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Original Article

The accurate surgical margin before surgery for malignant musculoskeletal tumors: a retrospective study

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Abstract: There is no accurate volume measurement method for evaluating the response to chemotherapy in malignant musculoskelal tumors, and there is no specific preoperative evaluation method to evaluate surgical margins. Twenty-five cases of malignant musculoskeletal tumors treated from Mar 2012 to Mar 2014 were analyzed. Through the use of a connective slice-scan and augmented virtual reality technique, accurate measurement of the tumor volume and determination of surgical margins according to the standard proposed by Kawaguchi were easily reached. Specimens were sent for a pathological examination to determine the tumor type. The preoperative surgical margin was compared with the postoperative surgical margin. Curative resection or wide resection facilitated by the preoperative imaging data occurred in 92% of patients; only one case resulted in intralesional resection for malignant tumor progression, and one case resulted in marginal resection for femoral nerve invasion. There was no significant difference between the predicted margin before the operation and final margin after the operation (P>0.05). Our results demonstrate that application of continuous imaging data with enough sectional anatomy detail can provide a scientific basis for measuring the size of a tumor and identifying the tumor's surgical margins in multiple dimensions using an augmented virtual reality technique.

Keywords: Malignant musculoskeletal tumors, surgical margin, volume measurement, connective slice-scan technique, augmented virtual reality technique

Introduction

A malignant musculoskeletal tumor is a series of malignant tumors developed in bones and soft tissues and originated from mesenchyme tissues. Recurrence is the most important factor that affects the prognosis and is usually related to the surgical margin. Archiving a wide surgical margin was quite important to avoid recurrence [1, 2]. Enneking WF developed the concept of "anatomic compartment" to evaluate surgical margins in the 1980s, and the term is now set as a standard for surgical margin evaluation [3]. The Enneking/MSTS criterion focuses on the anatomic compartment; however, many tumors break through one compartment, making it inappropriate to apply this evaluation method. Consequently, a new evaluation system was drafted in 1989 by the Bone and Soft Tissue Tumor Committee of the Japanese Orthopedic Association (JOA) [4]. In this method, a surgical margin was classified into four types based on the distance between the surgical margin and the reactive zone of the tumor. These surgical margin classifications (in order of surgical extent) are curative wide margin (curative margin), wide margin, marginal margin, and intralesional margin. The surgical margin is said to be curative if the margin is more than 5 cm outside the reactive zone. It is referred to as wide if the margin is less than 5 cm. Similarly, a margin that is in the reactive zone is considered marginal, and a margin passing through a tumor as intralesional. Moreover, a wide margin is classified as adequate (at least 2 cm outside the reactive zone) or inadequate (1 cm). Kawaguchi N designed an updated evaluation system to differentiate surgical margins according to the barrier theory.

However, these findings are obtained from analyzing the therapeutic results of cases that

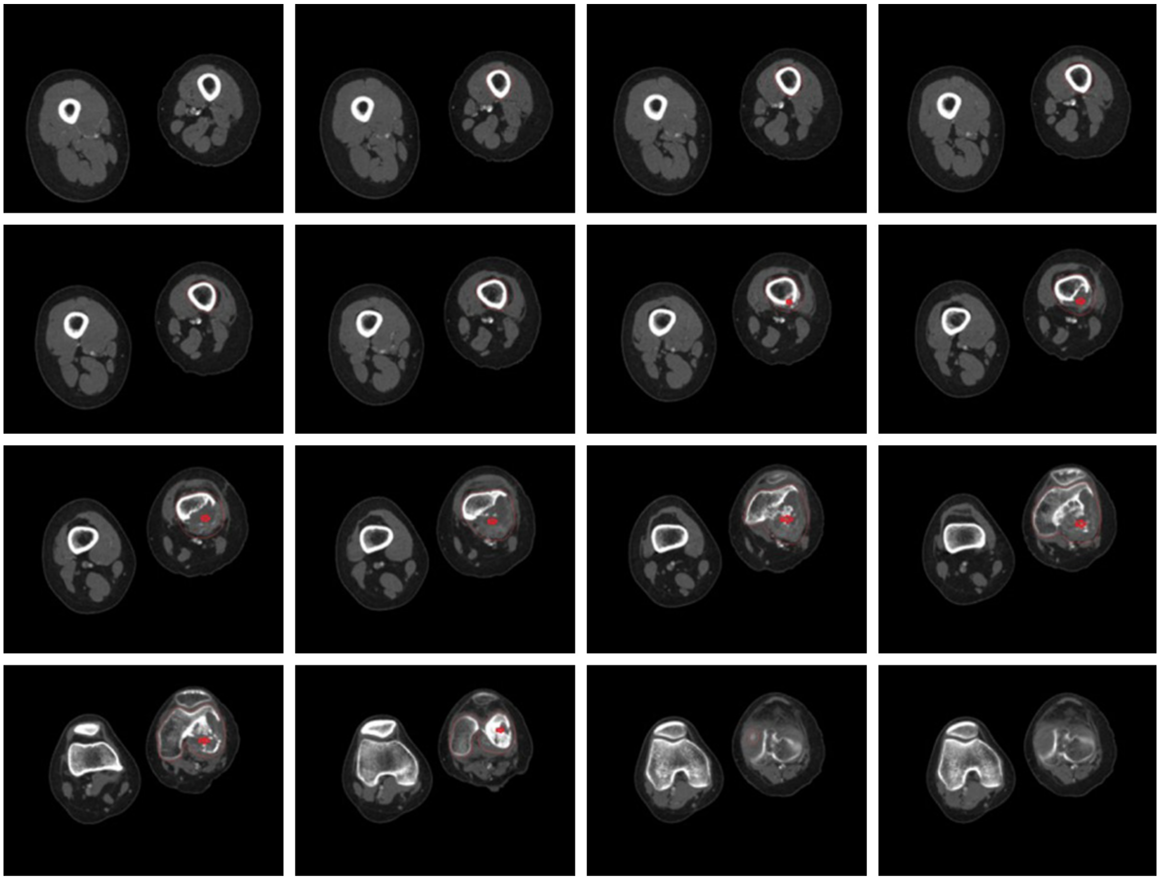

Figure 1. Connective slice-scan of computerized tomographic angiography images and connective analysis of axial images for an osteosarcoma around knee joint.

involve surgical procedures and that are evaluated manually after the operation. There is no satisfactory method to evaluate the accurate surgical margin preoperatively and to make a precise operation plan. Therefore, we are the first to develop a novel method of designing an accurate surgical margin before operations for malignant bone and soft tissue tumors: a slice-scan and augmented reality technique. This study was a prospective cohort study of surgical margins in malignant bone and soft tissue tumors before surgery. The surgical margin was designed and optimized by the treating surgical oncologists (Jinpeng He & Caihong Yang) according to Kawaguchi's criteria [4, 5]. Then, the preoperative surgical margin was assessed by the same surgical oncologists according to the anatomic examination of those tumors. The consistency between the surgical margin in the plan and the surgical margin after the operation was compared to assess the validity of this surgical margin designation system.

Materials and methods

Clinical materials

Twenty-five patients (13 males and 12 females) admitted to our hospital from Mar 2012 to Mar 2014 were diagnosed with 25 cases of malignant bone and soft tissue tumors. The youngest was 15 years old, the oldest was 68 years old, and the average age was 40.8 years. All patients received CTA and MRI examinations before the operation. The post-operative pathological examination revealed seven cases of osteosarcoma with different subtypes, four cases of primitive neuroectodermal tumor (PNET), two cases of malignant solitary fibrous tumor (MSFT), one case of malignant fibrous histiocytoma (MFH), one case of liposarcoma, two cases of synovial sarcoma, one case of extraskeletal myxoid chondrosarcoma (EMC), one case of chondrosarcoma, one case of myxofbrosarcoma, one case of undifferentiated spindle cell sarcoma, and four cases of giant cell tumor of

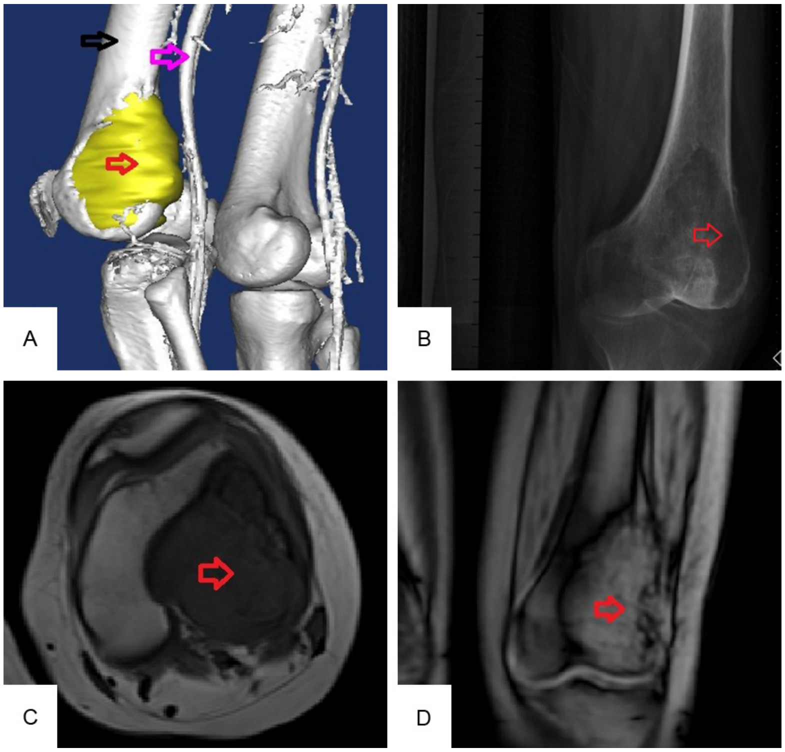

Figure 2. 3D reconstruction images, MRI and X-ray of an osteosarcoma around knee joint. (A. 3D reconstruction image; B. X-ray; C. Axial image on MRI; D. Coronal image on MRI).

bone (GCT). CT, MRI (1.5T, General Motors Corporation), MATERIALISE MIMICS 10.01 (Belgium, MATERIALISE), and the Geomagic studio 12.0 software (USA, Geomagic) were utilized. All patients signed an informed consent form before inclusion in this study.

Connective slice-scan technique

All CT scans were performed with a GE 64-row multislice spiral computerized tomographic (CT) scanner. The scans were operated at 120 kV, 240 mA, and a 0.625 mm slice thickness. Computerized tomographic angiography (CTA) and MRI of the extremities were used to establish the image diagnosis and analysis of the bone and soft tissue tumor. The images were examined slice by slice manually before the operation (**Figure 1** and Supplementary Movie 1). The tumor was verified according to the CTA and MRI images. The oncology margin was identified on the CTA images while referred to the MRI images. If the density of the tumors differed from that of the surrounding tissues, that is, with different Hounsfield values on the CTA images, the oncological margin could be selected automatically. If not, we had to verify the oncological margin line manually. A connective review of all scans provided enough information to verify the oncological margin, especially for those that were difficult to differentiate from the surrounding tissues (**Figure 1** and Supplementary Movie 1).

Augmented virtual reality technique

The acquired data sets were reconstructed in MATERIALISE MIMICS using the bone reconstruction algorithm of the inbuilt software. An image segmentation technique (Mimics v. 10.0, Materialise, Leuven, Belgium) was used to generate patient-specific 3-dimensional models of the tumors and important anatomic structures. The geometry of each bone was extracted by segmentation of the axial CT image, implementing a semi-automatic tool with minor manual adjustments. This created a 3D surface mask of the bones. The surface masks of other anatomic structures were created in a similar manner (**Figure 2A**). The oncological margin was identified manually slice by slice with a reference to the MRI and X-ray images, as shown in **Figure 2**. The oncological margin was reconstructed by MATERIALISE MIMICS to make a digital 3D image for augmented virtual reality (Supplementary Movie 2). The arteries and veins were reconstructed at the same time, to create a better operation plan.

Classification of the surgical margins

All patients were divided into two groups according to their extent of tumor invasion. Once a tumor was restricted to one compartment, the surgical margin was designated as the margin of this compartment (Supplementary Movie 3). If the tumor was not restricted to one compartment, then the surgical margin was classified into the following four types: curative wide margin (curative margin), wide margin, marginal

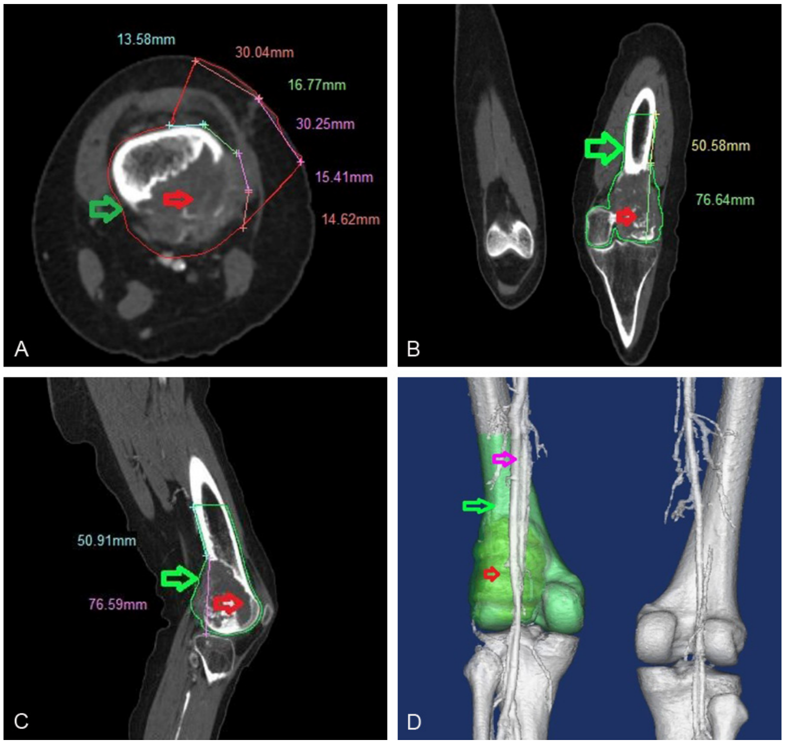

Figure 3. The construction and optimization of the surgical margin in different directions within this reconstruction system. (A. The surgical margin on axial image included a resection of the biopsy channel; B. The surgical margin on coronal image; C. The surgical margin on sagittal image; D. The surgical margin on augmented virtual reality image).

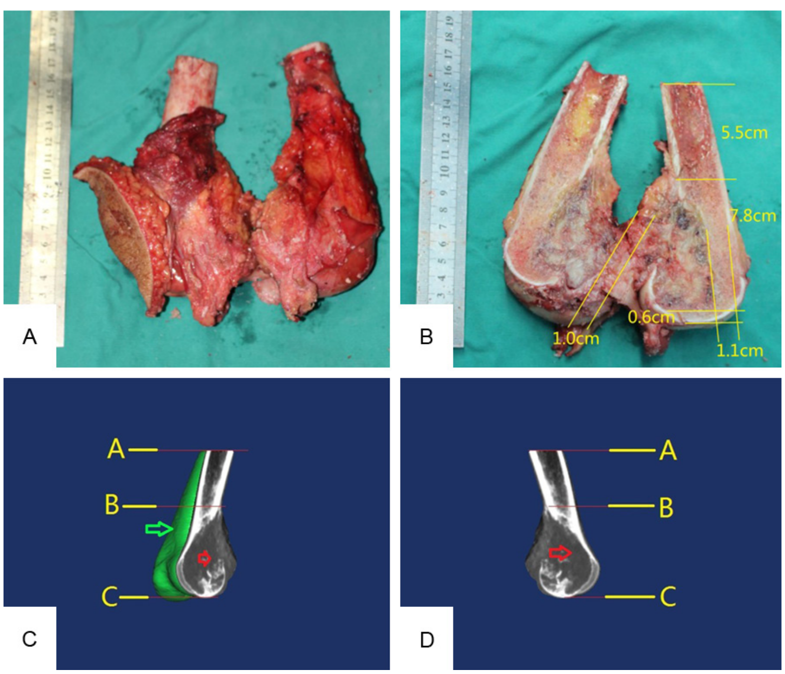

Figure 4. The comparison of virtual surgical margin to grossly evaluation for an osteosarcoma around knee joint. (A. Photo of split tumor; B. Measurement of surgical margin in practice; C and D. Virtual surgical split of the tumor).

margin, and intralesional margin. However, any existing barriers were calculated according to the thickness and invasive condition of this barrier. A thick barrier implies physically strong membranous tissues of various thicknesses with a white luster through which the underlying tissue cannot be seen. For instance, the iliotibial band, joint capsule, and peritoneum of an infant or young child fall into the thick-barrier group. By contrast, a thin barrier means weaker membranous tissue through which the underlying tissue can be seen, yet which contains healthy fascia of an individual muscle, for example, the peritoneum in adults, the vascular sheath and the epineurium [6]. We classified the margin into four types: the curative margin, the wide margin, the marginal margin and the intralesional margin. To facilitate the evaluation of the accurate margin, the barrier was presumed to be equal to 2 or 3 centimeters based on the thickness. A thick barrier was set as a margin equal to 3 cm, whereas a thin barrier was defined as a margin of 2 cm; 1 cm was subtracted if a barrier was invaded but not penetrated. The compartment margin was also evaluated according to the measurement in every direction and identified using the Kawaguchi method. The surgical margin was said to be curative if the margin was more than 5 cm outside the reactive zone and was referred to as wide if the margin was less than 5 cm. Similarly, a margin that was in the reactive zone was considered

Table 1. Comparison of the surgical margins archived in malignant bone and soft tissue tumors

No.	Sex	Age	Location	Diagnosis	TNM	Margin/cm	Designed margin	Final margin
1	F	21	Femur	Osteosarcoma	T1N0M0	1.3	Wide margin	Wide margin
2	F	40	Thigh	PNET	T1N0M0	3.5	Wide margin	Wide margin
3	F	55	Tibia	Osteosarcoma	T2N0M0	3.1	Wide margin	Wide margin
4	F	55	Thigh	MSFT	T2N0M0	2.7	Wide margin	Wide margin
5	F	59	Upper arm	MFH	T3N0M0	6.3	Curative margin	Curative margin
6	F	23	Calf	SCS	T3N0M0	0	Marginal margin	Intralesional margin
7	F	15	Calf	PNET	T2N0M0	3.2	Wide margin	Wide margin
8	F	19	Femur	GCT	T2N0M0	3.3	Wide margin	Wide margin
9	F	41	Thigh	PNET	T1N0M0	4.2	Wide margin	Wide margin
10	F	19	Tibia	Osteosarcoma	T1N0M0	5.9	Curative margin	Curative margin
11	F	52	Femur	GCT	T2N0M0	5.3	Curative margin	Curative margin
12	F	23	Femur	GCT	T2N0M0	2.7	Wide margin	Wide margin
13	M	43	Thigh	Synovial sarcoma	T2N0M0	6.3	Curative margin	Curative margin
14	M	40	Haunch	EMC	T2N0M0	2.1	Wide margin	Wide margin
15	M	21	Femur	Osteosarcoma	T2N0M0	8.1	Curative margin	Curative margin
16	M	38	Thigh	PNET	T2N0M0	3.5	Wide margin	Wide margin
17	M	64	Upper arm	MSFT	T1N0M0	2.7	Wide margin	Wide margin
18	M	68	Haunch	Chondrosarcoma	T3N0M0	0.5	Wide margin	Marginal margin
19	M	58	Tibia	GCT	T1N0M0	2.6	Wide margin	Wide margin
20	M	43	Thigh	PNET	T1N0M0	1.1	Curative margin	Curative margin
21	M	62	Thigh	Liposarcoma	T3N0M0	2.1	Wide margin	Wide margin
22	M	47	Thigh	Synovial sarcoma	T1N0M0	7.9	Curative margin	Curative margin
23	M	31	Clavicle	Osteosarcoma	T3N0M0	1.5	Wide margin	Wide margin
24	M	32	Pubis	Osteosarcoma	T1N0M0	2.4	Wide margin	Wide margin
25	M	52	Thigh	MF	T1N0M0	3.1	Curative margin	Curative margin

F, female; M, male.

marginal, and a margin passing through a tumor as intralesional. Moreover, a wide margin was classified as adequate (at least 2 cm outside the reactive zone) or inadequate (1 cm).

Evaluations of the surgical margins in the plan

The surgical plan was created to maximize the margin and minimize the loss of tissue and function. These digital surgical margins were sketched one by one on the basis of the oncological margin. After a global evaluation of all images, a surgical plan was created according to the clinical experience and CTA & MRI images (**Figure 3**). Then, an estimated surgical margin was sketched on every slice of the images. The final surgical margin depended on the worst margin archived in different directions. For example, a curative margin was archived on the upper side, a wide margin was archived on the lower side, and a marginal margin was archived in the other direction; we defined this margin as a marginal margin instead of a curative margin or wide margin, following the same principle as the Cannikin Law. A global evaluation of the 3D surgical margin was revised according to the axial/coronary/sagittal images, especially avoiding principal blood vessels and nerves.

Evaluation of the surgical margins in every specimen after the operation

All patients received a gross evaluation after removal of the tumor in time, and the results were recorded (**Figure 4A**, **4B**). Every removed tumor was separated along with the long axis of the tumor. External and internal surface pictures taken by shooting the cameras in the vertical orientation were recorded with a caliper laid beside the tumor. All manual measurements were taken post-operatively, and manual measurements were made by refereeing the caliper length (**Figure 4A**, **4B**). To evaluate the

Figure 5. MRI images for the patient of osteosarcoma around clavicle.

accuracy of the surgical margin obtained by this method preoperatively, the surgical margin in the plan was compared with those obtained by the conventional manual approach in practice (**Figure 4**).

Microscopic evaluation of the pathological sections

All removed tumors were fixed by formalin and embedded in paraffin and made into paraffin sections. The incised edge of the specimens was blindly checked by pathologists.

Statistical analysis

All analyses were conducted using SPSS 17.0 software (SPSS Inc., Chicago, USA). The data were expressed as $\bar{x} \pm s$. The homogeneity of variance was tested by Levene method in each group. If the variance is homogeneous, the single factor analysis of variance and t test are used to compare the sample means. The non-parametric test is used if the variance is not uniform. P values < 0.05 were considered indicative of a significant difference.

Results

All surgeries were conducted according to the 3D surgical plan before the surgery. The surgical margins in practice were measured in different directions. Twenty-three cases received a surgical margin in consistent with the 3D surgical plan, which included a compartment margin, a curative margin, a wide margin and one case with a marginal margin (**Table 1**); there were no significant differences between the surgical margin in the preoperative plan and the postoperative surgical margin (P=0.157). This case of a marginal margin was short of normal tissues to be resected to archive a higher margin type. Only two cases proved to be without a sufficient margin; one of them was diagnosed as a benign tumor by a pathologist at another hospital and received an intralesional margin resection for malignant transformation after several recurrences and complete enclosure of the tibia nerve/artery/vein. The other was diagnosed as a chondrosarcoma and resected in an intralesional margin for enclosure of the femoral nerve. Five (20%) of 25 patients received an amputation to archive a satisfactory surgery margin, with a limb salvage rate of 80%. One patient with multiple times recurrent MFH was misdiagnosed as having a hematoma, at another hospital. She received a wide resection at first but relapsed within one month; interscapulothoracic amputation was ultimately applied. One patient with aGCT with intertrochanteric femoral pathological fracture was treated using reduction and internal fixation primarily. There was an extremely large recurrent lesion surrounding her hip before the union of her intertrochanteric femoral fracture. Two cases of synovial sarcoma were treated by amputation-one for invading all the thigh muscles and extending outside the skin. One of the patients received an amputation for not having a wide margin by 3D surgical margin evaluation. Two patients with osteosarcoma and myxofbrosarcoma received a knee joint disarticulation and an amputation, respectively, both for not having a wide margin by 3D surgical margin evaluation. 23/25 (92%) of patients received a satisfactory surgery margin on the basis of the 3D surgical plan and negative incised margins by pathological examination.

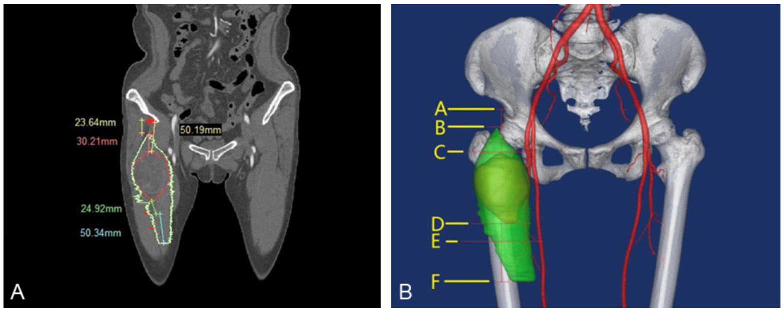

Figure 6. Optimization of the surgical margin before operation for malignant solitary fibrous tumor within 3D reconstruction system. (A. Measurement of the surgical margin in plan; B. Virtual display of the surgical margin in plan).

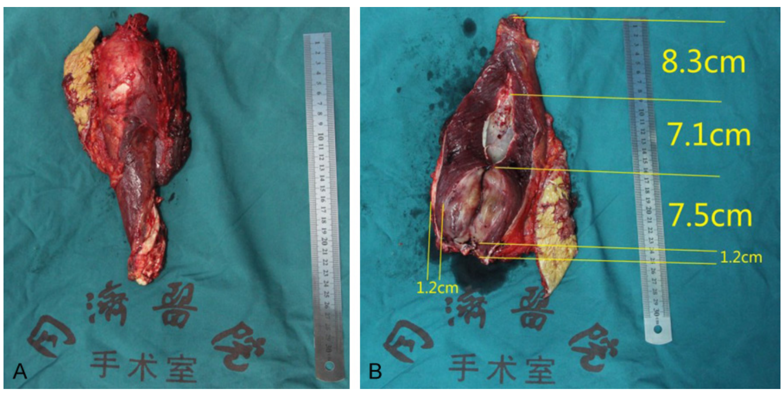

Figure 7. Measurement of surgical margin in practice for malignant solitary fibrous tumor after operation. (A. Split photo of the tumor; B. Measurement of surgical margin after operation).

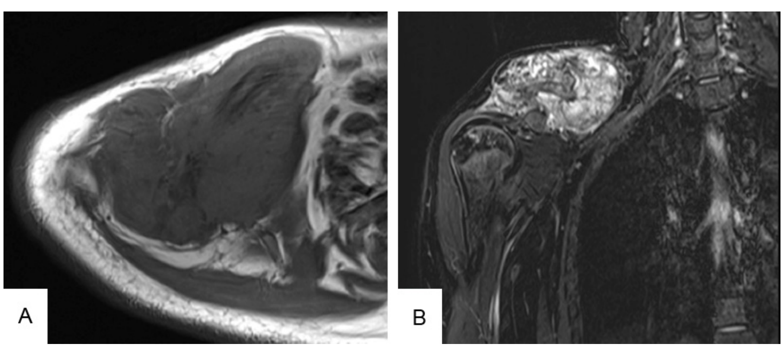

Figure 8. MRI images for malignant solitary fibrous tumor in a thigh.

All resected samples underwent measurement, dissection and illustration after the operation.

Until Dec 2017, the follow-up time after the surgery-treatment was 6 to 64 months (median 42 months). And 10 of them (60%) were still alive. In patients still alive, their minimum follow-up time had reached 48 months. However, the others lost follow up for change of their telephone numbers. Two local recurrences (13.33%) at initial tumor site occur in one case of malignant solitary fibrous tumor (MSFT) and one case of spindle cell sarcoma (SCS). At metastasis, lungs were again involved in three cases (two in PNET and one in osteosarcoma). Distant metastasis was also present in another three cases (multiple metastases in synovial sarcoma, limb metastases in spindle cell sarcoma and mediastina metastasis in osteosarcoma). A patient with GCT met a complication of prosthesis loosening at the fourth year past operation and received a revision surgery. Other complications were not observed.

Classical case presentation

Case 1: A female, 55 years old, underwent an MRI revealing an MSFT in the right thigh (**Figure 5**); a sarcoma was diagnosed as a preliminary diagnosis by needle biopsy. The tumor existed in one muscle compartment and could be removed through the anatomic compartment. The upper surgical margin was 3 cm at most, the lower surgical margin was over 5 cm, and the border surgical margin surrounding this tumor mass was no more than 1 cm with a thin barrier (**Figure 6A**). Therefore, we removed the muscle involving a wide margin that was only archived. Because a reactive region existed, a lower margin 5 cm away from the tumor border was planned. Then, we constructed the resection region in every axial image in the CTA. A 3D digital model of the tumor and the resection region was reconstructed by Mimics (**Figure 6B**). After the operation, the removed tissues were photographed and split into two parts. The measurement was

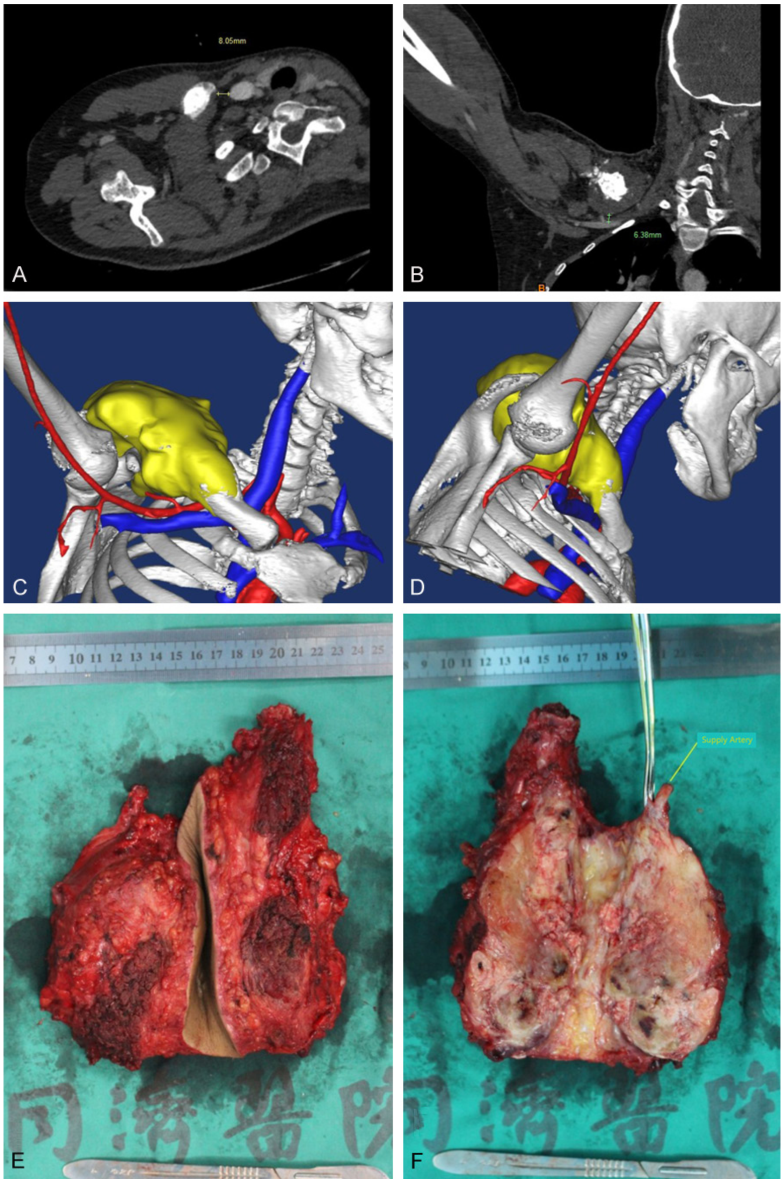

Figure 9. Presentation of the important anatomic structures on CT, virtual image and sample pictures. (A and B. Measurement on CT; C and D. Virtual display of the artery; E and F. Measurement on tumor sample photos).

performed according to the split photo (**Figure 7A**). The upper surgical margin was 1.2 cm in fact (but with a thin barrier), the lower surgical margin was 8.3 cm, and the border surgical margin surrounding this tumor mass was 1.2 cm (with a thin barrier) (**Figure 7B**). Therefore, we could remove this muscle that involved a wide margin that was archived only with a surgical margin of 3.2 cm.

Case 2: A male, 31 years old, underwent a CTA and MRI revealing an osteosarcoma in the right clavicle (**Figure 8**); the osteosarcoma was confirmed as a preliminary diagnosis by surgery biopsy. The distance between the subclavian artery and the tumor was measured in different directions on CTA images (**Figure 9A**, **9B**). The closest distance was measured as 0.6 cm (**Figure 9A**, **9B**). We made a 3D reconstruction to demonstrate the relationship of the tumor to the surrounding blood vessels and anatomical structure characteristics (**Figure 9C**, **9D**, Supplementary Movie 4). Moreover, the blood supply artery of the tumor was also clearly shown and provided a reminder to the surgeon in case of uncontrolled bleeding (**Figure 9C**, **9D**, Supplementary Movie 4). After the operation, the removed tissues were photographed and split into two parts, and the measurement was made according to the split photo (**Figure 9E**). The surgical margin was less than 1 cm in fact (**Figure 9F**). Therefore, an inadequate wide margin was ultimately archived. The blood supply artery was depicted in photos. The pathological examination revealed osteosarcoma.

Discussion

There is no specific preoperative evaluation method to evaluate surgical margins. This study designed a precise and individualized surgical margin preoperatively by the 3D reconstruction technique, to provide reliable reference data for resecting malignant bone and soft tissue tumors. Recent progress and neoadjuvant chemotherapy advances have dramatically improved the disease-specific survival rate and limb salvage rate in the treatment of malignant bone and soft tissue tumors [7]. The surgical margin is an important factor affecting the prognosis of malignant bone and soft tissue tumors [8, 9]. We developed this 3D system to evaluate the surgical margin before the operation and to optimize the surgical plan. The distance from the tumor to the incised margin in the plan was measured in every direction before the operation, and the incised margin in the plan was modulated according this measurement to archive an optimized surgical margin. The best choice of surgical margin had a maximal resection margin but, at the same time, minimal functional loss [10, 11].

Neoadjuvant chemotherapy was widely recommended as an important part of standard comprehensive treatment for many malignant bone and soft tissue tumors [12, 13]. As an increasing number of neoadjuvant chemotherapy protocols were studied, the evaluation methods of neoadjuvant chemotherapy have become the focus of the research in recent years [14]. General clinical characteristics evaluations include the tumor invasion region, calcification, bone destruction, edema, necrosis, hemorrhage and fibrosis. The tumor necrosis rate (TCNR) was established by Huvos [15] & Rosen [16] and admitted as the gold standard in evaluating the response to chemotherapy. However, it is not a commonly applied method in clinics because of the extensive time spent measuring the necrosis rate and the inability to measure repeatedly. Taking this into consideration, the volume evaluation system was widely used and generally accepted as the best choice to evaluate the response to chemotherapy. The Cooperative Ewing's Sarcoma Study (CESS 81) established the first volume evaluation system according to the tumor shape. If the tumor was shaped like a cylinder, the volume was calculated by the formula $V=\pi(r_1+r_2)^2*h/4$ [17]. If the tumor was shaped like an ellipsoid, the volume was calculated by the formula $V=\pi*a*b*c/6\approx a*b*c*0.52$ [18]. Abudu [19] updated the CESS method according to the tumor location, and the ellipsoid model formula was certified as the standard volume calculating system. However, it is only an approximate estimation of the tumor volume but not the actual volume. Shin first developed a summary method with the formula $T=\sum Ts*t$ by MRI images. We developed this 3D volume-calculating system, which has the same effect as Shin's method but with a higher accuracy due to thinner layer reconstruction. This system was proven to have a higher accuracy than the ellipsoid model method. It also indicated that higher dimensional measurements were significantly better predictors of overall survival [20].

The impact of therapy on quality of life is predicated on an ability to preserve those structures necessary for function, to match patient expectations with oncological appropriate treatments, and to design a rehabilitation program that can be followed over the long term to sustain function [21]. Amputation is therefore widely used as the curative treatment protocol in malignant musculoskeletal tumors in extremities without distant metastasis [22]. Not surprisingly, a comparison of amputation with limb salvage showed no survival benefit for amputation [23]. Therefore, it is important to define a consolidated standard for the indication of limb salvage. Here, we established this surgical margin system to formulate a quantized indication criterion for limb salvage. Surgical margins were evaluated before surgery in all patients to determine the operation plan. If an intralesional margin turns out to be an inevitable event for malignant musculoskeletal tumors, amputation will be the preferred choice. Otherwise, a limb salvage operation should be designed for patients most likely to have a marginal/wide/curative margin, except for those with repeated relapse after resection.

Here, we applied this technology to study the surgical margin, including a virtual operation process. Augmented reality (AR) can be used in surgery as a navigation tool, by creating a patient-specific virtual model through 3D software manipulation of DICOM imaging (e.g., CT scans) [24]. Indeed, the 3D-CT digital models revealed that a surgical plan can be created under a comprehensive and detailed assessment; 3D digital models and 3D surgical margins provide a way to employ precise robotic surgery with automatic registration. How can we archive a wide margin without amputation for malignant musculoskeletal tumors? This method offered a feasible way through a carefully designed surgical margin before the operation. Three-dimensional surgical margins were carefully determined by the cooperation of experienced surgeons and radiologists in the axial, sagittal and coronal directions. However, we compared the planned surgical margins on augmented reality reconstructions in a small group of patients to their final surgical margins without a comparison group such as amputation or limb salvage without using this method.

In conclusion, this is the starting point to develop this method and thereby assist surgeons to create a surgery plan with an accurate three-dimensional surgical margin before surgery. Many improvements should be added, and a novel pathway should be found to archive the final point in the better treatment of malignant musculoskeletal tumors. The use of continuous imaging data with a sufficient amount of sectional anatomy details can provide a more scientific basis for measuring the size of a tumor and identifying the surgical margins of the tumor in multiple dimensions by an augmented virtual reality technique. The surgical margin before an operation is a deciding factor for the indication of limb salvage.

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Disclosure of conflict of interest

None.

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Supplementary Movie 1. Connective slice scan and analysis of the osteosarcoma.

Supplementary Movie 2. Augmented virtual display of the osteosarcoma and the bones, popliteal artery and vein.

Supplementary Movie 3. Connective slice scan of the malignant solitary fibrous tumor.

Supplementary Movie 4. Augmented virtual display of the osteosarcoma. The artery was marked in red, and the vein was marked in blue. The tumor was marked in yellow, and the bone was marked in white.