DIPLOMARBEIT

30 years of growing endoprostheses in children with malignant bone tumours

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Abstract

Thirty years ago, children with primary malignant bone sarcomas of the extremities were treated with amputation in nearly all cases. Due to the predilection age in the second decade of life, a special challenge in limb-salvage surgery is the continuing growth potential. Therefore, the first extendible growing prosthesis was implanted in 1976. To reduce the high risk of infection due to the recurrent minimally invasive lengthening procedures and the need of general anaesthesia, non-invasive growing prostheses were developed.

The aim of this diploma thesis was first to analyse the complication rates and morbidity of patients who received an expandable prosthesis at the Department of Orthopeadics and Orthopaedic Surgery of the Medical University of Graz, Graz, Austria and second to perform a systematic literature review about growing prostheses.

Data from the Department of Orthopeadic Surgery Graz was analysed by conducting a retrospective database review. Twelve patients fulfilled the inclusion criteria. Due to the low number of cases a literature review was done additionally to supplement and compare our results regarding lengthening procedures and complications.

In our patients' collective (mean age 9.7 years (range 5.0- 14.0)) eight patients were treated by minimally invasive expandable prostheses and four patients by non-invasive prostheses. The mean follow-up was 88.0 months (range 6.0- 232.0). The mean number of minimally invasive lengthening procedures per patient was 3.3 (range 0.0 to 10.0). Mean total lengthening was 36.2 mm (range 0.0 to 131.9). Complications were classified according to modified Henderson et al. In our patients' collective the most common complication was deep infection. In our dataset neither amputation nor local recurrence occurred, However, three patients died of disease due to pulmonary metastases at initial diagnosis.

In literature review, 23 studies with 489 participants were included (mean age 10.1 years (range 2.0- 16.0)) with a mean follow-up of 56.0 months (range 2.0 to 282). The most common complication according to modified Henderson et al. was deep infection. Amputation was necessary in 24 cases (5.0%), local recurrence was present in 24 patients (50%) and 95 patients died of disease (19.7%). Mean number of lengthening procedures per patient was 5.1 (2.1- 40.0) with a mean total lengthening of 40.3 mm (1.5- 82.0).

Growing prostheses are a good alternative to amputation or rotationplasty regarding a good MSCS score. However, high rates of infection in minimally invasive growing prostheses and the high rate of prosthetic failures in non-invasive growing prostheses show a necessity of further development to meet the demands of a growing child.

Kurzfassung

Vor 30 Jahren wurden Kinder mit malignen Knochentumoren mittels Amputation versorgt. Das Prädilektionsalter für maligne Knochentumore liegt im 2. Lebensjahrzehnt. Das Größenwachstum in diesem Alter stellte eine große Herausforderung für die extremitätenerhaltende Chirurgie dar. Die Implantation der ersten minimal invasiven Wachstumsprothese brachte einen großen Durchbruch, obwohl die Infektionsrate durch die Invasivität dieses Verlängerungsmechanismus sehr hoch war. Mit der Einführung und Erstimplantation einer non-invasiven Wachstumsprothese erhoffte man sich die Verringerung der Infektionen.

In dieser Diplomarbeit wurden Daten der Universitätsklinik für Orthopädie und orthopädische Chirurgie an der Medizinischen Universität Graz, Graz, Österreich retrospektiv erhoben und bezüglich des Verlängerungsmechanismus, häufiger Komplikationen und des Implantat-Überlebens untersucht. Da nur zwölf Patienten die Einschlusskriterien erfüllten, wurde zusätzlich eine Literaturrecherche durchgeführt. Die erhobenen Komplikationen wurden nach einer modifizierten Klassifikation nach Henderson et al. eingeteilt um eine bessere Vergleichbarkeit zu erzielen.

In unserem Patientenkollektiv mit dem mittleren Alter von 9.7 Jahren (5.0-14.0) wurden acht Patienten mit einer minimal invasiven Prothese versorgt und vier mit einer non-invasiven Prothese. Die mittlere Anzahl an Verlängerungen pro Patient mit minimal invasiven Prothesen belief sich auf 3.3 (0.0- 10.0). Die Gesamtverlängerung belief sich im Mittel auf 36.2 mm (0.0- 131.9) während eines mittleren Follow-Up von 88 Monaten (6.0- 232.0). Die häufigste Komplikation war der periprothetische Infekt. Drei Patienten starben an Lungenmetastasen, jedoch kam es weder zu einer Amputation noch zu einem Lokalrezidiv.

Im Rahmen der Literaturrecherche konnten 23 Studien mit einem Patientenkollektiv von insgesamt 489 Patienten mit dem mittleren Alter von 10.1 Jahren (2.0- 16.0) eingeschlossen werden. Das Follow-Up belief sich im Mittel auf 56.0 Monate (2.0- 282) mit der mittleren Anzahl von 5.1 Verlängerungen pro Patient (2.1- 40.0). Die durchschnittliche Verlängerung belief sich auf 40.3 mm (1.5- 82.0). Die häufigste Komplikation war der periprothetische Infekt. Die Amputationsrate lag bei 5.0%, 95 Patienten starben (19.7%) und in 24 Patienten kam es zu Lokalrezidiven (5.0%).

Obwohl die Infektionsraten vor allem in minimal invasiven Prothesen noch sehr hoch sind und es bei non-invasiven Prothesen noch an einer Verbesserung der hohen mechanischen Versagensrate bedarf um den Ansprüchen zu entsprechen, ist der berechnete MSTS score durchaus befriedigend.

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Abbreviations

a.p.	anterior – posterior
AWD	alive with disease
COSS	Cooperative Osteosarcoma Study Group
CT	computer tomography
e.g.	for example (Latin exempli gratia)
EICESS	European Intergroup Cooperative Ewing’s Sarcoma Study
EMBASE	Excerpta Medica database
et al.	and others (Latin et alii)
EURAMOS	European and American Osteosarcoma Study Group
EVAIA	vincristin (V), actinomycin D (A), ifosfamid (I), doxorubicin (A) and etoposide (E)
HMRS	Howmedica Modular Resection System
GMRS	Global Modular Replacement System
HR	high risk
i.e.	that is (Latin id est)
IGF	insulin-like growth factors
JTS	Juvenile Tumour System
LPS	Limb Preservation System
MAP	methotrexate (M), cisplatin (P) and doxorubicin (A)
MAPIE	methotrexate (M), doxorubicin (A), cisplatin (P), ifosfamide (I) and etoposide (E)
MAPinf	methotrexate (M), cisplatin (P) and doxorubicin (A) and interferon-a (inf)
MedLine	Medical Literature Analysis and Retrieval System Online
MRI	magnetic resonance imaging

MSTS score	Musculoskeletal Tumour Society score
mTOR	mechanistic Target of Rapamycin
n.a.	not available
NED	no evidence of disease
OVID	Ovid Technologies
PAS	periodic acid-Schiff reaction
PARP	Poly (ADP- ribose) polymerase
PNET	primitive neuroectodermal tumour
PubMed	Public Medicine
RCT	randomized controlled trial
SR	standard risk
VAC	vincristin (V), actinomycin D (A) and cyclofosfamide (C)
VAI	vincristin (V), actinomycin D (A) and ifosfamide (I)
VAIA	vincristin (V), actinomycin D (A), ifosfamid (I) and doxorubicin (A)
VIDE	vincristin (V), ifosfamide (I), doxorubicin (D) and etoposide (E)

1 Introduction

1.1 Growing prostheses

1.1.1 History of growing prostheses

Before the 1970’s children with malignant bone tumours were almost always treated with amputation due to a lack of treatment possibilities (1). With the introduction of effective polychemotherapy, the 5-year survival rate increased from 11% up to 60- 70% and the need for limb salvage surgery increased (1). The major challenge with children with malignant bone tumours is their continuing growth potential. As osteosarcoma and Ewing’s sarcoma are frequently localized in the distal femur and proximal tibia, limb-length discrepancy will result after the resection of the growth plate until adulthood (2). To compensate this discrepancy, multiple revision surgeries in which the whole prosthesis was changed, had to be performed until the skeletal maturity was achieved in the past (2). By this the complication rate was increased, i.e. the infection rates of soft tissue failure (2). Therefore the first expandable prosthesis with a screw jack system (Mark I, Stanmore Implants, Middlesex, UK) was designed and implanted in 1976 (2). It replaced the distal femur with a knee hemiarthroplasty and was lengthened minimally invasive under general anaesthesia (3).

In 1982 this system was replaced by the redesigned “Mark II” prosthesis (2). This system consisted of two distinct components with a ball bearing system (3). As the Mark II prostheses showed failures of the lengthening mechanism in the form of breakage of the ball bearings due to the high pressure at implantation, this prosthesis was replaced by the Mark III model in 1986 (2, 3).

In 1983 the Lewis Expandable Adjustable Prosthesis (Dow Corning Wright Corporation, Memphis, TN, USA) was created having a fixed stem with a screw extension mechanism (4).

With the introduction of the Repiphysis (Wright Medical Technology, Arlington, TN, USA) in 1984, originally known as the Phenix Prosthesis (Phenix Medical, Paris, France), the first non-invasive expandable prosthesis was available. Expansion was reached by induction of an external electromagnetic field that heated an antenna in the implant. This antenna weakened the polyethylene locking mechanism, allowing a spring to expand (4).

In 1987 the minimally invasive Growing Kotz prosthesis (HMRS) (Howmedica Modular Replacement System) (Stryker Howmedica Osteonics, Kalamazoo, MI, USA) was introduced. The included growth module had a threaded spindle activated by a gear pair. When skeletal maturity was completed, the extendable module could be replaced by the components of the adult prosthesis (4).

The Mark IV prosthesis was used from 1988- 1992 and lengthened with external C washers (3). With Mark V (introduced in 1993), there was another minimally invasive growing prosthesis available (3).

In the early 2000s a non-invasive growing prostheses was used which was lengthened by 100 degrees flexion of the knee joint (5).

The newest generation of expandable prostheses has non-invasive lengthening mechanisms. Non-invasive growing prostheses are gold standard nowadays. There are three manufactures that produce non-invasive growing prostheses: Stanmore Implants (6) (Stanmore, Middlesex, United Kingdom) producing the JTS (Juvenile Tumour System), Implantcast (7) (Buxdehude, Germany) producing MUTARS Xpand and Wright Medical Technology (8) (Arlington, TN, USA) producing the Repiphysis Limb Salvage System.

1.1.2 Indications for growing prostheses

The idea of a non-invasive lengthening mechanism is to reduce the number of open revision surgeries to decrease the need for general anesthesia and complications like prosthetic joint infection (2). It is generally accepted that minimally invasive and non-invasive growing prostheses are implanted if a leg-length discrepancy greater than three to four centimetres is calculated until adulthood (3).

For the implantation of a growing prosthesis the diameter of the shafts in the lower extremities has to be 9 mm, minimum (9). Each type of expandable prostheses has a specific minimal resection length requirement (**Table 1**). Especially in the young children, when most growth is still anticipated, the required resection length might exceed tumour extension and could result in the need for wider resection than necessary for oncological reasons (9). Children older than eight years usually have enough bone stock (9). However, there are no strict criteria regarding minimum age and a consensus does not exist among experts. Some orthopedic oncologists do not consider the implantation of a growing prosthesis if metastatic disease is present at the time of surgery (9). Furthermore, some centres primarily implant so-called “Dummy” prosthesis-growing prostheses without a motor-as they prefer to implant the costly motor at a later stage when survival is more likely.

1.1.3 Types of Growing Prostheses

1.1.3.1 Minimally invasive growing prostheses

HMRS (**Figure 1 A & B, Figure 2 A & B**)

HMRS prosthesis (Howmedica Modular Replacement System) (Stryker Howmedica Osteonics, Kalamazoo, MI, USA) was developed and was raw coated to ensure extracortical “bone bridging” (10). Furthermore the design of the fixed hinge was improved (10). The growing module is lengthened by a minimally invasive procedure. The growing module has an inner part with a spindle driven by gears, which move a titanium sleeve. Although the system is self-locking due to a thread pitch, there is an additional locking screw (4). By unlocking this screw access is released and can be turned. So lengthening of the prosthesis is possible by 1 mm per turn without the necessity of using spacers (11).

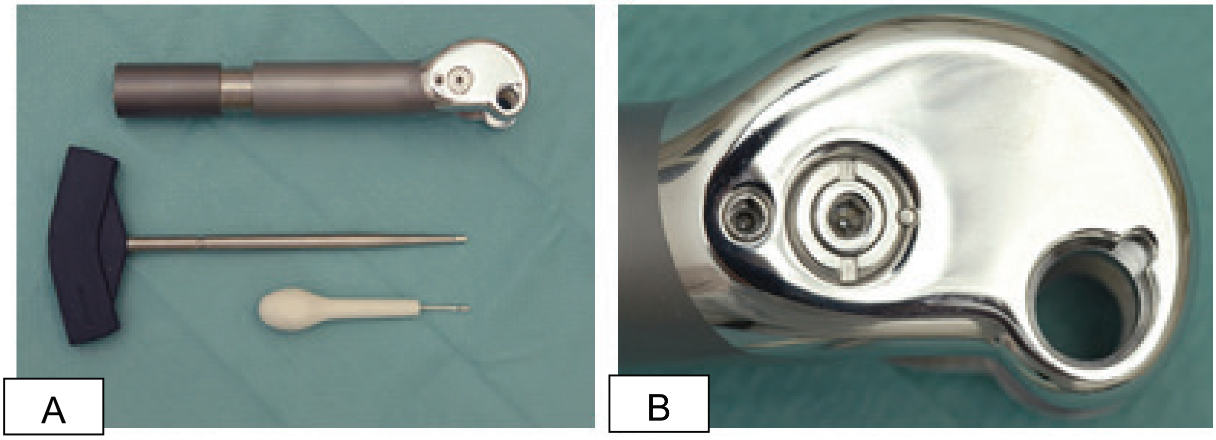

Figure 1 A & B: A: (top down) HMRS growing prosthesis with the lengthening screwdriver and the instrument for unlocking the fixation screw**. B:** left: aperture with fixation screw, right: lengthening screw

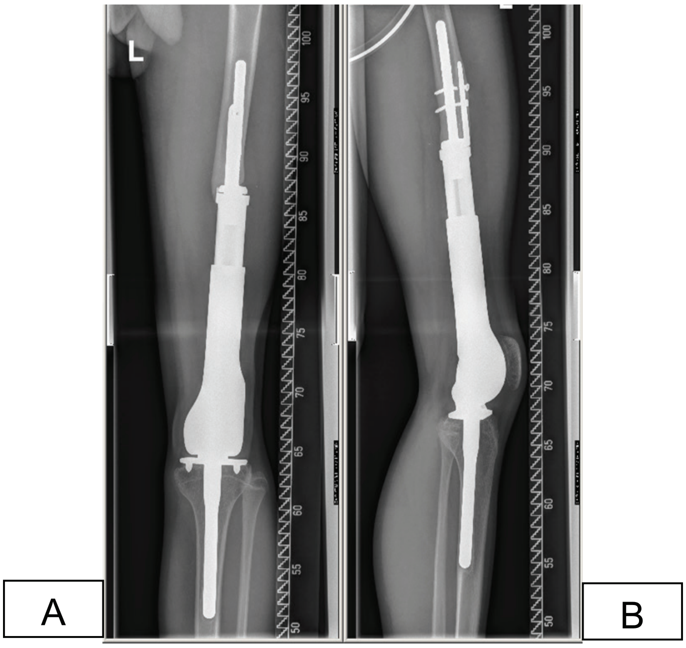

Figure 2 A & B: X-rays a/p and lateral: male patient from Department of Orthopedic Surgery Graz, **A**: 14 years old; **B**: 4 years following implantation of a minimally invasive HMRS prosthesis

Stanmore Mark I- V

Mark I (Stanmore Implants, Middlesex, UK) was the first growing prosthesis implanted in bone sarcoma patients (2). This type of prosthesis replaced the distal femur with a knee hemiarthroplasty which consisted of two condyles articulating the unaffected tibia plateau (3). It was lengthened minimally invasive under general anesthesia with a hex key (3). A screw jack system enabled the lengthening with minimal exertion of force. The rotation of this screw allows expansion or collapse of the device (3).

This system was replaced by a newer prosthesis with a lengthening mechanism of stacked ball bearings in 1982 (Mark II) (2). This system consisted of two distinct components (3). One component was implanted in the unaffected part of the joint and could be extended during the growth of the child whereas the second component was passive with a sliding femoral or tibia stem to minimize injuries to the growth plate and allowed continuing growth (3). As the Mark II prostheses showed high mechanical failure rates, such as fractures of the ball bearing system and the extension mechanism, the Mark III model replaced these prostheses in 1986. Compared to the previous system, in this prosthesis the 6 mm ball bearings were used as a spacer, and a distraction device was used to achieve lengthening so the incision had to be larger which resulted in higher infection rates (2, 3). The Mark IV prostheses were used from 1988- 1992 and were lengthened with external C-washers made in 6 mm increments. These C-washers in different sizes were inserted to lengthen the prosthesis step by step. During the lengthening procedure the smaller C-collar was explanted and replaced by the next size (3). This was possible every sixth week without any injuries to vessels or nerves (3).

The Mark V prosthesis (introduced in 1993) is the result of further development of the previously minimally invasive growing prostheses manufactured by Stanmore implants. After problems with the instability of the knee hemiarthroplasty and the unreliable lengthening mechanism in Mark I, fractures of the ball bearings under pressure in Mark II and III, collar dislocation and implant fractures of Mark IV, Mark V was based on a worm screw mechanism which allowed lengthening of one millimetre per ten turns unidirectional to minimize the risk of prosthetic collapse (3).

1.1.3.2 Non-invasive growing prostheses

	extension (mm)	**minimum resection length (mm)**
REPIPHYSIS ®	35.0	123.0- 147.0
	60.0	148.0- 173.0
	85.0	174.0- 199.0
	110.0	> 200.0
MUTARS Xpand ®	50.0	170.0
	75.0	195.0
	100.0	220.0
Non-invasive JTS Implants (Stanmore)	50.0	170.0
	70.0	190.0
	90.0	210.0

Table 1: maximal extension length of the prostheses and minimal resection length for implantation

MUTARS® Xpand- Implantcast (**Figure 3 A & B**)

MUTARS® Xpand is available in three different sizes. The smallest model needs a minimal resection length of 170 mm and has a maximal dimension of 50 mm. The second largest prosthesis has a minimum resection length of 195 mm and a maximum extension of 75 mm. The biggest model needs a resection of 220 mm, minimum and can be extended up to 100 mm (**Table 1**). This type of prosthesis works with a motor which is attached to the prosthesis and can be activated by an external electromagnetic field using a subcutaneous antenna as the transmitter (12). It combines a modular endoprosthesis with a telescopic component and a motordrive unit. Due to this technique, an individual non-invasive lengthening is possible continuously or in small steps without injuring the neurovascular structures or soft tissues. There is no need for further open lengthening procedures under general anesthesia and therefore infection rates were thought to be reduced (12). With MUTARS Xpand reconstructions of the total, proximal or distal femur as well as the proximal tibia are possible (9). Many of these prostheses are custom-made which means that the growing prosthesis is designed for a specific patient. When the lengthening of the prosthesis is completed, all the components can be shifted by conventional MUTARS parts.

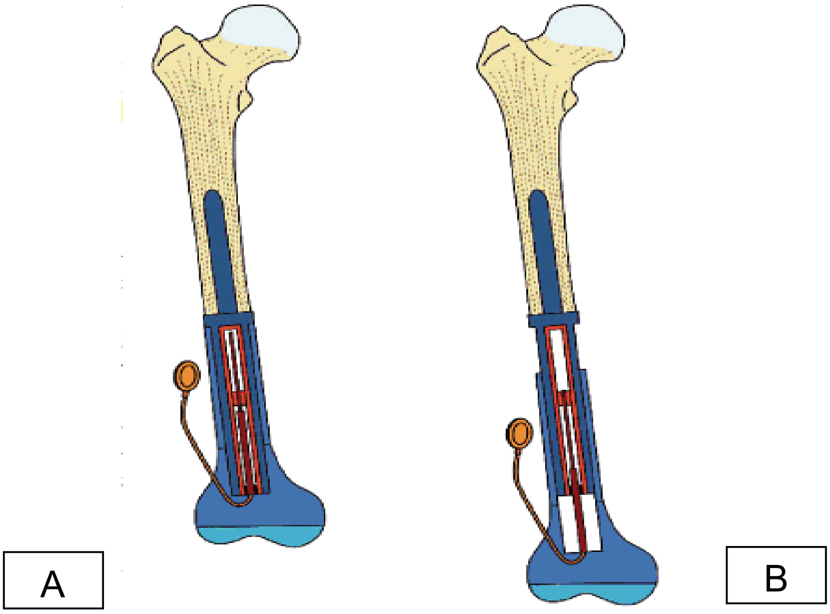

Figure 3 A & B: schematic representation of the MUTARS Xpand (12) (prosthesis and subcutaneous antenna); **A:** not lengthened; **B:** lengthened

A new non-invasive implant type of Implantcast is the MUTARS BioXpand. The lengthening is based on callus distraction which relies on the fact that tissue proliferates under continuous tension. With controlled bone distraction of one millimetre per day under axial standing, a bone formation of high quality occurs (12).

MUTARS BioXpand uses an articular component, a shaft substitute (available in different lengths) and a component with the host bone segment. After tumour resection, a fixed intramedullary polished nail is preliminary implanted. As soon as a leg length discrepancy of 3- 4 cm is reached (12), the intramedullary nail is explanted and a cortical osteotomy is performed. A motorized lengthening nail is implanted for performing distraction. The energy is, similar to MUTARS Xpand, supplied by a subcutaneous antenna. On average, a new callus is full weight bearing after four to six months. This procedure can be repeated any time, but the expandable prosthesis has to be replaced by a standard tumour prosthesis when skeletal maturity is reached (12).

<u>Stanmore- JTS non-invasive extendible prosthesis</u> (**Figure 4 A, B & C**)
The latest Stanmore extendible endoprosthesis is a non-invasive implant called Juvenile Tumour System (JTS). It is available in different sizes, beginning with 50 mm of extension capacity where a 170 mm resection length is needed. The next size is available with up to 70 mm expansion where a resection length of 190 mm is needed. The last size can be lengthened up to 90 mm and a resection length of 210 mm is required (**Table 1**).

A small jet gearbox that leads to the extension lengthens the JTS implant. For lengthening procedures, the limb has to be placed into the external drive unit. The drive unit produces a rotating magnetic field at 3000 rounds per minute by passing electric current into an electric coil. The rotation is caught by the magnet and is passed through the gearbox to extend the implant that grows 1 mm every four minutes, which is slow enough to stretch the soft tissues (6).

This type of implant can achieve a very precise lengthening, and in the case of overlengthening the implant length can easily be reduced (6).

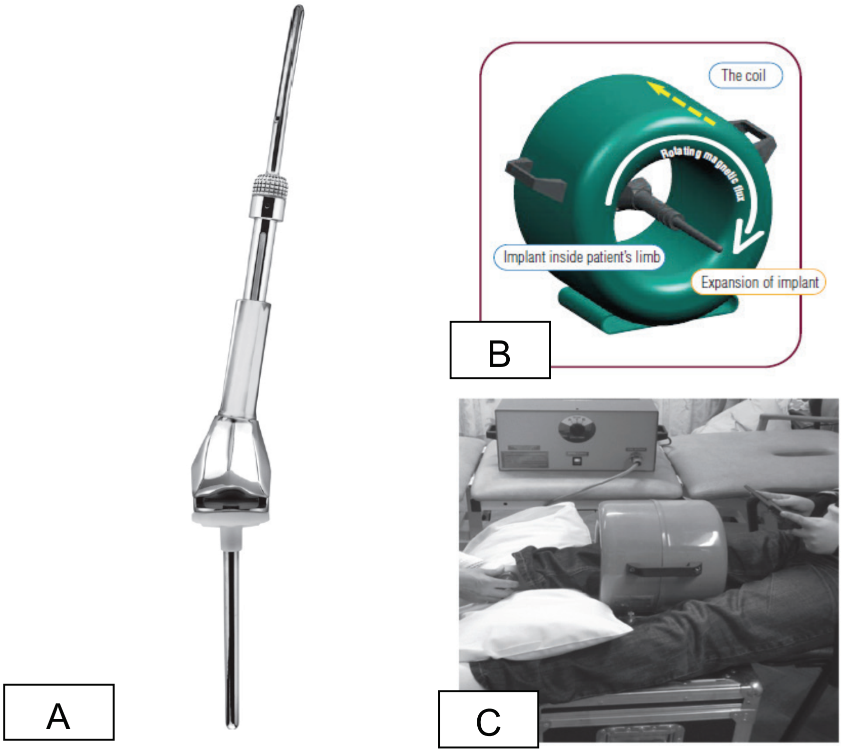

Figure 4 A, B & C: A: JTS growing prosthesis (37); **B:** schematic representation of the external electromagnetc field (36), **C:** lengthening procedure by the external electromagnetic field (37)

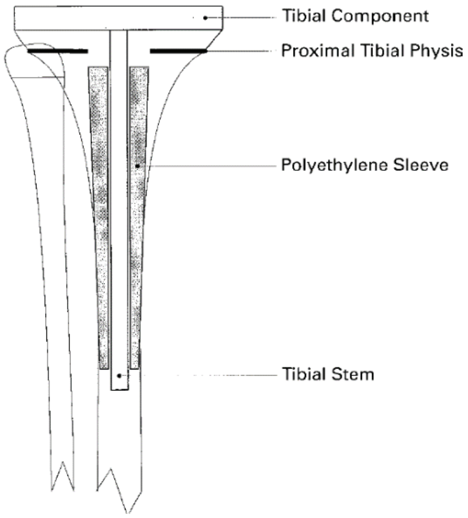

Figure 5 (48): principle of the sliding component

Repiphysis Limb Salvage System (**Figure 6 A, B & C**)

Repiphysis growing prostheses are available in four different dimensions. Expansion capacities beginning with a minimum resection length of 123 mm and an expansion of 35 mm. The second one needs 148- 173 mm resection length and can be extended up to 60 mm. The third dimension has a maximum extension of 85 mm and needs a resection length of 174- 199 mm. The largest one needs a resection length of more than 20 cm and can be extended to 11 cm (**Table 1**). The Repiphysis prosthesis was the first non-invasive growing prosthesis commercially available worldwide which allowed outpatient expansion by using an electromagnetic field. (13)

The expansion mechanism has a tubular part that is fitted in a polymer tube, with a spring compressed between the two closed tubes. The polymeric tube penetrated by a ring which locks the two tubes, allowing expansion of the spring due to the stored energy. (14)

For expansion, the annular protuberance is heated by an electromagnetic field generated by a coil applied around the extremity. Twenty seconds are usually needed to achieve expansion. After the expansion, the electromagnetic field is turned off, the system is cooled by blood flow, and the two tubes are linked in the expanded position. (14)

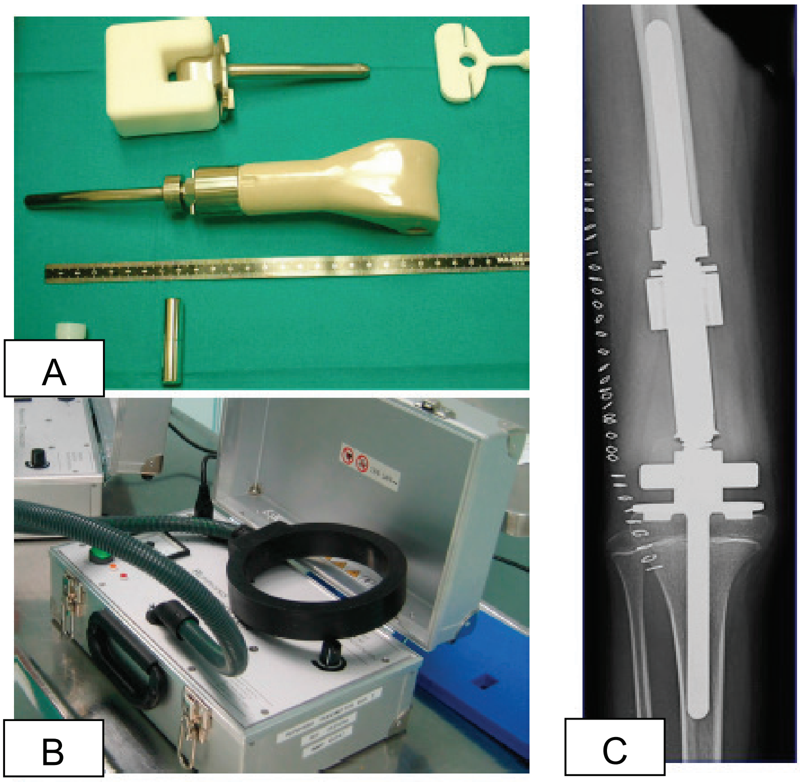

Figure 6 A, B & C: A: Repiphysis Limb Salvage System before implantation (13); B: lengthening mechanism (13); C: implanted Repiphysis Limb Salvage System (13)

Intercondylar stepless-extension module (**Figure 7**)

This type of prosthesis is lengthened by knee flexion which induces rotation of a switch unit (5). A gear wheel (**Figure 7** a) is rotated by an flexion angle of 100 degrees in knee joint which is translated to a threaded spindle (d) (5). This positioning is held by a spring (c) via a carrier (b) by 20 degrees. The threaded spindle causes an elongation of the prostheses of 0.056 mm per turn (e) (5).

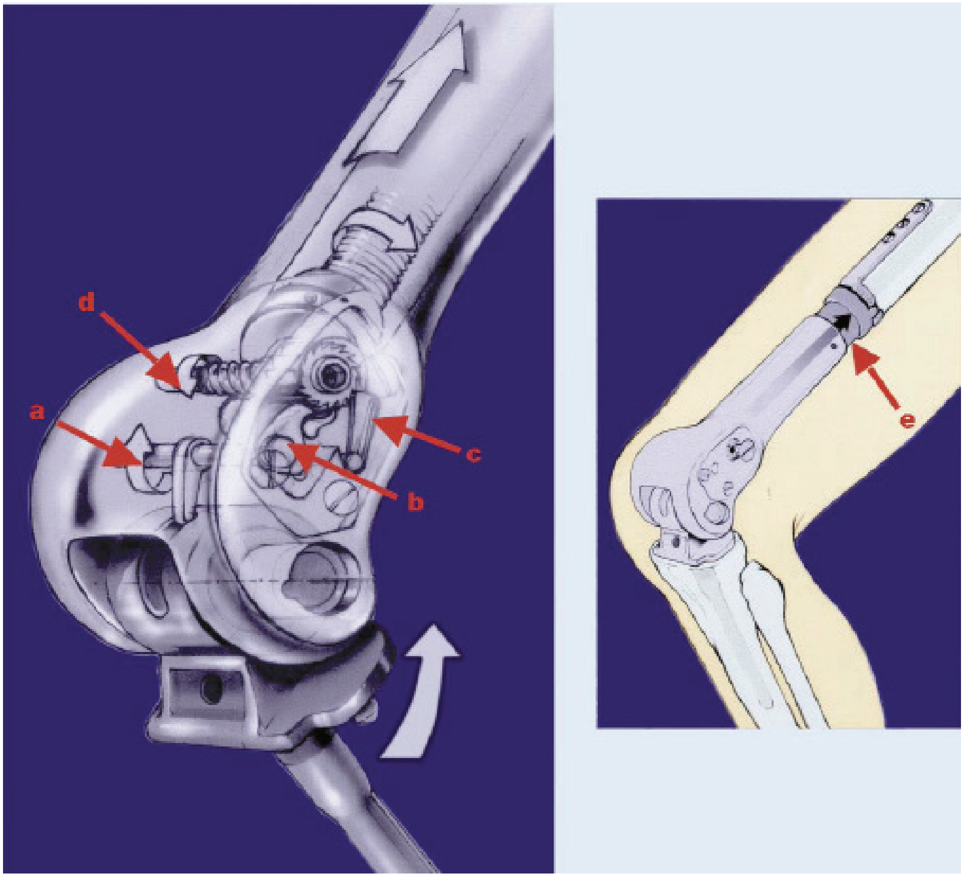

Figure 7 (5): interconylar stepless-extension module

1.2 Bone Sarcoma in Paediatric Patients

Pediatric bone sarcomas account for 0.2% of all neoplasms (15). The incidence is 1.1 in the male population and 0.8 in the female population per 100 000 inhabitants per year. (15, 16) The lifetime risk for the diagnosis of primary bone cancer is 0.1% (16). Regarding the predilection age the first peak occurs during the second decade of life, while the second occurs in patients older than 60 years (15). The most common types of primary malignant tumours of bone are osteosarcomas (35%), followed by Ewing’s sarcoma (16%) (15). Most primary bone sarcomas arise “de novo” from mesenchymal or neuroectodermal precursor cells that can differentiate into osteoblastic, chondroblastic and/or fibroblastic way but some primary bone sarcomas develop in connection with precursor lesions. These lesions could be non-neoplastic lesion which undergo malignant transformation or primary benign neoplasms that could be the source of a malignant neoplastic process (15). An example for precursor lesions with a high risk for getting osteosarcoma is the familiar retinoblastoma syndrome (15). The clinical presentation of bone tumours is non- specific, including pain, swelling and general discomfort (15). Therefore, early diagnosis is sometimes difficult and some patients may present with a pathological fracture at initial diagnosis. The imaging of bone sarcoma includes conventional radiographs, MRI (with contrast medium) including the adjacent joint to detect skip metastasis, CT in selected cases and bone scans as well as chest CT to detect metastatic spread (15). Conventional radiographs are mandatory to characterize the aggressiveness of a lesion. Characteristic radiological signs indicative for bone sarcomas are the Codman Triangle, mixed osteolytic and osteoblastic areas or a sunburst phenomenon (17). To establish a definitive diagnosis, taking histological samples is crucial. Therefore MRI imaging is not only needed to characterize the malignant potential of the lesion but also to plan the biopsy with regard to a potential future resection (15). After preoperative chemotherapy, the resected specimen has to be tested for the percentage of vital tumour cells which is defined as the “Regressionsgrad” (18). Depending on the percentage of vital cells after neoadjuvant chemotherapy, Salzer-Kutschnik et al. (18) classified six different regression grades to evaluate response to chemotherapy. Regression 1° means no vital tumour cells are left. Regression 2° implies that several vital tumour cells exist or that there is a cell-cluster of 0.5 mm. Regression 3° means that there is a vital tumour with < 10% of the total tumour mass. Regression 4° describes a vital tumour with 10- 50% of the original tumour mass. Regression 5° implies that there is > 50% of the tumour left and with more than regression 6° neoadjuvant chemotherapy did not have any effect on tumour cells (18).

Regarding resection margins of bone sarcoma a surgical staging system introduced by Enneking et al. (19) is used. Resection margins are classified into intralesional margin, marginal, wide and radical (19). Intralesional resection is the subtotally excision of a lesion and a tumour mass is left “in situ” e.g. curettage of a bone lesion. Marginal resection means resection of a tumour including the capsule without a cuff of healthy tissue. Wide resection margins are considered the gold standard in orthopedic oncology for malignant tumours meaning that the tumour is resected en bloc with a cuff of normal tissue. Radical margins would imply extracompartimental en bloc resection of the entire compartment (19).

Postoperative therapy

The tumour aftercare in curative therapy intention starts with controls in short intervals within the first three years with MRI with contrast medium, ultrasound of the abdomen, chest-CT and/or chest X-rays every three months. From the fourth postoperative year on, the intervals of the control examinations can be prolonged to six months, after the 5th postoperative year the intervals are yearly. The end of the postoperative care is reached with the 11th year after operation.

1.2.1. Osteosarcoma

Osteosarcoma belongs to the group of osteogenetic tumours which is characterized by osteoid production (15). There are six major types of osteosarcomas. The most common one is conventional osteosarcoma, followed by teleangiectatic osteosarcoma, small cell osteosarcoma, secondary osteosarcoma, parosteal osteosarcoma and periosteal osteosarcoma. (15)

Osteosarcomas are the most frequent bone sarcomas and can arise in any bone. However the predilection site of primary osteosarcomas is the metaphysis of long bones of children (in about 90%) (15), with the distal femur as the most common site (15).

Regarding gender, boys have a higher incidence than girls and regarding the origin, dark skinned children develop an osteosarcoma more often than Caucasian children (20, 21). The probable reason for the higher incidence in boys may be the larger volume of bone formed during a longer growth period compared with girls (22).

The etiology of osteosarcoma is mostly unknown. Due to the peak incidence in young adolescents, a coincidence with rapid bone growth seems probable. This is supported by the fact that pediatric bone sarcoma patients are often taller than their age-peers and that girls are affected in younger ages than boys due to the girls' more advanced skeletal age (22). In the specific case of teleangiectatic osteosarcoma, pathological fractures are reported in one-fourth of the cases (15), which could be explained by the higher aggressiveness of this type of osteosarcoma. In a small number of cases, osteosarcoma can be ascribed to other tumours or non- neoplastic conditions, although they are often linked with conventional osteosarcoma. So called "secondary osteosarcomas" arise from pre-existing abnormalities, in most cases Paget's disease (2% of all osteosarcomas (22)) or radiation changes (3% of osteosarcomas (22)) (15). These "secondary osteosarcomas" are the reason for the second peak incidence at the age of around 65 (15). Most osteosarcomas contain clonal chromosomal aberrations which comprise an abundance of numerical and structural alterations (15). Genetic susceptibility for osteosarcoma is given when a hereditary retinoblastoma (RB) has been reported. In 30- 40% sporadic osteosarcoma shows alteration of the RB1 gene and in these cases, the prognosis seems to be poorer than in the cases without alterations of the RB1 gene (15). Li-Fraumeni syndrome, characterized by a mutation of the TP53 germline, is associated with a higher risk of developing osteosarcoma (15).

Treatment for osteosarcoma is multidisciplinary including wide resection of the tumour, neoadjuvant and adjuvant polychemotherapy, radiation only in selected cases and supportive care (15). Without systemic treatment, metastatic spread is very likely, as at initial diagnosis micrometastases may already be present. 80- 90% of all patients will develop metastases, mostly pulmonary or locally, if chemotherapy is not administered (17, 23). Polychemotherapy for osteosarcoma in children is given within study protocols like EURAMOS 1 (**Figure 8**). This was a randomized open label, controlled clinical study of parallel groups with the intention to optimize therapy for osteosarcoma patients. The study question of EURAMOS 1 was to investigate whether it was possible to improve the outcome for both good and poor responders through the addition of either interferon alpha (for good responders) or etoposide and ifosfamide (for bad responders) to adjuvant chemotherapy (23, 24). All patients in this study received a ten-week of neoadjuvant chemotherapy with MAP, followed by surgery of the sarcoma (24). The histological response to the neoadjuvant chemotherapy is an important prognostic feature, as accordingly patients are stratified into risk arms with different adjuvant chemotherapy regimens (17). Patients are classified as good responders to neoadjuvant chemotherapy when > 90% of the tumour is necrotic (25). Poor responders have a necrosis of < 90% (25). “Poor responders (>10% viable tumour) are randomized to receive either MAP for 18 weeks or MAPIE (methotrexate, doxorubicin, cisplatin, ifosfamide and etoposide) regime for 29 weeks. Good responders (<10% viable tumour) will be randomized between MAP for 18 weeks or MAPinf, consisting of MAP for 18 weeks followed by maintenance therapy with interferon-a, which is continued for up to two years from diagnosis” (24).

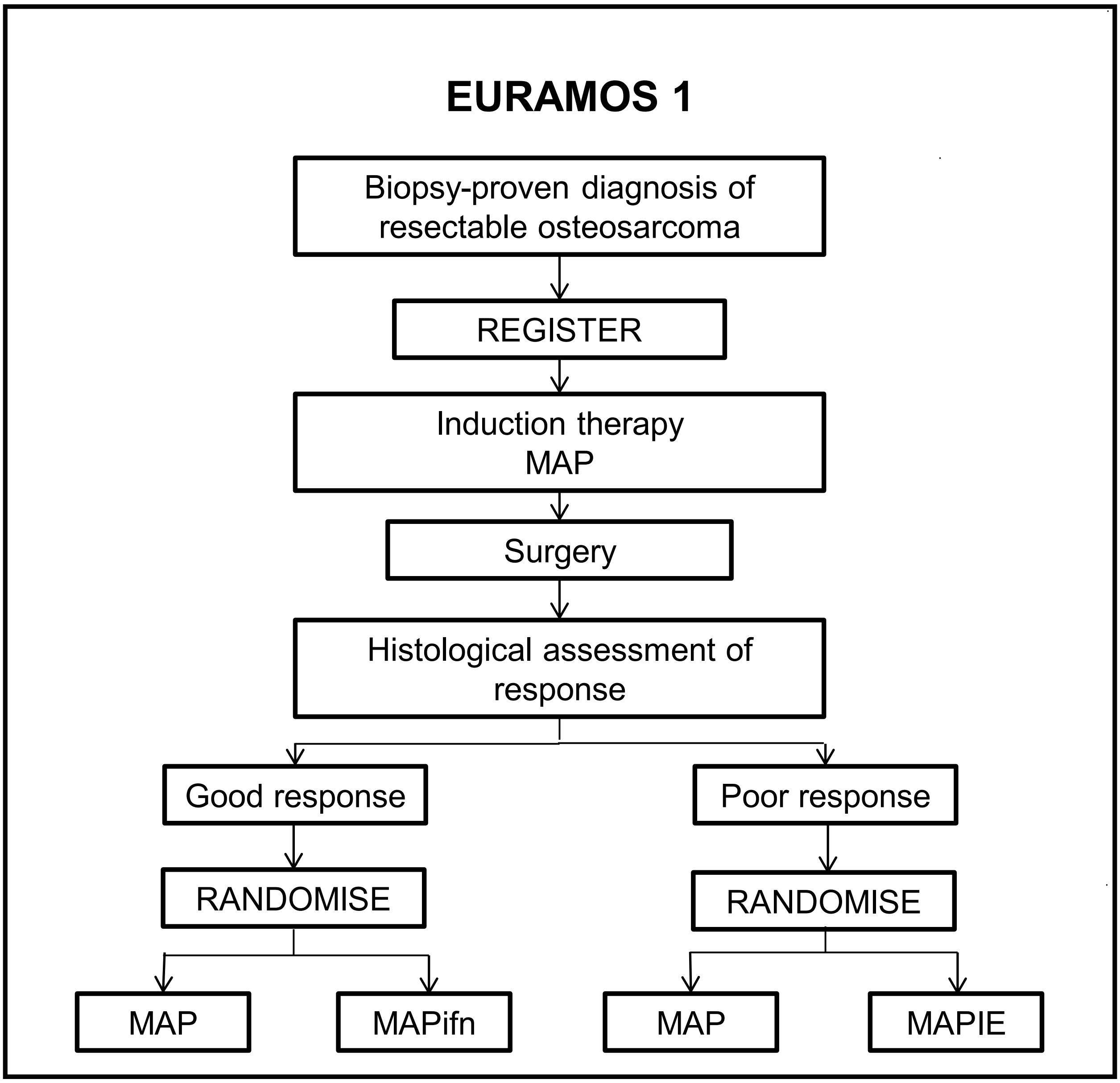

Figure 8: schema for EURAMOS 1 study treatment

The precursor study of EURAMOS 1 was COSS-96. There were two risk groups: high and standard risk. The preoperative chemotherapy was the same in all patients. It was given for nine weeks and it consisted of doxorubicin, methotrexate, ifosfamide and cisplatin. The adjuvant chemotherapy for standard risk patients lasted for 19 weeks with doxorubicin, methotrexate, ifosfamide and cisplatin. In the case of high risk patients, the postoperative chemotherapy lasted for 17 weeks with etoposide instead of cisplatin (26).

Although osteosarcomas are not very radiosensitive, new data show, that radiotherapy is useful in patients treated with multiagent chemotherapy without the possibility of total resection or patients who have microscopic residual tumour foci following attempted resection (17).

In the first half of the 20th century the 5-year survival rate of osteosarcoma was below 20% (25) due to lung metastases (17). Within the introduction of polychemotherapy and advanced surgical treatment, the 5-year survival rate in children with localized osteosarcoma increased up to 60% (25). In children with pulmonary metastases at initial diagnosis the five- year-survival rates still remain poor at 25- 30% (25).

The most sensitive indicator of survival is the response to the pre-operative chemotherapy.

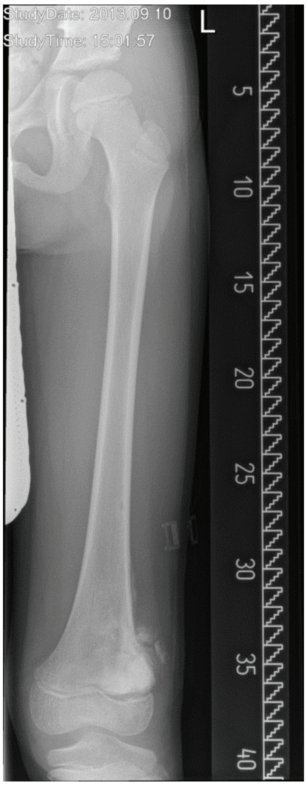

Figure 9: 10 year old male patient of the Department of Orthopaedic Surgery Graz: X-ray a.p. of the left femur- osteosarcoma of the distal femur

1.2.2. Ewing's sarcoma

Ewing's sarcoma is a blue round cell sarcoma with different degrees of neuroectodermal differentiation (15).

Ewing's sarcoma/PNET is the second most common bone and soft tissue sarcoma in children but it only amounts for 6- 8% of primary malignant bone tumours. In contrast to osteosarcoma, Ewing's sarcoma tends to arise in the diaphysis or metaphyseal-diaphyseal portion of long bones, in the pelvis or ribs (15). At initial diagnosis, Ewing's sarcoma is localized in 70- 80% (23). The male to female ratio is 1.4 to 1 and 80% of the patients are younger than 20 years (15). In Ewing's sarcoma a characteristic chromosomal translocation (recurrent t(11;22) (q24;q12)) can be detected in 85% of the cases (15). Similar to the clinical presentation of osteosarcoma, the symptoms of Ewing's sarcoma are unspecific. There is often pain and swelling at the affected area, clinical symptoms are fever, anemia and leukocytosis (15).

The most common radiographic feature of Ewing's sarcoma is an ill-defined osteolytic lesion, which involves the diaphysis. Bone destruction is often associated with "onion-skin" like multilayered periosteal reaction. The overlying cortex of the tumour is alternating thinned or thickened and a soft tissue component may be present (15). Similar to osteosarcoma CT scans and MRI are necessary to detect these radiological features (15). Regarding the histopathology, Ewing's sarcoma is mostly arranged in uniform round cells with round nuclei containing fine chromatin (15). The cytoplasm is either scanty clear or eosinophilic and contains PAS positive glycogen in most cases. Primitive intercellular junctions are often seen (15). As predictive parameters for overall survival tumour stage, anatomic location, EWS/ETS fusion status (the most common "type 1 gene fusion"- EWS exon 7 fuses with FLI1 exon 6 - has the best prognosis), the size of the tumour as well as the presence of metastases at initial diagnosis have been identified (15). For localized ES the five-year survival rate ranges from under 10% (23) for patients treated with radiation or surgery only up to 60- 75% (23) with the addition of polychemotherapy. Due to occult micrometastases in > 90% of all cases Ewing's sarcoma is considered a systemic disease (15).

Ewing's sarcomas are, in contrast to osteosarcomas, radiation sensitive. Therefore local radiation therapy is a part of the multidisciplinary treatment of these tumours and can even be considered as an alternative to surgical resection in difficult locations such as the spine or the pelvis. A radiation dose between 45 and 60 Gy is usually used, depending on the time of radiation therapy (pre- or postoperative) and the type of combination (local monotherapy or polytherapy in combination with chemotherapy) (23).

Regarding chemotherapy children are currently treated according to the EWING 2008 study protocol (**Figure 10**). The antineoplastic agents used in this study are vincristin (V), ifosfamide (I), doxorubicin (D) and etoposide (E) (VIDE) (27). These agents are used in six cycles of induction therapy (27). If necessary, a radiation therapy can be added to preoperative therapy if the tumour has a difficult localization for wide resection. Thereafter, surgery and/or radiation therapy follows. The implementation of postoperative radiation therapy depends on the resection margins and the response to neoadjuvant polychemotherapy (27). For adjuvant chemotherapy the patients are divided into three different groups: standard risk patients (R1), high risk patients (R2) and very high risk patients (R3) (27). Standard risk patients have a localized tumour with a tumour mass < 200 ml or good histological response (< 10% of vital tumour cells) (27). These patients obtain eight adjuvant cycles of vincristine, actinomycin D and cyclofosfamide (VAC for female patients) or vincristin, actinomycin D and ifosfamide (VAI, for male) (27). Before starting the consolidation therapy, a randomization if an additional therapy with fenretinid and/or zoledronacid should be given (27). The high risk group has a poorer histological response or pulmonary metastases at initial diagnosis and receives either eight cycles of VAI or high dose busulfan/melphalan therapy with following retransfusion of autologous stem cells (27). Patients in the R3 group have primary bone metastases with or without pulmonary metastases or metastases in other locations (27). They are treated with eight cycles of VAC or a high dose chemotherapy with trosulfan and mephalan followed by retransfusion of autologous stem cells and eight cycles of VAC (27). The aim of the study is to find out if the long-term survival rate after using agents like fenretinid/zoledronacid (R1), a high dose busulfan/melphalan therapy with following retransfusion of autologous stem cells (R2) or trosulfan and mephalan followed by transfusion of autologous stem cells (R3) is increased (27).

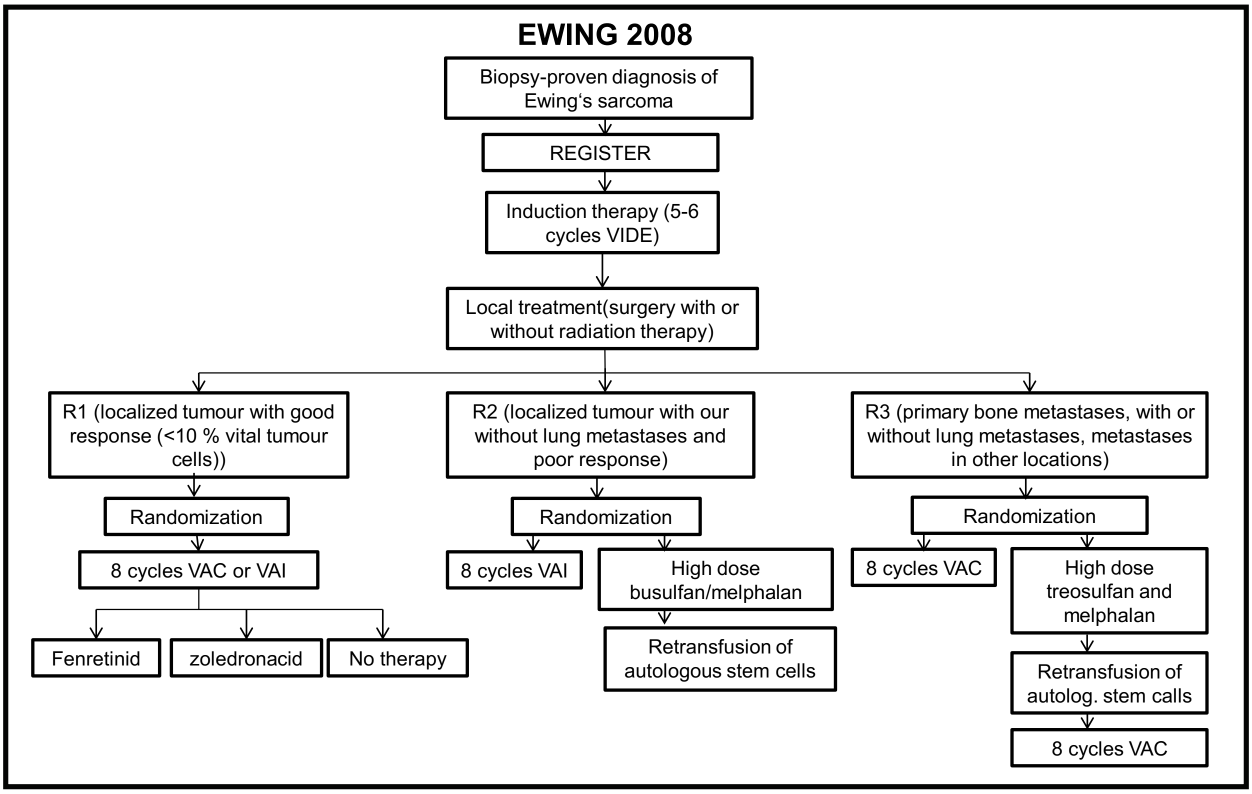

Figure 10: schema for EWING 2008 study treatment

One precursor study was EURO-E.W.I.N.G. in 1999 with the agents doxorubicin (D), cyclophosphamide (C), ifosfamide (I), vincristine (V), actinomycin D (A) and etoposide (E) (23, 28). In this study the maximum tolerated dosage within the shortest possible intervals of VIDE should be tested. (28) The patients were divided into risk groups depending on the prognostic factors like the site of metastases and the size of the primary tumour. After surgery or radiotherapy, further seperation in high and standard risk groups followed depending on the histological response to VIDE. Standard risk patients were treated either with VAC or with VAI while high risk patients received VAI or a high-dose chemotherapy (a combination of busulphan and melphalan) (28). The aim of this study was to verify adverse reactions and toxicities of the intensive induction of VIDE in all groups. Adverse reactions like myelosuppression, fever and infection were often reported. During VIDE courses given to over 800 patients nine deaths were reported (28).

Experimental studies with IGF-receptor-antibodies, antiangiogenetic agents like Bevacizumab, mTOR- antagonists like Rapamycin, PARP- inhibitors and bisphophonates are currently under examination (23).

Another precursor study was EICESS-92. There were two separate prospective randomized trials defined by stage and tumour mass according to the patient risk groups. The standard risk group (SR) included patients with a tumour volume < 100 ml and the high risk group (HR) consisted of patients with a tumour mass > 100 ml or metastatic disease (29). The SR group received four cycles of vincristine (V), dactinomycine (A), ifosfamide (I) and doxorubicin (A) followed by local therapy (surgery) (29). Thereafter, 10 cycles of either VAIA or VACA (vincristin (V), datinomycin (A), cyclophosphamide (C) and doxorubicin (A)) were given. For HR group patients, four cyles of either VAIA or EVAIA (VAIA plus etoposide (E)) were used preoperatively. The adjuvant polychemotherapy lasted for 10 cyles of VAIA or EVAIA (29).

2 Special part

2.1 Aim of the Study

In limb-sparing surgery of malignant bone tumours, endoprosthetic reconstruction or biological reconstruction are the treatment options to replace large bony defects after wide resection. One possibility to compensate for an increasing leg length discrepancy in the growing child is the use of growing prostheses.

The aim of this diploma thesis was first to analyse the morbidity rate of patients who received a growing prosthesis at the Department of Orthopaedic and Orthopaedic Surgery at the Medical University of Graz, Austria, and second to perform a systematic literature review about growing prostheses.

2.2 Patients and Methods

To answer our first study question, data from the Department of Orthopaedic Surgery was analysed by conducting a retrospective database review. Twenty-four patients who had received a growing prosthesis between 1993 and 2014 were identified by local database research (Archimed and Auraweb). Inclusion criteria were the age between 0 and 18 years, the location of the tumour in the proximal or distal femur or in the proximal tibia and implantation of a (non-invasive or minimally invasive) growing prosthesis after bone sarcoma resection. Exclusion criteria were follow-up (AWD or NED) less than 12 months from the implantation of the growing prostheses.

Twenty-six paediatric patients underwent resection of osteosarcoma or Ewing's sarcoma at our department. In two patients a conventional adult endoprosthesis was implanted and therefore these patients were excluded. Of 24 patients 12 fulfilled all the inclusion criteria. The reasons for exclusion of the other 12 patients were a lack of documentation of the lengthening procedures (n= 9), follow-up less than 12 months (n= 1), further oncological treatment in another centre (n= 1) and one patient was excluded due to a lack of information regarding oncological and histological data.

reason for exclusion	*number of patients*
no information about lengthening procedures	9
follow-up less than 6 months for patients who survived (AWD)	1
follow-up at different centre	1
lack of oncological data	1

Table 2: reasons for exclusion in own patient's collective

The following clinical data was documented for the included patients: sex, date of birth, date of initial diagnosis, age at initial diagnosis, histology and localization of the tumour, duration and type of chemotherapy, metastases at initial diagnosis and localization of metastases, date of the implantation of the growing prosthesis, type of growing prosthesis, number of postoperative revisions and complications, type of revision, date of first revision, implant survival, implantation of a new prosthesis, date of death, follow-up and status at last follow-up, radiotherapy, local recurrence and treatment of local recurrence as well as types of lengthening procedures which consists of the minimally invasive lengthening, non-invasive lengthening and lengthening during revision. The numbers of lengthening procedures as well as the total lengthening amount were documented. Medical records were searched for and information about leg length discrepancy. In our patients three different types of lengthening of a growing prosthesis existed: minimally invasive, non-invasive and lengthenings during a revision surgery, which means that the prosthesis or parts of the prosthesis had been changed to lengthen the leg within the framework of a revision surgery because of a relevant leg length discrepancy.

The functional outcome was assessed retrospectively with the Musculoskeletal Tumour Society Score (MSTS) in % at the last follow-up which includes the pain of the patient, the function of the affected limb, the emotional acceptance, the walking ability, the gait and the supports the patients might need.

Revision surgeries were classified according to the categories of modified Henderson et al. (30). As Henderson et al. (30) (**Table 3**) classified exclusively the first revision surgery in this study all revisions were classified.

General category	***Mode***	***Subcategory***	***description***
mechanical	Type 1 (soft-tissue failure)	A (functional)	Limited function owing to insufficient ligamentous attachment
		B (coverage)	Aseptic wound dehiscence
	Type 2 (aseptic loosening)	A (early)	Aseptic loosening < 2 years after implantation
		B (late)	Aseptic loosening > 2 years after implantation
	Type 3 (structural failure)	A (implant)	Implant breakage or wear; expandable implant lengthening malfunction
		B (bone)	Peri-prosthetic osseous fracture
Non- mechanical	Type 4 (infection)	A (early)	Infected implant < 2 years after implantation
		B (late)	Infected implant > 2 years after implantation
	Type 5 (tumour progression)	A (soft- tissue)	Soft-tissue progression of tumour with endoprosthetic contamination
		B (bone)	Bony progression of tumour with endoprosthetic contamination
Paediatric	Type 6 (paediatric failures)	A (physeal arrest)	Growth arrest resulting in longitudinal or angular deformity
		B (joint dysplasia)	Dysplastic joint resulting from articulation with implant

Table 3: adapted from Henderson et al. (30)

For diagnosis in all cases an incision biopsy was made to verify tumour type. After the completion of neoadjuvant chemotherapy according to the appropriate study protocols like COSS- 96, EURAMOS 1 (osteosarcoma), EURO- EWING, EICESS-92 (Ewing's sarcoma), and/or radiation therapy, resection was performed. Operation followed under general anaesthesia and Ewing's sarcoma or osteosarcoma was resected with wide resection margins for all patients. All patients received MUTARS Xpand (Buxdehude, Germany) or HMRS (Stryker Howmedica Osteonics, Kalamazoo, MI, USA). The operative technique in tumours of the distal femur starts with the positioning of the patient in a supine position and a long median incision which crosses the knee along the medial parapatellar area and distal to the tibial tubercule. This incision allows the wide exposure of the distal half of the femur, the sartorial canal, knee, popliteal fossa and the proximal half of the tibia. When the proximal tibia is resected, a gastrocnemius flap is used. The geniculate vessels are ligated and transected to develop the interval between the popliteal vessels and the posterior femur. The interval between M. rectus femoris and M. vastus medialis is used to approach the distal femur. M. vastus intermedius is left intact over the distal femur. If needed, either a portion of M. vastus medialis or a portion of M.vastus lateralis is left covered by soft tissue. Then the joint capsule is opened to remove the menisci and ligaments. Osteotomy of the distal femur follows about three to four cm beyond the proximal tumour extension (if the tumour is located at the distal femur) and the tibial osteotomy is done subsequently. After the resection of the tumour, the preoperatively chosen growing prosthesis with the largest possible stem diameter is implanted. First, the trial articulation is done with the femoral stem, body, condyle components, axle and the tibial components. Then the modular prosthesis is assembled. Linea aspera and the Tuberositas tibiae show the correct axis for anatomically correct implantation. (31)

Thereafter, the patients got antibiotic prophylaxis using cefuroxime for 24 hours after the operation. Postoperatively, all patients received a standardized individual physiotherapy regimen. The follow-up was regularly and patients were lengthened when the leg-length discrepancy was at least 1.5 cm for the minimally invasive implants and individually for non-invasive implants.

2.3 Literature review

Due to the low number of patients treated with a growing prosthesis at the Department of Orthopaedic Surgery in Graz an additional literature review was performed. Studies which focussed on the outcome of the different types of growing prostheses with a special interest in complication rates, implant survival, local recurrences and the lengthening procedures including the total amount of lengthening at skeletal maturity were identified.

To answer our research questions, two separate systematic literature reviews were performed searching MedLine (via PubMed) and EMBASE (via OVID) for relevant studies published up to January 2015. The search algorithm was “(growing OR expandable OR extendable) AND (complication OR revision OR outcome) AND Sarcoma”. 446 studies retrieved by the search algorithm and nine additional studies included by surveying bibliographies and manual literature research. Thirty-nine studies were duplicates, six were non-English articles, 16 were case reports or literature reviews and 351 did not contain data of growing prostheses and had to be excluded. Further 20 studies did not contain data on growing prostheses exclusively (including also outcome data on conventional endoprostheses or upper extremity) (**Figure 11**). If an article contained both data on conventional and growing prostheses, the study was included if data could be extracted on growing prostheses exclusively. 23 studies fulfilled the following inclusion criteria: (1) studies with data about exclusively growing prostheses (either minimally invasive or non-invasive) implanted in children after the resection of primary malignant bone tumours, (2) English language publications in a peer reviewed journal, (3) reporting outcome data of growing prosthesis.

Regarding the level of evidence, no RCT or observational study was retrieved. 19 retrieved studies were retrospective analyses and four were non-randomised prospective case series.

The criteria of special interest were the time of implantation of growing prostheses, the number of participants of the study, the mean age of the patients (including the range), the number of patients with local recurrences, the type and the localization of the tumour, the mean follow-up, the number of deaths, the type of the prosthesis (minimally invasive, non-invasive), the number of revision procedures independent of the affected patients, the number of amputations at last follow-up, the complications (classified according to the modified Henderson classification (30) (**Table 3**)), the mean number of lengthening procedures by patient, the mean total lengthening in mm and the mean MSTS score in %.

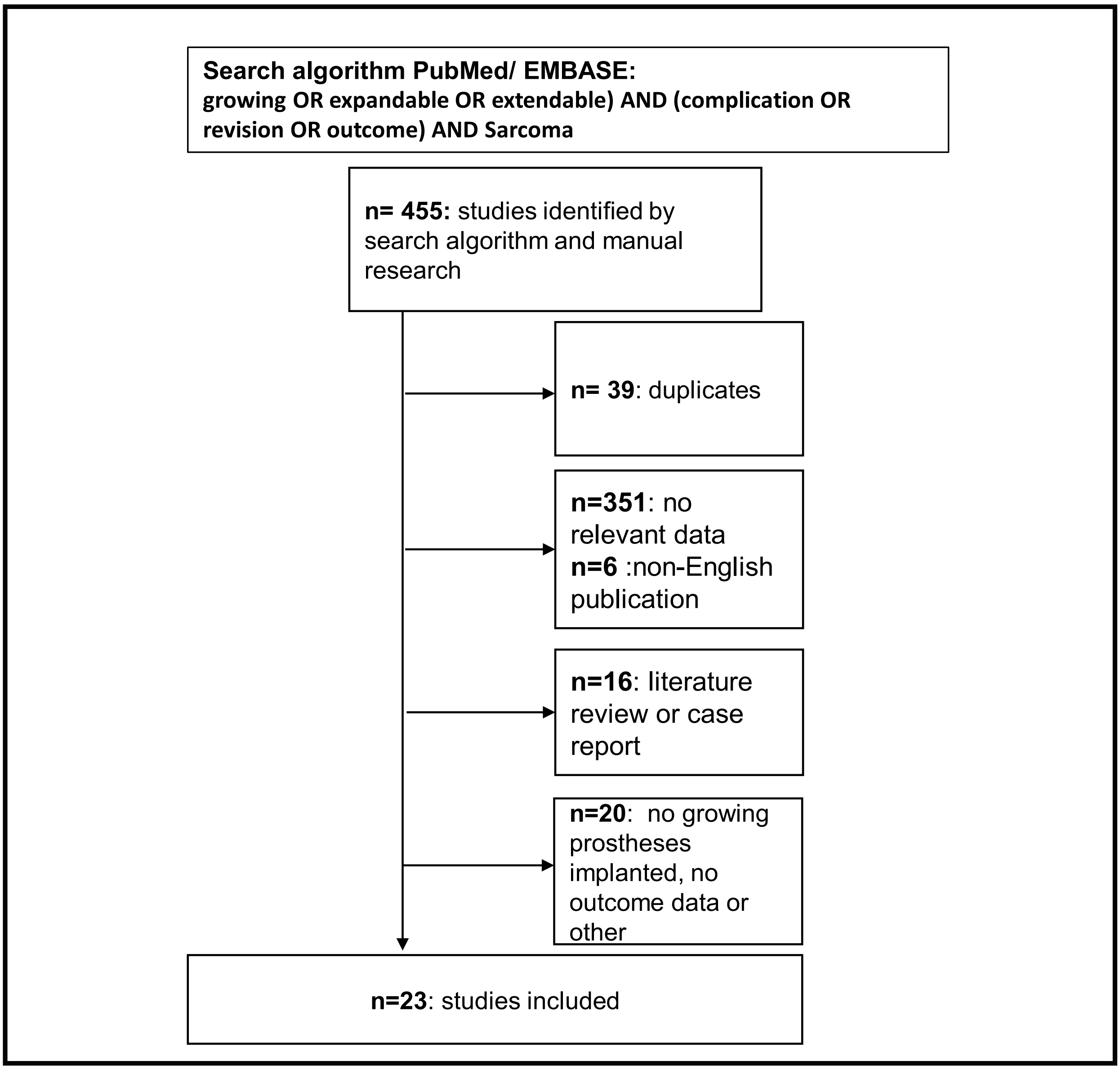

Figure 11: search algorithm and findings in PubMed and EMBASE, numbers and reasons for excluded studies, number of included studies

Statistical analysis

For both our clinical data and the literature review categorical variables are presented as absolute and relative frequencies, numerical variables as means and ranges. Complications were first analyzed descriptively without respect to chronology and second according to modified Henderson et al. (30). This implies that only those surgical interventions in which major parts of the prosthesis are changed or amputation is carried out, are considered as revision surgeries, e.g. debridement and washouts, biopsies, scar tissue excision are excluded. For our own data we calculated oncological survival from initial diagnosis until last follow-up or death of disease. Event-free survival (implantation of growing prosthesis until first surgical intervention (any type of surgical intervention including revision of the implant but excluding planned minimally invasive lengthening) and implant survival (implantation of growing prosthesis until first revision surgery (including revision of major parts of the

prosthesis and “planned” change of prosthesis due to exhausted lift) using Kaplan-Meier curves. We included change of prostheses due to achieved maximum expansion capacity as revision as the patients underwent open surgery including a high risk of infection as well as the need of general anaesthesia.
All statistical calculations were performed using IBM SPSS 22 and Excel (Microsoft). Two-sided p-values <0.05 were considered statistically significant.

3 Results

3.1 Results of own data set

In the group of 12 patients in whom a growing prosthesis was implanted at the Department of Orthopaedics and Orthopaedic Surgery, Medical University of Graz, Austria, three were female and nine male with a mean age of 9.7 years (range 5.0- 14.0) at initial diagnosis (**Table 4**). The tumour was located in the distal femur in seven patients, in the proximal tibia in three cases and in the proximal femur in two cases. In one case, the total femur was replaced by a growing prosthesis. Seven patients suffered from osteosarcoma and five from Ewing’s sarcoma.

Four patients were treated according to COSS- 96, three patients received therapy according to EURAMOS 1, two children were treated according to EURO- EWING and three patients according to EICESS- 92. None of these 12 patients exhibited a local recurrence.

The mean duration of chemotherapy was 7.4 months (range 5.0- 11.0). At initial diagnosis, two patients already suffered from lung metastases, one patient died after 14 months, the second patient after 30 months despite the resection of lung metastases.

Ten out of twelve patients were primarily treated with a functioning growing prosthesis. In two patients, a Dummy prosthesis was implanted and replaced by a definitive growing prosthesis three days later in one patient and two years later in the second patient.

Eight patients had HMRS growing prostheses of which two were custom-made. Four patients received MUTARS® Xpand.

During the implantation of the prostheses, there were intraoperative complications in one patient as sundries were missing due to human error.

The mean follow-up was 88.0 months (range 6.0- 232.0). At last follow-up three patients were dead of disease, two were alive with disease and 7 had no evidence of disease. The mean MSTS score was 77.6% (range 43.0- 97.0) at last follow-up.

Patients with minimally invasive growing prostheses

Eight patients received a minimally invasive growing prosthesis (HMRS) (**Table 4**). The mean age of these patients at initial diagnosis was 12.8 years (range 3.0- 12.0). The histology was osteosarcoma in four patients and Ewing's sarcoma in four patients. The localization of the tumour was the proximal femur in two cases, the distal femur in three cases and the proximal tibia in three cases. Four patients received chemotherapy according to COSS-96, two according to EURO-EWING and two according to EICESS-92 and the mean duration of chemotherapy was 7.0 months (range 6.0- 11.0), while in one patient the date of the end of the chemotherapy was not given. One patient suffered from lung metastases at initial diagnosis. The mean follow-up time for the eight patients with HMRS prostheses was 117.0 months (range 6.0- 232.0) and the status at last follow-up was no evidence of disease in six cases and death of disease in two cases. The mean MSTS score of the minimally invasive lengthened patients was 80.0% (range 43.0- 97.0%).

Patients with non-invasive growing prostheses

Four patients were primarily treated with MUTARS Xpand (**Table 4**). The mean age of patients at initial diagnosis was 8.5 years (range 6.0- 10.0). The histology of the primary malignant bone tumour was osteosarcoma in three patients and Ewing's sarcoma in one patient. In all four patients the tumour was located in the distal femur. The patients with osteosarcoma received polychemotherapy according to EURAMOS1 and the patient with Ewing's sarcoma received chemotherapy according to EICESS-92. The mean duration of chemotherapy was 8.0 months (range 7.0- 9.0) and in one patient the date of the end of the chemotherapy was not available. One of the patients with a non-invasive growing prosthesis had lung metastases at initial diagnosis. The follow-up ranged from 11.0 months to 60.0 months (mean 29.0 months). At the last follow-up, one patient was dead of disease, two patients were alive with disease and one had no evidence of disease. For all of these patients the implanted growing prosthesis was the initial prosthesis. Two patients were first treated with a Dummy instead of a functioning motor. The mean MSTS score of the non-invasive lengthened children was 72.8% (range 47.0- 87.0).

type of lengthening mechanism	**minimally invasive n= 8**	**non-invasive n= 4**	**total n= 12**
mean age at implantation (years) (range)	10.3 (5.0- 14.0)	8.5 (6.0- 10.0)	9.7 (5.0-14.0)
histology			
osteosarcoma	4	3	7
Ewing's sarcoma	4	1	5
localization			
proximal femur	2	0	2
distal femur	3	4	7
proximal tibia	3	0	3
type of prosthesis			
HMRS (Stryker Howmedica Osteonics, Kalamazoo, MI, USA)	8	0	8
MUTARS Xpand (Implantcast, Buxdehude, Germany)	0	4	4
mean duration of chemotherapy (months) (range)	7.0 (6.0- 11.0)	8.0 (7.0- 9.0)	7.4 (5.0-11.0)
chemotherapy			
COSS- 96	4	0	4
EURO- EWING	2	0	2
EICESS- 92	2	1	3
EURAMOS1	0	3	3
lung metastases at initial diagnosis	1	1	2
amputations	0	0	0

mean follow-up (months) (range)	117.0 (6.0- 232.0)	29.0 (11.0- 60.0)	87.6 (6.0-232.0)
mean MSTS score (%) (range)	80.0 (43.0- 97.0)	72.8 (47.0- 87.0)	77.6 (43.0- 97.0)
status at last FU			
DOD	2	1	3
AWD	0	2	2
NED	6	1	7

Table 4: patients' characteristics regarding type of lengthening mechanism

3.1.1 Complications and surgical interventions

Ten out of twelve patients had at least one revision surgery (**Table 5**). Mean number of surgical interventions per patient was 3.5 (range 0.0- 14.0). As the most common complication, eight deep infections occurred in 4 patients (two patients had one deep infection, another patient had two deep infections and a fourth had four) followed by fracture of prosthetic components (n= 2), exchange of a Dummy prosthesis (n= 2), aseptic loosening (n= 1) and periprosthetic fracture (n= 1). One patient had five and two patients one surgical interventions due to soft tissue failure.

Reasons for revisions were classified according to modified Henderson et al. criteria (30) (**Table 5**). There were four children suffering from 8 deep infections as two patients even received a new implant. One had aseptic loosening of the prosthesis. There were five implant failures and one of the patients had a structural bone failure. There was neither a tumour progression nor a pediatric failure in this collective (**Table 5**). Deep infection occurred in two patients with localization of the primary malignant bone tumour in the distal femur (in one patient two times in one patient once), in one patient with localization in the proximal tibia (once) and in one patient with affection of the proximal femur (deep infection occurred four times in this patient).

Apart from revision surgeries there were 26 other events that led to a surgical intervention (mean 2.2 per patient, range 0.0- 5.0) (**Table 5**). Other surgical interventions were related to the lengthening mechanism (n= 9), the implantation of a new motor due to an exhausted lift (n= 1), minimally invasive lengthening due to the collapse of the prostheses (5 times in three patients), implantation of missing sundries after human error (n= 1) or Dummy explantation

(2 patients). Superficial wound necrosis occurred in 10 cases, explantation of the spacer in three cases and operations after recurrent patella or hip luxations (4) (**Table 5**).

Revisions of the minimally invasive prostheses

Eight patients were treated with minimally invasive HMRS growing prostheses. Seven of these patients went through at least one surgical intervention. Mean number of surgical intervention per patient was 5.0 (range 1.0- 14.0). According to the modified classification of Henderson et al. (30) there were five structural failures of the prosthesis, one structural failure of the bone and six deep infections. Other surgical interventions were superficial wound necrosis in eight cases, explantation of the spacer three times and open reduction of the dislocated hip or patella in four cases. Three prostheses were exchanged due to recurrent collapse of the HMRS prostheses, one due to infection and one due to an exhausted lift. Five times there was minimally invasive lengthening due to collapse of the prosthesis in three patients. Ten surgical interventions were related to the lengthening mechanism. In this context we detected three patients with a complete collapse of the minimally invasive HMRS (Howmedica Modular Resection System) growing prosthesis following bone sarcoma resection between 2003 and 2005. The loosening of the adjustment screw was seen in all three patients. Despite a technically correct tightening of the fixation screw the growing module re-collapsed and severe limb-length inequality occurred. This ultimately resulted in loss of prosthesis in all three patients. During in-vitro testing of the explanted prostheses we were able to lengthen the growing module although the fixation screw was locked.

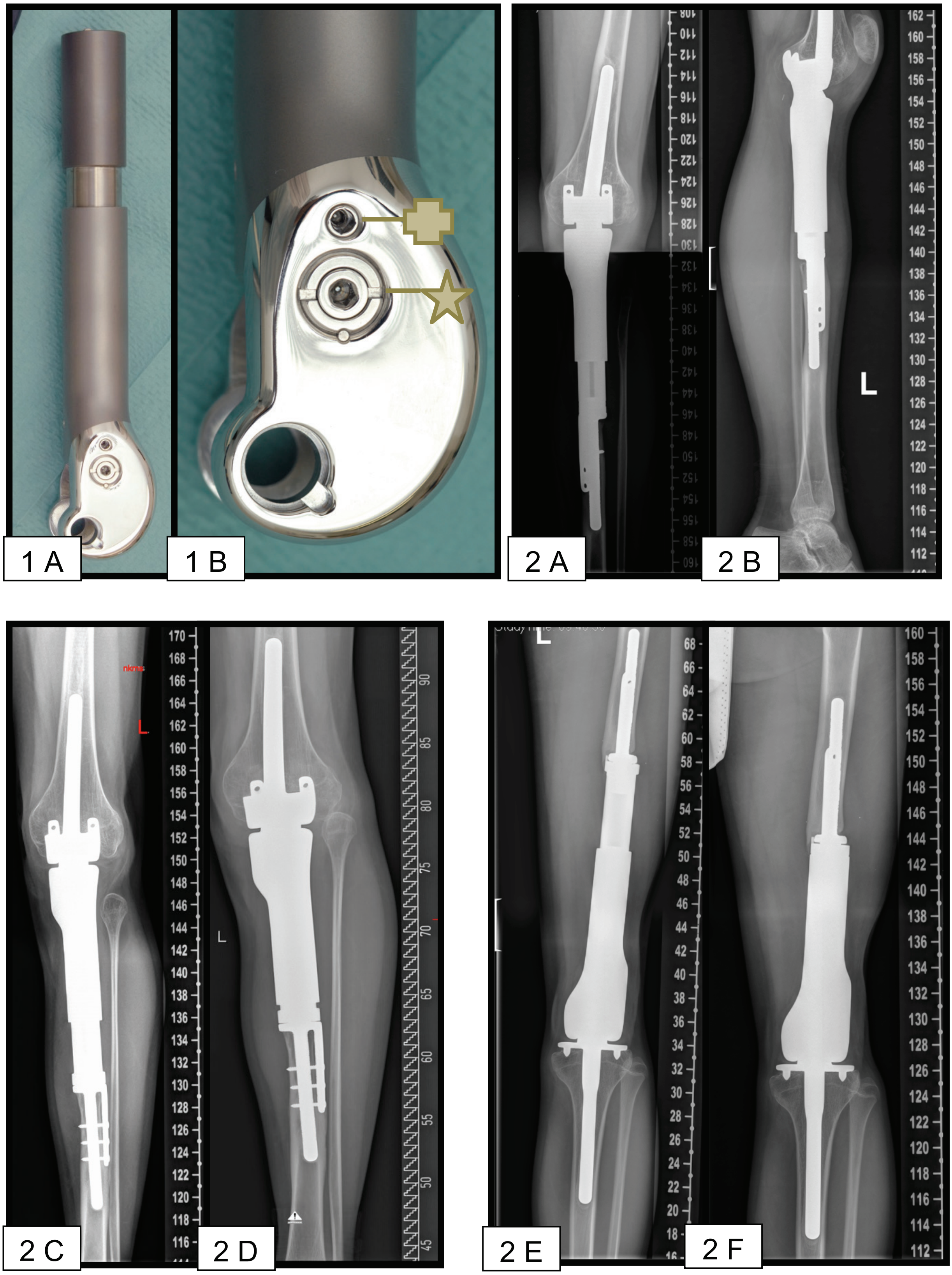

Figure 12: 1 A & B: A: showing an explanted HMRS growing prosthesis, **B:** showing the aperture for the adjustment (star) and the fixation screw (plus), **2 A & B:** patient 1: before and after collapse, **2 C & D:** patient 2: before and after collapse, **2 E & F:** patient 3: before and after collapse

Revisions of the non-invasive prostheses

In four patients a non-invasive growing prosthesis was implanted (MUTARS Xpand) (**Table 4**). Regarding modified Henderson et al. (30) there were two cases of deep infection in one patient. Other surgical interventions were related to the lengthening mechanism in four cases: change from Dummy to a functioning motor (n= 2), implantation of missing sundries due to human error (n= 1) and change of prosthesis due to exhausted hub (n= 1). Surgical intervention non-related to lengthening mechanism was superficial wound necrosis (n= 2). In total, there were seven revision surgeries in three patients. The mean number of revision surgeries per patient was 3.5 (range 1.0- 3.0).

lengthening mechanism	minimally invasive n= 8	non-invasive n= 4	total n = 12
reason for revision			
exchange of the Dummy	0	2	2
deep infection	6	2	8
implantation of a new prosthesis due to exhausted hub	0	1	1
fracture of prosthetic components	2	0	2
aseptic loosening	1	0	1
periprosthetic fracture	1	0	1
total	**10**	**5**	**15**
complications according to modified Henderson et al. (30)			
Henderson 1 A	0	0	0
Henderson 1 B	0	0	0
Henderson 2	1	0	1
Henderson 3 A	5	0	5
Henderson 3 B	1	0	1
Henderson 4	6	2	8
Henderson 5	0	0	0
Henderson 6	0	0	0
total	**14**	**2**	**15**
other surgical interventions			
related to lengthening mechanism			
lengthening due to collapse of the prosthesis	5	0	5
implantation of a new prosthesis (exhausted hub)	0	1	1
change Dummy to motor	0	2	2
implantation of missing sundries	0	1	1
non related to lengthening mechanism			
superficial wound necrosis	8	2	10
explantation of spacer	3	0	3
reduction of dislocated patella/hip	4	0	4
total	**20**	**6**	**26**

Table 5: reasons for revisions regarding type of lengthening mechanism

3.1.2 Implant and event-free survival

Kaplan-Meier survival curves showed a mean time to the first unplanned surgical intervention (= event-free-survival) of 16.1 months (range 0.0- 55.0). Event-free-survival was 37% at three years and decreased to 0% at five years according to Kaplan-Meier. The mean time to first revision of the prosthesis (= implant-survival) according to Kaplan-Meier was 42.3 months (range 1.0- 115.0). Implant survival was 80% at three years and 52% at five years. Five patients received one new prosthesis and another patient had two. MUTARS Xpand in three cases and conventional adult endoprostheses (GMRS) in three cases. (**Figure 12, Figure 13**)

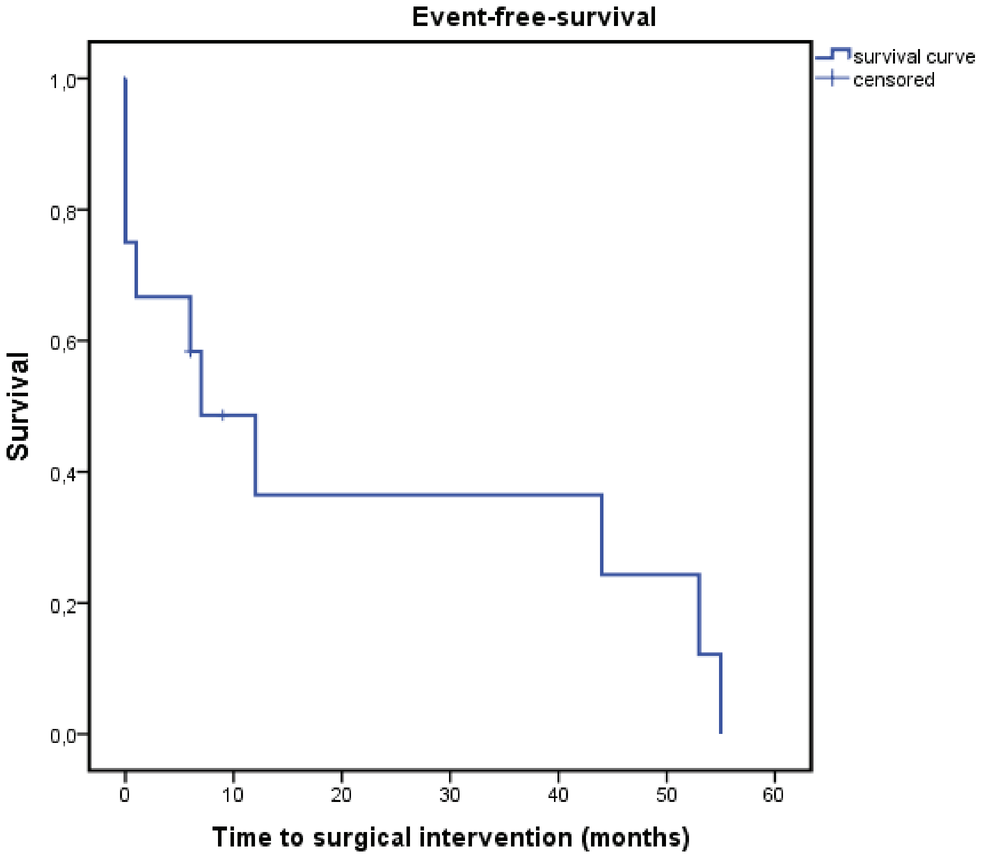

Figure 13: event- free- survival (months)

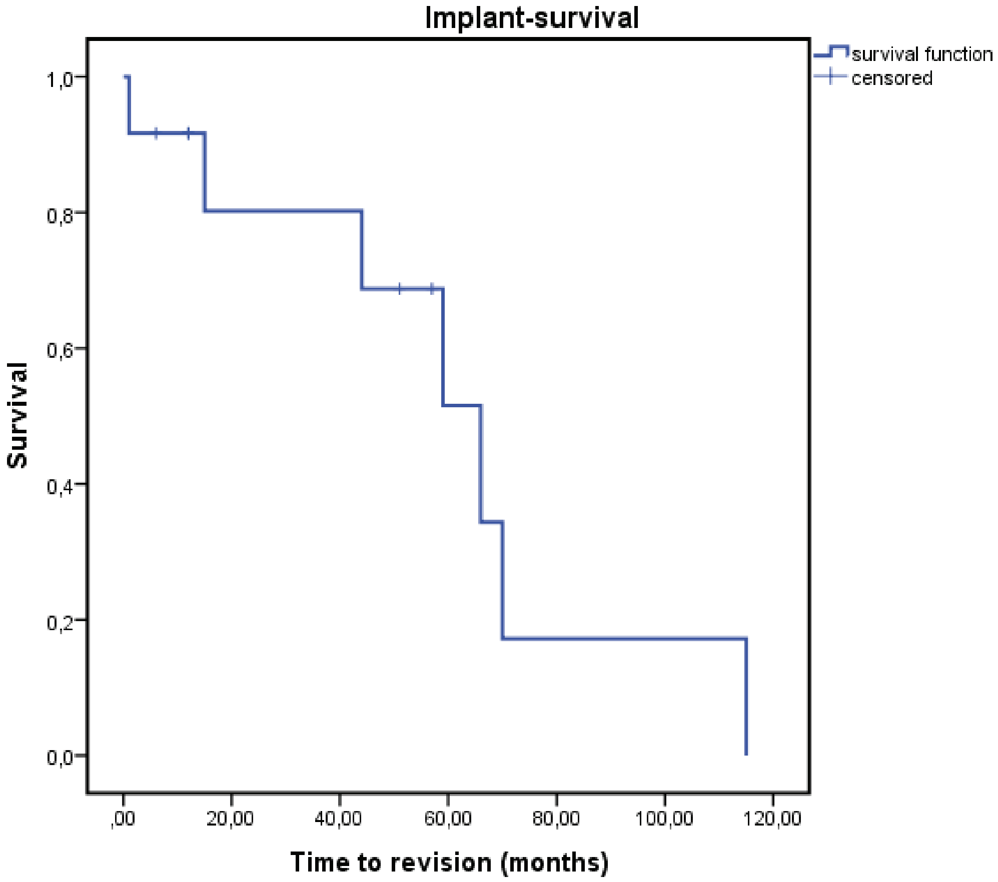

Figure 14: implant survival in months

Prosthetic-survival for minimally invasive prostheses

At one and three years postoperatively the event-free-survival was 47% and 0% at five years. At 12 months, 100% of HMRS prostheses had survived, at three years 86% and at five years 54%, according to Kaplan-Meier analysis. HMRS implants were revised to MUTARS Xpand in two cases (due to exhausted hub and deep infection) and conventional endoprosthesis GMRS in three cases (due to collapse of the prosthesis).

Prosthetic-survival for non-invasive prostheses

Due to the low number of implanted prostheses and limited follow-up time, Kaplan-Meier curves were not calculated. Two Dummies were implanted initially, one due to missing sundries which was replaced by a motor three days following initial implantation and one received the functioning motor 14 months following implantation. At last follow-up, one patient underwent exchange of the whole prosthesis due to exhausted lift.

3.1.3 Lengthening Procedures

Six patients underwent minimally invasive lengthening, one patient underwent non-invasive lengthening, one patient was exclusively lengthened during a revision surgery and one patient underwent minimally invasive lengthening as well as lengthening during revision surgery. Four patients did not undergo any lengthening due to death of disease before leg length discrepancy was present (3) and one patient had moved abroad (**Table 6**).

Minimally invasive lengthening procedures:

The mean age at first lengthening was 11.6 years (range 10.0- 14.0) whereas the mean age at last lengthening was 16.0 years (range 14.0- 19.0) (**Table 8**). For two patients data on lengthening was not available. The amount of each lengthening ranged between 10.0- 19.8 mm (mean 14.9 mm) and patients underwent between three and ten lengthening procedures in total (mean 5.2). Lengthening was started when a leg-length discrepancy between 10.0 and 100.0 mm was present (mean 29.5 mm). The total amount of lengthening summed up to a mean of 72.8 mm (range 43.2- 131.9 mm) per patient at last follow-up. One patient underwent intraoperative lengthening with a lengthening of 6 cm length due to nearly exhausted lift of the growing prostheses as soft tissue situation allowed stretching without injuring vessels or nerves. Extension failed in three patients due to loosening of the fixation screw described above, finally leading to the need for revision of the implants.

Non-invasive lengthening procedures

One patient underwent non-invasive lengthening procedures. After implantation the patient's families were instructed to the lengthening procedures in order to perform lengthening at home. The elongation schemata were given from the Department of Orthopaedic Surgery of Graz. Three patients did not undergo lengthening as no leg-length discrepancy was observed until last follow-up (n= 1), one patient died of disease before leg length discrepancy was present (n= 1) or as the patient left the country and was lost to follow-up before lengthening (n= 1). One patient had change of the growing module following four years of initial surgery due to achieved maximum elongation capacity. The patient reached a total expansion of 70 mm after five years (**Table 6**).

type of lengthening	minimally invasive n=5	non-invasive n= 1	Total n= 6
mean age at first lengthening (years) (range)	**11.6 (10.0- 14.0)**	**6.0**	**10.6 (6.0- 14.0)**
mean age at last lengthening (years) (range)	**16.0 (14.0- 19.0)**	**15.0**	**15.8 (14.0-19.0)**
mean number of lengthenig procedures per patient (range)	**5.2 (3.0- 10.0)**	.	**.**
lengthening per procedure (mm) (range)	**14.9 (10.0- 19.8)**	.	**.**
mean total lengthening (mm) (range)	**72.8 (43.2- 131.9)**	**70.0**	**72.3 (43.2- 131.9)**
lengthening during revision surgery	2.0	0.0	2.0

Table 6: details on lengthening procedures

3.2 Results literature review

Twelve studies were included after browsing PubMed and EMBASE and nine additional studies were included by manual search. The results are listed and summarized in the appendix. The year of publication reaches from 1993 to 2015. The total number of included patients was 489 and among the studies the numbers ranged from four in the study of Beebe et al. (32) to 71 of Schinhan et al. (33). The mean age of all patients was 10.1 years (range 3.0- 16.0). The mean follow-up for the included studies ranged from 2.0 months to 132.0 months. Overall the longest follow-up was 282.0 months (33) in one patient.

A majority (n= 387, 79.1%) of patients was diagnosed with osteosarcoma, 63 patients (12.8%) with Ewing's sarcoma, seven patients had other tumour entities (34–38) and for one study with 32 patients details on entity were not given (11) (**Table 7**). Regarding the localization of the tumours the most common site was the distal femur in 244 cases (49.9%) followed by the proximal tibia with 77 cases (15.7%). Two groups (11, 35) did not publish any fact about localization. Two authors classified only as "femoral" without any specification (39, 40). Another two groups did not publish any facts about localization.

Apart from two studies where the use of chemotherapy was not documented (32, 41), neoadjuvant chemotherapy was given in all cases. Neoadjuvant radiotherapy was used for Ewing's sarcoma patients in four studies (35, 37, 42, 43). In eight studies, no radiotherapy was used (3, 13, 14, 33, 36, 44–46) whereas in eleven studies (11, 32, 34, 38–41, 47–50) it was not mentioned if radiotherapy was used or not. A total of 24 local recurrences (5.0%) (3, 11, 13, 33, 37, 42, 46, 49, 50) were observed. In seven studies no local recurrences were observed in 489 included patients. In seven studies local recurrences were not documented (32, 34–36, 39, 41, 48). 95 out of 489 included patients died of disease (19.4%). Amputation of the affected limb was necessary in 24 patients (5.0%) (3, 13, 37, 38, 41–43, 47, 49, 50). In five studies the number of amputations was not documented (11, 33–35, 39).

Regarding the lengthening mechanism a total of 272 patients in 13 studies underwent minimally invasive lengthening (3, 11, 33, 35, 42–45, 47–50), whereas 210 implanted expandable prostheses in 12 studies (2 studies implanted both non-invasive and minimally invasive prostheses) were lengthened non-invasively (11, 13, 14, 32, 33, 36–41, 46). For seven patients, the type of lengthening mechanism was not given (34). In the following, the data will be analysed in three groups: minimally invasive lengthening only, non-invasive lengthening and both minimally and non-invasive lengthening.

Patients with minimally invasive lengthening

In 192 patients (39.8%) a minimally invasive growing prosthesis was implanted (3, 34, 35, 42–45, 47–50) (**Table 7**). The mean age at the time of implantation was 10.3 years (range 2.0- 16.0) and the mean follow-up was 65.7 months (range 3.0- 92.0). The localization of the primary malignant bone tumour was the distal femur in 130 patients (67.7%), the proximal tibia in 25 cases (13.0%), the proximal femur in 11 patients (5.7%) and the total femur in nine cases (4.7%). In 17 patients specifics about the localization were not given (35). The type of primary malignant bone tumour was osteosarcoma in 157 patients (81.7%), Ewing's sarcoma in 31 patients (16.1%) and other types in four patients (2.1%). Amputation was necessary due to infection in six cases, due to local recurrence in seven cases and due to disappearing bone disease in one case (7.3%), local recurrence was present in 12 cases (6.3%) and 48 patients died of disease (25.0%).

Patients with non-invasive lengthening

Non-invasive growing prostheses were implanted in 187 patients (88.8%) (13, 14, 32, 36–41, 46). The age at the time of implantation ranged from 5.0- 16.0 years with a mean of 10.5 years. The mean follow-up was 40.4 months (range 12.0- 140.0).The localization was the distal femur in 107 patients (57.2%), the proximal tibia in 37 (19.8%), the total femur in 11 patients (5.9%), the proximal femur in nine cases (4.8%) and the femur in general without any specifities in 23 cases (12.3%). Regarding the type of tumour, 166 children suffered from osteosarcoma (88.8%), 19 from Ewing's sarcoma (10.2%) and two from other tumour entities (1.1%). Amputation followed in 10 cases (four times due to infection, five times due to local recurrence and one time due to arterial thrombosis) (5.3%), local recurrence was present in six patients (3.2%) and 28 patients died of disease (15.0%).

Patients in studies with minimally and non-invasive lengthening

There were two studies in which 103 patients with both minimally (n= 79) and non-invasive growing prostheses (n= 24) were included (21.3%) (11, 33) (**Table 7**).The mean age at implantation was 9.5 years (range 4.0- 16.0), the localization of the tumour was the femur (no further information of localization) in 54 patients (52.4%), the proximal tibia in 15 patients (14.6%), other in two patients (1.9%) and in 32 patients the localization was not given (31.1%). The mean follow-up was 90.0 months (range 2.0- 282). The primary malignant tumour was osteosarcoma in 58 cases (56.3%), Ewing's sarcoma in 13 cases (12.6%) and in 32 cases the tumour entity was not given 31.1%). There were no amputations performed, local recurrence occurred in six cases (5.8%) and 19 patients died of disease (18.4%).

type of lengthening	**minimally invasive**	**non-invasive**	**minimally + non-invasive**	**studies with both**	**total**
number of patients	**192 (39.8%)**	**187 (38.8%)**	**379 (78.6%)**	**103 (21.3%)**	**482**
number of patients with type of lengthening not given					**7 (1.4%)**
mean age (years) (range)	**10.3 (2.0- 16.0)**	**10.5 (5.0- 16.0)**	**10.4 (2.0- 16.0)**	**9.5 (4.0- 16.0)**	**10.1 (2.0- 16.0)**
mean follow-up (months) (range)	**65.7 (3.0- 92.0)**	**40.4 (12.0- 140.0)**	**52.0 (3.0-140.0)**	**90.0 (2.0- 281.8)**	**55.8 (2.0- 281.8)**
localization					
proximal femur	11 (5.7%)	9 (4.8%)	20	0 (0.0%)	74 (15.1%)
distal femur	130 (67.7%)	107 (57.2%)	244	0 (0.0%)	244 (49.9%)
total femur	9 (4.7%)	11 (5.9%)	20	0 (0.0%)	20 (4.1%)
femur (general)	0 (0.0%)	23 (12.3%)	23	54 (52.4%)	23 (4.7%)
proximal tibia	25 (13.0%)	37 (19.8%)	62	15 (14.6%)	77 (15.7%)
localization not given	17 (8.9%)	0 (0.0%)	17	32 (31.1%)	49 (10.0 %)
other	0 (0.0%)	0 (0.0%)	2	2 (1.9%)	2 (0.4%)

primary malignant tumour					
osteosarcoma	157 (81.7%)	166 (88.8%)	329	58 (56.3%)	387 (79.1%)
Ewing's sarcoma	31 (16.1%)	19 (10.2%)	50	13 (12.6%)	63 (12.8%)
other	4 (2.1%)	2 (1.1%)	7	0 (0.0%)	7 (1.4%)
unknown	0 (0.0%)	0 (0.0%)	0	32 (31.1%)	32 (6.5%)
amputations	**14 (7.3%)**	**10 (5.3%)**	**24 (6.3%)**	**0 (0.0%)**	**24 (5.0%)**
local recurrence	**12 (6.3%)**	**6 (3.2%)**	**18 (4.7%)**	**6 (5.8%)**	**24 (5.0%)**
death of disease	**48 (25.0%)**	**28 (15.0%)**	**76 (20.0%)**	**19 (18.4%)**	**95 (19.4%)**

Table 7: patients characteristics literature review

Minimally invasive lengthening

For minimally invasive lengthening HMRS prostheses (Stryker Howmedica Osteonics, Kalamazoo, MI, USA) in 48 patients (25.0%) (35, 44, 47), Stanmore prostheses (Stanmore Implants, Middlesex, UK) were used in 132 children (66.3%) (3, 45, 45, 47–50) and Lewis growing prostheses (Dow Corning Wright Corporation, Memphis, TN) were used in 12 patients (6.0%) (33, 34, 43, 47).

The mean number of lengthening procedures of patients with minimally invasive growing prostheses was 6.3 (range 2.1- 11.8) with a mean total lengthening of 39.2 mm (range 1.5 mm- 69.7 mm) per patient. In five studies of minimally invasive growing prostheses, the mean number of lengthening procedures per patient was not given (34, 35, 43, 48). The mean total lengthening per patient was not documented in (3, 34, 35, 48, 49)..

The mean MSTS score of patients with minimally invasive growing prostheses was 73% (range 16.0- 100.0%). In four studies, the mean MSTS score was not analysed (34, 43, 44, 48).

The mean survival rate was calculated differently in most of the studies and therefore comparison was not possible, details can be seen in the appendix.

Leg-length discrepancy of ≥ 1 cm was present in six studies in 25%- 71% of patients (3, 34, 35, 45, 48, 49). However, cut off values that classified a leg-length discrepancy were different among studies and therefore have to been analysed separately. Tillman et al. (3) described 9% of patients with a leg length discrepancy > 1 cm but < 2 cm, Grimer et al. (49) observed 40% with 1 cm leg-length discrepancy. Details are shown in the appendix. Growth charts to calculate growth potential were used in four studies (44, 47, 49, 50).

Complications with minimally invasive growing prostheses were classified according to modified Henderson et al. (30) (**Table 8**). The patients with minimally invasive growing prostheses showed one soft tissue complication (0.5%) (44), 30 aseptic loosenings (15.0%) (3, 14, 35, 42, 44, 45, 48–50), 12 structural failures of the prosthesis (6.0%) (14, 34, 42, 45, 47, 48, 50), and six structural failures of bone in two studies (3.0%) (14, 44, 49). There were 30 deep infections in nine studies (15%) (3, 14, 34, 35, 44, 45, 47–50), one case of tumour progression (0.5%) (42) and one case of paediatric failure (0.5%) (34). In one study the complications were not documented (5.2%) (43).

Non-invasive lengthening

For non-invasive lengthening Repiphysis prostheses (Wright Medical Technology, Arlington, TN, USA) were used in a total of 91 patients (48.7%) (11, 13, 14, 32, 36, 38–41, 46), JTS prostheses (Stanmore Implants, Elstree, UK) were used in 96 children (51.3%) (11, 36–38) (**Table 8**).

Mean number of lengthening procedures in patients with non-invasive growing prostheses was 5.6 (range 3.0- 40.0) with a mean total lengthening of 35 mm (range 19.2 mm- 82.0 mm) per patient. In one study of non-invasive growing prostheses, the mean number of lengthening procedures and the mean total lengthening per patient were not mentioned (39) (**Table 8**).

The range of the MSTS score of patients with non-invasive growing prostheses reached from 26.6% to 100.0% with a mean of 81%.

The mean survival rate was calculated differently in most of the studies, for details please see appendix.

Leg-length discrepancy of ≥ 1 cm was present in 3 studies in 1.8%- 100% of patients (13, 32, 38). However, cut off values that classified a leg-length discrepancy were different among studies. Staals et al. (13) observed 10% with 1 cm leg-length discrepancy, 20% with 1.5 cm, 10% with 2 cm, 10% with 2.5 cm, 20% with 3 cm and 10% with 3.5 cm leg-length discrepancy. Picardo et al. (38) described > 2 cm leg length discrepancy in 1.8% of their cases. For details see appendix. The use of growth charts or growth prediction methods was not documented in any study.

Regarding the complications classified according to modified Henderson et al. (30), the patients with non-invasive growing prostheses showed 18 aseptic loosenings (9.6%) in six studies (13, 14, 39–41, 46), 32 structural failures of the prosthesis (17.1%) in six studies (13, 14, 37, 38, 40, 41), and 11 structural failures of bone (5.9%) in four studies (14, 38, 39, 46). There were 14 deep infections (7.5%) in six studies (13, 14, 37, 38, 40, 46). In one study, a paediatric failure in form of joint dysplasia occurred (38).

type of prosthesis	minimally invasive	non-invasive	minimally invasive + non-invasive	studies with both	total
HMRS (Stryker Howmedica Osteonics, Kalamazoo, MI, USA)	48 (25.0%)	-	48 (12.7%)	79 (76.7%)	127 (25.9%)
Stanmore (Stanmore Implants, Middlesex, UK)	132 (66.3%)	-	132 (34.8%)	0 (0.0%)	132 (26.9%)
Lewis (Dow Corning Wright Corporation, Memphis, TN, USA)	12 (6.0%)	-	12 (3.2%)	1 (0.9%)	13 (2.6%)
Repiphysis (Wright Medical Technology, Arlington, TN, USA)	-	91 (48.7%)	91 (24.0%)	15 (14.2%)	106 (21.7%)
JTS (Stanmore Implants, Elstree, UK)	-	96 (51.3%)	96 (25.3%)	7 (6.8%)	103 (21.1%)
MUTARS Xpand (Implantcast, Buxdehude, Germany)	-	0 (0. 0%)	0 (0.0%)	1 (0.9%)	1 (0.2%)
Type of prosthesis not given	7 (3.5%)	0 (0. 0%)	7 (1.8%)	0 (0.0%)	7 (1.4%)
lengthening procedures					
mean number of lengthening per patient (range)	6.3 (2.1- 11.8)	5.6 (3.0- 40.0)	6.0 (2.1- 40.0)	3.5 (0.0- 14.0)	5.1 (2.1- 40.0)
mean number of lengthening not given	51 (26.6%)	13 (7.0%)	64 (16.9%)	0	71
mean total lengthening (mm) (range)	39.2 (1.5- 69.7)	35.0 (19.2- 82.0)	37.1 (1.5- 82.0)	49.4 (28.0- 70.8)	40.3 (1.5- 82.0)
mean total lengthening not given	115 (59.9%)	13 (7.0%)	128 (33.8%)	0	135
MSTS score (%) (range)	73.0 (16.0- 100.0)	81.0 (26.6-100.0)	77.0 (16.0- 100.0)	83.0 (23.3- 100.0)	79.0 (16.0- 100.0)
MSTS score not given	40 (20.8%)	0	40 (10.6%)	0	47

complications					
Henderson 1 A	1 (0.5%)	0 (0.0%)	1 (0.3%)	35 (34.0%)	36
Henderson 1 B	0 (0.0%)	0 (0.0%)	0 (0.0%)	26 (25.2%)	26
Henderson 2	**30 (15.0%)**	**18 (9.6%)**	48 (12.4%)	**15 (14.6%)**	63
Henderson 3 A	**12 (6.0%)**	**32 (17.1%)**	44 (11.4%)	**31 (30.1%)**	75
Henderson 3 B	6 (3.0%)	11 (5.9%)	17 (4.4%)	19 (18.4%)	36
Henderson 4	**30 (15.0%)**	**14 (7.5%)**	44 (11.4%)	**34 (33.0%)**	78
Henderson 5	1 (0.5%)	0 (0.0%)	1 (0.3%)	4 (3.9%)	5
Henderson 6 A	1 (0.5%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	1
Henderson 6 B	0 (0.0%)	1 (0.5%)	1 (0.3%)	0 (0.0%)	1
Complications not given	10 (5.2%)	0	10 (2.6%)	0	10
total	**91**	**76**	**157**	**164 (49.6%)**	**331**

Table 8: implant types, specific data on lengthening procedures and complications separated minimally and non-invasive

Studies with inclusion of both minimally and non-invasive lengthening

There were two studies where minimally and non-invasive growing prostheses were implanted (11, 33) (**Table 8**, **Table 9**). 80 patients were lengthened minimally invasively (77.7%) and 23 non-invasively (22.3%). 79 HMRS prostheses and one Lewis prosthesis with a minimally invasive lengthening mechanism were used, 15 Repiphysis, seven JTS and MUTARS Xpand prostheses (Implantcast, Buxdehude, Germany) in one patient (33) were used with a non-invasive lengthening mechanism. The survival rate was only given in Ruggieri et al. (11) with 78% implant survival at four years following implantation and 66% at six years.

Regarding the complications there were 35 soft tissue complications (34.0%) in one study (33), 26 aseptic wound dehiscence (25.2%), 15 aseptic loosenings (14.6%) in both studies, 31 structural failures of the prostheses (30.1%), 19 structural failures of the bone (18.4%), 34 deep infections (33.0%) and four cases of tumour progression (3.9%) (33).

Regarding leg length discrepancy Ruggieri et al. (11) observed a leg-length discrepancy in 18.7% of their patients whereas Schinhan et al. (33) did not document leg-length discrepancy. The mean number of lengthening procedures per patient added up to 3.5 procedures (range 0.0- 14.0) with a mean total lengthening of 49.4 mm (range 0.0- 165.0). The mean MSTS score was 83% (range 23.3- 100.0). The mean follow-up was 90.0 months (range 2.0- 281.8).

author and title	**Ruggieri et al.**- Outcome of expandable prostheses in children. (11)		**Schinhan et al.**- Extendible Prostheses for Children After Resection of Primary Malignant Bone Tumour (33)	
year of publication	2013		2015	
mean age of patients (years) (range)	9.0 (5.5- 13.0)		10.0 (4.0- 16.0)	
mean follow-up (months) (range)	49.0 (2.0- 176.0)		132.0 (27.0- 281.8)	
death of disease	7		12	
type of lengthening	**minimally invasive**	**non-invasive**	**minimally invasive**	**non-invasive**
number of patients	10 (31.3%)	22 (68.8%)	70 (98.6%)	1 (1.4%)
<u>type of implant</u>				
HMRS	10 (31.3%)	0 (0. 0%)	69 (97.2%)	0 (0. 0%)
Lewis	0 (0. 0%)	0 (0. 0%)	1 (1.4%)	0 (0. 0%)
Repiphysis	0 (0. 0%)	15 (46.9%)	0 (0. 0%)	0 (0. 0%)
JTS	0 (0. 0%)	7 (21.9%)	0 (0. 0%)	0 (0. 0%)
MUTARS Xpand	0 (0. 0%)	0 (0. 0%)	0 (0. 0%)	1 (1.4%)
mean number of lengthening procedures (range)	2.6 (0.0- 14.0)		4.4	

mean total lengthening (mm) (range)	28.0 (4.0- 165.0)	70.8 (0.0- 224.0)
<u>complications</u>		
Henderson 1 A	0 (0. 0%)	35 (49.3%)
Henderson 1 B	0 (0. 0%)	26 (36.6%)
Henderson 2	5 (15.6%)	15 (21.1%)
Henderson 3 A	2 (6.3%)	29 (40.8%)
Henderson 3 B	1 (3.1%)	18 (25.4%)
Henderson 4	3 (9.4%)	31 (43.7%)
Henderson 5	0 (0. 0%)	4 (5.6%)
Henderson 6 A	0 (0. 0%)	0 (0. 0%)
Henderson 6 B	0 (0. 0%)	0 (0. 0%)
MSTS (%) (range)	85.3 (70.0- 100.0)	87.8 (23.3- 100.0)

Table 9: comparison of the studies with both types of lengthening mechanism used

4 Discussion

The first growing prosthesis was implanted in 1976 and lengthened minimally invasively. This mechanism was replaced by non-invasive systems in 1984. At the Department of Orthopedics and Orthopedic Surgery of Graz a total of 24 children have received a growing prosthesis since 1993, 12 of whom were included in this study with a mean follow-up of 88.0 months (range 6.0- 232.0 months). We aimed to identify the most common failure modes following the implantation of a growing prosthesis in our group and in literature by performing a systematic literature review. To the best of our knowledge, this is the first systematic literature review about growing prostheses.

4.1 Prosthetic survival

Due to the differences between numbers of implanted minimally invasive prostheses and non-invasive prostheses (8: 4), the shorter follow-up for non-invasive prostheses, the fact that three of the non-invasive prostheses never have been lengthened and the low number of patients, a reasonable comparison of lengthening procedures, implant-survival and event-free-survival in our data set is not possible. However, it is important to mention that the event-free-survival in non-invasive growing prostheses was poor with 0.0% survival rate at five years related to technical errors when starting the implantation of non-invasive growing prostheses. In detail one Dummy prosthesis had to be implanted due to missing sundries and was replaced with a motor three days following the initial implantation. The second patient was primarily treated with a Dummy prosthesis which was explanted 14 months following implantation. In literature, there is no data of implanting Dummies at primary surgery but after discussion with experts, we know that Dummies are sometimes implanted for to socioeconomic aspects, as costs are reduced if the motor is not implanted at primary surgery. At a later stage, when the prognosis is more favorable and survival of the patients is more likely, a functioning motor is implanted.

In literature the mean survival rate was calculated differently (appendix). For example Schindler et al. (42) reported a mean time to first revision of 69.3 months, an implant-survival rate of 93.9% at one year, 65.2% at five years and 0% at 10 years for Stanmore minimally invasive prostheses. This is comparable to results in our data set. The mean event-free-survival was analysed in three studies including exclusively non-invasive growing prostheses (13, 14, 39) reaching from a mean of 2.6 months in Ness et al. (39) to a mean of 62.0 months in Staals et al. (13).

4.2 Complications

Henderson et al. (30) developed a classification system designed to address for failure of limb-salvage surgery. Therefore the complication primary occurred are categorised into mechanical failure (soft tissue failure, graft-host nonunion, structural failure), non-mechanical failure (infection, tumour progression) and paediatric failures in bone tumour patients.

4.2.1 Non-mechanical complications

The most important complications in our own patients' collective regarding modified Henderson et al. (30) were deep infections in eight cases. Despite the high rate of deep infections, none of our patients underwent amputation. The high rate of deep infections in our collective may be caused by the neoadjuvant chemotherapy which all of the patients obtained and compromises the immune system (44). Similarly, in the clinical studies included, the complication that most frequently occurred was deep infection according to modified Henderson et al. (30). In literature deep infection often followed superficial wound dehiscence (37, 38) often seen in patients with a primary malignant bone tumour in the proximal tibia due to difficult soft tissue conditions and a lack of sufficient soft tissue coverage (3, 37, 38, 49). However, a correlation of localization of the primary bone sarcoma and deep infection could not be calculated from the included studies as data quality was poor. Additionally, the same authors described that infection rates decreased since using gastrocnemius flaps for soft tissue coverage at the proximal tibia (3, 37).

Three patients died of distant metastases (25%) and there were no local recurrences or amputations in our dataset. In literature, the rate of patients that died of disease was slightly lower than in our dataset (19.4%) whereas local recurrence occurred in 5.0% of patients and amputation was necessary in 5.0%. Reasons for amputations were local recurrence in 12 cases (3, 13, 33, 37, 38, 49), infection in 10 cases (3, 35, 37, 39, 49), disappearing bone disease in one case (49) and arterial thrombosis in one (36). However, **Figure 15** shows the decreasing amputation rate due to advanced appearance of expandable prostheses.

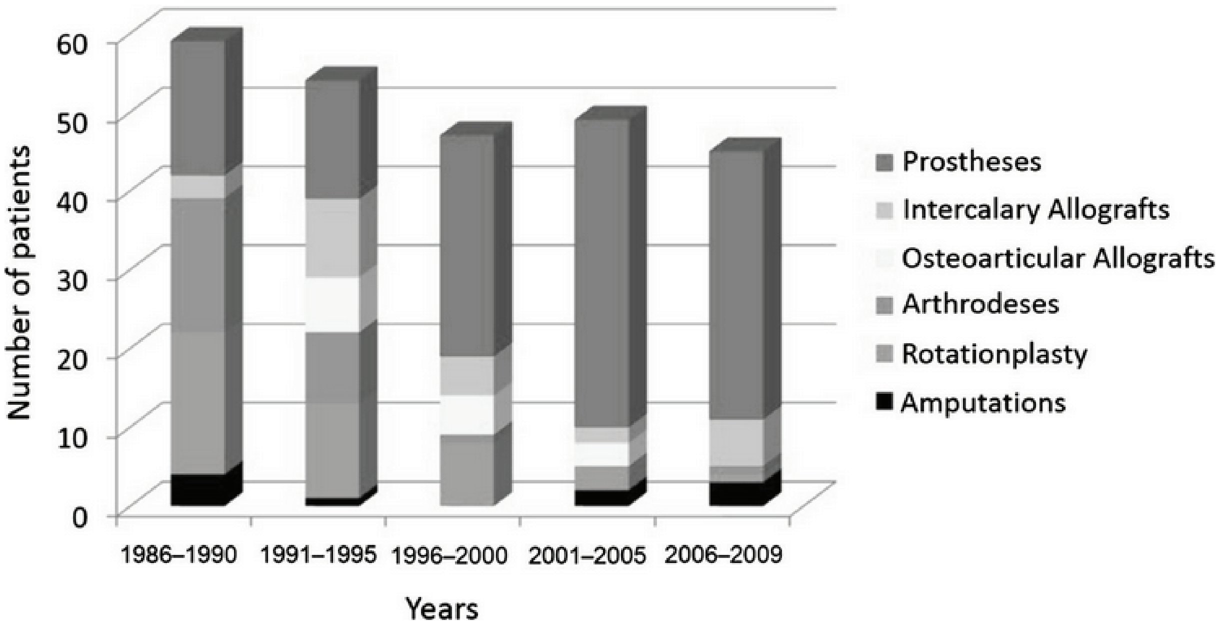

Figure 15 (51): use of prostheses in children with malignant bone sarcoma in the distal femur in comparison to other treatment options

4.2.2 Mechanical failure

Regarding mechanical failure the most common complications were fractures of prosthetic components in our dataset and structural failure and aseptic loosening in clinical studies.

4.2.2.1 Aseptic loosening

The reasons for aseptic loosening are multifactorial. On the one hand there is the reshaping of the femur during growth as the reshaping leads to a change of the bone in the form of thickness increase (52). On the outer surface of the bone there is an imbalance between osteoclasts and osteoblasts for the benefit of osteoblasts whereas in the inner part of the bone the osteoclasts predominate who form the medullary cavity (52). Due to the central position of the stem in the femur or the tibia, the resulting wide medullary cavity facilitate aseptic loosening. On the other hand, the constrained character of the knee component, the biochemical reactions to metal and polyethylene wear as well as the high mechanical demands on a growing prosthesis could lead to aseptic loosening (36, 38, 42). Other knee prostheses without lengthening mechanisms are implanted in patients of a higher age group and are, in contrast to children, less bodily active. One possibility to reduce the number of aseptic loosening is the use of, hydroxy- apatite- coated collars to permit offloading the stem to optimize bony ingrowth of the prosthesis (36, 42).

4.2.2.2 Structural failure

The most common complications regarding mechanical failure in our own dataset were related to the lengthening mechanism. The complications most often seen in this context were the collapses of the HMRS prostheses and the need to revise the prostheses. In literature, structural bone and prosthetic failure rate was highest in non-invasive growing prostheses (5.9% and 17.1%). Due to the low number of non-invasive prostheses and their short-term follow-up in our dataset structural failure is not comparable with literature whereas the rates for structural prosthetic failure in minimally invasive prostheses are higher in our dataset (31.3% versus 6.0%). The reason for exchange of minimally invasive growing prostheses in our dataset was the recurrent collapse of the lengthening mechanism in three of the implanted HMRS prostheses. Loosening of the adjustment screw was seen in all three cases. Despite the technically correct tightening of the fixation screw the growing module re-collapsed repeatedly and severe limb-length inequality occurred. In-vitro testing of the explanted prosthesis showed that lengthening was possible although the fixation screw was locked. If this type of mechanical failure in this model of minimally invasive growing prosthesis had not occurred, eight surgical interventions and three exchanges of the prosthesis could have been avoided. Every additional surgical intervention includes an increased risk for infection of 2- 5% (42) and the need for general aneasthesia. This contradicts the idea of a growing prosthesis. Additionally, costs for the operations and a new prosthesis have also to be taken into account. The use of exclusively HMRS prostheses in our dataset may be the reason for the higher rate of structural prosthetic failure.

4.3 MSTS score

The MSTS score in our own dataset was 80.0% (43.0- 97.0%) in patients with minimally invasive growing prostheses and 72.8% (range 47.0- 87.0%) in patients with non-invasive prostheses. This can be most likely attributed to the different follow-up times in our dataset. In contrast, in the literature review the mean MSTS score was higher in non-invasive growing prostheses (81.0, range 73.0- 94.0%) than in minimally invasive ones (**Table 8**). However, considering the high numbers of revisions and the involved long time of immobilisation in both, minimally and non-invasive growing prostheses, the MSTS scores are good. These MSTS scores have to be interpreted with caution as it could not be extracted from the available literature whether MSTS scores were calculated prospectively during routine follow-up or retrospectively from clinical noted and follow-up times were heterogeneously. Comparing the functional outcome of growing prostheses to rotationplasty, Benedetti et al. (51) reported similar functional outcomes with a mean MSTS score of 82% at last follow-up in their study including 25 patients treated with rotationplasty with a mean age of 23.8 years at last follow-up (range 16.3- 31.3).

4.4 Comparison of minimally and non-invasive prostheses

In our own patient collective comparison of minimally invasive and non-invasive implants does not seem reasonable since follow-up times were very heterogeneous and only four patients with a non-invasive prosthesis were included in our own data set.

Analysing the retrieved clinical studies, results were extracted for studies with implantation of exclusively minimally invasive, non-invasive growing prostheses and for studies that included both. Of the included studies the number of both, minimally and non-invasive implants was similar. An extra part of the analysis will be the two studies which included children with minimally invasive expandable prostheses as well as children with non-invasive prostheses.

The similar mean age in patients with minimally invasive prostheses and patients with non-invasive prostheses (10.3 versus 10.5 years) wallows for comparison of these types of prostheses.

The mean follow-up of 66.0 months in minimally invasive was longer than in non-invasive prostheses with 40.0 months, however both follow-up times are short- to mid-term and there is a lack of information regarding long-term results of growing prostheses in current literature. Due to the different follow-up times- as minimally invasive growing prostheses have been longer available than non-invasive ones- outcome and complication rates are difficult to compare.

Regarding complications, minimally invasive prostheses showed higher rates of deep infection (15.0%) as well of aseptic loosening (15.0%) than non-invasive prostheses. The higher rate of deep infection in minimally invasive prostheses may be caused by recurrent anaesthesia and local incision for lengthening. However, structural failures, bone as well as prosthesis, were present more often in non-invasive growing prostheses (17.1% and 5.9%). The reason for that may be the learning curve using non-invasive prostheses and the involved mistakes at implantation as well as the high biochemical demands on growing prostheses. Amputation rates were higher in minimally invasive growing prostheses as the majority of authors reported necessity of amputation after local recurrence. This could be explained by the longer availability of minimally invasive prostheses and the involved development of cytotoxic tumour treatment according to different chemotherapy protocols. Nevertheless it is important to mention, that there was none complication documented in a study of 10 children with minimally invasive Lewis expandable prostheses with a mean follow-up of 29.5 months (43). The rate of local recurrence is higher in minimally invasive prostheses (6.3% versus 3.2%) which could be explained by the advanced surgical technique in limb-salvage surgery, the improved preoperative planning including improved cross sectional imaging techniques and the enhanced neoadjuvant chemotherapies.

After classifying the different types of complications according to modified Henderson et al. (30) it was remarkable that there were hardly any complications regarding tumour progression or paediatric failures (in five cases tumour progression (33, 42), in one case joint stiffness (34) and one growth arrest resulting deformity (38)). The reason for the low number of revisions due to tumour progression may be explained by the use of neoadjuvant chemotherapy, advanced imaging techniques resulting in better preoperative planning of wide margins and increased experience with limb-salvage surgery of orthopaedic oncologists (5, 15, 19, 38). The reason for the barely existing or documented paediatric failures may be the difficulty of proofing physical arrest and resulting leg-length discrepancy as this is a long-term complication. Furthermore, specific X-rays like full leg exposures are not done on a regular basis and difficult to obtain in retrospective analysis. Only two authors focused on physical arrest and the resulting problems (48, 53). Arteau et al. (53) investigated 23 patients with distal femoral replacement using a cemented or a smooth tibial stem. In 10 patients, leg-length discrepancy worsened during growth whereas the tibial physis in the operated limb grew an average of 4.0 mm less per year (53). In five patients a tibial leg-length discrepancy of ≥ 20.0 mm was present at last follow-up (53). In two skeletally mature patients the leg length discrepancy was more than 20.0 mm (53). Reported problems included angular deformity at the proximal part of the tibia in three patients (53).

Regarding the type of prostheses implanted, most children were treated with Stanmore (26.9%) prostheses followed by HMRS (25.9%) and Repiphysis (21.7%) In only one case MUTARS Xpand was implanted. However, the high number of implanted HMRS prostheses no case of collapse of the lengthening mechanism was reported.

The mean number of lengthening procedure per patient was similar among minimally and non-invasive growing prostheses. The mean total lengthening of minimally invasive growing prostheses was slightly higher than the mean total lengthening of non-invasive prostheses (39.2 versus 35.0 mm). The younger patients and the longer availability of minimally invasive extendible prostheses can explain the differences. However, no data about total lengthening was reported in 115 patients (59.9%) which may modify the results. The amount of lengthening compensates around 4 cm, which is the minimum of expected growth before the implantation of a growing prostheses. However, it is very likely that there are patients who undergo any lengthening or only a minimal amount of lengthening. We do not know exactly, asabout one fourth of authors did not provide information about the amount of total lengthening.

The outcome of the MSTS score is slightly improved in non-invasive prostheses than in minimally invasive ones.

4.5 Comparison studies including both lengthenings with literature and own data set

There were two studies in which patients were treated with both minimally and non-invasive growing prostheses (11, 33) which are separately analysed.

4.6 Comparison with Schinhan et al.

In this context, the study of Schinhan et al. (33) should be scrutinised (**Table 10**). The authors of this study published their 27 years of experience with extendible prostheses for children after resection of primary malignant bone tumours. The mean follow-up of Schinhan et al. (33) was 131.6 months (range 27.0- 282.0) and therefore considerably longer than in our data set and the remaining clinical studies. Despite the long follow-up only a mean of 4.4 lengthening procedures per patient were performed. Schinhan et al. (33) reported a mean elongation of 14.4 mm per procedure. The mean total lengthening was 70.8 mm in Schinhan et al. (33) (range 0.0- 224.0 mm) which is higher than mean total lengthening in our data set (36.2 mm, range 0.0- 131.9 mm) because there was a lower mean follow-up in our patients collective. The mean MSTS score was highest in Schinhan et al. (33) (87.8%, range 23.3-100.0) followed by literature review (79.8%, range 27.0- 100.0) and in our data set 77.6% (range 43.0- 97.0). Schinhan et al. (33) does provide a very in depth analysis of complications including “subluxation of hip joint”, “spontaneous shortening of the elongation mechanism” and “dysfunction of automatic elongation” In our data set, a part of the occurred complications not classified according to modified Henderson et al. (30) could be classified similar to Schinhan et al. (33) (**Table 10**). They also reported one case of spontaneous shortening of lengthening mechanism which could be equated with the collapse of the HMRS prostheses in our patients collective. The type of the affected prosthesis was not specified. In Schinhan et al. (33) the most common complication according to modified Henderson et al. (30) was soft tissue complication in the form of functional soft tissue failure followed by deep infection and structural failure of the implant. In contrast, the most common complication occurred in literature review was aseptic loosening followed by deep infection and structural failure of the implant. However, in our data set the most frequent occurred complication according to Henderson et al. (30) was deep infection followed by aseptic loosening. Despite the high rate of complications, amputation had to be carried out in only 2.8% as compared with the high rate of deep infection which was 43.7% (33).

	own data set	**literature review**	**Schinhan et al. (33)**
number of patients	12	418	71
mean age of patients at implantation (years) (range)	9.7 (5.0- 14.0)	9.8 (2.0- 16.0)	10 (4.0- 16.0)
mean follow-up (months) (range)	87.6 (6.0- 232.0)	51.0 (2.0- 176.0)	131.6 (27.0- 282.0)
mean number of lengthening procedures per patient (range)	.	4.8 (2.1- 40.0)	4.4
mean total lengthening (mm) (range)	36.2 (0.0- 131.9)	34.1 (1.5- 165.0)	70.8 (0.0- 224.0)
mean MSTS score (%)	77.6 (43.0- 97.0)	79.8 (27.0- 100.0)	87.8 (23.3- 100.0)
complications			
Henderson 1 A	0 (0.0%)	1 (0.2%)	35 (49.3%)
Henderson 1 B	0 (0.0%)	0 (0.0%)	26 (36.6%)
Henderson 2	1 (8.3%)	53 (12.7%)	15 (21.1%)
Henderson 3 A	5 (41.7%)	46 (11.0%)	29 (40.8%)
Henderson 3 B	1 (8.3%)	18 (4.3%)	18 (25.4%)
Henderson 4	8 (61.5%)	47 (11.2%)	31 (43.7%)
Henderson 5	0 (0.0%)	0 (0.0%)	4 (5.6%)
Henderson 6 A	0 (0.0%)	1 (0.2%)	0 (0.0%)
Henderson 6 B	0 (0.0%)	1 (0.2%)	0 (0.0%)
other			
nerve lesion	0 (0.0%)	0 (0.0%)	7 (9.8%)
aneurysm	0 (0.0%)	0 (0.0%)	2 (2.8%)
sub-/dislocation hip	3 (0.7%)	0 (0.0%)	19 (26.8%)
spontaneous shortening of lengthening mechanism	7 (1.7%)	0 (0.0%)	1 (1.4%)
jamming	0 (0.0%)	0 (0.0%)	1 (1.4%)
dysfunction of automatic elongation	0 (0.0%)	0 (0.0%)	1 (1.4%)
amputations	0 (0.0%)	22 (5.2%)	2 (2.8%)
local recurrence	0 (0.0%)	22 (5.2%)	3 (4.2%)
death of disease	3 (25.0%)	83 (19.9%)	12 (16.9%)

Table 10: comparison own data set, literature review and study of Schinhan et al. (33)

As outlined above, Schinhan et al. (33) used minimally invasive prostheses as well as non-invasive prostheses.

4.7 Comparison of implant types

Having a look at different types of non-invasive growing prostheses, two were used most frequently: Repiphysis on one hand (48.7%) and Stanmore JTS on the other hand (51.3%) (**Table 11**). The similar number of participants, the similar time of follow-up, the slightly older patients treated with JTS and the similarity of tumour localization makes it possible to compare these two types of prostheses. Four short- and three mid-term studies with each a small patients collective (< 20) and high complication rates used exclusively Repiphysis prostheses (13, 14, 32, 39–41, 46). Saghieh et al. (14) described the necessity of oral analgetics during lengthening procedures due to pain and burn, as well as Neel et al. (41). Staals et al. (13) reported even use of general anaesthesia as well as muscle relaxation. Furthermore, Staals et al. (13) described a loss of lengthening after the same exposure time to the electromagnetic field after the first three lengthening procedures of each prosthesis. This was might related to the compressed spring which loses stored energy and expansion capacity. Summarised major problems in Repiphysis prostheses are structural failure of the prostheses and the need of exchange after skeletal maturity (14) so that Staals et al. (13) disadvise from using this type of non-invasive prosthesis.

Three studies including a total of 96 patients implanted the non-invasive JTS Stanmore prosthesis (36–38) with a relatively big patients' collective in two (55 and 34 patients) (37, 38). In Picardo et al. (38) an infection rate of 10.9% occurred. Most of the infections affected the patients with proximal tibia reconstruction (25%). However, the introduction of silver coated implants reduced the infection rates from 17.6 to 5.9% In this study, there was no correlation between the age of the patients at primary implantation of a growing prosthesis or the site of the primary tumour to the complications. Hwang et al. (37) reported an infection rate of 18% which results mostly from early infections following wound healing problems. In contrast to Repiphysis, the major problem in JTS prostheses are deep infections. However, no analgetics and no anaesthesia during lengthening procedure was necessary in any of the mentioned studies and the prostheses can stay in situ and has not to be changed after skeletal maturity (14, 38).

Regarding the non-invasive extendible prostheses produced by Implantcast (MUTARS Xpand) no study has been published regarding outcome or complication rates so far, Schinhan et al. (33) reported on 1 MUTARS Xpand, however no further details could be extracted from their study.

type of implant	**Repiphysis** (Wright Medical Technology, Arlington, TN, USA)	**JTS** (Stanmore Implants, Elstree, UK)	**total**
authors	(13, 14, 14, 32, 39–41, 46)	(36–38)	
number of patients	91 (48.7%)	96 (51.3%)	187
mean age of patients (years) (range)	10.0 (6.0- 11.0)	11.5 (5.0- 16.0)	10.8 (5.0- 16.0)
mean follow-up (months) (range)	42.7 (12.0- 140.0)	35.1 (14.0- 104.0)	38.9 (12.0- 140.0)
localization of the tumour			
proximal femur	0 (0. 0%)	9 (9.4%)	9
distal femur	42 (46.1%)	65 (67.7%)	107
femur (general)	23 (25.3%)	0 (0.0%)	23
total femur	4 (4.4%)	7 (7.3%)	11
proximal tibia	22 (24.2%)	15 (15.6%)	37
primary malignant bone tumour			
osteosarcoma	86 (94.5%)	80 (83.3%)	166
Ewing's sarcoma	5 (5.5%)	14 (14.6%)	19
other	0 (0.0%)	2 (2.1%)	2
amputations	3 (3.3%)	4 (4.2%)	7
local recurrence	3 (3.3%)	3 (3.1%)	6
dead of disease	10 (11 .0%)	18 (18.8%)	28
complications			
Henderson 1 A	0 (0.0%)	0 (0.0%)	0
Henderson 1 B	0 (0.0%)	0 (0.0%)	0
Henderson 2	18 (19.8%)	0 (0.0%)	18
Henderson 3 A	26 (25.6%)	6 (6.3%)	32
Henderson 3 B	5 (5.5%)	6 (6.3%)	11
Henderson 4	6 (6.6%)	8 (8.3%)	14
Henderson 5 A	0 (0.0%)	0 (0.0%)	0
Henderson 5 B	2 (2.2%)	0 (0.0%)	2
Henderson 6 A	0 (0.0%)	0 (0. 0%)	0
Henderson 6 B	0 (0.0%)	1 (1.0%)	1
lengthening			
mean lengthening procedures per patient	4.2 (0.0- 14.0)	10.2 (1.0- 40.0)	7.2 (0.0- 40.0)
mean total lengthening (mm)	42.3 (0.0- 99.0)	31.9 (3.5- 161.5)	37.1 (0.0- 161.5)
MSTS score (%) (range)	82.0 (30.0- 100.0)	78.1 (26.6- 100.0)	80.1 (26.6- 100.0)

Table 11: comparison Repiphysis and JTS non-invasive growing prostheses regarding performed literature review

4.8 Limitations of the study

There are several limitations of our clinical study and the performed literature review. First, the number of included patients in our data set is very small. Especially the low number of implanted non-invasive prostheses and the even lower number of performed lengthening procedures made a comparison with minimally invasive prostheses not possible. Second, all data were collected retrospectively including the MSTS scores and classification according to modified Henderson et al. (30). Third, regarding literature, a main drawback of this study are the heterogeneous follow-up times among the included studies which limits the comparison of studies. Fourth, mostly retrospective studies were available for inclusion in this systematic review. Fifth, as complications were not documented chronologically, the original version of the Henderson et al. (30) classification could not be applied. Finally, only limited data on lengthening procedures, implant survival and leg-length discrepancy was available and therefore outcome parametres have to been interpreted with caution.

5 Conclusion

Growing prostheses are a good alternative to amputation or rotationplasty in children with resection of primary malignant bone tumours providing a reasonable functional outcome both in minimally invasive and non-invasive implant types. Whether non-invasive growing prostheses show decreased rates of deep infections and truly reduce the numbers of surgical interventions in long-term follow-up remains unclear. However, a tendency towards lower amputation and deep infection rates was shown for the non-invasive growing prostheses. The results of this study have to be interpreted with caution due to the lack of long-term follow-up and prospective studies.

Due to the tendency towards lower amputation and deep infection rates, the risk for infection due to minimally invasive lengthening could may be avoided by the increasing appearance of non-invasive growing prostheses although there is the need of development to meet the mechanical and structural demands of a growing child.

6 Appendix

Author	Year of publication	timeframe of implantation of the growing prostheses	number of participants	mean age of patients (years) (range)	osteo-sarcoma	Ewing`s sarcoma	proximal femur	distal femur	proximal tibia	total femur	local recurrence
Israelsen et al. (34)	2011	2000-2010	7	8.9 (7-10)	6	0	0	7	0	0	n.a.
Yoshida et al. (35)	2010	1973-2008	17	11.9 (7-16)	14	2	n.a.	n.a.	n.a.	n.a.	n.a.
Tillman et al. (3)	1997	1976-1993	54	10 (3-14)	48	6	0	54	0	0	6
Schiller et al. (44)	1995	1986-1991	6	11 (9.2-13.7)	5	1	0	5	1	0	0
Ness et al. (39)	2014	1992-2013	13	10.5 (1.4)	12	1	0	9	4	0	n.a.
Ruggieri et al. (11)	2013	1996-2010	32	9 (5.5-13)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	3
Beebe et al. (32)	2010	2003-2005	4	9.8 (9-11)	3	1	0	2	1	1	n.a.
Saghieh et al. (14)	2010	2002-2008	17	10.5 (7-13)	16	1	0	10	7	0	0
Yoshida et al. (47)	2008	n.a.	28	10.1 (5-14)	25	3	1	22	3	2	0
Gupta et al. (36)	2006	2004-2004	7	12.1 (9-15)	6	0	0	7	0	0	n.a.
Neel et al. (41)	2003	1998-2001	15	11 (7-15)	15	0	0	10	4	1	n.a.
Schindler et al. (45)	1998	1988-1996	6	8 (2-12)	3	3	0	0	0	6	0
Schindler et al. (42)	1997	1983-1990	18	11 (8-14)	17	1	0	18	0	0	2
Eckardt et al. (43)	1993	1985-1987	10	10.3 (6-13)	8	2	1	7	1	1	0
Cool et al. (48)	1997	1976-1993	24	10.1 (5.8-14)	20	4	0	24	0	0	n.a.
Grimer et al. (49)	2000	1983-1998	20	9.9 (5-14)	14	3	0	0	20	0	2
Hwang et al. (37)	2012	2002-2009	34	11 (7-14)	31	3	1	25	3	5	3
Belthur et al. (50)	2003	1983-1996	9	8 (3-11)	3	6	9	0	0	0	2
Gitelis et al. (40)	2003	1998-2002	18	10.7 (8-16)	18	0	n.a.	14	4	n.a.	0
Staals et al. (13)	2015	2002-2007	15	8 (6-11)	14	1	0	15	0	0	2
Schinhan et al. (33)	2015	1986-2015	71	10 (4-16)	58	13	54		15		3
Beebe et al. (46)	2010	2003-2008	9	10 (7-12)	8	1	0	5	2	2	1
Picardo et al. (38)	2012	2002-2009	55	11.4 (5-16)	43	11	8	33	12	2	0

Author	DOD	mean follow-up (months) (range)	Henders on 1: soft tissue	Henders on 2: aseptic loosening	Henders on 3: Structural failure	Henders on 4: number of infections	Henders on 5: tumour progression	Henders on 6: paediatric failure	mean time to first revision (months) (range)	mean time to loss of prosthesis (months) (range)	mean survival rate (%)
Israelsen et al. (34)	n.a.	42 (6-110)	0	0	1	3	0	1	n.a.	n.a.	n.a.
Yoshida et al. (35)	5	81 (12-192)	0	1	0	2	0	0	n.a.	n.a.	n.a.
Tillman et al. (3)	21	112 (63-155)	0	13	0	11	0	0	n.a.	n.a.	n.a.
Schiller et al. (44)	0	59 (36-74)	1	1	1	3	0	0	n.a.	n.a.	n.a.
Ness et al. (39)	n.a.	>18	0	12	1	0	0	0	2.6 (0.7-402)	n.a.	n.a.
Ruggieri et al. (11)	7	49 (2-176)	0	5	3	3	0	0	n.a.	n.a.	78% at 4 years, 66% at 6 years
Beebe et al. (32)	0	31.5 (15-42)	0	0	0	0	0	0	n.a.	n.a.	n.a.
Saghieh et al. (14)	2	62 (19-82)	0	2	8	3	0	0	32.0 (22.0-59.0)	n.a.	n.a.
Yoshida et al. (47)	3	61	0	0	4	1	0	0	12.0	22.0	n.a.
Gupta et al. (36)	1	20.2 (14-30)	0	0	0	0	0	0	n.a.	n.a.	n.a.
Neel et al. (41)	1	21.5 (12-33)	0	1	7	0	0	0	n.a.	n.a.	n.a.
Schindler et al. (45)	1	49.2 (10.8-118.8)	0	1	2	1	0	0	n.a.	n.a.	n.a.
Schindler et al. (42)	4	73.5 (3-158)	0	6	3	0	0	0	69.3 (8.0- 108.0)	69.3 (8.0- 108.0)	93.9% at 1 year, 65.2% at 5 years, 0% at 10 years
Eckardt et al. (43)	3	42519,00	n.a	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Cool et al. (48)	1	56.4 (30-94.8)	0	3	1	1	0	0	n.a.	n.a.	n.a.
Grimer et al. (49)	5	>60	0	3	5	7	0	0	n.a.	n.a.	n.a.
Hwang et al. (37)	7	44 (15-86)	0	0	2	6	0	0	n.a.	n.a.	n.a.
Belthur et al. (50)	4	75.4 (19-152)	0	2	1	1	0	1	n.a.	n.a.	n.a.
Gitelis et al. (40)	0	24. Aug	0	1	5	1	0	0	n.a.	n.a.	n.a.
Staals et al. (13)	5	104 (78-140)	0	1	8	1	2	0	62.0 (48.0- 79.0)	n.a.	n.a.
Schinhan et al. (33)	12	131.6 (27.2-281.8)	61	15	37	31	4	0	n.a.	n.a.	n.a.
Beebe et al. (46)	2	37.2 (16-78)	0	1	2	1	0	0	n.a.	n.a.	n.a.
Picardo et al. (38)	10	41.2 (22-104)	0	0	10	2	0	1	n.a.	n.a.	n.a.

Author	minimal invasive lengthening	non- invasive lengthening	number of revision procedures (independent of the number of affected patients)	number of amputations at last follow-up	mean number of lengthening procedures per patient (range)	mean total lengthening (mm) (range)	patients with leg-lenght discepancy (%)	Mean MSTS score (%) (range)
Israelsen et al. (34)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	71.0%	n.a.
Yoshida et al. (35)	17	0	n.a.	n.a.	n.a.	n.a.	27.0%	85 (52-96)
Tillman et al. (3)	54	0	17	4	08. Jan	n.a.	19.0% > 1 cm but < 2 cm	72 (47-80)
Schiller et al. (44)	6	0	53	0	10	13.2 (4.5-19.5)	n.a.	n.a.
Ness et al. (39)	0	13	13	n.a.	n.a.	n.a.	0.0%	73 (30-90)
Ruggieri et al. (11)	10	22	9	n.a.	2.6 (0-14)	28 (4-165)	18.7%	79 (30-100)
Beebe et al. (32)	0	4	0	0	4.7 (2-7)	41.7 (12-69.9)	100.0%	78 (56,7-90)
Saghieh et al. (14)	17	0	7	0	4.8 (0-6)	19.2 (0-65)	29.4% < 1 cm	85.3 (70-100)
Yoshida et al. (47)	28	0	2	1	2.1 (1-4.1)	35.4 (9.9-70)	n.a.	73.6 (44-100)
Gupta et al. (36)	0	7	1	0	6.6 (1-14)	25 (4,25-55)	n.a.	67 (37-97)
Neel et al. (41)	0	15	8	1	4 (0-10)	33.9 (0-60)	n.a.	93.5 (70-100)
Schindler et al. (45)	6	0	4	0	11.8 (3-10)	63.4 (40-137)	33.0% > 1 cm	77.3 (67-90)
Schindler et al. (42)	18	0	10	2	4.3 (2-6)	52 (30-70)	100.0%	43.3 (16-59)
Eckardt et al. (43)	10	0	2	1	n.a.	1.5 (0-5.4)	70 .0% < 1 cm	n.a.
Cool et al. (48)	24	0	5	0	n.a.	n.a.	25.0%	n.a.
Grimer et al. (49)	20	0	15	5	6,8	n.a.	40.0% = 1 cm	83
Hwang et al. (37)	0	34	8	3	5 (1-15)	32 (4-80)	n.a.	85 (60-100)
Belthur et al. (50)	9	0	5	2	4.8 (1-11)	69.7 (7-104)	33.0% < 1 cm	77.6
Gitelis et al. (40)	0	18	7	0	4,1	38 (10-76)	n.a.	83.5
Staals et al. (13)	0	15	12	2	4,6	39 (17-7)	93.0%	81 (53-97)
Schinhan et al. (33)	64	7	184	2	4,4	70.8 (0-224)	n.a.	87.8 (23.3-100)
Beebe et al. (46)	0	9	2	0	3 (0-10)	82 (12-99)	n.a.	79.6 (43-100)
Picardo et al. (38)	0	55	13	1	11.3 (1-40)	38.6 (3.5-161.5)	1.8% > 2 cm	82.3 (26.6-10)

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