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ORIGINAL ARTICLE

Post-chemotherapy robot-assisted retroperitoneal lymph node dissection for metastatic germ cell tumors: safety and perioperative outcomes

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Abstract

Purpose To evaluate the feasibility, safety, and early oncologic outcomes after post-chemotherapy robot-assisted retroperitoneal lymph node dissection (PC-RARPLND) for metastatic germ cell tumors (mGCT).

Methods We retrospectively analyzed patients from four tertiary centers who underwent PC-RARPLND for mGCT, from 2011 to 2021. Previous treatment of mGCT, intraoperative and postoperative complications, and early oncologic outcomes were assessed.

Results Overall, 66 patients were included. The majority of patients had non-seminoma mTGCT (89%). Median size of retroperitoneal lymph node (RLN) before surgery was 26 mm. Templates of PC-RARPLND were left modified, right modified, and full bilateral in 56%, 27%, and 14%, respectively. Median estimated blood loss and length of stay were 50 mL [50–150] and 2 [1–3] days. Four patients (6.1%) had a vascular injury, only one with significant blood loss and conversion to open surgery (OS). Two other patients had a conversion to OS for difficulty of dissection. No patient had transfusion, most frequent complications were ileus (10.6%) and symptomatic lymphorrea (7.6%) and no complications grade IIIb or more occurred. With a median follow-up of 16 months, two patients had a relapse, all outside of the surgical template (one in the retrocrural space with reascending markers, one in lungs).

Conclusion PC-RARPLND is a challenging surgery. In expert centers and for selected patients, it seemed safe and feasible, with a low morbidity. Further prospective evaluation of this procedure and long-term oncologic results are needed.

Keywords Testicular cancer · Testicular germ cell tumor · Robot-assisted retroperitoneal lymph node dissection · Minimally invasive surgery · Post-chemotherapy robot-assisted retroperitoneal lymph node dissection

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Abbreviations

GCT	Germ cell tumor
RLN	Retroperitoneal lymph node
RPLND	Retroperitoneal lymph node dissection
RARPLND	Robot-assisted retroperitoneal lymph node dissection

Introduction

Testicular germ cell tumors (GCT) occur mostly in young patients, and are highly curable, even in case of metastatic spread [1–3]. The management requires multidisciplinary collaboration and high expertise. In case of retroperitoneal lymph node metastasis, upfront cisplatin-based

chemotherapy is mostly proposed, with three or four cycles of BEP according to IGCCCG risk group. Subsequently, post-chemotherapy retroperitoneal lymph node dissection (RPLND) is indicated for supracentimetric residual mass (non-seminoma GCT) or more than 3 cm hypermetabolic masses (seminoma GCT).

Robot-assisted surgery has become widely used for radical prostatectomy [4], partial nephrectomy [5], and is increasing also for radical cystectomy [6]. For urologists with extensive experience in robotic surgery, RPLND may represent the next challenge, keeping in mind that no compromise regarding the extent of surgery due to the surgical approach could be accepted [7].

Logically, robot-assisted RPLND started initially for stage I diseases [8], avoiding the potential difficulties of chemotherapy-induced modifications of the tissues. However, most of RPLNDs in Europe are nowadays planned in a post-chemotherapy setting [9], considering the superiority of adjuvant chemotherapy upon primary RPLND [10], the chemosensitivity of seminomas, and the rareness of stage IIA non-seminoma germ cell tumor with negative markers. Post-chemotherapy RPLND remains a demanding surgery, and open RPLND is undoubtedly the standard [3]. Evidently, PC-RARPLND will not replace open PC-RPLND for all cases, as the great extent of the disease frequently precludes a minimally invasive approach [11]. However, in selected cases, PC-RARPLND is proposed in more and more expert centers to improve perioperative outcomes [12].

Oncological concerns have been previously published regarding PC-RARPLND [13], suggesting that pneuperitoneum could alter the natural history of surgical relapses, describing paracolic recurrences or peritoneal carcinomatosis. Nevertheless, recent reports showed favorable oncological outcomes, without unusual recurrences [14–16]. Moreover, surgical safety is an important aspect to be questioned, since operating close to the large vessels could be associated with major bleeding complications, delicate to control in a robot-assisted laparoscopic setting.

Until now, no prospective trial has been published in this setting, and small retrospective series only started to emerge recently. Therefore, there is an unmet need for a comprehensive and contemporary analysis of a large PC-RARPLND series. Thus, the aim of this study was to describe our multicenter experience in patients managed with R-RPLND regarding perioperative and early oncological outcomes.

Methods

Study population

All patients who underwent post-chemotherapy robotic retroperitoneal lymph node dissection for metastatic germ cell tumor in four tertiary care centers from 2011 to August 2021, were retrospectively included. Patients with previous RPLNDs were excluded. RARPLNDs were classified "post-chemotherapy" when patients classically finished chemotherapy 4–6 weeks before surgery, or when patients had a history of successful first-line chemotherapy for stage II disease, and relapsed thereafter (considering that tissues had been significantly modified by the exposure of multiple cycles of chemotherapy in this setting). All patients were staged with CT scans before and after chemotherapy, and serum tumor markers (α-fetoprotein, human chorionic gonadotropin, and lactate dehydrogenase). Before surgery, all patients were discussed at multidisciplinary meetings including urologists, radiologists, medical oncologists, and radiation therapists. Institutional review board approved the study (ROBOTESTIS-IPC-2021-039). Follow-up was performed according to international guidelines: serum tumor markers every 3 months and CT scans every 6 months during the first 2 years, with reduced frequency thereafter.

Surgical technique

Every procedure was done by experienced robotic surgeons (FB, JCB, GR, ND, JBB, GV, JW). Patient positioning (decubitus dorsal or decubitus lateral) and port placement depended on surgeon's preference. The extension of the templates was decided by each surgeon and depended on the size and location of the mass(es) in imaging. Postoperative drainage depended on surgeon's preference.

Outcomes of interest

Preoperative data [histology of tumor at orchiectomy, history of chemotherapy, initial stage of the disease or relapse, location and size of the mass(es)], perioperative (length of surgery, estimated blood loss, intraoperative complications), and postoperative data (complications, pathologic results, relapse) were collected and analyzed. Regarding pathological results, patients were divided into three exclusive categories: necrosis/fibrosis only, teratoma (with or without necrosis/fibrosis, but without viable tumor), and viable tumor (whether concomitant teratoma or not). Postoperative complications were assessed using the Clavien–Dindo classification.

Statistical analysis

Descriptive statistics included frequencies and proportions for categorical variables. Means, medians, and ranges were reported for continuously coded variables. The statistical significance of differences in medians and proportions was evaluated with the Kruskal–Wallis and Chi-square tests. Univariable and multivariable logistic regression models

tested the relationship between complications (all complications and severe complications) and several variables, namely age, body mass index (BMI), time between orchiectomy and lymph node dissection, type of preoperative chemotherapy, number of cycles of chemotherapy, type of lymph node dissection, intraoperative blood loss, intraoperative patient positioning, operative time, and histological type. They were included in the multivariable models if significantly associated with the outcome in the univariable analysis.

For all statistical analyses, R software environment for statistical computing and graphics (version 3.4.3) was used. All tests were two sided with a level of significance set at $p < 0.05$.

Results

Patient characteristics

Overall, 66 patients, with a median age of 34 years, were included (Table 1). The majority of patients had non-seminoma germ cell tumors (59 patients, 89%).

The majority of patients had lymph node metastasis at the initial diagnosis of the disease (53 patients, 80%) and

Table 1 Patient characteristics before robot-assisted retroperitoneal lymph node dissection (RARPLND) (66 patients)

Characteristic	Value
Age median [IQR]	36 [27–45]
BMI median [IQR]	25 [22–28]
Time between orchiectomy and RARPLND (months) median [IQR]	8 [5–15]
Primary tumor side	
Left testis	39 (59.1%)
Right testis	25 (37.9%)
Retroperitoneum	2 (3.0%)
Histology (orchiectomy or biopsy in another site)	
Pure seminoma germ cell tumor	7 (10.6%)
Non seminoma germ cell tumor	59 (89.4%)
History	
Retroperitoneal lymph node at initial diagnosis	52 (78.8%)
Retroperitoneal relapse after initial stage I disease	10 (15.1%)
Retroperitoneal relapse after successful first-line chemotherapy for stage II/III disease	4 (6.1%)
IGCCCG prognostic group	
Good	43 (65.2%)
Intermediate	18 (27.3%)
Poor	5 (7.5%)
Size of biggest retroperitoneal mass (mm, great axis)	
10–19	17 (25.8%)
20–29	20 (30.2%)
30–39	12 (18.2%)
40–49	4 (6.1%)
50–59	6 (9.1%)
≥ 60	6 (9.1%)
No data	1 (1.5%)
Number of supracentimetric retroperitoneal mass	
1	41 (62.1%)
> 1	25 (37.9%)
Localization of main mass	
Latero or preaortic	38 (57.7%)
Retro-aortic	1 (1.5%)
Interaortocaval	16 (24.2%)
Latero or precaval	8 (12.1%)
Retrocaval	1 (1.5%)
Iliac	2 (3.0%)

13 patients (20%) had retroperitoneal lymph node relapse after initial stage I disease, or after successful first-line chemotherapy for stage II/III disease (metachronous relapse, median time of the relapse: 9 months). The proportions of patients with good, intermediate, and poor IGCCCG prognostic classification were, respectively, 65%, 27%, and 7.5%.

Surgeries and postoperative results

The median size of the largest retroperitoneal mass was 25 mm in great axis; six patients (9.1%) had a retroperitoneal mass of more than 50 mm (Table 1). The location of largest mass was mainly pre or latero aortic (38 patients, 58%).

Median operative time was 200 min [108–248] and estimated blood loss was 50 mL [IQR 50–150] (Table 2). Most patients had a modified template RARPLND (45 patients, 68%). No additional procedures (such as organ resection, or aorta/vena cava resection or reconstruction) were needed.

Regarding intraoperative complications, four patients (6.0%) had a vascular injury (two vena cava, two aorta), only one had an estimated blood loss of more than 500 mL, and no one had blood transfusion. Three patients (4.5%) had a conversion to open surgery: one for active bleeding, and two for difficulty of dissection (one was a post-chemotherapy seminoma, the other one a primary retroperitoneal tumor).

Regarding postoperative complications, seven patients (11%) had a postoperative ileus, five during hospitalization and two after. Five patients (7.6%) had lymphatic complications (symptomatic lymphocele needing paracentesis or drainage, lymphatic flow through trocar orifice); all of these complications occurred after hospitalization. Six patients (9.1%) needed re-hospitalization.

Three patients (3.5%) had a IIIa Clavien–Dindo complication (percutaneous drainage of lymphocele), there was no IIIb or more Clavien–Dindo complications.

In univariable analyses predicting intraoperative and early postoperative complications within 30 days (14 events), blood loss (Odds ratio [OR]: 1.01, 95% confidence interval [95% CI] 1.0–1.01, $p=0.02$), lateral intraoperative patient positioning toward the right side (OR: 0.2, 95% CI 0.03–0.7, $p=0.03$), and operative time (OR: 1.01, 05% CI 1.0–1.01, $p=0.02$) reached independent predictor status. None of the other tested variables, namely age, BMI, time between orchiectomy and lymph node dissection, type of preoperative chemotherapy, number of cycles of chemotherapy, type of lymph node dissection, and histological type reached independent predictor status.

In multivariable analyses (including blood loss, patient positioning, operative time) predicting intraoperative and early postoperative complications within 30 days, no factor reached independent predictor status.

In univariable analyses predicting severe (Clavien–Dindo ≥ IIIa) intraoperative and early postoperative complications within 30 days (3 events), no variable reached independent predictor status.

Pathology and early oncologic outcomes

Median number of lymph nodes in pathological reports was 10 [6–17]. Teratoma, necrosis, and viable tumor was found in 53%, 39%, and 7.6% of the cases, respectively.

With a median follow-up of 16 months, two patients had a relapse: one in the retrocrural space associated with reascending serum tumor markers and equivocal lung nodules months after PC-RARPLND, managed with second-line chemotherapy, with complete response; the other patient had multiple lung metastases 5 months after surgery and died 1 month later.

Discussion

Since there is a gap in the literature for a thorough and updated examination of a large PC-RARPLND series, the purpose of our study was to outline our multicenter experience with PC-RARPLND in terms of perioperative and early oncological outcomes. Our study showed that PC-RARPLND for selected cases was a feasible procedure with acceptable complication rates. In addition, no adverse or unusual oncological events occurred.

In the light of our results, PC-RARPLND should still only be performed by highly experienced robotic surgeons knowing that major vessel injury could occur and need to be managed with efficacy and safety [17]. A 6.0% rate of vessel injury was observed, but only one patient had significant bleeding with the need to an open conversion. This underlines the added value of the robotic procedure in selected cases as it provides important advantages such as short length of stay, low estimated blood loss, and small skin incisions.

The majority of patients had a modified template resection. This proportion is a consequence of a stringent selection of favorable patients for the robotic approach. A full bilaterally retroperitoneal lymph node resection is not mandatory for selected patients as described by Heidenreich et al. [18, 19]. The safety of modified template resection was recently validated by Gerdtsson et al. [20].

Our results are in accordance to the recent and growing data regarding PC-RARPLND, which are all retrospective series. Regarding intraoperative and postoperative outcomes, Fankhauser et al. reported a 3% conversion rate to open surgery, and a blood transfusion rate of 3% in the largest cohort so far reported [14]. Regarding oncological outcomes, recurrence rates ranged from 0 to 16.1% [14, 15, 21, 22].

Several limitations of our study need to be mentioned. First, our study is based on a retrospective analysis with all

Table 2 Characteristics of surgery and postoperative results (66 patients)

Characteristic	Value
Median operative time median [IQR] (extremes)	200 [108–268] (45–529)
Patient positioning	
Lateral decubitus	35 (53.0%)
Dorsal decubitus	31 (47.0%)
Type of RLNP	
Left modified	37 (56.1%)
Right modified	18 (27.3%)
Bilateral	9 (13.6%)
Other	2 (3.0%)
Estimated blood loss median [IQR] (extr)	50 [50–150] (0–1600)
Vascular injury (aorta, vena cava, lumbar vessel)	4 (6.0%)
Vena cava	2 (3.0%)
Aorta	2 (3.0%)
Reason of conversion in open surgery	
Active bleeding	1 (1.5%)
Difficulty of dissection	2 (3.0%)
Postoperative nights median [IQR] (extr)	2 [1–3] (1–13)
Postoperative complications (during or after hospitalization)	
Transfusion	0 (0%)
Ileus	7 (10.6%)
Lymphorrea/lymphocele	5 (7.6%)
Symptomatic hematoma	0 (0%)
Complications according to Clavien–Dindo (0–30 days), *n* (%)	
II	6 (9.1%)
IIIa	3 (4.5%)
IIIb/IV/V	0 (0%)
Pathologic results	
Total number of lymph nodes median [IQR]	10 [6–17]
Number of positive lymph nodes	
0	38 (57.6%)
1	20 (30.3%)
> 1	8 (12.1%)
Positive surgical margins	0 (0%)
Teratoma	35 (53.0%)
Necrosis/fibrosis only	26 (39.4%)
Viable tumor	5 (7.6%)
Adjuvant chemotherapy	
No	64 (97.0%)
Yes	2 (3.0%)
Surgery of residual mass in another territory	
Lung	1 (1.5%)
Cervical lymph node	1 (1.5%)
Relapse	2 (3.0%)

of its inherent limitations leading to selection and data collection bias. We cannot exclude that some adverse events had been missed, especially small complications resulting in outpatient visits if patients had been re-admitted to other facilities not visible to the surgical team. Second, the template of RARPLND was chosen by each surgeon and varied between patients and centers. Additionally, information regarding antegrade ejaculation was not available and follow-up was only intermediate, as centers only recently started to perform this procedure robotically. Lastly, a comparison to a control group treated with open surgery was not available.

Conclusion

In this multicenter study, we saw that for selected cases and in expert hands, PC-RARPLND seemed to be a feasible and reasonably safe procedure, with no adverse oncological results. Prospective evaluation or ideally a comparative randomized trial versus open surgery should be performed to have more consistent data regarding the safety and oncologic efficacy of this procedure.

Author contributions NB: protocol/project development, data collection or management, data analysis, manuscript writing/editing; FB: data collection or management/ manuscript writing/editing; GV: data collection or management/ manuscript writing/editing; SK: data analysis/manuscript writing/editing; GR: manuscript writing/editing; JCB: manuscript writing/editing; JBB: manuscript writing/editing; AK: data collection or management; AMDV: data collection or management; AF: manuscript writing/editing; JW: manuscript writing/editing; ASB: data collection or management; ND: manuscript writing/editing; MR: protocol/project development; TM: protocol/project development, manuscript writing/editing.

Data availability The data that support the findings of this study are available from the corresponding author, Nicolas Branger, upon reasonable request.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals This is a retrospective analysis, no interventional actions were done, only data collection.

Informed consent Institutional review board approved the study (ROBOTESTIS-IPC-2021–039), waiving the need of an informed consent, considering the retrospective characteristic of this study.

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