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ORIGINAL ARTICLE

Minimally invasive retroperitoneal lymph node dissection for men with testis cancer: a retrospective cohort study of safety and feasibility

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Abstract

Purpose To describe the perioperative safety, functional and immediate post-operative oncological outcomes of minimally invasive RPLND (miRPLND) for testis cancer.

Methods We performed a retrospective multi-centre cohort study on testis cancer patients treated with miRPLND from 16 institutions in eight countries. We measured clinician-reported outcomes stratified by indication. We performed logistic regression to identify predictors for maintained postoperative ejaculatory function.

Results Data for 457 men undergoing miRPLND were studied. miRPLND comprised laparoscopic ($n=56$) or robotic ($n=401$) miRPLND. Indications included pre-chemotherapy in 305 and post-chemotherapy in 152 men. The median retroperitoneal mass size was 32 mm and operative time 270 min. Intraoperative complications occurred in 20 (4%) and postoperative complications in 26 (6%). In multivariable regression, nerve sparing, and template resection improved ejaculatory function significantly (template vs bilateral resection [odds ratio (OR) 19.4, 95% confidence interval (CI) 6.5–75.6], nerve sparing vs non-nerve sparing [OR 5.9, 95% CI 2.3–16.1]). In 91 men treated with primary RPLND, nerve sparing and template resection, normal postoperative ejaculation was reported in 96%. During a median follow-up of 33 months, relapse was detected in 39 (9%) of which one with port site (< 1%), one with peritoneal recurrence and 10 (2%) with retroperitoneum recurrences.

Conclusion The low proportion of complications or peritoneal recurrences and high proportion of men with normal postoperative ejaculatory function supports further miRPLND studies.

Keywords Retroperitoneal lymph node dissection · RPLND · Germ cell tumours · Testis cancer · Robotic surgery

Introduction

Open retroperitoneal lymph node dissection (RPLND) is the standard of care for non-seminomatous germ cell tumour (GCT) patients with either a post-chemotherapy retroperitoneal residuals mass or late recurrence [1]. Primary RPLND is a potential treatment option for stage II [2–6] or an adjuvant option for stage I non-seminoma [7–9]. Likewise for patients with stage I NSGCT relapsing on surveillance with retroperitoneal disease, primary RPLND has been shown to be an effective option [5]. To decrease the morbidity of and improve visualisation during nerve sparing, some centres have introduced minimally invasive retroperitoneal lymph node dissection (miRPLND); however, only limited data regarding the perioperative safety, functional and oncological outcomes of miRPLND are available.

Materials and methods

This retrospective analysis identified men diagnosed with GCTs and treated with miRPLND. Baseline variables included age, BMI, primary tumour site, histology, International Germ Cell Cancer Collaborative Group prognostic group, the use of chemotherapy and retroperitoneal lymph node size before RPLND. Intraoperative variables

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included the duration of the procedure, the number of ports, CO_2 pressure, the type of vessel sealing/clipping, template boundaries, nerve sparing, estimated blood loss, the use of drainage, intra-operative complications and the reason for open conversion. Postoperative variables included complications or readmissions, the length of stay, the use and type of thromboprophylaxis and the number of red blood cell transfusions. Pathological variables included the number of resected lymph nodes and involvement with teratoma or vital cancer. Any RPLND performed after at least two cycles of cisplatin-based chemotherapy was defined as post-chemotherapy RPLND, whereas any RPLND performed after no or only one cycle of chemotherapy was defined as pre-chemotherapy RPLND. Oncological variables included the use of additive chemotherapy, time to recurrence and cancer-specific survival. Follow-up was based on clinical notes and radiological reports without central review by the study team. Ejaculation status was retrieved from medical charts.

A description of all cases and a comparison between pre- and post-chemotherapy RPLND was performed. No primary outcome was defined as this was intended as a descriptive case series to show feasibility and challenges of miRPLND. Categorical variables are presented as percentages, while the results for non-normally distributed variables are presented as median and interquartile ranges (IQR) and ranges. Given the exploratory nature of this retrospective analysis with numerous variables and no prior sample size calculation, we refrained from formal statistical testing for differences between pre- and post-chemotherapy RPLND. A multivariable regression analysis was performed to analyse the influence of nerve sparing, template resection and disease setting. The ethical committee approved this retrospective cohort study (BASEC ID 2020–02,237). Statistical analysis was performed using R version 3.1.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

After the exclusion of 23 patients with a non-germ cell or missing histology, 457 men from 16 institutions in eight countries treated with miRPLND between 2008 and 2020 were studied (Supplementary Fig. 1, Table 1). Laparoscopic RPLND was performed on 56 and robotic RPLND on 401 men. Pre-chemotherapy RPLND was performed on 305, including recurrence after one dose of adjuvant carboplatin in eight and after one cycle of adjuvant BEP in one. Post-chemotherapy RPLND was performed on 152 men. The median retroperitoneal mass sizes for pre- and post-chemotherapy RPLNDs were 32 (IQR 20–45) and 32 mm (IQR 20–53).

Perioperative outcomes

A median of five ports (range 4–7) were placed, and the median CO_2 gas pressure used was 15 mmHg (range 12–20). The median operative time was 270 min (IQR 210–355). Haemostasis was achieved with a combination of manual or robotically applied non-absorbable polymer clips, a harmonic scalpel, advanced bipolar or harmonic vessel seal devices and human gelatine thrombin matrix sealant. The median intra-operative blood loss was 75 mL (IQR 50–153), with red blood cell transfusions in 11 men (3%) (Table 2). Conversion to open surgery was necessary in 15 men (3%) due to intra-operative complications in six, access problems in five and the extent of disease in four. Intra- and post-operative complications occurred in 20 (4%) and 33 (7%) patients, respectively (Table 2). The highest Clavien–Dindo complication was 3a/b in 3 (< 1%) and 1–2 in 30 (7%). A postoperative drain was placed in 95 men (21%). The median overall length of stay was two days (IQR 2–3), and 20 men (4%) were readmitted within the first 30 days.

Oncological outcomes

In men with pre-chemotherapy RPLND, a median of 19 lymph nodes (IQR 13–29) were resected: further chemotherapy was used after surgery in 78 men (17%) (Table 2). During a median follow-up of 33 months (IQR 12–61), relapse was detected in 22 men (7%) after a median follow-up time to recurrence of 11 months (IQR 3–17). Of these, there was one port-site metastasis (< 1%) and recurrence in the retroperitoneum in eight (3%). In the subgroup of men treated with laparoscopic surgery, 5/56 (9%) demonstrated recurrence, including 1/56 (2%) in the retroperitoneum.

In men with post-chemotherapy RPLND, a median of 19 lymph nodes (IQR 13–29) were resected: post-surgical chemotherapy was used in 78 (17%). During a median follow-up of 23 months (IQR 7–50), relapse was detected in 17 men (11%). Sites of recurrence included the peritoneum around the sigmoid in one patient (< 1%) and the retroperitoneum in two patients (1%) (Table 2).

Postoperative ejaculatory dysfunction

Detailed information concerning surgical templates, nerve sparing, and ejaculatory function was available for 281/457 men (61%). Of 281 men with information recorded, ejaculation was maintained in 187 (85%). In multivariable regression, nerve sparing and template resection improved the chance to maintain ejaculatory function (unilateral vs bilateral template resection [OR 16.5, 95% CI 6.3–52.8], nerve sparing vs non-nerve sparing [OR 3.7, 95% CI 1.6–8.9])

Table 1 Baseline characteristics of 457 patients treated with minimally invasive RPLND

	Overall cohort $n=457$ (100%)	Pre-chemotherapy $n=305$ (67%)	Post-chemotherapy $n=152$ (33%)
Number of patient by country (%)			
United States of America	250 (55)	171 (56)	80 (52)
Italy	80 (18)	40 (13)	40 (26)
United Kingdom	48 (11)	47 (15)	2 (1)
Germany	32 (7)	24 (8)	8 (5)
Canada	29 (6)	18 (6)	11 (7)
Switzerland	9 (2)	4 (1)	5 (3)
Turkey	5 (1)	0	5 (3)
France	4 (1)	1 (< 1)	3 (2)
Median age [IQR] (range)	30 (25–38) (16–72)		
Median body mass index (kg/m2) [IQR] (range)	26 (25–38) (16–72)	26 (24–29) (18–44)	26 (23–29) (19–61)
Primary site			
Testis	452 (99%)	305 (100%)	147 (97%)
Retroperitoneum	4 (< 1%)	0	4 (3%)
Pelvis	1 (< 1%)	0	1 (< 1%)
Histology			
Non-seminoma/Mixed germ cell tumour	365 (80%)	224 (73%)	141 (93%)
Seminoma	82 (18%)	76 (25%)	6 (4%)
Scar	10 (2%)	5 (2%)	5 (3%)
Minimally invasive technique			
Robotic-assisted	401 (88%)	283 (93%)	118 (78%)
Laparoscopic	56 (12%)	22 (7%)	34 (22%)
Median diameter of largest retroperitoneal mass (mm) [IQR] (range)	32 (20–45) (0–198)	31 (20–44) (0–163)	34 (20–53) (0–198)
IGCCCG prognostic group			
Good	229 (50%)	109 (36%)	120 (79%)
Intermediate	19 (4%)	2 (< 1%)	17 (11%)
Poor	13 (3%)	0 (0%)	13 (9%)
Missing	196 (43%)	194 (64%)	2 (1%)

IGCCCG international germ cell cancer collaborative group, *IQR* interquartile range from 25 to 75% percentiles

(Table 3). In the subgroup of 91 men treated with primary RPLND, nerve sparing and template resection, normal ejaculation were reported in 87 (96%).

Discussion

As evidence about long-term morbidities associated with radio- or chemotherapy in GCT patients continues to develop [10], several groups have considered surgery as a treatment option for stage I or II disease [2–5, 7–9]. Given the morbidity of open RPLND, important technical modifications have been introduced: First, extra-peritoneal [11] and minimally invasive approaches, conventional laparoscopic [5] and robot-assisted [6] techniques, have been established to try to decrease treatment related complications and shorten the overall period of post-treatment recovery. Second, nerve sparing RPLND and template resection are now commonly used to improve ejaculatory function [7–9]. The rationale for miRPLND is based on newly acquired and comprehensive surgical experience in robot-assisted laparoscopy for renal, bladder and prostate cancer. It thus has the potential to alter the risk/benefit ratio of traditional treatment paradigms with broader consideration of using surgery to reduce patient exposure to radio- and chemotherapy.

Intra- and postoperative complications after open RPLND are common [12, 13]. In this international cohort of selected patients with stage I or low-volume stage II GCT, only a low proportion of men undergoing miRPLND suffered from intra- and postoperative complications which is in line in a recent comparative study comparing open versus miRPLND [14]. Furthermore, a low median blood loss of 75 mL was observed. However, case selection in this condition is fundamentally important, particularly in the post-chemotherapy

Table 2 Perioperative, pathological and oncological outcomes stratified by disease setting

Perioperative outcomes	Overall cohort $n=457$	Pre-chemotherapy $n=305$	Post-chemotherapy $n=152$
Median operative time (minutes) [IQR] (range)	270 (210–335) (85–826)	260 (205–314) (87–600)	290 (215–361) (85–826)
Median intra-operative blood loss (mL) [IQR] (range)	75 (50–153) (0–6000)	50 (50–150) (0–4000)	100 (50–220) (0–6000)
Number of patients receiving red blood cell transfusion(s) (%)	11 (3%)	2 (< 1%)	9 (6%)
Number of patients with blood loss > 1500 mL (%)	12 (2%)	3 (< 1%)	9 (6%)
Number of patients and reasons requiring conversion to open surgery (%)	15 (3%)	7 (2%)	8 (5%)
Complications	6 (1%)	3 (< 1%)	3 (2%)
Access problems	5 (1%)	3 (< 1%)	2 (1%)
Extent of disease	4 (1%)	1 (< 1%)	3 (2%)
Number of patients and type of reported intra-operative complications (%)	20 (4%)	11 (4%)	20 (13%)
Bleeding	12 (3%)	6 (3%)	6 (3%)
Ureteric injury	4 (< 1%)	3 (< 1%)	1 (< 1%)
Anaesthetic problems	2 (< 1%)	1 (< 1%)	1 (< 1%)
Bowel injury	1 (< 1%)	1 (< 1%)	0
Thoracic duct injury	1 (< 1%)	0	0
Number of patients with postoperative complications (%)	33 (7%)	18 (6%)	15 (10%)
Ascites and/or pleural effusion	11 (2%)	7 (2%)	4 (2%)
Deep vein thrombosis	7 (2%)	2 (< 1%)	5 (3%)
Fever	3 (< 1%)	3 (< 1%)	0
Wound infection	3 (< 1%)	2 (< 1%)	1 (< 1%)
Rhabdomyolysis	2 (< 1%)	0	2 (1%)
Clostridium difficile infection	2 (< 1%)	0	2 (1%)
Incisional hernia	2 (< 1%)	2 (< 1%)	0
Compartment syndrome of the legs	1 (< 1%)	0	1 (< 1%)
Pneumonia	1 (< 1%)	1 (< 1%)	0
Bleeding	1 (< 1%)	1 (< 1%)	0
Median length of stay [IQR] (range)	2 (2, 3) (0–38)	2 (2–4) (0–38)	3 (2–4) (0–38)
Number of patients readmitted within 30 days (%)	20 (4%)	14 (5%)	6 (4%)
Pathological and oncological outcomes			
Median number of resected lymph nodes [IQR]	19 (13–29)	19 (13–28)	20 (13–29)
Median follow-up after RPLND in months [IQR]	29 (10–58)	33 (12–61)	23 (7–50)
Number of patients and site of recurrence (%)	39 (9%)	22 (7%)	17 (11%)
Port site	1 (< 1%)	1 (< 1%)	0
Peritoneum around sigmoid	1 (< 1%)	0	1 (< 1%)
Any retroperitoneum	10 (2%)	8 (3%)	2 (1%)
Retroperitoneum only	5 (1%)	5 (2%)	0
Retroperitoneum and chest	1 (< 1%)	1 (< 1%)	0
Retroperitoneum, chest and liver	2 (< 1%)	1 (< 1%)	1 (< 1%)
Retroperitoneum and neck	1 (< 1%)	1 (< 1%)	0
Retroperitoneum lung, brain and liver	1 (< 1%)	0	1 (< 1%)
Chest only	4 (1%)	2 (< 1%)	2 (1%)
Chest and contralateral testicle	1 (< 1%)	1 (< 1%)	0
Neck or clavicular lymph nodes	2 (< 1%)	2 (< 1%)	0
Chest and neck or clavicular lymph nodes	1 (< 1%)	1 (< 1%)	0
Mediastinum	3 (< 1%)	2 (< 1%)	1 (< 1%)
Mediastinum and neck or clavicular lymph nodes	1 (< 1%)	1 (< 1%)	0
Mesenterial lymph nodes	1 (< 1%)	1 (< 1%)	0
Pelvic lymph nodes	2 (< 1%)	2 (< 1%)	0

Table 2 (continued)

Perioperative outcomes	Overall cohort $n=457$	Pre-chemotherapy $n=305$	Post-chemotherapy $n=152$
Retrocrural	2 (< 1%)	1 (< 1%)	1 (< 1%)
Brain	1 (< 1%)	0 (< 1%)	1 (< 1%)

IQR interquartile range from 25 to 75% percentiles

Table 3 Multivariable regression analysis for preservation of ejaculatory function

Variable	OR	95% CI	*p* value
Unilateral vs. bilateral template	16.5	6.3–52.8	< 0.01
Nerve-sparing vs. non-nerve sparing	3.7	1.6–8.9	< 0.01
Primary vs. post-chemotherapy	1.5	0.7–3.2	0.31

OR Odds ratio, *CI* Confidence interval

setting where peri-tumoral fibrosis is well established. Injury to major vessels with potential for rapid, high-volume blood loss or damage to contiguous intraabdominal organs may still occur. Thus, only surgeons with experience in RPLND for testis cancer, working in high-volume centres experienced in open surgery and emergency conversion from laparoscopic/robotic exposure should consider attempting miRPLND.

The first major concern regarding miRPLND represents less extensive resection in critical areas which could translate into a higher risk of recurrence. Our median node yield of 19 is comparable to population level data of the United States with a median of 17 nodes [15] but is lower compared to series at high-volume institutions reporting a median node yield of 35 for open post-chemotherapy RPLND [16] and of 28 [17] or 38 [18] for primary RPLND in stage 1. However, within a limited follow-up, we observed a similar relapse rate compared to contemporary open series. For example, in the primary miRPLND subgroup, we observed relapse in 7% which is comparable to 5% in Beck et al. [19],) or 9% in Masterson et al. [20]. In the post-chemo miRPLND subset, we observed relapse in 11%, similar to Masterson et al. [20] with 13%. Nevertheless, as higher lymph node counts may lead to better oncological outcomes [15], a critical and prospective audit of the used surgical technique and templates of miRPLNDs within prospective trials or registries is justified.

The second major concern regarding miRPLND is the risk of peritoneal seeding with minimally invasive surgical approaches and a pneumoperitoneum which has previously been reported in randomised trials in cervical and bladder [21, 22] cancer patients and recent reports in men undergoing miRPLND [23]. In the entire cohort of 457 men, only two peritoneal-type seeding events were observed: one port-site recurrence (primary) and one para-sigmoid recurrence (post-chemo). While it is impossible to compare the frequency of this very rare event with open RPLND, these types of recurrences do occur in open RPLNDs as well [24]. Therefore, our data provide an important short-term oncological outcome supporting further studies of miRPLND in selected cases [18]. Those oncological results together with the high proportion of men with normal ejaculation after primary RPLND with nerve sparing approaches support further studies on surgery in men with stage I or II GCT.

This study has several inherent limitations. First, comparisons with open, laparoscopic, or robotic RPLND should be performed as randomised controlled trials; nevertheless, given the rarity of most events of interest, and a requirement for large sample sizes and the rarity of the disease, such a trial is unlikely to be feasible. The men in this cohort had a low tumour burden/median lymph node size and represent a highly selected group. Therefore, further data should be collected to define which anatomical location, mass configuration is suitable for miRPLND. For example, a high degree of circumferential great vessel involvement [25–27], IGCCCG prognostic group, tumour diameter or number of cycles of chemotherapy [26] have been described to predict the necessity for great vessel resection or reconstruction in open RPLND which could be predictive in miRPLND as well.

Given the limitations of the data presented herein, our aim is to present a "proof of concept paper", not to analyse the long-term oncological outcome or propose that miRPLND be considered as a new standard of care in stage I or low-volume stage II GCT. Our data do confirm that this procedure is feasible in selected cases and that peri and post-operative complications are acceptably low, although we accept that the current cohort relies on retrospective chart reviews, which may miss perioperative complications when compared to prospective assessment [28]. Future clinical assessment of miRPLND should now be considered and this assessment should include better definition of the type of case for consideration, utilisation of prospective standardised assessments of complications (as recommended by the European Association of Urology [29]), clearer definition of key surgical steps [30] and technical modifications assessment of long-term oncological outcomes and (importantly, development of patient-reported outcome measures, particularly in relation

to ejaculatory function. Until then, open RPLND remains the standard of care, especially in large-volume disease.

Conclusion

This report, using multi-centre international data from expert centres has shown that miRPLND can be performed safely in selected cases. The low rate of complications and peritoneal recurrences, and high proportion of men with retained postoperative ejaculatory function support further, more detailed, and comprehensive studies of this approach to the treatment of men with high-risk testis cancer.

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Declarations

Conflict of interest The authors have no conflicts of interest to declare.

Ethical approval This article does not contain any studies/experiments with human participants or animals performed by any of the authors.

Consent for publication All persons gave their informed consent to use their data (de-identified) for this retrospective study.

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