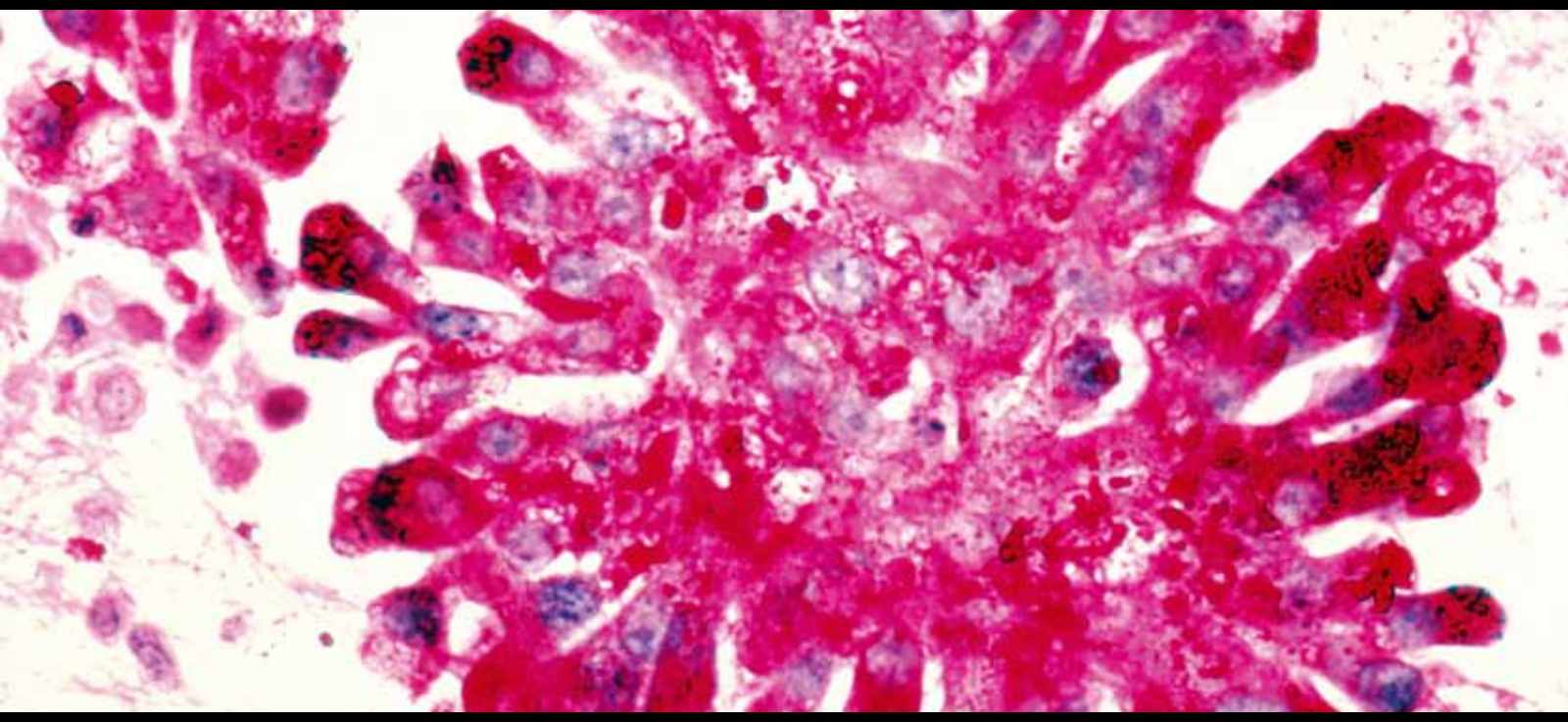
Recent Developments in the Surgical Treatment of Bone Tumors and Their Impact on Quality of Life

Guest Editors: Hans Rechl, G. Douglas Letson, and Pietro Ruggieri



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Sarcoma

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Editorial Board

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Editorial

Recent Developments in the Surgical Treatment of Bone Tumors and Their Impact on Quality of Life

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The management of bone tumors has rapidly evolved over the last decades. Before the 1970s, amputation and arthrodesis were almost exclusively performed at the surgical theaters of tertiary tumor centers. Currently, with the evolutions in diagnostic imaging, surgical techniques, metallurgy, and adjuvant therapies, more than 90% of bone sarcomas patients are treated with limb salvage surgery. It is well documented in the related literature that limb salvage surgery does not compromise the survival of the patients. The main indication for limb salvage is the ability to obtain wide-margin (microscopically negative) surgical resection. A relative contraindication is local recurrence in a patient that previously had limb salvage surgery, except if the recurrence can be excised with wide margins. Various reconstruction options have been described following bone tumors resection with limb salvage, including megaprosthetic and biological reconstructions with allografts and vascularized bone autografts. However, what is the impact of bone tumors surgical resections and their reconstructions on the quality of life of tumor patients? This special issue tries to address the recent developments in the surgical treatment of bone tumors and their impact on quality of life. Expert authors in tumor surgery present their experience and knowledge on this subject.

The treatment of bone sarcomas is based on the tumor's biology and location and the patient's expectations [1]. The reconstruction options are technically demanding, may require lengthy treatment protocols, and may be associated with complications, which are not acceptable in cancer patients. These constraints have triggered a need for new therapeutic concepts to design and engineer structural and functional bone grafts. The goal is for long-term repair and optimum clinical outcome using techniques to replace tissues with inert biological devices such as tissue engineering constructs [2, 3]. The study of Dr. B. M. Holzapfel et al. is within this context. The authors discuss the implementation of tissue engineering concepts in treatment strategies of bone defects following bone tumor resection and outline their future prospects and possible application spectrum.

Massive bone allografts may be used as alternative to megaprosthetic reconstructions for bone defects after tumor resection. However, the rate of complications, namely, infection, fracture, and nonunion, may range up to 30%. Decreasing nonunion may minimize surgical exposure and permit earlier rehabilitation of the patients. While congruous osteotomy cuts are desirable, exact matching surfaces are rarely achieved using a freehand technique [4]. Computer-assisted navigation may provide for more accurate osteotomies resulting in more congruent allograft-host junctions, potentially decreasing nonunion rates [5, 6]. Dr. A. Lall et al. suggested that the limited contact achieved using standard freehand techniques may increase the rate of nonunion, while in contrast, computer-assisted navigation may increase the contact area and improve the rate of union. In their study, the authors quantified the average surface contact areas across

simulated intraoperative osteotomies using both a freehand and a computer-assisted navigation technique following application of a limited-contact dynamic compression plate. They found that using a freehand technique, contact areas of only 30% were obtained. However, using computer-assisted navigation the average contact area increased to more than 43%. Therefore, future development of an oncology software package and oncology-related navigation hardware may serve an important role in decreasing nonunion rates in limb salvage surgery and allograft reconstruction.

Peripheral dedifferentiated chondrosarcomas are rare high grade malignant connective tissue tumors [7]. The radiographic characteristics of these lesions have been reported in descriptive terms in limited series [8, 9]; however, objective quantification of their imaging characteristics has not been performed. Dr. E. R. Henderson et al. studied a clinical series of patients with peripheral dedifferentiated chondrosarcomas aiming to define imaging criteria to facilitate better recognition of these uncommon tumors. The authors found that the imaging characteristics described for central dedifferentiated chondrosarcomas are similar to peripheral tumors. They observed mineralization in all tumors except one, a preexisting exostosis in half cases and corticomedullary continuity in only 7% of cases, and no difference on the incidence of mineralization or other characteristics based on tumor location. The authors suggest that peripheral mineralization with a bimorphic pattern on CT scan and the presence of a soft-tissue mass should be considered worrisome for a peripheral dedifferentiated chondrosarcoma, particularly in the setting of multiple hereditary exostoses.

Chondrosarcoma is the most common malignant tumor of the foot, followed by Ewing's sarcoma and osteosarcoma [10]. A relatively long delay in diagnosis has been reported for tumors of the foot. Additionally, foot sarcomas rarely develop metastases; this may be attributed to a less aggressive behavior of bone tumors at the foot compared to similar histologies in other sites of the skeleton [11–13]. Dr. M. Brotzmann et al. studied a series of patients with sarcomas of the foot. They confirmed previous reports that sarcomas in this location show a distinct biological behavior compared to the same tumor at other skeletal sites; foot sarcomas grow slower and are less aggressive than those at other anatomical locations. Interestingly, a delayed time to diagnosis is observed; however, the prognosis is similar to other locations.

The pediatric skeleton is unique because of the growing physes and the smaller bones that complicate reconstructions following tumor resection. Biological reconstructions are considered the goal standard in this age group [14, 15]. Dr. L. Bellanova et al. describe a technique to decrease the resection margins in the tibia, ensuring that the margins are adequate. They used rapid prototyping and manufactured a patient-specific instrument as a guide for tumor resection and a second for the bone allograft osteotomy to adjust the allograft to fit the resection gap accurately. Histological sections of the resected specimens showed tumor free margins. The presented technique may improve the surgical accuracy and patient safety in surgical oncology.

We congratulate the authors for their important contributions to this special issue. We believe that this issue will inform the readers on the recent developments in the surgical treatment of bone tumors and their impact on the quality of life of these patients and will enhance the literature on the management of patients with bone sarcomas.

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Clinical Study

Dedifferentiated Peripheral Chondrosarcoma: A Review of Radiologic Characteristics

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Introduction. Peripheral de-differentiated chondrosarcomas are among the rarest malignant mesenchymal tumors. This tumor's descriptive radiographic characteristics are reported but objective quantification does not exist. This investigation surveyed imaging of peripheral de-differentiated chondrosarcomas to facilitate better recognition of these uncommon tumors. *Methods.* Database interrogation for peripheral de-differentiated chondrosarcomas was performed; 23 patients were identified and imaging for 18 was reviewed. A musculoskeletal radiologist reviewed all studies for mineralization characteristics; presence of pre-existing osteochondromas; preserved corticomedullary continuity; adjacent cortical obliteration; soft-tissue mass; tumor necrosis; and presence of a cartilage cap. Tumor luminance was measured with computer software. *Results.* Mineralization was present in 17 tumors. Preexisting exostoses were evident in nine cases, corticomedullary continuity was preserved in three cases. There was no difference in mineralization or other characteristics based on tumor location. Mean tumor luminance was 94.9 candela/m^2. *Conclusions.* The imaging characteristics described for central de-differentiated chondrosarcomas are similar to the peripheral form of this tumor. Peripheral mineralization with a bimorphic pattern on CT scan and the presence of a soft-tissue mass should be considered worrisome for a peripheral de-differentiated chondrosarcoma, particularly in the setting of multiple hereditary exostoses.

1. Introduction

Dedifferentiated chondrosarcoma is an uncommon tumor that is known to arise from preexisting, low-grade cartilage lesions [1–5]. This tumor demonstrates bimorphic histology with a well-differentiated cartilaginous component and a dedifferentiated, noncartilaginous component [4]. These lesions comprise approximately 11% of chondrosarcomas and generally occur in association with a central chondrosarcoma [3]. Because of its cartilaginous origin, dedifferentiated chondrosarcoma may also occur in the setting of a preexisting exostosis; however, the occurrence is rare [6]. When single-institution, redundant reporting is considered, approximately 60 discrete cases of peripheral dedifferentiated chondrosarcoma have been reported in limited series with an emphasis on descriptive reporting of histologic subtypes and patient survival [3, 4, 6–18].

A consistent radiographic appearance of conventional, central dedifferentiated chondrosarcoma is recognized and described [19]; as a result radiologists and surgeons trained in musculoskeletal imaging are able to identify these lesions successfully. The typical radiographic description of a central dedifferentiated chondrosarcoma is a lesion that originates within bone with an area of cortical breach and subsequent soft-tissue mass demonstrating a bimorphic pattern with mineralized and unmineralized areas; pathologic fracture is common [19]. Unlike the more common, central lesions, peripheral dedifferentiated chondrosarcomas arise from preexisting exostoses or, extracortically, and may appear as

a peripheral chondrosarcoma without the features of its dedifferentiated counterpart [19].

Descriptive reporting of radiologic findings has been undertaken in some case reports and limited series; however, objective quantification of radiographic characteristics for peripheral dedifferentiated chondrosarcoma has not been performed. The varied descriptions of this tumor have included comparisons to a normal osteochondroma, a low-grade chondrosarcoma, and a conventional dedifferentiated chondrosarcoma [19, 20]. The purposes of this investigation were to quantify and describe the radiographic findings of a large series of patients with peripheral dedifferentiated chondrosarcomas to determine whether this tumor has a distinct, recognizable radiographic appearance.

2. Patients and Methods

After Investigational Review Board and Ethics Committee approvals were obtained, the senior investigator's institutional database was queried for patients treated between 1980 and 2012 with a diagnosis of peripheral dedifferentiated chondrosarcoma; 23 patients were identified. Five patients were encountered only in consultation, and no imaging studies were available, leaving 18 patients for consideration.

The mean age of the patients at the time of operation was 46.4 years (range from 22.9 to 70.0 years). There were 13 men and five women. Nine patients' tumors arose from an exostosis in the setting of multiple hereditary exostoses (MHE), eight lesions arose from a preexisting solitary exostosis, and one lesion arose peripherally without an exostosis. The cartilaginous component of the tumors was chondrosarcoma in all patients. The histologic subtype of the dedifferentiated, noncartilaginous component was malignant fibrous histiocytoma-like (MFH) in 11 patients, osteosarcoma-like in five patients, and spindle-cell sarcoma-like in two patients. There was one lesion of the sternum, two of the scapula, three of the humerus, five of the pelvis, four of the femur, two of the tibia, and one of the fibula.

Preoperative imaging studies of the lesion included plain radiographs alone for five patients; a computed tomography (CT) scan alone for one patient; plain radiographs and CT for eight patients; and plain radiographs, CT, and magnetic resonance imaging (MRI) for four patients. An attending-level musculoskeletal radiologist evaluated all imaging studies. Plain radiographs were assessed for the presence of mineralization, whether mineralization appeared to encompass greater or less than 50% of the tumor area, a bimorphic pattern of mineralization, the presence of a soft-tissue mass, evidence of a preexisting exostosis, evidence of preserved corticomedullary continuity when an exostosis was present, extracompartmental extension, and erosion of the adjacent cortex. CT and MRI scans were assessed for the presence of mineralization, whether mineralization was central, peripheral, or both; a bimorphic pattern of mineralization; the presence of a soft-tissue mass; evidence of a preexisting exostosis; preserved corticomedullary continuity; extracompartmental extension; erosion of the adjacent cortex; the presence and thickness of a cartilage cap, and necrosis.

Tumor luminance was measured in an effort to objectively quantify tumor mineralization content on plain radiographs. Luminance is a measurement of brightness with units of candela per square meter; it is measured on a scale of zero, or completely black, to 255, or completely white. Luminance has been used in previous investigations to measure trabecular and soft-tissue density with both radiography and ultrasound [21, 22]. Radiographs intended for analysis were displayed on a conventional light box (Dupix, Milano, Italy) and photographed with a 12-megapixel digital camera at 50 cm range (Canon A1100IS, Canon USA, Lake Success, NY, USA). Digital images were saved as Joint Photographic Experts Group (JPEG) files without compression and were opened with GNU Image Manipulation Program version 2.8 (GIMP Developers, Groton, MA, USA). The manual selection tool was used to trace the periphery of the tumor, and the histogram function was used to measure the mean luminance of the tumor. The selection was then inverted to measure the mean luminance of the surrounding soft tissues. Luminance of the soft tissues was subtracted from tumor luminance to yield a measurement of net tumor luminance. These numbers were recorded in a spreadsheet (Microsoft Excel for Mac 2011, Microsoft Inc., Redmond, WA, USA). Means were compared statistically with the Student's t test.

3. Results

Plain radiographs revealed mineralization was seen in 16 of 17 cases; in eight cases it appeared to be bimorphic (Table 1). Mineralization appeared to occupy more than half of the tumor area in 10 patients and less than half in six patients. A soft-tissue mass was seen in 14 of 17 cases. Preexisting exostoses at the tumors' origin could be identified in eight of 17 cases; corticomedullary continuity appeared to be preserved in three cases. Thirteen cases showed evidence of adjacent cortical erosion. No patients had a pathologic fracture.

Dedifferentiated, noncartilaginous histologic subtypes of patients in this series included 11 with MFH-like components, five with osteosarcoma-like components, and two patients with a spindle-cell sarcoma-like components. Mineralization was seen in 10 of 11 patients with MFH-like tumors, and in all patients with osteosarcoma-like and spindle-cell-like tumors, there was no statistical difference between groups (Table 1).

There were eight axial lesions, seven of which demonstrated mineralization. All appendicular lesions showed mineralization. There was no difference in the occurrence of mineralization when results were divided by tumor location (Table 2).

Computed tomography demonstrated mineralization in 12 of 13 scans, it was thought to be bimorphic in 11 cases. The only CT to not demonstrate mineralization was the case which did not show mineralization on plain radiographs. Cross-sectional imaging showed the mineralization to be peripheral-only in four cases and central and peripheral in eight cases; there were no cases of central-only mineralization. A soft-tissue mass was identified in all 13 CT scans. A preexisting exostosis was seen in six CT scans; four of these

Table 1: Plain radiograph findings by histologic subtype.

	Mineralization				Soft-tissue mass			Exostosis		Tumor luminance
	Present	<50%	>50%	Bimorphic	Present	Extracompartmental	Cortical obliteration	Present	Corticomedullary continuity	
MFH-like subtype	9	2	7	4	10	10	8	7	1	103.9
OSA-like subtype	5	3	2	3	5	5	4	3	2	90.4
SCS-like subtype	2	1	1	1	2	2	1	1	0	67.6

Abbreviations: malignant fibrous histiocytoma (MFH); osteosarcoma (OSA); spindle-cell sarcoma (SCS).

Table 2: Plain radiograph findings by tumor location.

	Mineralization				Soft-tissue mass			Exostosis		Tumor luminance
	Present	<50%	>50%	Bimorphic	Present	Extracompartmental	Cortical obliteration	Present	Corticomedullary continuity	
Axial	6	2	4	5	7	7	8	5	2	93.2
Appendicular	10	4	6	3	10	10	5	6	1	95.8

Abbreviations: malignant fibrous histiocytoma (MFH); osteosarcoma (OSA); spindle-cell sarcoma (SCS).

Table 3: CT findings by histologic subtype.

	Mineralization				Soft-tissue mass				Exostosis		
	Present	Peripheral	Central	Bimorphic	Present	Extracompartmental	Cortical obliteration	Necrosis	Present	Corticomedullary continuity	Cartilage cap
MFH-like subtype	6	6	2	6	7	7	7	2	2	1	1
OSA-like subtype	4	4	2	3	4	4	3	1	3	2	1
SCS-like subtype	2	2	2	2	2	2	1	0	1	0	1

Abbreviations: malignant fibrous histiocytoma (MFH); osteosarcoma (OSA); spindle-cell sarcoma (SCS).

exostoses were identified on the corresponding plain radiographs, and two were not identified on plain radiographs. Corticomedullary continuity was preserved in three cases with identifiable exostoses. Central necrosis was identified in three CT and MRI studies performed with contrast. A cartilage cap was identified in three lesions. There was no difference when results were divided by histologic subtype or tumor location (Tables 3 and 4).

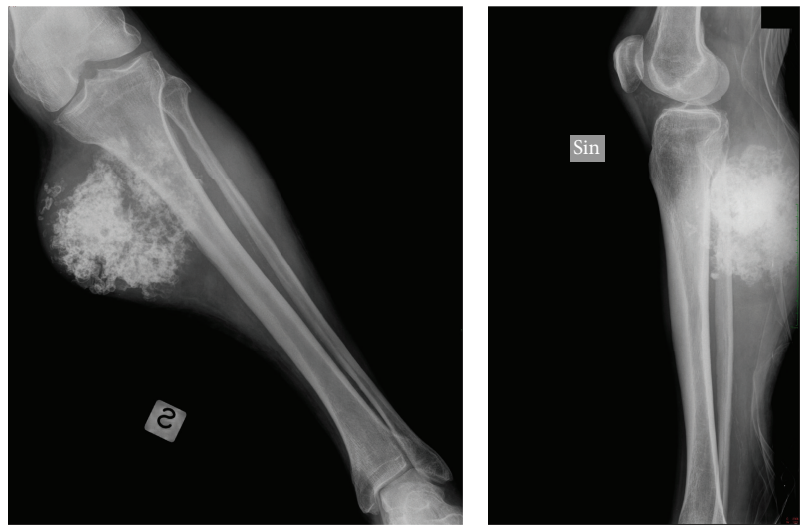
Tumor luminance was measured on plain radiographs in 14 cases. Mean tumor luminance without soft-tissue subtraction was 138.7 candela/m^2 (range, 70.5 to 201.2). Mean adjacent soft-tissue luminance was 43.8 candela/m^2 (range from 11.1 to 140.0); therefore mean luminance for the tumors alone was 94.9 candela/m^2 (range from 59.4 to 129.0), indicating that tumor opacity on radiographs was approximately 37%. When compared by histological subtype, MFH-like and OSA-like tumor luminance showed no statistical difference ($P = 0.49$). When spindle cell-like tumors were compared to MFH-like and OSA-like, the difference approached significance ($P = 0.14$), however, limited patient numbers precluded robust statistical analysis (Table 1).

4. Discussion

Anderson and coauthors reported the earliest description of a peripheral dedifferentiated chondrosarcoma and noted that its radiographic characteristics were consistent with osteochondroma [20]. Since that time small series of peripheral dedifferentiated chondrosarcomas have been published with descriptive accounts of this tumor's radiographic appearance but without objective quantification of findings. The present study demonstrates that mineralization is present in the majority of peripheral dedifferentiated chondrosarcomas (Figure 1). Mineralization patterns, best visualized with CT scan, are usually central and peripheral or peripheral-only (Figure 2). A bimorphic mineralization pattern was demonstrated more reliably with CT than plain radiographs; however,

Table 4: CT findings by tumor location.

	Mineralization				Soft-tissue mass				Exostosis		
	Present	Peripheral	Central	Bimorphic	Present	Extracompartmental	Cortical obliteration	Necrosis	Present	Corticomedullary continuity	Cartilage cap
Axial	6	6	5	5	7	7	7	2	2	2	2
Appendicular	6	6	3	6	6	6	4	1	4	1	1



(a) (b)

Figure 1: (a) AP and (b) lateral radiographs of tibia and fibula demonstrating a peripheral dedifferentiated chondrosarcoma with mineralization and a soft-tissue mass.

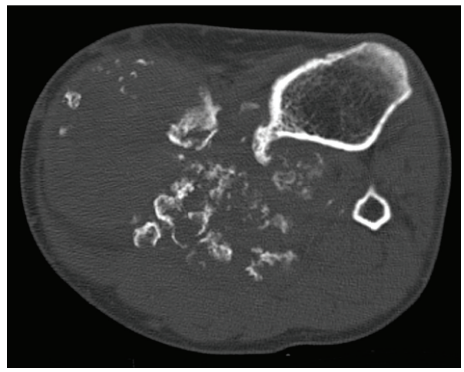
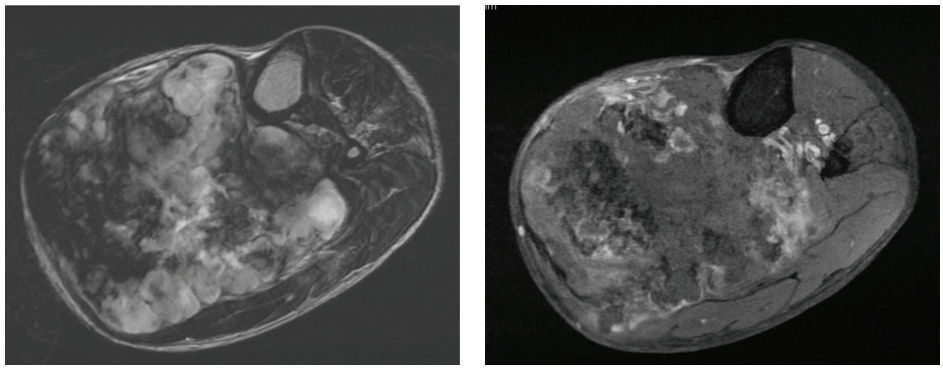


Figure 2: Axial CT scan of tibia and fibula demonstrating a peripheral dedifferentiated chondrosarcoma with central and peripheral, bimorphic mineralization, destruction of the prior exostosis, and a soft-tissue mass.

it cannot be relied upon as a definite indicator of tumor dedifferentiation. Obliterations of the preexisting exostosis or adjacent cortex are common findings; however, the presence of a soft-tissue mass on CT or MRI was the most consistent radiographic feature associated with peripheral dedifferentiated chondrosarcomas (Figure 3).

The radiographic characteristics of conventional, central chondrosarcomas are known and include deep endosteal scalloping, cortical destruction, and a soft-tissue mass [23]. Garrison and coauthors were the first to describe a large series of secondary chondrosarcomas arising from osteochondromas. Radiographic features consistent with malignant degeneration included an indistinct superficial border, the presence of a partially mineralized soft-tissue mass, and frequent destruction of the underlying osteochondroma [13]. Wuisman and coauthors mentioned only blurring of the bone borders as an indicator of malignant transformation [24]. Ahmed and coauthors, in a series of 107 patients with secondary chondrosarcomas arising from exostoses, documented irregular margins, heterogeneous mineralization, and a soft-tissue mass as positive indicators of malignant change in an osteochondroma [25]. Altay and coauthors reported a series of 32 patients with malignant degeneration of an osteochondroma but did not comment on radiological features [26].

Mercuri and coauthors reported that the imaging characteristics of central dedifferentiated chondrosarcoma depended on the preexisting cartilage tumor [19]. They noted that when the noncartilaginous component was small, the imaging findings often reflected a conventional chondrosarcoma. When the dedifferentiated, noncartilaginous component was larger, however, the tumor often demonstrated no discernible radiographic characteristics of a cartilaginous neoplasm. The two features they found most commonly on plain radiographs were permeative osteolysis and a soft-tissue



(a) (b)

Figure 3: Axial MRI scan of tibia and fibula demonstrating a peripheral dedifferentiated chondrosarcoma with soft-tissue mass and heterogeneous T2 weighted (a) and T1 weighted with contrast (b) enhancement.

mass. The largest series to address radiographic features of central dedifferentiated chondrosarcomas was published by Littrell and coauthors [16]. The authors reported cortical destruction, chondroid matrix, soft-tissue mass, and tumor bimorphism were the most common findings associated with these tumors; as in the present study, CT was more sensitive in detecting the mineralized component as well as demonstrating bimorphism. Radiographic characteristics described by Johnson and coauthors included a lytic lesion with cortical destruction and a soft-tissue mass [27].

Several case series of dedifferentiated chondrosarcoma have included mixed reporting of central and peripheral tumors. Discrete accounts of radiologic features for peripheral dedifferentiated chondrosarcoma include few case reports and limited case series. Cortical destruction was the first described harbinger of de-differentiation [17]. Bertoni and coauthors published the earliest series of peripheral dedifferentiated chondrosarcomas and described a preexisting osteochondroma, cortical destruction, and a soft-tissue mass as consistent findings among all tumors [6]. Staals and coauthors described the largest series of peripheral dedifferentiated chondrosarcomas. Radiographs of all patients demonstrated indistinct borders, heterogeneous mineralization, and a soft-tissue mass [7]. Bimorphic mineralization was noted in half of their patients and, similar to the current study, was more evident with CT than plain radiographs.

The current investigation confirms that the primary radiologic features of central dedifferentiated chondrosarcoma, soft-tissue mass, heterogeneous mineralization, and bimorphism are similar to the less common peripheral lesion morphology (Figure 1). Secondary features of central tumors including intramedullary mineralization with an extramedullary, radiolucent soft-tissue mass and pathologic fracture [19] are uncommon with peripheral lesions, likely due to the origin of the lesion outside of the medullary space.

Over one-half of the cases in the current series showed an MFH-like histologic morphology. This finding diverges from the largest reports of central dedifferentiated chondrosarcoma where MFH-like features comprised from 4% to 22% of the total cases, and osteosarcoma-like characteristics usually dominate [2, 3, 16, 28]. Other reports have documented a rate of MFH-like histologic subtypes greater than 50% in the peripheral form of dedifferentiated chondrosarcoma, indicating that the peripheral form may have a predilection for this morphology [7, 12, 15].

This investigation has limitations that warrant discussion. Our study details the radiologic findings of eighteen patients treated over a 33-year interval, during which imaging technology changed substantially, creating a heterogeneous mix of radiographic studies. While our case number is small and underpowered to truly ascertain statistical differences in the radiographic appearances of these rare lesions, this study represents the largest and only investigation dedicated to peripheral dedifferentiated chondrosarcoma imaging, and we believe that the results justify reporting. Measurement of tumor luminance in this investigation was an attempt to quantify tumor opacity, and therefore its mineralized content is relative to the surrounding soft tissues. Further investigations correlating this technique with quantitative CT are required to determine its usefulness and validate the results; however, the authors believe that it may prove a useful technique for quantitifying mineralization in the absence of advanced, three-dimensional imaging. The authors acknowledge that luminance in isolation does not provide radiologists and surgeons with objective criteria for ruling peripheral dedifferentiated chondrosarcoma in or out as a diagnosis; however, it does provide an objective starting point for comparison to other tumors that could lead to such parameters.

5. Conclusion

In general the imaging characteristics described for central dedifferentiated chondrosarcomas are applicable to the peripheral form of this tumor. Peripheral mineralization with a bimorphic pattern on CT scan and the presence of a soft-tissue mass should be considered worrisome for a peripheral dedifferentiated chondrosarcoma, particularly in the setting of multiple hereditary exostoses.

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Research Article

Do Malignant Bone Tumors of the Foot Have a Different Biological Behavior than Sarcomas at Other Skeletal Sites?

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We analyze the delay in diagnosis and tumor size of malignant bone tumors of the foot in a retrospective study. We compared the oncological and surgical long-term results with identical tumor at other anatomical sites in order to analyze the biological behavior of sarcomas that are found in the foot. Thirty-two patients with a histologically proven malignant bone tumor (fifteen chondrosarcomas, nine osteosarcomas, and eight Ewing sarcomas) between the years 1969 and 2008 were included. The median follow-up was 11.9 years. The overall median time gap between the beginning of symptoms and diagnosis in the study group was 10 months. Ewing sarcoma presented with the longest delay in diagnosis (median of 18 months), followed by osteosarcoma (median of 15 months) and chondrosarcoma (median of 7.5 months). The delay in diagnosis of these tumors was significantly longer than that of equivalent tumors at other skeletal sites, but the 5- and 10-year survival rates and the occurrence of distant metastases were comparable. In contrast, the average size of foot tumors was 5- to 30-fold less than that of tumors analyzed at other skeletal sites. This study indicates that sarcomas of the foot demonstrate a distinct biological behavior compared to the same tumor types at other skeletal sites.

1. Introduction

Bone tumors of the foot are rare and represent only 3%–6% of all bone tumors [1–5]. They are benign in 75%–85% of cases and malignant in 15%–25% [2, 5, 6]. The bone most commonly affected is the calcaneus, followed by metatarsal and phalangeal bones [1, 7]. Chondrosarcoma is the most frequent malignant tumor of the foot, followed by Ewing sarcoma and osteosarcoma [1, 2]. Although there is no thick soft tissue layer to potentially cover a developing mass, a relatively long delay in diagnosis has been reported for such tumors [8]. However, despite a high rate of misdiagnoses, which may lead to incorrect first-line treatment, foot sarcomas rarely develop metastases [5, 9]. It was hypothesized that this might be due to a less aggressive behavior of bone tumors at the foot compared to other sites of the skeletal system [7, 9].

Although amputation of the foot is hardly an acceptable surgical solution for many patients with sarcomas, the resection margins commonly contain residual tumor tissue after initial excision and biological reconstruction. The desire to make a functionally optimal reconstruction and the complexity of this anatomical region can easily lead to an inadequate resection. Wide surgical margins, however, are an important factor for the oncological outcome of malignant bone tumors [9, 10].

The aim of this retrospective study was to evaluate the delay in diagnosis, the tumor size, and the long-term survival rate of patients with malignant bone tumors of the foot. To our knowledge, there is a lack of information regarding these factors in the literature. The results were compared with data from equivalent tumors in the literature both at the foot and also at other skeletal sites.

2. Materials and Methods

After approval of the local ethical committee (Reference no. EK 143/08), we retrieved records of 32 patients diagnosed between 1969 and 2008 with a primary bone tumor of the foot from the database of the Bone Tumor Reference Center

(BTRC) in Basel. The dataset included age, gender, histology, grade, anatomical site, size (volume) of the tumor, metastases, recurrence, and treatment modalities. In order to obtain detailed information on the chronology of symptoms and patient survival rate, a questionnaire was sent to the patients' general physicians. All patient data are provided in Table 1.

We distinguished between low- (G1) and high-grade (G2 + G3) sarcomas, and all diagnoses were confirmed by a reference pathologist. The tumor volume was calculated roughly respecting its geometrical shape (ellipsoidal or cylindrical) from plain X-rays and computed tomography (CT)/magnetic resonance imaging (MRI) scans, depending on the tumor configuration and presence/absence of a soft tissue component. The interval between diagnosis and the events local recurrence-free survival (LRFS) and metastasis-free survival (MFS) were calculated. Delay in diagnosis was defined as the time period between the first clinical symptoms and the diagnosis, which was based on histology after biopsy.

Adequate treatment of high-grade tumors was considered to be bioptic diagnosis followed by neoadjuvant chemotherapy (in cases of Ewing sarcoma and osteosarcoma) and wide or radical resection (for all kinds of sarcomas). Intralesional resections were considered to be inadequate treatment in all cases. Surgical procedures were classified as radical, wide, marginal, and intralesional, according to Enneking's classification [10].

Data analysis was performed using SPSS 11.5 software (SPSS Inc., Chicago, IL, USA). Data description was primarily based on median and quartile values for continuous endpoints. Binary endpoints were characterized by frequencies. Interindividual comparisons between patient subgroups were based on the two-sample Wilcoxon test for continuous endpoints and Fisher's exact test for binary endpoints. Survival analysis was based on the Kaplan-Meier method and Logrank test. In addition to the overall survival rate (OS), LRFS and MFS were calculated as a function of various clinical parameters. P values < 0.05 were considered statistically significant.

3. Results

3.1. Delay in Diagnosis. The overall median delay in diagnosis of our cases was 10 months (IQR 3–18 months, range 3–128 months). Ewing sarcoma showed the longest delay between onset of symptoms and diagnosis (Table 2). Patients with a delay in diagnosis of >12 months and <12 months did not show a significant difference in the 5-year (86% versus 74%) and 10-year (63% versus 54%) survival rates ($P = 0.24$).

The rate of metastasis when correlated to a delay in diagnosis of >6 or <6 months and >12 or <12 months revealed no significant influence of the delay in diagnosis on the occurrence of subsequent metastasis ($P = 0.69$ for 6 months and 0.44 for 12 months).

3.2. Tumor Size, Survival Rate, and Treatment

3.2.1. Chondrosarcoma. The median size of the low-grade chondrosarcomas of the foot was 3.1 mL (IQR 2.0–4.5 mL, range 1.2–158 mL), and all patients with low-grade chondrosarcomas ($n = 9$) were alive at last follow-up. The 5- and 10-year survival rates of these patients were 100% and 86%, respectively (Table 3).

High-grade chondrosarcomas ($n = 6$) had a median size of 16.7 mL (IQR 4–18, range 0.9–45) and showed a 66% ($n = 4$) patient overall survival rate. The 5- and 10-year survival rates of these patients were 83% and 66%, respectively. Patients with chondrosarcomas undergoing radical surgery had significantly better 5- and 10-year survival rates than patients undergoing other surgical treatments ($P < 0.01$).

Two patients with high-grade chondrosarcoma treated with intralesional resection had local recurrences and subsequently amputation in both cases. Both patients died of metastatic disease.

3.2.2. Ewing Sarcoma. The overall survival in patients with Ewing sarcoma was 37.5%, including two patients with no evidence of disease (NED) and one patient alive with disease (AWD). The median size was 14.4 mL (IQR 4.5–36, range 0.9–60). The 5- and 10-year survival rates were 71% and 28%, respectively (Table 3). All patients ($n = 8$) were treated with neoadjuvant chemotherapy according to the current protocols.

Two patients with Ewing sarcoma presented with metastases at the time of diagnosis. In one patient, chemotherapy and surgical treatment of the metastases were successful. The second patient developed recurrent metastases after 55 months, received radiotherapy, and died 2 months later.

The remaining six patients developed distant metastases after a median of 42 months (range 8–70). One patient died 2 months after occurrence of systemic spread without further treatment. Three patients were treated with chemotherapy and the remaining two with radiotherapy following surgery. Five of these six patients died after a median of 8 months (range 2–30). The one surviving patient was treated by resection of the lung metastases and additional chemotherapy.

There were two local recurrences, one of which appeared after a marginal and the second after a radical resection. These patients were treated with amputation or radiotherapy, and both died of metastatic disease.

3.2.3. Osteosarcoma. The overall survival rate of patients with low-grade osteosarcoma ($n = 4$) was 75%, and the median tumor size was 50 mL (IQR 8–101, range 2.5–134). Both 5- and 10-year survival rates of these patients were 67% (Table 3). The only nonsurvivor of this group developed metastatic disease after 7 months and died 19 months later.

The median size of high-grade osteosarcomas of the foot ($n = 5$) was 14.4 mL (IQR 4.5–36, range 3–280). The overall survival rate was 40%, with 5- and 10-year survival rates of 80% and 60%, respectively.

None of the patients with osteosarcoma presented with metastases at the time of diagnosis. After a median of 39 months (IQR 15.3–60, range 4–63), a total of five patients developed distant metastases. In three cases, local surgery was performed, and in the remaining cases, chemotherapy was applied. Only one patient treated surgically was still

Table 1: Patient data.

ID number/ gender	Tumor	Grading G1–G3[1]	Age[2]	Tumor size[3] (volume[4])	Tumor site	Primary metastasis	Late metastasis time[5]	Delay in diagnosis[5]	Operative treatment[6]	Recurrence/ time[5]	Survival time[2]	Follow-up[2]	Adequate therapy	Status[7]
1/♀	Chondrosarcoma	G 1	59.5	1.5 × 2.0 × 1.0 (3.0)	Calcaneus	No	No	6.0	4	No	13.91	13.91	No	NED
2/♀	Chondrosarcoma	G 2	72.6	4.0 × 1.0 × 1.0 (4.0)	Phalanx Dig. IV	No	No	Unknown	1	No	15.58	15.58	Yes	DOC
3/♂	Chondrosarcoma	G 1	72.9	3.4 × 3.0 × 4.0 (40.8)	Calcaneus	No	No	1.0	4	No	9	9	No	DOC
4/♀	Chondrosarcoma	G 1	52.3	1.5 × 1.0 × 1.0 (1.5)	Phalanx Dig. III	No	No	Unknown	1	No	8.58	8.58	Yes	NED
5/♂	Chondrosarcoma	G 2	22.0	1.2 × 0.8 × 1.0 (0.9)	Phalanx Dig. II	No	No	3.0	1	No	12.25	12.25	Yes	NED
6/♂	Chondrosarcoma	G 1	66.7	1.8 × 1.4 × 1.2 (3.0)	Dig. V	No	No	128.0	1	No	18.25	18.25	Yes	NED
7/♀	Chondrosarcoma	G 1	36.4	2.0 × 1.6 × 1.0 (3.2)	Os metatarsale II	No	No	10.0	1	No	8.83	8.83	Yes	NED
8/♂	Chondrosarcoma	G 1	66.7	6.5 × 6.1 × 4.0 (158.0)	Calcaneus	No	No	9.0	3	No	11.91	11.91	Yes	NED
9/♀	Chondrosarcoma	G 1	39.5	2.0 × 1.5 × 1.5 (4.5)	Phalanx Dig. I	No	No	5.0	1	No	26.33	26.33	Yes	NED
10/♂	Chondrosarcoma	G 2	62.5	Unknown	Calcaneus	Yes	No	10.00	4	Yes/8	6.91	—	No	DOD
11/♀	Chondrosarcoma	G 2	67.6	3.0 × 6.0 × 1.0 (18.0)	Os metatarsale II	No	No	13.0	1	No	8.66	8.66	Yes	NED
12/♂	Chondrosarcoma	G 1	28.1	2.0 × 1.0 × 1.0 (2.0)	Phalanx Dig. III	No	No	1.0	1	No	13.83	13.83	Yes	NED
13/♂	Chondrosarcoma	G 2	20.0	2.5 × 2.5 × 2.7 (16.7)	Phalanx Dig. III	No	No	Unknown	1	No	7.41	7.41	Yes	NED
14/♂	Chondrosarcoma	G 3	68.9	3.0 × 5.0 × 3.0 (45.0)	Calcaneus	Yes	Yes/3	9.0	4	Yes/4	0.5	—	No	DOD
15/♂	Chondrosarcoma	G 1	29.4	1.2 × 1.0 × 1.0 (1.2)	Phalanx Dig. III	No	No	1.0	1	No	20.83	20.83	Yes	NED
16/♀	Osteosarcoma (central chondroblastic)	G 2	39.4	4.0 × 1.8 × 2.0 (14.4)	Os metatarsale IV	No	Yes/63	1.0	1	No	11.5	11.5	Yes	NED
17/♀	Osteosarcoma (parosteal)	G 2	69.3	3.0 × 1.0 × 1.0 (3.0)	Os metatarsale I	No	Yes/4	4.0	1	No	2.6	—	Yes	DOD
18/♂	Osteosarcoma (parosteal)	G 1	43.3	4.0 × 2.5 × 1.0 (10.0)	Os metatarsale I	No	No	9.0	2	No	2.0	2.0	Yes	NED
19/♀	Osteosarcoma (central)	G 1	22.8	8.0 × 4.2 × 4.0 (134.0)	Calcaneus	No	No	16.0	4	Yes/6	17.58	17.58	No	NED
20/♂	Osteosarcoma	G3	49.8	3.0 × 3.0 × 4.0 (36.0)	Phalanx Dig. I	No	Yes/59	18.0	1	No	25.00	—	No	DOD

Table 1: Continued.

ID number/ gender	Tumor	Grading G1–G3[1]	Age[2]	Tumor size[3] (volume[4])	Tumor site	Primary metastasis	Late metastasis time[5]	Delay in diagnosis[5]	Operative treatment[6]	Recurrence/ time[5]	Survival time[2]	Follow-up[2]	Adequate therapy	Status[7]
21/♀	Osteosarcoma (central)	G 1	57.5	6.0 × 6.0 × 2.5 (90.0)	Talus	No	Yes/7	19.0	1	No	2.33	—	Yes	DOD
22/♀	Osteosarcoma	G 3	14.8	7.0 × 8.0 × 5.0 (280.0)	Os metatarsale I	No	No	15.0	1	No	10.08	10.08	Yes	NED
23/♀	Osteosarcoma	G 2-3	45.1	3.0 × 1.5 × 1.0 (4.5)	Phalanx Dig. I	No	Yes/19	2.0	1	No	6.08	—	Yes	DOD
24/♀	Osteosarcoma (central)	G 1	47.0	2.5 × 1.0 × 1.0 (2.5)	Os metatarsale II	No	No	23.0	1	No	8.5	8.5	Yes	NED
25/♂	Ewing sarcoma	G 3	19.0	3.5 × 3.5 × 1.0 (12.3)	Calcaneus	No	Yes/8	Unknown	1	Yes/ unknown	2.58	—	Yes	DOD
26/♂	Ewing sarcoma	G 3	11.4	4.0 × 3.5 × 3.2 (45.0)	Calcaneus rechts	No	No	5.0	4	No	18.25	18.25	No	NED
27/♀	Ewing sarcoma	G 3	16.8	4.0 × 1.2 × 1.0 (4.8)	Os metatarsale III	No	Yes/70	11.0	1	No	6.41	—	No	DOD
28/♂	Ewing sarcoma	G 3	9.8	1.2 × 0.8 × 1.0 (0.9)	Os metatarsale I	Yes	No	34.0	2	No	11.91	11.91	Yes	NED
29/♂	Ewing sarcoma	G 3	18.8	4.0 × 1.5 × 1.5 (9.0)	Os metatarsale IV	Yes	Yes/55	24.0	3	Yes/48	4.25	—	No	DOD
30/♂	Ewing sarcoma	G 3	11.6	5.0 × 3.0 × 4.0 (60.0)	Os metatarsale I	No	Yes/49	3	1	No	5.91	—	Yes	DOD
31/♂	Ewing sarcoma	G 3	51.7	3.0 × 4.0 × 4.0 (48.0)	Os metatarsale IV	No	Yes/36	26.0	1	No	5.5	—	Yes	DOD
32/♀	Ewing sarcoma	G 3	17.7	4.3 × 2.9 × 1.9 (24.0)	Calcaneus	No	Yes/15	18.0	1	No	3.0	3.0	Yes	AWD

[1]Low grade = Gl; high grade = G2/G3; [2]age in years; [3]size in cm; [4]volume in mL; [5]in months; [6]radical = 1; wide = 2; marginal = 3; intralesional = 4; [7]DOC: death of other cause; DOD: death of disease; AWD: alive with disease; NED: no evidence of disease.

Table 2: Delay in diagnosis at the foot (the present study) and at the other sites (the literature).

Diagnosis	Time of delay in diagnosis (in months)	
	Median results of the present study	Average results from other sites in the literature
Chondrosarcoma	7.5 (IQR 1.5–12.2, range 1–128)	10 (G1-G2) 5 (G3) [25]
Osteosarcoma	15 (IQR 3–18.5, range 1–23)	3.5 [17] 5.2 [30] 6.4 [11]
Ewing sarcoma	18 (IQR 5–26, range 3–34)	8.5 [12] 9.6 [11] 8.1 [30] 3–9 [13]

Abbreviations used: IQR–interquartile range. The superscripts listed in the last column of the table refer to references.

Table 3: Five- and 10-year survival rates of sarcomas of the foot compared with rates at other skeletal sites.

Diagnosis		Results of the present study		Results from other sites in the literature	
	Grading	5-year survival rate	10-year survival rate	5-year survival rate	10-year survival rate
Chondrosarcoma	G1 ($n = 9$)	100%	86%	89%–96% [25, 31]	89% [25]
	G2/G3 ($n = 6$)	83%	66%	53%–62% [25, 31]	38%–53% [25]
Osteosarcoma	G1 ($n = 4$)	67%	67%	66% [32]	—
	G2/G3 ($n = 5$)	80%	60%	60%–80% [26, 31]	20%–49% [26, 31]
Ewing sarcoma	G3 ($n = 9$)	71%	28%	50%–70% [19, 27, 31]	20%–50% [19, 27, 31]

The superscripts listed in the last two columns of the table refer to references.

alive after follow-up of 11.5 years, and the other patients died from metastatic disease. All osteosarcoma patients without metastases were still alive at the time of the latest follow-up.

One patient with low-grade osteosarcoma developed local recurrence after an intralesional resection and was further treated with amputation. The patient refused to undergo the recommended chemotherapy. The patient is still alive without significant impairment of his daily activities.

3.3. Local Recurrence. Patients treated with radical resection ($n = 22$) had better 5- and 10-year survival rates compared to those treated with local resection ($n = 10$): 87% versus 72% and 63% versus 49% ($P = 0.62$).

Local recurrence was found in five patients (15.6%) after a median of 8 months (IQR 5.5–18, range 4–48). We found one local recurrence in the group treated with radical resection (Ewing sarcoma). Local recurrence was associated with an adverse outcome and showed a statistically significant influence on 5- (40% versus 90%) and 10-year (20% versus 68%) survival rates ($P = 0.043$).

Four of five patients with local recurrence received inadequate prior treatment. In only one case, a local recurrence occurred despite adequate therapy. Three patients developed subsequent distant metastases.

3.4. Overall Treatment. Twenty-three patients (72%) underwent adequate treatment. Of the nine patients receiving inadequate therapy, 7 received insufficient local resection (intralesional/marginal resection). The latter comprised 2 low-grade chondrosarcomas and 5 high-grade sarcomas (2 chondrosarcoma, 1 osteosarcoma, and 2 Ewing sarcomas). One patient with osteosarcoma refused to undergo chemotherapy, and one patient with Ewing sarcoma had an inadequate neoadjuvant chemotherapy.

3.5. Metastases. Twelve patients developed distant metastases after a median of 27.5 months (IQR 13–51.3, range 3–70). Four patients presented with metastases already at the time of diagnosis ($P = 0.039$). Patients with metastases at the time of diagnosis had worse 5- and 10-year survival rates (40% and 20%) than those without (89% and 65%). Patients with late metastases had a significantly lower survival rate compared to patients without metastases (58% versus 100% after 5 years and 17% versus 88% after 10 years; $P = 0.01$).

4. Discussion

In the recent years, we have observed several patients with malignant bone tumors of the foot with a long delay in diagnosis. In this study, we wanted to elucidate whether such a delay may reflect characteristic biological differences between bone sarcomas of the foot and their counterparts at other skeletal sites. To our knowledge, there is only one study in the literature reporting on the delay in treatment of tumors of the foot but not in comparison to tumors at other sites of the skeletal system [1].

Because the foot has only a thin soft tissue envelope, one would suspect swelling caused by a tumor to lead to an immediate clinical recognition. However, we observed a long overall delay in diagnosis in the foot, especially in high-grade tumors.

Ewing sarcomas, which usually are rapidly and aggressively growing lesions, showed the longest delays (median of 18 months). This is 2–6 times longer than delays in Ewing sarcomas located at other sites of the skeleton [2, 11–13]. These findings are consistent with Adkins et al. [14] and Metcalfe and Grimer [15] reporting on a delay of 11,75 and 14 months. In addition, the sizes of sarcomas in our patients were considerably smaller than those at other sites.

Delays seen in diagnosis of osteosarcomas in our study (median of 15 months), as with Ewing sarcomas, were considerably longer (4.5- to 14-fold) than reported for osteosarcomas at other sites [2, 11, 12, 16, 17]. Likewise, the volume of these tumors was much smaller than reported for tumors at other sites.

In contrast to Ewing sarcomas, the more slowly growing chondrosarcomas showed the shortest median delay in diagnosis with 7.5 months. This is almost comparable to the delay in diagnosis of chondrosarcomas at sites other than the foot.

Several authors argue that the rarity of bone tumors in this special anatomical location is a major cause for the long delay in diagnosis of bone tumors of the foot [8, 9, 18]. In our opinion, this argument is not very convincing, since bone tumors are rare anyway. First symptoms as pain and swelling are unspecific and frequently misinterpreted as being of inflammatory or posttraumatic nature. The variety of differential diagnoses explains the long delay in diagnosis of bone tumors in general but not the striking difference between tumors of the foot and those at other skeletal sites.

Zeytoonjian et al. [9] tumors found a death rate of 8% in primary malignant bone tumors of the foot compared to 27% in tumors in other anatomical locations.

In this study, the death rate (34%) was higher but in the same range of sarcomas at other sites. However, despite the higher death rate, the long delay, and a relatively large proportion of cases with inadequate treatment, the OS is not significantly worse. It has been assumed that primary malignant bone tumors of the foot may have less deleterious effects than those located at other sites, but this is not completely understood [1, 3, 4, 9, 19]. Results of our study indicate that these tumors in foot may have certain basic biological differences from those at other sites.

The delay in diagnosis of primary malignant bone tumors of the foot is—especially for high-grade tumors—considerably longer than that at other sites (Table 2). In contrast, the average volume is tumors significantly smaller than reported for other sites (Table 4). For chondrosarcomas localized in the rest of the skeleton, the size is 20–30-fold, for osteosarcomas 3–10-fold, and for Ewing sarcomas 5-6-fold higher according to the literature [20–24]. The difference is even more striking if the time of development is taken into consideration. Based on these assumptions, a rough calculation of 12-month tumor development in chondrosarcomas would, for example, result in a tumor volume of 30 mL at the foot and of 800 mL at other sites. Although the evidence of such estimations is not very strong, the difference is so obvious that it allows the assumption that tumors of the foot exhibit a different biological behavior and grow much slower. This could explain the long delays in diagnosis. The survival rate of malignant bone tumors of the foot is affected by metastases at the time of diagnosis, the occurrence of distant metastasis, and local recurrence of the primary tumor. In these respects, sarcomas in the foot do not differ from those at other sites. Such factors normally significantly worsen the prognosis, but this was not found in our study. However, the long delay in diagnosis found in this study did not correlate with a higher rate of primary metastases.

The risk of developing a local recurrence is eight times higher with an inadequate compared to an adequate therapy. Local recurrence is associated with a significantly decreased survival rate and a higher occurrence of metastases. Consequently, the prognosis worsens. In our series, there was a significantly lower survival rate for patients with distant metastases ($P = 0.01$). In summary, patients with a local recurrence have a worse survival rate, accompanied by a higher rate of distant metastases. This phenomenon is well known in the literature too [19, 25].

As expected, comparing adequate versus inadequate treatments indicated a positive influence of adequate treatment on the survival rates in this study. These rates imply an unequivocal but not significantly better prognosis ($P = 0.26$). One reason for the high number of patients with an inadequate treatment is the long follow-up of the study; diagnoses and treatments were performed in the 1970s and 1980s. Meanwhile, the treatment regimens have markedly changed—for example, multimodal therapy regimes including chemotherapy—and have led to significant improvements in the outcome for patients with sarcomas [2, 3, 14, 19, 26–28].

The main cause for an inadequate therapy was an insufficient surgical procedure. In 7 of 9 patients with inadequate therapy in our study, an intralesional or marginal resection was performed most likely caused by the specific anatomical challenges in this location (e. g. small compartments). Compared to intralesional, marginal, or wide resections, we found a significantly lower rate of local recurrences and higher survival rates in patients who underwent radical surgical treatment. This is in accordance with the results of other studies considering radical surgery as the best option for local tumor control too [9, 18, 28, 29]. Despite radical resection, patients with foot sarcomas usually do not have significant functional restrictions after surgery and rehabilitation.

An unknown factor is the latency of the tumor (i.e. time between the emergence of the first tumor cell and the appearance of symptoms). It is quite probable that the latency of sarcomas of the foot is shorter than that at other sites. In such a case, tumors in long bones and the trunk would be larger at clinical manifestation than comparable tumors of the foot. Likewise, the longer latency at other sites could be attributed to a masking by the relatively thick soft tissue layers in the leg and trunk. The indeterminacy of latency is a weakness in the calculation of tumor growth before diagnosis. As cell growth is exponential, detectable increases in tumor volume require much more time in small compared to large tumors. Nevertheless, the observed differences between

Table 4: Average volume of tumors in the foot and at other anatomical sites.

Diagnosis	Median/average volume of tumor at diagnosis	
	Median volume in the present study	Average volume from other sites reported in the literature
Chondrosarcoma	21.2	400 [20]
		600 [25]
Osteosarcoma	63.8	182 [21]
		650 [22]
		242 [23]
Ewing sarcoma	25.5	145 [27]
		144 [24]

The superscripts listed in the last column of the table refer to references.

tumor growth in the foot and other sites are striking. It is likely that—despite the unknown latency factor—this reflects a differential biological behavior.

One major limitation of this study is that almost one half of the patients were diagnosed and treated before the end of the 1980s when chemotherapeutic regimes and imaging modalities were improved dramatically. Further limitations derive from the retrospective design and the small patient population. Sarcomas of the foot are rare, but the number of patients in this series is within the range (6–87 patients) of those in other reports [1, 3, 6, 8, 15]. In contrast, the long median follow-up of 11.9 years is the strength of this study.

In conclusion, primary malignant bone tumors of the foot appear to grow slower and to be less aggressive than those at other anatomical locations. We observed a long delay in diagnosis of foot sarcomas, which is in contrast to the general assumption that the thin soft tissue layer of the foot should allow an immediate clinical recognition. Interestingly, despite the delay in diagnosis, the prognosis is similar to that of tumors at other skeletal locations. From a systematic comparison of reported delays in diagnosis and tumor volumes at other sites, we conclude that malignant tumors of the foot grow at an approximately 10–20-fold slower rate than tumors at other sites of the body, and this property indicates a distinct biological behavior of bone tumors in this special anatomic location.

Disclosure

All authors disclose that they have no financial or personal relationships with other people or organizations that could inappropriately influence (bias) their work.

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Clinical Study

Surgical Guides (Patient-Specific Instruments) for Pediatric Tibial Bone Sarcoma Resection and Allograft Reconstruction

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To achieve local control of malignant pediatric bone tumors and to provide satisfactory oncological results, adequate resection margins are mandatory. The local recurrence rate is directly related to inappropriate excision margins. The present study describes a method for decreasing the resection margin width and ensuring that the margins are adequate. This method was developed in the tibia, which is a common site for the most frequent primary bone sarcomas in children. Magnetic resonance imaging (MRI) and computerized tomography (CT) were used for preoperative planning to define the cutting planes for the tumors: each tumor was segmented on MRI, and the volume of the tumor was coregistered with CT. After preoperative planning, a surgical guide (patient-specific instrument) that was fitted to a unique position on the tibia was manufactured by rapid prototyping. A second instrument was manufactured to adjust the bone allograft to fit the resection gap accurately. Pathologic evaluation of the resected specimens showed tumor-free resection margins in all four cases. The technologies described in this paper may improve the surgical accuracy and patient safety in surgical oncology. In addition, these techniques may decrease operating time and allow for reconstruction with a well-matched allograft to obtain stable osteosynthesis.

1. Introduction

The tibia is a common site for the most frequent malignant primary bone tumors in children, osteosarcoma (tibia is affected in 27% of cases), and Ewing's sarcoma (8% of cases) [1, 2]. Improvements in diagnosis and therapeutic techniques have increased interest in limb-salvage surgery. However, several studies have suggested that limb-salvage surgery may increase local recurrence in the case of inappropriate excision margins [3]. To achieve local control of disease and to improve oncological results, wide resection margins are mandatory. However, a wide surgical excision results in a large residual bone defect that requires restoration [4]. We propose a new technique to decrease the width of the excision margins with patient-specific instruments (PSIs). In this method, the resection is carefully planned prior to surgery, based on magnetic resonance imaging (MRI) and computed tomography (CT), which are used to define the trajectories of the resection and create PSIs.

The function of the reconstructed limb is of major interest, especially in young and physically active patients who place high demands on their limbs. The limb reconstruction must also be durable because life expectancy for many of these patients is several decades [4]. Limb reconstruction for such large defects can be performed by various techniques, including endoprosthetic reconstruction, osteoarticular allografting, vascularized autografting, bone transport with distraction osteogenesis, or reimplantation of the tumor-bearing bone segment after the devitalization of the tumor cells (by heating, freezing, or extracorporeal irradiation) [5].

Massive bone allografting presents several drawbacks: relatively long rehabilitation due to immobilization and partial loss of weight bearing, difficulties in obtaining size-matched allografts for small patients, an absence of expandability, and a relatively high incidence of complications [6]. Despite these

drawbacks, allografting offers several advantages, including the ability to reattach the ligamentous and tendinous structures of the host to the graft. An accurate reconstruction of the soft-tissue attachments at the host-allograft junction can lead to improved results [7]. Other advantages include the biologic incorporation (at least partial) of the graft and the preservation of the joint, the juxta-articular bone, and the growth plates [8]. These advantages make massive bone allografting convenient for intercalary, osteoarticular, and arthrodesis operations, as well as for allograft-prosthetic composite reconstruction in an extra-articular resection. In fact, bone allografting is the most common option for intercalary reconstruction, with a survival rate as high as 75% to 89% at 10 years [6, 9–12].

The concept of using a patient-specific template was introduced in the 1990s by Radermacher et al. [13] for pedicle screw placement, total knee arthroplasty, decompression of cervical spine, and triple osteotomy of the pelvis. They performed CT-based preoperative planning and conceived a template to fit the bone surface. The template was manufactured by milling because rapid prototyping was not yet well developed and was far more expensive. Later, Salako et al. used guided intrapedicular screws to install instrumentation on the spine. This mechanism allowed the surgeon to drill in the optimal direction, and it decreased the rate of screw misplacement [14]. In maxillofacial reconstruction surgery, the use of a PSI to guide the osteotomies allowed the surgeon to avoid important structures, such as dental nerves and components of the vascular anatomy. This concept was used by Leiggener et al. [15] for mandible reconstruction with a free fibula osseous flap. Using CT angiography, the authors manufactured a guide by rapid prototyping (SLS). They performed a complex mandible reconstruction with this method, choosing the best sites on the donor (fibula) and recipient (mandible) with regard to function, aesthetics, and blood supply. Modabber et al. [16] concluded that this technique significantly decreased shaping time during surgery and will likely impact the survival of the flap. Several authors have used a patient-specific template technique to treat other conditions, such as a cubitus varus deformity, a malunited forearm fracture, and a distal-radial fracture combined with tibial deformities. After preoperative planning, a rapid-prototyped model was manufactured to correct each deformity. This technique improves the accuracy and ease of the surgical act [17, 18].

In the present paper, we describe the use of PSIs for resecting aggressive tibial sarcomas and reconstructing the anatomy with an intercalary or osteoarticular allograft. First, we detail the preoperative planning process. Next, we describe how PSIs are used to perform the resections and to adjust the allografts. Finally, we present several clinical cases and their outcomes.

2. Materials and Methods

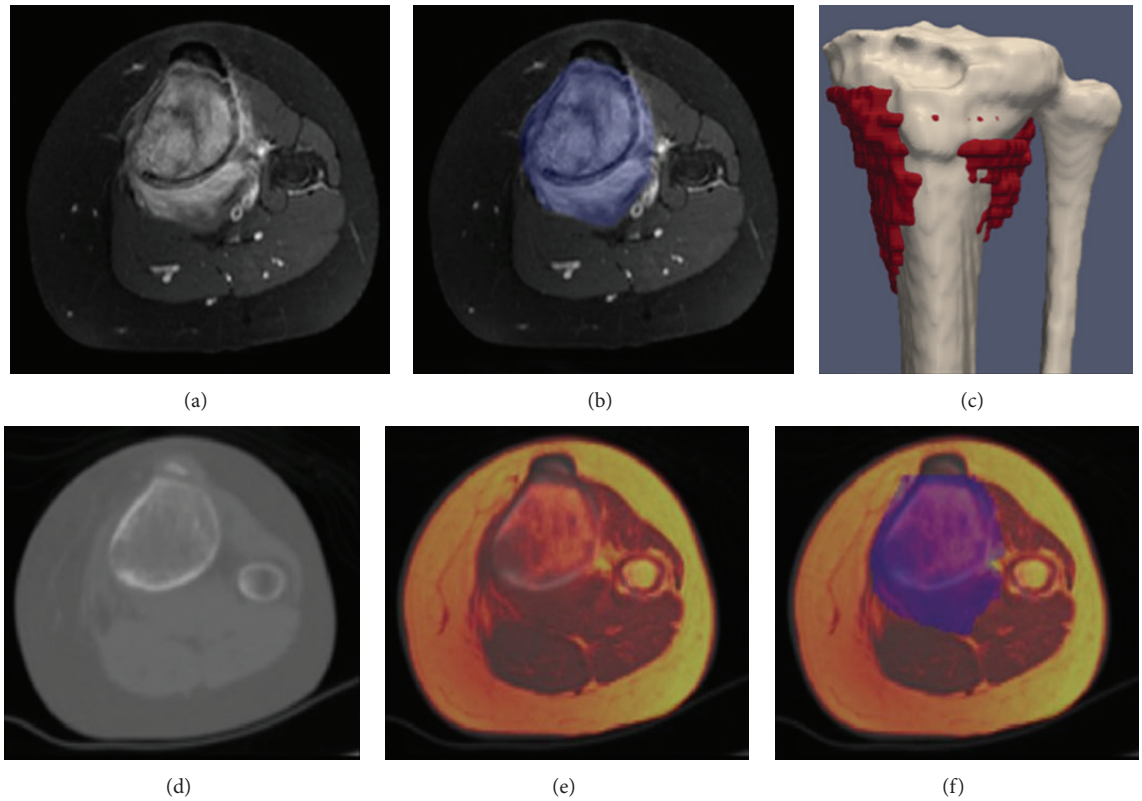
2.1. Preoperative Planning for Tumor Resection. Preoperative images of the patients were acquired for diagnoses. Anatomical images were obtained by CT from a Brilliance 40 CT scanner (Philips, the Netherlands; 0.5 mm spacing between slices, 1 mm slice thickness, 120 kV peak voltage, and 99-mA tube current) and by MRI from a 1.5 T NTScan Intera (Philips, the Netherlands, 4 mm spacing between slices, 3 mm slice thickness, 550 ms TR, and 14 ms TE).

Preoperative planning required delineation of each tumor. An MRI series that clearly showed the boundaries of the tumor was selected. The tumor was manually delineated on each slice on which it was visible, using the open-source software ITK-Snap 2.0 (http://www.itksnap.org/) [19]. The obtained delineation, referred to as the tumor volume, was saved for later use.

A multimodal registration algorithm was used to merge, simultaneously, the MRI series with the CT images (image fusion) and the tumor volume (Figure 1). 3D models of the bone and the tumor volume were extracted from the 2D slices, and a combined 3D image of the tibia and tumor (red in Figure 1) was obtained. The 3D models were used to position the resection planes (target planes) that represented the trajectories of the saw blade. With the assistance of a haptic device and a specific software program developed in the author's laboratory, the planes were initially brought into contact with the tumor and then translated back with a surgeon-defined security margin of at least 5 mm. This method ensured a controlled safe margin during the surgery. The resection plane data were saved for use in the next two stages of preoperative planning.

2.2. Preoperative Planning for Allograft Cutting. To select the best-fitting allograft among the tibial allografts from the local bone bank, CT images of all available tibia allografts were acquired (Somatom Definition AS, Siemens; 0.35-mm slice thickness, 0.7 mm spacing between slices, 120 kV peak voltage, and 99 mA tube current). A monomodal registration was performed between CT scans from the tibia of the patient and the various allografts. The optimal allograft was chosen as the one that best bridged the bone defect created by the resection. Particular attention was paid to the articular surface in the case of an osteochondral allograft. The resection planes defined in the previous stage of preoperative planning were transferred toward the allograft with the registration algorithm (Figure 3). This process ensured that the resection planes were identical for the patient and for the allograft, with a well-matched allograft to fit the bone defect.

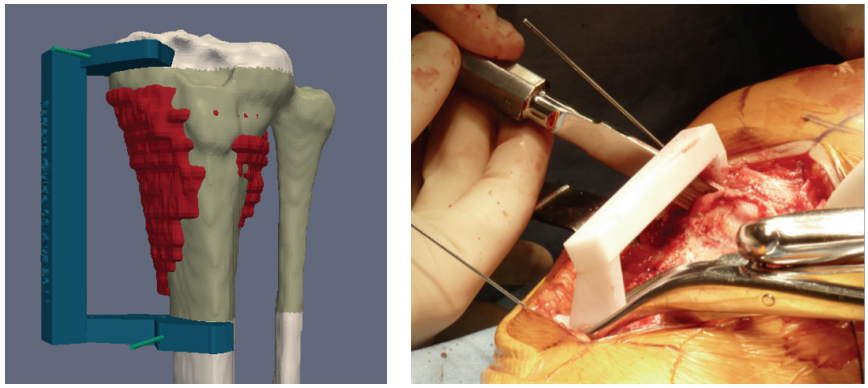
2.3. Patient-Specific Instruments. Two PSIs were created for each patient: one for the tumor resection and a second one for the allograft cutting. The PSIs were virtually designed with a computer-aided design software package (Blender 2.63.11). Each PSI was endowed with a specific surface that could be fit onto a unique position on the bone surface. The instruments contained small holes that were specifically designed for 2 mm Kirschner wires (K-wires). These K-wires allowed the instrument to be pinned onto the bone surface. A flat surface materialized the resection planes and permitted the clinician to guide the saw blade during the osteotomies.



(a) (b) (c)

(d) (e) (f)

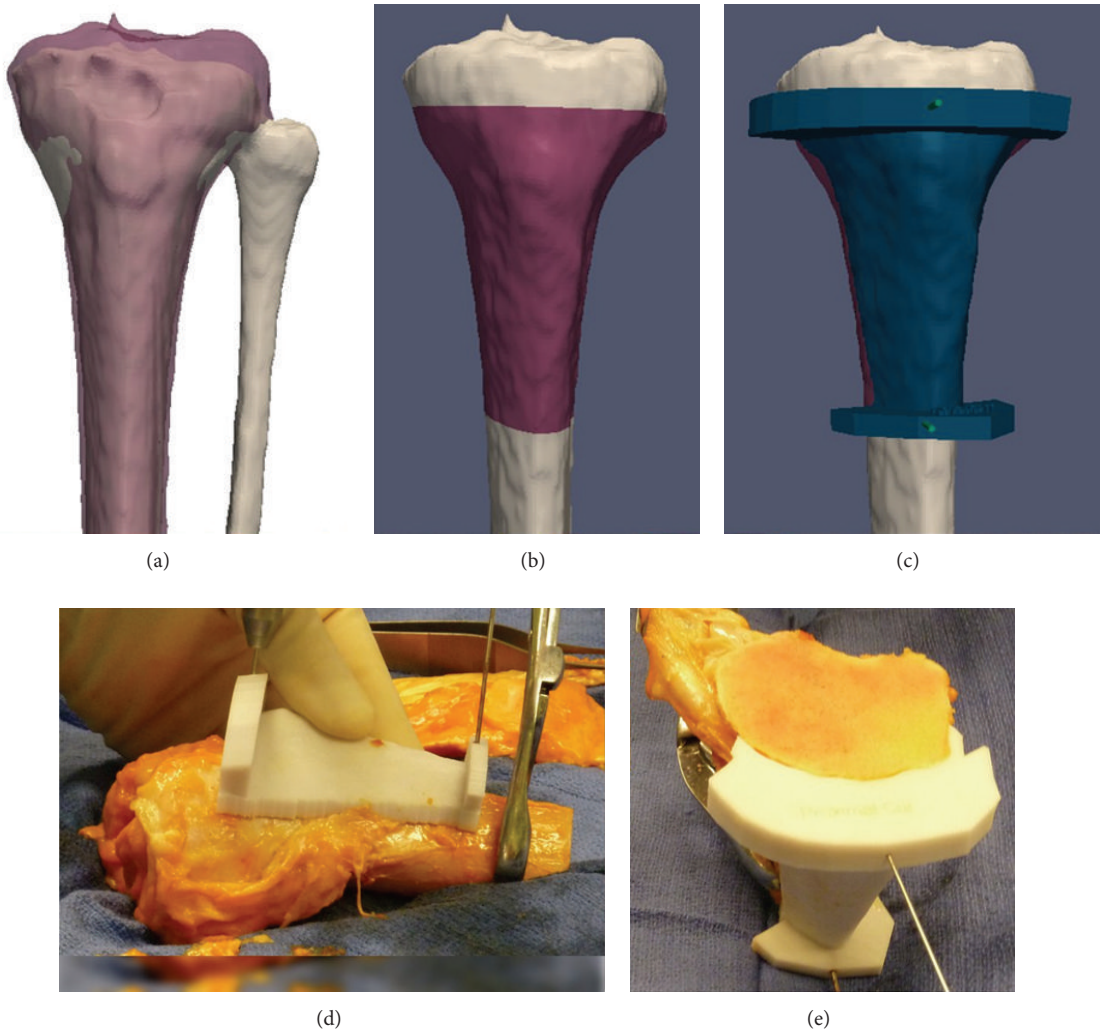
Figure 1: 11-year-old patient with tibia metastasis of a femoral osteosarcoma. (a) MRI showing the osteosarcoma invading the proximal tibia. (b) Tumor is delineated in blue on each slice of MRI where it is visible. (d) CT scan. (e) Merging of MRI and CT. (f) MRI-CT merging with the delineation of the tumor. (c) 3D reconstruction of the tibia with the delineated tumor visible (red).



(a) (b)

Figure 2: Images from the patient shown in Figure 1. (a) Target resection planes have been designed according to the osteosarcoma (red) with a safe margin. The green zone is included between the two planes. A 5 mm distance (margin) between the plane and tumor was selected to spare epiphysis, whereas a 10 mm margin was chosen distally. K-wires are represented by green cylinders. A PSI was created to guide the saw blade and to respect the planes. (b) PSI has been postitioned at the surface of the exposed tibia, and the surgical saw has been placed on the PSI to follow the target planes.

The PSIs were produced by rapid prototyping with Selective Laser Sintering (SLS) technology in a biocompatible material (Polyamide, Figure 2). This additive manufacturing technology consists of building a 3D object by adding material layer by layer. A laser draws a 2D shape on the surface of a powder bed, locally fusing the powder to create a solid section. A new layer of powder is spread on top of the surface, and the process is repeated until the entire object is built.



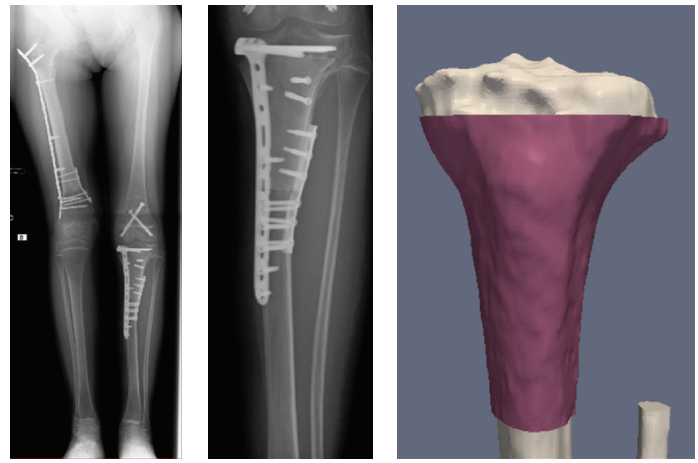
(a) (b) (c)

(d) (e)

Figure 3: Images from the patient shown in Figures 1 and 2. (a) Merging of the allograft CT and the tibial CT of the patient. (b) Target planes have been transferred to the allograft. The pink zone is the planned cut allograft. (c) A PSI has been virtually created (blue) and is shown pinned to the bone with two K-wires (green cylinders). (d) PSI has been positioned on the surface of the tibial allograft. (e) Allograft after cutting with the saw.

2.4. Patient Series (Table 1). Four patients were operated on for tibial bone sarcoma resection and allograft reconstruction with PSIs. Two patients presented with primary tibia sarcomas (one with osteosarcoma and one with Ewing's sarcoma), one patient had a local recurrence of tibial osteosarcoma, and one patient had a tibial metastasis from a contralateral femoral osteosarcoma. The ages at operation ranged from 9 years and 9 months to 18 years and 2 months. Imaging assessment consisted of plain radiograph, CT, MRI, and positron emission tomography (PET)-CT with fluorodeoxyglucose-18. The latter revealed no distant metastases. Neurological deficits and systemic symptoms, such as fever or weight loss, were absent. The diagnosis was confirmed by an incisional biopsy and histological evaluation of the tissue. Patients received multiagent, neoadjuvant, and adjuvant chemotherapy, according to the Euramos, Euro-Ewing, OS2005, and OSII-TTP protocols.

2.5. Assisted Surgery. The patients were placed in decubitus. A medial-tibial approach was used in three patients and a lateral approach in the last patient (because the biopsy had been performed laterally). The open-surgical biopsy tract was excised with the tumor, as an ellipse. A progressive soft-tissue dissection was performed to isolate the tumor with the planned margin and with the preservation of the anterior tibial tuberosity. Both PSIs (one for the patient and one for the allograft) were sterilized by standard autoclaving the day before the surgery. The resection PSI was positioned on the tibia and rigidly fixed with two K-wires at proximal and distal locations (Figure 2). A safe margin of 5 mm was chosen (3.5 mm after resection because of material loss due to saw blade cutting, i.e., the kerf). Proximal and distal osteotomies were performed with a surgical saw that was guided by the PSI. The tibial resection lengths ranged from 8 to 16.4 cm.



(a) (b) (c)

Figure 4: Images from the patient shown in Figures 1, 2, and 3. (a) Full-length standing radiograph showing the final result. (b) Magnified view of the reconstruction site: the intercalary allograft is inserted between the spared epiphysis and diaphysis. Osteosynthesis is performed with two plates. (c) Virtual simulation of reconstruction with allograft (pink) inserted into the patient's tibia (white).

Table 1: Summary of 4 cases of tibial resection with PSI.

	Case 1	Case 2	Case 3	Case 4
Patient information				
Age (y)	18.2	12.5	11.2	9.8
Sex	M	M	F	M
Sarcoma type	OS (local occurrence)	EWS (primary)	OS (tibial metastasis of a femoral OS)	OS (primary)
Resection				
Type	Intercalary	Intercalary	Intercalary	Osteoarticular
Length (cm)	8.0	11.8	8.2	16.4
Preservation	Preservation of epiphysis	Preservation of proximal tibial growth plate	Preservation of epiphysis; sacrifice of growth plate	Epiphysiodesis of contralateral proximal tibia
Results				
Local complications	None	Transient common fibular nerve palsy	None	Sepsis requiring allograft replacement
Time to host-allograft junction union (mo)	4	9	12	None
Followup (mo)	17	19	14	10
Final patient outcome	Excellent; walking without assistance	Excellent; walking without assistance	Excellent; walking without assistance	Poor after initial procedure; good final result; walking with a brace

M: male; F: female; OS: osteosarcoma; EWS: Ewing's sarcoma.

Extemporaneous biopsies were taken from both the distal and proximal sites in the tibia to ensure the adequacy of the margins. After the pathologic confirmation of the safe margin, reconstruction was undertaken. During tumor excision, a second surgeon prepared the allograft to reconstruct the resulting surgical defect. After soft-tissue dissection, the allograft-specific instrument was pinned onto the graft. The instrument was created such that the osteotomy planes of the graft were receded 1.5 mm to compensate for the kerf.

The adjusted allograft was placed on the bone defect, and osteosynthesis was performed with an NCB titanium 9-hole plate in three cases, and with two plates (an L-plate and a 6-hole plate) in one case (Figure 4). In two patients, a contralateral proximal tibia epiphysiodesis was performed at the same time to avoid a consecutive progressive leg-length discrepancy. A brace was applied for all patients in the postoperative period.

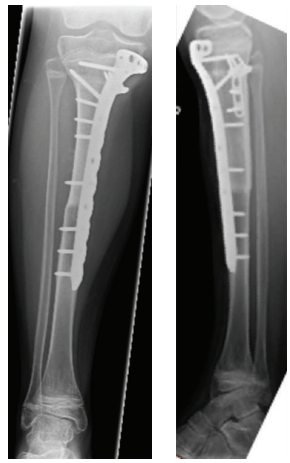
3. Results

The mean total surgical time was 250 minutes from the time of skin incision to the end of skin closure. Preoperative

preparation, including general anesthesia, epidural catheter insertion, patient positioning, and draping, lasted a mean of 73.5 minutes.

One patient developed transient common fibular nerve palsy, which was confirmed by electromyography. Skin necrosis and wound dehiscence occurred in the patient with the osteoarticular allograft at one postoperative month, necessitating a lateral gastrocnemius flap. The allograft was ultimately found to be infected by *Enterococcus faecium* and *Pseudomonas* and was explanted 3 months after the reconstruction. An antibiotic-impregnated cement spacer was inserted, and a new reconstruction was performed 4 months later with a new PSI to guide the allograft cutting.

Histological examination of the removed sarcoma confirmed osteosarcoma in three patients and Ewing's sarcoma in one patient. All resection margins appeared to be tumor-free. Postoperative radiograph, CT scan, and MRI results revealed satisfactory host-graft contact and no evidence of recurrent disease. The explanted, infected allograft was not consolidated with the host tissue. For the other three patients, radiological union was obtained at the graft-host junction at 4, 9, and 12 months. Partial weight bearing was allowed after 6 weeks and full weight bearing after 3 months, except for one patient for whom partial weight bearing was allowed immediately.



(a) (b)

Figure 5: 12-year-old boy with EWS sarcoma of the proximal tibia. Result of the reconstruction with preservation of the growth plate: radiographic anteroposterior and lateral view.

4. Discussion

This paper reports a novel method of bone sarcoma surgery that is supported by the use of PSIs. The PSI assistance was used not only for tumor resection but also for massive allograft cutting, allowing for optimal reconstruction. This technique was applied to 4 patients.

In surgical oncology, obtaining a wide margin during a tumor resection is crucial to avoid local recurrence. However, limb-salvage surgery requires the preservation of a functioning limb at the expense of obtaining safe margins [3]. Accurate preoperative localization of the tumor provides full control over the safe margins, and PSIs improve the accuracy of the resection during the surgery. The combination of these techniques allows resection with adequate but minimal safe margins, thus preventing unnecessary resection and preserving, when needed, articular cartilage in young patients. In one of the patients presented here, the target margins were defined at 3.5 mm, which allowed for the preservation of the growth plate (Figure 5). This outcome would not have been possible without the assistance of PSIs.

The literature reports discrepant results for tibia allografting reconstruction, ranging from excellent outcomes with full incorporation and osteointegration of the allograft and durable joint function to a high rate of failure and complications, including accelerated and advanced arthritis, fractures, nonunion, and infection [20]. The PSI technique allows the allograft to be cut with a high degree of accuracy, producing a transplant of the optimal shape to bridge the bone defect. Moreover, the allograft can be adjusted simultaneously (by another surgeon) or prior to the tumor resection, thereby decreasing the operating time and improving patient safety. The precise tumor and allograft cuttings obtained by PSIs yield strong contact at host-graft junctions, resulting in a stable osteosynthesis. The mechanical stability of the graft facilitates improved and more rapid healing and bone fusion due to the increased growth of blood vessels into the graft [21].

The production of PSIs requires medical images to be sent to an engineer who performs the preoperative planning. This process presents a challenge because it is crucial to maintain the security of the medical data of the patient. In addition, an open communication between the surgeon and the engineer is important. Furthermore, the engineer must have a strong clinical background to understand the medical context and the prerequisites of the PSI that will be generated. The PSI must be localized to a unique site on the bone surface that will be exposed by the surgical approach without adding unnecessary surgical approaches, skin incisions, or dissection. Surgeons will be asked to anticipate the constraints of the surgery (e.g., surgical approach, access to bone surface, and presence of soft tissue). The engineer must respect these clinical data and determine a trade-off between the invasiveness of the PSI and its stability on the bone surface. In our series of patients, accurate positioning of the instruments was easily achieved for each case, and the instruments were stable.

5. Conclusions

The techniques described in this paper may help to improve patient safety and surgical accuracy for the resection of bone sarcomas of the tibia and for the accompanying reconstruction at these sites. In addition, these techniques may potentially benefit surgery for bone sarcomas at other sites such as the pelvis.

Acknowledgment

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Review Article

Can Bone Tissue Engineering Contribute to Therapy Concepts after Resection of Musculoskeletal Sarcoma?

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Resection of musculoskeletal sarcoma can result in large bone defects where regeneration is needed in a quantity far beyond the normal potential of self-healing. In many cases, these defects exhibit a limited intrinsic regenerative potential due to an adjuvant therapeutic regimen, seroma, or infection. Therefore, reconstruction of these defects is still one of the most demanding procedures in orthopaedic surgery. The constraints of common treatment strategies have triggered a need for new therapeutic concepts to design and engineer unparalleled structural and functioning bone grafts. To satisfy the need for long-term repair and good clinical outcome, a paradigm shift is needed from methods to replace tissues with inert medical devices to more biological approaches that focus on the repair and reconstruction of tissue structure and function. It is within this context that the field of bone tissue engineering can offer solutions to be implemented into surgical therapy concepts after resection of bone and soft tissue sarcoma. In this paper we will discuss the implementation of tissue engineering concepts into the clinical field of orthopaedic oncology.

1. Introduction

Bone has to carry major loads. To fulfil this task it is created as a composite material, which comprises primarily of collagen, noncollageneous proteins, and hydroxyapatite. Its complex structure contains a wealth of mechanically relevant details [1]. Bone is a composite in several senses that is, being a porous material, a polymer-ceramic mixture, a lamellar material, and a fibre-matrix material. Its mechanical properties will therefore depend on each of these aspects of composition and structure. In general, bone displays a high intrinsic regenerative capacity following trauma or disease. Therefore, the majority of fractures heal spontaneously by a recapitulation of the pathway of normal fetal skeletogenesis,

including endochondral and intramembraneous ossification [4]. Refinements in surgical techniques, implant design and postoperative care have significantly improved treatment outcomes of complex fractures and defects as caused by high-energy trauma, disease, developmental deformity, and revision surgery. However, there are conditions in which bone regeneration is compromised or in which bone regeneration is required in a large quantity.

A situation of the latter entity is the resection of malignant bone and soft tissue sarcoma. This can result in large defects where regeneration is needed in a quantity far beyond the normal potential of self-healing [5]. Furthermore, an adjuvant therapeutic regimen or local factors such as postoperative seroma or infection can account for a limited intrinsic regenerative potential [6]. Therefore, reconstruction of these defects is still one of the most demanding procedures in orthopaedic surgery.

2. Common Treatment Strategies for Bone Defects

Treatment protocols of bone and soft tissue sarcoma are based not only on the tumour biology and location, but also on the patient's needs and age [7]. The primary surgical goal should be to obtain adequate surgical margins in order to ensure local tumor control [8–10]. With the introduction of multimodal therapeutic concepts and improved reconstruction techniques, limb salvage procedures have largely replaced ablative surgery [11–14], but only few of them can restore the original anatomical and functional conditions. For the reconstruction of skeletal defects after tumor resection, both biological techniques (e.g., autografts, allografts, or rotationplasty) and prostheses are used. These procedures, mainly bone grafting and metallic implants, are well established and the comparative advantages and disadvantages have been discussed at length in the literature [15–17]. Problems of autologous bone grafting can be donor site morbidity and limitation of the graft mass. For graft harvesting, additional personnel and time are needed. The use of allografts or xenografts carries the risk of immunomediated rejection, transmission of infectious diseases, or graft sequestration. In addition, the acquisition costs of allo- or xenografts are rather high. Graft devitalisation and consecutive absorption processes can lead to decreased mechanical stability. Failures usually result from incomplete transplant integration, particularly in critical sized defects. Due to the dense nature of cortical allografts, revascularisation and cellular invasion is impeded. This limited ability for revascularization and remodelling is believed to be responsible for the high complication rate associated with allografts [18]. Other biologic approaches used for the reconstruction of bone defects include distraction osteogenesis, segment transport, or the Masquelet technique, but all of these methods are technically demanding and they require lengthy treatment protocols, which can be highly inconvenient for patients [19, 20]. The limitations of these conventional biological reconstruction techniques are exacerbated in cancer patients, who are often elderly, have localised or systemic osteoporosis and suffer from impaired wound healing as a consequence of an adjuvant therapeutic regimen. The high tensile strength and fatigue resistance of metal would make it suitable for load-bearing applications, but the large mismatch in Young's modulus between metal and bone can lead to peri-implant bone resorption, a phenomenon known as stress shielding [21]. Furthermore, tumor endoprostheses exhibit a higher complication rate than standard implants with infection or aseptic loosening as the most common failure modes [22].

These constraints have triggered a need for new therapeutic concepts to design and engineer unparalleled structural and functioning bone grafts to replace current treatment options. To satisfy the need for long-term repair and good clinical outcome, a paradigm shift is needed from methods to replace tissues with inert medical devices to more biological approaches that focus on the repair and reconstruction of tissue structure and function [23]. It is within this context that the field of bone tissue engineering can offer solutions to be implemented into surgical therapy concepts after resection of bone and soft tissue sarcoma. While this has already led to a variety of novel therapeutic concepts particularly in the field of craniofacial surgery [3, 24], only few called smart biomaterials have found their way into clinical application in the field of orthopaedic surgery.

In the following passages, we will discuss the implementation of tissue engineering concepts into treatment strategies of bone defects caused by musculoskeletal sarcoma. From a material science and especially clinical point of view, the future prospects and possible application spectrum will be outlined.

3. Tissue Engineering Constructs (TECs)

The field of tissue engineering is embodied in the collective vision of its early pioneers Langer and Vacanti, whose diverse yet symbiotic research approaches as an engineer and surgeon led to the commencement of this interdisciplinary field. Their seminal 1993 paper remains one of the most influential and cited works in the field [25]. The application of the principles of biology and engineering to the development of functional substitutes for damaged tissue has seen laboratories worldwide forging impressive multidisciplinary teams to focus on restoring, maintaining, or improving the function of a wide range of human tissues. While progress has been made to deliver bench to bedside solutions, the rate at which tissue engineering has seen innovations translated to the clinic has been slower than originally expected and the urgency for tissue-engineered products which achieve these ideals remains high [26–28].

The fundamental concept underlying tissue engineering is to combine a scaffold with living cells and/or biologically active molecules to form a "tissue engineering construct" (TEC) which promotes the repair and/or regeneration of tissues [29, 30]. A suitable scaffold should (i) possess a porous interconnected pore network (pores and pore interconnections should be at least 400 μm to allow vascularisation) with surface properties optimised for the attachment, migration, proliferation, and differentiation of cell types

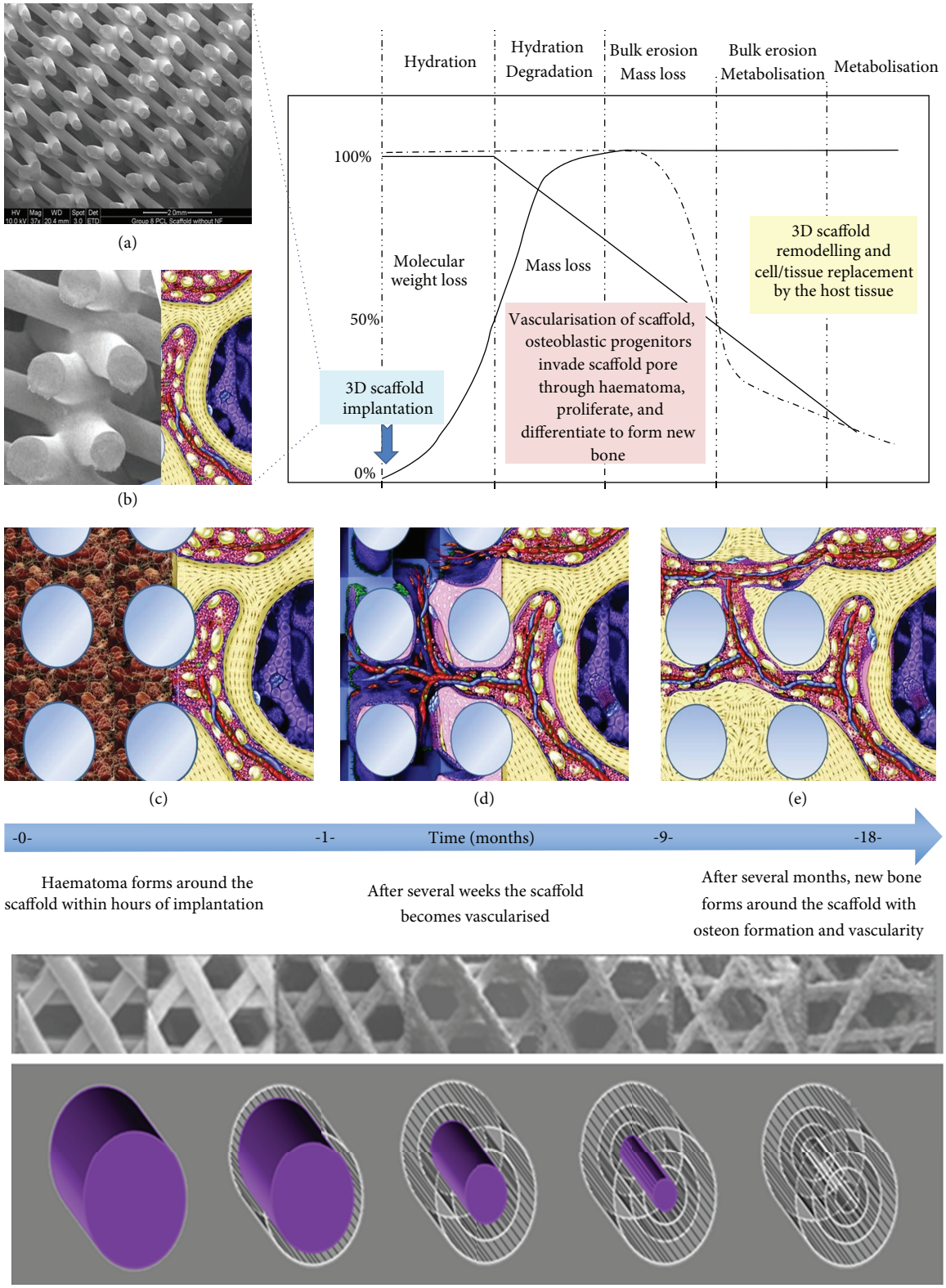
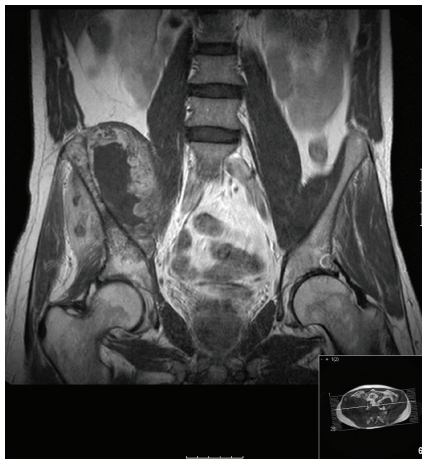


Figure 1: Schematic illustrating the interdependence of molecular weight loss and mass loss of a slow-degrading composite scaffold plotted against time. Scaffold implanted at $t = 0$ with lower figures showing a conceptual illustration of the biological processes of bone formation over time. After implantation the scaffold is immediately filled with haematoma followed by vascularisation. New bone is formed gradually within the scaffold. As the scaffold degrades over time, there is increased bone remodelling within the implant site until the scaffold pores are entirely filled with functional bone and vascularity (partially adapted from [2]). The lower part of the figure shows the schematic visualisation of how medical-grade poly-ε-caprolactone/tricalcium phosphate (mPCL-TCP) degrades via long-term bioerosion processes.



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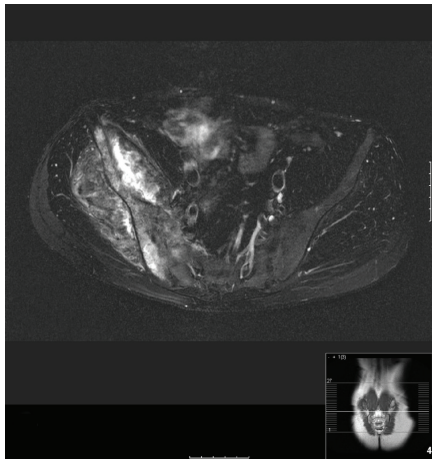

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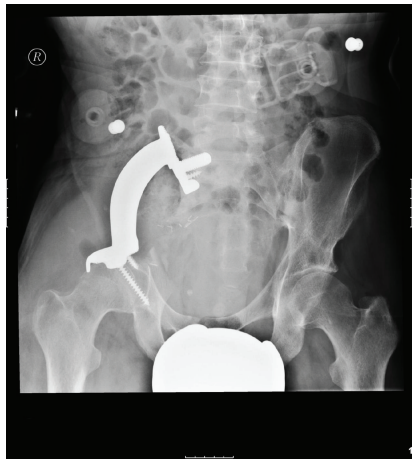

(c)

Figure 2: 34 year old patient with a large destructive soft tissue mass of the right hemipelvis. Coronal T1-weighted (a) and axial T2-weighted (b) MRI images demonstrate calcific lobules and punctuated foci with low signal intensity representing calcifications, which are typical for chondroid matrix. Histological analysis revealed a dedifferentiated chondrosarcoma. After resection of the affected bone a custom-made pelvic metal prosthesis was fitted into the defect. Radiograph one year postoperatively (c) shows a stable prosthesis, the functional and clinical outcome of the patient was good.

of interest (depending on the targeted tissue) and enable flow transport of nutrients and metabolic waste, (ii) be biocompatible, and (iii) be biodegradable with a controllable rate to complement cell/tissue growth and maturation [23, 31]. The design of these scaffolds also needs to consider physicochemical properties and morphology. External size and shape of the construct are of importance, particularly if the construct is customised for an individual patient. The work by groups focussing on scaffold design and fabrication utilising additive manufacturing technologies has advanced the tissue engineering field tremendously over the past few years [32]. The ability to create scaffolds in a layer-by-layer manner enables a computer-aided design to be directly translated from a clinical scan (i.e., a patient CT or MRI scan) to produce customised and/or patient-specific scaffolds to fit any anatomical defect site [33, 34].

4. Regeneration and Remodelling of TECs

After scaffold implantation, continuous cell and tissue remodelling is essential to achieve and maintain stable biomechanical conditions, vascularization, and integration within the host site [2]. Importantly, TECs should stimulate and support both the onset and the continuance of bone ingrowth as well as subsequent remodelling and maturation by providing optimal stiffness and external and internal geometrical shapes. Scaffolds must provide sufficient initial mechanical strength and stiffness to substitute for the loss of mechanical function of the diseased, damaged, or missing tissue. Furthermore TECs must degrade at a rate which is compatible with new tissue ingrowth and maturation [35]. It is essential to understand and control this scaffold degradation process for successful tissue formation, remodelling and maturation at the defect site. In the early days of tissue engineering, it was believed that scaffolds should degrade and vanish as the tissue is growing [36]. Though, tissue ingrowth and maturation differ temporally from tissue to tissue and, furthermore, tissue ingrowth does not equate to tissue maturation and remodelling. In other words, a defect filled with an immature tissue should not be considered as "regenerated." Hence, many scaffold-based strategies have failed in the past as scaffold degradation was more rapid than tissue remodelling and/or maturation [37]. Our concept of using a slow degrading composite scaffold fabricated with pores and pore interconnections with a size larger than 400 μm is illustrated in Figure 1.

5. Translating Bone Tissue Engineering Concepts into the Clinical Field of Orthopaedic Oncology

Bone defects after resection of musculoskeletal tumours represent a considerable surgical challenge, are associated with high socioeconomic costs and highly influence patients' quality of life. These problems may be approached from the perspective of the nature of the graft material with which the surgeon works. The mission of our interdisciplinary group is to coordinate efforts between researchers and clinicians

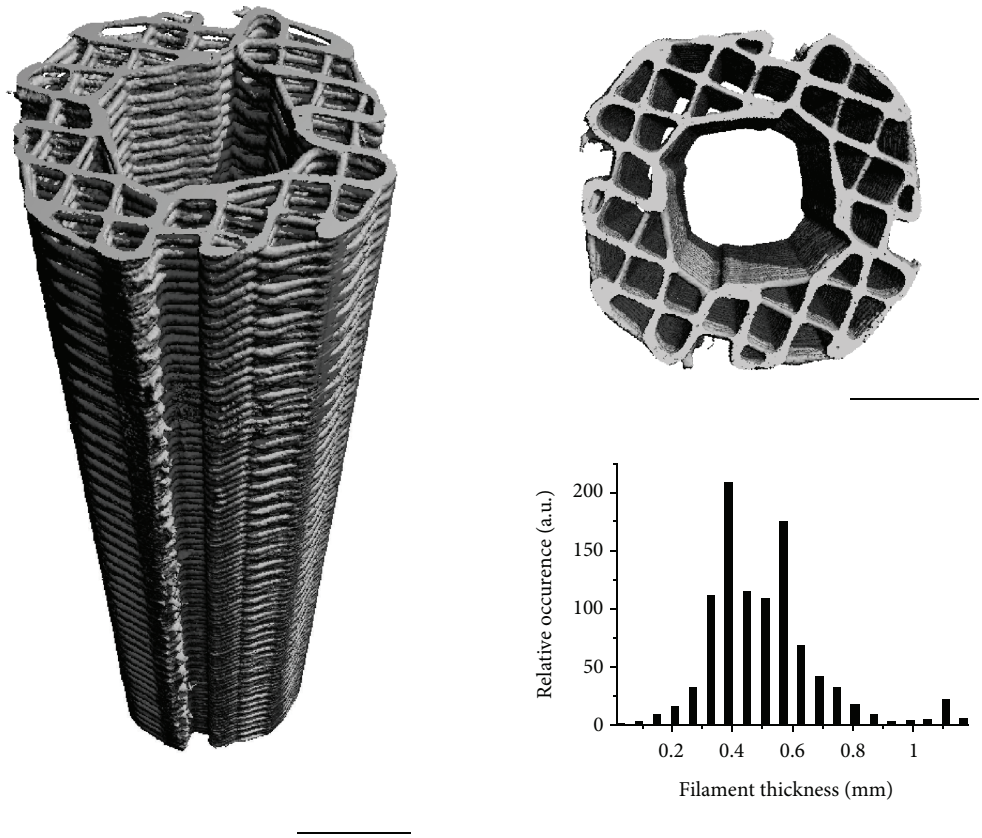

Figure 3: Side and top view of a PCL scaffold for tibia segmental defect regeneration, visualised by microcomputed tomography. The fabrication technique results in scaffolds with well-controlled architecture as evidenced by the narrow filament thickness distribution, leading to a porosity (volume fraction available for tissue ingrowth) of 60%, with interconnected pores. Scale bars are 5 mm.

in the area of bone tissue engineering and the translation of tissue engineering platforms into orthopaedic oncology. Laboratories in Singapore, Germany, and Australia have spent the last decade in close collaboration translating a concept of bone tissue engineering based on slowly biodegradable composite scaffolds comprising medical grade poly (epsilon-caprolactone) (mPCL) and calcium phosphates from bench to bedside [38–45]. After a large series of *in vitro* experiments, we consequently performed small animal studies using mouse, rat, and rabbit models which demonstrated the ability of composite scaffolds in combination with BMPs or cells to promote bone regeneration within ectopic sites or bone defects [35]. Another key project of our group has been the development of a large animal model for bone regeneration research. We recently have established and fully characterised a critically sized defect model in sheep tibiae to evaluate different tissue-engineering-based treatment strategies [46, 47].

In the following section, we will describe a part of the rationale and road map of how our multidisciplinary research team is approaching the first steps to translate bone tissue engineering concepts into orthopaedic oncology.

Our clinical partners have used custom-made metal prostheses for the treatment of pelvic defects after sarcoma resection for more than 20 years [48, 49]. Since 1988, the general production process of the prosthesis has only changed in details but has developed according to the technological advances available. In the first step a 1 : 1 pelvic model is made using data acquired via high-resolution computed tomography. The model is cut out from a block of polyurethane by a five axial CNC-milling machine. In the next step the surgeon uses this model to define the levels of osteotomy with special regard to the later surgical margins. According to the planned osteotomy planes and the acquired CT-data not only the custom-made prosthesis but also special osteotomy guides are constructed by the manufacturer to ensure accurate fitting of the prosthesis. The series reported from our institution showed encouraging results (Figure 2) [50].

Although these massive endoprostheses provide orthopaedic oncologists with many reconstructive options, failure rates are still high. Especially in younger patients a reconstructive method would be desirable that does not rely on the use of permanent metal implants but rather on bioactive materials enabling customised reconstruction and supporting natural healing processes. Using computer-aided design (CAD) and fused deposition modelling (FDM) technologies, we are able to produce bioresorbable composite scaffolds fabricated from mPCL, either with or without reinforcement using up to 20 wt% β-tricalcium phosphate (TCP)

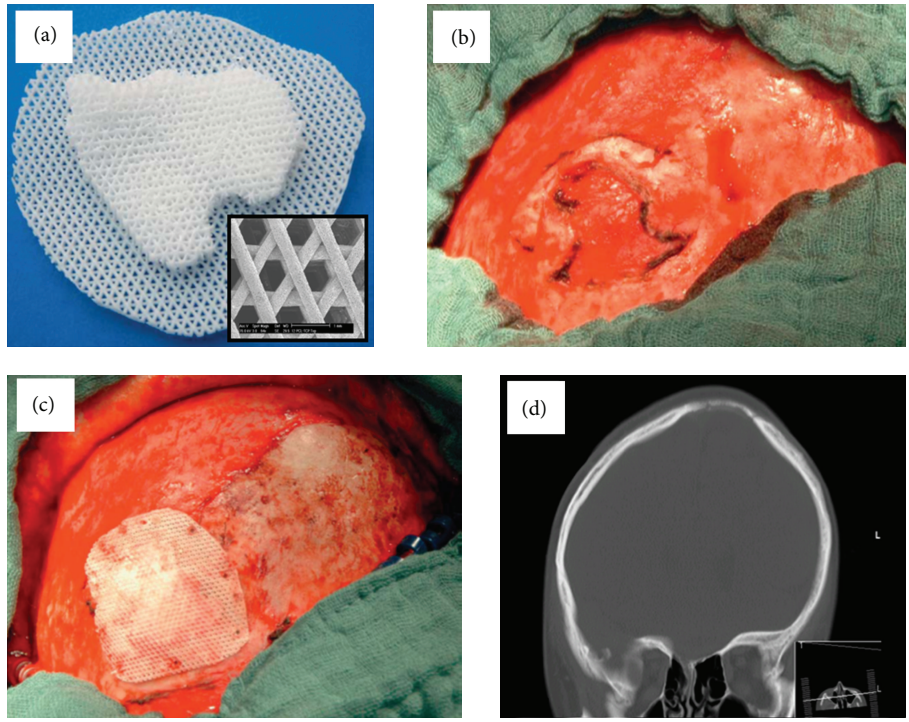

Figure 4: Clinical application of a cell-free polycaprolactone-calcium phosphate scaffold for bone regeneration in a calvarial defect. Scaffold designed using CT imaging data and fabricated by fused deposition modeling (a). Calvarial defect (b). Defect after implantation of the scaffold (c). CT images showing bony consolidation of the defect after 6 months (d). Reproduced with permission from Georg Thieme Verlag (2012) [3].

for bone tissue engineering applications at load-bearing sites (Figure 3).

This scaffold exhibits mechanical and structural properties comparable to cancellous bone and can be specifically adapted to the clinical needs with a fully interconnected pore network structure [45, 51]. A detailed description of the fabrication protocol has been given elsewhere [34, 39, 44]. These scaffolds are already in clinical use and are FDA approved for craniofacial applications [3] (Figure 4).

In principle, the fabrication process of our scaffolds as depicted in Figure 5 is similar to that described for the patient-specific and individually customised pelvic metal implants. Preoperatively, high-resolution CT data is processed via a 3D medical imaging software (e.g., InVesalius 3.0) supporting the medical DICOM/PACS format to generate a virtual model of the pelvis. In the next step, the data set is converted into a Standard Tessellation Language format (STL) which is the standard format for rapid prototyping applications. Accordingly, a model is built from an acrylonitrile butadiene styrene (ABS) polymer using a 3D fabricator (FDM3000, Stratasys, Eden Prairie, USA) based on fused deposition modeling technology. The model facilitates the haptic perception and orientation both before and during surgery. In close collaboration with the orthopaedic surgeon, the levels of osteotomy are marked in both the virtual and the physical model. Considering the dimensions of the tumor it should be possible to achieve tumor-free resection margins. As it has been previously described for the customised metal implants [50], based on the virtual model, special osteotomy guides can be manufactured to facilitate the later resection and implantation process of the scaffold. As the dimensions of the prospective bony defect are exactly known, the dimensions of the scaffold can be virtually adjusted. Moreover, the form of the scaffold can be adapted to the clinical needs. In the first step, we mirror the healthy side of the pelvis to the affected one to achieve near-physiological conditions. Afterwards the scaffold is armed with flanges and an intramedullary peg to improve its primary stability. Then, Skeinforge software is employed to generate the printing toolpath, which is subsequently modified to introduce porosity allowing tissue ingrowth. An infill density of 0.2 is chosen, corresponding to 80% porosity. Furthermore, the perimeter sections of the toolpath are removed using a custom algorithm to generate open pores to the exterior of the scaffold. According to this modified toolpath the scaffold is then manufactured using again a 3D fabricator. We used a commercially available MakerBot Replicator with poly(D,L-lactide (PDLLA) as biomaterial. PDLLA is a biodegradable thermoplastic polymer which has been successfully applied for fixation in maxillofacial reconstructions before [52, 53] and has been made available for several additive manufacturing techniques such as fused deposition modeling (as in this application) and stereolithography [54]. During surgery, the flanges are fixed with resorbable tacks or screws. Additionally, the contact area between the scaffold and the host bone can be covered with fibrin glue which can serve

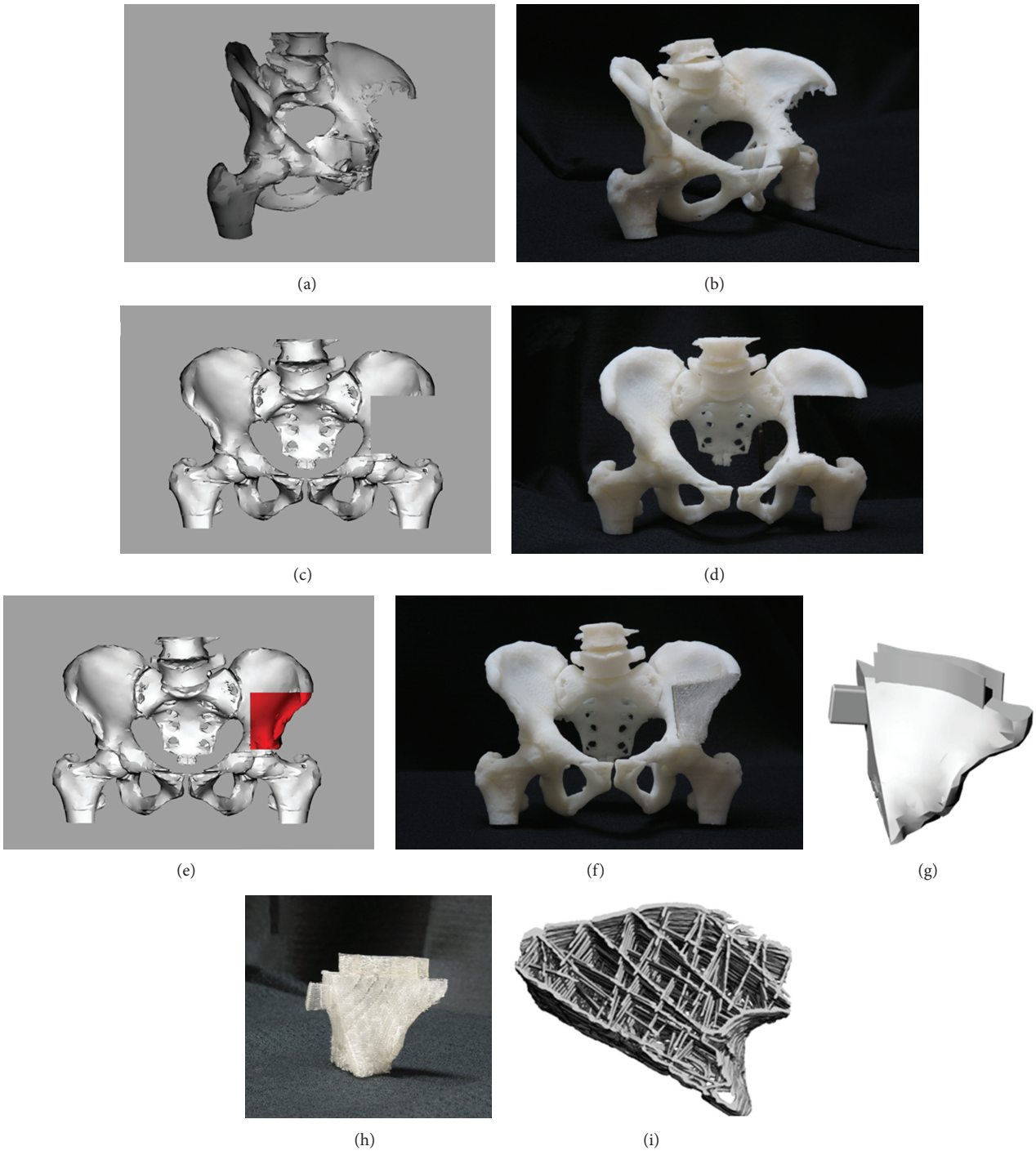

Figure 5: Schematic illustration of the scaffold manufacturing process. A 3D computer-aided designed (CAD) model of the patient's pelvis is fabricated according to data obtained by high-resolution CT ((a), (b)). Using this prototype, the surgeon indicates the osteotomy planes needed to achieve tumour-free resection margins, after which the CAD model is virtually resected ((c), (d)). A scaffold model is then derived by mirroring the healthy side of the pelvis and adjusting the size to fit into the defect ((e), (f)). The scaffold can be armed with flanges or an intramedullary peg to enhance its primary stability ((g), (h)) and exhibits a porous internal architecture to allow for tissue ingrowth and regeneration (i).

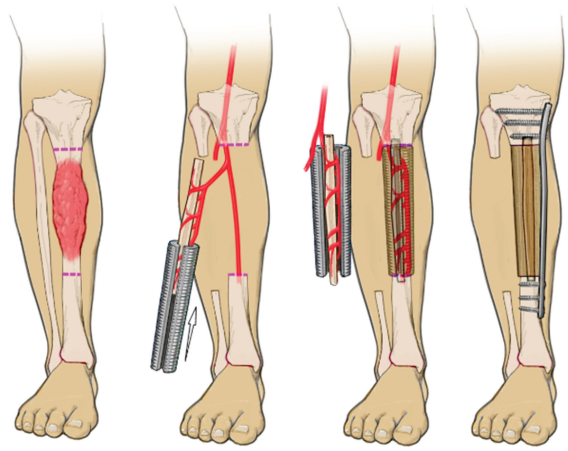

Figure 6: In orthopaedic oncology, vascularised fibula transfer is considered as one of the most suitable techniques for the reconstruction of critically sized defects of the tibia diaphysis due to the mechanical strength, the predictable vascular pedicle, and the hypertrophic potential of the fibula. Combining the autograft with a large bone allograft can enhance the biomechanical properties of the construct. However, the use of allografts can be associated with significant drawbacks such as immunomediated rejection, graft sequestration or transmission of infectious diseases. In addition, the acquisition costs are rather high. A novel biological approach could be to combine an intramedullary fibular autograft with a customised tissue engineered bone construct. After tumor resection (a) a customised mPCL/TCP tube is placed around the vascularised fibula (b) to fill the defect. Together with an internal fixation device, it ensures load distribution and primary stability. Secondary stability is achieved by osseointegration of both the fibula and the porous scaffold (c).

as a biomimetic template promoting migration of osteogenic cells.

The presented therapy strategy combines the advantages of both CAD/CAM procedures and tissue engineering concepts. Technically, it is not restricted to the application in defects caused by pelvic tumors but can also be transferred to other bony defect sites (Figure 6).

6. Outlook

Though, small bony defects such as cysts are relatively easy to handle in the routine clinical setting, the management of large defects in load-bearing bones presents a particular challenge in reconstructive surgery and particularly in orthopaedic oncology. In this opinion paper, tissue engineering has been suggested as an alternative strategy to regenerate bone in patients with musculoskeletal sarcoma. We have developed an integrated holistic approach for the reconstruction of bone defects caused by musculoskeletal tumours using patient-specific scaffolds with well-defined macro- and microarchitecture. Though promising case reports have been presented in the literature [3, 55], large clinical studies, which can show the efficacy of this approach in the clinical setting, are still missing. To tackle major bone tissue engineering problems in orthopaedic oncology, researchers have to perform functional assessment of the biological and biomechanical parameters of the regenerated bone. Furthermore, to allow a comparison between different studies, animal models, fixation devices, surgical procedures, and methods of taking measurements need to be standardised to achieve an efficient accumulation of reliable data as a foundation for future developments.

Acknowledgments

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Research Article

Comparison of Surface Area across the Allograft-Host Junction Site Using Conventional and Navigated Osteotomy Technique

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Bulk allograft reconstruction plays an important role in limb-salvage surgery; however, non-union has been reported in up to 27% of cases. The purpose of this study is to quantify average surface contact areas across simulated intraoperative osteotomies using both free-hand and computer-assisted navigation techniques. Pressure-sensitive paper was positioned between two cut ends of a validated composite sawbone and compression was applied using an eight-hole large fragment dynamic compression plate. Thirty-two samples were analyzed for surface area contact to determine osteotomy congruity. Mean contact area using the free-hand osteotomy technique was equal to 0.21 square inches. Compared with a control of 0.69 square inches, average contact area was found to be 30.5% of optimal surface contact. Mean contact area using computer-assisted navigation was equal to 0.33 square inches. Compared with a control of 0.76 square inches, average contact area was found to be 43.7% of optimal surface contact. Limited contact achieved using standard techniques may play a role in the high rate of observed non-union, and an increase in contact area using computer-assisted navigation may improve rates of bone healing. The development of an oncology software package and navigation hardware may serve an important role in decreasing non-union rates in limb salvage surgery.

1. Introduction

Allograft reconstruction has become increasingly important as the ability and interest in limb-salvage surgery for the treatment of bone tumors has grown over the past 50 years [1]. Despite its numerous benefits, allograft use has been associated with well-recognized complications, most notably, infection, fracture, and non-union. While infection and fracture may occur either postoperatively or as delayed events, non-union is by definition an early complication, which may be significantly influenced by operative technique.

Although congruous osteotomy cuts are thought to be desirable, exact matching surfaces are rarely achieved using a free-hand technique. This has previously been reported by McGrath et al., who demonstrated that end-cutting intramedullary reamers produced a significantly greater contact area across transverse osteotomies as compared with hand-cutting techniques [2]. With the advent of computer-assisted surgical navigation, whereby increased surgical precision and real-time surgeon feedback is feasible, higher accuracy may be achieved when compared to a freehand technique [3, 4].

Bulk allograft incorporation is likely a complex event, depending upon graft preservation, anatomic location, host vascularity, immunologic host response, and mechanical properties that include the fixation employed and the geometry of the allograft-host junction. [5]. Increased contact surface area across the allograft-host junction has

Table 1: Types of pressure sensitive films (Pressurex).

Types	Pressure range
Micro	0.14–1.4 kg/cm^2
Zero	0.5–2 kg/cm^2
Ultra low	2–6 kg/cm^2
Super low	5–25 kg/cm^2
Low	25–100 kg/cm^2
Medium	100–500 kg/cm^2
High	500–1300 kg/cm^2
Super high	1300–3000 kg/cm^2

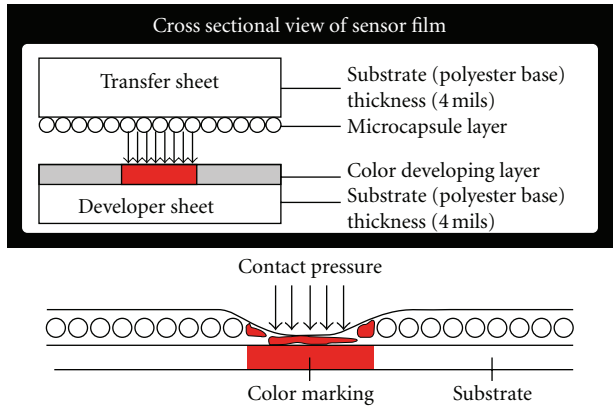


Figure 1: Cross sectional view of PRESSUREX film illustrating mechanism of color mapping from contact pressure.

been shown to provide a mechanical advantage, increasing stability as measured by torsional stiffness, maximum torque and maximum displacement [6]. Similarly, contact surface area across the allograft-host junction site may also play an important role in allograft-host junction site healing which, in turn, would serve to lower morbidity and monetary cost associated with non-union.

The purpose of the current study was to quantify average surface contact areas across a simulated allograft-host junction site using both a free-hand and computer-assisted osteotomy techniques. We hypothesized that the computer-assisted technique will result in significantly improved congruity and contact area across the allograft-host junction site.

2. Materials and Methods

A 1 cm segment was removed from validated composite femoral sawbones (Pacific Research Laboratories, Vashon, WA) by 2 experienced orthopedic oncologic surgeons, by making two transverse osteotomies using a Stryker System 6 operative sagittal saw (Stryker, Mahwah, NJ) using either a standard free-hand technique or a CT-navigated technique (O-arm Surgical Imaging System, Medtronic, Minneapolis, MN) for real-time intraoperative feedback. Free-hand technique cuts were performed in a conventional manner, with the surgeon using his discretion regarding saw position, angle, and alignment. No jigs or cutting blocks were utilized and other present persons made no input or adjustment. The CT-navigated technique was performed by affixing a 100 mm percutaneous reference navigation pin in the distal metaphysis of the sawbone and attaching the reference frame in routine manner. The O-Arm was used to localize the sawbone by obtaining antero-posterior and lateral fluoroscopic images in order to center and properly position the gantry. A CT scan was then obtained and the imaging was reviewed to ensure adequacy. The saw was navigated by affixing a SUR-TRAC navigation frame and registering the tip of the saw in keeping with the manufacturer's recommendations. Following removal of the osteotomized segment, pressure sensitive paper [Fuji Pressurex Ultralow Film (28–85 PSI, 2–6 kg/cm^2)] was positioned between the remaining sawbone ends, which served as a simulated allograft-host junction site (SAHJS).

Pressurex, a mylar based film, contains a layer of microcapsules which upon the application of force are designed to rupture, producing an instantaneous and permanent high resolution "topographical" image of pressure variation across the contact area (Figure 1). Pressure film can be applied between any two surfaces that touch, mate, or impact [7]. The procedure of pressure film application simply involves applying the pressure and removal of the pressure. Similar to Litmus paper, the color intensity of the film is directly related to the amount of pressure applied to it. Pressure ranges being investigated determine the specific type of film used as shown in Table 1.

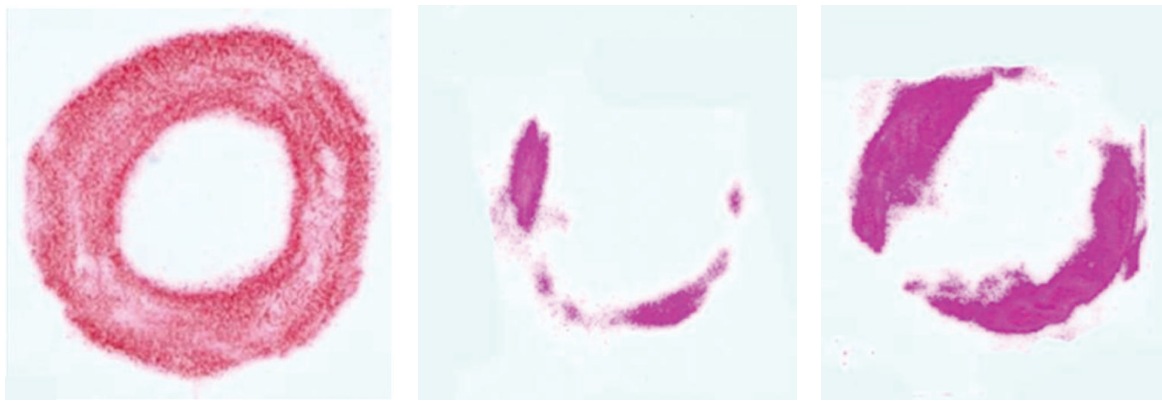
Compression across the SAHJS was achieved by first fixing the plate to one side of the SAHJS using a single fully-threaded non-locking cortical screw placed centrally within the plate's hole. Next, an eccentrically placed fully-threaded non-locking cortical screw was inserted on the opposite side of the SAHJS and compression ensued with complete seating of the screw. The pressure indicating film (28–85 PSI, 2–6 kg/cm^2) acts as a force-sensing resistor between the cut ends of femoral sawbones under compression plating (Figure 2). Hardware was then removed with care in order to protect the pressure sensitive paper from scuffing or manipulation prior to analysis. A total of 32 samples were obtained using the free-hand technique and 22 samples were obtained using computer-assisted navigation.

Film analysis was performed using the Topaq system, which permits for high resolution full-color representation of pressure distribution along the Pressurex film, serving to represent osteotomy congruity. Utilizing an adapted flatbed scanner, the system scans and interprets the pressure sensitive film to determine the pressure applied at any given point across the surface at resolutions of up to 1000 dots per inch (DPI) [7]. Software statistics and personalized finite element modeling permit for 3D reconstruction of sawbone contact area geometry and provide quantitative values for both contact area and force.

Control samples were created by applying pressure sensitive film to one end of a perpendicularly cut femoral

(a) (b)

Figure 2: Scheme of femoral sawbones under compression plating at the simulated allograft-host junction site (SAHJS). Images demonstrating 100% contact (a), minimal contact with gapping (b).



(a) (b) (c)

Figure 3: Scanned raw images of PRESSUREX film after contact at the allograft-host junction site made using the free-hand technique. Of the 32 samples, contact area achieved is seen in red for control (ideal) at 0.69 sq. in. (a), minimal contact at 0.07 sq. in. (b), and maximal contact at 0.36 sq. in. (c).

sawbone using either free-hand or computer assisted navigation. These samples were calculated by assuming that all available surface area across the 2-dimentional cortical surface was in fact utilized and indeed made contact with the opposing bone. This theoretically represents the greatest possible contact area for a transverse osteotomy given the size of the sawbone. Pressurex film was then manually compressed to provide a quantifiable measurement of surface contact. The control sample was defined as the maximum available cortical bone contact surface area and did not include the area representing the intramedullary space. Controls differed, using the free-hand technique (0.69 sq. in.) versus computer-assisted navigation (0.76 sq. in), due to quantitative calculations of the Topaq system. The percent contact area was calculated relative to a control sample with optimal contact area.

3. Statistics

Mean absolute and percentage values were compared between the free-hand and CT-navigated groups with the two sample t-test. A two-tailed P value of less then 0.05 was considered statistically significant.

Table 2: Freehand osteotomy.

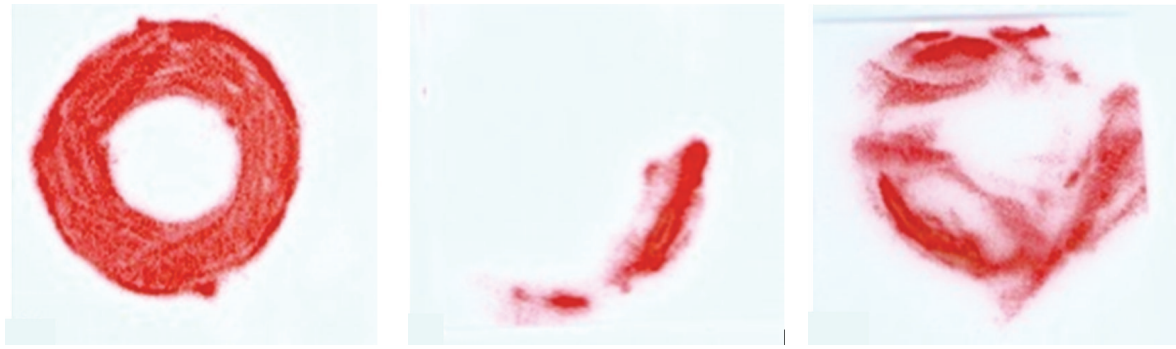
Absolute Value (sq. in.)		Percentage % [(Abs value/Control) 100]	
Mean	0.21	Mean	30.5%
Range	Min: 0.07	Range	Min: 10.1%
	Max: 0.36		Max: 52.2%

Statistical analysis of contact area measured ($N = 32$) using free-hand osteotomy technique. Control = 0.69 sq in.

4. Results

Analysis of the 32 Pressurex samples using the free-hand technique showed a mean contact area of 0.21 sq. in. (range 0.07 to 0.36). As shown in Figure 3, compared with a control of 0.69 sq. in., the mean contact area represents 30.5% of optimal surface contact (range 10.1% to 52.2%) (Table 2).

Analysis of the 22 Pressurex samples using computer navigation showed a mean contact area of 0.33 sq. in. (range 0.12 to 0.69). As shown in Figure 4, compared with a control



(a) (b) (c)

Figure 4: Scanned raw images of PRESSUREX film after contact at the allograft-host junction site made using the computer-assisted navigation technique. Of the 22 samples, contact area is seen in red for control (ideal) at 0.76 sq. in. (a), minimal contact at 0.12 sq. in. (b), and maximal contact at 0.69 sq. in. (c).

Table 3: Computer-assisted navigation osteotomy.

Absolute Value (sq. in.)		Percentage % [(Abs value/Control) 100]	
Mean	0.33	Mean	43.7%
Range	Min: 0.12	Range	Min: 15.8%
	Max: 0.69		Max: 90.8%

Statistical analysis of contact area measured ($N = 22$) using computer-assisted technique. Control = 0.76 sq in.

of 0.76 sq. in., the mean contact area represents 43.7% of optimal surface contact (range 15.8% to 90.8%) (Table 3).

A comparison of the two techniques demonstrated the absolute mean contact area was 0.21 sq. in. using free-hand versus 0.33 sq. in. using CT-navigation ($P = .002$). Mean percent contact area was 30.5% using free-hand versus 43.7% using CT-navigation ($P = .01$).

5. Discussion

Bone allograft transplantation has played an important role in skeletal reconstruction for more than one hundred and twenty years. As a bone restoring procedure, it provides soft tissue insertions to which host tendon and capsule can be attached and it can delay the need for joint resurfacing for many years. While early challenges revolved around availability of donor bone, recent focus has shifted to safety, bone-banking standards, and the technical processes of donor screening, bone preparation, and storage [8]. Current and future allograft concerns will likely revolve around optimizing union and implant longevity. Non-union, infection, and fracture serve as the major limitations of bulk allograft use.

Nonunion of the allograft-host junction is a well-recognized and well-described complication. Hornicek et al. reported non-union rates ranging from 11%, in patients not receiving chemotherapy, to rates of 27% for patients undergoing chemotherapy [9]. Similarly, in a large series of over 700 allografts spanning 20 years, Mankin et al. reported an overall nonunion rates of 17% [10].

Nonunion of allograft-host junctions is a multifactorial event and is both biologically dependent and technique dependent. Allograft bone is not living bone, so osseous union is entirely dependent upon unidirectional healing. This process, creeping substitution, occurs via cutting cones whereby osteoclast-mediated resorption is pursued by osteoblast-mediated bone formation [11–13]. The process is slow and dependent upon intimate contact between allograft-host bone. Gapping, which is tolerated under typical fracture conditions, is likely a substantial barrier to osseous union in allograft-host bone healing [14]. We believe that technical considerations to limit gapping or conversely, maximize bony approximation are thought to be critical.

Location of non-union plays an important role in that diaphyseal bone has been recognized to heal at a slower rate and have a higher rate of nonunion than metaphyseal bone [15]. Although this discrepancy is likely related to inherent differences between metaphyseal cancellous bone and diaphyseal cortical bone, there is invariably more surface area available for healing within the metaphyseal region, underscoring the relevance of maximizing contact to bone healing.

Modifications in surgical preparation of the bone have been reported. The step-cut is a well-recognized technique, which increases surface area and inherent stability across the allograft-host junction site. However, it is technically more demanding and does not permit for rotational adjustment following the osteotomy, possible reasons which explain why it has become less popular in recent years. Healey et al., 2009, proposed a surgical technique in cases whereby limited remaining bone stock could be supplemented with a structural allograft, which was interposed or telescoped into the remaining host bone [16]. This served to maximize surface contact between host and allograft bone and permit, in turn, use of more conservative prosthesis.

In the current study, computer-assisted navigation was employed, allowing for more accurate transverse osteotomies, thereby increasing contact area at the allograft-host interface. However, even under controlled simulated conditions, absolutely congruent osteotomies are technically

difficult to create. Average bony contact areas using navigated techniques were recorded at 43.7%, 13.2% greater than the free-hand technique ($P = .01$). This finding may help explain the observed rate of non-union when using free-hand osteotomy techniques and supports the notion that an increased contact area may promote bone healing.

Limitations of this study include the simulated study design, which may not entirely parallel the intraoperative human condition as well as the small number of samples collected. It is possible that a discrepant amount of bone was lost in one technique compared with the other and that this, in turn, impacted the congruency of the osteotomies. However, since bone loss is largely a function of saw blade cutting characteristics and since the same saw blade design was standardized throughout the study this was felt to be of minimal impact. Our technique of compression plating was standardized as well and intended to recapitulate the intraoperative maneuver whereby a compression screw is fully seated in order to achieve a finite amount of compression across a fracture site or osteotomy site. The compression obtained is not further affected by the placement of additional non-compression screws and for this reason additional screw placement was not deemed necessary. In addition, it is recognized that the deviation from a perfectly congruous osteotomy can take on many orientations and angles. We did not attempt to classify or categorize each sample but rather chose to quantify the resulting contact area as a means of comparing the two techniques. This model does not exactly recapitulate the intraoperative clinical situation in that surrounding soft tissue structures are not present and the entire length of the bone is clearly visualized. This may serve to artificially improve the free hand technique in particular, as adjustments based on visual cues would seemingly be easier. Finally, it is unknown whether the measured improvement in bone-on-bone contact area would in fact translate into improved biologic outcomes of bone-allograft-bone constructs and therefore the clinical relevance remains currently unclear.

In conclusion, although biology and blood supply are most likely more important than perfect mechanical congruency for the successful union at the allograft-host junction site, osteotomies generated with computer-assisted navigation, when compared to free-hand technique, have a significant increase in contact area when apposed. We speculate that increased contact may in turn improve union rates. Likewise, previous studies have reported on enhanced rates of bony union at the allograft-host junction by improvements in contact area [17]. Obvious benefits of this could include decreased morbidity, revision surgery rates, and associated cost.

Going forward, it is likely that navigated-techniques will play an important role in the planning of, execution of, and reconstruction following complex tumor surgery. Which system and how it is employed or developed remains to be seen. An optimal system would permit for preoperative planning and therefore preoperative custom implant fabrication. In addition, it would allow for easy intraoperative registration, a high degree of accuracy, and easy-to-use user interface. Blending CT and MRI would likely be beneficial as well. Although basic oncology navigation software has recently become available, its continued development and enhancement as well as incorporation of navigated instrumentation such as wide osteotomes and sagittal saw blades are essential.

Conflict of Interests

The authors declare that they have no conflict of interests.

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