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Preservation of Ejaculation in Patients Undergoing Nerve-Sparing Post-Chemotherapy Retroperitoneal Lymph Node Dissection for Metastatic Testicular Cancer

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Abstract

Purpose—We evaluated clinical parameters associated with recovery of ejaculation following nerve-sparing post-chemotherapy retroperitoneal lymph node dissection (PC-RPLND) for non-seminomatous germ cell tumor.

Methods—We queried our institutional database for all patients who underwent nerve-sparing PC-RPLND between 1995 and 2005 using a bilateral template. Nerve-sparing was carried out whenever technically feasible and oncologically prudent. Antegrade ejaculation was defined as any seminal fluid expulsion and was determined by patient report. We evaluated recovery of antegrade ejaculation based on clinical and pathologic parameters and fit a logistic regression model to determine which pre-operative variables are associated with antegrade ejaculation.

Results—A total of 341 patients had PC-RPLND during the study period, 136 (40%) with nerve sparing techniques. Post-operative antegrade ejaculation was reported by 107/136 (79%) of patients with information available. On the multivariable analysis, a right-sided primary testicular tumor (OR 0.4, 95% CI: 0.1, 1.0, p=0.044) and residual masses ≥5 cm (OR 0.1, 95% CI: 0.0, 0.7, p=0.020) were associated with retrograde ejaculation. However, 40/54 (74%) with right-sided primary tumors and 4/9 (44%) with mass ≥5 cm reported antegrade ejaculation. The 5-year relapse free survival was 98% with a median follow up of 39 months (IQR 19, 66).

Conclusions—Nerve-sparing PC-RPLND is associated with excellent functional return of antegrade ejaculation, is feasible in select patients with bulky disease, and has excellent oncologic outcomes.

Keywords

Testicular Cancer; Chemotherapy; Surgery; Ejaculation; Retroperitoneal Lymph Node Dissection

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Introduction

The multidisciplinary approach to treating metastatic nonseminomatous germ cell tumors (NSGCT) has led to a greater than 90% cure rate overall. Post-chemotherapy retroperitoneal lymph node dissection (PC-RPLND) is an integral component in the management of advanced NSGCT. Following induction chemotherapy, approximately 40% of patients undergoing PC-RPLND will harbor teratoma, 10–15% will have residual viable NSGCT, and the remaining patients will have fibrosis or necrosis.[1] Some investigators have attempted to predict necrosis or fibrosis based on preoperative information to spare some the morbidity of PC-RPLND.[2, 3] However, either viable NSGCT or teratoma is present in the retroperitoneum in up to 30% of patients with minimal or no radiographic evidence of disease.[3] Teratoma is chemo-resistant, may have adverse local effects, result in late recurrence, and/or undergo malignant transformation in 6–14% of cases.[4–6] Finally, an uncontrolled retroperitoneum requires lifelong surveillance, and late relapses are associated with poor prognosis.[7, 8] Currently, there are no reliable criteria to predict fibrosis and obviate the necessity for PC-RPLND.

The morbidity associated with PC-RPLND has diminished over time,[9] but potential anejaculation continues to be a concern among young men with testicular cancer. To address the problem of anejaculation following primary RPLND, modified template dissections[10, 11] and/or nerve sparing techniques[12, 13] have been developed and broadly applied for low stage disease. Approximately 95% of patients can expect antegrade ejaculation following nerve sparing primary RPLND. Some have applied similar modified template resections in the PC-RPLND setting to reduce anejaculation. Recent reports suggest extra-template disease may be found in up to 32% of PC-RPLND candidates.[14] Therefore, we currently perform bilateral PC-RPLND (with or without the contralateral iliac nodal package) in which the sympathetic chains, postganglionic sympathetic nerve fibers and hypogastric plexus are prospectively identified and spared whenever feasible and oncologically safe. The purpose of this report is to evaluate the return of antegrade ejaculation following nerve-sparing PC-RPLND for NSGCT and to determine which clinical parameters are associated with functional recovery.

Methods and Materials

We obtained approval through our Institutional Review Board for this analysis prior to initiating this study. We queried our prospectively-collected testis cancer database for all patients who underwent nerve-sparing PC-RPLND from March 1995 to April 2005 by a single surgeon (JS) and extracted the following clinicopathologic data: age, clinical stage, International Germ Cell Cancer Collaborative Group (IGCCCG) risk classification,[15] chemotherapeutic agents received, second-line chemotherapeutic agents received, date and extent of PC-RPLND (bilateral with vs. bilateral without contralateral iliac nodes), radiographic size of residual retroperitoneal mass, number of nodes resected, final pathology of PC-RPLND specimen, and disease status. Patients who underwent re-operative surgery were excluded. Patients are interviewed regarding ejaculatory and fertility status during follow-up clinic visits. We defined antegrade ejaculation as any discharge of seminal fluid at the time of ejaculation by patient report. The retroperitoneal nodal size was determined by the transverse diameter of the largest retroperitoneal mass and categorized into <2 cm, 2–5 cm, and ≥5 cm for analysis. The anatomic nodal regions included in the template were pre/paracaval, retrocaval, interaortocaval, pre/paraaortic, retroaortic and the ipsilateral iliac nodal packages. The contralateral iliac lymph nodes were included at the surgeon's discretion.

To identify pre-operative factors associated with recovery of ejaculation in men undergoing a nerve-sparing PC-RPLND, we fit a multivariable logistic regression model treating ejaculation recovery as a binary variable. We evaluated 5-year probability of freedom from recurrence using the Kaplan-Meier method. All statistics were performed using Stata (College Park, TX). P-values <0.05 were considered statistically significant. Instances of missing data were excluded from analysis.

Results

A total of 341 patients underwent PC-RPLND by a single surgeon during the study period. Nerve-sparing PC-RPLND was performed in 136 (40%) patients at the surgeon's discretion. The clinical and pathologic characteristics of patients undergoing bilateral PC-RPLND with and without nerve-sparing technique are reported in Table 1. Patients in whom a nerve-sparing technique was performed tended to present initially with a lower-volume of metastatic disease and a higher proportion were classified as good risk by IGCCCG criteria.

For men who underwent a nerve-sparing bilateral PC-RPLND, 36 (27%) patients had the contralateral iliac nodes resected, and in the remaining 100 (73%) patients the contralateral iliac lymph nodes were not resected. The retroperitoneal histology revealed fibrosis in 82 (61%) patients, teratoma in 54 (39%) patients, and no patients had residual viable germ cell tumor. A total of 107/136 (79%) reported antegrade ejaculation postoperatively. No patients were treated with sympathomimetic agents in this study. Recovery of antegrade ejaculation decreased with increasing residual mass size: 86/104 (83%) with masses <2 cm, 16/22 (73%) with masses 2–5 cm, and 4/9 (44%) with masses ≥5 cm had return of ejaculation. On multivariable analysis evaluating predictors of antegrade ejaculation for men undergoing a nerve-sparing PC-RPLND (Table 2), a right-sided testicular primary tumor (OR 0.4, 95% CI: 0.1, 1.0, p=0.044) and a residual mass size ≥5 cm (OR 0.1, 95% CI: 0.0, 0.7, p=0.020) were negatively associated with recovery of ejaculation.

At a median follow-up of 39 months, there were 2 (2%) systemic relapses in the cohort of patients undergoing a nerve-sparing PC-RPLND. The 5-year relapse-free survival was 98% (95% CI: 0.93, 0.99).

Discussion

PC-RPLND is an integral part of the management of advanced NSGCT. Because testicular cancer is a disease of young men, the sexual and reproductive side-effects of treatment can have a profound impact on quality of life. The current study shows that nerve-sparing PC-RPLND was feasible in approximately half of patients undergoing PC-RPLND and results in preservation of antegrade ejaculation in nearly 80% of patients without compromising oncologic efficacy.

Ejaculation requires seminal emission, bladder neck closure, and rhythmic contraction of the bulbocavernosal muscles to propel the ejaculate through the urethra. The sympathetic nerves arising from T12-L2 are responsible for seminal emission and bladder neck closure, while the pudendal nerves mediate the rhythmic contraction of the bulbocavernosal muscles. On the right, the post ganglionic sympathetic fibers arise from the right sympathetic trunk, which is located posterior to the vena cava. These fibers travel anteriorly along the posterior surface of the inferior vena cava to the interaortocaval space and course over the anterior aorta. On the left, the sympathetic fibers arise from the left sympathetic trunk posterior to the aorta and travel anteriorly along the surface of the aorta. The left and right postganglionic fibers coalesce in the hypogastric plexus at the level of the inferior mesenteric artery, where they organize into the hypogastric nerves which again coalesce in

the pelvic plexus in the presacral region and travel via the pelvic nerves to their target organs.

Modified templates were initially described to reduce postoperative anejaculation following primary RPLND in patients with Stage 1 NSGCT based on anatomic mapping studies.[16, 17] However, various templates have been adapted and applied in the postchemotherapy setting based on those initial reports.[14] Previously, Jacobsen and colleagues reported antegrade ejaculation in 76% of select patients who underwent a unilateral template PC-RPLND compared to 11% of patients in whom a modified bilateral RPLND was performed.[18] In this study, preservation of antegrade ejaculation was increased to 89% when a nerve-sparing unilateral template dissection was performed. However, the oncologic efficacy of limited modified templates for men undergoing a PC-RPLND remains unknown. Recently, Carver et al reported that, 7–32% of patients who underwent a PC-RPLND had disease outside the boundaries of a modified template depending on which template was applied.[14] Even among patients with residual masses smaller than 2cm, 19/62 (15%) patients had disease outside the boundaries of a modified template dissection. The uncontrolled retroperitoneum may place patients at risk for relapse with viable germ cell tumor or teratoma. Furthermore, re-operative retroperitoneal surgery is associated with a higher morbidity and is curative for only approximately 50% of patients.[19]

Previously, Coogan et al reported on a select group of patients undergoing nerve-sparing PC-RPLND and 62/81 (76.5%) patients had antegrade ejaculatory recovery.[20] In the current study, we found that 79% of patients recovered antegrade ejaculation following bilateral nerve-sparing PC-RPLND. With bilateral nerve-sparing PC-RPLND, risk of late recurrence is minimized and ejaculatory recovery is maximized. On multivariable analysis, residual mass size ≥5 cm conferred a negative association with return of antegrade ejaculation. Nevertheless, 4/9 patients with residual masses ≥5 cm reported antegrade ejaculation demonstrating that nerve-sparing PC-RPLND can be effectively performed in the setting of bulky nodal disease, albeit with lower recovery rates. Similarly, right-sided primary lesions had a negative impact on recovery of ejaculation. This may reflect the technical complexities of preserving postganglionic fibers of the hypogastric plexus in the presence of interaortocaval and/or precaval masses, which are more common in right-sided primary tumors. Nevertheless, the recovery rate was 74% for right-sided lesions. There were only 2 systemic recurrences in our cohort, with a 5- year relapse-free survival of 98%. This excellent prognosis indicates that nerve-sparring procedures do not increase the risk of relapse for patients in the post-chemotherapy setting.

Conclusion

Nerve-sparing is feasible in an increasing number of patients undergoing PC-RPLND. It is associated with an excellent recovery of antegrade ejaculation, and does not compromise oncologic efficacy of the operation.

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Table 1

Overall Characteristics of Post Chemotherapy RPLND Patients

		Non-Nerve-Sparing		Nerve-Sparing Study Cohort		p-Value
		#	%	#	%	
n		205		135		
Age, yrs	Median (IQR)	34	(27, 41)	30	(24,35)	<0.001
Laterality	Left	87	(42%)	81	(60%)	0.001
	Right	112	(55%)	54	(40%)	
	Bilateral	1	(0%)	0	(0%)	
	Extragonadal Disease	5	(3%)	0	(0%)	
Clinical Stage	l	14	(7%)	10	(7%)	<0.001
	lS	3	(1%)	3	(2%)	
	lla	14	(7%)	31	(23%)	
	llb	48	(23%)	40	(30%)	
	llc	47	(23%)	20	(15%)	
	lll	79	(39%)	31	(23%)	
IGCCCG Risk	Good	131	(64%)	113	(84%)	0.001
	Intermediate	35	(17%)	15	(11%)	
	Poor	38	(19%)	7	(5%)	
	Missing	1	(0%)	0	(0%)	
Chemo Intent	Induction	193	(94%)	126	(93%)	0.96
	Relapse	11	(5%)	7	(5%)	
	Missing	1	(1%)	2	(2%)	
Chemo Regimen	BEP	93	(45%)	28	(21%)	<0.001
	EP	108	(53%)	107	(79%)	
	Other	4	(2%)	0	(0%)	
2nd Line Chemo		37	(18%)	7	(5%)	0.001

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		Non-Nerve-Sparing		Nerve-Sparing Study Cohort		p-Value
		#	%	#	%	
Elevated Marker		42	(20%)	7	(5%)	<0.001
PC-RP Nodal Size	<2cm	88	(43%)	104	(77%)	
	2–5cm	54	(26%)	22	(16%)	
	>5cm	54	(26%)	9	(7%)	
	missing	9	(4%)	0	(0%)	
Template	Bilateral With Contralateral Iliacs	138	(67%)	36	(27%)	0.001
	Bilateral Without Contralateral Iliacs	54	(26%)	99	(73%)	
	Other	12	(6%)	0	(0%)	
	Missing	1	(1%)			
Number of Nodes	Median (IQR)	25	(20, 40)	27	(19,39)	0.083
Pathology	Fibrosis/Necrosis	100	(49%)	82	(61%)	<0.001
	Teratoma	80	(39%)	53	(39%)	
	Viable Germ Cell	25	(12%)	0	(0%)	

IQR: interquartile range, IGCCCG: International Germ Cell Cancer Collaborative Group, RP: retroperitoneal, PC-RPLND: post-chemotherapy retroperitoneal lymph node dissection

Table 2

Multivariate Analysis of Factors Associated with Post-Operative Recovery of Ejaculation after Nerve-Sparing PC-PRLND

	OR	95% CI	P-value
Age (per year)	1.0	1.0, 1.1	0.2
[*]**Right Sided Primary**	0.4	0.1, 1.0	0.044
[†]**Intermediate/Poor IGCCCG Risk**	2.4	0.5, 11.9	0.4
Second Line Chemotherapy	0.5	0.1, 3.3	0.5
Elevated STM at PC-RPLND	0.3	0.0, 2.3	0.2
[‡]**PC Residual RP Mass Size 2–5 cm**	0.3	0.1, 1.2	0.1
≥5 cm	0.1	0.0, 0.7	0.020

[*] Compared to Left sided primary

[†] Compared to good IGCCCG risk

[‡] Compared to <2 cm PC residual RP mass

IGCCCG: International Germ Cell Cancer Collaborative Group, STM: serum tumor marker, PC-RPLND: post-chemotherapy retroperitoneal lymph node dissection, PC: post-chemotherapy, RP: retroperitoneal