

# Multimodality Treatment of Germ Cell Tumors of the Mediastinum

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## KEYWORDS

- Germ cell tumors • Mediastinal tumors
- Nonseminomatous germ cell cancer
- Thoracic surgery • Chemotherapy

Although the majority of germ cell tumors originate in the gonads, 5% to 10% arise within the anterior mediastinum, which represents the second most common site of origin. Various theories have been proposed to explain the pathogenesis of extragonadal germ cell tumors. The most widely accepted theory involves primordial germ cells, which are “misplaced” during embryonic migration through midline structures. Teratoma, one of the “Four Ts” used as a mnemonic for the main differential diagnoses of primary tumors arising in the anterior-mediastinal compartment, actually represents three histologic categories (mature teratoma, seminomatous, and nonseminomatous germ cell tumors) that have distinct biologic behavior. Mature teratomas are the most common germ cell tumor arising in the mediastinum, representing 60% to 70% of all mediastinal germ cell tumors. Mature teratomas are benign, with surgery representing curative therapy. Primary mediastinal seminomas constitute less than half of all malignant primary mediastinal germ cell tumors and have high cure rates with cisplatin-based chemotherapy alone. Nonseminomatous germ cell cancers comprise the main category of the malignant germ cell tumors arising in the mediastinum (PMNSGCT). The treatment of testicular nonseminomatous germ cell tumors with cisplatin-based chemotherapy regimens, followed by surgical resection of residual disease, is considered one of the most successful paradigms

of multimodality cancer therapy, with greater than 80% long-term survival.

It has been well established that although histologically similar to their more commonly occurring testicular counterparts, PMNSGCT have a distinctly worse prognosis and therefore have been categorized as “poor risk,” along with other subsets of testicular nonseminomatous germ cell tumors.<sup>1</sup> The relatively poorer prognosis is attributed to a different biologic behavior, including the known association with Klinefelter syndrome and the propensity for hematologic dyscrasias, which are not observed in patients with nonseminomatous testicular cancer.<sup>2,3</sup> This article discusses the multimodality treatment strategy for PMNSGCT.

## DIAGNOSIS

The vast majority of PMNSGCTs occur in males 20 to 40 years of age, with extremely rare cases of PMNSGCT occurring in females. Most patients present symptomatic with chest pain, cough, superior vena cava syndrome, and shortness of breath secondary to a rapidly growing anterior mediastinal mass. CT scans usually demonstrate a large heterogeneous mass, with occasional evidence of necrosis and hemorrhage.<sup>4</sup> Local invasion into either lung, left brachiocephalic vein, superior vena cava, and pericardium is common, and even direct cardiac chamber or proximal great artery involvement

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can occasionally be present. Associated pericardial and pleural effusions are also common but typically not malignant in nature. For any young adult male presenting with a mass in the anterior mediastinal compartment, obtaining serum tumor markers (STM), alpha fetoprotein (AFP) and human chorionic gonadotropin (hCG), is an essential component of clinical evaluation, as significant elevation of either STM is diagnostic for PMNSGCT. Biopsy in these cases is not only unnecessary, but can be misleading because of sampling error within these typically large and heterogeneous neoplasms. Cytologic confirmation with CT-guided fine-needle aspiration is necessary in rare PMNSGCT patients presenting with normal STMs or patients with minor elevations of hCG, which can be present in pure-seminomatous germ cell cancer.

Histologically, these neoplasms are comprised of at least one nonseminomatous germ cell cancer subtype (yolk sac cancer, embryonal carcinoma, or choriocarcinoma in order of frequency), and frequently mixed with some form of teratomatous pathology, ranging from mature teratoma to teratoma with immature elements (stromal atypia), and finally, frank malignant degeneration of teratoma into the so-called "non-germ cell" cancer (sarcomas and epithelial carcinomas).<sup>5</sup>

Metastatic disease is present in 20% to 25% of cases before chemotherapy, with lung being the most common site, followed by neck, liver, bone, and central nervous system (CNS). Chest and abdominal CT scans are standard imaging tests for staging, with other radiologic studies including positron emission tomography (PET) scan and CNS MRI obtained on an individual basis. Gated MRI and echocardiogram can be helpful to determine the presence of great vessel or cardiac involvement, but subtle invasion may not be apparent until postchemotherapy surgical resection is undertaken. A scrotal examination is recommended during evaluation. However, an isolated metastasis to the anterior mediastinum from a testis cancer is distinctly rare in the authors' institution's experience.

## CHEMOTHERAPY

After diagnosis and staging, primary surgical therapy for PMNSGCT is inappropriate. PMNSGCTs are usually large and infiltrative neoplasms. Surgical resection as initial therapy will therefore rarely achieve local control and does not treat metastatic disease when present. Appropriate therapy typically begins with cisplatin-based chemotherapy. The combination of BEP (bleomycin, etoposide, and cisplatin) has historically been the standard chemotherapy for poor-risk nonseminomatous

germ cell tumors including PMNSGCT. The relatively lower incidence of benign histology following cisplatin-based chemotherapy for PMSNGCT, as compared with most testicular nonseminomatous germ cell tumors, has prompted exploration of different chemotherapeutic strategies. However, Walsh and colleagues<sup>6</sup> from MD Anderson Hospital reported on 20 PMNSGCT patients who received a very intensive chemotherapy regimen, with eight different agents in various combinations. Although there was high chemotherapy-related morbidity in this series, the 2-year survival rate of 58% was encouraging, particularly because several patients who had failed first-line therapy were included in this study. Subset analysis of 28 PMNSGCT patients from a multicenter phase II German study using high-dose VIP (etoposide, ifosfamide, and cisplatin) with autologous stem-cell rescue for first-line therapy in poor-risk nonseminomatous germ cell tumor patients showed an impressive 68% 2-year overall survival.<sup>7</sup> A recent multi-institutional trial randomized 219 poor-risk nonseminomatous germ cell tumors patients, which included 58 PMNSGCT patients, to either four cycles of standard BEP or two cycles of BEP followed by high-dose carboplatin-based chemotherapy with autologous stem-cell rescue for first-line therapy.<sup>8</sup> Unfortunately, no overall survival advantage was found in the experimental arm in any subset, including the patients with PMNSGCT.

A recent randomized trial comparing BEP to VIP for poor-risk nonseminomatous germ cell tumors including PMNSGCT demonstrated statistically equivalent survival.<sup>9</sup> To eliminate the possibility of bleomycin-induced pulmonary toxicity before a major thoracic surgical procedure, the authors have used VIP combination chemotherapy for the past 2 years. Since initiating this change, the authors' institution has gone from a 14% rate of postoperative pulmonary failure, which carried 50% mortality in these otherwise young and healthy patients after BEP, to no patients experiencing postoperative respiratory failure out of 21 patients to date who received preoperative VIP.

Following chemotherapy, there is typically resolution of pleural and pericardial effusions and a significant decrease in STMs. There is also typically a reduction in tumor dimensions. However, a residual mediastinal mass (RM) is still invariably present. In the authors' and other institutions' experience, the RM pathologically contains complete tumor necrosis only in a distinct minority of cases.<sup>10,11</sup> Therefore, teratoma, persistent nonseminomatous germ cell cancer, and non-germ cell cancer is pathologically present in most RMs for which surgery is indicated. Unfortunately, there is

no role for postchemotherapy PET scanning to determine the need for removal of a RM, as teratoma does not demonstrate hypermetabolic activity similar to complete necrosis. PET additionally lacks sensitivity to identify microscopic foci of persistent nonseminomatous germ cell cancer or non-germ cell cancer. Optimally, STMs normalize and surgery is planned after adequate functional and hematologic recovery, which usually occurs between 4 and 6 weeks following completion of chemotherapy.

A controversial area has been the role of surgery in the presence of elevated serum tumor markers following chemotherapy. At the authors' institution a decade ago, PMNSGCT patients with persistently elevated STMs were treated with second-line cisplatin-based chemotherapy before considering surgery, similar to the current treatment paradigm for testicular nonseminomatous germ cell tumors. While second-line cisplatin-based chemotherapy has a 50% "salvage" rate for nonseminomatous germ cell tumors arising in the testes, there has been a very poor response rate for PMNSGCTs.<sup>12</sup> Additionally, there unfortunately appears to be relatively poor sensitivity and specificity of STMs after chemotherapy to detect pathologic evidence of residual viable malignancy in PMNSGCT patients. In a recent study from the authors' institution involving 166 PMNSGCT patients who underwent postchemotherapy resection of residual disease, elevation of either STM was present in 39% patients at the time of surgery.<sup>13</sup> However, only 57% of these patients pathologically demonstrated evidence of malignancy, with either persistent nonseminomatous germ cell cancer or pure non-germ cell cancer. Even 39 patients who presented to surgery with rising STMs had just a 67% chance of pathologically demonstrating persistent nonseminomatous germ cell cancer in the RM. In this study, all but only eight patients with either AFP or hCG levels greater than 1,000 uniformly demonstrated pathologic evidence of persistent nonseminomatous germ cell cancer. Forty-three percent of patients with elevated STMs at the time of surgery, therefore, pathologically demonstrated only benign disease (necrosis/teratoma) and would likely not have benefited from additional chemotherapy. In contrast, 32% of patients with normal STMs at the time of surgery demonstrated pathologic evidence of viable malignancy in the RM, with either persistent nonseminomatous germ cell cancer or pure non-germ cell cancer. Given the historically poor response of second-line chemotherapy, the imperfect correlation of postchemotherapy STM levels to pathologic findings, and the ability for surgery to "salvage" patients with residual malignancy, the authors have subscribed to the policy of surgically removing

any residual disease if deemed resectable after first-line cisplatin-based chemotherapy, regardless of STM status.<sup>10,14,15</sup> The authors do believe that two additional cycles of adjuvant cisplatin-based chemotherapy should be considered after recovery if there is pathologic evidence of viable nonseminomatous germ cell cancer in the surgical specimen and the patient had demonstrated response to first-line cisplatin-based therapy.

Occasionally, PMNSGCT patients will demonstrate the so-called "growing teratoma syndrome," with paradoxical growth of a mediastinal mass associated with a rapid decrease of STMs during chemotherapy.<sup>16</sup> The authors agree that chemotherapy should be discontinued and surgery undertaken if feasible in these situations. Of note however, although teratoma is pathologically identified in many of these cases, 57% of patients presenting for surgery at the authors' institution with this clinical scenario have pathologically demonstrated areas of nongerml-cell cancer or even occasionally persistent nonseminomatous germ-cell cancer in the RM.<sup>10</sup> Approximately 5% of patients with PMNSGCT will, unfortunately, demonstrate progressive serologic and radiographic disease during or shortly after first-line chemotherapy and are considered poorly operable to inoperable. The authors are currently investigating the use of high-dose carboplatin-based chemotherapy with tandem stem cell transplant in these cases.

## SURGERY

The basic premise of the authors' surgical approach involves a complete en-bloc removal of the RM, thymus, and surrounding involved structures. An approach (sternotomy, posteriolateral thoracotomy, bilateral anterior thoracotomies with transverse sternotomy or the "clam shell" incision) is planned based on size and location of the RM.<sup>17,18</sup> Cardiopulmonary bypass circuits are routinely available in case cardiac or great vessel involvement is encountered, requiring bypass support. Surgery for PMNSGCT is technically demanding, as preoperative chemotherapy renders surrounding mediastinal tissues fibrotic, obscuring normal anatomic planes. The effectiveness of cisplatin-based chemotherapy for germ cell cancer, however, also usually results in extensive tumor necrosis that is more marked around the periphery. This finding usually allows a complete resection, which minimizes operative morbidity by preserving critical structures that abut but are not densely adherent to or directly involved with the RM, such as lung, great veins, phrenic nerves, and occasionally cardiac chambers where the pericardial barrier has been violated. An

extrapleural dissection is considered sufficient if the RM abuts but does not invade the chest wall. If the RM is simply adherent to the visceral pleura of either lung without invasion, removing a small rim of lung parenchyma with the RM is usually adequate to obtain a tumor-free margin. Frank invasion of the RM into pulmonary parenchyma or hilum usually requires formal anatomic resection. Similarly, phrenic nerves can usually be separated from an adjacent RM with scalpel dissection, although dense adherence or direct involvement requires en bloc removal. Diaphragmatic plication is performed only if an ipsilateral lobectomy or pneumonectomy is not required with phrenic nerve resection. If only one (usually the left) brachiocephalic vein is removed en-bloc with the RM, venous reconstruction is usually not performed, as upper extremity venous insufficiency in these cases is typically temporary and minor. If both brachiocephalic veins are removed with the RM, then unilateral brachiocephalic reconstruction, preferably the right, is performed using an externally-stented polytetrafluoroethylene vascular prosthesis. The superior vena cava is similarly reconstructed with externally-stented polytetrafluoroethylene vascular prosthesis, and autologous pericardium is used to patch partial superior vena cava defects. Right atrial and partial pulmonary artery defects are repaired with thin-walled polytetrafluoroethylene prosthetic patches. Intraoperative frozen section analyses of surgical margins are obtained in cases where critical structures abutting the RM are preserved or visibly close surgical margins exist. When required, the timing of pulmonary metastastectomy is individualized, based on several factors, including the surgical approach to the RM, the magnitude of pulmonary resection required to remove the RM, and the magnitude of pulmonary resection required for metastastectomy.

In the authors' recently published surgical experience involving 158 PMNSGCT patients, a sternotomy was used to remove residual disease in 50%, "clam-shell" incision in 27%, and posterior lateral thoracotomy in 23% of the cases, respectively.<sup>10</sup> Adjacent organs removed en bloc with the RM in this series are shown in **Table 1**. The pericardium was the most common adjacent organ adherent to or frankly involved with the RM. As there is no appreciable morbidity from pericardial resection, no attempt was made at separating the RM from the pericardium, which was removed en bloc in 117 patients, typically with a 1-cm to 2-cm tumor-free margin. En bloc pulmonary resection was required in 56% patients. Lobectomy and pneumonectomy were performed in 50 and 9 cases, respectively, with the remainder of patients

**Table 1**  
Organs removed en bloc

Pericardium	117 (74.1)
Lung	88 (55.7)
Wedge/segment	29 (18.4)
Lobectomy	50 (31.6)
LU	33
RU±M13	
Pneumonectomy	9 (5.7)
Left	6
Right	3
Phrenic nerve	50 (31.6)
Great vein	39 (24.7)
Left BC	31
Right BC/SVC	19
Cardiac chamber	6 (3.8)
Right atrium	4
Diaphragm	4 (2.5)
Separate metastastectomy	
Pulmonary	19 (12.0)
Non pulmonary	16 (10.1)

Adjacent organs removed en bloc with the RM and metastatic resections after cisplatin-based chemotherapy in 158 PMNSGCT patients. Number of patients given with percentage of series in parenthesis.

*Abbreviations:* BC, brachiocephalic; LU, left upper; RU ± M, right upper with or without middle, SVC, superior vena cava.

From Kesler KA, Rieger KM, Hammoud ZT, et al. A 25-year single institution experience with surgery for primary mediastinal nonseminomatous germ cell tumors. *Ann Thorac Surg* 2008;85:373; with permission.

undergoing sublobar resections. The ipsilateral phrenic nerve was removed with the RM in 50 patients. A great vein was excised with the RM in 39 patients and prosthetic venous reconstruction performed in 10 of these cases. Two patients underwent patch repair of a superior vena cava defect. Cardiopulmonary bypass was required in six patients; four of these required excision and patch repair of the right atrial free wall and two underwent patch repair of the main pulmonary artery. Nineteen patients required pulmonary metastastectomy and 16 patients have undergone staged extrathoracic metastastectomy for either synchronous or metachronous disease including bone ( $n = 5$ ), cervical lymph node ( $n = 4$ ), and central nervous system ( $n = 3$ ).

To decrease the risk of pulmonary complications, efforts are made to minimize intravenous fluid administration and oxygen levels during and immediately after surgery, particularly for patients who have received bleomycin. The vast majority

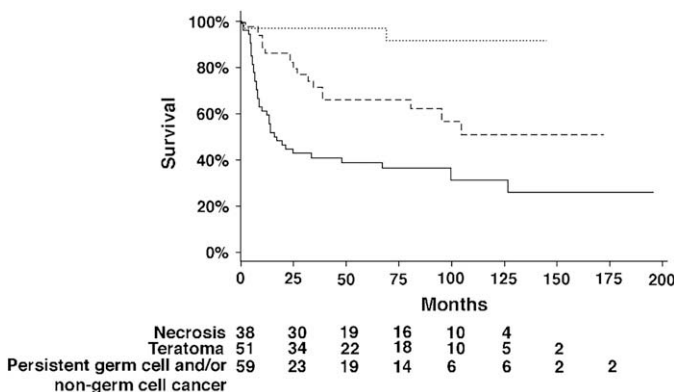
of postchemotherapy nonseminomatous germ cell tumor patients will present to surgery with a baseline sinus tachycardia, which is not treated with fluid or pharmacologic blockade if blood pressure and urine output remain adequate. Patients who presented to surgery with elevated STMs have STMs measured before hospital discharge and at a 1-month follow-up visit. The authors' routine long-term follow-up includes chest radiographs and STMs on an every 6-month basis for the first 5 years, then yearly thereafter for most patients. For patients pathologically demonstrating a component of teratoma, the authors additionally use CT imaging during follow-up, as surgery for early recurrence of teratoma has a high success rate. In contrast, teratoma, particularly with immature elements, has a propensity to degenerate into malignant histology over time, which carries a significantly worse prognosis despite aggressive surgery.

## SURVIVAL

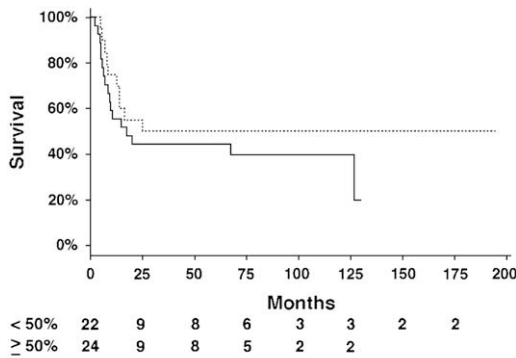
It is well established that the overall survival outcome after multimodality treatment of PMNSGCTs is inferior when compared with nonseminomatous germ cell tumors originating in the testes. Goss and colleagues<sup>19</sup> reported on a 14-year experience in Toronto with 24 PMNSGCT patients, and found a 47% survival at 5 years. A multicenter retrospective study from Spain, involving 27 PMNSGCT patients, reported a 32% 5-year survival; however, 12 of these patients had metastatic disease at the time of presentation.<sup>20</sup> Fizazi and colleagues<sup>21</sup> reviewed 38 PMNSGCT patients, 29 of whom were referred for primary treatment to their institution. Only 10 of these patients have remained disease-free after a median follow-up of 89 months. Inferior survival has been mainly attributed to a higher incidence of cisplatin-refractory nonseminomatous germ cell cancer, including

degenerative non-germ cell cancer present in PMNSGCT, as compared with testes nonseminomatous germ cell tumors. Other factors include the propensity of PMNSGCT patients to develop hematologic malignancies, which are usually fatal.<sup>3,22</sup>

The authors have found that the worst pathology identified in the RM following chemotherapy is independently predictive of long-term survival (Fig. 1).<sup>10,14</sup> Patients who pathologically demonstrate complete tumor necrosis with no evidence of teratoma or viable cancer have an excellent long-term prognosis, with only a rare late death secondary to recurrent disease. In the authors' series, patients with pathologic evidence of teratoma, with or without tumor necrosis, demonstrate intermediate survival. Although considered benign, teratoma in PMNSGCT cases not infrequently contain immature elements. When present, occult teratoma metastases therefore do have potential to degenerate into malignant histology. "Salvage" surgical therapy, where viable nonseminomatous germ cell cancer or non-germ cell cancer are pathologically identified in the RM, results in relatively worse but possible long-term survival, even in the face of rising STMs.<sup>23</sup> From institutional data, patients with less than 50% of the RM containing viable malignancy have an approximate 50% long-term survival following aggressive surgery, which is diminished when greater than or equal to 50% of the RM contains viable malignancy (Fig. 2). Other reports have also found heterogeneous survival for PMNSGCT patients. The Memorial Sloan Kettering Cancer Center reported a series of 49 PMNSGCT patients, 32 of whom underwent surgical resection of residual disease after platin-based chemotherapy.<sup>11</sup> Complete tumor necrosis was identified in 12% of surgical specimens, where teratoma and viable cancer were found in 66%. The overall 2-year survival for their series was 38%. However, an 81%



**Fig. 1.** Long-term survival based on worst pathologic category identified in the RM after cisplatin-based chemotherapy and complete surgery. The pathologic category was independently predictive of survival by multivariable analysis. Numbers represent patients at risk. Necrosis shown by dotted line; teratoma shown by interrupted line; Persistent germ cell cancer or non-germ cell cancer shown by solid line. (From Kesler KA, Rieger KM, Hammoud ZT, et al. A 25-year single institution experience with surgery for primary mediastinal nonseminomatous germ cell tumors. *Ann Thorac Surg* 2008;85:374; with permission.)



**Fig. 2.** A trend toward improved long-term when the amount of viable persistent germ-cell cancer or non-germ cell cancer was less than 50% of the RM (*dotted line*) as compared with 50% or greater (*solid line*). Numbers represent patients at risk. (From Kesler KA, Rieger KM, Hammoud ZT, et al. A 25-year single institution experience with surgery for primary mediastinal nonseminomatous germ cell tumors. *Ann Thorac Surg* 2008;85:374; with permission.)

survival rate was found in patients demonstrating pathology of necrosis or teratoma. A large multicenter review of extragonadal nonseminomatous germ-cell tumor patients, including 287 with PMNSGCT, reported an overall 5-year survival of 45%.<sup>24</sup> Two year survival varied widely in this study, from 34% in the subset of patients who presented visceral metastases to 84% in younger patients without metastases and normal hCG at the time of diagnosis. Only 49% of PMNSGCT patients underwent postchemotherapy surgery in this review. Teratoma and complete necrosis was present in 26% and 37% of patients, respectively; however, the pathology of any excised residual disease was not analyzed with respect to survival outcome.

## SUMMARY

Germ cell tumors originating in the anterior mediastinal compartment represent a rare but biologically interesting group of neoplasms. Knowledge of the specific biologic behaviors and therapeutic strategies for the three histologic types is important. PMNSGCT represent the most challenging group of malignant germ cell tumors and survival outcome is dependant on both successful chemotherapy and surgery to remove residual disease when feasible. The authors currently believe non-bleomycin-containing regimens will reduce operative risks in this regard. New chemotherapy strategies that reduce the incidence of persistent nonseminomatous germ cell or non-germ cell cancer

need continued investigation. Although overall survival is inferior to nonseminomatous germ cell tumors of testicular origin, favorable subsets with pathologic evidence of either necrosis or teratoma have been identified. An aggressive surgical approach after cisplatin-based chemotherapy can result in long-term survival, even in patients with persistent nonseminomatous germ cell or non-germ cell cancer, and is warranted in these otherwise young and healthy patients.

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