

Post-chemotherapy retroperitoneal lymph node dissection for non-seminomatous germ cell tumors: A single-surgeon, Canadian experience

Joshua King¹; Jun Kawakami, MD²; Daniel Heng, MD³; Chun Loo Gan, MBBS, FRACP³

¹Biological Sciences, University of Lethbridge, Lethbridge, AB, Canada; ²Division of Urology, Department of Surgery, Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada; ³Division of Medical Oncology, Department of Oncology, Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada

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Abstract

Introduction: Post-chemotherapy retroperitoneal lymph node dissection (PCRPLND) has a well-established role in the management of residual retroperitoneal masses >1 cm in patients with advanced non-seminomatous germ cell tumor (NSGCT). Herein, we report our single-surgeon surgical experience in a Canadian tertiary hospital.

Methods: We identified 57 patients with NSGCT who received primary chemotherapy and PCRPLND from 2010–2016. Surgical complication rate was graded with Clavien-Dindo classification. Chi-squared testing was used in testing for differences in proportion of PCRPLND tumor histology vs. the historical cohorts. Chi-squared testing was also used to analyze the association between primary orchiectomy tumor histology and post-chemotherapy residual mass (PCRM) tumor histology.

Results: The overall complication rate was 23% (n=13), of which four were Clavien-Dindo grade IIIb and one was grade IVa. Fourteen percent of patients required additional procedure for resection of adjacent organs intraoperatively. There was a statistically significant difference in the distribution of PCRPLND tumor histologies (Chi-squared p=0.0187), with a lower rate of viable tumor (7%) and higher rate of teratoma (63%) compared to historical cohorts. The absence of teratoma in the primary orchiectomy specimen was associated with the findings of fibrotic/necrotic tissue in the PCRM (Chi-squared p=0.0005).

Conclusions: Our series demonstrated that the rate of viable tumor in PCRM appears lower than published historical series, and this possibly reflects the improvement in chemotherapy delivery in a contemporary series. The high rate of teratoma in the PCRM calls for ongoing need for PCRPLND. Grade III and IV surgical complications are considered rare in our series.

Introduction

Testicular cancers are the most common solid tumor malignancies of young adult men. In Canada, the projected incidence of testicular cancers was estimated to be 1100 cases in 2017, including 45 deaths. The age-standardized incidence rate was estimated at 6.1/100 000 males, with a five-year survival rate of 96%.¹

Germ cell tumors (GCTs) comprise 95% of malignant tumors arising in the testes. GCTs are broadly divided into seminoma and non-seminoma because they have different prognostic and treatment algorithms.

The 1997 International Germ Cell Cancer Collaborative Group (IGCCCG) classification stratify patients with advanced GCTs by risk: good (91% five-year overall survival [OS] rate), intermediate (75–83% five-year OS rate), and poor risk (42–54% five-year OS rate).² In 2006, a pooled analysis of chemotherapy trials reported survival in the good-, intermediate-, and poor-risk groups to be 94%, 83%, and 71%, respectively.³ Outcomes were improved compared with the 1997 analysis.³

The use of retroperitoneal lymph node dissection (RPLND) in the management of GCTs has evolved over the years, especially since the discovery of highly efficacious chemotherapeutic agents such as cisplatin in 1970s. Principally, there is a shift away from the use of primary RPLNDs in the management of early-stage GCTs, mainly due to the widespread uptake of active surveillance as the management strategies in stage I disease and use of induction chemotherapy in stage II disease.^{4,5} The majority of RPLNDs today are performed in the post-chemotherapy setting.⁶

Post-chemotherapy retroperitoneal lymph node dissection (PCRPLND) has a well-established role in the management of residual masses >1 cm in patients with advanced non-seminomatous germ cell tumor (NSGCT) with negative serum tumour markers.⁷ The main rationale for PCRPLND is that residual masses >1 cm in advanced NSGCT have a 50–70% chance of harboring viable tumors or teratoma. Historically, histopathological evaluation of resected

specimens shows necrosis, teratoma, and viable malignancy (with or without teratoma) in 40%, 45%, and 15% of cases, respectively.⁸ Each of the histopathology findings is of prognostic value and guides further management. Teratoma is known to be chemo-resistant, and it has the potential for malignant transformation and late relapse,⁹ and PCRPLND is often curative in this setting. Viable tumors may prompt intervention with salvage chemotherapy. There are many attempts at identifying predictive factors for viable tumors or teratoma at surgery,¹⁰ but the utility of various predictive models is not widely adopted.

As the only center for RPLND surgery in Southern Alberta, Canada, we performed a retrospective data collection and analysis of patients who had undergone an open RPLND between 2010 and 2016. Our objective is to present our surgical experience and to evaluate the histopathology from the PCRPLNDs performed at our institution.

Methods

The electronic medical records of a single surgeon at the Southern Alberta Institute of Urology (SAIU) were searched for any patients who had undergone an open RPLND for advanced GCTs between 2010 and 2016.

Inclusion criteria

All patients have either NSGCTs on histology or elevation of serum alpha-feto protein (AFP). They must have received primary chemotherapy prior to surgery and had post-chemotherapy retroperitoneal masses greater than 1 cm in short axis. Patients who received salvage chemotherapy prior to surgery were excluded, which aligned with previous published surgical series.⁹⁻¹² Data were collected by review of electronic medical records, preoperative tumour markers results, radiology reports, operative findings, and histopathology report.

Data collection

Patient's demographic data were collected. Histology of the orchiectomies and resected retroperitoneal specimens were collected from the pathology reports. Patients were stratified into good-, intermediate-, or poor-risk groups based on the IGCCCG classification. Data on the type of chemotherapy regimens used and number of cycles of chemotherapy delivered were also collected. Complications of surgery were defined as any documented surgical complication in the operative report or clinical notes. Intraoperative blood loss was included in intraoperative complications. The severity of complications was graded according to the Clavien-Dindo classification of surgical complications, which ranges from grade 1–5.¹³ Additional procedures were defined as any

additional surgical procedure that occurred simultaneously during the PCRPLND and this information was collected.

The histology of post-chemotherapy residual mass (PCRM) was recorded and a Chi-squared test was used to test for the statistical significance of the occurrence of observed histology against the reported histology proportion (40% necrosis, 45% teratoma, and 15% viable tumors) according to prior published series. Chi-squared testing was used in testing for differences in proportion of post RPLND tumor histology in this cohort vs. the most comprehensive cohort available.⁸ Chi-squared testing was also used in evaluating the association between the primary tumor histology and the histological findings at PCRM.

Results

A total of 64 patients were identified. Of these, seven patients were excluded, as four patients underwent primary RPLND, one patient was considered a desperation case, and two patients have pure seminoma histology in the primary tumor. Therefore, a total of 57 patients with advanced NSGCTs who had received primary chemotherapy prior to RPLND met the inclusion criteria for the study. All patients underwent radical orchiectomy. The baseline characteristics are outlined in Table 1. Median followup is 52.4 months.

The median age of patients is 29 years. Overall, the majority of our patients are of IGCCCG good-risk ($n=32$, 56%). The number of patients who were intermediate or poor-risk are $n=14$ (25%) and $n=11$ (19%), respectively.

The most common ($n=47$, 83%) primary chemotherapy regimen used was bleomycin, epirubicin, and cisplatin (BEP) for 3–4 cycles, depending on the IGCCCG risk group. Three good-risks patients received epirubicin and cisplatin (EP), five patients received etoposide, ifosfamide, and cisplatin (VIP), while two patients received alternative individualized chemotherapy regimens due to comorbidities.

Surgery was performed in all patients due to residual retroperitoneal mass of >1 cm on computed tomography (CT) imaging. The operative approach was bilateral, full-template, infrahilar RPLND via an anterior transabdominal approach. Nerve-sparing techniques were used where possible, but this was limited by significant tissue scarring in the surgical field post-chemotherapy.

There were no perioperative deaths; 14% of patients required additional procedure for resection of adjacent organs intraoperatively. The overall complication rate was 23% ($n=13$), of which nine were Clavien-Dindo grade I–II, four were Clavien-Dindo grade IIIb, and one was grade IVa (Table 2). Of note, 77% ($n=10$) of complications occurred intraoperatively and 23% ($n=3$) occurred postoperatively. There were three cases of wound dehiscence, which occurred at day 2, day 4, and day 10 postoperatively. All three cases required re-operations. One patient suffered from

Table 1. Baseline demographics and patient characteristics

Variable	n (%)
Age, median (mean)	29 (30)
Clinical stage pre-chemotherapy	
1s	1 (2%)
2a	5 (9%)
2b	19 (33%)
2c	9 (16%)
3a	4 (7%)
3b	9 (16%)
3c	10 (18%)
Site of primary tumor	
Right	28 (49%)
Left	28 (49%)
Bilateral	1 (2%)
Patient characteristics pre-chemotherapy	
Good risk	32 (56%)
Intermediate risk	14 (25%)
Poor risk	11 (19%)
Mean size of retroperitoneal tumor \pm SD	5.6 \pm 3.3 cm
Blood loss range	0.1-6 L
Organs removed without complications	8 (14%)
Median followup	52.4 months
Retroperitoneal histology	
Teratoma	36 (63%)
Necrosis	17 (30%)
Viable cancer	4 (7%)

SD: standard deviation.

infarcted kidney requiring intraoperative nephrectomy and postoperative hemodialysis.

The overall histopathology analyses are presented in Table 1. The chance of teratoma was highest for those patients who had IGCCCG good-risk disease, as shown in Fig. 1. Of note, 63% (n=36) were pure teratoma, 30% (n=17) were fibrosis/

Table 2. Descriptions and grading of surgical complications

Grade	Complication	n
I	Damage of IVC or aorta	1
	Damage of renal vein	1
II	Damage of IVC or aorta	3
	Thrombosis and blood transfusion	2
	Chyle leakage/infection	1
	Blood transfusion	1
IIIb	Wound dehiscence (postoperative)	3
IVa	Renal infarct requiring temporary dialysis and intensive care unit	1
Total		13 (22.8%)

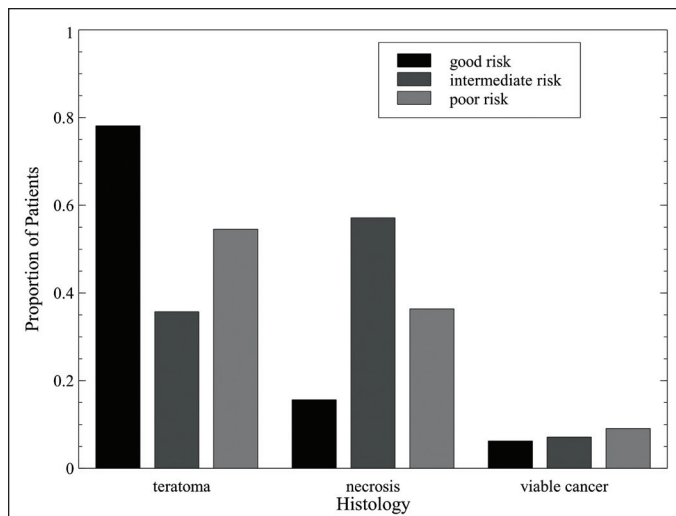
IVC: inferior vena cava.

necrosis, and 7% (n=4) were viable tumors. Of the four viable tumours, three patients had yolk sac tumors and one patient had seminoma with an embryonal component. When comparing these frequencies to those seen in historical cohorts,⁸ there was a statistically significant difference in the distribution of histologies (Chi-squared $p=0.0187$). The presence of teratoma in the orchiectomy specimens is associated with the findings of teratoma in the PCRM (Chi-squared $p=0.0047$). On the contrary, the absence of teratoma is associated with the findings of fibrotic/necrotic tissue in the PCRM (Chi-squared $p=0.0005$)

Discussion

Despite a lack of randomized control trial evidence, there is almost universal agreement that PCRPLND should be offered to all advanced NSGCTs patients with post-chemotherapy residual mass of >1 cm on CT imaging and normal serum tumor markers. The practice is supported by retrospective surgical series,^{12,14} which demonstrated high proportion of residual teratoma or viable tumors at PCRPLND and the presumption that untreated teratoma or viable tumors would progress. On the other hand, it is generally accepted that observation is an appropriate management option for patients with advanced NSGCTs who achieved clinical complete response (CR) (normalization of tumour markers and resolution of all radiographic disease) following first-line chemotherapy.^{15,16}

The histopathological evaluation of resected specimens from traditional series shows necrosis, teratoma, and viable malignancy (with or without teratoma) in approximately 40%, 45%, and 15% of cases, respectively.⁸ Compared to historical data, our series shows an interesting observation of: a lower proportion of viable malignancy of 7% (n=4); a higher proportion of teratoma at 63% (n=36); and a lower proportion of fibrosis/necrosis at 30% (n=17). This is consistent with some of the more contemporary surgical series in the early 2000s.¹⁷ Our series is relatively recent, capturing patients who received PCRPLND from 2010–2016.

**Fig. 1.** Histopathologic outcome stratified by IGCCCG risk group.

As the tertiary referral center for testicular cancer in Alberta, Canada, we have a high volume of patients with testicular cancer per year. It is our policy to discuss all testicular cancer patients at a tumor board, allowing a multidisciplinary approach to patient's care and a streamlined treatment pathway. This standardizes our approach to the treatment of advanced testicular cancer in an effort to optimize outcomes. The importance of maintaining optimal chemotherapy dose intensities is emphasized, possibly resulting in lower number of viable tumors other than teratoma. Secondly, with improvement in CT imaging techniques and the availability of subspecialty radiologists, it is possible that this results in better patient selection for PCRPLND. Thirdly, we routinely perform post-chemotherapy restaging scan eight weeks from completion of chemotherapy, allowing maximal chemotherapy effect and potentially avoiding false-positive results. Lastly, men are presenting with less advanced metastatic NSGCT and the stage migration, together with effective therapy, may result in lower rates of viable tumors.⁹ On the other hand, selection bias may be contributing to the findings of high rate of teratoma and low rate of viable tumors in our series. Compared to historical series, patients who did not achieved CR post-chemotherapy but have <1 cm masses are currently managed with surveillance in most centers, including our center. PCRPLND is offered only when the retroperitoneal mass grows, potentially increasing the likelihood of finding teratoma and decreasing the likelihood of finding fibrosis at PCRPLND specimens. The low rate of viable GCT in PCRPLND specimens in our series could be due to small sample size. Despite these limitations, the apparent high proportion of teratoma in our series highlights the importance of PCRPLND as an integral part of patients' management, as these tumours are often chemo-resistant and PCRPLND is associated with 10-year probability of freedom from recurrence of 80%.¹¹

There have been numerous attempts made at examining clinical predictors of histology in the PCRM, in the hope to identify a subgroup of patients who can safely be observed. A number of studies have looked at the predictors of teratoma in the PCRM, and it has been consistently demonstrated that teratoma in the primary tumor is associated with higher rate of teratoma in the PCRM.^{18,19} In our series, 76% of patients who had teratoma in the PCRM had teratoma in the primary tumor, and we showed that the presence of teratoma in the primary tumor is associated with higher rate of teratoma in the PCRM, consistent with the literature. Other groups examined the clinical predictors for necrosis in the PCRM, including absence of teratoma in the primary tumour, normal prechemotherapy tumour markers, small residual mass, and a large diminishment in mass size during chemotherapy.^{10,19} Our data is in line with this, where the absence of teratoma in the primary tumor was associated with presence of fibrosis/necrosis in the PCRM. However, due to the inability

to reliably predict necrosis in the whole cohort of patients, these predictive models remain experimental and are not routinely used in clinical practice. Perhaps more importantly, patients with advanced testicular cancer can be both under- or overtreated, due to a number of potential administrative and systemic issues that may affect our ability to correctly identify patients who truly require PCRPLND. In many tertiary Canadian centers, medical oncologists are often the decision-makers when it comes to referring patients for PCRPLND. Meticulous review of post-chemotherapy CT scans by a urologist familiar with the primary landing zones for testicular cancer is often not done and often reliant on radiologists. The definition of pathological lymph node that is subcentimeter is variable and not well-defined, leading to misclassification of some patients having a CR when they likely only had a partial response (PR). Even when the urologic oncologist has a predetermined protocol of offering PCRPLND on all PCRM of >1 cm on CT scans, the system is dependent on getting the patient referred to them for consideration of surgery. Potential solutions to circumvent this systemic issue are to discuss all advanced testicular patients at a tumor board, by having a dedicated genitourinary radiologist to review pre-chemotherapy and post-chemotherapy scans, and to generate an automatic referral to uro-oncologist for PCRPLND if the decision for referral to PCRPLND is made at tumor board.

Traditionally, RPLND is associated with high morbidity and mortality.²⁰ With improvement in surgical expertise, anesthetic techniques, and improvement in chemotherapy resulting in smaller tumors, major complications are now less common when surgery is performed in high-volume academic centers.

Many of the published surgical series used non-standardized definitions of complications, therefore, comparing complication rates cross-study may be misleading. Within this limitation, the overall complication rate of 23% in our series appeared to be at the lower end of the spectrum from published surgical series, which ranges from 20–35%.^{21–23} The mortality rate of 0% is encouraging.

Historically, increased risk of pulmonary complications was recognized in patients who received bleomycin or had bulky retroperitoneal disease.²¹ In our series, serious pulmonary complications were not observed. The rate of additional procedures required intraoperatively (14%) in our series also appears lower than previously published series.^{24–26}

Limitations

Being a retrospective study, our study has several limitations. The identification of complications may potentially be missed if the event was not documented in the patient's clinical chart. However, the provincial electronic medical record system exists and, thereby, minimizes the rate of undeclared

complications. When there is doubt in grading the severity of a particular complication, the treating surgeon is consulted to clarify the actual event. This may cause recall or classification bias; however, the final decision about the grading of severity lies in the judgement of an independent reviewer (CLG), who used Clavien-Dindo surgical complications grading system as a reference. Our study has a relatively short followup and some longer-term complications may not be captured. Lastly, as a single surgeon-derived surgical series, our results may not be generalizable to the wider audience, however, this study may provide a reference point for future study of PCRPLND in Canada.

Conclusions

PCRPLND is an integral part of the multidisciplinary management of advanced testicular patients. Our series demonstrated that the rate of viable tumor and fibrosis/necrosis in PCRM appears lower than published historical series. The high rate of teratoma in the PCRM calls for ongoing need for RPLND in the management of patients with post-chemotherapy residual mass >1 cm. Grade 3 and 4 surgical complications are considered rare in our series.

Competing interests: Dr. Kawakami has been a speaker and proctor for Minogue Medical; and is a stockholder in and advisor for Vibe Bioscience. Dr. Heng has been a consultant for BMS, Ipsen, Merck, Novartis, Pfizer, and Roche. The remaining authors report no competing personal or financial interests related to this work.

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Correspondence: Dr. Jun Kawakami, Division of Urology, Department of Surgery, Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada; kawakamijun@me.com