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The Total Number of Retroperitoneal Lymph Nodes Resected Impacts Clinical Outcome Following Chemotherapy for Metastatic Testicular Cancer

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Abstract

Background—Following the multidisciplinary management of metastatic germ cell tumor, approximately 10 to 15% of patients with the histologic finding of fibrosis or teratoma will suffer disease recurrence. We evaluated the prognostic significance of the total number of lymph nodes obtained at post-chemotherapy retroperitoneal lymph node dissection (PC-RPLND).

Materials and Methods—From 1989 to 2006, a total of 628 patients underwent PC-RPLND and were found to have either fibrosis or teratoma. Following Institutional Review Board approval, complete clinical and pathologic data were obtained from our prospective testis cancer surgical database. A Cox proportional hazards regression model was constructed to evaluate the association of the total number of lymph nodes obtained at PC-RPLND on disease recurrence.

Results—On pathologic evaluation, 248 (57%) patients had fibrosis and 184 (43%) patients had teratoma. The median number of lymph nodes resected was 25 (IQ range 15, 37). On multivariable analysis, increasing post-chemotherapy nodal size and decreasing lymph node counts were significant predictors of disease recurrence ($p=0.01$, 0.04 , respectively). For patients with 10 nodes removed, the predicted 2 year relapse free probability was 90%, compared to 97% when 50 nodes were removed.

Conclusion—Our data suggests that the total number of lymph nodes removed and analyzed is an independent predictor of disease recurrence following PC-RPLND. This has implications both for the urologist to assure completeness of resection and for the pathologist to meticulously assess the pathologic specimens.

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Keywords

testis cancer; surgery; chemotherapy; lymph node count

Introduction

Testicular cancer is the most common malignancy in men 20 to 35 years of age and accounts for approximately 1% of all male malignancies.¹ Through the appropriate utilization of clinical trials, effective treatment paradigms have been developed for the management of all stages of testicular cancer. Most men presenting with advanced metastatic non-seminomatous germ cell tumor (NSGCT) are managed with cisplatin-based chemotherapy followed by post-chemotherapy surgery. This multidisciplinary approach to the management of germ cell tumors of the testis has resulted in overall survival rates of greater than 90% overall.¹

Following post-chemotherapy retroperitoneal lymph node dissection (PC-RPLND), residual viable GCT and teratoma are present in approximately 15% and 40% of patients, respectively.² We have previously demonstrated that over recent years patients with the histologic finding of fibrosis or teratoma have an improved 2-year probability of freedom from disease recurrence greater than 90%, and the improvement in clinical outcome is significantly associated with surgical templates and technique.³

Previous studies in bladder, colon, and prostate cancer have demonstrated that the number of lymph nodes resected significant impacts on freedom from disease recurrence in patients with node positive and negative malignancies.⁴⁻⁸ These data have potential implications for establishing an appropriate number of lymph nodes for adequate therapeutic efficacy and pathologic staging.

Traditionally, bilateral infrahilar RPLND templates have been recommended for patients undergoing PC-RPLND to maximize oncologic efficacy. This approach however, may be associated with significant ejaculatory morbidity due to interruption of the sympathetic nerves and hypogastric plexus. In an effort to reduce retrograde ejaculation, modified unilateral templates limiting contralateral dissection have been described in the post-chemotherapy setting with limited data demonstrating therapeutic efficacy.^{9,10} Modified template dissections limit anatomic regions of dissection and thus may result in a reduced number of lymph nodes resected by the surgeon and analyzed by the pathologist. Furthermore, we have recently demonstrated that 7% to 32% of patients will have disease outside the boundaries of a modified template dissection depending on the anatomic limits of dissection.¹¹ The purpose of our study was to examine the impact of the number of lymph nodes resected and analyzed, a surrogate for extent of surgery, on freedom from disease recurrence in men with fibrosis or teratoma at PC-RPLND.

Materials and Methods

There were 695 patients who underwent PC-RPLND from 1989 to 2006 at Memorial Sloan-Kettering Cancer Center. On pathologic evaluation, 628 patients had histology of fibrosis or teratoma. Patients with viable GCT at the time of PC-RPLND were excluded from the current study, as adjuvant chemotherapy is administered in select patients, which affects clinical outcome independent of surgery. Of the 628 patients with fibrosis or teratoma, the total number of lymph nodes removed and analyzed was available for 485 (77%) patients. We further excluded 53 patients who were missing retroperitoneal nodal size, leaving 432 patients in our study cohort. This study was approved by the Institutional Review Board at Memorial Sloan-Kettering Cancer Center.

Clinical and pathologic data were obtained from our prospective surgical database. Pre- and post-chemotherapy retroperitoneal nodal size was determined by the transverse diameter of the largest mass on CT imaging. IGCCCG risk classification was assigned based on the previous defined criteria.¹² A full bilateral or modified template RPLND was performed based on the discretion of the surgeon. Intra-operative pathologic specimens were sent to our pathology department according to anatomic region of dissection (para-aortic, interaortocaval, paracaval, left iliac, right iliac). Total nodal count was reported by the original pathology review. Individual lymph nodes were counted for the anatomic specimens and each grossly abnormal residual mass was reported as one lymph node regardless of size.

The probability of freedom from relapse following PC-RPLND was estimated using Kaplan-Meier methods. Cox proportional hazards regression was used to evaluate the association between the number of lymph nodes removed during PC-RPLND and relapse-free survival following PC-RPLND, with adjustment for covariates. Due to the limited number of events, prior to performing any analyses we selected pre-RPLND nodal size and histology to be covariates. The number of lymph nodes removed and nodal size were entered as continuous variables; histology was categorized as fibrosis versus teratoma. The association between the number of lymph nodes removed and pre-RPLND nodal size was determined with simple linear regression. To explore whether there was a threshold for nodes removed, above which there was no apparent benefit of removing additional nodes, we fitted a Cox regression model entering nodes removed with restricted cubic splines with knots at the tertiles to relax linearity assumptions. We then plotted the predicted relapse-free probability at 2 years against nodes removed, which would allow for observation of a plateau if it existed. All statistical analyses were conducted using Stata 9.0 (Stata Corp., College Station, TX).

Results

Clinical and pathologic parameters

On pathologic evaluation, 248 (57%) patients had fibrosis and 184 (43%) patients had teratoma. Pre- and post-chemotherapy patient characteristics according to histology are shown in Table 1. There were no observed differences in pre-chemotherapy characteristics between men with fibrosis or teratoma, with the exception that a higher proportion of men with teratoma had elevated serum tumor markers prior to initiation of chemotherapy. The post-chemotherapy nodal size was smaller for fibrosis patients (median of 1.0 cm for fibrosis and 2.0 cm for teratoma). Overall, the median number of nodes removed was 25 (interquartile range 15, 37) and was similar among patients with teratoma and fibrosis. Classifying patients according to the median number of lymph nodes resected (< 25 and ≥ 25 lymph nodes) there was no statistical difference in the distribution of IGCCCG risk classification, the requirement for second-line chemotherapy, or post-chemotherapy retroperitoneal histology (data not shown). Increasing residual mass size was associated with a lower total number of lymph nodes resected as these masses typically represent a coalescence of multiple lymph nodes and are counted by the pathologist as one lymph node ($p < 0.001$, Figure 1).

Total lymph node count is associated with clinical outcome

Overall, there were 30 patients who relapsed following PC-RPLND, 17 in the teratoma group and 13 in the fibrosis group. The sites of relapse, not mutually exclusive, were the retroperitoneum in 8 patients, lungs in 12 patients, liver in 4 patients, and 9 patients presented with elevated serum tumor markers. The median follow-up for relapse-free patients was 3.2 years. On multivariable analysis, the number of nodes removed was significantly associated with relapse following PC-RPLND when controlling for post-

chemotherapy residual mass size and histologic findings (Table 2). Removing more nodes was protective of relapse (hazard ratio 0.74 per 10 nodes removed; 95% C.I. 0.55, 0.99; $p=0.039$).

We next examined whether there was a threshold for nodes removed, above which there was no apparent benefit of removing additional nodes. Due to the limited number of events, and given the results of the multivariable model, we controlled only for nodal size in this analysis. The predicted relapse-free probability at 2 years with increasing nodal count is shown in Figure 3a for a typical patient (nodal size of 1.4cm). From this model, we see no evidence to identify a threshold for nodes removed. For patients with 10 nodes removed, the predicted 2-year relapse-free probability from the model was approximately 90%; this increased to approximately 95% when 30 nodes were removed and to approximately 97% when 50 nodes were removed (Figure 2). Although the curve appears to flatten out starting at 20 nodes, this is likely a statistical artifact due to over-fit. Moreover, the relapse-free probability starts to increase again past 40 nodes. As a check, we fit a model using a quadratic term for nodes removed instead of cubic splines, which confirmed that outcome continued to improve past 20 nodes. Because these analyses controlled for post-chemotherapy residual mass size, the association between increasing lymph node counts associating with improved clinical outcome, holds for both small and large masses.

Discussion

This study is the first to demonstrate that the total number of retroperitoneal lymph nodes resected and analyzed impacts the probability of freedom from recurrence for patients with metastatic NSGCT undergoing PC-RPLND. These results have implications both for the urologist to assure completeness of resection and for the pathologist to meticulously assess the pathologic specimens. Importantly, our data demonstrate that even in patients with a favorable clinical outcome (i.e., the histologic finding of fibrosis or teratoma in the retroperitoneum) total lymph node count is a significant predictor of disease recurrence.

Previous studies in other malignancies have demonstrated that the number of lymph nodes resected significantly impacts on freedom from disease recurrence in patients with node positive and negative malignancies.⁴⁻⁸ Studies of patients with node negative and node positive colon cancer have reported that disease-free and overall survival is improved with increasing total lymph node counts.⁴ Additionally, for patients undergoing radical cystectomy for bladder cancer, the total number of lymph nodes removed is a predictor of overall survival for patients with both node positive and node negative disease.^{7,8} These studies demonstrate the importance of lymphadenectomy for both therapeutic efficacy and appropriate pathologic classification and may assist in establishing guidelines regarding the appropriate number of lymph nodes which must be resected and analyzed.

In our current study we have demonstrated that the total lymph node count has a significant impact on the clinical outcome for men with metastatic NSGCT following treatment with chemotherapy. On multivariable analysis controlling for histology and retroperitoneal nodal size, the number of lymph nodes removed was significantly associated with relapse following PC-RPLND. Removing more nodes was protective of relapse (hazard ratio 0.74 per 10 nodes removed; 95% C.I. 0.55, 0.99; $p=0.039$). For patients with 10 lymph nodes removed, the predicted 2-year relapse-free probability was approximately 90%; this increased to approximately 95% when 30 lymph nodes were removed and to approximately 97% when 50 lymph nodes were removed. Thus limiting the anatomic boundaries of retroperitoneal lymph node dissections, even in patients with a favorable histology, may have detrimental effects on the number of lymph nodes resected and analyzed, and may compromise therapeutic efficacy.

In an effort to reduce the morbidity of PC-RPLND several investigators have evaluated the role of modified unilateral templates in the post-chemotherapy setting.^{9,10} These modified templates limit the contralateral lymph node dissection, resulting in a higher probability of recovery of antegrade ejaculation compared to patients undergoing a bilateral PC-RPLND. However, there is limited data demonstrating equivalent therapeutic efficacy for patients undergoing modified template RPLND. We have previously reported that 7% to 32% of patients will have disease outside the boundaries of a modified template dissection.¹¹ Furthermore, with nerve-sparing techniques, antegrade ejaculation is preserved in a similar proportion of men undergoing a bilateral RPLND.^{15,16} Additionally, modified template dissections limit anatomic regions of dissection and thus may be associated with a reduced number of lymph nodes resected by the surgeon and analyzed by the pathologist. Therefore, limiting the anatomic regions of a PC-RPLND may be associated with a higher risk of recurrence and a lower accuracy of histologic classification and pathologic staging.

Total lymph node counts are influenced by the anatomic boundaries of surgical template, patient variability, anatomic surgical labeling of the specimens (en bloc vs separate packets), and pathologic processing.^{13,14} The association of increasing nodal counts and freedom from disease recurrence is likely not only secondary to complete surgical resection, but also more accurate pathologic staging. Therefore, it is important for the pathologist to meticulously analyze the surgical specimens to provide a comprehensive report on histologic classification and pathologic staging.

Our data demonstrate that even in patients with predicted favorable clinical outcome (i.e., the histologic finding of fibrosis or teratoma in the retroperitoneum) the total number of lymph nodes resected is a significant predictor of disease recurrence. This observation has implications both for the urologist to assure completeness of resection and for the pathologist to meticulously assess the pathologic specimen. Therefore, we continue to recommend a bilateral PC-RPLND with nerve-sparing technique (when nerve-sparing is technically feasible) as the most prudent and efficacious approach to the management of metastatic NSGCT.

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Figure 1.
Total number of lymph nodes removed according to retroperitoneal nodal size

Figure 2.

Predicted 2-year relapse-free probability by number of nodes removed, adjusting for nodal size. Dashed line: number of nodes modeled with cubic splines; Solid line: number of nodes modeled with a quadratic term. Unadjusted Kaplan-Meier estimates of the 2-year relapse-free probability for patients with x nodes removed are given as a scatter-plot.

Table 1
Pre- and post-chemotherapy characteristics for patients with the histologic finding of
teratoma or fibrosis at PC-RPLND

Data are given as median (IQR) or frequency (proportion)

	Overall N=432	Teratoma N=184	Fibrosis N=248
Pre-chemotherapy characteristics			
Elevated AFP (>15)	250 (58%)	139 (76%)	111 (45%)
Elevated HCG (>2)	300 (69%)	151 (82%)	149 (60%)
RP Nodal Size			
Median (IQR)	3.2 (2.0, 6.0)	4.0 (2.0, 6.2)	3.0 (2.0, 5.0)
0–1 cm	25 (6%)	11 (6%)	14 (6%)
1–2 cm	90 (21%)	32 (17%)	58 (23%)
2–5 cm	167 (39%)	68 (37%)	99 (40%)
5–10 cm	65 (15%)	32 (17%)	33 (13%)
10 cm	40 (9%)	23 (13%)	17 (7%)
IGCCCG risk category			
Good	330 (76%)	136 (74%)	194 (78%)
Moderate	50 (12%)	25 (14%)	25 (10%)
Poor	49 (11%)	20 (11%)	29 (12%)
Clinical Stage			
I (relapse after surveillance)	45 (10%)	28 (15%)	17 (7%)
IS	7 (2%)	6 (3%)	1 (0.4%)
IIa	57 (13%)	21 (11%)	36 (15%)
IIb	105 (24%)	44 (24%)	61 (25%)
IIc	69 (16%)	35 (19%)	34 (14%)
III	149 (34%)	50 (27%)	99 (40%)
Received second line chemotherapy	30 (7%)	11 (6%)	19 (8%)
Post-chemotherapy patient characteristics			
Elevated AFP (>15)	22 (5%)	16 (9%)	6 (2%)
Elevated HCG (>2)	29 (7%)	17 (9%)	12 (5%)
RP Nodal Size			
Median (IQR)	1.4 (0.6, 3.0)	2.0 (1.0, 5.0)	1.0 (0.5, 2.0)
0–1 cm	142 (33%)	36 (20%)	106 (43%)
1–2 cm	120 (28%)	43 (23%)	77 (31%)
2–5 cm	105 (24%)	58 (32%)	47 (19%)
5–10 cm	48 (11%)	33 (18%)	15 (6%)
10 cm	17 (4%)	14 (8%)	3 (1%)
Received adjuvant chemotherapy	2 (0.5%)	1 (0.5%)	1 (0.4%)
PC-RPLND patient characteristics			
Age at surgery (years)	30 (24, 36)	27 (23, 34)	31 (25, 36)
Number of nodes removed	25 (15, 37)	25 (16, 39)	26 (15, 37)

AFP: alpha-feto protein, HCG: human chorionic gonadotropin, IGCCCG: International Germ Cell Cancer Collaborative Group, RP: retroperitoneum, PC-RPLND: post-chemotherapy retroperitoneal lymph node dissection

Table 2

Multivariable Cox proportional hazards regression to evaluate predictors of relapse following PC-RPLND

	Hazard Ratio (95% C.I.)	p-value
Pre-surgery RP nodal size	1.11 (1.02, 1.20)	0.013
Histology: (teratoma vs fibrosis)	1.42 (0.63, 3.20)	0.4
Lymph node count *	0.74 (0.55, 0.99)	0.039

* Hazard ratio is given in units of 10 nodes

RP: retroperitoneum