Surgical salvage therapy for malignant intrathoracic metastases from nonseminomatous germ cell cancer of testicular origin: Analysis of a single-institution experience

Kenneth A. Kesler, MD,^a Jamison L. Wilson, MS,^a Jason A. Cosgrove, MS,^a Jo Ann Brooks, DNS,^a Ahdy Messiha, MS,^a Naomi S. Fineberg, PhD,^b Lawrence H. Einhorn, MD,^c and John W. Brown, MD^a

Background: Cisplatin-based chemotherapy followed by surgical extirpation of residual benign disease represents the usual sequence of curative therapy for metastatic nonseminomatous germ cell cancer of testicular origin. Occasionally, residual disease is malignant in the form of either a persistent nonseminomatous germ cell cancer tumor or degeneration into non-germ cell cancer. We reviewed our institution's experience with patients undergoing salvage operations to remove malignant intrathoracic metastases.

Methods: From 1981 through 2001, 438 patients with nonseminomatous germ cell cancer had operations to remove residual intrathoracic disease after cisplatin-based chemotherapy at Indiana University Hospital. A subset of 134 patients who underwent 186 surgical procedures to remove malignant metastases is the basis of this review. Fifty-nine patients had removal of pulmonary metastases, 49 had removal of mediastinal metastases, and 26 had removal of both pulmonary and mediastinal metastases. Surgical pathology demonstrated 84 patients with persistent nonseminomatous germ cell cancer tumors, 38 with degeneration into non-germ cell cancer, and 12 with both malignant pathologic categories.

Results: There were 4 (3.7%) operative deaths. The overall median survival was 5.6 years, with 55 (42.3%) patients alive and well after a mean follow-up of 5.1 years. Seventeen variables were analyzed by using Cox regression. Of these, older age, pulmonary metastases (vs mediastinal metastases), and 4 or more (vs 1) total intrathoracic metastases were significantly ($P \leq .01$) predictive of inferior long-term survival.

Conclusions: Salvage thoracic surgery to remove malignant metastases from nonseminomatous germ cell cancer tumors of testicular origin can result in long-term survival in select patients. We identified variables that influence survival in this subset.

From the Indiana University School of Medicine, Department of Surgery, Thoracic Division,^a Medicine and Biostatistics Divisions,^b and Medical Oncology Division,^c Indianapolis, Ind.

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Address for reprints: Kenneth A. Kesler, MD, Indiana University School of Medicine, Department of Surgery, Thoracic Division, 545 Barnhill Dr, EH 215, Indianapolis, IN 46202 (E-mail: kkesler@iupui.edu.).

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Nonseminomatous germ cell tumors (NSGCTs) of testicular origin are the most common neoplasm in young male subjects less than 35 years of age.¹ Approximately 8000 new cases will be diagnosed in the United States each year, with the worldwide incidence doubling during the past 40 years.² Despite the increasing incidence of testicular NSGCTs, mortality rates have dramatically decreased since the advent of cisplatin-based chemotherapy. Cisplatin-based chemotherapy alone results in 70% to 80% durable cure for patients presenting with disseminated disease. It is estimated that 10% to 20% of patients with testicular NSGCTs who present with or subsequently have supradiaphragmatic metastases will require at least one thoracic surgical procedure in the form of either mediastinal dissection, pulmonary metastasectomy, or both, to remove residual disease after chemotherapy.³ The vast majority of these cases will involve removal of benign disease in the form of mature teratoma, tumor necrosis, or both, with an excellent long-term prognosis anticipated.⁴⁻⁶ The subset of patients who undergo removal of

malignant disease, or so-called salvage operations, includes patients with persistent NSGCTs after first- or second-line chemotherapy, late NSGCT relapse, and NSGCT degeneration into non-germ cell cancer (NGCCA).^{6,7} We undertook an institutional review of patients who underwent thoracic surgery to remove malignant metastases from NSGCTs of testicular origin to determine variables predictive of outcome.

Materials and Methods

Patient Variables

Institutional records of 483 patients with the diagnosis of testicular NSGCT who underwent removal of residual intrathoracic disease after cisplatin-based chemotherapy between 1981 and 2001 were reviewed after institutional review board approval. We identified a subset of 134 patients who had undergone at least one thoracic surgical procedure to remove malignant metastases. The following variables were recorded when available: age, serum tumor markers (STMs; α -fetoprotein and the β subunit of human chorionic gonadotropin [bHCG]) at diagnosis and at the time of surgical intervention, stage at presentation (I, testes; II, retroperitoneum; III, supradiaphragmatic; III advanced, liver or brain metastases), testicular pathology (NSGCT cell type or types, the presence of teratoma or NGCCA), second-line chemotherapy (cisplatin-based or high-dose cisplatin-based therapy plus autologous stem cell transplantation) before surgical intervention, concomitant or separate retroperitoneal lymph node dissection (RPLND), worst pathology of RPLND (necrosis, teratoma, persistent NSGCT, or NGCCA), presence and location of extrathoracic malignant metastases, time from diagnosis to the first thoracic surgical procedure to remove malignant disease, number of thoracic surgical procedures to remove malignant metastases, location and number of intrathoracic malignant metastases (lung, mediastinum, or both), type of pulmonary resection (wedge, lobectomy, and/or pneumonectomy), location and type of mediastinal dissection (upper-middle-lower visceral, anterior, and/or paravertebral sulcus compartments⁶⁻⁸), adjacent organs removed, pathology of malignant metastases (persistent NSGCT [persistent nonseminomatous germ cell cancer], NGCCA [degeneration into sarcoma, primitive neuroectodermal tumor, adenocarcinoma, and/or undifferentiated carcinoma], or both persistent NSGCT and NGCCA), operative morbidity and mortality, and status at last follow-up.

Indications and Techniques of Surgical Intervention

Our indications and techniques for thoracic surgery to remove residual disease after chemotherapy for both routine and salvage cases have previously been described.^{6,7} In summary, salvage thoracic surgery was typically performed for patients suspected of having malignant pathology, which included persistent NSGCTs after first- or second-line chemotherapy, late NSGCT relapse (>2 years after initial chemotherapy), and/or degeneration into NGCCA. The 2 former indications are usually identified on the basis of the increase of STM levels, and thus biopsy of intrathoracic masses on computed tomographic (CT) scanning in this clinical setting is rarely necessary. The latter indication to remove NGCCA can be more difficult to determine preoperatively because STM levels are frequently normal. However, NGCCA pathology

can also be anticipated without biopsy on the basis of similar pathology from prior nonthoracic surgery, such as RPLND; a noncystic appearance on CT imaging; or both.⁷ We have advocated surgical therapy for all patients suspected of having teratomatous pathology after chemotherapy regardless of the extent of intrathoracic disease because not only are conservative surgical techniques that spare pulmonary parenchyma, intrathoracic nerves, and blood vessels appropriate, but also the prognosis is excellent after successful surgical intervention.⁶ In contrast, we have maintained a more conservative approach to patient selection when malignant disease is suspected, reserving salvage thoracic surgery for patients with a limited number of intrathoracic or extrathoracic metastases. Although positron emission tomographic (PET) scanning has low diagnostic yield for the majority of patients with benign residual disease, such as teratoma or necrosis, PET imaging can identify areas of malignant disease and is of value for both diagnostic and therapeutic decision-making purposes in these cases.⁹ The ultimate decision to offer surgical intervention in this series was made on an individual patient basis and collectively by medical oncologists and thoracic surgeons. In general, surgical intervention was offered if more than one area of intrathoracic malignant disease could be removed at a relatively low operative risk level or only one area of malignant disease was identifiable that required a major surgical procedure, such as pneumonectomy or en bloc removal of a great vessel. CT evidence, PET evidence, or both, of multiple sites of malignant disease would typically contraindicate surgical intervention.

In contrast to benign residual disease, not only are the indications for thoracic surgery more conservative for patients with NSGCTs with malignant disease, but a more aggressive surgical oncologic approach is occasionally necessary. Residual teratomatous disease in the lung can frequently be excised with precision electrocautery techniques, which spares parenchyma.¹⁰ In this series, for patients in whom malignant disease was suspected, however, standard wedge resection techniques were used that included a surgical margin of normal lung tissue. Because of the location or extent of pulmonary disease, anatomic resection in the form of lobectomy or pneumonectomy was occasionally required. For mediastinal disease, a more aggressive surgical approach compared with the more common situation in which teratoma is present was also occasionally necessary, removing portions of adherent adjacent organs, great vessels, or both. Intraoperative frozen section analysis was also used to assess surgical margins after removal of suspected malignant disease if resection of additional adjacent tissue could be performed without adding significant morbidity.

Our routine for postoperative care has been described in detail elsewhere.⁷ In summary, because most patients received bleomycin as part of first-line cisplatin-based chemotherapy regimens, both perioperative fluid administration and inspired oxygen concentrations were minimized. If persistent NSGCT elements were present after first-line chemotherapy, then administration of 2 additional cycles of cisplatin combination chemotherapy was given postoperatively after satisfactory recovery.^{11,12} Patients who pathologically demonstrated NGCCA or patients who received second-line cisplatin-based chemotherapy before surgical intervention were not given adjuvant cisplatin-based chemotherapy.

TABLE 1. Demographics at surgical intervention

AFP, ng/mL (n = 126)	
Normal	81 (64.3)
25-100	19 (15.1)
101-1000	15 (11.9)
1001-10,000	11 (8.7)
bHCG, ng/mL (n = 123)	
Normal	92 (74.8)
1.5-1000	29 (23.6)
1001-50,000	2 (1.6)
Previous thoracic surgery procedures for benign disease	
None	105 (78.4)
1	24 (17.9)
≥2	5 (3.7)
No. of thoracic surgery procedures to remove malignant disease	
1	90 (67.2)
2	37 (27.6)
3	6 (4.5)
4	1 (0.7)
No. of lung metastases removed	
None	49 (36.6)
1	43 (32.0)
2	15 (11.2)
3	10 (7.5)
≥4	17 (12.7)
Type of pulmonary resection*	
Wedge	65 (76.5)
Segment-lobe	24 (28.2)
Pneumonectomy†	14 (16.5)
No. of mediastinal metastases removed	
None	59 (44.0)
1	64 (47.8)
2	7 (5.2)
≥3	4 (2.9)
Type of mediastinal dissection*	
Visceral	
Upper	33 (44.0)
Middle	39 (52.0)
Lower	27 (36.0)
Anterior	4 (5.3)
Paravertebral sulcus	8 (10.6)
Adjacent organs	15 (20.0)
Descending aorta	3
Brachiocephalic artery	3
Chest wall–diaphragm	5
Esophageal wall	2
SVC–great vein	2

The number of patients is given, with the percentage of known variables in parentheses. AFP, α -Fetoprotein; bHCG, β subunit of human chorionic gonadotropin; SVC, Superior vena cava. *Percentage of subset undergoing either pulmonary or mediastinal surgery. †Pneumonectomy or equivalent with 2 lobectomies.

Statistical Analysis

Kaplan-Meier analysis was used to calculate survival from the time of the first intrathoracic surgical procedure to remove malignant disease. Seventeen variables potentially predictive of long-

term survival were evaluated. Univariate assessments of discrete risk factors possibly predictive of survival were made by using the Kaplan-Meier method with log-rank tests. The Cox proportional hazard model was used to calculate hazard ratios for both continuous and discrete variables.

Results

Demographics at Diagnosis

The mean age at diagnosis was 27.8 years (range, 14-57 years). From available data, 45 (19.2%) patients had either stage I or II disease, and 87 (65.9%) patients demonstrated stage III disease. Of the patients with stage III disease, 46 patients had mediastinal disease, and 60 patients had lung metastases. The most common testicular pathology was embryonal carcinoma, which was present in 88 (68.2%) patients. Teratoma was present in 78 (60.5%) patients, whereas 13 (10.1%) patients demonstrated NGCCA in testis pathology. Eighty-one (60.4%) patients received second-line cisplatin-based chemotherapy (high-dose chemotherapy with autologous stem cell transplantation, n = 17) for progressive disease either during or shortly after first-line cisplatin-based chemotherapy.¹³ One hundred ten (82.1%) patients underwent RPLND before thoracic surgery, with 60 demonstrating either persistent NSGCT or NGCCA in the surgical specimen. Thirty-four patients underwent RPLND in conjunction with the thoracic surgical procedure. Twenty-two of these patients demonstrated malignant pathology in both the RPLND and thoracic surgical specimens. Thirteen patients underwent surgical intervention to remove malignant metastases outside of the chest and abdomen (7 in the neck, 2 in the brain, and 4 at other sites).

Surgical Intervention and Pathology

The average time from diagnosis to the first thoracic surgical procedure to remove malignant disease was 4.1 years (range, 0.7-24.5 years). However, slightly more than half of the series, 68 (50.7%) patients, underwent thoracic surgery for malignant disease within 2 years of diagnosis, with the remaining 66 (49.3%) patients undergoing thoracic salvage surgery 2 or more years after initial diagnosis. Of the 130 patients who had known STM status at the time of the first thoracic surgery to remove malignant disease, 72 (55.4%) presented to surgical intervention with increased STM levels, and 58 (44.6%) had normal STM levels (Table 1). There were a total of 186 thoracic surgical procedures to remove malignant disease. Fifty-nine (44.0%) patients had malignant disease removed from the lung, 49 (36.6%) underwent mediastinal dissection, and 26 (19.4%) had malignant disease removed from both the lung and the mediastinum. Fifty-six (41.8%) patients had one metastasis removed from the lung or mediastinum, 34 (25.4%) had 2 areas of malignant disease removed, 16 (11.9%) had 3 areas of malignant disease removed, and the remaining 28 (20.9%) had 4 or more areas of malignant intrathoracic disease removed. Eighty-four (62.7%) patients pathologically demonstrated

TABLE 2. Cox regression analysis of survival

Variable	Hazard ratio	Confidence interval	P value
At diagnosis			
Age	1.05	1.02-1.09	<.01*
AFP	0.82	0.66-1.02	.08
bHCG	0.97	0.71-1.31	.84
Stage	0.75	0.55-1.02	.07
Lung disease	1.02	0.50-2.05	.96
Mediastinal disease	1.10	0.57-2.14	.77
Testes pathology			
Teratoma	0.77	0.46-1.28	.31
NGCCA	1.21	0.52-2.81	.66
At surgical intervention			
From diagnosis to cancer surgery (y)	0.99	0.94-1.05	.76
AFP	0.73	0.38-1.42	.35
bHCG	1.39	0.80-2.39	.24
Extrathoracic cancer removed	0.69	0.42-1.15	.15
No. of thoracic operations for cancer	0.94	0.64-1.38	.75
Location of cancer	2.05	1.16-3.62	.01*
No. of lung metastases	1.33	0.73-2.42	.35
No. of mediastinal metastases	2.02	0.88-4.68	.12
No. of lung and mediastinal metastases	1.56	1.12-2.18	.01*
Pathology	0.75	0.46-1.22	.25

Variables at surgical intervention: *bHCG*, normal versus increased; *preoperative AFP*, 0 to 100 ng/mL versus greater than 100 ng/mL; *location of cancer*, mediastinum only versus lung only versus both mediastinum and lung; *lung metastases*, 1 versus 2 or more; *no. of mediastinal metastases*, 1 versus 2 or more; *no. of lung and mediastinal metastases*, 1 versus 2 or 3 versus 4 or more; *pathology*, NSGCT vs NGCCA vs both NSGCT and NGCCA. *AFP*, α -Fetoprotein; *bHCG*, β subunit of human chorionic gonadotropin; *NGCCA*, non-germ cell cancer. * $P \leq .01$.

persistent NSGCTs, 38 (28.4%) demonstrated NGCCA, and 12 (8.9%) demonstrated both types of malignant pathology. Finally, 35 patients who pathologically demonstrated persistent NSGCTs after first-line chemotherapy received 2 additional cycles of cisplatin-based chemotherapy after surgical intervention.

Outcomes

The overall surgical mortality was 4 patients (3.6% of patients and 2.2% of surgical procedures), all of whom died as a result of respiratory (acute respiratory distress syndrome–pneumonia) complications. Two of these 4 patients underwent pneumonectomy. One operative death followed a lobectomy, and the remaining death occurred after multiple pulmonary wedge resections. Twenty patients (14.9% of patients and 10.7% of procedures) had significant nonfatal complications, including 8 patients successfully treated for acute respiratory distress syndrome–pneumonia, 7 patients with prolonged air leak (>10 days), and 3 patients with prolonged chyle leak (>10 days). One patient had transient lower extremity weakness after extensive lower visceral mediastinal dissection, and 1 patient required temporary dialysis. The overall median survival was 5.8 years, with 55 (42.3%) patients alive and well after an average follow-up of 5.1

years (range, 0.1-18.1 years). Twelve patients are alive with disease after a mean follow-up of 2.6 years (range, 0.3-8.5 years). Of the 62 patients who have died during follow-up, 53 died of disease, 2 died of nondisease, and 7 died of unknown causes. One patient has been lost to follow-up. Considering the 65 patients who experienced recurrent disease, 31 were found to have the first evidence of recurrence within the thorax, and 23 had recurrence in an extrathoracic location.

Of 17 variables analyzed, older age, the requirement for pulmonary metastasectomy, and removing 4 or more intrathoracic metastases predicted significantly diminished survival (Table 2). There was significantly better survival comparing patients who only underwent mediastinal metastasectomy compared with that among patients after lung metastasectomy or with removal of malignant disease from both the mediastinum and the lung ($P = .04$, Figure 1). Twenty-six (53.1%) of 49 patients are alive and well who underwent removal of mediastinal disease only compared with 31 (36.4%) of 85 who are alive and well after removal of lung disease with or without removal of mediastinal disease. Considering the patients who underwent removal of pulmonary metastases, 43 underwent resection of 1 pulmonary metastasis, with a median survival of 3.5 years. The 42

Figure 1. Survival on the basis of the anatomic site of resection. Patients who underwent removal of disease from the mediastinum only are represented by the *solid line* (median survival, 11.4 years; confidence interval [CI], 6.8-16.1), patients who underwent removal of disease from both the mediastinum and lung are represented by the *dashed line* (median survival, 3.2 years; CI, 1.6-4.7), and patients who underwent removal of disease from the lung only are represented by *interrupted dots* (median survival, 2.8 years; CI, 0.4-5.3). Patient numbers at risk are given per 2.5-year intervals.

Figure 2. Survival on the basis of the number of lung metastases removed. Patients who underwent removal of 1 lung metastasis are represented by the *solid line* (median survival, 3.5 years; CI was not able to be determined because of large number of survivors and length of survival), and patients who underwent removal of 2 or more lung metastases are represented by the *dashed line* (median survival, 2.5 years; CI, 1.0-3.9). Patient numbers at risk are given per 2.5-year intervals.

patients who underwent removal of 2 or more pulmonary metastases demonstrated a median survival of 2.5 years (Figure 2). Although this difference was not statistically significant ($P = .48$), patients undergoing resection of 2 or more pulmonary metastases had a shorter duration of follow-up. Of the patients who underwent removal of mediastinal metastases, there was a trend toward better survival in the 64 patients who underwent removal of 1 area of malignant disease compared with the 11 who underwent removal of 2 or more malignant areas ($P = .06$, Figure 3). Combining both anatomic areas, 56 patients who underwent one metastasectomy in the lung or mediastinum had significantly better survival than did the 28 patients who had 4 or more areas of metastatic disease removed ($P < .01$). The 50 patients who had 2 or 3 areas of malignant disease removed demonstrated intermediate survival ($P = .08$ vs 1 area and $P = .09$ vs ≥ 4 areas, Figure 4). Overall, 30 (53.6%) of 56 patients who underwent a single metastasectomy either from the lung or mediastinum are alive and well at last follow-up, whereas only 8 (28.6%) of 28 patients are alive and well who underwent removal of 4 or more total areas of malignant disease. Eighteen (36.0%) patients are alive and well who had 2 or 3 total areas of metastatic disease re-

moved. With respect to pathology, the 84 patients who demonstrated persistent NSGCTs had a median survival of 8.1 years and appeared better than the 38 patients with NGCCA or the 12 patients who had both malignant pathologic categories. However, this was not statistically significant ($P = .24$, Figure 5). Finally, on the basis of Cox regression analysis, there were trends toward inferior survival in patients who required removal of malignant extrathoracic disease ($P = .15$) and patients who presented to surgical intervention with increased bHCG levels ($P = .24$, Table 2).

Discussion

Patients with nonseminomatous germ cell cancer who have malignant residual disease, including persistent NSGCTs after first- or second-line chemotherapy, late NSGCT relapse, and NSGCT degeneration into NGCCA, represent approximately 10% to 13% of all patients with testicular NSGCTs.¹⁴ The concept of surgical salvage for malignant residual disease has been well established after RPLND over the past decade because the retroperitoneum represents the first echelon of lymphatic drainage and therefore the most common anatomic site of metastases. Foster and coworkers¹⁵ recently reported on 58 patients with viable NSGCT in RPLND specimens and found

Figure 3. Survival on the basis of the number of mediastinal metastases removed. Patients who underwent removal of 1 mediastinal metastasis are represented by the *solid line* (median survival, 11.4 years; CI, 5.4-17.5), and patients who underwent removal of 2 or more mediastinal metastases are represented by the *dashed line* (median survival, 2.2 years; CI, 0.9-3.5). Patient numbers at risk are given per 2.5-year intervals.

a 33% five-year survival. Other series have reported similar disease-free survival rates after salvage RPLND.^{16,17} Despite the mediastinum representing the second echelon of lymphatic drainage, 53% of our patients undergoing removal of malignant disease only in the mediastinum were alive and well at the time of last follow-up. Although there likely exists selection bias in patients undergoing salvage mediastinal dissection compared with patients undergoing salvage RPLND, this finding alone establishes the salvage potential of thoracic surgery for select patients with NSGCT.

In contrast to mediastinal metastases, hematogenous metastases to the lung were found to have a statistically inferior prognosis, with 36% of our series alive and well after removal of malignant pulmonary disease. Other series have reported the presence of viable NSGCT cancer compared with benign residual disease in resected pulmonary metastases to result in poor but possible long-term survival. Liu and colleagues,⁴ reporting on a 28-year experience of pulmonary metastasectomy for testicular NSGCT from Memorial Sloan Kettering Cancer Center, found 70 (44%) of 157 patients had pathologic evidence of viable cancer. This subset demonstrated 43% long-term survival, which was an independent predictor of poor outcome. Anyanwu and associates¹⁸ reported on 104 patients undergoing 117 thoracic

Figure 4. Survival on the basis of the number of lung and mediastinal metastases removed. Patients who underwent removal of 1 lung or mediastinal metastasis are represented by the *solid line* (median survival, 11.5 years; CI was not able to be determined because of the large number of survivors and length of survival), patients who underwent removal of 2 or 3 lung or mediastinal metastases are represented by *dashed lines* (median survival, 5.7 years; CI, 1.9-9.4), and patients who underwent removal of 4 or more lung or mediastinal metastases are represented by *interrupted dots* (median survival, 2.2 years; CI, 1.1-3.3). Patient numbers at risk are given per 2.5-year intervals.

surgical procedures to remove pulmonary metastases from NSGCTs of testicular origin, which included 38 (36%) patients with viable tumor cells. The overall 5-year survival in this series was 59%, with inferior survivals for the subset of patients with viable cancer. A study from the Royal Brompton Hospital involving 141 patients undergoing thoracic metastasectomy, including removal of both pulmonary and mediastinal residual disease, for NSGCTs of testicular origin found 46 (32%) patients to demonstrate malignant pathology.¹⁹ This subset had a 51% five-year survival that was significantly inferior to that of patients pathologically demonstrating either teratoma or necrosis. Although not specifically analyzing patients with malignant pathology, these authors also found significantly inferior survivals for patients undergoing pulmonary metastasectomy compared with those patients who underwent removal of residual mediastinal disease only.

We identified other variables that were predictive of outcome. In our series, although a fewer number of malignant metastases removed specifically from either

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Figure 5. Survival on the basis of lung and mediastinal pathology. Patients pathologically demonstrating persistent NSGCTs are represented by the *solid line* (median survival, 8.1 years; CI, 0.1-17.4), patients pathologically demonstrating NGCCA are represented by the *dashed line* (median survival, 4.5 years; CI, 0.9-8.1), and patients demonstrating both persistent NSGCTs and NGCCA are represented by *interrupted dots* (median survival, 2.4 years; CI, 2.1-2.7). Patient numbers at risk are given per 2.5-year intervals.

the lung or mediastinum appeared to result in improved survival, this difference did not reach statistical significance, probably because of low patient numbers. When the total number of metastases removed from both anatomic sites was analyzed, however, significantly better survival was found in patients who had removal of only 1 area compared with patients undergoing resection of 4 or more areas. This finding, in addition to the trend toward decreased survival in patients who additionally had extrathoracic malignant disease removed, validates our selection strategy of offering salvage thoracic surgery to patients requiring removal of more than one area of malignant disease only when associated with low surgical risks. We reserve higher-risk operations, such as large pulmonary resections or complex mediastinal dissections involving removal of great vessels, to patients with an isolated area of malignant disease. Although it did not reach statistical significance in our series, there also appeared to be better survival in those patients pathologically demonstrating persistent NSGCTs compared with patients with NGCCA. We attribute this finding to an institutional observation that persistent NSGCTs represent a neoplasm with a less aggressive biologic behavior, including a relative responsiveness to adjuvant chemo-

therapy compared with degenerative NGCCA. In this regard, because patients with degenerative NGCCA frequently do not demonstrate increased STM levels, it is not surprising that increased preoperative α -fetoprotein or bHCG levels did not predict a poor outcome in this subset analysis. The presence of both persistent NSGCT and degenerative NGCCA elements in pathologic specimens appeared to represent the most aggressive form of malignant disease, with no long-term survivors in our series to date.

There are several limitations of this study. First, we could not determine which patients under the category of persistent NSGCT were nonresponders to initial cisplatin-based chemotherapy or relapsed late. The distinction between the 2 subgroups can be occasionally difficult, particularly because many of these patients received initial evaluation and chemotherapy at outside institutions before referral. Regardless, because nearly half of our patients underwent salvage thoracic surgery within 2 years of diagnosis and initial chemotherapy, we believe there is likely a well-balanced distribution of both subgroups represented in the persistent NSGCT category. Moreover, because the time from diagnosis to salvage thoracic surgery was not predictive of outcome, we speculate that these 2 clinical scenarios, both of which result in pathologic evidence of persistent NSGCT, might not have significantly dissimilar outcomes. We did not have sufficient data to determine whether disease recurring within the thorax represented a failure of local surgical control or occurred in other areas of the lung, mediastinum, or both, as a result of disease progression. It is our general impression that the surgical approach we use to remove residual malignant disease in the lung and mediastinum has resulted in few local recurrences; however, further study is needed. Small numbers of patients with long-term follow-up after resection of multiple areas of malignant disease, although reflecting an institutional trend over the study period toward a more aggressive thoracic surgical approach in these patients, precludes statistical analysis to determine ultimate efficacy. Finally, we are unable to determine what fraction of these patients pathologically demonstrated malignant disease as an incidental finding, which was not anticipated before surgical intervention. These patients would arguably have the best prognoses and potentially therefore favorably influence survival outcome.

Salvage thoracic surgery to remove malignant refractory disease represents a situation in which a significantly poorer long-term survival is anticipated. However, an aggressive surgical approach is selectively justified in these otherwise young and healthy patients, with prolonged survival being possible. We have defined risk factors associated with long-term survival.

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