Osteosarcoma in adolescents and adults: survival analysis with and without lung metastases

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Background: Survival data are still limited and controversial about adult patients with osteosarcoma as older group of patients has mostly been excluded from the historical trials.

Patients and methods: Patients with osteosarcoma, from 1986 to 2003, in a single center, were reviewed. Survival according to a cutoff age of 40 was studied. Patients with lung metastases were identified. Variables at first lung involvement including time to first lung metastases, multiplicity and size of the metastatic lesions and use of chemotherapy were all analyzed.

Results: A total of 247 patients, with age range of 14–77 years, were reviewed. Five-year survival is 66% with no difference between patients <40 or ≥40 years. Eighty-five patients, with either synchronous or metachronous lung involvement, have 3-year postlung metastases survival (PLMS) of 30%. Forty-seven patients (55.3%) underwent lung resection with 3-year PLMS of 38% compared with 16% for nonoperated patients ($P = 0.00023$). Patients who developed lung metastases within a year and have fewer than four lung lesions have better PLMS ($P < 0.0001$ for both).

Conclusions: Older patients have identical survival to pediatric population and should have a similar management approach. Complete metastectomy is the key issue for prolonged survival. Time to lung metastases and number of lung lesions are the most important prognostic factors.

Key words: adult patients, lung metastasis, osteosarcoma, survival

introduction

The overall survival (OS) of nonmetastatic osteosarcoma has improved significantly since mid-1970s with the development of effective chemotherapy combinations. Only 15% of patients are cured with surgery alone [1]. Randomized clinical trials have demonstrated that addition of chemotherapy to complete surgical resection has increased the cure rate to the range of 58%–76% [2–4]. However, these outcome data cannot be generalized to all patients with osteosarcoma. Older group of patients has been excluded from the historical trials because they were thought to have worse prognosis. Therefore, survival data are still limited and controversial about adult patients.

Recurrence still occurs, after optimal induction treatment, in 30% to 40% of cases with >80% of relapses involve the lungs. Synchronous pulmonary metastasis, on the other hand, constitutes >80% of all metastatic cases at presentation [5]. Complete surgical resection of all pulmonary nodules may produce long-term survival in about 30% of patients with isolated pulmonary metastases [6, 7]. Many retrospective studies tried to address the prognostic factors associated with the pulmonary metastases, but again, adult patients constituted small percentage of population in most of the previous studies, and there was no separate analysis for the pattern of relapse and survival data in this group of patients.

We present here our single-center experience of all adolescent and adult patients with both synchronous and metachronous pulmonary metastases from osteosarcoma. To the best of our knowledge, this is the largest series of nonpediatric population of osteosarcoma with pulmonary metastases. The aim is to find the prognostic factors associated with the first lung involvement and their impact on survival.

patients and methods

patients and initial therapy

All patients with high-grade osteosarcoma, who had all or part of their treatment at Mount Sinai Hospital, Toronto, Canada, from 1986 to 2003, were included in this review. Patients were identified using an institutional cancer registry.

Patients are given neo-adjuvant chemotherapy unless if thought preoperatively to have low-grade osteosarcoma. Adjuvant chemotherapy is given routinely to all patients. First-line chemotherapy is a combination of doxorubicin and cisplatin. Additional chemotherapeutic drugs, e.g. high-dose methotrexate, ifosfamide, etoposide or vincristine, are added to some patients. Most patients with synchronous isolated pulmonary metastases have metastectomy procedures after the surgery of the primary tumor.

detection and treatment of lung metastases

After completion of adjuvant chemotherapy, patients are checked regularly to detect pulmonary metastases with alternating chest X-ray and computed...
tomography (CT) scan every 6 weeks in the first year, every 3 months in the second and third year then every 6 months thereafter. On suspicion of lung relapse, complete restaging with CT scan of the chest and bone scan was required. Most patients with isolated pulmonary metastases had attempted surgical resection. Decision to give preoperative chemotherapy is individualized. Subsequent lung relapses are managed in a similar way, and except for inoperability, there is no limit to the number of lung operations.

**data collection**

Data concerning patient demographics and extent of disease at presentation were collected. Variables at the first lung involvement (e.g. time to first lung metastases, use of chemotherapy with the lung operation, multiplicity and laterality of lesions and size of the largest nodule) are all analyzed. The number of lung lesions, laterality and size of largest lesion are defined according to the surgical pathology reports and not the radiology reports.

**statistics**

Survival was identified for all patients then according to a cutoff age of 40 years. The probability of lung metastases at a point in time was calculated using the cumulative incidence function with death without lung metastases as competing risks. The curves were compared using log-rank test.

Time to first lung metastases was calculated from the date of complete surgical resection to the date of relapse. Postlung metastases survival (PLMS) was calculated as a difference between the date of death or last follow-up and the date of the first lung metastases. The percent survival was calculated using Kaplan–Meier methods. The difference between the two curves was tested using log-rank test.

Approval from the Research Ethics Board in Mount Sinai Hospital was received for conducting this study.

**results**

**patient characteristics**

Among the identified 247 cases, 209 (84.6%) were localized at presentation and 38 patients (15.4%) were found to have synchronous distant metastases.

Characteristics of the 85 patients with lung metastases were reported in Table 1. The median age, at the onset of lung involvement, is 29 years (range 14–77) with 71 patients of them (83.5%) are ≥18 years old. There are 53 male patients (62.4%). Overall, 78 patients (91.8%) received chemotherapy at least once during the course of disease, in whom, 74 patients (90%) had neo-adjuvant chemotherapy before the surgery of the primary site, with only 26 of them had achieved ≥90% necrosis at the primary site. Twenty-two (43.1%) of the 51 patients with metachronous lung involvement developed lung metastases within the first year. The median time to first lung metastases is 10 months (range 2–56 months).

**treatment of lung metastases**

Details of surgical treatment for lung metastases are summarized in Table 2. Surgery for lung metastases was carried out in 47 patients (55.3%), with more than once in 24 patients (28.2%). Thirty-four (40%) had no lung surgery because of presence of other organ metastases or inoperability. Five operated patients (10.6%) had incomplete resection and no information on status of resection in seven (14.9). Of the 35 patients (74.5%) with complete surgical resection, 30 (85.7%) relapsed with median relapse-free interval (RFI) of 4 months, with only one relapsed after the first year. RFI before the next relapse is unknown for three patients.

**variables related to first lung involvement**

For the purpose of precision and consistency, the information on multiplicity, laterality and size of largest lung lesion along with the margin status was taken exclusively from the pathology reports. Thus, only the operated cases (47 cases) were included in this analysis (Table 3).

Eighteen (38.3%) and 25 (53.2%) were found to have one to three and four or more nodules, respectively. Bilateral lesions were reported in 32 (68.1%) and data missing in three (6.4%). Twenty (42.6%) had nodules larger than 1 cm, 13 (27.7%) had ≤1 cm and no data for 14 patients (29.8%). In total, only 21 of

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**Table 1. Characteristics of cases with both synchronous and metachronous lung metastases (85 patients)**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up (since the onset of lung metastases)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>2.7 years</td>
</tr>
<tr>
<td>Range</td>
<td>0.1–16.25 years</td>
</tr>
<tr>
<td>Age at first lung metastasis</td>
<td></td>
</tr>
<tr>
<td>Median age</td>
<td>29 years</td>
</tr>
<tr>
<td>Range</td>
<td>14–77 years</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>53 (62.4)</td>
</tr>
<tr>
<td>Female</td>
<td>32 (37.6)</td>
</tr>
<tr>
<td>Timing of lung metastasis</td>
<td></td>
</tr>
<tr>
<td>Synchronous</td>
<td>33 (38.8)</td>
</tr>
<tr>
<td>Metachronous</td>
<td>52 (61.2)</td>
</tr>
<tr>
<td>Location of primary tumor</td>
<td></td>
</tr>
<tr>
<td>Extremities</td>
<td>70 (82.4)</td>
</tr>
<tr>
<td>Non-extremities (trunk/girdles)</td>
<td>15 (17.6)</td>
</tr>
<tr>
<td>Percentage of necrosis (primary site)</td>
<td></td>
</tr>
<tr>
<td>≥90%</td>
<td>26 (30.6)</td>
</tr>
<tr>
<td>&lt;90%</td>
<td>48 (56.5)</td>
</tr>
<tr>
<td>No preoperative chemotherapy</td>
<td>11 (12.9)</td>
</tr>
<tr>
<td>Presence of nonpulmonary metastases</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>28 (32.9)</td>
</tr>
<tr>
<td>No</td>
<td>57 (67.1)</td>
</tr>
<tr>
<td>Presence of local recurrence</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7 (8.2)</td>
</tr>
<tr>
<td>No</td>
<td>78 (91.8)</td>
</tr>
<tr>
<td>Time to first lung metastases (only patients with metachronous lung metastases—52 patients)</td>
<td></td>
</tr>
<tr>
<td>≥12 months</td>
<td>24 (46.2)</td>
</tr>
<tr>
<td>&lt;12 months</td>
<td>27 (51.9)</td>
</tr>
<tr>
<td>Not applicablea</td>
<td>1 (1.9)</td>
</tr>
</tbody>
</table>

*aThis patient has synchronous bone metastases and metachronous lung involvement.*
the operated patients (44.7%) had perioperative chemotherapy (before or after lung surgery).

survival results for all patients
As the date of diagnosis was missing for three patients, this analysis was carried out on 244 patients. The 5-year OS is 66%. There was no difference in survival between patients younger or older than 40 years (65% and 71%, respectively; \( P = 0.63 \)). On the other hand, the status at presentation has significant impact on survival. Nonmetastatic cases at presentation have significantly better outcome with 5-year OS of 75% compared with only 21% for the metastatic cases at presentation \( (P < 0.0001) \).

probability of lung metastasis
This analysis was carried out on 206 of the nonmetastatic cases at presentation (three patients were excluded because the date of diagnosis was missing). The probability of lung metastasis at 5 years for all of them is 28%. Our analysis showed no change in the

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\begin{array}{|c|c|}
\hline
\text{Variables} & \text{n} \ (\%) \\
\hline
\text{Number of lung metastases} & \\
\leq 3 \text{ lesions} & 18 \ (38.3) \\
> 3 \text{ lesions} & 25 \ (53.2) \\
\text{Unknown} & 4 \ (8.5) \\
\hline
\text{Laterality} & \\
\text{Bilateral} & 32 \ (68.1) \\
\text{Unilateral} & 12 \ (27.7) \\
\text{Unknown} & 3 \ (6.4) \\
\hline
\text{Size of the largest lung nodule} & \\
> 1 \text{ cm} & 20 \ (42.5) \\
\leq 1 \text{ cm} & 13 \ (27.7) \\
\text{Unknown} & 14 \ (29.8) \\
\hline
\text{Perioperative chemotherapy} & \\
\text{Yes} & 21 \ (44.7) \\
\text{No} & 25 \ (53.2) \\
\text{Unknown} & 1 \ (2.1) \\
\hline
\end{array}
\]

5-year probability of lung metastasis between patients younger or older than 40 years (29% and 23%, respectively; \( P = 0.6 \))

survival results for patients with lung metastases (85 patients)
The median follow-up is 2.7 years (range 0.1–16.25). Of the 85 cases, 58 (68.2%) died of disease, 12 (14.1%) are still alive with disease and 15 (17.6%) are alive with no evidence of disease. The PLMS, for all of them, is 30% at 3 years (Figure 1A), with no difference between cases with synchronous versus metachronous metastases (3-year PLMS is 30% in both groups; Figure 2B). Patients, who underwent lung resection, had significantly superior PLMS of 38% compared with nonoperated patients with only 16% \( (P = 0.00023) \).
Figure 2A–E illustrates the PLMS according to the variables at first lung involvement. Patients with three or less lung lesions have much better outcome with 3-year PLMS of 69% (95% confidence interval (CI) 49% to 96%) compared with 18% (95% CI 7% to 43%) for patients with more than three lung lesions (P < 0.0001). Although not statistically significant, there is trend toward superior PLMS in patients with unilateral versus bilateral lung lesions (P = 0.091) and patients with largest lesion £1 cm size versus larger lesions (P = 0.072). There is no difference in survival between patients who received chemotherapy with the lung resection and patients who did not (P = 0.63).

PLMS for patients with metachronous lung metastases is significantly affected by the time to first lung metastases. Patients who developed lung metastases within the first year have worse 3-year PLMS of 5% (95% CI 0.8% to 35%) compared with 52% (95% CI 35% to 78%) for those having lung involvement after 1 year (P < 0.0001) (Figure 1E).

discussion

This is a retrospective study of all adolescent and adult cases of osteosarcoma with synchronous and metachronous pulmonary metastases from single institution. It represents, to our best knowledge, the largest series of separately reported nonpediatric cases with lung metastases. The age range at first lung involvement is 14–77 years with the vast majority (83.5%) of them are 18 years or older. The Cooperative Osteosarcoma Study Group [8] and the study of Ferrari et al. [9] are the largest series, published so far, of relapsed osteosarcoma. Patients older than 18 years constitute only less than half of patients in both studies. Moreover, there was no separate analysis for the adult population, in particular, regarding the prognostic factors at the time of lung metastasis. Cases of synchronous metastases were not included in both studies.

Although treatment concepts, prognostic factors and outcome, for the typical young patients with localized osteosarcoma, have been studied extensively and outlined accurately in the literature, the amount of evidence-based information about the older patients with or without metastases remains limited and controversial. The notion that older patients have worse outcome has emerged from the expectations that this group may not tolerate aggressive therapeutic approaches in addition to the increased proportion of unfavorable axial lesions. This, along with the low incidence
of osteosarcoma at advanced age, has led over the years to exclude older patients from the historical trials of osteosarcoma [5, 10–13].

This study has two different survival analyses. The first survival analysis included 244 patients with both localized and metastatic osteosarcoma. The 5-year OS for all patients is 66% with no difference between patients younger and older than 40 years (P = 0.63). Moreover, there was no difference in the probability for lung metastasis between patients under and over 40 years (P = 0.6). The reported outcome in older patients (over 40 or 50 years) is inconsistent and hugely variable in the literature. Bielack et al. [5] analyzed 1702 patients with both metastatic and nonmetastatic osteosarcoma and reported similar survival rate with 5-year OS of 65.1% and 55% for patients <40 and ≥40 years, respectively (P = 0.012), knowing that only 54 patients were 40 years or older. Similar result has been obtained in retrospective Japanese review [14] of 64 patients older than 50 years, with OS of 55.5%. The results from the paper by Bacci et al. [10] showed that the outcome of 29 patients aged 40–60 years did not seem to be worse than patients under 40 years. They had a survival rate of 62%. By far, the largest study of osteosarcoma over the age of 40 [15] included 481 cases of nonmetastatic osteosarcoma and reported less 5-year survival of only 46%. Our survival results in adolescent and adults were identical to those of pediatric population.

The second survival analysis included 85 patients with lung metastases (both synchronous and metachronous metastases). The aim is to identify the outcome after the pulmonary metastasis and to outline the prognostic factors related to the first lung involvement. The PLMS is 30% at 3 years and it is identical for both synchronous and metachronous metastases. This is compatible with the published results of the previous large series. The postrelapse survival in the COSS study [8] was 23% and 18% at 5 and 10 years, respectively, and it was 33% and 28% at 3 and 5 years, respectively, in the review of Ferrari et al. [9]. It is worth mentioning that both studies included patients with all sites of relapse and not restricted to lung metastasis. Accounting for 90% of all metastatic cases, only patients with lung metastasis (with or without other sites of involvement) were included in our study.

Out of 85 patients, 47 patients (55.3%) underwent at least one thoracic surgery. Thirty-four (40%) had no lung surgery because of presence of other organ metastasis or inoperability. Out of the operated patients, only five patients (10.6%) were documented to have incomplete resection. The rate of complete resection is variable in the literature, ranging between 38.6% and 92% [8, 9, 16–18].

Achieving complete remission (CR) after the first lung metastasizes is the only prerequisite for potentially prolonged survival. Since the only therapy that may lead to CR is complete surgical resection, it makes sense that operated cases have, by far, superior survival. In our study, the operated cases have 3-year PLMS of 38% compared with 16% in nonoperated cases. Our result for nonoperated cases is higher than expected and, certainly, than what has been reported in the literature. Long-term survival of 0% has been constantly reported in the previous studies [8, 9, 17, 18–21]. We have this discrepancy in our report because few patients presented with lung lesions and were entered in the database as metastatic at presentation, but their lung lesions disappeared completely with the neoadjuvant chemotherapy and they survived with no relapse. The survival rate for operated cases was identical to that described in many reports [8, 9, 17–22]. It is obvious that resectability, which makes complete resection feasible, is the key issue. Patients deemed unresectable are, at first, not offered the curative treatment.

Regarding the variables related to the lung metastases, the time to first lung metastases (in 31 patients) and the number of pulmonary lesions have significant impact on PLMS. Patients having lung metastases within the first year have three PLMS of 5% compared with 52% for patients relapsing after 1 year (P < 0.0001). On the other hand, having three or less lung lesions have much better outcome with 3-year PLMS of 69% compared with 18% for four or more lesions (P < 0.0001). Time to lung metastases and number of lung lesions, as the main prognostic variables for operated cases, have gained almost consensus in the previous large reports [8, 9, 20, 23, 24].

Unilaterality and smaller lung lesions, defined as largest lesion ≤1 cm, although not statistically significant, may have some impact on PLMS (P = 0.991 for laterality and P = 0.072 for the size of lung lesions). This negative result maybe attributed to the small number of analyzed patients (12 versus 32 in the laterality analysis and 13 versus 20 in the size of lesion analysis). Laterality of lung lesions, as being prognostic factor, has received less support from the literature with much fewer reviews, actually, investigated its impact on survival [8]. Although there were no many reports about the impact of the size of lesions on survival, it has been found, in general, that the increased tumor burden has negative effect on resectability and, subsequently, on survival [8].

The role chemotherapy for lung metastases is not defined. We collectively assessed the effect of chemotherapy before and after the surgery for both synchronous and metachronous lung metastases. That entails collective assessment of both first- and second-line chemotherapy. The previous reports investigated only the role of second-line chemotherapy for relapsed cases. Some reports failed to find any advantage of adding chemotherapy to the lung resection [8, 9, 17]. Ferrari et al. [9] found that unresectable patients who were treated with chemotherapy had a postrelapse survival significantly longer than that observed in patients who refused chemotherapy. In this study, we examined the role of perioperative chemotherapy for the first lung involvement and found no effect. Theoretically, patients with high tumor burden, usually, are treated, in addition, to the surgical resection with chemotherapy. Those patients have presumably worse prognosis and, therefore, chemotherapy is thought to, at least, even the survival to that for patients with less tumor burden who do not frequently receive chemotherapy.

In conclusion, our study showed that adolescent and adult patients have identical survival results to those of the pediatric population and certainly adds to the cumulative evidences that support the aggressive management approaches in this group of patients. The prognostic indicators related to the first lung metastases are also similar to those described extensively, in the literature, for the younger population. Complete surgical resection is the key issue for prolonged survival and should be
considered for any age group. Time to lung metastases and number of lung lesions have the clearest impact on the survival after pulmonary involvement. Laterality and size of lesions may have marginal impact and the role of chemotherapy remains undefined.

references