ACTA ONCOLOGICA
2018, VOL. 57, NO. 8, 1084–1093
https://doi.org/10.1080/0284186X.2018.1449249

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ORIGINAL ARTICLE

Limited post-chemotherapy retroperitoneal resection of residual tumour in non-seminomatous testicular cancer: complications, outcome and quality of life

Anna Hartmann Schmidt[a], Morten Høyer[a], Bent Frode Skov Jensen[b] and Mads Agerbaek[a]

[a]Department of Oncology, Aarhus University Hospital, Aarhus, Denmark; [b]Department of Cardio-Thoracic and Vascular Surgery, Vascular Section, Aarhus University Hospital, Aarhus, Denmark

ABSTRACT

Background: Resection of residual masses after chemotherapy plays a crucial role in management of patients with germ cell tumours (GCTs). The extent of surgery is controversial and we present the experiences from Aarhus University Hospital over a 20-year period. The aim was to evaluate survival, complications, working ability and quality of life (QOL) following a limited surgical procedure performed to resect residual masses in non-seminomatous testicular cancer patients after chemotherapy.

Material and methods: A consecutive patient cohort of 109 patients having surgery between 1993 and 2013 was investigated. Hospital records were reviewed and complications were graded according to the Clavien-Dindo classification. QOL data were assessed in a cross-sectional analysis using the European Organisation for Research and Treatment of Cancer (EORTC), QLQ-C30 version 3.0. Patients were matched 1:1 with controls to evaluate the influence of surgical resection on the QOL.

Results: With a median follow-up of 10.3 years, 11 relapses in retroperitoneum were recorded in 10 patients (9%), and four patients (5%) died of disease progression. The majority of relapses in patients considered having no evidence of disease (NED) after primary retroperitoneal surgery occurred 10 + years after treatment and was outside the field of the elective lymph node dissection. Twenty-seven (44%) grade I, 15 (24%) grade II, 7 (11%) grade IIIa and 13 (21%) grade IIIb complications were recorded. No grade IV and V complications were observed. Twenty-three patients (20%) reported loss of antegrade ejaculation. We found no significant differences between patients and controls regarding QOL.

Conclusion: The survival outcome and complication rate are favourable and are comparable to studies involving full and modified template lymph node dissection. We find that limited resection constitutes an applicable and safe procedure. Limited surgical resection did not influence the patients' long-term QOL. Longer follow-up might be considered.

ARTICLE HISTORY
Received 14 December 2017
Accepted 28 February 2018

Introduction

Testicular cancer remains the most common malignancy in males aged between 15 and 35 years. The vast majority are germ cell tumours (GCTs), encompassing seminoma (SGCT) and non-seminoma GCT (NSGCT). The incidence of testicular cancer has nearly tripled during the last 50 years and, for unknown reasons, one of the highest incidences of this malignancy is found in Denmark [1].

After first-line chemotherapy, 20–50% of NSGCT patients harbour residual tumours in the retroperitoneal space consisting of teratoma, necrosis or viable malignant tumour components, the latter being less frequent [2]. Because no diagnostic procedures have been able to discriminate between these entities with acceptable precision, radical resection is recommended for residual masses larger than 10 mm [3,4].

International guidelines have changed several times during this 20-year period, but a full bilateral template lymph node dissection has for long been considered standard care in case of post-chemotherapy residual masses. The modified templates and nerve-sparing procedures have now gained acceptance in selected patients [5–9] and laparoscopic techniques are evolving [10]. Some centres still consider the full template lymph node dissection the preferred procedure. Others prefer using the modified template in patients with unilateral residual disease in good prognostic group according to the International Germ Cell Consensus Classification [11]. The subject is controversial, and the interest for minimally invasive approaches is growing. Long-term follow-up studies on limited resection are warranted [8,12].

At Aarhus University Hospital, the policy regarding surgical consolidation after chemotherapy has remained unchanged during the period. A radical resection is performed after chemotherapy for NSGCT of any residual mass measuring 10 mm or more in longest diameter. No template resection of clinically and radiologically uninvolved lymph nodes is done. The conservative approach is chosen in order to reduce the risk of intra- and post-operative complications. This report presents the results in a consecutive cohort of 109 patients undergoing retroperitoneal limited resection for

CONTACT Mads Agerbaek madsager@rm.dk Department of Oncology, Aarhus University Hospital, Palle Juul-Jensens Blvd. 99-8200, Aarhus N, Denmark

residual tumour mass after chemotherapy for NSGCT. The aim of this study was to evaluate oncological results, survival, complications and the impact of this conservative procedure on quality of life (QOL) and working ability with a long (up to 20 years) follow-up.

Material and methods

Study population

The study population consisted of a consecutive patient cohort including all 109 patients having surgical resection of a residual tumour mass in the retroperitoneal space following cisplatin-based chemotherapy for NSGCT between 1993 and 2013. Ten patients (9%) were included even though complete resection was deemed impossible and the purpose of surgery was debulking. All patients received chemotherapy in accordance with international standards: three cycles of bleomycin, etoposide and cisplatin (BEP) to patients in good prognostic group (according to IGCCC) and four cycles to patients in intermediate or poor prognostic group. In case of contraindications against bleomycin, four cycles of etoposide and cisplatin (EP) were administered. Aarhus University Hospital, Denmark, is one of the two Danish tertiary referral centres responsible for all residual retroperitoneal surgery in testicular cancer. All patients underwent surgery at the Department of Cardio-Thoracic and Vascular Surgery, Vascular Section, Aarhus University Hospital. Because of the often-intimate relations between residual tumours and the vascular system, surgery in our centre has traditionally been performed at the Vascular Surgery Section by a specially trained vascular surgeon, assisted by a urologist when needed.

On top of the 109 patients receiving surgery after chemotherapy, five NSGCT patients receiving retroperitoneal surgery as a diagnostic procedure were included in the QLQ and complication analysis but not in the oncologic outcome assessment. They did not show malignant NSGCT relapse on histology (one lipoma, one teratoma with rhabdomyosarcoma and three teratomas). A group of 101 patients, who received chemotherapy but not surgery in the same time period, acted as controls in the assessment of QOL.

Surgical technique

To determine the need for and extent of surgical resection, every patient with residual tumours was evaluated at a tumour board consisting of a uro-oncologist, a specially trained vascular surgeon and a radiologist. A urologist was involved when needed.

The exact surgical procedure was individualised according to the location of the residual tumour. Overall principles included ureteral catheters placed by a cystoscopic procedure in order to ease identification and avoid damage of the ureters when the residual mass was in close proximity to the ureters. To expose the retroperitoneal space, transverse section was most often performed, typically above the umbilical level. In a few cases, longitudinal sections were chosen instead. If the masses were located behind the kidney, a medial rotation of the kidney and colon was done. Perioperative histological examination (frozen section) was performed on tumour material. If histology revealed necrosis or inflammation, the gross tumour was removed with respect to nearby structures. If GCT or teratoma was found, all visible tumour tissue, cyst walls and intimately adherent related structures were removed.

Data collection

Information on the individual patients was retrospectively reviewed from the hospital records. A computed tomography (CT) or magnetic resonance imaging (MRI) scan was performed before surgery and one month postoperatively. Scans and descriptions were examined.

Complications were defined as present when reported in the hospital records and/or the patient received relevant treatment according to the records. The postoperative complications were ranked according to the Clavien-Dindo classification of surgical complications from grade I to V based on the therapy used to correct the specific complication [13,14]. Although this classification is not strictly validated to score late postoperative complications beyond 90 days, we have chosen to use this scoring system based on lack of a validated alternative. The classification is specified in Table 1. The study was approved by the Danish Health and Medicines Authority and the Danish Data Protection Agency.

Quality of life and ability to work questionnaire

Between March and May 2015, 1.5–21.5 years after surgery, the patients were contacted by letter. QOL data were recorded using the European Organisation for Research and

Table 1. Classification of surgical complications.

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimes are drugs, such as antiemetics, antipyretics, analgetics, diuretics, electrolytes and physiotherapy.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications.
Grade III	Requiring surgical, endoscopic or radiological intervention.
Grade IIIa	Intervention not under general anaesthesia.
Grade IIIb	Intervention under general anaesthesia.
Grade IV	Life-threatening complication.
Grade IVa	Single-organ dysfunction (including dialysis).
Grade IVb	Multi-organ dysfunction.
Grade V	Death of a patient.

Abbreviated version of Clavien-Dindo classification of surgical complications [13].

Treatment of Cancer (EORTC), QLQ-C30 version 3.0 [15,16]. Another questionnaire recorded basic health information, work/study activity, educational level and health conditions with a possible causal relation to chemotherapy and surgery.

The following scales were incorporated and were all analysed; physical functioning, role functioning, cognitive functioning, emotional functioning, social functioning, fatigue, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties, nausea and vomiting and global health/QOL.

Matching of operated patients and controls

To be able to investigate the specific impact of retroperitoneal surgery on QOL, work/study activity and health conditions possibly related to chemotherapy and surgery, the patients were matched with controls 1:1. Controls were GCT patients with retroperitoneal metastases treated with chemotherapy and achieving complete response; 88 patients with NSGCT and 13 patients with SGCT. Matching criteria were age, number of cycles of chemotherapy and year of treatment. The patients and controls received identical questionnaires.

Statistical analysis

Differences between groups were tested with Chi-square test. If number of observations in a group were <10, Fisher's exact test was used. Differences in age groups were tested with Student's *t*-test.

Analyses of EORTC QLQ-C30 were performed after transforming data into continuous scales ranging from 0 to 100, where 100 indicated best function on scales regarding functioning and the opposite on symptoms scales. Missing values were handled as recommended by the EORTC [17]. A difference of >10 was considered clinically significant [18]. Groups of operated patients and controls in EORTC QLQ-C30 scales were compared using Wilcoxon's rank sum test. All tests were two-sided, and p values $<.05$ were considered statistically significant. Statistical analyses were performed using STATA 13.1 (StataCorp LP, College Station, TX, USA).

Results

Survival analysis

One patient refused to participate in the study leaving 109 patients for analysis. Characteristics of the patients, oncological treatment and surgeries performed are presented in Table 2.

A total of 14 patients also had residual tumour masses outside the retroperitoneal space. Six in the lung, two in the mediastinum, three in the neck, one in the spine, one in the axilla and one patient had residual tumour both in the mediastinum and in the lung. These patients had resection of the tumour mass in the retroperitoneal as well as in the additional site. In this analysis, we only focus on the retroperitoneal surgery.

An overview of the study is presented in Figure 1. In total, 109 patients went through 131 operations. Ninety-seven (89%) had no evident disease (NED) on postoperative scans and serum markers, while 12 patients (11%) were found partly unresectable and still had residual masses. Of the 97 patients with NED after primary surgery, seven patients (7%) experienced a later retroperitoneal relapse. None of these patients died of relapsing GCT. However, one patient experienced a late relapse out of field with somatic transformation to sarcoma. He received additional chemotherapy but died of the disease.

Of the 12 patients found partly unresectable, 10 had debulking or desperation surgery. Three patients progressed and died. One patient survived with unresectable remains of teratoma after the second retroperitoneal surgery. Eight patients achieved NED following additional chemotherapy and surgery, three of the eight due to retroperitoneal relapse.

A total of 14 patients (13%) required repeated surgery. Nine patients (8%) required two, three patients (3%) three, one patient (1%) four and one patient (1%) five surgeries. In total, 22 operations were repeated surgeries due to either relapsing tumours or lacking NED after previous surgery.

We defined a relapse as radiologically visible tumour or rising markers occurring after a patient achieved NED postoperatively. Histology of the surgical specimen representing the 11 relapses in retroperitoneum is presented in Table 3. Three patients had viable GCT, four had teratoma and two had necrosis. Furthermore, one had GCT and teratoma and one had somatic transformation of teratoma to sarcoma. The patient with two relapses had teratoma at the first and necrosis at the second relapse. Median time period from surgery to relapse was 57 months with a range of 251 months.

The seven relapses among the 97 patients with NED after primary retroperitoneal surgery were diagnosed at 1, 12, 137, 211, 227, 248 and 252 months of follow-up.

Six patients had relapse outside the retroperitoneal space, i.e., in the cervical and mediastinal lymph nodes, in the bones, lung or spleen or had increased tumour markers without radiologically detectable tumour. All patients were treated with chemotherapy and/or surgery. One patient died of progressing cancer, one achieved stable disease (unresectable) and the remaining four achieved NED.

Surgical complications

Table 4 shows intra- and post-operative complications. Intraoperative complications were defined as complications occurring during the time of surgery. Post-operative complications were defined as occurring within 30 d, after 30 d and after 90 d post-operatively including the Clavien-Dindo score. Of the complications recorded within 90 d after surgery, 20 (48%) were grade I, 13 (31%) grade II, five (12%) grade IIIa and four (10%) grade IIIb according to the Clavien-Dindo classification. Of the complications occurring more than 90 d

Table 2. Patient characteristics.

Characteristic, $n = 109$ patients	Median or number (range) or (%)
Age at diagnosis	27.1 (15.3–64.4)
Follow-up (months)	124 (10–377)
IGCCC prognostic group[a]	
Good	59 (54)
Intermediate	29 (27)
Poor	20 (18)
Unknown	1 (1)
Stage of disease	
Stage II	55 (50)
Stage III	53 (49)
Unknown	1 (1)
Primary site	
Left testis	49 (45)
Right testis	43 (39)
Extragonadal origin	17 (16)
Additional metastatic sites	
Lung	21 (19)
Mediastinal lymph nodes	10 (9)
Cervical or axillary lymph nodes	11 (10)
Liver	6 (6)
Spleen	1 (1)
Brain	1 (1)
Soft tissues	1 (1)
Other	1 (1)
First line chemotherapy	
BEP[b], 3 cycles	54 (50)
BEP, 4 cycles	38 (35)
EP[c], 4 cycles	6 (6)
Other combinations (BEP + Taxol, Einhorn and others)	11 (10)
Number of residual masses removed	$n = 109$ operations
1	83 (76)
2	20 (18)
3	6 (6)
Size of residual tumour (biggest diameter), cm	
<2	13 (12)
2–3.9	38 (35)
4–5.9	24 (22)
≥ 6	34 (31)
Unknown	1 (1)
Localisation	
Above renal vessels	25 (23)
Between renal vessels and bifurcation of aorta	107 (98)
Below bifurcation of aorta	41 (38)
Histology of residual tumour	
Teratoma	63 (58)
Necrosis	35 (32)
GCT	7 (6)
Teratoma and GCT	3 (3)
Other	1 (1)
Days at hospital after surgery	6 (3–34)
Operating time, minutes	120 (44–248)

[a]Prognostic group according to the International Germ Cell Consensus Classification [11].
[b]BEP: bleomycin, etoposide and cisplatin; [c]EP: etoposide and cisplatin

after surgery, seven (35%) were grade I, two (10%) grade II, two (10%) grade IIIa and nine (45%) grade IIIb. No grade IV and V complications were recorded. In a patient-based analysis, 18% had grade I, 11% grade II, 4% grade IIIa and 4% grade IIIb complications occurring within 90 d after surgery. Of complications occurring more than 90 d postoperatively, 6% had grade I, 2% grade II, 2% grade IIIa and 8% grade IIIb complications.

Grade I and II complications are treated conservatively or medically, while grade III requires invasive intervention. Grade IV is life-threatening, while grade V is fatal.

Retrograde ejaculation was registered in hospital records for 14 patients (12%), one patient having the condition before treatment.

Quality of life and ability to work

Seven patients had died and two had emigrated at the time of the study. In total, 106 operated patients and 101 controls were eligible for the cross-sectional questionnaire survey and were contacted. Sixty-seven patients and 60 controls responded corresponding to an overall response rate of 62%.

Operated patients and controls

Operated patients and controls were well matched regarding prognostic group ($p = .26$). However, despite efforts to age-match operated patients and controls, operated patients were slightly younger (40.3 years [95% CI: 37.9;

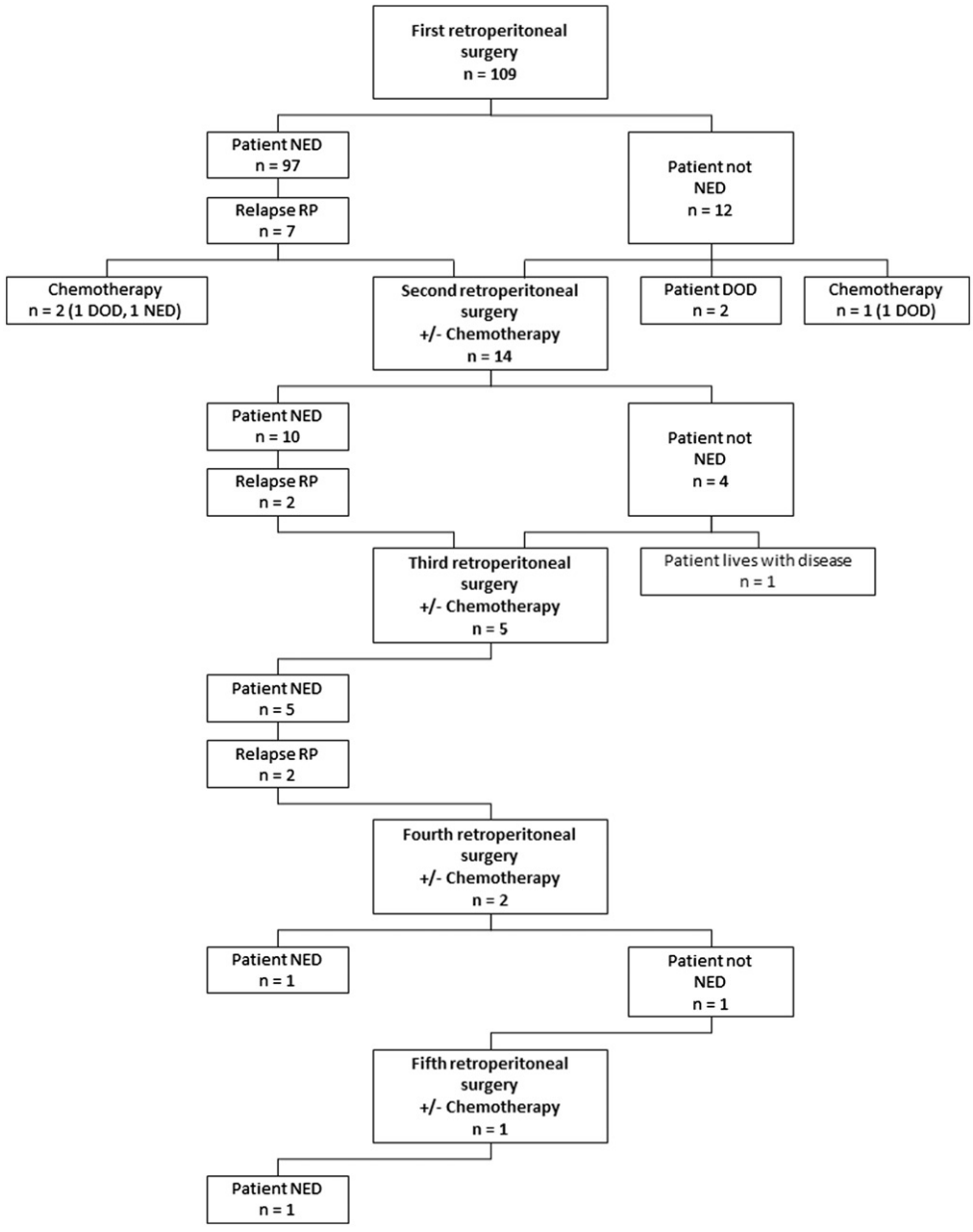

Figure 1. Overview of oncological survival and surgeries performed. NED: no evident disease; RP: retroperitoneum; DOD: died of disease.

Table 3. Pathology of relapsing tumour mass in retroperitoneum.

Histology	*n* (%)
GCT	3 (30)
Teratoma	4 (40)
Necrosis	1 (10), 1 (100)[a]
GCT and teratoma	1 (10)
Somatic transformation of teratoma to sarcoma	1 (10)

Histology of relapse in retroperitoneum.
GCT: germ cell tumour
[a]One second relapse occurred with the histology of necrosis.

42.9]) than the controls (44.2 years [95% CI: 41.9; 46.7]) ($p = .03$).

Table 5 shows differences between operated patients and controls regarding basic information, work/study activity and somatic symptoms. There were no statistically significant differences between operated patients and controls regarding all items listed in Table 5. Sixty-one (91%) of the operated patients and 54 (90%) of the controls were working/studying at the time of investigation.

In the cross-sectional survey, 17 operated patients (25%) and four controls (7%) reported loss of antegrade ejaculation ($p = .009$). Considering the relatively high number, the operated patients and controls were contacted to confirm the condition. Nine operated patients (13%) and one control (2%) confirmed incomplete retrograde ejaculation, and five operated patients (7%) confirmed complete retrograde ejaculation. Two operated patients and one control were not reachable for further information.

When combining answers from questionnaires and hospital records, 23 operated patients (20%) reported loss of antegrade ejaculation.

Table 6 presents the distribution of the scales of EORTC QLQ-C30. We found a statistically significant difference

Table 4. Intra[a]- and post-operative complications[b].

	n (%)	–	–	Treatment	CD
Intraoperative complications, $n = 25$					CD
Renal infarction	1 (4)	–	–	None	–
Injury of renal artery	1 (4)	–	–	Reconstructed	–
Injury of renal vein	5 (20)	–	–	Reconstructed	–
Injury of ureter	2 (8)	–	–	Reconstructed	–
Injury of suprarenal vein	1 (4)	–	–	Closed	–
Injury of inferior caval vein	7 (28)	–	–	Reconstructed	–
Injury of aorta	2 (8)	–	–	Reconstructed	–
Injury of iliac artery	1 (4)	–	–	Reconstructed	–
Injury of small intestine	5 (20)	–	–	Reconstructed	–
	<30 d, *n* (%)	>30 d, *n* (%)	>90 d, *n* (%)		
Postoperative complications, $n = 62$					
Bowel obstruction					
Mechanic	1 (2)	–	3 (5)	Surgery	IIIb
Paralytic	1 (2)	1 (2)	1 (2)	Conservative treated	II
Ascites/abdominal abscess	1 (2)	–	1 (2)	PD	IIIa
Abdominal hernia	–	–	9 (15)	3 NT	I
				6 Surgery	IIIb
Denervation/atrophy of abdominal muscles	–	–	3 (5)	NT	I
Lung complications (Atelectasis, pleural effusion and pneumonia)	8 (13)	–	–	1 Physiotherapy	I
				1 PD	IIIa
				6 AB	II
Lymphocele	6 (10)	9 (15)	1 (2)	14 NT	I
				2 PD	IIIa
Hydronephrosis with or without acute renal failure	3 (5)	2 (3)		3 NT	I
				1 Nephrostomy and medically treated	IIIa
				1 Nephrostomy and JJ-catheter	IIIb
Wound infection	2 (3)	–		1 No AB	I
				1 AB	II
Haematoma under cicatrice	1 (2)	–		Treated during surgery due to bowel obstruction	IIIb
Keloid formation in cicatrice	–	–	2 (3)	1 NT	I
				1 Injections of steroid	II
Decubitus	1 (2)	–		Cleansing and repositioning	I
Temperature and CRP increasing with no focus	4 (6)	–		AB	II
Repeated surgery due to bleeding	1 (2)	–		Haemostasis – bleeding stopped	IIIb
Nausea and vomiting, patient not able to eat	1 (2)	–		Gastroscopy verified oesophageal ulcer – medically treated/stomach tube	IIIa

Intra- and post-operative complications, postoperative complications divided in occurrence <30 d, >30 d and >90 d after surgery including the Clavien-Dindo score.
CD: Clavien-Dindo classification of surgical complications; AB: antibiotic treatment; PD: percutaneous drainage; NT: no treatment
[a]Intra-operative complications defined as complications occurring during the time of surgery.
[b]Post-operative complications defined as complications occurring after surgery.

concerning nausea and vomiting (p=.04). However, the absolute difference in scores was less than 10 points, which is considered the limit of clinical importance. We did not find statistically significant differences regarding other scales listed in Table 6.

Discussion

Surgical resection of residual masses after chemotherapy remains an integrated and important part of treatment for metastatic testicular cancer [3,6,8,9].

Due to the diversity in reporting results of retroperitoneal dissection for NSGCT, comparison of survival outcome and complications across studies is difficult. Our study is retrospective, and reviewing hospital records dating back to 1993 was a challenge. Overall, the records were comprehensive and were meticulously reviewed. We found the data reliable as very little information was missing. To obtain comparable data, we found two retrospective studies reporting experience with retroperitoneal dissection for NSGCT, none of them reporting on criteria for choosing between treatment options. A study from Montreal, in which a bilateral retroperitoneal dissection for NSGCT was performed in 73 patients, four patients received extended template, two patients received right or left unilaterally modified template and 33 of the 73 patients received nerve-sparing procedure. The patients were included if normal post-chemotherapy serum tumour marker levels were present, if no prior surgical attempts to resect retroperitoneal tumours had been performed, if the tumour mass was considered resectable and if the histology was NSGCT [19]. In the second study, from Lyon, in which 151 consecutive patients with NSGCT received lymph node dissection, 75 had full template lymph node dissection and 76 had modified template dissection [20].

Compared to template lymph node dissection, gross tumour resection could be expected to result in more

Table 5. Differences between operated patients and controls regarding basic information, work/study activity and somatic symptoms.

Subject	Operated patients, frequencies	Controls, frequencies	p^*
Living with a partner	Yes/no 18/49	Yes/no 12/48	.36
Drinking alcohol	Yes/no 12/55	Yes/no 8/52	.63
Smoking habits	Yes/no/has smoked 7/40/20	Yes/no/has smoked 13/34/13	.18
Co-morbidity	None/1 illness/2 illnesses/3 + illnesses 47/15/3/2	None/1 illness/2 illnesses/3 + illnesses 43/15/2/0	.75
Educational level	No education/trained/university 5/27/35	No education/trained/university 10/26/24	.20
Being fired from work	Yes/no 7/60	Yes/no 7/51	.78
Having to change job	Yes/no 9/57	Yes/no 7/52	.80
Professional help during rehabilitation	Yes/no 11/56	Yes/no 7/52	.61
Sick leaves	0-9/10-24/25 +[a] 47/10/4	0-9/10-24/25 +[a] 50/2/2	.06
Limitations at work	None/a few/some/several/a lot/not able to work 48/3/3/5/1/0	None/a few/some/several/a lot/not able to work 43/4/5/0/1/1	.10
Symptoms affect quality of work	Not at all/a little/quite a bit/very much 49/8/4/0	Not at all/a little/quite a bit/very much 43/8/2/1	.79
Symptoms affect quantity of work	Not at all/a little/quite a bit/very much 50/7/3/1	Not at all/a little/quite a bit/very much 46/5/3/0	.96
Self-ranked ability to work	1/2/3/4/5/6/7[b] 0/1/4/7/12/34	1/2/3/4/5/6/7[b] 1/0/4/5/12/32	.96
Ability to work the coming 2 years	Yes/not sure/no 54/6/1	Yes/not sure/no 52/2/0	.28
Loss of hearing/tinnitus	Yes/no 31/34	Yes/no 29/29	.80
Neuropathy	Yes/no 28/39	Yes/no 27/31	.60
Problems getting or maintaining erection	Not at all/a little/quite a bit/very much 44/15/4/4	Not at all/a little/quite a bit/very much 34/15/6/3	.76
Trying to conceive after treatment	Yes/no 31/36	Yes/no 29/28	.61
Ability to conceive	Yes/no 27/4	Yes/no 23/6	.41
Fertility treatment	Yes/no 17/14	Yes/no 13/15	.52

p^*:patients versus controls (Chi-square test or Fisher's exact test)
[a]number of sick days during the past year.
[b]1 indicates lowest ability to work and 7 indicates the best ability to work.

Table 6. Quality of life.

Scale	Operated patients mean (95% CI)	Controls mean (95% CI)	p^*
Global health status/QOL	76 (71–82)	74 (69–80)	.44
Physical functioning	93 (89–97)	96 (94–99)	.46
Role functioning	88 (82–94)	94 (90–97)	.56
Emotional functioning	85 (80–90)	89 (85–92)	.80
Cognitive functioning	86 (81–91)	84 (79–89)	.42
Social functioning	90 (85–96)	92 (88–96)	.52
Fatigue	19 (12–26)	17 (12–22)	.49
Nausea and vomiting	4 (1–8)	1 (0–1)	.04
Pain	10 (5–16)	9 (5–13)	.48
Dyspnoea	10 (4–15)	9 (5–14)	.49
Insomnia	15 (9–22)	16 (10–22)	.40
Appetite loss	5 (1–9)	4 (1–8)	.91
Constipation	5 (1–9)	3 (0–6)	.86
Diarrhoea	7 (3–12)	5 (2–8)	.59
Financial difficulties	12 (5–19)	8 (2–14)	.47

Mean and 95% CI of EORTC QLQ-C30 for operated patients and controls.
p^*: operated patients versus controls (Wilcoxon's rank sum test).

relapses in the retroperitoneum. This, however, does not seem to be the case. In Montreal, 2.7% and in Lyon 10% relapsed in the retroperitoneal space compared to 9% in the Aarhus cohort [19,20]. In the Lyon study, 17 patients (11%) ultimately died from disease progression compared to four (4%) in our study [20]. In the Montreal series, the estimated 5-year survival rate was 91.2% indicating a fatality rate around 8–9% [19]. One other study from Ankara, Turkey, reported oncological survival on limited resection of residual masses. In this study, 75 patients had a resection of residual masses alone, and only two (3%) had relapse in the retroperitoneal space. Overall survival rate in the Turkish study was

89% compared to 96% in this study [21]. A study from Indiana, USA, reports long-term follow-up data (10 years) on 100 patients receiving either left- or right-modified template surgery after primary chemotherapy for NSGCT [22]. Patients were included if they presented limited residual retroperitoneal disease and normal serum tumour markers after chemotherapy. Desperation and re-resections were excluded. This group corresponds to the 97 patients in this study, who had NED after surgery. The Indiana study reports a 10-year survival of 99% corresponding to the survival rate in the group of 97 patients in this study. Four patients (4%) in the Indiana study had relapse in the inguinal canal or in the retroperitoneal or retrocrural space compared to seven (7%) of the 97 patients in our study.

The rate of relapse and death due to disease progression does not seem to be negatively influenced compared to full template and modified template resections practiced elsewhere.

The removal of residual masses in the retroperitoneum is a major operation, and a number of both intra- and post-operative complications are to be expected. In face of the widespread use of these procedures, relatively few clinical studies have focused on intraoperative complications. Those that have, report on the need for additional procedures such as nephrectomy or repair of ureters and vascular resections in terms of replacement or reconstruction due to injury of the inferior vena cava, aorta, iliac artery and renal vessels [19,23,24]. In the post-operative setting, pulmonary complications including pneumonia and atelectasis, lymphocele, wound infections, gastrointestinal complications including bowel obstruction (paralytic and mechanic), urinary tract infection and hernia are among the common complications reported. Of more rare complications, retroperitoneal bleeding, renal infarction, pancreatitis and pulmonary complications, such as pulmonary emboli and respiratory failure, femoral neuropathy, lymphedema of leg, leg ischemia, iliac deep vein thrombosis, renal artery thrombosis, multi organ-failure and death are reported [19,20,23–25].

Five (7%) cases of nephrectomy and eight (11%) cases of vascular resection were reported in the Montreal study [19]. In Lyon, vascular resection was performed in 10 patients (7%), and two patients (1%) had nephrectomies [20]. In this study, 17 cases of vascular resection (15%) were performed. In the light of the number of patients studied, we consider the rate of vascular resections to be similar in the three studies. In the Montreal study, the Clavien-Dindo scoring was reported, and 12.3% of the patients experienced grade I complications, 7% grade II, 15.4% grade III, 4.2% grade IV, while there were no grade V complications. Grade I complications are by nature associated with significantly more uncertainty in retrospective studies than grade II and above. This is simply because of diversity in the documentation in hospital records of minor deviations from the normal post-operative course. Compared to our study, we found more patients having grades I–III (34.7% vs. 54%) but no patients having grade IV complications. No time perspective of the Clavien-Dindo score was given in the Montreal study, but median follow-up time was 47 months compared to 124 months in our study. A large part of the reported grade IIIb complications in our study were hernias and mechanic bowel obstructions, which can occur late in the follow-up period and thus partly can be explained by the longer follow-up. Lymphocele developed at similar rates; 10.9% of the patients in the Montreal study and 14.6% in the Lyon study compared to 14% in our study. The Lyon study does not report Clavien-Dindo scores but found intestinal occlusion (4.6% vs. 2%) and haemorrhagic complications (1.9% vs. 1%) slightly more often than in our study [19,20].

Repeated operative procedures are more likely to induce complications and in itself represent a risk factor for a poor oncological result [6]. In the Montreal study, no patients with prior attempt of retroperitoneal resection were included, and in the Lyon study, only three patients received repeated surgery. Considering that 22 of the 131 operations performed in this study were repeated surgeries, a higher rate of complications was to be expected. However, the complication rates found in this study conclusively seem to be comparable with the few other investigations available in the literature.

Loss of antegrade ejaculation is a well-known complication experienced after surgery in the retroperitoneal space [26]. In all, we found that 80% of the operated patients maintained antegrade ejaculation. Three controls and one patient reported retrograde ejaculation, the latter reporting presence of the condition before surgery. This demonstrates that chemotherapy might play a role in losing the ability to have antegrade ejaculation. Cisplatin is known to cause peripheral neuropathy, but the effects on the autonomic nervous system are controversial [27,28]. Retrograde ejaculation due to cisplatin has, to our knowledge, not previously been described. Two operated patients in our study have successfully used Imipramine to restore retrograde ejaculation. There are reports on Imipramine used to restore antegrade ejaculation [29], and the achievement in our study confirms the relevance of this drug.

When full template lymph node dissection is performed, only 25% maintain antegrade ejaculation [30]. In the Lyon data based on full template or modified resection, 62% maintained antegrade ejaculation [20]. When nerve-sparing procedure is performed, available data suggest that antegrade ejaculatory function can be preserved in between 89 and 79% of patients [6,26,30,31]. Of the 75 patients undergoing limited surgery in Ankara, ejaculatory status was known for 62 patients; 95.2% had preserved ejaculatory function [21].

Preserving ejaculation obviously correlates with the extent of surgery performed. This cohort, representing consecutive patients with both advanced and limited residual disease, compares favourably with the available studies reporting on ejaculatory function with template resections.

Considering QOL, we found no statistically significant differences between patients having retroperitoneal surgery and controls in any areas concerning work and study. This indicates that the surgical intervention does not influence the occupational possibilities of patients after treatment for testicular cancer.

We only found one scale, nausea and vomiting, to show statistically significant differences between the surgical patients and the controls. Differences less than 10 (on a scale of 100) are considered clinically irrelevant. Given that the

absolute difference was three, the difference is considered not clinically significant. One scale, role functioning, did differ between five and 10 in mean score, but the difference was not statistically significant.

We did not find disparities in any of the QOL scales by more than 10 points in either surgical patients or controls when comparing QOL to healthy Danish men in the age 40–49 [32]. If anything, differences indicated less pain, less insomnia and better functioning (except cognitive functioning) in GCT patients. The size of this cohorts does not, however, allow detailed analysis to rule out minor differences. The response rate among candidates in this study was 62%, which is in line with what has been achieved in other retrospective cohort analyses, and we consider it sufficient material to evaluate the chosen end points regarding QLQ.

In summary, we found no significant, clinically relevant differences between the operated patients and controls. The tumour resections without elective lymph node removal performed in this study thus do not seem to affect later QOL.

The EUA guidelines recommend resection of any residual tumour >10 mm as has been done in the present series. All primary metastatic sites should be resected and, if possible, nerve-sparing procedure should be performed. Lumpectomy, mere resection of residual tumour, is, however, not recommended [9]. Due to lack of evidence of clinical benefits by removing clinically uninvolved lymph nodes, the procedure in Aarhus has been to remove all residual tumours >10 mm with no further template resection. Targets for surgical removal were decided on an individual basis at a tumour board conference evaluating pre-chemotherapy and immediate post-chemotherapy scans.

The majority of late relapses showed teratoma on histology as expected. Ten patients had 11 relapses, nine were in field of prior surgery and two were out of field. In six patients, bulky, locally advanced disease had compromised complete resection, and template resection of other areas would not have prevented these infield relapses. Of the remaining four patients, two relapsed in the field of prior surgery, two outside the field. Relapse outside the field was for one patient inside the target area for full template resection, the other one in the pelvis. Thus, in our series, only one patient would obviously have benefitted from template lymph node resection and probably have avoided relapse.

Standard follow-up after treatment of testicular cancer in Denmark is five years after achieving NED. This period is extended to ten years if a relapse occurs. In case of multiple relapses, control will be life-long. The number of very late relapses in this cohort, however, raises questions regarding the need for longer follow-up in a wider category of patients.

The tumour resection of all residual elements >10 mm, without elective lymph node dissection, applied systematically in this consecutive cohort study is associated with a relatively low risk of complications. The survival does not seem inferior to that obtained in studies applying template resections. We find that gross tumour resection appears an applicable and safe procedure for patients with residual retroperitoneal tumour after chemotherapy for testicular cancer. The surgery as such did not seem to influence the long-term QOL or occupational status. Further data on limited surgery with long-term follow up are needed. We are aware of the inherent heterogeneity and the relatively small size of this cohort and advocate for further studies on limited surgery.

Disclosure statement

The authors report no conflicts of interest.

Funding

This work was supported by Aarhus University.

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