Abstract

Objective: Pulmonary resection in metastatic pediatric solid tumors is an accepted method of treatment. The purpose of this study was to determine the clinical course, outcome and prognostic factors after surgery. Methods: A retrospective analysis from 1985 to 2006 of 52 patients less than 17 years old at the time of tumor diagnosis and submitted to thoracotomy for pulmonary metastatic disease was performed. Three had nodules excised which proved to be benign at histology and were excluded from further analysis. There were 28 males and 21 females with median age of 13.2 years [2—36] at the time of metastasectomy. The primaries were osteosarcoma (25), Ewing’s sarcoma (6), Wilms’ tumors (4), hepatoblastoma (3) and miscellaneous (11). Pulmonary metastases were encountered either at the time of initial diagnosis (18%) or occurring within 1 month to 22 years. Disease free interval (DFI) was equal or less than 2 years in 31 (63%) patients and more than 2 years in 18 (37%). Results: Patients had one (24), two (16), three (2), four or more (7) metastasectomies resulting in a total of 95 thoracotomies. Wedges (75%) were performed more frequently than anatomic resections (25%). The number of resected metastatic nodules ranged from 1 to 45, median 3. There were no perioperative deaths. There were six complications: pneumothoraces requiring chest tube drainage in two cases. Resection was incomplete in four cases. The mean drainage time and hospital length of stay were 2.7 and 5 days, respectively. Using the date of pulmonary resection as the starting point, 5-year survival rate was 25%. By univariate analysis, we found that a significantly longer survival was observed for patients with a complete resection ($p = 0.004$), with two or less metastases ($p = 0.0004$), with unilateral metastases ($p = 0.001$) or when the DFI was more than 2 years ($p = 0.003$). By multivariate analysis, we showed that the number of pulmonary metastases was an independent predictor of survival. Conclusion: We conclude that resection of pulmonary metastases of pediatric solid tumors is a safe and effective treatment that offers improved survival benefit in carefully selected patients within a multidisciplinary approach for pediatric cancer. Prognosis related criteria that support patient selection for surgery are identified.

Keywords: Pulmonary metastases; Thoracotomy; Prognostic parameter; Childhood

1. Introduction

The majority of pediatric pulmonary neoplasms are secondary in origin. Primary solid tumors of childhood, such as osteosarcomas, Ewing’s sarcoma, hepatoblastoma, and Wilms’ tumor commonly spread to the lungs and pulmonary metastases has a major impact on prognosis [1,2]. Children are a special population with specific characteristics with respect to history, number of metastases and evolution of the disease. Moreover, due to the low incidence of this pathology, it is very difficult to put together a large enough number of procedures to obtain any statistics related to complications after surgery, mortality, long-term results of surgical resection and finally to define prognostic factors. While many retrospective reports have consistently shown prolonged survival after surgical resection among selected patients with isolated pulmonary metastases [3] particularly for osteosarcoma [4—7], prognostic factors associated with improved survival are still controversial [6,7]. We undertook this study to determine operative morbidity, long-term follow-up and prognostic factors of pulmonary metastasectomy in children and adolescents. The study was performed in a retrospective fashion using data from every thoracotomy performed for pediatric tumor at our institution over a period of 21 years.
2. Materials and methods

From January 1985 to December 2006, 52 patients with metastatic pediatric solid tumors underwent resection of pulmonary metastases at our institution. Three had nodules excised which proved to be benign at histology and were excluded from further analysis. Histologic diagnoses were granuloma in one case and hyperplastic pulmonary lymph node in two cases. The primaries were osteosarcoma (25), Ewing’s sarcoma (6), Wilms’ tumor (4), hepatoblastoma (3) and miscellaneous (11) (Table 1). There were 28 males and 21 females. All patients were under 17 years of age at the time of the excision of the primary tumor. Patients were evaluated by physical examination, chest X-ray, chest computed tomography (CT) scan, abdominal ultrasound and bone scan as necessary. Patients were selected for resection of pulmonary metastases if they met the following criteria: primary tumor completely eradicated and without local recurrence, no evidence of extrapulmonary metastatic disease and all pulmonary metastases resectable with a low operative risk and sufficient pulmonary reserve to withstand complete resection, regardless of volume or location of pulmonary disease. The therapeutic control for patients with lung metastases was based on the combination of chemotherapy and surgery. Chemotherapy was always administered to these patients with systemic disease. This could be done before metastasectomy during the treatment of the primary or after histologic confirmation of the metastatic disease with thoracic surgery for patients with a long DFI. Chemotherapy protocols varied depending on tumor histology and period of administration. Radiotherapy was seldom used: 13 postoperative indications. Radiotherapy was administered in case of incomplete resection (four patients), extended resection to the mediastinum or to the chest wall (seven patients), metastatic nodal involvement (one patient) and for a patient with numerous pulmonary metastases from an Ewing sarcoma. Median age at pulmonary metastasectomy was 13.2 years (2—36). The median time interval between the resection of the primary tumor and the occurrence of pulmonary metastases (DFI) was 16 months (range 0—264 months). In nine cases (18%), metastases were diagnosed at evaluation of the primary tumor. All operations were performed through a posterolateral thoracotomy performed in a muscle-sparing fashion. Neither median sternotomy nor video-assisted thoracoscopic surgery (VATS) were performed. Selective intubation using a double lumen tube was seldom used depending on the age of the patient. Thorough palpation of the lung was carried out to detect metastases not identified by CT scan. Resection of the metastases was as conservative of the lung parenchyma as possible, essentially wedges and segmentectomies. Lobectomy and pneumonectomy were used only for patients with metastases in the hilum. Procedures for lung resection might be combined, such as wedge and segmentectomy or wedge with lobectomy. Systematic lymph node dissection was not carried out. In 28 patients (57%) there was bilateral involvement and metastases were removed through bilateral synchronous [5] or sequential [13] thoracotomies depending on the surgeon’s choice. Sequential approach was preferred when anticipating technical difficulties for numerous or central lesions and it was permitted to give chemotherapy after the first surgery and to schedule the second thoracotomy if there was no progression of the metastatic disease. Ten patients did not have contralateral exploration because of extensive and rapid disease progression (eight cases) or because of disappearance of pulmonary nodules under chemotherapy (two cases). All 49 patients were analyzed for gender, age, DFI, number and type of pulmonary resection, tumor histology, unilaterality and number of pulmonary metastases, time frame of resection, completeness of resection, 30-day mortality and long-term survival. Complete resection was defined as no tumor cell at the surgical margin of the resected lung that was examined macroscopically and histologically. Moreover, resection was considered incomplete for patients who were found to have nodules that were too numerous to count and only had a biopsy performed. Follow-up data was obtained through December 2006 and no patients were lost at follow-up. Children and adolescents were regularly reviewed in the surgical and oncology clinics. All have undergone routine chest X-ray and CT if there were clinical or radiological concerns to identify recurrence. The date and site of first relapse were recorded.

2.1. Statistical analysis

Probability of survival was analyzed by the Kaplan—Meier method using the date of pulmonary resection as the starting point. The significance of differences between subgroups was calculated using the log-rank test. The influence of the year of diagnosis and the number of metastases on the evaluation of the death rate have been explored with and without categorization (i.e. keeping them continuous); in the latter case, the effects of the covariates were modeled using smoothing splines (pspline function of S+ software, reference Therneau, modeling survival data, chapter 5, Springer 2000). Comparison of various characteristics between groups was made using t tests (means) or \( \chi^2 \) tests (proportions/categorical variables). For the multivariate analysis of prognostic factors, the Cox model was used and continuous covariates have been categorized. Values of \( p \) less than 0.05 were considered statistically significant. Statistical analyses were performed using S+ software version 6.

3. Results

In this group of 49 patients, 95 thoracotomies were performed. Patients had one (24), two (16), three (2), four or

<table>
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<tr>
<th>Histologic type of the primary tumor</th>
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<td>Osteosarcoma</td>
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<td>Ewing sarcoma</td>
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<td>Wilms’ tumor</td>
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<td>Neuroblastoma</td>
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<td>Hemangioendothelioma</td>
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more (7) metastasectomies. Wedge resections were performed in 71 occasions, 16 surgeries were segmentectomies (with wedge in two cases), 4 lobectomies (with wedge in three cases, and bronchoplasty in one case) and 4 pneumonectomies. Resection was enlarged to the diaphragm in four cases, to the pericardium in two cases and to the ribs in one case. Cardiopulmonary bypass (CPB) was necessary in one patient in order to resect an intra-atrial tumor thrombus. The median number of metastases diagnosed by CT scan was 2 (1—25). All surgery confounded, the median number of metastases resected at surgery was 3 (1—45). There were no surgery related deaths. Postoperative course was complicated by pneumothoraces in six cases, requiring chest tube drainage in two cases. Resection was incomplete in four cases at the first operation. There were no other complications of the procedure. Mean chest tube drainage was 2.7 days (1—7) with a mean hospital stay of 5 days (2—9). Repeat thoracotomy in recurrent lung metastases was not associated with an increase in morbidity or an increase of chest tube drainage or hospital stay. The median follow-up after lung surgery was 21 months (range 1 month to 21 years). One-year, 5-year and 10-year survival and their 95% confidence interval were 60% (48—76%), 25% (15—42%) and 19% (9—36%), respectively (Fig. 1). Using a univariate analysis, age, gender, repeated thoracotomy, type of pulmonary resection had no statistically significant impact on survival. We did not find significant impact of histology on survival duration. Four groups were compared: osteosarcoma (n = 25), Ewing sarcoma (n = 6), Wilms’ tumor (n = 4) and others histologies were pooled together (n = 14). Five-year survival was 26% (13—53%), 50% (22—100%), 25% (5—100%) and 14% (4—51%), respectively, p = 0.17. Obviously, except for the osteosarcoma group, the small number of patients by groups limit the power of the study to draw definitive conclusion. Analyzing
the year of surgery as a continuous covariate in the model, it could be shown that the relative risk of death decreased since 1995 but it did not achieve statistical significance (Fig. 2).

Four significant factors in that univariate analysis were found. The 1-year estimated survival rate in patients with incomplete resection is 25% compared with 64% with complete resection ($p = 0.004$). At 5 years, the survival rate for patients with a DFI of 2 years was more was 49% and the survival rate for patients with a DFI of less than 2 years was 13% ($p = 0.003$) (Fig. 3). Fig. 4 demonstrates a statistically significant difference in survival rates between patients with unilateral metastases and those with bilateral metastases (49% vs 7%, $p = 0.001$). Five-year survival rate in patients with two or less metastases was 42% compared with 5% in patients with more than two metastases ($p = 0.0004$). Analyzing the number of metastases as a continuous covariate, the relative risk of death increases by two times with four metastases and four times when nine metastases or more are resected as compared to one (Fig. 5). In a multivariate analysis considering both DFI and the number of metastases, only the number of metastases could be found as a significant prognostic factor.

Patterns of failure were mainly metastatic. Site of first recurrence was essentially thoracic (lung—pleura—chest wall) in 11 cases (30%). There were also 16 patients showing a thoracic plus distant progression of the disease (43%). New metastases outside the thorax were seen in four cases. Local recurrences were found infrequently alone (8%) or associated with pulmonary metastases (8%).

4. Discussion

The present study was conducted to describe criteria for selecting patients with isolated pulmonary metastases in an attempt to identify patients who would benefit from surgical resection. In a univariate analysis of a series of 95 thoracic surgical procedures in 49 patients, the results suggest that a complete surgical resection, the duration of DFI, the unilaterality and number of metastases are significant prognostic factors for survival after metastasectomy. There is almost a uniform agreement that the ability to completely resect metastatic nodules will be associated with an improved outcome compared with patients with incomplete resection [3,4,7—10]. One tenet of good cancer surgery is complete resection of all tumors. In our series, incomplete resection was documented in four patients after initial resection, and they all died rapidly during follow-up. This is consistent with other studies on surgery for pulmonary metastases from osteosarcoma where complete resection of
all tumor sites is considered to correlate with improved long-term results [5,10–12]. Indeed, few if any patients who develop pulmonary metastases have been saved with chemotherapy alone [5,13]. Meyers et al. [11] showed in a group of 62 patients presenting synchronous pulmonary metastases of osteosarcoma that complete resection of the primary tumor and all sites of metastatic disease was correlated with overall survival. All 35 patients undergoing incomplete resection of all sites of measurable disease died. Kager et al. [12] analyzed 202 patients who presented with metastases at diagnosis of osteosarcoma and found that the completeness of surgical resection had a significant impact on survival in multivariate analysis. Conversely, Harting et al. [6], reported on a series of 137 patients and resection margins did not significantly affect survival. In addition to resectability, the univariate analysis of our data identified three further favorable prognostic factors, i.e. DFI of 24 months or greater, unilaterality of lesions and metastases fewer or equal than two. With these findings, we reconfirmed the data derived from the International Registry of Lung Metastases [3]. Pastorino and colleagues reviewed the long-term results after resection of pulmonary metastases from various primaries based on more than 5000 patients collected from several institutions and found that DFI of 36 months or greater and a solitary metastases were associated with improved survival. The longer the interval between resection of the primary tumor and the development of chemotherapy-resistant metastases the better chance of survival [7,14–16]. A shorter DFI might indicate a more aggressive neoplasm and therefore predict a shorter survival. On the basis of our analysis, we found that tumor burden of pulmonary metastases (as defined by number, extension and short DFI) is a significant prognostic factor. It would seem logical that the presence of a large number of metastases would have a more severe prognosis for patients undergoing metastasectomy than for those with few metastases. Indeed, in a large study of 576 patients with metastatic osteosarcoma, Kempf-Bielack et al. [7] found the number of lesions and laterality of pulmonary disease to be statistically significant prognostic factors. Others [5] have noted a correlation between tumor burden and survival. In our study, patients with more than two metastases had a significantly shorter 5-year survival rate. Moreover, the relative risk of death increases twice with four metastases, and four times with nine metastases or more in comparison with one metastasis. This is in accordance with previous published data using various cut-off points for the number of resected metastases [5,7,8,12,13,17,18]. On the other hand, the number of metastases was not of prognostic significance in other even larger studies [6,16,19] and there is still debate on this issue. McCarrville et al. [20] reported good results in a relatively small series of children who had undergone multiple thoracotomies for management of pulmonary metastases of osteosarcoma. They found no statistically significant difference between survival for patients having one versus five or six thoracotomies. In our series, only four long-term survivors (more than 5 years from initial thoracotomy) underwent more than one thoracotomy (two, four and six repeated thoracotomies in 2, 1, and 1 cases, respectively). Analyzing reoperative metastasectomy for sarcomatous pediatric histologies, Temeck et al. [9] concluded that repeat metastasectomy can salvage a subset of patients who retain favorable prognostic determinants, i.e. complete resection and few metastases to resect. Our results are in accordance with this conclusion and despite a worse prognosis, multiple metastasectomies may be required to achieve permanent cure and that repeated surgery can be safe and effective over the long term in some cases. In our series, patients with bilateral disease had a shorter survival period. Furthermore, of our 12 patients presently alive without recurrence, 8 have had unilateral metastases initially. In addition, only 47% of patients with unilateral disease at first thoracotomy relapsed in the contralateral hemithorax. These data suggest that patients with radiographically determined unilateral disease do not require exploration of the opposite hemithorax. By multivariate analysis, the number of metastases is an independent significant prognostic factor of survival after metastasectomy. This may be helpful in selecting patients for resection of pulmonary metastases.

Several studies concerning surgery for pulmonary metastases from pediatric solid tumors have been published and the 5-year survival rates reported ranged from 20% to 40% [6,7,21]. In the present studies, patients with complete resection of all pulmonary metastases had a 5-year survival probability of 28% which compares with other studies and confirms the poor prognosis of these patients with metastatic disease. Surgical procedures for resection in our study included unilateral thoracotomy, staged or synchronous thoracotomy but not median sternotomy. Sternotomy was never done except in the case necessitating CPB, because it does not allow a good access to basal and posteriorly located lung segments. However, the thoracic access chosen have not been reported to influence long-term survival if all metastases were resected. The number of thoracotomies was not associated with an increase of postoperative morbidity and mortality rates. We, among others [3,22], believe that open thoracotomy with thorough palpation of the lung remains mandatory even in the light of modern CT scan sensitivity. There is often a discrepancy between the number of radiologically visible metastases and palpable nodules, and many more metastases are identified during surgery than by CT scan [9,15,23]. Kayton et al. [22], in a retrospective study comparing number of lesions identified by CT scan and the number of metastases found at thoracotomies for metastatic osteosarcoma, found that CT scan underestimated the total number of histologically proven osteosarcoma metastases in 35% of thoracotomies. This is in accordance with data published from the International Registry of Lung Metastases in which pre-operative radiology for 2988 patients of all histologies underestimated the number of metastases in 25% [3]. Our results confirmed this experience and we found consistently more metastases at surgery than visualized at CT scan and this corroborates the concept of using open surgery. The video-assisted approach identifies only superficial, visible metastases and is only of diagnostic value. Moreover, CT imaging is unable to distinguish benign from malignant pulmonary disease or surgical scarring of the pulmonary parenchyma in patients who have had multiple thoracotomies, demonstrating the need for histopathological confirmation. In their series of patients with Wilms’ tumor and
pulmonary disease, Ehrlich et al. [24] demonstrated that only 82% of patients with isolated pulmonary lesions and 69% with multiple lesions at CT scan had tumor proven on surgical biopsy. In this group 33% of patients with pulmonary lesions but with negative biopsy had unneeded pulmonary radiotherapy. Thus, thoracotomy for biopsy of pulmonary nodules can resolve diagnostic uncertainty and may save patients from the toxicity of potentially unnecessary adjuvant chemotherapy or radiotherapy.

The pattern of failure is mainly metastatic. Local long-term recurrence is rare in our series. New metastases in the lungs and sometimes pleural and chest wall implants were the most frequent findings. In a group of 576 patients treated for osteosarcoma Kempf-Bielack et al. [7] reported a recurrence rate of 87%. Eighty-one percent of those patients had lung metastases. As was observed in other reports [7], we found late relapses developed more than 5 years after initial treatment (three cases) and even after 20 years (one case) highlighting the need for long-term follow-up.

There are several limitations to our analysis. First of all the retrospective design and the number of 49 patients limits the power of our study to delineate prognostic factors. Second it is an inhomogeneous group regarding the primaries, and chemotherapeutic regimes have evolved substantially over the last 20 years. However given the incidence of the disease among children, this cohort represents a relatively large study group and period of treatment and histology were not found to be significant prognostic factors of survival.

We conclude that the resection of pulmonary metastases of pediatric solid tumors is a safe and potentially curative treatment. The absence of mortality and the low morbidity rate justify an aggressive approach to surgical resection in combination with chemotherapy. Good surgical candidates for pulmonary resection are those showing a long DFI and a small number of pulmonary metastases. Five-year survival is influenced by resectability and metastatic pulmonary involvement. Repeat resection for recurrent lung metastases is warranted.

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References


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Appendix A. Conference discussion

Dr L. Lang-Lazdunski (London, United Kingdom): Do you administer the chemotherapy before or after your thoracotomy?

Dr Tronc: All patients had chemotherapy mainly before surgery. Patients with very long disease free interval had chemotherapy only after surgery with histologic confirmation of metastatic disease.

Dr D. Waller (Leicester, United Kingdom): Did you do any thoracoscopic surgery in this population?

Dr Tronc: We did not. We do exclusively thoracotomies.

Dr Waller: Is it because of the size of the children?

Dr Tronc: In part yes. The smaller size of children’s anatomical structures restricts access for thoracoscopy. Moreover, selective intubation cannot be realized easily for the younger children. Thoracoscopy can identify only visible metastases, knowing that osteosarcoma metastases are often located deep in the parenchyma.

Dr Waller: Is it because you don’t believe in the CT scan?

Dr Tronc: Well, it is a historical series which began in 1985. CT scan at this time did not accurately detect all metastases.

Dr Waller: What about now, do you believe your CT scans now?

Dr Tronc: CT scan is now more precise. However, we found consistently more metastases at thoracotomy than detected by CT scan with median two metastases detected with CT scan and median three metastases resected during surgery. Considering this discrepancy we do open surgery.

Dr Waller: You believe you have to palpate the lung to be sure there are no metastases?

Dr Tronc: Yes.

Dr Waller: Well, then may I ask you why you don’t palpate both lungs and perform a sternotomy on all your patients?

Dr Tronc: In our experience we have never performed bilateral thoracotomies in patients with radiographically determined unilateral disease. We resect the metastases, give chemotherapy and we see what happens after. If contralateral metastases appear we resect them as much possible. We do not perform sternotomy because it does not allow a good access of posterior lung segments.

Dr M. Saute (Petach-Tikva, Israel): What was the pathology of the four patients that went to pneumonectomy?

Dr Tronc: These patients had central lesions close to the hilum and so we were rushed to do pneumonectomy.

Dr Saute: What was the pathology in these patients?

Dr Tronc: Two patients had osteosarcoma, one a rhabdomyosarcoma and one a Wims’ tumor. One of these patients had the longest disease free interval of the series, more than 20 years. At this time follow-up was abandoned and he came to the hospital with a very big central lesion.

And the second question is?

Dr Saute: Did you perform single-stage bilateral thoracotomy?

Dr Tronc: Yes, but infrequently, five cases in this series. We prefer to do staged thoracotomies. After the first operation chemotherapy is given and second chemotherapy is scheduled if there is no progression of the metastatic disease.

Dr Saute: Because, in general, the children, they tolerate very nicely bilateral thoracotomy.

Dr Tronc: Yes, it’s true.

Dr S. Solberg (Oslo, Norway): Have you ever considered doing laser resections on the metastases as many of them have many metastases and they may come back? You haven’t had that in your material now as I understand.

Dr Tronc: At this time, no.

Dr Solberg: And you haven’t missed that, you haven’t wanted to do that, wanted a laser knife?

Dr Tronc: I have no experience with laser resection and to date we have not this material.