Resection of Malignant Mediastinal Germ Cell Tumors

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Kenneth A. Kesler

Introduction

The anterior mediastinum represents the second most common site of germ cell tumor origin. Nonseminomatous germ cell cancers comprise the main category of malignant germ cell tumors arising in the mediastinum (PMNSGCT). Although histologically similar to their testicular counterparts, PMNSGCT have an overall worse prognosis and therefore have been categorized as "poor-risk" nonseminomatous tumors.

Most PMNSGCT occur in men 20–40 years of age, with extremely rare cases occurring in women. Most patients present with symptoms due to a rapidly growing anterior mediastinal mass. CT scans typically demonstrate a large heterogeneous mass. Local invasion into lung, great vein, and pericardium is common. Chest wall invasion or direct cardiac chamber/proximal great artery involvement also occasionally is present. Pericardial and pleural effusions are common but typically not malignant in nature. For any young male adult presenting with a mass in the anterior compartment, obtaining serum tumor markers (STMs; alpha fetoprotein and human chorionic gonadotropin) is an essential component of clinical evaluation, as a significant elevation in either STM is diagnostic for PMNSGCT. In these cases, biopsy not only is unnecessary but may be misleading because of sampling error within these typically large and heterogeneous neoplasms.

Histologically, these neoplasms are composed of at least one nonseminomatous germ cell cancer subtype (yolk sac cancer, embryonal carcinoma, or choriocarcinoma) and frequently are mixed with some form of teratomatous pathology, ranging from mature teratoma to teratoma with immature elements ("stromal atypia") and, finally, to frank malignant degeneration of teratoma into so-called non–germ cell cancer (sarcomas and epithelial carcinomas). Metastatic disease is present in 20–25 % of cases prior to chemotherapy, with lung being the most common site. Chest and abdominal CT scans are standard imaging tests for staging with other radiologic studies, including positron emission tomography (PET) and central nervous system MRI scans obtained on an individual basis. Gated MRI or echocardiography may help determine the presence of great vessel or cardiac involvement; however, invasion may be subtle and apparent only at the time of surgical resection. We therefore have cardiopulmonary bypass capabilities available for these cases.

After diagnosis and staging, surgical resection for PMNSGCT as initial therapy rarely will achieve local control and does not treat metastatic disease if present. Appropriate therapy typically begins with cisplatin-based chemotherapy. More recently, VIP (etoposide, ifosfamide, and cisplatin) combination chemotherapy has been recommended to eliminate the possibility of bleomycin-induced pulmonary toxicity before a major thoracic surgical procedure. Following chemotherapy, there typically is resolution of pleural and pericardial effusions and a significant decrease in STMs, as well as a reduction in tumor dimensions. However, a residual mediastinal mass (RM) invariably still is present and pathologically contains complete tumor necrosis in only a distinct minority of cases. Therefore, teratoma, persistent nonseminomatous germ cell, or non–germ cell cancer is pathologically present in most RMs, which is an indication for surgery. Unfortunately, postchemotherapy PET scanning has no role in determining the need for RM removal, as teratoma does not demonstrate hypermetabolic activity similar to complete necrosis. PEt also lacks sensitivity for identifying microscopic foci of persistent nonseminomatous germ cell 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. Although prechemotherapy STMs are highly diagnostic for PMNSGCT, unfortunately postchemotherapy STMs lack predictive value for either

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residual malignant or benign pathology. Additionally, second-line chemotherapy has a very poor response rate for PMNSGCT refractory to first-line therapy. Therefore, it has been our policy to recommend surgery for patients deemed operable after first-line chemotherapy with persistently elevated or even rising STMs. In this same regard, resection of the RM must proceed carefully with frozen section control of close surgical margins, even in patients with normal preoperative STMs, as up to a third of these patients will pathologically demonstrate malignant elements.

Figure 35.1

The basic premise of our surgical approach involves complete en bloc removal of the RM, thymus, and surrounding involved structures. Surgery for PMNSGCT is technically demanding because 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 that minimizes operative morbidity by preserving critical structures that abut but are not densely adherent to nor directly involved with the RM, such as lung, great veins, phrenic nerves, and occasionally cardiac chambers in which the "pericardial barrier" has been violated. In general, we believe an aggressive approach to remove all visible residual disease, but balanced dissection sparing critical structures with generous use of frozen section analysis, is warranted. This approach has allowed resection of virtually all RMs, including extremely large ones, with tumor-free margins. Although all PMNSGCT arise in the anterior mediastinal compartment, the exact location, size, and degree of adjacent organ involvement of postchemotherapy masses are variable. Therefore, the most critical decision initially is determination of the surgical approach. A median sternotomy, bilateral anterior thoracotomy with transverse sternotomy (the so-called clamshell incision), or anterolateral thoracotomy is chosen to optimize dissection around critical structures likely to be encountered during surgery. Based on referred cases to our institution, we currently use the sternotomy and clamshell approaches with approximately equal frequency. A thoracotomy approach is used for less common lateralized RMs, in which there is no substernal component. A sternotomy approach typically is employed for a midline RM or a midline RM with modest to moderate extension into the right chest. With the use of sternal retractors to mobilize internal thoracic arteries for coronary bypass procedures and instruments designed for minimally invasive pulmonary surgery, en bloc right upper and middle lobectomies, if necessary, can be accomplished through this approach

Figure 35.2

A clamshell approach provides the exposure required for midline tumors with significant extension into the right chest. This approach also is used for a substernal RM with anything more than slight extension into the left chest, as the heart makes it difficult to remove a large RM significantly invading the left lung. The patient is positioned supine with both arms crossed, padded, and then secured to an ether screen above the head. Following resection, it is important to perform longitudinal stabilization with short-length but threaded Kirschner pins carefully placed across the transverse sternotomy in addition to standard sternal wires to avoid painful sternal nonunion and secondary subluxation. On a final note, rare patients with both significant substernal and pleural space involvement in which the RM extends inferiorly to the diaphragm may benefit from a sequential sternotomy then thoracotomy approach, as inferior dissection is difficult through a clamshell incision

Figure 35.1

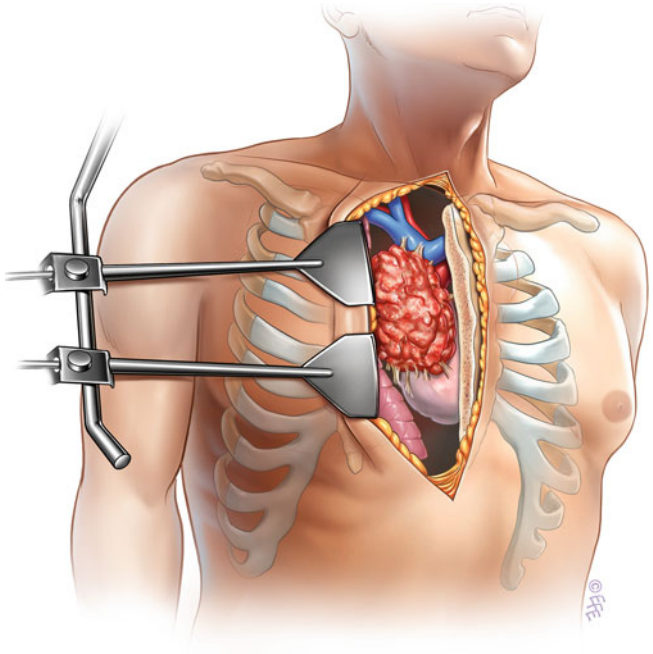


Figure 35.2

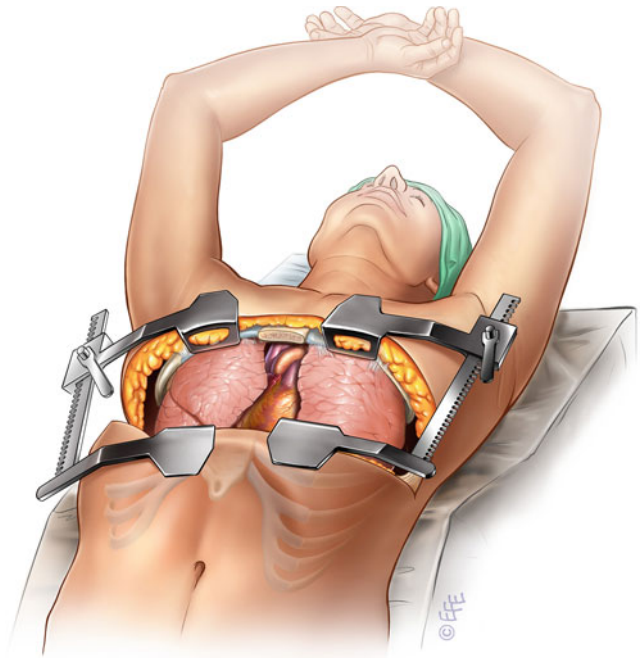


Figure 35.3

For most patients who do not demonstrate CT evidence of frank chest wall/sternal involvement, we begin with an extrapleural dissection until it can be determined that the RM does or does not involve the parietal pleura. The pleural space is entered at any point if the RM is found not to be adherent. If the RM is adherent, then at least a 1-cm rim of visibly normal parietal pleura is removed en bloc. Unfortunately, given the variability in location, size, and degree of the adjacent organ involvement of postchemotherapy masses, there is no consistent step-by-step surgical routine. In general, however, a surgical strategy proceeding from the easiest to the most difficult works best. Typically, we begin by dissecting adherent lung tissue from the RM, particularly if this involves lysis of filamentous adhesions or a stapled wedge resection removing a rim of lung parenchyma more densely adherent to the RM. Stapled wedge resection may be facilitated by passage of a red rubber catheter between the RM and pulmonary hilum for elevation and lateral retraction of the lung parenchyma before stapler division. Invasion of the RM into a significant amount of pulmonary parenchyma or pulmonary hilum usually requires formal anatomic resection**,** which may be done at this point or after further dissection. In our institution's experience, more than half of PMNSGCT patients require some form of en bloc pulmonary resection. Formal lobectomy has been required in approximately a third of patients, wedge resection in 20 %, and total pneumonectomy in 5 %. We typically proceed with dissection of uninvolved tissues superior and inferior to the RM. The thymic horns rarely are involved and may be mobilized from the neck easily. Below, the pericardial fat is mobilized along with uninvolved contiguous thymic tissue to within 1 cm of the RM. Typically, the RM is densely adherent to the pericardium. Because there is little downside to pericardectomy, no attempt is made to separate the RM from the pericardium and the pericardium removed en bloc with a 1-cm tumor-free margin. Inspection of underlying cardiac structures, including a determination of whether the RM has transgressed the pericardial barrier, is made at this time. Occasionally, inflammatory adhesions to the epicardial surface are present and may be lysed with frozen section control. Division of the pericardium around the inferior aspect of the RM also may facilitate dissection around more critical structures, such as great veins and phrenic nerves. Following resection, pericardial reconstruction should be performed for most defects, using either fenestrated thin-walled polytetrafluoroethylene or absorbable mesh to eliminate the possibility of cardiac herniation

Figure 35.3

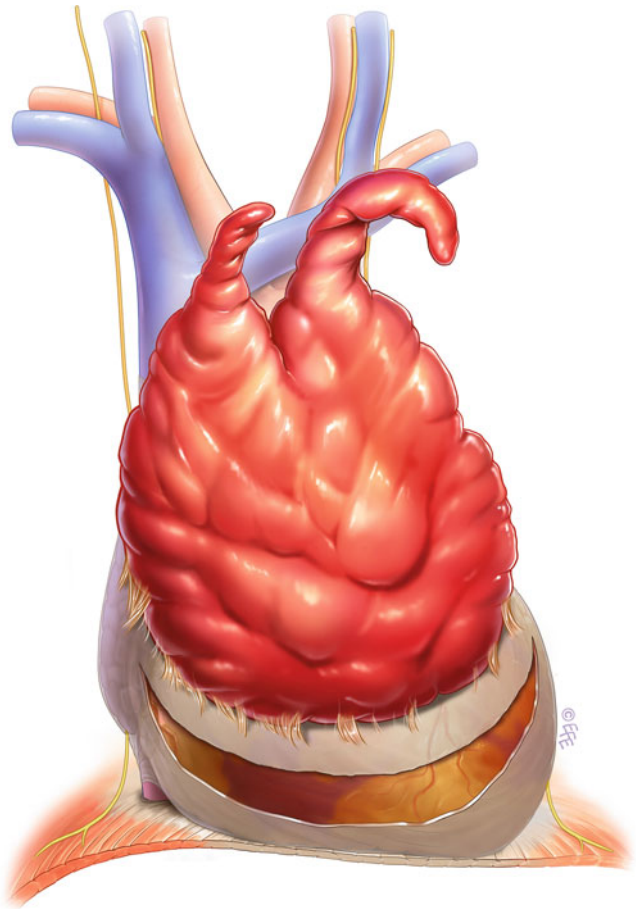


Figure 35.4

Many RMs are close to the left brachiocephalic vein. If there is no evidence of frank invasion, an attempt may be made to spare the left brachiocephalic vein with frozen section control; however, if the RM is found to be densely adherent to the left brachiocephalic vein, then en bloc removal without reconstruction is warranted, as there typically is only minor left upper extremity venous insufficiency in these cases. If both brachiocephalic veins or the superior vena cava (SVC) are removed en bloc with the RM, which in our experience has been necessary in approximately 10 % of cases, then we prefer unilateral right brachiocephalic to SVC reconstruction using an externally stented polytetrafluoroethylene vascular prosthesis. More recently, when available, we been utilizing descending thoracic aortic homografts for great vein reconstruction as homograft conduits have excellent tissue handling, wall compliance, and patency. Care must be taken to avoid injury to the right phrenic nerve if it has been preserved during clamping of the right brachiocephalic vein and SVC. Although somewhat more difficult than left brachiocephalic reconstruction, we believe that the "straight, short, and downward" course of a right brachiocephalic to SVC vascular prosthesis, along with a higher venous flow if the left brachiocephalic vein is not reconstructed, will promote patency. Partial SVC defects may be reconstructed with a patch of autologous pericardium

Figure 35.5

One phrenic nerve almost always is found close to the RM. If there is clear evidence of frank unilateral phrenic nerve invasion, either at the time of surgery or with preoperative CT evidence of diaphragmatic paralysis, then early en bloc phrenic nerve resection will facilitate the remaining dissection, including exposure of hilar structures. More commonly, however, the ability to spare or the necessity to remove a phrenic nerve near the RM can be determined only at the time of surgery. In these cases, phrenic nerve dissection is best deferred until the later stages of the surgical procedure. The pericardiophrenic fat pat usually is densely adherent and at times imperceivably "blends" into the fibrotic soft tissue surrounding the RM. In these cases, an attempt to free the phrenic nerve with frozen section control may be challenging but minimizes short- and long-term morbidity. The phrenic nerve initially is identified proximal and distal to the area of the RM. Careful blunt dissection with the tip of a "cold" electrocautery blade or clamp may facilitate developing a plane between the phrenic nerve and RM, controlling pericardiophrenic bleeding with topical hemostatic agents after resection if necessary. Again, frozen section control of close surgical margins in which the phrenic nerve has been preserved is obtained. En bloc phrenic nerve resection has been required in almost one third of our surgical cases. Bilateral phrenic nerve removal has never been necessary in our experience and should be avoided at all costs. Prophylactic diaphragmatic plication should be considered after the RM is removed. Although not mandatory we have more recently been performing modest plications if an ipsilateral lobectomy or pneumonectomhy is required with phrenic nerve resection. While diaphragmatic plication is not absolutely necessary after lobectomy or pneumonectomy, more recently we have been performing moderate plications in these cases

Figure 35.4

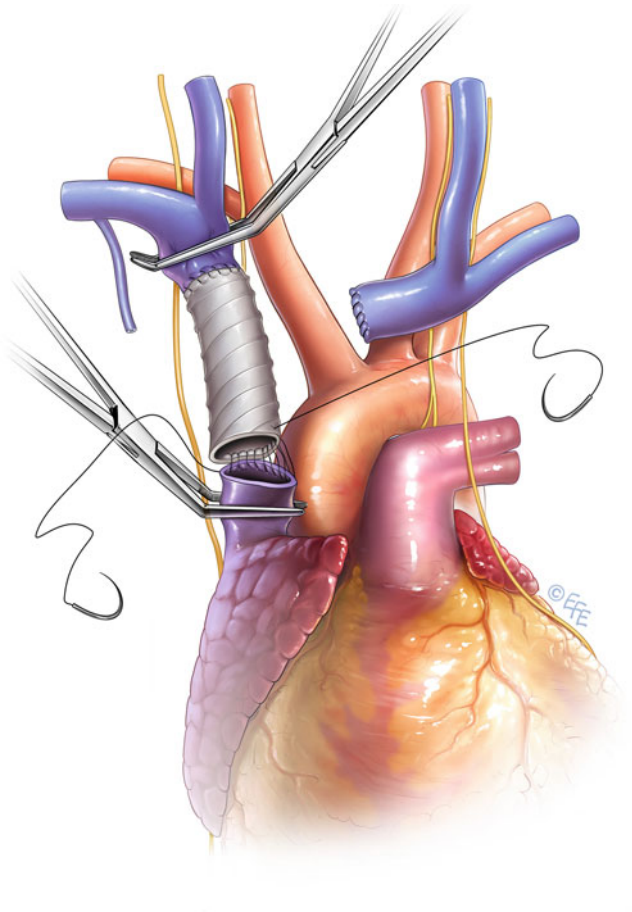
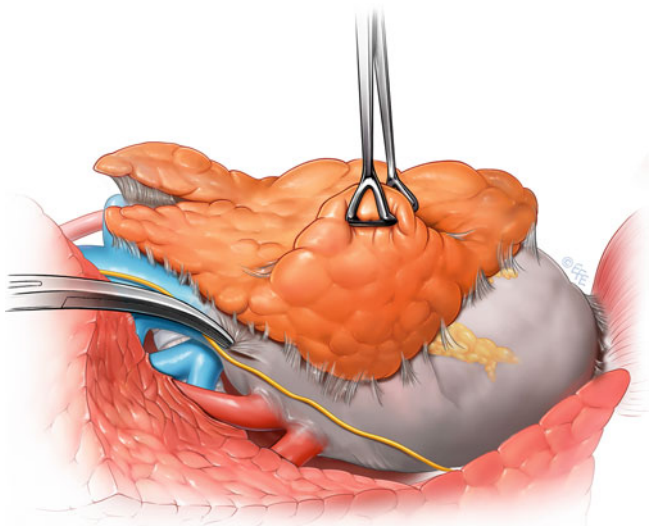


Figure 35.5



Conclusion

Cardiopulmonary bypass has been required in approximately 5 % of cases. Most of these patients required excision and patch repair of the right atrial free wall; however, two patients underwent patch repair of the main pulmonary artery. These excisions and repairs usually can be performed with normothermic cardiopulmonary bypass using bicaval venous cannulation, allowing the heart to beat "empty" with control of the coronary sinus return through a cardiotomy sucker.

When required, the timing of pulmonary metastasectomy 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 metastasectomy. Pulmonary metastasectomy usually can be accomplished at the time of surgery to remove the RM; however, we do not hesitate to stage pulmonary metastasectomy after recovery if deemed prudent. Finally, approximately 10 % of patients in our surgical series have undergone staged extrathoracic metastasectomy for either synchronous or metachronous metastases to other organs, including bone, cervical lymph node, and central nervous system.

Patients who presented to surgery with elevated STMs have these markers measured before hospital discharge and at the 1-month follow-up visit. Our routine long-term follow-up for most patients includes chest radiographs and STMs every 6 months for the first 5 years, then yearly. For patients pathologically demonstrating a component of teratoma in the resected RM, additional CT imaging during follow-up is justified because surgery for early recurrence of teratoma has a high success rate.

The "worst" pathology identified in the RM following chemotherapy is independently predictive of long-term survival. 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 our 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. If present, therefore, occult teratoma metastases do have the potential to degenerate into malignant histology. "Salvage" surgical therapy in which viable nonseminomatous germ cell or non–germ cell cancer is pathologically identified in the RM results in relatively worse but possible long-term survival, even in the face of rising STMs.

PMNSGCT represent a challenging group of malignant germ cell tumors, and survival depends on both successful chemotherapy and surgery to remove residual disease when feasible. New chemotherapy strategies, which reduce the incidence of persistent nonseminomatous germ cell and/or non–germ cell cancer, need continued investigation. Postchemotherapy mediastinal surgery typically is demanding. Choosing a surgical approach that provides optimal exposure of the RM and surrounding structures is paramount. An aggressive but balanced surgical approach can remove extremely large RMs with tumor-free margins and is warranted in these young, otherwise healthy patients.

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