Pathologic concordance of resected metastatic nonseminomatous germ cell tumors in the chest

Laura L. Donahoe, MD, MSc,[a] Gregory J. Nason, MD, MSc,[b] Philippe L. Bedard, MD,[c] Aaron R. Hansen, MBBS,[c] Michael A. S. Jewett, MD,[b] Robert J. Hamilton, MD, MPH,[b] and Marc de Perrot, MD, MSc[a]

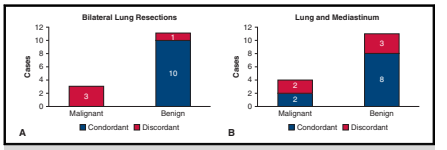
ABSTRACT

Objective: Men with metastatic nonseminomatous germ cell tumors (NSGCTs) often present with residual chest tumors after chemotherapy. We examined the pathologic concordance of intrathoracic disease and outcomes based on the worst pathology of disease resected at first thoracic surgery.

Methods: A retrospective analysis was performed of consecutive patients undergoing thoracic resection for metastatic NSGCT in our institution between 2005 and 2018.

Results: Eighty-nine patients (all men) were included. The median age was 29 years (interquartile range [IQR], 23-35 years). Primary sites were testis (n = 84; 94.4%) and retroperitoneum (n = 5; 5.6%). Eighty-seven patients received chemotherapy before undergoing surgery. Nineteen patients (21.3%; group 1) had malignancy resected at first surgery (OR1), and the other 70 patients had benign disease at OR1 (78.7%; group 2). Concordant pathology between lungs was 85.2% in group 1 and 91% in group 2, and between lung and mediastinum was 50% in group 1 and 72.7% in group 2. Despite no teratoma at OR1, 3 patients (15.8%) in group 2 had resection of teratoma (n = 2) or malignancy (n = 1) at future surgery. After a mean follow-up of 65.5 months (IQR, 23.1-89.2 months) for group 1 and 47.7 months (IQR, 13.0-75.1 months) for group 2, overall survival was significantly worse for group 1 (68.4% vs 92.9%; $P = .03$).

Conclusions: The wide range of pathology resected in patients with intrathoracic NSGCT metastases requires careful decision making regarding treatment. Pathologic concordance between lungs is better than that between lung and mediastinum in patients with intrathoracic NSGCT metastases. Aggressive surgical management should be considered for all residual disease due to the low concordance between sites and the potential for excellent long-term survival even in patients with chemotherapy-refractory disease. (J Thorac Cardiovasc Surg 2021;161:856-68)



Intrathoracic pathologic concordance is better between lungs for patients with resection of benign disease (A) than between lung and mediastinum for all patients (B) but remains low overall.

CENTRAL MESSAGE

Pathology is often discordant between intrathoracic nonseminomatous germ cell tumor metastases. Aggressive surgical management of intrathoracic disease should be considered due to the potential for excellent long-term survival.

PERSPECTIVE

Patients with intrathoracic metastases from nonseminomatous germ cell tumors often have multiple anatomic sites of disease with differing pathologies. Knowledge of concordance rates between sites could be used to determine whether further surgery is needed, yet our series has shown that intrathoracic sites are often not concordant, and aggressive surgery should be considered for all residual disease.

See Commentaries on pages 869, 870, and 871.

Testis cancer is one of the most commonly diagnosed cancers in young men, yet has a very high survival when treated aggressively. In Canada in 2019, it was the second most commonly diagnosed cancer in the 15- to 29-year age

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From the Divisions of [a]Thoracic Surgery, [b]Urology, and [c]Medical Oncology and Hematology, Princess Margaret Cancer Center, University Health Network, University of Toronto, Toronto, Ontario, Canada.

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Address for reprints: Laura L. Donahoe, MD, MSc, Toronto General Hospital, 9N-950, 200 Elizabeth St, Toronto, Ontario, Canada M5G 2C4 (E-mail: laura.donahoe@uhn.ca).

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Abbreviations and Acronyms

AFP = alpha-fetoprotein
βHCG = beta-human chorionic gonadotrophin
IGCCCG = International Germ Cell Cancer Collaborative Group
NSGCT = nonseminomatous germ cell tumor
OR = thoracic resection
PNET = primitive neuroectodermal tumor
RPLND = retroperitoneal lymph node dissection
STM = serum tumor marker
VIP = ifosfamide, etoposide, cisplatin

group, with an incidence of 13% of all cancers, yet accounted for only 3% of the cancer deaths in this age group.[1] Although the incidence of testis cancer is rising, with an annual percent change of 1.3 over a 20-year period, the annual percent change in age-standardized mortality rate has fallen at a rate of 1.9% per year over that same period.[1]

Most patients who present with testis cancer have early-stage disease, yet up to 40% present with advanced metastatic disease and require much more aggressive treatment plans.[2] Patients are stratified into prognostic categories based on diagnosis of seminoma germ cell tumor or nonseminomatous germ cell tumor (NSGCT) and by clinical factors, such as anatomic sites of metastases (liver, bone, and brain for NSGCT; nonpulmonary viscera for seminoma) and the magnitude of elevation of the serum tumor markers (STMs) beta human chorionic gonadotrophin (βHCG), alpha-fetoprotein (AFP), and lactate dehydrogenase.[3]

The role of the thoracic surgeon in treating NSGCTs is in the presence of residual intrathoracic tumors after treatment with chemotherapy, which can be present in up to 30% of patients with testicular NSGCT.[4,5] The recommended treatment regimen for patients with metastatic disease is 3 or 4 cycles of a cisplatin-etoposide–based chemotherapy regimen, followed by restaging and resection of residual tumors >1 cm for patients with normal STM levels.[3] Tumors <1 cm are more likely to be necrotic or fibrotic, and thus do not require resection if they remain of stable size, as they pose no threat to life.[6] The goal of resecting tumors >1 cm is to prevent future transformation of teratoma into somatic malignancy, avoid the development of benign growing teratoma, or control viable disease in patients with persistently elevated STM post-chemotherapy and disease that can be fully resected with salvage surgery. For patients with normal STM post-chemotherapy, it is impossible to differentiate between teratoma and necrosis using imaging; thus, for some patients, resection is diagnostic as opposed to therapeutic.

The timing of surgery also can be influenced by the histology, in that residual malignancies require expedited resection, whereas resection of nongrowing mature teratoma lesions can be delayed. Patients often have multiple sites of metastatic disease, but the histology of residual disease at one site (eg, retroperitoneal lymph nodes) might not correspond with disease at another site (eg, pulmonary masses). Thus, a finding of necrosis at one site with reliable data showing concordance with other intrathoracic sites may prevent some patients from undergoing unnecessary surgery for remaining sites of residual disease. However, there is a paucity of data in the literature on pathologic concordance between lung resections and between lung and mediastinal resections for these patients.

The primary objective of this study was to examine the intrathoracic pathologic concordance of resected masses for patients with metastatic NSGCT who had multiple sites of thoracic resections at their first surgery post-chemotherapy. Given the wide range of potential histologies of residual masses, we hypothesized that there would be a great variability in the lesions resected, with imperfect concordance between sites of resection, thus making it difficult to determine which patients may avoid surgery.

METHODS

A retrospective analysis was performed, including all patients who had resection of intrathoracic metastatic NSGCT between 2005 and 2018 at University Health Network (Princess Margaret Cancer Centre and Toronto General Hospital). The study was approved by the Research Ethics Board (Approval 14-8396; March 4, 2015). The need for written informed consent from patients for publication was waived owing to the study's retrospective and noninterventional nature. Patients with primary mediastinal NSGCT were excluded due to the different treatment protocols and universally worse prognosis. Data on the pathology of the primary testicular tumor was collected when available, as many patients had undergone their orchiectomy at an outside center. The pathologies of the primary tumor were grouped based on histology, with mixed NSGCT defined as containing germ cell tumor components with or without teratoma.[7]

The multidisciplinary testicular cancer clinic is a high-volume referral center that includes urology, medical oncology, radiation oncology, and thoracic surgery and treats patients from both regional and interprovincial sites. Often patients can be seen by all specialists in a single visit. This close working group also allows case-by-case discussion and treatment planning of all complex cases. Some patients are referred early in their disease course and receive all chemotherapy at our center, and others are treated at outside centers and referred for management of residual disease or for salvage treatment. Patients are typically treated with cisplatin-etoposide and bleomycin as first-line chemotherapy; however, in some cases with extensive intrathoracic disease, non–bleomycin-containing chemotherapy regimens are used owing to the potential need for pulmonary resection and concerns about bleomycin lung toxicity. In general, these patients are treated with cisplatin-etoposide and ifosfamide (VIP). In patients found to have residual masses after first-line chemotherapy, a decision to proceed with surgical resection is based on STM levels. Immediate surgery is planned for all patients with normal post-chemotherapy STM levels. Patients with persistently elevated STMs proceed to 2 cycles of TIP (cisplatin, ifosfamide, and paclitaxel), followed by high-dose carboplatin-etoposide with autologous stem cell support for 2 cycles, in accordance with previously described protocols.[8]

Many patients are discussed on a case-by-case basis by the multidisciplinary team, as some patients with mildly elevated markers after first-line chemotherapy will proceed to surgery if there are limited sites of disease

that are completely resectable. In patients who present with late relapses, upfront surgery is preferred if possible, owing to poor outcomes with second-line chemotherapy.[9]

The decision for combined versus sequential resection of intrathoracic and retroperitoneal disease is based on the complexity of surgery required, the presence of retrocrural disease, and availability of operating room time.[10] Intrathoracic retrocrural disease is typically approached through a combined procedure to facilitate the transabdominal transcrural resection of these tumors with or without a sternotomy.[11,12]

Follow-up after surgery is according to our institutional protocol and consists of measurement of STM every 3 months for the first 2 years, every 6 months for year 3, and yearly from years 4 to 10. Imaging follow-up includes a chest-abdomen-pelvis computed tomography (CT) scan every 6 months for year 1, at year 2, and at year 10. Chest radiography is performed annually from years 3 to 5.

The patients were divided into 2 groups based on the worst pathology found at their first thoracic resection. Group 1 includes patients with malignant disease (viable germ cell malignancy or somatic transformation), and group 2 includes patients with benign disease (immature and mature teratoma, necrosis, and other benign pathology).

Demographic data are reported as median and range. Categorical variables were compared by the χ^2 or Fisher's exact test; continuous variables, by Student's *t* test. Survival was estimated using the Kaplan–Meier method, and comparisons were performed using the log-rank test. Survival was calculated from the date of the first thoracic resection. A P value <.05 was considered to indicate statistical significance.

RESULTS

Patients

Over the study period, 89 patients underwent intrathoracic resection of residual post-chemotherapy intrathoracic masses. All the patients were men, and the median age was 29 years (IQR, 23-35 years). There were no operative mortalities. Details of our surgical outcomes have been reported elsewhere.[10] Fifty patients (56.2%) were never-smokers (Table 1). The primary tumor was testicular in 84 patients (94.4%) and retroperitoneal in 5 (5.6%). When classified based on International Germ Cell Cancer Collaborative Group (IGCCCG) risk category, 27 patients (30.4%) were considered good risk, 30 (33.7%) were intermediate risk, 31 (34.8%) were poor risk, and in 1 patient the classification was not available. The pathology of the primary tumor was mixed NSGCT in 60 patients (67.4%) and variable in the remaining patients (Table 1). Seventy-six patients (86%) received chemotherapy with cisplatin-etoposide and bleomycin, 8 (9.0%) received VIP, 2 (2.2%) received etoposide-cisplatin, and 2 (2.2%) received no chemotherapy owing to early low-volume recurrence and normal STM levels. In 1 patient (1.1%), details of chemotherapy were not available, because the patient had been treated at an outside center 10 years before presenting with thoracic metastases.

Nineteen patients (21.3%) had a malignant tumor at the time of first thoracic resection (group 1, OR1), and 70 patients (78.7%) had benign disease at the time of first thoracic surgery (group 2, OR1). Compared with group 2, patients in group 1 were significantly older (median age, 32 years vs 28 years; $P = .01$), had a significantly longer interval between primary diagnosis and first thoracic surgery (median, 2.0 years [IQR, 1.0-13.5 years] vs 1.0 years [IQR, 0.0-1.0 years]; $P < .0001$), and were significantly more likely to undergo sequential retroperitoneal lymph node dissection (RPLND) rather than combined surgery (73.7% vs 21.5%; $P < .0001$). Moreover, patients in group 1 had a significantly higher rate of elevated STM levels before OR1 (52.6% vs 20.0%; $P = .04$). Among the patients with elevated STM levels in each group, those in group 1 had significantly higher levels of βHCG compared with those in group 2 (Table 2). There were no significant between-group differences in the site of origin of the primary tumor, initial IGCCCG risk classification, site of first thoracic resection, or total number of thoracic resections (Table 2).

TABLE 1. Characteristics of the entire cohort (N = 89)

Characteristic	Value
Male sex, n (%)	89 (100)
Age, y, median (IQR)	29 (23-35)
Smoking history, n (%)	
No	50 (56.2)
Yes	26 (29.2)
Ex-smoker	13 (14.6)
Site of origin of primary, n (%)	
Testis	84 (94.4)
Extragonadal (retroperitoneal)	5 (5.6)
Pathology of primary, n (%)	
Mixed NSGCT	61 (68.5)
Not determined (neoadjuvant chemotherapy)	10 (11.2)
Embryonal	7 (7.9)
Seminoma	3 (3.4)
Immature teratoma	3 (3.4)
Choriocarcinoma	2 (2.3)
Yolk sac	1 (1.1)
Yolk sac and high-grade rhabdomyosarcoma	1 (1.1)
Teratoma and PNET	1 (1.1)
Initial IGCCCG risk, n (%)	
Good	27 (30.4)
Intermediate	30 (33.7)
Poor	31 (34.8)
Not available	1 (1.1)
Bleomycin chemotherapy, n (%)	76 (86)

IQR, Interquartile range; *NSGCT*, nonseminomatous germ cell tumor; *PNET*, primitive neuroectodermal tumor; *IGCCCG*, International Germ Cell Cancer Collaborative Group.

Tumor Histology

The histologies of malignancies resected at OR1 in group 1 included somatic transformation in 8 cases (42.1%), choriocarcinoma in 5 (26.3%), embryonal carcinoma in 3 (15.8%), and yolk sac tumor in 3 (15.8%). The median time between first diagnosis and thoracic surgery was

TABLE 2. Characteristics of groups 1 and 2

Characteristic	Group 1 (N = 19)	Group 2 (N = 70)	*P* value
Age, y, median (IQR)	32 (26-41)	28 (22-34)	.01
Site of origin of primary, n (%)			.93
Testis	18 (94.7)	66 (94.3)	
Retroperitoneal	1 (5.3)	4 (5.7)	
Time from diagnosis to surgery, y, median (IQR)	2.0 (1.0-13.5)	1.0 (0.0-1.0)	<.0001
Elevated serum tumor markers, n (%)			.04
Yes	9 (52.6)	14 (20.0)	
No	10 (47.4)	54 (77.1)	
Not available	0	2 (2.9)	
Elevated preoperative serum tumor markers, median (IQR)			
βHCG, IU/L	41.0 (2.0-296.0)	1.5 (1.0-3.75)	<.0001
AFP, ug/L	5.0 (3.0-16.0)	7.0 (6.0-37.5)	
LDH, U/L	183 (172-184)	195 (158-216)	
Initial IGCCCG risk, n (%)			
Good	3 (15.8)	24 (34.3)	.24
Intermediate	7 (36.8)	23 (32.9)	
Poor	9 (47.4)	22 (31.4)	
Not available	0	1 (1.4)	
Site of resection			.32
One lung	9 (47.4)	28 (40.0)	
Bilateral lung	3 (15.8)	5 (7.2)	
Mediastinum	3 (15.8)	25 (35.7)	
Lung and mediastinum	4 (21.0)	12 (17.1)	
Total number of thoracic resections, n (%)			.16
1	11 (57.9)	52 (74.3)	
2	7 (36.8)	11 (15.7)	
3	0	5 (7.1)	
4	0	2 (2.9)	
8	1 (5.3)	0	
RPLND, n (%)			<.0001
Simultaneous	1 (5.3)	33 (47.1)	
Sequential	14 (73.7)	15 (21.5)	
None	4 (21.0)	22 (31.4)	

IQR, Interquartile range; *βHCG*, beta-human chorionic gonadotrophin; *AFP*, alpha-fetoprotein; *LDH*, lactate dehydrogenase; *IGCCCG*, International Germ Cell Cancer Collaborative Group; *RPLND*, retroperitoneal lymph node dissection.

7.5 years for patients with somatic transformation and 2.0 years for patients with active germ cell malignancy, although this difference was not statistically significant ($P = .24$). The rate of somatic transformation was significantly higher in the patients with normal STM levels before surgery (7 of 10 [70.0%] vs 1 of 9 [11.0%]; $P = .02$). Four of the 10 patients (40.0%) with normal STM levels had viable germ cell malignancy present, 1 of whom also had somatic transformation. Two of the 10 patients with normal STM levels had been treated with second-line chemotherapy before surgery, and thus normalized their STM levels after systemic treatment. The 9 patients with elevated STM levels all had viable germ cell malignancy present, and 6 of the 9 patients (66.7%) had rising STM levels at the time of surgery (Figure 1). Seven of the 9 patients with elevated STM levels had been treated with second-line chemotherapy before surgery. In this group, 4 of the 5 patients who had choriocarcinoma resected underwent high-dose chemotherapy and stem cell transplant before surgery. The 2 patients who did not receive second-line chemotherapy had slightly elevated markers (AFP, 16 μg/L; βHCG, 20 IU/L).

The histology of benign disease resected at OR 1 in group 2 included teratoma in 46 cases (65.7%), necrosis in 16 cases (22.9%), nonspecific benign lesions in 6 cases (8.6%), and immature teratoma in 2 cases (2.8%). The histology of the nonspecific benign lesions included fibrosis in 2 cases and granuloma, focal organizing pneumonia, xanthoma and normal lymph nodes, and sarcoidosis in 1 case each. Among 14 patients (20.0%) with elevated STM levels at OR1, 10 underwent simultaneous RPLND, with concordant chest and RPLND pathology in 8 (teratoma in both sites) and discordant pathology in 2 (sarcoidosis in chest and necrosis in RPLND; teratoma in chest and yolk sac tumor in RPLND). Of the remaining 4 patients with elevated STM levels at OR1, 3 did not have RPLND at any point (1 necrosis, 2 teratoma) and 1 had sequential RPLND (teratoma resected from both surgeries) (Figure 1). Of these 14 patients, 9 had only mild elevation of 1 marker at the time of surgery (AFP <10 μg/L in 6 patients and βHCG <10 IU/L in 3 patients). Three of the 14 patients with persistently elevated STM levels had been treated with second-line chemotherapy before surgery. Five of the 56 patients with normal STM levels had been treated with second-line chemotherapy before surgery, and thus normalized their STM levels after systemic treatment.

Eight patients in group 1 (42.1%) had more than 1 thoracic resection, including 2 surgeries in 7 patients (36.8% of group 1) and 8 surgeries in 1 patient (5.3% of group 1). Details of the pathology from the additional resections are shown in Table 3. Eighteen patients in group 2 (25.7%) had more than 1 thoracic resection, including 2 surgeries in 11 patients (15.7% of group 2), 3 surgeries in 5 patients (7.1%), and 4 surgeries in 2 patients (2.9%). Of the patients in group 2 who had multiple thoracic resections, 3 had malignancy resected at future surgeries (Figure 2). Nineteen patients in group 2 had no neoplastic disease at OR1 (ie, only necrosis or benign disease), but 3

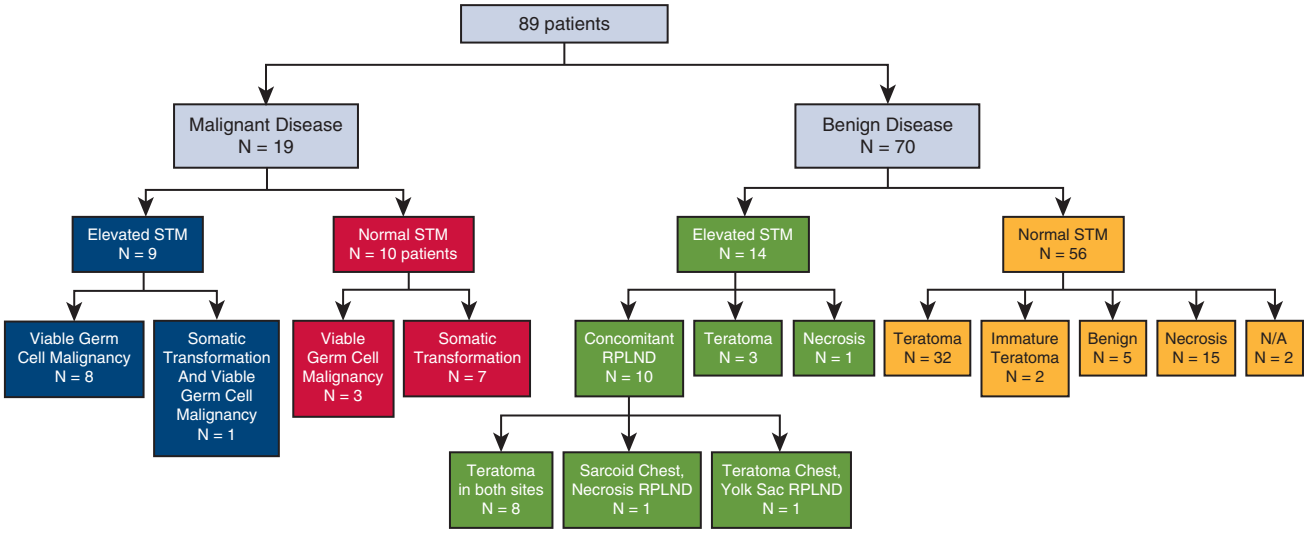

FIGURE 1. Pathology of patients with residual intrathoracic disease post-chemotherapy. *STM*, Serum tumor marker.

of these patients went on to have resection of disease (1 malignant, 2 teratomas) at OR2.

A total of 3 patients in group 1 and 11 patients in group 2 had bilateral lung resections at OR1. None (0%) of the 3 patients in group 1 had concordant pathology between lungs. In group 2, 10 of the 11 patients (90.1%) had concordant pathology, including 7 with bilateral teratomas and 3 with bilateral necrosis (Figure 3, *A*). The discordant pathology resected in groups 1 and 2 is shown in Table E1.

A total of 4 patients in group 1 and 11 patients in group 2 had lung and mediastinal resections at OR1. Two of these patients (50%) in group 1 had concordant pathology between the lung and mediastinum (1 with embryonal carcinoma, 1 with spindle cell neoplasm) (Figure 3, *B*). In group 2, 8 of the 11 patients (72.7%) had concordant pathology (6 teratoma, 1 necrosis, 1 benign). The discordant pathology resected in groups 1 and 2 is shown in Table E1.

Only 1 patient (5.3%) in group 1 had simultaneous thoracic resection and RPLND, and the pathology was concordant between both sites (choriocarcinoma in mediastinum and RPLND). Fourteen patients (73.7%) in group 1 had sequential thoracic resection and RPLND, of whom 3 (21.4%) had concordant pathology between the chest and RPLND (embryonal carcinoma, transformed adenocarcinoma, yolk sac tumor). The remaining 11 patients (78.6%) had discordant pathology between the chest and RPLND, of whom only 2 patients had malignant disease in the retroperitoneum (Table E2). There was no significant difference in the interval between RPLND and thoracic resection for patients with concordant pathology (median,

TABLE 3. Group 1 (malignant disease at OR1) pathological results of all thoracic resections

Patient	OR1	OR2	OR3	OR 4 and 5	OR 6 and 7	OR 8
1	Right lung, choriocarcinoma	Left lung, necrosis				
2	Mediastinum, synovial sarcoma	Pleura and right lung, immature teratoma				
3	Left lung, embryonal carcinoma	Right lung, teratoma	Pleura, PNET	Mediastinum, PNET	Left lung, PNET	Mediastinum, PNET
4	Right lung, choriocarcinoma	Left lung, choriocarcinoma				
5	Left lung, somatic transformation	Right lung, teratoma				
6	Left lung, yolk sac	Bilateral lungs, teratoma				
7	Left lung, choriocarcinoma	Lymph nodes, teratoma				
8	Right lung, embryonal carcinoma	Right lung, choriocarcinoma				

OR, Thoracic resection; *PNET*, primitive neuroectodermal tumor.

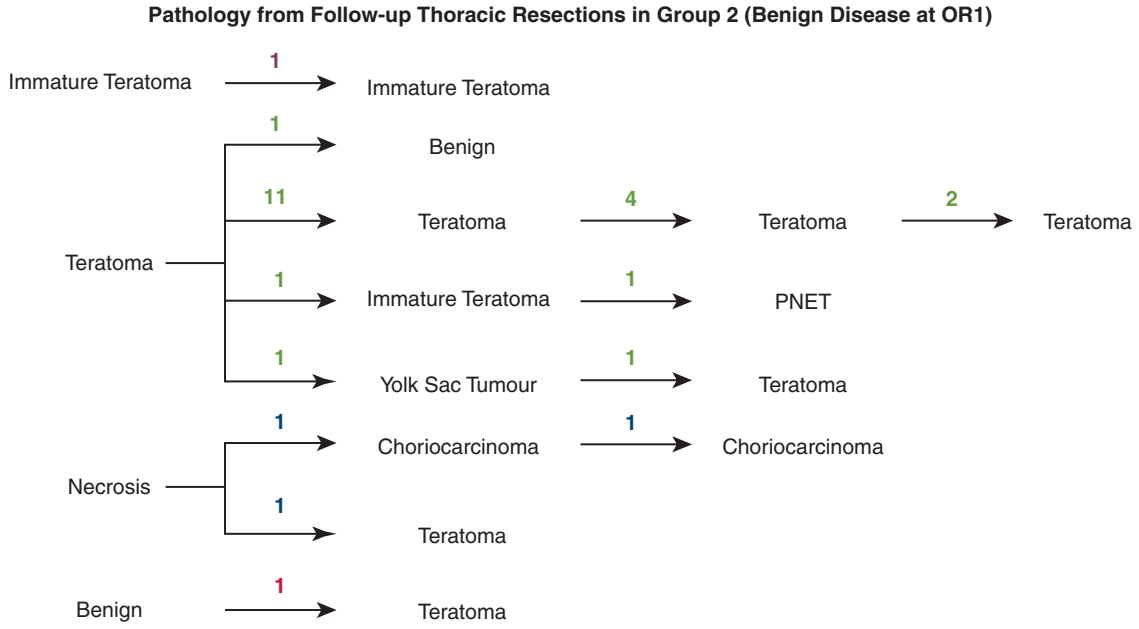

FIGURE 2. Pathology of all patients who had benign disease at first surgery (group 2) and underwent more than 1 thoracic resection. *OR1*, First thoracic resection; *PNET*, primitive neuroectodermal tumor.

23.5 months; IQR, 4.1-72.5 months) and discordant pathology (median, 30.3 months; IQR, 2.6-160.5 months; $P = .64$).

Thirty-three patients (47.1%) in group 2 had simultaneous thoracic resection and RPLND. The pathology was concordant in 27 of these 33 patients (81.8%) and discordant in 6 patients (28.2%). Two patients with discordant pathology had benign disease in the chest and malignancy in the RPLND (Table 4). Fifteen patients (21.5%) in group 2 had sequential thoracic resection and RPLND. The pathology was concordant in 12 of these 15 patients (80%) and discordant in 3 patients (20%) (Table 4). There was no significant difference in the interval between RPLND and thoracic resection between patients with concordant pathology and those with discordant pathology (median, 168.5 months [IQR, 127.2-207.7 months] vs 99.0 months [IQR, 64.5-213.0 months]; $P = .77$).

The overall pathologic concordance rate for all patients who had thoracic resection and RPLND was 68.3% (43 of 63 patients). There was a significant difference in the pathologic concordance between thoracic resection and RPLND in group 1 (4 of 15 patients; 26.7%) and group 2 (39 of 48 patients; 81.3%; $P = .0002$). In examining patients who had lung resections, pathologic concordance with RPLND was 18.8% (3 of 16) in group 1 and 39.2% (11 of 28) in Group 2. Only 2 patients with concordance between lung and RPLND had necrosis/fibrosis in both sites.

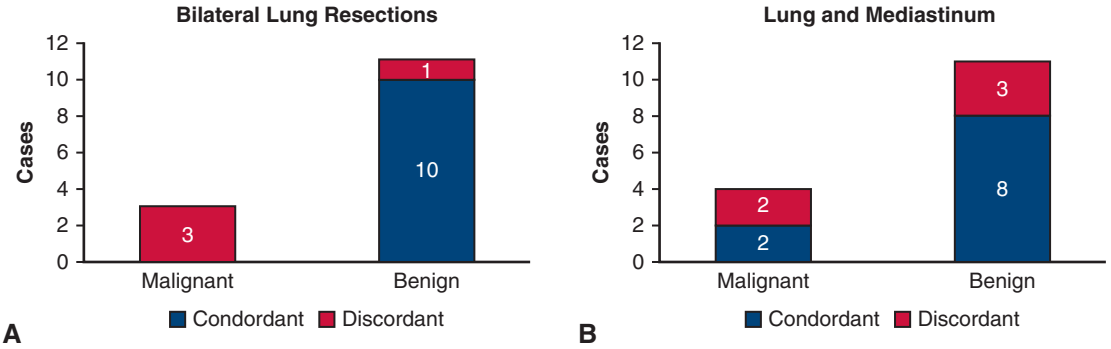

FIGURE 3. A, Pathological concordance between lungs for patients in group 1 (malignant disease at first thoracic resection) and group 2 (benign disease at first thoracic resection). B, Pathological concordance between lung and mediastinum for patients in group 1 and group 2.

TABLE 4. Group 2 (benign disease at OR1) and RPLND pathology

Type	Concordant		Discordant	
	Chest and RPLND pathology		Chest pathology	RPLND pathology
Simultaneous (n = 33)	Teratoma	22		
	Necrosis	3		
	Benign	2		
			Necrosis	Teratoma
			Necrosis	Teratoma
			Necrosis	Teratoma
			Teratoma	Necrosis
			Sarcoid	Yolk sac
			Necrosis	Yolk sac
Sequential (n = 15)	Teratoma	9		
	Necrosis	3		
			Teratoma	Immature teratoma
			Granuloma and focal organizing pneumonia	Teratoma
			Teratoma	Necrosis

RPLND, Retroperitoneal lymph node dissection.

Survival

There was no significant between-group difference in the duration of follow-up (group 1: median, 58.1 months [IQR, 23.1-89.2 months]; group 2: median, 25.9 months [IQR, 13.0-75.1 months]; $P = .18$). Overall survival at 10 years was significantly worse for group 1 compared with group 2 (68.4% [13 of 19] vs 92.9% [65 of 70]; $P = .03$) (Figure 4, *A*). A significant difference in overall survival was seen when comparing patients with elevated and normal STM in groups 1 and 2 (Figure 4, *B*). Interestingly, although not significantly different, patients classified as good initial risk by the IGCCCG criteria showed a trend toward worse 10-year survival (good, 70.7%; intermediate, 87.0%; poor, 84.5%; $P = .48$). Survival was poorest in patients with malignant disease and normal STM levels and best in patients with benign disease and normal STM levels. Patients with malignant disease and elevated STM levels, as well as patients with benign disease and elevated STM levels, had excellent survival, reaching 75.0% and 83.3%, respectively, at 10 years. There was no significant difference in overall survival for patients in group 1 when comparing viable germ cell tumor and transformed malignancy (Figure 4, *C*) and for patients in group 2 when comparing immature and mature teratoma and necrosis (Figure 4, *D*).

DISCUSSION

Intrathoracic NSGCT metastases represent a very diverse group of lesions that require individualized management in the context of a broader goal of cure. These men are all young, with a mean age of 29 years in our series, and although most patients have a testis primary tumor, a small proportion present with metastatic disease from an extragonadal (retroperitoneal) primary tumor. It is well established that resection of residual intrathoracic metastases postchemotherapy has a survival benefit and should be part of the treatment algorithm for all patients with persistent residual chest tumors after chemotherapy.[13] Patients often present with multiple sites of disease, as shown in our series of 89 patients, with disease present in 1 lung in 37 patients (41.6%), bilateral lungs in 8 patients (9.0%), mediastinum in 28 patients (31.4%), and both lung and mediastinum in 16 patients (18.0%). The histology of resected intrathoracic disease has been shown to have a significant impact on survival, with worse outcomes for patients with residual viable malignancy.[4,5,14-19]

The rationale for resecting residual disease postchemotherapy in patients with normal STM levels concerns the risk that these lesions may be teratomas. Although by definition teratomas are benign, it has been well documented that these lesions have the potential to degenerate and transform into other types of somatic malignancies when left in situ.[20] This transformation can occur many years after chemotherapy and present a persistent risk in these young patients who otherwise will have excellent long-term survival. Thus, although teratomas do not pose an immediate risk to life, over many years they have the potential to grow and transform into often aggressive, noncurable malignancies.[21] Current imaging techniques are unable to differentiate between necrosis and teratoma; thus, surgery is required for diagnostic purposes in all patients

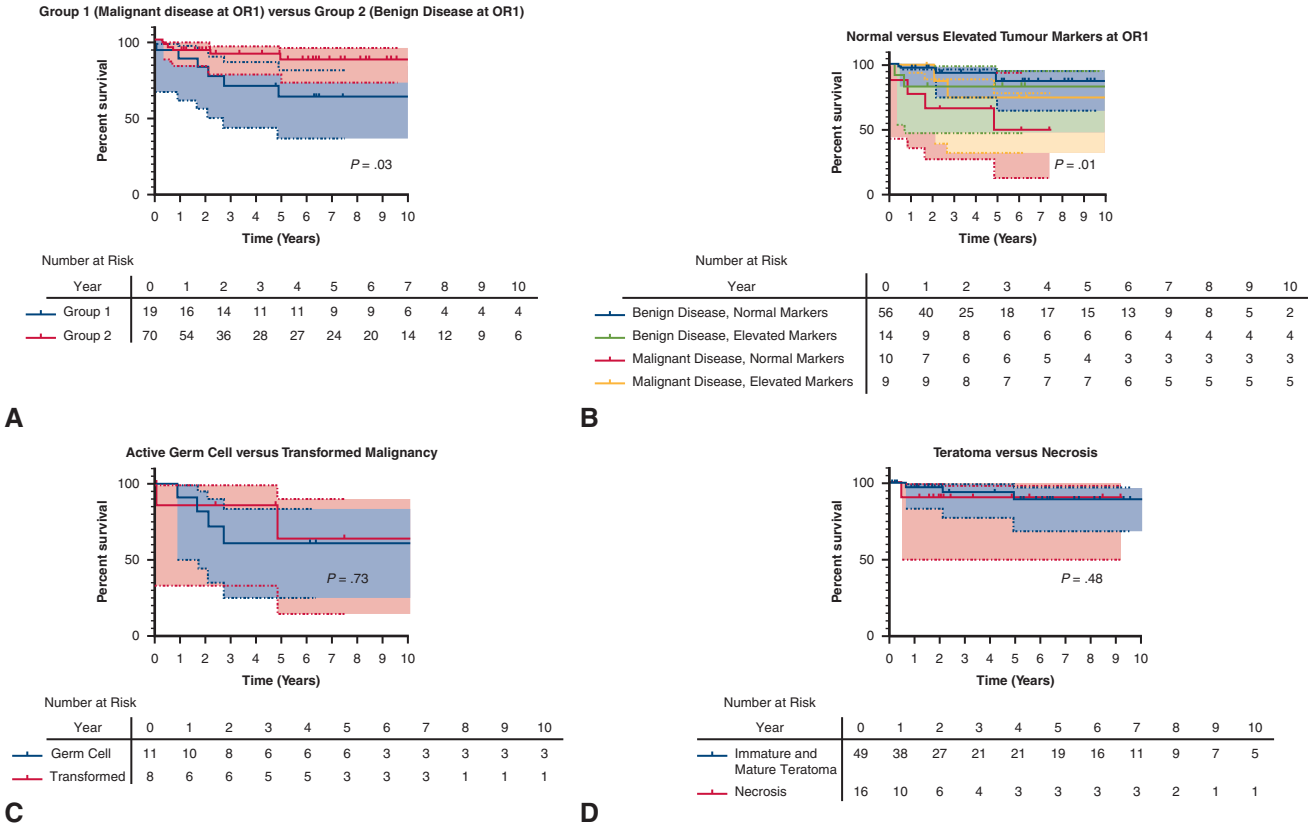

FIGURE 4. A, Overall survival for patients in group 1 (malignant disease at first thoracic resection) and group 2 (benign disease at first thoracic resection). B, Overall survival for group 1 and group 2 based on preoperative serum tumor markers. C, Overall survival for patients in group 1 based on the malignant pathology (viable germ cell vs somatic transformation). D, Overall survival for patients in group 2 based on the benign pathology (teratoma vs necrosis). *OR1*, First thoracic resection.

with residual tumors.[22] Reliably predicting disease in one site based on the histology of previously resected disease from another site could save patients with only necrosis in residual lesions (reportedly 15%-71% of cases) from unnecessary surgery.[5,15,16,23-25] Patients who underwent bilateral lung resections in our series had no concordance between the right and left lungs in group 1 and 91% concordance in group 2. Patients who underwent lung and mediastinal resections had a concordance rate of 50% in group 1 and 73% in group 2. Rates reported in the literature for concordance between intrathoracic sites range from 80% to 95% for bilateral lungs and from 67% to 72% for lung and mediastinum, although these series do not differentiate based on resection of malignant and benign disease.[15,26] In a series reported by Besse and colleagues,[26] 19 of 20 patients (95%) with necrosis in one lung had necrosis in the contralateral lung, leading to a recommendation to perform staged pulmonary resections, with watchful waiting for the contralateral lung in patients with necrosis resected from the first lung. In our series, we found that 2 patients had benign disease in one lung (1 teratoma and 1 necrosis) and malignant disease contralaterally, and both patients had elevated STM levels. Thus, although necrosis in one lung has been shown to often predict necrosis contralaterally, we found that it does not rule out the possibility of a contralateral malignancy, and that STM levels can be helpful in choosing between sequential and staged pulmonary resection.

Rates of concordance between thoracic and RPLND specimens range from 25% to 83%, with higher overall concordance for RPLND and mediastinum.[5,24-28] Concordance rates are higher for patients who have simultaneous RPLND compared with those with staged RPLND (72% vs 43%).[17] Concordance rates also differ based on the RPLND pathology, with higher rates for patients with necrosis in the retroperitoneum.[29] For patients with necrosis only in the RPLND specimen, one series showed an 89% probability of necrosis in the lung and found that 56% of patients with necrosis in the lung would be spared thoracotomy if the patient had no teratoma in the primary tumor and RPLND was performed first.[23] In our series, only 2 patients had necrosis/fibrosis in the lung and RPLND; thus, the minority

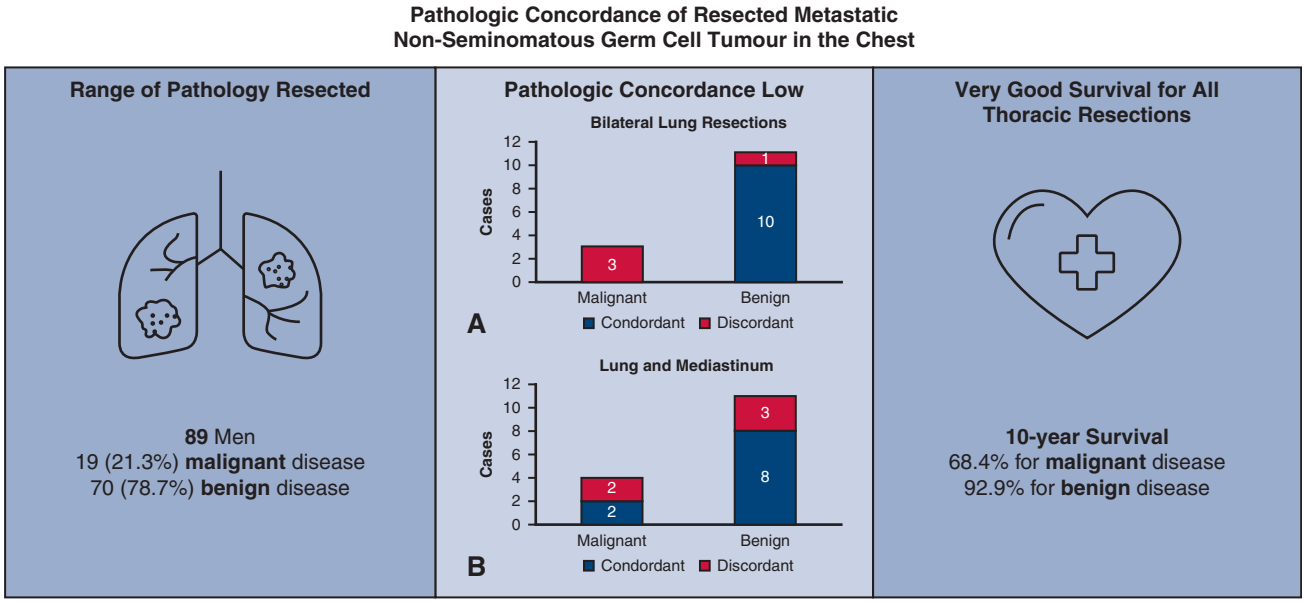

FIGURE 5. Men with intrathoracic metastases from nonseminomatous germ cell tumors have a range of pathology from malignant to benign disease and often present with disease at multiple sites. Pathological concordance is better between lung than between lung and mediastinum but still remains low. All patients should be considered for aggressive surgical resection owing to the good long-term survival even in patients with active malignancy.

of our patients would have been saved a thoracic resection had this paradigm been followed.

Elevated STM levels may predict worse outcomes after resection of intrathoracic disease, although some previous studies have shown no correlation.[4,15,18] In comparing the 2 groups in our series, as expected, group 1 (malignant disease) had a significantly higher rate of elevated STM levels before thoracic resection compared with group 2 (benign disease). Nine patients (52.6%) in group 1 had normal STM levels despite having viable malignancy owing to a higher rate of somatic transformation; therefore, normal STM levels should not be considered reassuring in patients with concerning findings on imaging. It is noteworthy that 14 patients (20.0%) in group 2 had elevated STM levels before surgery despite having benign disease, although their STM levels were significantly lower than those seen in group 1. Among these 14 patients, 10 had simultaneous RPLND with teratoma resected from the chest and retroperitoneum in 9 cases, and only 1 had viable malignancy resected from the RPLND. Thus, mildly elevated STM levels can originate from teratoma and be associated with excellent prognosis.

There was a significant difference in overall survival between group 1 and group 2 when stratified by STM level (normal vs elevated). The worst survival was observed in patients with malignant disease and normal STM, likely because most of these patients had somatic transformation. Although the difference was not statistically significant, patients with somatic transformation had a longer median interval between first diagnosis and thoracic resection, which highlights the importance of continuing long-term follow-up for these patients. It also may suggest a delay in diagnosis of disease recurrence; thus, surgeons must have a high index of suspicion for recurrent disease in patients who present with late intrathoracic tumors. In group 1, survival was not significantly different between patients with normal and elevated STM levels, possibly because 3 of the 10 patients with normal STM levels had only viable germ cell malignancy and no somatic transformation. The survival of patients with malignant disease and elevated STM remained very good, reaching 75.0% at 10 years even though 6 of the 9 patients had rising STM levels at the time of surgery, confirming the value of salvage surgery in these patients.[30] In a review of 134 patients who underwent resection of malignant disease, Kesler and colleagues[19] found that patients with non–germ cell cancer had a trend toward worse overall survival compared with those with residual NSGCT resected, emphasizing that somatic transformation carries the worst survival, and that aggressive resection of residual teratoma is warranted to prevent this phenomenon.

As outlined above, 3 patients in group 2 who initially had no neoplastic disease at OR1 went on to undergo resection of disease at future surgeries, 1 of whom had malignancy resected. Thus, it is imperative that these patients be followed closely and considered for future resection in the setting of intrathoracic recurrence and not be reassured by the presence of necrosis at the first operation.

Our study has several limitations, including the retrospective nature of the data collection and its single-center design. We did not include information about adjuvant

chemotherapy use or disease-free survival, which may impact the decision to proceed with salvage surgery. The analysis is limited by small numbers of patients, because the disease is so rare. Finally, our center is a referral center for NSGCT, and thus our findings might not be generalizable to other settings.

CONCLUSIONS

Patients with intrathoracic metastases from NSGCT have complex disease requiring thoughtful individualized treatment plans. Intrathoracic pathologic concordance is better for patients with benign disease resected at their first thoracic surgery and better between lungs than between lung and mediastinum. A contralateral lung malignancy cannot be ruled out by the presence of benign disease in one lung; thus, measurement of preoperative STM levels is crucial when planning for sequential versus staged pulmonary resection. Although survival is worse in patients with malignant disease, the 10-year survival remains very good, particularly in patients undergoing salvage surgery (Figure 5). Thus, all patients with intrathoracic NSGCT metastases should be considered for aggressive surgical resection with curative intent at experienced centers.

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: https://aats.blob.core.windows.net/media/20AM/Presentations/Pathologic%20Concordance%20of%20Resected%20M.mp4.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: nonseminomatous germ cell tumor, thoracic metastases, lung metastases, surgery, pathologic concordance

Discussion

Presenter: Dr Laura L. Donahoe

Dr Kenneth A. Kesler *(Indianapolis, Ind)*. Dr Donahoe and her colleagues are to be congratulated on an excellent study. Their study gives us important messages that can't be understated. These are otherwise young and healthy patients with overall very good prognoses provided that the correct treatment strategies are taken, which typically include aggressive surgery after cisplatin-based chemotherapy to remove residual disease. Additionally, disseminated germ cell tumor patients need careful long-term follow-up, including serial CT scans and serum tumor markers with removal of recurrent disease, when appropriate, to maintain optimal outcomes.

There are a few items I would to discuss. First is the management of patients with elevated serum tumor markers after first-line cisplatin-based chemotherapy. Germ cell tumors that originate in the mediastinum have very poor response to second-line chemotherapy, but metastatic germ cell tumors from the testes to the lung or mediastinum with elevated markers after first-line chemotherapy have a 50% success rate of normalizing serum markers with second-line chemotherapy. Only approximately 20% of testicular cancer patients will have elevated serum markers after first-line chemotherapy, so half of these patients (or 10% of overall cases) will resolve viable germ cell cancer with second-line chemotherapy, which can significantly improve expected survival from the malignant curve up to the benign curve, as you nicely demonstrated. Accordingly, second-line chemotherapy can be very beneficial in select cases.

Fourteen patients in your series had pathologic evidence of viable germ cell cancer in the lung or mediastinum. I suspect that most of these patients presented to surgery with elevated serum tumor markers. Do you take patients with elevated serum tumor markers after first-line chemotherapy directly to surgery or do you offer second-line chemotherapy? If you do offer second-line chemotherapy, what is your regimen of choice, as there are a few options?

Dr Laura L. Donahoe *(Toronto, Ontario, Canada)*. Thank you very much for the question. For context, at our center, I work very closely with our medical oncologists and our urologist—myself and one of my partners. I do most of the germ cell surgery, and we have a multidisciplinary clinic with 2 oncologists and a urologist. In general, patients receive second-line chemotherapy if they have positive markers, but the benefit of our close working group is that we really discuss a lot of cases and take it on a case-by-case basis. So if somebody has mildly elevated tumor markers after first-line chemotherapy and, for instance, only a single site of intrathoracic disease, then that would be somebody who we would consider going to surgery rather than putting them through second-line chemotherapy.

But you know, we really discuss each patient—unless they have a very obvious high burden of disease. Protocol-wise, we use 2 cycles of TIP, and then high-dose carboplatin and etoposide, with autologous stem cell support for two cycles.

Dr Kesler. We also subscribe to your strategy of offering surgery to patients with intrathoracic disease and low-level serum tumor marker elevation. Many of these patients will normalize serum tumor markers after surgery even with "benign" teratoma pathology, and second-line chemotherapy can then be reserved for cases of persistent or recurrent marker elevation postoperatively.

Along these lines, I would like to know your specific surgical approach to patients with anticipated malignant disease, such as patients with chemorefractory or late relapse germ cell cancer and malignant (somatic) transformation into non–germ cell cancer. Our institution reported outcomes of this patient subset and found that resecting 4 or more areas of malignant disease had significantly worse

survival outcomes than resecting 1 area. We are therefore reluctant to offer surgery in cases where there are numerous areas of malignancy. While PET is typically not helpful for management of germ cell tumors, we have found PET useful to determine the location/number of malignant areas which in turn helps decide operability. Did you look at the number of malignant areas removed versus survival, or do you have a rough cutoff with respect to the number of malignant areas present and patient operability?

Dr Donahoe. Thank you. We have all of that data and the numbers look very nice—the simple resections from each case. But I would say that in each of these surgeries, I just looked at the worst pathology, but we resect multiple other lesions. So even though the worst pathology may have been malignancy, you're right, the question is how many sites and how many other locations they had resected at the same surgery.

We do have that data and will look at that for certain, because it will be interesting to look at the survival difference between number of sites resected with malignant disease. In terms of a cutoff number, I would say that we don't have an absolute cutoff; it's taken on a case-by-case basis. We are quite aggressive (and our oncologists are quite aggressive) with referring for surgery. Especially in a patient with salvage, we would resect if we can resect, provided that the patient can tolerate it. Even if it seems like a really large number of sites, if there really are no other options, we may try resecting. We have used PET scans in those cases to help differentiate, which we found very helpful. So again, if a patient has a large number of sites, there is no specific cutoff, but we would exhaust all systemic therapy options before proceeding to resection. But again, if it's a small number, we would be more willing to resect earlier.

Dr Kesler. Finally, I would like to discuss the role of contralateral pulmonary metastasectomy in the face of unilateral pulmonary metastasectomy pathologically demonstrating tumor necrosis only. I agree with your premise that it is an imprecise science to predict pathology in the lung and the mediastinum after chemotherapy. We can get some strong clues, however—for example, in patients with significantly elevated serum tumor markers is predictive of viable germ cell cancer. Patients with malignant (somatic) transformation (non–germ cell cancers) are a little trickier, as they are typically serum tumor marker–negative, but most of these patients will pathologically demonstrate non–germ cell cancer in orchiectomy or retroperitoneal surgical specimens. When patients have these factors suggestive of possible malignancy, we agree that an aggressive bilateral pulmonary metastasectomy approach is typically appropriate.

But in the usual scenario of patients who normalize their serum tumor markers after first-line chemotherapy, with no evidence of non–germ cell cancer in the orchiectomy or retroperitoneal surgical specimens, we do try to avoid the costs and morbidity of performing pulmonary metastasectomy for tumor necrosis only. Your data and other reports referenced in your manuscript have shown excellent—over 90%—pathologic concordance with tumor necrosis only identified in residual bilateral lung abnormalities. In the usual scenario, we typically perform unilateral metastasectomy in the lung most involved to minimize sampling error, and if pathology shows complete tumor necrosis, feel comfortable observing the contralateral lung. These patients will be carefully observed anyway with serial CT scans and serum tumor markers.

How do you do perform bilateral pulmonary metastasectomies? Do you operate on both lungs under the same anesthetic or use a staged approach where you know the pathology of one lung before operating on the other?

Dr Donahoe. Thank you. For the patients who have normal tumor markers and whom we can fairly confident that they do not have active malignancy, for most patients, we would do a staged approach. We have looked at our data in terms of simultaneous resection with doing retroperitoneum at the same time as doing the chest resection, but in general, for the lung, if they just have lung disease, we usually do a staged approach.

But we do have a number of patients who actually come from out of province, and in those patients, we've done them simultaneously just because of the logistics of having them travel a great distance for surgery. Of our patients, we have 3 who had bilateral lung resections with necrosis, and at least 1 of those was an out-of-province patient, so we wanted to facilitate that. We tend to do a staged approach, but again it's on a case-by-case basis.

Dr Kesler. Going back to the typical scenario, I don't see where your data conclusively demonstrate that observing the contralateral lung after unilateral pulmonary metastatectomy pathologically demonstrates tumor necrosis only adversely affects survival. I would like your thoughts on this, however. Again, congratulations on an excellent study.

Dr Donahoe. Thank you very much. I think we just want to alert people to the idea that every patient with metastatic disease in the chest should be considered for aggressive surgery. We had very few patients who had benign disease in one side and malignant disease on the other side. And in the patient who developed malignant disease afterward, it was a single nodule that grew a couple of months after his first surgery.

We want to raise the point that in all patients, it's not necessarily the same thing; even if patients had necrosis in the first instance, if they have a new growing nodule, you need to be aware that they need close follow-up and aggressive treatment. But as we discussed, in these patients who have residual disease bilaterally and normal tumor markers, I think we would also agree that we'd feel confident doing a staged approach, starting with one side (the worst side, as you mentioned). If it's just necrosis, then

we do close follow-up and resect if the nodules are growing. Thank you very much.

Dr Kesler. Thank you.

Dr Shanda H. Blackmon *(Rochester, Minn)*. Have you considered the role of circulating tumor cells or cell-free DNA in this population, especially when their tumor markers go down?

Dr Donahoe. We don't have any studies on that ongoing at this time, but that is a really interesting question.

Dr Blackmon. I think that's a great area for future exploration, especially for germ cell tumors. Of course, you might still want to resect remaining teratomas, but knowing if there was residual tumor might guide further chemotherapy.

Dr James D. Luketich *(Pittsburgh, Pa)*. I have a question regarding your follow-up. Is it primarily marker-driven? Every *x* number of months? Are they always getting CAT scans and PET scans in addition? Or do you wait for that marker first?

Dr Donahoe. For chest disease, we tend to follow up with CT scans for the first year or so, but in general it is marker-driven follow-up. We don't do any PET scans—again, we only use this in a select few patients preoperatively if we have extensive disease, and it's salvage just to see which lesions are more active. But even in follow-up, we don't do PET scans for these patients, and usually it's just a marker-driven.

Dr Luketich. I think outside of really busy centers like yours and Ken's, there's a lot of PET scanning that can be done at times. It can be confusing. Do you have any data about the role of PET scan and its limited role? And maybe it shouldn't be used at all; as you mentioned, you use it rarely. I think it probably gets used more frequently than it's needed elsewhere. Any general comments about how you're using it?

Dr Donahoe. I agree; we don't use it. It's not part of our workup at all. I've been involved for 4 years now, and I've done about half the patients we reported and I used it once, and that was actually not a patient in this series, and he was very salvage, with very widespread disease.

Dr Luketich. That was a very nice presentation, Dr Donahoe. Thank you, Dr Kesler, for your comments.

TABLE E1. Discordant pathology

Between lungs	Right	Left
Malignant discordant		
1	Fibrosis	Choriocarcinoma
2	Choriocarcinoma	Necrosis
3	Embryonal	Teratoma
Benign discordant		
1	Fibrosis	Teratoma
Between lung and mediastinum	**Lung**	**Mediastinum**
Malignant discordant		
1	Teratoma	Yolk sac, embryonal, PNET
2	Teratoma	PNET
Benign discordant		
1	Teratoma	Necrosis
2	Fibrosis	Necrosis
3	Fibrosis	Teratoma

PNET, Primitive neuroectodermal tumor.

TABLE E2. Group 1, sequential RPLND discordant pathology

Patient	Chest pathology	RPLND pathology
1	Synovial sarcoma	Embryonal carcinoma
2	Embryonal	Teratoma
3	Choriocarcinoma	Necrosis
4	PNET	Teratoma
5	Somatic transformation and choriocarcinoma	Teratoma
6	Carcinoid	Teratoma
7	Yolk sac	Necrosis
8	Choriocarcinoma	Teratoma
9	Yolk sac	Teratoma
10	Spindle cell	Teratoma
11	Somatic transformation	Embryonal carcinoma

RPLND, Retroperitoneal lymph node dissection; *PNET*, primitive neuroectodermal tumor.