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Cohort Study

Limited utility of intraoperative frozen sections in primary malignant tumours involving long bones - A multicenter analysis of 475 cases

Niranj G. Radhamony [a,*], Subin Sugath [b], Bibi Dhanan [c], Jayasree Kattoor [d], Nanda Kachare [e]

[a] Royal Stoke University Hospital, Stoke on Trent, UK
[b] Aster Medcity, Kochi, Kerala, India
[c] Abeer Medical Center, Farwaniya, Kuwait
[d] Regional Cancer Centre, Thiruvananthapuram, India
[e] Aster Medcity, Kochi, Kerala, India

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ABSTRACT

Background: In the surgical removal of primary malignant tumours involving long bones, intraoperative frozen sections are used to ascertain the adequacy of tumour clearance. However, with the improved imaging modalities that provide better foreknowledge of the tumour extent, it is possible that the arduous task of performing frozen sections can be safely avoided. This would not only save procedural time but also reduce hospital costs. Presently, there are no clear guidelines regarding the modality required intraoperatively to assess tumour margins in these cases. Hence, in our retrospective multicentre analysis, we aimed at determining the usefulness of frozen sections in these cases.

Materials and methods: Our study is a 3-centre retrospective analysis of 475 cases (513 tumour margins) involving the surgical removal of primary malignancies of long bones. The preoperative Magnetic Resonance Imaging (MRI) and intraoperative assessment of the split specimen of the tumours were used to determine marginal clearance in all the cases in addition to frozen sections in 410 of the margins.

Results: Of the 410 frozen sections (centres 1 and 2), only one margin was reported positive and another reported indeterminate. All other margins were reported negative. In the first case, a 2 cm additional bone-cut was done whereas in the second, the procedure was proceeded based on the intraoperative agreement without re-cutting the margin. All these margins were negative in the final histopathology. In addition, in Centre 3, where frozen sections were not available, all the 103 cases had negative margins in the final histopathology.

Conclusion: In primary malignancies involving long bones, intraoperative decision making with the aid of MRI has been sufficiently accurate in identifying the required tumour margin without frozen sections. Hence, the added time and cost incurred by doing an additional procedure can be avoided in these cases.

1. Introduction

Primary malignancies of bone affect about 3600 people in the United States and about 550 people in the United Kingdom every year [1,2]. In the extremities, whether these tumours are managed by amputation or by limb salvage procedures, our main aim is to provide margins free from neoplastic cells. There are various methods that help us to ascertain the adequacy of tumour clearance in these cases.

One of the methods considered greatly reliable regarding the adequacy of tumour clearance is intraoperative histopathologic consultation in the form of frozen-sections. Here, the tissue to be tested is frozen before being viewed under the microscope. Most major bone cancer treatment centres use this modality to determine the adequacy of tumour clearance [3]. However, the actual usefulness of this procedure in aiding surgical clearance of tumour margins and decision making is unproven, and there are no published protocols on the method to be adopted intraoperatively to get negative tumour margins involving long bone tumours [4–6]. Moreover, there is scarce data on the rates of positivity of frozen sections intraoperatively that mandate recuts and the rates of presence of marginal tumour cells in the final histopathology of resection specimens in these cases. Another fact which discourages the usage of frozen sections is that it is technically challenging to freeze the

* Corresponding author.
E-mail addresses: niranj.gr@gmail.com (N.G. Radhamony), bhaskarsubin@gmail.com (S. Sugath), bibidhanan@yahoo.co.in (B. Dhanan), jayasreeramdas@gmail.com (J. Kattoor), drnandadk@rediffmail.com (N. Kachare).

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marrow when they are too liquefied or too hard as in cancellous or fibrosed bone [7].

Recent data shows that the refinements in imaging modalities, especially the Magnetic Resonance Imaging (MRI), have shown more promise in delineating the tumours in bones more precisely [8]. Newer techniques such as image navigation have improved our ability to make carefully planned osteotomies based on the preoperative imaging studies [9,10]. Such detailed information beforehand has enabled the surgeons to decrease the acceptable margin size further while still getting adequate oncological clearance [11,12]. Hence, it is important to critically evaluate the diagnostic role of frozen sections. This can promote evidence-based guidelines that save operating time and cost thereby improving overall patient care.

Considering the above concerns, the present multicentric retrospective observational study aimed at finding out the number of tumour resection margins involving long bone malignancies that had come positive, and how far did they correlate with the final histopathology. Subsequently, we analysed how accurately one can rely on the preoperative MRI images along with gross split specimen examination in providing the required tumour clearance.

2. Material and methods

Our study is a multicentre retrospective analysis of 475 cases of primary malignant tumours involving long bones managed surgically at three different hospitals. The cases were performed from January 2001 to December 2017. The study obtained institutional ethics committee approval (AM/EC/70–2018), and the work has been reported in line with the STROCSS criteria [13]. The data about these cases were gathered from the hospital records, and the tumour type, procedure performed, frozen section result and the final histopathology of the resection margins were noted. We included amputations and limb salvage surgeries where a bony resection was made for malignant tumours involving long bones. Metastatic lesions, tumours involving flat bones including pelvis and cases where the entire bone was resected as in total femur prosthesis replacement were excluded.

All the cases had an MRI scan performed preoperatively. The scans had been performed either at the operating hospital or at other private scan centres. The quality of the images was either 1.5 T (T) or 3 T, and cases performed based on both the qualities were included. The images considered for planning surgical bone cuts were made based on the pre-chemotherapy T1 weighted MRI sequences as they exclude bone marrow edema [14]. Intraoperatively, the tumours were resected by leaving a 2 cm margin from the tumour extent as seen in these MRI images (Fig. 1). Intraoperatively, this measurement was made from the joint line which was assessed either by palpation or by fluoroscopy. Frozen section samples were then sent by scooping out the marrow at the bone cut margins and by spreading them on glass slides. These were transferred immediately to the histopathology department where the frozen sections were performed immediately. Meanwhile, the resected gross specimen was split (Figs. 2 and 3), and analysed for adequacy of tumour clearance. This assessment was correlated with the frozen section result that arrived, and based on the agreement regarding the adequacy of tumour clearance, the operations were completed. Had the frozen section results come positive, an additional 2 cm resection was made and frozen sections repeated. Although the included cases belonged to varied pathological types as per preoperative needle histopathology and MRI, no qualitative differences between the tumour types were considered to decide on the tumour resection margins.

Fig. 1. Preoperative pre-chemotherapy T1 weighted MRI image representing a 2 cm margin for resection.

Among the 513 tumour margins involved, 410 margins were subjected to frozen sections intraoperatively to confirm the marginal clearance (centres 1 and 2). In the rest of the cases (centre 3), frozen section facility was not available, however these cases were included to correlate how many cases reported positive margins in the final histopathology. In this particular centre, cases that were expected to have narrow margins anticipating the need for frozen section analysis for clearance were not operated, and referred to centre 1.

Based on the frozen section reports obtained, the margins were classified as negative, positive, or indeterminate. The final pathologic report of the specimen about marginal clearance was considered confirmative.

3. Results

Out of the 410 margins (including 38 intercalary resections 76 margins) subjected to frozen section analysis, all except two were reported negative. Among these two cases, one was reported positive and the other was indeterminate. In the positive case, which was an Ewing's sarcoma of the tibia, a 2 cm additional bone resection was made, and the marrow margin after revised resection was reported negative on performing a repeat frozen section. Surprisingly, the margin which was initially reported as positive was finally found to be negative on subsequent biopsy. In the other case where the frozen section report was indeterminate, the operation was proceeded based on the intraoperative findings without a bone re-cut. Here again, the final histopathology showed a negative margin. This case was again a case of Ewing's sarcoma of the tibia. Among the remaining cases where frozen sections were not performed (centre 3), all the cases showed negative margins for tumour cells on the final histopathology. This shows that only preoperative MRI images and intraoperative findings were sufficient to provide marginal clearance in these cases.

Regarding the time taken for frozen section analysis, the maximum

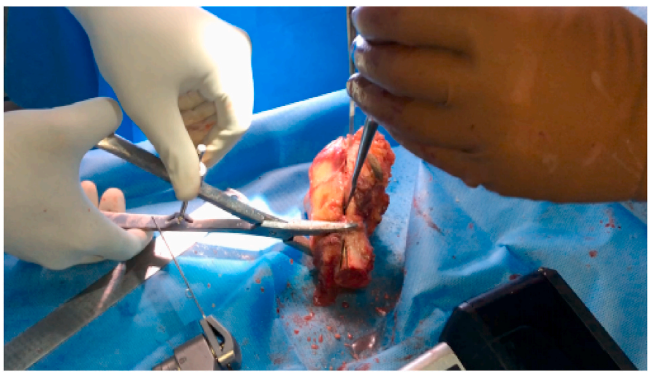

Fig. 2. Performing intraoperative gross split specimen.

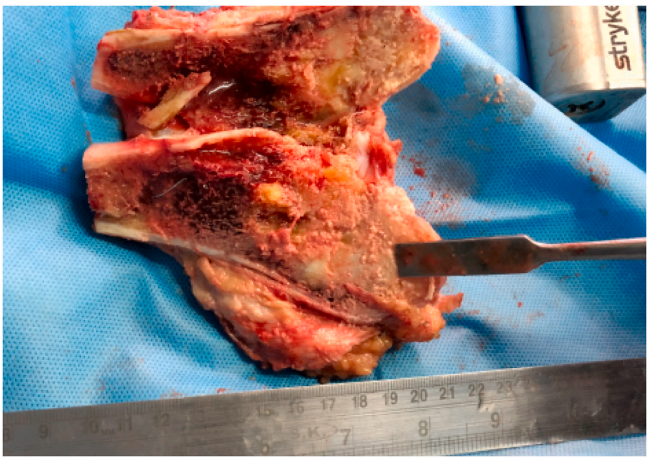

Fig. 3. Performing intraoperative gross split specimen.

documented time was 45 min and the minimum was 15 min although we were unable to trace this timing from all the cases retrospectively.

The distribution of cases is shown in Table 1 and the frequency of cases based on the pathological types is shown in Table 2. Notably, even though alveolar soft-part sarcoma (ASPS), clear cell sarcoma, angiosarcoma, liposarcoma and osteoliposarcoma are malignant tumours with predominant soft tissue component, these were included along with primary malignancies of long bones as there were significant long bone involvement in these cases requiring curative resections.

4. Discussion

In bone tumour resection surgeries, intraoperative pathological consultation by frozen section is frequently sought to confirm the diagnosis and to determine the adequacy of marginal clearance [14,15]. In centres where frozen section study is not available, preoperative MRI images and intraoperative assessment of the resected split specimen are relied upon for deciding the margins for tumour clearance. However, there are no clear guidelines regarding the method to be followed intraoperatively in bone tumour resection surgeries to get tumour free margins. While the advantage of frozen sections in providing adequate tumour clearance is clear in soft tissue sarcomas [16], a convincing evidence on their application in long bone sarcoma resection is missing. Bone tumours of flat bones like pelvic bones are frequently associated with significant soft tissue involvement and hence can be considered as a continuum to soft tissue sarcomas. Therefore, long bone tumours can be considered as a separate entity. Clearly, there are no studies evaluating an algorithm required for obtaining tumour free margins during long bone tumour resections, and none have proven the necessity of frozen sections in providing tumour clearance in such a scenario. With this background, we retrospectively analysed 475 cases of long bone tumours from 3 different institutes regarding the usefulness of frozen sections in these cases.

Table 1
Inclusion of cases and centres.

475 Cases of long bone tumours 3 centres 2001–2017		
Frozen section performed Centres 1 and 2 372 cases 334 + (38 intercalary resection x2) = 410 margins		No frozen sections Centre 3
Centre 1 354 margins	Centre 2 56 margins	103 cases (103 margins) Final histopathology negative for tumour cells in all the cases

Table 2
Distribution of cases based on pathological types.

S. No	Tumour type	Number of cases
1	Osteosarcoma	393
2	Condrosarcoma	26
3	Ewing's sarcoma	7
4	Undifferentiated pleomorphic sarcoma	10
5	Osteoliposarcoma	6
6	Clear cell sarcoma	3
7	Synovial sarcoma	8
8	Angiosarcoma	6
9	Alveolar soft part sarcoma	3
10	Liposarcoma	9
11	Fibrosarcoma	4
Total		475

In centre 3, where frozen sections were not available, the decision on tumour margins were made based on the MRI images and intraoperative morphology of the tumours alone. During the considered period, 103 malignant long bone tumours were resected in this centre and all of them had a negative tumour margin on the final histopathology. Thus, in all our cases it is clear that the final histopathology correlated with the initial intraoperative decision about bone cuts during tumour resection. These results correlate well with the findings of Meyer et al. [14] who noticed that frozen sections contributed very less in the decision making of these tumour resections.

The capability of MRI in accurately determining the extent of skeletal tumours with respect to marginal clearance has been previously discussed in various studies [17–21]. According to studies, the pre-chemotherapy T1 weighted images of MRI have been precise in delineating the intramedullary extent of tumours [17,22–26]. Other sequences like Short Tau Inversion Recovery (STIR) and T2 weighted images tend to overestimate the extent of tumours. This happens due to marrow edema [17,23–25]. This corresponds to our study where we used pre-chemotherapy T1 images to plan the intraoperative bone cuts.

Even though frozen sections are relied upon for deciding intraoperative marginal status in many tumour surgery centres, a lot of factors result in inconclusive tissue diagnosis during frozen sections. These include hypocellularity of the smears and nonrepresentative samples [27]. The hypocellularity can be due to fibrosis or due to application of inadequate pressure on preparing the imprint slides. Specifically, for bone tumours, both hard cortical bones and the cheesy bone marrow are challenges in creating a frozen substrate on which the microtome is used to prepare adequate slices in order to perform frozen sections. All these factors contribute to indeterminate results at times while doing frozen sections. Another factor that discourages the use of frozen sections is the time required for the procedure. On an average, a frozen section study takes 20–25 min [27], which prolong the overall operative duration. In our analysis, the time taken was noted to be from 15 to 45 min.

In our study, given that all the marrow margins were negative on the final histopathology except in two instances, we conclude that MRI evaluation along with the appearance of intraoperative gross split specimen helps in reliable surgical decisions and that the information from the frozen section analysis was non-contributory in these instances. The results of this study confirm that there is no evidence to support frozen section assessment as superior to MRI and intraoperative assessment in operative decisions of long bone tumours. Hence, in today's healthcare practice it is important that we avoid unnecessary or redundant practices that don't add any value.

Our study has some limitations. First, we analysed the usefulness of frozen sections in long bone tumours only which means that the results of the study cannot be considered for flat bones and those with extensive soft tissue involvement. The duration between the MRI images performed in the pre-chemotherapy period and the time of surgery varied and this was not analysed. Moreover, the quality of MRI images (1.5T versus 3 T) were not considered and in either types, the bone resection

margins was 2 cm. These could have resulted in non-uniformity of cases considered. Second, regarding the assessment of bone marrow margins on the gross specimen, these split sections could be done only in one plane which may not represent the most accurate extent of the tumour thereby resulting in false interpretations. Third, sinde there are no universally accepted guidelines on the amount of bone required at marrow margins to be considered negative, the surgeon's discretion regarding recut has been considered correct. Sometimes, this may be at the expense of making extra bone cuts, and when there are no consequences, it was considered acceptable. A final limitation is that the patient outcome has not been recorded and there is no long-term follow-up regarding local recurrence or metastasis in these cases.

To conclude, although frozen section reporting is a good armamentarium desirable in tumour resection surgeries, when it comes to tumours involving long bones, the combined agreement based on the MRI and intraoperative findings can provide adequate marginal clearance. Therefore, frozen sections could be safely avoided in these cases, and the time and cost incurred by an additional intra operative procedure such as frozen sections can be avoided.

Location of the study

The study included data gathered from three hospitals in India.

Centre 1- Regional Cancer Centre, Thiruvananthapuram, Kerala, India
Centre 2- Aster Medcity, Kochi, Kerala, India
Centre 3- SUT hospitals, Thiruvananthapuram, Kerala, India

Ethical approval

Yes. AM/EC/70-2018.

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CRediT statement

Niranj G Radhamony: Conceptualization, Methodology, Writing-Original draft preparation. **Subin Sugath**: Conceptualization, Methodology, Validation, Writing- Reviewing and Editing, Supervision, Project Administration. **Bibi Dhanan:** Conceptualization, Methodology, Writing- Original draft preparation. **Nanda Kachare:** Conceptualization, Methodology, Validation, Writing- Reviewing and Editing. **Jayasree Kattoor**: Conceptualization, Methodology, Validation, Writing- Reviewing and Editing.

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Guarantor

Niranj Ganeshan Radhamony, 18 Sharman Close, Stoke on Trent, UK. niranj.gr@gmail.com.

Declaration of competing interest

The authors do not have any conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2021.103108.

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