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ORIGINAL ARTICLE

Surgeon's perception of margins in spinal en bloc resection surgeries: how reliable is it?

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Abstract
Purpose and Background En bloc resections aim at surgically removing a tumor in a single, intact piece, fully encased by a continuous shell of healthy tissue—the "margin". Intraoperative continuous assessment of the plane of resection regarding the tumor's margins is paramount. The goal of this study was to evaluate the accuracy of experienced spinal tumor surgeons' perception of these margins.
Methods A retrospective analysis of a prospectively collected data of 1681 patients affected by spine tumors of whom 217 en bloc resections was performed. Surgeons' intraoperative assessment was compared to the histopathological assessment.
Results Most were primary—163 (42 benign and 121 malignant), metastases occurred in 54 cases. 'Wide' margins were obtained in 126 cases; 'marginal' in 60 cases, and 'intralesional' in 31 cases. Surgeons assessed clear margins in 109 cases and contaminated in 108 cases. When considering marginal margins as a contaminated resection, the surgeon's assessment of clear resection had a sensitivity of 76.89%, specificity of 86.81%, PPV and NPV (positive and negative predictive values) were 88.99 and 73.15%, respectively. Inter-observer agreement was 0.62. When considering marginal margins as a clear resection, the surgeon's assessment of clear resection had a sensitivity of 64.5%, specificity of 100%, PPV and NPV were 100 and 0%, respectively. Inter-observer agreement was 0.29.
Conclusion Surgeons are fairly accurate in their intraoperative assessment of clear margins achieved; however, this accuracy is not perfect and exploring ways to improve this intraoperative assessment is of major importance possibly impacting the outcome of the treatment.

Keywords Margins · Spine tumors · En bloc resection · Intraoperative assessment · Recurrence

Introduction

En bloc resections [1] are the procedures aiming at surgically removing a tumor in a single, intact piece, fully encased by a continuous shell of healthy tissue, which is defined as the "margin". As described by Enneking [2] for bone tumors, there are four types of surgical margins, each directly relates to the oncological prognosis of the patient. The different types were termed intralesional, marginal wide and radical with regard to the tumor's pseudocapsule and the chance of remaining tumor cells after excision.

Intralesional/Intracapsular margins means that the lesion has been removed from within the tumor's pseudocapsule, or that the tumor pseudocapsule has been violated during the en bloc resection procedure: in this case, the pathologist can demonstrate vital tumor on the surface of the specimen. As a consequence, we can expect that gross tumor is left in the wound.

Marginal margins mean that the lesion has been removed en bloc, and the plain of dissection has been extracapsular either between the pseudocapsule and the

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reactive zone or within the reactive zone. These margins are composed of reactive tissue and might contain satellite cells and skip lesions.

Wide margins mean that the lesion has been removed en bloc, and that the plain of resection has been peripheral to the reactive zone through normal tissue, but still in the compartment of the lesion (Figs. 1, 2, 3).

Radical margins mean that the entire lesion together with the entire compartment has been removed.

EN bloc resection can be performed in the spine [3–10], where anatomical and surgical constraints make them technically demanding. Either multiple surgical approaches or a widely enlarged single posterior approach must be planned for the complete removal of the tumor without violation of its margins. The requirement of a margin encasing the tumor can, at times, be met by resecting relevant anatomical structures [11–16] (pleura, dura, muscles, nerve roots, nerves, vessels and so on).

Radical resection in the spine would mean in intracompartmental tumors, resection of the tumor with the whole vertebra of occurrence: this would obviously include the content of the spinal canal. Alternatively, in case of tumor expansion in the canal, which is an extracompartmental space, the term "radical" is not applicable. In any case, the term "radical" has no role in the spine.

Intentional transgression of oncological principles [1, 7, 17] may be considered, the advantage in terms of reduced morbidity and better functional results being weighed against the higher risk of recurrence. In a recent study published by our group [18] focusing on the morbidity of 220 en bloc resection conducted between 1990 and 2015, a 45.45% complications were observed. This high rate requires continuous attention and effort to understand and reduce the morbidity of this operation. To that extent, limiting the surgical resection while maintaining the oncological principles could reduce this high reported morbidity of this procedure.

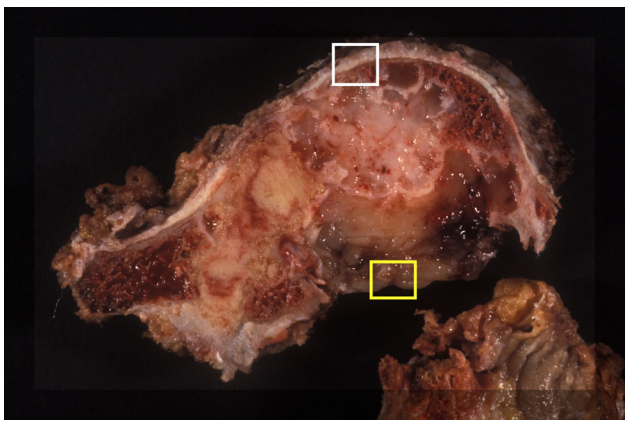

Fig. 1 Resected specimen, Marginal resected area—*yellow rectangle*, wide resected area—*white rectangle*

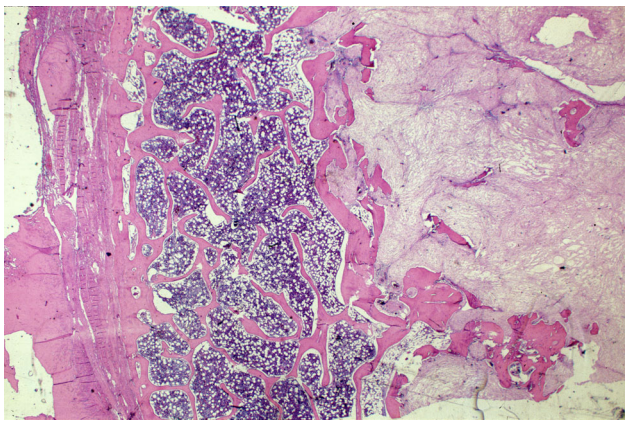

Fig. 2 Histological slide—wide resected area

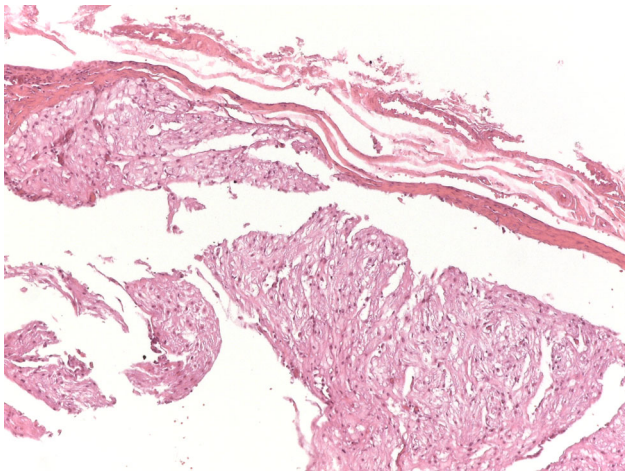

Fig. 3 Histological slide—marginal resected area

En bloc resection has proved effective in improving the prognosis of primary bone tumors of the spine [3, 17, 19–21] and the quality of life and sometimes survival time of patients with selected isolated metastases, such as renal cell carcinoma [22, 23] and thyroid cancer not responsive to medical oncology [24]. The local control of the disease is markedly increased when margins are tumor free, where if an en bloc resection is achieved the local control rises to 92.3% in giant cell tumor (GCT) [25], to 78% in chordoma (CH) [20] and to 82% in chondrosarcoma (CHS) [21], compared with the local control achieved in the same studies by intralesional surgery: 72.2% in GCT [22, 25] 22% in CH [20] and 0% in CHS [21]. In a recent study, reporting a series of 103 patients, both marginal and intralesional resections were shown to be an independent risk factors for local recurrence with hazard ratio (HR) of 9.45 and 38.62, respectively [17].

The oncological importance of achieving clear margins mandates both preoperative planning as well as intraoperative continuous assessment of the plane of resection with regard to the tumor's margins. The surgeon's experience

combined with the pre-operative planning is paramount to the success of the procedure.

The goal of this study was to evaluate the accuracy of experienced spinal tumor surgeons' perception of the achievement of clear (tumor free) margins. This was done by comparing the surgeons' intraoperative assessment of the achievement of clear margins, with a gold standard pathological assessment that was performed post-operatively. This comparison was done in one of the world's largest spine oncology centers, evaluating a series of 220 consecutive cases of en bloc resections.

Materials and methods

From January 1990 to July 2015, 1681 consecutive patients with spine tumors were diagnosed and treated in a single institution. 220 en bloc resections were performed on 216 patients by the senior author (S.B.) and his team. All cases underwent full clinical radiographic and histological study, and were classified according to the Enneking staging system [1] and the WBB surgical staging system [26]. Surgery was planned accordingly. From the beginning of the period, all available data were inserted into a purpose-built database for use in a prospective study.

Factors that were reviewed for this study included the intraoperative surgeon's assessment of the surgical margins, classified as clear or contaminated, and the postoperative pathological examination performed by a trained pathologist classifying the margins as wide, marginal and intralesional. As the diagnosis of marginal margins can only be made by histopathological analysis, two assessments were performed. The first considering marginal margins together with wide margins as clear resection, while the second considering this resection together with intralesional margins as contaminated.

Statistical analyses

A correlation between the surgeons' assessment and the histopathological assessment was performed. For every patient, a comparison of the two assessments was made. Parameters that were calculated were the positive predictive value (PPV), negative predictive value (NPV), sensitivity, specificity, and kappa statistics for agreement between the surgeons' and the histopathological assessments.

For all analyses, SPSS 23.0 statistical software was used (SPSS Inc, Chicago, Illinois).

Terminology for resections [1, 26]:

1. The surgeon's perception of oncological margins was classified as:
   a) Contaminated—if the intraoperative assessment was that the tumor was violated during the procedure of en bloc resection
   b) Clear—if the intraoperative assessment was that the resection was done without violation of the tumor's capsule, and that the surgical dissection was performed through healthy tissue.
2. The histopathological evaluation of the resected specimen enabled en bloc resections to be further subclassified as:
   a) Intralesional—if the tumor was violated by intentional or accidental transgression to spare important neuro-vascular structures, thereby causing a part of the tumor to remain in the patient and tumor spillage.
   b) Marginal—if only tumoral pseudocapsule covered the tumor.
   c) Wide—if a cuff of peripheral healthy tissue, better if it is a dense fibrous cover (e.g., fascia), or an anatomical barrier not yet infiltrated (e.g., pleura), fully covered the tumor.
3. Two separate statistical analyses were performed with regard to the histopathological classification of marginal margins.
   d) Marginal margins were considered a potential tumor violation and were regarded together with intralesional resection as contaminated margins.
   e) Marginal margins were considered en bloc resection without tumor violation and were regarded together with wide resection as clear margins.

Results

From January 1990 to July 2015, 1681 consecutive patients with spine tumors were diagnosed and treated in the same institution. A total of 220 en bloc resections were performed on 216 patients during that period.

217 cases had both, a surgeon's assessment of the oncological margins achieved as well as a complete post-operative pathological evaluation.

The study group consisted of 111 males and 102 female patients with an average age of 44.1 ± 18 (range 3–82 years). Most of the tumors were primary—163 cases (42 benign and 121 malignant), while 54 cases were metastases. The location of the tumor was lumbar in 113 cases, thoracic in 94 and cervical in 10.

Regarding the margins determined by the pathologist following the examination of the final specimen,

Table 1 Statistical analysis

	Marginal = contaminated	Marginal = clear
True positive	97	109
True negative	79	31
False positive	12	0
False negative	29	60
PPV	88.99%	100%
NPV	73.15%	0%
Sensitivity	76.98%	64.5%
Specificity	86.81%	100%
Kappa statistics	0.62	0.29

intralesional resections were performed in 31 cases; of them, 5 were benign (GCT, osteoblastoma) and 26 were malignant or metastatic. Marginal margins resections were done in 60 cases; 7 of them were benign tumors (GCT, osteoblastoma) and 53 cases were malignant or metastatic. Wide resection was reported in 126 cases; of them, 31 cases were benign and 95 were malignant or metastatic.

The surgeon's assessed the margins as clear in 109 cases of them the histopathological analysis was marginal in 12, 99 wide, no intralesional margins were determined. Contaminated resections were assessed by the surgeons in 108 cases of them, the histopathological assessment determined 29 as wide, 48 as marginal and 31 as intralesional margins.

When considering the histopathological assessment of marginal margins as a contaminated resection, the surgeon's assessment of clear resection had a sensitivity of 76.89%, and specificity of 86.81%, the PPV and NPV were 88.99 and 73.15%, respectively (Table 1). Kappa statistics for inter-observer agreement was 0.62.

When considering the histopathological assessment of marginal margins as a clear resection, the surgeon's assessment of clear resection had a sensitivity of 64.5%, and specificity of 100%, the PPV and NPV were 100 and 0%, respectively (Table 1). Kappa statistics for inter-observer agreement was 0.29.

The agreement between the surgeons and the histopathological assessment did not differ regarding the various pathologies treated.

Local recurrence

When stratified according to the tumor's staging and aggressive characteristics, all 10 cases of recurrence following intralesional resection were classified as extracompartmental tumors—Enneking stages IB (in 2 cases) and IIB (in 8 cases), with a diagnosis of osteogenic sarcoma, chordoma, chondrosarcoma and Ewing sarcoma. In the 11 cases of local recurrence following marginal margins achieved resection, all but one case of intracompartmental stage IA Ewing sarcoma were extracompartmental tumors, Enneking stages IB (in six cases), IIB (in three cases), IIIB (one case). In the nine cases of local recurrence following wide resection achieved, all but one case of stage three Giant cell tumor were malignant tumors, six cases were extracompartmental (Enneking stages IB in three cases, IIB in three cases), one metastatic case (Enneking stage IIIA) and one case of intracompartmental low-grade chordoma stage IA.

As both perception and prognosis are different considering the various histotypes of the tumors, following the histopathological stratification of the tumors, local recurrence of the tumor occurred in 10 cases out of 26 (38.46%) intralesional histopathologically diagnosed, 11 cases out of 53 (20.75%) histopathologically diagnosed as marginal margins, and in 8 cases out of 95 (8.42%) histopathologically diagnosed as wide resection. No local recurrence occurred following intralesional or marginal resections of benign tumors, only one local recurrence occurred following wide resection of stage 3 GCT.

Discussion

En bloc surgical resection of spine tumor has the potential benefit of local control of the disease, thereby allowing an optimal oncological treatment and improving patient survival. For that, an aggressive and potential morbid surgical procedure is performed with the goal of completely removing the tumor en bloc preferably with all pathological tissue including satellite tumor cells.

The surgeon's experience and intraoperative evaluation of the lesion's borders is paramount for the successful complete resection of the tumor. However, it is unclear how accurate this assessment is. This was the impetus of this study.

As described by Enneking [1], marginal resection is in fact a complete en bloc resection of the tumor through its reactive zone, with the possibility of missing satellite tumor cells in the wound. To that extent, the prognostic meaning of such margins differs between benign tumors such as Osteoblastoma, where marginal margins would be an acceptable oncological resection, and malignant aggressive tumors such as Osteosarcoma, where wide margins would be preferred. When addressed accordingly, where marginal margins achieved in the histopathological evaluation are considered complete resection with clear margins, the surgeon's perception of achieving clear margins had a PPV and specificity of 100%. That means that the surgeon's assessment correlated with the histopathological evaluation, and that with regard to resection achieving the oncological goals, the intraoperative surgeon's assessment correlated with the pathological status

greatly. To that extent, the NPV and sensitivity were 34.07 and 64.5%, respectively, and the Kappa statistics was 0.29. This means that there was a significant disagreement between the two methods, but this disagreement was mostly regarded to the surgeons that assessed clear margins as contaminated in several cases and were "over careful" or "pessimistic" in that aspect. This "over-pessimistic" intraoperative assessment might cause the surgeon to expand the surgical resection for better oncological results while increasing the morbidity of the procedure.

As the resection of spinal tumors involves at times the sacrifice of vital anatomical structures, accurate planes of resection that is based on the best possible assessment of tumor's margins is critical to avoid unnecessary sacrifices. Furthermore, as local recurrence is closely related to any remaining malignant cells, knowing intraoperatively of the margins, allows the surgeon to expand the resection if required.

Local recurrence

The main target of en bloc resection is local and systemic control of the disease, and the achievement of this goal justifies the high level of morbidity reported to be related to this procedure. The risk of local recurrence is directly related to the margin of resection [1, 27], where when performing intralesional surgery reduces the possibility of local control [3–9, 11, 17, 19–23, 25, 28].

In this series, the local recurrence rates following stratification according to the potential local recurrence of the tumors, were 38.46, 20.75 and 8.42% for intralesional, marginal and wide resections, respectively. Furthermore, local recurrence occurred following marginal margins almost exclusively in extracompartmental tumors, suggesting that in these cases, marginal margins should be addressed as contaminated resection. These data are not surprising as it is expected that the more the resection is close to the tumor, and the more the tumor is violated the higher the chances of local recurrence. However, that higher rate of local recurrence when marginal resection was achieved supports the notion that some satellite tumor cells are in fact present in the reactive zone, and therefore the tumor's resection could not be regarded as a tumor free margin enbloc.

Correlation

When analyzing marginal margins as histopathologically diagnosed, to be related with an incomplete tumor resection or a contaminated resection, the surgeon's accuracy in assessing the clear resection was reduced. In this case, the PPV and specificity were 88.99 and 86.81%, respectively. Furthermore, the NPV and sensitivity increases and were 73.15 and 76.98%, respectively, and the Kappa statistics was 0.62. This means that the surgeons' assessment did not completely correlate with the histopathological results, although the overall agreement improved. This disagreement was related to underassessment of contaminated margins, meaning that in more then 10% of the cases, margins were regarded as clear when they were in fact contaminated.

As it is almost impossible for the surgeon to differentiate between wide and marginal margins during surgery, a more clinically relevant distinction between either marginal or intralesional and wide resection was performed in this study. This distinction, of either clear or violated margins, represents better the surgical parameters upon which the surgeon should base his intraoperative decisions and planes of resection.

The difference between the surgeons' and the histopathological assessments should, preferably be reduced to minimum, as some of the intraoperative as well as the post-operative paradigms might be influenced by this assessment. Having the best possible idea as for the contamination of the margins should be pursued.

It is of note, that there was no use of intraoperative pathological frozen section analysis. The use of such intraoperative technique might improve the intraoperative assessment, and perhaps could result in further widening of the surgical resection. The influence of these, in terms of patient outcome, morbidity and tumor local control, is not known and should be further explored.

Conclusions

The surgical techniques of en bloc resections dramatically improve local control in aggressive benign and low-grade malignant bone tumors [3, 5–7, 9, 29]. Oncologic criteria should guide the decision-making process regarding bone tumors of the spine [1, 3–9, 11, 17, 19–23, 25, 26, 28, 30, 31]. The complete resection of the tumor, in one intact piece, without contamination of the surgical field is the key point for the success of this procedure. Therefore, determination of clear vs. contaminated margins is the most important factor during both, the surgical resection as well as the postoperative oncological treatment.

This study evaluates the accuracy of margins assessment done by experienced tumor surgeons recorded in a large single-center series of en bloc resections.

The data support the conclusion that experienced surgeons are fairly accurate in their intraoperative assessment of clear margins achieved. As for their assessment of contamination, their assessment is less accurate and "over-pessimistic". As this accuracy is not perfect, exploring ways to improve this intraoperative assessment is of major

importance with a possible impact on the outcome of the treatment.

Compliance with ethical standards

Conflict of interest None.

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