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ORIGINAL ARTICLE **CME**

Association of Osteosarcoma Necrotic Volumes with Tumour Size and Lung Metastasis: Revealed by Magnetic Resonance Imaging

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ABSTRACT

Objective: *Osteosarcoma is the most frequent skeletal malignancies in children and adolescents. Studies indicate that hypoxia of such solid tumours has a major prognostic impact; severe and long-lasting hypoxia results in tumour necrosis. Therefore presence of necrosis can be correlated with prognosis. This study was designed to determine any correlation between tumour necrosis volume, tumour volume, and lung metastasis.*

Methods: *This was a cross-sectional study involving 33 patients with osteosarcoma admitted to the Hospital Universiti Sains Malaysia from October 2001 to September 2008. They each underwent magnetic resonance imaging and their respective measurements of tumour volume and tumour necrosis volume were done using OsiriX software. Computed tomography was used to detect lung metastasis.*

Results: *A total of 73% of patients presented with lung metastasis. There was no significant association between tumour necrosis volume and lung metastasis ($p = 0.115$). There was a significant association between tumour volume and lung metastasis ($p = 0.036$). A significant correlation was noted between tumour necrosis volume and tumour volume ($p < 0.001$).*

Conclusion: *Tumour necrosis volume cannot be used as prognostic factor. There was, however, an association between tumour volume and prognosis.*

Key Words: *Bone neoplasms; Necrosis; Osteosarcoma; Prognosis; Tumor burden*

中文摘要

骨肉瘤的腫瘤壞死區域體積與腫瘤大小及肺轉移的關係：磁共振表現

M Nor Azam、NM Nik Munirah、W Zulmi

目的：骨肉瘤是小童及青年人最常見的惡性骨腫瘤。研究指出這類腫瘤缺氧會影響預後，而嚴重及長時間缺氧會導致腫瘤壞死，所以說腫瘤壞死與預後有關。本研究嘗試探討腫瘤壞死區域的體積、腫瘤大小及肺轉移的關係。

方法：參與者為2001年10月至2008年9月期間入住馬來西亞理科大學醫院的33名骨肉瘤患者。每名病人都會接受磁力共振造影，得出的腫瘤壞死區域體積和腫瘤大小均會用OsiriX軟體分析，並用CT觀察病人肺轉移的情況。

結果：共有73%的病人出現肺轉移。結果顯示，腫瘤壞死區域體積和肺轉移並無明顯關係（$p = 0.115$），可是腫瘤大小和肺轉移明顯相關（$p = 0.036$），而腫瘤壞死區域體積和腫瘤大小亦有顯著關係（$p < 0.001$）。

結論：腫瘤壞死區域體積不能被用作預後。但腫瘤大小可被用作預後。

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INTRODUCTION

Osteosarcoma is the most frequent skeletal malignancy in children and adolescents. The conventional type arises in the intramedullary cavity of bones and accounts for about 75% of all osteosarcomas. These tumours penetrate and destroy bone cortex and extend into surrounding soft tissues. Most arise from random and unpredictable errors in the DNA of growing bone cells during times of intense bone growth, and currently there is no effective way to prevent this type of cancer. With the proper diagnosis and treatment, most patients with osteosarcoma do recover.

Several recent investigations indicate that hypoxia in solid tumours has a major prognostic impact. This has been demonstrated in head and neck cancers, gliomas, adult soft tissue sarcomas, and Ewing's sarcoma.[1] Hypoxia leads to various reactions at a cellular level, such as increased gene expression and increased genomic instability, which can promote tumour aggressiveness. Severe and long-lasting hypoxia results in necrosis. Therefore presence of necrosis can be correlated with prognosis.

This study was designed to determine any correlation between tumour necrosis volume (TNV), tumour volume (TV), and lung metastasis. TNV and TV were measured using OsiriX software. Lung metastases were assessed by computed tomography (CT). A previous study by Dunst et al[1] had demonstrated a correlation between TNV, TV, and lung metastasis in patients diagnosed to have Ewing's sarcoma. In brief, this study showed an increasing frequency of metastasis with increasing amounts of tumour necrosis. Since osteosarcoma is the most frequent skeletal malignancies in children, demonstration of correlations between these three entities may help predict patient prognosis.

METHODS

This was a cross-sectional study involving osteosarcoma patients from October 2001 to September 2008 seen in the Hospital Universiti Sains Malaysia (HUSM) using data from patient radiological records, medical records, and histopathological records. The source population involved patients who were referred from tertiary centres or admitted to the HUSM for investigation and management of osteosarcoma.

Patients were selected for study based on inclusion and exclusion criteria. The inclusion criteria were: (1) referral and treatment in HUSM from October 2001 to September 2008 for osteosarcoma, and (2) having a pre-chemotherapy contrast-enhanced magnetic resonance imaging (MRI) in the HUSM as well as CT of the thorax. Patient exclusion criteria included (1) recurrence, (2) MRI being contraindicated (e.g. due to surgical clips), (3) being pregnant, (4) pre-chemotherapy MRI not performed in the HUSM, and (5) having no CT of the thorax to evaluate lung metastasis. Patient demographic data retrieved from the MY Radiological Information System, Picture Archiving Communication System, and patients folder in record office included: gender, race, site of tumour, date of MRI pre-chemotherapy, and date of CT thorax. Relevant histopathological examination dates and results were obtained from the histopathology computer database (Pathos) in the Department of Pathology, HUSM. All the patients in this series had histopathologically confirmed classical osteosarcoma.

Magnetic Resonance Examination

Each patient had undergone MRI according to a standard protocol, using a 1.0 Tesla MR system (Signa Horizon LK, General Electric Medical Systems, Milwaukee, USA) at the HUSM. A body or surface coil was applied as indicated. Standard sequences were taken and included: T1-weighted spin echo (TR msec/TE msec = 400-600/10-70), T2-weighted fast spin echo (TR msec/TE msec = 3500/80-120) and contrast-enhanced T1-weighted sequence using manual injection of a bolus of 0.1 mmol per kg body weight gadopentate dimeglumine (Magnevist; Schering, Berlin). This was

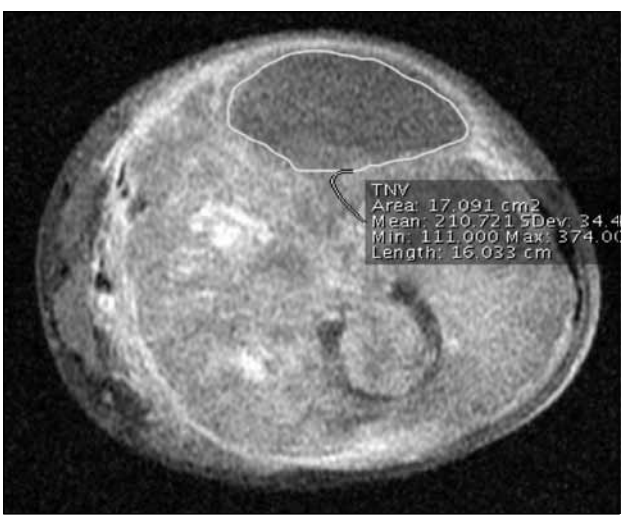

Figure 1. In this image, tumour necrotic area is shown as non-enhanced area within the tumour in post-contrast magnetic resonance imaging. Tumour necrotic area for this patient is 17.091 cm².

followed by a saline flush of 10 ml. Contrast-enhanced multiplanar images were used for assessment of TV and TNV.

TNV was measured thrice and the mean was calculated. Later, TV was measured thrice and the mean was calculated. All data were entered in a Microsoft Excel 2007 program and transferred to the Statistical Package for the Social Sciences (Windows version 12.0; SPSS Inc, Chicago [IL], USA).

Measurement of Tumour Volume and Tumour Necrosis Volume

A Mac Pro 3, 1 Quad-Core Intel Xeon desktop computer with built in OsiriX v.3.0.2 32 bit was used for measurement of TV and TNV. OsiriX provided tools for drawing and outlining the region of interest (ROI) directly on the images, in all slices of the visualised tumour or tumour necrotic area (Figure 1). After the ROI was drawn, estimated tumour area was shown in cm^2. The necrotic area was taken as the non-enhanced region within the tumour. OsiriX software facilitated linking of regions drawn on contiguous slices to enable calculating a volume. Before ROI measurements were possible, the same default name was set to all regions.

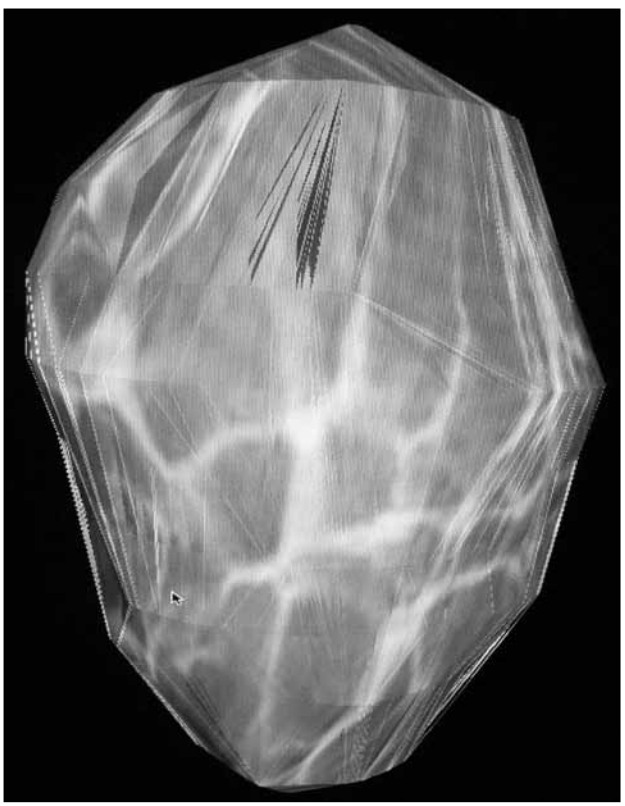

Figure 2. Tumour volume is shown in three dimensions.

Thereafter, ROI measurements could be followed. Method of ROI measurement entailed outlining the outermost boundaries of the tumour density and tumour necrotic area on the contrast-enhanced axial T1-weighted image. Differentiating tumour margin from the perilesional oedema is quite challenging. However discrepancies can be minimised if measurement is undertaken in post-contrast images as the perilesional oedema is not enhanced post-gadolinium. After manual outlining of ROI in multiple slices, pressing the 'compute volume' button on the OsiriX would automatically calculate the TV and TNV in cm^3 (Figure 2); three readings were taken for each and mean volumes were calculated.

Presence of lung metastasis was assessed by CT of the thorax in the HUSM (GE Light Speed Plus multi-detector CT four-slice scanner) or elsewhere provided the official report was available. The status of pulmonary metastasis was recorded in the SPSS database.

Statistical Analysis

All data were analysed and using SPSS (Windows version 12) statistical software. TNV and TV were expressed as mean (standard deviation). Association between median TNV/ TV ratios in patients with and without lung metastasis were determined using the Mann-Whitney test taking $p < 0.05$ as statistically significant. Correlation between TV and TNV was tested using Spearman's correlation test. Tumour necrosis percentage was categorised as showing necrosis in less than or more than 20% of the TV. These two categories were based on a study by Björnsson et al.[2] Fisher's exact test was used to determine correlation between TV and TNV in these osteosarcoma patients.

RESULTS

In all, 33 patients met the inclusion criteria to enter this study; their ages ranged from 6 to 28 (mean, 15) years, and 22 (67%) were male. There were 27 (82%) Malays, and six from other ethnic groups (3 Chinese, 1 Indian, 1 Thai, and 1 Orang Asli). A total of 24 (73%) patients had lung metastasis at presentation.

The femur was the commonest site of their osteosarcoma; 18 (55%) of the patients had femoral involvement, and in 7 (21%), 5 (15%), 2 (6%), 1 (3%), it involved the tibia, humerus, radius, and fibula, respectively. A total of 28 (85%) patients had TNV/TV ratios of less than 20%; in five (15%) patients, it was higher.

Table 1. Association between tumour necrosis volume (TNV) and tumour volume (TV) with lung metastasis.

Variable	Median (interquartile range: difference between 1st and 3rd quartile)		p Value*
	Metastasis, n = 9	No metastasis, n = 24	
TNV (cm^3)	39.2 (99.7)	13.7 (66.7)	0.115
TV (cm^3)	566.0 (400.0)	228.7 (233.4)	0.036

* Mann-Whitney test.

Table 2. Correlation between tumour necrosis volume (TNV) and tumour volume (TV) using Spearman's correlation test.

	ρ*	p Value†
Correlation between TNV and TV	0.726	<0.001

* Spearman's correlation coefficient.
† Spearman's correlation.

There was no statistically significant association between TNV and lung metastasis ($p = 0.115$). However, there was statistically significant association between TV and lung metastasis ($p = 0.036$; Table 1).

There was a significant (linear) correlation between TNV and TV ($p < 0.001$). The observed ρ (Spearman's correlation coefficient) was 0.726, suggesting good correlation (Table 2).

DISCUSSION

Deterioration of diffusion and disturbed microcirculation lead to inadequate supply of oxygen to the tumour cell thus causing tumour necrosis. Males are affected more frequently than females (ratio = 1.3:1).[3] No apparent relationship between race and incidence of osteosarcoma was found.[4] Known predictors including metastases at presentation, anatomic site (extremity or axial), histological response to preoperative chemotherapy (based on the resected specimen), serum levels of alkaline phosphatase and lactate dehydrogenase all appear to have a significant role on outcomes and survival.[5] Giaccia[6] reported that hypoxia of tumour cells can promote their aggressiveness.

Our study showed that there was no association between TNV and lung metastasis. In contrast, Dunst et al[1] in 2001 suggested that the presence of necrosis had prognostic impact in Ewing's sarcoma. There was an increasing frequency not only of metastases but especially a larger frequency of unfavourable metastases with increasing amounts of necrosis. These authors noted that those with no tumour necrosis had an excellent prognosis and that none relapsed after therapy.[1] Difference between their results and our findings could be due to some differences in sample size, methodology, or type of tumour itself.

Our sample size was smaller (33 patients) whereas Dunst et al[1] reported on 79 patients. Though both series dealt with sarcoma family neoplasms, their distribution and characteristics could be quite different. Similarly, techniques for measuring TNV also differed. In Dunst et al series,[1] necrotic areas were measured in three dimensions using T1-weighted images post-gadolinium (non-enhanced areas post-gadolinium were taken as necrosis). Our study made use of the latest technology (OsiriX) and by directly outlining ROI over the tumour necrotic area. The ROI should be drawn in all slices of the visualised tumour or tumour necrotic area to obtain the most accurate result. OsiriX helped to link regions drawn on contiguous slices to calculate a volume. Study by Björnsson et al[2] in 1993 which involved 20 patients seen at the Mayo Clinic between 1963 and 1972 also suggested that relative volume of spontaneous necrosis may reflect a given tumour's growth rate and thus its biological aggressiveness. All six patients with spontaneous necrosis involving more than 20% of tumour died. Five of 14 patients with necrosis amounting to less than 20% were long-term, disease-free survivors. A highly necrotic osteosarcoma would be expected to spread earlier, and independently of other clinicopathological variables. Tumour necrosis was measured using gross specimens.

Tumour size was another controversial parameter postulated to affect the prognosis of patients with osteosarcomas. Our study showed that there was an association between TV with lung metastasis. Similarly, a study by Munajat et al[7] in 2008 suggested that TV was directly associated with occurrence of lung metastasis. TV and lung metastasis were predictors of patient survival and prognosis.[1] According to this study, 10 to 20% of patients with an osteosarcoma had gross metastatic disease in the lung, whilst occult micrometastases were already present at the time of diagnosis in 80 to 90%. In osteosarcoma patients, presence of metastasis was an indication of an unfavourable prognosis. The study by Munajat et al[7] included 70 patients of whom 33 (47%) had evidence of lung metastases. This compared to 24 of 33 in our study. Though our study size was small, its results were comparable. The proportion of patients having lung metastasis when the primary tumour volume exceeded 371 cm^3 was 69%, compared to 34% in those with smaller tumours. Tumour dimensions were measured

using MRI by outlining the outermost boundaries of the lesion. The length, width, and depth of the tumour were measured and the volumes calculated using the formula for an ellipsoidal mass (π/6) x length x depth x width. In our study, ellipsoidal formula was not used. Instead, direct measurement by using ROI and automatic volume calculation depended on OsiriX software.

Another extensive study by Bielack et al[8] evaluating prognostic factors for osteosarcoma showed that the tumour size was of independent prognostic impact; a staggering 1702 patients were reported between 1980 and 1998 (18 years' span). Our study only involved patients from 2001 till 2008 (6 years' span). Tumours measuring at least one-third of the length of the involved bone were defined as large and all others were considered small.

A study by Ahrens et al[9] showed that TV and response to chemotherapy are the most important prognostic factors in patients with localised disease at presentation. In contrast, Ozger et al[10] concluded that survival rates of tumours smaller and bigger than the median size of 10 cm were not significantly different. This study included 180 primary osteosarcoma patients (metastatic or non-metastatic) treated and followed up regularly from 1995 to 2005. Only maximum diameter of tumour was taken into consideration for evaluation of tumour size. Whereas, our study measured TV in three dimensions instead of a single dimension.

Our study showed a significant correlation between TNV and TV, which was consistent with the results of by Dunst et al[1] in Ewing's sarcoma patients. Median TV increased with amount of necrosis. On the other hand, this study also demonstrated an association between TNV and presence of lung metastasis.

As for the limitation and recommendations of the study, liaising with other centres / hospitals was needed to obtain more patients. OsiriX was an excellent tool for measurement of TNV and TV, but as with any new software, much malfunctioning was encountered, especially in analysing large TVs. Future software updates may abolish this problem and increase efficiency and productivity.

CONCLUSION

Many techniques were available for the measurement of TNV and TV. They include: dynamic contrast MRIs, diffusion-weighted imaging, static MRI, and direct examination of gross tumour samples by a pathologist. Measurements of TNV and TV by using static MRI with OsiriX software were used in this study. There was no association between TNV and the incidence of lung metastasis. However, there was an association between TV and frequency of lung metastasis. We also found that larger TVs correlated well with TNV.

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