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TOPIC PAPER

Primary robotic RLPND for nonseminomatous germ cell testicular cancer: a two-center analysis of intermediate oncologic and safety outcomes

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Abstract

Objective To evaluate the intermediate-term oncologic outcomes and safety profile of the largest case series of primary robotic retroperitoneal lymphadenectomy for low-clinical-stage non-seminomatous germ cell testicular cancer.

Methods This was a two-center retrospective analysis of robotic RPLND cases for low-clinical-stage (stage I–IIB) non-seminomatous germ cell testicular cancer in the primary setting. Demographic, perioperative, operative and oncologic variables were collected between March 2008 and May 2019. Descriptive analyses were performed and presented as medians with interquartile ranges for continuous variables and frequency and proportions for categorical variables. A survival analysis of time to recurrence was performed using Cox proportional hazards model. Using logistic regression, risk factors for complications were analyzed. Both univariate and multivariate analyses were performed.

Results A total of 58 patients (CS 1 = 56, CS IIA = 2, CS IIB = 0) were identified. The median follow-up was 47 months and the 2-year recurrence-free survival rate was 91%. The five recurrences were all out of the performed dissection template (pelvis = 1 and lung = 4). Only five patients (29%) with occult metastasis underwent adjuvant chemotherapy. The median operative time was 319 min [interquartile range (IQR) 276–355 min], estimated blood loss was 100 ml (IQR 75–200 ml), node count was 26 (IQR 20–31), and length of stay 2 d (IQR 1–3 days). There were 2 (3.3%) intraoperative complications, 19 (32.7%) 30-day postoperative complications to include 14 (24.1%) Clavien grade I, 4 (6.9%) Clavien grade II, 1 (1.7%) Clavien grade III and 0 Clavien grade IV complications. No statistical significance was found on multivariate or univariate analysis for survival analysis of time to recurrence and risk factors for complications.

Conclusions This study represents the largest case series of primary R-RPLND for the treatment of low-stage non-seminomatous germ cell tumors (NSGCT). With 47 months of follow-up and a low rate of adjuvant chemotherapy, intermediate oncologic efficacy appears to be comparable to the gold standard open approach.

Keywords Testicular cancer · Retroperitoneal lymph node dissection · Robotic surgery · RPLND · NSGCT

Introduction

According to the National Comprehensive Cancer Network (NCCN), retroperitoneal lymph node dissection (RPLND) is a management option for testicular non-seminomatous germ cell tumor (NSGCT) for clinical-stage (CS) I–IIB disease [1]. RPLND is an ideal option for patients who wish to avoid the known and unknown long-term toxicities of platinum-based chemotherapy [2, 3], and for those wanting to decrease the 5-year relapse rate of 30% observed of patients with clinical stage I disease who choose active surveillance [4]. Another advantage of RPLND is the treatment of chemorefractory retroperitoneal teratoma.

Disclaimer: The views expressed in this paper are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the U.S. Government.

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Open RPLND (O-RPLND) remains the gold standard approach for NSGCT; however, it can result in significant post-operative morbidity and hospitalizations lasting 6 days or more [5]. Minimally invasive RPLND for low-stage testicular NSGCT has shown promise as a less morbid alternative to the traditional open approach. The first primary laparoscopic RPLND (L-RPLND) was described by Rukstalis and Chodak in 1992 [6]. This approach has been found to offer faster recovery times, reduced blood loss and decreased morbidity compared to O-RPLND [7–9].

After being approved in 2000 by the United States Food and Drug Administration for general laparoscopic surgery, there has been continuous expansion of robot-assisted surgery for both upper and lower urinary tract disease in urology. Robot-assisted laparoscopy offers the benefits of an operator-controlled camera, high-definition 3D magnified view of 10–12 times, wristed instrumentation with 7 degrees of freedom and tremor filtration [10]. These same benefits also make robotic surgery attractive for RPLND. The first robotic RPLND (R-RPLND) was reported by Davol et al. [11] on an 18-year-old man with mixed GCT. Since the original description, early results demonstrate an acceptable safety and early oncologic profile compared to open and laparoscopic techniques, making R-RPLND potentially an excellent option for the treatment of low-clinical-stage testicular NSGCT [9, 12–14].

Despite these early reports showing potential benefits to minimally invasive RPLND, longer term outcomes are limited. The primary aim of the present study is to report intermediate-term oncologic outcomes of the largest case series of R-RPLND for low CS NSGCT. Secondarily, we aim to describe the safety profile and identify risk factors for complications.

Methods

Study design

Medical charts for all patients who underwent a primary R-RPLND for low-CS (I–IIB) nonseminomatous germ cell testicular cancer between May 2008 and May 2019 at two institutions were retrospectively reviewed. This retrospective review was approved by the Institutional Review Board at Naval Medical Center San Diego (NMCSD.2012.0155) and performed in accordance with the institution guidelines. Of note, patients presenting with low-CS testicular NSGCT were offered all management choices, including active surveillance, chemotherapy, and RPLND, consistent with current guidelines [1]. Exclusion criteria for R-RPLND included bulky retroperitoneal disease and multiple lymph nodes concerning for the presence of metastatic disease (CS IIC or greater). Patients were excluded from analysis if they underwent RPLND for pathology other than CS I-IIB NSGCT or in the post-chemotherapy setting.

Surgical technique

R-RPLND was completed in a manner previously described by Santomauro et al. and Cheney et al. [12, 15]. In brief, the approach to R-RPLND was performed via a supine, low-abdominal, transperitoneal approach with moderate Trendelenburg (15°) and a total of six ports across the lower abdomen (one robotic camera port, three working robotic ports, and two 12-mm assistant ports). The spermatic cord on the side of the primary tumor is dissected first. Next, the retroperitoneum was exposed by incising the peritoneum and creating a retroperitoneal 'hammock'—a key step in the success of the supine, low-abdominal approach (Fig. 1). The operation progresses by establishing the superior extent of the lymph node dissection by exposing the left renal vein and right renal artery, followed by the use of a split-and-roll technique. Sympathetic nerve roots are prospectively identified and preserved as they cross over the lumbar veins of the inferior vena cava.

Early in our experience, patients underwent a modified unilateral template dissection based on the primary tumor location. Given the better understanding of the retroperitoneal neuroanatomy gained through experience with R-RPLND and recent data demonstrating that original mapping studies supporting the modified template underestimated the extent of retroperitoneal metastases [16, 17], a bilateral template with prospective nerve sparing was performed in the most recent 40 cases.

Staging and postoperative surveillance

American Joint Committee on Cancer guidelines (8th ed.) were used for clinical and pathologic staging [18]. Follow-up for nonseminoma testicular cancer treated with primary RPLND was performed using the NCCN Guidelines and included a history and physical examination, tumor marker assessment, axial imaging of the abdomen and pelvis, and plain films of the chest [1].

Data analysis

Demographic, perioperative, and oncologic data were analyzed using descriptive statistics. Continuous variables were presented as medians with interquartile ranges (IQR) and categorical variables were assessed using frequencies and proportions. Independent factors thought to predict complications were analyzed using logistic regression. These factors included age, BMI, R-RPLND template, clinical stage, and nodal count. Complications were defined as any deviation from the normal post-operative

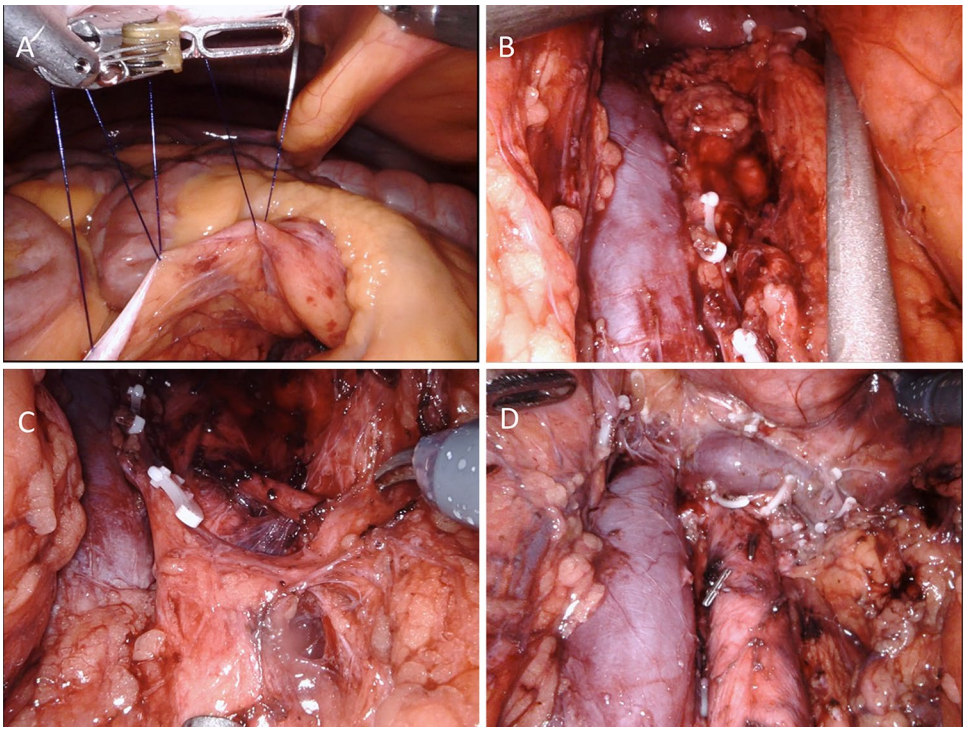

Fig. 1 **a** Hammock sutures, **b** initial exposure, **c** prospective nerve sparing and identification of inferior mesenteric artery, **d** completed dissection

course, in accordance with the Clavien–Dindo classification system. A survival analysis of time to recurrence was performed using Cox proportional hazards model. Time to recurrence was defined as the time lapse between the surgical date of R-RPLND and the date the recurrence was identified. Independent variables were clinical stage, presence of lymphovascular invasion, presence of > 40% embryonal tumor on testicular pathology, presence of teratoma on testicular pathology, surgical template, and node count. Both univariate and multivariate analyses were completed. Statistical significance was defined as $\alpha \leq 0.05$. STATA®12 (College Station, TX) was utilized for the statistical analysis.

Results

Baseline patient characteristics

During the study period, 56 (97%) and 2 (3%) R-RPLNDs were performed for CS I and CS IIA disease, respectively. There were no primary R-RPLNDs performed for CS IIB during our study period. A total of 16 cases were performed by one surgeon at the Mayo Clinic and 42 cases were performed by two surgeons at the Naval Medical Center San Diego. Baseline tumor characteristics are presented in Table 1.

Operative outcomes

In 69% of cases, a bilateral template was used, while a right-sided template and a left-sided template were used in 17% and 14% of cases, respectively (Table 1). The median operative time was 319 min (IQR 276–355 min), estimated blood loss (EBL) was 100 ml (IQR 75–200 ml), median node yield was 26 (IQR 20–31), length of stay was 2 days (IQR 1–3 days) and post-operative morphine equivalents were 22 mg (IQR 12–57). Overall 47 (81%) patients underwent a nerve-sparing procedure while 7 (12%) and 4 (7%) had no nerve sparing or unknown status, respectively.

Complications

Complications are detailed in Table 1. There were 31% low-grade (Clavien I–II) complications and 1.7% high-grade (Clavien III–IV) complications overall. One intraoperative complication early in the series was a renal artery injury that required open conversion. Robotic and open repair was unsuccessful so a right nephrectomy was performed. For that case alone, the estimated blood loss was 4 l and 354 mg post-operative morphine equivalents were used. The other intraoperative complication was a ureteral injury which required primary repair and stent placement. The Clavien grade II complications included two cases of pneumonia, one episode of scrotal edema requiring pharmacologic diuresis, and pancreatitis requiring readmission

Table 1 Demographics and perioperative outcomes

Patient and tumor characteristics ($n=58$)	Median (IQR)/ frequency (%)
Age (years)	26 (22–33)
BMI (kg/m^2)	26 [23–28]
Primary tumor laterality	
Right	31 (54)
Left	25 (43)
Bilateral	2 [3]
Clinical stage	
IA	35 (60)
IB	21 (36)
IIA	2 [3]
IIB	0 (0)
LVI	
Yes	23 (40)
No	35 (60)
> 40% embryonal	
Yes	33 (57)
No	25 (43)
Risk factors if CS I	
None	14 [25]
LVI only	9 [16]
> 40% Embryonal only	20 (36)
Both	13 [23]
Teratoma present	
Yes	39 (67)
No	19 (33)
Teratoma present if 0 risk factors	
Yes	12 (86)
No	2 [14]
Operative outcomes ($n=58$)	Median (IQR)
Operative time (min)	319 (276–355)
Estimated blood loss (ml)	100 (75–200)
Node yield	26 (20–31)
Length of stay (days)	2 [1–3]
Dissection template	
Bilateral	40 (69)
Right	10 [17]
Left	8 [14]
Nerve sparing	
Yes	47 (81)
No	7 [12]
Post-operative morphine equivalents (mg) (unknown in $n=15$)	22 (12–57)
Intraoperative and postoperative complications	Frequency (%)
Overall	21 (36)
Intraoperative	2 (3.3)
Open conversion	1 (1.7)
Ureteral injury	1 (1.7)
30-D postoperative	19 (32.7)

Table 1 (continued)

Intraoperative and postoperative complications	Frequency (%)
Clavien I	14 (24.1)
Clavien II	4 (6.9)
Clavien III	1 (1.7)
Clavien IV	0 (0)

to the hospital. The Clavien grade III complication was a symptomatic lymphocele requiring percutaneous aspiration. There were no other adverse sequelae for any of these cases. Using logistic regression, risk factors for complications were analyzed. Both univariate and multivariate analyses revealed no statistically significant risk factors for the development of complications.

Pathologic stage and node status

The pathologic outcomes are found in Table 2. In short, 17 patients (29%) were found to have pathologically involved retroperitoneal lymph nodes, indicating pathologic stage II disease, including 15 (27%) and 2 (100%) CS I and CS IIA patients, respectively. Pathologic stage was pN1 in 13 patients (33%) and pN2 in 4 patients (7%).

Oncologic and functional outcomes

Overall the median follow-up was 47 months (IQR 21–73), including 47 months (IQR 21–73) and 45 months (IQR 21–70) and 47 months (IQR 25–70) for pathologic stage I patients, pathologic stage II patients and pathologic stage II patients who did not receive adjuvant chemotherapy, respectively (Table 2). Among the 17 pathologic stage II patients, 5 patients (29%) received adjuvant chemotherapy while 12 patients (71%) were managed with surveillance. The 2-year recurrence-free survival rate for the entire cohort was 91%. The five recurrences were all out of the performed template. Two patients had recurrences at 6.3 and 20.9 mo, respectively, in the lung. One patient had a pelvic relapse outside of the dissection template that was identified and surgically removed via a robotic pelvic lymph node dissection 1.4 months after the initial R-RPLND surgery. The recurrence-free survival at 2 years was 92% (11/12) for patients with pathologic stage II disease managed with surveillance. All patients are alive and free of disease. Using a Cox proportional hazards model a survival analysis of time to recurrence was performed. Both univariate and multivariate analyses revealed no statistically significant independent variable. Of 54 patients with evaluable data, 44 (81%) had normal antegrade ejaculation at last follow-up.

Discussion

This retrospective, two-center study analyzed the intermediate-term oncologic outcomes and perioperative morbidity and complications in the largest case series of primary R-RPLND for low CS NSGCT. At 47 months of follow-up, there were five recurrences, all of which were out of the dissection template. Among the 17 pathologic stage II patients, 5 patients (29%) received adjuvant chemotherapy and the recurrence-free survival at 2 years was 92% (11/12) for patients managed with surveillance. All patients are alive with no evidence of disease. There were no clinically relevant predictors of recurrence or complications with multivariate analysis. As in other minimally invasive surgeries in urologic oncology, our series demonstrates a shorter recovery time which translated into shorter hospital stays.

The intent of the R-RPLND is to match the oncologic efficacy of O-RPLND while providing the benefits of a minimally invasive approach. Data regarding the oncologic outcomes for R-RPLND have been limited by small cohort size and short-term follow-up. Despite these shortcomings, we see a trend in intermediate-term oncologic equivalence among the three largest case series, including this study, with a recurrence-free survival of 91–100% [13, 14]. The five recurrences in this study were all out of field. Four patients had a distant recurrence in the lung and one patient had a pelvic relapse outside of the bilateral dissection template. A survival analysis of time to recurrence was performed and both univariate and multivariate analyses revealed no statistically significant independent variables for recurrence. These oncologic results are comparable to recurrence-free rates of 92.5% for O-RPLND and 95.4% for L-RPLND based on findings reported in a systematic review including > 800 patients from 34 series spanning 1992–2008, with a 63-month follow-up [19].

Another criticism of the oncologic efficacy of primary R-RPLND for low-CS NSGCT is the liberal use of adjuvant chemotherapy, which is often avoided in pN1 marker-negative disease. Pearce et al. and Cheney et al. reported an adjuvant chemotherapy rate of 62 and 44%, respectively. In this study, five patients (29%) with occult metastasis underwent adjuvant chemotherapy which is lower than reported rates in open series (54%) [20].

Table 2 Clinicopathological outcomes

Pathologic outcomes	Frequency (%)
pN+	
All ($n=58$)	17 [29]
CS IA ($n=35$)	7 [20]
CS IB ($n=21$)	8 (38)
CS IIA ($n=2$)	2 (100)
Final pN stage	
pN0	41 (71)
pN1	13 [22]
pN2	4 [7]
pN+ among CS I	
No risk factors ($n=14$)	2 [14]
LVI alone ($n=9$)	2 [22]
> 40% embryonal alone ($n=20$)	5 [25]
Both ($n=13$)	6 (46)
−LVI ($n=34$)	7 [21]
+LVI ($n=22$)	8 (36)
Oncologic and functional outcomes	**Median (IQR)/frequency (%)**
Months of follow-up	
All	47 (21–73)
Pathologic stage I	47 (21–73)
Pathologic stage II	45 (21–70)
Pathologic stage II (no chemo)	47 (25–70)
Adjuvant chemotherapy (if pN+)	
Yes	5 [29]
No	12 (71)
Number of positive nodes	
−Adjuvant chemotherapy	1 [1, 2]
+Adjuvant chemotherapy	2 [1–3]
Recurrence-free survival	
2 years (all patients)	91%
2 years (pN+ and −adjuvant chemotherapy)	92%
Normal ejaculation (unknown in $n=4$)	
Yes	44 (81)
No	10 [19]

Controversy regarding the boundaries of RPLND for testicular cancer persists today as the result of the development of the modified template and nerve-sparing technique. Nayan et al. suggests that increased lymph node yield (LNY) represents a more thorough dissection and may be associated with a reduced risk of relapse [21]. In addition, others have demonstrated higher LNY in higher volume surgeons, suggesting that surgical experience is important [22]. However, historically LNYs are subjective, dependent on center, processing, and pathologist. Our median lymph node yield was 26 (IQR 20–31) which is comparable to other robotic series [23].

We noted several advantages in the R-RPLND approach in our series when compared to open series in the literature. First, the median estimated blood loss was 100 ml (IQR 75–200 ml) compared to 207–450 ml in primary O-RPLND series [5, 24]. The significant difference in blood loss could be a function of the tamponading effects of pneumoperitoneum on venous bleeding [25]. Second, our median LOS of 2 days is significantly shorter than 4.1–6 days experienced in other series undergoing the conventional approach [5, 26]. Some O-RPLND series have managed to reduce the LOS to a mean of 3 days using an extraperitoneal open approach [27]. The reduced LOS stay in the robotic and open

extraperitoneal approach is primarily due to the lower rates of post-operative ileus which translate into earlier return of bowel function.

Our perioperative outcomes compare favorably to other contemporary open and robotic RPLND series in the literature. The median operative time was 319 min (IQR 276–355 min) compared to the median operative time of 243 min from a systematic review that included 111 patients who underwent primary R-RPLND for low CS (I-IIB) NSGCT [23] One systematic review of L-RPLND reported an operating time of 204 min for L-RPLND and 186 min O-RPLND. Normal antegrade ejaculation was reported in 44/54 (81%) patients with evaluable data at the last follow-up. Despite all surgeons in this study being experienced in robotic techniques, the longer operative time and decreased rates of antegrade ejaculation is likely a reflection of the evolution of the R-RPLND technique and early learning curve associated with this procedure. To date, there are no reports on the R-RPLND learning curve; however, it is generally accepted that the learning curve for robotic surgery is faster than laparoscopic surgery [28].

Our intraoperative complication rate of 3.4% is comparable to the rate of 4–6.3% and 5% in other R-RPLND and contemporary O-RPLND series, respectively [5, 9, 12, 14]. The open conversion rate in this series of 1.7% is similar to a large contemporary primary R-RPLND series of 2.0% [14]. Our case requiring open conversion was a renal artery injury that failed minimally invasive and open management.

O-RPLND series experience a postoperative complication rate of 9–24%, which is comparable to our series [5, 26, 29, 30]. 74% (14/19) postoperative complications were classified as Clavien–Dindo grade 1 complications, including 5 cases of early post-operative fever, all of which had an unremarkable workup. A subset analysis of our case series suggests that complication rates decreased over time which could reflect the R-RPLND learning curve and/or implementation of patient-centered, evidence-based, multidisciplinary team developed pathways in patients undergoing R-RPLND. Further studies on the R-RPLND learning curve and enhanced recovery after surgery (ERAS) protocols in R-RPLND are needed to determine the impact on peri-operative complications.

This study is limited by the inherent pitfalls of a retrospective study to include unmeasured confounding variables and selection bias as well as differences in peri-operative management, surgical technique, pathologic processing and adjuvant chemotherapy between institutions. Despite some evolution in the surgical technique over time, differences were minimized through strong collaboration and discussions where best practices and improved processes were shared. Furthermore, R-RPLND represents an advanced robotic technique and these results may not be applicable to all centers or all surgeons, as has been suggested by centers of excellence for open RPLNDs. We support future studies and trials to evaluate the learning curve, safety and longer term oncologic efficacy of R-RPLND.

Conclusion

In conclusion, this study of 58 patients represents the largest known case series of primary R-RPLND for the treatment of low-stage non-seminomatous germ cell tumors (NSGCT). Our findings suggest that R-RPLND offers comparable intermediate-term oncologic equivalence and an acceptably low morbidity profile. Unlike previous R-RPLND series which have been criticized by their liberal use of adjuvant chemotherapy, our study shows an acceptably low rate as seen in open series. Despite the consistent encouraging results of R-RPLND for low CS NSGCT, it is essential to obtain longer follow-up to characterize the true value of R-RPLND.

Author contributions NRR: data collection or management, data analysis, and manuscript writing/editing. SPS: protocol/project development, data analysis, and manuscript writing/editing. HMA: data collection or management, data analysis. MTM: data analysis and manuscript writing/editing. MGS: data collection or management, data analysis, and manuscript writing/editing. MSC: data analysis and manuscript writing/editing. JOL': protocol/project development. EPC: protocol/project development and manuscript writing/editing.

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Compliance with ethical standards

Conflict of interest SPS, MGS, and JOL have served as surgical proctors for Intuitive Surgical, Inc.

Ethical approval All procedures performed in this retrospective study involving human participants were in accordance with the ethical standards of the NMCSD Institutional Review Board (NMCSD.2012.0155) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent A waiver of informed consent was granted for this retrospective registry study in accordance with ethical standards and after approval of the NMCSD Institutional Review Board (NMCSD.2012.0155).

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