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ORIGINAL ARTICLE

Spontaneous necrosis and additional tumor necrosis induced by preoperative chemotherapy for osteosarcoma: a case–control study

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Abstract
Background Extent of spontaneous necrosis in untreated osteosarcoma may imply tumor aggressiveness. Reports regarding this issue are scarce and there are several points to be clarified; (1) the correlation between tumor size and extent of spontaneous necrosis displayed was conflicting, (2) whether there is difference in necrosis rate between intra- and extra-medullary portion of tumor is not described, if it does, its relation with other clinico-pathologic variables, (3) in patients with surgical treatment only, >20 % spontaneous necrosis was a poor prognostic factor, however, whether that cutoff is still valid in chemotherapy cohort remains to be determined, (4) expected additional tumor necrosis by chemotherapy was made by simply comparing the necrosis rates of untreated and treated osteosarcoma cohort.
Methods We evaluated spontaneous necrosis in 43 osteosarcoma patients (39 Stage IIB, 4 Stage III). We evaluated overall necrosis rate and separately evaluated the necrosis rate of intra- and extra-medullary portion of tumor. These results were compared with other clinico-pathologic variables. To evaluate additional tumor necrosis induced by neoadjuvant chemotherapy, case (38 without preoperative chemotherapy)–control (76 with preoperative chemotherapy) study was performed.
Results The mean spontaneous necrosis rate was 23 %. Overall spontaneous necrosis was not associated with tumor volume. Necrosis rate of extramedullary tumors was higher in cases of large tumors ($p = 0.02$). In patients with upfront surgery followed by chemotherapy, 5-year event-free survival rate of patients with >20 and <20 % spontaneous necrosis were 82 ± 17 and 79 ± 18.5 %, respectively ($p = 0.75$). After chemotherapy, regardless of tumor volume and location, control group tumors showed an increase in the tumor necrosis of approximately 50 %.
Conclusion In chemotherapy era, the extent of spontaneous necrosis has no relation with survival. The expected additional tumor-killing effect of preoperative chemotherapy is around 50 % of initial tumor volume.

Introduction

The percentage of tumor necrosis resulting from preoperative chemotherapy is regarded the most powerful prognostic factor for osteosarcoma [1]. The most predictive cutoff for favorable or unfavorable response to chemotherapy is greater or lesser than 90 % necrosis and this translates into the difference in survival rates [2]. Currently, approximately 30–40 % of patients with localized osteosarcoma experience relapse with unfavorable prognosis. However, almost 50 % of patients with osteosarcoma show poor response to preoperative chemotherapy [3]. This gap between the relapse rate and poor response rate necessitates an understanding of the role of tumor necrosis in untreated osteosarcoma and in the evaluation of post-chemotherapy necrosis in pathologic specimen.

In a few reports on spontaneous necrosis in untreated osteosarcoma, there are several points to be clarified [4–7]. Firstly, the amount of spontaneous necrosis varied widely across studies. Secondly, besides differences in the methods of tumor size measurement (maximal diameter, cross-sectional area), the correlation between tumor size and extent

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of spontaneous necrosis displayed was conflicting [4, 6]. Moreover, whether there is a difference in necrosis rate between intra- and extra-medullary portion of tumor is not well-described. Thirdly, because a highly necrotic tumor is expected to spread rapidly, in one study with surgical treatment only, patients with osteosarcomas >20 % spontaneous necrosis show poorer survival than <20 % spontaneous necrosis [4]. However, in the chemotherapy era, whether that 20 % cutoff remains as a valid predictor of survival is not evaluated. Finally, by simply comparing the necrosis rates of untreated and treated osteosarcoma cohort, it was established that marked additional tumor necrosis could result from preoperative chemotherapy.

Therefore, we evaluated; (1) the relationship between clinico-pathologic variables and overall/intra- and extra-medullary spontaneous necrosis, (2) in the upfront surgery followed by chemotherapy cohort, whether there is a difference in the survival rate at 20 % spontaneous necrosis cutoff, (3) the expected additional tumor necrosis by preoperative chemotherapy (case–control study).

Materials and methods

From August 2006 to December 2012, we performed immediate surgery followed by chemotherapy on 43 osteosarcoma patients. The selection of patients in this study was randomly assigned and had informed consent regarding treatment strategy guidelines. There were 17 males and 26 females with a mean age of 21 years (range 8–64 years). The tumors were located in the femur in 25 patients, tibia in 12 patients, humerus in 4 patients, fibula in 1 patient and pelvis in 1 patient. According to the classification system of Enneking, 39 patients had Stage IIB tumors and 4 had Stage III tumors. The mean follow-up duration was 32 months (range 12–87 months). Follow-up duration was defined as the period from the date of surgery to the date of death or last visit. Of the 43 patients, 33 (77 %) were continuously disease free, 5 (14 %) showed no evidence of disease after metastasectomy, 4 (7 %) were alive with disease, and 1 (2 %) died of distant metastasis. This study was approved by our institutional research review board.

To accomplish the aims of this study, two analyses were conducted. In the first analysis, we analyzed the spontaneous necrosis rates of the untreated osteosarcoma (the necrosis rates of intramedullary and extramedullary tumors were determined separately). We also assessed the relationship between spontaneous necrosis and clinico-pathologic variables: age, gender, primary tumor location, pathologic subtype, tumor volume, and pattern on plain radiography (radiolucent, radiopaque, mixed). Tumor volumes were calculated using MR images, as described by Gobel et al. [8] using the formula: tumor volume = 0.53 × tumor length × tumor width × tumor depth. At time of tumor resection, we applied surgical margin identical to that of tumors with preoperative chemotherapy. After resection, we examined the cross-sections of the tumor in the most maximal dimension and divided into smaller sections for visualization (2 × 2 cm). Each individual section was independently examined and the viable parts of the tumor were marked on the glass slide. The microscopic examination of the necrosis was expressed by Huvos grades; grade 1, <50 % necrosis; grade 2, most of the tumor is necrotic; grade 3, 90–99 % necrotic; grade 4, totally necrotic. The slides of tumor tissue were reviewed by two pathologists (MSK, JSK). In the case of a discrepancy between the findings of 2 examiners, the amount of necrosis was determined by consensus. The percentage of necrosis was calculated by dividing the necrotic area by the total tumor area.

Under the assumption that tumors with similar factors at presentation would have similar extent of spontaneous necrosis and chemotherapy-induced necrosis, we performed case–control study. To ensure homogeneous study group, we included 38 of 43 untreated osteosarcomas (4 patients with Stage III and 1 patient with a pelvic tumor were excluded) as case group. For control group, we extracted 78 patients from 567 stage IIB patients. Control group patients were matched with patients in the case group in terms of age, initial tumor size, and tumor location. We compared the percentage of tumor necrosis in the case (38 untreated) and control (76 with preoperative chemotherapy) groups according to the tumor volume cutoffs (50, 100, 200 cc) and location (proximal vs others). Tumors in the proximal humerus and proximal femur were defined as proximal tumors. All patients in the case and control groups received neo- and adjuvant chemotherapy with the same chemotherapeutic protocol as previously described [9].

Chi square test was used to determine the statistical significance. Analyses were performed using the SPSS ver. 13.0 (SPSS Inc, Chicago, IL, USA), and the significance level was set at $p < 0.05$.

Results

Correlation between spontaneous necrosis rate and tumor volume and survival

The mean spontaneous necrosis rate was 23 % (range 0–80 %). The necrosis was not evenly distributed; intramedullary tumors showed higher rates than extramedullary area (mean 29.3 vs 11.2 %). Overall spontaneous necrosis was not associated with clinco-pathologic variables examined (Table 1). However, the necrosis rate of extramedullary tumors was higher in case of large tumors