Is percent seminoma associated with intraoperative morbidity during post-chemotherapy RPLND?

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Introduction: *To evaluate whether varying degrees of seminomatous elements in the primary orchiectomy specimen would be predictive of patient morbidity during post-chemotherapy retroperitoneal lymph node dissection (PC-RPLND) since the desmoplastic reaction with seminoma is associated with increased intraoperative complexity.*

Materials and methods: *We retrospectively identified 127 patients who underwent PC-RPLND for residual retroperitoneal masses. Clinicodemographic, intraoperative, and 30 day postoperative outcomes were compared for patients with pure seminoma (SEM), mixed germ cell tumors (GCT) containing seminoma elements (NS+SEM), and tumors with no seminoma elements (NS). Multivariate logistic regression was used to determine independent predictors of intraoperative and postoperative 30 day complications.*

Results: *We excluded 19 patients who received chemotherapy prior to orchiectomy, 2 patients with primary extragonadal GCT, and 3 patients who underwent re-do RPLND, leaving 103 patients for analysis. Fourteen patients (13.6%) had SEM, 18 (17.5%) had NS+SEM, and 71 (68.9%) had only NS elements. SEM patients were older ($p = 0.03$), had more intraoperative blood loss ($p = 0.03$), and were more likely to have residual seminomatous components in their post-chemotherapy lymph node (LN) histology ($p = 0.01$). Percent seminoma in the orchiectomy specimen was an independent predictor of estimated blood loss > 1.5 liters (odds ratio: 1.04, 95% confidence interval: 1.01-1.07; $p = 0.013$) after adjusting for age, stage, IGCCC risk category, preop chemotherapy, number and largest LN removed, need for vascular or adjacent organ resection (including nephrectomy), and LN histology.*

Conclusions: *Higher percentage of seminoma in the orchiectomy specimen is associated with increased estimated blood loss during PC-RPLND. Percent seminoma, therefore, may be a useful prognostic tool for appropriate pre-surgical planning prior to PC-RPLND.*

Key Words: testicular cancer, germ cell tumor, seminoma, orchiectomy, retroperitoneal lymph node dissection, post-chemotherapy, blood loss

Introduction

Despite the relative chemo-sensitivity observed in testicular germ cell tumors (TGCTs), many patients are found to have residual disease following chemotherapy, necessitating a post-chemotherapy retroperitoneal lymph node dissection (PC-RPLND).[1-3] Following surgical resection of metastatic deposits, a relatively durable survival can be expected, especially in those meeting good or intermediate risk criteria as defined by the International Germ Cell Consensus Classification (IGCCC) system.[4-6] Although surveillance is considered in patients that have experienced a complete response to systemic chemotherapy, it is the combination of chemotherapy and surgical resection that is responsible for the low disease-specific mortality rates observed

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in patients with residual disease following medical therapies.[7,8]

PC-RPLND should be considered in patients with non-seminoma and residual retroperitoneal disease (particularly for a residual mass ≥ 1 cm in diameter) as there is a significant risk for identifying teratoma (35%-45%) and viable malignancy (10%-15%), although the presence of viable GCT compared to teratoma or fibrosis is dependent upon whether patients received standard induction or induction plus salvage chemotherapy regimens.[9] Recommendations for patients with pure metastatic seminoma differ secondary to higher rates of necrosis and fibrosis (80%) and limited viable malignancy (20%) in the final pathology specimens.[10-12] PC-RPLND in patients with pure metastatic seminoma is thus limited to residual disease ≥ 3 cm, or in those who demonstrate evidence of disease progression marked by tumor growth, increasing serum tumor markers, or increased metabolic activity on positron emission tomography (PET) performed at least 6-8 weeks following the completion of systemic chemotherapy.[13,14]

PC-RPLND may result in significant patient morbidity and intraoperative blood loss, and when performed with complete therapeutic intent, necessitates adjacent organ resection or excision of visceral sites of metastatic tumor in approximately 25% of cases.[15] When completed in high volume centers, however, this procedure is considered safe and comparable to primary retroperitoneal lymph node dissection (P-RPLND) with regards to postoperative complications.[15]

The increased desmoplastic reaction encountered in the fibrous residual masses of patients with pure metastatic seminoma represents a unique challenge and has previously been reported to increase the complexity of surgical dissection.[11,16] With increased technical difficulty and close proximity to vital organs and vasculature, PC-RPLND in patients with pure seminoma may result in increased intraoperative complications, blood loss, rates of organ resection, and postoperative complications.[11,16] Whether mixed nonseminatous tumors with seminomatous components, however, share similar characteristics in regards to operative complexity has not yet been established.

Our primary objective in this study was to evaluate the association between the percentage of seminomatous components in the primary orchiectomy specimen and markers of intraoperative morbidity during PC-RPLND, specifically focusing on the primary endpoints of blood loss and the need for vascular or adjacent organ resection (including nephrectomy). As a secondary endpoint, we also evaluated its association with postoperative outcomes, such as 30 day complications and length of stay (LOS). We hypothesized that percent seminoma in the orchiectomy specimen may serve as a potentially useful prognostic marker in the preoperative planning for these patients.

Materials and methods

Following Institutional Review Board (IRB) approval, we retrospectively identified patients who underwent PC-RPLND at our institution for residual retroperitoneal masses following radical orchiectomy and the completion of at least one cycle of cisplatin-based induction chemotherapy between 1992 and 2014. All PC-RPLNDs were performed for residual masses via an open approach and involved a full bilateral template dissection bordered by the renal vessels superiorly, the ureters laterally, and the bifurcation of the common iliac vessels inferiorly. When indicated, a retrocrural, suprarenal, presacral, or pelvic node dissection was performed to remove all residual sites of disease. Involved abdominal viscera or vascular structures were also resected with subsequent reconstruction when necessary to achieve a disease-free status with no visible sites of metastases.

Preoperative clinical and demographic characteristics were identified for each patient including age (in years), body mass index (BMI in kg/m^2), side of the primary testicular tumor, percent seminoma in the orchiectomy specimen, disease stage, IGCCC risk category, last preoperative chemotherapy regimen, number of chemotherapy cycles before surgery, and most recent line of chemotherapy given. All primary orchiectomy specimens were reviewed by our pathologists with expertise in genitourinary malignancies, and post-chemotherapy imaging as well as tumor marker assessment was performed at our facility approximately 2-4 weeks prior to surgery. Staging was re-assigned according to the 2010 American Joint Committee on Cancer system (AJCC).

Intraoperative outcomes such as operative time, estimated blood loss (EBL), use of a blood transfusion, size of largest residual lymph node (LN) mass removed, and number of LNs removed were recorded for each analytic case in the study population. Markers of intraoperative complexity such as vascular or adjacent organ resection (including nephrectomy) were also noted.

Postoperative outcomes, including LN or residual mass histology, complications, and LOS were also recorded. Complications were captured via retrospective chart review of the patient's postoperative course (i.e.

progress notes and discharge summary) and subsequent clinic visits up to 30 days after PC-RPLND. The Clavien-Dindo classification (CDC) was used to categorize 30 day complications with high grade complications defined as Clavien > IIIa. The highest grade was assigned to patients with multiple complications during the 30 day postoperative period. LOS, defined from the time of PC-RPLND until the date of initial discharge, was also captured via chart review.

Continuous variables were reported as means and standard errors (SEs), and categorical variables were reported as frequency counts and percentages. We used the one-way ANOVA test to determine any difference in means between groups, and the chi-square test was used for proportions. We also tested for multicollinearity between variables using the variance inflation factor (VIF). Univariate and multivariate logistic regression analysis were used to determine the association of relevant demographic, clinical, and pathological features with the primary outcome of EBL > 1.5 liters, which represented the highest quartile in the study population, as well as the need for vascular or adjacent organ resection (including nephrectomy). Clinically significant variables were included in the adjusted multivariate model as well as any variable that was statistically different between groups on univariate analysis. Secondary analysis was also performed to determine any relevant association with postoperative outcomes such as 30 day complication rates and LOS. Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS) software package version 21.0 (IBM Corporation, Armonk, NY, USA). All tests were 2-sided with a p value < 0.05 considered as statistically significant.

Results

We retrospectively identified 127 patients who underwent PC-RPLND by four different surgeons for residual retroperitoneal masses for metastatic testicular cancer. Thirty-five patients were treated from 1992-2003, and 92 were treated from 2004-2014. We excluded 19 patients who received chemotherapy prior to orchiectomy, 2 patients with primary extragonadal (retroperitoneal) GCT, and 3 patients who underwent re-do RPLND, leaving 103 for analysis. All patients had negative tumor markers at the time of surgery except three who underwent "desperation" PC-RPLND in the setting of elevated tumor markers after failure of 1st and 2nd line chemotherapy.

In the radical orchiectomy specimen, 14 patients (13.6%) had pure seminoma (SEM), 18 (17.5%) had mixed germ cell tumors containing seminoma elements (NS+SEM), and 71 (68.9%) had tumors with no seminoma elements (NS). The preoperative clinical and demographic features of our study population are listed in Table 1. Patients with SEM were older than NS+SEM and NS patients (mean age: 37.3 versus 29.8 versus 30.6 years, respectively; p = 0.03) but were similar with respects to all other collected variables including disease stage (p = 0.18), IGCCC risk category (p = 0.15), and preoperative chemotherapy used (p = 0.22).

The intraoperative and postoperative outcomes of our study population are listed in Table 2. Patients with SEM had more intraoperative blood loss during PC-RPLND than NS+SEM and NS patients (mean EBL: 2108 mL versus 1838 mL versus 1023 mL, respectively; p = 0.03) and were more likely to have residual seminomatous components in their post-chemotherapy LN histology (14% versus 6% versus 0%, respectively; p = 0.01). The rate of intraoperative blood transfusion (47% versus 33% versus 44%, p = 0.61) and vascular or adjacent organ resection (including nephrectomy) was no different across groups (32% versus 29% versus 24%, p = 0.77). The overall complication rate was 28.8% (n = 30) with 8 patients (7.6%) experiencing a high grade complication during the 30 day postoperative period. There were no intraoperative or postoperative deaths in our study cohort. Furthermore, 30 day postoperative complications (p = 0.53) and mean LOS (p = 0.13) did not differ between groups.

When evaluating a primary endpoint of EBL during PC-RPLND, it did not appear to differ across disease stage (p = 0.38) or IGCCC risk category (p = 0.10) although poor risk patients experienced more intraoperative blood loss than good or intermediate risk patients (mean EBL: 1895 mL versus 1138 mL versus 1032 mL, respectively), Figure 1. On multivariate analysis after adjusting for age, stage, IGCCC risk category, number of preop chemotherapy cycles received, largest LN removed, number of LNs removed, need for vascular or adjacent organ resection (including nephrectomy), and LN histology, percent seminoma in the orchiectomy specimen remained an independent predictor of EBL > 1.5 liters (odds ratio [OR]: 1.04, 95% confidence interval [CI]: 1.01-1.07; p = 0.013), Table 3. Percent seminoma, however, did not show any significant association with rates of intraoperative blood transfusion (p = 0.99) and vascular or adjacent organ resection (including nephrectomy) (p = 0.50), which was another variable significantly associated with excessive blood loss (OR: 9.85, 95% CI: 1.27-76.2; p = 0.028).

On secondary analysis, percent seminoma did not show any relationship with postoperative complications (p=0.44) or high-grade complications (p = 0.91) within 30

TABLE 1. **Preoperative clinical and demographic characteristics**

	SEM (n = 14)	NS+SEM (n = 18)	NS (n = 71)	p value
Mean age, yrs (SE)	37.3 (3.0)	29.8 (1.7)	30.6 (1.1)	0.03
Mean BMI, kg/m^2 (SE)	30.5 (2.7)	28.0 (2.2)	29.2 (1.1)	0.76
Side, no. (%)				0.20
Right	7 (50)	10 (56)	25 (35)	
Left	5 (36)	7 (39)	43 (61)	
Unknown	2 (14)	1 (6)	3 (4)	
Mean %seminoma on orchiectomy specimen, (SE)	100 (0)	31 (7)	0 (0)	< 0.01
Disease stage, no. (%)				0.18
IIA	1 (7)	3 (17)	4 (6)	
IIB	0 (0)	1 (6)	8 (11)	
IIC	5 (36)	1 (6)	11 (16)	
IIIA	0 (0)	2 (11)	8 (11)	
IIIB	6 (43)	6 (33)	16 (23)	
IIIC	2 (14)	5 (28)	24 (34)	
IGCCC risk category, no. (%)				0.15
Good	9 (64)	7 (39)	33 (47)	
Intermediate	5 (36)	5 (28)	15 (21)	
Poor	0 (0)	6 (33)	23 (32)	
Last preop chemo regimen, no. (%)				0.22
BEP	9 (64)	15 (83)	46 (65)	
EP	3 (21)	2 (11)	6 (9)	
TIP	2 (14)	1 (6)	8 (11)	
VIP	0 (0)	0 (0)	11 (16)	
Mean preop chemo cycles, (SE)	4.3 (0.4)	4.1 (0.2)	4.3 (0.2)	0.87
Last preop chemo line of therapy, no. (%)				0.23
1st	12 (86)	17 (94)	55 (78)	
2nd	2 (14)	1 (6)	16 (23)	

SEM = seminoma; NS+SEM = seminoma elements; NS = no seminoma elements; SE = standard error; BMI = body mass index; IGCCC = International Germ Cell Consensus Classification

days of surgery. Percent seminoma also did not correlate with prolonged LOS > 8 days (uppermost quartile) (p = 0.46) in our study population.

Discussion

PC-RPLND is critical to the management paradigm for many patients with metastatic testicular cancer. It carries with it, however, the risk of significant morbidity including the resection of adjacent organ parenchyma and vasculature as well as significant blood loss. Furthermore, patients undergoing PC-RPLND represent a heterogeneous group secondary to differences in risk group stratification, the amount of chemotherapy administered, tumor histology, and the volume and location of residual disease.

Although the majority of patients with clinical stage II or III SEM experience a partial or complete response to chemotherapy or radiation, anywhere from 60% to 75% will have residual masses on post-treatment imaging.[17] In most cases, residual radiographic disease represents necrosis or fibrosis, but upwards of 15% to 20% of patients with more well defined residual masses > 3 cm in diameter harbor viable residual malignancy, and a properly timed PET scan following the completion of chemotherapy can help identify the presence of viable tumor and thus the need for surgical resection.[13] In the setting of post-chemotherapy

TABLE 2. **Intraoperative and postoperative outcomes**

	SEM (n = 14)	NS+SEM (n = 18)	NS (n = 71)	p value
Mean operative time, minutes (SE)	401 (54)	517 (61)	410 (19)	0.08
Mean EBL, mL (SE)	2108 (664)	1838 (569)	1023 (134)	0.03
Intraoperative blood transfusion, no. (%)	9 (47)	7 (33)	35 (44)	0.61
Mean total LNs removed, (SE)	20 (3.0)	22 (3.4)	19 (1.5)	0.71
Mean largest LN removed, cm (SE)	8.6 (0.7)	10.4 (1.5)	8.5 (0.7)	0.39
Vascular or adjacent organ resection (including nephrectomy), no. (%)	6 (32)	6 (29)	19 (24)	0.77
Retroperitoneal histology, no. (%)				0.001
Necrosis/fibrosis	12 (86)	5 (28)	20 (28)	
Teratoma	0 (0)	9 (50)	37 (52)	
Viable germ cell tumor	2 (14)	4 (22)	14 (20)	
+Seminoma in retroperitoneum, no. (%)	2 (14)	1 (6)	0 (0)	0.01
Postoperative complication (30 day), no. (%)				0.53
None	9 (64)	11 (61)	54 (76)	
I	1 (7)	1 (6)	5 (7)	
II	3 (21)	4 (22)	8 (11)	
III	1 (7)	1 (6)	4 (6)	
IV	0 (0)	1 (6)	0 (0)	
Mean LOS, days (SE)	7.0 (1.0)	10.6 (3.6)	6.7 (0.5)	0.13

SEM = seminoma; NS+SEM = seminoma elements; NS = no seminoma elements; SE = standard error; EBL = estimated blood loss; LN = lymph node; LOS = length of stay

metastatic pure seminoma, a complete resection is often difficult and labor-intensive due to increased peritumoral fibrosis.[11] Often, resection of the residual masses cannot be safely completed, and up to 40% of cases may require additional surgeries at the time of resection.[16] For this reason, it has been proposed that post-chemotherapy seminoma patients are subjected to increased intraoperative and postoperative morbidity as well as short term complications. It is currently unclear, however, if patients with mixed primary GCTs that contain some component of seminoma share similar negative surgical implications with pure seminoma patients in the post-chemotherapy setting as compared to patients with stage II-III nonseminoma without a seminoma component. In this study, we analyzed whether increasing volume (or percentage) of seminomatous elements in the primary orchiectomy specimen would be associated with markers of surgical complexity during PC-RPLND including EBL and the need for vascular and adjacent organ resection (including nephrectomy). Nephrectomy, either planned or from resulting injury to the renal hilum, represents the most common additional procedure required in the setting of PC-RPLND (5%-31%), and as such serves as an excellent surrogate marker for increased surgical complexity in patients undergoing

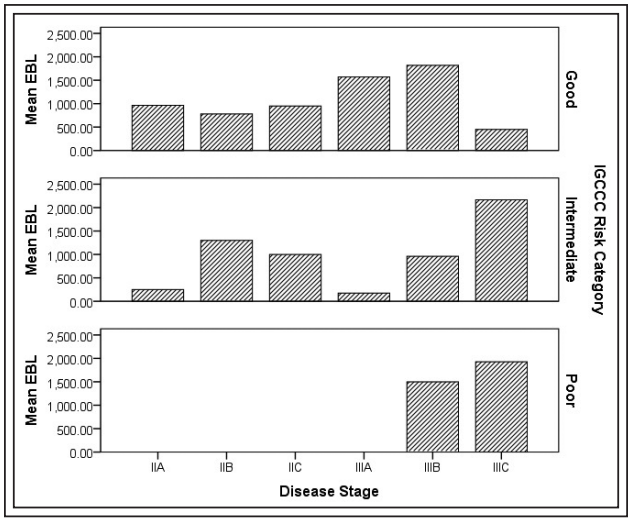

Figure 1. Intraoperative blood loss during PC-RPLND across disease stage and IGCCC risk category.

TABLE 3. **Predictors of EBL > 1.5 liters**

	Odds ratio	Multivariable 95% CI		p value
		Lower	Upper	
Age > 40 years (reference: age < 40)	0.74	0.06	9.65	0.82
% seminoma at orchiectomy, per 1%	1.04	1.01	1.07	0.013
Disease stage III (reference: stage II)	0.25	0.01	7.11	0.42
IGCCC risk category				
Intermediate (reference: good)	2.65	0.10	67.3	0.56
Poor (reference: good)	22.0	1.02	477	0.05
Preop cycles of chemotherapy	1.45	0.82	2.57	0.21
Largest LN size, cm	1.13	0.94	1.36	0.19
Total LNs removed	0.96	0.87	1.06	0.43
+Vascular or adjacent organ resection (including nephrectomy)	9.85	1.27	76.2	0.028
LN histology				
Teratoma (reference: necrosis/fibrosis)	3.98	0.37	42.6	0.25
Viable GCT (reference: necrosis/fibrosis)	1.53	0.11	21.5	0.75

EBL = estimated blood loss; IGCCC = International Germ Cell Consensus Classification; LN = lymph node

PC-RPLND.[18-21] We also evaluated as a secondary outcome the association between percent seminoma in the primary testicular tumor and postoperative morbidity including complications and length of hospitalization after surgery.

Interestingly, percent seminoma in the primary orchiectomy specimen was a very strong predictor of EBL during PC-RPLND even after controlling for other relevant clinicodemographic and intraoperative factors. Patients with SEM had more than twice as much blood loss as patients with NS (mean EBL: 2108 mL versus 1023 mL), and for every 20% increase in the percent seminoma in the orchiectomy specimen, the risk of intraoperative blood loss > 1.5 liters during PC-RPLND increased almost two-fold (OR: 1.8). Even though operative time was also strongly associated with EBL (p = 0.001), we did not include it in our multivariate model due to strong collinearity between the two variables (VIF = 4.5). Additionally, percent seminoma did not correlate with the risk of intraoperative blood transfusion (p = 0.99). This is important because the administration of a perioperative blood transfusion has been associated with an immunosuppressive effect and a greater risk of disease recurrence, worse cancer-specific mortality, and worse overall survival in other abdominal malignancies such as pancreatic, liver, bladder, and kidney.[22-25] Whether this trend could similarly hold true for metastatic testicular cancer patients is largely unknown. The apparent discordance between EBL and blood transfusions may be secondary to varying preoperative patient hemoglobin levels or differing anesthesia thresholds as to when an intraoperative blood transfusion is necessary. Finally, percent seminoma showed no relationship with the need for vascular or adjacent organ resection (including nephrectomy) (p = 0.50). Our study, however, may be underpowered to accurately evaluate this outcome since it only occurred in a small number of patients in each group.

Surprisingly, percent seminoma in the primary orchiectomy specimen was not associated with any marker of postoperative outcome including 30 day complications, high grade complications, or LOS. Again, this analysis may be underpowered and limited by small numbers, so definitive conclusions regarding these endpoints cannot be made from this study. It is important to note, however, that the overall complication rates observed in our study population are reflective of those reported in previous PC-RPLND series (27%-32%) as well as those observed during primary RPLND (20%-24%).[26-28]

Percent seminoma of the primary testicular tumor may play a role in intraoperative blood loss due to the concordance between percent seminoma in the primary orchiectomy specimen and the prevalence

of seminomatous components in retroperitoneal and other abdominal metastatic sites during RPLND. Patients with SEM had a higher rate of viable seminomatous components on residual mass histology after PC-RPLND, and although rare, we did encounter a single case of residual seminoma in the LN of a NS+SEM patient with 70% seminoma in the primary testicular tumor. The true correlation between these two pathological characteristics cannot be assessed from this study since LN histology was assessed after chemotherapy, thus affecting the degree of viable GCT and seminoma in the retroperitoneum. A strong argument can be made, however, that an increasing percentage of seminomatous components in the testicular tumor will lead to a greater likelihood of seminomatous components in abdominal metastatic deposits, thus leading to a more complex RPLND.

The small sample size of this study population as well as the limited number of patients with SEM and NS+SEM is an inherent limitation. Our group was also significantly heterogeneous including patients that underwent 1st and 2nd line chemotherapy prior to PC-RPLND with varying disease stages and IGCCC risk classifications. Additionally, 3 patients in our study population underwent "desperation" PC-RPLND in the setting of elevated tumor markers (1 NS+SEM, 2 NS), although this unique cohort was too small to consider a subgroup analysis.

Additionally, although all PC-RPLNDs were performed through an open approach with a full bilateral template dissection, nerve-sparing technique was not standardized and complete data on ejaculatory status was not available. There also may be significant inter-surgeon variability in the quality of PC-RPLND (and subsequent intraoperative outcomes) although we did not specifically look at this measure of quality control due to limited numbers across some surgeons. Our reported LN yield, however, was comparable to prior PC-RPLND series' in the literature, and it did not seem to vary between groups. Furthermore, LN yield can be quite variable in the post-chemotherapy setting due to difficulty assessing nodal counts secondary to matted lymphadenopathy, and thus the largest diameter of the residual mass is more commonly utilized for reporting purposes.

We have made several significant assumptions that are difficult to prove given the current management paradigm for patients with advanced testicular cancer. First, we assumed that patients with seminoma in their primary orchiectomy specimen had some component of seminoma in sites of distant metastases. Contrary to the first assumption, we also assumed that patients with "true" NS had no seminomatous GCT elements in distant metastatic sites. Finally, we suggested that there could be a linear relationship between the volumes of seminoma (when present) in primary testicular tumors and the volume of seminomatous elements in metastatic sites prior to the administration of chemotherapy. We also confirmed appropriate categorization of SEM patients by ensuring AFP levels were within normal range throughout their preoperative course. This avoided the misclassification of patients prior to PC-RPLND as SEM, which can occur in up to 30% of cases when residual retroperitoneal disease has been found to harbor nonseminomatous germ cell elements.[11] Despite these strict classification criteria, discordance may still exist from using histology of the primary orchiectomy specimen as representative of the type of retroperitoneal disease present prior to chemotherapy.[29]

A final limitation of this study is the exclusion of 19 patients who received chemotherapy prior to orchiectomy, a treatment pattern that has been shown to result in rates of necrosis and fibrosis in up to 50% of primary tumors.[30,31] Although this reduced our sample size significantly, this criteria for exclusion was necessary in order to avoid bias in our study objectives and minimize incorrect categorization of patients.

Conclusions

PC-RPLND for SEM is associated with increased intraoperative blood loss compared to PC-RPLND for NS, possibly due to a higher prevalence of seminomatous disease in the abdominal metastatic sites. Furthermore, there may be a relationship between increasing percentage of seminoma in the primary orchiectomy specimen and expected EBL during surgery. Despite the increased operative complexity observed in patients undergoing surgery for SEM, there was no apparent association with rates of vascular reconstruction or adjacent organ resection (including nephrectomy), postoperative 30 day complications, high grade complications, or LOS, indicating that this procedure is safe regardless of the primary GCT characteristics. □

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