Outcomes Following Surgery for Primary Mediastinal Nonseminomatous Germ Cell Tumors in the Cisplatin Era

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ABBREVIATIONS

NSGCT-Nonseminomatous germ cell tumor

PMNSGCT-Primary mediastinal nonseminomatous germ cell tumor

STM-Serum tumor markers

AFP-Alphafetoprotein

ßHCG-Beta human chorionic gonadotropin

CNS-Central nervous system

SVC-Superior vena cava

VIP-Etoposide, ifosfamide, cisplatin

ARDS-Acute respiratory distress syndrome

CENTRAL PICTURE (FIGURE 4 GRAPHICAL ABSTRACT)

Diagnostic approach, treatments, short and long-term outcomes of 255 PMNSGCT patients.

CENTRAL MESSAGE

Avoiding bleomycin containing chemotherapy in the treatment of PMNSGCT is important. Pre- and post-chemotherapy pathology as well as postoperative STM are independent predictors of long-term survival.

PERSPECTIVE STATEMENT

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. This study represents the largest single institutional series in the cisplatin-era to define short and long-term outcomes after surgery.

ABSTRACT

Objective: Treatment of primary mediastinal nonseminomatous germ cell tumors (PMNSGCT) involves cisplatin-based chemotherapy followed by surgery to remove residual disease. We undertook a study to determine short and long-term outcomes.

Methods: A retrospective analysis of PMNSGCT patients who underwent surgery at our institution from 1982 to 2017 was performed.

Results: A total of 255 patients (mean age 29.2 years) were identified. Acute respiratory distress syndrome (ARDS) occurred postoperatively in 27 (10.9%), which was responsible for all 11 (4.3%) postoperative deaths. Of patients who developed ARDS, more patients received bleomycin-containing chemotherapy (n=25/169, 14.8%) than non-bleomycin regimens (n=2/77, 2.6%) (p=0.004). With respect to variables independently predictive of long-term survival, evidence of choriocarcinoma prior to chemotherapy (n=12) was determined to be an adverse factor (p=0.006). In contrast, biopsy-proven elements of seminoma (n=34) was predictive of improved survival (p=0.04). The "worst" pathology identified in the residual mediastinal mass after chemotherapy: necrosis in 61 (25.0%), teratoma in 84 (34.4%), and malignant (persistent germ cell or non-germ cell cancer) in 97 (39.8%), impacted overall survival (p<0.001). Additionally, teratoma with stromal atypia (n=18) demonstrated decreased survival compared to teratoma without atypia (n=66, p=0.031). Patients with malignancy involving >50% of the residual mass (n=47) had a 2.3-fold increased risk of death compared to ≤50% malignancy (n=45,

p=0.008). Finally, elevated postoperative serum tumor markers (n=40) was significantly predictive of adverse survival (*p* <0.001).

Conclusion: In the treatment of PMNSGCT, avoiding bleomycin-containing chemotherapy is important. Pre- and post-chemotherapy pathology as well as postoperative STM are independent predictors of long-term survival.

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INTRODUCTION

Although the majority of nonseminomatous germ cell tumors (NSGCT) originate in the gonads, 5 to 10% arise within the anterior mediastinum, which represents the most common site of extragonadal origin. The treatment of testicular NSGCT with cisplatin-based chemotherapy regimens, followed by surgical resection of residual disease is considered one of the most successful models for multi-modality cancer therapy with greater than 80% overall long-term survival. It has been well established, however, that although histologically and serologically identical to their testicular counterparts, primary mediastinal nonseminomatous germ cell cancers (PMNSGCT) represent a biologically distinct subset of NSGCT with a 40 to 50% overall survival which places PMNSGCT in a "poor risk" category along with other subsets of testicular NSGCT. (1-4) Moreover, surgery can be challenging, as chemotherapy typically results in fibrosis of mediastinal tissues surrounding residual disease. We undertook a retrospective study representing a 10-year update of our previous institutional report to further define short and long-term outcomes after surgery for PMNSGCT. (6)

MATERIALS AND METHODS

Study Design and Patient Selection

A prospective institutional database was queried to identify PMNSGCT patients who underwent surgery following cisplatin-based chemotherapy from 1982 to 2017. A retrospective analysis was undertaken on all identified patients. Data collection consisted of institutional/outside hospital record review and patient/family contact. The study protocol was approved by the Institutional Review Board of Indiana University and informed consent waived.

Institutional Treatment Strategy

Our institutional practice has been to establish a diagnosis of PMNSGCT by obtaining serum tumor markers (STM) in young adult male patients presenting with an anterior mediastinal mass. Any elevation in alphafetoprotein (AFP) or significant elevation in ß-human chorionic gonadotropin (ßHCG) >100 unit/liter is considered diagnostic. In patients with diagnostic STM elevation, prompt cytologic confirmation can be obtained where CT-guided biopsy is deemed feasible but surgical biopsy is not performed. Biopsy, either CT-guided or surgical when CT-guided is not considered feasible, is obtained in cases where AFP is normal and ßHCG marginally elevated, potentially indicative of seminoma. While many patients were diagnosed and subsequently received first and occasionally second-line chemotherapy at the discretion of outside facilities, our

institutional practice remained consistent over the study interval with surgery to remove a residual mediastinal mass, if deemed operable, after first-line cisplatin-based chemotherapy, regardless of STM status. Rare patients were deemed inoperable including for example patients with extensive great vessel or middle mediastinal involvement. This strategy included patients who presented with metastatic disease which resolved after chemotherapy. An individualized approach was utilized for patients with metastatic disease which did not resolve with first-line chemotherapy. For patients with normal STM after first-line chemotherapy, non-pulmonary and pulmonary metastases were resected when feasible, particularly if deemed to represent teratoma. Extrathoracic metastases were typically removed as a staged procedure before or after mediastinal surgery. Surgery was 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, was given prior to considering surgery. (7) Patients with elevated STM after first line chemotherapy due to an isolated central nervous system (CNS) metastasis were treated with stereotactic radiation and/or surgery with CNS disease control prior to removal of mediastinal disease. While the vast majority of patients in this series received four cycles of cisplatin-based chemotherapy prior to surgery, rare patients demonstrated the “growing teratoma syndrome,” defined by a rapidly growing symptomatic mediastinal mass with decreasing STM prior to completion of four chemotherapy cycles. (8) In these cases, chemotherapy was discontinued and urgent surgery undertaken.

The details of our technique to remove residual mediastinal disease have been described previously. (6,8) In brief, an approach was selected to optimize exposure of technically difficult areas anticipated during surgery. Surgical removal involved en bloc dissection of the residual mass and surrounding involved structures. A balanced surgical approach was utilized however, sparing critical structures such as phrenic nerves, main pulmonary arteries, great veins, and cardiac chambers where the residual mass abutted but did not grossly invade with frozen section margin control. In cases where phrenic nerves were removed en bloc, prophylactic diaphragm plication was performed on an individual basis. (Video) With respect to the great veins, reconstruction was done in all cases where en bloc superior vena cava (SVC) resection was required. If one innominate vein was involved, ligation was performed without reconstruction. A single vein reconstruction technique was used for cases where bilateral innominate veins required removal, preferably the right innominate to SVC with ligation of the left innominate vein. Our conduit preference for great vein reconstruction has changed over time. Over last 6 years of this series, cryopreserved descending thoracic aortic allografts were utilized. While rarely needed, cardiopulmonary bypass capabilities were made available for select patients. Perioperative fluid and oxygen administration were kept to a minimum, particularly in patients who received bleomycin prior to surgery.

Patients who presented to surgery with elevated STM had STM measured prior to hospital discharge and at one month postoperatively. Patients with pathologic evidence of viable NSGCT and normal postoperative STM were 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. (7) Routine long-term follow-up included 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 demonstrated a component of teratoma, CT imaging was additionally utilized during follow-up. Patients with recurrent disease were treated on an individual basis, with surgery favored for teratoma and limited areas of malignancy.

Statistical Analysis

Percentages were calculated using known values of each variable as the denominator. Survival was calculated from the date of surgery. Patients who died within 30-days following surgery or prior to hospital discharge were considered operative deaths and excluded from long-term survival analysis. Univariate, bivariate, and multivariable analyses were used to examine the primary endpoints of operative mortality and overall survival. In the univariate analyses, continuous variables were described using mean (±SD) and percentage. In bivariate analyses, chi-square and Fisher's exact tests were utilized as deemed appropriate to identify variables potentially predictive of all-cause mortality. The Kaplan-Meier method was used to calculate survival by "worst" pathology groups (necrosis, teratoma, and malignant). (6) A secondary survival analyses using the Kaplan-Meier method was also performed comparing outcomes of patients with teratoma with and without pathologic evidence of cellular atypia and patients with >50% and

≤50% of the residual mass containing viable cancer. Bivariate Cox proportional-hazard models were used to examine the association between overall survival and each potential variable predicting survival. Multivariable analyses were done using a stepwise estimation method with Cox proportional-hazard model specifying 0.20 as the significant level for removal from the final model and 0.05 for addition to the model. Finally, due to the small sample size, robust variances were utilized to establish inferences about significance of the Cox model. (10) (Stata/SE 14.2, StataCorp 2015 Release 14, College Station, TX)

RESULTS

Demographics at Presentation

A total of 255 patients were identified. Average age was 29.2 ± 8.4 years. All but 5 patients were male (98.0%). Baseline STM status and presence of metastatic disease is given in Table I. In summary, 226 (95.8%) patients had elevated STM, AFP or ßHCG, at the time of diagnosis. Seventy-eight (34.1%) patients presented with evidence of metastatic disease. Two hundred and twenty-five patients (92.2%) underwent mediastinal biopsy prior to receiving chemotherapy (n=82, CT-guided and n=97, surgical biopsy). Of the patients who underwent biopsy, 183 (81.3%) demonstrated NSGCT subtypes, including 129 (57.3%) with yolk sac tumors. Forty-two (18.7%) and 12 (5.3%) patients had embryonal carcinoma and choriocarcinoma, respectively. Other pathology was identified in 98 (43.6%) patients, including teratoma (n=52), seminoma (n=34) and malignant transformation into nongerm cell cancer (n=12).

Chemotherapy and Preoperative STM Status

All patients received cisplatin-based chemotherapy prior to surgery. One hundred and sixty-nine (69.7%) patients received bleomycin-containing combination chemotherapy. Twenty-nine of these patients had ≤ 2 bleomycin cycles while most (n=132) had ≥ 3 cycles (mean 3.5 ± 0.98 cycles). Seventy-seven patients received non-bleomycin

containing regimens, the majority of whom (n=70, 90.9%) received etoposide, ifosfamide and cisplatin (VIP). One patient received initial high-dose chemotherapy with bone marrow transplant on a clinical trial. Sixteen (6.6%) patients received second-line chemotherapy prior to surgery including one patient who received high-dose chemotherapy with stem cell rescue. Eight (3.3%) patients demonstrated a "growing teratoma syndrome" and underwent surgery prior to completing 4 cycles of chemotherapy. Overall, 149 (61.3%) patients presented to surgery with normal STM. Of the 94 patients with documented elevations in STM at surgery, 84 had elevated AFP and 8 had elevated ßHCG. Forty-six patients had rising STM at the time of surgery. Of note, 21 patients underwent a previous attempt at postchemotherapy resection at outside hospitals prior to referral.

Surgery

The operative approaches utilized (in order of frequency) were: median sternotomy (47.1%), "clamshell" with transverse sternotomy (31.0%), anterolateral thoracotomy (17.7%), and sternotomy combined with separate thoracotomy (2.9%). Table II lists adjacent structures and suspected metastatic disease removed. The vast majority of patients (n=228, 93.4%) had at least one adjacent organ removed en bloc with the residual mass. The most common involved structures included pericardium (n=195, 79.9%) and lung (n=165, 72.3%). Phrenic nerve and great vein resections were required in 30.3% and 26.2% of cases respectively. Cardiopulmonary bypass was utilized in 4 patients who required pneumonectomy due to central pulmonary artery involvement

(n=2) and right atrial free wall resection with patch reconstruction (n=2). Six patients underwent a contralateral pulmonary metastatectomy as a planned staged procedure after recovery from initial surgery. Overall, all but 3 patients had R0 resections, with R1 and R2 resections in 2 and 1 patients, respectively.

Postoperative Acute Respiratory Distress Syndrome and Mortality

Twenty-seven (10.9%) patients manifested acute respiratory distress syndrome (ARDS) postoperatively. Of the patients who developed ARDS, significantly more patients had received bleomycin-containing chemotherapy (n=25, 92.6%) than those who had received chemotherapy regimens without bleomycin (n=2, 7.4%) (p=0.004, significance adjusted to the extent of pulmonary resection). There were 11 (4.4%) total postoperative deaths, all of whom died secondary to respiratory failure. Thus, ARDS-related mortality was 40.7% (11/27 patients). All postoperative deaths occurred in patients who received bleomycin (n=11, 6.5%), compared to no deaths in patients receiving non-bleomycin regimens (p=0.019). With respect to mortality in patients who received bleomycin, there was no significant different comparing patients who received ≤ 2 or ≥ 3 cycles (p=0.108). Of the 12 patients who required pneumonectomy, 6 died (50.0%) and, of these, 4 received >2 cycles of bleomycin.

Postoperative Pathology and Adjuvant Chemotherapy

The longest tumor dimension averaged 11.8 ± 5.3 cm. The "worst" histology pathologically identified in the residual mediastinal mass was categorized as: complete necrosis (n=61, 25.0%), teratoma (with or without stromal atypia) (n=84, 34.4%), and malignant (persistent germ cell or malignant transformation into nongerm cell cancer) (n=97, 39.8%) patients. (Table III) With respect to preoperative STM, elevated STM had 47.8% sensitivity and 70.0% specificity for pathologic evidence of viable NSGCT in the residual mass.

Thirty-four (13.9%) patients underwent removal of mediastinal lymph nodes (n=9) or residual pulmonary nodules (n=28). Of these, 14 (41.1%) patients pathologically demonstrated necrosis, 9 (26.5%) demonstrated teratoma, and 4 (11.8%) patients had evidence of malignancy. Fifteen patients underwent removal of extrathoracic metastatic disease, and the "worst" pathology identified in these specimens was necrosis in 6 (40.0%), teratoma in 2 (13.3%), and malignancy in 5 (33.3%). Sixty-three patients received adjuvant cisplatin-based chemotherapy. Five patients underwent pulmonary metastatectomy for recurrent disease. Three of these patients pathologically demonstrated NSGCT, with teratoma and non germ cell cancer found in the other two patients respectively.

Survival Analysis

In operative survivors, mean and median follow-up period were 52 and 26 months respectively, with a range of 1 to 255 months.. At the time of last follow-up, 151 patients

were alive, and 91 patients had died**.** Nineteen patients were lost to long-term follow-up. Cancer was the most frequently determined cause of death (n = 79) with 4 patients dying of bone marrow dyscrasias, mainly acute myeloid leukemia. The cause of death was unknown in 7 cases and a cardiac event in 1 patient. Of patients who died of disease, and the site of first recurrence was known, an intrathoracic recurrence was identified in 12 patients, an extrathoracic recurrence in 13 patients, and both intrathoracic and extrathoracic metastases developed n 22 patients.

Multiple variables were analyzed with respect to long-term survival. (Table IV) Although larger tumor diameter was associated with higher mortality by univariate analysis, this variable did not remain significant in the multivariate model. (Table V) By univariate analyses, normal STM at time of surgery was protective **(**n=149, 61.1%) (*p*=0.001). Conversely, rising preoperative markers (n=46, 18.9%) and elevated AFP (n=84, 34.4%) at surgery were predictors of death (*p*=0.005 and *p*=0.001, respectively), as were elevated postoperative STM (n=40, 16.4%, *p* <0.001). However, only elevated postoperative STM remained significantly predictive of adverse survival by multivariate analysis (HR=3.41, *p*<0.001). Patients with biopsy evidence of choriocarcinoma prior to chemotherapy (n=12, 5.3%) had significantly poorer survival by multivariate analysis compared to patients pathologically demonstrating yolk sac tumor or embryonal carcinoma (HR=3.07, *p*=0.006). In contrast, biopsy-proven elements of seminoma before chemotherapy was independently predictive of improved survival (HR=0.43, *p*=0.04). When eliminating patients who underwent either intrathoracic or extrathoracic metastasectomy with necrosis pathology, our data did not support prognosis based on proposed staging. (11)

The “worst” pathology category identified in the residual mass following chemotherapy significantly impacted long-term survival, with patients pathologically demonstrating complete tumor necrosis having excellent survival, patients with teratoma having intermediate survival, and patients with malignancy identified having inferior survival (p<0.001) (Fig 1). Additionally, teratoma with stromal atypia (n=18) demonstrated decreased overall survival compared to teratoma without atypia (n=66, p=0.031) (Fig 2). Finally, patients with malignancy involving >50% of the residual mass (n=47) had a 2.3-fold increased risk of death compared to patients with malignancy involving ≤50% (n=45, p=0.008) (Fig 3).

DISCUSSION

Primary mediastinal nonseminomatous germ cell tumors represent a rare but important malignancy. Histologically, these neoplasms are typically mixed, comprised of at least one nonseminomatous germ cell cancer subtype (yolk sac tumor, embryonal carcinoma, choriocarcinoma) usually with 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. The admixture contains variable amount of these nonseminomatous histologies, as well as malignant seminoma on occasion.

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. The magnitude of postchemotherapy surgery for PMNSGCT is, however, typically high, with potential for pulmonary-related morbidity. Pulmonary toxicity is a well-known consequence of bleomycin. Over the past 15 years, our institution has been using a VIP regimen as the chemotherapy of choice for PMNSGCT, although we continue to operate on patients referred from outside facilities who have received bleomycin-containing regimens. (12) We have previously cited 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. (13) In this current update, our institution has gone from a 14.8% rate of postoperative pulmonary failure, which carried 40.7% mortality in these otherwise young and healthy patients after bleomycin-containing regimens, to an incidence of 2.6% in patients who received VIP. While over this study interval there have been clear improvements in ARDS management including protective ventilation strategies and extracorporeal membrane oxygenation, which may reduce the mortality of ARDS, ARDS remains a complication with significant associated morbidity. Chemotherapy strategies, which minimize the risks of ARDS , therefore remain important.

Ideally, STM normalize after chemotherapy, and surgery to remove residual disease is planned in 4 to 6 weeks allowing bone marrow and functional 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. Response rates of standard cisplatin-based salvage chemotherapy for PMNSCGT are notoriously poor, however. (14) Moreover, while elevated STM are diagnostic of PMNSGCT, these data demonstrate postchemotherapy STM lacked high sensitivity or specificity for residual NSGCT. Finally, the propensity of PMNSGT 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 have therefore subscribed 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. (15,16)

Serum tumor markers appear to remain important from a prognosis standpoint. By univariant analysis, our current 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. Our institutional approach now utilizes high-dose chemotherapy in patients with rising postoperative STM with an expectation of low but improving cure rates. (7) A multicenter review of extragonadal NSGCT patients, including 341 with PMNSGCT, identified pretreatment elevated ßHCG and non-pulmonary visceral metastases as adverse risk factors. (4) 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 ßHCG was a surrogate for the presence of choriocarcinoma which is independently predictive in our series. Conversely, pure mediastinal seminomas have extremely high cure rates with cisplatin-based chemotherapy alone. (3,4) While all patients in our series had serologic or pathologic evidence of NSGCT, it is perhaps not surprisingly the subset of cases with tumors containing a malignant seminoma component had significantly improved survival.

Two staging systems have been proposed for PMNSGCT. A modification of the AJCC TNM stage for soft tissue tumors, and a novel staging system described by Moran and Suster. (3,11) The latter system involves 3 stages (I-tumor without local invasion or metastases, II with local invasion and without metastases, and IIIA intrathoracic metastases/IIIB extrathoracic metastases) which seems more clinically relevant. There were, however, limitations to this study, including a relatively small patient number and no provision of treatment specifics. A collaborative, multi-institutional study also reported inferior survival in patients presenting with non-pulmonary visceral metastases. (3) When eliminating patients who had metastatic disease removed pathologically demonstrating tumor necrosis only, the Moran staging system was not predictive in our series. Similarly, intrathoracic or extrathoracic metastatic disease at the time of presentation, or removed after chemotherapy, was not predictive. Unfortunately, attempts to develop a reliable staging system for PMNSGCT will be confounded by both relatively small patient numbers as compared to stages established for other solid tumors and the wide spectrum of benign and malignant pathology in the primary tumor and metastatic disease, when present, following chemotherapy.

Although overall long-term survival averages 40 to 50%, individual survival after surgery for PMNSGCT has been reported to widely range 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. (6,17) Patients who demonstrate complete tumor necrosis have an excellent long-term prognosis with only a rare late death secondary to recurrent disease. (Fig 4, Graphical abstract) 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. (18,19) Teratoma with stromal atypia arguably represents the precursor to nongerm cell cancer. While sarcomas predominate, the spectrum of nongerm cell pathology in our series is a testimony to the pluripotent nature of these tumors. Interestingly, the subset of patients who pathologically demonstrated teratoma with stromal atypia had long term survival similar to patients with residual malignancy, which diminished overall survival in the teratoma category in our series. 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 nongerm cell cancer) could be contributing factors to this finding.

This study further validates the ability of surgery to “salvage” patients with pathologic evidence of malignancy in the form of either viable NSGCT and/or nongerm cell cancers with poor but possible long-term survival in these cases. Impressively, the subset of patients with <50% of the residual mass containing viable malignancy had long-term survival equivalent to the overall survival of patients whose “worst” pathology was

teratoma. Survival in this current study was, however, significantly diminished when ≥50% of the residual mass contains viable malignancy. This observation was a trend in our 2008 report, which has become statistically significant with additional patients in this updated institutional experience. (6)

Limitations of this study include the single institution and retrospective natures. Accordingly, referral and other biases may exist. Given the outside nature of many referrals, preoperative diagnosis and management strategies were not uniform, and data collection, including long-term follow up, was not complete. In this regard, we were unfortunately not able to determine the specific cause of late deaths in all cases. Besides disease-related mortality, other potential causes of late death include myelodysplastic syndromes and cardiovascular disease, which PMNSGCT patients appear susceptible. (20,21) Although mortality due to recurrent disease was most probable in these typically otherwise young and healthy patients, accurate disease-specific survival could therefore not be calculated. An underlying strength of this study is however that our institution's case selection, surgical approaches, and perioperative care have remained remarkably constant over the study interval. Finally, it is estimated that 10 to 20% of PMNSGCT patients will be inoperable due to metastatic disease, significant intrathoracic disease, or acute myeloid leukemia. Specific numbers of patients who did not undergo postchemotherapy surgery over this time interval cannot be determined, however. Inclusion of such cases would clearly negatively impact overall survival.

PMNSGCT 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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LEGENDS AND FIGURES

Video. We use one of our more challenging PMNSGCT cases, to demonstrate the key aspects of our surgical techniques to remove a residual mediastinal mass following cisplatin-based chemotherapy.

Figure 1. Long-term survival in 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). Shaded areas represent respective confidence intervals. Survival was significantly longer in those patients with necrosis, followed by teratoma and then malignancy ($p<0.001$). The numbers represent patients at risk per given time interval.

Figure 2. Long-term survival in operative survivors with primary mediastinal nonseminomatous germ cell tumors with teratoma as the "worst" pathology based on the presence or absence of microscopic atypia in the residual mediastinal mass. Shaded areas

represent respective confidence intervals. Survival was significantly worse amongst those patients with atypia identified in the residual mass (p=0.031). The numbers represent patients at risk per given time interval.

Figure 3. Long-term survival of operative survivors with primary mediastinal nonseminomatous germ cell tumors in the subset of patients pathologically demonstrating malignancy (persistent germ cell or transformation into nongerm cell cancer) based on the amount of cancer in the residual mass, ≤50% or >50% viable persistent germ cell or nongerm cell cancer. Shaded areas represent respective confidence intervals. Survival was significantly worse amongst those patients with >50% viable tumor cells (p=0.006). The numbers represent patients at risk per given time interval.

Figure 4 (Graphical abstract). Diagnostic approach, treatments, short and long-term outcomes of 255 PMNSGCT patients.