

Post-chemotherapy laparoscopic retroperitoneal lymph node dissection is feasible for stage IIA/B non-seminoma germ cell tumors

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Abstract

Objective To assess the efficacy, outcome and complications of post-chemotherapy laparoscopic retroperitoneal lymph node dissection (L-RPLND) for stage IIA/B testicular germ cell tumor (GCT) patients in comparison with open RPLND (O-RPLND).

Methods L-RPLND was performed in 14 patients with stage IIA/B non-seminoma GCTs among 154 non-seminoma patients who received RPLND after completion of chemotherapy with tumor marker normalization at our institution between 1998 and 2013. Their outcomes were compared with those of 14 patients with stage IIA/B non-seminoma GCTs treated with O-RPLND during the same period. Clinical parameters were compared between L-RPLND and O-RPLND.

Results There were no significant differences in the background characteristics of the two groups except for follow-up duration (36 months for L-RPLND, 70 months for O-RPLND; $p = 0.02$). Blood loss during surgery was significantly less for the L-RPLND group than for the O-RPLND group (155 mL for L-RPLND, 700 mL for O-RPLND; $p < 0.001$). Parameters related to post-operative recovery were significantly better for the L-RPLND group than for the O-RPLND group. Histopathological examination showed no difference between the two groups. Neither group had disease recurrence.

Conclusion Post-chemotherapy L-RPLND with a bilateral template and nerve-sparing method was safe, effective, and showed a high preservation rate of antegrade ejaculation with no deterioration of outcomes compared to O-RPLND.

Keywords Germ cell tumors · Laparoscopic retroperitoneal lymph node dissection · Non-seminoma · Post-chemotherapy · Stage IIA/B

Introduction

Post-chemotherapy retroperitoneal lymph node dissection (PC-RPLND) is an essential part of the management of advanced testicular germ cell tumors (GCTs), especially non-seminoma GCTs. Open RPLND (O-RPLND) is recommended in the current guidelines [1, 2]. After the first report of laparoscopic RPLND (L-RPLND) by Rukstalis, its indication has been extended from staging to therapy [3–7]. We have also reported our preliminary experience [8]. The technical feasibility of the approach has been reported by several investigators [6, 9]; however, most reports, including ours, showed the feasibility of L-RPLND without comparing it to their own O-RPLND series.

In this study, intra- and post-operative clinical parameters of our consecutive series of L-RPLND and O-RPLND were compared.

Patients and methods

Patients

Between June 1998 and December 2013, 175 post-chemotherapy RPLNDs were performed at our institution.

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Table 1 Patient characteristics

	Total, <i>n</i> = 28	Laparoscopic, <i>n</i> = 14	Open, <i>n</i> = 14	<i>p</i> value	All cases during the same period, <i>n</i> = 154
Age (years)	30 (18–56)	32.5 (19–56)	29.5 (18–42)	0.38	31 (17–56)
IGCCC					
Good	23 (82.1 %)	13 (92.9 %)	10 (71.4 %)	0.30	63 (40.9 %)
Intermediate	4 (14.3 %)	1 (7.1 %)	3 (21.5 %)		45 (29.2 %)
Poor	–	–	–		33 (21.5 %)
Not evaluable	1 (3.6 %)	–	1 (7.1 %)		13 (8.4 %)
Prior chemotherapy					
Induction	29 (87.9 %)	14 (100 %)	12 (83.3 %)	0.14	91 (59.1 %)
Salvage	4 (12.1 %)	0 (0 %)	2 (16.7 %)		63 (40.9 %)
Median follow-up (months)	50.5	36	70	0.02	55

IGCCC International Germ Cell Consensus Classification

L-RPLND was started in September 2009. Before starting L-RPLND for stage IIA/B GCTs (stage IIC excluded), O-RPLND was a standard procedure at our institution. Laparoscopic or open RPLND was chosen by patient preference after starting L-RPLND. Of 154 non-seminoma patients with RPLND, L-RPLND and O-RPLND were performed in 14 patients each with stage IIA/B during this period. All patients had induction or salvage chemotherapy and obtained serum tumor marker (STM) normalization. Patients who obtained true complete response were excluded from this study. Patient characteristics are summarized in Table 1. A significant difference was observed only in median follow-up (36 months for L-RPLND vs 70 months for O-RPLND; $p = 0.02$). The Institutional Review Board approved the performance of L-RPLND, and written, informed consent was obtained from all patients.

Surgical procedure

O-RPLND was performed with a full bilateral template with a nerve-sparing technique according to our previous report [10]. L-RPLND was performed bilaterally using the extraperitoneal approach, as in our report [8]. Briefly, the patient was placed in the supine position. We developed the retroperitoneal space between the psoas muscle and the ureter until the ipsilateral great vessel could be seen. A prospective identification and sparing of the sympathetic nerves was carried out in all patients. The first two patients who underwent L-RPLND had a unilateral modified template to ensure the safety of L-RPLND. Drainage tubes were removed after the amount of discharge decreased to <100 ml in the L-RPLND and 500 ml in the O-RPLND group.

Follow-up strategy

The usual follow-up strategy was as follows—baseline serum tumor marker (STM) levels and computed

tomography (CT) were carried out 4 weeks after the last surgery. Blood tests including STM levels, CT (chest to pelvis), and physical examinations were then repeated every 3 months in the first year. In viable cancer cases, STM levels were measured every month in the first year. In the 2nd and 3rd years, STM levels and CT were checked every 3 or 4 months. In the 4th and 5th years, STM levels and CT were checked every 6 months. After 5 years, medical check-ups were performed annually.

Statistical analysis and assessment of complications

Statistical differences between the two groups were analyzed by the chi-squared test for dependent variables, Fisher's exact probability test, and Mann–Whitney's *U* test, as appropriate.

Intra- and post-operative complications were categorized using the Clavien–Dindo classification (10). We defined antegrade ejaculation as any discharge of seminal fluid at ejaculation by patient report.

Results

Peri-operative variables (Table 2)

Median tumor sizes before treatment and before RPLND were not significantly different between L-RPLND and O-RPLND groups. Blood loss during surgery was significantly less in the L-RPLND group than in the O-RPLND group. Operation time showed no significant difference between L-RPLND and O-RPLND groups because a bilateral template was used for L-RPLND. No conversion to open surgery was required with L-RPLND.

Times to initiation of oral intake and walking after surgery were significantly shorter in the L-RPLND group than in the O-RPLND group. The median period to permission of

Table 2 Comparison of intra- and post-operative parameters

	Total (28)	Laparoscopic (14)	Open (14)	<i>p</i> value
Pre-chemotherapy tumor size (mm)	25 (10–50)	24.5 (18–30)	28.5 (10–50)	0.60
Pre-RPLND tumor size (mm)	20 (5–32)	19 (5–25)	16.5 (6–32)	0.87
Blood loss (mL)	508 (little–1,357)	155 (little–710)	700 (260–1,357)	<0.001
Operation time (min)	412 (220–639)	439 (223–600)	407.5 (220–639)	0.38
Time to oral intake				
Median post-operative days	2 (1–4)	1 (1–2)	2 (1–4)	0.001
Time to starting to walk				
Median post-operative days	1 (1–3)	1 (1–2)	2 (1–3)	0.009
Time to permission of discharge				
Median post-operative days	9 (4–28)	7 (4–28)	10.5 (7–22)	0.042
Histology of RPLND				
Necrosis	14 (50.0 %)	7 (50.0 %)	7 (50.0 %)	0.15
Teratoma	11 (39.3 %)	7 (50.0 %)	4 (28.6 %)	
Viable cancer	3 (10.7 %)	0	3 (21.4 %)	
Antegrade ejaculation	27/28 (96.4 %)	13/14 (92.9 %)	14/14 (100 %)	0.31

RPLND retroperitoneal lymph node dissection

Table 3 Post-operative complications

Clavien–Dindo classification grade	L-RPLND (14)				O-RPLND (14)			
	1	2	3a	4a	1	2	3a	4a
Lymphatic cyst		–	1	–		–	–	–
Chyle leak	5	1	–	–	–	–	–	–
Sub-ileus	–	–	–	–	–	1	–	–
Surgical site infection	–	–	–	–	3	–	–	–
Acute respiratory distress syndrome	–	–	–	–	–	–	–	1

L-RPLND laparoscopic retroperitoneal lymph node dissection, *O-RPLND* open retroperitoneal lymph node dissection

discharge was also significantly shorter in the L-RPLND group than in the O-RPLND group.

On histopathological examination, both types of RPLND showed similar proportions of necrosis, teratoma, and viable cancer. Three viable cancer cases were found in the O-RPLND group and the histology of those cases were embryonal carcinoma, seminoma and unknown malignancy, respectively. Two of three patients who only underwent induction chemotherapy had 2 cycles of adjuvant chemotherapy.

With regard to antegrade ejaculation, uni- or bilateral nerve-sparing RPLND was performed in all patients. All but one patient in each group had antegrade ejaculation.

Complications

Peri-operative complications are summarized in Table 3.

Intervention by percutaneous puncture was required in one case with a lymphatic cyst. In this case, inflammation of the lymphatic cyst occurred on the 10th day after surgery. Chyle leaks were more often observed in the

L-RPLND group; however, the chyle leaks disappeared within a few days by taking a conventional low-fat diet. On the other hand, surgical site infections, including fat necrosis, were observed only in the O-RPLND group.

One O-RPLND case developed acute respiratory distress syndrome 2 days after surgery and required intensive care unit treatment.

Clinical outcomes

There was no disease recurrence in either group at the time of writing, with a median follow-up of 36 months for the L-RPLND group and 70 months for the O-RPLND group.

Discussion

For residual mass resection after chemotherapy for advanced testicular GCTs, post-chemotherapy RPLND is mandatory [1, 2]. O-RPLND with a full template is standard procedure. Nerve sparing is often not possible because

of encasement of the residual mass to be excised. In addition, post-chemotherapy RPLND is a complex, high-risk procedure that sometimes requires vascular procedures and often requires complete mobilization of the vena cava and aorta. Because of these morbidity and complicated surgical procedures of O-RPLND, less invasive surgery that does not adversely affect disease-free survival is required, especially in early stage GCTs.

L-RPLND began as a diagnostic tool for stage I GCTs [3, 4]. After confirmation of its safety, its indication has been extended to include therapy [5, 6, 9]. A unilateral, modified template with an intra-abdominal approach has been a common procedure in most reports of L-RPLND. In the early L-RPLND era, a modified template was not part of standard post-chemotherapy RPLND. Therefore, bilateral L-RPLND using a nerve-sparing technique was developed [11]. The accumulated experience of bilateral L-RPLND with nerve sparing [12–14] has shown that its safety and oncologic outcomes have been comparable to those of O-RPLND.

Although the follow-up duration was significantly shorter for L-RPLND than for O-RPLND, the major complications and oncologic outcomes were comparable. In fact, no recurrence has occurred to date. Our extra-retroperitoneal surgical procedure with nerve sparing [8] was based on the reports of Arai et al. [7], LeBlanc et al. [11] and Steiner et al. [12]. No open conversions or major complications occurred. Times to initiation of oral intake and walking after surgery were significantly shorter for L-RPLND than for O-RPLND patients. In addition, the length of hospital stay was also significantly shorter for L-RPLND patients.

Kenney and Tuerk reviewed the reported complications [15]. Their report showed that vascular injury and hemorrhage were the most common complications of post-chemotherapy L-RPLND. With regard to post-operative complications, no ileus and no wound infections were observed, but retrograde ejaculation was reported. Winter et al. reported that tumor size and International Germ Cell Consensus Classification (IGCCC) [16] predicted additional vascular procedures such as inferior vena cava interventions or aortic prosthesis [17]. Intermediate or poor prognosis showed a significantly higher risk of intervention than good prognosis, and residual tumor size >5 cm had a higher risk. In the present study, neither ileus nor bowel injury were observed. In this study, chyle leak was the most frequent complication and observed more in the L-RPLND group than in the O-RPLND group. In the L-RPLND group, the drainage tube was usually removed after starting a normal diet. On the other hand, patients in the O-RPLND group usually start meals three or four days after surgery and the drainage tube is usually removed before starting meals due decreased lymphatic fluid. Since chyle leaks are usually

observed more frequently after starting a meal, early timing of starting a diet in L-RPLND patients might be associated with the frequent occurrence of chyle leaks. This may be preventable by using a clip to seal the lymphatic vessels and by a low fat diet. In fact, when we started to use clips, the number of chyle leaks decreased. Steiner et al. reported that chyle leaks were not observed after introducing a low fat diet [18]. In addition, no additional vascular procedure and nephrectomy were observed with our strict indication of post-chemotherapy L-RPLND. In this study, we performed L-RPLND in patients with stage IIA/IIB and mainly IGCCC good prognosis (93.3 %). Therefore, this indication would be acceptable for post-chemotherapy L-RPLND. With regard to ejaculation, there was no significant difference between L-RPLND and O-RPLND ($p = 0.89$). This means that bilateral nerve-sparing post-chemotherapy L-RPLND is feasible for the management of advanced GCTs. The reported retrograde ejaculation rate was 0–5 % with primary RPLND for stage I non-seminoma and up to 12.5 % with post-chemotherapy L-RPLND [15]. The present result with post-chemotherapy L-RPLND with a bilateral template, which is a more complicated procedure, was identical to that with primary L-RPLND.

Bilateral RPLND using a laparoscopic or open method is the standard method for the management of post-chemotherapy residual masses. However, the extent of RPLND has been discussed [19–21]. Recently, Vallier et al. reported a validation study to determine whether a modified template would be reasonable [22]. They wrote that a unilateral modified template resection during post-chemotherapy RPLND was suitable if pre-chemotherapy metastases were found in the primary landing zone of the tumor-bearing testicle and if the post-chemotherapy residual masses were <5 cm in diameter. Otherwise, a full bilateral template RPLND is recommended. With the accumulated evidence, the modified template is now suitable for well-defined small residual masses after chemotherapy. In this situation, less invasive surgery was desired for low-stage GCT patients for resection of post-chemotherapy residual masses. Although bilateral L-RPLND was recognized to be safe and effective, modified unilateral L-RPLND might be a standard of care for stage IIA/B, low-volume, well-defined residual masses after chemotherapy. Our first case of L-RPLND with a modified template has not developed recurrence or metastasis to date.

In recent advances in L-RPLND, patients with more advanced GCTs such as infiltrating great vessels could be candidates for L-RPLND. Aufderklamm et al. showed bilateral L-RPLND in patients with vascular infiltration is feasible and reproducible when laparoscopic vascular surgery can be reliably handled [23].

From these findings, less invasive L-RPLND with a modified template would be a feasible procedure for stage

IIA/IIB GCTs and bilateral L-RPLND with more complicated cases with infiltrating great vessels might be one of the treatment options.

Despite the limitations of this study, i.e., the small number of patients and short follow-up, the safety and comparable oncologic outcomes of L-RPLND and O-RPLND seem clear.

In conclusion, post-chemotherapy L-RPLND with a bilateral template and nerve-sparing method was safe, effective, and showed a high preservation rate of antegrade ejaculation without adversely affecting the outcome compared to O-RPLND. Modified L-RPLND might become a standard method for post-chemotherapy management of patients with stage IIA/B non-seminoma GCTs.

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Compliance with ethical standards

Conflict of interest We have no financial disclosures or conflicts of interest and no funding sources.

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