

## **Surgical complications in Post-Chemotherapy Retroperitoneal lymph node dissection for Non-Seminoma Germ Cell Tumour: a population-based study from the Swedish Norwegian Testicular Cancer Group**

Axel Gerdtsson <sup>a,b</sup>, Ulf Håkansson <sup>c</sup>, Magnus Törnblom <sup>d,e</sup>, George Jancke <sup>f</sup>, Helene F. S. Negaard <sup>g</sup>, Ingrid Glimelius <sup>h</sup>, Dag Halvorsen <sup>i</sup>, Ása Karlsdóttir <sup>j</sup>, Hege Sagstuen Haugnes <sup>k,l</sup>, Kristine Engen Andreassen <sup>g</sup>, Signe Melsen Larsen <sup>m</sup>, Göran Holmberg <sup>n</sup>, Rolf Wahlqvist <sup>m</sup>, Torgrim Tandstad <sup>o,p</sup>, Gabriella Cohn-Cedermark <sup>q,r</sup>, Olof Ståhl <sup>s,t</sup>, Anders Kjellman <sup>a,u</sup>

<sup>a</sup>Department of Clinical Science, Intervention and Technology, Division of Urology, Karolinska Institutet, Stockholm, Sweden; <sup>b</sup>Department of Urology, Skåne University Hospital, Malmö, Sweden; <sup>c</sup>Gastrocenter, Lund, Sweden; <sup>d</sup>Department of Clinical Science and Education, Section of Urology, Karolinska Institutet, Södersjukhuset, Stockholm, Sweden; <sup>e</sup>Department of Surgery, Visby County Hospital, Visby, Sweden; <sup>f</sup>University Hospital, Linköping, Sweden; <sup>g</sup>Department of Oncology, Oslo University Hospital, Oslo, Norway; <sup>h</sup>Department of Immunology, Genetics and Pathology, Unit of clinical and experimental oncology, Uppsala University, Sweden; <sup>i</sup>Department of Urology, St. Olavs University Hospital, Trondheim, Norway; <sup>j</sup>Department of Oncology, Haukeland University Hospital, Bergen, Norway; <sup>k</sup>Department of Oncology, University Hospital of North Norway, Tromsø, Norway; <sup>l</sup>Department of Clinical Medicine, UIT- The Arctic University of Norway, Tromsø, Norway; <sup>m</sup>Department of Urology, Oslo University Hospital, Oslo, Norway; <sup>n</sup>Department of Urology, Sahlgrenska University Hospital, Gothenburg, Sweden; <sup>o</sup>The Cancer Clinic, St. Olavs University Hospital, Trondheim, Norway; <sup>p</sup> Department of clinical and molecular medicine, the Norwegian university of science and technology, Trondheim, Norway; <sup>q</sup>Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden; <sup>r</sup>PO Bäckencancer, Karolinska University Hospital, Stockholm, Sweden; <sup>s</sup>Department of Oncology, Skåne University Hospital, Lund, Sweden; <sup>t</sup>Department of Clinical Sciences, Lund University, Lund, Sweden; <sup>u</sup> Department of Urology, Pelvic Cancer, Karolinska University Hospital, Stockholm, Sweden

Contact information for corresponding author: Axel Gerdtsson, Jan Waldenströms gata 5, 21421 Malmö, Sweden, +46 733 793 795, +46 40 337352 (fax number), [axel.gerdtsson@ki.se](mailto:axel.gerdtsson@ki.se),

Keywords: Complications; Non-seminoma; PC-RPLND; Retrograde ejaculation, Testicular cancer

Word count of text: 2528

Word count of the abstract: 269

## **Abstract**

**Background** Reports on perioperative complications after Post-Chemotherapy Retroperitoneal lymph node dissection (PC-RPLND) for Non-Seminoma Germ Cell Tumour (NSGCT) are from experienced single centres, with a lack of population-based studies.

**Objective** To assess the complications of bilateral and unilateral PC-RPLND.

**Design, Setting, Participants** Prospective, population-based observational multicentre study that included all patients with NSGCT that underwent PC-RPLND in Norway and Sweden 2007 to 2014. In total 318 patients, 87 underwent bilateral PC-RPLND and 231 unilateral PC-RPLND. Median follow-up 6 years.

**Outcome measurements and statistical analysis** Bilateral and unilateral PC-RPLND were compared for the outcome intra- and postoperative complications (graded by Clavien-Dindo) and retrograde ejaculation (with or without nerve-sparing surgery). Complications were reported as absolute counts and percentages. The  $\chi^2$ -test was used for comparisons

**Results and Limitations** The incidence of intraoperative complications was higher for bilateral PC-RPLND compared to unilateral PC-RPLND (14% vs. 4.3%,  $p=0.003$ ), with ureteral injury as the most frequent reported complication (2% of the patients). Postoperative complications were more common after bilateral than unilateral PC-RPLND (45% vs 25%,  $p=0.001$ ) with Clavien  $\geq 3$  reported in 8.3% and 2.2% respectively ( $p=0.009$ ). Lymphatic leakage was the most common complication occurring in 11% of the patients. Retrograde ejaculation occurred more frequently after bilateral than unilateral surgery (59% vs 32%, ( $p<0.001$ )). Limitation of the study include reporting of retrograde ejaculation, which was based on chart review.

**Conclusions** Intraoperative complications and postoperative complications including retrograde ejaculation are more frequent after bilateral PC-RPLND compared to unilateral PC-RPLND.

## **Patient Summary**

Lymph node dissection in patients with testicular cancer puts the patient at risk of complications. In this study we present the complications after lymph node dissection.

## **Introduction**

Testicular cancer (TC) is the most common cancer among young men with a particularly high incidence in Northern Europe. In 2017, Norway had an age-standardized incidence of 10.8/100 000 males and Sweden 7.6/100 000 males (1, 2). The 10-year cancer-specific survival rates in Norway and Sweden for disseminated non-seminoma germ cell tumour (NSGCT) are high, with rates at 95%, 90% and 67% in good, intermediate and poor prognosis, respectively (3). This high survival for metastatic NSGCT has been achieved through more than 30 years of collaboration between Oncologists and Urologists in the binational collaboration Swedish and Norwegian Testicular Cancer Group (SWENOTECA) (4).

The cornerstone in the treatment of metastatic NSGCT is cisplatin-based chemotherapy. Current guidelines recommend post-chemotherapy retroperitoneal lymph node dissection (PC-RPLND) to rule out viable cancer and to remove teratoma in patients with residual retroperitoneal lymph node enlargement  $\geq 1$ cm (5). The dissection revealed fibrosis/necrosis in 45%, teratoma in 45% and viable cancer in 10% in a study from Memorial Sloan-Kettering Cancer Center 1989-2002 (6). The standard PC-RPLND technique has been a full bilateral approach irrespective of clinical abdominal stage and previous chemotherapy (5). However, to reduce the risk of complications and long-term consequences such as retrograde ejaculation, less extensive templates, originally developed for primary RPLND have been used in the PC-RPLND setting for residual tumour  $< 5$ cm (7, 8, 9). Still, PC-RPLND will always be followed by a high risk of complications due to desmoplastic reaction in the retroperitoneal space. Due to the young age at diagnosis and the good prognosis, treatment-related adverse effects is an important health concern.

Previous reports on PC-RPLND have reported intraoperative complications in 12% (10). Additional surgical procedures occurred in 18-33% with nephrectomy as the most common additional procedure (4.6-7.3%) (7, 11, 12). Postoperative complications ranged from 3.7-32% (7, 10, 11, 13). The most common postoperative complication was ileus (0.5-21%) (10, 11). The prevalence of retrograde ejaculation after PC-RPLND ranges from 2-15% after unilateral and 21-75% after bilateral PC-RPLND (7, 10, 14, 15). These reports were from experienced single centres with various inclusion criteria.

To our knowledge, no population-based series have evaluated complications in an unselected patient population. The aim of this study was to assess the intra-and postoperative complications after unilateral and bilateral PC-RPLND. We herein present a binational prospective, population-based observational multicentre study of the complications after PC-RPLND.

## **Material and methods**

All patients with newly diagnosed TC aged above 16 years and who initiate treatment for TC in Sweden or Norway are prospectively included in the SWENOTECA database. In this study, all patients with NSGCT included in the SWENOTECA database, who underwent PC-RPLND in Sweden and Norway between September 1, 2007 and September 1, 2014, were included, in total 318 patients. The only exclusion criterion was patients with extragonadal tumour or previous RPLND. During the study period, 11 centres performed PC-RPLND in Sweden and Norway (supplementary Table 1).

## **Chemotherapy**

Patients were staged according to Royal Marsden clinical staging system and prognostic group were defined according to International Germ Cell Cancer Collaborative Group (IGCCCG) (16, 17). Patients with clinical stage (CS) 2-4 received chemotherapy prior to PC-RPLND according to SWENOTECA IV (1995-2012) and SWENOTECA VIII (2012-2014) protocols (18, 19).

### **PC-RPLND**

In 2007, the guidelines (SWENOTECA IV) stated that all patients with abdominal lymph nodes  $> 2$  cm on staging CT should be selected for PC-RPLND after completion of chemotherapy, regardless of residual disease (18). After revision of the guidelines in 2012 (SWENOTECA VIII), only patients with residual tumour  $\geq 1$ cm were selected for PC-RPLND (19). Desperation surgery was performed in selected cases.

Patients with residual tumour  $> 5$  cm (abdominal stage C and D) were planned for bilateral PC-RPLND. Patients with residual tumours in interaortocaval nodes (area 2 and 5)  $< 5$  cm were selected for bilateral surgery if left-sided TC, while a unilateral right-sided PC-RPLND was performed in case of right-sided TC. The remaining patients underwent unilateral PC-RPLND if the residual tumours were located in the unilateral template.

### **Templates**

The retroperitoneal space was divided in 12 areas (Figure 1). A right-sided unilateral PC-RPLND involved areas 1,2,3,4,5,7,9. A left sided unilateral PC-RPLND involved areas 2,3,6,8,10. A bilateral PC-RPLND involved 1,2,3,4,5,6,7,8 and either 9 or 10 depending on left or right-sided testicular tumour. Suprahilar dissection (areas 11 and 12) was only

performed in case of residual tumour involvement post-chemotherapy in these areas. To preserve some of the nerves from the sympathetic trunk, area 5 was avoided in left-sided unilateral surgery, whereas area 6 was spared for the right-sided.

### **Data collection**

The data was prospectively collected for each patient in a Case Report Form (CRF). Data included which areas were dissected and nerve-sparing technique was recorded for left and right side as yes, no, partial or not relevant. Bilateral RPLND and unilateral RPLND with dissection of areas on both sides of the aorta, was defined as being nerve-sparing if at least one side was performed in such manner. Intraoperative complications, extended surgery performed, intraoperative bleeding and operating time were noted in the CRF. Extended surgery was defined as surgery performed to make the patient tumour free whereas intraoperative complication was defined as an unforeseen event that was not planned before surgery. Appendectomy, orchidectomy and testicular prosthesis removal were not considered as extended surgery.

Length of hospital stay was recorded as number of postoperative nights at the hospital and postoperative complications (0-30 days and 31-90 days after surgery) with the Clavien-Dindo classification (20), date, therapy given and International-Classification of Diseases 10<sup>th</sup> version (ICD-10) codes. The pathologist reported if the areas contained benign nodes (fibrosis/necrosis), teratoma or viable cancer.

### **Follow-up**

Each patient had follow-up at an oncology department according to SWENOTECA guidelines (18, 19). Follow-up was continued until 31 December 2016, unless the patient was deceased,

or lost to follow-up. Information on date of diagnosis, clinical stage according to Royal Marsden and prognostic group according to the IGCCCG, chemotherapy and retrograde ejaculation was collected from the SWENOTECA database. The collected data was validated through chart review. The latest notation in the chart on retrograde ejaculation was used for the retrograde ejaculation variable.

### **Data analysis**

Descriptive characteristics were presented as number (percent) for categorical variables such as clinical stage, prognostic group, chemotherapy, nerve-sparing surgery, extended surgery, intra-, postoperative complication and retrograde ejaculation. Continuous variables such as operation time, intraoperative blood loss, postoperative nights, number of dissected areas were presented as median (interquartile range; IQR). Non-parametric test  $\chi^2$  was used to test the difference between intra- and postoperative complications and retrograde ejaculation between bilateral and unilateral PC-RPLND. The data was analysed using SPSS software v24. A two-sided p-value  $<0.05$  were considered as significant.

National/regional ethics committees approved the study.

## **Results**

### **Baseline characteristics**

In total 318 patients underwent PC-RPLND, 87 of the patients (27%) with bilateral PC-RPLND and 231 of the patients (73%) with unilateral PC-RPLND. Median follow-up time was 72 months (IQR 48-92). Median age, abdominal stage and prognostic group are shown in Table 1. Dose-intensified chemotherapy was given to 34% (30/87) of the patients prior to bilateral PC-RPLND compared to 19% (43/231) of unilateral PC-RPLND patients. High dose

chemotherapy (HD) and consolidation with an autologous stem cell transplantation was given to 5.7% (18/318) (Table 1).

### **PC-RPLND**

No difference was seen in rate of bilateral PC-RPLND compared to unilateral during the study period, however the number of PC-RPLND performed each year decreased after the guidelines changed. All PC-RPLND's were performed with an open transperitoneal approach except for four patients with thoracolaparatomy and one performed with robotic surgery. Median operating time was longer and blood loss was higher for bilateral PC-RPLND than for unilateral PC-RPLND (Table 2). A nerve-sparing technique was used in 23% (18/80) of bilateral PC-RPLND surgeries and in 64% (136/211) of the unilateral PC-RPLND. For complete tumour removal 16% (14/87) of the patients with bilateral PC-RPLND and 10% (24/231) of the patients with unilateral PC-RPLND had extended surgery. The most common organ resection was nephrectomy (6/318, 1.9%) (Table 2, supplementary Table 2).

### **Intraoperative and postoperative complications**

Any intraoperative complication was reported in 22/318 (6.9%) of all patients and was more frequently reported in bilateral PC-RPLND (12/87, 14 %) compared with unilateral PC-RPLND (10/231, 4.3%) ( $p=0.003$ ). Ureteral injury was the most frequently reported complication (6/318, 2%). Injury of aorta and/or IVC occurred in 5/318 (1.6%) of the patients. (Table 3, Supplementary Table 3)

During 0-30 days of follow-up 39/87 (45%) of the patients after bilateral PC-RPLND compared to 58/231 (25%) after unilateral PC-RPLND had a complication ( $p=0.001$ ). Clavien  $\geq 3$  complications occurred in 9.2% (8/87) of the patients with bilateral PC-RPLND and



2.2% (5/87) ( $p=0.009$ ) after unilateral PC-RPLND. The most frequently reported complications were lymphatic leakage (35/318, 11%) and wound infection (12/318, 3.8%) (Table 3, Supplementary Table 4). Four patients underwent second surgery during the 31-90 days of follow-up. One patient for ileus, one for lymphatic leakage and wound rupture, one for lymphatic leakage and one had a nephrectomy due to a ureteral injury. One patient (0.3%) died post-operatively due to major bleeding after vertebrae resection.

There was no annual change over time, or before or after the guidelines changed, in intra- and postoperative complications. No difference was seen in rate of intra- and postoperative complication between right and left sided unilateral PC-RPLND. However all four adrenalectomies and nephrectomies performed, occurred in left unilateral PC-RPLND.

### **Retrograde ejaculation**

Information on post-surgery retrograde ejaculation was available for 88% (280/318). After bilateral PC-RPLND 42/71 (59%) of the patients reported retrograde ejaculation compared to 67/209 (32%) after unilateral PC-RPLND ( $p<0.001$ ). Nerve-sparing surgery showed lower rates of retrograde ejaculation both for bilateral and unilateral PC-RPLND (Table 3).

Retrograde ejaculation was related to extent of surgery in areas 2, 3, 5 and 6. If only area 3 and 6 (paraaortic areas) or 2 and 5 (interaortocaval areas) were dissected 8/66 (12 %) had retrograde ejaculation. After dissection of area 3+6 or 2+5 and one contralateral area of the aorta (areas 2 or 3) 30/89 (34%) of patients had retrograde ejaculation. After dissection of all four areas (2+3+5+6), 71/125 (57%) of patients had retrograde ejaculation ( $p<0,001$ ) (Table 3). Retrograde ejaculation was more common after unilateral left compared to unilateral right-sided PC-RPLND. (25 vs 38%,  $p=0.041$ ) The difference was due to how the surgery was performed. If the surgery was performed in a strict unilateral approach with no area dissected

of the contralateral side of the aorta there was no difference between left and right unilateral PC-RPLND in rate of retrograde ejaculation.

### **Histology**

Histology after PC-RPLND revealed fibrotic/necrotic lymph nodes in 44%, 45% had teratoma and 11% had viable cancer. (Table 3).

### **Discussion**

This is the first prospective population-based study reporting on PC-RPLND complications. Herein, we present outcomes for all NSGCT patients who underwent PC-RPLND surgery in Norway and Sweden during a seven-year period. The operating time and intraoperative blood loss are comparable to contemporary high-volume centres (7, 10, 11, 12). An intraoperative complication were more frequent in bilateral PC-RPLND and corresponds to 12% after bilateral PC-RPLND reported by Subramanian et al (13). The number of PC-RPLND each year decreased after the guidelines changed, probably due to primary PC-RPLND for CS2 Mk- and avoiding PC-RPLND in patients with residual tumour <1cm after chemotherapy.

In this population-based report, extended surgery was less frequently performed compared to previous reports. Heidenreich et al reported adjunctive procedures (“to ensure complete resection”) in 24% of 54 patients after bilateral and 16% of 98 patients after unilateral PC-RPLND (7). Others report additional surgery in 18-33% (11, 12). However, the inclusion criteria for the studies and which procedures were defined as additional procedure are different from ours.

Postoperative complications (0-30 days) occurred in this study in 25% and 45% of patients operated with unilateral and bilateral surgery respectively. Most patients had a grade I or II complication and Clavien  $\geq 3$  were reported in 2.2% and 8.3% after unilateral and bilateral surgery, respectively. Cary et al reported a perioperative complication rate of only 3.7%, but included primary surgery of retroperitoneal disease with 17% of patients with CSI at diagnosis (10). Clavien classification was used but only one patient had a Clavien I complication. In a study by Subramanian et al, 32% had a complication after PC-RPLND classified by the Clavien-Dindo. Most were in Clavien I (16%) (13). Other series report complication rates at 6.7% and 32% (7, 13, 21). The different studies have various inclusion criteria as well as chemotherapy given prior to PC-RPLND, and did not report according to Clavien-Dindo classification.

Herein, 59% and 32%, respectively for bilateral and unilateral PC-RPLND had retrograde ejaculation. Nerve-sparing surgery was only feasible in 23% and 64%, respectively for bilateral and unilateral PC-RPLND, which is lower than numbers from other studies.

Heidenreich et al reported that nerve-sparing surgery was feasible in 67% of patients (55% in bilateral PC-RPLND and 75% in unilateral PC-RPLND) and Pettus et al 40% in bilateral PC-RPLND (7, 15). Even if nerve-sparing surgery were feasible in a large number of patients, 75% had retrograde ejaculation after bilateral PC-RPLND in the Heidenreich study and 21% after unilateral PC-RPLND (7). Pettus et al report that nerve-sparing surgery were feasible in 40%, but only 9 patients had a residual mass  $>5$ cm (15). Nerve-sparing PC-RPLND is difficult to perform in patients with a large residual mass. Cho et al reported that only 2% of their patients, operated with modified unilateral approach had retrograde ejaculation (21), of whom 94% of patients were in CS2A. Patients selected for unilateral approach differs between studies as well as the boundaries for unilateral template dissection. In this study area

2 and 3 were dissected in both right and left unilateral PC-RPLND. This means that the contralateral nerves are not being preserved when using our present templates for unilateral surgery unless the surgery was performed with a nerve-sparing operating technique. If no areas of the contralateral side of the aorta are dissected, retrograde ejaculation occurred at 12% after PC-RPLND. When one contralateral area is added to the dissection the rate increased to 34% and when all four areas are dissected 57% of patients experienced retrograde ejaculation. Centralization of PC-RPLND may increase the number of patients being operated with nerve-sparing surgery. RPLND has been centralized to 3 centres in Norway, and since 2017, to 2 centres in Sweden .

The limitation of this study is that the information on retrograde ejaculation is from database and chart review and not self-reported. Another limitation is that complications that occurred after discharge from the hospital (that performed PC-RPLND), might have been missed since some patients have been referred from other hospitals than those who performed PC-RPLND. A third-party validation of the complications after PC-RPLND has not been accomplished.

The major strength of this study is the population-based, prospective design with a selection of only NSGCT patients who underwent PC-RPLND. Another strength is the high degree of completeness, since all patients that underwent PC-RPLND for 7 years are included. Complications are graded by the Clavien-Dindo and intra-operative complications are reported separately.

## Conclusion

This population-based binational study shows that intraoperative complications as well as postoperative complications and retrograde ejaculation is more frequent after bilateral PC-

RPLND compared to unilateral PC-RPLND. However, the selection of patients for bilateral dissection is different than for the unilateral approach with a higher proportion of patients with large residual masses, thus making nerve-sparing surgery less feasible.

## References

1. [dataset] The National Board of Health and Welfare. Statistical database. 2019 <https://www.socialstyrelsen.se/statistics/statisticaldatabase/cancer>
2. [dataset] Cancer Registry of Norway. Cancer in Norway 2017 - Cancer incidence, mortality, survival and prevalence in Norway. Oslo: Cancer Registry of Norway, 2018. <https://www.kreftregisteret.no/globalassets/cancer-in-norway/2017/cin-2017.pdf>
3. Olofsson SE, Tandstad T, Jerkeman M, et al. Population-based study of treatment guided by tumor marker decline in patients with metastatic nonseminomatous germ cell tumor: a report from the Swedish-Norwegian Testicular Cancer Group. *J Clin Oncol.* 2011;29(15):2032-9.
4. Tandstad T, Stahl O, Hakansson U, et al. The SWENOTECA group: A good example of continuous binational and multidisciplinary collaboration for patients with testicular cancer in Sweden and Norway. *Scand J Urol.* 2016;50(1):9-13.
5. D Albers P, Albrecht W, Algaba F, et al. Guidelines on Testicular Cancer: 2015 Update. *Eur Urol.* 2015;68(6):1054-68.
6. Carver BS, Serio AM, Bajorin D, et al. Improved clinical outcome in recent years for men with metastatic nonseminomatous germ cell tumors. *J Clin Oncol.* 2007;25(35):5603-8.
7. Heidenreich A, Pfister D, Witthuhn R, et al. Postchemotherapy retroperitoneal lymph node dissection in advanced testicular cancer: radical or modified template resection. *Eur Urol.* 2009;55(1):217-24.
8. Beck SD, Foster RS, Bihrl R, et al. Is full bilateral retroperitoneal lymph node dissection always necessary for postchemotherapy residual tumor? *Cancer.* 2007;110(6):1235-40.
9. Hiester A, Nini A, Fingerhut A et al. Preservation of Ejaculatory Function After Postchemotherapy Retroperitoneal Lymph Node Dissection (PC-RPLND) in Patients With Testicular Cancer: Template vs. Bilateral Resection. *Front Surg.* 2019;17;5:80
10. Cary C, Masterson TA, Bihrl R, et al. Contemporary trends in postchemotherapy retroperitoneal lymph node dissection: Additional procedures and perioperative complications. *Urol Oncol.* 2015;33(9):389 e15-21.
11. Djaladat H, Nichols C, Daneshmand S. Adjuvant surgery in testicular cancer patients undergoing postchemotherapy retroperitoneal lymph node dissection. *Ann Surg Oncol.* 2012;19(7):2388-93.
12. Mosharafa AA, Foster RS, Koch MO, et al. Complications of post-chemotherapy retroperitoneal lymph node dissection for testis cancer. *J Urol.* 2004;171(5):1839-41.
13. Subramanian VS, Nguyen CT, Stephenson AJ, et al. Complications of open primary and post-chemotherapy retroperitoneal lymph node dissection for testicular cancer. *Urol Oncol.* 2010;28(5):504-9.
14. Baniel J, Foster RS, Rowland RG, et al. Complications of post-chemotherapy retroperitoneal lymph node dissection. *J Urol.* 1995;153(3 Pt 2):976-80.
15. Pettus JA, Carver BS, Masterson T, et al. Preservation of ejaculation in patients undergoing nerve-sparing postchemotherapy retroperitoneal lymph node dissection for metastatic testicular cancer. *Urology.* 2009;73(2):328-31; discussion 31-2.
16. Peckham MJ, McElwain TJ, Barrett A, et al. Combined management of malignant teratoma of the testis. *Lancet.* 1979;2(8137):267-70.
17. International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group. *J Clin Oncol.* 1997;15(2):594-603.

18. [dataset] SWEDISH & NORWEGIAN TESTICULAR CANCER PROJEKT  
“SWENOTECA. Behandling av non-seminomatös testikelcancer. SWENOTECA III och IV. 1999. <https://www.swenoteca.org/old-management-programs>
19. [dataset] SWENOTECA group. SWENOTECA VIII. A cancer care program. Non-seminomatous Germ Cell Tumours (NSGCT), V2; 2016.  
<https://www.swenoteca.org/nonseminoma>
20. [dataset] D. Mitropoulos, W. Artibani, M. Graefen, et al. EAU guidelines on Reporting and Grading of Complications after Urologic Surgical Procedures. 2016.  
<https://uroweb.org/wp-content/uploads/EAU-Guidelines-Reporting-Complications-2016.pdf>
21. Cho JS, Kaimakliotis HZ, Cary C, et al. Modified retroperitoneal lymph node dissection for post-chemotherapy residual tumour: a long-term update. *BJU Int.* 2017;120(1):104-8.

**Table 1. Baseline characteristics of study participants, according to bilateral and unilateral PC-RPLND.**

	<i>Bilateral PC-RPLND</i>	<i>Unilateral PC-RPLND</i>
<i>Number of cases</i>	87	231
<i>Age, years (IQR)</i>	31 (25-38)	29 (24-35)
<b><i>Royal Marsden Clinical Stage</i></b>		
<i>CSMK+</i>	0 /86	1/229
<i>CSII</i>	33/86 (38%)	141/229 (62%)
<i>CSIII</i>	13/86 (15%)	10/229 (4%)
<i>CSIV</i>	40/86 (47%)	77/229 (34%)
<b><i>Abdominal stage</i></b>		
<i>A</i>	4/86 (4.7%)	28/229 (12%)
<i>B</i>	34/86 (40%)	134/229 (59%)
<i>C</i>	26/86 (30%)	50/229 (22%)
<i>D</i>	22/86 (26%)	17/229 (7.4%)
<b><i>IGCCCG prognostic group</i></b>		
<i>Good</i>	37/86 (43%)	154/228 (68%)
<i>Intermediate</i>	22/86 (26%)	38/228 (17%)
<i>Poor</i>	27/86 (31%)	36/228 (16%)
<b><i>Chemotherapy <sup>a</sup></i></b>		
<i>Standard</i>	57/87 (66%)	188/231 (81%)
<i>Dose intensified (no HD)</i>	24/87 (28%)	31/231 (13%)
<i>Dose intensified (HD)</i>	6/87 (6.9%)	12/231 (5.2%)
<i>MK+</i>	12/85 (14%)	24/229 (10%)

Data are presented as numbers (%) unless otherwise specified.

Abbreviations: IQR=Inter quartile range, IGCCCG= International Germ Cell Consensus Classification, HD= High dose, MK+=elevated tumour markers at time of surgery

a, The SWENOTECA treatment algorithm was based on response evaluation and multiple step dose intensification in case of unsatisfactory tumour marker decline or response.

Standard initial treatment of metastatic NSGCT consists of BEP (Bleomycin, etoposide and cisplatin). Response evaluation after 2 cycles determined further treatment, good responders continued to receive additionally 1-2 cycles of BEP, whereas treatment was intensified in a step-wise manner for poor responders with addition of ifosfamide or paclitaxel in standard dose chemotherapy or high dose treatment with stem cell rescue.



**Table 2. Details regarding PC-RPLND surgery**

	<i>Bilateral PC-RPLND</i>	<i>Unilateral PC-RPLND</i>
<i>Duration of surgery, minutes (IQR)</i>	300 (214-405)	185 (150-240)
<i>Intraoperative bleeding, millilitres (IQR)</i>	700 (300-1800)	300 (200-700)
<i>Postoperative nights (IQR)</i>	8 (7-11)	7 (6-8)
<i>Number of dissected areas (IQR)</i>	8 (7-9)	5 (4-6)
<i>Dissection of areas 2,3,5,6<sup>a</sup></i>		
<i>Not over aortic midline</i>	1/87 (1%) <sup>b</sup>	70/231 (30%)
<i>One contralateral area</i>	4/87 (4,6%)	91/231 (39%)
<i>Two contralateral areas</i>	82/87 (94%)	70/231 (30%)
<i>Nerve-sparing technique (percent)</i>	18/80 (23%)	136/211 (64%)
<i>Suprahilar dissection (area 11 or 12)(percent)</i>	16/87 (18%)	19/231 (8.2%)
<i>Extended surgery (percent)</i>	14/87 (16%)	24/231 (10%)

a, Dissection in areas where sympathetic nerves are present. In our templates areas 2,3,5,6. “Not over aortic midline” means dissection of area 2 and 5 in a right sided unilateral PC-RPLND but not of 3 and 6. For a left sided unilateral PC-RPLND this corresponds to dissection of area 3 and 6 but not 2 and 5. “One contralateral area” means dissection of area 2 and 5 in a right sided unilateral PC-RPLND plus area 3 or 6. For a left sided unilateral PC-RPLND this corresponds to dissection of area 3 and 6 and 2 or 5.

b, Two patients had aborted surgery; one due to extensive extra lymphatic spread to iliopsoas and vena cava not seen on preoperative Computed tomography (CS4D poor prognosis), and the second due to aortic rupture (CS2D poor prognosis). Two patients had major retroperitoneal fibrosis and the surgery was considered non-radical (one unilateral and one bilateral). These four patients were included in the analysis.

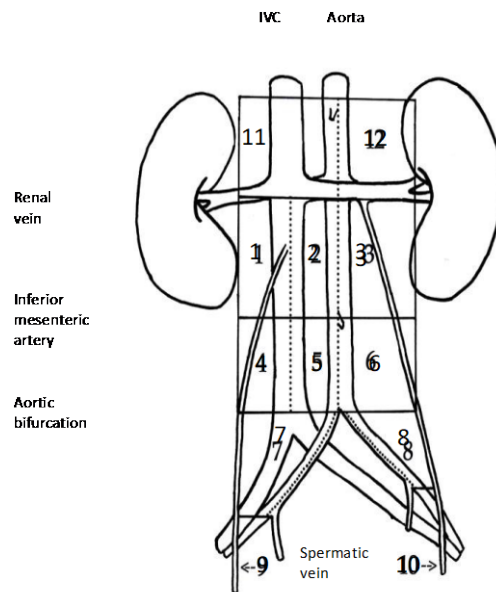
**Table 3. Intra- and postoperative complications after PC-RPLND.**

<i>Outcome</i>	<i>Bilateral PC-RPLND</i>	<i>Unilateral PC-RPLND</i>	<i>p-value</i>
<i>Intraoperative complication</i>	12/87 (14%)	10/231 (4.3%)	p=0.003
<i>Patients with any postoperative complication (0-30 days)</i>	39/87 (45%)	58/231 (25%)	p=0.001
<i>Patients with Clavien-Dindo <math>\geq 3b</math> (0-30 days)</i>	8/87 (9.2%)	5/231 (2.2%)	p=0.009
<i>Clavien-Dindo (0-30 days) <sup>a</sup> I</i>	7 (8%)	18 (7.8%)	
<i>II</i>	23 (26%)	24 (10%)	
<i>IIIa</i>	10 (11%)	16 (6.9%)	
<i>IIIb</i>	6 (6.9%)	4 (1.7%)	
<i>IV</i>	1 (1.1%)	2 (0.9%)	
<i>V</i>	1 (1.1%)	0 (0%)	
<i>Retrograde ejaculation</i>	42/71 (59%)	67/209 (32%)	
<i>Retrograde ejaculation (nerve-sparing technique)</i>	5/14 (36%)	36/130 (28%)	
<i>Not over aortic midline <sup>b</sup>, Retrograde ejaculation</i>	-	8/66 (12%)	
<i>Retrograde ejaculation (nerve-sparing technique)</i>		2/35 (6%)	
<i>One contralateral area, Retrograde ejaculation</i>	1/3 (33%)	29/86 (34%)	
<i>Retrograde ejaculation (nerve-sparing technique)</i>	0/1	23/69 (33%)	
<i>Two contralateral areas, Retrograde ejaculation</i>	41/68 (60%)	30/57 (53%)	
<i>Retrograde ejaculation (nerve-sparing technique)</i>	5/13 (38%)	11/26 (42%)	
<i>Fibrosis/necrosis/benign</i>	38/87 (44%)	102/231 (44%)	
<i>Teratoma</i>	37/87 (43%)	106/231 (46%)	
<i>Cancer</i>	12/87 (14%)	23/231 (10%)	

Intra- and postoperative complications after PC-RPLND. p-values calculated using  $\chi^2$ -test. a, all complications occurring during 0-30 days. A patient could have more than 1 complication.

b, Retrograde ejaculation depending on extent of dissection. Dissection in areas where sympathetic nerves are present. In our templates areas 2,3,5,6. "Not over aortic midline" means dissection of area 2 and 5 in a right sided unilateral PC-RPLND but not of 3 and 6. For a left sided unilateral PC-RPLND this corresponds to dissection of area 3 and 6 but not 2 and 5. "One contralateral area" means dissection of area 2 and 5 in a right sided unilateral PC-RPLND plus area 3 or 6. For a left sided unilateral PC-RPLND this corresponds to dissection of area 3 and 6 and 2 or 5.

**Figure 1. Templates for PC-RPLND**



Area	Cranial	Caudal	Lateral	Medial
1	RRV	Level of IMA	Right renal hilus/ureter	IVC midline
2	LRV	Level of IMA	IVC midline	AA midline
3	LRV	Level of IMA	Left renal hilus/ureter	AA midline
4	Level of IMA	Level of AA bifurcation	Right ureter	IVC midline
5	Level of IMA	AA bifurcation	IVC midline	AA midline
6	Level of IMA	AA bifurcation	Left ureter	AA midline
7	AA bifurcation	CIA bifurcation	Right ureter	CIA
8	AA bifurcation	CIA bifurcation	Left ureter	CIA
9	Right spermatic vein			
10	Left spermatic vein			
11		RRV	Level of Right renal hilus	AA midline
12		LRV	Level of Left renal hilus	AA midline

Template dissection. Bilateral PC-RPLND

D ■+■ + Spermatic vein.

Boundaries for right sided unilateral PC-RPLND ■ + Spermatic vein.

Boundaries for left sided unilateral PC-RPLND ■ + Spermatic vein.

Abbreviations: RRV=Right Renal Vein, LRV=Left Renal Vein, SMA=Superior Mesenteric Artery, IMA=Inferior Mesenteric Artery, IVC=Inferior Vena Cava, AA=Aortic Artery, CIA=Common Iliac Artery

Supplementary Table 1 Hospitals who performed PC-RPLND 2007-2014

	<i>Unilateral<sup>a</sup></i>	<i>Bilateral</i>
<b>Norway</b>		
<i>Aker Hospital, Oslo</i>	28 (24%)	8 (29%)
<i>Haukeland University Hospital, Bergen</i>	19 (16%)	5 (18%)
<i>The Norwegian Radium Hospital, Oslo</i>	43 (37%)	10 (36%)
<i>St Olav's University Hospital, Trondheim</i>	15 (13%)	2 (7%)
<i>University Hospital of North Norway, Tromsø</i>	12 (10%)	3 (11%)
<b>Sweden</b>		
<i>Karolinska University Hospital, Stockholm</i>	28 (25%)	15 (25%)
<i>Lund University Hospital, Lund</i>	8 (7%)	0
<i>Linköping University Hospital, Linköping</i>	6 (5%)	14 (24%)
<i>Malmö University Hospital, Malmö</i>	26 (23%)	20 (34%)
<i>Sahlgrenska University Hospital, Göteborg</i>	27 (24%)	5 (8.5%)
<i>Uppsala University Hospital, Uppsala</i>	19 (17%)	5 (8.5%)

<sup>a</sup>, Percentage of all cases per country performed with unilateral or bilateral post-chemo-retroperitoneal lymph node dissection (PC-RPLND)

Supplementary Table 2 Extended surgery

<i>Extended surgery</i>	<i>Unilateral</i>	<i>Bilateral</i>
<i>Lymph node dissection:</i>		
<i>Neck</i>	1	1
<i>Inguinal</i>	1	0
<i>Mediastinal</i>	1	0
<i>Mesenteric</i>	2	2
<i>Retrocrural</i>	1	1
<i>Supraclavicular</i>	1	0
<i>Hepatoduodenal ligament</i>	0	1
<i>Organ resection:</i>		
<i>Adrenalectomy</i>	4	0
<i>Resection renal vein</i>	1	0
<i>Resection of IVC</i>	1	1
<i>Thrombectomy IVC</i>	1	0
<i>Aortic embolectomy</i>	0	1
<i>Liver resection</i>	1	1
<i>Hemi hepatectomy</i>	1	0
<i>Colon resection</i>	0	1
<i>Duodenal resection</i>	0	1
<i>Nephrectomy</i>	4	2
<i>Ureteral resection</i>	2	0
<i>Vertebral tumour resection</i>	0	2
<i>Resection lung metastasis</i>	1	0
<i>Thoracotomy</i>	2	2
<i>Biopsy:</i>		
<i>Biopsy IVC</i>	1	0
<i>Liver biopsy</i>	0	1
<i>Omental biopsy</i>	1	0
<i>Mesenteric biopsy</i>	0	1

Supplementary Table 3 Intraoperative complication

<i>Intraoperative complication</i>	<i>Unilateral</i>	<i>Bilateral</i>
<i>Aortic perforation</i>	1	0
<i>Aortic injury</i>	0	1
<i>Aortic rupture</i>	0	1
<i>IVC injury</i>	0	4
<i>Transfusion</i>	4	2
<i>Renal artery injury</i>	2	1
<i>Renal vein injury</i>	1	1
<i>Ureteral injury</i>	2	4
<i>Duodenal injury</i>	0	2

Supplementary Table 4 Postoperative complications 0-30 days

<i>Postoperative complications 0-30 days</i>	<i>Unilateral</i>	<i>Bilateral</i>
<i>Clavien I</i>		
<i>Abdominal wall hematoma</i>	1	1
<i>Bell's palsy</i>	1	0
<i>Delayed wound healing</i>	1	0
<i>Drop foot</i>	0	1
<i>Fever</i>	1	0
<i>Hypokalaemia</i>	1	0
<i>Lymphatic leakage (prolonged drain removal)</i>	5	3
<i>Nausea</i>	1	1
<i>Numbness toes</i>	1	0
<i>Pain</i>	1	1
<i>Retroperitoneal bleeding at drain removal</i>	0	1
<i>Sub ileus</i>	1	0
<i>Wound secretion</i>	4	0
<i>Clavien II</i>		
<i>Postoperative transfusion</i>	2	7
<i>Clostridium difficile</i>	0	2
<i>Deep vein thrombosis</i>	1	0
<i>Depression</i>	0	1
<i>Epileptic seizures from embolus</i>	1	0
<i>Fever</i>	2	3
<i>Gastritis</i>	1	0
<i>Nausea</i>	0	1
<i>Pneumonia</i>	3	4
<i>Pulmonary oedema</i>	1	0
<i>Pulmonary embolus</i>	2	0
<i>Renal artery stenosis(hypertension)</i>	1	0
<i>Renal infarction</i>	3	0
<i>Urinary tract infection</i>	1	0
<i>Ventricular retention</i>	1	0
<i>Wound infection</i>	6	5
<i>Clavien IIIa</i>		
<i>Lymphatic leakage</i>	16	9
<i>Hydronephrosis</i>	0	1
<i>Peptic ulcer</i>	1	0
<i>Clavien IIIb</i>		
<i>Ileus</i>	0	2
<i>Compartment syndrome</i>	0	1

<i>Lymphatic leakage</i>	1	1
<i>Wound infection</i>	1	0
<i>Wound rupture</i>	2	2
<i>Clavien IV</i>		
<i>Acute renal failure</i>	1	0
<i>Postoperative bleeding</i>	1	0
<i>Respiratory failure</i>	0	1
<i>Clavien V</i>		
<i>Postoperative bleeding</i>	0	1