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CONTEMPORARY LYMPH NODE COUNTS DURING PRIMARY RETROPERITONEAL LYMPH NODE DISSECTION

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Abstract

Objective—Recent observations suggest that surgeon volume is associated with lymph node counts during retroperitoneal lymph node dissection (RPLND). We report our contemporary single-surgeon experience with lymph node counts during primary RPLND for nonseminomatous germ cell tumors (NSGCT).

Methods—Using the Memorial Sloan-Kettering Testis Cancer Database, we identified 124 consecutive patients treated with primary RPLND by a single experienced surgeon for NSGCT between 2004 and 2008. Predictors of positive nodes and number of positive nodes were evaluated with logistic and linear regression models adjusting for year of surgery and clinical stage.

Results—Positive lymph nodes were observed in 37 (30%) while 87 (70%) patients were pN0. Mean total node count was 51 (SD= 23) during the 5 year study period. Mean node counts for the paracaval, interaortocaval, and paraaortic regions were 8 (SD= 6), 17 (SD= 9), and 26 (SD= 15), respectively. In a multivariate analysis, higher total node count was significantly associated with finding positive nodes (odds ratio 1.02 for each additional node counted; p=0.037) and finding multiple positive nodes (coefficient 0.04 for each additional node counted; p=0.004). Year of surgery (p<0.001) was associated with higher total node counts, while clinical stage and pathologist were not (p>0.5 for each).

Conclusion—The average total node count for a primary RPLND by an experienced surgeon is approximately 50 nodes with nearly half of the nodes originating in the paraaortic region. These

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results will be useful when assessing the adequacy of lymph node dissections for testis, renal, and upper tract urothelial malignancies.

Keywords

Testicular neoplasms; Lymph node excision; Neoplasm staging; Retroperitoneal space; Lymph nodes

Introduction

There is a substantial volume of literature demonstrating that the number of lymph nodes removed has significant prognostic value for many malignancies including bladder,¹ lung,² esophageal,³ pancreatic,⁴ breast,⁵ gastric,⁶ and colon cancers.^{7, 8} While the mechanisms underlying the association between survival and lymph node count remain unknown for many of these malignancies, it seems intuitive for testicular cancer- a malignancy that primarily spreads via the lymphatic channels. Thus, when the decision to perform a primary RPLND is made, it is important that both the diagnostic and therapeutic benefits of the operation be maximized. This will not only identify patients who would benefit from adjuvant chemotherapy but it will also serve to prevent overtreatment for those who do not need chemotherapy. However, an uncontrolled retroperitoneum potentially increases the risk of late relapse,⁹ need for reoperation,¹⁰ salvage chemotherapy, and malignant transformation of unresected teratoma.

We recently evaluated our experience with primary retroperitoneal lymph node dissection (RPLND) and found that surgeon volume, among other features, was significantly associated with higher lymph node counts during primary RPLND.¹¹ The aim of the current study is to evaluate normal lymph node counts by a single experienced surgeon in the contemporary era. These results should prove useful when evaluating the adequacy of a lymph node dissection in clinical trials for not only testis cancer but other malignancies where retroperitoneal lymphadenectomy is a critical component in the overall management, such as renal cell carcinoma, various gynecological malignancies, and upper tract urothelial carcinoma.

Materials and Methods

Patient Selection

After obtaining Institutional Review Board approval, we queried the MSKCC Testis Cancer Registry and identified 124 consecutive patients treated with primary RPLND by a single experienced surgeon for NSGCT between the years 2004 and 2008. The MSKCC Testis Cancer Registry is prospectively maintained with >100 variables collected and recorded for all patients who undergo RPLND at MSKCC. For this project, charts were reviewed for all patients to ensure that the location and number of lymph nodes recorded in the registry was accurate.

Clinical and Pathologic Features

The clinical and pathologic features studied included lymph node counts from the paracaval, interaortocaval, and paraaortic regions, total lymph node count, pathologist, clinical stage, primary tumor histology, year of surgery, pathologic stage, number of positive nodes, location of positive nodes, and timing and location of relapse. For simplicity and when performed, right iliac lymph nodes were added to the paracaval node region, interiliac lymph nodes were added to the interaortocaval region, and left iliac nodes were added to the paraaortic region. A high volume pathologist was defined as evaluating >10 primary RPLND's over the study time period.

Operative Description

All patients undergoing primary RPLND were treated by a single surgeon with similar limits of dissection. Given that the oncologic efficacy of template-limited dissection has recently been reassessed due to concerns regarding extra-template disease,^{12, 13} all patients were treated with a nerve-sparing bilateral template dissection. A midline abdominal incision is utilized and the small bowel along with the ascending colon are mobilized out of the abdomen. Following, this, the descending colon is mobilized medially by incising the white line of Toldt for improved access to the paraaortic region. A split and roll technique is employed removing the paracaval, interaortocaval, and paraortic lymph nodes while lumbar veins and arteries are ligated. The ipsilateral iliac nodes, with respect to primary tumor side, are removed and the contralateral iliac nodes are removed if frozen section is positive. Rarely, interiliac nodes are removed if they are palpably abnormal. Post-ganglionic sympathetic nerves are dissected free from the sympathetic trunk down to the hypogastric plexus, typically sparing one side only. Upper limits of dissection include the skeletonized renal vessels and crus of the diaphragm while lower limits include the external iliac vessels on the ipsilateral side and the bifurcation of the great vessel on the contralateral side. The nodal packets are received in pathology from the operating room in a fresh state. Using visual inspection, palpation and blunt dissection with a scalpel blade, the adipose tissue is dissected free and all firm, rubbery areas suspicious for a lymph node are then separated and submitted for microscopic examination. If no nodes are palpated, the tissue is submitted for microscopic examination in its entirety. Microscopic evidence of at least a partial nodal capsule is required to constitute a node; a collection of lymphocytes without a nodal capsule is considered insufficient to count as a node.

Statistical Analysis

The clinical and pathologic features were summarized with mean and standard deviation (SD) or frequency and percentage as appropriate. Associations with higher lymph node counts were evaluated using linear regression models both in a univariate and a multivariate model adjusting for year of surgery, clinical stage (stage I vs II), and pathologist (high volume vs low volume). To evaluate features associated with the finding of positive nodes, we performed logistic regression models with total node count adjusting for year of surgery and clinical stage. We then evaluated if total node count is associated with number of positive nodes using linear regression models univariately and after adjusting for clinical

stage and year of surgery. Statistical analyses were performed with Stata v8.2 and p-values <0.05 were considered statistically significant.

Results

A summary of baseline features for the 124 patients studied is detailed in Table 1. Mean (SD) age at RPLND was 31 (9). The most common primary tumor histology was mixed NSGCT with embryonal predominance, noted in 68 (55%) patients. Only 9 (7%) patients were clinical stage IA while the remaining were IB (n=73, 59%) or IIA (n=42, 34%). Overall, positive lymph nodes were found in 37 (30%) patients, including 30 (81%) with viable tumor only, 5 (14%) with viable tumor and teratoma, and 2 (5%) with teratoma only. Positive nodes were found in 0, 17 (23%), and 20 (48%) patients with clinical stage IA, IB, and IIA NSGCT, respectively.

A summary of node counts by region is detailed in Table 2. Mean (SD) total lymph node count was 51 (23). Approximately half of the total node count originated in the paraaortic region which had a mean (SD) of 26 (15) nodes. The paracaval region had the least number of nodes with a mean (SD) of 8 (6) nodes. The only feature predictive of higher total lymph node count on univariate or multivariate analysis was year of surgery; on average, 5.1 additional nodes were counted with each increasing year during the study time frame (95% CI 2.5 – 7.7, $p<0.001$). Both univariately and on multivariate analysis, high volume pathologist and clinical stage were not significantly associated with higher total node counts ($p>0.5$ for each).

We then evaluated features associated with positive nodes (vs pN0) at time of RPLND. As demonstrated in Table 3, clinical stage and total node count were significantly associated with positive nodes while year of surgery was not. The odds of finding positive nodes was >3 for patients with clinical stage II compared with clinical stage I NSGCT ($p=0.003$). Each additional lymph node removed was associated with a nearly 2% increase odds of finding a positive node ($p=0.037$).

Next, we evaluated if total node count is associated with the absolute number of positive nodes. A total of 37 patients had positive nodes; among them, 11, 9, 7, and 10 had 1, 2, 3, and >3 positive nodes. One notable patient with clinical stage IB NSGCT had 37 positive nodes among 112 counted. In a linear regression model, higher total node count was significantly associated with higher total positive nodes (coefficient 0.04 for each additional node counted; 95% CI 0.01 – 0.07; $p=0.004$; Figure 1). Higher total node count remained significantly associated with higher number of positive nodes even after adjusting for year of surgery and clinical stage in a multivariate analysis (coefficient 0.04 for each additional node counted; 95% CI 0.01 – 0.07; $p=0.004$).

At last follow-up, all patients were still alive and 12 patients relapsed. Median follow-up for patients who did not relapse was 1.6 years. Most relapses were in the lung (n=9, 75%) and no patient had a relapse in the paracaval, interaortocaval, paraaortic, or iliac regions. Due to the limited number of relapses and 100% survival at last follow-up, outcome analyses were not performed.

Discussion

We present our contemporary experience with lymph node counts during primary RPLND for patients treated at MSKCC over the last 5 years. To our knowledge, this is the first single-surgeon investigation of normal lymph node counts during primary RPLND. Mean total node count was 51 with nearly half of lymph nodes originating in the paraaortic region. We also observed that higher total node count is significantly associated with not only finding positive nodes but finding multiple positive nodes in a multivariate analysis. These findings have important clinical implications since observation is generally recommended for pN1 disease while chemotherapy is given for pN2 and/or pN3 (which includes >5 positive nodes) or greater NSGCT.¹⁴ One notable patient in this study had 37 positive nodes (among 112 nodes counted) despite a normal preoperative CT scan highlighting the fact that a full bilateral RPLND with nerve sparing techniques maximizes both diagnostic and therapeutic goals of surgery with the benefit of minimizing ejaculatory morbidity and reducing the need for chemotherapy and its associated long-term sequelae.^{15, 16} These results should provide a benchmark when assessing the adequacy of a lymph node dissection in clinical trials and for standardization of what represents a full bilateral RPLND versus a more “regional” dissection. For example, if a paracaval lymph node dissection is performed for a right renal mass, 8 lymph nodes should be counted on average; however, if a paraaortic lymph node dissection is performed for a left upper tract TCC, 26 lymph nodes should be counted on average.

Historically, RPLND was associated with ejaculatory morbidity due to interruption of the sympathetic trunks, hypogastric plexus, or postganglionic efferent nerve fibers. In effort to minimize these side effects, multiple modified templates were proposed which limited the contralateral dissection to preserve antegrade ejaculation. However, the oncologic efficacy of template-limited dissection has recently been reassessed due to concerns regarding extra-template disease.^{12, 13} In fact, recent observations suggest that 3 – 23% of patients (depending on template utilized) with clinical stage I or IIA NSGCT actually harbor extra-template disease.¹³ Moreover, with improved surgical technique utilizing a nerve sparing approach, there is near uniform preservation of antegrade ejaculation without the need to modify a standard bilateral template.¹⁷ Thus, a properly performed RPLND has both a diagnostic and therapeutic role for high risk clinical stage I and clinical stage IIA NSGCT patients.

Recently, laparoscopic RPLND has been reported as technically feasible, associated with improved pain, and shorter convalescence.^{18–21} In a recent meta-analysis of 34 contemporary laparoscopic RPLND articles, the mean lymph node count was 16 (among the 3 articles that reported node count).¹⁸ It should be noted, however, that modified templates were utilized in all of the laparoscopic RPLND reports¹⁸ although more recent laparoscopic RPLND data suggest that a nerve-sparing bilateral template RPLND is technically feasible in experienced hands.¹⁶ However, 16 lymph nodes is less than what we observed in the paraaortic region alone with an open technique. Furthermore, our results demonstrating that higher total node counts predict for finding not only positive nodes but multiple positive nodes suggests that a more limited dissection invites the risk of improper staging and reduces the therapeutic efficacy for patients with pathologic II NSGCT. Every effort should

be made to not only remove the lymph nodes but to evaluate them morphologically as this has important ramifications when deciding upon adjuvant chemotherapy following primary RPLND.

In a recent randomized controlled trial comparing primary RPLND to chemotherapy in the community setting, Albers et al reported that disease recurrence following RPLND was significantly higher compared with one cycle of bleomycin, etoposide, and cisplatin.²² Among 191 patients treated with primary RPLND, 13 recurrences were noted including 9 who recurred in the retroperitoneum or scrotal region.²² Notably, all recurrences following RPLND occurred within 17 months and unilateral templates were utilized in all cases. While our follow-up data is maturing, we did not observe a single recurrence in the paracaval, interaortocaval, or paraaortic regions at a mean of 1.6 years following RPLND with a bilateral nerve-sparing dissection. As stated by Albers et al, the results of their trial demonstrate the importance of experienced surgeons if RPLND is used as a treatment option.²² It should also be noted that chemotherapy or observation for stage I NSGCT requires surveillance of the retroperitoneum. Recent evidence suggests that radiation exposure from repeated computerized tomography may increase the risk of secondary malignancies.^{23–25} In fact, Tarin et al suggest that the relative risk of a secondary malignancy in a surveillance protocol for clinical stage I NSGCT patients is approximately 15 compared with primary RPLND.²⁴ In our practice, pN0 patients only receive one scheduled CT scan following primary RPLND assuming chest x-ray and tumor markers remain normal.

This report is not without limitations. While the data was collected in a prospective fashion, it was analyzed retrospectively and is subject to the many inherent biases associated with this approach. It should be noted that nodal counts may vary across institutions based on differences in pathologic preparation, technique, effort to find nodes, and philosophy about what constitutes a node. As part of a quality assurance, the pathology reports for all 124 patients identified were reviewed to ensure the accuracy regarding the number and location of lymph node counts. Furthermore, while a single surgeon who utilized similar boundaries of dissection over the study time period, node counts increased over the last 5 years. We believe this observation likely reflects increased emphasis on nodal counts by all pathologists for many malignancies that occurred during the last 10 years.^{1–8}

One additional point deserves mention. While chemotherapy has revolutionized the field of testis cancer, providing cure for many of the most advanced stages, it should be emphasized that chemotherapy is not without long term adverse consequences.²⁶ Increased risk of endothelial dysfunction, infertility, pulmonary fibrosis, cardiovascular disease, and secondary malignancies are recently reported long-term side effects of chemotherapy for NSGCT.^{26, 27} A properly performed RPLND can obviate the need for chemotherapy for most patients with pN1 disease, reduce the need for intense radiographic surveillance, and reduce the risk of malignant transformation from unresected teratoma.^{9, 10, 28} For these reasons, we advocate a thorough dissection, including the paracaval, interaortocaval and paraaortic regions, which should yield on average 50 lymph nodes in contemporary times for patients undergoing primary RPLND.

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Figure 1.

Relationship between total number of nodes removed and number of positive nodes at primary RPLND ($p=0.004$).

Table 1

Summary of baseline features for 124 patients treated with primary RPLND for NSGCT.

Feature	No. (%)
Primary Tumor	
Right	74 (60)
Left	50 (40)
Primary Histology	
Mixed	106 (85)
Pure Embryonal	17 (14)
Pure Teratoma	1 (1)
Clinical Stage	
IA	9 (7)
IB	73 (59)
IIA	42 (34)
Year of RPLND	
2004	26 (21)
2005	15 (12)
2006	27 (22)
2007	22 (18)
2008	34 (27)
pN Stage	
N0	87 (70)
N1	22 (18)
N2	15 (12)
RPLND Histology	
Benign	87 (70)
Viable GCT (only)	30 (24)
Viable GCT and Teratoma	5 (4)
Teratoma (only)	2 (2)

Table 2

Node count by region for 124 patients treated with primary RPLND

Feature	Mean (SD)
Paracaval Lymph Node Count	8 (6)
Interaortocaval Lymph Node Count	17 (9)
Paraaortic Lymph Node Count	26 (15)
Total Lymph Node Count	51 (23)

*
SD = Standard Deviation

Table 3

Univariate and multivariate features predictive of positive lymph nodes in 124 patients treated with primary RPLND

Feature	Univariate		Multivariate	
	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Year of Surgery	1.0 (0.7 – 1.3)	0.8	0.8 (0.6 – 1.1)	0.3
Clinical stage (I vs II)	3.5 (1.5 – 7.8)	0.002	3.5 (1.5 – 8.1)	0.003
Total lymph node count	1.02 (1.00 – 1.03)	0.049	1.02 (1.00 – 1.04)	0.037