Thoracotomy for Postchemotherapy Resection of Pulmonary Residual Tumor Mass in Patients With Nonseminomatous Testicular Germ Cell Tumors*

Aggressive Surgical Resection Is Justified

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In patients with disseminated nonseminomatous testicular germ cell tumors (NSTGCT), a retroperitoneal residual tumor mass (RRTM) and/or a pulmonary residual tumor mass (PRTM) are often present after successful treatment with cisplatin-based polychemotherapy. Results and complications of postchemotherapy resection of PRTM were studied and survival was calculated. In the period 1979 to 1996, 31 patients with a median age of 28 years (range, 17 to 44 years) underwent 32 thoracotomies for the resection of a PRTM. A solitary lesion was encountered nine times (28.1%) and multiple lesions were encountered 23 times (71.9%). The median size was 15 mm (range, 2 to 60 mm). There were only three major postoperative complications (9.6%): prolonged ventilation, pneumothorax, and pneumonia. In 16 patients (51.6%), the resected PRTM showed mature teratoma, while in four patients (12.9%) it showed viable cancer. In 11 patients only necrosis and/or fibrosis were found (35.5%). Resection of an RRTM had been performed prior to thoracotomy in 20 patients. There was dissimilarity between the histologic features of the resected RRTM and PRTM in 10 of the 20 patients (50%). During a median follow-up of 80 months (range, 2.5 to 203 months), five patients died from metastatic disease (16.1%). The 5-year survival rate was 86.8% and the 10-year survival rate was 82.2%. Owing to the dissimilarity between the histologic features of the postchemotherapy resected RRTM and PRTM in 50% of the patients, all sites of pulmonary residual disease must be resected in patients with disseminated NSTGCT, irrespective of the histologic features of previously resected retroperitoneal residual disease. This approach offers minimal morbidity and a high 10-year survival rate.

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Abbreviations: NSTGCT = nonseminomatous testicular germ cell tumors; PRTM = pulmonary residual tumor mass; RRTM = retroperitoneal residual tumor mass

The main selection criteria for pulmonary metastasectomy in patients with disseminated cancer are the following: no detectable metastatic site other than the lungs; the possibility of complete resection of all nodules; and adequate pulmonary reserves to tolerate resection. Other variables that may be of prognostic value include tumor histologic features, the number of metastatic lesions present, and the disease-free interval between primary treatment and pulmonary recurrence.3 Patients with chemoresistant tumors, such as renal cell carcinoma, soft-tissue sarcoma, colorectal carcinoma, and melanoma benefit from early surgical intervention, because pulmonary metastasectomy is the only curative treatment...
option.5-5 In contrast, for patients with disseminated chemotherapy-sensitive tumors, such as testicular germ cell tumors, the primary treatment consists of chemotherapy. Any residual disease, including pulmonary metastases, can be removed surgically afterwards.6

Testicular cancer is the most common solid tumor that affects men aged between 20 and 35 years.7-8 Lymphatic drainage of the testes occurs via the lumbar lymph nodes, adjacent to the fourth to the second lumbar vertebrae. Hematogenic spread of testicular cancer may follow two routes: a direct route from the testis to the lungs, or an indirect route via the lumbar lymph nodes through the thoracic duct to the supraclavicular lymph nodes, and from there via the subclavian vein to the lungs. Nowadays, patients who present with disseminated nonseminomatous testicular germ cell tumors (NSTGCT) are treated with cisplatin-based polychemotherapy after initial orchidectomy.9 The introduction of cisplatin has improved the prognosis of these patients considerably.10,11 However, after a complete biochemical response to polychemotherapy, metastatic disease often remains in the retroperitoneum and/or the lungs. In this particular group of patients, surgical resection of these residual tumor masses is necessary to distinguish pathologically among necrosis, fibrosis, mature teratoma, or viable cancer.12 Leaving masses with residual viable cancer in situ involves a serious risk. The presence of viable cancer directs the decision to administer additional second-line chemotherapy.13 Similarly, masses that contain mature teratoma may start to grow during follow-up: the so-called growing teratoma syndrome.14 Resection may then be more complicated than it would have been shortly after the completion of chemotherapy.

At the University Hospital Groningen, the Netherlands, resection of pulmonary residual tumor masses (PRTM) is performed after primary chemotherapy in patients with PRTM who have become serum tumor marker negative or who have a mature teratoma component in their primary tumor. This article describes the results and the complications of postchemotherapy resection of a PRTM in patients with disseminated NSTGCT, treated with orchidectomy and cisplatin-based polychemotherapy.

**Materials and Methods**

Between July 1979 and March 1996, 474 consecutive patients with disseminated NSTGCT were treated at the University Hospital Groningen, the Netherlands. Clinical staging was performed by physical examination, chest radiograph, serum tumor markers α-fetoprotein and human choriogonadotropin, and CT scans of the abdomen and chest.15 In the early years, bilateral lymphangiography and tomography of the lungs also formed part of the staging procedure. From 1986 onwards, only CT scanning has been performed, because it enables more accurate clinical staging than can be achieved with the former diagnostic procedures.16,17

Of these 474 patients, 73 had pulmonary metastases (stage IV according to the Peckham et al18 classification). All these patients were treated with cisplatin-based polychemotherapy. A total of four remission-induction courses were administered; each course had a duration of 3 weeks. Chemotherapy was administered with the use of a venous access port (Strato/Infusaid Inc; Norwood, Mass).19 After completion of the polychemotherapy, the patients’ conditions were clinically restaged with CT scans of the abdomen and chest and monitored for serum tumor markers. If a patient had become serum tumor marker negative, but still had residual retroperitoneal and/or pulmonary disease, resection of the residual tumor mass was performed. Indications for the resection of a retroperitoneal residual tumor mass (RRTM) have been described previously.19 Indications for the resection of a PRMT partly depended on the histologic features of resected RRTM.20 If the resected RRTM contained necrosis and/or fibrosis only, as a rule, pulmonary metastasectomy was not performed and the patients were followed up as outpatients, unless no further regression occurred. Resection of the PRMT was performed if the resected RRTM contained mature teratoma or if no surgical evaluation of the retroperitoneum had been performed. If the resected RRTM contained viable tumor, second-line chemotherapy was administered. It was necessary for all the patients who underwent resection of a PRMT to have adequate pulmonary reserves to tolerate resection.

The standard surgical approach to resect a PRMT was posterolateral thoracotomy. In individual cases, median sternotomy, anterolateral thoracotomy, or transverse incision was performed. If possible, metastasectomy was performed by minimal resection or wedge resection. To achieve complete resection in some patients, lobectomy was necessary. Perioperative prophylactic antibiotic therapy was given. Anesthetic management included continuous monitoring of oxygen saturation and intermittent arterial blood gas analysis. After induction, the fraction of inspired oxygen (FIO2) was maintained at the lowest level possible to still allow adequate oxygenation (21 to 25%).21 Generally, epidural catheters were inserted in the operating room prior to thoracotomy for postoperative pain control. The first attempts at extubation were made within 24 h of surgery. IV, IM, and oral analgesics were used as required.

Pulmonary complications were divided into two categories based on their severity. Major complications included the need for mechanical ventilatory support for >4 days, pneumothorax requiring secondary closed chest tube drainage, and pneumonia documented by positive sputum culture. Minor complications included the need for mechanical ventilatory support for 2 to 4 days, air leakage for <1 week, minor pneumothorax requiring no further treatment, and atelectasis in the absence of infection. Other complications were defined as minor if they did not lead to more than 2 days prolongation of hospitalization.

Tumors were classified in accordance with the nomenclature of the World Health Organization.22 The histologic features of the resected PRMT were compared to those of the primary testicular tumor and to the histologic features of the resected RRTM if resection of an RRTM had been performed and if the patient had not been treated with chemotherapy in the period between resection of the RRTM and PRMT. Survival was calculated from the date of the first PRMT resection to July 1, 1996, or to the date of death of the patient. Survival probability was estimated by the Kaplan-Meier method. The statistical analyses were conducted using a software package (EGRET; Statistics and Epidemiology Corporation; Seattle).
RESULTS

In the group of 73 patients with stage IV disease, 31 patients (42.5%) underwent postchemotherapy PRTM resection. The operation was not indicated in the other 42 patients (57.5%) because they had a radiologically complete pulmonary response, or their serum tumor markers had failed to normalize, or RRTM resection had revealed viable cancer. A total of 32 thoracotomies were performed. One patient underwent two operations. The second thoracotomy was an elective operation for the management of metastases in the contralateral lung, after the other lung had been operated on 4 weeks earlier.

The median age of the 31 patients was 28 years (range, 17 to 44 years). The median interval between the last dose of combination chemotherapy and PRTM resection was 109 days (range, 31 days to 9 years). In two of these patients, the interval was very long, namely 6 and 9 years, respectively. In both patients, only a PRTM was detected, without any retroperitoneal disease. In 20 patients (64.5%), RRTM resection was performed between polychemotherapy and PRTM resection. The median interval between RRTM resection and PRTM resection was 81 days (range, 0 days to 8.9 years). In two patients, PRTM resection was performed in the same session as the RRTM resection. The surgical approach in these two patients was laparotomy with median sternotomy (3.1%) and laparotomy and left posterolateral thoracotomy (3.1%), respectively. In the other 30 thoracotomies, the surgical approach was 13 left posterolateral thoracotomies (40.6%), nine right posterolateral thoracotomies (28.2%), six median sternotomies (18.8%), one anterolateral thoracotomy on the left and right (3.1%), and one transverse incision with transverse sternotomy (3.1%). Minimal resection was performed in six thoracotomies (18.8%), wedge resection in 24 thoracotomies (75.0%), lobectomy in one thoracotomy (3.1%), and wedge resection together with lobectomy in the remaining thoracotomy (3.1%). In nine cases a solitary lesion was removed (28.1%) and in 23 cases multiple lesions (71.9%) were removed. The median number of metastases removed was two (range, 1 to 15) and the median size was 15 mm (range, 2 to 60 mm).

Perioperative Complications

There were five complications in four patients (12.9%). In two patients, a small air leak was accepted at the time of chest closure. In one of these patients and in one another patient, an accidental arterial lesion caused major bleeding. In the remaining patient, separate ventilation of both lungs was not possible because of retention of secretions. In this patient, suction by bronchoscopy was performed.

Major Postoperative Complications

Three major complications occurred (9.6%). Prolonged mechanical ventilation for 5 days was necessary in one patient who underwent resection of bilateral PRTM by median sternotomy. A second patient needed closed chest tube drainage for a pneumothorax 1 day after right posterolateral thoracotomy. The third patient developed pneumonia 3 days after left posterolateral thoracotomy. This patient was treated successfully with antibiotics. There was no procedure-related mortality.

Minor Postoperative Complications

There were 11 minor postoperative complications (35.5%). One patient required prolongation of postoperative ventilation for 1 day, because of insufficient oxygenation. Two patients experienced air leakage for 2 and 3 days, respectively. In two patients, a small postoperative pneumothorax occurred for which no further treatment was necessary. Atelectasis without infection was diagnosed in one patient and another patient had an allergic reaction to the prophylactic antibiotics; neither of them needed any further treatment. One patient had a frozen shoulder on the right side after right posterolateral thoracotomy. This was treated successfully with physiotherapy. Postoperative neurologic complications consisted of transient paresthesia in two patients and of unilateral miosis in one patient.

In this group of 31 patients, the median postoperative period of hospitalization was 8 days (range, 4 to 14 days). Perioperative and postoperative complications are shown in Table 1.

In all 31 patients, complete resection of the PRTM was achieved; 20 of them had also undergone a laparotomy. However, although CT scanning of the abdomen had revealed a small RRTM, in three patients no abnormalities were found at laparotomy and therefore resection was not performed. So, a total of 17 patients eventually underwent a resection of RRTM. There was a complete radiologic response in the retroperitoneum in 11 patients. Therefore, laparotomy was not performed and they underwent thoracotomy alone.

The histologic features of the primary tumor, the resected RRTM, and the resected PRTM are shown in Table 2.

Mature teratoma was found in the PRTM in 16 patients (51.6%). Four of the 20 patients (20.0%) who had undergone both RRTM and PRTM resection had mature teratoma in the RRTM, but not in the PRTM, while three patients (15.0%) had mature
teratoma in the PRTM, but not in the RRTM. In four patients (12.9%), histologic examination of the resected PRTM revealed viable cancer, despite normalization of the serum tumor markers. In three of them, the malignant components were choriocarcinoma, embryonal carcinoma, and yolk sac tumor, respectively; no viable cancer was found in the RRTM of any of them. In the remaining patient, the resected PRTM revealed a second primary malignancy, consisting of chondrosarcoma and rhabdomyosarcoma. These components were also found in the resected RRTM. In this particular patient, the indication to perform thoracotomy was therefore slightly different; surgery was also aimed to be curative.

Five patients had necrosis and/or fibrosis only in the resected RRTM. In three of these five patients, necrosis was also found in the PRTM. In the other two patients, mature teratoma and embryonal carcinoma, respectively, were found in the PRTM. In the latter two patients, the decision to resect the PRTM was made at the same time as the decision to resect the RRTM. In one patient, both resections were performed in the same session; in the other patient, the interval between resection of RRTM and PRTM was 21 days. There was dissimilarity between the histologic findings at the two sites in 10 of the 20 patients (50.0%) who had undergone both RRTM and PRTM resection.

The median follow-up duration was 80 months (6.7 years); the range was 2.5 to 203 months. During the course of follow-up, five patients died (16.1%) from metastatic disease after 2.5, 9, 25, 26, and 65 months, respectively. One of these patients suffered massive GI tract bleeding of unknown origin during second-line polychemotherapy treatment. At the time of this study, the remaining 26 patients (83.9%) were alive with no evidence of disease. Figure 1 shows the Kaplan-Meier survival curve of the 31 patients after their first pulmonary metastasectomy. Five-year survival rate was 86.8% (95% confidence interval, 68.5 to 94.8%) and the 10-year survival rate was 82.2% (95% confidence interval, 62.0 to 92.3%).

**DISCUSSION**

The indication for PRTM resection in patients with NSTGCT is different from that of patients with
pulmonary metastases from other malignancies. In general, surgery is the only curative option for patients with chemoresistant tumors. For example, after curative resection of pulmonary metastases in patients with pulmonary metastases from soft-tissue sarcomas, a 5-year survival rate of 25% can be achieved.23 Testicular cancer reacts very well to cisplatin-based-polychemotherapy. In patients with NSTGCT, postchemotherapy resection of residual radiographically detectable abnormalities is important, because it enables a histologic diagnosis. Resection of metastases with mature teratoma is necessary to exclude the risk of the growing teratoma syndrome;14 similarly, it is not desirable to leave masses with residual viable cancer in situ. Therefore, resections of RRTM and PRTM are well established and effective adjunctive procedures in patients with NSTGCT.

It is generally recommended that after chemotherapy, all patients with resected viable cancer should undergo second-line polychemotherapy, with the aim of improving recurrence-free survival.15,24-27 Nevertheless, despite this salvage polychemotherapy treatment, the recurrence-free survival of these patients is substantially poorer than that of patients whose metastases contain necrotic debris or fibrosis.9,12 Moreover, Steyerberg et al28 found that the incomplete resection of residual tumor was associated with a significantly poorer prognosis than complete resection. The current study describes 31 patients who underwent complete resection of a PRTM. At present, 26 of them are alive without any evidence of disease, despite the fact that viable cancer was found in the metastases of 3 of them (11.5%). In two patients, late pulmonary metastases were detected after 6 and 9 years, respectively. Both patients are still alive, without any evidence of disease. Baniel et al29 described 47 patients with testicular germ cell cancer who suffered relapses >5 years after the successful management of their initial disease. They stated that surgery is the preferred mode of therapy for late recurrence, because chemotherapy is only moderately successful in these cases.

Overall 10-year survival rates of 23% and 30% have been reported among patients with pulmonary metastases from cancer at various primary sites.2-4,23 The high recurrence-free 10-year survival rate of the patients (82.2%) in the current study indicates that in patients with NSTGCT, complete resection of a PRTM can form an extremely effective curative approach. These findings also confirm those reported by other authors, although the long-term recurrence-free survival rates vary from 50 to 87% after surgery in adjunct to chemotherapy.28,30,31 Besides the advantages of the procedure, thoracotomy also has disadvantages. The perioperative complication rate of 12.9%, the postoperative major complication rate of 9.6%, and the postoperative minor complication rate of 35.5% are comparable with those mentioned in the literature, in which the complication rates range from 6.3 to 39%.2,6,32-35 These complications include pneumonia in 3.8 to 22%, prolonged thoracic drainage for >1 week in 3.2
to 17.3%, wound infection in 3 to 11.3%, postoperative hemorrhage leading to reoperation in 1 to 3%, secondary closed chest tube drainage in up to 5%, and prolonged mechanical ventilation in 3.2 to 7.5.

In our study, no procedure-related mortality occurred. However, in the literature, mortality rates of up to 5.3% have been reported.6,36,37

At the University Hospital Groningen, the Netherlands, the current decision to resect a PRTM in patients with both residual retroperitoneal lymph and pulmonary disease is partly made on the basis of the histologic diagnosis of the resected RRTM, eg., necrosis/fibrosis or mature teratoma. The results of this study indicate that this may not be a sound policy, because in 10 of the 20 patients (50.0%), the histologic findings in the resected RRTM were different from those in the PRTM. In four of these patients (20.0%), mature teratoma was found in the resected RRTM, but not in the resected PRTM; in three patients (15.0%), mature teratoma was found in the resected PRTM, but not in the resected RRTM; in three patients (15.0%), viable cancer was found in the resected PRTM but not in the resected RRTM. Other authors have also indicated that the histologic features at one resected site do not necessarily predict the histologic features at other sites in patients with multiple distant metastases. Brenner et al35 have described 24 patients who underwent simultaneous resection of residual postchemotherapy masses in the retroperitoneum and chest. They reported that in six patients (25%), the pathologic findings in the chest differed from those in the abdomen. Tiffany et al36 described 25 patients with stage III NSTGCT who underwent both retroperitoneal lymph node dissection and thoracotomy. The histologic findings at the two sites were dissimilar in 35%. In the separate series described by Donohue and Rowland,15 Qvist et al,30 and Mandelbaum et al,40 there was dissimilarity between the thoracotomy and laparotomy histologic features in 29%, 47%, and 29%, respectively. Table 3 shows an overview of recent experience with dissimilarities in the histologic features of resected RRTM and PRTM.

**Table 3—Dissimilarities in the Histologic Features of the Resected Residual Retroperitoneal and Pulmonary Tumor Masses**

<table>
<thead>
<tr>
<th>Source, yr</th>
<th>No. of Patients</th>
<th>No. (%) of Dissimilarities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mandelbaum et al,40 1983</td>
<td>24</td>
<td>7 (29)</td>
</tr>
<tr>
<td>Donohue and Rowland,13 1984</td>
<td>24</td>
<td>7 (29)</td>
</tr>
<tr>
<td>Tiffany et al,36 1986</td>
<td>23</td>
<td>8 (35)</td>
</tr>
<tr>
<td>Qvist et al,30 1991</td>
<td>15</td>
<td>7 (47)</td>
</tr>
<tr>
<td>Brenner et al,35 1996</td>
<td>24</td>
<td>6 (25)</td>
</tr>
<tr>
<td>Present study</td>
<td>20</td>
<td>10 (50)</td>
</tr>
</tbody>
</table>

et al,30 described 39 patients who underwent 47 separate procedures for pulmonary parenchymal nodules. Three of the eight patients who underwent bilateral thoracotomy (37.5%) showed different histologic features in the masses resected from each lung.30 Recently, Steyerberg et al11 have demonstrated that necrosis was found at thoracotomy in 89% of those patients with necrosis at retroperitoneal lymph node dissection. In the present study, only three of the five patients (60%) with necrosis and/or fibrosis in the resected RRTM also had necrosis in the PRTM. The resected PRTM of the other two patients showed mature teratoma and embryonal carcinoma, respectively. If there was only necrotic and/or fibrotic tissue in the retroperitoneum, the percentage of necrotic tissue in the chest differs from 50 to 100% in the literature.13,35,38-43

Because the histologic features of the PRTM cannot be predicted in all patients based on the histologic features of the resected RRTM, it is justified to perform a pulmonary resection, even in patients with necrosis in the retroperitoneum.

The current retrospective study demonstrates that an aggressive surgical approach to residual pulmonary disease in disseminated NSTGCT after cisplatin-based polychemotherapy is highly justified. All the sites of residual disease must be resected, irrespective of the histologic results of the initial RRTM resection. An aggressive approach to testicular cancer using combined treatment modalities offers the best recurrence-free and overall survival, with minimal treatment-related morbidity and no mortality.

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