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ORIGINAL ARTICLE

Robotic retroperitoneal lymph node dissection for primary and post-chemotherapy testis cancer

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Abstract

The role of retroperitoneal lymph node dissection (RPLND) in testicular cancer is well established in both the primary and post-chemotherapy setting. The aim of this study was to report our 2 years oncological outcomes of robotic RPLND. A retrospective review was performed of all patients undergoing robotic RPLND by a single surgeon at Princess Margaret Cancer Centre. Demographic, perioperative, and oncologic data were analyzed using descriptive statistics. Between September 2014 and June 2020, 141 patients underwent an RPLND [33 (23.4%) were primary, 108 (76.6%) were post-chemotherapy]. 27 (19.1%) patients underwent a robotic bilateral template nerve-sparing RPLND. RPLND indication was primary (i.e. pre-chemotherapy) in 18 (66.7%), and post-chemotherapy in 9 (33.3%) patients. Stage at RPLND was 2A ($n=15$, 55.6%), 2B ($n=9$, 33.3%), 2C ($n=1$, 3.7%) and 3 ($n=2$, 7.4%). Median OR time (incision to closure) was 525 min and blood loss was 200 ml. Nerve sparing was performed in all but one case. Six (22.2%) adjuvant procedures were performed including two (7.4%) vascular repairs. Median length of stay was 2 days. Viable tumor was detected in 17 (63%) and teratoma in 9 (33.3%). Median follow-up was 31.3 months. No adjuvant chemotherapy was given. Three patients (11.1%) relapsed: 2 out-of-field and 1 with both in-field and out-of-field disease. Robotic RPLND can be performed safely. Long-term follow-up of series such as ours, enriched with patients with viable disease and/or teratoma, and not treated with adjuvant chemotherapy is required to ensure oncological outcomes are comparable to the open approach.

Keywords Germ cell tumor · Testis cancer · Robotic · RPLND

Introduction

Retroperitoneal lymph node dissection (RPLND) is a primary management option for nonseminomatous germ cell tumors clinical stage I-2B disease [1–3] and those with clinical stage I disease that relapsed on surveillance [4]. Likewise, after chemotherapy, RPLND has an established role in resecting residual disease [5]. The advantage of primary RPLND is the avoidance of toxicities associated with chemotherapy [6]. Post chemotherapy, there is a survival advantage to resecting residual disease [7].

The disadvantage of RPLND is the associated morbidity. The majority of RPLNDs are performed through a large midline incision with a length of stay around 5–7 days. The reported complication rate in the primary setting is ~ 10–20% [8].

The first reported laparoscopic RPLND was described in 1992 [9]. Since then robotic RPLND has evolved with the first case described in 2006 [10]. The literature to date has

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consisted of a number of case series confirming feasibility [11–16]. However, oncologic efficacy remains relatively unproven given the number of patients in the published series with stage I disease who ended up not having any disease in their retroperitoneum, and the prevalent use of adjuvant chemotherapy for those who did. Very few studies have reported on patients with Stage 2/3 disease or in the post-chemotherapy setting.

The aim of this study was to report the oncologic outcomes of robotic RPLND in both the primary and post-chemotherapy setting.

Methods

Following institutional board review, a retrospective review was performed of all patients who underwent a robotic RPLND by a single surgeon at a tertiary testis cancer center.

When we initiated the robotic RPLND program we had two goals: (a) to continue to adhere to the multidisciplinary decision-making principles regarding which patients should have an RPLND and (b) to replicate the extent of dissection of an open RPLND.

All new patients referred to the testis cancer clinic, patients with new relapse, significant disease change, or those having completed chemotherapy are discussed at our weekly multidisciplinary meeting with radiation oncology, medical oncology, and urologic oncology. Once an RPLND was deemed the most appropriate treatment plan, patients were offered a robotic approach with full disclosure that robotic RPLND is an evolving technique. Though each case was considered individually, in general our selection criteria included: (a) primary RPLND for clinical stage IIA/B (≤ 3 cm) disease; (b) primary RPLND for patients who have progressed on surveillance to a clinical stage IIA/B (≤ 3 cm) equivalent; and (c) post-chemotherapy RPLND for patients with residual masses less than 3 cm without large (approximately $> 70\%$) tumor volume reduction from the pre-chemotherapy volume.

Surgical technique

Our surgical technique has been described in detail previously [17] but briefly we perform a transperitoneal approach with the patient in the supine position. Our technique is modeled after that of Dr. James Porter [16, 18]. The patient is placed in a slight Trendelenburg position and the robot is docked over the patient's head. The posterior peritoneum is incised along the root of the mesentery from the appendix heading cephalad and medial to the duodenum up to the crossing point of the inferior mesenteric vein, at the level of the renal veins. The bowel is then anchored ventrally to the abdominal wall using Biosyn sutures. We start the lymphadenectomy with the paracaval nodes, rolling the inferior vena cava (IVC) medially and dissecting as far medial as the sympathetic chain. IVC retraction is facilitated through vessel loops. Small vessels off the IVC are controlled with bipolar cautery, larger lumbar veins are secured with Hemo-lok clips. As with our open technique, lumbar arteries are skeletonized and preserved unless involved with disease. It is at this point that nerve sparing is accomplished by identifying the sympathetic chain, the right-sided postganglionic sympathetic fibers, and the hypogastric plexus. All tissue is completely removed circumferentially around the vena cava. Subsequently, the dissection moves to include the para-aortic nodes both above and below the inferior mesenteric artery (IMA), which is preserved. The aorta is retracted medially and all tissue underneath the aorta is excised. The left sympathetic chain is identified and left-sided postganglionic sympathetic fibers coursing under the IMA are identified and preserved down to the hypogastric plexus. Limits of the dissection include cephalad to the renal arteries, caudad to the point of the ureter crossing the common iliacs, posteriorly to the anterior spinous ligament and/or psoas fascia, and laterally to the ureters. The procedure concludes by dissecting and removing the ipsilateral spermatic cord down to the level of orchiectomy ligation.

Follow-up

Patients are followed, depending on histology, with regular clinic visits for history and physical examinations, tumor marker assessment and surveillance imaging.

Statistical analysis

Demographic, perioperative, and oncologic data were analyzed using descriptive statistics. Continuous variables were presented as medians and categorical variables were assessed using frequencies and proportions. Complications were defined as any deviation from the normal post-operative course, in accordance with the Clavien–Dindo classification system. Time to relapse was defined as the time between robotic RPLND and date of relapse. Statistical significance was defined as $\alpha \leq 0.05$. STATA®12 (College Station, TX) was utilized for the statistical analysis.

Results

Between September 2014 and 2020—141 patients underwent an RPLND [33 (23.4%) primary, 108 (76.6%) post-chemotherapy]. 27 (19.1%) patients underwent a robotic RPLND.

The median age was 28.6 years (range 21.8–54.2). The indication for RPLND was primary in 18 (66.7%) and

post-chemotherapy in 9 (33.3%). Stage at diagnosis was clinical stage 1 (CSI) in 15 (55.6%), CSIS in 1 (3.7%), CS IIA in 6 (22.2%), CSIIB in 3 (11.1%) and CSIII in 2 (7.4%). Stage equivalent at RPLND was CS2A in 15 (55.6%), CS2B in 9 (33.3%), CS2C in 1 (3.7%) and CS3 in 2 (7.4%). Baseline characteristics are presented in Table 1.

The median operative time (incision to closure) was 525 min (range 420–600). The median blood loss was 200 ml (range 50–6000). One (3.7%) patient required a blood transfusion. Nerve-sparing procedure was performed in 26 (96.3%) patients. One patient was converted intra-operatively to an open procedure due to bleeding which required a repair of the renal artery. Six (22.2%) adjuvant procedures were performed including two (7.4%) vascular repairs. The median length of stay was 2 days (range 1–8). Peri-operative details are presented in Table 2.

Viable tumor was detected in 17 (63%) patients, teratoma in 9 (33.3%) patients and fibrosis/necrosis in 1

Table 1 Baseline tumor characteristics of patients undergoing robotic RPLND

	Combined ($n=27$)	Primary ($n=18$)	Post chemotherapy ($n=9$)
Age (years) (median)	28.6 (21.8–54.2)	33.8 (25–51)	25.7 (21.8–54.2)
BMI (kg/m^2) (median)	25.6 (20.1–38.5)	26.4 (20.1–38.5)	24.9 (20.9–35)
Laterality of primary tumor			
Right	12 (44.4)	8 (44.4)	4 (44.4)
Left	15 (55.6)	10 (55.6)	5 (55.6)
Histology at orchiectomy			
Non-seminoma	24 (88.9)	15 (83.3)	9 (100)
Seminoma	3 (11.1)	3 (16.7)	0 (0)
Clinical stage at diagnosis			
1	15 (55.6)	13 (72.2)	2 (22.2)
1S	1 (3.7)	0 (0)	1 (11.1)
2A	6 (22.2)	3 (16.7)	3 (33.3)
2B	3 (11.1)	2 (11.1)	1 (11.1)
2C	0 (0)	0 (0)	0 (0)
3	2 (7.4)	0 (0)	2 (22.2)
Stage equivalent at RPLND*			
2A	15 (55.6)	12 (66.7)	3 (33.3)
2B	9 (33.3)	5 (27.8)	4 (44.4)
2C	1 (3.7)	1 (5.6)	0 (0)
3	2 (7.4)	0 (0)	2 (22.2)
Lympho-vascular invasion			
Yes	10 (37)	6 (33.3)	4 (44.4)
No	17 (63)	12 (66.7)	5 (55.6)
Embryonal > 40%			
Yes	19 (70.4)	12 (66.7)	7 (77.8)
No	8 (29.6)	6 (33.3)	2 (22.2)
Teratoma			
Yes	13 (48.1)	6 (33.3)	7 (77.8)
No	14 (51.9)	12 (66.7)	2 (22.2)
Size of primary tumor (cm) (median)	3.5 (1.3–6.5)	3.2 (1.3–4.6)	4.2 (2–6.5)
Markers at diagnosis			
Normal	20 (74.1)	18 (100)	2 (22.2)
Abnormal	7 (25.9)	0 (0)	7 (77.8)
Chemotherapy regimens			
BEP×4		N/A	5 (55.6)
BEP×3		N/A	4 (44.4)
Other		N/A	0 (0)

*Stage equivalent represents the updated staging at the time of RPLND. E.g. if a patient with stage I disease relapsed with a 2 cm retroperitoneal node and then underwent RPLND they would be a stage equivalent IIA

Table 2 RPLND details

	Combined ($n=27$)	Primary ($n=18$)	Post chemotherapy ($n=9$)
Operative time* (mins) median	525 (420–600)	525 (420–600)	500 (435–585)
Bloods loss (ml) median	200 (50–6000)	200 (50–500)	100 (50–6000)
Transfusion rate	1 (3.7)	0 (0)	1 (11.1)
LOS (days) median	2 (1–8)	2 (1–4)	2 (1–8)
Nodal yield median	33 (7–86)	37 (7–86)	32 (14–59)
Nerve sparing			
Bilateral	18 (66.7)	13 (72.2)	5 (55.6)
Unilateral	8 (29.6)	4 (22.2)	4 (44.4)
None	1 (3.7)	1 (5.6)	0 (0)
Size of mass on CT pre RPLND (cm)	1.7 (1.1–3.6)	1.8 (1.1–3.1)	1.7 (1.3–3.6)
Adjuvant procedures			
Mediastinal resection	1 (3.7)	0 (0)	1 (11.1)
Hernia repair	2 (7.4)	1 (5.6)	1 (11.1)
Adhesiolysis	1 (3.7)	1 (5.6)	0 (0)
Vascular repair of renal artery	1 (3.7)	0 (0)	1 (11.1)
Vascular repair of IVC	1 (3.7)	1 (5.6)	0 (0)
Conversion to open	1 (3.7)	0 (0)	1 (11.1)
30 days readmission rate	1 (3.7)	0 (0)	1 (11.1)
30–90 days readmission rate	4 (14.8)	2 (11.1)	2 (22.2)
Complications			
Ascites requiring drain	3 (11.1)	2 (11.1)	1 (11.1)
Ascites requiring embolization	1 (3.7)	0 (0)	1 (11.1)
Clavien–Dindo			
1	1 (3.7) (Pneumothorax from central venous catheter)	1 (5.6)	0 (0)
2	0	0 (0)	0 (0)
3a	3 (11.1) (Ascites interventions)	2 (11.1)	1 (11.1)
3b	0	0 (0)	0 (0)
4	0	0 (0)	0 (0)
Follow-up in months from RPLND	31.3 (4.3–73.3)	31.7 (4.3–73.3)	31.3 (5.7–50.4)
Recurrence post RPLND	3 (11.1)	2 (11.1)	1 (11.1)
Infield	1 (3.7) BEP × 3	1 (5.6)	0 (0)
Out field	2 (7.4)—SBRT to Brain, BEP × 3	1 (5.6)	1 (11.1)
Adjuvant chemotherapy	0 (0)	0 (0)	0 (0)
Pathology of RPLND			
Viable tumor	17 (63)	17 (94.4)	0 (0)
Teratoma	9 (33.3)	1 (5.6)	8 (88.9)
Fibrosis/Necrosis	1 (3.7)	0 (0)	1 (11.1)

* = operative time is represented as incision to closure

(3.7%) patient. Median follow-up was 31.3 months (range 4.3–73.3). No patient received adjuvant chemotherapy.

Three (11.1%) patients recurred following robotic RPLND, Table 3: two out-of-field and one with both in- and out-of-field disease. The first out-of-field recurrence was a patient who developed rising tumor markers and a 11 mm mediastinal node 12 months following robotic primary RPLND (viable embryonal carcinoma)—he received BEP × 3 and remains disease-free 15 months following chemotherapy. The next out-of-field patient had rising markers following post-chemotherapy RPLND- his imaging revealed brain metastases. He underwent stereotactic radiotherapy 3 weeks following RPLND and remains disease-free 20 months later. One patient developed a combined in- and out-of-field recurrence. He initially underwent a left radical orchiectomy for a 4.6 cm classic seminoma. Markers were normal at diagnosis. He was enrolled in surveillance for clinical stage 1 disease. Subsequently he developed a

Table 3 Characteristics of patients who relapsed following robotic RPLND

Age at RPLND (years)	Indication	Stage at diagnosis	Reason for primary RPLND	Orchiectomy histology	Size of nodal mass (cm)	Nodal yield	RPLND histology	Time to relapse (months)	Location of relapse	Treatment of relapse	Follow-up from RPLND (months)
21.8	Post chemotherapy	3C	n/a	NSGCT	1.8	42	Teratoma	1	Brain	SBRT	21
35.1	Primary	1A	Stage 1 progression	Seminoma	1.2	41	Viable tumor	3	Retroperitoneum	BEP×3	21
28.4	Primary	1A	Stage 1 progression	Seminoma	1.2	63	Viable embryonal carcinoma	12	Mediastinal	BEP×3	27

recurrence in his retroperitoneum 21 months later. He underwent a primary robotic RPLND for a 1.9 cm periaortic node. The robotic RPLND was uneventful—operating time was 500 min, blood loss 200 ml, no intraoperative complications. He was discharged on day 3. Histology revealed 12/43 nodes positive for seminoma. After a multidisciplinary consultation, a shared decision was made not to give adjuvant chemotherapy but to survey. Initial follow-up imaging at 4 months demonstrated no residual lymphadenopathy. At 15 months post RPLND a slow marker rise prompted imaging which revealed an enlarged retrocrural node and left-sided para-aortic nodes. He received BEP×3 and has stable disease 6 months following chemotherapy.

Discussion

We report a case series of bilateral primary and post-chemotherapy robotic RPLND performed by an experienced RPLND surgeon at a high-volume testis cancer center. This report of consecutive cases since program initiation demonstrates feasibility, safety and provides important data on oncologic efficacy. It also serves to remind of the complexity of these cases and the need for them to be managed at experienced centers.

Given the morbidity of open RPLND, robotic RPLND is evolving as a technique. Despite the first report of robotic RPNLD in 2006, there are still only a few small series in the literature. These series all endorse feasibility and safety of the technique, the oncologic efficacy of robotic RPLND remains largely unknown [11–16] as most of the patients included either did not have viable disease in their retroperitoneum, or those that did were treated with adjuvant chemotherapy. This leaves very few cases where the robotic RPLND was the sole therapeutic intervention such that we can evaluate its ability to cure as a monotherapy.

Although our series also reports the early outcomes with no learning curve run-in, it is strengthened by the fact that nearly all had either viable disease (63%) or teratoma (33.3%) and that a third were post-chemotherapy RPLNDs. Despite this fact, we observed only 3 (11.1%) relapses; 2 (7.4%) after primary RPLND and 1 (3.7%) after post-chemotherapy RPLND. These rates are similar to that seen after primary and post-chemo open RPLNDs from high-volume centers [19, 20].

We do however report one relapse that was both in-field and out-of-field in location. Having an in-field relapse is an uncommon occurrence after RPLND and implies inadequacy of dissection [21]. There were no technical concerns with this particular case; it was thought to be a thorough and complete dissection. We take this event seriously and acknowledge that this should be monitored closely in ours and other series to be reported. If robotic RPLND were to

yield a higher than expected rate of in-field relapse, this would be a reason to consider abandoning it.

The largest robotic RPLND series reported to date only contain primary RPLNDs. In 2017, Pearce et al. [12] reported the early outcomes of 47 primary RPLNDs across 4 centers in the United States. The majority (89%, $n=42$) were CSI. Positive nodes were detected in 17% ($n=8$) and 12% ($n=5$) received adjuvant chemotherapy. Despite the predominant low stage of their series, they reported one out-of-field recurrence with a 2-year recurrence free survival of 97%. More recently, Rocco et al. [14] reported a study of 58 primary RPLNDs with nearly 4-year follow-up. Again, this was a predominantly low-stage series with 97% ($n=56$) being CSI disease. Only 17 (29%) had disease in the nodes at RPLND, a third of which received adjuvant chemotherapy. The 2-year recurrence free survival was 91% with 5 patients developing out-of-field recurrences. Recently, Taylor et al. [22] reported a multicenter series of 49 patients who underwent primary robotic RPLND with a 15 months follow-up. Positive nodes were detected in 42% while 18% had adjuvant chemotherapy. Similarly this was predominantly a low stager series with 83% being CSI disease. In contrast to our series, less than half underwent a bilateral template.

Aside from oncologic outcomes, we observed a short length of stay (2 days median), limited blood loss (200 ml median) and a low complication rate (3.7% minor, 11.1% major). The large primary robotic RPLND series likewise demonstrated short median lengths of stay (ranging from 1 to 2 days), low rates of blood loss (ranging from 50 to 100 ml), and low complication rates (6.4% and 1.7% Clavien–Dindo ≥ 3). For comparison, open RPLND series from high-volume centers have typically shown longer lengths of stay, more blood loss, and similar complication rates (ranging from 2 to 16%) [8, 19, 20, 22, 23].

Despite these better non-oncologic parameters, it is important to note that both Pearce et al. and Rocco et al. [12, 14] experienced one vascular injury requiring conversion to open. The case in Rocco's series ultimately required a nephrectomy. Similarly, in our series, in one of our early cases we had one conversion due to a vascular injury which was repaired but lead to significant blood loss and transfusion. Thus, while overall robotic RPLND does appear to have a lower overall complication rate in comparison to open RPLND, it is not without risk of serious injuries requiring conversion to open surgery due to vascular or visceral injury. This needs to be highlighted to patients as part of the consent process and serve as a reminder of the importance that these cases be attempted by surgeons experienced with the nuances of both robotic and open RPLND.

There is scarce published literature regarding post-chemotherapy robotic RPLND. There have been few series published with more than 10 patients [13, 14]. The largest series, that by Singh et al. reported successful outcomes of 13 patients (12 underwent a unilateral template) with no recurrence at 23 months. They did however note 3 patients had persistent chyle leak requiring intervention (lymphangiography for one and surgery for 2). In our post-chemotherapy subset, one patient who underwent concomitant sternotomy and mediastinal resection at robotic RPLND required lymphatic embolization due to ongoing ascites despite low-fat diet and repeated paracenteses. With our data added to the small published post-chemotherapy series this highlights the feasibility of robotic post-chemotherapy RPLND in highly selected patients but large studies with longer follow-up are clearly required.

There is some skepticism regarding robotic RPLND. Recently, Calaway et al. [21] reported a case series of 5 patients referred to Indiana University with recurrent disease following robotic RPLND. One was an in-field recurrence and 4 had unusual recurrence locations. Sheinfeld et al. [24] replied echoing the concerns as the Memorial Sloan-Kettering Cancer Centre group has also seen unusual relapse locations after robotic RPLND. They feel these unusual recurrences are likely underreported. Porter et al. [25] responded suggesting unconventional recurrences are not inherent to the robotic approach.

Indeed there needs to be caution, as with any evolving technique to ensure safety standards [26]. While we do have one case of both in- and out-of-field relapse, we have yet seen the unconventional relapse locations suggested by Calaway. We feel this is something that needs to be tracked and reported by centers performing RPLND and if indeed this is occurring even at centers with high-volume open and robotic RPLND experience, then safety of robotic RPLND should be questioned.

Our study has limitations including the relatively small number of patients, the retrospective nature, that it is a single surgeon experience and the fact it represents highly selected patients. Despite the small numbers, the fact the majority of patients had pathologic disease at RPLND and none received adjuvant chemotherapy means our data is meaningful to oncologic efficacy of robotic RPLND. Furthermore, our series adds to the post-chemotherapy robotic RPLND literature.

Conclusion

In our series of both primary and post-chemotherapy bilateral robotic RPLND we observed that it can be performed safely and with at least short-term oncologic efficacy without the need for adjuvant chemotherapy. Long-term follow-up of series such as ours, enriched with patients with viable disease and/or teratoma, and not treated with adjuvant chemotherapy is required. Our series also highlights the importance of these cases being treated at centers experienced

with the nuances of testis cancer care, and in particular with both open and robotic RPLND.

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Declarations

Conflict of interest Robert Hamilton: Advisory Board—Bayer, Amgen, Janssen, Astellas. Research Funding—Bayer (ARASENS trial), Janssen (SPARTAN trial). Speaking Honoraria—Abbvie. Meeting Travel—Roche. Sources of Funding: None. No other conflicts of interest to declare.

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