GENERAL THORACIC SURGERY

PRIMARY MEDIASTINAL NONSEMINOMATOUS GERM CELL TUMORS: THE INFLUENCE OF POSTCHEMOTHERAPY PATHOLOGY ON LONG-TERM SURVIVAL AFTER SURGERY

Kenneth A. Kesler, MD[a]
Karen M. Rieger, MD[a]
Kristen N. Ganjoo, MD[b]
Matt Sharma, MD[b]
Naomi S. Fineberg, PhD[c]
Lawrence H. Einhorn, MD[b]
John W. Brown, MD[a]

Objectives: The treatment of nonseminomatous germ cell tumors with cis-platin-based chemotherapy followed by aggressive surgical resection of residual disease is one of the most successful models for multimodality cancer therapy. We reviewed the case histories of 91 patients treated at our institution from 1981 to 1998 with primary mediastinal nonsemino-matous germ cell tumors to evaluate variables that may influence survival after surgery. *Methods:* Twelve of the 91 patients did not undergo postchemotherapy resection because of progressive disease. Seventy-nine of them underwent 82 thoracic surgical procedures and are the basis of this review. The majority (71/75) had elevated serum tumor markers, 75% (n = 50) of which returned to normal levels after first- or second-line chemotherapy. *Results:* There were 3 operative deaths and 1 late death, attributed to pulmonary complications. Twenty-four patients died of recurrent disease and 3 of leukemia, for an overall survival of 61% after an average follow-up of 48 months. The pathologic findings of complete tumor necrosis (n = 19) and benign teratoma (n = 28) in the surgical specimen predicted excellent and good long-term survival, respectively, which was statistically better than that of patients having persistent nonseminomatous germ cell tumors (n = 24) or carcinoma-tous/sarcomatous degeneration (n = 8). *Conclusions:* Primary nonsemi-nomatous germ cell tumors of the mediastinum can be cured with a mul-timodality therapy, particularly in the subset of patients with postchemotherapy pathologic findings of tumor necrosis and teratoma. Survival is poor but possible in patients with unfavorable pathologic findings after chemotherapy, currently justifying an aggressive surgical approach in patients with otherwise operable disease. (J Thorac Cardiovasc Surg 1999;118:692-701)

Nonseminomatous germ cell tumors originating in the mediastinum (PMNGCTs) are rare, accounting for only 1% to 3.5% of mediastinal tumors.[1] They represent biologically interesting models for multimodali-

ty cancer therapy. The treatment of nonseminomatous germ cell tumors (NSGCTs), regardless of origin, with cisplatin-based chemotherapy regimens, and in particular cisplatin/etoposide-containing regimens, followed by aggressive surgical resection of residual disease, currently is one of the most successful paradigms of multi-modality cancer therapy.[2] However, although histologically and serologically identical to more common testicular counterparts, PMNGCTs have a distinctly poorer prognosis. Our institution has previously reported a 57% 5-year survival in a select group of 28 patients with PMNGCT after successful first-line chemotherapy and surgery.[3] Other series have reported long-term survivals ranging between 32% and 44%, which are clearly inferior to the 70% to 80% reported survivals in patients

with metastatic NSGCT of testicular origin after multi-modality therapy.[4-6] We retrospectively reviewed our 16-year experience with patients with PMNGCT in an attempt to analyze variables that may predict long-term survival after postchemotherapy resection of residual disease.

Patients and methods

From 1981 to 1998, 92 patients were admitted to Indiana University Hospital with the diagnosis of PMNGCT. The patients included 91 male patients and 1 female patient; however, 12 (13%) of these patients did not undergo post-chemotherapy resection because of progressive disease. Seventy-nine of these patients underwent 82 thoracic surgical procedures and are the basis of this review. All but 1 of the patients undergoing resection were male. Ages ranged between 12 and 46 years (mean 27.9 ± 8.3 years). The vast majority, 96% (71/75), had an elevated serum tumor marker (STM), either alpha-fetoprotein (AFP, 70/74) or beta human chorionic gonadotropin (bHCG, 34/71) (Table I). For most patients, diagnosis is currently confirmed and categorized pathologically by fine needle aspiration biopsy. However, 11 patients had serologic diagnosis only. Three patients who had complete resections before admission were not included in this review. Radiographic evidence of extramediastinal metastatic disease was present in 25% (n = 20) of patients, including lung (n = 11), bone (n = 4), cervical lymph nodes (n = 6), and retroperitoneal lymph nodes (n = 2).

First-line chemotherapy consisted of regimens containing cisplatin/etoposide in 94% (n = 74) of this series, with the other 5 patients receiving regimens containing either cis-platin/vinblastine sulfate (Velban) (n = 3) or cisplatin/other drugs (n = 2). Three patients underwent 2 cycles of cis-platin/etoposide/bleomycin followed by 2 cycles of high-dose carboplatin-based chemotherapy with autologous stem cell rescue after randomization to the experimental arm of the current phase III intergroup trial for high-risk germ cell cancer as first-line therapy. First-line chemotherapy was administered at our institution in 38 patients; the other 41 received first-line chemotherapy at outside hospitals. Second-line chemotherapy was given to 8 patients (10%) who demonstrated either radiographic and/or serologic progressive disease with first-line therapy. Second-line chemotherapy consisted of high-dose carboplatin-based chemotherapy with autologous stem cell rescue in 3 patients, vinblastine sulfate, ifosfamide, and cisplatin in 1, and etoposide, ifosfamide, and cisplatin in 4. All patients received second-line chemotherapy at our institution.

In 51 patients STMs returned to normal limits after first-line chemotherapy; however, a rising STM was noted in 4 of these patients and surgery was deferred until completion of second-line chemotherapy (Table II). STMs subsequently returned to normal limits in 4 of these patients but not in 2 patients who received high-dose carboplatin-based chemo-therapy with autologous stem cell rescue. Of the 28 patients in whom STMs did not return completely to normal limits, 4

Table I. *Patient characteristics*

	No. of patients	*Percent of series*
AFP levels (ng/mL)		
Normal	4	5
21-100	6	8
101-1,000	8	10
101-10,000	34	43
>10,000	22	28
bHCG levels (ng/mL)		
Normal	39	49
2-100	16	20
101-10,000	11	14
1,001-10,000	3	4
>10,000	2	3
Pathology		
Yolk sac	40	51
Embryonal	17	22
Teratoma	23	29
Choriocarcinoma	4	5
Other	7	9
Sarcoma	4	
Carcinoma	2	
Other	1	

Some patients had more than one pathologic diagnosis demonstrated by prechemotherapy biopsy including all patients with teratomatous elements *(teratoma)*. *AFP,* Alpha-fetoprotein; *bHCG,* beta human chorionic gonado-tropin; *PNET,* primitive neuroectodermal tumor.

received second-line chemotherapy. The STM returned to normal limits in 1 patient but not in the other 3, 1 of whom received high-dose carboplatin-based chemotherapy with autologous stem cell rescue. Fifty patients, therefore, had normal STMs at operation and 29 had elevated STMs. It is our current institutional approach to perform resection in patients with PMNGCT who have elevated STMs after first-line chemotherapy if anatomically feasible. The results with second-line chemotherapy in this patient population have been dismal.[7]

Hospital records were reviewed and other variables recorded, which may be predictive of long-term survival, including AFP at diagnosis, before, and immediately after the operation (normal, 21-100, 101-1,000, 101-10,000 and > 10,000 ng/mL), bHCG at diagnosis, before, and immediately after the operation (normal, 2-100, 101-1,000, 1,001-10,000 and > 10,000 ng/mL), and prechemotherapy pathology (yolk sac, embryonal, teratoma, choriocarcinoma, and other pathology [sarcoma, carcinoma, and primitive neuroectodermal carci-noma], Table I).

Seventy-seven of these patients underwent thoracic surgery for removal of residual disease at our institution, and 2 under-went surgery elsewhere after successful first-line chemothera-py at Indiana University Hospital. Thoracic surgery was typi-cally delayed for 4 weeks after chemotherapy, which allowed the patient and, in particular, the bone marrow to recover. Surgery for PMNGCT is technically demanding because pre-operative chemotherapy often renders surrounding mediasti-

Table II. *Chemotherapy treatment and STM elevation as compared with pathologic category of residual disease*

STM after initial CTx	2nd-line CTx	STM after 2nd-line CTx	Residual mass pathology
Normal (n = 51)	No (n = 47)	N/A	Necrosis (n = 10)
			Teratoma (n = 2)
			NSGCT (n = 9)
			Carcinoma/sarcoma (n = 7)
	Yes (n = 4)	Normal (n = 2)	Necrosis and teratoma
		Elevated (n = 2)[*]	NSGCT (n = 2)
Elevated (n = 28)	No (n = 24)	N/A	Necrosis (n = 7)
			Teratoma (n = 6)
			NSGCT (n = 10)
			Sarcoma (n = 1)
	Yes (n = 4)	Normal (n = 1)	Necrosis (n = 1)
		Elevated (n = 3)[*]	Persistent (n = 3)

STM after initial CTx, Serum tumor marker levels after first-line chemotherapy; *2nd-line CTx,* if second-line chemotherapy was administered; *STM after 2nd-line CTx,* serum tumor marker level after second-line chemotherapy; *N/A,* STM after second-line chemotherapy was not applicable in patients who did not receive second-line chemotherapy; *Residual mass pathology,* pathologic category of residual mass after the operation; *NSGCT,* persistent NSGCT.
[*]Number of patients treated with high-dose carboplatin-based chemotherapy with autologous stem cell rescue for second-line therapy.

nal tissues fibrotic, obscuring normal anatomic planes. Our surgical technique involving aggressive en bloc removal of the residual mass after chemotherapy and surrounding adherent structures has been previously described and was used in the majority of these cases.[3] In summary, the epicenter of the residual mass is located in the anterior mediastinum and typically is adherent to adjacent pericardium requiring en bloc removal. Not infrequently, the residual mass is also adherent to the mediastinal surfaces of the lung, great veins, phrenic nerves, and occasionally the cardiac chambers. Over the past year, we have modified our surgical approach. After exposure of the residual mass, "4-quadrant" core biopsy specimens are judiciously obtained with a Core needle (Anchor Products, Addison, Ill), avoiding tumor "spillage," and pathologically analyzed by frozen section. If benign disease (either necrosis or teratoma) is confirmed, then efforts are made to carefully separate the phrenic nerve within the periphrenic fat pad from the residual mass by means of sharp dissection with a No. 15 blade scalpel. Similarly, great venous or large anatomic pulmonary resections are avoided in these cases, if possible. If a more conservative resection has been performed, frozen section analysis of phrenic nerve, great vein, and/or pulmonary margins is also obtained before chest closure. In light of potentiating bleomycin lung toxicity, efforts are made during and after the operation to minimize fluid administration. The vast majority of these patients will be operated on after chemotherapy with baseline sinus tachycardia (heart rate 100-120 beats/min), which is not treated with fluid and/or pharmacologic blockade if blood pressure and urine output remain adequate.

Operative variables were recorded for each patient, including the number of thoracic surgical procedures required to achieve complete extirpation of residual disease and the thoracic surgical approach used for removal of the residual mass (sternotomy, left or right thoracotomy, and/or bilateral anterior thoracotomies with transsternal extension [clamshell]). The requirement for en bloc pericardium, pulmonary (wedge,

lobectomy, or total pneumonectomy), phrenic nerve, great vein, cardiac chamber, and/or diaphragm resection, and finally the need for separate pulmonary metastasectomy was obtained from operative records. Surgical disease was recorded as 1 of 5 categories (necrosis, teratoma, persistent NSGCT, sarcomatous degeneration, or carcinomatous degeneration). In cases in which mixed surgical disease was present, the "worst case" pathologic category was recorded (eg, necrosis with a focus of persistent NSGCT = persistent NSGCT). Operative morbidity, mortality, and status at last follow-up examination (alive, dead, or alive with disease) were obtained from hospital records or by contacting referring physicians when necessary. If late death occurred, whether primarily attributable to local recurrence, distant recurrence, treatment-related disease (ie, pulmonary fibrosis caused by bleomycin), or non–treatment-related disease (ie, acute leukemia), the cause was recorded when information was available.

With respect to the effect on long-term survival, age at presentation, the only continuous variable, was analyzed by Cox regression. Kaplan-Meier analysis was used to calculate survival and to determine the effect on survival of the following discrete variables: STM at presentation, preoperatively, and postoperatively; the presence of extramediastinal disease; the presence of pulmonary metastases; and preoperative and postoperative disease. Variables that were found to be predictive of survival with a P value < .10 were entered into a multivariate analysis using the Cox regression to identify a set of variables that were independently predictive.

Results

Seventy-nine patients underwent 82 thoracic surgical procedures (Table III). In 67% the approach was through a median sternotomy (n = 53), a left thoracotomy approach was used in 17 patients, a clamshell incision in 7, and a right thoracotomy in the remaining 2 patients. Forty-five patients required en bloc pericar-

Table III. *Surgical approach and other organs removed with the residual mass*

	No. of patients	Percent
Approach to residual mass		
Sternotomy	53	67
Left thoracotomy	17	22
Right thoracotomy	2	3
Clamshell	7	9
En bloc resection		
Pericardium	45	57
Pulmonary	46	
Wedge	32	41
Lobectomy	9	11
LUL	8	
RUL, RML	1	
Pneumonectomy	5	6
Left	4*	
Right	1	
Phrenic nerve	18	23
Left	14	
Right	4	
Great vein	19	24
Left innominate vein	10	
SVC/right innominate vein	9	
Cardiac chamber	4	5
Right atrium	2*	
Left atrium	1	
Left ventricle	1	
Diaphragm	3	4
Pulmonary metastasectomy	6	8

LUL, Left upper pulmonary lobe; *RUL,* right upper pulmonary lobe; *RML,* right middle pulmonary lobe; *SVC,* superior vena cava.
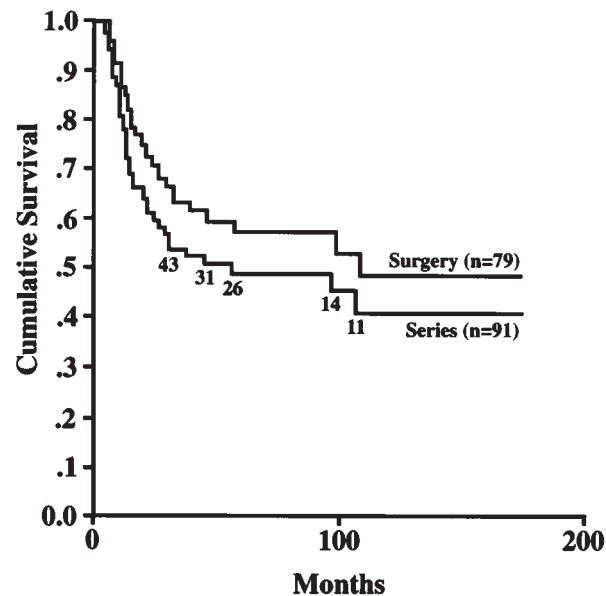*Cardiopulmonary bypass without cardiac arrest was used (n = 2).

Fig 1. Long-term survival for patients who underwent postchemotherapy resection of residual disease *(Surgery)* and all presenting patients *(Series),* including patients who were not operated on, at the Indiana University Medical Center (1982-1998). Numbers represent patients at risk for death, which are the same for both curves at each break point.

dial resection (57%). Pulmonary resection was required in 46 (58%) patients, with most (n = 32) undergoing wedge resection of adjacent lung. En bloc lobectomy and pneumonectomy were performed in 9 and 5 patients, respectively. One left pneumonectomy was performed with cardiopulmonary bypass support because of tumor involvement of the main pulmonary artery. The ipsilateral phrenic nerve was removed with the residual mass in 18 patients. Prophylactic diaphragmatic plication was typically performed in these patients unless a substantial amount of lung had been removed (ie, lobectomy or pneumonectomy). The left innominate vein was removed in 10 patients and was not reconstructed unless a patent superior vena cava or right innominate vein was removed as well (n = 3). In these patients, orthotopic great venous reconstruction was accomplished with an externally stented polytetrafluoroethylene vascular prosthesis* placed from the remaining left innominate vein to the superior vena cava–right atrial junction. Four patients required cardiac chamber resection. A large area of right atrium was replaced with a patch of autogenous pericardium in 1 patient with the aid of cardiopulmonary bypass, and the atrial involvement was limited to the appendages, allowing primary closure without bypass, in 2 other patients. In a final patient, sarcomatous degeneration involving the lateral wall of the left ventricle required partial-thickness myocardial resection including a circumflex coronary artery branch without cardiopulmonary bypass. Seven patients required pulmonary metastasectomy; 4 of these operations were performed at the time of extirpation of the residual mass, and the other 3 were sequentially performed at a separate thoracotomy (34, 51, and 200 days after the initial operation). Four patients required staged extrathoracic surgical procedures, including cerebral metastasectomy (n = 1), cervical lymphadenectomy (n = 2), and retroperitoneal lymphadenectomy (n = 1).

Three operative deaths occurred (4%), all attributable to pulmonary complications. One patient died of adult respiratory distress syndrome after en bloc right upper/middle lobe wedge resection and superior vena cava resection and the other 2 died of bacterial pneu-

*Gore-Tex vascular prosthesis, registered trade name of W. L. Gore & Associates, Inc, Flagstaff, Ariz.

Table IV. *The influence of analyzable discrete variables on survival*

Prognostic variable	Mean survival (mo)	Alive/total patients (%)	P value
AFP before chemotherapy (ng/mL)			
>10,000	99 ± 12	31/52 (60)	0.39
<10,000	103 ± 14	15/22 (68)	
AFP after chemotherapy (ng/mL)			
Normal	104 ± 11	34/55 (62)	<0.01
21-100	44 ± 8	9/17 (53)	
101-1,000	—	5/5 (100)	
1,000-10,000	9 ± 4	0/2 (0)	
STM preop			
Normal	105 ± 12	32/50 (64)	0.38
Elevated	85 ± 13	16/29 (55)	
Normal postop	117 ± 13	14/18 (78)	<0.01
Elevated postop	16 ± 4	1/8 (13)	
Extramediastinal disease			
Absent	104 ± 12	38/59 (64)	0.49
Present	73 ± 12	10/20 (50)	
Lung metastases			
Absent	105 ± 10	43/68 (63)	0.23
Present	62 ± 17	5/11 (46)	
No surgery	98 ± 24	3/4 (75)	<0.01
Surgery	34 ± 11	2/7 (29)	
Prechemotherapy teratoma			
Present	110 ± 20	14/23 (61)	0.45
Absent	89 ± 9	34/56 (61)	

AFP after chemotherapy, Levels after first-line chemotherapy; *STM preop, normal,* AFP < 21 ng/mL and bHCG < 2 ng/mL; *elevated,* AFP > 21 ng/mL or bHCG > 2 ng/mL; *normal and elevated,* normal and elevated markers of those patients in whom either marker was elevated at operation and in whom postoperative STM data were available; *extramediastinal disease,* disease in lung parenchyma separate from primary, cervical, or retroperitoneal lymph nodes or brain at presentation; *lung metastases present, no surgery,* chemotherapy cured pulmonary metastases; P *value,* lung metastases absent versus present, but no surgery, versus present with surgery; *lung metastasis present, surgery,* pulmonary metastases requiring surgery; *prechemotherapy teratoma,* evidence of teratomatous elements in mediastinal mass before chemotherapy.

Table V. *Independent predictors of death by Cox regression analysis*

Prognostic variable	Hazard ratio (95% CI)	P value
Residual mass pathology		
Teratoma	5.6 (0.7-44.9)	.10
Persistent NSGCT	15.2 (2.0-116.6)	.01
Carcinoma	6.6 (0.4-108.6)	.18
Sarcoma degeneration	22.2 (2.4-203.6)	.01
AFP after chemotherapy		
21-100	1.3 (0.5-3.3)	.59
101-1,000	<0.1 (no deaths)	.98
1,001-10,000	6.5 (1.3-33.2)	.03

Residual mass pathology and AFP postchemotherapy hazard ratios calculated with "tumor necrosis" and "normal" as reference groups, respectively. *CI,* Confidence interval; *NSGCT,* nonseminomatous germ cell tumor; *AFP,* alpha-fetoprotein.

monias, which occurred in 2 of the 5 patients requiring pneumonectomy. Operative morbidity occurred in 6 of the 79 other patients having thoracic surgical procedures: prolonged air leaks (>10 days) necessitating the patient's discharge with indwelling chest tubes connected to 1-way valves (n = 3), nonfatal pneumonia (n = 1), upper gastrointestinal hemorrhage requiring endoscopic intervention (n = 1), and return to the operating room for minor bleeding (n = 1). There were 28 late deaths, the majority (86%) of which were due to recurrent cancer. In 5 of the 18 (28%) patients in whom information was available, local recurrence at the initial site in the mediastinum was the cause of death. All 5 of these patients had persistent NSGCT in the resid-

ual mass, equating to a 21% (5/24) incidence of mediastinal recurrence with this pathologic category. Three late deaths were attributed to acute leukemia and 1 to pulmonary fibrosis. Three patients are currently alive with disease. Excluding 2 patients lost to long-term follow-up (both of whom had teratoma in the residual mass), 43 of 77 (56%) patients are alive and free of disease after an average follow-up interval of 60.8 months (range 4-175 months) (Fig 1).

Comparing survivors and nonsurvivors, age at presentation had no predictive value (mean 27.7 years vs 28.2 years, respectively; *P* = .8). Table IV demonstrates the influence of discrete variables on survival. AFP level in excess of 10,000 ng/mL at the time of diagnosis had a somewhat poorer prognosis than lower AFP levels (mean survival 99 vs 103 months, respectively). Only 2 patients, both of whom were long-term survivors, had a bHCG level greater than 10,000 ng/mL; therefore this variable could not be included in the survival analysis. The presence of extramediastinal disease at the time of presentation did tend to diminish mean survival (73 months vs 104 months for patients without extramediastinal disease); however, this variable was not significantly predictive. There was a similar trend toward poorer survival in patients who had pulmonary metastases as compared with those who did not, but this variable did not reach statistical significance in our series (*P* = .2). Interestingly, patients who had pulmonary metastases that were successfully treated with chemotherapy and did not require subsequent metastasectomy (n = 4) had a mean survival that was inferior but statistically equivalent to that of 68 patients who did not have pulmonary metastases (98 ± 24 vs 105 ± 10 months, respectively). Survival in these 2
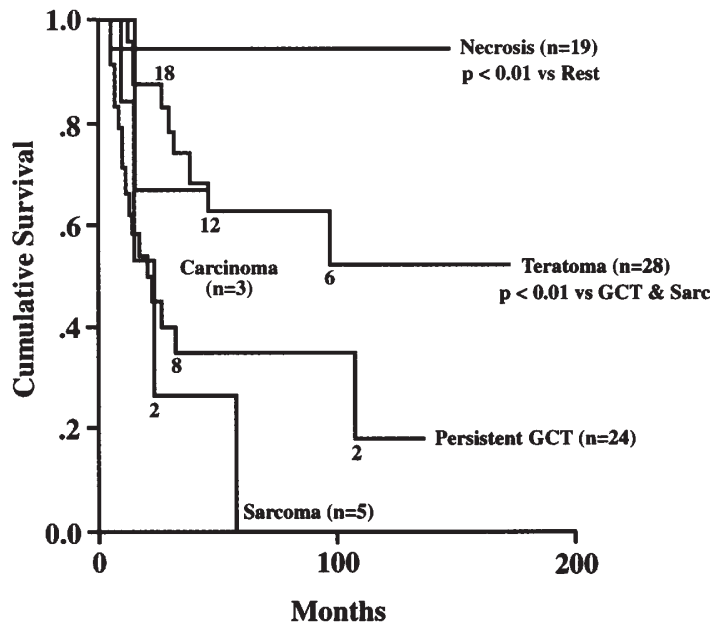
Fig 2. Long-term survival based on postchemotherapy pathologic category. Numbers represent patients at risk for death.

groups was statistically better than survival in the 7 patients who required subsequent pulmonary metastasectomy ($P < .01$).

Prechemotherapy pathologic tumor type was not significantly predictive of survival. Of patients who underwent prechemotherapy biopsy, only 4 had elements of choriocarcinoma, which is believed to be a poor prognostic factor, precluding statistical analysis. However, 3 of these patients are alive and well. On the other hand, patients having teratomatous elements, believed to be a positive prognostic finding, demonstrated no survival advantage as compared with patients without teratomatous elements (Table IV). An AFP level greater than 1000 ng/mL after first-line chemotherapy was found to be negatively predictive of survival, which was significant as compared with lower postchemotherapy levels ($P < .01$). With respect to STMs in general, 32 of 50 (64%) patients with preoperative normal STMs are surviving as compared with only 16 of 29 (55%) patients who had elevated STMs at operation. This difference failed to reach statistical significance in our series ($P = .4$). STMs did not return completely to normal limits before the operation in 26 patients. Postoperatively, they did return to normal limits in 18 patients, and survival was significantly better in these 18 than in the 8 in whom STMs did not return to normal (mean survival 117 vs 16 months; $P < .01$).

The pathologic finding of complete tumor necrosis in

the residual mass predicted excellent survival (mean 139 ± 8 months). Only 1 late death was attributable to pulmonary fibrosis among 19 patients, which was statistically significant as compared with the other pathologic categories ($P < .01$) (Fig 2). The finding of teratoma (n = 28) predicted intermediate survival (mean 111 ± 16 months, $P < .01$ vs persistent NSGCT and sarcomatous degeneration). Late deaths occurred in 8 patients having teratoma in the residual mass, 3 from leukemia and the other 5 from tumor recurrence. One of the 20 surviving patients with teratoma is currently alive with disease. Twenty-four patients had pathologic evidence of NSGCT in the residual mass with a mean survival of 52 ± 12 months. Fifteen deaths occurred in this group, 3 postoperative and 12 cancer related. Of the 8 survivors in this group, 7 are free of disease. Survival was poor in patients having sarcomatous degeneration (n = 5), with no survivors past 57 months. Four of these patients have died of recurrent disease and the only survivor is not disease free. Three patients were found to have carcinomatous degeneration in the residual mass, 2 of whom are alive and well. Low patient numbers in this group precluded statistical comparison with the other pathology groups, however.

Finally, 3 discrete variables—pathologic category of the residual mass, AFP level after first-line chemotherapy, and the presence of pulmonary metastases necessitating surgery—were entered into a multivariate sur-

vival analysis. Pathologic category and AFP level were found to be independent predictors of postoperative survival (Table V). AFP levels greater than 1000 ng/mL increased the hazard ratio for death by a factor of 6.5 as compared with normal AFP levels. Sarcomatous degeneration and persistent NSGCT in the residual mass increased the chance of death by factors of 22.2 and 15.2, respectively, as compared with tumor necrosis only. The risk of death was increased 5.6-fold in patients having benign teratoma after chemotherapy, but this difference did not reach statistical significance from the tumor necrosis category.

Discussion

NSGCTs originating in the testes represent a true success story of multimodality therapy, with a better death-to-case ratio than cancers of the thyroid or Hodgkin's lymphoma. Cisplatin/etoposide-based chemotherapy regimens with or without surgical extirpation of residual disease will result in cure in 70% to 80% of cases. Despite identical histologic features, the relative inability of standard cisplatin/etoposide/ bleomycin chemotherapy to achieve similar results for PMNGCT reflects the distinctly different biologic behavior. Known associations with Klinefelter's syndrome and the propensity for hematologic malignant diseases to develop, which are usually fatal, further support the unique biologic nature of PMNGCT.[8,9]

The interesting biologic nature of PMNGCT, and NSGCT in general, with respect to potential for conversion to a wide variety of pathologic diagnoses after cisplatin-based chemotherapy, has been previously described.[10] Although low AFP levels after chemotherapy were significantly predictive of survival after surgery, it is perhaps not surprising that the pathologic findings of either necrosis or benign teratoma in the residual mass were more predictive. A similar concept is currently recognized in the treatment of more frequently occurring thoracic malignant tumors, such as lung and esophageal cancers, with statistically better survival found in the subset of patients who have had a complete pathologic response to neoadjuvant therapy.[11,12]

New therapeutic strategies are necessary in the treatment of patients with PMNGCT to achieve survivals equivalent to those of testicular NSGCT. Of the 79 patients who underwent surgery in our series, 41% or 32 patients had persistent cancer in the residual mass after standard cisplatin-based chemotherapy regimens. In a preliminary report, Walsh and coworkers[13] have recently reported on 8 of 10 patients surviving 2 years after a very aggressive 8-drug chemotherapy regimen followed by surgery. At our institution, we strongly

encourage enrollment in the phase III intergroup trial for high-risk germ cell cases, which includes PMNGCT, randomizing patients to receive either 4 cycles of cisplatin/etoposide/bleomycin chemotherapy (standard arm) or 2 cycles of cisplatin/etoposide/ bleomycin chemotherapy followed by 2 cycles of high-dose carboplatin/etoposide/cyclophosphamide with autologous stem cell rescue (experimental arm). The experimental arm in this phase III study is based on promising data from Motzer and coworkers,[14] reporting 22 cases of high-risk germ cell tumor, including 5 patients with PMNGCT who received high-dose carboplatin/etoposide chemotherapy with autologous stem cell rescue as first-line therapy.[14]

Previously, we[3] had emphasized the importance of normalization of STM before surgical extirpation of residual disease in patients with PMNGCT, including, if necessary, the use of second-line chemotherapy in patients whose markers remained elevated after first-line therapy. Second-line chemotherapy is anticipated to cure between 25% and 50% of testicular NSGCTs. Unfortunately, however, less than 5% of refractory PMNGCTs are curable with second-line chemotherapy including patients undergoing autologous stem cell rescue and high-dose carboplatin-based chemotherapy.[7] These data have changed our treatment algorithm with respect to patients whose STM levels have not returned to normal but who otherwise have anatomically operable residual disease as determined by computed tomographic imaging after first-line chemotherapy. Of the 24 patients in our series with histologic evidence of persistent NSGCT in the residual mass, 8 have survived and 7 of these patient remain free of disease, demonstrating the ability of surgery to "salvage" select patients. This is analogous to the ability of retroperitoneal lymph node dissection to "salvage" chemorefractory NSGCT of testicular origin.[15] In addition to aggressive surgical extirpation of visible disease with wide surgical margins, patients found to have persistent NSGCT in the residual mass currently also receive 2 additional cycles of cisplatin/etoposide chemotherapy if they demonstrated a favorable serologic response to chemotherapy before the operation. Equally important, these data demonstrate the less than perfect sensitivity of elevated STM corresponding to persistent NSGCT after chemotherapy. Although 29 patients had elevated markers at operation in our series, only 15 had persistent NSGCT in the residual mass, with 6 patients having teratoma and 7 having necrosis only. Further chemotherapy in these later 13 patients obviously would have increased morbidity without therapeutic benefit. There was an equal lack of STM specificity as

9 of the 50 patients having normal STMs at operation were found to have persistent NSGCT in the residual mass. Given the incomplete sensitivity and specificity of STM levels for persistent NSGCT, in addition to the limited benefit of second-line chemotherapy in the treatment of PMNGCT, we currently believe that operable patients should undergo surgical extirpation of residual disease after first-line chemotherapy, regardless of STM status.

Although the success of chemotheraputic regimens in PMNGCT is important, skilled thoracic surgery after chemotherapy is an equally important component for successful multimodality therapy. We have previously emphasized an aggressive approach to surgical extirpation of residual disease.[3] However, we have recently taken a more conservative but complete resectional approach with patients whose STMs are normal (or near normal) and in whom intraoperative frozen section analysis has demonstrated benign histologic characteristics. In these patients, representing nearly two thirds of our series, efforts are currently being made to spare phrenic nerves, which are typically adherent to the residual mass, and avoid large anatomic pulmonary resections where possible. The majority of these patients, although young and otherwise healthy, have received bleomycin-containing chemotherapeutic regimens, which predictably result in varying degrees of pulmonary fibrosis. The relatively high incidence of prolonged air leaks in this series also supports the notion that the remaining lung tissue is relatively noncompliant and expands poorly to fill space after the residual mass is removed. Efforts to spare pulmonary function are underscored by all 3 operative deaths being directly attributed to pulmonary complications, 2 involving total pneumonectomy. We do believe, however, that complete removal of any residual mass that contains necrosis is imperative. We have recently treated a patient who initially underwent subtotal resection of a residual left hilar mass histologically demonstrating tumor necrosis only at an outside hospital. A large recurrent mass containing sarcomatous degeneration subsequently developed 2 years later, and he underwent intrapericardial pneumonectomy at our institution. This patient died of the disease 8 months after this secondary thoracic surgical procedure. Although a microscopic focus of sarcoma could have been present in the residual mass left unresected, it is equally possible that a histologic finding of tumor necrosis does not uniformly predict cellular nonviability. The finding of 7 patients in our series who had complete tumor necrosis histologically but low levels of STM elevation that normalized postoperatively lends further support to incomplete correlation of postchemotherapy histologic findings and potential biologic behavior. In conclusion, we believe that complete extirpation of the residual mass after chemotherapy is important regardless of histologic type, with wide surgical margins including great vein and limited cardiac chamber resection if necessary, and in particular when persistent NSGCT, carcinomatous degeneration, or sarcomatous degeneration is present.

The results of multimodality solid tumor therapy, including therapy for PMNGCT, depend on both successful chemotherapy and surgery. In this regard, PMNGCT, although rare, represents an excellent treatment model for more common thoracic malignant tumors. New surgical and chemotherapy strategies are currently being investigated to minimize operative morbidity and improve long-term survival equivalent to NSGCT of nonmediastinal origin.

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Discussion

Dr Scott J. Swanson *(Boston, Mass).* With this paper, once again the group from Indiana has put together a large amount of data concerning a relatively uncommon tumor, that of PMNGCT. They are to be congratulated for pursuing an intensive multimodal approach that includes aggressive surgery, and their perioperative mortality of less than 5% and low morbidity are outstanding.

Their paper presents several interesting issues, from which I have 4 questions. Their prior report in 1990 demonstrated that the STMs AFP and bHCG have inadequate sensitivity and specificity. With this larger series of 79 patients, they now report that even in the face of elevated markers patients should be operated on after first-line chemotherapy, as 13 out of 29 patients with elevated markers had favorable histology at resection. Also they showed that those patients with complete necrosis in the residual mass after chemotherapy had the best survival, a mean survival of 139 months. In addition, they showed that those patients with pulmonary metastases that completely responded to chemotherapy and did not require resection did as well as those patients who did not have pulmonary metastases.

Over the past year, as he mentioned, Dr Kesler and his colleagues have adopted an approach of 4-quadrant biopsy during resections. If on rapid sectioning a favorable histologic tumor type is noted, they will limit their surgical resection by saving the phrenic nerve and limiting the pulmonary and great vessel resections. In addition, they observed that patients who had extramediastinal disease did not fare less well statistically than those with disease limited to the mediastinum.

With these issues in mind, my questions for Dr Kesler are as follows: First, clearly the biology of this tumor is different from the standard thoracic carcinoma that we see commonly. Is radical resection really necessary as advocated by your group for those tumors showing complete necrosis? In those cases, what is the contribution of surgery? Have you specifically noted any different outcome in the group over the past year where a lesser resection is carried out?

Second, are other biomarkers available that may be more sensitive and specific than AFP and bHCG? In cases in which AFP remains greater than 1000 ng/mL before surgery, are there any other novel therapies to be considered before resection, for example, antiangiogenic therapy?

Third, is there a role for other functional tests, such as positron emission tomographic (PET) scanning, to determine the timing and need for surgery?

Finally, given that 20% of these tumors with persistent NSGCT histology showed local recurrence, is there a role for adjuvant therapy, such as high-dose radiation in the form of seeds or newer agents such as photodynamic therapy?

Dr Kesler. Thank you for your kind comments and insightful questions.

First, we currently believe that if either tumor necrosis or benign teratoma is demonstrated on intraoperative core biopsy, then phrenic nerves and/or great veins that are attached to but not grossly involved by the residual mass may be spared. We would also make efforts to avoid pneumonectomy if reasonable in these cases. We still emphasize that all visible evidence of residual disease must be removed despite "benign" pathology on frozen section. In this respect, aggressive surgery is still mandatory. To date we have not been "burned" by false negative intraoperative pathologic analysis or local recurrence using this approach; however, further study is needed.

Second, we are not aware of any other STMs that have more sensitivity or specificity for this disease. Patients with AFP levels greater than 1000 ng/mL at operation certainly represent a desperate situation. The results of second-line chemotherapy, however, are very poor in NSGCTs originating in the mediastinum; therefore, the oncologists at our institution would still recommend surgery if anatomically feasible in these patients.

PET scanning has been studied for the evaluation of germ cell tumors in general and found to be only moderately sensitive. Moreover, we are not at all convinced that tumors demonstrating complete tumor necrosis histologically, and therefore PET scan "negative," would have long-term biologic inactivity. We therefore believe that complete extirpation of residual disease would be necessary regardless of PET scan findings. In summary, PET scanning to determine preoperative planning has not been helpful.

Finally, patients who have persistent germ cell cancer in the resected residual mass are currently treated with 2 cycles of platinum-based chemotherapy after the operation only if they responded to platinum-based chemotherapy before the operation. If they did not respond preoperatively, we unfortunately believe that no further standard chemotherapy would be of value, although investigational drug regimens may be offered.

Dr David J. Sugarbaker *(Boston, Mass).* I wonder, Dr Kesler, whether you could resolve for me one conflict that I have regarding your presentation. You mentioned your procedure of 4 core biopsies to determine whether you are dealing with teratoma or a more malignant residual variant after chemotherapy. At the Dana-Farber Cancer Institute, we have found that these tumors are often variegated, with areas of teratomatous change as well as areas of more malignant residual disease. I wonder whether that procedure will not lead you to a suboptimal resection in patients with residual malignant disease. Could you comment on that?

Dr Kesler. Dr Sugarbaker, we certainly do have concerns about using a more conservative resectional approach, and we agree that residual masses after chemotherapy may not

demonstrate homogeneous histologic features. However, two thirds of these patients will ultimately be shown to have some form of benign histology only throughout the residual mass. Moreover, for patients demonstrating viable germ cell cancer in the completely resected specimens, we have observed that the malignant histology is not infrequently harbored closer to the mass epicenter as opposed to the margins. In either of these scenarios, we currently believe that removal of adjacent phrenic nerves and/or great veins will only increase postoperative morbidity without improving cure rates. Certainly, regardless of a benign intraoperative biopsy report, if a residual mass cannot be rather readily dissected from great vein adventitia or periphrenic fat, then a more radical mediastinal dissection is performed without hesitation. Finally, thus far our pathologists have been extremely accurate at analyzing intraoperative core biopsy specimens. In summary, we currently believe that an aggressive but "balanced" surgical approach is justified in these cases, although, again, more studies and follow-up are needed.

Dr Valerie W. Rusch *(New York, NY).* I want to emphasize a couple of your comments and also ask you a question. At Memorial Sloan-Kettering Cancer Center we would endorse your policy of offering salvage resection to patients who have completely resectable disease but still have elevated markers, particularly an elevated AFP level. In addition, our preliminary experience with PET scanning indicates that this does not accurately restage the disease after chemotherapy.

How do you handle the patient who has negative 4-quadrant biopsy specimens intraoperatively but elevated STMs preoperatively?

Dr Kesler. Dr Rusch, as up to 50% of the patients in this series admitted for surgery with elevated STMs had complete tumor necrosis or benign teratoma, the finding of viable germ cell cancer is not a foregone conclusion. Most of these patients had only modest elevation of STMs (<100 ng/mL), however. Patients harboring only small foci of active germ cell cancer within the residual mass likewise usually had only minor marker elevation before the operation. In either of these cases, a conservative but complete resection after biopsy should not compromise cure. Certainly, however, if a patient comes to surgery with significant STM elevation and a poor radiographic response to chemotherapy, we would directly proceed with wide mediastinal resection without core biopsy, assuming a large volume of viable germ cell cancer is remaining.

Dr Mark J. Krasna *(Baltimore, Md).* Since you have such a vast experience, I think we all have taken an aggressive approach, thanks to the Indiana group's leadership.

One question that seems to beckon is a converse of Dr Sugarbaker's question: Why not perform biopsies on everybody, and why not do it before you open the chest? If there is any residual disease, why not give more chemotherapy at that time? Clearly you have shown that the best predictor for ultimate survival is the complete response. You are telling us that there is no second-line chemotherapy. Give more of the same and then do your 4-quadrant biopsy after you have had a second or a third course of the several cycles of chemotherapy.

Dr Kesler. Dr Krasna, our oncologists have demonstrated that the results of currently available second-line chemotherapy for this disease are abysmal, effective in less than 7% of patients after standard first-line platinum/etoposide regimens fail. In our series, we were able to surgically cure or "salvage" nearly 30% of our patients with persistent germ cell cancer found histologically within the resected specimen. For this reason, we do not believe that a second biopsy after first-line chemotherapy is indicated if resection is anatomically feasible.

Dr L. Penfield Faber *(Chicago, Ill).* One comment struck me as being controversial—the fact that you make the diagnosis initially on a needle biopsy specimen. It has been my understanding that a large piece of tissue is needed to confirm the exact histologic characteristics of these tumors. In other words, a seminomatous tumor may have mixed histologic features and, therefore, your treatment program could be incorrect if you are doing only a needle biopsy. You may diagnose a seminoma when the tumor is really a mixed tumor with yolk sac and seminomatous elements. I always do an anterior mediastinotomy and biopsy a block of tissue for accurate histologic determination. Would you comment on the accuracy of needle biopsy in determining histologic type?

Dr Kesler. Dr Faber, our cytologists are proficient at differentiating nonseminomatous from seminomatous tumors on fine needle aspiration biopsy alone. We also believe it would not be totally unreasonable to empirically treat a young man who has an anterior mediastinal mass and markedly elevated STMs with standard chemotherapy for PMNGCT without biopsy. We certainly agree with your point that differentiating nonseminomatous from seminomatous germ cell tumors, or other primary mediastinal tumors for that matter, remains critical in some patients. In these cases, core biopsy performed percutaneously under computed tomographic guidance or an open Chamberlain approach would be justified if fine needle aspiration biopsy was inconclusive or unavailable.