



Review article

Assessment of resection margins in bone sarcoma treated by neoadjuvant chemotherapy: Literature review and guidelines of the bone group (GROUPOS) of the French sarcoma group and bone tumor study group (GSF-GETO/RESOS)



Anne Gomez-Brouchet^{a,*}, Eric Mascard^b, Aurore Siegfried^a, Gonzague de Pinieux^c, Nathalie Gaspar^d, Corinne Bouvier^e, Sébastien Aubert^f, Perrine Marec-Bérard^g, Sophie Piperno-Neumann^h, Béatrice Marieⁱ, Frédérique Larousserie^j, Christine Galant^k, Fabrice Fiorenza^l, Philippe Anract^m, Jérôme Sales de Gauzyⁿ, François Gouin^o, the GROUPOS (GSF-GETO RESOS)

^a Département de pathologie, IUCT-oncopole, CHU de Toulouse and université de Toulouse, 1, avenue Irène Joliot Curie, 31059 Toulouse cedex 9, France

^b Département de chirurgie orthopédique pédiatrique, hôpital-Necker, 149, rue de Sèvres, 75015 Paris, France

^c Service d'anatomie et cytologie pathologiques et université de Tours, CHRU de Tours, Avenue de la République, 37170 Chambray-lès-Tours, France

^d Département de cancérologie de l'enfant et l'adolescent, Gustave-Roussy cancer campus, 114, rue Edouard Vaillant, 94800 Villejuif, France

^e Département de pathologie, CHU la Timone, 278, rue Saint-Pierre, 13005 Marseille, France

^f Université de Lille - institut de pathologie, centre de biologie pathologie, 1, rue Philippe Marache, 59000 Lille, France

^g Département d'oncologie pédiatrique, IHOPE/Centre Léon Bérard, 28, promenade Léa et Napoléon Bullukian, 69008 Lyon, France

^h Département d'oncologie médicale, institut Curie, 26, rue d'Ulm, 75005 Paris, France

ⁱ Département de Pathologie, CHU Nancy, 25, rue Lionnois, 54000 Nancy, France

^j Service de pathologie et université Paris Descartes, AP-HP, hôpital Cochin, 27, rue du Faubourg Saint-Jacques, 75014 Paris, France

^k Service d'anatomie pathologique des cliniques universitaires Saint-Luc, 10, avenue Hippocrate, 1200 Brussels, Belgium

^l Département de chirurgie orthopédique, CHU de Limoges, 2, avenue Martin Luther King, 87000 Limoges, France

^m Département de chirurgie orthopédique, CHU de Cochin, AP-HP, 27, rue du Faubourg Saint-Jacques, 75014 Paris, France

ⁿ Département de chirurgie orthopédique pédiatrique, hôpital-Mère-Enfant, CHU Toulouse, 330, avenue de Grande Bretagne, 31300 Toulouse, France

^o Centre Léon-Bérard, CHU Nantes, Nantes/Inserm, UMR 1238, Phy-Os, université de Nantes, 28, rue Laennec, 69008 Lyon France

ARTICLE INFO

Article history:

Received 20 June 2018

Accepted 7 December 2018

Keywords:

Margins

Osteosarcoma

Ewing sarcoma

Chemotherapy

Bone sarcoma

ABSTRACT

Background: Standardized reports are essential to meeting the bone sarcoma reference center certification requirements of the French National Cancer Institute (INCa). The usual classifications of the Musculoskeletal Tumor Society (MSTS), the American Joint Committee on Cancer (AJCC/IUCC) TNM R classification and the American College of Pathologists, are inexact inasmuch as they fail to include chemotherapy impact on tumor cells in assessing surgical margins. This leads to inconsistent interpretation by teams managing bone sarcoma. The present literature analysis sought to assess the limitations of existing classifications for purposes of standardized reporting of the management of surgical specimens from patients with osteosarcoma or Ewing sarcoma receiving neoadjuvant chemotherapy, by addressing the following questions: 1) What is the prognostic value of margins and chemotherapy response in the classifications? 2) What are the histologic changes induced by chemotherapy, with what impact on interpretation of margins?

Method: A PubMed literature analysis was performed, targeting the prognostic value of resection margin assessment, in September 2018. French bone pathology group (*Groupe français des pathologistes osseux*) and international guidelines on bone specimen management were referred to so as select items for a standardized report. Eight of the 523 articles retrieved met the study eligibility criteria.

Results: Minimal distance between tumor and surgical margin, with a >2 mm threshold, seemed to be the optimal parameter for predicting local recurrence. Good chemotherapy response and appendicular skeletal location were associated with lower risk of local recurrence. None of the available classifications take into account the microscopic changes induced by chemotherapy in interpreting resection margins.

* Corresponding author at: Département de pathologie et université de Toulouse, CHU of Toulouse, IUCT oncopole, institut de pharmacologie et de biologie structurale CNRS UMR5089, 1, avenue Joliot-Curie 31059 Toulouse cedex 9, France.

E-mail address: brouchet.anne@chu-toulouse.fr (A. Gomez-Brouchet).

Discussion: To standardize practice, GROUPOS developed a standardized report for bone sarcoma specimens, considering the histopathologic changes in the tumor after neoadjuvant chemotherapy. The TNM R system was adapted and a threshold of > 2 mm was chosen as an acceptable limit to qualify surgical resection as safe (R0). R1 status (≤ 2 mm) was subdivided into subgroups a, b and c, to include margin measurement in relation to the post-chemotherapy scar: R1a, resection within the scar; R1b, resection in healthy tissue, ≤ 2 mm from the scar and/or residual viable cells; and R1c, resection within the lesion in contact with viable cells or within coagulation necrosis areas. The GROUPOS members drew up this standardized report so as to ensure a common language, improving bone sarcoma management in specialized centers. Reliable data can thus be established for national and international multicenter studies.

Level of evidence: IV.

© 2019 Elsevier Masson SAS. All rights reserved.

1. Introduction

In France, the organization of management of bone sarcoma is based on the RESOS network, approved by the French National Cancer Institute (INCa) in January 2012 [1]. Surgery should be performed in a reference center, by a surgeon specialized in bone surgery; microscopic analysis of the diagnostic biopsy sample and surgical specimen should be performed by a pathologist specialized in bone pathology [1–4]. Local recurrence risk depends on chemotherapy response and resection quality [1–5].

The Musculoskeletal Tumor Society (MSTS) classification of margins, based on Enneking et al.'s classification [6], the AJCC/UICC (American Joint Committee on Cancer) TNM R system [7–9] and minimal tumor-to-margin distance according to the College of American Pathologists & the Association of Directors of Anatomic and Surgical Pathology [10,11], lack precision and lead to heterogeneity in pathology reports and in margin interpretation by teams managing bone sarcoma [12]. The classifications fail to consider the impact of chemotherapy on margin measurement, whereas most high-grade bone sarcomas (osteosarcoma, Ewing sarcoma) are treated by neoadjuvant chemotherapy. The aim of the present literature review was to assess the limitations of the reference classifications so as to draw up a standardized report of bone sarcoma resection after chemotherapy by addressing the following questions:

- What is the prognostic value of margins and chemotherapy response in the classifications?
- What are the histologic changes induced by chemotherapy, with what impact on interpretation of margins?

2. Method

The PubMed literature review using the search-term “surgical margins and bone sarcoma” was performed by a pathologist (AGB) and a surgeon (EM). Only articles published in English since 2013 and taking into account the most recent WHO bone tumor pathology classification, still applicable in 2018 [13], were selected (Fig. 1). Out of a total 523 articles, 379 written before 2013 were eliminated. Out of the remaining 144 articles from the period 2013–2018, the following were excluded:

- 48 dealing with soft-tissue sarcoma and other cancers and bone tumor in dogs;
- 25 with fewer than 150 patients (including case reports);
- 39 on surgical techniques or radiation therapy;
- 16 not analyzing the prognostic value of margins;
- 8 that were not accessible (Fig. 1).

All the selected studies were of non-randomized retrospective series. Five of the 8 remaining articles met all eligibility criteria, and enabled question 1 to be addressed. None of the studies took account of chemotherapy-induced changes in classifying surgical margins. Items to be included in a standardized report were selected in the light of the French Bone Pathology Group (*Groupe français des pathologistes osseux*: GFPO) guidelines for the management of bone sarcoma specimens and French and international guidelines. The other 3 articles from our selection enabled question 2 and the Discussion to be addressed.

The three classifications studied in the literature served as references for meeting our objectives: the MSTS (Musculoskeletal

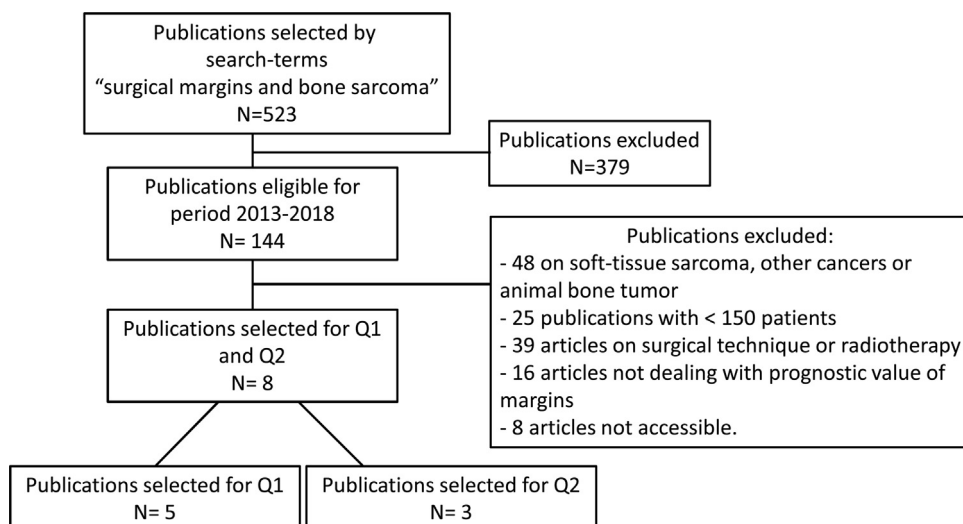


Fig. 1. Flowchart of article selection for the 2 study questions.

Table 1
Enneking's classification WF/MSTS [6].

Stage	Grade	Tumor	Metastasis
IA	G1 low grade	T1 intact cortex (intracompartmental)	M0
IB	G1 low grade	T2 ruptured cortex with soft-tissue extension	M0
IIA	G2 high grade	T1 intact cortex (intracompartmental)	M0
IIB	G2 high grade	T2 ruptured cortex with soft-tissue extension	M0
IIIA	G1 or G2	T1	M1
IIIB	G1 or G2	T2	M1

Table 2
Bone tumor TNM classification (AJCC/IUCC) [7–9,13].

Stage	Tumor (T)	Node (N)	Metastasis (M)	Grade (G)
IA	T1 (≤ 8 cm)	N0	M0	Low grade
IB	T2 (> 8 cm)	N0	M0	Low grade
IIA	T1	N0	M0	High grade
IIB	T2	N0	M0	High grade
III	T3 (multifocal tumor at primary site)	N0	M0	All grades
IVA	All T	N0	M1 (Lung)	All grades
IVB	All T	N1	All M	All grades
	All T	All N	M1b (other sites)	All grades

Table 3
Residual tumor classification.

Rx: tumor residue not determinable
 R0: no tumor residue: curative resection
 R1: microscopic tumor residue
 R2: macroscopic tumor residue

Tumor Society) classification of margins, based on Enneking et al.'s classification [6], the (AJCC/UICC) (American Joint Committee on Cancer) TNM R system [7–9], and minimal tumor-to-margin distance according to the College of American Pathologists & the Association of Directors of Anatomic and Surgical Pathology [10,11].

2.1. Enneking's classification and MSTS margin classification

In 1980, Enneking et al. [6] published a surgical bone tumor staging classification to define complete tumor resection. Three stages (Table 1) are distinguished, on histologic criteria (histologic tumor subtype and grade according to Goyanna et al. [14]), anatomic criteria (anatomic site and extension within the various anatomic compartments: intra- and extra-compartmental tumor), and progression criteria (lymph node and distant metastasis).

Enneking et al.'s [6] definition of surgical margins is based on this classification, with 4 types: intralesional, marginal (margins with a high percentage of microscopic residual tumor), wide, and radical (Fig. 2).

2.2. AJCC/IUCC TNM staging and R system

AJCC/IUCC TNM staging assesses tumoral extension [7–9], based on tumor grade, tumor size and metastatic status (Table 2). In 1978, the AJCC recommended that staging be completed by the R classification, where R refers to residual tumor [15]. This classification thus became a subsidiary within the AJCC/IUCC TNM system [16,17]. It comprises 4 groups (Rx, R0, R1 and R2) for residual tumor within the resection margin (Table 3), R1 designating a resection in contact with tumor cells [18].

2.3. Margins according to the American College of Pathologists

The American College of Pathologists and the Association of Directors of Anatomic and Surgical Pathology recommend using the distance between the tumor and the nearest margin [10,11].

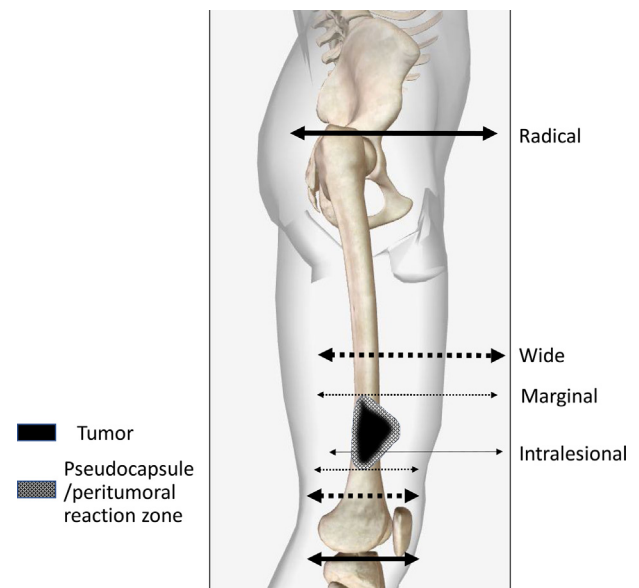


Fig. 2. Definition of margins according to Musculoskeletal Tumor Society (Enneking): Intralesional: resection within tumor. Marginal: resection in pseudocapsule/peritumoral inflammatory reaction area. Wide: en-bloc resection including pseudocapsule/peritumoral inflammatory reaction area, with margin in healthy tissue and intracompartmental resection (a compartment comprising an entire anatomic entity: bone or muscle body). Radical: en-bloc resection including pseudocapsule/peritumoral inflammatory reaction area and all involved muscles and bones; longitudinally, resection through or beyond proximal and distal joints of the bone and beyond tendon and muscle insertions; transversally, resection beyond fascia, or periosteum in intraosseous tumor.

3. Results

3.1. What is the prognostic value of margins and chemotherapy response in the classifications?

Cates [19], reporting a cohort of 186 osteosarcomas, recently assessed the 3 margin measurement systems in terms of local recurrence-free survival; the MSTS and tumor-to-margin distance systems were the most effective, with reduced risk for distances > 2 mm.

Hasley et al.'s meta-analysis [20] of margin measurement assessment in bone and soft-tissue sarcoma, with 22 articles totaling 498 patients, showed that local recurrence was less frequent

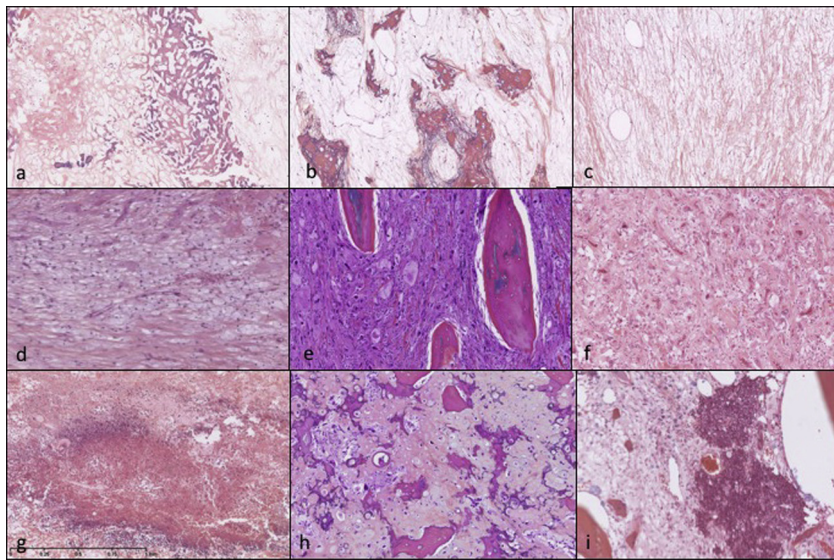


Fig. 3. Microscopic lesions associated with chemotherapy response. a: Complete response in osteosarcoma patient, with residual osteoid/chondroblastic matrix showing acellular gaps; b, c d: Complete response with residual edematous territories (b), fibrous territories (c) or foamy macrophage-rich territories (d); changes observed in osteosarcoma with low tumoral bone production, such as fibroblastic osteosarcoma or Ewing family sarcoma; e, f: Atypical residual cells; g: Coagulation necrosis; h: Poor response in osteosarcoma, with residual chondroblastic territories; i: Poor response in Ewing sarcoma, with residual round cells.

Table 4
Birmingham classification.

1a Necrosis $\geq$ 90% and margins $>$ 2 mm
1b Necrosis $\geq$ 90% and margins $\leq$ 2 mm
2a Necrosis $<$ 90% and margins $>$ 2 mm
2b Necrosis $<$ 90% and margins $\leq$ 2 mm

in bone sarcoma than in soft-tissue sarcoma (17.7% versus 28.1%), and that Enneking's system was the most effective in predicting local recurrence rates, comparing marginal versus wide or radical margins (respectively, 50.48% and 7.22%), but that the significance of marginal margins was unclear, as they could be either both positive or negative. Chemotherapy significantly reduced the risk of local recurrence, from 26.67% to 3.64% [20].

Jeys et al. [21] included response to chemotherapy in the assessment of local recurrence risk and survival in osteosarcoma, with a new 4-group classification according to chemotherapy response, setting a threshold of $>$ 2 mm for measuring margins (Table 4). In a cohort of 389 osteosarcoma patients, poor responders with $\leq$ 2 mm margins had 20-fold greater risk of local recurrence than good responders with $>$ 2 mm margins; there was a significant difference in overall survival according to chemotherapy response but not according to margin measurement.

Loh et al. [22], in 181 conservative limb procedures, reported that reducing bone osteosarcoma resection margins from 5 cm to 1.54 cm did not impair overall survival, whereas metastasis at diagnosis and poor chemotherapy response significantly impaired overall and recurrence-free survival. Finally, He et al. [23], in a meta-analysis of 1,559 osteosarcoma patients, confirmed that inadequate or marginal margins were associated with higher local recurrence rates, although the definition of “adequacy” varied between the large number of studies analyzed; pelvic location was an independent risk factor for local recurrence.

3.2. What are the histologic changes induced by chemotherapy, with what impact on interpretation of margins?

The reference classifications do not consider the chemotherapy-induced changes in classifying surgical margins. Except for the GFPO guidelines on bone specimen management [24], we found

no studies describing histologic changes related to chemotherapy in bone sarcoma or defining the acceptable distance between surgical margin and post-chemotherapy scar in assessing risk of local relapse.

When effective, chemotherapy induces histologic changes related to tumor-cell necrosis. Necrosis consists of a “scar” with no tumor cells. The scar is different in osteosarcoma and Ewing sarcoma (Fig. 3a–d) [24]. Cells with atypical nucleus and microvacuolized cytoplasm (Fig. 3e and f) should be considered viable. The distinction between spontaneous necrosis and post-chemotherapy coagulation necrosis (with persistent phantom cells) is impossible to draw, and the two aspects should both be categorized as areas of non-response to treatment (Fig. 3g).

Macro- and micro-scopic management of bone specimens [24] is governed by a protocol (Fig. 4) assessing:

- chemotherapy response;
- resection margin quality;
- any intravascular embolism [25].

The average level of the response to chemotherapy was calculated according to the protocol (Fig. 4). No previous studies provided a histologic definition of margins in relation to chemotherapy scar. Two studies of, respectively, 20 long-bone Ewing sarcomas and 55 bone sarcomas (Ewing and osteosarcoma), however, showed that T1 MRI sequences obtained after chemotherapy were the best for planning bone resection, with a safety margin of 1–2 cm [26,27].

4. Discussion

In the present literature review, the GROUPOS aimed to identify items for a standardized report (Appendix A) for bone sarcoma specimens following chemotherapy. Analysis revealed no consensus on the definition of microscopic resection margins. It is, however, essential to have common definitions shared by the medical and surgical teams managing bone tumors. The reference classifications, implemented ahead of chemotherapy in bone sarcoma treatment, show limitations. The main drawback of Enneking et al.'s definitions [6] is the subjectivity of the surgeon's and pathologist's assessment in the “marginal” area; the drawback of the

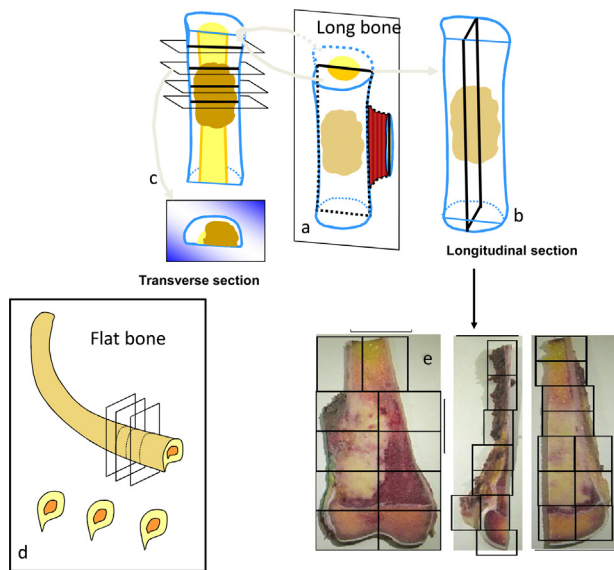


Fig. 4. Macroscopic specimen management. Long bone: section parallel to long axis (a) and perpendicular, longitudinal (b) or transverse (c) cuts. Flat bone: Series of parallel slices (d), or as in long bone if volume permits. Cuts performed using a saw. Coronal and sagittal sections are made. The surgical resection is divided into several equal territories (e) and the percentage of viable cells is calculated in each territory. The percentage of viable cells should be noted on a plan of the surgical resection, which will be scanned, if possible, in the definitive report. The average percentage of residual tumor cells is calculated by summing the percentages in every territory and dividing by the number of territories.

American College of Pathologists definitions is that they do not provide a threshold for the distance between tumor and margin that would identify patients at high risk of local recurrence [10,11]. In France, GSF-GETO GROUPOS uses the 2013 WHO bone tumor classification [13] and the AJCC/IUCC TNM R system to assess margins [9]. The AJCC/IUCC TNM R system is imprecise in its definition of R0,

failing to specify the minimal distance defining complete curative resection (R0). Moreover, the definition of R1 is not applied consistently between teams: for some, it is a margin in contact with tumor cells, for others a margin of < 1 mm, while others again include the invasive and bulging character of the tumor to differentiate narrow margins between R1 and R0 [28,29]. And finally, none of the classifications includes chemotherapy response in defining margins: the chemotherapy “scar” is not taken into consideration in assessing margins, and the threshold distance between this scar and the surgical margin is not defined. Taken alone, these classifications are inadequate and lead to differences in interpretation of margins and hence in treatment.

4.1. What is the prognostic value of margins and chemotherapy response in the classifications?

Cates [19] showed that, with distances greater than 2 mm between tumor and margin, local recurrence risk for osteosarcoma ceases to diminish. Hasley et al.’s meta-analysis [20] of margin assessment in bone and soft-tissue sarcoma confirmed that the significance of marginal margins on Enneking et al.’s classification [6] is unclear, associated for some teams with positive and for others with negative status. Hasley et al. [20] and Loh et al. [22] showed that chemotherapy significantly reduced local recurrence risk. The Birmingham classification, which includes chemotherapy response and a 2 mm threshold in assessing local recurrence risk and survival in osteosarcoma, is interesting, proving the importance of taking chemotherapy response into account in assessing risk of local recurrence [21].

4.2. What are the histologic changes induced by chemotherapy, with what impact on interpretation of margins?

We illustrated the histologic changes induced by chemotherapy with various examples of osteosarcoma and Ewing sarcoma in good and poor responders. Interestingly, osteosarcoma, unlike

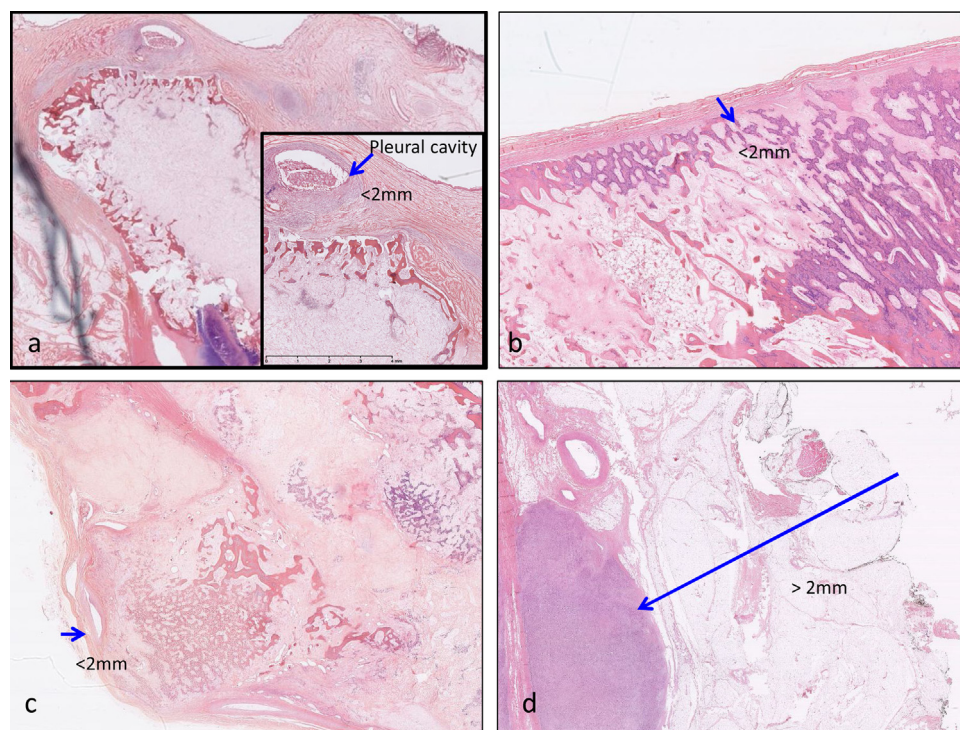


Fig. 5. R0 margins according to GROUPOS. R0 margin (blue arrow). a: < 2 mm from intact pleural cavity wall; b: < 2 mm in osteosarcoma with periosteum as natural pleural cavity wall; c: R0 margins < 2 mm in high-grade osteosarcoma.

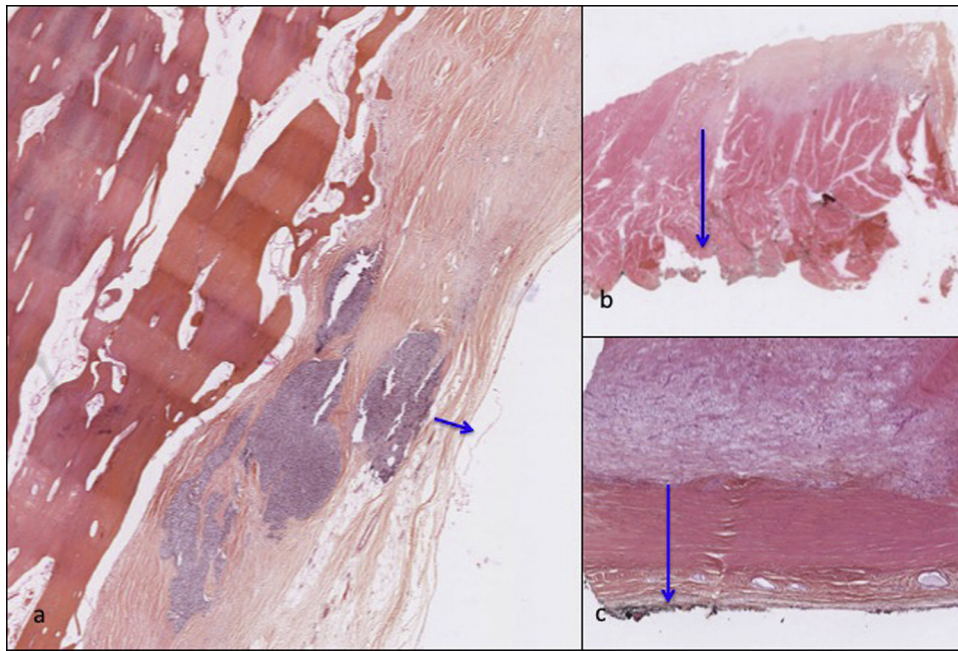


Fig. 6. R1b margin (blue arrow); margin in healthy tissue and ≤ 2 mm from viable Ewing sarcoma cells (a), and < 2 mm from scar (b, c).

Ewing sarcoma, shows soft-tissue extension that is often limited by the periosteum. Good chemotherapy response in osteosarcoma patients with low bone production and in Ewing sarcoma patients shows the same morphological signature, in the form of edematous, fibrous or foamy macrophage-rich territories. Atypic cells and coagulation necrosis territories (with phantom cells) should be considered viable.

T1-weighted MRI following chemotherapy is the sequence of choice for reliable bone resection planning outside of tumoral or scar zones [26,27]. There are no radiologic studies defining a minimal distance for planning soft-tissue resection, and no studies specify how margins should be assessed with regard to scar tissue and post-chemotherapy remodeling or what is the prognostic significance of such margins.

4.3. Proposed standardized pathology report form

To achieve a common language between teams, GROUPOS drew up a simple standardized pathology report form applicable in osteosarcoma and Ewing sarcoma, including margin measurement with respect to the chemotherapy scar, with a threshold of > 2 mm, based on the literature. It is essential that the surgeon and pathologist dealing with the specimen should be experts in bone tumor pathology and should work in close collaboration.

According to GROUPOS and GSF-GETO/RESOS guidelines, the standardized pathology report should specify (Appendix A):

- Patient data: name, age, gender, history;
- tumor size and topology, with a frozen sample: superficial, intramedullary, epiphyseal, metaphyseal or diaphyseal;
- single or multiple location;
- surgeon's name, and date of surgery.

The surgeon should provide the pathologist with a diagram and all elements needed for an exhaustive report:

- neoadjuvant treatment (chemotherapy, radiotherapy);
- monobloc or morselized resection;
- any visible tumoral pseudocapsule or "scar-like" tissue;

- any tumor breach (site located, whether the tumor was breached or not, possibly with adjacent cuts);
- any in-situ tumor residue.

The surgeon should use sutures to locate territories to be analyzed in detail (or preferably examine the specimen with the pathologist), and indicate any breaches, areas in which the tumor and pseudocapsule are visible, any skip metastasis, joint extension or intraoperatively suspect aspect.

The pathologist, aided by imaging (on CD or the institution's data network) and the surgeon's landmarks, can thus ink the specimen, sample the areas liable to be invaded, and perform macroscopic assessment, detailing specimen size and sectioning method (Fig. 4), backed up by photographs.

Microscopic examination:

- Mean percentage residual cells after chemotherapy should be calculated, determining areas with the highest rates of viable tumor cells. Interpretation of chemotherapy response needs to take account of the histologic sub-type of the tumor and its cell density on biopsy prior to chemotherapy. Patients with less than 10% residual tumor cell rates count as good responders and those with $\geq 10\%$ as poor responders (Fig. 3h, i). A photocopy of the map of the viable cell rate calculation on a grid of the specimen should be drawn up and may be scanned for inclusion in the final report, or should at least be archived in the patient's file.
- Bone and soft-tissue margins should be measured, with the minimal distance (in mm) between tumor and margin, specifying the type of tissue involved at the margin.
- Any embolism should be noted.

In its conclusion, the report should detail margins with respect to the chemotherapy scar on the AJCC/UICC TNM R system. As mentioned above, a threshold of > 2 mm (or ≤ 2 mm with natural anatomic barrier) between tumor and dissection plane was chosen to define healthy (R0) margins (Fig. 5). R1 status (≤ 2 mm margin with possible microscopic residue) was subdivided into 3 groups to take account of margins with respect to the chemotherapy scar: R1a, R1b (Fig. 6), and R1c (Table 5).

Table 5

Definition of margins according to GROUPOS.

R1 and R0 status determined by pathologist, R2 by surgeon. Morselized tumor cannot be R0
R0: healthy margins > 2 mm (or ≤ 2 mm with natural anatomic barrier) from tumor (viable cells or scar)
R1: Resection ≤ 2 mm with possible microscopic residue, including distance from chemotherapy scar
R1a: resection within scar, without viable cells
R1b: resection in healthy tissue, ≤ 2 mm from scar or residual viable cells
R1c: microscopically intralesional resection or in coagulation necrosis territory (phantom cells)
R2: Macroscopically intralesional resection

4.4. Study limitations

The present study had several limitations, and notably assessment of the use and reproducibility of the standardized report form, which is presently being validated in the OS 2006 cohort; reproducibility will be assessed in ongoing and future bone tumor studies (EURO EWING 2012 and SARC 13).

5. Conclusion

Literature analysis of resection margin classification in bone tumor surgery showed the limitations of the systems most often used to classify “narrow” margins and their failure to take account of post-chemotherapy histologic remodeling. The analysis enabled a standardized pathology report form to be drawn up, establishing a common language, in order to improve management of bone sarcoma in specialist centers, allow data entry in the French national data-base (NETSARC, RESOS), and facilitate good quality multicenter studies in the various European and international networks. The use of the document and assessment of local recurrence rates according to the three groups it newly defines is currently under validation in the OS 2006 cohort, a phase-3 randomized clinical trial associating Zometa™ (zoledronic acid) to conventional treatments (poly-chemotherapy and surgery) in osteosarcoma.

Disclosure of interest

François Gouin reports personal fees from Amgen, others from Atlantha, Saint Herblain France, others from Zimmer/HipCare, outside the submitted work.

Funding

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

Contribution

The authors belong all to GSF-GETO groups (*Groupe français des sarcomes* and *Groupe d'étude des tumeurs osseuses*): Pathologists: A. Gomez-Brouchet, A. Siegfried, G. de Pinieux, C. Bouvier, S. Aubert, B. Marie, F. Larousserie, C. Galant; Surgeons: E. Mascard, F. Fiorenza, P. Anract, J. Sales de Gauzy, F. Gouin; Oncologists: N. Gaspar, P. Marec-Bérard, S. Piperno-Neumann. All authors have participated to discuss and revise the manuscript

Appendix A. Standardized report form assessing response to chemotherapy after surgical resection of bone tumor

SURGERY

Date:

Name of center and of surgeon:

TUMOR BANK: yes/no

BIOPSY AND DIAGNOSIS:

Date:

Diagnosis and registration n° in pathology laboratory:

Molecular biology: yes/no

MACROSCOPIC EXAMINATION

A) TOPOGRAPHY

- Intramedullary tumor and/or soft-tissue location or extension:- Superficial tumor

B) SIZE

- Of specimen:

- Of tumor:

C) MACROSCOPIC TUMOR DESCRIPTION:

Solitary/ Multiple:

Whitish/reddish/bluish:

Ossified/ Cystic/ Necrotic/ Hemorrhagic/...:

D) METHODOLOGY: Include macroscopic photographs of specimen (if possible)

Number of blocks on bone specimen:

Number of blocks in tumor zone:

MICROSCOPIC EXAMINATION:

A) PERCENTAGE RESIDUAL TUMOR CELLS AFTER NEOADJUVANT CHEMOTHERAPY

- mean percentage residual tumor cells:...

- (...% is the highest percentage of residual tumor cells; in the block: ...)

- Vascular invasion: yes/no

B) DESCRIPTION OF SCAR = TREATMENT RESPONSE ZONE

- Fibrosis, edema, foamy macrophages, coagulation necrosis

C) MICROSCOPIC DEFINITION OF MARGINS

- R2: Macroscopically intralesional resection

- R1: Microscopically incomplete resection

R1a: Resection within scar (fibrosis, edema, foamy macrophages, inflammatory cells)

R1b: Resection within normal tissue, ≤ 2 mm from scar and/or residual viable cells

R1c: Microscopically intralesional resection or in residual tumor site or coagulation necrosis area (phantom cells)

- R0: Resection > 2 mm from tumor or, < 2 mm with natural separation barrier

D) MARGIN ASSESSMENT

R0/R1/R2

Margins in soft tissue: relation to scar (fibrosis, edema, foamy macrophages, inflammatory cells), relation to residual tumor cells:

Bone margins: to scar (fibrosis, edema, foamy macrophages, inflammatory cells), relation to residual tumor cells:

CONCLUSION

GOOD/ POOR responder

.....% residual tumor cells

RESECTION quality: R0/R1 (a, b, c)/R2

References

- [1] INCa - Recommandations et référentiels: procédure de labellisation, 2010. www.unicancer.fr.
- [2] Gerrand C, Athanasou N, Brennan B, Grimer R, Judson I, Morland B, et al. British Sarcoma Group UK guidelines for the management of bone sarcomas. *Clin Sarcoma Res* 2016;6:7.
- [3] Grimer R, Athanasou N, Gerrand C, Judson I, Lewis I, et al. UK Guidelines for the management of bone sarcomas. *Sarcoma* 2010;2010:3162–74.

- [4] Dahan M, Anract P, Babinet A, Larousserie F, Biau D. Proximal femoral osteosarcoma: Diagnostic challenges translate into delayed and inappropriate management. *Orthop Traumatol Surg Res* 2017;103:1011–5.
- [5] Bacci G, Longhi A, Versari M, Mercuri M, Briccoli A, Picci P. Prognostic factors for osteosarcoma of the extremity treated with neoadjuvant chemotherapy: 15-year experience in 789 patients treated at a single institution. *Cancer* 2006;106:1154–61.
- [6] Enneking WF, Spanier SS, Goodman MA. A system for the surgical staging of musculoskeletal sarcoma. *Clin Orthop Relat Res* 1980;153:106–20.
- [7] Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE. The eighth edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more “personalized” approach to cancer staging. *CA Cancer J Clin* 2017;67:93–9.
- [8] Greene FL, Sobin LH. A worldwide approach to the TNM staging system: Collaborative efforts of the AJCC and UICC. *J Surg Oncol* 2009;99:269–72.
- [9] Wittekind C, Compton CC, Greene FL, Sobin LH. TNM residual tumor classification revisited. *Cancer* 2002;949:2511–6.
- [10] Abdul-Karim FW, Bauer TW, Kilpatrick SE, Raymond KA, Siegal GP. Association of directors of anatomic and surgical pathology. Recommendations for the reporting of bone tumors. *Hum Pathol* 2004;35:1173–8.
- [11] Rubin BP, Antonescu CR, Gannon FH, Hunt JL, Inwards CY, et al. Protocol for the examination of specimens from patients with tumors of bone. *Arch Pathol Lab Med* 2010;134:e1–7.
- [12] Hoang K, Gao Y, Miller BJ. The variability in surgical margin reporting in limb salvage surgery for sarcoma. *Iowa Orthop J* 2015;35:181–6.
- [13] Fletcher CDM, Bridge JA, Hogendoorn P, Mertens F, editors. WHO Classification of tumours of soft tissue and bone. IARC WHO Classification of Tumours, 5, Fourth Edition IARC; 2013.
- [14] Goyanna R, Torres ET, Broders AC. Histological grading of malignant tumors; Broder's method. *Hospital (Rio J)* 1951;39:791–818.
- [15] Fleming ID, Cooper JS, Henson DE, et al., editors. American Joint Committee on Cancer Staging and End Results Reporting. Manual for staging of cancer. American Joint Committee on Cancer. Philadelphia: J.B. Lippincott; 1978.
- [16] Bearhs OH, Henson DE, Hutter RVP, Kennedy BJ, editors. American Joint Committee on Cancer manual for staging of cancer. 4th edition Philadelphia: J.B. Lippincott; 1992.
- [17] Fleming ID, Cooper JS, Henson DE, et al., editors. American Joint Committee on Cancer manual for staging of cancer. 5th edition Philadelphia: J.B. Lippincott; 1997.
- [18] Sobin LH, Fleming ID. TNM Classification of malignant tumors, fifth edition (1997). Union Internationale Contre le Cancer and the American Joint Committee on Cancer. *Cancer* 1997;80:1803–4.
- [19] Cates JM. Reporting surgical resection margin status for osteosarcoma: Comparison of the AJCC MSTs, and Margin Distance Methods. *Am J Surg Pathol* 2017;41:633–42.
- [20] Hasley I, Gao Y, Blevins AE, Miller BJ. The significance of a “close” margin in extremity sarcoma: a systematic review. *Iowa Orthop J* 2018;38:123–30.
- [21] Jeys LM, Thorne CJ, Parry M, Gaston CL, Sumathi VP, Grimer JR. A novel system for the surgical staging of primary high-grade osteosarcoma: The Birmingham Classification. *Clin Orthop Relat Res* 2017;475:842–50.
- [22] Loh AH, Wu H, Bahrami A, Navid F, McCarville MB, et al. Influence of bony resection margins and surgicopathological factors on outcomes in limb-sparing surgery for extremity osteosarcoma. *Pediatr Blood Cancer* 2015;62:246–51.
- [23] He F, Zhang W, Shen Y, Yu P, Bao Q, et al. Effects of resection margins on local recurrence of osteosarcoma in extremity and pelvis: Systematic review and meta-analysis. *Int J Surg* 2016;36:283–92.
- [24] Gomez-Brouchet A, Bouvier C, Decouvelaere AV, Larousserie F, Aubert S, et al. Place of the pathologist in the management of primary bone tumors (osteosarcoma and Ewing's family tumors after neoadjuvant treatment). *Ann Pathol* 2011;31:455–65.
- [25] Benezech S, Chabaud S, Chambon F, Dijoud F, Chotel F, Marec-Berard P. Prognostic Value of Vascular Invasion in Pediatric Osteosarcomas. *Pathol Oncol Res* 2016;22:847–52.
- [26] Thévenin-Lemoine C, Destombes L, Vial J, Wargny M, Bonneville P, et al. Planning for bone excision in Ewing Sarcoma: Post-chemotherapy MRI more accurate than pre-chemotherapy MRI Assessment. *J Bone Joint Surg Am* 2018;100:13–20.
- [27] Thompson MJ, Shapton JC, Punt SE, Johnson CN, Conrad EU3rd. MRI identification of the osseous extent of pediatric bone sarcomas. *Clin Orthop Relat Res* 2018;476:559–64.
- [28] Quirke P, Dixon MF. The prediction of local recurrence in rectal adenocarcinoma by histopathological examination. *Int J Colorectal Dis* 1988;3:127–31.
- [29] Lintz F, Moreau A, Odri GA, Waast D, Maillard O, Gouin F. Critical study of resection margins in adult soft-tissue sarcoma surgery. *Orthop Traumatol Surg Res* 2012;98:S9–18.