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Tumor Volume Change after Chemotheraphy as a Predictive Factor of Disease Free Survival for Osteosarcoma

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Change in tumor volume after chemotherapy appears to have a prognostic significance for the outcome of osteosarcoma. A newly developed volume measurement method based on three-dimensional summation with a proved reproducibility was utilized to measure osteosarcoma tumor volume. This retrospective analysis included 38 patients with biopsy-proven, nonsurface, skeletal high-grade osteosarcoma. The treatment was started by using three cycles of preoperative chemotherapy with cisplastin (100 mg/m^2) and adriamycin (30 mg/m^2). The tumor volume was measured before and after preoperative chemotherapy using three-dimensional magnetic resonance image measurement. The percentage of tumor necrosis was assessed by pathologic exam. After three cycle of postoperative chemotherapy, the patients were followed up at regular interval. For the 23 good responder patients, the mean survival time was 73.2 months (95% confidence interval 61.9 - 84.5 months), and for the 15 poor responder patients, the mean survival time was 50.8 months (95% confidence interval 38.6 - 63.1 months) (p<0.05). For the 14 patients with increased tumor volume after chemotherapy, the mean survival time was 47.5 months (range: 36.3 - 58.6 months) and for the 24 patients with stable or decreased tumor volume, the mean survival time was 74.3 months (range: 63.79 - 84.88 months) (p<0.05). Among the various factors, histopathologic response and tumor volume change after chemotherapy predicted disease free survival (p<0.05). Change in the tumor volume that was measured with a reproducible method and the histopathologic response after chemotherapy were the important predictors of disease free survival for osteosarcoma patients.

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INTRODUCTION

With the introduction of aggressive chemotherapy for high-grade osteosarcoma, the long term survival rate for patients with localized osteosarcoma has dramatically improved.[1] The metastasis free survival rate after systemic chemotherapy has risen to 60% to 70% compared with 10% to 15% after local treatment alone[2-4] Preoperative and postoperative chemotherapy in combination with limb salvage surgery often offers acceptable functional results and survival.[5] Among the numerous prognostic factors,[6-12] the histological response of tumor to preoperative chemotherapy is the most important predictor of disease free survival.[1,10] Therefore, it is important to determine whether the tumor truly has had a response to chemotherapy during the courses of preoperative chemotherapy. Knowing the susceptibility of tumor to preoperative chemotherapy renders valuable information to the physician for selecting the proper options for definitive surgery and the postoperative chemotherapeutic regimens. However, it is still impossible to determine the responsiveness of tumor to preoperative chemotherapy without a resected specimen because the responsiveness of tumor is currently determined by assessment of the histological response of the resected specimens.[13] Hence, many researchers have tried to elucidate correlation of the tumor volume change with the histopathological response after chemotherapy.[6,13] There have been problems with previous studies including the simple assumption that the maximal length of tumor represents tumor volume, calculation of tumor volume by using an ellipsoid formula and calculation of

volume without any acceptable reproducibility. Therefore, a more accurate method has been deemed necessary to determine the exact measurement of tumor volume. Accordingly, the authors have tested the feasibility of volumetric measurement of osteosarcoma volume with a three dimensional summation method from magnetic resonance imaging, and then we proved that tumor volume change after chemotherapy was well correlated with the histopathological response along with having an acceptable reproducibility of our measurement method.[14] With a solid correlation between the histopathological response and tumor volume change after chemotherapy, the survival analysis of patients with osteosarcoma is mandatory to prove an independent effect of tumor volume change after chemotherapy for the disease free survival rate. Therefore, the objectives of the current study was to test the prognostic significance of the actual tumor volume change after chemotherapy for the disease free survival rate of patients with osteosarcoma.

MATERIALS AND METHODS

This retrospective analysis included 38 patients with biopsy-proven, nonsurface, skeletal high-grade osteosarcoma, and these patients were followed up for an average of 48 months (range: 5 to 80 months). At the start of this study, 41 patients were enrolled, however, 3 patients were excluded due to their failure to maintain follow up after definitive surgery. The tumors were located in the distal femur in 15 patients, in the proximal tibia in 10 patients, in the proximal humerus in 10 patients, and in other locations including the proximal femur, middle femur and distal tibia in 3 patients. The histologic subtypes of the tumors were osteoblastic osteosarcoma in 34 patients and chondroblastic osteosarcoma in 4 patients. The baseline investigation included plain radiography and magnetic resonance imaging (MRI) of the primary bone lesion for the initial staging and measurement of the pretreatment tumor volume. MRI studies were performed on 1.5 Telsta superconducting systems (General Electrics Horizon, Milwaukee, WI; Siemens Vision, Munich, Germany). Magnetic resonance images were acquired in the axial, sagittal, and coronal planes using T1 weighted (TR/TE: 300 - 700 ms/10 - 20 ms), and T2 weighted (TR/TE: 2000 - 3500 ms/60 - 990 ms) conditions. In addition, T1 weighted (TR/TE: 300 - 700 ms/12 - 20 ms) gadolinium diethylene triamine penta-acetic acid enhanced spin echo sequences were also obtained. A 15 to 30 cm field of view was used, and the matrix size was 256 × 256. Metastatic tumors were screened by plain chest radiograph, radionuclide bone scan and computed tomography (CT) of the chest. Staging was done according to the surgical staging system of the Musculoskeletal Tumor Society.[15] In this system, high-grade intracompartmental lesion were staged as IIA, and a high-grade lesion with extracompartmental extension were staged as IIB. Stage IA, IB and III lesions were excluded from the study. There were three cases of stage IIA osteosarcoma and the remaining cases were stage IIB osteosarcoma. The treatment started using three cycles of preoperative chemotherapy with an intraarterial infusion of cisplastin (100 mg/m^2) and an intravenous administration of doxorubicin (30 mg/m^2). Follow-up radiographs and MRI of the tumors were taken to assess the tumor volume change. After definitive surgeries including resection and prosthetic replacement, resection with arthrodesis and amputation, three cycles of postoperative chemotherapy were then done. To detect the development of metastatic lesions during the follow-up periods, chest radiograph and CT of the chest were performed at regular intervals.

All images of MRI were scanned, digitized and transferred to MatLab program (MatLab, Mat Work Inc, Natick, MA, USA) using a special file conversion. The absolute tumor volume (cm^3) was calculated by the summation of each tumor area multiplied by the slice thickness using three-dimensional summation software (MatLab) after employing a scale correction as described previously.[14] The total tumor volume was calculated from the outermost boundaries of the tumor. Intraosseous tumor volume was calculated from the tumor that was inside the interrupted cortical envelope. Extraosseous tumor volume was calculated by subtracting the intraosseous volume from the total tumor volume. Relative tumor volumes were defined as absolute volumes divided by

body surface area 16 to normalize for each patient's stature.[16] Tumor volume change was defined as the difference in tumor volume between the preoperative chemotherapy and the postoperative chemotherapy.

After surgical resection of the tumor, the specimen was cut into slices. The percentage of histologically viable tumor was scored as previously described.[17] If the percentage of necrosis was less than 90% (Huvos Grades I and II), the patient was considered to be a poor responder. If more than 90% of necrosis was found (Huvos Grades III and IV), the patient was regarded as a good responder. In this study, 25 patients were good responders and 13 patients were poor responders.

As reported previously,[14] the percent coefficiency of variation (CV) for the intra-observer variability ranged from 1.2 - 3.8%, and for the inter-observer variability ranged from 1.4 - 4.5% for the T1WIs, T2WIs, and GdEIs. Based on these ranges of measurement variability, the significant tumor volume change was defined as more than 4.5% changes in the volume compared with the pretreatment tumor volume. Therefore, patients with a change in tumor volume within 4.5% of the preoperative volume were grouped together as having stable tumor volume. Patients with increases or decreases in tumor volume of more than 4.5% of the preoperative volume were grouped together as having increased tumor volume or decreased tumor volume, respectively.

All data were analyzed and tested using statistical software SPSS (SPSS Inc, Chicago, IL, USA). The correlation of the volume changes with the histopathologic response were analyzed using Pearson's correlation analysis. The tumor volume changes between the good and poor responders were evaluated by the Mann-Whitney test. Kaplan-Meyer survival analysis with log rank statistics and Cox regression analysis as a multivariate analysis were also performed. Failures were defined by the occurrence of metastasis, local recurrence and tumor related death. *P* value below 0.05 was considered statistically significant.

RESULTS

Among the 38 patients who were available for follow-up, fourteen patients developed pulmonary metastases or local recurrences. Of the 14 patients with recurrence or metastasis, only seven patients were still alive at the end of their follow-up period. In the good responder group, six patients out of 25 developed metastases or recurrences. In the poor responder group, eight patients out of 13 showed metastases or recurrences. In the good responder group, four patients (16%) out of 25 actually showed an increased tumor volume, while in the poor responder group, ten patients (77%) out of 13 actually showed an increased tumor volume after chemotherapy.

For patients having increased tumor volume, nine patients (64%) out of 14 patients developed metastases or recurrence. For patients having stable or decreased tumor volume, five patients (21%) out of 24 patients showed metastases or recurrences.

Using the Kaplan Meyer's method, the estimated mean disease free survival rates were calculated. For the 25 good responder patients, the mean survival time was 73.2 months (95% confidence interval 61.9 - 84.5 months), and for the 13 poor responder patients, the mean survival time was 50.8 months (95% confidence interval 38.6 - 63.1 months) ($p<0.05$) (Fig. 1).

For the 14 patients having increased tumor

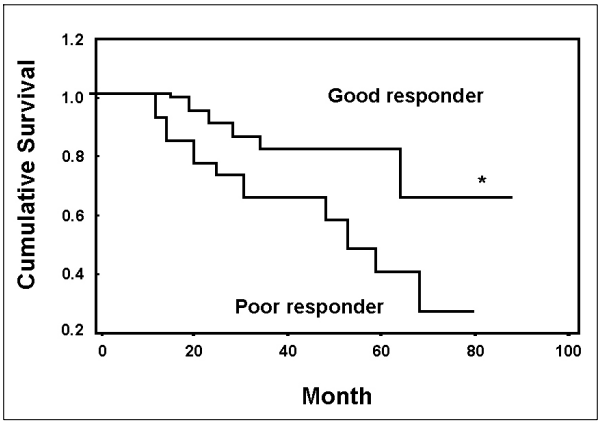

Fig. 1. Kaplan-Meier analysis for disease free survival of the good histopathologic responder group vs. the poor histopathologic responder group. Failure was defined as local recurrence, distant metastasis and tumor related death. Good responders showed a mean survival of 73.2 months (95% confidence interval 61.9 - 84.5 months), and the poor responder showed a mean survival of 50.8 months (95% confidence interval 38.6 - 63.1 months). *$p<0.05$.

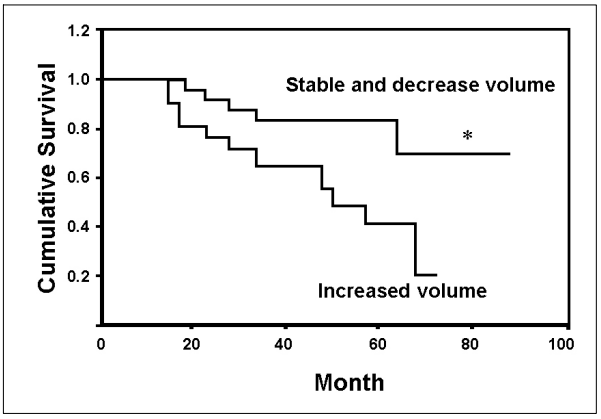

Fig. 2. Kaplan-Meier analysis for disease free survival of the stable or decreased tumor volume group vs. the increased tumor volume group. Failure was defined as local recurrence, distant metastasis and tumor related death. The stable or decreased tumor volume group showed a mean survival of 74.3 months (95% confidence interval 63.7 - 84.8 months), and the increased tumor volume group showed a mean survival of 47.5 months (95% confidence interval 36.3 - 58.6 months). *$p<0.05$.

volume after chemotherapy, their mean disease free survival was 47.5 months (95% confidence interval 36.3 - 58.6 months) and for the 24 patients with stable or decreased tumor volumes, their mean disease survival was 74.3 months (95% confidence interval 63.7 - 84.8 months) ($p<0.05$) (Fig. 2). Cox regression analysis as a multivariate analysis was performed to test the significance of each factor in predicting disease free survival. Among the various factors including gender, age, histologic type, location of tumor, type of limb salvage surgery, histopathologic response after chemotherapy and tumor volume change after chemotherapy, only the histopathologic response and tumor volume change after chemotherapy predicted disease free survival ($p<0.05$).

DISCUSSION

This retrospective study on tumor volume change investigated the prognostic significance of volume change on the disease free survival in osteosarcoma, and the study provide clinically relevant information in regards to decision making during the course of preoperative chemotherapy. In this study, the actual tumor volume change after preoperative chemotherapy proved to be not only correlated with the histopathologic response, but it also predicted the disease free survival.

Several reports have dealt with the significance of tumor size on the prognosis.[1,3,6-8] Nevertheless, most of these previous studies utilized relative measurements of tumor volume that were really just an easily available approximation of volume. In the past, tumor volume has been measured using the ellipsoid mass formula with the visible dimensions from plain radiographs and MRI,[6,13,17-19] or with the single largest diameter of a resected specimen 8 with the few exceptions being the studies that used direct three-dimensional volume measurement by CT[20] and MRI.[21] Tumor volume may be more accurately measured using a three-dimensional technique, since tumors tend to have an irregular shape that does not fit well into the ellipsoid formula. Although a three-dimensional volumetric method with MRI was applied for tumor volume measurement in a previous report,[21] the study had the following shortcomings: a small number of patients, the lack of a reproducible analysis of their measurement methods, and there was no data for comparison between the histopathologic response and volume change. In contrast to the previous reports, the authors of this study developed a method to measure the actual tumor volume using T2 weighted MRI images with a proven acceptable reproducibility.[14] In this current study, the long term disease free survival was plotted according to the histopathologic response and actual tumor volume change after preoperative chemotherapy.

Tumor volume increase, as defined by a 4.5% increase compared to the prechemotherapy tumor volume, independently affected the disease free survival in an adverse fashion. Furthermore, among the various prognostic factors, only the tumor volume change and histopathologic response after preoperative chemotherapy provided for independent prediction of disease free survival for patients with osteosarcoma. Therefore, the authors recommend that the actual tumor volume change be used as an indicator for predicting the histopathologic response and disease free survival, and also these parameters can be used as clinical guidelines for selecting the definitive

surgical options.

The limitation of this study was our inability to differentiate viable tumor tissue from necrotic, hemorrhagic tissue and inflammation when calculating tumor volume. The total tumor volume was measured, which included viable tumor, necrosis, hemorrhage and inflammation without considering tumor viability. In the future, studies concerning the dynamic imaging of osteosarcoma combined with the exact volumetric measurement of specific areas will be necessary.

In this study, change in the tumor volume after preoperative chemotherapy was measured with reproducible three-dimensional magnetic resonance imaging, and disease free survival was analyzed with various factors including gender, age, histologic type, location of tumor, type of limb salvage surgery, histopathologic response after chemotherapy and tumor volume change after chemotherapy. The histopathologic response and change in tumor volume after chemotherapy represent the statistically independent predictors of disease free survival.

In conclusion, the change in tumor volume, as measured with a reproducible method, was an important predictor of disease free survival in osteosarcoma, and this provides a clinically relevant guideline for the early detection of chemoresistance and the selection of definitive surgical options.

REFERENCES

1. Glasser DB, Lane JM, Huvos AG, Marcove RC, Rosen G. Survival, prognosis, and therapeutic response in osteogenic sarcoma. Cancer 1992;69:698-708.
2. Bacci G, Ferrari S, Delepine N, Bertoni F, Picci P, Mercuri M, et al. Predictive factors of histologic response to primary chemotherapy in osteosarcoma of the extremity: Study of 272 patients preoperatively treated with high-dose methotrexate, doxorubicin, and cisplatin. J Clin Oncol 1998;16:658-63.
3. Goorin AM, Abelson HT, Frei III E. Osteosarcoma: Fifteen years later. N Engl J Med 1985;313:1637-41.
4. Rosen G, Caparros B, Huvos AG, Kosloff C, Nirenberg A, Cacavio A, et al. Preoperative chemotherapy for osteogenic sarcoma: selection of postoperative adjuvant chemotherapy based on the response of the primary tumor to preoperative chemotherapy. Cancer 1982;49: 1221-30.
5. Rosen G, Murphy ML, Huvos AG, Gutierrez M, Marcove RC. Chemotherapy, en bloc resection and prosthetic bone replacement in the treatment of osteogenic sarcoma. Cancer 1976;37:1-11.
6. Bieling P, Rehan N, Winkler P, Helmke K, Maas R, Fuchs N, et al. Tumor size and prognosis in aggressively treated osteosarcoma. J Clin Oncol 1996;14:848-58.
7. Bronstrom LA, Strander H, Nilsonne U. Survival on osteosarcoma in relation to tumor size and location. Clin Orthop 1982;167:250-4.
8. Hudson M, Jaffe R, Jaffe N, Ayala A, Raymond AK, Carrasco H, et al. Pediatric osteosarcoma: Therapeutic strategies, results, and prognostic factors derived from a 10-year experience. J Clin Oncol 1990;8:1988-97.
9. Meyers PA, Heller G, Healey J, Huvos A, Lane J, Marcove R, et al. Chemotherapy for nonmetastatic osteosarcoma. The Memorial Sloan-Kettering experience. J Clin Oncol 1992;10:5-15.
10. Pochanugool L, Subhadharaphandou T, Dhanachai M, Hathirat P, Sangthawan D, Pirabul R, et al. Prognostic factor among 130 patients with osteosarcoma. Clin Orthop 1997;345:206-14.
11. Scranton P, DeCicco F, Totten T, Yunis EJ. Prognostic factors in osteosarcoma: A review of 20 years experience at the University of Pittsburgh Health Center hospital. Cancer 1975;36:2179-91.
12. Taylor WF, Ivins JC, Dahlin DC, Edmonson JH, Pritchard DJ, et al. Trends and variability in survival from osteosarcoma. Mayo Clin Proc 1978;53:695-700.
13. Holscher HC, Bloem JL, Van der Woude HJ, Hermans J, Nooy MA, Taminiau AH, et al. Can MRI predict the histopathologic response in patients with osteosarcoma after the first cycle of chemotherapy? Clin Radiol 1995; 50:384-90.
14. Shin KH, Moon S-H, Suh J-S, Yang WI. Tumor volume change as a predictor of chemotherapeutic response in osteosarcoma. Clin Orthop 2000;376:200-8.
15. Enneking WF, Spanier SS, Goodman M. Current concepts review: Surgical staging of musculoskeletal sarcoma. J Bone Joint Surg Am 1980;62:1027-30.
16. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. 1916 (classical article). Nutrition 1989;5:303-11.
17. Huvos AG, Rosen G, Marcove RC. Primary osteogenic sarcoma: Pathologic aspects in 20 patients after treatment with chemotherapy, en bloc resection, and prosthetic bone replacement. Arch Pathol Lab Med 1977; 101:14-8.
18. Erlemann R, Sciuk J, Bosse A, Ritter J, Kusnierz-Glaz CR, Peters PE, et al. Response of osteosarcoma and Ewing sarcoma to preoperative chemotherapy: Assessment with dynamic and static MR imaging and skeletal scintigraphy. Radiology 1990;175:791-6.
19. Holscher HC, Bloem JL, Nooy MA, Taminiau AH, Eulderink F, Hermans J, et al. The value of MR imaging in monitoring the effect of chemotherapy on bone sarcoma. Am J Roentgenol 1990;154:763-9.
20. Welling RM, Davies AM, Pynsent PB, Carter SR,

Grimer RJ. The value of computed tomographic measurements in osteosarcoma as a predictor of response to adjuvant chemotherapy. Clin Radiol 1994;49:19-23.
21. Hanna J, Parham DM, Fairclough DL, Meyer WH, Le AH, Fletcher BD, et al. Assessment of osteosarcoma response to preoperative chemotherapy using dynamic FLASH gadolinium-DTPA-enhanced magnetic resonance mapping. Invest Radiol 1992;27:367-73.