

## Mediastinal Germ Cell Tumors: Updates in Diagnosis and Management

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Synopsis:

Primary mediastinal nonseminomatous germ cell tumors represent a rare but important malignancy, which occur in otherwise young and healthy patients. Treatment is challenging and involves cisplatin-based chemotherapy followed by surgery to remove residual disease. Avoiding bleomycin containing chemotherapy in the treatment of primary mediastinal

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nonseminomatous germ cell tumors is important. Pre- and post-chemotherapy pathology as well as postoperative serum tumor markers are independent predictors of long-term survival.

Key words (5-8): Germ cell tumors, Mediastinal tumors, Nonseminomatous germ cell cancer, Thoracic surgery, Chemotherapy

Key Points (3-5, indicating the main teaching points/defining features for the whole article (approximately 25 words each, with a total of 125 words):

- Primary mediastinal nonseminomatous germ cell tumors represent a rare but important malignancy, which occur in otherwise young and healthy patients.
- Treatment is challenging and involves cisplatin-based chemotherapy followed by surgery to remove residual disease.
- Avoiding bleomycin containing chemotherapy in the treatment of primary mediastinal nonseminomatous germ cell tumors is important.
- Pre- and post-chemotherapy pathology as well as postoperative serum tumor markers are independent predictors of long-term survival.

## INTRODUCTION

The mediastinum is the most common site of extragonadal origin of germ cell tumors, with 5 to 10% of germ cell tumors arising primarily within the anterior mediastinum and accounting for 15-20% of all anterior mediastinal tumors. (1, 2) Mediastinal germ cell tumors are comprised of three distinct histologic types. Teratoma (mature and immature subtypes), seminoma, and nonseminomatous germ cell tumors. Mature teratomas comprise 60-70% of mediastinal germ cell tumors and are considered benign, and surgical resection is curative. Immature teratomas behave more aggressively and have poor outcomes as compared to their mature counterparts. Primary mediastinal seminomas represent about 40% of malignant mediastinal germ cell tumors. Seminomas are sensitive to chemotherapy and have excellent cure rates with cisplatin-based treatment. Primary mediastinal nonseminomatous germ cell tumors (PMNSGCT) represent the majority of malignant mediastinal germ cell tumors. These tumors are typically aggressive with a poor-risk profile, and overall long-term survival averages 40-50%. (3) Treatment for PMNSGCT consists of cisplatin-based chemotherapy followed by surgical resection of residual tumor mass. The remainder of this section focuses on the diagnosis and contemporary multimodality strategy for the treatment of PMNSGCT.

### Pathogenesis

Primary mediastinal nonseminomatous germ cell tumors represent a rare but important malignancy, accounting for 1% of all mediastinal tumors and the majority of malignant germ cell tumors of the mediastinum. These tumors occur almost exclusively in young adult males, most commonly between the ages of 20-40 years.

Histologically, these neoplasms are typically mixed, and contain at least one nonseminomatous germ cell cancer subtype (yolk sac tumor, embryonal carcinoma, choriocarcinoma) as well as

some form of teratomatous pathology, ranging from mature teratoma to teratoma with immature or “atypical” elements, and occasionally frank malignant transformation of teratoma into so-called “nongerm cell” cancers (sarcomas and epithelial carcinomas). The admixture contains variable amounts of these nonseminomatous histologies, as well as malignant seminoma, on occasion.

## DIAGNOSIS

Patients with PMNSGCT are usually symptomatic on presentation. Clinical findings are consistent with a growing mediastinal mass, such as cough, shortness of breath, chest pain or superior vena cava syndrome. CT imaging usually reveals a large heterogenous mass in the anterior mediastinum (Figure 1). These are aggressive tumors with local invasion into surrounding structures common at the time of presentation. Metastatic disease was present at diagnosis in 32% of 244 patients in our recent institutional series, with lung being the most common site, followed by mediastinal and extrathoracic lymph nodes, liver, and central nervous system (CNS). (4) Chest and abdominal CT scans are standard imaging tests for staging, with other radiologic studies, including positron emission tomography (PET) scan and MRI, acquired on a case-by-case basis.

Obtaining serum tumor markers (STM) on a young male presenting with an anterior mediastinal mass is essential to establish a diagnosis of PMNSGCT. Any elevation in alphafetoprotein (AFP) or significant elevation in  $\beta$ -human chorionic gonadotropin ( $\beta$ HCG) >100 unit/liter is diagnostic of PMNSGCT. In patients with diagnostic STM elevation, prompt cytologic confirmation can be obtained with CT-guided biopsy, if desired. Biopsy, either CT-guided or surgical when CT-guided is not feasible, is obtained in cases where AFP is normal and  $\beta$ HCG marginally elevated, potentially indicative of seminoma.

## TREATMENT

### Chemotherapy

The treatment strategy for PMNSGCT is multimodal therapy with cisplatin-based chemotherapy as initial treatment followed by surgical resection of residual tumor. Development of cisplatin-based combination chemotherapy for NSGCT has been responsible for vastly improved long-term survival rates as compared to outcomes in the pre-cisplatin era. Four courses of bleomycin, etoposide, and cisplatin chemotherapy have traditionally been considered the standard of care for patients with “poor-risk” NSGCT, including PMNSGCT. However, the magnitude of post-chemotherapy surgery for PMNSGCT is usually high and carries significant risk of pulmonary-related morbidity, including development of acute respiratory distress syndrome (ARDS). Pulmonary toxicity is a well-known consequence of bleomycin. In order to avoid the compounding effect of bleomycin on the postoperative pulmonary risk associated with mediastinal and intrathoracic resection, over the past 15 years, our institution has been using a VIP regimen as the chemotherapy of choice for PMNSGCT. We have experienced a reduction in postoperative respiratory failure in PMNSGCT patients who received non-bleomycin containing regimens as compared to patients who received bleomycin, despite similar extent of surgery including pulmonary resections.(5, 6) We recently updated our institutional experience and demonstrated a 14.8% rate of postoperative pulmonary failure, which carried 40.7% mortality in these otherwise young and healthy patients, after bleomycin-containing regimens, compared to an incidence of 2.6% in patients who received VIP. (4) Postoperative pulmonary complications and ARDS carry significant associated morbidity. Therefore, following chemotherapy strategies that minimize the risks of ARDS remains important.

## Surgery

Ideally, STM levels normalize after chemotherapy, or at least significantly decrease, and tumor dimension shrinks. However, there always remains a residual mediastinal mass, the majority of which contain residual disease for which surgical resection is indicated. Most residual tumor masses contain teratoma, persistent nonseminomatous germ cell cancer, and non-germ cell cancer cells, and complete tumor necrosis is found in only a minority of cases. (7) Surgery to remove residual disease is typically planned 4 to 6 weeks following chemotherapy to allow for patient recovery. The standard of care for testicular NSGCT patients who relapse serologically shortly after first-line chemotherapy involves second-line chemotherapy, prior to considering surgery. However, response rates of standard cisplatin-based salvage chemotherapy for PMNSGCT are notoriously poor. (8) Moreover, while elevated STM are diagnostic of PMNSGCT, postchemotherapy STM lack high sensitivity or specificity for residual NSGCT. Finally, the propensity of PMNSGCT to transform into nongerm cell cancers, which are typically STM negative as well as refractory to chemotherapy, further questions the role of second-line chemotherapy prior to surgery. We, therefore, subscribe to a policy of removing residual disease if deemed operable, regardless of STM status, as the overall results of surgical “salvage” in patients with residual malignancy after first-line chemotherapy appear to be superior as compared to response rates of second-line chemotherapy. (9, 10)

Patients are rarely considered to be inoperable, however, extensive great vessel or middle mediastinal involvement may preclude safe resection. For patients with persistent metastatic disease after first-line chemotherapy, we utilize an individualized approach. Those patients with normal STM after first-line chemotherapy, non-pulmonary and pulmonary metastases are resected when feasible, particularly if suspicious for teratoma. Extrathoracic metastases are typically removed as a staged procedure before or after mediastinal surgery. Surgery is

undertaken for select patients with elevated STM and limited areas of pulmonary metastases deemed resectable at the time of surgery to remove the residual mediastinal mass. For patients with elevated STM after first-line chemotherapy and systemic or extensive pulmonary metastases, second-line chemotherapy, more recently in form of high-dose chemotherapy with peripheral stem cell transplantation, should be given prior to proceeding with surgery. (11) Patients with elevated STM after first line chemotherapy due to an isolated central nervous system (CNS) metastasis can be treated with stereotactic radiation and/or surgery with CNS disease control prior to removal of mediastinal disease. Rare patients demonstrate a “growing teratoma syndrome,” defined by a rapidly growing symptomatic mediastinal mass with decreasing STM prior to completion of four chemotherapy cycles. (12) In these cases, chemotherapy is discontinued, and urgent surgery undertaken.

Surgery can be challenging, as chemotherapy results in fibrosis of mediastinal tissues surrounding residual disease. Our technique to remove residual mediastinal tumor has been described. (13) We start by selecting an approach (median sternotomy, “clamshell” with transverse sternotomy, anterolateral thoracotomy, or sternotomy combined with separate thoracotomy) to optimize exposure of technically difficult areas anticipated during surgery. Surgical removal involves en bloc dissection of the residual mass and surrounding involved structure with an ultimate goal of obtaining an R0 resection (Table 1). A balanced surgical approach is utilized to spare critical structures such as phrenic nerves, main pulmonary arteries, great veins, and cardiac chambers where the residual mass abuts but does not grossly invade, using intraoperative frozen section for margin control. In cases where phrenic nerves are removed en bloc, prophylactic diaphragm plication can be performed on an individual basis. With respect to the great veins, reconstruction is done in all cases where en bloc superior vena cava resection is required. If one innominate vein is involved, ligation can be performed without reconstruction. A single vein reconstruction technique is used for cases that require bilateral

innominate vein removal, preferably the right innominate to superior vena cava with ligation of the left innominate vein. Our conduit preference for great vein reconstruction is cryopreserved descending thoracic aortic allografts. Cardiopulmonary bypass capabilities should be made available for select patients with great vessel or cardiac involvement. Perioperative fluid and oxygen administration should be kept to a minimum, particularly in patients who may have received bleomycin prior to surgery.



Table I. Anatomical Structures Removed with Residual Mass

Variable (Total n=244)	No. (%)
Organs removed, any	228 (93.4)
1	37 (15.2)
>1	191 (78.3)
Pericardium	195 (79.9)
Phrenic nerve	74 (30.3)
Right phrenic nerve	19 (7.8)
Left phrenic nerve	51 (20.9)
Diaphragm plication	15 (6.1)
Great vein, any	64 (26.2)
Right innominate	12 (4.9)
Left innominate	54 (22.1)
Superior vena cava	25 (10.2)
Inferior vena cava	1 (0.4)
Cardiac Chamber	9 (3.9)
Right atrium	5 (2.2)
Left atrium	2 (0.9)
Left ventricle	2 (0.9)
Chest wall	9 (3.9)
Diaphragm	8 (3.5)
Pulmonary Resection	165 (72.3)
Segment or wedge	77 (33.8)
Lobectomy	55 (24.1)
1	35 (15.4)
>1	20 (8.8)
Pneumonectomy	12 (5.3)

Table I. Anatomic structures removed en bloc with the residual mass after chemotherapy in 244 operative survivors with primary mediastinal nonseminomatous germ cell tumors.

Data from: Outcomes Following Surgery for Primary Mediastinal Nonseminomatous Germ Cell

Tumors in the Cisplatin Era. Kesler, Kenneth A. et al. The Journal of Thoracic and

Cardiovascular Surgery, Published online April 22, 2020

## Follow up

Patients who present to surgery with elevated STM should have STM measured prior to hospital discharge and at one month postoperatively. Patients with pathologic evidence of viable NSGCT and normal postoperative STM should be given two additional cycles of etoposide/cisplatin. Current practice includes consideration of high-dose chemotherapy for patients with persistently elevated postoperative STM and recurrent PMNSGCT. (11) Routine long-term follow-up includes chest radiographs and STM every 2 months for the first year, every 4 months for the second year, every 6 months years 3 through 5, then annually. For patients who pathologically demonstrate a component of teratoma, CT imaging is also recommended during follow-up. Patients with recurrent disease are treated on an individual basis, with surgery favored for teratoma and limited areas of malignancy.

## Outcomes

Serum tumor markers appear to remain important from a prognosis standpoint. By univariate analysis, our recent study demonstrated that preoperative elevated AFP, elevated STM in general, and rising STM were predictive of poor survival while normal STM was protective. Even though elevated postchemotherapy STM did not remain statistically significant in the multivariate model, persistent elevation of STM after surgery, likely indicative of residual microscopic NSGCT, was predictive of adverse survival.(4) Our institutional approach now utilizes high-dose chemotherapy in patients with rising postoperative STM with an expectation of low but improving cure rates. (11) A multicenter review of extragonadal NSGCT patients, including 341 with PMNSGCT, identified pretreatment elevated  $\beta$ HCG and non-pulmonary visceral metastases as adverse risk factors. (14) Of note, less than half of PMNSGCT patients in this study underwent postchemotherapy surgery. Although prechemotherapy tumor histology

was not provided, it is plausible that elevated  $\beta$ HCG was a surrogate for the presence of choriocarcinoma, which was independently predictive in our recent series. Conversely, pure mediastinal seminomas have extremely high cure rates with cisplatin-based chemotherapy alone. (3,4) While all patients in our recent series had serologic or pathologic evidence of NSGCT, it is perhaps not surprising that the subset of cases with tumors containing a malignant seminoma component had significantly improved survival.

Although overall long-term survival averages 40 to 50%, individual survival after surgery for PMNSGCT has been reported to range widely, with rates reported between 30-90%. Similar to prechemotherapy pathology, pathology identified in resected mediastinal masses can be quite variable and mixed, potentially containing elements of tumor necrosis, teratoma, and malignancy. Current and previous studies from our institution as well as a report from Memorial Sloan Kettering Cancer Center continue to demonstrate the pathology identified in the residual mass following chemotherapy is independently predictive of long-term survival and largely responsible for variable survival rates (Figure 2). (4, 5, 15) Patients who demonstrate complete tumor necrosis have excellent long-term prognosis. Patients with pathologic evidence of teratoma, with or without tumor necrosis, demonstrate intermediate survival. The poorer prognosis of PMNSGCT as compared to testicular NSGCT is not only due to a relative resistance to cisplatin-based chemotherapy but a higher propensity of teratoma in PMNSGCT to undergo malignant transformation into nongerm cancers. (16, 17) Teratoma with stromal atypia arguably represents the precursor to nongerm cell cancer. While sarcomas predominate, the spectrum of nongerm cell pathology in residual mass lesions is a testimony to the pluripotent nature of these tumors. Interestingly, the subset of patients who pathologically demonstrate teratoma with stromal atypia have long term survival similar to patients with residual malignancy, which diminishes overall survival in the teratoma category. We speculate that pathologic sampling error in large residual masses where small areas of frank nongerm cell

cancer are missed, or perhaps observer variability (severe atypia vs. frank nongerml cell cancer) could be contributing factors to this finding.

Surgery has the ability to “salvage” patients with pathologic evidence of malignancy in the form of either viable NSGCT and/or nongerml cell cancers with poor but possible long-term survival. Impressively, patients with <50% of the residual mass containing viable malignancy have been shown to have long-term survival equivalent to the overall survival of patients whose “worst” pathology was teratoma. However, survival significantly diminishes when ≥50% of the residual mass contains viable malignancy. (4, 5)

### Conclusion

Primary mediastinal nonseminomatous germ cell tumors represent a challenging group of malignant germ cell tumors. Avoiding bleomycin-containing chemotherapy prior to these major thoracic surgical procedures is important. Pre- and post-chemotherapy pathology, as well as postoperative STM, are independent predictors of long-term survival. Although overall PMNSGCT survival remains inferior to testicular NSGCT, an aggressive surgical approach can be justified in these otherwise young and healthy patients.

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## FIGURES

Figure 1. Illustrative chest CT images of patients presenting with PMNSGCT demonstrating heterogenous tumors arising from the anterior mediastinum.

Figure 2. Long-term survival in a series of 244 operative survivors with primary mediastinal nonseminomatous germ cell tumors based on the “worst” pathologic diagnosis microscopically identified in the residual mass (necrosis, teratoma or malignant).

Data from: Outcomes Following Surgery for Primary Mediastinal Nonseminomatous Germ Cell Tumors in the Cisplatin Era. Kesler, Kenneth A. et al. *The Journal of Thoracic and Cardiovascular Surgery*, Published online April 22, 2020