Growth Characteristics of Pulmonary Metastases from Human Sarcomas

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ABSTRACT

The relationship between volume increases of pulmonary metastases and their doubling time values was studied in patients with osteogenic sarcomas, soft tissue sarcomas, and malignant melanomas. From 60 patients (18 with osteogenic sarcomas, 24 with soft tissue sarcomas, and 18 with malignant melanomas), a total of 197 metastases were measured and 362 doubling time values were calculated. The overall median for doubling time was 32 days. The smaller metastases grew significantly faster (median, 26 days) when compared to the growth rate for the larger metastases (median, 47 days). The measured doubling time values seemed to vary similarly among them, since analysis of the growth rate for small metastases from all three types of cancers showed essentially similar values for the median doubling time. The recorded respective median values for doubling time of pulmonary metastases were 26 days for osteogenic sarcomas, 26 days for soft tissue sarcomas, and 24 days for malignant melanomas. A similar tendency was observed for larger metastases, in which somewhat larger differences were found when respective values for the median were compared. Subsequently, the time interval between initial diagnosis and the onset of pulmonary metastases and the time lapse from the appearance of metastases to patient’s death were calculated and compared for all three instances studied. The comparison of time intervals from initial diagnosis to the onset of metastases obtained in all three instances revealed differences of duration, but the time interval passing from the appearance of metastases to patient’s death appeared similar for all three types of cancers studied. The presented data indicate that similar growth control mechanisms operated in the pulmonary metastatic growth processes in all three instances reported.

INTRODUCTION

Data relative to the growth behavior of human cancers can provide more adequate information for use in the clinical management and therapeutic scheduling of cancer patients. Information regarding the natural history of human tumor growth and their metastases is, however, inherently limited by the clinical availability of lesions for observation and study. Under such circumstances, virtually any approach that expands our knowledge of neoplastic growth, based on clinical data, deserves consideration. From previous studies on the growth rate of pulmonary metastases for the 3 different types of cancers, studied by the method of doubling time determination (4), it was found that the arithmetic mean for doubling time of pulmonary metastases of osseous and soft tissue sarcomas was 42 days, with a 99% range extending from 2 to 967 days (12). Similar values were reported in 15 cases of different types of sarcomas (including 8 osteogenic sarcomas), in which the values for doubling time ranged from 10 to 120 days, and in another series with 23 patients who had soft tissue sarcomas (including 16 fibrosarcomas), in which the reported values for doubling time ranged from 13.5 to 257 days (1). In other studies, a reported series of 13 cases with osteogenic sarcomas had the range of values extended from 17 to 253 days (2) and/or from 11 to 360 days (3), while the described series of soft tissue sarcomas had a range in doubling time values between 5 and 340 days (6). In a sequential study of pulmonary metastases from the cases of malignant melanomas, the reported values for doubling time ranged from 14 to 112 days, with an arithmetic mean of 6 weeks, or 42 days (8). The above-reported data have shown extremely large ranges for doubling time values in the studies of growth rates from pulmonary metastases. Accordingly, the present study sought to provide additional basic information on the growth rate of pulmonary metastases from cases of osteogenic and soft tissue sarcomas and malignant melanomas. For this purpose, the method of doubling time determination was used. Through these parameters, we attempted to determine whether or not a correlation existed between the momentary size of metastases and the corresponding doubling time value and whether there are any similarities among the variations in the growth rates of pulmonary metastases for the 3 different types of cancers.

MATERIALS AND METHODS

This report deals with a retrospective study of chest radiograms from 60 patients with histologically proven sarcomas. We investigated 18 cases of osteogenic sarcomas, 24 cases of soft tissue sarcomas, and 8 cases of malignant melanomas.

The 18 patients with osteogenic sarcomas had 54 metastatic growths that were measured 74 consecutive times. We determined 126 values for doubling time. Among the 24 patients with soft tissue sarcomas, there were 15 fibrosarcomas, 5 rhabdomyosarcomas, 1 leiomyosarcoma, 1 liposarcoma, 1 hemangiopericytoma, and 1 angiosarcoma. Altogether, 62 metastases were measured on 79 consecutive dates and 116 values were calculated. In 18 patients with malignant melanomas, 81 metastases were measured 51 consecutive times, and 120 values for doubling time were determined.

A total of 362 values for doubling time were calculated from 197 metastases. A single value for doubling time was obtained for 104 metastatic growths, 2 values for 52 growths, 3 values for 22 growths, 4 values for 12 growths, 5 values for 3 growths, 6 values for 3 growths, and 7 values for 7 metastatic growths. The shortest observation period was 19 days, and the longest was 812 days. The largest measured metastatic growth had a diameter of 135 mm. The ages of patients ranged from 12 to 90 years, and those with osteogenic sarcomas for the most

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part were younger; the oldest was 55. All patients were hospitalized at this Institute in Yugoslavia from 1962 to 1971 and did not receive either radiotherapy or chemotherapy. Therefore, our findings may be considered typical for the natural course of pulmonary metastatic growths.

In each instance, a spherical metastatic growth was selected at random for the study. At least 2 diameters, one vertical and one horizontal, were measured, on standard 150 focus-skin distance in posteroanterior X-ray chest projection for each metastasis.

The values for doubling time were calculated by the method of Collins et al. (4) and by using the values for calculated doubles related to the changing diameter reported by Twardzik and Sklaroff (14).

Median doubling time value for each group was determined, and the correlation coefficient between the diameters of metastases and the studied doubling time median value was calculated.

The significance of differences was tested by using nonparametric significance tests.

RESULTS

Table 1 summarizes the statistical analysis of 362 doubling time values obtained by studying the growth rate of pulmonary metastases originating from 60 cases with osteogenic sarcomas, soft tissue sarcomas, and malignant melanomas. Since a correlation between the metastatic growth increase of volumes and the corresponding lengthening of doubling time values was postulated, changes of doubling time values relative to the volume increases were studied from data obtained in all 3 instances and were considered together as a single group. The calculated value for the median for all 362 doubling time values was 32 days (coefficient of asymmetry, +1.00). The observation range was 540 days (ranging from 4 to 544 days). The 362 values for doubling time were subsequently studied relative to the size of metastases. Small metastases with diameters of up to 14.9 mm had the median for doubling time values of 26 days (observation period was 540 days), while large metastases with diameters from 15.0 to 135.5 mm had the median for doubling time values of 47 days (with an observation range of 365 days). The values for the median doubling time for large metastases indicated a consistently slower growth rate, while the small metastatic growths exhibited faster rates of growth and expansion. The difference in values for the doubling time median for small and large metastases was statistically significant ($p = 0.010$). It appears that the deceleration of the growth rate occurred in all probability when the metastatic growths approached a size of about 15 mm in diameter. Besides the 2 described groups of metastatic growths, i.e., the smaller, fast-growing metastases and larger, slowly growing metastases, a third group of extremely slowly growing metastases could be identified. In this series of 362 values for doubling time, 46 observations were noted (12.7% of all observations) with doubling time over 100 days and with a median value of 146 days (observation range, 397 days). It should be noted that metastases with doubling time values over 100 days are size independent, i.e., at the moment of measurement, slowly growing metastases could be identified in the group of smaller, as well as in the larger metastatic growths.

From the above data, it may be concluded that the doubling time value parameter is significantly correlated to the size of metastases by the fact that, with the increasing size of pulmonary metastatic growth, the doubling time was significantly lengthened.

The data in Table 2 describe the growth behavior ranges of pulmonary metastases derived from osteogenic sarcomas, soft tissue sarcomas, and malignant melanomas, respectively. The median for 126 doubling time values for pulmonary metastases originating from osteogenic sarcomas was 29 days, and for 116 doubling time values of soft tissue sarcomas, it was 42 days. For 120 doubling time values of malignant melanomas, the median was 31 days. The median doubling time in pulmonary metastases from soft tissue sarcomas (42 days) is substantially higher when compared with corresponding values for osteogenic sarcomas and/or malignant melanomas. This difference is caused by the fact that, in the series of doubling time values for soft tissue sarcomas, a higher percentage of doubling values over 100 days (18.9%) was included, while the percentage of slowly growing metastases was smaller in the other 2 groups, in which the osteogenic sarcomas group had 10.3% of all observations, and the malignant melanomas group had 9.2% of observations. However, differences among the reported values for doubling time medians of the 3 series of measurements are not statistically significant, and no statistically significant difference between the observed groups was found using the Kruskal-Wallis test ($p > 0.050$). This finding indicates that the growth rate of pulmonary metastases varies similarly in all 3 types of cancers studied. The observed similarities for the median values become even more evident when median values for doubling time of smaller metastases were reciprocally compared. In fact, in the osteogenic sarcoma group, the doubling time median for smaller metastases was 26 days, for soft tissue sarcomas, it was 26 days, and for malignant melanomas, it was 24 days.

Statistical analysis of this parameter again showed no signif-

### Table 1

<table>
<thead>
<tr>
<th>Groups of metastases</th>
<th>Diameter of metastases (mm)</th>
<th>No. of doubling times</th>
<th>Mean</th>
<th>Ranges</th>
<th>67%</th>
<th>95%</th>
<th>Median</th>
<th>Asymmetry coefficient</th>
<th>Correlation coefficient*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>3.0–135.5</td>
<td>362</td>
<td>34.5</td>
<td>14.1–84.7</td>
<td>5.7–208.0</td>
<td>32</td>
<td>+1.00</td>
<td>+0.24*</td>
<td></td>
</tr>
<tr>
<td>Small</td>
<td>3.0–14.9</td>
<td>179</td>
<td>25.2</td>
<td>10.9–58.3</td>
<td>4.7–135.0</td>
<td>26</td>
<td>+0.84</td>
<td>+0.05</td>
<td></td>
</tr>
<tr>
<td>Large</td>
<td>15.0–135.5</td>
<td>183</td>
<td>47.0</td>
<td>20.2–109.6</td>
<td>8.7–255.5</td>
<td>47</td>
<td>+0.90</td>
<td>+0.16*</td>
<td></td>
</tr>
</tbody>
</table>

* Coefficient of correlation between the diameter of metastases and doubling-time values and $p$ values. ** $p < 0.01$. The coefficients of correlation are statistically significant. The significance of differences are $p = 0.010$ and $p = 0.050$, respectively, for $b$ and $c$. 

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significant differences among the 3 groups of smaller metastases ($p > 0.050$). Somewhat larger differences for doubling time median values were observed, however, for the larger metastases. The differences among the 3 values for the median again were not statistically significant ($p > 0.050$). Thus, according to the presented data, the growth rate of pulmonary metastases deriving from 3 different types of malignant neoplasms in all 3 instances were comparably varying, regardless of the tumor type from which the observed pulmonary metastases originated.

The survival time period from diagnosis of the cancers to the onset of pulmonary metastases and the time interval to subsequent death of the patient were studied for all 3 groups (Table 3).

In 18 patients with osteogenic sarcomas, the mean value for the time interval between the initial diagnosis to the onset of pulmonary metastases was 238 days, while the mean time interval from the appearance of pulmonary metastases to the patient’s death lasted 215 days. In 20 patients with soft tissue sarcomas, the average survival time from diagnosis to the onset of pulmonary metastases was considerably longer, i.e., 419 days, while the mean survival interval from the appearance of metastases to the patient’s death was 249 days and was similar to the corresponding value for the osteogenic sarcoma cases (215 days). The mean interval between diagnosis and appearance of pulmonary metastases was longest (557 days) in 16 patients with malignant melanomas. The period between the onset of metastases and the patient’s death was shortest in this series of malignant melanomas and averaged 173 days.

Time interval values for the 3 tumor groups, from diagnosis to the onset of metastases, showed a statistically significant difference for osteogenic sarcomas and soft tissue sarcomas (see Table 3). A statistically significant difference was also found between the values for osteogenic sarcomas and malignant melanomas. By contrast, differences in values for time interval from the appearance of pulmonary metastases to patient’s death were not statistically significant among the 3 groups. This finding also agrees with closely similar doubling time values for pulmonary metastases from all 3 tumor types investigated. Thus, according to the above-indicated data, the time lapse between initial diagnosis of the tumor to the appearance of pulmonary metastases varied among the 3 tumor types studied, and the patient’s survival after the appearance of pulmonary metastases was also similar and averaged 4 to 8 doubling time values.

**DISCUSSION**

From the data presented in this report, it appears that growth characteristics of pulmonary metastases from osteogenic sarcomas, soft tissue sarcomas, and malignant melanomas vary similarly during their development. In all 3 instances, the smaller metastases grew faster when compared to larger metastases. A deceleration of the growth rates appeared to occur when the diameter of the metastatic growth reached a value of about 15 mm. These generally agree with data reported in

## Table 2

<table>
<thead>
<tr>
<th>Group of metastases</th>
<th>Diameter of metastases</th>
<th>No. of doubling times</th>
<th>Med</th>
<th>Range</th>
<th>Asymmetry coefficient</th>
<th>Correlation coefficient</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteogenic sarcomas</td>
<td>All</td>
<td>3.0–135.5</td>
<td>126</td>
<td>29</td>
<td>0.95</td>
<td>0.32</td>
<td>0.010</td>
</tr>
<tr>
<td></td>
<td>Small</td>
<td>3.0–14.9</td>
<td>66</td>
<td>26</td>
<td>1.09</td>
<td>0.18</td>
<td>0.050</td>
</tr>
<tr>
<td></td>
<td>Large</td>
<td>15.0–135.5</td>
<td>60</td>
<td>36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soft tissue sarcomas</td>
<td>All</td>
<td>3.0–111.0</td>
<td>116</td>
<td>42</td>
<td>0.98</td>
<td>0.21</td>
<td>0.050</td>
</tr>
<tr>
<td></td>
<td>Small</td>
<td>3.0–14.9</td>
<td>44</td>
<td>26</td>
<td>0.85</td>
<td>0.33</td>
<td>0.050</td>
</tr>
<tr>
<td></td>
<td>Large</td>
<td>15.0–111.0</td>
<td>72</td>
<td>55</td>
<td>0.95</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>Malignant melanomas</td>
<td>All</td>
<td>3.0–58.0</td>
<td>120</td>
<td>31</td>
<td>0.97</td>
<td>0.31</td>
<td>0.010</td>
</tr>
<tr>
<td></td>
<td>Small</td>
<td>3.0–14.9</td>
<td>69</td>
<td>24</td>
<td>0.72</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Large</td>
<td>15.0–58.0</td>
<td>51</td>
<td>50</td>
<td>0.87</td>
<td>0.44</td>
<td>0.010</td>
</tr>
</tbody>
</table>

*Coefficient of correlations between the diameter and doubling time values and $p$ values.

## Table 3

<table>
<thead>
<tr>
<th>Primary site</th>
<th>No. of patients</th>
<th>Time (geometric mean days ± 67% range)</th>
<th>Range</th>
<th>$p$</th>
<th>Time (geometric mean days ± 67% range)</th>
<th>Range</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteogenic sarcomas</td>
<td>18</td>
<td>238 (106–538)</td>
<td>0.050</td>
<td></td>
<td>215 (121–380)</td>
<td>&gt;0.050</td>
<td></td>
</tr>
<tr>
<td>Soft tissue sarcomas</td>
<td>20</td>
<td>419 (193–906)</td>
<td>&gt;0.050</td>
<td></td>
<td>249 (105–594)</td>
<td>&gt;0.050</td>
<td></td>
</tr>
<tr>
<td>Malignant melanomas</td>
<td>16</td>
<td>557 (230–493)</td>
<td>&lt;0.050</td>
<td></td>
<td>173 (95–314)</td>
<td>&gt;0.050</td>
<td></td>
</tr>
</tbody>
</table>

*For periods of time from diagnosis to the appearance of pulmonary metastases, and $p$ values: between Groups 1 and 2, $p = 0.050$; between Groups 2 and 3, $p > 0.050$; between Groups 1 and 3, $p < 0.050$.

*For the period of time ranging from the appearance of pulmonary metastases to the patient’s death, differences among the 3 groups were statistically not significant ($p > 0.050$).
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other studies (6, 7, 11, 13). Our observed variations in the growth rates may be ascribed to the interaction of biological factors, such as properties of neoplastic growth, tumor vascularization (5), the subsequent appearance of central necrosis, on one hand, and to factors of the environments of the tumors represented by surrounding pulmonary tissue, on the other (7). The occurrence of these factors forms an integrated growth system, the nature of which is still poorly understood. Such a postulated mechanism could be supported also by the observation in the present study, that survival rates of patients from the appearance of pulmonary metastases to their death, were similar in all 3 patient groups studied, i.e., for osteogenic and soft tissue sarcomas and malignant melanomas. The wide range of doubling time values reported by others (1, 2, 9, 10, 13), and found also in the present series, that ranged from 4 to 544 days often obscures the clinical usefulness of these data. Consequently, we must point out that, among the growing metastases, a small proportion of extremely slow-growing metastatic growths are always present, and their doubling time values are longer than 100 days. In the present study, this proportion ranged from 9.2 to 18.9% of all observations. The presence of this small number of doubling time values over 100 days in this series also contributed to the nonsymmetrical distribution of the values recorded.

It is possible that, in these slowly growing metastases, a compromised blood supply forces the cells into a prolonged G1 or even a G0 phase, with subsequent deceleration of their replication and growth. Alternatively, these slowly growing metastases may arise from subpopulations of tumor cells with a relatively low growth potential for cell replication and growth. According to the information gathered for the growth of pulmonary metastases originating from osteogenic and soft tissue sarcomas and/or malignant melanomas, it appears there are similar variations in their growth trends in all 3 studied instances. Consequently, it may be valid, therefore, to speculate that closely similar mechanisms govern the growth rates of pulmonary metastases in all 3 types of cancers studied.

REFERENCES

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