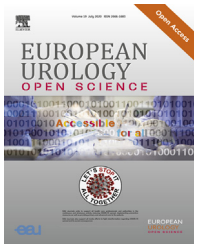
EUROPEAN UROLOGY OPEN SCIENCE 33 (2021) 83–88

available at www.sciencedirect.com
journal homepage: www.eu-openscience.europeanurology.com



European Association of Urology

Testis Cancer

# Outcomes of Postchemotherapy Retroperitoneal Lymph Node Dissection from a High-volume UK Centre Compared with a National Data Set

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**Article info**

***Article history:***
Accepted September 9, 2021

***Associate Editor:***
Guillaume Ploussard

***Keywords:***
Retroperitoneal lymph node dissection
Germ cell tumours
Testis cancer
Postchemotherapy
Outcomes
Centralisation
Blood transfusion

**Abstract**

***Background:*** Retroperitoneal lymph node dissection (RPLND) is essential for the treatment of metastatic germ cell tumours of the testis. Recommendations on the referral and management of complex urological cancers in the UK includes centralisation of services to regional centres.
***Objective:*** To review contemporary PC-RPLND outcomes at a high-volume centre with a complex case-mix, and compare with national registry data.
***Design, setting, and participants:*** We retrospectively reviewed the medical records of PC-RPLNDs performed for germ cell tumours at our centre between July 2012 and September 2018.
***Outcome measurements and statistical analysis:*** Primary outcomes were Clavien 3 + complications, histology, rates of positive margin, relapse, in-field recurrences, and mortality. Secondary outcomes were blood loss, operation time, blood transfusion, adjuvant procedures, length of stay, and lymph node count. Surgical and histological outcomes of all RPLNDs for testicular cancers were compared with national RPLND registry data. For statistical difference, $\chi^2$ testing was used.
***Results and limitations:*** A total of 178 procedures were performed, including 31 (17%) redo RPLNDs. Clavien 3+ complications occurred in 11 (7%). Histological findings in non-redo cases were the following: necrosis 24%, teratoma 62%, viable germ cell tumour 11%, and dedifferentiated cancers 3%. Rates of positive margin, relapse, and in-field recurrence were 11%, 17%, and 2%, respectively. Overall survival was 89% at a median of 36 mo. The median blood loss was 650 ml (350, 1250), with a transfusion rate of 8%. Nephrectomy, vascular reconstruction, and visceral resection was required in 12%, 6%, and 3% respectively. The median inpatient stay was 6 d

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http://dx.doi.org/10.1016/j.euros.2021.09.005

(5, 8) and the median node count was 35 (20, 37). A comparison of all RPLNDs with national data showed no statistical difference in primary outcomes. Our blood transfusion rate was significantly lower (12% vs 21%, $\chi^2$ [1, $N$ = 322] = 4.296, $p$ = 0.038).

***Conclusions:*** Centralisation led to high quality of RPLND in UK. Within that, our series (the largest in the UK) demonstrates no significant difference in outcomes despite higher complexity cases. Our blood transfusion rates are in fact lower than national figures. Complex RPLNDs should be performed in high-volume centres where possible.

***Patient summary:*** In the UK, retroperitoneal lymph node dissections (RPLND) are centralised to specialist centres and the quality of surgery is high, with low complications and good histological outcomes. When compared to national data, we found no significant difference in the majority of outcomes from our high-volume centre despite our complex case-mix.



## 1. Introduction

Retroperitoneal lymph node dissection (RPLND) is an essential component of the multimodal treatment of metastatic germ cell tumours (GCTs) of the testis. Following the completion of multiagent chemotherapy, a number of men have residual tumour masses, most commonly in the retroperitoneum. In metastatic nonseminomatous GCTs, assuming normalisation or plateau of tumour markers, residual masses of the retroperitoneum are required to undergo resection, along with involved adjacent structures and lymph node tissue surrounding the great vessels. The rationale for this is that residual masses may contain chemoresistant GCTs or more commonly may be teratoma differentiated (TD). TD is not itself biologically aggressive but has the potential to undergo malignant dedifferentiation into highly aggressive somatic malignancies if left in situ. Alternatively, the finding of necrosis/fibrosis only indicates a complete response to chemotherapy.

In 2002, the National Institute for Clinical Excellence (NICE) published recommendations on the referral and management of complex urological cancers in the UK [1]. The key recommendations were the centralisation of services to regional centres, with treatment planned through multidisciplinary team (MDT) meetings involving oncologists, radiologists, pathologists, and urological surgeons, all specialised in the field. For testicular cancer, it was recommended that services should be based on geographical areas covering a population of 2–4 million each. Ten years later, the British Association of Urological Surgeons (BAUS) commissioned an audit of RPLND surgery across the UK, the first, and to our knowledge, the only reporting of national data [2]. This showed that RPLNDs had centralised to 17 centres performing a mean of nine RPLNDs (a median of six per surgeon) annually. It demonstrated that, despite the vast majority of RPLNDs in the UK being performed in the postchemotherapy (PC) setting, the quality of surgery is high, with low complication rates and good histological outcomes.

Other series report complication rates for open PC-RPLNDs between 12% [3] and 25% [4], and between 9% [5] and 12% [6] for Clavien-Dindo $\geq$3 complications within 30 d. Deaths are rare (0.26% in one large series from the USA [7]). The median operating time is 3–4 h, and blood loss is typically 300–500 ml [5,8]. Transfusion rates vary between 3% and 26% [5,9,10]. Adjuvant nephrectomy is required in 5–22% and major vascular reconstruction in 3–10% of cases [2,5,7,11]. The median length of stay is typically 5–6 d [2,4,5]. Generally speaking, operative outcomes vary with the complexity of surgery required.

The histological finding of necrosis/fibrosis occurs in 47–67% of PC-RPLNDs, TD-only malignancy occurs in 20–40%, and a minority of cases have residual viable GCTs [5–7,11–13]. Data from the BAUS registry, however, reported a very low necrosis-only rate of 23% and TD-only rate of 41% (although 14% were recorded as “other” and data were missing in a further 10%) [2]. Small residual masses $<$1 cm contain necrosis in up to 70% of cases, and it has been shown that these can safely be observed [11]. Incomplete resection is an independent predictor of relapse [14]. Redo RPLNDs and RPLNDs for late relapses are more likely to yield teratomas or viable GCTs due to chemoresistant disease.

Of the men who undergo PC-RPLNDs, 13% will relapse following completion of treatment [5]. In addition to the International Germ Cell Cancer Collaborative Group (IGCCCG) prognostic groups for metastatic GCTs [15], PC-RPLND histological findings are also predictive of survival: The 5-yr cancer-specific survival is excellent at 98% for both necrosis and TD. It is lower at 78% when viable GCT ($\pm$TD) is found [6].

Within an already regionalised system, our centre additionally receives complex cases (massive residual masses, growing teratoma, and redo RPLNDs) from other centres and networks. We aimed to review PC-RPLND surgical, histological, and survival outcomes at our high-volume centre and compare these with the national UK registry data. The primary outcomes were Clavien-Dindo $\geq$3 complications; proportions of necrosis, TD, and viable

GCT (±TD) and dedifferentiated malignancy on PC GCT histology; positive surgical margin rate; relapse rate; in-field recurrence; and overall survival. Secondary surgical outcomes were blood loss, operation time, requirement for blood transfusion or adjuvant procedures, length of stay, and lymph node count.

## 2. Patients and methods

We retrospectively reviewed all PC-RPLNDs performed for GCTs at our centre between July 2012 and September 2018. Cases were identified using our surgical booking diary. Our institutional electronic patient record system (which incorporates in- and outpatient records, correspondence, operation reports, pathology and radiology reports, and MDT outcomes) was interrogated. Additional operative parameters were sourced from our anaesthetic electronic record system. Complications within 60 d following surgery were identified by reviewing operative records, and postoperative in- and outpatient records, and cross-referenced with our departmental morbidity and mortality meeting reports. Relapse and survival data were obtained from medical records, external correspondence, and our supraregional MDT records.

Perioperative and histological outcomes were compared with the BAUS registry data, with data submitted from our centre being removed to prevent duplication of cases. As the registry included primary RPLNDs and those for non-GCT testicular cancer, these cases were also included. To assess for statistical difference, $\chi^2$ testing was used.

## 3. Results

Our centre performed at total of 178 PC-RPLNDs for GCTs, including 31 (17.4%) redo operations. Patients' preoperative characteristics are summarised in Table 1.

Operative outcomes are summarised in Table 2. The median operation time was 240 (210–300) min. Forty-four patients (24.7%) required one or more adjuvant surgical procedures, including nephrectomy (12.4%), vascular resection/reconstruction (5.6%), and visceral resection (2.8%). Four patients were identified as having inoperable disease at the time of surgery. Blood loss data were available for 137 patients, with a median blood loss of 650 (350–1250) ml. Fourteen (7.8%) patients received blood transfusion associated with their procedure. Eighty-six (48.3%) patients experienced a complication within 60 d, including 13 (7.3%) Clavien-Dindo ≥3 greater complications. There were no returns to the operating theatre. Two deaths within 60 d were attributable to disease progression, with both being inoperable at surgery. The median length of stay was 6 (5–8) d.

The median lymph node count was 35 (20–37). Twenty (11.2%) patients had positive surgical margins.

A review of the histology for the 147 men who underwent PC-RPLND exclusive of redo cases shows a necrosis/fibrosis rate of 23.8%, whilst TD, viable GCT ± TD, and dedifferentiated cancers accounted for 61.9%, 10.9%, and 3.4%, respectively.

Key oncological outcomes from our centre are summarised in Table 3. At a median follow-up of 36 mo, 31 (17.4%) patients had relapsed. Men who had benign histology at RPLND had a relapse rate of 2.5%, whilst the rates were 11.2%, 53.6%, and 57.1% for TD, viable GCT ± TD, and dedifferentiated malignancy, respectively. Thirteen patients relapsed at multiple sites, and the most common site of recurrence was the lungs (32%). Four (2.2%) relapsed in the retroperitoneal template.

At the time of review, 19 (10.6%) patients are deceased. The median time to death was 13 mo. Five of these patients had incomplete resection at RPLND, and all but one were confirmed to have disease relapse before their death.

Overall survival rates based on RPLND histology were 100%, 99.0%, 60.1%, and 57.1% for necrosis-only, TD-only, viable GCT ± TD, and dedifferentiated malignancy, respectively.

Thirty-one patients had a redo RPLND. This typically involved resection of a residual or recurrent mass, although eight had a bilateral template dissection with a median lymph node count of 33. The majority had their initial RPLNDs at other centres. Redo histologies were as follows: necrosis 16%, TD 36%, viable GCT ± TD 42%, and dedifferentiated malignancy 6%. Redo RPLNDs had a relapse rate of 42% and a mortality rate of 16% in the follow-up period.

Relapse was associated with IGCCCG intermediate- or poor-prognosis disease, requirement for second-line systemic treatment before surgery and elevated TM at surgery, as well as viable GCT or dedifferentiated malignancy on histology.

A total of 197 RPLNDs were included for comparison of surgical outcomes with the remainder of those reported in the BAUS registry study (Table 4). There was no significant

**Table 1 – Patient characteristics of consecutive PC-RPLNDs for GCTs at our centre (RMH) between July 2012 and September 2018**

| | | |
|---|---|---|
| Total PC-RPLNDs | | 178 |
| Age, median (IQR) | | 32 (27–42) |
| Histology before RPLND, *n* (%) | NSGCT | 176 (98.9) |
| | Seminoma | 2 (1.1) |
| AJCC prognostic stage group at diagnosis, *n* (%) | I/IS | 30 (16.9) |
| | II | 55 (30.9) |
| | III | 93 (52.2) |
| IGCCCG prognosis, *n* (%) [16] | Good | 91 (51.1) |
| | Intermediate | 34 (19.1) |
| | Poor | 53 (29.8) |
| Redo RPLND, *n* (%) | No | 147 (82.6) |
| | Yes | 31 (17.4) |

AJCC = American Joint Committee on Cancer; GCT = germ cell tumour; IGCCCG = International Germ Cell Cancer Collaborative Group; IQR = interquartile range; NSGCT = nonseminomatous GCT; PC = postchemotherapy; RMH = Royal Marsden Hospital; RPLND = retroperitoneal lymph node dissection.

**Table 2 – Operative outcomes of PC-RPLNDs performed between July 2012 and September 2018**

| | | |
|---|---|---|
| Total PC-RPLNDs | | 178 |
| Median operation time (min) | | 240 (210–300) |
| Median estimated blood loss (ml) | | 650 (350–1250) |
| Blood transfusion (units) [a], *n* (%) | 0 | 154 (86.5) |
| | 1–2 | 10 (5.6) |
| | >2 | 4 (3.9) |
| Adjuvant procedures, *n* (%) | Nephrectomy | 22 (12.4) |
| | Vascular resection/reconstruction | 10 (5.6) |
| | Visceral resection | 5 (2.8) |
| Clavien-Dindo complication within 60 d, *n* (%) | 0 | 92 (51.7) |
| | 1–2 | 73 (41.0) |
| | 3a | 6 (3.3) |
| | 3b | 0 |
| | 4a | 5 (2.8) |
| | 4b | 2 (1.1) |
| Median length of stay (d) | | 6 (5, 8) |

PC = postchemotherapy; RPLND = retroperitoneal lymph node dissection.
[a] Intra- and postoperative transfusions.

**Table 3 – Rate of relapse, in-field recurrence, and survival by histological outcome of postchemotherapy retroperitoneal lymph node dissection (PC-RPLND) at a median follow-up of 36 mo**

| PC-RPLND histology | *N* | Positive surgical margin (%) | Relapses (%) | In-field relapses (%) | Overall survival (%) |
|---|---|---|---|---|---|
| Benign/necrosis | 40 | 0 (0%) | 1 (2.5%) | 0 (0%) | 40 (100%) |
| TD | 98 | 7 (7.1%) | 11 (11.2%) | 2 (2.0%) | 97 (99.0%) |
| Viable GCT ± TD | 28 | 9 (32.1%) | 15 (53.6%) | 0 (0%) | 17 (60.1%) |
| Dedifferentiated malignancy | 7 | 4 (57.1%) | 4 (57.1%) | 2 (28.6%) | 4 (57.1%) |
| Inoperable | 4 | NA | NA | NA | 1 (25.0%) |
| Total | 178 | 20 (11.2%) | 31 (17.4%) | 4 (2.2%) | 159 (89.3%) |

GCT = germ cell tumour; NA = not available; TD = teratoma differentiated.

**Table 4 – Comparison of operative and histological outcomes from our centre (RMH) with national data from BAUS audit [2] following removal of RMH submitted data**

| Outcome | | BAUS audit[a] | RMH | $\chi^2$ | *p* value |
|---|---|---|---|---|---|
| Adjuvant procedures | Nephrectomy | 11/125 (8.8%) | 22/197 (11.2%) | (1, *N* = 322) = 0.477 | 0.490 |
| | Vascular resection/reconstruction | 2/125 (1.6%) | 10/197 (5.1%) | (1, *N* = 322) = 2.593 | 0.107 |
| | Visceral resection | 3/125 (2.4%) | 5/197 (2.5%) | (1, *N* = 322) = 0.003 | 0.955 |
| Blood transfusion required | | 26/125 (20.8%) | 24/197 (12.2%) | (1, *N* = 322) = 4.296 | 0.038 |
| Positive margin | | 11/126 (8.7%) | 22/193 (11.4%) | (1, *N* = 319) = 0.598 | 0.438 |
| Overall complications | | 16/66 (24.2%) | 92/197 (46.7%) | (1, *N* = 263) = 10.303 | 0.001 |
| Clavien-Dindo ≥3 complications | | 1/66 (1.5%) | 14/197 (7.1%) | (1, *N* = 263) =2.876 | 0.0899 |
| Median length of stay (d) | | 6 | 6 | NA | NA |
| RPLND histology | TD | 54/114 (47.4%) | 103/193 (53.3%) | (4, *N* = 311) = 8.192 | 0.0848 |
| | Necrosis | 29/114 (25.4%) | 47/193 (24.4%) | | |
| | GCT ± TD | 15/114 (13.2%) | 31/193 (16.1%) | | |
| | Dedifferentiated | 6/114 (5.3%) | 8/193 (4.1%) | | |
| | Other | 10/114 (8.8%) | 4/193 (2.1%) | | |

BAUS = British Association of Urological Surgeons; GCT = germ cell tumour; RMH = Royal Marsden Hospital; RPLND = retroperitoneal lymph node dissection; TD = teratoma differentiated.
[a] Data obtained via correspondence with a coauthor.

difference in histology findings, positive margin rate, or length of stay. There was a trend towards more Clavien 3+ complications at our centre (7.1% vs 1.5%) as well as more vascular resections or reconstructions (5.1% vs 1.6%), but neither reached significance. Our transfusion rate was significantly lower than national figures (12% vs 21%, $\chi^2$ [1, $N = 322$] = 4.296, $p = 0.038$).

## 4. Discussion

Our centre is the largest in the UK and averages 35 RPLNDs per year, compared with the national average of nine cases. This reflects referral of complex cases from other centres beyond our geographically defined regional network. The complexity of our caseload is highlighted by the high

proportion of redo RPLNDs and our high rate of vascular reconstruction.

Overall complication rate (46.7% vs 26.5%) and Clavien 3+ complication rates (7.1% vs 1.5%) appear to be higher in our series than in BAUS audit figures. Published series report overall complication rates for open RPLNDs of 12–25% [3,4], and 9–12% [5,6] for Clavien 3+ complications within 30 d. Discrepancies between the national data set and our series almost certainly reflect incomplete reporting to the BAUS registry evidenced by the low rate of follow-up data with absent complication data for nearly two-thirds of patients beyond the initial operation and inpatient stay. Our series captured all surgical complications within 60 d and thus is a more accurate reflection of outcomes. Our Clavien 3+ complication rate is comparable with that of international series from high-volume specialist centres.

Despite the complexity of our caseload, our transfusion rate was significantly lower (12% vs 21%, $\chi^2$ [1, $N = 322$] = 4.296, $p = 0.038$) than that reported in the national audit. National figures are consistent with recently published multinational data, which showed that retroperitoneal tumour resections and open radical nephrectomies are both in the top ten procedures most likely to be associated with a blood transfusion, with rates of 26.5% and 26.6%, respectively [10]. Transfusion rate is a surrogate marker of surgical quality. In other urological procedures, the requirement for a transfusion is reduced in high-volume centres. Our centre adheres to guidelines for packed red blood cell (PRBC) transfusion and yet has a lower rate of transfusion than either of these two series [16]. In addition to the cost and availability issues, PRBC administration is known to cause transfusion reactions and transfusion-related lung injury, and has been associated with poorer oncological outcomes in multiple malignancy types, including urological malignancy [17]. The immunosuppressive effect of transfusions has long been established [18] and has been hypothesised as the cause for poorer cancer outcomes. However, since the circumstances under which PRBCs are given are also associated with poorer cancer outcomes, a causative relationship has not yet been established beyond controversy. Whilst no specific data are available relating to GCTs, minimisation of transfusions associated with RPLNDs should be considered through centralisation of complex PC-RPLNDs to high-volume centres.

From the perspective of surgical outcomes, this evidence supports the BAUS and NICE initiatives to centralise complex urological cancer surgery and highly complex RPLNDs being performed in only a handful of centres nationally. This review focuses on surgical outcomes, rather than on GCT outcomes as a whole. The surgical benefits of centralising RPLNDs to a small number of centres must be balanced against the possibility of substandard care, which may occur with the absence of an RPLND surgeon in regional MDTs. It should also be acknowledged that RPLNDs for testis cancer comprise one component of the practice of a urologist specialising in complex retroperitoneal surgery. The outcomes of caval thrombectomy, locally advanced or recurrent renal cancer, and RPLNDs for other malignancies are beyond the scope of this analysis.

The rate of necrosis/fibrosis on PC-RPLND is considerably lower at our centre (24%) and in the BAUS registry (25%) than widely reported elsewhere (47–67%) [5–7,11–13]. Several attempts have been made to devise and validate tools to reliably predict patients who have a benign residual mass after chemotherapy, and thus can avoid potentially morbid surgery without an oncological benefit. No clearly defined parameters have been established, and thus variations in practice are likely to occur.

The low necrosis/fibrosis rate across the UK may reflect several potential factors. Cases are centralised to a limited number of centres where all PC cases are reviewed by an MDT, with treatment decisions based on consensus discussions between oncologists, urological surgeons, and radiologists experienced in managing advanced GCTs. This approach favours a conservative approach to case selection, allowing observation of small or equivocal residual masses suspected not to harbour TD or viable cancer, until complete resolution. Patients whose residual masses fail to continue regressing or progress subsequently are reconsidered for surgery. A further consideration is that a nationalised health system operates in the UK. Remuneration is thus not on a fee for service basis, which removes the incentive for surgical interventions compared with health systems where remuneration and incomes relate to case volume. Nevertheless, low-volume TD may remain dormant for many years, and long-term outcome data on those observed are required to validate what would appear to be a conservative approach to PC-RPLND both in our centre and across the UK.

Many of our cases are redo RPLNDs. These patients have higher proportions of TD and viable GCTs, and consequently, worse relapse and death rates than other PC-RPLNDs. A review of the initial date of diagnosis in this group revealed 18 men who were diagnosed >10 yr ago, including seven diagnosed >20 yr ago. As such, their initial surgery may not have been performed in a manner that is standard now. A median lymph node yield of 33 in a subset of these patients where a bilateral template dissection was performed at the redo procedure indicates that their original RPLND has been inadequate. These findings again support the centralisation of RPLNDs to specialist centres using standardised resection techniques. It also shows the timeframe that is required to assess the full effect of centralisation. It may still take some years before the effects of improving outcomes in urological cancers confine this finding to history.

Our quoted relapse rates may underestimate the true relapse rate. Many of our patients are referred from outside our regional catchment area and return to the care of their local oncologist for surveillance. Additionally, patients in this young demographic relocate out of catchment for several social reasons. Privacy laws prevent these patients from being traced or approached directly by our centre. Whilst local treating oncologists will often refer back to our centre if patients relapse, this may not always occur, and hence relapses or mortality may be under-reported here.

## 5. Conclusions

We report the UK's largest series of RPLNDs and have compared it with a national data set. The latter was compromised by limited data related to outcomes, specifically complications beyond the surgical procedure and initial hospitalisation. Despite the complexity of cases at out centre, no significant difference was seen in most outcomes. Importantly, our rate of blood transfusion, a surgical quality measure, is nearly half that of national rates. RPLNDs are performed in 17 centres across the UK, which had a population of 64 million at the time of the BAUS registry data collection, and many centres perform fewer than ten cases per year. Even within an already centralised system, high-volume centres appear to offer the best care. However geographically and logistically challenging, complex cases should be performed in larger centres.

## CRediT authorship contribution statement

**Adam K Pearce:** Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing - original draft, Visualization, Project administration. **David Manson-Bahr:** Investigation, Writing - review & editing. **Alison Reid:** Writing - review & editing. **Robert Huddart:** Writing - review & editing. **Erik Mayer:** Writing - review & editing. **David L Nicol:** Conceptualization, Writing - review & editing, Supervision.

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