Transition from Tumor Tissue to Bone Marrow in Patients with Appendicular Osteosarcoma after Neoadjuvant Chemotherapy

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Abstract

Background: Limb-salvage surgery is the standard procedure for the treatment of appendicular osteosarcoma. Precise resection is the trend in limb-salvage surgery. The aim of this study was to evaluate a large series of cases to identify the histological relationship between the tumor and marrow and determine the intramedullary transition type and width from the tumor to normal marrow in patients with osteosarcoma after neoadjuvant chemotherapy.
Methods: One hundred and six osteosarcoma specimens were evaluated. The tissue specimens were sectioned through the coronal axis by an electronic saw. The tissue was immersed in formalin solution for fixation and subsequently decalcified. The interface between the tumor and normal bone marrow was grossly determined and submitted for microscopic evaluation to detect the relationship between the tumor and bone marrow and identify the transition type and width. All histological slides were examined by experienced orthopedic pathologists.
Results: Histologically, the interface between the tumor and normal bone marrow was classified into two patterns: "clear" and "infiltrated." The clear pattern, characterized by a clear boundary between the tumor and marrow, was identified in sixty cases (56.6%). A subtype of the clear type, characterized by fibrous bands between the tumor and marrow, was found in 13 cases (12.3%). The infiltrated pattern, characterized by a boundary with tumor cell clusters embedded in the marrow, was found in 46 cases (43.4%). The infiltrating depth varied from 1 to 4 mm (mean, 2.6 ± 0.7 mm). No tumor cells were observed in the normal bone marrow areas next to the interface.
Conclusions: The transition from osteosarcoma tissue to bone marrow after neoadjuvant chemotherapy can be divided into two histological patterns: clear and infiltrated. The greatest infiltration width was 4 mm from tumor to normal marrow in this study. This depth should be considered in the presurgical plan.

Key words: Bone Marrow; Limb-salvage Surgery; Osteosarcoma; Pathology

Introduction

Limb-salvage surgery is the standard procedure for the treatment of appendicular osteosarcoma. Determination of the tumor boundary is essential for surgical planning. The osteotomy plane is determined by the tumor extension. Surgical techniques for limb salvage surgery have greatly improved in the recent years.[1] Precise resection is the trend in limb-salvage surgery.[2] Neoadjuvant chemotherapy has been proven to increase the local control of osteosarcoma.[3,4] Intramedullary osteosarcomas extend into the normal marrow, and a histological understanding of how the tumor extends into the marrow could help in surgical planning. In the present study, we evaluated a large series of cases to identify the histological relationship between tumor tissue and bone marrow and determine the intramedullary transition type and width from the tumor to normal marrow in patients with osteosarcoma after neoadjuvant chemotherapy.

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Methods

Ethical approval

This study was approved by the Medical Ethics Committee of Beijing Jishuitan Hospital.

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The enrollment criterion for this study was surgical treatment of an osteosarcoma in an extremity. The exclusion criteria were osteosarcomas with skip lesions found by imaging or pathological examination, pathological fractures, and tumors in a narrow bone such as the fibula or radius. One hundred and six osteosarcomas of the extremity were evaluated in this study from March 2012 to April 2015. The patients were diagnosed with osteosarcoma through imaging studies and biopsy examinations. All patients had conventional osteosarcoma and received neoadjuvant chemotherapy according to our center's protocol, which included high-dose methotrexate, ifosfamide, cisplatin, and adriamycin. There were 69 male and 37 female patients. Their median age was 15 years (range, 9–62 years). The tumors were located in the distal femur (n = 60), proximal tibia (n = 37), proximal humerus (n = 8), and distal tibia (n = 1). All tumors were located in the metaphyseal region, and the transition from tumor tissue to marrow could be evaluated in all cases.

Tissue specimens were sectioned through the coronal axis of the osteosarcomas by an electronic saw. Since the specimens were taken at different times, they were treated separately. The tissue sample was immersed in formalin solution for 24 h for fixation and subsequently decalcified. The interface between the tumor and normal bone marrow was grossly determined and submitted for microscopic evaluation. The 1.0 × 0.5 × 0.5 cm section that was obtained constituted nearly 50% of the tumor area and 50% of the normal bone marrow area; another three sections next to the normal bone marrow area were sampled for evaluation as well [Figure 1]. After hematoxylin and eosin staining, microscopic evaluation was performed to identify the relationship between the tumor and bone marrow and determine the transition type and width. Experienced orthopedic pathologists examined all histological slides using a photomicrograph (BX41; Olympus Corporation, Tokyo, Japan). Grossly, the interface section included half tumor and half marrow in the longitudinal axis. Therefore, the transition width was evaluated from the central line of the tissue section to the most distal tumor cells on the marrow side.

Results

Histologic evaluation of treated osteosarcoma focuses on residual osteosarcoma cells on a background of necrosis, calcification, or fibrosis. Histologically, the interface between the tumor and normal bone marrow can be classified into two patterns according to the relationship between the tumor and marrow. The first pattern is characterized by a clear boundary and is termed the "clear" transition type. This type was found in sixty cases (56.6%) [Figure 2]. The tumor cells did not cross the central line, and a clear boundary was present between the tumor and marrow. In addition, 13 cases showed a thin collagenous–fibrous septum of <0.5 mm between the tumor and bone marrow [Figure 3]. The second pattern is called the "infiltrated" type. An infiltrating boundary with tumor cell clusters embedded in the marrow was found in 46 cases (43.4%) [Figure 4]. In this pattern, the infiltrating depth varies from 1 to 4 mm. The mean depth was 2.6 ± 0.7 mm. No tumor cells were found in the normal bone marrow areas next to the interface.

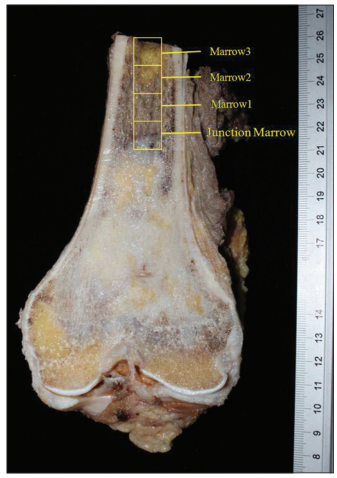

Figure 1: Schematic diagram of a specimen.

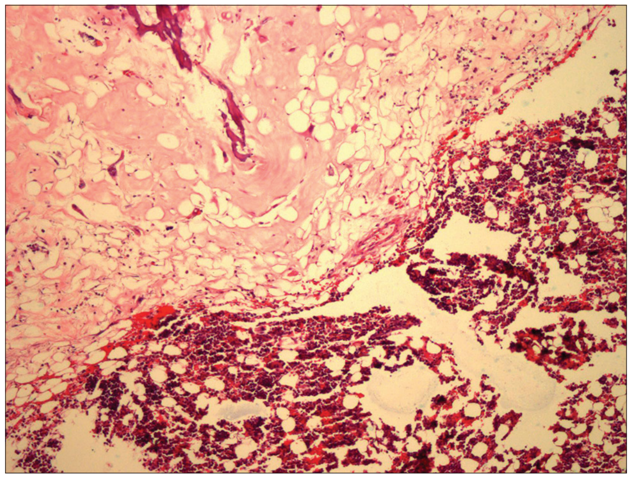

Figure 2: Clear transition pattern, H & E staining, original magnification ×100. The marrow cells are below and the tumor cells are above the boundary line. The boundary is very clear.

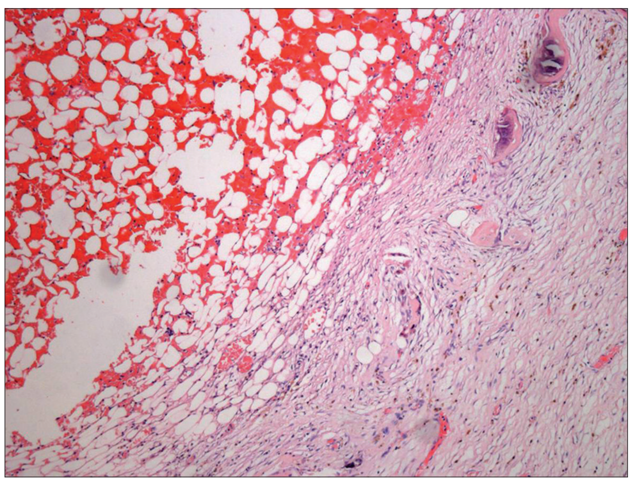

Figure 3: Subtype of clear transition pattern, H & E staining, original magnification ×100. Fibrous bands are present between the tumor and marrow.

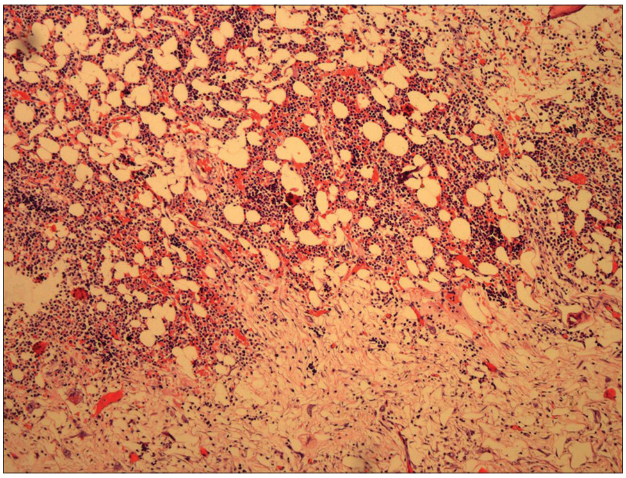

Figure 4: Infiltrated transition pattern, H & E staining, original magnification ×100. Clusters of tumor cells have infiltrated the marrow cells. The boundary is unclear.

Discussion

Osteosarcoma is the most common primary malignant bone tumor and occurs with greatest frequency in the appendicular skeleton.[5,6] Preferred management involves limb-sparing surgery following neoadjuvant chemotherapy.[7-11] Studies have demonstrated that the surgical margin is closely associated with local recurrence.[12-14] Presurgical planning is very important to achieve adequate margins. Local recurrence has been shown to be a high-risk factor for survival.[15]

Bony resection planning is based on the tumor extension. Previous studies have shown that magnetic resonance imaging, especially T1-weighted imaging, can accurately estimate the intramedullary extent of osteosarcoma.[16,17] However, information on the histological transition from tumor tissue to marrow cannot be found in literature. In the present study, we observed a clear boundary between the tumor and marrow in 56.6% of cases. The tumor infiltrated into the marrow in 43.4% of cases, and the greatest infiltration width was 4 mm. This finding provides histological evidence that tumor cells can infiltrate into the marrow, but no more than 4 mm away from the gross boundary.

The bone marrow margin adjacent to the osteotomy site is commonly evaluated to assess the margin status after surgical treatment of osteosarcoma. Several studies have demonstrated that narrow but negative margins can result in good outcomes, showing local recurrence and distant disease rates comparable with those in cases involving wider margins.[18,19] However, these reports provide no histological evidence of how far the tumor cells can infiltrate into the marrow.

The optimal distance between the osteotomy and intraosseous tumor has not been established. In our routine clinical work, we usually place the osteotomy plane 3 to 5 cm away from the tumor based on the presurgical imaging to obtain an adequate surgical margin. This is a safe distance that accounts for possible instrument-induced manual error during bone resection as well as length measurement-related error upon imaging of the specimen. Loh *et al*.[20] found no significant increase in adverse survival outcomes after reducing the bony resection margins to 1.5 cm in the longitudinal plane in patients with osteosarcoma of the extremity.[20] The results of the present large series study indicate that, when skip lesions are excluded, the histological transition area from the osteosarcoma tissue to the marrow cannot exceed 4 mm. In practice, the histological tumor infiltration length is only one important factor to consider when determining where to cut the bone based on imaging findings. More studies are needed to elucidate the correlation between imaging findings and specimen characteristics as well as the manual error of osteotomy compared with the presurgical plan.

Our study has several limitations. First, all specimens were osteosarcomas treated with neoadjuvant chemotherapy. The effect of chemotherapy on the results of this study is unknown. A control group without neoadjuvant chemotherapy was unavailable. Second, all specimens in this study were taken from a wide long bone. The results cannot be extended to narrow long bones such as the fibula or radius.

In conclusion, this study has shown that the transition from osteosarcoma tissue to bone marrow after neoadjuvant chemotherapy can be divided into two histological patterns: clear and infiltrated. The widest infiltrated depth was 4 mm from the tumor to normal marrow. This depth should be considered in the presurgical plan.

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Conflicts of interest

There are no conflicts of interest.

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