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Management and follow-up of Ewing sarcoma patients with isolated lung metastases☆

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ABSTRACT

Background: Ewing sarcoma (ES) is the second most common pediatric malignant bone tumor with a wide spectrum of clinical presentations. Although metastatic disease to the lungs is often the cause of death, isolated lung metastases at diagnosis are not frequent. The specific role of chemotherapy, surgery, and lung radiation has not been clearly defined. We investigated prognostic factors and the impact of the different treatment modalities in a cohort of patients with ES with isolated lung metastases.

Materials and methods: Thirty-eight patients with ES and isolated lung metastases were treated using modern multimodal therapy during the period 2000–2014. According to the imaging characteristics of lung nodules patients were allocated into one of four treatment groups: "0" without nodules, "1" one solitary nodule of <0.5 cm or several nodules of <0.3 cm, "2" solitary nodule of 0.5–1 cm or multiple nodules of 0.3–0.5 cm, "3" one pulmonary/pleural nodule of >1 cm, or more than one nodule of >0.5 cm. Factors predictive of outcome were analyzed. Overall survival was estimated by Kaplan–Meier methods and compared using long-rank test and Cox models.

Results: Treatment of the lung metastases was performed in 23 cases (60.5%): twenty patients underwent lung surgery, 6 of them received additional postoperative whole lung radiation; three patients received lung radiation only. Malignant cells were found in all lung nodules of patients from group "3", in 5 (62.5%) patients from group "2", and none of the group "1". There was a correlation between histological response of the primary tumor and outcome. Three-year estimates of EFS and OS were 45.19% and 60.7%, respectively. Patients with good response measured by chest CT had significantly better EFS than patients with poor response (81% vs. 27.66%, respectively, $p = 0.006$).

Conclusions: Metastatectomy may have a role in the treatment of highly selected patients with ES and isolated lung metastases depending on the histologic response to therapy. Further studies are needed to better define the use of surgery and the response-adapted criteria in the upfront management of this population.

Ewing sarcoma is a small round blue cell tumor with varying degrees of neuroectodermal differentiation and a wide spectrum of clinical presentation. Most patients have micrometastases already at the time of diagnosis [1], and although metastatic disease to the lungs is often the cause of death in patients with progressive disease, only 10% of patients present with isolated lung metastases at the time of diagnosis [2]. The outcome for patients with metastatic disease is very poor, and typically less than 30% of them survive; however, patients with isolated lung metastases have a better outcome, with long term survival rates in excess of 45–50% in most series [2–7]. The specific roles of chemotherapy, surgery of the lung metastases, and lung irradiation in this group of patients have not been clearly defined.

Few studies have addressed the treatment of this small group of patients with isolated lung metastases with particular attention to the impact of the different treatment modalities. In the case of osteosarcoma

☆ This manuscript is dedicated to the memory of Professor Wojciech Wozniak, a long-time Head of the Department of Pediatric Oncology at The Mother and Child Institute in Warsaw; a great surgeon, a pioneer of pulmonary metastatectomy in children with bone tumors, and more importantly a wonderful man and friend.

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and some other sarcomas, surgical resection of lung nodules is the standard of care and currently such procedure is an indispensable component of multimodal modern approaches [1,8,9]. However, the role of metastatectomy in patients with Ewing sarcoma and lung metastases has not been well defined; this is probably because this malignancy is very radiosensitive, and radiation therapy is an integral component in the treatment of those patients. In many Ewing sarcoma protocols whole lung radiation is considered the standard care procedure in the presence of lung disease; however, its ultimate impact on survival is not clear [1,3,10]. Similarly, various studies have suggested a potential role of myeloablative therapy with hematopoietic stem cell transplant (HSCT) in metastatic ES, but also without an evident impact on outcome [5]. A randomized study is currently ongoing comparing the efficacy of whole lung radiation and HSCT in this group of patients.

In this study, we sought to evaluate the results of a multidisciplinary approach in patients with Ewing sarcoma with isolated lung metastases and to analyze prognostic factors and the impact of the different treatment modalities in the disease control and outcome.

1. Materials and methods

1.1. Patients and methods

This retrospective study included thirty-eight patients with Ewing sarcoma and isolated lung metastases at the time of diagnosis and who were treated during the period 2000–2014 at 5 institutions of the Polish Group for Paediatric Solid Tumours. All patients had standard tumor imaging using CT, MRI, bone scan or PET, prior to treatment, after 3 courses of induction, and at the end of the neoadjuvant treatment, as clinically indicated. According to the lung nodules detected in each of the time points patients were allocated into one of four groups as defined by the Euro-Ewing protocol: "0" without nodules, "1" one solitary nodule of <0.5 cm or several nodules of <0.3 cm, "2" solitary nodule of 0.5–1 cm or multiple nodules of 0.3–0.5 cm, "3" one pulmonary/pleural nodule of >1 cm, or more than one nodule of >0.5 cm. All patients had to have histological confirmation of ES at the time of diagnosis. Diagnosis of ES was performed using standard immunohistochemical definitions; cytogenetic and molecular studies were not performed. Good histology response was defined as ≥90% necrosis, and poor histology response was defined as <90% necrosis. All patients had lung function evaluation performed before and after lung surgery. Performance status was defined by the Karnofsky and Lansky scores. Demographic, treatment, and outcome data were collected. Informed consent was obtained from all patients or their guardians before treatment. Approval for this retrospective study was obtained from all the relevant institutions in compliance with the international regulations for protection of human research subjects.

1.2. Treatment

All patients were treated according to the Euro-EWING regimen [11]. Neoadjuvant chemotherapy included vincristine, ifosfamide, doxorubicin, and etoposide (VIDE), followed by risk group- and response-adapted adjuvant chemotherapy with vincristine, actinomycin D, and cyclophosphamide/ifosfamide (VAI/VAC) after local control. Local control was performed after 6 courses of VIDE, and included surgery, radiation or both. Patients with unresectable disease, microscopic residual after surgery, or poor histological response received 45.0–54.0 Gy. For patients with complete tumor resection, with good response to chemotherapy (≥90% necrosis), small tumor volume, and absence of metastasis radiation was not recommended. Following lung control, patients who had residual disease in the lungs after 6 cycles of VIDE were reclassified, and those from groups "2" or "3" underwent thoracotomy for resection. Decisions on the group "1" patients were taken individually based on histological response of the primary tumor when available, and a discussion in a multidisciplinary team. Patients with complete response of all nodules in CT after six courses of VIDE did not have additional lung treatment. Patients with residual disease in the lung nodules from group "2" and "3", as well as those from group "1" and additional poor histological response of the primary tumor underwent lung surgery. Radiation therapy (15 Gy for patients <14 years of age and 18 Gy for patients ≥14 years) was recommended for patients with active disease on pathology after thoracotomy, and in cases not undergoing lung surgery. However, treatment was individualized. For the patients with positive margin of resection of the primary tumor, and those with completely resected large tumors or poor histological response a consolidation with high-dose therapy (busulfan and melphalan regimen) and autologous hematopoietic stem cell transplant (aHSCT) was recommended.

1.3. Statistical methods

Overall survival (OS) was defined as the time interval from the date of diagnosis to the date of death or last follow-up. Event-free survival (EFS) was defined as the time interval from the date of diagnosis to the date of disease progression, recurrence, second malignancy, or death, or to the date of last follow-up for patients without events. Time to progression (TTP) was defined as the time interval from the date of initial biopsy to the date of disease relapse or progression. Result distributions were estimated using the Kaplan–Meier method. Factors were examined as predictors of OS using log-rank test. The multivariate Cox proportional hazards model was applied to evaluate multiple factors as predictors of OS. $P \leq 0.05$ was regarded as significant. Statistical analysis was performed using STATA 10.0 for Windows.

2. Results

2.1. Patient characteristics and treatment

Between 2000 and 2014, 212 patients with Ewing sarcoma were referred for treatment, among whom thirty-eight (17.9%) had isolated lung metastases. The patients' clinical and treatment characteristics are shown in Table 1. The median age at the time of diagnosis was 13.1 years (range 4.2–18.9 years). There were no significant differences in the clinical characteristics between patients >10 and ≤10 years. Twenty patients had axial location of the primary tumor. Local control of the primary tumor was performed in 37 patients, with definitive irradiation only in 2 patients; one patient did not receive local control of the primary tumor because of parental refusal. Twenty-eight patients achieved a good histological response to induction chemotherapy.

Table 1
Patient characteristics (n = 38).

Age	≤10 years	>10 years
Total number	8	30
Sex		
Female	5	14
Male	3	16
Primary tumor location		
Axial	3	17
Limb	5	13
Histology result of primary tumor[a]		
Good	8	20
Poor	0	7
No treatment of primary tumor	0	1
Consolidation with HSCT		
Yes	5	12
No	3	18
Treatment of lung metastases		
Surgery	3	11
RT	0	3
Surgery and RT	1	5
No lung-directed treatment	4	11

N, number; HSCT, hematopoietic stem cell transplant.
[a] Three patients did not have surgery, two of them had RT.