

Research Progress on the Evaluation and Clinical Value of Negative Surgical Margins in Osteosarcoma

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Abstract: Achieving negative surgical margins is a critical objective in osteosarcoma management, directly linked to reduced local recurrence and improved survival. This review comprehensively examines the evaluation techniques and clinical significance of these margins. We discuss the ongoing debate surrounding the optimal margin width and the impact of neoadjuvant chemotherapy on this standard. The application of conventional imaging (X-ray, CT, MRI) and advanced technologies (radiomics, fluorescence imaging, robot-assisted surgery) for margin assessment is analyzed. Furthermore, we explore treatment strategies to secure negative margins. By synthesizing current evidence, this article aims to guide clinicians in margin selection and highlights future directions for improving oncological outcomes.

Keywords: osteosarcoma, negative surgical margins, imaging technology, CT, MRI

Introduction

Osteosarcoma¹⁻³ is the most common primary malignant bone tumor, accounting for approximately 35.5% of all malignant bone tumors.^{1,4} It exhibits a bimodal age distribution, with peak incidences in adolescents (median age: 15–20 years) and older adults (>65 years). Histologically, it is defined as a high-grade spindle cell neoplasm where malignant cells produce osteoid.⁵ Osteosarcomas are broadly categorized into two groups: primary (idiopathic, with no identifiable cause) and secondary (resulting from predisposing conditions, such as Paget's disease, prior radiotherapy and so on). The appendicular skeleton is the most common site of involvement, particularly around the knee joint, with the distal femur and proximal tibia being the most frequently affected locations. Management requires a multidisciplinary approach, combining systemic chemotherapy and local surgical therapy.⁵

Surgical margin status is a critical determinant of prognosis. Multiple studies have established that a positive surgical margin (indicating residual tumor cells at the resection edge) is an independent predictor of higher local recurrence (approximately 30.5%) and poorer overall survival.⁶⁻⁸ The achievement of a negative margin is influenced by several factors, including tumor location, size, stage, response to neoadjuvant chemotherapy, surgical technique, and the accuracy of intraoperative pathological assessment. Therefore, a primary goal of osteosarcoma surgery is to obtain a precise negative margin to minimize local recurrence and improve patient survival. Significant progress has been made in evaluating and achieving negative margins in osteosarcoma, particularly through advances in imaging, surgical techniques, and multidisciplinary care. The introduction of 3D printing and computer-assisted surgery has further enhanced surgical precision. However, accurately determining the tumor boundary remains a technical challenge. Comparative studies have revealed that traditional imaging modalities have limitations: X-rays often underestimate, while Emission Computed Tomography (ECT) tends to overestimate the actual tumor size compared to pathological findings. This indicates that reliance on these conventional methods alone can lead to inaccurate surgical margin assessment. As noted in a systematic review by Haitham Shoman,⁹ emerging technologies hold high potential for intraoperative margin

detection. For instance, combining radiomics with intraoperative navigation can provide more accurate tumor boundary information, thereby improving the rate of achieving negative margins. This article examines the assessment of osteosarcoma margins by analyzing traditional and emerging imaging techniques, along with their clinical applications. It aims to synthesize current evidence to assist clinicians in making informed decisions regarding margin selection.

Application of Conventional Imaging in Osteosarcoma Margin Assessment

Conventional X-ray serves as a preliminary imaging modality for evaluating osteosarcoma margins.¹⁰ It effectively demonstrates characteristic features such as bone destruction, periosteal reaction and soft tissue masses, and aids in assessing tumor location, size, and relationship with surrounding structures.¹¹ However, its utility in determining negative margins is limited by several factors. Firstly, due to its low soft-tissue resolution, X-ray fails to clearly delineate the tumor boundary from adjacent soft tissues, compromising assessment accuracy. Secondly, it is insensitive to early micro-metastases within the bone marrow;¹² thus, a radiographically normal appearance at the margin cannot reliably exclude the presence of tumor cells. Lastly, interpretation is highly subjective and varies significantly with the reader's experience.

Compared with CT and MRI, X-ray is notably inferior for assessing tumor margins and soft tissue invasion.^{11,13,14} This was corroborated by a retrospective study of 39 osteosarcoma patients, which categorized margins into 1 cm, 2 cm, and 3 cm groups,¹⁴ the study found that the average difference between X-ray measurements and pathological findings was 1.09 cm (standard deviation: 0.79 cm), whereas for MRI, it was only 0.71 cm (standard deviation: 0.70 cm). Importantly, MRI demonstrated a smaller measurement error than X-ray in 84% of cases (32/38), a difference that was statistically significant ($p < 0.001$).

While X-ray is inferior to CT and MRI for margin assessment,¹³ each cross-sectional modality has distinct characteristics. Computed Tomography (CT) offers high spatial resolution for visualizing bony structures and tumor boundaries, making it valuable for assessing cortical bone, medullary cavity, and soft tissue invasion. However, its ability to define the precise boundaries of osteosarcoma and detect distant satellite lesions remains limited.

Magnetic Resonance Imaging (MRI) is widely regarded as superior for this purpose.^{15,16} A retrospective study by Mei Jing¹³ of 29 osteosarcoma patients quantitatively compared imaging findings with histological measurements. The results demonstrated that the tumor invasion ranges measured by MRI (lateral: 73.3 ± 27.7 mm; longitudinal: 123.6 ± 36.5 mm) were remarkably closer to the histological gold standard (lateral: 72.9 ± 26.1 mm; longitudinal: 119.8 ± 34.8 mm) than those from CT (lateral: 70.1 ± 22.7 mm; longitudinal: 84.4 ± 30.3 mm) or X-ray. This study confirmed that MRI in most cases depicts the true invasion range of osteosarcoma, offering a significant advantage over both CT and X-ray.

Bone scintigraphy (or ECT) provides a comprehensive survey of the skeletal system, which aids in detecting distant satellite lesions. However, it offers considerably lower accuracy than MRI for defining tumor resection margins. This was demonstrated in a study by Dong Yang,¹¹ which analyzed 19 osteosarcoma patients who underwent preoperative X-ray, MRI, bone scan, and pathological examination. During the study, tumor size was measured macroscopically, and specimens were sectioned into 10 mm thick slices based on anatomical landmarks before being further divided into 1×1 cm pieces for routine pathological analysis. The results revealed a statistically significant difference between pathological findings and both X-ray and ECT measurements, whereas no significant difference was observed between pathological and MRI measurements. This finding further validates the superior accuracy of MRI in evaluating osteosarcoma margins.

MRI is established as a crucial modality for evaluating the invasion range of osteosarcoma, owing to its high soft-tissue resolution which clearly delineates the tumor's relationship with surrounding structures.^{17,18} T1-weighted imaging, in particular, is instrumental in determining the surgical resection range.¹⁷ A study by Han¹⁷ involving 17 patients demonstrated that surgical plans based on T1WI resulted in no significant difference from postoperative histopathological findings when a 2–3 cm margin was used as the standard, whereas X-ray and CT measurements showed statistically significant discrepancies ($P < 0.05$).

Despite its widespread use in preoperative planning, uncertainty remains in MRI ability to predict the precise intraosseous extent of osteosarcoma.¹⁹ The accuracy of MRI interpretation is critical, as it directly influences the

Table 1 Comparison of Conventional Imaging Modalities for Osteosarcoma Margin Assessment

Imaging Modality	Advantages	Limitations	Key Findings
X-ray	- Low cost, widely available. - Good for initial assessment of bone destruction and periosteal reaction.	- Poor soft-tissue resolution, cannot delineate tumor-muscle interface. - Insensitive to marrow infiltration. - Highly operator-dependent.	- Significantly underestimates tumor extent compared to pathology.¹⁰ - Average measurement error vs pathology: ~1.09 cm.¹⁰
CT	- Excellent spatial resolution for bony anatomy. - Clear depiction of cortical destruction and matrix mineralization.	- Limited accuracy for defining intra-medullary and soft-tissue boundaries. - Poor detection of skip/satellite lesions.	- Tends to underestimate longitudinal tumor extent compared to MRI and histology.¹³ - Less accurate than MRI for surgical planning.
MRI	- Superior soft-tissue contrast. - Gold standard for assessing intramedullary and extraosseous extent. - Multiplanar capability.	- May overestimate tumor due to peritumoral edema - Accuracy is sequence-dependent and influenced by reader experience.	- Measurements show the closest correlation with histological tumor size.^{17,18} - T1-weighted sequences are most reliable for determining resection range.¹⁷
Bone Scan (ECT)	- Provides a whole-body survey. - Excellent for detecting distant bone metastases.	- Very low specificity and spatial resolution. - Cannot reliably define the precise margins for resection.	- Tends to overestimate the true pathological tumor margin.¹¹ - Primarily used for staging, not for primary margin planning.

achievement of negative margins and the risk of local recurrence.²⁰ Furthermore, peritumoral edema and inflammation can obscure the true tumor boundary on MRI, potentially leading to an overestimation of disease extent.²¹ A retrospective study by Matthew¹⁹ of 55 patients quantified this variability, reporting a mean difference of 8.26 ± 11.0 mm ($r = 0.516$) between T1WI and pathological margins, and 7.96 ± 11.5 mm ($r = 0.494$) for T2-weighted sequences, underscoring the challenges in achieving perfect correlation with histology.

Multimodal image fusion technology integrates complementary data from different imaging modalities to provide a more comprehensive assessment of tumors. In osteosarcoma surgery, the fusion of CT and MRI is most common, combining CT high-resolution bony anatomy with MRI superior soft-tissue contrast. This synergy allows for a more precise delineation of the tumor extent and its spatial relationship to critical surrounding structures. The clinical benefits of this approach were demonstrated in a retrospective study by Du²² of 48 primary pelvic osteosarcoma patients. Compared to the control group ($n=27$), the image fusion group ($n=21$) exhibited significantly improved surgical outcomes. The procedure time was substantially shorter (Type III: 144.0 ± 31.6 vs 248.2 ± 56 minutes; Type IV: 173.0 ± 42.0 vs 306.1 ± 62 minutes; both $p < 0.01$), and intraoperative blood loss was markedly reduced (484.8 ± 226.3 vs 836.1 ± 359.8 mL, $p < 0.01$). Crucially, the incidence of R1 margins (microscopically positive margins with residual tumor cells) and local recurrence was significantly lower in the fusion group (4.8% [1/21] vs 22.2% [6/27], $p = 0.040$). The study concluded that CT-MRI image fusion enhances surgical precision, leading to shorter operations, reduced blood loss, and a lower recurrence rate by facilitating the achievement of adequate surgical margins.

Table 1 lists the advantages, limitations, and key findings of the conventional imaging techniques mentioned above for osteosarcoma margin assessment.

Application of New Imaging Technologies in the Evaluation of Surgical Margins of Osteosarcoma

Radiomics is an emerging approach that addresses the limitations of traditional margin assessment by extracting high-dimensional, quantitative features from medical images. By analyzing peritumoral imaging characteristics, it can assist in delineating tumor boundaries and guiding resection.²³ For instance, a study²³ on 113 soft tissue sarcoma patients developed a predictive model based on texture, shape, and intensity features, achieving 96% accuracy in distinguishing tumor from normal tissue. Furthermore, radiomics can preoperatively stratify recurrence risk. A multicenter study²⁴ of 80

osteosarcoma patients constructed a CT-based radiomics nomogram, which demonstrated good discriminatory ability (training cohort C-index: 0.779; validation cohort C-index: 0.710), highlighting its potential for clinical application across institutions.

Fluorescence imaging, utilizing agents like methylene blue or 5-ALA, offers a real-time solution for identifying ambiguous margins and satellite lesions.^{25,26} A pivotal study in a mouse osteosarcoma model revealed the efficacy of methylene blue fluorescence angiography. In the assisted group, none of the 11 mice (0%) experienced recurrence post-resection, whereas recurrence occurred in 9 out of 11 mice (81.8%) in the non-assisted group. Critically, the presence of any residual fluorescence signal at the margin was associated with a 100% recurrence rate, validating its utility as an intraoperative guide for achieving negative margins.²⁷ Robot-assisted surgery^{22–25} enhances margin control through a stable 3D visual field, wristed instrumentation, and features like motion scaling and tremor filtration. These capabilities facilitate precise tumor excision while preserving normal tissue.²⁸ A study comparing surgical plans for femoral head osteosarcoma resection found that computer-aided plans (a key component of robotic systems) yielded a larger resection volume ($96 \pm 10 \text{ mm}^3$ vs $88 \pm 7 \text{ mm}^3$) and significantly reduced the calculated risk of positive margins compared to standard CT-based planning.

Strategies to Achieve Negative Surgical Margins in Osteosarcoma

The primary objective of osteosarcoma surgery is to achieve a negative surgical margin through wide resection,²⁹ which entails removing the tumor with a surrounding cuff of healthy tissue. Attaining this goal hinges on a systematic, multi-stage strategy integrating preoperative planning, intraoperative execution, and postoperative assessment.³⁰ Preoperatively, the response to neoadjuvant chemotherapy guides surgical aggressiveness, as significant tumor necrosis may permit a more conservative resection.^{7,31} High-resolution MRI defines the tumor's soft-tissue and intraosseous extent, while CT optimally visualizes bony destruction for reconstruction planning.^{17,18,21} These data can be integrated via 3D reconstruction³² and image fusion²² to create a patient-specific surgical roadmap. Intraoperatively, this plan is executed using navigation systems for real-time guidance, fluorescence imaging (eg indocyanine green)³³ for visualizing tumor boundaries, and robotic assistance for enhanced precision. Where available, intraoperative frozen section analysis provides immediate feedback,^{34,35} allowing for further resection if needed. Ultimately, success relies on multidisciplinary collaboration among orthopedic oncologists, radiologists, and pathologists to optimize both oncologic and functional outcomes.

The Width of Resection Margins in Osteosarcoma: Clinical Research and Application

Standard of Margin Width

The optimal width for surgical margins in osteosarcoma remains a critical yet unresolved issue in bone tumor management.^{36,37} While wide resection is a cornerstone of successful treatment, a clear consensus on what constitutes an “adequate” margin is lacking.²² This ambiguity leads to variability in clinical practice and may impact patient prognosis. Current definitions of “wide resection” are largely descriptive and lack quantitative criteria. Furthermore, while various assessment schemes exist in orthopedic pathology, it is uncertain which is most suitable for osteosarcoma. The minimum distance required for effective local tumor control has not been definitively established.³⁸ Supporting the importance of a generous margin, a review of 200 pediatric osteosarcoma cases by Loh³⁹ found that a margin of $\geq 1 \text{ cm}$ was associated with longer patient survival.

Impact of Neoadjuvant Chemotherapy on Margin

Neoadjuvant chemotherapy is a standard component of osteosarcoma treatment,⁴⁰ administered to reduce tumor volume, control micro-metastases, and facilitate limb-salvage surgery.³¹ However, the impact of neoadjuvant chemotherapy on the margin of osteosarcoma and how to determine the optimal margin width remain issues of great concern in clinical practice. Currently, there is no unified standard for the optimal margin width after neoadjuvant chemotherapy for osteosarcoma. Some studies set $> 2 \text{ mm}$ as a safe limit;³¹ while other studies believe that the margin can be appropriately

reduced on the basis of adequate chemotherapy. The key challenge lies in balancing tumor control and functional preservation. A retrospective study by Li⁷ of 47 osteosarcoma patients provided critical insight: while positive margins were an independent risk factor for local recurrence (57.1%), there was no significant difference in recurrence rates between close and wide margins (8.3% vs 10.7%, respectively). This finding indicates close margin may be oncologically safe following effective neoadjuvant chemotherapy, offering a valuable reference for complex limb-salvage procedures.

Relationship Between Local Recurrence and Margin in Osteosarcoma

The margin status is a paramount determinant of local recurrence and overall survival in osteosarcoma. A study of 1126 patients with extremity osteosarcoma by Bacci⁴¹ confirmed that surgical margin is an independent prognostic factor for local recurrence, emphasizing that limb-salvage surgery is contingent upon achieving an adequate margin. Further quantifying this risk, Bertrand⁴² found that margins >1 mm were associated with a significantly increased risk of local recurrence compared to wider negative margins (risk ratio = 8.006). The long-term impact is underscored by a retrospective analysis by Carlos,²⁶ which showed that patients with negative initial margins had a significantly higher 5-year recurrence-free survival rate than those with positive margins (33.3% ± 13.6% vs 7.1% ± 4.9%, $P = 0.015$). The same study highlighted that complete surgical resection at the time of recurrence was crucial, with a 5-year post-recurrence survival rate of 41.7% ± 14.2% for resected patients versus no survivors in the non-resected group ($P = 0.001$). These studies collectively affirm that negative margins in initial surgery are vital for preventing recurrence, and that aggressive surgical intervention remains key to managing recurrent disease.

Summary and Outlook

In conclusion, achieving negative margins is the primary surgical goal in osteosarcoma, critical for reducing recurrence and improving survival. This review underscores three key aspects: First, accurate assessment requires moving beyond conventional imaging to advanced techniques like radiomics and fluorescence guidance. Second, the definition of an “adequate” margin width continues to evolve and lacks a universal standard. While evidence suggests a margin of ≥1 cm may be optimal, the influence of effective neoadjuvant chemotherapy is reshaping this paradigm,⁶ potentially making close margins oncologically safe in this context. Finally, success ultimately relies on a multidisciplinary approach that seamlessly integrates preoperative planning, intraoperative technology, and pathological verification. Future efforts should focus on standardizing and personalizing this comprehensive strategy, which holds the promise of further improving survival rates and functional outcomes for osteosarcoma patients.^{38,43}

Funding

This work was supported by the Tianjin Municipal Education Commission Scientific Research Plan Project, China (Grant No. 2023YXZX20).

Disclosure

The authors report no conflicts of interest in this work.

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