Mediastinal metastases from testicular nonseminomatous germ cell tumors: Patterns of dissemination and predictors of long-term survival with surgery

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Objectives: The purpose of this study was to determine the pattern of mediastinal dissemination of nonseminomatous germ cell tumors of testicular origin and evaluate variables that may influence survival with mediastinal dissection in patients with metastatic nonseminomatous germ cell tumors.

Methods: From 1981 to 2000, a total of 421 patients were seen at our institution for extirpation of residual lung or mediastinal disease after cisplatin-based chemotherapy for metastatic testicular nonseminomatous germ cell tumors. We reviewed 268 of these patients, with a mean age of 26.8 years, who required at least one surgical procedure to remove residual mediastinal disease. Pathologic types of resected residual mediastinal disease were necrosis (15%), teratoma (59%), persistent nonseminomatous germ cell cancer (15%), and non-germ cell carcinomatous degeneration (11%). Twelve variables were evaluated by univariate analyses, and four variables potentially statistically significant at $P < .10$ were subsequently entered into a Cox regression model.

Results: All patients demonstrated metastases to the visceral mediastinum. Fewer patients also demonstrated metastases to the paravertebral sulcus or anterior compartments (16% and 7%, respectively). Overall 5- and 10-year survivals were $86\% \pm 2\%$ and $74\% \pm 4\%$, respectively. According to multivariate analysis, disease-related survival was negatively influenced by an elevated preoperative β -human chorionic gonadotropin level ($P = .028$) and adverse pathologic characteristics of residual mediastinal disease ($P = .006$).

Conclusions: Testicular nonseminomatous germ cell tumors follow a predictable pattern of mediastinal dissemination, primarily following the course of the thoracic duct and its major tributaries. Patients who require surgery to remove residual mediastinal disease after cisplatin-based chemotherapy for metastatic nonseminomatous germ cell tumors have good to excellent long-term survivals. These results justify an aggressive surgical approach, including multiple surgical procedures if clinically indicated.

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Nonseminomatous germ cell tumors (NSGCTs) of testicular origin are the most common neoplasm in male patients younger than 40 years.¹ It is estimated that 8000 new cases will be diagnosed in the United States each year, with the worldwide incidence doubling during the past 40 years. In addition, according to birth cohort data, testicular NSGCT is being diagnosed at a younger age.² Despite the increasing incidence of testicular NSGCT, mortality rates have dramatically fallen by an estimated 70% since the advent of cisplatin-based chemotherapy regimens in the 1970s.^{3,4} The paradigm of cisplatin-based chemotherapy followed by surgery to remove residual disease is currently viewed as the most successful multimodality cancer treatment model, that against which other solid cancer treatments are compared.

Although hematogenous metastases to the lung, bone, or brain may occur, testicular NSGCT most frequently metastasizes through the lymphatics to the retroperitoneum and may subsequently metastasize to contiguous mediastinal lymphatics. Cisplatin-based chemotherapy alone suffices for a cure for most patients with supradiaphragmatic metastases. In approximately 10% to 20% of testicular NSGCT cases with presentation or subsequent development of supradiaphragmatic metastases, at least one thoracic surgical procedure, in the form of either mediastinal dissection or pulmonary metastasectomy, is required to remove persistent radiographic abnormalities after chemotherapy.⁵ Few studies have reported clinical outcomes of this select population with testicular NSGCT treated with surgery to remove residual intrathoracic disease.⁶⁻⁹ These reports have mainly focused on patients undergoing pulmonary metastasectomy for hematogenous metastases. The purpose of this retrospective study was to determine the patterns of mediastinal dissemination, determine outcomes with resection of mediastinal metastases, and analyze variables that may influence long-term survival with mediastinal dissection in patients with testicular NSGCT.

Material and Methods

Patient Identification and Variables

Institutional records of 421 patients with the diagnosis of testicular NSGCT who underwent removal of residual intrathoracic disease after cisplatin-based chemotherapy between 1980 and 2000 were reviewed to select the subset of patients who had undergone at least one surgical procedure to remove residual mediastinal disease. The following variables were recorded when available: age at diagnosis, date of diagnosis, serum tumor marker (STM, α -fetoprotein [AFP] and the β subunit of human chorionic gonadotropin [β hCG]) levels at diagnosis and at surgery, stage at presentation (I, testes; II, retroperitoneum; III, supradiaphragmatic; III advanced, liver, brain, or bone metastases), the presence of pulmonary metastases, testicular pathologic type, the need for second-line chemotherapy before surgery, the number and surgical approaches to remove residual intrathoracic disease, the need for concomitant or

separate retroperitoneal lymph node dissection (RPLND) and modified neck lymph node dissection (MND), the location of mediastinal metastases (anterior compartment; paravertebral sulcus; and middle or visceral compartment, which was subdivided into three additional compartments, upper middle, thoracic inlet to tracheal carina, mid middle, tracheal carina to dome of the diaphragm, and lower middle or retrocrural, dome of diaphragm to crus), the need to remove adjacent intrathoracic organs or pulmonary metastases, "worst" pathologic category of all residual mediastinal disease (necrosis, no viable tumor; teratoma, mature or immature teratoma; persistent NSGCT; non-germ cell cancer, degeneration into sarcoma, primitive neuroectodermal tumor, and adenocarcinoma), and postoperative morbidity or mortality.¹⁰

Indications and Techniques of Mediastinal Surgery

Indications for surgery were based on multiple factors, including disease stage at presentation, the serologic and radiographic response to chemotherapy, and the pathologic findings of RPLND if performed.¹¹ Moreover, rarely were efforts made to obtain either a tissue or cytologic diagnosis before surgery, because benign and malignant pathologic types of residual or recurrent mediastinal masses were typically predicted by clinical and radiographic findings. In general, after completion of cisplatin-based chemotherapy, patients underwent restaging with STMs and computed tomographic (CT) body scans. Most patients had normalization of previously elevated STMs and either a significant reduction or resolution of all radiographic evidence of disease in the retroperitoneum and chest. Patients with demonstrated progression of disease during or soon after first-line chemotherapy were given second-line platin-based chemotherapy (eg, vinblastine, ifosfamide, and cisplatin, or high-dose platin-based chemotherapy with autologous stem cell rescue). If significant radiographic abnormalities remained in the retroperitoneum and chest, then RPLND was typically performed first. If RPLND pathologic examination demonstrated elements of persistent NSGCT, then second-line chemotherapy was usually administered before removal of residual mediastinal disease. Because there is a high correlation between the pathologic findings of tumor necrosis in residual retroperitoneal and intrathoracic masses after successful first-line chemotherapy, we would usually radiographically observe persistent mediastinal abnormalities if necrosis alone was found in the RPLND specimen.¹² If more extensive residual mediastinal disease was present after second-line chemotherapy, then mediastinal dissection was performed even if RPLND pathologic examination demonstrated tumor necrosis as bulky areas of residual necrosis that might contain viable cells with future growth or malignant degeneration potential that would be refractory to further chemotherapy. Bulky residual mediastinal masses suspected of containing tumor necrosis not infrequently represent situations where dissection is technically difficult because of obscured tissue planes. Adjacent and even adherent intrathoracic organs, such as the great arteries, trachea, and esophagus, were typically spared, however, to avoid morbidity. Thoracic surgery was mainly performed for residual low-density cystic mediastinal masses suspected of containing teratoma, either after recovery from chemotherapy or when identified during follow-up. Given the high potential for cure as well as the ability to more readily dissect teratomatous masses from major intrathoracic organs and nerves without sacrifice, surgery was

indicated regardless of the extent of residual mediastinal disease in this setting. Salvage thoracic surgery was performed for persistent NSGCT (usually signified by significant STM elevation) after second-line chemotherapy or for degeneration into non-germ cell cancer, both situations that are typically refractory to additional chemotherapy. Surgery was performed as a salvage strategy only in patients with radiologic evidence of limited mediastinal disease, either after recovery from second-line chemotherapy or when malignant mediastinal disease was seen during follow-up. Moreover, a more aggressive surgical approach was not infrequently necessary, with removal and if necessary reconstruction of adherent or frankly involved adjacent organs or great vessels. In further contrast to resections of teratomatous masses, intraoperative frozen-section analysis was used to assess surgical margins after removal of chemorefractory disease.

Specific surgical approaches for all mediastinal compartments harboring residual disease were selected to minimize the overall number of thoracic procedures necessary while optimizing exposure to remove residual disease.¹¹ Moreover, to reduce the overall number of surgical procedures, one thoracic surgical procedure was not infrequently performed in conjunction with RPLND or MND. In summary, residual disease in the upper middle mediastinum (and anterior mediastinum when present) was approached through a median sternotomy. If extension of residual disease into the thoracic inlet was present or concomitant MND was performed, then a cervicosternotomy approach was used. With upper middle mediastinal disease limited to the upper and lower paratracheal spaces, a standard right-sided posterolateral thoracotomy through the 4th or 5th intercostal space was performed. For isolated mid middle mediastinal disease, a standard right-sided posterolateral thoracotomy through the 5th or 6th intercostal space was used. Lower middle mediastinal disease, if isolated, was approached through an oblique thoracotomy over the 7th or 8th ribs or through a thoracoabdominal or transabdominal approach in conjunction with RPLND if contiguous with retroperitoneal lymphadenopathy. If both RPLND and mediastinal dissection involved nonbulky and noncontiguous disease, then both RPLND and mediastinal dissection were commonly performed during the same anesthetic period through separate abdominal and thoracic incisions.⁵ Because most patients received bleomycin as part of first-line cisplatin-based chemotherapy regimens, perioperative fluid administration and inspired oxygen concentrations were minimized.

Follow-up and Statistical Analysis

After successful removal of all residual intrathoracic disease, patients demonstrating tumor necrosis, persistent NSGCT, or non-germ cell cancer were followed up with serial STM measurements and routine chest radiographs. If persistent NSGCT elements were present in residual mediastinal disease removed after first-line chemotherapy, then two additional courses of cisplatin combination chemotherapy were usually administered. Patients with demonstrating pathologic evidence of teratoma were also followed up with serial CT body scans. Any new mediastinal or lung abnormalities detected during long-term follow-up were removed according to the previous indication criteria. Referring physicians were contacted if there was no institutional record of follow-up within 6 months of review. Patients were categorized as alive and

TABLE 1. Patient demographic characteristics and disease profile at time of diagnosis

Variable	No.	%
Race (n = 268)		
White	250	93.3
Other	18	6.7
AFP (ng/mL, n = 227)		
0-25	42	18.5
26-100	29	12.8
101-1000	59	25.9
1001-10,000	78	34.4
>10,000	19	8.4
βhCG (ng/mL, n = 233)		
0-1.5	45	19.3
1.6-1000	94	40.3
1001-50,000	64	27.5
>50,000	30	12.9
Stage (n = 258)		
I (testes)	24	9.3
II (retroperitoneum)	46	17.8
III (above diaphragm)	170	65.9
III advanced (liver, bone, brain)	18	7.0
Lung metastases (n = 192)		
Present	118	61.5
Absent	74	38.5
Testicular pathology (n = 265)		
Seminoma	64	24.2
Yolk sac	84	31.7
Embryonal	184	69.4
Choriocarcinoma	44	16.6
Teratoma	189	71.3
Other	66	24.9

well, alive with disease, dead of disease, dead of non-disease-related causes, or unavailable follow-up.

Kaplan-Meier analysis was used to calculate overall survival, survival by pathologic category, and disease-free survival from the time of diagnosis. All variables potentially predictive of long-term survival were evaluated by Cox regression to establish hazard ratios. Variables that were found to be predictive of survival with a *P* value less than .1 were entered into a multivariate analysis model with Cox regression to identify a subset of variables that were independently predictive of survival.

Results

There were 268 patients found who underwent at least one surgical procedure to remove residual disease in the mediastinum after chemotherapy. The remaining 153 patients underwent surgery to remove pulmonary metastases only and were therefore excluded from review. The mean age was 26.8 ± 7.6 years (range 12-58 years). These patients underwent a total of 455 procedures to remove intrathoracic disease from 4 to 251 months from the time of diagnosis (median 12 months). One hundred forty-two patients (53.0%) underwent one procedure, 80 patients (29.9%) underwent two procedures, 35 (13%) underwent three procedures, and 11 patients (4.1%) underwent four to six proce-

TABLE 2. Preoperative STM status

Variable	No.	%
STMs (n = 257)		
Normal	176	68.4
Elevated	91	31.6
AFP (ng/mL, n = 257)		
0-25	216	84.0
26-100	20	7.8
101-1000	11	4.2
1001-10,000	10	4.0
>10,000	0	0.0
β hCG (ng/mL, n = 257)		
0-1.5	213	82.9
1.6-1000	44	17.1
1001-50,000	0	0.0
>50,000	0	0.0

Levels reported represent the highest values before removal of any intrathoracic disease.

dures. Ninety-eight percent of patients (n = 210/215) demonstrated elevated STM levels at diagnosis, with near equal frequencies of AFP (n = 185/227, 81.5%) and β hCG (n = 188/233, 80.7%) elevation (Table 1). All patients had a component of NSGCT cancer found in the testicular pathologic examination, with most (69.4%) demonstrating embryonal cell carcinoma, 21.3% demonstrating elements of teratoma, and 24.2% demonstrating seminomatous germ cell cancer. Most patients (n = 170, 65.9%) were seen with supradiaphragmatic (stage III) disease; however, the other 98 patients manifested mediastinal disease either during or after cisplatin-based chemotherapy. Ninety-four (35.1%) patients received second-line chemotherapy before removal of residual intrathoracic disease. Before all surgical procedures, 176 patients (68.4%) had normalization of STM levels. The other 91 (31.6%) patients underwent surgery with elevated STM levels, with most of these patients demonstrating minor elevations only (Table 2). Eighty-four (31.3%) patients underwent MND, 55 of which procedures (12.1%) were done in conjunction with mediastinal surgery. The vast majority of patients in this series (239, 89.2%) underwent RPLND, and 141 thoracic surgical procedures (31.9%) were performed in conjunction with RPLND.

The distributions of mediastinal metastases and surgical approaches are shown in Table 3. In summary, all patients had residual disease removed from the middle mediastinum, with most (67.5%) undergoing a mid middle mediastinal dissection (carina to dome of diaphragm). A smaller fraction of patients also had disease removed in the paravertebral sulcus and anterior mediastinal compartments (15.7% and 7.1%, respectively). Slightly more than half of these procedures (51.2%) were carried out through a posterolateral thoracotomy approach, and 14.5% were carried out through a thoracoabdominal approach in conjunction with RPLND. Eighty-one patients underwent removal of upper middle

TABLE 3. Anatomic distribution of residual mediastinal disease and surgical approach

Variable	No.	%
Anatomic location		
Anterior	19	7.1
Middle or "visceral"	268	100.0
Upper	119	44.4
Mid	181	67.5
Lower	125	46.6
Paravertebral sulcus	42	15.7
Surgical approach		
Thoracotomy		
Right	128	28.1
Left	110	24.1
Thoracoabdominal		
Right	39	8.1
Left	27	5.9
Transabdominal	60	13.2
Clam shell	3	0.6
Sternotomy	81	17.8
Thoracoscopy	7	1.5

Percentage of mediastinal compartment is expressed as a fraction of the total number of patients undergoing mediastinal dissection (n = 268). Percentage of surgical approaches is expressed as a fraction of the total number of intrathoracic surgical procedures (n = 455).

mediastinal disease through a sternotomy, and 60 underwent a transabdominal approach to remove residual lower middle mediastinal disease. Fifteen patients (5.6%) with either persistent NSGCT or non-germ cell cancer required removal of a major vascular structure (n = 12), superior vena cava or brachiocephalic vein (n = 6), subclavian or carotid artery (n = 3), descending thoracic aorta (n = 3), or a significant portion of the esophageal muscular wall (n = 3). Seven patients underwent separate thoracoscopy procedures to remove peripheral pulmonary metastases only. Some form of pulmonary resection was required to remove intrapulmonary or hilar disease in a total of 128 cases (47.8%). Pulmonary wedge resections were most commonly performed, with 109 patients (40.7%) undergoing mediastinal dissection and 38 patients (14.1%) and 10 patients (3.7%) requiring lobectomy and pneumonectomy, respectively.

Operative morbidity and mortality were low among these otherwise young and healthy male patients. There were 3 operative deaths (1.1% of patients). Two patients died of adult respiratory distress syndrome after lobectomy and pneumonectomy for extensive residual middle mediastinal and hilar disease. Both of these patients had only necrosis in the resected specimens. One patient died of complications related to gastric perforation after a combined thoracoabdominal approach to remove residual teratoma. Thirty-two (11.9%) patients had nonfatal postoperative complications, including the following: pneumonia, significant atelectasis, or more than 48 hours of mechanical ventilation (n = 9);

Figure 1. Long-term overall and disease-free survivals for 268 patients who underwent postchemotherapy resection of residual mediastinal disease. *Numbers* represent patients at risk at 2.5-year increments. See text for details.

chylothorax persistent for longer than 10 days ($n = 8$); air leakage prolonged for longer than 10 days ($n = 8$); bleeding necessitating reoperation ($n = 4$); atrial arrhythmias ($n = 3$); pleural space infection ($n = 3$); recurrent nerve palsy ($n = 2$); and pulmonary embolism ($n = 2$). Of significant note, 6 patients manifested postoperative lower extremity paresis or paraplegia after circumferential lower descending thoracic aorta dissection to remove residual masses containing teratoma. Of these patients, 4 demonstrated significant improvement of neurologic function and 2 did not.

At last follow-up 200 patients were alive, and 169 were both alive and free of disease. Fifty-seven patients had died (47 of the disease, 7 of other or unknown causes, and 3 of operative causes as previously described). Sixteen patients are unavailable for follow-up. The overall 5- and 10-year survivals were $86\% \pm 2\%$ and $74\% \pm 4\%$, respectively (Figure 1). The overall 5- and 10-year disease-free survivals were $80\% \pm 3\%$ and $63\% \pm 4\%$, respectively. The worst pathologic classification of residual mediastinal disease was necrosis in 14.9% ($n = 39$), teratoma in 58.8% ($n = 154$), persistent NSGCT in 15.6% ($n = 41$), and non-germ cell cancer in 10.7% ($n = 28$). The pathologic finding of complete tumor necrosis in residual mediastinal disease predicted excellent survival (mean 190 ± 11 months), which was statistically superior to that associated with non-germ cell cancer (mean 123 ± 20 months, $P = .007$) but not statistically significantly different from those of the other two pathologic categories of teratoma (mean 181 ± 10 , $P = 0.196$) and persistent NSGCT (mean 202 ± 23 , $P = .147$;

Figure 2) The finding of teratoma in residual mass pathologic examination also predicted better survival than did that of non-germ cell cancer ($P = .008$) but not that of persistent NSGCT ($P = .80$). The subset of patients with pathologically demonstrated either tumor necrosis or teratoma had an overall $78.3\% \pm 4.4\%$ 10-year survival. Disease-free survival according to worst mediastinal pathologic class is shown in Figure 3. Patients with tumor necrosis demonstrated superior mean survival (115 ± 7 months), which was again statistically better than that of patients with non-germ cell cancer (79 ± 10 months, $P < .001$) and also significantly better than that of patients with persistent NSGCT (106 ± 6 months, $P = 0.042$). Mean disease-free survival of patients with teratoma (105 ± 4 months) was not statistically different from that of patients with necrosis ($P = .189$), however. Finally, residual mass pathologic type of teratoma predicted better statistical disease-free survival than did that of non-germ cell cancer ($P < .001$) but not that of persistent NSGCT ($P = .268$).

The univariate analysis of 12 variables that potentially could influence survival is depicted in Table 4. Other than adverse pathologic type of residual mediastinal disease, an older age at diagnosis appeared to have a significantly negative impact on survival ($P = .014$). There were 15 patients older than 40 years at the time of diagnosis, and 7 (46.7%) of these patients have died (2 of disease, 1 of operative causes, and 4 of non-cancer-related causes or unknown causes). In contrast, there were 14 patients younger than 14 years of age with only 2 late deaths, both

Patients at Risk

Necrosis	25	18	14	10
Teratoma	108	83	57	36
Persistent NSGCT	37	29	21	18
Non-Germ Cell Cancer	18	11	8	4

Figure 2. Long-term survival according to worst postchemotherapy pathologic category. *Numbers* represent patients at risk at 2.5-year increments. See text for details.

attributable to disease. There was a trend toward elevation in either STM level at the time of surgery predicting diminished survival ($P = .115$), and an elevated preoperative β hCG did reach statistical significance in this regard ($P = .036$). In contrast, however, an elevated AFP at time of surgery was not predictive ($P = .760$). There were 44 patients who had elevated β hCG levels at time of surgery, and 16 of these patients (36.4%) have died (15 of disease and 1 of non-cancer-related causes). The need for separate removal of residual pulmonary disease after chemotherapy was not predictive of an adverse outcome ($P = .764$); however, removal of residual lung disease containing either persistent NSGCT or non-germ cell cancer was predictive by univariate analysis ($P = .012$). Finally, in a Cox regression model, older age at diagnosis ($P = 0.005$), elevated β hCG level at surgery ($P = .028$), and more serious pathologic class of residual mediastinal disease ($P = .006$) were the only variables found to be independently predictive of poorer long-term survival.

Discussion

Intrathoracic NSGCTs, whether primary mediastinal NSGCTs (PMNSGCTs) or, more commonly, NSGCTs metastatic to the mediastinum from the testes, provide unique and interesting biologic tumor models. Elevated STM levels usually correlate with the presence of viable NSGCT. There is distinctly better survival after excision of residual disease

metastatic to the mediastinum from testicular NSGCT than with PMNSGCT, however. We found an 86% 5-year survival in this series, as compared with a 56% survival after chemotherapy and surgery for PMNSGCT, which clearly demonstrates their different biologic behaviors despite similar histologic characteristics.¹³ Chemotherapy in our previously reported PMNSGCT series converted active NSGCT to either necrosis or teratoma in 59% of cases.¹³ In contrast, these current data demonstrate that cisplatin-based regimens converted mediastinal metastases from NSGCT of testicular origin into necrosis or teratoma histologic type in 74% of surgical cases. The difference in the biologic response to chemotherapy is further amplified by the fact that the vast majority of all residual masses in patients with PMNSGCT are resected after chemotherapy, as opposed to only a minority of residual mediastinal masses suspected of containing necrosis in patients with testicular NSGCT.¹² Moreover, patients with testicular NSGCT who show evidence of persistent NSGCT in residual mediastinal disease also appear to have a better long-term survival after salvage surgery, with a mean survival of 202 months, as opposed to a mean survival of only 52 months after salvage surgery for PMNSGCT. Regardless of the site of origin, the curability of NSGCTs establishes these diseases as models of successful multimodality therapy after which treatments of other intrathoracic and extrathoracic solid human cancers are patterned.

Figure 3. Long-term disease-free survival according to worst postchemotherapy pathologic category. *Numbers* represent patients at risk at 2.5-year increments. See text for details.

TABLE 4. Univariate analysis of survival

Variable	Hazard ratio	95% Confidence interval	P value
Age at diagnosis	1.04	1.01-1.08	.014
AFP at diagnosis	1.09	0.85-1.38	.507
β hCG at diagnosis	0.76	0.55-1.06	.102
Stage at diagnosis	1.10	0.77-1.57	.618
Teratoma (testes)	1.22	0.68-2.17	.507
Normal STMs at surgery	0.65	0.38-1.11	.115
AFP at surgery	0.95	0.68-1.32	.760
β hCG at surgery	1.86	1.04-3.31	.036
Residual lung disease removed	1.08	0.64-1.83	.764
Malignant lung disease removed	2.11	1.18-3.77	.012
Malignant mediastinal disease removed	1.69	0.98-2.91	.060
Pathologic type of mediastinal disease	1.55	1.14-2.12	.006

STM, AFP, and β HCG levels at surgery represent the highest values before removal of any intrathoracic disease. Residual lung disease removed refers to cases in which separate pulmonary resection was required, and malignant lung disease or mediastinal disease removed refers to removal of either persistent NSGCT or non-germ cell cancer.

In addition, PMNSGCT originates in the anterior mediastinal thymic tissues. Mediastinal metastases from NSGCT of testicular origin, however, appear to follow a predictable pattern of dissemination mainly along the distribution of the

thoracic duct and its major lymphatic tributaries. We favor using the mediastinal compartments described by Shields,¹⁰ who designates the middle mediastinum as consisting of the visceral mediastinum from the thoracic inlet to the diaphragmatic crura. In this designation, the middle mediastinum includes not only the ascending and aortic arch, brachiocephalic vessels, and esophagus superiorly, but the descending thoracic aorta, adjacent azygos vein, and esophagus to the diaphragmatic crura inferiorly. This designation is more logical from embryologic, anatomic, and pathologic standpoints with respect to keeping all the major lymphatic vessels within the middle mediastinum than is the more frequently used designation in which major arteries and adjacent lymphatics course through at least two of the mediastinal compartments with somewhat arbitrary boundaries.¹⁴ Moreover, subdividing the middle or visceral mediastinum into roughly equal thirds (upper, mid, and lower) dictates optimal surgical approaches to remove residual intrathoracic disease.¹¹ Although the residual disease appears to rather uniformly disseminate throughout the major lymphatics of the middle or visceral mediastinum, occasionally metastases are also present in the anterior compartment and paravertebral sulcus, presumably as a result of branch lymphatic spread probably contributed by malignant obstruction of more cephalic lymphatic vessels. We found, however, no cases of isolated metastases in the anterior mediastinal compartment or paravertebral sulcus without

middle mediastinal metastases. NSGCT isolated to the anterior compartment in a patient with a history of testicular NSGCT should therefore be considered a second primary neoplasm.

Operative morbidity and mortality were low among these otherwise young and healthy male patients, particularly as mediastinal dissection usually did not require removal of major intrathoracic organs or nerves. Bleomycin, commonly used with cisplatin and etoposide in combination therapy for the treatment of metastatic NSGCT, is known to cause pulmonary fibrosis and an associated reduction in diffusing capacity. Bleomycin is typically administered to a maximum of 360 units. Unfortunately, this may have contributed to 2 of the 3 postoperative deaths that followed anatomic pulmonary resections. Although teratoma can usually be dissected from adjacent major hilar airways and blood vessels, tumor necrosis, persistent NSGCT, and non-germ cell cancer often cannot be readily dissected from adjacent structures. In cases in which anatomic pulmonary resection may be necessary, we are currently limiting the total bleomycin dose to 300 units. Most of our non-fatal complications were also pulmonary in nature. Further study is indicated to clarify bleomycin-related morbidity and mortality and to determine optimal bleomycin dose, particularly when large pulmonary resection is anticipated. Of significant note was the complication of lower extremity paresis or paraplegia, which occurred in our series after circumferential thoracic aortic dissection in the lower middle mediastinum (retrocrural) compartment for removal of residual teratoma.¹⁵ This complication fortunately did not occur in the 3 patients who underwent descending thoracic aortic removal and prosthetic vascular graft replacement; however, those patients were also at risk. Although it is technically challenging, to avoid the risk of spinal cord ischemia we are currently attempting to spare larger diameter intercostal arteries in this compartment when anatomically and oncologically feasible. Certainly, appropriate preoperative counseling regarding the potential for neurologic complications is warranted if circumferential lower descending thoracic aortic dissection or resection is planned that would result in the sacrifice of any pair (or pairs) of intercostal arteries during tumor removal.

Long-term survival was found to be excellent with removal of residual mediastinal disease, particularly if the pathologic class was necrosis or teratoma. This finding justifies an aggressive thoracic surgical approach in these cases, which not infrequently require multiple surgical procedures to remove bilateral residual disease or disease that appears during subsequent radiographic follow-up. Prolonged survival also appears possible with resection of limited areas of persistent NSGCT or non-germ cell cancer within the mediastinum. There have been few previous reports on the outcomes of patients with testicular NSGCT

with resection of residual intrathoracic disease after cisplatin-based chemotherapy. Liu and colleagues⁸ reported on 143 patients with testicular NSGCT with hematogenous metastasis to the lung who underwent pulmonary metastasectomy with 71% 5-year survival. Cagini and colleagues⁹ and Anyanwu and associates⁶ also published series consisting primarily of patients with testicular NSGCT who underwent pulmonary metastasectomy, reporting 5-year survivals of 77% and 59%, respectively. Although previous reported survival has been excellent for stage III (supradiaphragmatic) disease, it does appear to be somewhat inferior to our overall survival of 86% at 5 years for patients with stage III disease undergoing surgery to primarily remove residual disease disseminated from the retroperitoneum into the mediastinal lymphatic tissues.

Multivariate analysis found elevated preoperative β hCG levels, pathologic status of residual mediastinal disease, and older age at the time of diagnosis as independent risk factors for poor long-term outcome. Elevated β hCG level usually signifies the presence of persistent choriocarcinoma or embryonal cell carcinoma in residual disease and has been previously reported to have a significantly negative impact relative to elevated preoperative AFP levels on survival before RPLND.^{16,17} Adverse pathologic status, which includes persistent NSGCT or non-germ cell cancer, has also been previously reported to adversely affect long-term survival in patients with NSGCT with intrathoracic metastases after surgery.^{6,8,9} The presence of either persistent NSGCT or non-germ cell cancer in the mediastinum is not infrequently suspected before surgery on the basis of multiple variables, including CT characteristics of more solid (versus low-density cystic) areas, high preoperative STM levels, late relapse, or history of other areas from the retroperitoneum or neck having been removed and found to harbor malignant pathologic processes. Our 10-year survival data for these poor-risk patients also demonstrate that long-term survival is possible when surgical candidates with limited malignant mediastinal disease are carefully chosen. Patients who sustained a late relapse with masses not infrequently containing chemotherapy-refractory pathologic processes, such as persistent NSGCT or non-germ cell cancer, also underscore the need for longer (>5 year) disease-free survival analysis. Finally, age has not previously been found to be an independent risk factor for long-term survival after treatment for metastatic NSGCT of testicular origin. In the subgroup of patients at least 40 years old, 5 of the 7 patients who died had either operative, late non-cancer-related, or late unknown causes of death, which may have erroneously skewed statistical analysis of this variable, at least with respect to disease-related survival. Certainly, patients with disease diagnosed at or after the age of 40 years would be expected to be at greater risk for non-cancer-related death after long-term follow-up than would younger patients.

Although many patients with a diagnosis of NSGCT of testicular origin are first seen with stage III disease, only a minority ultimately require surgical removal of residual mediastinal disease after cisplatin-based chemotherapy. Patients who do undergo mediastinal dissection have residual disease distributed throughout the lower, mid, or upper middle or visceral mediastinum from the thoracic inlet to the diaphragmatic crura, with residual disease in the mid middle mediastinum being most common. Residual disease in the paravertebral sulcus and anterior mediastinal compartment occurs much less frequently. Long-term survival of patients who demonstrate either necrosis or teratoma in residual mediastinal disease is excellent, which clearly justifies an aggressive surgical approach, even when extensive mediastinal or circumferential descending thoracic aortic involvement is present. Bilateral or multiple thoracic surgical procedures are not infrequently necessary. Operative morbidity and mortality are low because sparing of adjacent organs and nerves is usually possible, particularly with residual teratomatous disease. As a referral center for testicular NSGCT cases, we continue to evaluate an increasing number of patients with chemotherapy-refractory disease. Salvage operations to remove mediastinal disease in these cases represent situations in which significantly poorer long-term survival is anticipated; however, an aggressive surgical approach is justified for selected patients.

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References

1. Bosl GJ, Motzer RJ. Testicular germ-cell cancer. *N Engl J Med*. 1997;337:242-53.
2. McKiernan JM, Goluboff ET, Liberson GL, Golden R, Fisch H. Rising risk of testicular cancer by birth cohort in the United States from 1973 to 1995. *J Urol*. 1999;162:361-3.
3. Levi F, La Vecchia C, Boyle P, Lucchini F, Negri E. Western and eastern European trends in testicular cancer mortality. *Lancet*. 2001;357:1853-54.
4. Einhorn LH. Testicular cancer as a model for curable neoplasm. *Cancer Res*. 1981;41:3275-80.
5. Kesler KA, Donohue JP. Combined urologic and thoracic approaches for advanced or disseminated testis cancer. *Atlas Urol Clin North Am*. 1999;7:79-94.
6. Anyanwu E, Krysa S, Buelzebruck H, Vogt-Moykopf I. Pulmonary metastasectomy as secondary treatment for testicular tumors. *Ann Thorac Surg*. 1994;57:1222-8.
7. Fadel E, Court B, Chapelier AR, Droz JP, Dartevelle P. One-stage approach for retroperitoneal and mediastinal metastatic testicular tumor resection. *Ann Thorac Surg*. 2000;69:1717-21.
8. Liu D, Abolhoda A, Burt ME, Martini N, Bains MS, Downey RJ, et al. Pulmonary metastasectomy for testicular germ cell tumors: a 28 year experience. *Ann Thorac Surg*. 1998;66:1709-14.
9. Cagini L, Nicholson AG, Horwich A, Goldstraw P, Pastorino U. Thoracic metastasectomy for germ cell tumours: long term survival and prognostic factors. *Ann Oncol*. 1998;9:1185-91.
10. Shields TW. The mediastinum, its compartments, and the mediastinal lymph nodes. In: Shields TW, LoCicero J 3rd, Ponn RB, editors. General thoracic surgery, vol 2. 5th ed. Philadelphia: Williams & Wilkins; 1999. p. 1983-6.
11. Kesler KA. Surgical techniques for nonseminomatous germ cell tumors metastatic to the mediastinum. *Chest Surg Clin North Am*. 2003;12:749-68.
12. Steyerberg EW, Donohue JP, Gerl A, Toner GC, Schraffordt Kooops H, Fossa SD, et al. Residual masses after chemotherapy for metastatic testicular cancer: the clinical implications of the association between retroperitoneal and pulmonary histology. *J Urol*. 1997;158:474-8.
13. Kesler KA, Rieger KM, Kristen N, Ganjoo KN, Sharma M, Fineberg NS, et al. Primary mediastinal nonseminomatous germ cell tumors: the influence of postchemotherapy on long-term survival after surgery. *J Thorac Cardiovasc Surg*. 1999;118:692-701.
14. Strollo DC, Rosado de Christenson ML, Jett JR. Primary mediastinal tumors. Part I—tumors of the anterior mediastinum. *Chest*. 1997;112:511-22.
15. Leibovitch I, Nash PA, Little JS, Foster RS, Donohue JP. Spinal cord ischemia after post-chemotherapy retroperitoneal lymph node dissection for nonseminomatous germ cell cancer. *J Urol*. 1996;155:47-51.
16. Murphy B, Breeden ES, Donohue JP, Messemer J, Walsh W, Roth BJ, et al. Surgical salvage of chemorefractory germ cell tumors. *J Clin Oncol*. 1993;11:324-9.
17. Wood DP, Herr HW, Motzer RJ, Reuter V, Sogari PC, Morse JM, et al. Surgical resection of solitary metastases after chemotherapy in patients with nonseminomatous germ cell tumors and elevated serum tumor markers. *Cancer*. 1992;70:2354-7.

Discussion

Dr Joe B. Putnam, Jr (Houston, Tex). Kesler and colleagues have carefully presented a retrospective review of 268 patients with mediastinal metastases from testicular NSGCT. This article focuses on metastatic NSGCT rather than PMNSGCT or combined PMNSGCT and metastatic NSGCT. These patients underwent a successful combined multimodality approach with chemotherapy followed by multiple resections. Univariate analysis of suspected prognostic factors and then Cox regression analysis of significant factors was undertaken. Kesler and colleagues demonstrated excellent long-term survival in patients receiving this multimodality therapy. However, patients who were older or those with elevated preoperative β hCG or adverse pathologic class within the residual mediastinal disease (eg, nonseminomatous germ cell cancer) had significantly reduced survival.

I have several questions for Dr Kesler. First, was an attempt at diagnosis made before the initiation of therapy, and how were such diagnoses obtained during the 20-year study period? Second, were there any unusual characteristics of the patients with non-germ cell cancer? Should these patients undergo biopsy before resection, or should different chemotherapy be used before or after resection if such a diagnosis is made? Third, significant neurologic complications occurred in patients undergoing extensive circumferential lower descending thoracic aortic dissection. I presume that extracorporeal support was routine. Should these patients be excluded from resection or have the resection modified? Finally, patients with metastatic NSGCTs have complicated courses, and multiple combined medical and surgical treatments are required for a successful outcome. Should these patients be treated at centers with experience in this type of surgery, or can they be appropriately treated at most general hospitals?

Dr Kesler. Most of these patients have their cancer diagnosed at the time of orchiectomy and initially staged with abdominal, pelvic, and chest CT scans only. Clinical parameters, such as serum tumor marker status, CT appearance (low-density cystic vs solid) and histologic class of RPLND residual disease can usually

predict mediastinal pathologic type after chemotherapy. In routine cases, STM levels normalize after first-line chemotherapy and disease is restaged with repeated CT scans. Any residual low-density cystic masses within the mediastinum almost always represent teratoma and are surgically treated with a conservative type of resection without the need for either prechemotherapy or postchemotherapy biopsy. For less common situations in which patients have serologic or CT evidence of chemorefractory disease in the mediastinum, such as persistently elevated STM levels after second-line chemotherapy or after late relapse, we more frequently use combined CT and positron-emission tomographic scanning as opposed to biopsy, because this will accurately localize disease as well as assure us that there only is a limited amount of disease (one or two areas) present before surgery. In addition, surgery is typically done with frozen-section analysis of the surgical margin in these chemorefractory cases. In summary, we only rarely encounter situations in which open or fine-needle aspiration biopsy of a mediastinal mass in a patient with a history of testicular NSGCT would change recommendations for surgical removal. The pathologic type of residual disease may, however, determine the degree of surgical aggressiveness.

Neurologic injury did occasionally occur after circumferential removal of teratoma surrounding the lower descending thoracic aorta. Fortunately, this complication usually resulted in some degree of paraparesis, as opposed to frank paraplegia. We attribute this complication to division of the paired intercostal arteries during circumferential aortic dissection, which does not require circulatory support or aortic occlusion. Somewhat ironically, neurologic injury did not occur in 3 patients undergoing radical mediastinal dissections, including en bloc removal of the descending thoracic aorta for isolated areas of primitive neuroectodermal tumor degeneration. These latter operations were performed with aortic occlusion and left atrial to left femoral artery heparin-coated bypass pump circuits. Despite the potential for neurologic morbidity, we still recommend and do not hesitate to perform surgery after appropriate preoperative consultation for these otherwise young and healthy patients who have good to fair potential for cure only with surgical therapy. During circumferential removal of teratoma surrounding the descending thoracic aorta, we do make every effort to spare any intercostal arteries encountered during the dissection in an attempt to minimize the risk of neurologic complications. We unfortunately, however, have not found sparing any intercostal arteries that course directly through teratomatous masses to be technically feasible.

Similar to any other solid human cancer, the best results are usually going to be found at centers that treat large numbers of patients. Having said that, though, there is certainly no reason that a surgeon who is familiar with mediastinal anatomy and mediastinal surgical techniques could not successfully remove a teratomatous residual mass in the mid middle mediastinum along the distribution of the thoracic duct, which our data demonstrate to be the most frequently encountered scenario. Cases in which residual teratoma is dispersed throughout the upper middle mediastinum after chemotherapy are more technically demanding, and careful attention must be paid to sparing great vessels and intrathoracic nerves to avoid long-term morbidity in these young patients. Our specific surgical techniques to remove residual mediastinal disease

from metastatic testicular NSGCT will be presented in a future edition of *The Surgical Clinics of North America*.

Dr W. Roy Smythe (*Houston, Tex*). Dr Kesler, thank you for allowing us to learn from your unparalleled experience with this disease. I have a couple of questions. First, I noticed that one of your independent predictors of bad outcome was the presence of elevated STM levels at the time of resection. Has this changed your approach in patients with elevated STM levels? Do you now send the patients back to the medical oncologists for consideration of additional chemotherapy if STM levels are still elevated when patients are being considered for surgical resection? Second, many of these patients have concomitant parenchymal pulmonary metastasis along with their mediastinal disease. How does the presence of residual parenchymal metastasis affect your decision whether to operate on these patients?

Dr Kesler. Unlike treatment of PMNSGCT, in which we believe that second-line chemotherapy has at best a limited role, second-line chemotherapy for metastatic NSGCT of testicular origin, in the form of high-dose platin-based chemotherapy with stem cell rescue, can achieve salvage in as many as 50% of patients with failure of first-line chemotherapy. Even with aggressive second-line chemotherapy, however, anywhere from 10% to 20% of patients will continue to have STM level elevation, which usually signifies the presence of persistent testicular NSGCT. These are cases in which CT and positron-emission tomographic scans may be helpful to locate the areas of persistent NSGCT. If there are limited (one or two) areas of mediastinal metastases containing viable NSGCT amenable to surgical therapy after second-line chemotherapy, we would offer the patient "salvage surgery" with a low but real chance of cure. Multiple areas in the mediastinum (or the lung, for that matter) with persistent NSGCT after high-dose platin-based chemotherapy with stem cell rescue would unfortunately be considered an incurable situation. Degeneration into sarcomatous or neuroectodermal cancer typically does not increase STM levels, and it is also refractory to chemotherapy. Again, with limited areas of mediastinal disease, we believe that surgery offers the only chance of cure.

Pulmonary metastases from hematogenous spread are common in this patient population and occurred in nearly half of our patients with mediastinal metastases. Most of these patients underwent staged bilateral pulmonary metastasectomy procedures with ipsilateral residual mediastinal disease removed during the same surgical procedure. Most such patients can be rendered disease free, particularly if there are only a few peripheral areas of residual teratomatous disease present. Rare patients with pulmonary nodules too numerous to count would typically have residual mediastinal disease removed along with larger pulmonary masses containing teratoma, with parenchymal sparing techniques used if at all possible. Most residual lung disease would be observed with serial CT scans, and selected nodules would be removed if growth was subsequently demonstrated.

Dr Joseph B. Shrager (*Philadelphia, Pa*). I also found your presentation particularly interesting, because, like a lot of people in this room, I occasionally see one of these cases, but not enough to have a good feel for the disease. These tumors often tend to be really socked into the mediastinum, and so when one does the resection, I think one generally finds that one's margins are close. Although they may be pathologically negative, you nevertheless

know that in fact they are very close, and there's no way to know that a few cells haven't been left behind. With the understanding that these tumors are relatively radioresistant, would you nevertheless ever radiate one of these afterward? Also, is there anything you do other than limit oxygen for people who have had bleomycin to try to prevent some of the pulmonary toxicity afterward?

Dr Kesler. As long as postchemotherapy residual disease contains only teratoma, we believe that conservative resection with removal of all visible disease but without the need for microscopic surgical margin analysis is completely sufficient. In fact, our main surgical efforts in these cases are focused on sparing all intrathoracic vessels and nerves, thereby minimizing morbidity. We believe that for the most part thoracic radiation therapy has no role in this disease, with perhaps the very rare exception of sarcomatous degeneration where surgical extirpation is not possible.

We believe that bleomycin does increase postoperative pulmonary morbidity and subsequent mortality, particularly among patients who require large anatomic pulmonary resections. We therefore try to limit the total bleomycin dose if a large pulmonary resection is anticipated after combination chemotherapy. Regardless of the need for concomitant pulmonary resection, we simply make efforts to minimize the inspired oxygen concentration and are judicious with perioperative fluid administration in the case of any patient who has received this chemotherapy agent before any thoracic surgical procedure.

Dr Robert J. Ginsberg (*Toronto, Ontario, Canada*). I have a couple of questions. As the standard of care at your center for the primary testicular tumors, you mentioned retroperitoneal node dissection. Do all your patients undergo retroperitoneal node dissection? If they do, do you do synchronous operations? There are many centers that accept a diagnosis of total necrosis after induction therapy with normal STM levels and do not do retroperitoneal

node dissections, the "wait and see" policy. Have you ever used that for the posterior mediastinum or in the middle mediastinum?

Dr Kesler. Nearly 90% of the patients in our series underwent RPLND at some point, with nearly a third of thoracic surgical procedures being performed at the same time as RPLND. The high frequency of retroperitoneal disease in this series is not surprising, given the lymphatic drainage patterns from the retroperitoneum directly into the visceral mediastinum through the thoracic duct. Commonly, if residual masses that are low density and cystic, typical of residual teratoma, are present in the retroperitoneum and mediastinum, both RPLND and mediastinal dissection would be performed during the same general anesthesia. Occasionally a combined laparotomy and sternotomy approach can actually facilitate dissection of retrocrural (low middle mediastinum) disease, as can left or right thoracoabdominal incisions. If separate abdominal and thoracic incisions are required, we frequently have our urologic surgeons proceed with RPLND first; if RPLND is uneventful, we then perform a mediastinal dissection during the same anesthetic session. Exceptions to this combination approach include massive residual retroperitoneal or mediastinal disease that requires extensive and prolonged surgery and the requirement of an anatomic pulmonary resection. In these cases, removal of intrathoracic disease is typically performed during a later surgical procedure after satisfactory recovery from RPLND to avoid morbidity, particularly after bleomycin combination chemotherapy. In contrast to PMNSGCT, in which any radiographic abnormality remaining after chemotherapy is surgically removed, no matter how minor or suspicious for complete tumor necrosis the area may be, we do observe most mediastinal abnormalities after first-line chemotherapy if the abnormality is solid appearing, STM levels have normalized, and RPLND pathologic examination has demonstrated complete necrosis only.