Tumour volume and lung metastasis in patients with osteosarcoma

I Munajat, W Zulmi, MZ Norazman, WI Wan Faisham
Department of Orthopaedics, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia

ABSTRACT

Purpose. To assess the association between tumour volume and occurrence of lung metastasis in patients with osteosarcoma and to determine the cut-off value.

Methods. Records of 70 patients with histopathologically confirmed primary osteosarcoma in the extremities who had magnetic resonance imaging and computed tomography of the thorax less than one month before treatment were reviewed, with reference to the official report of tumour dimensions and lung metastasis by radiologists. The status of lung metastasis was assessed. Tumour volume was measured using the formula for an ellipsoidal mass.

Results. Of the 70 patients with osteosarcoma, 33 (47%) had evidence of lung metastasis. Tumour volume was directly associated with occurrence of lung metastasis (p=0.048). The proportion having lung metastasis when the primary tumour volume exceeded 371 cm$^3$ was 69%, compared to 34% in those with smaller tumours.

Conclusion. Larger tumours are more likely to correlate with lung metastasis. Both features are predictive of patient survival and prognosis.

Key words: osteosarcoma; neoplasm metastasis; tumor burden

INTRODUCTION

Lung metastasis from osteosarcomas is a major cause of death. Most osteosarcoma patients present with micrometastasis in the lungs (treatable with adjuvant chemotherapy). The number, site, and size of the metastasis determine the overall management and prognosis. Tumour volume has been used to predict patient survival and the occurrence of lung metastasis on plain radiographs. Magnetic resonance imaging (MRI) can delineate tumour margins and tumour volume can be measured more accurately, using the formula for an ellipsoidal mass, and thereby predict the occurrence of lung metastasis.

We aimed to assess whether tumour volume is associated with the occurrence of lung metastasis in patients with osteosarcoma. The cut-off value of tumour volume was determined in relation to the occurrence of lung metastasis.
MATERIALS AND METHODS

This was a cross-sectional study of patients’ medical, radiological and histopathological records. Between January 1999 and September 2004, 70 patients aged 13 to 60 years with osteosarcoma fulfilled the inclusion criteria. They had histopathologically confirmed primary osteosarcoma in the extremities, including pelvic and shoulder girdles. Moreover, they had undergone MRI and computed tomography (CT) of the thorax one month before treatment, and a corresponding official report of the tumour dimensions and lung metastasis by radiologists was available.

Tumour dimensions were calculated by radiologists based on the MRI by marking the outermost boundaries of the lesion visible on T1-weighted, T2-weighted, or gadolinium-enhanced T1-weighted images. The length (in coronal or sagittal view), width (in coronal or axial view) and depth (in sagittal or axial view) were measured and the volumes calculated using the formula for an ellipsoidal mass:

\[
\text{volume} = \frac{\pi}{6} \times \text{length} \times \text{depth} \times \text{width}. 
\]

The presence of lung metastasis was assessed by radiologists using CT with a standard cutting distance of 5 mm.

Data were analysed using the Statistical Package for Social Sciences (SPSS, Chicago [IL], US). The association between tumour volume and the occurrence of lung metastasis was analysed using independent \( t \) tests between means. A \( p \) value of <0.05 was considered statistically significant. The cut-off value of tumour volume was determined by the largest area under the receiver operating characteristic (ROC) curve.

RESULTS

The femur was the most commonly affected, accounting for 47% of all sites (Table 1). Of the 70 patients with osteosarcoma, 33 (47%) had evidence of lung metastasis, whereas 37 (53%) did not. Primary tumour volumes in patients with and without metastases were significantly different (\( p=0.048 \), independent sample \( t \) test, Table 2). The cut-off value of tumour volume was determined by the largest area under the receiver operating characteristic (ROC) curve.

DISCUSSION

Tumour volume and lung metastasis are predictive factors for patient survival and prognosis. It is
reported that at presentation, 10 to 20% of patients with an osteosarcoma have gross metastatic disease in the lung.\cite{5} Occult micrometastases are already present at the time of diagnosis in 80 to 90% of patients.\cite{5} Patient survival depends on several factors including treatment approach. The presence of clinically detectable metastatic disease confers an unfavourable prognosis.\cite{6} Death from osteosarcoma is usually the result of progressive lung metastasis with respiratory failure secondary to widespread disease.\cite{7}

Radiography, CT, structural and functional MRI, Doppler sonography, and 99mTc scintigraphy have been used to estimate the tumour size in one-dimension (tumour length or tumour diameter), 2-dimension (tumour plane), or 3-dimension (tumour volume).\cite{3,4} Radiography and CT tend to underestimate the tumour size because of inadequate visualisation of the soft tissue and poor differentiation between the tumour and adjacent soft tissue. MRI measurements combined with the ellipsoidal formula has high sensitivity (89\%) and specificity (73\%).\cite{4} MRI is the better modality for defining the tumour margin and delineating the soft-tissue component, making it feasible to measure changes in tumour volume in response to preoperative chemotherapy.\cite{8} MRI has the same degree of precision for measuring tumour mass as histological examination.\cite{9} Nonetheless, a bias may arise when calculating the tumour planes and volumes as ideal ellipsoids.\cite{2} Visual estimation of the tumour volume using the ellipsoid approximation on T1-weighted images is not as accurate as using a computerised measurement.\cite{9}

Tumour volume is reported to correlate with the rate of lung metastasis in tumours of $>400 \text{ cm}^3$ (without any ROC curve analysis)\cite{10} and $>150 \text{ cm}^3$.\cite{3} However, in the latter study the measurements of tumour volume were made on 2 plane radiographs, which may be less representative than volumes inferred from MRI.

There is strong evidence for interdependence of tumour size and site. The commonest affected site is around the knee, which is associated with greater growth velocity than anywhere else.\cite{3,11} Smaller tumours are often found in the tibia and larger ones are usually situated in the distal femur and have a worse prognosis.\cite{12} Tumours in the distal femur, because of their deep location and surrounding muscle compartments, may grow larger than those in the tibia before becoming symptomatic. Late presenters certainly have longer duration of symptoms and usually have larger tumours. In our study, the cut-off value for tumour volume was higher, probably because of late presentations and more accurate measurement of the tumour volume.

Changes in tumour volume may be closely related to its biological behaviour.\cite{3,4,8} Tumour size reflects the tumour burden and/or the extent of disease. A large primary tumour is more likely to be associated with distant metastasis. In patients with osteosarcoma, significant prognostic factors for lung metastasis include tumour burden (size) and the proportion of the tumour manifesting necrosis after preoperative chemotherapy.\cite{13} Patients having tumours with a diameter of $>15 \text{ cm}$ have 3.4 folds higher risk of death, whereas with tumour diameters of $<15 \text{ cm}$ survival is better.\cite{14}

Patients exhibiting small or stable tumour volumes are those whose histology responds favourably to therapy, with a positive predictive value of 88\%,\cite{4} but predictive values have not been derived for tumour volumes and lung metastasis. In our study, an increase in tumour volume represented an increase in the chance of lung metastasis with a positive predictive value of 69\%. The rates of lung metastasis were 34\% and 69\% in patients with the tumour volume of $<371 \text{ cm}^3$ and $\geq371 \text{ cm}^3$, respectively. This is consistent with another study reporting a lower rate of lung metastasis of 12\% in patients with tumour volumes of $\leq150 \text{ cm}^3$, and a much higher rate of 44\% in those with volumes of $>150 \text{ cm}^3$.\cite{3}

### ACKNOWLEDGEMENT

We thank Dr Mohd Ayub Sadiq for his help in statistical analysis.

### Table 3

<table>
<thead>
<tr>
<th>Tumour volume (cm$^3$)</th>
<th>Lung metastasis</th>
<th>Predictive value</th>
<th>Rate of metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Positive</td>
</tr>
<tr>
<td>≥371</td>
<td>18</td>
<td>8</td>
<td>18/26 (69%)</td>
</tr>
<tr>
<td>&lt;371</td>
<td>15</td>
<td>29</td>
<td>15/44 (34%)</td>
</tr>
</tbody>
</table>

Sensitivity=18/33 (55\%) Specificity=29/37 (78\%)

<table>
<thead>
<tr>
<th>Tumour volume (cm$^3$)</th>
<th>Lung metastasis</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;150</td>
<td>12%</td>
<td>88%</td>
<td>18%</td>
</tr>
<tr>
<td>≥150</td>
<td>44%</td>
<td>34%</td>
<td>66%</td>
</tr>
</tbody>
</table>
REFERENCES