The prognosis factors in children undergoing pulmonary metastatectomy

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A retrospective analysis was performed to determine the prognosis factors affecting survival in children who underwent pulmonary metastatectomy. Seventeen patients who underwent pulmonary metastatectomy between 2000 - 2006 were evaluated retrospectively by means of age, sex, primary diagnosis, time of metastasis appearance, number of nodules found on imaging examinations, type of management, surgical data, and outcome. Video-assisted thoracoscopic surgery (VATS) was used in 11 patients, and all patients underwent thoracotomy consequently. The nodule was composed of tumor cells in 13 (76%) patients and had positive surgical margins in 5 (38%). The time of metastasis appearance, number of metastases and completeness of the nodule excision did not affect survival (p=0.31, p=0.87 and p=0.56, respectively). Nodule size >1 cm was associated with dismal survival (p=0.008).

Time elapsed until the diagnosis of pulmonary metastasis, number of metastases and the completeness of metastatectomy do not have an impact on survival. The only significant prognosis factor is the size of the largest metastatic nodule. The presence of a metastatic nodule >1 cm is associated with a worse outcome in pediatric patients. VATS is an adjunct method to thoracotomy in the surgical management of pulmonary metastasis in children.

Key words: pulmonary metastasis, metastatectomy, surgery, child, video-assisted thoracoscopic surgery.

The lungs are the primary site of metastasis for some tumors in children such as osteosarcoma, Wilms’ tumor and soft tissue sarcomas. Systemic chemotherapy usually causes regression of pulmonary metastasis. However, surgery is indicated to determine the nodule histology and for total excision of pulmonary nodules.

When a pulmonary metastatectomy is considered, the surgeon should be sure of the following: the patient must be free of recurrent or residual disease in the primary tumor site or of extrapulmonary metastatic disease; radiological visualization of the pulmonary metastasis has been made; no residual metastases will be left after the operation, and no residual pulmonary insufficiency will occur postoperatively¹-⁷. The absence of alternative therapy that is superior to surgery has also been considered as a criterion when deciding surgery in this situation⁸-¹⁰.

Video-assisted thoracoscopic surgery (VATS) or thoracotomy is used to perform metastatectomy. Some authors prefer VATS because the technique is minimally invasive without a troublesome incision causing postoperative pain, longer hospitalization time and scarring on the incision line¹⁰-²⁰. Thoracotomy is superior to VATS by ease of detection and excision of deeply located nodules, as it allows palpation of lung tissue¹,⁷,²¹-²⁸.

Various prognosis factors have been suggested in adults with pulmonary metastasis. However, these prognosis factors as concerns a pure pediatric patient population that underwent pulmonary metastatectomy have been evaluated previously in only a few reports²⁹-³². Therefore, a retrospective analysis was performed to determine the prognosis factors affecting survival in children with pulmonary metastasis.
who were treated by metastatectomy in a reference center.

**Material and Methods**

The patients who underwent excision of a pulmonary metastasis between 2000 and 2006 were evaluated retrospectively. The charts of the patients were reviewed for clinical features, radiological examinations and details of surgery. The age and sex, primary diagnosis, time elapsed from admission to development of metastasis, number of nodules found on imaging examinations, type of management, surgical findings and details of surgery, and outcome were noted. Patients who were referred for resection of pulmonary metastasis were evaluated accordingly with our previously published patient selection algorithm.

**Technique of Video-Assisted Thoracoscopic Surgery (VATS)**

Video-assisted thoracoscopic surgery was performed by applying standard rules. The patient was placed in the decubitus position on the side opposite to the location of the metastasis. Single lung ventilation technique was applied. Thoracoscopy was performed initially. The pleural space and the lung surface were evaluated through two ports: a 5 mm camera port and a 5 mm working port. The location and number of metastatic nodules were noted. The nodule was excised together with surrounding healthy tissue using electrocautery. The surface was checked for bleeding and air leak and controlled by cautery, and then a chest tube was placed. Conversion to the thoracotomy was decided if the metastases could not be visualized on thoracoscopy. The lung surface was inspected and the lung was palpated carefully for nodules. If the nodule was superficial, a wedge resection was performed with surrounding normal-appearing tissue. A segmentectomy or lobectomy was preferred if the nodule was located deeply or the remaining part of the lung lobe could not be expanded after resection, respectively. A chest tube was placed at the end of the thoracotomy.

The data were expressed as mean ± standard deviation (SD). The relations between the number or the size of the metastatic nodule and survival and the relation between the time of appearance of the nodule and survival were analyzed using Student’s t test and chi-square test. P values lower than 0.05 were considered to be significant.

**Results**

Seventeen patients were included. The clinical and surgical data are summarized in Table I and Table II. The male to female ratio was 12/5 and the mean age was 11.9 years (range: 5-17 years). The primary diagnoses were osteosarcoma (n=3), Ewing’s sarcoma (n=2), Wilms’ tumor (n=2), clear cell sarcoma (n=1), renal cell carcinoma (n=1), mesoblastic nephroma (n=1), primitive neuroectodermal tumor (n=1), neurogenic sarcoma (n=1), and hepatocellular carcinoma (n=1). The details of the patients and their outcomes are summarized in Table I and Table II.

**Table I. Summary of Clinical Data**

<table>
<thead>
<tr>
<th>Case no</th>
<th>Age (year)</th>
<th>Sex</th>
<th>Primary disease</th>
<th>Time interval to metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12</td>
<td>M</td>
<td>Wilms’ tumor</td>
<td>8 years</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>M</td>
<td>Wilms’ tumor</td>
<td>1 year</td>
</tr>
<tr>
<td>3</td>
<td>5.5</td>
<td>F</td>
<td>Clear cell sarcoma</td>
<td>17 months</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>M</td>
<td>Renal cell carcinoma</td>
<td>Present at admission</td>
</tr>
<tr>
<td>5</td>
<td>7</td>
<td>F</td>
<td>Mesoblastic nephroma</td>
<td>2 years</td>
</tr>
<tr>
<td>6</td>
<td>15</td>
<td>M</td>
<td>Osteosarcoma</td>
<td>7 months</td>
</tr>
<tr>
<td>7</td>
<td>13</td>
<td>M</td>
<td>Osteosarcoma</td>
<td>22 months</td>
</tr>
<tr>
<td>8</td>
<td>15</td>
<td>F</td>
<td>Osteosarcoma</td>
<td>2 years</td>
</tr>
<tr>
<td>9</td>
<td>17</td>
<td>M</td>
<td>Ewing’s sarcoma</td>
<td>Present at admission</td>
</tr>
<tr>
<td>10</td>
<td>17</td>
<td>M</td>
<td>Ewing’s sarcoma</td>
<td>3 years</td>
</tr>
<tr>
<td>11</td>
<td>13</td>
<td>M</td>
<td>Hodgkin lymphoma</td>
<td>7 months</td>
</tr>
<tr>
<td>12</td>
<td>15</td>
<td>M</td>
<td>Non-Hodgkin lymphoma</td>
<td>5.5 years</td>
</tr>
<tr>
<td>13</td>
<td>12</td>
<td>M</td>
<td>Hepatocellular carcinoma</td>
<td>Present at admission</td>
</tr>
<tr>
<td>14</td>
<td>7</td>
<td>F</td>
<td>PNET</td>
<td>19 months</td>
</tr>
<tr>
<td>15</td>
<td>11</td>
<td>F</td>
<td>PNET</td>
<td>3.5 years</td>
</tr>
<tr>
<td>16</td>
<td>10</td>
<td>M</td>
<td>Neurogenic sarcoma</td>
<td>3 months</td>
</tr>
<tr>
<td>17</td>
<td>16</td>
<td>M</td>
<td>Rhabdomyosarcoma</td>
<td>5 months</td>
</tr>
</tbody>
</table>

tumor (PNET) (n=2), lymphoma (n=2), hepatocellular carcinoma (HCC) (n=1), malignant nerve sheath tumor (n=1), and rhabdomyosarcoma (RMS) (n=1). All patients received chemotherapy, and except for two lymphoma patients, underwent surgical excision for control of the primary tumor. Radiotherapy was used in cases with Wilms’ tumor (n=1), Ewing’s sarcoma (n=2), Hodgkin disease (n=1), PNET (n=1), and RMS (n=1).

Pulmonary metastasis was present at the time of admission in three patients and none of them underwent metastatectomy as an initial mode of treatment. The metastatic nodule appeared within a mean time of 2.27 years (range: 3 months – 8 years) in the remaining 14 cases. No significant relation was found between the appearance time and survival (p=0.31).

The number of nodules detected on computed tomography (CT) did not correlate with the number of nodules found on histopathological examination in 3 patients (17.6%). The CT underestimated the number of nodules. The mean number of metastases was 2.12±1.9 (range: 1 - 8). The number of metastases and survival time did not reveal a statistical significance (p=0.87).

Video-assisted thoracoscopic surgery (VATS) was used in 11 patients. The operation was started with thoracoscopy and then converted to mini-thoracotomy in 9 patients to find all nodules or to excise the nodule completely. One patient with lymphoma underwent only VATS for diffuse nodular involvement. VATS was also used to perform wedge resection in one of the osteosarcoma patients in whom the procedure was converted to thoracotomy.

All patients underwent thoracotomy, in one of them it was a staged thoracotomy. Wedge resection (n=12), segmentectomy (n=2),

<table>
<thead>
<tr>
<th>Case no</th>
<th>Location</th>
<th>No</th>
<th>Size (cm)</th>
<th>Type of excision</th>
<th>Histopathology</th>
<th>Margin</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LI</td>
<td>1</td>
<td>3x3.5</td>
<td>TT + wedge res.</td>
<td>Wilms’ tumor</td>
<td>+</td>
<td>DOD</td>
</tr>
<tr>
<td>2</td>
<td>LS, LI</td>
<td>3</td>
<td>1 / 0.2-0.3</td>
<td>TS / TT + wedge res.</td>
<td>Wilms’ tumor</td>
<td>-</td>
<td>FOD</td>
</tr>
<tr>
<td>3</td>
<td>RI</td>
<td>1</td>
<td>0.5</td>
<td>TT + wedge res.</td>
<td>No active tumor</td>
<td>-</td>
<td>?</td>
</tr>
<tr>
<td>4</td>
<td>RI</td>
<td>4</td>
<td>0.2</td>
<td>TS / TT + wedge res.</td>
<td>RCC</td>
<td>-</td>
<td>FOD</td>
</tr>
<tr>
<td>5</td>
<td>LI</td>
<td>1</td>
<td>2x3</td>
<td>TS / TT + lobectomy</td>
<td>Cellular MN</td>
<td>-</td>
<td>DOD</td>
</tr>
<tr>
<td>6</td>
<td>RS, M</td>
<td>4</td>
<td>1.2x0.3 / 0.3 / 0.2</td>
<td>TS / TT + wedge res.</td>
<td>Osteosarcoma</td>
<td>+</td>
<td>DOD</td>
</tr>
<tr>
<td>7</td>
<td>RS</td>
<td>1</td>
<td>1x0.5</td>
<td>TT + wedge res.</td>
<td>Osteosarcoma</td>
<td>-</td>
<td>FOD</td>
</tr>
<tr>
<td>8</td>
<td>RS</td>
<td>1</td>
<td>0.4</td>
<td>TS / TT + wedge res.</td>
<td>Osteosarcoma</td>
<td>-</td>
<td>FOD</td>
</tr>
<tr>
<td>9</td>
<td>LI</td>
<td>1</td>
<td>1x0.5</td>
<td>TS / TT + wedge res.</td>
<td>Ewing’s sarcoma</td>
<td>-</td>
<td>DOD</td>
</tr>
<tr>
<td>10</td>
<td>RI</td>
<td>3</td>
<td>1.5 / 1 / 3</td>
<td>TT + wedge res.</td>
<td>Ewing’s sarcoma</td>
<td>+</td>
<td>DOD</td>
</tr>
<tr>
<td>11</td>
<td>LS</td>
<td>1</td>
<td>0.5x0.5</td>
<td>TS / TT + wedge res.</td>
<td>Lymphoma</td>
<td>+</td>
<td>FOD</td>
</tr>
<tr>
<td>12</td>
<td>RS, RI</td>
<td>8</td>
<td>0.2x0.3</td>
<td>TS + biopsy</td>
<td>No active tumor</td>
<td>-</td>
<td>FOD</td>
</tr>
<tr>
<td>13</td>
<td>RI</td>
<td>1</td>
<td>0.4</td>
<td>TS / TT + wedge res.</td>
<td>No active tumor</td>
<td>-</td>
<td>DOD</td>
</tr>
<tr>
<td>14</td>
<td>RS</td>
<td>1</td>
<td>1x1</td>
<td>TT + segmentectomy</td>
<td>PNET</td>
<td>-</td>
<td>DOD</td>
</tr>
<tr>
<td>15</td>
<td>LI</td>
<td>1</td>
<td>2.5x2</td>
<td>TT + wedge res.</td>
<td>PNET</td>
<td>-</td>
<td>DOD</td>
</tr>
<tr>
<td>16</td>
<td>RI</td>
<td>1</td>
<td>1</td>
<td>TT + segmentectomy</td>
<td>No active tumor</td>
<td>-</td>
<td>?</td>
</tr>
<tr>
<td>17</td>
<td>LS, LI</td>
<td>3</td>
<td>2x3 / 4</td>
<td>TT + LI lobectomy + LS wedge biopsy</td>
<td>RMS</td>
<td>+</td>
<td>DOD</td>
</tr>
</tbody>
</table>

The numbers of nodules in the remaining patients were as follows: 3 nodules in 3 patients, 4 nodules in 2 patients and 8 nodules in 1 patient. The nodules were located in the superior lobe of the right lung (n=8), middle lobe (n=2), lower lobe of the right lung (n=13), hilum of the right lung (n=1), upper lobe of the left lung (n=4), and lower lobe of the left lung (n=8).

The mean size of the excised metastatic nodules was 1.44±1.24 cm (range: 0.2 – 4 cm). All patients with a metastatic nodule size >1 cm died of disease (6/6); however, only 2 patients with nodule size <1 cm (2/7) died. There was a statistically significant relation between the size of the largest metastatic nodule (>1 cm) and survival (p=0.008).

Histopathological examination revealed that the metastasis was composed of tumor cells in 13 patients (13/17), and surgical margins were positive for tumor cells in 5 of them (5/13). No active tumor cells were found in the remaining 4 patients (4/17). Surgical margins were free of tumor in 8 of 13 patients with tumor-positive metastasis, and 4 of them died (50%). Surgical margins were positive for tumor in 5 of 13 patients, and 4 of them died (80%). However, survival rates did not differ with regard to surgical margins (p=0.56).

The mean follow-up period was 2 years (range: 1 – 4 years). Six patients are alive (35%), 5 patients are free of disease and 1 patient is under chemotherapy. Nine patients died of disease, of which, 8 had tumor-positive metastasis (89%). The remaining 2 were lost to follow-up.

Regarding the tumor positivity of the metastasis (n=13, 76%), 5 patients (5/13) are alive (4 are free of disease (4/13) and 1 is receiving chemotherapy), and 8 patients (8/13) died. Regarding tumor negativity of the metastasis (n=4, 24%), 1 patient is living, 1 patient died of disease and 2 patients (1 with disease, 1 without disease at the time of last contact) were lost to follow-up.

Discussion

Pulmonary metastasis is usually encountered in the adult patient population, and thus most of the knowledge on this subject has been derived from adult series. The adult series contain a limited number of pediatric cases. A brief review of the medical literature provided only a few articles concerning the prognostic factors in a pure pediatric patient group that underwent pulmonary metastatectomy.

Various prognostic factors have been suggested in adults with pulmonary metastasis, such as number of nodules, size of nodule, uni- or bilaterality, number of involved lung lobes, time to development of metastasis and timing of surgery, histology of the primary tumor, completeness of excision, age of patient, need for conversion to open surgery, recurrence at the primary tumor site, and necessity for repeated thoracotomies. It is really impossible to derive a common conclusion from these reports because some of them also contain pediatric patients, and some of them have been composed of at least two groups of patients with different primary pathologies.

Although of limited number, the pure pediatric reports have suggested prognostic factors are similar, as: number of nodules, uni- or bilaterality, increase in nodule size, time to development of metastasis and timing of surgery, nodal involvement, completeness of excision, age of patient, and type of primary tumor. Additionally, most contain at least two groups of patients with different primary pathologies.

The present report is based on the results of pediatric pulmonary metastatectomy patients with various primary pathologies, such as Wilms’ tumor, clear cell sarcoma, renal cell carcinoma, mesoblastic nephroma, osteosarcoma, Ewing’s sarcoma, PNET, lymphoma, HCC, malignant nerve sheath tumor, and RMS. This report suggests no prognostic effect of time of metastasis appearance, number of metastases or completeness of the excision. However, nodule size >1 cm was found prognostic and associated with dismal outcome.

Various reports have suggested that increased numbers of nodules affect prognosis adversely, while others mention no relation between survival and the number of nodules as encountered in our report. Interestingly, two patients who underwent metastatectomy for 8 and 4...
nODULES, respectively, are still alive and free of disease. Many authors concluded that a longer disease-free interval (DFI) has a positive impact on survival\(^4,6,9,23,24,26,29,31,32\); however, some contrary findings have been reported by others\(^7,25,35,39\). We considered the patients whose pulmonary nodules were seen after the diagnosis of malignancy and determined that DFI was not a prognostic factor. The limited number of patients and different types of primary pathologies may explain this finding.

The size of the metastatic nodules may influence survival\(^2,25\), while some reports were unable to determine such an influence\(^24,26,29\). We showed that there was a relation between the size of the metastatic nodule and survival. The size of the nodule, which is the only factor we found to be correlated with survival, may reflect the short doubling time, which is the indicator of the malignant character of the tumor\(^2\). On the other hand, it should be kept in mind that the series were composed of many different malignancies, which have different biological behavior and various survival rates.

Computed tomography (CT) of the chest is a frequently used imaging method when determining the size and numbers of the metastatic nodules. However, it is known that CT may not show all of the pulmonary nodules. CT may overlook pulmonary nodules especially those <0.5 cm. It has been reported that 25% of cases have more nodules palpated during thoracotomy than are shown on chest CT\(^27\). Similar conclusions have been reached in other reports\(^3,11,15,18,21,22,31\). It should be kept in mind that the type of CT is of utmost importance. Spiral CT has a higher accuracy in defining pulmonary nodules\(^10,20\). CT underestimated the number of pulmonary nodules in 17.6% of patients in the present series.

Complete excision of the metastases has been suggested as a significant prognostic factor in many reports\(^4-6,9,23,25,29,31,32,40\). Although completeness of excision did not reach a statistically significant importance in the present series, the surgeon always faces the impression of a demand to resect the metastasis completely. Therefore, the surgeon should plan surgery to resect all metastases with free surgical margins.

The type of the primary tumor may affect the management of pulmonary metastasis. The pulmonary involvement or metastasis of lymphoma, Wilms’ tumor, HCC, and Ewing’s sarcoma may be managed initially with chemotherapy and/or radiotherapy instead of primary pulmonary surgery\(^41\). Surgical excision is decided if pulmonary metastases do not disappear after chemotherapy and/or radiotherapy. On the other hand, initial total excision of all tumoral foci may be crucial for better survival rates in patients with osteosarcoma and soft tissue sarcoma\(^2,4,8,14,21,25,35\).

The pediatric surgeon should be familiar with the usage of VATS and thoracotomy techniques for the diagnosis and treatment of pulmonary nodules. VATS has some advantages like limited surgical trauma with a consequent reduction in postoperative morbidity and pain, more rapid postoperative recovery, decreased length of hospital stay, lower medical costs, earlier resumption of work\(^38\), and cosmetic benefits. However, VATS does not allow tactile examination of the lung tissue and is usually useful for detection of superficially located lesions. Since the nodule may be overlooked even on CT, a deeply seated lesion cannot be diagnosed when only VATS is used. Some marking or pointing out procedures such as CT-guided transthoracic needle placement\(^10,13,14,19\), injection of radioactive material to the nodules followed by use of tracer during VATS\(^12\), injection of blue dye to the pleural surface of the nodule\(^10,12,14\), and use of tactile probe during VATS\(^11,14,16\) were recommended for proper localization and complete excision of the nodules. Additionally, a new technique has been recommended as palpation of both lungs through a transxiphoid incision during excision of the pulmonary nodules by VATS\(^18\). In contrast, most authors think that direct palpation of lung tissue is essential to not overlook associated nodules, and thoracotomy has been recommended\(^4,12\).

In our series, in 9 cases, it was thought that exploration would not be sufficient during VATS and the procedure was converted to mini-thoracotomy to evaluate the lung tissue manually. Significant rates of conversion from VATS to thoracotomy have been reported previously for the same reason\(^12-15,17,19-21\).
Although this kind of approach has a scientific basis since more nodules have been found when the VATS procedure was converted to thoracotomy\textsuperscript{20,28}, the consequent effect on survival should also be considered. Some recent studies concluded that there was no difference between thoracotomy and VATS based on patient survival\textsuperscript{11,38}. They concluded that the nodules missed by CT, and which could not be seen during VATS, were too small to influence prognosis, and thus, their excision by thoracotomy did not alter the outcome\textsuperscript{13,38}. This explanation seems logical; however, they selected patients with single peripheral nodule for VATS\textsuperscript{16,19,38}. These selection criteria may also reflect the good outcome of the patients.

The criteria for choosing VATS or thoracotomy have been defined recently in a pediatric group of patients according to the number and localization of the metastatic nodules\textsuperscript{15}. VATS has been recommended in children having <3 nodules and peripherally located nodules. The other cases have been considered to be suitable for thoracotomy\textsuperscript{15}.

We used VATS as an adjunct method to open surgery in this series. VATS was performed initially to overview the pleural cavity and lung surfaces and then proceeded to preferably limited open surgery for complete evaluation of all lung tissue by manual examination.

Repeated thoracotomies were required in 25.8% of patients when they presented with recurrence\textsuperscript{7}, and recurrent thoracotomies do not have an adverse prognostic effect\textsuperscript{2,5-7,25}. Second thoracotomies were used in three patients presenting with recurrence in our series. It seems rational to perform repeat thoracotomies in patients who meet the surgical criteria for pulmonary metastatectomy\textsuperscript{3}.

Time elapsed until the diagnosis of pulmonary metastasis, number of metastases and the completeness of metastatectomy do not have an impact on survival. The only significant prognostic factor is the size of the largest metastatic nodule. The presence of a metastatic nodule >1 cm is associated with worse outcome in pediatric patients. VATS is an adjunct method to open surgery in the management of pulmonary metastasis in children. The pediatric surgeon should be familiar with the VATS technique as well as open thoracotomy.

REFERENCES


