasiveness of the implant design, with a relatively large diameter polyethylene sleeve passing through the proximal tibial physis. Also, excessive stress loads through the medial compartment due to altered mechanical axis could have played a role, although in none of the cases, evident malpositioning of the implant could be detected on the postoperative radiographs. Finally, asymmetrical damage to the proximal tibial physis could have occurred due to excessive trimming of the proximal tibia or cementation of the polyethylene sleeve. Since we started to use the uncemented fixed hinge (JTS-FH) component instead of the rotating hinge (JTS-RH) component, no varus deformities or other types of mechanical failure have occurred, although the follow-up of the JTS-FH is too short to draw conclusions.

Both the HMRS-CHF and JTS-FH components have shown excellent preservation of tibial growth, that was around 90% compared to the contralateral tibia for both components. Again, the JTS-FH has a relatively short follow-up, and needs confirmation of these results at longer term.

Conclusion

Pediatric tibial components have been designed specifically to allow for continuous tibial growth, in children who undergo distal femoral replacements. The implant design and fixation method differs from the adult-type tibial components. This study shows that pediatric components used throughout the last decades have been frequently associated with mechanical

failure. Especially mechanical failure to aseptic loosening has been a major issue for these components. Nevertheless, the latest HMRS/GMRS custom pediatric components and the JTS fixed hinge components have shown good implant survival results. The current study also shows that tibial growth with these implants, is preserved for about 90%.

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CHAPTER 3
EXPANDABLE MEGAPROSTHESIS FOR BONE RECONSTRUCTION IN CHILDREN

3.1 INTRODUCTION

With the introduction of effective chemotherapy in the treatment for Osteosarcoma and Ewing sarcoma, and the subsequent prognostic improvement, the need for limb salvage surgery increased for pediatric patients with these pathologies. As most bone sarcomas in children arise around the knee, close to the most important growth plates in the lower limb, the surgical resection of these tumors, in case of limb salvage surgery, has huge consequences for final limb length. To overcome this problem, expansion mechanisms of the reconstructive implants had to be developed.

3.2 IMPLANT DESIGN AND EVOLUTION

Before the introduction of expandable implants, distal femoral reconstructive implants required either complete substitution of the whole prosthesis, or substitution of a large part of the reconstruction, to compensate for the loss of growth. For young children this meant they had to undergo multiple major surgeries until the end of skeletal growth.
The first-generation expandable prostheses was introduced in the 70s and 80s (Figure 1), and still required open surgery with extensive soft tissue dissection for lengthening. In 1976, the first expandable prosthesis with a screw jacket system, the Mark I (Stanmore Implants , Middlesex, UK) was designed and implanted in the United Kingdom. The successors, Mark II to Mark IV, were also invasive growers that initially were lengthened through a ball-bearing mechanism and later with C-washers. In the US, in 1983, the Lewis Expandable Adjustable prosthesis (Dow Corning Wright Corporation, Memphis TN, USA) was created with a screw-driven expansion mechanism. These prostheses had a high failure rate over the time required for multiple lengthening procedures.

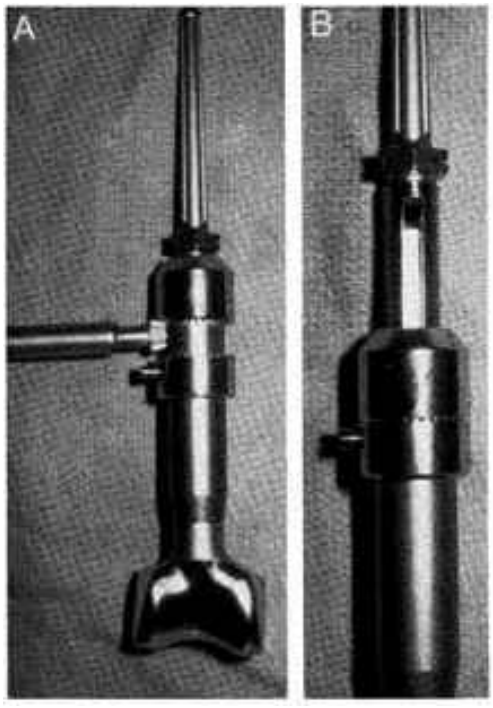

Fig. 1 Early design expandable prosthesis

The second generation expandable implants further reduced the invasiveness of the lengthening surgeries. In 1987, a minimally invasive prosthesis was introduced, that was compatible with the Kotz Modular Femur Tibia Reconstruction System (KMFTR, Stryker Howmedica Osteonics, Rutherford NJ, USA) and later with the Howmedica Modular Resection System (HMRS) and the Global Modular Resection System (GMRS) of the same company. The prosthesis lengthens through a telescopic mechanism of a titanium sleeve on an inner spindle, activated by a screwdriver, with a mini-invasive approach (Figure 2 and 3).

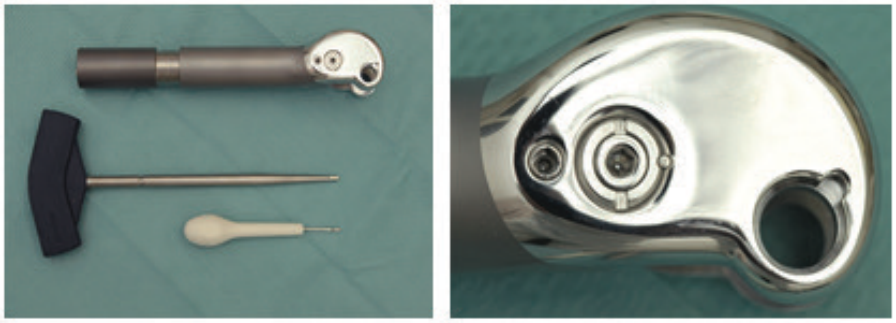

Fig. 2 Howmedica custom expandable prosthesis, compatible with the HMRS modular system.

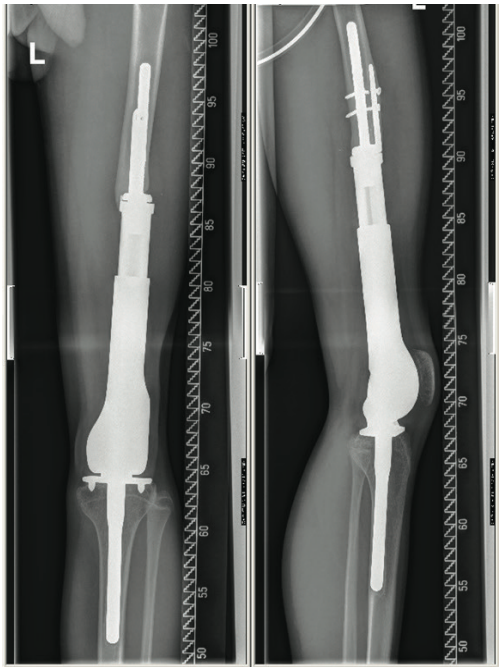

Fig. 3 Howmedica expandable prosthesis

An important advantage of this prosthesis is the possibility to increase and decrease its length, and the possible integration with the Howmedica modular systems. In this way, lengthening can be repeated and revision surgery at skeletal maturity may be less invasive. The lengthening mechanism is reliable, the stem can be either cemented or uncemented. The tibial component is a fixed hinge smooth stem pediatric tibial component. One mm lengthening is applied by one turn with the screwdriver. Usually 1,5cm lengthening is applied each procedure. Postoperative knee stiffness and neurovascular stretching are possible complications. Sometimes, a tick fibrotic layer in the soft tissues around the implant prevents the mechanism from expansion . In this case, the fibrotic layer needs to be removed surgically, in order to continue further lengthening.

In the 90s, early attempts to create non-invasive expandable prostheses were made. In Austria, Professor Kotz and coworkers developed a non-invasive growing prosthesis that lengthened by a 100 degrees flexion movement of the knee joint, but this implant was clearly less successful than the mini-invasive KMFTR expandable system and its successors (Figure 4).

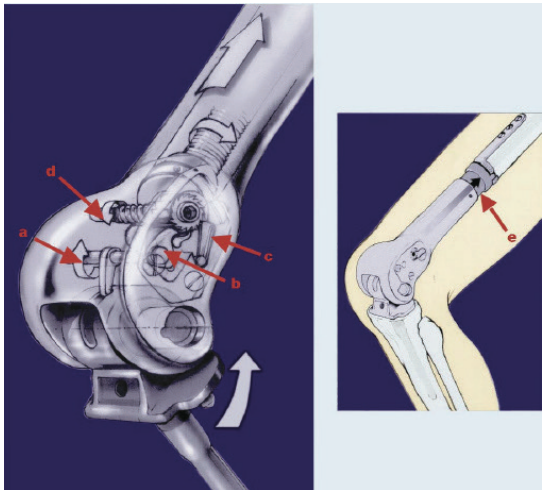

Fig. 4 The Intercondylar stepless extension module, lengthened by knne flexion >100°

The Phenix Prosthesis (Phenix Medical, Paris, France) was originally designed in France but its technology was later used and commercialized in the Repiphysis prosthesis (Wright Medical Technology, Arlington TN, USA) to become the very first non-invasive expandable prosthesis, in 1984 (Figure 5). Expansion was obtained in an electromagnetic field, that through the heating of a polyethylene locking mechanism, gradually released an internal spring. The Repiphysis Limb Salvage System was approved by the FDA in 2002. In the meantime, there have been numerous reports and series describing high complication rates for this specific implant.

Fig. 5 The Phenix non-invasive expandable prosthesis, used an external electromagnetic field for lengthening field.

Stanmore implants introduced in 1993 the Mark V, a non-invasive growing prosthesis, which became a precursor of their successful non-invasive grower in the following decade. Currently, the most frequently used non-invasive expandable prostheses on the market is the Stanmore Juvenile Tumor System (Stanmore Implants Worldwide, Middlesex, UK). The implant was introduced in 2002 and, for lengthening, it uses an electric current to produce a rotating magnetic field, that is captured by a magnet within the implant, and extended to an internal gearbox (Figure 6). This implant can articulate with either a fixed hinge or a rotating hinge

tibial component. One important advantage of this implant is that it can both expand and reduce its length. Lengthening is performed in the outpatient clinic and can be repeated in small steps.

Fig. 6 The Stanmore JTS non-invasive growing prosthesis is currently one of the most frequently used expandable implants. It can be lengthened in an outpatient setting, through an external electromagnetic field.

Another popular expandable non-invasive grower currently on the market is the MUTARS Xpand prosthesis (Implantcast, Buxtehude, Germany). This implant, produced in Germany, was introduced in 2005 and lengthening is motor-driven and activated by an external electromagnetic field that uses a subcutaneous antenna as transmitter (Figure 7). At skeletal maturity, the expandable components are supposed to be substituted by adult-type MUTARS components. The MUTARS BioXpand is a new type of expandable system. It uses the principle of distraction osteogenesis through an expandable nail connected to an articular component to lengthen the host bone by approximately 1mm per day. It takes around 4 to 6 months to mature the newly formed bone. The procedure can be repeated, but again, at the end of skeletal growth the implant has to be replaced by adult type components.

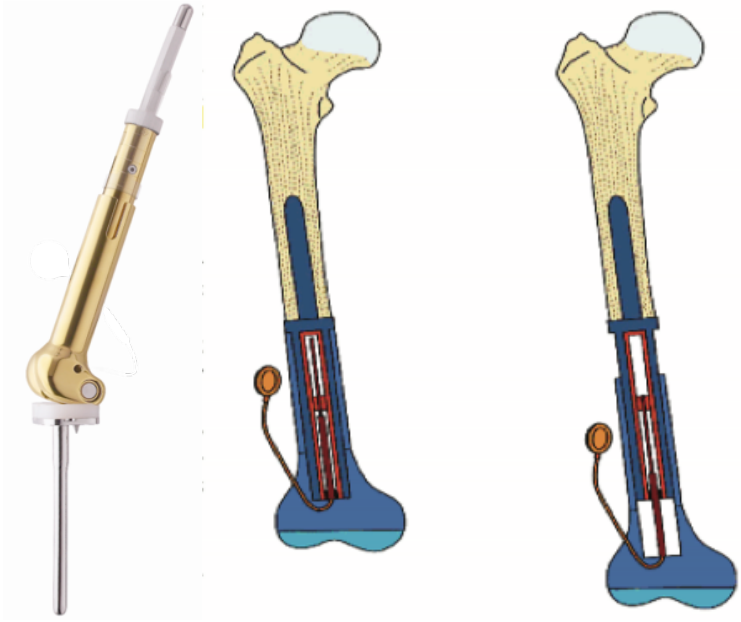

Fig. 7 The MUTARS BioXpand is a non-invasive expandable implant. It uses an external electromagnetic field and a subcutaneous antenna as transmitter.

3.3 INDICATIONS, COMPLICATIONS AND CONCERNS

The idea of implanting an expandable prosthesis is to reduce the number of operations necessary to compensate for the expected growth loss. This reduces not only the traumatic burden of surgeries, general anesthesia, hospitalizations and rehabilitations for these fragile patients, but also reduces the risk of periprosthetic joint infections. Generally, it is accepted that expandable implants are used when there is an expected final limb length discrepancy of at least 3-4 cm. For lesser expected limb length discrepancies there are cheaper and safer alternatives as: shoe lifts, contralateral epiphysiodesis, the use of specific growth preserving tibial components and 'overlengthening' of the distal femoral segment at the time of reconstruction. The last technique can be safely executed for 1-1,5 cm without risking neurovascular damage.

Although there is not complete consensus about the minimum age of patients eligible for expandable implant reconstruction, a certain amount of residual bone stock and diameter of the endomedullary canal is thought to be required for adequate implant fixation. Also, the lengthening potential of the implant is directly related to the length of the prosthetic body and thus, to the resection length. Therefore, the space required to obtain enough lengthening potential to compensate for growth loss, may become a problem in very young patients. For the same reason, in some patients, it might be necessary to resect more bone than actually would be required to obtain a safe oncologic margin.

A questionnaire under orthopedic surgeons of the European Musculoskeletal Oncology Society (EMSOS) showed that on average, a minimum age of 6,5 years and an expected limb length discrepancy of 3-4 cm, was thought to be required.

Many orthopedic surgeons have chosen not to use the expandable implants because of their high costs or limited availability in some countries. Currently, the price of non-invasive expandable implants varies probably between 20.000 and 35.000 euros in most European countries, which is much higher than that of non-expandable modular or mini-invasive expandable implants. According to the FDA evaluation for the Stanmore JTS implant, the cost of a non-invasive outpatient clinic based lengthening procedure is estimated to be around 267 USD per lengthening, compared to approximately 8,000 USD if surgery is required. Therefore, a non-invasive implant, although much more expensive than an invasive grower, seems cost-effective. Although for a complete analysis it would be necessary to calculate separate complication risks for the different types of implants. Some centers prefer to implant a so-called 'Dummy'-prosthesis without the motor at index surgery, and implant the expensive motorized prosthesis at a later stage, when long survival has become more likely. Also, two thirds of the participants in the EMSOS survey, preferred not to implant this expensive prosthesis in metastatic patients.

Another important issue is the need for future revision surgery of the Implantcast systems, to substitute pediatric components with adult-type components at completed growth. Also, the non-modularity or low versatility of the Stanmore system, especially in case of conversion to a definite adult-type implant at skeletal maturity has raised concerns.

Overall, the high complication rates of expandable prosthesis has raised many concerns. After the enthusiasm from the initial reports on the first mini-invasive expandable implant, the Repiphysis Limb Salvage System, there has been a impressive number of complications described on this specific implant. Problems with the lengthening procedure in an outpatient setting, frequent loosening and implant breakage, and extensive bone loss from reactive bone resorption have characterized the literature on this implant after the first few years.

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3.4.1
Are complications associated with the Repiphysis expandable distal femoral prosthesis acceptable for its continued use?

Abstract

Background Reconstruction of the distal femur after resection for malignant bone tumors in skeletally immature children is challenging. The use of megaprostheses has become increasingly popular in this patient group since the introduction of custom-made, expandable devices that do not require surgery for lengthening, such as the Repiphysis® Limb Salvage System. Early reports on the device were positive but more recently, a high complication rate and associated bone loss have been reported.

Questions/Purposes We asked: (1) what are the clinical outcomes using the Musculoskeletal Tumor Society (MSTS) scoring system after 5-year minimum follow-up in patients treated with this prosthesis at one center; (2) what are the problems and complications associated with the lengthening procedures of this implant; and (3) what are the specific concerns associated with revision of this implant?

Methods At our institute, between 2002 and 2007, the Repiphysis® expandable prosthesis was implanted in 15 children (mean age, 8 years; range, 6−11 years) after distal femoral resection for malignant bone tumors. During this time, the general indication for use of this implant was resection of the distal femur for localized malignant bone tumors in pediatric patients. Alternative techniques used for this indication were modular prosthetic reconstruction, massive (osteoarticular or intercalary) allograft reconstruction, or rotationplasty. Age and tumor extension were the main factors to decide on the surgical indication. Of the 15 patients who had this prosthesis implanted during reconstruction surgery, five died with the implant in situ or underwent amputation before 5 years follow-up and the remaining 10 were evaluated at a minimum of 5 years (mean, 104 months; range, 78−140 months). No patients were lost to follow-up. These 10 patients were long-term survivors and underwent the lengthening program. They were included in our study analysis. The first seven lengthening procedures were attempted in an outpatient setting; however, owing to pain and burning sensations experienced by the patients, the procedures failed to achieve the desired lengthening. Therefore, other procedures were performed with the patients under general anesthesia.

We reviewed clinical data at index surgery for all 15 patients. We further analysed the lengthening procedures, implant survival, radiographic and functional results, for the 10 long-term survivors. Functional results were assessed according to the MSTS scoring system. Complications were classified according to the International Society of Limb Salvage (ISOLS) classification system.

Results Nine of the 10 survivors underwent revision of the implant for mechanical failure. They had a mean MSTS score of 64% (range, 47%−87%) before revision surgery. At final follow-up the 10 long-term surviving patients had an average MSTS score of 81% (range, 53%−97%). In total, we obtained an average lengthening of 39 mm per patient (range, 17–67 mm). Exact expansion of the implant was unpredictable and difficult to control. Nine of 10 of the long-term surviving patients underwent revision surgery of the prosthesis—eight for implant breakage and one for stem loosening. At revision surgery, six patients had another type of expandable

prosthesis implanted and three had an adult-type megaprosthesis implanted. In five cases, segmental bone grafts were used during revision surgery to compensate for loss of bone stock.

Conclusions We could not comfortably expand the Repiphysis® prosthesis in an outpatient setting because of pain experienced by the patients during the lengthening procedures. Furthermore, use of the prosthesis was associated with frequent failures related to implant breakage and stem loosening. Revisions of these procedures were complex and difficult. We no longer use this prosthesis and caution others against the use of this particular prosthesis design.

Introduction

Limb salvage after tumor resection in a skeletally immature child, particularly in the lower limb, is challenging. The primary goal of surgical treatment is complete removal of the tumor with adequate margins. Reconstruction is particularly difficult because of the relatively small anatomic size, reduced growth in the surgically treated limb resulting in a potential limb-length discrepancy, and the high functional and mechanical demands of young, active patients [1, 14, 21]. Expandable prostheses have been developed to address the problem of limb-length discrepancy, compensating for lost growth potential and maintaining good function of the treated joint [5,19, 24, 25].

The introduction of expandable prostheses that can be lengthened without the need for invasive surgery or general anesthesia made this type of reconstruction increasingly popular. The Repiphysis® prosthesis was the first expandable endoprosthesis commercially available worldwide, with a lengthening mechanism that did not require any surgery. The device was introduced by Wright Medical Technology (Arlington, TN, USA) and received approval from the FDA in 2002. The Repiphysis® Limb Salvage System was later acquired by MicroPort Orthopedics Inc (Arlington, TN, USA), which is the current manufacturer of the implant [20]. Initially, there were positive reports on short-term results of the implant [6, 11, 17, 26], but there have been increasing concerns regarding high complication rates and poor function at longer follow-up [3, 4, 16, 22].

We therefore analyzed our experience with the Repiphysis® prosthesis in 10 patients younger than 12 years, who had survived 5 or more years after treatment for a malignant bone tumor of the distal femur. We asked (1) what are the clinical outcomes using the Musculoskeletal Tumor Society (MSTS) scoring system after 5-year minimum follow-up in patients treated with this expandable prosthesis; (2) what are the problems and complications associated with the lengthening procedures of the implant; and (3) what are the specific concerns associated with revision of the implant?

Patients and Methods

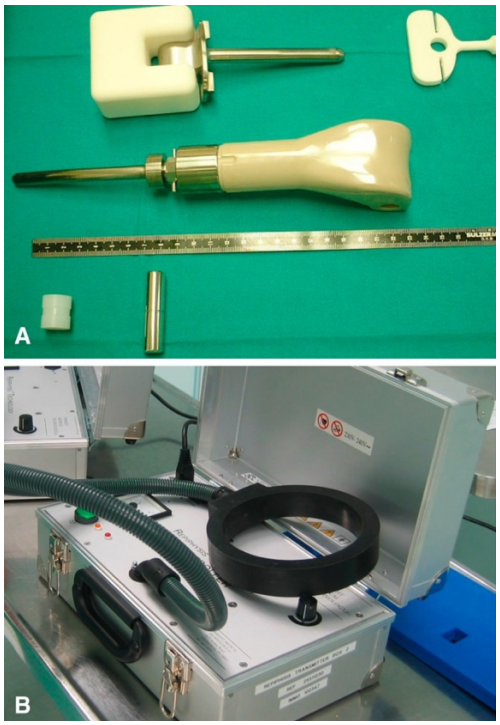
We performed retrospective clinical and radiographic evaluations of all pediatric patients (younger than 12 years) who underwent reconstruction of the distal femur with the Repiphysis® custom-made expandable prosthesis after resection, between 2002 and 2007 at one institute, for a malignant bone tumor. The patients in this study were identified from an observational prospective study.

Between 2002 and 2007, at our institution, the Repiphysis® custom-made, expandable prosthesis was implanted in 15 patients who underwent resection of the distal femur for a malignant bone tumor. The series included nine male and six female patients, with a mean age of 8 years (range, 6−11 years). The diagnosis was high-grade osteosarcoma in 14 patients and

Ewing's sarcoma in one. All patients received pre- and postoperative chemotherapy according to well-established protocols [9, 10].

During that period, our general indications for using this implant were resection of the distal femur for localized malignant bone tumors in pediatric patients. During the same time, for similar indications, we used an adult-type of modular prosthesis in five patients (all 12 years old), a modular megaprosthesis with a smooth tibial stem in eight patients (between 9 and 12 years old), one intercalary reconstruction after resection through the epiphysis, four rotationplasties (in patients younger than 7 years or with very large tumors), two other types of expandable prostheses (mechanical lengthening through a small incision), and two osteoarticular allografts. Age and tumor extension were the main factors leading to the decision to use this expandable implant. In general, we opted for the expandable prosthesis when patients were between 7 and 12 years old, had an expected potential limb length discrepancy of at least 4 cm, good clinical and radiographic response to preoperative chemotherapy, possibility to save the primary neurovascular bundle, and with at least 8 cm of longitudinal tumor extension from the joint line. This might have resulted in a selection bias compared with other approaches.

One patient died because of drug toxicity during chemotherapy. Two patients had a local recurrence and underwent an above knee amputation at 6 and 19 months after the index surgery. Each died of diffuse disease at 11 and 28 months follow-up, respectively. Three other patients had lung metastases during follow-up. Two of them died at 20 and 28 months after the primary surgery (one of the patients had undergone implant removal at 8 months follow-up because of a postoperative infection). None of these patients underwent the lengthening program and their functional results, complications, or revision procedures are not included in this study. The other patient who had lung metastasis is alive and in complete remission 85 months after thoracotomy and wedge resection of the lung nodules. Ten long-term surviving patients underwent the lengthening program and we evaluated implant survival and functional outcome for these patients only. Mean follow-up of this group of patients was 104 months (range, 78−140 months).



The Repiphysis® custom-made, noninvasive expandable prosthesis uses a telescopic lengthening mechanism composed of a titanium tube embedded in a polyethylene housing cylinder (Fig. 1).

Fig. 1A-B (A) The Repiphysis® prosthesis and **(B)** the generator of the external electromagnetic field are shown.

The energy to lengthen the implant is stored in a compressed spring inside the titanium tube. The end of the titanium tube is flared and engages in the polyethylene cylinder, locking it into place. When lengthening is required, an external electromagnetic field is generated by a coil, which is placed circumferentially to the extremity at the level of the implant. The coil heats and softens the polyethylene cylinder, allowing for the titanium tube to disengage from its housing. At this stage, the compressed spring partially releases and expands, sliding the titanium tube out of the polyethylene cylinder, lengthening the implant. Once the flared part of the tube reaches a new and cooler portion of polyethylene, it is locked back in place, limiting further expansion [18, 20, 26]. According to the manufacturer [20], it takes approximately 20 seconds to obtain a 0.8-mm expansion of the prosthesis, but this is variable and further lengthenings are estimated in a table in the manufacturer's instructions. It is not possible to reverse the lengthening obtained with each expansion. It is recommended that the procedure be performed under fluoroscopic guidance. Lengthening of the device can be performed without anesthesia or sedation in an outpatient setting according to the manufacturer [20] and Ness et al. [18]. The maximum expansion capacity of the prosthesis depends on the length of the prosthesis, and indirectly, on the length of the resected bone. According to oncologic principles, the resection level was at least 2 cm proximal to the tumor extension, as measured on preoperative MR images. The custom-designed prosthesis was usually between 0.5 and 1 cm longer than the planned distal femoral resection segment to gain some initial lengthening at the time of reconstruction. In this series the prosthesis varied in length from 126 mm to 202 mm, with a lengthening capacity ranging from 3.5 cm to 11 cm.

All study patients underwent distal femur resections for bone sarcomas, according to oncologic principles, and wide surgical margins were achieved in all cases. Cement was used to fix the stem of the femoral component in all but one patient. In this patient's reconstruction surgery, a plasma-coated, uncemented stem was inserted in the femoral canal; with the records available in this retrospective study, we were unable to ascertain why this approach was chosen for this patient. In all cases, the proximal tibia was shaved minimally and the stem was inserted in a press-fit manner to cause the least possible damage to the proximal tibial growth plate, as it maintains growth at the level the proximal tibial physis [8, 17]. Postoperatively, the patients were instructed to immediately bear weight as tolerated but to refrain from impact activities.

We retrospectively studied the medical records for clinical details (including age, sex, weight, tumor site, diagnosis, and resection length), and implant characteristics (implant length, stem diameter, stem length, expansion capacity). Furthermore, we analyzed clinical, radiographic, and oncologic outcomes. Functional results were assessed in patients who had survived their disease at final follow-up, according to the MSTS scoring system [7]. We focused specifically on implant survival, complications, limb-length discrepancy, lengthening procedures, and revision surgery. Complications were classified according to the International Society of Limb Salvage (ISOLS) classification system [13].

Results

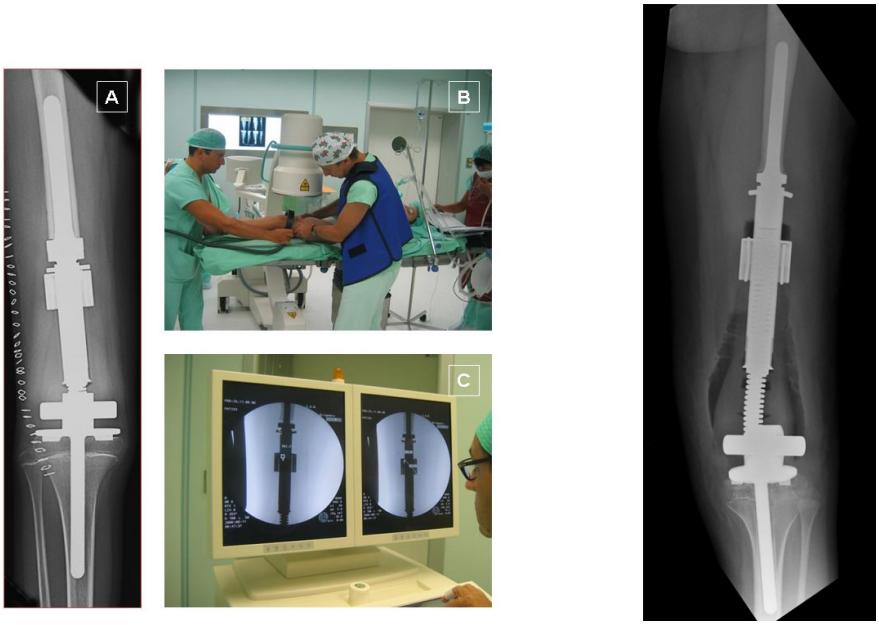
Table 1. Patient data

Pt nr	Age, (yrs)/ sex	Oncologic outcome	Followup (months)	Revision surgery/explantation Repiphysis	Time to revision (months)	Reason for revision	MSTS at revision surgery (%)
1	9/M	CDF	140	Expandable	49	Breakage	47
2	11/M	DOD	20				
3	8/F	DOD	11	AKA		LR	
4	9/F	CDF	126	Adult type	79	Breakage	47
5	8/M	CDF	101	Expandable	55	Loosening	87
6	11/M	DOD	28	AKA		LR	
7	8/M	CDF	114	Expandable, bone	67	Breakage	77
8	7/M	CDF	110	Expandable, bone	48	Breakage	63
9	9/F	NED	100	Adult type, bone	71	Breakage	77
10	7/F	CDF	96				
11	6/M	CDF	96	Expandable	61	Breakage	50
12	9/M	DTOX	2				
13	9/M	DOD	28	Cement spacer	8	Infection	
14	8/F	CDF	81	Adult type, bone	56	Breakage	57
15	7/F	CDF	78	Expandable, bone	76	Breakage	73

CDF=continuously disease free; NED=noevidence of disease; DTOX=death due to chemotherapy toxicity; DOD=deth of disease; Epandable=revision with another type of expandable prosthesis; Adult type=Revisione with a modular conventional megaprosthesis; AKA=above-knee-amputation; LR= local recurrence; bone=segmental massive bone allograft; MSTS=Musculoskeletal Tumor Society functipoonal score.

Nine of 10 patients underwent revision of their prosthesis for mechanical failure. Before revision these nine patients had a mean MSTS score of 64% (range, 47%−87%). At final follow-up, the 10 long-term surviving patients had an average MSTS score of 81% (range, 53%−97%). We then focused our review of patient data on implant survival and revision surgery (Table 1). The first seven lengthening procedures (in three patients) were attempted in an outpatient setting with the patients receiving no anesthesia. However, these procedures were unsatisfactory because of the difficulties for patients who reported sudden pain and burning sensations during lengthening. Moreover, it became clear that without complete muscle relaxation, only limited lengthening was achievable. The following 39 lengthening procedures were performed with the patients under general anesthesia on a day-hospital basis (Fig. 2). In all procedures, the manufacturer guidelines for the prosthesis were observed and instructions for the duration of each lengthening session were strictly followed. A total lengthening of 390 mm was obtained in 46 lengthening sessions which means an average lengthening of 39 mm per patient (range, 17–67 mm) (Table 2). Although the procedures were performed in a standardized manner, great variability of expansion ranging from 0 to 20 mm was observed.

Post-lengthening inflammation of the thigh with pain, stiffness, febrile responses, and radiographic appearance of a radiolucent layer around the prosthetic body (Fig. 3) was observed in six patients and became a consistent set of findings after their third lengthening procedure. Their temperature varied between 38º and 39 º Celsius and disappeared spontaneously within 3 days without antibiotic treatment.



Nine patients had clinical and radiographic signs of implant failure (metallic debris in the soft tissues, progressive stem loosening, breakage of the spring, or implant instability) and underwent complete revision of the primary implant at a mean of 62 months (range, 48−79 months) after the index procedure. In all but one case, the femoral stem was revised with a noncemented stem, which fits either an expandable or modular adult-type prosthesis of the implant system we have most experience with, in our department. In the remaining case, a custom-made expandable prosthesis of a different system was manufactured to fit a well-fixed cemented stem from the Repiphysis® implant.

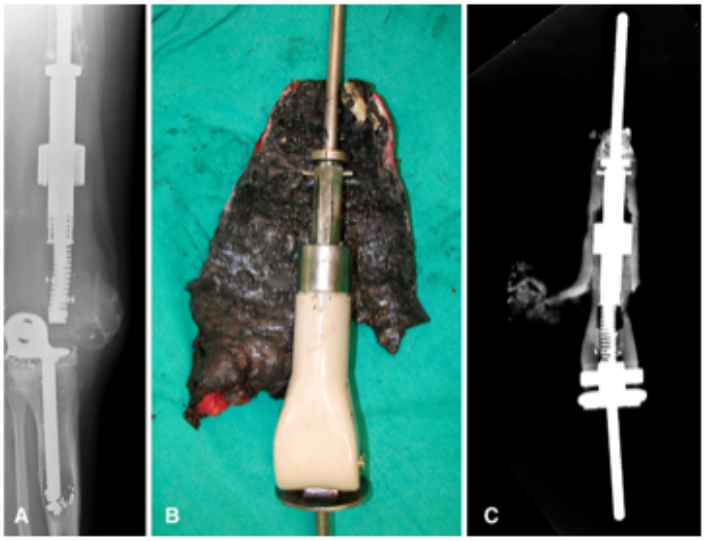


Fig. 4A-C (A) The radiograph shows signs of implant failure including metallic debris in the soft tissues and breakage of the spring. **(B)** The explanted prosthesis shows the periprosthetic membrane with extensive metallosis and a dark greenish-gray pseudocapsule. **(C)** The radiograph shows the removed implant at revision surgery.

Table 2. Follow up data

Patient number	Age (years)/ sex	Total lengthening	Revision of Repiphysis®	Further revisions (months from Repiphysis® revision)	Final limb length discrepancy	MSTS at final followup (months)
1	9/M	17 mm	Expandable	Adult type (95)	-1.5 cm	16
2	11/M *					
3	8/F *					
4	9/F	31 mm	Adult type		-3 cm	26
5	8/M	48 mm	Expandable	DAIR for infection (9)	0 cm	27
6	11/M *					
7	8/M	43 mm	Expandable, bone		-1.5 cm	23
8	7/M	67 mm	Expandable, bone	Expandable (26), adult type (62)	-2 cm (EPD)	22
9	9/F	31 mm	Adult type, bone		-1 cm	26
10	7/F	23 mm			-3.5 cm	
11	6/M	40 mm	Noninvasive expand		-2.5 cm	26
12	9/M *					
13	9/M *		Cement spacer			
14	8/F	50 mm	Adult type, bone		0 cm	29
15	7/F	40 mm	Expandable, bone	Expandable	-3 cm	23

Expandable = mini-invasive mechanically expandable prosthesis; Noninvasive expand = noninvasive expandable prosthesis; bone = segmental massive bone allograft; DAIR = débridement, antibiotics, and implant retention; EPD = epiphysiodesis; MSTS = Musculoskeletal Tumor Society; * = Did not undergo lengthening

The most common cause of revision was spring breakage (eight patients [89%]), an ISOLS type 3A complication. A consistent finding during revision surgery was the presence of extensive metallosis with a dark greenish-gray pseudocapsule surrounding the prosthesis (Fig. 4). One patient underwent revision surgery for aseptic femoral stem loosening after 55 months, an ISOLS type 2B complication. In five cases during revision surgery, a segmental allograft was used around the residual host bone-stem interface to compensate for lost bone stock in the short residual proximal femur segment and to improve the femoral stem fixation (Fig. 5).

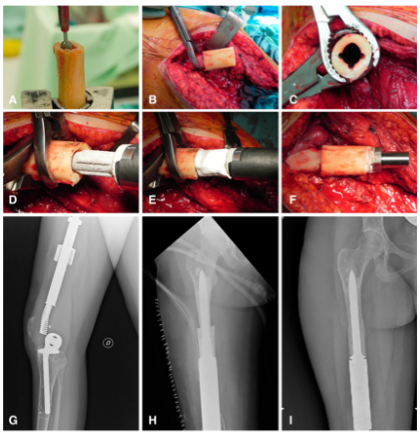


Fig. 5A–I The intraoperative photographs show (A) preparation of the segmental cortical allograft; (B) application of the allograft to the host bone; (C) preparation of the stem wings distally in the segmental cortical allograft; (D) stem introduction; (E) the distal part of the stem with a thin mantle of cement, just before complete introduction; and (F) final stem placement. The plain radiographs show (G) the prosthesis before revision, (H) immediately postoperative, and (I) 40 months after revision surgery

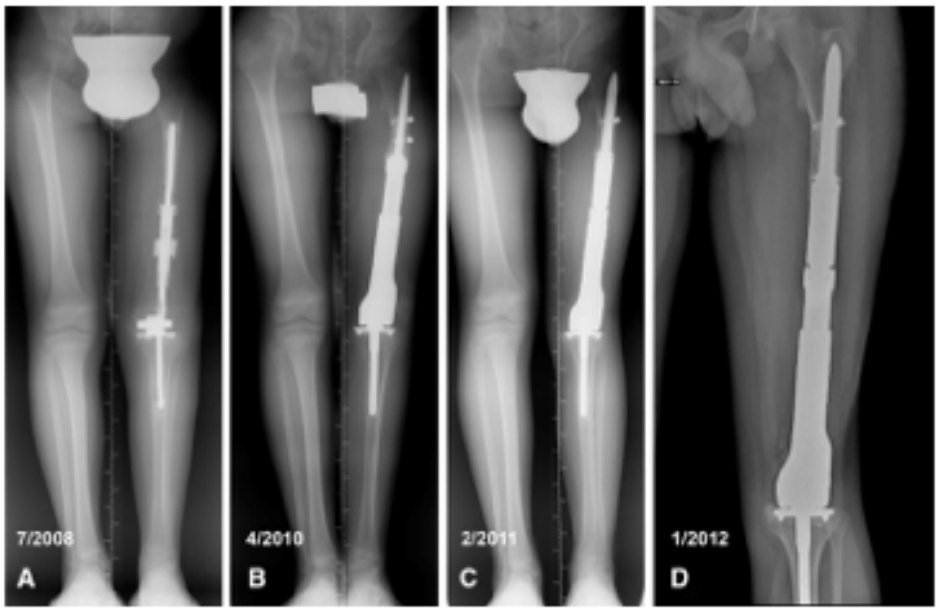


Fig. 6A–D Sequential radiographs show (A) spring breakage of the Repiphysis[1] prosthesis in 2008, followed by (B) revision surgery in 2010 with another type of expandable prosthesis, and radiographic controls after expanding the new prosthesis in (C) 2011 and (D) 2012.

The five male patients who needed revision surgery for implant failure were still skeletally immature (11−13 years old) at the time of the revision surgery. Their implants were revised with other types of expandable megaprostheses (Fig. 6). Four had their implants revised to an expandable prosthesis that can be lengthened through a small incision, and one had a prosthesis implanted that can be lengthened without surgery through application of an electromagnetic field. Three of these patients required further implant revision and their final limb length discrepancy ranged from 1.5 to 2.5 cm. Three female patients (13−15 years old at revision surgery) underwent revision surgery with implantation of an adult-type megaprosthesis and had a final limb length discrepancy ranging from 0 to 3.5 cm. Another female patient (13 years old) with 5-cm limb shortening at the time of revision surgery had implantation of a mini-invasive expandable prosthesis. In one patient, a contralateral epiphysiodesis of the distal femur and proximal tibia was performed to avoid progression of the limb length discrepancy.

Discussion

Limb-salvage surgery in skeletally immature children is a challenging problem for orthopedic surgeons because of the need to create a functional and durable reconstruction, minimize postsurgical complications, and address the problem of potential limb length discrepancy [24]. The introduction of less-invasive expandable prostheses is purported to allow for implant expansion without further surgical interventions and without use of general anesthesia, making this type of reconstruction increasingly popular in the treatment of skeletally immature children with malignant bone tumors of the extremities [6, 11, 12, 15, 17, 26, 27]. However, we found that use of a particular expandable prosthesis was associated with many complications, resulting in failure of the prosthesis, inability to achieve lengthening, and the need for surgical interventions and revisions.

There are limitations to our study. Five of our patients died within short follow-up, so only 10 patients are included in our study. However, findings from the 10 patients were sufficiently concerning to lead us to recommend against the use of the Repiphysis® prosthesis. Other

limitations included possible selection bias of cases as there are several reconstructive options for the specific reconstruction site in the age group of our patients, all with different surgical techniques, possible complications, rehabilitation programs, costs, and functional goals.

Our series confirms the tendency that with longer follow-up, the functional results deteriorate, owing to mechanical failure. However, the improved MSTS scores at final follow-up (on average 81%), compared with scores at revision (average, 64%), show that complex revision surgery can restore function. Our study included 10 patients with a mean age of 8 years and a minimum follow-up of 5 years (mean of nearly 9 years). To our knowledge, this study presents the longest follow-up of the Repiphysis® implant published to date. The Repiphysis® expandable prosthesis was the first noninvasive expandable endoprosthesis commercially available. Originally called the Phenix prosthesis (Phenix Medical, Paris, France), it has been used in Europe since the early 1990s and in the United States since the late 1990s [23]. Early reports showed promising preliminary results [11, 17, 26], with good-to-excellent function and a relatively low complication rate. MSTS scores in the early series with relatively short follow-up varied from 81.7% to 90% [2, 11, 17, 18, 22], but in the only previous series with an average follow-up of more than 6 years, the final MSTS score was on average 67% [4] (Table 3).

Table 3. Summary of literature on outcomes of Repiphysis® expandable prosthesis

Study	Number of patients	Followup (months)	Cases revised (%)	MSTS scores (%)
Wilkins & Souberain [26]	6	14	2/7 (29)	NA
Neel et al. [17]	15	21.5	8/15 (53)	90
Gitelis et al. [11]	16	24.8	7/16 (44)	83.5
Beebe et al. [2]	12	38	7/12 (58)	81.7
Ness et al. [18]	13	46	6/13 (46)	73
Saghieh et al. [22]	12	61.7	7/12 (58)	90
Cipriano et al. [4]	10	72	8/10 (80)	67
Current study	10	104	9/10 (90)	81

MSTS = Musculoskeletal Tumor Society; NA = Not Available

With respect to lengthening of the device, our study revealed a complication of the prosthesis that to our knowledge has not been previously reported. The Repiphysis® expandable prosthesis failed to expand for us as stated by the manufacturer, therefore only partially maintaining the noninvasiveness. Owing to pain and burning sensations the patients felt around the implant during the lengthening procedures, these had to be performed with the patients receiving general anesthesia. This has not been reported in previous studies of this implant. Wilkins and Souberain [26] mentioned very mild discomfort during the lengthening procedures which could be managed with oral analgesics. Patient age could partially explain the difficulties in pain management with our patients. Our patients were younger, with a mean age of 8 years at index surgery, whereas in other series the patients were older than 10 years [2, 4, 11, 18, 22]. Furthermore, the amount of lengthening was unpredictable and difficult to control. We performed 46 expansions in 10 patients, with an average of 8.4 mm per expansion. However, we observed gradual reduction of lengthening capacity. Generally, after the first three lengthening procedures of each prosthesis, the same exposure time to the electromagnetic field led to less lengthening. This might be related partially to the compressed spring, which as it gradually gets released, loses stored energy and expansion capacity. In addition, the increasing resistance of a thick fibrotic tissue around the implant, as seen in all revision surgeries, might influence the lengthening capacity. Although the problem of metallosis and periprosthetic fibrosis has been reported [3, 4], the difficulties controlling the amount of lengthening has not

been addressed, although Gitelis et al. [11] mentioned one case of failure with lengthening. Another potential disadvantage of this implant is that there is no possibility to reverse the lengthening achieved in case of overlengthening. We have not experienced overlengthening in our patients, but there is a potential risk for nerve damage through stretching if this happens accidentally, which cannot be resolved easily by shortening the implant.

Nine of 10 long-surviving patients underwent revision surgery of the implant, all but one because of mechanical failure of the implant. All revision surgeries were performed between 4 and 7 years after implantation of the prosthesis. The relatively early failures, before obtaining complete lengthening, and generally before the patients reached skeletal maturity, led to the need for revision with a second expandable implant in six patients. It was possible to revise the implant with an adult-type megaprosthesis in only three female patients. The most common complications of the Repiphysis® expandable implant have been reported [3, 4, 16, 22]. Infection, spring breakage, aseptic loosening, and fracture are well-recognized problems that often lead to revision of the implant, and with longer follow-up the percentage of revision surgeries seems to increase. In our study, one implant was removed for early postoperative infection and one implant was revised because of aseptic loosening. However, the most frequent reason for revision was prosthetic failure attributable to spring breakage (eight cases). Younger patient age and longer follow-up in our current series compared with previous studies [2, 11, 17, 22] might have influenced the results. Longer follow-up obviously exposes the implant to more risks of failure. Younger age at index surgery could influence the results through less compliance by the patient and a relatively more pronounced change of body weight and length. In addition, the biologic properties of bone (such as elasticity, bone turnover, tendency for stress shielding) are age dependent.

Cipriano et al. [4] stressed that extensive loss of bone stock in the metadiaphyseal area was frequent and an important complication of the implant. The bone loss might be attributable to extensive stress shielding of a cemented stem in young patients with high bone remodeling. Metal and polyethylene debris associated with high wear of the implant material might play a role in osteolytic processes resulting in stem loosening and bone loss, both of which increase the complexity of future operations. The manufacturer of the Repiphysis® implant suggests using cement for the femoral stem fixation [20] which can lead to more bone loss and the need for revision surgery. A well-fixed stem could be left in place and used to attach another implant, but this requires a custom-made adapter with the Repiphysis®, thereby increasing the costs and complexity of this relatively expensive implant system. In the series of Cipriano et al. [4], two patients had to undergo revision surgery with a total femoral replacement owing to extensive bone loss. We noticed similar loss of bone stock. We could avoid implanting total femoral replacements, but we used segmental allografts in five cases to achieve good proximal stem fixation of the revision implant and avoid use of an adapter component or total femoral implant.

In our series, the Repiphysis® prosthesis was associated with frequent failures and problems during lengthening procedures. Although lengthenings in our patients were in the range of values reported by others [2, 4, 11, 22], the majority of our procedures were painful for the patients if anesthesia was not used. We also were not able to control the amount of expansion during each lengthening procedure and the amount of expansion tended to decrease with time. We confirm that the implant showed unacceptable fragility and mechanical failure before obtaining the complete limb lengthening expected, with the need for revision with a second expandable implant. Furthermore, revision was a complex and difficult procedure although the functional results for our patients were improved. We have not used the Repiphysis® prosthesis since 2008 and have been using another type of expandable implant. Based on our findings and those of others [3, 4, 16], we caution against the use of this particular prosthesis.

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3.4.2
Stanmore non-invasive extendible endoprosthesis in the treatment of bone sarcoma in the preadolescent

Abstract
Aims The aim of this study is to assess outcomes of patients ≤12 years who undergo Stanmore non-invasive extendible endoprosthetic replacement of the distal femur (DFNIEPR).
Patients and Methods
101 children (mean age 9.6 years) were included. All complications which required further surgery were recorded. Clinical and functional outcomes were evaluated with Musculoskeletal Tumour Society Scores at mean follow-up of 64 months (range 6-174).
Results Thirty-one (30.7%) patients died at mean of 33 months.
Forty had prosthesis removed after a mean of 43 months (range, 7-103). Attaining of the full lengthening potential before skeletal maturity was the most frequent reason for revision surgery, particularly in those with smaller lengthening potential (p=0.039).
Implant survival rate for other causes was 61.7% at 5 years and 45.0% at 10 years. At final follow up mean MSTS score was 26 (range 13 to 29). Twenty-two (21.5%) patients had a final limb-length discrepancy >2 cm.
Conclusions DFNIEPR produces a good functional outcome, with prevention of major limb-length discrepancy at skeletal maturity in the majority of the cases.
We suggest patient selection criteria to account for stage of disease due to the high cost of the NIEPR, and high percentage requiring revision, and a 60% mortality rate in those patients presenting with distant disease burden.

Introduction
Nowadays, the treatment of primary malignant bone tumors in children aims not only to preserve the limb but also to minimize complications and maximize function.
Tumors in children frequently involve the distal femur (DF) metaphysis, thus requiring the resection of the physis. Since the annual growth potential that DF physis accounts for in the pre-adolescent is 9-10mm [1], the normal contralateral limb growth will result in a significant limb length discrepancy (LLD) in the operated limb at skeletal maturity. Therefore, preserving limb length equality after resection of the DF growth plate represents one of the main challenges of limb-salvage surgery in skeletally immature patients.

To compensate for the resulting LLD, different generations of extendible endoprosthesis (EPR) have been developed. Non-invasive extendible EPR (NIEPR) allow the implant to be extended on an outpatient basis by closed technique during follow-up. They theoretically reduce the number of operations and the need for anesthesia and they allow a more planned and progressive lengthening of the devices than minimally invasive EPR.

Stanmore Implants Worldwide (Elstree, United Kingdom) has developed a NIEPR that lengthens via an internal magnetic gearbox activated by an external magnetic field. [2-4] Using electromagnetic induction, gradual, painless controlled extension can be undertaken in the outpatient clinic. However, most of the studies in the literature report only short to mid-term outcomes of this implant. [4-6] Furthermore, previous series comprised a wide range of ages, including patients close to skeletal maturity, and multiple types of implants. [5, 7-9]

The aim of this multicentric retrospective study is to assess mid- to long-term survival and functional results of Stanmore DF NIEPR in patients younger than 12 years.

Materials and methods

A retrospective review of the prospectively maintained oncology databases of three specialist institutions was undertaken for all patients with a bone sarcoma of the DF treated by resection and reconstruction with Stanmore NIEPR. Patients treated between 2002 and March 2017 were included in the study. We included only patients younger than 12 years old in order to analyze a homogeneous cohort in terms of growing potential, as these can benefit the most from the lengthening potential of EPR.

A total of 101 patients aged ≤12 years at the time of diagnosis were included in the study.
Their mean age at the time of surgery was 9.5 years (range, 5 to 12). The diagnosis was osteosarcoma in 98 (91.5%) patients and Ewing's sarcoma in 9 (8.5%) patients. **(Table 1)**

TABLE 1 Patients' characteristics at baseline

Characteristics		n (%)
Sex	Male	50 (49.5)
	Female	51 (50.5)
Age at diagnosis, y		Mean 9.6 (range, 5-12)
Histology	Osteosarcoma	93 (92.0)
	Ewing sarcoma	8 (8.0)
Metastasis at diagnosis	Yes	26 (25.7)
	No	75 (74.3)
Length of resection, mm		Mean 202 (range, 160-330)

Twenty-six (24.3%) patients had metastasis at the time of diagnosis (21 to the lungs, two skip bone metastasis and one both to lungs and sternum). All patients received neoadjuvant chemotherapy. Three patients affected by Ewing sarcoma received additional radiotherapy in the neo-adjuvant setting due to the large size of the tumour.
The lengthening mechanism has been described previously.[4] The extending mechanism of the implant comes in three sizes, allowing 50 mm, 70 mm or 90 mm of extension and these are attached to the stem and joint of the implant. In details, the minimum length of the implant to have an amount of growth of 50mm is 190 mm, 210 mm for a lengthening potential of 70 mm and 230 mm for 90 mm. In three patients 177 mm customized prostheses with a lengthening potential of 50 mm were planned **(Figure 1).**

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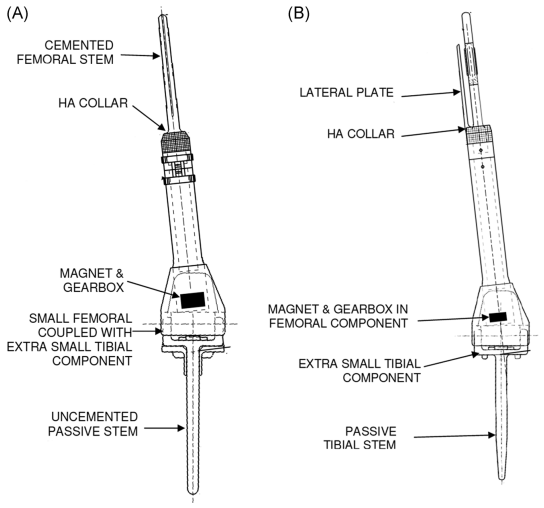

The femoral stem was either cemented or uncemented with the collar of the prosthesis coated with hydroxyapatite [10]. The joint articulation had a rotating or fixed-hinge knee with a passive sliding tibial component (Stanmore Modular Individualized Lower Extremity System (SMILES); Stanmore Implants Worldwide). **(Figure 1)**

In most of the cases the tibial component consisted of an ultrahigh molecular weight polyethylene sleeve fixed into the intramedullary cavity below the epiphysis and a metallic component which slides in the sleeve as the tibia grows thus allowing continued growth of the epiphysis.[11] On surgeon request, a fixed hinged with smoothed tibial stem was provided.

Usually, patients were over lengthened at the index operation to add additional length opportunity. A patient-by-patient decision was necessary, considering the LLD pre-operatively and intraoperative knee flexion.

Lengthening was started after completion of chemotherapy if the limb length discrepancy was > 2cm. [5] Lengthening was planned based on long leg x-rays. A lengthening of 4-6 mm was performed every procedure depending on LLD.

Lengthening was only performed if the patient could fully extend and flex the knee to 90°. Routine radiographs were performed after every lengthening procedure to confirm its success. When the prosthesis had been maximally lengthened, exchange of components was necessary for further growth: the telescopic shaft, magnet and gearbox were exchanged, leaving the fixation in the femur and tibia undisturbed.

In some other cases, a contralateral epiphysiodesis was performed to prevent LLD. A case-by-case decision was taken, taking into account LLD, the age of the patient and an estimation of the final height.

All complications which required a further surgeries were recorded and classified according to Henderson et al. [12]

At final follow-up, functional results of surviving patients with implant in situ were evaluated according to the Musculoskeletal Tumour Society Score (MSTS). Limb-length discrepancy was evaluated on lower limbs plain panoramic radiographs at last follow-up.

The Kaplan-Meier method was used to estimate overall survival (OS). Overall survival interval was defined as the time between surgery and death or last follow-up, whichever came first. The implant failure rate was defined as removal of the NIEPR for any reason, and it was calculated by competing risk analysis with NIEPR censored at the time of failure or last follow-up. Infection free and amputation free-rates were also calculated by Kaplan-Meier survival analysis. Categorical variables were compared between groups by contingency tables and chi square test. Significance was set with P values <0.05 in all statistical analyses, which were completed using the Statistical Package for Social Science (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.).

Results

Mean bone resection length was 202 mm (range, 160-330). Prosthesis characteristics are reported in **table 2**.

TABLE 2 Prosthesis characteristics

Prosthesis characteristics	n (%)
Length of the femoral stem, mm	Mean 120 (range, 50-130)
Lengthening potential, mm	
50	53 (52.5%)
70	21 (20.8%)
90	27 (26.7%)
Hinge	
Fixed	13 (12.9%)
Rotating	88 (87.1%)
Stem fixation	
Cemented	100 (90.0%)
Uncemented	1 (1.0%)

The lengthening potential of the prosthesis was not related to the age of the patients (p=0.651); however, a higher lengthening potential was obviously observed in longer femoral resections (p<0.001).

All but one patient with fixed hinge prosthesis were 8 years old or younger. Mean age in the "fixed hinge" group was 7.4 (range, 5-10) while in the "rotating hinge" group was 8.3 (range, 7-12) (p=0.113).

The estimated overall survival for all the patients was 68.3% at 5 years and 60.9% at 10 years.

A total of 31 patients died of metastatic disease at a mean of 33 months (range, 9 to 102) post-operatively. In particular, 16 patients out of 26 (61.5%) who presented with metastasis at diagnosis died after a mean of 20 months (range, 5 to 28). Five of these patients did not receive any lengthening procedure due to progressive metastasis after surgery.

In all, 47 (46.5%) patients underwent additional operations (including procedures not requiring prosthesis removal) related to the endoprosthetic reconstruction. **(Table 3)**

TABLE 3 Outcome and complications of EPRs

		n (%)
Any further surgery required (patients)	Yes	47 (46.5)
	No	54 (53.5)
Implant revision surgery required	Yes	40 (39.6)
	No	61 (60.4)
Prosthesis at final follow-up	DF NIEPR	87 (86.1)
	DF EPR	7 (6.9)
	DF EPR+proximal tibia expandable NIEPR	1 (1.0)
	Total femur EPR	1 (1.0)
	Amputation	5 (5.0)
Number of further surgeries	0	54 (53.5)
	1	28 (27.7)
	2	12 (11.9)
	3	6 (5.9)
	4	1 (1.0)
Type of complications[13]	- Type 1. Soft tissue complications	
	A functional	7
	B coverage (wound dehiscence)	2
	- Type 2. Aseptic loosening	9
	- Type 3.	
	A. Implant failure	7
	B. Periprosthetic fracture	5
	- Type 4. Infection	7
	- Type 5. Tumor progression	
	A. Soft tissue	3
	B. Bone	6
	- Type 6. Pediatric failures (lengthening potential achieved)	25 (21)
Follow-up, mo	Mean (range)	64 (6-174)
Status at follow-up	NED	69 (68.3)
	AWD	1 (1.0)
	DOD	31 (30.7)
MSTS	Mean (range)	26 (13-29)
Limb-Length Discrepancy (>2 cm)	Yes	22 (21.5)
	No	79 (78.5)

Abbreviations: AWD, alive with disease; DOD, died of disease; DF, distal femur; EPR, endoprosthetic replacement; NED, no evidence of disease; NIEPR, noninvasive extendible EPR.

One patient underwent also proximal tibia resection for a metachronous skip metastasis and reconstruction with a minimally-invasive growing EPR.

Forty (39.6%) patients required prosthesis removal after a mean of 43 months (range, 7-103). Estimated implant survival rate was 52.4% at 5 years and 32.6% at 10 years. **(Figure 2)**

In details, 23 out of 55 (41.8%) patients with a follow up longer than 5 years and 6 out of 17 (35.3%) with a follow up longer than 10 years have never changed the original EPR.

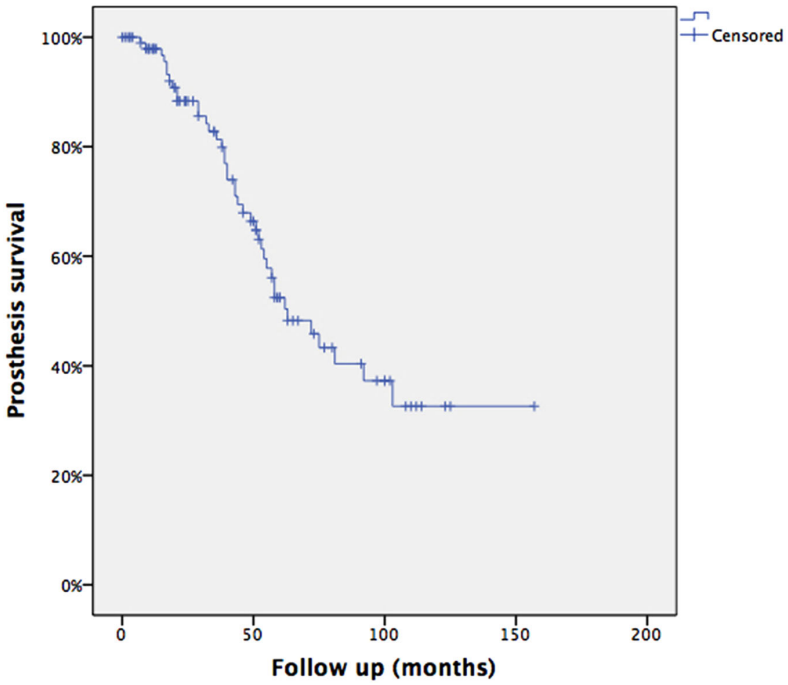

FIGURE 2 Kaplan-Meier survival analysis curve showing EPR survival rate. EPR, endoprosthetic replacement [Color figure can be viewed at wileyonlinelibrary.com]

Twenty-one patients required their prostheses to be removed due to the full NIEPR lengthening potential being reached before skeletal maturity. It was observed more frequently with lesser lengthening potential (50 mm) of the prosthesis (p=0.036). In 18 out of 21 cases (85.7%) a new NIEPR was implanted.

In addition, prosthesis was removed for aseptic loosening (after a mean of 60 months, range 39-92) and prosthetic infection in 9 and 7 patients, respectively. Other complications that required NIEPR removal were local recurrence (5 patients), implant failure (4) and periprosthetic fracture (2). In details, Causes of implant failure included hinge breakage (4 cases), bushing failure (2 cases) and fracture of the collar-prosthesis junction (in one case).

Estimated implant survival rate for causes other than attaining the lengthening potential was 61.7% at 5 years and 45.0% at 10 years. **(Figure 3)**

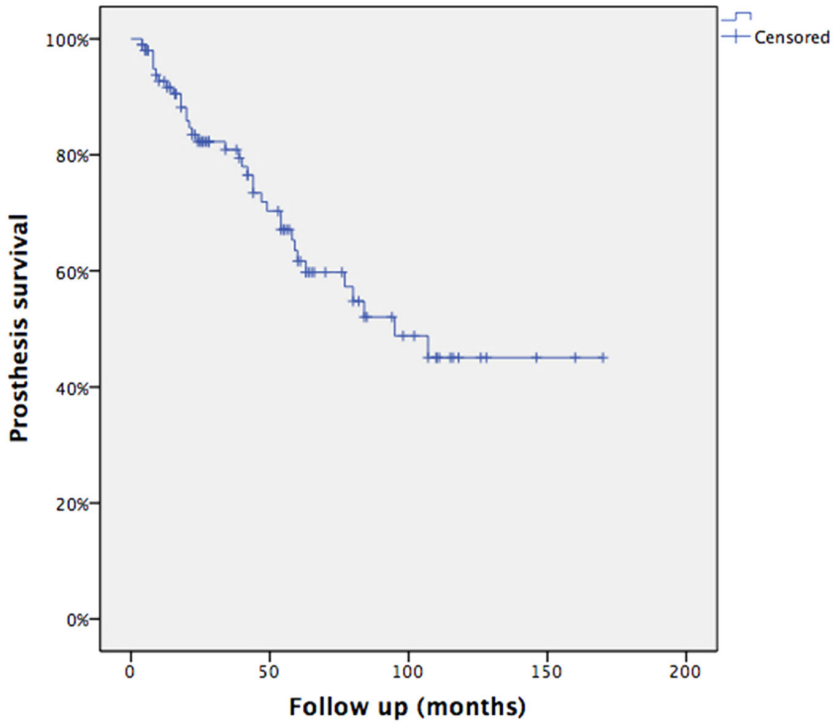

FIGURE 3 The Kaplan-Meier survival analysis curve showing EPR survival rate for causes other than attaining the lengthening potential. EPR, endoprosthetic replacement [Color figure can be viewed at wileyonlinelibrary.com]

No correlation was found between the complication rate and the age at insertion and length of resection.

Seven patients developed deep infection at a mean of 29 months (range, one to 63) postoperatively; two of these were managed successfully by washout and a six-week course of antibiotics. Three patients required a two-stage revision surgery and two required a one-stage revision; one of these had an infection recurrence and was amputated.

Estimated infection-free survival was 94.7% at 5 years and 90.7% at 10 years.

Five patients had secondary amputations (4 above-the-knee amputations and one hip disarticulation) either because of local recurrence (4) or infection (one). Limb preservation rates of 95.0% at 5 years and 92.0% at 10 years were observed.

In 15 (14%) patients a contralateral epiphysiodesis was performed. Nevertheless, 24 (22.0%) patients showed at last follow-up a limb-length discrepancy >2 cm.

At final follow-up, 4 patients had 10° limitation in knee extension. Knee flexion was up to 100° in 74 cases, between 60° and 80° in 22 cases and <60° in 5 cases.

Functional evaluation of the 63 surviving patients with NIEPR in site at the last follow-up revealed a mean MSTS score of 26 (range 13 to 29).

Discussion

Limb salvage surgery represents a challenge in skeletally immature patients in whom further growth is anticipated. This is particularly evident in very young patients with sarcomas in the distal femur where removal of the more important growth plate of the lower limb may be required to adequately remove the tumour. This will result in significant limb length inequality at maturity. The use of a NIEPR is one of the most commonly used methods of compensating for LLD after a wide resection of a distal femur bone sarcoma in a child.

A limitation to NIEPR is the contraindication to magnetic resonance imaging (MRI). Even if MRI is not considered the gold-standard to follow up patients with a megaprosthesis, in cases of NIEPR it can destroy the actuator device and should not be done as lengthening device may fail. [13]

In this study we evaluated the outcome and complications of 101 Stanmore NIEPR prostheses implanted in three tertiary referral centers.

To the best of our knowledge this is the largest series reporting the use of DF NIEPR in patients younger than 12 years old.
We found that approximately half of the patients required additional surgeries with 39.6% requiring revision of the NIEPR. Our finding is similar to that reported by Henderson et al. who reported 38% of revision-rate for all causes in a series including different models of NIEPR.[8] However, the most frequent cause leading to NIEPR removal was the achievement of the maximum lengthening potential of the implant before skeletal maturity, as previously reported by Gilg et al. [7]
Since the lengthening potential is related to the size of the prosthesis, we don't consider this as a complication but as a predictable event in NIEPR, particularly in very young children in whom a small prosthesis is implanted. [14] A possible and valid alternative to NIEPR in very young patients might be rotationplasty. Nevertheless, we believe that its indication should be reserved to cases of large tumours involving the vascular bundle. It is rarely accepted by the parents.
Even though patient's age has already been described as a limiting factor since enough bone stock has to be available to insert a prosthesis with a reasonable lengthening potential [14], we didn't find a significant correlation between lengthening potential and the age of the patients. However, a higher lengthening potential was obviously correlated to longer femoral resections. This suggests that even in young children, a longer resection is sometimes performed in order to place a NIEPR with a longer lengthening potential.

In this study the majority of patients received a rotating hinged joint. However, in 13 relatively young patients (12 $\leq$8 years old), a fixed hinge joint was preferred by the surgeon, because of the supposed less invasiveness on the growth plate for this type of implant. Compared with a rotating hinge component, the fixed hinge tibia creates a smaller diameter central defect to the physis and requires less bone sacrifice of the tibial joint surface.

In our series, estimated infection-rate (6% and 10% at 5 and 10 years, respectively) was lower than that reported in most of previous studies, which reported infection rates up to 18% for all sites NIEPR. [5, 15-19] However, only 12.5% of DF NIEPR developed a deep infection in the series of Gilg et al. [7] These data emphasizes the reduced risk of infection after distal femur NIEPR when compared to other sites. [7]
Also, infection did not seem to be related to secondary surgeries with only two patients developing infection after NIEPR revision. All other cases of infection occurred as first complication after the initial implantation of the implant.

Only 9 patients in our series needed revision surgery for aseptic loosening after a mean of 69 months (range, 39-140). This data is lower than that reported by Ness et al. [16] but is similar to other series reporting on Stanmore NIEPR. [5, 7] The most likely reason for this difference is our use of hydroxyapatite-coated collars, which has been shown to reduce aseptic loosening dramatically.[5]

Although complications were frequent, they often could be managed successfully without an amputation. In this study 4 out of 5 amputations were due to a local recurrence.
One patient had a periprosthetic fracture, which was managed through the implantation of a total femur EPR. Even if this data seems very low, our series report 5 years mean follow up and we may expect a higher number of patients needing a total femur EPR at longer term follow up.

The ideal goal of NIEPR is to avoid LLD at skeletally maturity. Although 15 patients had an epiphysiodesis and 18 patients had a new NIEPR for lengthening potential achieved, 22% of the patients in this series had a LLD of more than 2 cm at final follow-up.
Limb length discrepancy is particularly predictable in very young patients. Contralateral knee epiphysiodesis can be effective in particular in those cases in which a final LLD between 2 and 4 cm is expected. [20] Even though the real role and the right timing of epiphysiodesis in NIEPR patients

is not yet clear, this is the first series which evaluates it. Moreover, the revision of the prosthesis to a new NIEPR can be a viable but more expensive option to continue the lengthening of the femur. However, a case-by-case decision is mandatory. A strict follow up of these patients is necessary in order to detect very early progressive LLD and decide, together with patient families, how to correct it.

Our functional outcomes were excellent with a mean MSTS scoring system of 26. This is similar to data previously reported in similar smaller series. [2, 8, 21] MSTS score is a subjective scale and these encouraging results underline how patients are generally satisfied after DF NIEPR. Henderson et al. [22] studied the emotional acceptance of limb salvage with expandable prostheses in children, concluding that the level of happiness is similar to patients without tumour and have a good level of social functioning. In this study, NIEPR achieved reasonable limb-length equality and a good functional outcome for nearly all our long-term survivors.

The main limitation of this study is that it is a retrospective analysis without a control group. Limited follow-up restricted data collection, as several patients had died as a result of their disease. Nevertheless, it is a multi-institutional study, which includes a large homogeneous cohort of patients aged 12 years old or younger with a distal femur Stanmore NIEPR. Moreover, we report a series with a mean follow up longer than 5 years.
In our opinion, a few questions need to be further addressed in future studies. These include the final outcome of NIEPR in patients 5 and 10 years after skeletal maturity as well as the shortest femur resection to allow implantation of a NIEPR?

In consideration of the high costs of NIEPR and also considering that more than 60% of patients with metastasis at diagnosis died, we suggest a careful patients' selection which should also include stage of the disease. [14] However, it must be taken into account that only 10–20% of patients have macroscopic evidence of metastatic disease, whereas 80–90% of patients with osteosarcoma are assumed to have micrometastatic disease at initial diagnosis [23], so that the final decision may be difficult.
In case of a predictable poor prognosis a less expensive modular EPR with an initial over lengthening may be suggested.

Although NIEPR in young children seem technologically very exciting, it is characterized by a high rate of revision surgeries. Therefore, it is important to inform patients and their families about the significant risk of further surgeries associated with this type of implant.

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CHAPTER 4

EUROPEAN DATABASE EXPANDABLE PROSTHESES

4.1 INTRODUCTION

Over the last 20 years, the use of expandable prostheses for the reconstruction of children after bone tumor resection, has increased significantly.
These implants are nowadays considered the main reconstructive option for children in a certain age group and for selected bone segments. However, Gilg et al showed that there is no absolute consensus on indications, and a third of orthopedic oncologists in Europe, do not use expandable implants at all, probably due to the limited availability, high costs, and relatively high complication rates. Mechanical failure, infection risk, stem loosening, growth loss, joint stiffness, are all complications reported in expandable prosthesis, that are likely to diminish gradually over time, as surgeon's experience and implant design improve. However, for reconstructions performed in a highly selected patient group with very rare diseases, the production of scientific data is bound to be slow and weak if only single centers studies are performed as 'many have done a few, but only a few have done many' of these reconstructions.
For this reason, a European EMSOS study, focusing on expandable megaprosthesis of the distal femur was started in 2018. In this study, data from all European centers involved in musculoskeletal oncology was collected, to increase general knowledge regarding procedure/implant complications and the final functional outcome for patients.
All EMSOS members who have implanted (minimally invasive and non-invasive) expandable prostheses of the distal femur were invited to participate and share their cases in a centralized database. The following study is the result of this project.

EMSOS study on expandable distal femur megaprosthesis

Background

Expandable prostheses have become an important reconstructive technique in the treatment of children with bone sarcomas of the lower limb. According to a recent EMSOS survey, more than 60% of orthopedic oncologists have used this technique. However, less than 5% of these consultants have implanted more than 5. Therefore, scientific data on these implants remains limited. The literature on expandable implants is limited to small series, or mono-institutional studies with inevitable selection bias. According to these reports, complications are common and outcome is difficult to predict compared to adult-type megaprostheses.

We therefore proposed to perform an international European study on expandable prostheses of the distal femur. The objective of this study was to obtain scientific data on this rare indication, to provide our patients with reliable data on complications, functional outcome and need for further surgery.

Methods

We invited all members of the European Muscuuloskeletal Oncology Society to participate to this study by sending in data on their cases. All cases of expandable prosthesis of the distal femur were included, regardless of patient age, indication, and expansion mechanism.

Study period was between 1986 and 2019.

All complications which required a further surgeries were recorded and classified according to Henderson et al.

At final follow-up, functional results of surviving patients with implant in situ were evaluated according to the Musculoskeletal Tumour Society Score (MSTS). Limb-length discrepancy was evaluated on lower limbs plain panoramic radiographs at last follow-up.

The Kaplan-Meier method was used to estimate overall survival (OS). Overall survival interval was defined as the time between surgery and death or last follow-up, whichever came first. The implant failure rate was defined as removal of the expandable prothesis for any reason, and it was calculated by competing risk analysis with expandable prosthesis censored at the time of failure or last follow-up. Infection free and amputation free-rates were also calculated by Kaplan-Meier survival analysis. Categorical variables were compared between groups by contingency tables and chi square test. Significance was set with P values <0.05 in all statistical analyses, which were completed using the Statistical Package for Social Science (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.).

Results

A total of 299 patients were included from 15 different referral centers for orthopedic oncology in 9 different European countries (Italy, the Netherlands, Belgium, France, UK, Austria, Russia, Ukraine, Israel). Before the year 2000, expandable prostheses were very rarely used, with an annual incidence of less than four implants per year. After the year 2000 there was a quick, almost exponential, increase of the number of implants. Since 2010, there is a slow but gradual increase of the yearly implanted distal femoral expandable prostheses (Figure 1).

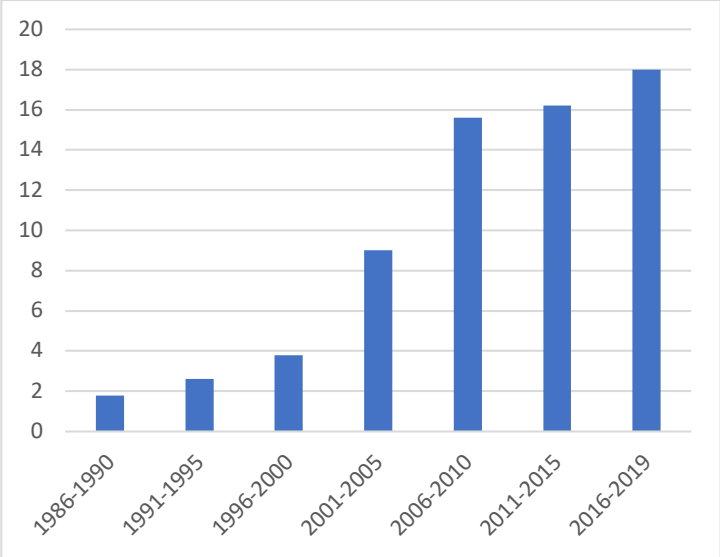

Figure 1. Expandable distal femoral prostheses implanted per year, according to the EMSOS database.

Median follow-up in this study was 80 months (range 8 to 287Months).
The mean age of patients at the time of surgery was 10 years (range, 4 to 63 years). The diagnosis was osteosarcoma in 271 (90.6%) patients, and Ewing sarcoma in 18 (6.0%) patients. Other diagnoses were chondrosarcoma (2 patients), PNET (2 patients), UPS (2 patients), and bone loss due to prosthetic loosening (3 patients) or infection (1 patient). Average tumor size (length) was 117 mm (range 35-238mm).
Fifty-two (17.4%) patients had metastatic disease at the time of diagnosis. All but six patients underwent (neo)adjuvant chemotherapy. Eleven patients received also radiotherapy.
Sixty (20%) of the implants required a (mini-invasive) surgical procedure for lengthening, the remainder were non-invasive growers. In almost two thirds (64%) a fixed hinge joint was implanted, the other implants had a rotating hinge design.
The most frequently used prosthesis was manufactured by Stanmore Implants Worldwide, followed by Stryker/Howmedica, Implancast and the Wright Repiphysis prosthesis (Table 1)

TABLE 1.

Prosthesis Manufacturer	**Nr (%)**
Implantcast	43 (14%)
Wright Repiphysis	38 (13%)
Stanmore	157 (53%)
Stryker/Howmedica	48 (16%)
Other	13 (4%)

Complications were classified according to the modified Henderson classification of implant failure. The most frequent reason for revision procedure was completion of lengthening potential (Table 2).

TABLE 2

Complication	Number of surgeries
Soft tissue complications	35
Aseptic Loosening	70
Structural failure	62
Infection	61
Tumor progression	20
Pediatric failures	102

KaplanMeier survival analysis of invasive versus non-invasive growing prostheses against infection, showed significantly (p=0,015) higher risk of infection for the implants that required a surgical procedure for lengthening (Figure 2). (88.2% vs 79.1% at 10 years)

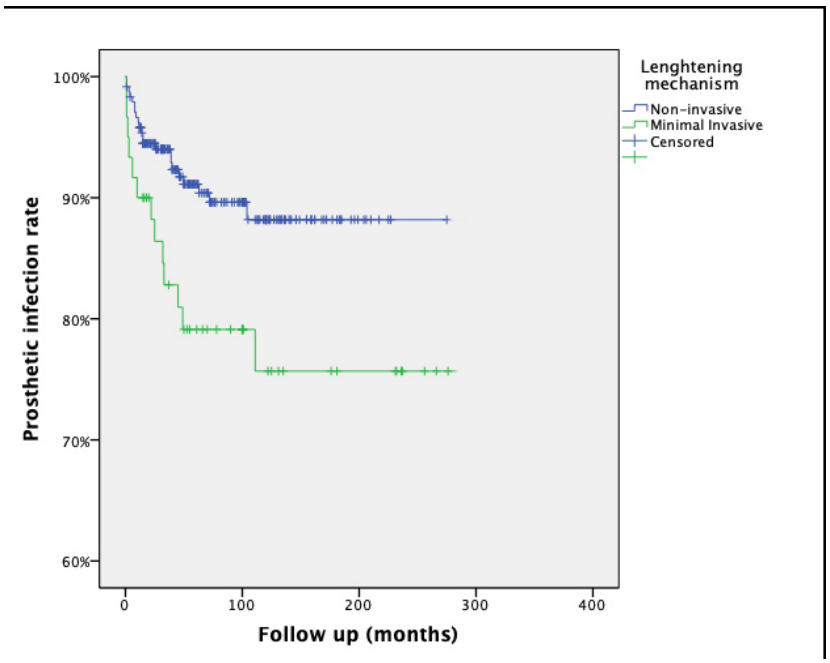

Fig. 2 Implant survival of invasive versus non-invasive prosthesis against infection showed better outcome for non—invasive expandable implants.

Looking at aseptic loosening, prostheses that were fixed with a cemented stem, did not significantly (p=0,394) differ in survival compared to prostheses with uncemented stems (Figure 3). (86.3% vs 80.4% at 10 years)

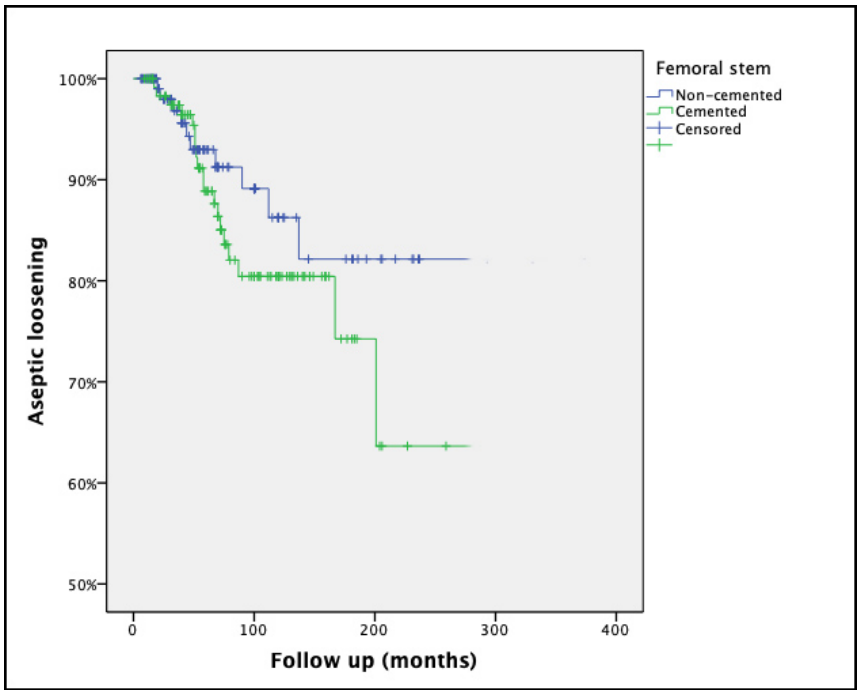

Fig. 3 Implant survival of cemented versus uncemented stem fixation did not show a significant difference.

Total length was more often (p=0,047) reason for implant revision in young children, when patients were divided in group up to and older than 10 years of age (Figure 4). (62.7% Vs 76.4%)

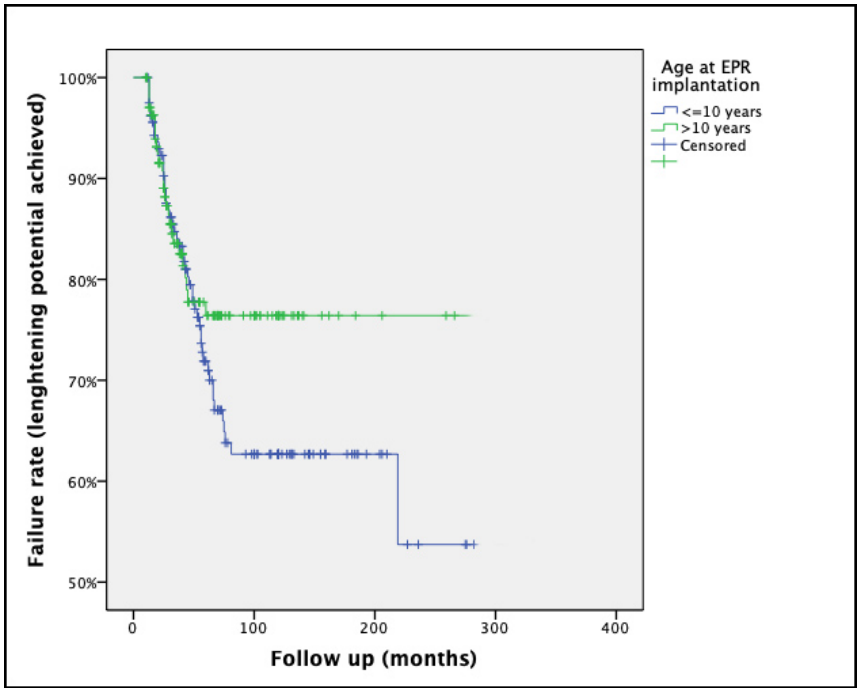

Fig. 4 Children up to 10 years had significantly higher risk for revision surgery due to completion of total length potential.

Comparing the different implants, the Wright Repiphysis prosthesis showed worse survival (57.9% at 5 years and 40.9% at 10 years), when looking at mechanical implant failure. The Stanmore, Stryker and Implantcast prostheses all had an implant survival of more than 80% at 5 and 10 years (Figure 5).

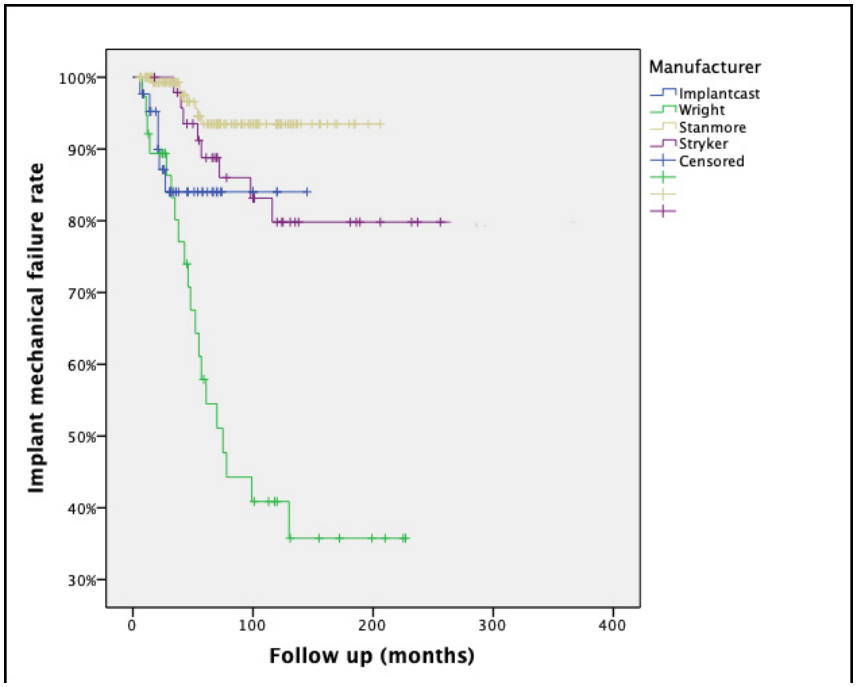

Fig. 5 Stanmore, Stryker and Implancast prostheses all showed implant survival over 80% agains mechanical failure. The Wright Repiphysis prosthesis did significantly worse.

At final follow-up, 76% of the patients had no evidence of disease. Average MSTS score was 25 (range 9-30). One hundred and eighty-eight (63%) of patients required further surgery, and one average each patient required 2,2 surgeries during the study period. Also, 12% (36 patients) eventually developed a deep infection of their prosthesis during follow-up, and a total of 20 patients (7%) required demolitive surgery.

Discussion

Expandable distal femoral replacements have been used since the 70s, when limb salvage surgery started to become more frequent, and required special reconstructions in children to overcome the problem of growth loss. However, the early expandable prosthetic designs showed disappointing results, and frequent complications. This, together with the high adaptive potential of children to demolitive surgery, made expandable reconstruction a rare indication before the end of the 21st century. Since the introduction of non-invasive expandable implants, the popularity of this reconstructive technique has increased significantly. This study showed how the incidence of this indication increased almost exponentially since the year 2000, and is still increasing, although at a slower rate, over the last decade. Reason for this, is certainly the improved implant design, with higher mechanical reliability and lower infection risk for the most recent generation of expandable implants. The mean age of patients was 10 years, which is in line with previous series of expandable implants. Very young patients, under the age of 5 or 6 years, require a lengthening potential that is not possible

to obtain with a single expandable implant. Furthermore, the small diameter and length of their residual femur, make a reliable implant fixation difficult. At the same time, for patients who are near skeletal maturity, loss of growth potential can be easily compensated by less invasive and less expensive measures such as, shoe lift, overlengthening at primary surgery, and contralateral epiphysiodesis, possibly in combination with a smooth stemmed pediatric tibial component.
The Stanmore JTS prosthesis was the most popular expandable distal femoral implant in this database. This implant has the advantage of a non-invasive lengthening mechanism. Stem fixation can be either cemented or uncemented and the hinge mechanism either fixed or rotating. The implant has shown reliability of the lengthening mechanism in an outpatient setting and overall implant survival was relatively high in most series. As in previous series, also in this study, the Stanmore expandable implant showed good overall survival. Both, Stryker and Implantcast showed similar durability to that of the Stanmore implants and no statistical difference between these implants could be detected. However, this analysis confirmed the poor implant survival for the Wright Repiphysis prosthesis, as was reported in previous series.
In this database, we did not find a significant difference for aseptic loosening, when comparing cemented and uncemented stem fixation.
The most frequent reason for implant revision was completion of the lengthening potential. As expected, this was more frequent in the younger patients. No compression-type implant fixation was used in this series.
Overall, the more modern implants showed relatively good outcomes, and functional scores, measured according to the MSTS scoring system, were on average good. Yet, the high need for further surgery, required for almost two thirds of the patients, with on average 2,2 surgeries, and subsequent high risk of infection (12%) and amputation (7%) during follow-up, warrant for further implant development, focusing on reducing the need for revision surgery.

Conclusion

This study represents the largest database on expandable megaprostheses ever presented. It shows how this reconstructive technique has been used more frequently over the last decades and still increases in popularity. Implants that are currently available on the market show overall good implant survival and good functional outcome, but repeat surgeries are frequent and major complications still represent a concern.

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CHAPTER 5

CONCLUSIONS

5.1 CURRENT STATUS AND FUTURE PERSPECTIVES OF EXPANDABLE PROSTHESES IN CHILDREN

It is inevitable that expandable prostheses will further increase in popularity over the next years. Through the last two decades important steps have been made in the reliability and durability of these implants. The lengthening mechanisms have been improved, and implant fixation is under continuous development. There is a tendency to reduce the classical rigid fixation with cementation or extensive press fit techniques, as this will eventually lead to bone loss because of remodeling or highly invasive revision surgery. Instead, stem fixation is probably moving towards a more natural fixation based on a gradual, but limited, osteointegration. In this perspective, excellent preliminary results have been obtained with a uncemented stem that is only partially covered with a hydroxyapatite layer.
At the same time, in consideration of the high complication rates for these implants, it is important to be aware of the likely need for further surgery during the patients' life, right from the start. Therefore, it is desirable to use an expandable implant that can be left in situ, possibly with only minor interventions, for a lifetime, without the need to substitute the whole implant into a different adult-type prosthesis. Surgical techniques using cylindrical allografts are available to restore bone stock and avoid the dramatic impact of conversion into a total femoral replacement or, even worse, amputation or disarticulation.
The fixed hinge tibial component with a thin smooth stem, seems to offer the best residual growth at the proximal tibial physis with excellent implant survival. However, further developments are required to overcome the problem of limited lengthening of the distal femoral component, especially in the patient group in which most expansion is required, children below the age of 6. It would be interesting to use a compression type of implant fixation in this patient group, in which the femoral diameter and residual length often is a limiting factor for endoprosthetic reconstruction. Also, the stem connection should be compatible with both a pediatric, expandable, distal femoral component and an adult-type distal femur component, without the need to remove the stem in case of revision after skeletal maturity.
The overall implant availability has to increase, to offer this type of reconstruction in all countries worldwide. To reach this objective, the implant costs need to be reduced. With upcoming new 3D printing manufacturing technology, this is likely to happen over the next few years. A second advantage of this technology is the reduction of production time. Which would make the surgical planning easier and more accurate. Also, personalized cutting guides could be useful to improve osteotomy and implant fitting accuracy, reducing the risk of stretching the neurovascular structures in case of planned overlengthening. Disposable, personalized reamers can help to improve canal preparation to increase stem grip, especially when uncemented fixation is used.
Finally, as for all rare diseases and rare surgical indications, it is important to collaborate between expert centers. When patient numbers are low, the only way to increase scientific knowledge, is by sharing our personal, limited experiences. This will avoid unnecessary experimentation on patients who already are in a weak position because of the aggressive diseases that they have to cope with at a very young age. International collaboration will be the key to rapid evolution of our innovative techniques, that eventually will be essential to further improve the quality of life for our patients.