Perioperative complications and oncological outcomes of post-chemotherapy retroperitoneal lymph node dissection in patients with germ cell cancer at two high-volume university centres in Switzerland - a retrospective chart review

Notarfrancesco, Marco ; Fankhauser, Christian D ; Lorch, Anja ; Ardizzone, Davide ; Helnwein, Simon ; Hoch, Dennis ; Hermanns, Thomas ; Thalmann, George ; Beyer, Jörg

Abstract: BACKGROUND: Post-chemotherapy retroperitoneal lymph node dissection (PC-RPLND) is an integral part of the management of patients with metastatic non-seminoma and residual masses >1 cm after chemotherapy. AIMS: To assess perioperative complications and oncological outcomes at two major referral centres in Switzerland. METHODS: This was a retrospective chart review of 136 patients with non-seminoma who underwent PC-RPLND between 2010 and 2020 at the university hospitals of Bern and Zürich. Patient, treatment and tumour characteristics as well as the types and frequencies of intra- and postoperative complications were registered and compared using the chi-square test. Oncological outcomes consisted of the time and location of relapses as well as progression-free and overall survival, which were compared using the log-rank test. RESULTS: Overall, 70 patients from Bern and 66 patients from Zürich were included; 5 patients had a previous retroperitoneal lymph node dissection (RPLND) (2 Bern, 3 Zürich). Vascular injuries were the most frequent intraoperative complication, occurring in 27/136 (19.9%) patients. Postoperative complications were observed in 42/136 (30.9%) patients, ileus being the most common. Perioperative mortality was 2.2%. A retroperitoneal mass ≥50 mm was significantly associated with intraoperative complications (p = 0.004) and increased resource demands (p = 0.021). Postoperative morbidity was higher according to age at post-chemotherapy retroperitoneal lymph node dissection ≥40 years (p = 0.028) and retroperitoneal mass ≥20 mm (p = 0.005). The median follow-up time was 37 months (interquartile range [IQR] 18-64 months). The median progression-free survival at 5 years was 76% (95% confidence interval [CI]: 64-85%) in Bern and 69% (95% CI: 54-80%) in Zürich (p = 0.464). The median overall survival at 5 years was 88% (95% CI: 76-94%) in Bern and 77% (95% CI: 60-87%) in Zürich (p = 0.335). Patients with progressive disease or a tumour marker increase before retroperitoneal lymph node dissection had significantly inferior progression-free and overall survival compared to non-progressing patients. The presence of teratoma in resected specimens did not confer inferior survival probabilities compared to necrosis only, whereas the presence of vital undifferentiated tumour conferred inferior progression-free and overall survival. Patients with a previous retroperitoneal lymph node dissection and patients operated for late relapses >2 years after chemotherapy also had significantly inferior progression-free and overall survival. CONCLUSIONS: We found a relevant rate of severe perioperative complications at PC-RPLND at even experienced high-volume centres. The oncological outcomes at two major university urological centres in Switzerland were similar and determined by preoperative risk factors and intraoperative histology.

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Summary

BACKGROUND: Post-chemotherapy retroperitoneal lymph node dissection (PC-RPLND) is an integral part of the management of patients with metastatic non-seminoma and residual masses >1 cm after chemotherapy.

AIMS: To assess perioperative complications and oncological outcomes at two major referral centres in Switzerland.

METHODS: This was a retrospective chart review of 136 patients with non-seminoma who underwent PC-RPLND between 2010 and 2020 at the university hospitals of Bern and Zürich. Patient, treatment and tumour characteristics as well as the types and frequencies of intra- and postoperative complications were registered and compared using the chi-square test. Oncological outcomes consisted of the time and location of relapses as well as progression-free and overall survival, which were compared using the log-rank test.

RESULTS: Overall, 70 patients from Bern and 66 patients from Zürich were included; 5 patients had a previous retroperitoneal lymph node dissection (RPLND) (2 Bern, 3 Zürich). Vascular injuries were the most frequent intraoperative complication, occurring in 27/136 (19.9%) patients. Postoperative complications were observed in 42/136 (30.9%) patients, ileus being the most common. Perioperative mortality was 2.2%. A retroperitoneal mass ≥50 mm was significantly associated with intraoperative complications (p = 0.004) and increased resource demands (p = 0.021). Postoperative morbidity was higher according to age at post-chemotherapy retroperitoneal lymph node dissection ≥40 years (p = 0.028) and retroperitoneal mass ≥20 mm (p = 0.005). The median follow-up time was 37 months (interquartile range [IQR] 18–64 months). The median progression-free survival at 5 years was 76% (95% confidence interval [CI]: 64–85%) in Bern and 69% (95% CI: 54–80%) in Zürich (p = 0.464). The median overall survival at 5 years was 88% (95% CI: 76–94%) in Bern and 77% (95% CI: 60–87%) in Zürich (p = 0.335). Patients with progressive disease or a tumour marker increase before retroperitoneal lymph node dissection had significantly inferior progression-free and overall survival compared to non-progressing patients. The presence of teratoma in resected specimens did not confer inferior survival probabilities compared to necrosis only, whereas the presence of vital undifferentiated tumour conferred inferior progression-free and overall survival. Patients with a previous retroperitoneal lymph node dissection and patients operated for late relapses >2 years after chemotherapy also had significantly inferior progression-free and overall survival.

CONCLUSIONS: We found a relevant rate of severe perioperative complications at PC-RPLND at even experienced high-volume centres. The oncological outcomes at two major university urological centres in Switzerland were similar and determined by preoperative risk factors and intraoperative histology.

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Introduction

Germ cell tumours (GCT) are the most common solid malignancy in men 20 to 35 years of age and account for approximately 1% of all male malignancies [1]. An estimated 470 men were newly diagnosed with GCT every year in Switzerland between 2013 and 2017 [2].

Non-seminoma patients with metastatic disease are typically treated with cisplatin-based chemotherapy. Nevertheless, 25% to 50% of these patients will have residual retroperitoneal masses after chemotherapy [3, 4].

Guidelines recommend post-chemotherapy retroperitoneal lymphnode dissections (PC-RPLND) of residual retro-

peritoneal masses >1 cm (post-chemotherapy retroperitoneal lymph node dissection) for non-seminoma [5–7]. The ra-tionale for PC-RPLND is to remove lymph nodes that may contain viable cancer in 15% and teratoma in 45% of pa-tients [8]. Being resistant to chemotherapy, teratomas have the potential to grow, transform into malignancy, and re-lapse at a later time, if left unresected [9, 10]. The multidis-ciplinarity of this approach results in overall survival rates exceeding 90% and serves as a model for the treatment of other solid tumours [11].

Studies from high-volume centres report outcomes of PC-RPLND with complication rates ranging from 4% to 35% and a mortality rate of approximately 1% [12–18]. To our knowledge, there have been no such reports from Switzerland so far.

This study aimed to evaluate surgical complication rates and oncological outcomes after PC-RPLND at two university hospitals in Switzerland.

Patients and methods

As a quality control measure at the two participating institutions, we performed a retrospective chart review of in- and outpatient admissions of newly diagnosed germ cell tumour patients, tumour board protocols and operating room schedules at the departments of urology of the university hospitals in Bern and Zürich to identify all patients who underwent post-chemotherapy retroperitoneal lymph node dissection for germ cell tumours from 2010 to 2020. Subsequently, we reviewed all medical records of identified patients to capture information at baseline, pre and post surgery, and at follow-up using structured paper-based case report forms. A list of variables captured in the case report forms can be obtained by the corresponding author. Attempts were made to obtain missing clinical information by contacting referring or follow-up institutions. Data from patients with a second PC-RPLND during the study period were also captured but not included in the final data analysis. All captured data was subsequently entered by one of the authors (MN) into a central SPSS database (IBM SPSS Statistics, IBM Corp., Chicago, IL, USA, Version 28.0.1.1). Plausibility checks and extensive data cleaning to correct entry errors were performed by two of the authors (MN and JB) before analysis. The database was locked to entries on April 22nd 2022.

Baseline and pre-operative characteristics included the site and histology of the primary tumour, clinical staging information, the International Germ Cell Cancer Collaborative Group (IGCCCG) prognostic classification, number of cycles and type of chemotherapy, and serum tumour marker levels pre-chemotherapy and pre-operatively. Normal serum tumour marker levels were defined as alpha-fetoprotein (AFP) less than 10 µg/l and human chorionic gonadotropin (H CG) less than 5 U/l. The size of a retroperitoneal mass at diagnosis and before retroperitoneal lymph node dissection was determined by measuring the largest short-axis diameter of the retroperitoneal mass on computed tomography (CT) imaging. Measurements in the craniocaudal axis were not considered.

According to the guidelines of the European Germ Cell Cancer Consensus Group (EGCCCG), PC-RPLND was indicated in non-seminoma patients with residual retroperitoneal masses larger than 1 cm [5]. Surgical templates were chosen by the lead surgeon according to guidelines based on the sidedness of the primary tumour, the location and the size of the residual mass. Surgical reports were reviewed for information on the resection area (template), additional procedures and intraoperative complications. Further perioperative outcomes included intraoperative blood loss, operative time and length of hospital stay. Postoperative complications were recorded until the day of discharge and graded according to the classification by Clavien and Dindo [19]. If a patient had more than one complication, the highest grading was taken for further analysis. Postoperative ileus was radiologically confirmed, defined as the requirement for a nasogastric tube, or defined when the passage of flatus or stool and tolerance of an oral diet did not occur until day 4 postoperatively. [20]. All available records were analysed for late complications and readmission up to 90 days after surgery.

Outcomes of interest were the occurrence of intraoperative complications (defined as an estimated blood loss ≥1000 ml, any reported intraoperative injuries or the need for relaparotomy), the occurrence of any postoperative complication, increased resource demands (defined as a length of postoperative stay in the intensive care unit >1 day, total length of postoperative stay >7 days or readmission within 90 days) and oncological outcomes. Oncological outcomes consisted of type and localisation of relapse and progression-free and overall survival probabilities. Progression-free survival (PFS) started on the day of PC-RPLND and ended on the day of documented progression or death. Progression was defined as serological or radiological, whichever occurred first. Overall survival (OS) started on the day of PC-RPLND and ended on the day of the last follow-up visit. A patient was declared lost to follow-up if we were unable to obtain information about his follow-up status despite contacting follow-up institutions, or if he did not return to the follow-up institution for further visits. Patients lost to follow-up were censored at the time of their last contact. Missing data is indicated in the tables wherever appropriate. We undertook no measures to replace or do substitute calculations for any missing values.

Descriptive statistical analyses were performed on relevant parameters. Significance was tested using Pearson's χ^2-test of independence and Fisher's exact test for categorical variables and the Mann-Whitney U test for metric variables. PFS and OS probabilities were analysed using the Kaplan-Meier method. The significance of survival analyses was tested using the log-rank test. A two-sided p-value of <0.05 was considered significant. All tests were performed using the SPSS (IBM SPSS Statistics, IBM Corp., Chicago, IL, USA, Version 28.0.1.1) and STATA (StataCorp LLC, College Station, TX, USA, Version 10.1, 2008) software packages. Due to the design of the study, all statistical analyses must be considered hypothesis-generating.

The study was approved by the local ethical committee (BASEC ID 2020-02237). All patients gave written general consent.

Results

Patients and baseline characteristics

A total of 136 patients were identified and included in the study: 70 patients from Bern and 66 patients from Zürich. They underwent a total of 141 PC-RPLND; 5 second PC-RPLNDs were excluded from the analysis.

The overall median (range) age at PC-RPLND was 31.3 (17.3–69.8) years; 101/136 (74.3%) of patients were <40 years old. The primary site of the tumour was the testis in 94.6% of patients, and 89.7% of histopathology results at orchiectomy revealed non-seminoma. PC-RPLND for patients with pure seminoma at initial diagnosis was performed in 10/136 (7.4%) patients. The histopathological results of the resected specimens of those 10 seminoma patients eventually showed teratoma in 2, seminoma in 2, and necrosis or fibrosis in the remaining 6.

Preoperative variables

All patients received systemic chemotherapy before RPLND consisting of a median (range) of 4 (1–18) treatment cycles: 118/136 (86.8%) received first-line chemotherapy, 15/136 (11.0%) had one additional salvage chemotherapy, 2 had a second salvage chemotherapy, and 1 was treated with a third salvage chemotherapy before PC-RPLND. Overall, 12/136 (8.8%) patients received high-dose chemotherapy, either upfront or in addition to conventional-dose chemotherapy. No significant association existed between treatment with high-dose chemotherapy and the occurrence of intra- or postoperative complications. The median time from the end of chemotherapy to PC-RPLND was shorter for Zürich than for Bern (2.1 months vs 6.2 months, p <0.001).

Overall, preoperative AFP levels were elevated in 16/136 (11.8%) patients, and HCG levels were elevated in 6/136 (4.4%) patients. Half of all the patients with elevated tumor markers had increasing markers before surgery.

The size of the residual retroperitoneal mass before PC-RPLND did not significantly differ between Bern and Zürich. Preoperative imaging studies showed increasing size in 38/136 (27.9%) of all patients compared to previously obtained images.

Data on patients' baseline and preoperative characteristics are shown in table 1 and supplementary tables 1 and 2.

Surgical variables

Overall, 77/136 (56.6%) patients had a stable partial response with negative tumour markers after chemotherapy. In 26/136 (19.1%) patients, a growing teratoma syndrome was suspected. Overall, 20/136 (14.7%) patients had a relapse more than 2 years after the initial remission and were considered a late relapse before surgery; 5/136 (3.7%) were treated as a redo procedure, i.e., they had undergone a previous retroperitoneal lymph node dissection before the study period elsewhere (see table 2).

Table 1:
Patients' baseline and preoperative characteristics.

			Bern	Zürich	Overall
			n = 70 (51.5%)	n = 66 (48.5%)	n = 136 (100%)
Age at PC-RPLND (years), median (range)			30.7 (17.3–63.8)	31.8 (17.6–69.8)	31.3 (17.3–69.8)
Body mass index at PC-RPLND (kg/m^2), median (range)			25.9 (17.7–39.5)	25.5 (19.6–36.5)	25.6 (17.7–39.5)
Site of primary tumour, number (%)	Gonadal		67 (95.7)	62 (93.9)	129 (94.9)
	Primary retroperitoneal		3 (4.3)	4 (6.1)	7 (5.1)
Histopathology subtype and pattern in primary tumour, number (%)	Pure seminoma		7 (10.0)	3 (4.5)	10 (7.4)
	Non-seminoma/mixed germ cell tumour		61 (87.1)	61 (92.4)	122 (89.7)
	Non-seminoma with teratomatous elements		35 (50.0)	35 (53.0)	70 (51.5)
	Burned-out tumour/scar only		2 (2.9)	2 (3.0)	4 (2.9)
Type of chemotherapy regimen before PC-RPLND, number (%)	Primary chemotherapy		56 (80.0)	62 (94.0)	118 (86.8)
	First salvage chemotherapy		13 (18.6)	2 (3.0)	15 (11.0)
	Second and third salvage chemotherapy		1 (1.4)	2 (3.0)	3 (2.2)
Time from end of chemotherapy to PC-RPLND (months), median (range)			6.2 (0.5–54.2)	2.3 (0.5–327.6)	3.8 (0.5–327.6)
Serum tumour markers at PC-RPLND	AFP elevated (≥10 µg/l)	Number (%)	9 (12.9)	7 (10.6)	16 (11.8)
		Increasing marker levels	5 (7.1)	3 (4.5)	8 (5.9)
		Median (range)	253.8 (19.7–853)	48.0 (12.8–13,860)	97.0 (12.8–13,860)
	HCG elevated (≥5 U/l)	Number (%)	4 (5.7)	2 (3.0)	6 (4.4)
		Increasing marker levels	3 (4.3)	–	3 (2.2)
		Median (range)	62.0 (5.0–691.0)	157.5 (8.0–307.0)	62.0 (5.0–691.0)
Largest diameter of retroperitoneal mass at PC-RPLND (mm), median (range)*			33.0 (8–160)	31.0 (8–126)	32.0 (8–160)
Trend of retroperitoneal mass before PC-RPLND, number (%)	Increasing		21 (30.0)	17 (25.8)	38 (27.9)
	Decreasing		20 (28.6)	37 (56.1)	57 (41.9)
	Stable		29 (41.4)	9 (13.6)	38 (27.9)
	Mixed response		–	2 (3.0)	2 (1.5)
	Missing values		–	1 (1.5)	1 (0.7)

PC-RPLND: post-chemotherapy retroperitoneal lymph node dissection; AFP: alpha-fetoprotein; HCG: human chorionic gonadotropin

* Corresponds to the largest short-axis diameter (anterior–posterior [sagittal] and lateral [transverse] axis). Measurements in the craniocaudal (longitudinal) axis were not considered.

Open surgery was performed in 129/136 (94.9%) patients, with 1 robotic PC-RPLND in Bern and 4 laparoscopic and 2 robotic PC-RPLND in Zürich. No conversion to open surgery was required in those 7 patients. Overall, the median (range) operating time was 300 (90–975) minutes (275 minutes in Bern vs 310 minutes in Zürich, p = 0.014). In 26/136 (19.1%) patients, the intervention required ≥7 hours. The median (range) estimated intraoperative blood loss was 500 (0–21,500) ml. In 98/125 (78.4%) procedures, the blood loss was <1000 ml, resulting in 112/125 (89.6%) patients who did not need any red blood cell transfusions. Detailed information on the surgical variables is presented in supplementary tables 3 and 4.

Overall, 32/136 (23.5%) patients had a total of 52 major additional procedures during PC-RPLND (figure 1). Vascular resections of smaller vessels than the aorta or inferior vena cava (IVC) were not counted. More aortic resections and repairs were performed in Zürich than Bern (9/66 [13.6%] vs 2/70 [2.9%], p = 0.021). The rate of caval resection and repair was almost identical at the two centres (6/70 [8.6%] in Bern and 6/66 [9.1%] in Zurich). A nephrectomy was performed in 6/136 (4.4%) of patients.

The most frequent intraoperative complication at both centres was a vascular injury (19.9% overall, 23.3% in Bern and 18.3% in Zürich; figure 2 and supplementary table 5). The most frequently injured vessel was the renal vein in 10/136 (7.4%) of patients, followed by the IVC in 7/136 (5.1%), and the aorta in 6/136 (4.4%). Gastrointestinal and urogenital injuries were rare, with overall rates of 2.3% and 1.6%, respectively. Overall, more intraoperative complications occurred in patients with a pre-operative retroperitoneal mass ≥50 mm (20/32 [62.5%] vs 31/93 [33.3%], p = 0.004) and those who underwent a bilateral template (27/49 [55.1%] vs 24/77 [31.2%], p = 0.008).

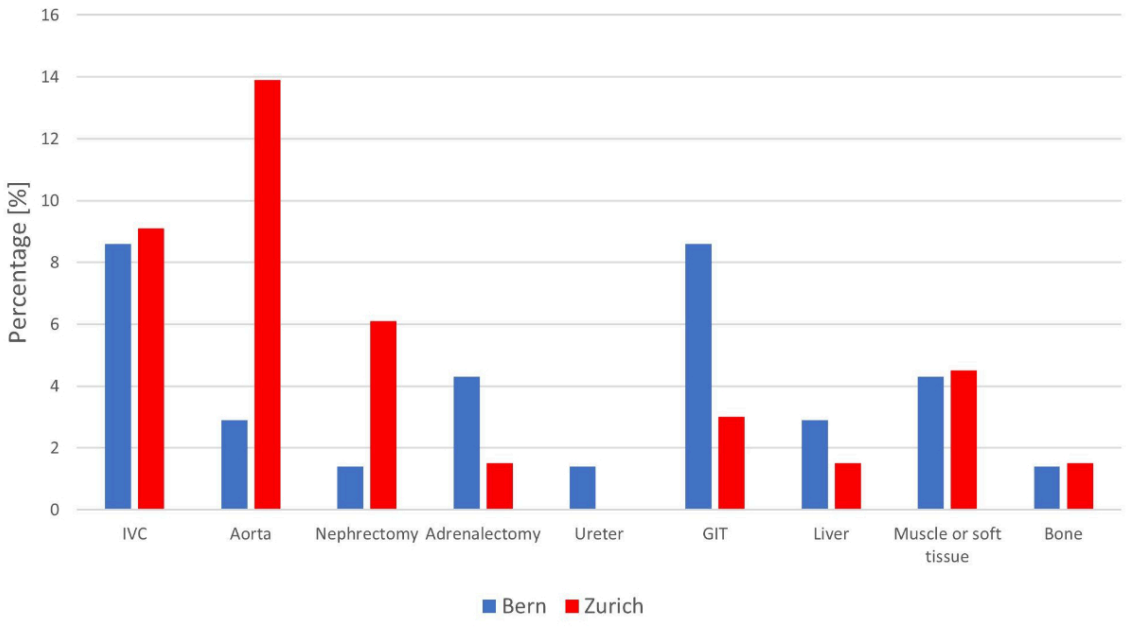
Table 2:
Surgical data post-chemotherapy retroperitoneal lymph node dissection.

		Bern	Zürich	Overall
		n = 70 (51.5%)	**n = 66 (48.5%)**	**n = 136 (100%)**
Remission status/indication for PC-RPLND, number (%)	Partial response marker negative	35 (50.0)	42 (63.6)	77 (56.6)
	Progressive disease	24 (34.3)	20 (30.3)	44 (32.3)
	– Suspected growing teratoma syndrome	17 (24.3)	9 (13.6)	26 (19.1)
	Late relapse	11 (15.7)	9 (13.6)	20 (14.7)
	Redo RPLND*	2 (2.9)	3 (4.5)	5 (3.7)
Modus of surgery, number (%)	Open	69 (98.6)	60 (90.9)	129 (94.9)
	Minimal invasive	1 (1.4)	6 (9.1)	7 (5.1)
Operative time (minutes), median (range)		275 (140–740)	310 (90–975)	300 (90–975)
Estimated intraoperative blood loss (ml), median (range)		500 (30–21,500)	500 (0–8000)	500 (0–21,500)
Patients with intraoperative blood transfusion, number (%)		7 (10.0)	6 (9.1)	13 (9.6)
Retroperitoneal histology, number (%)	Mature teratoma	37 (52.9)	33 (50.0)	70 (51.5)
	Fibrosis/necrosis	21 (30.0)	20 (30.3)	41 (30.1)
	Vital GCT	12 (17.1)	13 (19.7)	25 (18.4)

PC-RPLND: post-chemotherapy retroperitoneal lymph node dissection; GCT: germ cell tumour

* Not including redo PC-RPLNDs of patients who underwent PC-RPLND twice in the study period

Figure 1: Additional procedures during post-chemotherapy retroperitoneal lymph node dissection by centre (IVC: inferior vena cava; GIT: gastrointestinal tract).



Postoperative variables and complications

The overall median (range) length of stay was 7 (2–60) days, with a median (range) of 1 (0–51) days in intermediate or intensive care. Overall, 9/136 (6.6%) patients were readmitted to the hospital within 90 days after PC-RPLND due to chylous ascites or lymphocele (n = 4), ileus (n = 3), sepsis (n = 1) and pain (n = 1; supplementary table 6).

A total of 81 complications were reported in 42/136 (30.9%) patients (figure 3 and supplementary table 7). More patients had reported complications in Zürich than in Bern (28/66 [42.4%] vs 14/70 [20.0%], p = 0.005). However, 94/136 (69.1%) of all patients had no postoperative complications reported. The reported complications were classified as major (≥Clavien III) in 13/42 (31%) patients, the most common being a postoperative ileus.

Three patients died of perioperative complications during their hospital stay, resulting in an overall mortality rate of 2.2%. One patient developed aspiration pneumonia and a central pulmonary embolism, one patient with wide resection of the aorta and inferior vena cava died from an infection of the vascular graft, and a third patient developed ventilator-associated pneumonia and fatal sepsis.

Histopathological findings

The histopathological report showed teratoma in 70 patients (51.5%), fibrosis or necrosis only in 41 (30.1%) patients, and viable cancer in 25 patients (18.4%; table

Figure 2: Intraoperative complications during post-chemotherapy retroperitoneal lymph node dissection by centre.

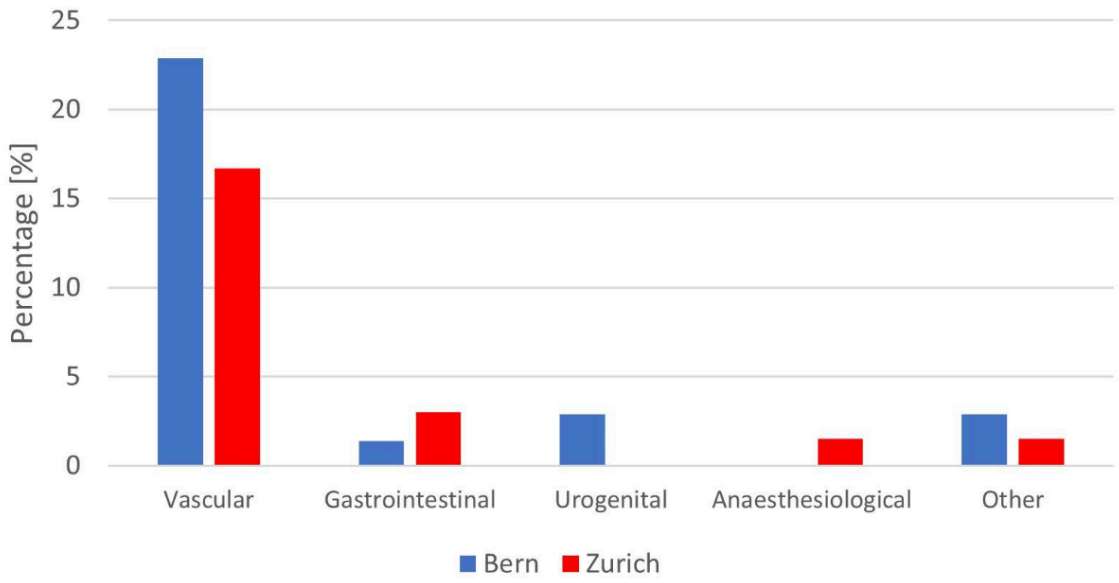
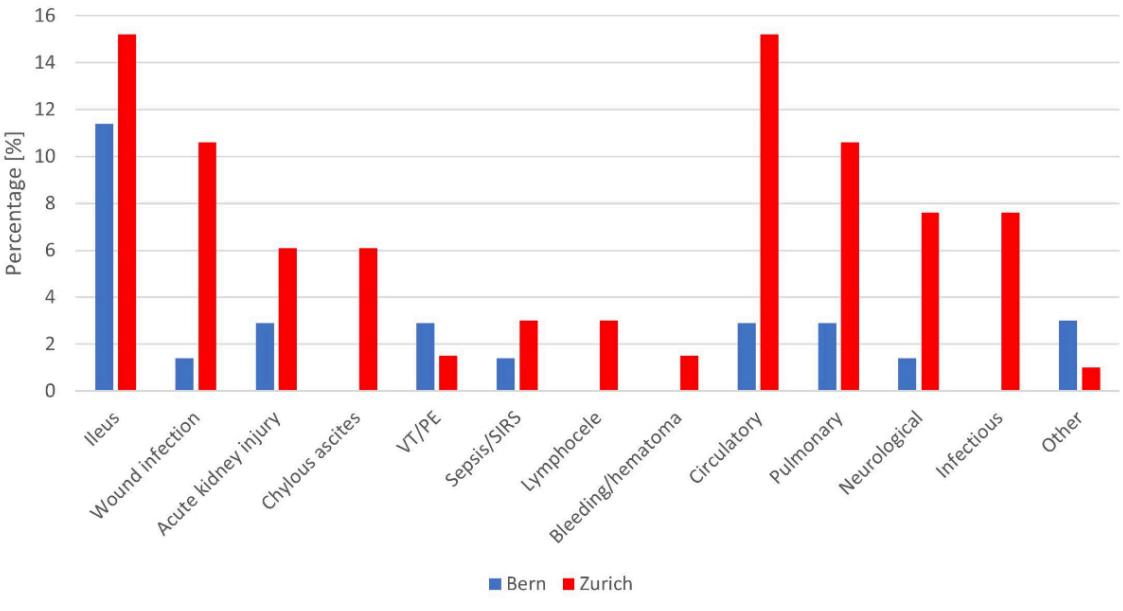


Figure 3: Postoperative complications after post-chemotherapy retroperitoneal lymph node dissection by centre (VT/PE: venous thromboembolism/pulmonary embolism; SIRS: systemic inflammatory response syndrome).



2), with no difference between the two centres. Teratoma was more frequently found in patients with a preoperative retroperitoneal mass ≥50 mm (25/33 [75.8%] vs 54/102 [52.9%], p = 0.021) and radiological progression of the mass prior to PC-RPLND (32/38 [84.2%] vs 48/98 [49.0%], p <0.001). Vital tumour occurred more frequently in patients with a preoperative retroperitoneal mass ≥50 mm (10/33 [30.3%] vs 15/102 [14.7%], p = 0.045) and elevated increasing serum tumour markers prior to RPLND (8/10 [80%] vs 17/126 [13.5%], p <0.001).

Oncological outcomes

The median (range) follow-up was 37.2 (0.1–142.1) months, with no difference between Bern and Zürich. Until April 22nd 2022, 26 (19%) patients were lost to follow-up and censored at the time of last contact.

Relapses during follow-up occurred in 28/136 (20.6%) patients (see supplementary table 8); 14/136 (10.3%) had a retroperitoneal relapse (7 after bilateral template, 7 after unilateral template), of whom 12/14 (85.7%) were in the former surgical field (in-field relapse). Another 15/136 (11.0%) patients had a relapse outside the retroperitoneum, including the liver, thorax, lung or brain, or tumour marker progression only. Of relapsing patients, 13/28 (46.4%) died due to disease progression. The median (range) time to relapse was 5.8 (0.7–56.1) months, and 26/28 (92.9%) relapses occurred within 24 months after PC-RPLND.

The occurrence of relapse was associated with a preoperative retroperitoneal mass ≥50 mm (12/33 [36.4%] vs 16/102 [15.7%], p <0.011), PC-RPLND performed for a late relapse (10/20 [50.0%] vs 18/116 [15.5%], p = 0.001) and the occurrence of vital cancer in the resected specimen at PC-RPLND (14/25 [56.0%] vs 14/111 [12.6%], p <0.001).

Overall survival and progression-free survival at 5 years were similar in Zürich and Bern (figure 4 and supplementary figure 1). Patients with progressive disease in the preoperative imaging or increasing elevated serum tumour markers before PC-RPLND had significantly inferior survival probabilities at 5 years compared to non-progressing patients (supplementary figures 2 to 5). The presence of teratoma in the resected specimens did not confer inferior survival probabilities compared to patients with necrosis or fibrosis, whereas patients with vital tumour had inferior progression-free and overall survival (figure 5 and supplementary figure 6). Patients who underwent RPLND for a late relapse also had significantly inferior progression-free and overall survival (supplementary figures 7 and 8).

Progression-free and overall survival were not statistically different in patients resected within 3 months after the end of chemotherapy compared to within 1 year among 74 patients with normal serum tumour markers and no radiological progression before surgery.

Discussion

This is the first analysis reporting on perioperative morbidity and oncological outcomes of patients with germ cell tumours undergoing PC-RPLND at two high-volume centres in Switzerland. In accordance with published results, expert surgery contributed to high long-term progression-free and overall survival probabilities of 72% and 84% at 5 years, respectively. However, despite surgical expertise, a significant rate of around 30% perioperative complications at PC-RPLND and a mortality rate of 2% supports the centralisation of such procedures, as has been suggested previously [13, 16, 18].

Vascular injuries represent the largest group among intraoperative complications, in around 20% of patients. This is not surprising because lymph nodes in the retroperitoneum are in direct proximity to the major abdominal vessels, and residual nodal masses may invade local structures, including the aorta and vena cava. In addition, a possible severe desmoplastic reaction induced by chemotherapy can impair the meticulous dissection of the layers around the vessels during PC-RPLND [21]. Thus, when performing PC-RPLND, expertise and familiarity with the specific surgical techniques of this intervention are essential.

The complication rate was higher in patients with larger preoperative retroperitoneal masses >5 cm, which is in accordance with published data. Heidenreich et al. reported complication rates of up to 41.7% in a group of 25 patients with a median mass size of 186 mm [22]. All 25 patients in this series underwent additional procedures (vascular, skeletal, pancreaticoduodenal surgery). In the subgroup of patients who underwent additional procedures during PC-

Figure 4: Kaplan–Meier analysis of overall survival probabilities by centre. Bern overall survival at 5 years 88% (95% CI: 76–94%), Zürich overall survival at 5 years 77% (95% CI: 60–87%), p = 0.335 for difference.

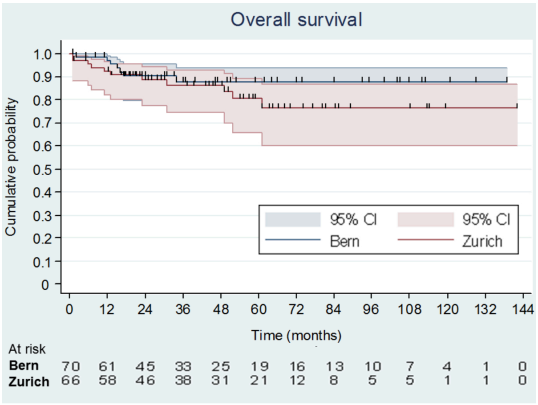
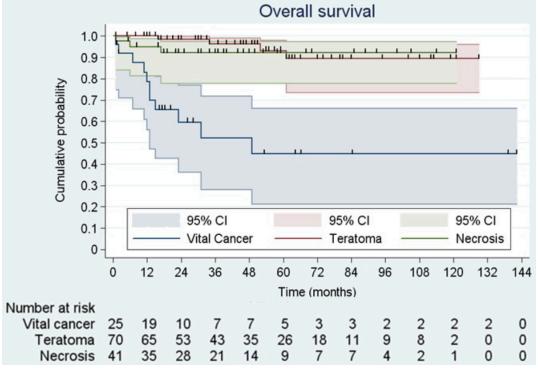


Figure 5: Kaplan-Meier analysis of overall survival after stratification for histology in the resected specimen. Vital cancer overall survival at 5 years 45% (95% CI: 21–66%); teratoma overall survival at 5 years 90% (95% CI: 73–96%); necrosis overall survival at 5 years 93% (95% CI: 78–97%); p <0.001 for difference between teratoma or necrosis and vital cancer



RPLND in our study cohort, the complication rate reached 56.3%.

Two systematic reviews have reported overall complication rates of 21.8% for PC-RPLND: 29% for unilateral and 52% for more extended bilateral template PC-RPLND, similar to our series [16, 23]. However, different definitions used by the various study groups, different grading of complications, and different accuracy in documenting the intra- and postoperative course may lead to variations in reporting of complications. This may have contributed to the observed differences in complication rates also at the two centres studied in our cohort [24].

Histopathological analysis of the resected specimen at PC-RPLND revealed vital cancer in 18.4% of patients, mature teratoma in 51.5%, and fibrosis or necrosis in 30.1%. Teratoma and viable cancer were more frequent in patients with large retroperitoneal masses before PC-RPLND and progression before PC-RPLND. Similar correlations have been identified by the German Testicular Cancer Study Group and others [25–29]. However, at present, no preoperative variable can be used safely to exclude patients with residual masses >1 cm from PC-RPLND.

Oncological outcomes at both institutions of the present cohort were similar and determined by preoperative risk factors and intraoperative histology. In contrast to teratoma or necrosis and fibrosis, vital cancer in the resected specimen was associated with significantly inferior survival probabilities, similar to patients with progressive disease before surgery and those undergoing PC-RPLND for late relapse. Therefore, according to guidelines, patients with residual masses >1 cm should be scheduled for PC-RPLND early and not later than 3 months after chemotherapy.

The quality of surgery and the meticulous dissection of the surgical template are of paramount importance for oncological outcomes but were difficult to measure in this retrospective analysis. Overall, 8.8% of patients experienced an in-field relapse. Enlarging the extent of resection would have potentially prevented a relapse in 2/14 patients who suffered abdominal relapses outside their initially chosen resection area (out-of-field-relapse).

A limitation of the present analysis is its retrospective nature. Particularly, adherence to published templates and the quality of surgery was difficult to assess retrospectively because we had to rely on written surgical reports, which did not always report all relevant information in a structured fashion. Furthermore, compared to published reports, patient numbers are small in Switzerland, making a more detailed comparison between the two centres difficult. In particular, the small sample size prevented a multivariable analysis, which would have been desirable to fully assess the contribution of individual variables impacting progression-free and overall survival. Follow-up data was incomplete in many patients, and 19.1% of patients had to be censored due to missing follow-up. Finally, we could not extract important quality-of-life data, such as retrograde ejaculation and long-term satisfaction with the procedure, which will be the subject of a prospective data collection.

In conclusion, we have demonstrated excellent oncological outcomes and acceptable rates of perioperative morbidity and mortality at two major urological centres in Switzerland, which were comparable to reports from major international centres.

Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest was disclosed.

References

1. Siegel RL , Miller KD , Fuchs HE , Jemal A . Cancer Statistics, 2021. CA Cancer J Clin. 2021 Jan;71(1):7–33. http://dx.doi.org/10.3322/caac.21654.
2. Bundesamt für Statistik / Nationale Krebsregistrierungsstelle. Krebs, Neuerkrankungen und Sterbefälle: Anzahl, Raten, Medianalter und Risiko pro Krebslokalisation. (2020).
3. de Wit R , Stoter G , Kaye SB , Sleijfer DT , Jones WG , ten Bokkel Huinink WW , et al. Importance of bleomycin in combination chemotherapy for good-prognosis testicular nonseminoma: a randomized study of the European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group. J Clin Oncol. 1997 May;15(5):1837–43. http://dx.doi.org/10.1200/JCO.1997.15.5.1837.
4. Culine S , Kerbrat P , Kramar A , Théodore C , Chevreau C , Geoffrois L , et al.; Genito-Urinary Group of the French Federation of Cancer Center (GETUG T93BP) . Refining the optimal chemotherapy regimen for good-risk metastatic nonseminomatous germ-cell tumors: a randomized trial of the Genito-Urinary Group of the French Federation of Cancer Centers (GETUG T93BP). Ann Oncol. 2007 May;18(5):917–24. http://dx.doi.org/10.1093/annonc/mdm062.
5. Krege S , Beyer J , Souchon R , Albers P , Albrecht W , Algaba F , et al. European consensus conference on diagnosis and treatment of germ cell cancer: a report of the second meeting of the European Germ Cell Cancer Consensus Group (EGCCCG): part II. Eur Urol. 2008 Mar;53(3):497–513. http://dx.doi.org/10.1016/j.eururo.2007.12.025.
6. Honecker F , Aparicio J , Berney D , Beyer J , Bokemeyer C , Cathomas R , et al. ESMO Consensus Conference on testicular germ cell cancer: diagnosis, treatment and follow-up. Ann Oncol. 2018 Aug;29(8):1658–86. http://dx.doi.org/10.1093/annonc/mdy217.
7. EAU Guidelines on Testicular Cancer. EAU Guidelines Office, Arnhem, The Netherlands, 2021.
8. C. T. Nguyen , A. J. Stephenson , Role of postchemotherapy retroperitoneal lymph node dissection in advanced germ cell tumors. Hematol Oncol Clin North Am 25, 593-604, ix (2011). http://dx.doi.org/10.1016/j.hoc.2011.03.002.
9. Motzer RJ , Amsterdam A , Prieto V , Sheinfeld J , Murty VV , Mazumdar M , et al. Teratoma with malignant transformation: diverse malignant histologies arising in men with germ cell tumors. J Urol. 1998 Jan;159(1):133–8. http://dx.doi.org/10.1016/S0022-5347(01)64035-7.
10. Oldenburg J , Alfsen GC , Waehre H , Fosså SD . Late recurrences of germ cell malignancies: a population-based experience over three decades. Br J Cancer. 2006 Mar;94(6):820–7. http://dx.doi.org/10.1038/sj.bjc.6603014.
11. Tandstad T , Kollmannsberger CK , Roth BJ , Jeldres C , Gillessen S , Fizazi K , et al. Practice Makes Perfect: The Rest of the Story in Testicular Cancer as a Model Curable Neoplasm. J Clin Oncol. 2017 Nov;35(31):3525–8. http://dx.doi.org/10.1200/JCO.2017.73.4723.
12. Mosharafa AA , Foster RS , Koch MO , Bihrle R , Donohue JP . Complications of post-chemotherapy retroperitoneal lymph node dissection for testis cancer. J Urol. 2004 May;171(5):1839–41. http://dx.doi.org/10.1097/01.ju.0000120141.89737.90.
13. Subramanian VS , Nguyen CT , Stephenson AJ , Klein EA . Complications of open primary and post-chemotherapy retroperitoneal lymph node dissection for testicular cancer. Urol Oncol. 2010;28(5):504–9. http://dx.doi.org/10.1016/j.urolonc.2008.10.026.
14. Winter C , Raman JD , Sheinfeld J , Albers P . Retroperitoneal lymph node dissection after chemotherapy. BJU Int. 2009 Nov;104(9b 9 Pt B):1404–12. http://dx.doi.org/10.1111/j.1464-410X.2009.08867.x.
15. Heidenreich A , Albers P , Hartmann M , Kliesch S , Kohrmann KU , Krege S , et al.; German Testicular Cancer Study Group . Complications of primary nerve sparing retroperitoneal lymph node dissection for clinical stage I nonseminomatous germ cell tumors of the testis: experience of the German Testicular Cancer Study Group. J Urol. 2003 May;169(5):1710–4. http://dx.doi.org/10.1097/01.ju.0000060960.18092.54.
16. Rosenvilde JJ , Pedersen GL , Bandak M , Lauritsen J , Kreiberg M , Wagner T , et al. Oncological outcome and complications of post-

chemotherapy retroperitoneal surgery in non-seminomatous germ cell tumours - a systematic review. Acta Oncol. 2021 Jun;60(6):695–703. http://dx.doi.org/10.1080/0284186X.2021.1905176.

17. Wells H , Hayes MC , O'Brien T , Fowler S . Contemporary retroperitoneal lymph node dissection (RPLND) for testis cancer in the UK - a national study. BJU Int. 2017 Jan;119(1):91–9. http://dx.doi.org/10.1111/bju.13569.
18. Cary C , Masterson TA , Bihrle R , Foster RS . Contemporary trends in postchemotherapy retroperitoneal lymph node dissection: additional procedures and perioperative complications. Urol Oncol. 2015 Sep;33(9):389.e15–21. http://dx.doi.org/10.1016/j.urolonc.2014.07.013.
19. Dindo D , Demartines N , Clavien PA . Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004 Aug;240(2):205–13. http://dx.doi.org/10.1097/01.sla.0000133083.54934.ae.
20. Vather R , Trivedi S , Bissett I . Defining postoperative ileus: results of a systematic review and global survey. J Gastrointest Surg. 2013 May;17(5):962–72. http://dx.doi.org/10.1007/s11605-013-2148-y.
21. Macleod LC , Rajanahally S , Nayak JG , Parent BA , Ramos JD , Schade GR , et al. Characterizing the Morbidity of Postchemotherapy Retroperitoneal Lymph Node Dissection for Testis Cancer in a National Cohort of Privately Insured Patients. Urology. 2016 May;91:70–6. http://dx.doi.org/10.1016/j.urology.2016.01.010.
22. Heidenreich A , Haidl F , Paffenholz P , Pape C , Neumann U , Pfister D . Surgical management of complex residual masses following systemic chemotherapy for metastatic testicular germ cell tumours. Ann Oncol. 2017 Feb;28(2):362–7. http://dx.doi.org/10.1093/annonc/mdw605.
23. Haarsma R , Blok JM , van Putten K , Meijer RP . Clinical outcome of post-chemotherapy retroperitoneal lymph node dissection in metastatic nonseminomatous germ cell tumour: A systematic review. Eur J Surg Oncol. 2020 Jun;46(6):999–1005. http://dx.doi.org/10.1016/j.ejso.2020.02.035.
24. Cary C , Foster RS , Masterson TA . Complications of Retroperitoneal Lymph Node Dissection. Urol Clin North Am. 2019 Aug;46(3):429–37. http://dx.doi.org/10.1016/j.ucl.2019.04.012.
25. Beck SD , Foster RS , Bihrle R , Ulbright T , Koch MO , Wahle GR , et al. Teratoma in the orchiectomy specimen and volume of metastasis are predictors of retroperitoneal teratoma in post-chemotherapy nonseminomatous testis cancer. J Urol. 2002 Oct;168(4 Pt 1):1402–4. http://dx.doi.org/10.1016/S0022-5347(05)64458-8.
26. Steyerberg EW , Vergouwe Y , Keizer HJ , Habbema JD , Group RS ; ReHiT Study Group . Residual mass histology in testicular cancer: development and validation of a clinical prediction rule. Stat Med. 2001 Dec;20(24):3847–59. http://dx.doi.org/10.1002/sim.915.
27. Carver BS , Bianco FJ Jr , Shayegan B , Vickers A , Motzer RJ , Bosl GJ , et al. Predicting teratoma in the retroperitoneum in men undergoing post-chemotherapy retroperitoneal lymph node dissection. J Urol. 2006 Jul;176(1):100–3. http://dx.doi.org/10.1016/S0022-5347(06)00508-8.
28. Albers P , Weissbach L , Krege S , Kliesch S , Hartmann M , Heidenreich A , et al.; German Testicular Cancer Study Group . Prediction of necrosis after chemotherapy of advanced germ cell tumors: results of a prospective multicenter trial of the German Testicular Cancer Study Group. J Urol. 2004 May;171(5):1835–8. http://dx.doi.org/10.1097/01.ju.0000119121.36427.09.
29. Fosså SD , Qvist H , Stenwig AE , Lien HH , Ous S , Giercksky KE . Is postchemotherapy retroperitoneal surgery necessary in patients with nonseminomatous testicular cancer and minimal residual tumor masses? J Clin Oncol. 1992 Apr;10(4):569–73. http://dx.doi.org/10.1200/JCO.1992.10.4.569.

Appendix

Supplementary table 1. Patients' baseline characteristics.

	Bern **n = 70 (51.5%)**	**Zurich** **n = 66 (48.5%)**	**Overall** **n = 136 (100%)**
Age at diagnosis (years), median (range)	29.3 (16.3–57.5)	28.9 (16.2–69.2)	29.2 (16.2–69.2)
<40 years, number (%)	58 (82.9)	54 (81.8)	112 (82.4)
≥40 years, number (%)	12 (17.1)	12 (18.2)	24 (17.6)
Body mass index (kg/m^2), median (range)	25.9 (17.7–39.5)	25.5 (19.6–36.5)	25.6 (17.7–39.5)
<30	58 (82.9)	56 (84.8)	114 (83.8)
≥30	12 (17.1)	10 (15.2)	22 (16.2)
Site of primary tumor, number (%)			
Left testis	34 (48.6)	33 (50.0)	67 (49.3)
Right testis	32 (45.7)	27 (40.9)	59 (43.4)
Bilateral	1 (1.4)	2 (3.0)	3 (2.2)
Retroperitoneum	3 (4.3)	4 (6.1)	7 (5.1)
Mediastinum	–	–	–
Size of primary tumor (mm), median (range)	40 (3–190)	40 (3–160)	40 (3–190)
Missing values	7	8	15
Histopathology subtype and patterns in primary tumor, number (%)			
Pure seminoma	7 (10.0)	3 (4.5)	10 (7.4)
Nonseminoma / mixed germ cell tumor	61 (87.1)	61 (92.4)	122 (89.7)
Seminoma	24 (39.3)	24 (36.4)	48 (35.3)
Embryonal carcinoma	38 (62.3)	45 (68.2)	83 (61.0)
Yolk sac tumor	30 (49.2)	30 (45.5)	60 (44.1)
Choriocarcinoma	11 (18.0)	11 (16.7)	22 (16.2)
Teratoma	35 (57.4)	35 (53.0)	70 (51.5)
Burned out tumor / scar only	2 (2.9)	2 (3.0)	4 (2.9)
Metastases at diagnosis, number (%)			
Retroperitoneal	60 (85.7)	55 (83.3)	115 (84.6)
Pulmonary	26 (37.1)	29 (44.0)	55 (40.4)
Mediastinal	15 (21.4)	17 (25.8)	32 (23.5)
Cervical	5 (7.1)	13 (19.7)	18 (13.2)
Liver	9 (12.9)	4 (6.1)	13 (9.6)
Bone	3 (4.3)	2 (3.0)	5 (3.7)
Cerebral	2 (2.9)	–	2 (1.5)
Other	9 (12.9)*	1 (1.5)†	10 (7.4)
Side of retroperitoneal metastases at diagnosis, number (%)			
Unilateral, ipsilateral to primary tumor	29 (41.4)	20 (30.3)	49 (36.0)
Unilateral, contralateral to primary tumor	–	–	–
Bilateral	30 (42.9)	30 (45.5)	60 (44.1)
No retroperitoneal metastases	9 (12.9)	10 (15.2)‡	19 (14.0)
Missing values	2 (2.9)	6 (9.1)	8 (5.9)
Maximum size of retroperitoneal mass at diagnosis (mm), median (range)§	57.0 (7–130)	40.0 (9–165)	49.0 (7–165)
No retroperitoneal metastases	8 (11.4)	10 (15.2)‡	18 (13.2)
Missing values	5 (7.1)	4 (6.1)	9 (6.6)

Serum tumor markers prechemotherapy			
AFP elevated (≥10 µg/l)			
Number (%)	40 (57.1)	31 (47.0)	71 (52.2)
Median (range)	137.0 (10.4–63951)	205.0 (17.1–36145.2)	139.5 (10.4–63951)
Missing values	13 (18.6)	13 (19.7)	26 (19.1)
HCG elevated (≥5 U/l)			
Number (%)	39 (55.7)	34 (51.5)	73 (53.7)
Median (range)	234.0 (6.8–1462779)	1785.0 (10.0–1232859)	1661.8 (6.8–1462779)
Missing values	14 (20.0)	13 (19.7)	27 (19.9)
Both elevated			
Number (%)	28 (40.0)	25 (37.9)	53 (39.0)
Clinical stage at diagnosis according to UICC, number (%)			
I	9 (12.9)	9 (13.6)‡	18 (13.2)
IIA, IIB	11 (15.7)	10 (15.2)	21 (15.4)
IIC	12 (17.1)	5 (7.6)	17 (12.5)
III	35 (50.0)	41 (62.1)	76 (55.9)
Unknown	3 (4.3)	1 (1.5)	4 (2.9)
IGCCCG risk classification, number (%)			
Good prognosis	29 (41.4)	24 (36.4)	53 (39.0)
Intermediate prognosis	13 (18.6)	20 (30.3)	33 (24.3)
Poor prognosis	18 (25.7)	11 (16.7)	29 (21.3)
No metastases (stage I)	9 (12.9)	9 (13.6)	18 (13.2)
Unclassified	1 (1.4)	2 (3.0)	3 (2.2)

* Including metastases in spinal cord (1), adrenal gland (2), spleen (1), femoral (1), inguinal (3) and pelvic (1) lymph nodes.

† Metastases in the stomach (1).

‡ One patient without retroperitoneal metastases had metastases in the lung at diagnosis and was therefore classified as clinical stage III B disease.

§ Corresponds to the maximum size of the short axis diameter (anterior-posterior (sagittal) and lateral (transverse) axis). Measurements in the craniocaudal (longitudinal) axis were not considered.

AFP alpha-fetoprotein, HCG human chorionic gonadotropin, UICC The Union for International Cancer Control, IGCCCG International Germ Cell Cancer Collaborative Group.

Supplementary table 2. Patients' characteristics prior to PC-RPLND.

	Bern n = 70 (51.5%)	**Zürich n = 66 (48.5%)**	**Overall n = 136 (100%)**
Type of chemotherapy regimen prior to PC-RPLND, number (%)			
Primary chemotherapy	56 (80.0)	62 (94.0)	118 (86.8)
First salvage chemotherapy	13 (18.6)	2 (3.0)	15 (11.0)
Second salvage chemotherapy	1 (1.4)	1 (1.5)	2 (1.5)
Third salvage chemotherapy	–	1 (1.5)	1 (0.7)
Number of chemotherapy cycles prior to PC-RPLND, median (range)	4.0 (1–10)	4.0 (1–18)	4.0 (1–18)
Type of chemotherapy, number (%)			
Conventional-dose chemotherapy only	61 (87.1)	63 (95.5)	124 (91.2)
High-dose chemotherapy*	9 (12.8)	3 (4.5)	12 (8.8)
Type of primary chemotherapy, number (%)			
BEP†	46 (65.7)	44 (66.7)	90 (66.2)
EP	5 (7.1)	3 (4.5)	8 (5.9)
VIP/PEI‡	4 (5.7)	8 (12.1)	12 (8.8)
High-dose chemotherapy upfront	3 (4.3)§	–	3 (2.2)
Other	7 (10.0)	3 (4.5)	10 (7.4)
No initial chemotherapy	5 (7.1)	8 (12.1)	13 (9.6)
Time from end of chemotherapy to PC-RPLND (months), median (range)	6.2 (0.5–54.2)	2.3 (0.5–327.6)	3.8 (0.5–327.6)
<12 months	53 (75.7)	58 (87.9)	111 (81.6)
≥12 months	15 (21.4)	8 (12.1)	23 (16.9)
Missing values	2 (2.9)	–	2 (1.5)
Serum tumor markers at PC-RPLND			
AFP elevated (≥10 µg/l)			
Number (%)	9 (12.9)	7 (10.6)	16 (11.8)
Median (range)	253.8 (19.7–853)	48.0 (12.8–13860)	97.0 (12.8–13860)
Missing values	–	7 (10.6)	7 (5.1)
HCG elevated (≥5 U/l)			
Number (%)	4 (5.7)	2 (3.0)	6 (4.4)
Median (range)	62.0 (5.0–691)	157.5 (8.0–307)	62.0 (5.0–691)
Missing values	2 (2.9)	5 (7.6)	7 (5.1)
Both elevated			
Number (%)	1 (1.4)	–	1 (0.7)
Increasing elevated serum tumor markers at PC-RPLND, number (%)			
AFP	5 (7.1)	3 (4.5)	8 (5.9)
HCG	3 (4.3)	–	3 (2.2)
Localization of retroperitoneal mass at PC-RPLND, number (%)			
Paracaval / precaval	21 (30.0)	17 (25.8)	38 (27.9)
Interaortocaval	25 (35.7)	21 (31.8)	46 (33.8)
Paraaortal / preaortal	48 (68.6)	43 (65.1)	91 (66.9)
Suprahilar	6 (8.6)	3 (4.5)	9 (6.6)
Iliac	13 (18.6)	5 (7.6)	18 (13.2)
Missing values	–	1 (1.5)	1 (0.7)
Largest diameter of retroperitoneal mass at PC-RPLND (mm), median (range)**	33.0 (8–160)	31.0 (8–126)	32.0 (8–160)
<20 mm	16 (22.9)	18 (27.3)	34 (25.0)
20–49 mm	37 (52.9)	31 (47.0)	68 (50.0)
≥50 mm	17 (24.3)	16 (24.2)	33 (24.3)
Missing values	–	1 (1.5)	1 (0.7)

Trend of retroperitoneal mass prior to PC-RPLND, number (%)			
Increasing	21 (30.0)	17 (25.8)	38 (27.9)
Decreasing	20 (28.6)	37 (56.1)	57 (41.9)
Stable	29 (41.4)	9 (13.6)	38 (27.9)
Mixed response	–	2 (3.0)	2 (1.5)
Missing values	–	1 (1.5)	1 (0.7)
Preoperative ASA status, number (%)			
1	2 (2.9)	7 (10.6)	9 (6.6)
2	35 (50.0)	43 (65.2)	78 (57.4)
3	31 (44.3)	15 (22.7)	46 (33.8)
4	1 (1.4)	–	1 (0.7)
Missing values	1 (1.4)	1 (1.5)	2 (1.5)

* Including both conventional and high dose chemotherapy.
† Including 14 patients that received three cycles of BEP and one cycle of EP.
‡ Including 2 patients that received one cycle of EP ahead of four cycles of VIP/PEI.
§ Upfront high-dose chemotherapy consisting of VIP (1) and Carboplatin/Etoposide (2).
** Corresponds to the maximum size of the short axis diameter (anterior-posterior (sagittal) and lateral (transverse) axis). Measurements in the craniocaudal (longitudinal) axis were not considered.
PC-RPLND post-chemotherapy retroperitoneal lymph node dissection, BEP Bleomycin, Etoposide, Cisplatin, EP Etoposide, Cisplatin, VIP/PEI Etoposide, Cisplatin, Ifosfamide, AFP alpha-fetoprotein, HCG human chorionic gonadotropin, ASA American Society of Anesthesiologists.

Supplementary table 3. Surgical data PC-RPLND.

	Bern n = 70 (51.5%)	Zurich n = 66 (48.5%)	Overall n = 136 (100%)
PC-RPLNDs per lead urologist, number (%)			
<2	5 (33.3)	–	5 (22.7)
2–4	5 (33.3)	1 (14.3)	6 (27.3)
5–9	2 (13.3)	1 (14.3)	3 (13.6)
≥10	3 (20.0)	5 (71.4)	8 (36.4)
<20	12 (80.0)	5 (71.4)	17 (77.3)
≥20	3 (20.0)	2 (28.6)	5 (22.7)
Surgeons from other specialties present during PC-RPLND, number (%)			
Visceral surgery	2 (2.9)	1 (1.5)	3 (2.2)
Vascular surgery	5 (7.1)	13 (19.7)	18 (13.2)
Both visceral and vascular surgery	–	8 (12.1)	8 (5.9)
Other	1 (1.4)	1 (1.5)	2 (1.5)
Modus of surgery, number (%)			
Open	69 (98.6)	60 (90.9)	129 (94.9)
Laparoscopic	–	4 (6.1)	4 (2.9)
Robotic	1 (1.4)	2 (3.0)	3 (2.2)
Conversion from laparoscopic or robotic to open, number (%)	–	–	–
Template, number (%)			
Right†	22 (31.4)	7 (10.6)	29 (21.3)
With IAC	21 (30.0)	7 (10.6)	28 (20.6)
Without IAC	1 (1.4)	–	1 (0.7)
Left‡	30 (42.9)	16 (24.2)	46 (33.8)
With IAC	21 (30.0)	15 (22.7)	36 (26.5)
Without IAC	9 (12.9)	1 (1.5)	10 (7.4)
Full bilateral	12 (17.1)	40 (60.6)	52 (38.2)
Suprahilar dissection	11 (15.7)	10 (15.2)	21 (15.4)
Pick-up lymphadenectomy	7 (10.0)	4 (6.1)	11 (8.1)
Nerve-sparing procedure	11 (15.7)	22 (33.3)	33 (24.3)
Missing data	58 (82.9)	37 (56.1)	95 (69.9)
Duration of the procedure (minutes), median (range)	275 (140–740)	310 (90–975)	300 (90–975)
<1.9 hrs	–	3 (4.5)	3 (2.2)
2–2.9 hrs	9 (12.9)	3 (4.5)	12 (8.8)
3–3.9 hrs	18 (25.7)	6 (9.1)	24 (17.6)
4–4.9 hrs	11 (15.7)	15 (22.7)	26 (18.4)
5–5.9 hrs	12 (17.1)	11 (16.7)	23 (16.9)
6–6.9 hrs	10 (14.3)	7 (10.6)	17 (12.5)
7–7.9 hrs	2 (2.9)	9 (13.6)	11 (8.1)
8–8.9 hrs	3 (4.3)	4 (6.1)	7 (5.1)
> 9 hrs	1 (1.4)	7 (10.6)	8 (5.9)
Missing values	4 (5.7)	1 (1.7)	5 (3.7)
Length of postoperative stay (days), median (range)			
Total	7 (4–60)	7 (2–39)	7 (2–60)
On IMC/ICU	1 (1–51)	1 (0–32)	1 (0–51)
On normal ward§	6 (2–20)	6 (0–21)	6 (0–21)

* Not including redo PC-RPLNDs of patients who underwent surgery twice in the study period.
† Defined as paracaval (right ureter to vena cava) and pre- and retrocaval space.
‡ Defined as paraaortal (left ureter to aorta) and pre- and retroaortal space.
§ Including patients who died on IMC/ICU and did not return to normal ward.
PC-RPLND post-chemotherapy retroperitoneal lymph node dissection, IAC interaortocaval space, IMC intermediate care, ICU intensive care unit.

Supplementary table 4. Additional procedures during PC-RPLND.

Type of additional procedure, number (%)	Bern n = 70 (51.5%)	Zurich n = 66 (48.5%)	Overall n = 136 (100%)
Caval resection/repair	6 (8.6)	6 (9.1)	12 (8.8)
Aortic resection/repair	2 (2.9)	9 (13.6)	11 (8.1)
Other vascular resection/repair	20 (28.6)	46 (69.7)	66 (48.5)
Inferior mesenteric artery only	6 (8.6)	5 (7.6)	11 (8.1)
Inferior mesenteric vein only	1 (1.4)	–	1 (0.7)
Inferior mesenteric artery and vein	–	1 (1.5)	1 (0.7)
Lumbar vessels only	7 (10.0)	23 (34.8)	30 (22.1)
Renal vessels only	3 (4.3)	6 (9.1)	9 (6.6)
Both inferior mesenteric artery and lumbar vessels	2 (2.9)	6 (9.1)	8 (5.9)
Both inferior mesenteric and lumbar vessels	–	1 (1.5)	1 (0.7)
Both renal and lumbar vessels	–	3 (3.0)	3 (2.2)
Side branches of inferior vena cava	1 (1.4)	–	1 (0.7)
Renal, lumbar and mesenteric vessels	–	1 (1.5)	1 (0.7)
Liver resection	2 (2.9)	1 (1.5)	3 (2.2)
Gastrointestinal resection	6 (8.6)	2 (3.0)	8 (5.9)
Ureteral resection	1 (1.4)	–	1 (0.7)
Nephrectomy	1 (1.4)	4 (6.1)	5 (3.7)
Adrenalectomy	3 (4.3)	1 (1.5)	4 (2.9)
Both nephrectomy and adrenalectomy	1 (1.4)	–	1 (0.7)
Muscle or vertebral resection	3 (4.3)	3 (4.5)	6 (4.4)
Other procedure, tumor related	8 (11.4)	14 (21.2)	22 (16.1)
Orchiectomy	3 (4.3)	8 (12.1)	11 (8.1)
Insertion of ureteral stenting	2 (2.9)	2 (3.0)	4 (2.9)
Open abdomen treatment	–	2 (3.0)	2 (1.5)
Removal of port-a-cath	2 (2.9)	–	2 (1.5)
Implantation of testicular prosthesis	1 (1.4)	1 (1.5)	2 (1.5)
Insertion of chest tube	–	1 (1.5)	1 (0.7)
Other procedure, tumor unrelated	5 (7.1)	1 (1.5)	6 (4.4)
Inguinal or umbilical hernia repair	3 (4.3)	–	3 (2.2)
Excision of skin tumor	2 (2.9)	1 (1.5)	3 (2.2)

Supplementary table 5. Intraoperative complications.

Type of intraoperative complication, number (%)	Bern n = 70 (51.5%)	Zurich n = 66 (48.5%)	Overall n = 136 (100%)
Vascular injury/bleeding complication	16 (22.9)	11 (16.7)	27 (19.9)
Aorta	2 (2.9)	2 (3.0)	4 (2.9)
Aorta and IVC	2 (2.9)	–	2 (1.5)
IVC	1 (1.4)	1 (1.5)	2 (1.5)
IVC and iliac vessels	1 (1.4)	–	1 (0.7)
IVC and renal vein	1 (1.4)	–	1 (0.7)
IVC and lumbar vessels	–	1 (1.5)	1 (0.7)
Renal vein	6 (8.6)	2 (3.0)	8 (5.9)
Renal artery	1 (1.4)	1 (1.5)	2 (1.5)
Renal vein and artery	–	1 (1.5)	1 (0.7)
Iliac vessels	2 (2.9)	1 (1.5)	3 (2.2)
Lumbar vessels	–	1 (1.5)	1 (0.7)
Other vessels	–	1 (1.5)	1 (0.7)
Gastrointestinal injury	1 (1.4)	2 (3.0)	3 (2.2)
Urogenital injury	2 (2.9)	–	2 (1.5)
Anaesthesiologic complication	–	1 (1.5)	1 (0.7)
Other	2 (2.9)	–	2 (1.5)
Intraabdominal spilling of cystic fluid	2 (2.9)	1 (1.5)	3 (2.2)

IVC inferior vena cava.

Supplementary table 6. Outcome characteristics.

	Bern **n = 70 (51.5%)**	**Zurich** **n = 66 (48.5%)**	**Overall** **n = 136 (100%)**
Length of postoperative stay (days), median (range)			
Total	7 (4–60)	7 (2–39)	7 (2–60)
On IMC/ICU	1 (1–51)	1 (0–32)	1 (0–51)
On normal ward*	6 (2–20)	6 (0–21)	6 (0–21)
Relaparotomy after PC-RPLND, number (%)	–	5 (7.6)†	5 (3.7)
Readmission within 90 days, number (%)			
In total	14 (20.0)	11 (16.7)	25 (18.4)
Due to complications	6 (8.6)	3 (4.5)	9 (6.6)
Due to further treatment	8 (11.4)	8 (12.1)	16 (11.8)
Follow-up			
Patients still alive at last follow-up, number (%)	63 (90.0)	55 (83.3)	118 (86.8)
Follow-up period (months), median (range)	34.3 (0.3–139.3)	45.5 (0.1–142.1)	37.2 (0.1–142.1)
Patients that died during follow-up period, number (%)	6 (8.6)	9 (13.6)	15 (11.0)
Time to death (months), median (range)	15.6 (12.3–34.4)	23.5 (5.7–61.3)	16.3 (5.7–61.3)
Patients with terminated follow-up, number (%)	3 (4.3)	–	3 (2.2)
Lost to follow-up, number (%)	14 (20.0)	12 (18.2)	26 (19.1)
Further treatment after PC-RPLND, number (%)			
Surveillance	54 (77.1)	41 (62.1)	95 (69.9)
Chemotherapy	4 (5.7)	1 (1.5)	5 (3.7)
Radiotherapy	–	1 (1.5)	1 (0.8)
Additional surgery‡	12 (17.1)	23 (34.8)	35 (25.7)
Relapse, number of patients (%)	12 (17.1)	16 (24.2)	28 (20.6)
Retroperitoneum	6 (8.6)	8 (12.1)	14 (10.3)
In field	5 (7.1)	7 (10.6)	12 (8.8)
Out of field	1 (1.4)	1 (1.5)	2 (1.5)
Other§	7 (10.0)	12 (18.2)	19 (14.0)
Time to relapse (months), median (range)	5.8 (0.7–31.3)	5.6 (0.9–56.1)	5.8 (0.7–56.1)

* Including patients who died on IMC/ICU and did not return to normal ward.
† Two out of five patients had an abdominal vacuum assisted closure (VAC) system and underwent second look surgery after PC-RPLND.
‡ Other than orchiectomy or PC-RPLND, including thoracic, vascular, visceral, and cervical procedures.
§ Including other abdominal sites (e.g. liver), thorax, lung, brain, and laboratory values.
IMC intermediate care, ICU intensive care unit, PC-RPLND post-chemotherapy retroperitoneal lymph node dissection.

Supplementary table 7.1. Summary of perioperative complications of PC-RPLND.

	Bern n = 70 (51.5%)	**Zurich n = 66 (48.5%)**	**Overall n = 136 (100%)**
No. patients with intraoperative complications (%)	20 (28.6)	16 (24.2)	36 (26.5)
No. patients with postoperative complications (%)	14 (20.0)	28 (42.4)	42 (30.9)
No. postoperative complications	22	59	81

PC-RPLND post-chemotherapy retroperitoneal lymph node dissection.

Supplementary table 7.2. Complications after PC-RPLND.

	Bern n = 70 (51.5%)	**Zurich n = 66 (48.5%)**	**Overall n = 136 (100%)**
Reported postoperative complications, number (%)			
Ileus/small bowel obstruction	8 (11.4)	10 (15.2)	18 (13.2)
Wound infection	1 (1.4)	7 (10.6)	8 (5.9)
Pneumonia/pulmonary complications*	2 (2.9)	7 (10.6)	9 (6.6)
Sepsis/SIRS	1 (1.4)	2 (3.0)	3 (2.2)
Chylous ascites	–	4 (6.1)	4 (2.9)
Lymphocele	–	2 (3.0)	2 (1.5)
Venous thromboembolism or pulmonary embolism	2 (2.9)	1 (1.5)	3 (2.2)
Bleeding or hematoma	–	1 (1.5)	1 (0.7)
Other complications	8 (11.4)	25 (37.9)	33 (24.3)
Circulatory complications†	2 (2.9)	10 (15.2)	12 (8.8)
Infectious complications‡	–	5 (7.6)	5 (3.7)
Neurological complications§	1 (1.4)	5 (7.6)	6 (4.4)
Acute kidney failure	2 (2.9)	4 (6.1)	6 (4.4)
Allergic reaction to drugs	1 (1.4)	–	1 (0.7)
Swelling of the scrotum	1 (1.4)	–	1 (0.7)
Panzytopenia	1 (1.4)	–	1 (0.7)
Urinary retention	–	1 (1.5)	1 (0.7)
Grading of worst complication/patient, number (%)			
Clavien I	7 (10.0)	13 (19.7)	20 (14.7)
Clavien II	4 (5.7)	5 (7.6)	9 (6.6)
Clavien IIIa	1 (1.4)	4 (6.1)	5 (3.7)
Clavien IIIb	–	1 (1.5)	1 (0.7)
Clavien IVa	–	1 (1.5)	1 (0.7)
Clavien IVb	1 (1.4)	2 (3.0)	3 (2.2)
Clavien V	1 (1.4)	2 (3.0)	3 (2.2)
No complication	56 (80.0)	38 (57.6)	94 (69.1)

* Including pneumonia, pulmonary edema, pleural effusion, (sero-)pneumothorax, acute respiratory distress syndrome (ARDS).
† Including partial or complete ischemia of the kidneys, liver, rectum, and spinal cord, and compartment syndrome.
‡ Including conjunctivitis, endocarditis, graft infections, clostridium difficile infection, and urinary tract infection.
§ Including delirium, leckage of cerebrospinal fluid and peripheric paraesthesias.
PC-RPLND post-chemotherapy retroperitoneal lymph node dissection, SIRS systemic inflammatory response syndrome.

Supplementary table 7.3. Postoperative complications classified according to Clavien-Dindo.

Grade	Complication	Frequency, n (%)
I	Ileus with NPO and supportive treatment	7
	Wound infection	4
	Chylous ascites	3
	Neurological complication (CSF leakage, paraesthesia left lower extremity)	2
	Circulatory complication (hypoperfusion kidney)	1
	Symptomatic lymphocele	1
	Acute renal failure with fluid management	1
	Srotal swelling	1
II	Ileus with TPN	3
	Panzytopenia	1
	Allergic reaction	1
	Infectious complication (C. difficile infection, conjunctivitis) with antibiotic treatment	2
	Neurological complication (delirium)	1
	Chylous ascites with TPN	1
IIIa	Circulatory complication (dissection renal artery) with stenting	2
	Urinary retention with placement of urinary bladder catheter	1
	Ileus with placement of nasogastric tube	1
	Pulmonary complication (seropneumothorax) with placement of chest tube	1
IIIb	Ileus with relaparotomy	1
IVa	Sepsis with resuscitative therapy	1
IVb	Multi-organ failure (compartment syndrome, rhabdomyolysis, acute renal failure and respiratory failure) with multiple fasciotomies, non-invasive ventilation, and hemodialysis	1
	Multi-organ failure (acute liver failure, acute renal failure) with hemodialysis	1
	Multi-organ failure (SIRS, pulmonary failure, acute renal failure) with invasive ventilation and hemodialysis	1
V	ARDS (aspiration pneumonia, pulmonary embolism) resulting in insufficient ventilation	1
	Incontrollable infection of vascular graft	1
	Multi-organ failure (ventilator-associated pneumonia, sepsis, ischemic ulcerative colitis, acute renal failure)	1
Total		42

Not all complications are listed above: If a patient had more than one complication, the complication with the highest grading according to the classification by Clavien and Dindo is listed.
NPO nothing per mouth, *CSF* cerebrospinal fluid, *TPN* total peripheral nutrition, *C. difficile* Clostridium difficile, *ARDS* acute respiratory distress syndrome.

Supplementary table 8. Characteristics of patients with relapses after PC-RPLND.

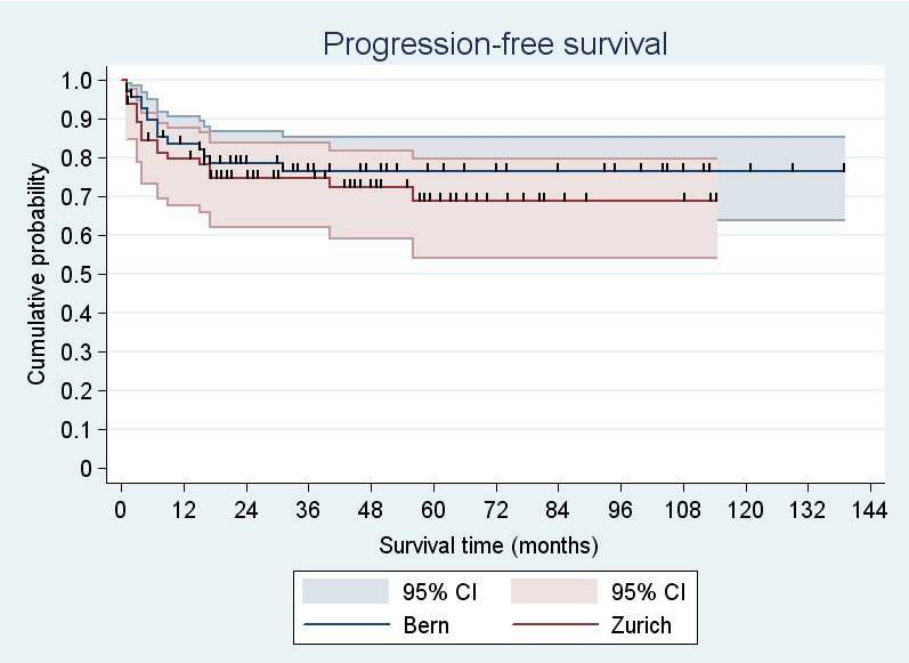
Centre	Patient number	Clinical stage at diagnosis	IGCCCG risk group	Largest diameter RP size preop (mm)	Template	Pathology of RP mass	Relapse site(s)	Time to relapse (months)	Treatment	Status
Bern	12	IIIC	poor	50	bilateral	vital cancer (yolk sac tumor)	liver	1.3	chemotherapy	alive without disease
	17	IIIC	poor	51	bilateral	necrosis	thorax	0.7	surgery	alive without disease
	20	IIC	good	60	bilateral	teratoma	thorax	14.7	surgery	alive without disease
	37	IIIC	poor	41	left - IAC	necrosis	brain	6.8	none	alive with active radiological disease
	38	IIIC	poor	45	right + IAC	vital cancer (choriocarcinoma)	liver	5.1	chemotherapy	dead to disease progression
	42	I	good	46	right + IAC	vital cancer (PNET), teratoma	thorax and RP (in field)	6.5	chemotherapy	dead to disease progression
	59	IIIC	poor	20	left - IAC	vital cancer (yolk sac tumor)	RP (out of field)	3.7	surgery	dead to disease progression
	203	IIB	good	60	left - IAC	teratoma	RP (in field)	31.3	surgery	alive without disease
	206	IS	n/a	30	left - IAC	teratoma	RP (in field)	4.1	surgery	lost to follow up (last visit: alive without disease)
	213	IS	n/a	60	bilateral	vital cancer (seminoma)	RP (in field)	4.9	chemotherapy	alive without disease
	218	unknown	good	160	bilateral	teratoma	RP (in field)	6.6	surgery	dead to disease progression
	223	IIIC	poor	41	right + IAC	necrosis	inguinal	9.1	surgery	alive without disease
Zurich	76	IIIB	intermediate	41	bilateral	teratoma	thorax	40.2	surgery	alive without disease
	78	IIIB	intermediate	51	bilateral, retrocrural	teratoma	pulmonary	16.6	surgery	alive with active radiological disease

	87	IIIB	intermediate	61	bilateral	teratoma	pulmonary	3.7	surgery	dead to disease progression
	100	IIIB	intermediate	22	bilateral	vital cancer (embryonal carcinoma)	pulmonary and RP (in field)	3.2	chemotherapy	dead to disease progression
	111	IIB	good	25	left + IAC	teratoma	thorax	3.0	surgery	alive without active disease
	116	IIIC	poor	84	bilateral	teratoma	thorax	17.2	surgery	dead to disease progression
	133	IIIC	poor	59	bilateral	vital cancer (embryonal carcinoma)	pulmonary	1.3	surgery	dead to disease progression
	134	III	unknown	73	left + IAC	vital cancer (malignant transformation of teratoma)	thorax and RP (in field)	6.9	radio- and chemotherapy	dead to disease progression
	138	IIIA	good	23	bilateral	vital cancer (malignant transformation of teratoma)	thorax, pulmonary, RP (in field)	4.0	chemotherapy	dead to disease progression
	141	IIA	good	36	bilateral	vital cancer (embryonal carcinoma)	RP (out of field)	14.8	surgery	alive with radiological disease
	150	IIA	good	29	bilateral	vital cancer (yolk sac tumor)	thorax	3.3	surgery	dead to disease progression
	154	IIA	good	28	right + IAC	vital cancer (seminoma)	RP (in field)	7.1	chemotherapy	alive without disease
	163	IIIB	intermediate	31	bilateral	necrosis	pulmonary and RP (in field)	0.9	chemotherapy	dead to disease progression
	173	IIIC	poor	97	left + IAC	vital cancer (renal cell carcinoma), teratoma	supraclavicular	56.1	surgery	alive with radiological disease
	177	I	n/a	17	left + IAC	teratoma	RP (in field)	4.3	surgery	lost to follow-up (last visit: alive without disease)
	178	IA	n/a	20	bilateral	vital cancer (rhabdomyo-sarcoma)	RP (in field), pulmonary, thorax	9.4	surgery	dead to disease progression

PC-RPLND post-chemotherapy retroperitoneal lymph node dissection, *IGCCCG* International Germ Cell Cancer Cooperative Group, *RP* retroperitoneal, *IAC* interaortocaval, *PNET* primary neuroendocrine tumor.

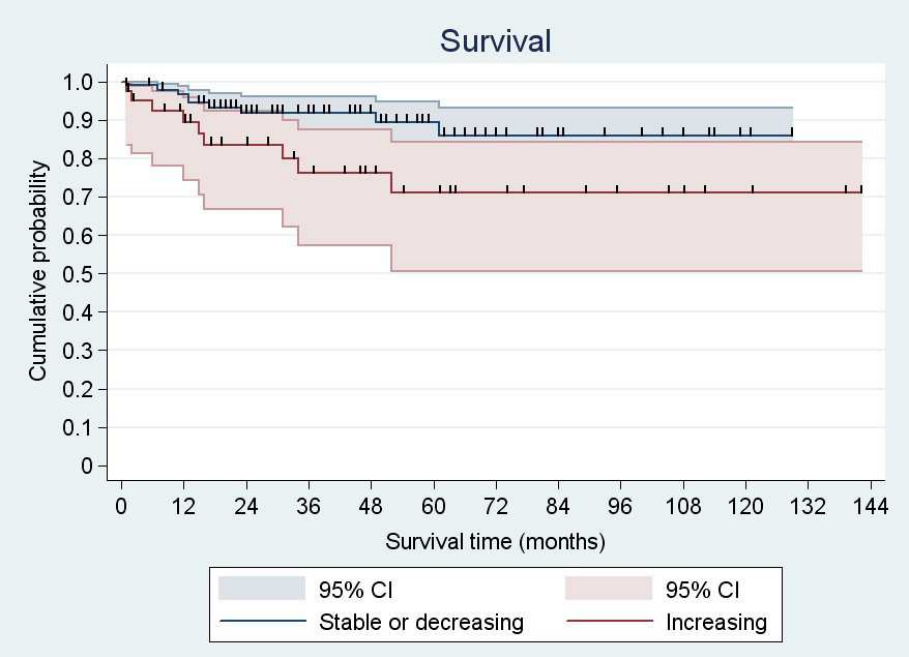
Supplementary figure 1

Kaplan-Meier analysis of progression-free survival after stratification for centre.
Bern progression-free survival at 5 years 77% (95% CI: 64–85%);
Zurich progression-free survival at 5 years 69% (95% CI: 54–80%), p = 0.468 for difference



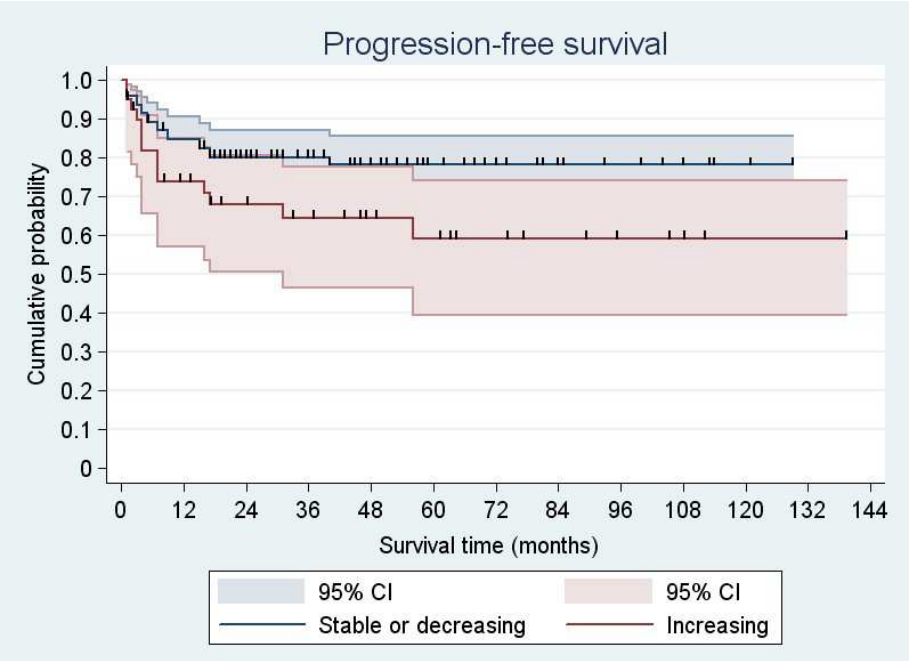
Supplementary figure 2

Kaplan-Meier analysis of overall survival after stratification for radiological progression prior to PC-RPLND.
Stable or decreasing on imaging overall survival at 5 years 89% (95% CI: 79–95%);
Increasing on imaging overall survival at 5 years 71% (95% CI: 51–84%), p = 0.045 for difference



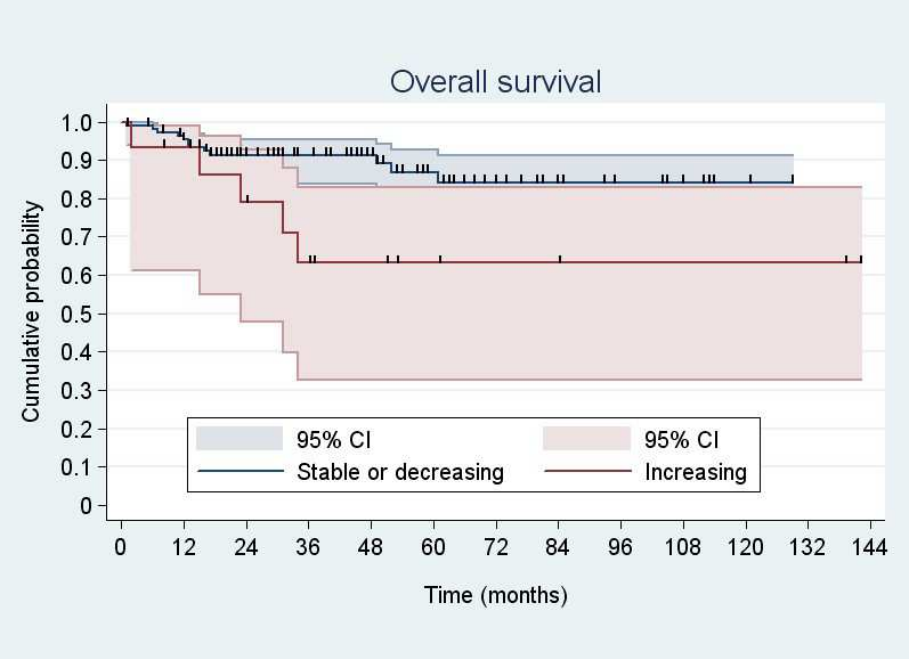
Supplementary figure 3

Kaplan-Meier analysis of progression-free survival after stratification for radiological progression prior to PC-RPLND.
Stable or decreasing on imaging: progression-free survival at 5 years 78% (95% CI: 68–86%); Increasing on imaging: progression-free survival at 5 years 60% (95% CI: 40–74%), p = 0.063 for difference



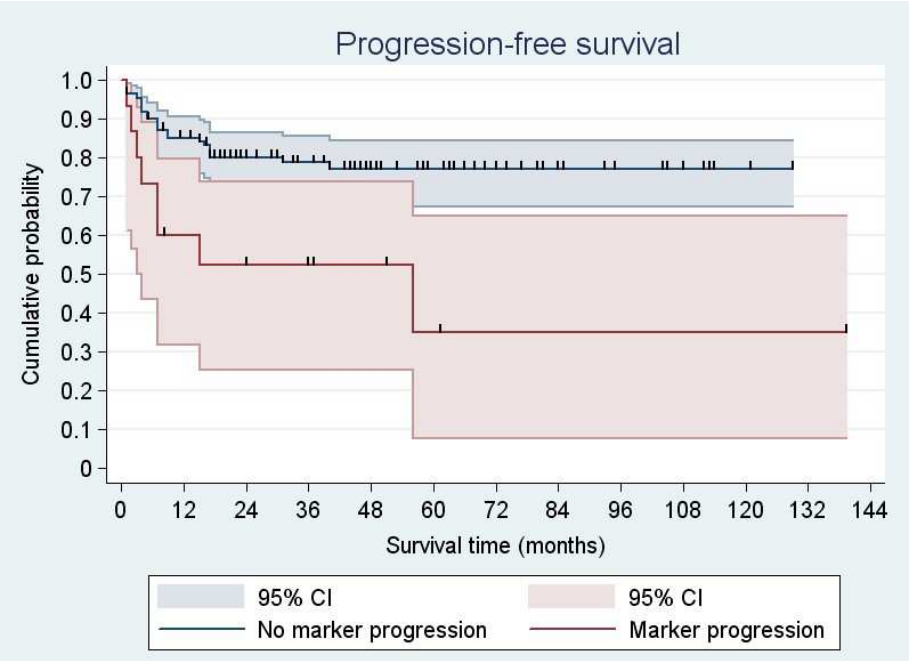
Supplementary figure 4

Kaplan-Meier analysis of overall survival after stratification for serological progression prior to PC-RPLND.
Stable or decreasing overall survival at 5 years 87% (95% CI: 76–93%);
Increasing overall survival at 5 years 63% (95% CI: 33–83%), p = 0.028 for difference



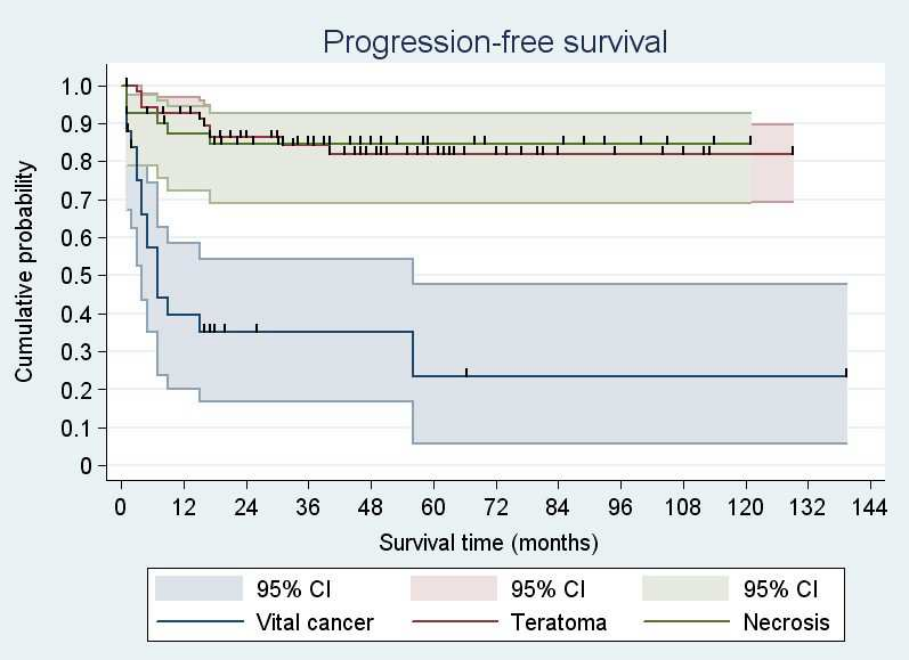
Supplementary figure 5

Kaplan-Meier analysis of progression-free survival after stratification for serological progression prior to PC-RPLND.
Tumor marker stable or decreasing progression-free survival at 5 years 77% (95% CI: 67–84%);
Tumor marker increasing progression-free survival at 5 years 35% (95% CI: 8–65%), p = 0.003 for difference



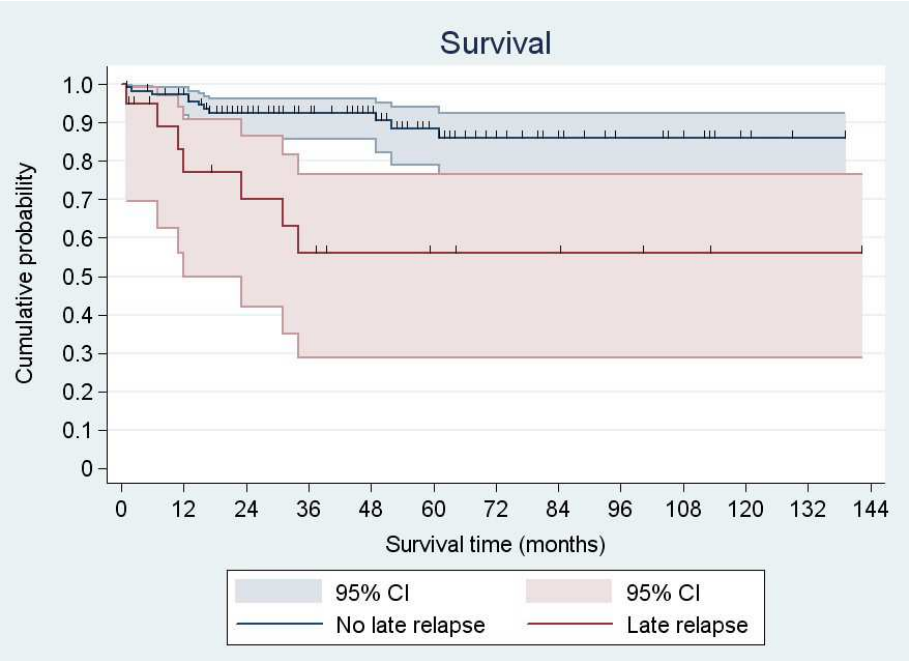
Supplementary figure 6

Kaplan-Meier analysis of progression-free survival after stratification for histology in the resected specimen.
Vital cancer progression-free survival at 5 years 23% (95% CI: 6–48%)
Teratoma progression-free survival at 5 years 82% (95% CI: 69–90%)
Necrosis progression-free survival at 5 years 85% (95% CI: 69–93%), p <0.001 for difference between teratoma or necrosis and vital cancer



Supplementary figure 7

Kaplan-Meier analysis of overall survival after stratification for late relapse.
No late relapse overall survival at 5 years 89% (95% CI: 79–94%);
Late relapse overall survival at 5 years 56% (95% CI: 29–76%), p <0.001 for difference



Supplementary figure 8

Kaplan-Meier analysis of progression-free survival after stratification for late relapse.
No late relapse progression-free survival at 5 years 79% (95% CI: 70–86%);
Late relapse progression-free survival at 5 years 34% (95% CI: 11–58%), p <0.001 for difference