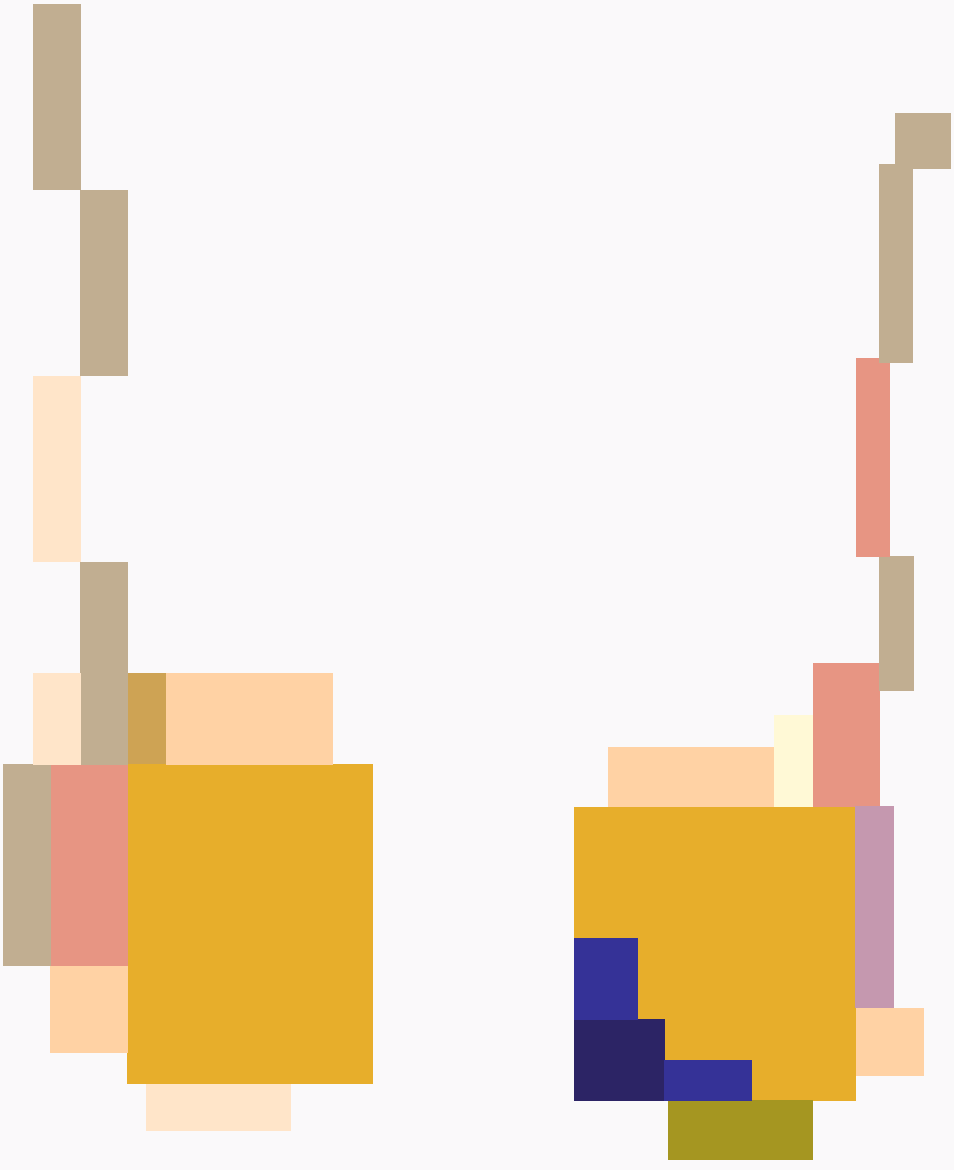
Advancements in the multimodal treatment of testicular germ cell tumor

Joost M. Blok



ADVANCEMENTS IN THE MULTIMODAL TREATMENT OF TESTICULAR GERM CELL TUMOR

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ADVANCEMENTS IN THE MULTIMODAL TREATMENT OF TESTICULAR GERM CELL TUMOR

Vooruitgang in de multimodale behandeling van testiculaire kiemceltumor
(met een samenvatting in het Nederlands)

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Chapter

General introduction and thesis outline

Introduction

Epidemiology and survival

Testicular germ cell tumor (TGCT) is a relatively rare form of cancer and accounts for approximately 1% of all male cancers [1]. It is mostly diagnosed at a young age, with peak incidence between 20 to 35 years. This makes TGCT the most common type of cancer among young men [2].

TGCT incidence has distinct geographical differences and primarily affects Caucasian men [3–5]. The age-standardized incidence rates (ASRs) are highest in Northern and Western Europe, with 6.7 and 7.8 cases per 100.000 men, respectively. The incidence is highest in Norway (9.9 per 100.000) and Denmark (9.4 per 100.000). In The Netherlands, approximately 800 new cases are diagnosed each year, corresponding to an ASR of 6.4 per 100.000 [1,6].

In contrast, the lowest incidence is observed in African and Asian populations, with multiple countries reporting ASRs <1 per 100.000. The fact that TGCT primarily affects Caucasian males is also reflected in epidemiological data from the United States, where TGCT is five times more common among white men (6.2 per 100.000) compared to black men (1.2 per 100.000) [1].
TGCT incidence is increasing worldwide, for which the reasons are mostly unknown [1,2,7]. In the past two decades, this increase was most evident in Southern Europe, with average increases of 6% per year in Croatia and Spain [1]. In The Netherlands, TGCT incidence increased with 4% per year between 1999 and 2008 [1]. It is estimated that the incidence will increase by an average of 13% in Europe over the period 2010-2035 [8].

The prognosis of TGCT in general is very favorable with an overall 5-year survival rate of approximately 95%. At initial presentation, the majority of patients have stage I disease, which has a 15-year cancer-specific survival rate higher than 99% [9,10].

Etiology

The 2016 World Health Organization classification system for TGCT recognizes three types of TGCTs [11]. Type I TGCTs are mostly diagnosed in prepubertal boys (< 14 years old) and can be further subdivided in benign teratoma and malignant yolk sac tumor. Type III TGCTs were previously known as spermatocytic seminoma and are predominantly diagnosed in elderly men. Both type I and type III TGCTs do not arise from the precursor germ cell neoplasia in situ (GCNIS) [7].

The most common type of TGCTs are type II TGCTs. These tumors arise from GCNIS, are always malignant and are histologically divided into morphologically homogeneous seminomatous germ cell tumor (SGCT or seminoma) and heterogeneous nonseminomatous germ cell tumor (NSGCT or nonseminoma). NSGCT is divided into several histolopathological subgroups: embryonal carcinoma, teratoma, yolk sac tumor and choriocarcinoma. NSGCTs can be composed of one or more of these subgroups. Tumors that contain both SGCT and NSGCT

elements are classified as NSGCT [3,7]. Approximately 60% of TGCTs are SGCT with peak incidence at 35 years. The remaining 40% are NSGCT with a peak incidence at 25 years. This thesis only considers type II TGCT.

Several risk factors for TGCT have been established. The factor that is most consistently associated with an increased risk is cryptorchidism, a congenital disorder in which the testicle has not descended into the scrotum. Men with cryptorchidism have an almost fivefold increased risk of developing TGCT [12]. Other risk factors are hypospadias (a congenital disorder in which the urethral opening is not at the tip of the penis but somewhere lower at the ventral side of the penis), impaired spermatogenesis, history of previous TGCT and family history of TGCT [7,13–16].

However, it is unlikely that these risk factors predispose to the development of TGCT. Instead, there is increasing evidence that cryptorchidism, hypospadias, impaired spermatogenesis and TGCT share a common causal pathway, which has led to the postulation of the testicular dysgenesis syndrome [15]. One suggested causal pathway is prenatal exposure to endocrine disrupting chemicals that impair androgen signaling in the fetus [17,18]. Whether postnatal environmental or lifestyle factors also play a role in TGCT development is still unclear.

Heritable factors play an important role in susceptibility to TGCT. The estimated heritability of TGCT approaches 50%, which is among the highest of all cancer types [19]. In comparison, kidney and urinary bladder have an estimated heritability of 8% and 7%, respectively.

The high hereditability is also reflected by the high familial risk. Sons of fathers with testicular cancer have a two to six times higher risk of developing TGCT, compared to the general population. The relative risk is even higher in siblings, where brothers of men with testicular cancer have a four to ten times higher risk of developing TGCT [13,20,21]. The higher familial risk among brothers than fathers-sons suggests the involvement of a recessive or X-linked mode of inheritance or the importance of shared environmental effects [13]. Although genetics play an important role in testicular cancer development, more than 97% of patients do not have a family history positive for TGCT [13].

Clinical presentation, diagnosis and staging

Clinical presentation

The most common presentation of testicular cancer is a unilateral painless testicular mass. Scrotal pain or discomfort can be present, which is a potential cause of delayed diagnosis. Acute testicular pain is less common and caused by intratumor hemorrhage or infarction. In the case of metastatic disease or extragonadal germ cell tumor, patients can present with back pain, abdominal mass, lymphadenopathy or weight loss, although most are asymptomatic. Approximately 1-5% of patients present with gynecomastia caused by elevated levels of human choriogonadotropin (HCG) [22].

There is a high variation in patient delay and doctor delay. Two main factors can cause patient delay. First, TGCT involves young men in a period of their life when they do not perceive themselves as susceptible to serious disease. Second, it affects an intimate organ associated with masculinity and sexual functioning which can cause embarrassment [23]. There are also two main factors that can cause doctor delay: the disease is very rare (the average Dutch general practitioner sees a patient with TGCT only once every 10 years) and other causes of scrotal swelling are much more common (e.g. epididymitis, trauma) [23].

Diagnostic evaluation

The diagnostic evaluation of a patient suspected of TGCT includes physical examination, scrotal ultrasound, measurement of serum tumor markers, radical orchiectomy, and contrast enhanced computed tomography (CT) scanning.

Scrotal ultrasound is necessary to confirm and characterize the testicular tumor. Although an ultrasound is not sensitive enough to confidently distinguish between the two TGCT subtypes, there are some radiographic differences. In general, SGCTs appear as homogeneous hypoechoic lesions without cystic areas. NSGCT, on the other hand, are typically inhomogeneous with calcifications and cystic areas and have more indistinct margins.

In addition to the tumor, microlithiasis can be seen in the surrounding testicular tissue or in the contralateral testicle. The clinical significance and natural history of testicular microlithiasis remains unclear [24]. Multiple studies have found an association between microlithiasis and GCNIS but the microlithiasis seen on scrotal ultrasound is not always found in the biopsy or orchiectomy specimen [25,26].

TGCTs can produce three types of tumor markers: HCG, α-fetoprotein (AFP) and lactate dehydrogenase (LDH). The serum levels of these markers can give an indication of the tumor histology and are used for disease staging, treatment monitoring and relapse detection.

HCG is secreted by embryonal carcinoma, choriocarcinoma and in some cases also by SGCT. Levels higher than 500 IU/L are indicative of an NSGCT [3]. The serum half-life of HCG is 1-3 days and its levels are elevated in 40-60% of patients with NSGCT [27–29].

AFP is secreted by embryonal carcinoma and yolk sac tumors, and is therefore never elevated in SGCT. Patients with elevated AFP levels should be considered as having NSGCT, even if histopathological analysis of the orchiectomy specimen only shows seminomatous elements. AFP has a serum half-life of 5-7 days and is increased in approximately 50-70% of patients with NSGCT [27–29].

LDH is of limited use since it is not specific and remains persistently elevated in 30% of patients with metastatic disease after complete remission [27].

Serum levels of at least HCG and AFP should be measured before, during and after treatment and also during follow-up. After orchiectomy, serum levels should decrease according to their half-lives, since plateauing or elevating levels can indicate active disease.

A radical inguinal orchiectomy is indicated before the initiation of further treatment, because the definitive diagnosis of TGCT is based on tumor histology. The orchiectomy can be postponed only if a patient requires chemotherapy without delay [30].

Finally, a contrast enhanced CT scan of the abdomen, thorax and pelvis is necessary to assess whether there are any lymphatic or distant metastases present. A 10 mm short-axis lymph node diameter is the most often used cut-off value for suspected lymph nodes. In the case of small (<2 cm) retroperitoneal or thoracic masses and negative tumor markers, restaging after six to eight weeks is recommended. In the case of contrast allergy, a non-contrast CT is indicated.

There are currently no indications for magnetic resonance imaging (MRI) or fluorodeoxyglucose-positron emission tomography CT scanning (FDG-PET/CT) for routine staging of TGCT. The accuracy of MRI is similar to CT but is more expensive and subject to greater artefacts. The only indication of FDG-PET/CT is the assessment of tumor activity in SGCT patients with postchemotherapy residual tumor >3 cm [31].

Table 1. TNM classification for TGCT [31]

pT	Primary Tumor
pTx	Primary tumor cannot be assessed (no radical orchiectomy has been performed)
pT0	No evidence of primary tumor (e.g. histological scar in testis)
pTis	Intratubular germ cell neoplasia in situ
pT1	Tumor limited to testis and epididymis without vascular/lymphatic invasion; tumor may invade tunica albuginea but not tunica vaginalis
pT2	Tumor limited to testis and epididymis with vascular/lymphatic invasion, or tumor extending through tunica albuginea with involvement of tunica vaginalis
pT3	Tumor invades spermatic cord with or without vascular/lymphatic invasion
pT4	Tumor invades scrotum with or without vascular/lymphatic invasion
N	**Regional Lymph Nodes (Clinical)**
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis with a lymph node mass 2 cm or less in greatest dimension or multiple lymph nodes, none more than 2 cm in greatest dimension
N2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence of extranodal extension of tumor
N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension

Table 1. TNM classification for TGCT [31] *(continued)*

pN	**Regional Lymph Nodes (Pathological)**		
pNx	Regional lymph nodes cannot be assessed		
pN0	No regional lymph node metastasis		
pN1	Metastasis with a lymph node mass 2 cm or less in greatest dimension and 5 or fewer positive nodes, none more than 2 cm in greatest dimension		
pN2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence of extranodal extension of tumor		
pN3	Metastasis with a lymph node mass more than 5 cm in greatest dimension		
M	**Distant Metastasis**		
Mx	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
M1b	Non-regional lymph node(s) or lung metastasis		
M1a	Distant metastasis other than non-regional lymph nodes and lung		
S	**Serum Tumor Markers (After Orchiectomy)**		
Sx	Serum marker studies not available or not performed		
S0	Serum marker study levels within normal limits		
	LDH (U/L)	**HCG (mIU/mL)**	**AFP (ng/mL)**
S1	<1.5 x ULN and	<5,000 and	<1,000
S2	1.5-10 x ULN or	5,000-50,000 or	1,000-10,000
S3	<10 x ULN or	<50,000 or	<10,000

ULN: Upper limit of normal range

Disease staging

TGCT primarily disseminates to the retroperitoneal lymph nodes. Hematogenic dissemination is possible and mostly seen in addition to lymphatic dissemination. The pattern of lymphatic dissemination is sequential according to the vertical route of the lymphatics in which regional lymph node metastases first arise in the retroperitoneum.

The pattern of lymphatic dissemination in the retroperitoneum depends on whether the primary tumor originated in the left or right testis. Tumors of the left testis initially disseminate to the para-aortic lymph nodes, followed by the inter-aortocaval nodes. A solitary inter-aortocaval lymph node metastasis in a patient with a left-sided TGCT is rare [32,33]. Right-sided tumors have a more heterogeneous pattern of dissemination. Their most common sites of dissemination are the inter-aortocaval, paracaval and precaval lymph nodes.

Table 2. Stage grouping [31]

Stage	T stage	N stage	M stage	S stage
Stage 0	pTis	N0	M0	S0
Stage I	pT1-T4	N0	M0	Sx
IA	pT1	N0	M0	S0
IB	pT2 - pT4	N0	M0	S0
IS	Any pT/Tx	N0	M0	S1-3
Stage II	Any pT/Tx	N1-N3	M0	Sx
IIA	Any pT/Tx	N1	M0	S0
	Any pT/Tx	N1	M0	S1
IIB	Any pT/Tx	N2	M0	S0
	Any pT/Tx	N2	M0	S1
IIC	Any pT/Tx	N3	M0	S0
	Any pT/Tx	N3	M0	S1
Stage III	Any pT/Tx	Any N	M1a	Sx
IIIA	Any pT/Tx	Any N	M1a	S0
	Any pT/Tx	Any N	M1a	S1
IIIB	Any pT/Tx	N1-N3	M0	S2
	Any pT/Tx	Any N	M1a	S2
IIIC	Any pT/Tx	N1-N3	M0	S3
	Any pT/Tx	Any N	M1a	S3
	Any pT/Tx	Any N	M1b	Any S

Dissemination to the contralateral side of the retroperitoneum is rare in left-sided tumors and associated with bulky disease. For right-sided primary tumors, however, retroperitoneal crossover is more common due to the natural pathway of lymphatics to the cisterna chyle [32,33]. From the retroperitoneal lymph nodes, tumor cells can disseminate via the thoracic duct to the mediastinum and the supraclavicular lymph nodes.

The lungs are the most common site of hematogenic tumor spread. There are two main routes of hematogenic spread: either directly via vascular invasion of the tumor in the testis, or indirectly via the retroperitoneal lymph nodes, cisterna chyli and thoracic duct to the subclavian vein. Dissemination to the liver, brain or bone is rare and associated with extensive metastatic disease and poor outcome [34].

Disease staging is based on the TNM classification and depends on the anatomical extent of the disease and prechemotherapy levels of tumor markers (Tables 1 and 2). Approximately two-thirds of patients initially present in Clinical Stage I (CS I) [35].

Patients with advanced disease are grouped according to the International Germ Cell Cancer Collaborative Group (IGCCCG) prognostic classification system (Table 3). This system is based on tumor histology, primary tumor site (TGCT versus extragonadal germ cell tumor), presence of metastases and levels of serum tumor markers (drawn shortly before to the initiation of chemotherapy and after orchiectomy). There are three prognostic groups for NSGCT patients and two for SGCT. The IGCCCG prognosis is one of the factors on which the treatment plan is based.

Table 3. IGCCCG prognostic-based staging system for metastatic germ cell cancer [31]

	Nonseminoma	Seminoma
Good prognosis group	*All of the following criteria* Testis/retroperitoneal primary No non-pulmonary visceral metastases AFP <1,000 ng/mL HCG <5,000 IU/L (1,000 ng/mL) LDH <1.5 x ULN	Any primary site No non-pulmonary visceral metastases Any marker level
Intermediate prognosis group	*Any of the following criteria* Testis/retroperitoneal primary No non-pulmonary visceral metastases AFP 1,000-10,000 ng/mL, or HCG 5,000-50,000 IU/L, or LDH 1.5-10 x ULN	Any primary site Presence of non-pulmonary visceral metastases Any marker level
Poor prognosis group	*Any of the following criteria* Mediastinal primary Presence of non-pulmonary visceral metastases AFP >10,000 ng/mL, or HCG >50,000 IU/L (10,000 ng/mL), or LDH >10 x ULN	No patients are classified as poor prognosis

Prognostic classification is primarily based on the levels of serum tumor markers immediately prior to administration of chemotherapy (same day).
AFP = alpha-fetoprotein; HCG = human chorionic gonadotrophin; LDH = lactate dehydrogenase; ULN = upper limit of normal range

Disease management

Management of localized disease

The management of localized TGCT (Clinical Stage I, CS I) depends on the tumor histology (SGCT or NSGCT) and risk of relapse. Long-term survival is expected in almost all cases, with reported survival rates of up to 100% [36–38]. However, a substantial proportion of CS I patients have microscopic metastases at the time of first presentation and will relapse without adjuvant treatment. This is the case in approximately 30% of NSGCT patients and 15% of SGCT patients [37–41].

Therefore, much attention has been given to identify risk factors for relapse, in order to select patients who would benefit from adjuvant treatment. In SGCT, patient selection is mainly based on two histopathological features of the primary tumor: presence or absence of rete testis invasion (RTI) and tumor size >4 cm [42]. Patients with one or two risk factors are considered high-risk. The relapse risk in patients with two risk factors is 30%, compared to 6% in patients without risk factors [43,44]. In NSGCT, risk stratification is based on the presence or absence of lymphovascular invasion (LVI) of the primary tumor. The five-year relapse risk with LVI is 50%, compared to 15-20% without LVI [30,31,45]. The presence of embryonal carcinoma in the primary tumor is another possible risk factor, although its prognostic value is still unclear [31].

The predominant treatment strategy of low-risk patients in Europe is surveillance [30,31]. This consists of repeated clinical assessment, CT-scans and measurement of serum tumor markers for at least 5 years. More than 90% of relapses occur within the first two years after orchiectomy. Therefore, the intensity of the follow-up visits can be decreased after this period. Many protocols for active surveillance exist and current European guidelines only recommend a certain minimal follow-up (Table 4).

High-risk SGCT is treated with either surveillance, adjuvant chemotherapy or adjuvant radiotherapy. Adjuvant chemotherapy (one cycle of carboplatin) reduces the recurrence rate from 15-30% to 9%, but strict follow-up with imaging and serum tumor markers is still necessary [30,37,46]. Adjuvant radiotherapy has similar results, but a possible higher risk of radiation-induced tumors. Therefore, adjuvant radiotherapy is only recommended if surveillance and adjuvant chemotherapy are not possible [30,31].

In high-risk NSGCT, there are two preferred treatment modalities: surveillance or adjuvant chemotherapy. Surveillance is associated with a relapse rate of 50%. Adjuvant therapy with one cycle of bleomycin, etoposide, cisplatin combination chemotherapy (BEP) results in a relapse risk of 2-3% [30,47], which suggests that adjuvant chemotherapy prevents >90% of relapses. There is no difference in survival between the two modalities, although salvage chemotherapy for relapse after surveillance is associated with serious short- and long-term side-effects [48–51]. High-risk patients can also be treated with primary retroperitoneal lymph node dissection (P-RPLND). This is an extensive surgical procedure associated with high morbidity and should

only be performed by experienced surgeons in high-volume centers. A recent randomized study in NSGCT CS I patients found a relapse rate of 1.6% after one cycle of BEP, compared to 8.4% after P-RPLND [52]. After more than 13 years follow-up, there were no significant differences in toxicities, apart from retrograde ejaculation, which was more frequent after P-RPLND. The excellent survival rate of surveillance with salvage treatment in case of relapse and the low relapse rate after adjuvant chemotherapy have diminished the role of P-RPLND in Europe [31].

Patients should be informed of all treatment options, including the potential advantages and disadvantages. The best treatment approach is tailored to the individual patient and based on shared-decision making with the patient and his health-care provider.

Table 4. Recommended minimal follow-up in CS I TGCT [31]

4a. Seminoma

Modality	Year 1	Year 2	Year 3	Years 4 & 5	After 5 years
Tumor markers	2 times	2 times	2 times	Once	Further follow-up according to survivorship care plan
Abdominopelvic CT imaging	2 times	2 times	At 36 months	At 60 months	

4b. Nonseminoma

Modality	Year 1	Year 2	Year 3	Years 4 & 5	After 5 years
Tumor markers	4 times	4 times	2 times	1-2 times	Further follow-up according to survivorship care plan
Chest X-ray	2 times	2 times	Once, in case of LVI	At 60 months, in case of LVI	
Abdominopelvic CT imaging	2 times	At 24 months	At 36 months	At 60 months	

Management of advanced disease

Patients with advanced disease are predominantly treated with three or four cycles of BEP combination chemotherapy, according to their IGCCCG risk category. Patients in the good IGCCCG prognosis category receive three cycles of BEP or, in the case of contra-indications against bleomycin, four cycles of etoposide and cisplatin (EP) chemotherapy. Patients in the intermediate and poor IGCCCG prognosis category receive four cycles of BEP.

Surgery after combination chemotherapy

A substantial proportion of patients who undergo cisplatin-based combination chemotherapy for metastatic TGCT have significant residual retroperitoneal disease with normalized tumor markers. This is the case in approximately one-third of patients with NSGCT [53,54].

Surgical resection of the residual mass is indicated if the mass is larger than 1 cm in diameter [31,55]. The rationale for this approach is that these masses contain vital cancer in 6-10% and teratoma in up to 50% of patients [56,57]. In the remaining 40-50% of patients, the residual mass contains only fibrosis or necrosis. Because there are currently no validated methods to reliably predict the histology of a residual mass, postchemotherapy retroperitoneal lymph node dissection (PC-RPLND) remains important in patients with significant residual disease [58].

There has been an ongoing debate concerning the anatomical extent of PC-RPLND for many years. Early lymphatic mapping studies have identified the primary landing sites of metastases in TGCT. In 1974, Ray et al. retrospectively analyzed the primary sites of metastatic involvement in a cohort of 283 patients undergoing RPLND [32]. The authors found that right-sided tumors disseminated predominantly to the inter-aortocaval (69% of cases) and precaval (31%) lymph nodes. For left-sided tumors, the predominant regions were para-aortic (99% of cases), and inter-aortocaval (20%) [32].

In 1987, Weissbach and Boedefeld investigated the localization of metastases in 214 clinical stage II patients [33]. In 84.5% of CS II patients with left-sided testicular germ cell tumor, the para-aortic lymph nodes were involved. In right-sided tumors, metastases were most commonly found in the inter-aortocaval (44%) region.

Both studies concluded that left-sided tumors show a more uniform pattern of dissemination than right-sided tumors. The primary landing zone for left-sided tumors is the left para-aortal region (between the aorta and left ureter). For right sided tumors, the primary landing zone is the right para-caval region (between the vena cava and the right ureter) or the interaortocaval region. In both cases, the cranial boundaries of the primary landing zone are the renal vessels and the caudal boundaries are the crossing of the ureter with the common iliac artery [32,33].

Historically, a bilateral template-based dissection was the standard approach in all patients undergoing PC-RPLND [58]. This procedure involves resecting all lymphatic tissue within the template, along with the residual tumor. The anatomical boundaries of the bilateral template are based on the early mapping studies: the renal vessels cranially, the ureters laterally and the crossing of the ureter with the common iliac artery caudally.

This approach, however, is associated with high morbidity, including ejaculatory dysfunction due to interruption of the sympathetic nerves and the hypogastric plexus. To reduce morbidity, modified unilateral templates limiting contralateral dissection have been developed, based on nodal mapping studies. Multiple modified templates with their own specific anatomical

boundaries have been proposed; their common denominator is that the lymphatic tissue on the contralateral retroperitoneal region is not resected. The literature on the perioperative morbidity of PC-RPLND is limited and more research on the identification of patients with a high risk of a perioperative complication is necessary.

In general, the modified template of right-sided tumors is bounded by the right ureter laterally and the aorta medially. Thus, the lymphatic tissue in the left-para-aortic region is not dissected. For left-sided tumors, the template consists of only the left-para-aortic region; it is bounded by the left ureter laterally and the aorta medially and does not include the interaortacaval region. The cranial and caudal boundaries of the modified (or "unilateral") templates are the same as in the bilateral template.

Although template-based resection (bilateral or modified) is advocated by current guidelines, some centers regard the resection of the residual mass only as oncologically equivalent [59]. With this approach, the residual mass and enlarged lymph nodes identified on imaging or during surgery are resected (residual mass resection, RMR). The tumor location prior to chemotherapy is taken into account and lymph nodes that were enlarged prior to chemotherapy are also resected. However, in contrast to template-based procedures, no template resection of clinically and radiologically unsuspicious lymph nodes is done.

Another development is the introduction of minimally-invasive (laparoscopic or robot-assisted) surgery in the postchemotherapy setting in order to reduce morbidity. It is important to bear in mind that the retroperitoneal specimen shows merely fibrosis or necrosis in up to half of patients with residual tumor [56,57,60]. Therefore, it could be argued that these patients have been unnecessarily exposed to the risks of PC-RPLND. Although large volume series are currently lacking, the minimal invasive approach is gaining recognition in the postchemotherapy setting. However, more research is necessary to establish the value and safety of minimally-invasive surgery, compared to open PC-RPLND.

Follow-up after curative therapy

Optimal follow-up is important for timely diagnosis of recurrences and monitoring of short- and long-term morbidity. Follow-up consists of outpatient visits for physical examination (including the contralateral testicle), serum tumor marker analysis, and radiological examinations.

As in CS I disease, there are multiple follow-up schedules and current guidelines state only a minimal amount of follow-up. Follow-up should be tailored to the individual patient, taking into account their relapse risk, comorbidities and personal preferences.

Patients with unilateral TGCT are at increased risk of developing TGCT in the contralateral testicle (CTGCT). This risk is approximately 12-18 times higher, compared with the general population. After 20-years, approximately 2-5% of patients with TGCT will have developed CTGCT [61–64]. A well-known risk factor for developing CTGCT is diagnosis of a first TGCT

before the age of 30 years [65–67]. The role of the histopathology of the first TGCT (NSGCT or SGCT) and prior treatment with chemotherapy are less clear.

Routine biopsy of the contralateral testis in all patients is not recommended. After all, the incidences of contralateral GCNIS and CTGCT are low, testicular biopsy and GCNIS treatment can cause significant morbidity and most metachronous CTGCTs are diagnosed at an early stage. Current European Association of Urology (EAU) and European Society for Medical Oncology (ESMO) guidelines advocate discussing the pros and cons of a contralateral biopsy in patients at high risk for contralateral GCNIS, i.e. patients <40 years with testicular volume <12 mL and/or with a history of cryptorchidism [31,68].

Another long-term risk of TGCT survivors is the development of a late relapse (LR), defined as a relapse more than two years after completion of systemic therapy. Relapses more than five years after systemic therapy are classified as very late relapse (VLR).

LR is a rare event, with an incidence of approximately 1-2% in SGCT and 3-4% in NSGCT. VLR is even more rare, occurring in only 0.5% of patients [69]. Due to the rarity of the event, only few well-established cohort studies have been published and not much is known about the risk factors, detection methods and prognosis.

Most VLRs are diagnosed due to symptoms, since patients are generally followed for a maximum of five years. Both LRs and VLRs do not respond well to chemotherapy, which makes the treatment challenging. In the case of LR (or VLR) without elevation of serum tumor makers, radical surgical resection of all lesions is indicated.

Thesis outline

Approximately 30% of CS I NSGCT patients have occult metastatic disease in their retroperitoneal lymph nodes. **Chapter 2** systematically reviews the current literature on the two main histopathological risk factors for these microscopic metastases: lymphovascular invasion (LVI) of the primary tumor and the presence of embryonal carcinoma in the primary tumor. The major limitation to diagnose occult metastatic disease is the inability of current imaging modalities to detect microscopic tumor spread. The sentinel node procedure, in which the first-echelon lymph node is resected and histopathologically examined, is standard of care in several types of cancer [70]. In **chapter 3** we describe the long-term results of the sentinel node procedure for TGCT in a cohort of 25 patients.

Chapter 4 systematically reviews the clinical outcome of PC-RPLND, distinguishing between open and minimally-invasive procedures. There is an ongoing debate on the anatomical boundaries of PC-RPLND. The standard approach used to be a bilateral template-based dissection in all patients. More recently, a modified (or unilateral) template-based dissection is accepted in selected patients. Although current guidelines recommend template-based resection, some centers regard the resection of the residual mass only as oncologically equivalent (residual mass resection; RMR). In this approach, the residual tumor, all lymph nodes that were enlarged prior to chemotherapy and all enlarged lymph nodes identified on imaging or during surgery is resected. **Chapter 5** compares the oncological outcome of template-based PC-RPLND to RMR. PC-RPLND is a technically challenging procedure and associated with significant morbidity. An additional procedure (e.g. nephrectomy or vascular reconstruction) is necessary in approximately one-third of patients. **Chapter 6** evaluates the perioperative morbidity of PC-RPLND in two intermediate volume hospitals and identifies risk factors to identify patients who are at high risk of perioperative morbidity. In addition to a trend towards less extensive dissection, there is also a trend toward minimally invasive procedures. Several large volume studies have reported on the outcome of laparoscopic PC-RPLND, but only few studies have reported on robot-assisted tumor resection. **Chapter 7** describes the results of robot-assisted residual mass resection (RA-RMR) in patients with residual tumor after chemotherapy for disseminated NSGCT.

Patients with TGCT have an increased risk of developing contralateral TGCT (CTGCT). It has been suggested that prior treatment with platinum-based chemotherapy decreases CTGCT risk. However, a relationship between CTGCT risk and platinum dose has not been assessed. In **chapter 8** we analyzed the association between prior chemotherapy and CTGCT, with a special emphasis on platinum dose.

Chapter 9 provides a general discussion of this thesis and **chapter 10** provides a summary in English and Dutch.

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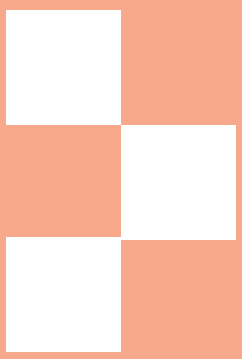
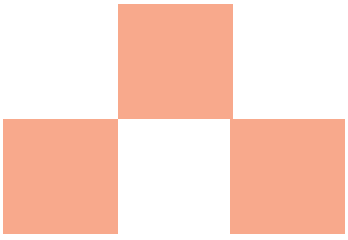
Part 1



Identification of microscopic metastases



2
Chapter

Lymphovascular invasion and presence of embryonal carcinoma as risk factors for occult metastatic disease in clinical stage I nonseminomatous germ cell tumor: a systematic review and meta-analysis

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Abstract

Objective

To systematically review the literature on the prognostic value of lymphovascular invasion (LVI) and embryonal carcinoma (EC) for occult metastatic disease in clinical stage I nonseminomatous germ cell tumor (CS I NSGCT).

Materials and Methods

The Pubmed, Embase (OVID) and SCOPUS databases were searched up to March 2019. Studies reporting on the association between LVI and/or EC and occult metastatic disease were considered for inclusion. The quality and risk of bias was evaluated by the Quality in Prognosis Studies tool.

Results

We screened 5,287 abstracts and 207 full-text articles. We included 35 studies in the narrative synthesis and 24 studies in a meta-analysis. LVI showed the strongest effect. Pooled rates of occult metastasis were 47.5% and 16.9% for LVI positive and LVI negative patients, respectively (odds ratio [OR] 4.33; 95% CI 3.55-5.30; p<0.001). Pooled rates of occult metastasis were 33.2% for EC presence and 16.2% for EC absence (OR 2.49; 95% CI; 1.64-3.77; p<0.001). Pooled rates of occult metastasis were 40.0% for EC >50% and 20.0% for EC<50% (OR 2.62; 95% CI 1.93-3.56; p<0.001).

Conclusions

LVI is the strongest risk factor for relapse. The prognostic value of EC is high, but there is no common agreement on how to define this risk factor. Both EC presence and EC >50% have similar ORs for occult metastasis. This shows that the assessment of EC presence is sufficient for the classification of EC.

Introduction

Approximately 30% of patients with nonseminomatous germ cell tumor (NSGCT) presenting with clinical stage I (CS I) have occult metastatic disease in their retroperitoneal lymph nodes [1]. These patients will relapse if treated with active surveillance (AS).

Several management strategies for CS I NSGCT exist. Primary retroperitoneal lymph node dissection (RPLND) is still a standard approach in the USA [2]. In Europe, its role is largely diminished, as it is associated with high morbidity and European follow-up is generally well organized [3]. Various guideline statements acknowledge non-risk-adapted AS as a preferred management strategy [3,4]. This approach limits overtreatment, and most relapsed patients can still be cured with salvage chemotherapy. However, salvage treatment consists of multiple cycles of bleomycin, etoposide, and cisplatin (BEP) chemotherapy and is associated with an increased risk of secondary malignancy [5] and cardiovascular disease [6].

The high survival rate and the long life-expectancy of patients has shifted focus to minimization of treatment-related morbidity. This includes a reduction of treatment-associated long-term toxicities caused by salvage therapy. Early identification of patients who have a high risk of relapse enables adjuvant treatment at an early stage. This prevents relapse, thereby avoiding the necessity of salvage treatment and reducing toxicity [7,8].

In order to select these high-risk patients, several risk-adapted strategies have been developed [7,9]. Patient selection is largely based on two histopathological features in the primary tumor: presence of lymphovascular invasion (LVI), and presence or predominance of the tumor subtype embryonal carcinoma (EC) [3,7,8,10,11].

High-risk patients can be offered treatment with one course of BEP [3]. This reduces the relapse risk by 90-95%, regardless of risk classification [7]. In a prospective study by the Swedish and Norwegian Testicular Cancer Group (SWENOTECA) the relapse risk after one course of BEP was 3.2% and 1.6% for patients with and without LVI, respectively [7].

As the presence of LVI and EC are important factors that aid clinical decision-making on adjuvant treatment in patients with CS I NSGCT, their prognostic value needs to be clarified. Several studies have investigated the association between these predictors and occult metastatic disease. However, a systematic review with meta-analysis is necessary to quantify the strength of these predictors more precisely. The aim of the present study was to systematically review the literature to establish the prognostic value of LVI and EC in CS I NSGCT.

Materials and Methods

Search strategy

This review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement and the recommendations of the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group [12,13]. The review protocol has been published in the International Prospective Register of Systematic Reviews (PROSPERO) database (registration number CRD42018107698).

A systematic PubMed, Embase (OVID) and SCOPUS literature search was conducted up to March 2019. An information scientist (E.W.) was involved in the design of the search strategy. The full search strategy is available as Supplementary File 1. Relevant references from selected studies were also considered. Two reviewers (J.B. and I.P.) independently screened all abstracts and full-text articles. Disagreement was resolved by discussion.

Study eligibility

Studies reporting on the individual association of LVI and/or EC with occult metastatic disease in CS I NSGCT patients treated with AS or primary RPLND were eligible for inclusion. Studies reporting on patients treated with adjuvant therapy or with a risk-adapted protocol were not included. Studies reporting on patients with pure seminoma, pediatric germ cell tumor (GCT), or bilateral testicular tumors were also not included. Reviews, case reports, conference papers, editorials, commentaries, and studies not in the English language were excluded. If multiple studies reported on the same patient cohort and reported the same outcome measures, only the most recent publication was included. If multiple studies possibly included the same patients (but not the same cohort), we included both studies in the narrative synthesis but included only the most recent study in the meta-analysis.

Studies making a distinction between vascular and lymphatic invasion were also included in the narrative synthesis but not in the meta-analysis. If it was not explicitly stated whether LVI or strictly vascular invasion (VI) was meant, the corresponding author was contacted.

Outcome measures of interest were relapse during AS or positive nodes on primary RPLND. LVI and EC were evaluated as a dichotomous variable (presence vs. absence). The percentage of EC was evaluated either as a continuous variable or as a categorical variable using different cut-off points. Studies reporting raw data were included in the meta-analysis. If the relapse rates were reported, these were converted to number of patients. AS studies with a median follow-up <24 months were included in the narrative synthesis but not in the meta-analysis.

Risk of bias assessment

Two reviewers (J.B. and I.P.) independently assessed the quality and risk of bias in the included studies using the Quality in Prognosis Studies (QUIPS) tool for six domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and

statistical analysis and reporting [14]. Disagreement was resolved by discussion. The highest score on one of the domains was taken as the overall grade of bias. In addition, the sources of funding for the included studies were evaluated. Publication bias was assessed using a funnel plot.

Data extraction and statistical analysis

Data from the articles was extracted independently by two reviewers (J.B. and I.P.). Baseline characteristics were summarized using descriptive statistics. Cochrane's Review Manager (version 5.3) was used for the meta-analysis and construction of the Forest plots in collaboration with a biostatistician (K.J.). Statistical heterogeneity was evaluated by calculating I^2.

Results

Our search identified 9,314 manuscripts (March 2019). After removal of duplicates, 5,287 studies were screened. Of these, 207 studies were selected for full-text evaluation. A total of 35 studies, reporting on 7,113 patients were included in the systematic review [1,10,15–47] (Figure 1, Table 1); 26 studies reported on patients treated with AS [1,15–38,46] and nine reported on patients treated with primary RPLND [10,39–45,47]. Of these studies, 14 included >150 patients [1,10,15,17,19,20,22,25,28,32,37,39,42,43].

The median age of the patients at time of diagnosis ranged from 25 to 31 years. In primary RPLND studies, the percentage of patients with pathological stage II was between 18.6% and 41.3%. In AS studies, overall relapse rates varied between 17.1% and 36.3%. Reported median follow-up duration ranged from 18 to 180 months.

A total of 24 studies could be included in a meta-analysis [1,10,15–17,21,22,24–31,34,39–43,45–47]. In these studies, the rate of occult metastatic disease ranged from 18.6% to 41.3%. The median follow-up for the 16 AS studies in the meta-analysis varied between 38 and 180 months.

In one study with an accrual period from 1982 to 1992, patients in the first two years underwent explorative laparotomy in conjunction with orchiectomy [28]. If no palpable lymph nodes were found during surgery, the lymph nodes were not resected and the patients were classified as CS I and treated with AS.

The overall risk of bias was moderate to high for all studies (Table S1). Symmetry shown in the funnel plots for studies on LVI and EC predominance indicates that there is a low risk of publication bias (Figure S1). The funnel plot for studies on EC presence showed asymmetry, which suggests that there may be some unpublished negative studies.

Table 1. Study criteria

Study	Inclusion period	Country	Inclusion criteria for surveillance	Patients (n)	Median age (range), years	Median follow-up (range), months	Overall metastatic rate (%)	Central pathology review	Overall risk of bias
Surveillance studies									
Gilbert (2016) [15]	NR	UK	NR	177	NR	NR	NR	Yes	High
Li (2015) [16]	1999-2013	China	NR	78	29.5 (14-56)	6.2 yrs (1-15)	23.1	Yes	High
Kollmannsberger (2015) [1]	1983-2012	Canada, Norway, Sweden, UK, USA	NR	1,139	30 (14-85)	62 (1-277)	19.4	No	High
Daugaard (2014) [17]	1984-2007	Denmark	Standard policy	1,226	30 (15-79)	180 (1-346)	31.2	No	Moderate
Keskin (2011) [18]	2002-2009	Turkey	Patient preference	70	27.8 (16-67)	18.5 (6-71)	17.1	Yes	High
Sturgeon (2011) [19]	1981-2005	Canada	Preferred management option, no pure choriocarcinoma	371	Mean 30.5 (13.2-76.6)	6.3 yrs (0.08-25.9)	28.0	Yes	Moderate
Kollmannsberger (2010) [20]	1998-2007	Canada	Preferred management option	223	29 (15-63)	52 (3-136)	26.5	Yes	Moderate
Atsu (2003) [21]	1978-2000	Turkey	Normalization of markers	132	28 (16-52)	38 (6-265)	24.2	Yes	High

Table 1. Study criteria *(continued)*

Study	Inclusion period	Country	Inclusion criteria for surveillance	Patients (n)	Median age (range), years	Median follow-up (range), months	Overall metastatic rate (%)	Central pathology review	Overall risk of bias
Daugaard (2003) [22]	1984-2002	Denmark	Standard policy	301	34 (15-72)	60 (1-226)	28.6	No	High
Alexandre (2001) [23]	1984-1996	France	Patient preference, not based on histopathologic characteristics	88	30.5 (15.9-55.7)	4.3 yrs (1-12)	27.3	Yes	Moderate
Roeleveld (2001) [24]	1982-1994	The Netherlands	No pure choriocarcinoma, no history of any previous tumor	90	Mean 30 (16-60)	8.1 yrs	25.6	Yes	Moderate
Colls (1999) [25]	1980-1997	New Zealand	Histologic NSGCT, seminoma with β-HCG ≥300 IU/L, or seminoma with elevated AFP	248	29 (16-77)	53 (1-185)	28.2	No	High

Table 1. Study criteria *(continued)*

Study	Inclusion period	Country	Inclusion criteria for surveillance	Patients (n)	Median age (range), years	Median follow-up (range), months	Overall metastatic rate (%)	Central pathology review	Overall risk of bias
Sogani (1998) [26]	1979-1987	USA	No T2-T4, no pure choriocarcinoma, no pure seminoma, no history of orchiopexy, no unreliability for close follow-up	105	26 (15-46)	11.3 yrs (2.4-16.8)	25.7	Yes	High
Maher (1998) [27]	1980-1993	UK	Standard policy	42	28 (18-53)	79.4 (30.6-183.2)	31.0	Yes	High
Gels (1995) [28]	1982-1992	The Netherlands	Standard policy	154	29 (15-66)	7 yrs (2-12)	27.3	No	Moderate
Nicolai (1995) [29]	1981 - 1984	Italy	Offered to all CS I patients, no tumor at cut end of spermatic cord	85	NR	132 (114-156)	29.4	Yes	High
Ondrus (1994) [30]	1984-NR	Slovakia	No seminoma or choriocarcinoma component	80	27 (13-58)	mean: 83.1 (61-110)	36.3	NR	High

Table 1. Study criteria *(continued)*

Study	Inclusion period	Country	Inclusion criteria for surveillance	Patients (n)	Median age (range), years	Median follow-up (range), months	Overall metastatic rate (%)	Central pathology review	Overall risk of bias
Tekgul (1995) [31]	1985-1994	Turkey	No tumor at cut end of spermatic cord, eligible for close and proper surveillance	58	31 (17-43)	39 (14-79)	29.3	Yes	High
Read (1992) [32]	1984 - 1987	UK and Norway	No tumor at cut end of spermatic cord	373	NR	5 yrs	26.8	Yes	Moderate
Sturgeon (1992) [33]	1981-NR	Canada	Preferred management option, no pure choriocarcinoma	105	28 (17-76)	60 (12-121)	35.2	Yes	Moderate
Rørth (1991) [34]	1980-1984	Denmark	Randomization	83	30 (17-64)	64 (33-103)	27.7	Yes	High
Wishnow (1989) [46]	1981-1987	USA	NR	82	NR	NR	29.3	Yes	High
Dunphy (1988) [35]	1981-1986	USA	NR	93	Mean 28 (16-54)	34 (12-61)	30.1	Yes	Moderate
Thompson (1988) [36]	1979-NR	New Zealand	No tumor at cut end of spermatic cord	36	27 (18-45)	36 (14-92)	33.3	Yes	High

Table 1. Study criteria *(continued)*

Study	Inclusion period	Country	Inclusion criteria for surveillance	Patients (n)	Median age (range), years	Median follow-up (range), months	Overall metastatic rate (%)	Central pathology review	Overall risk of bias
Freedman (1987) [37]	1979-1983	UK	NR	259	NR	30 (10-63)	27.0	Yes	Moderate
Hoskin (1986) [38]	1979-1985	UK	Histologic NSGCT or seminoma with elevated AFP, no tumor at cut end of spermatic cord	126	NR	42	28.6	Yes	Moderate
Primary RPLND studies									
Nicolai (2011)a [29]	2002-2007	Italy	NR	183	NR	NR	18.6	Yes	Moderate
Albers (2003)b [10]	1996-2002	Germany	CS I, randomization	165	Mean 31.3 (SD 8.3)	Mean 34.5 (12-64)	37.6	Yes	Moderate
Spermon (2002)a [40]	1986-1992	The Netherlands	NR	50	NR	NR	30.0	Yes	High
Sweeney (2000)b [43]	1990-1995	USA	NR	292	NR	46 (24-89)	30.5	Yes	Moderate
Albers (1997)b [47]	1983-1994	Germany	NR	78	NR	Mean 58.2 (8-149)	35.9	Yes	High
Albers (1995)a [45]	1992-1993	USA	CS I	90	NR	Mean 15.9 (5-27)	27.8	Yes	High

Table 1. Study criteria *(continued)*

Study	Inclusion period	Country	Inclusion criteria for surveillance	Patients (n)	Median age (range), years	Median follow-up (range), months	Overall metastatic rate (%)	Central pathology review	Overall risk of bias
Moul (1994)a [44]	1980-1993	USA	NR	92	NR	(1-10)	41.3	Yes	High
Klepp (1990)b [42]	1981-1986	Sweden, Norway	CS I, no previous malignancy	279	NR	50 (30-90)	37.6	Yes	Moderate
Fung (1988)a [41]	1979-1987	USA	NR	60	25 (15-56)	18 (NR)	33.3[d]	Yes	Moderate
Total	1978-2013			7,113[c]					

NR = not reported; β-HCG = β-human chorionic gonadotropin; AFP = alpha-fetoprotein; CS I = clinical stage I; NSGCT = nonseminomatous germ cell tumor; SD = standard deviation

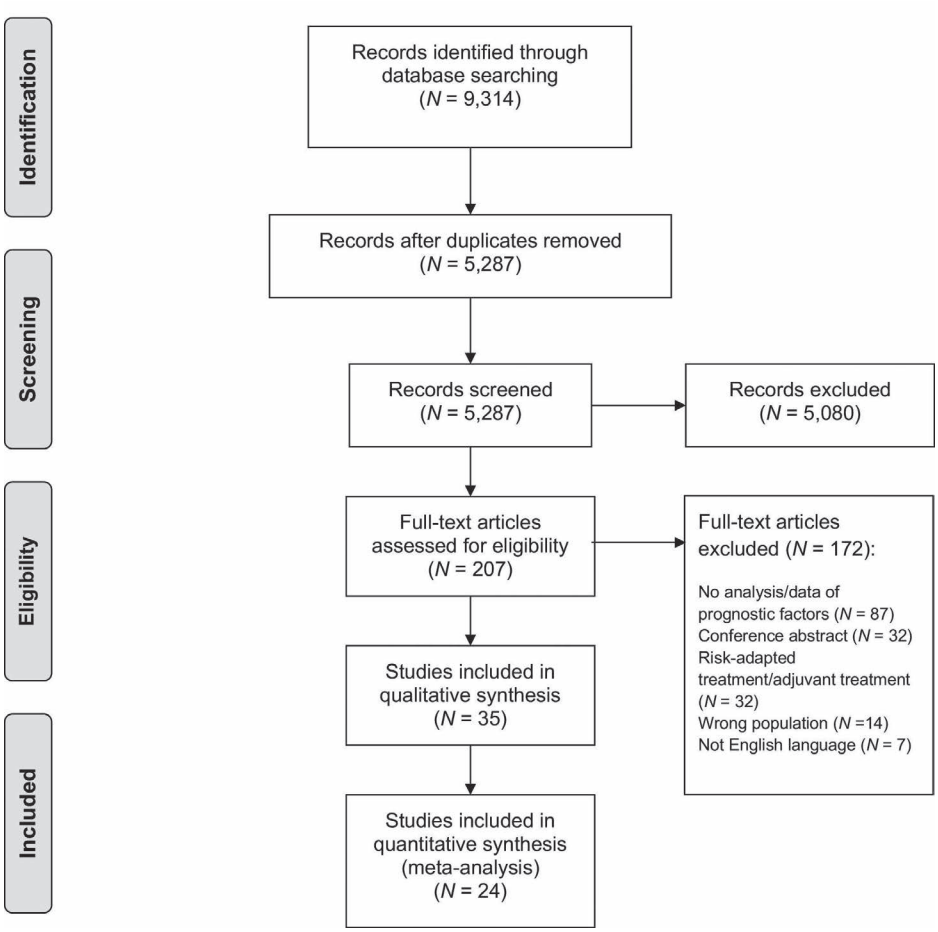
a = Study endpoint is pathological stage II

b = Study endpoint is pathological stage II or relapse after pathological stage I

c = Includes patients reported in multiple studies

d = 48.3% including patients with relapse after pathological stage I

Figure 1. PRISMA diagram



LVI as a risk factor for recurrence

All but one study reported the effect of LVI (Table 2) [1,10,15-44,46,47]. Six studies analyzed vascular and lymphatic invasion separately or mentioned only VI [28,32,36–38,44]. The proportion of patients with LVI ranged from 16.4% to 61.4%.

Studies with central pathology review reported a higher rate of LVI. The weighted average percentage of LVI-positive patients was 23.5% for studies without pathology review and 36.6% for studies with central pathology review.

The relapse rate for LVI-positive patients varied between 26.1% and 60.6%, and was <40% in four of 28 studies that reported on it [18,21,34,39]. The relapse rate for LVI-negative patients ranged from 10.9% to 37.0%. In RPLND studies, the rate of N+ was 25.8-65.3% and 11.9-25.8%

for patients with and without LVI, respectively. In all studies, the metastatic rate was higher for LVI-positive patients.

A total of 21 studies reported the univariable analysis of LVI [10,15–18,21,23–27,29,30,33,35,39–43,47], and this was statistically significant in 18 studies [10,15–17,23–27,30,33,35,39–43,47].

In all, 18 studies reported raw data and were eligible for inclusion in the meta-analysis (Figure 2A) [1,10,16,21,24–27,29,30,34,39–43,46,47]. These studies reported on 3,009 patients, of which 894 (29.7%) were LVI-positive. The pooled rate of occult metastatic disease for LVI-positive patients was 47.5%, compared to 16.9% for LVI-negative patients (odds ratio [OR] 4.33; 95% CI 3.55-5.30; ***P*** < 0.001).

Embryonal carcinoma as a risk factor for recurrence

A total of 27 studies analyzed the association between EC and relapse (Table 3) [10,15–24,26–31,33–35,40–43,45–47]. In 12 studies, EC was analyzed as present vs. absent. The percentage of EC was analyzed in several studies, but mostly as a categorical variable with different cut-off values. Two studies analyzed EC percentage as a continuous variable [15,47].

The percentage of EC-positive patients ranged from 69.7% to 87.1%. Rates of occult metastatic disease were 22.0%-34.6% and 0-38.5% for EC-positive and -negative patients, respectively.

A total of 10 studies reported raw data on the analysis of EC present vs. absent and were included in the meta-analysis (Figure 2B) [15,21,22,27,28,31,34,40,42,46]. These studies reported on 1,346 patients of whom 1,049 (77.9%) were EC positive. The pooled rates of occult metastasis were 33.2% and 16.2% for EC-positive and -negative patients, respectively (OR 2.49; 95% CI 1.64-3.77; ***P*** < 0.001).

One study analyzed the prognostic value of pure EC and found that it was significant (hazard ratio [HR] 1.74; 95% CI 1.10-2.74; ***P*** = 0.02) [19]. Patients classified as high risk, based on the presence of pure EC and/or LVI, had a 52% risk of relapse, compared to 15.8% of patients classified as low-risk.

Studies reporting on the predictive value of percentage of EC were of heterogeneous design. Four studies divided the study population in more than two categories, all using different cut-off values [15,24,29,45]. The association between percentage of EC and relapse was significant on univariable analysis in three studies.

Six studies analyzed EC percentage as a binary variable [10,16,20,23,41,47]. The cut-off value was 50% in five studies [10,16,20,41,47]. Three studies found no significant difference in occult metastasis between EC ≥50% and EC <50% [10,16,41] and two studies did not report on it, but showed a significant difference when we re-calculated the ORs [20,47].

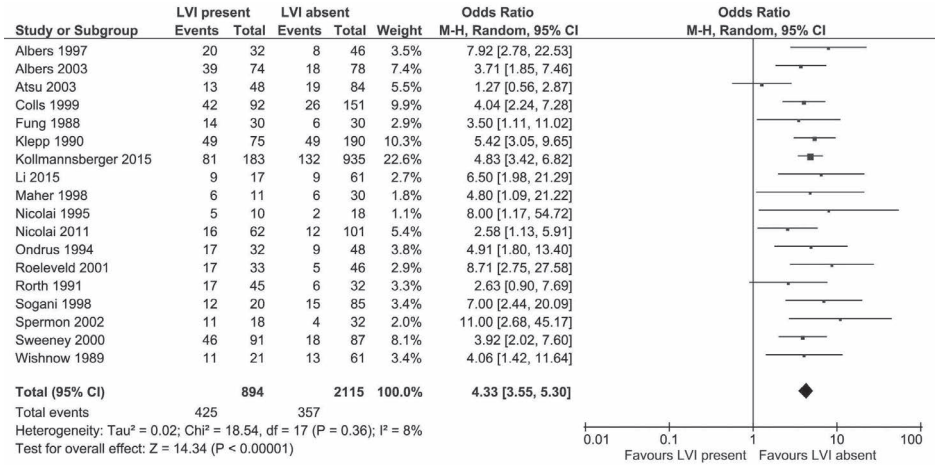
Alexandre et al. used 40% as a cut-off value and reported a significant difference in relapse-free survival on univariable analysis [23]. The relative risk (RR) for patients with EC >40% in comparison to patients with EC ≤40 was 3.5 (95% CI 1.4-8.7; ***P*** = 0.008), but this was not statistically significant on multivariable analysis.

Three of the four studies that divided EC percentage in more than two categories found a significant difference in occult metastatic disease occurrence [15,24,29]. Two studies included EC percentage in a multivariable model, and this was significant only in the study by Gilbert et al. [15]. However, the cut-off values in this study (<25%; 26-99%; 100%), were data-driven and not based on previous reports.

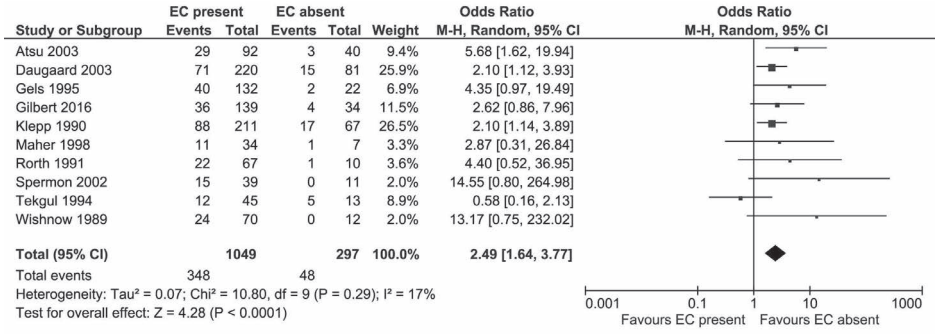
Gilbert et al. also analyzed EC percentage as a continuous variable [15]. In their model, which also included LVI, the OR for EC percentage was 1.011 (95% CI 1.002-1.019; ***P*** = 0.012). As mentioned before, Albers et al. also found a significant correlation between EC as a continuous variable and occult metastatic disease, but LVI and tumor proliferation rate were better predictors [47].

We included nine studies, reporting on 932 patients, in the meta-analysis comparing EC >50% with EC <50% (Figure 2C) [10,16,20,24,29,41,45–47]. Four studies used 50% as a cut-off value in their own statistical analysis [10,16,41,47]. The other studies reported sufficient raw data that it was possible to construct 2 x 2 tables and include them in the analysis. Pooled rates of occult metastasis were 40.0% and 20.0% for patients with EC >50% and EC <50%, respectively (OR 2.62; 95% CI 1.93-3.56; ***P*** < 0.001).

Figure 2. Forest plot of meta-analysis for (A) LVI presenc e, (B) EC presence, (C) EC >50%



A



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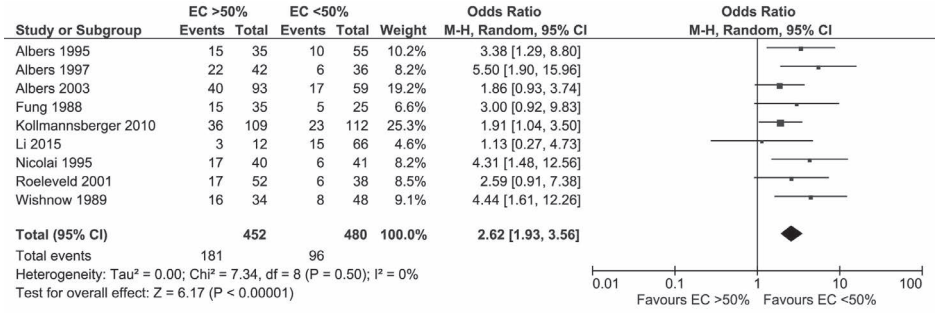

C

Table 2. Results of studies reporting on LVI

Author	Patients with LVI information (N)	LVI missing (%)	LVI positive (%)	Metastasis LVI present (%)	Metastasis LVI absent (%)	Reported univariable analysis	Method multivariable analysis	Reported multivariable analysis
Gilbert (2016)	177	0	36.7	2 yr RFR 58.3	2 yr RFR 88.3	*P*<0.001	Stratified log-rank test	N/A (stratified by LVI)
Li (2015)	78	0	21.8	52.9	14.8	OR 6.500 (1.984-21.291) *P*=0.002	Logistic regression analysis	OR 6.521 1.872-22.721 *P*=0.003
Kollmannsberger (2015)	1118	1.8	16.4	44.3	14.1	NR	NR	NR
Daugaard (2014)	683	44.3	24.9	42.6	26.4	HR 2.62 (2.03-3.39) *P*<0.001	Cox prop. hazards model	HR 1.57 1.64-2.99 *P*<0.001
Keskin (2011)	70	0	32.9	26.1	12.8	*P*=0.322	NR	NR
Nicolai (2011)	163	10.9	38.0	25.8	11.9	*P*=0.032	NR	NR

Table 2. Results of studies reporting on LVI *(continued)*

Author	Patients with LVI information (N)	LVI missing (%)	LVI positive (%)	Metastasis LVI present (%)	Metastasis LVI absent (%)	Reported univariable analysis	Method multivariable analysis	Reported multivariable analysis
Sturgeon (2011)	331	10.8	27.8	NR	NR	NR	Cox prop. hazards model	HR 3.22 2.17-4.78 *P*<0.0001 [a]
Kollmannsberger (2010)	206	7.6	29.1	50.0	13.0	NR	NR	NR
Albers (2003)	152	7.9	48.7	52.7	23.1	*P*=0.001	Logistic regression analysis	OR 3.7143 (1.8501-7.4566) *P*=0.0002
Atsu (2003)	132	0	36.4	27.1	22.6	*P*=0.7	Cox prop. hazards model	LVI NS
Daugaard (2003)	145	51.8	31.7	54.3	NR	NR	NR	NR
Spermon (2002)	50	0	36.0	61.1	12.5	*P*=0.001	Multivariate logistic model	*P*=0.001
Alexandre (2001)	84	4.5	47.6	NR	NR	RR 5.3 (2.0-14.2) *P*<0.001	Cox prop. hazards model	RR 3.8 1.4-10.4 *P*=0.008

Table 2. Results of studies reporting on LVI *(continued)*

Author	Patients with LVI information (N)	LVI missing (%)	LVI positive (%)	Metastasis LVI present (%)	Metastasis LVI absent (%)	Reported univariable analysis	Method multivariable analysis	Reported multivariable analysis
Roeleveld (2001)	79	12.2	41.8	51.5	10.9	*P*<0.001	Logistic regression analysis	*P*=0.0003
Sweeney (2000)	178	39.0	51.1	50.5	20.7	*P*<0.001	NR	NR
Colls (1999)	243	2.0	37.9	45.7	17.2	*P*<0.001	NR	NR
Sogani (1998)	105	0	19.0	60.0	16.5	*P*=0.0001	Cox prop. hazards model	OR 4.2 *P*=0.0005
Maher (1998)	41	2.4	26.8	54.5	20.0	*P*=0.025	NR	NR
Albers (1997)	78	0	41.0	62.5	17.4	*P*=0.0001	Maximum likelihood analysis	*P*=0.0101
Gels (1995)	VI: 154	0	VI: 23.4%	VI: 52.8	VI: 19.5	*P*<0.0001	Logistic regression analysis	OR 4.24, *P*=0.0001
Nicolai (1995)	28	67.1	35.7	50	11.1	*P*=0.069	NR	NR
Moul (1994)	92	0	VI: 41.3 LI: 21.7	VI: 76.3 LI: 85.0	VI: 16.7 LI: 29.2	VI: *P*=0.0001 LI: *P*=0.0001	Logistic regression analysis	VI: *P*=0.0002

Table 2. Results of studies reporting on LVI *(continued)*

Author	Patients with LVI information (N)	LVI missing (%)	LVI positive (%)	Metastasis LVI present (%)	Metastasis LVI absent (%)	Reported univariable analysis	Method multivariable analysis	Reported multivariable analysis
Ondrus (1994)	80	0	40.0	53.1	18.8	*P*=0.042	NR	NR
Tekgul (1995)	36	37.9	27.8	40.0	NR	*P*>0.05	NR	NR
Read (1992)	LI: 362 VI: 363	LI: 2.9 VI: 2.7	LI: 16.9% VI: 47.1%	2-yr RFR LI: 59% VI: 65%	2-yr RFR LI: 79% VI: 86%	LI: *P*<0.001 VI: *P*<0.0001	Cox prop. hazards model	VI: *P*<0.0001
Sturgeon (1992)	103	1.9	32.0	60.6	24.3	*P*=0.0002	NR	NR
Rørth (1991)	77	7.2	58.4	37.8	18.8	NR	NR	NR
Klepp (1990)	265	5.0	28.3	65.3	25.8	*P*<0.0001	Logistic regression analysis	*P*<0.0001
Wishnow (1989)	82	0	25.6	52.4	21.3	NR	NR	NR
Dunphy (1988)	93	0	34.4	53.1	18.0	*P*<0.01	Cox regression analysis	*P*=0.99
Fung (1988)	60	0	50.0	46.7	20.0	*P*=0.05	NR	NR
Thompson (1988)	34	5.6	VI: 29.4% LI: 52.9%	VI: 40.0% LI: 55.6%	VI: 29.2% LI: 6.3%	VI: *P*>0.1 LI: *P*<0.005	Cox regression analysis	Only LI significant

Table 2. Results of studies reporting on LVI *(continued)*

Author	Patients with LVI information (N)	LVI missing (%)	LVI positive (%)	Metastasis LVI present (%)	Metastasis LVI absent (%)	Reported univariable analysis	Method multivariable analysis	Reported multivariable analysis
Freedman (1987)	LI: 256 VI: 259	LI: 1.2 VI: 2.3	LI: 18.7% VI: 50.6%	2-year RFR LI+: 45% VI+: 57%	2-year RFR LI-: 80% VI-: 90%	LI: *P*<0.001 VI: *P*<0.001	Cox prop. hazards model	LI: <0.001 VI: <0.001
Hoskin (1986)	VI: 118 LI: 116	VI: 6.3 LI: 7.9	VI: 31.4% LI: 18.1%	VI: 45.9% LI: 57.1%	VI: 23.5% LI: 23.2%	VI: *P*<0.01 LI: *P*<0.005	Cox proportional hazards model	VI: NS LI: HR 3.7, *P*<0.01

RFR = relapse-free rate; LVI = lymphovascular invasion; LI = lymphatic invasion; VI = vascular invasion; HR = hazard ratio; NR = not reported; NS = not significant; RR = relative risk; OR = odds ratio; N/A = not applicable

a: With imputation of missing data.

Multivariable analyses

Twenty-one studies reported multivariable analysis, but with various levels of quality. Most studies used the Cox proportional hazards model, and six studies used logistic regression analysis [10,16,24,28,42,44]. Three studies reported HRs instead of ORs [15,17,19].

The presence of LVI was the most studied predictor and showed the strongest effect. The largest cohort, by Daugaard et al. (n = 1,226), found an HR of 1.57 (95% CI 1.22-2.02; P < 0.001) for LVI alone [17]. The Princess Margaret Cancer Center reported on a series of 371 patients treated between 1981 and 2005 [19]. LVI, regardless of other prognostic factors, was an independent predictor of relapse (HR 3.22; 95% CI 2.17-4.78; P < 0.0001) in this cohort. Albers et al. calculated the negative (NPVs) and positive predictive values (PPVs) for various combinations of histopathological risk factors [10]. The best prediction of a low-risk group was a combination of absent LVI and low proliferation rate. This resulted in a NPV of 86.5%. Patients with a combination of LVI presence, high proliferation rate, and EC ≥50% were the best predicted high-risk group (PPV 63.6%).

The independent predictive value of EC was analyzed in several studies, but different definitions were used. Sturgeon et al. was the only study to include the presence of pure EC in a multivariable analysis and found a significant association (HR 1.74; 95% CI 1.10-2.74; P = 0.02) [19]. The cohort by Daugaard et al. analyzed EC presence as a single risk factor and also found a significant association (HR 2.73; 95% CI 1.94-3.85; P < 0.001) [17]. In a Turkish study of 138 patients, the presence of EC led to a 3.7-fold increase of the relapse risk [21]. Three studies reported no significant association between presence of EC and relapse [28,31,42].

EC ≥50% was included in a multivariable analysis in two studies, with contradictory results [10,26]. Sogani et al. found that it was a significant predictor (OR 2.6; P = 0.016) [26], but it was not significant in the study by Albers et al. (P = 0.080) [10]. Gilbert et al. analyzed the predictive value of EC in various ways [15]. LVI and EC, either as a continuous variable or split into the three previously mentioned categories (≤25%; 26-99%; 100%), were independent predictors of relapse. Only when EC was analyzed as a binary variable (present/absent), the molecular marker C-X-C motif chemokine 12 (CXCL12), but not EC, was a significant negative predictor. As mentioned before, Albers et al. also found a significant correlation between EC as a continuous variable and occult metastatic disease, but LVI and tumor proliferation rate were better predictors [47].

Discussion

Our present study confirms that presence of LVI is the strongest predictor of occult metastatic disease in CS I NSGCT. The prognostic value of this parameter is affirmed by several large cohort studies and our present meta-analysis.

EC is an additionally useful risk prognosticator but agreement about the definition to be used is necessary. Our meta-analysis showed that the ORs for EC presence and EC ≥50% are quite

similar (2.49 vs. 2.62) and the relapse rates are approximately equal (33.2% vs. 40.0%). This small difference in prognostic value between EC presence and EC ≥50% suggests that the assessment of EC presence may be sufficient to identify high-risk patients.

A continuous correlation between EC and occult metastatic disease was found in both studies that investigated it [15,47]. The clinically most relevant cut-off value, however, is still up for debate. It is likely that the risk of occult metastatic disease is already high in the presence of only a small amount of EC and any further increase in EC percentage does not involve a relevant increase in clinical risk.

A meta-analysis from 2002 by Vergouwe et al. also investigated the predictive value of LVI and EC [48]. The results of that study are very much in line with our findings. LVI had the strongest predictive value (OR 4.7) and EC presence and EC >50% showed similar ORs for metastasis (OR 2.9 and 2.8, respectively).

Risk stratification of CS I NSGCT is important for patient counselling and when adjuvant treatment is considered. Several stratifications have been proposed. Since 1995, the SWENOTECA has identified high-risk patients on the basis of LVI presence or absence [7]. Lago-Hernandez et al. developed a 0, 1, and 2 scoring system to stratify patients according to LVI presence and EC predominance (defined as EC presence at a larger level than any other histologic type) [9]. Relapse rates were 25%, 41%, and 77% for 0, 1, and 2 risk factors, respectively. Daugaard et al. also explored the combination of different risk factors and found that 5-year relapse risk was highest for patients with EC + LVI + rete testis invasion (50%, HR 5.65) [17]. Risk for patients with LVI alone was 18% (HR 1.57) and 41% for patients with EC + LVI (HR 4.29).

The proportion of high-risk patients based on LVI and/or EC differed between the included studies. This may be due to selected patient groups and is not necessarily a reflection of differences between study populations. More specifically, not all AS studies reported on truly unselected AS populations. In both studies by Sturgeon et al., AS was offered as the preferred management method for all men with CS I NSGCT, but patients were allowed to choose [19,33]. This may have introduced bias, which is illustrated by the differences in proportion of LVI-positive patients and relapse rates between the two studies by Kollmannsberger et al. [1,20]. The data included in Kollmannsberger et al. (2015) is pooled from several institutions and almost half of the cohort comes from centers where patients can choose between AS and adjuvant therapy (SWENOTECA) [1]. Both the relapse rate (19.4%) and the proportion of LVI-positive patients (16.4%) in this study are low. In an earlier study by the same author , which reports on some of the same patients as the 2015 study and is also not a strictly AS population, the relapse rate and LVI percentage are higher (26.5% and 29.1%, respectively) [20].

We compared the weighted average of strictly AS studies with studies that reported no strict AS in a subgroup analysis. Weighted average relapse rates were 30.2% and 25.0% for strictly AS and non-strictly AS studies, respectively. The weighted rate of LVI-positive patients was

slightly higher for strictly AS patients (27.4% vs. 25.0%). Thus, studies that did not explicitly state that a strict AS protocol was followed, often reported on a selected population. This can give contradictory results.

The difference in rate of high-risk patients could also be due to a lack of reproducibility of LVI assessment by pathologists. This is reflected by the difference in rate of LVI between reports with and without central pathology review. In a series of 221 patients by Harari et al., reporting of LVI changed in 22% of cases after central pathology review [49]. Purshouse et al. reported that in 7.2% of patients with NSGCT the tumor prognostic factors were changed after central pathology review (5% for LVI status, 2.2% for EC >50% vs. <50%: 2.2%) [50]. These discrepancies emphasize the need for pathology review by an expert genitourinary pathologist.

Most studies investigated other possible histopathological risk factors in addition to LVI and EC. Tumor size, an important prognostic factor in seminoma, was significantly associated with relapse in the study by Roeleveld et al. (cut-off value: 5 cm; ***P*** = 0.039) [24]. Five other five other studies in our present study also assessed this factor, but none found a significant correlation with occult metastatic disease [16,28,35,36,38]. In a large series of 779 patients by Beck et al. (not included in our review) primary tumor size was not predictive of occult metastatic disease (***P*** = 0.167) [51].

Several studies reported on the tumor proliferation rate, which is one of the prognostic markers mentioned in the European Association of Urology (EAU) guidelines [3]. It is commonly expressed as rate of MIB-1-positive tumor cells and was an independent predictor of metastatic disease in a prospective trial by the German Testicular Cancer Study Group Trial [10]. In this study, MIB-1 scores were available for 152 patients. Using a cut-off value of 70%, the OR for metastatic disease was 2.75 (95% CI 1.28-5.91; ***P*** = 0.010). However, the PPV was relatively low at 43.0%. In an earlier study by the same author (but in a different patient cohort), the pathologic stage was correctly classified in 69% of cases (NPV 88%, PPV 55%) [47]. These findings are contradicted by a series of 149 specimens by Heidenreich et al., in which the MIB-1 score was not useful in predicting the pathological stage [52]. Gilbert et al. used the same cut-off values as the German trial and found no evidence of any prognostic value [15]. This could be explained by the fact that only five of 179 patients had MIB-1 staining in ≥70% cells. When MIB-1 staining was dichotomized (weak vs. high), it had some prognostic value on univariable analysis, but this was reduced after stratification for LVI (***P*** = 0.045). In the meta-analysis by Vergouwe et al., patients with MIB-1 staining >70% were at higher risk of occult metastasis (OR 4.7) [48]. However, the authors noted that this analysis was based on a low number of patients (***N*** = 212), the 70% cut-off value was data-driven, and, therefore, additional research is necessary.

One of the limitations of our study is the heterogeneity of included studies. Studies were heterogeneous in terms of study population, year of accrual, assessment of histopathological risk factors and methodological quality. Although studies reporting on a risk-adapted protocol were excluded, some studies reported on selected populations. Furthermore, only a few studies

performed central pathology review in the context of the study. Several single-center and some larger studies reported pathology review by an expert pathologist as part of standard care. Especially in low-volume centers, however, the quality of risk factor assessment might be low. In addition, most studies did not report the definition for LVI and several studies did not report the definition for EC predominance.

Missing data of the histopathological features of interest were high in a number of studies. Some retrospective studies only included patients with complete data without reporting the total number of patients treated during the study period. Therefore, missing data were not assessable in these studies. Most studies that reported missing data excluded these patients for further analysis. Imputation of missing data was only performed in the study by Daugaard et al., in which LVI status was unknown in 44% of the cohort [17].

In the present study, we were only able to analyze LVI and EC separately. It would be interesting to evaluate the predictive value of both factors together. For example, it was not possible to assess the difference in relapse risk between LVI-positive patients with EC >50% and LVI-positive patients without EC >50%. This requires an individual patient data meta-analysis of the series included in this review.

The major strength of our present review is the systematic approach that was applied. Our methodology is in line with the Cochrane reporting standards, such as the PRISMA statement and the QUIPS tool for risk–of-bias assessment. Furthermore, a high number of participants have been included in our meta-analysis and we paid special attention to avoid the inclusion of overlapping populations. Even though methodological heterogeneity might exist, statistical heterogeneity I^2 was low for all meta-analyses.

Conclusions

Our present review and meta-analysis show that LVI is the strongest predictor of occult metastatic disease in CS I NSGCT. The prognostic value of EC is high, but consensus on how to use this risk factor is necessary. A cut-off value of 50% is reported in only a few studies, with contradicting results. Both EC presence and EC >50% show similar ORs for occult metastasis. This suggests that the assessment of EC presence is sufficient for the classification of EC.

Table 3. Results of studies reporting on EC

Author	Patients with EC information (N)	EC missing (%)	Method of EC reporting	Patients per category (%)	Metastases for EC present (%)	Metastases for EC absent (%)	Reported univariable analysis	Method multivariable analysis	Reported multivariable analysis
Present vs. absent									
Gilbert (2016)	177	0	Present vs. absent	Present: 78.5	2-yr RFR Present: 74.3	2-yr RFR 89.2%	*P*=0.096	Stratified log-rank test (stratified by LVI) Cox regression model	*P*=0.243
Daugaard (2014)	1226	0	Present vs. absent	Present: 78.1	NR	NR	HR 3.00 (2.14-4.22) *P*<0.001	Cox prop. hazards model	HR 2.73 (1.94-3.85) *P*<0.001
Keskin (2011)	70	0	Present vs. absent	Present: 71.4	22.0	5.0	*P*=0.157	NR	NR
Atsu (2003)	132	0	Present vs. absent	Present: 69.7	31.5	7.5	*P*=0.003	Cox prop. hazards model	RR 3.7
Daugaard (2003)	301	0	Present vs. absent	Present: 73.1	32.3	18.5	NR	NR	NR
Spermon (2002)	50	0	Present vs. absent	Present: 78.0	38.5	0	*P*=0.02	NR	NR

Table 3. Results of studies reporting on EC *(continued)*

Author	Patients with EC information (N)	EC missing (%)	Method of EC reporting	Patients per category (%)	Metastases for EC present (%)	Metastases for EC absent (%)	Reported univariable analysis	Method multivariable analysis	Reported multivariable analysis
Maher (1998)	41	2.4	Present vs. absent	Present: 82.9	32.4	14.3	*P*=0.38	NR	NR
Gels (1995)	154	0	Present vs. absent	Present: 85.7	30.3	9.1	*P*=0.039	Logistic regression analysis	OR 3.49 *P*=0.110
Tekgul (1995)	58	0	Present vs. absent	Present: 77.6	26.7	38.5	NR	Cox prop. hazards model	*P*>0.05
Sturgeon (1992)	105	0	Present vs. absent	Present: 27.6	48.3	30.3	NR	NR	NR
Rørth (1991)	77	7.2	Present vs. absent	Present: 87.0	32.8	10.0	NR	NR	NR
Klepp (1990)	278	0.4	Present vs. absent	Present: 75.9	41.7	25.4	*P*=0.024	Logistic regression analysis	*P*=0.11
Dunphy (1988)	93	0	Present vs. absent	Present: 87.1	34.6	0	*P*=0.05	Cox regression analysis	*P*=0.05

Table 3. Results of studies reporting on EC *(continued)*

Author	Patients with EC information (N)	EC missing (%)	Method of EC reporting	Patients per category (%)	Metastases for EC present (%)	Metastases for EC absent (%)	Reported univariable analysis	Method multivariable analysis	Reported multivariable analysis
EC percentage									
Li (2015)	78	0	>50% vs. <50%	>50%: 15.4	>50%: 25.0	<50%: 22.7	OR 1.133 (0.272-4.726) *P*=0.864	NR	NR
Kollmannsberger (2010)	221	0.9	≥ 50% vs. <50%	≥ 50%: 49.3	≥50%: 33.0	<50%: 20.5	NR	NR	NR
Albers (2003)	152	7.9	≥50% vs. <50%	≥50%: 61.2	≥50%: 43.0	<50%: 28.8	*P*=0.088	Logistic regression analysis	OR 1.8646 (0.9286-3.7440) *P*=0.0798
Alexandre (2001)	84	4.5	>40% vs. ≤40%	>40%: 50.0	NR	NR	RR 3.5 (1.4-8.7) *P*=0.008	Cox prop. hazards model	EC NS
Albers (1997)	78	0	≥50% vs. <50%	≥50%: 53.9	≥50%: 52.4	<50%: 16.7	Continuous: *P*=0.001	Maximum likelihood analysis	Continuous: *P*=0.0242
Fung (1988)	60	0	≥50% vs. <50%	≥50%: 58.3	≥50%: 42.9	<50%: 20.0	*P*=0.10	NR	NR
Wishnow (1989)	82	0	All data given	>50%: 40.2	>50%: 47.1	<50%: 16.7	NR	NR	NR

Table 3. Results of studies reporting on EC *(continued)*

Author	Patients with EC information (N)	EC missing (%)	Method of EC reporting	Patients per category (%)	Metastases for EC present (%)	Metastases for EC absent (%)	Reported univariable analysis	Method multivariable analysis	Reported multivariable analysis
Multiple categories									
Gilbert (2016)	177	0	3 categories: ≤25% 26-99% 100% Continuous variable	≤25%: 45.2 26-99%: 31.6 100%: 23.2	2 yr RFR ≤25%: 88.4 26-99%: 76.4 100%: 57.5		3 categories: ≤25%: ref 26-99%: HR 1.679 (0.736-3.831) 100%: HR 3.118 (1.391-6.988) *P*=0.019 Continuous: HR 1.011 (1.002-1.019) *P*=0.012	Stratified log-rank test (stratified by LVI) Cox regression model	3 categories: *P*=0.006
Roeleveld (2001)	90	0	4 categories: 0-25% 25-50% 50-75% 75-100%	0-25%: 25.6 25-50%: 16.7 50-70%: 25.6 75-100%: 32.2 >50%: 57.8	0-25%: 21.7 25-50%: 6.6 50-70%: 47.8 75-100%:20.7 >50%: 32.7	<50%: 15.8	4 categories: *P*=0.032	Logistic regression analysis	4 categories: *P*=0.2196

Table 3. Results of studies reporting on EC *(continued)*

Author	Patients with EC information (N)	EC missing (%)	Method of EC reporting	Patients per category (%)	Metastases for EC present (%)	Metastases for EC absent (%)	Reported univariable analysis	Method multivariable analysis	Reported multivariable analysis
Nicolai (1995)	81	4.7	3 categories:: <50% 50-99% 100%	<50%: 50.6 50-99%: 37.0 100%: 12.3	<50%: 14.6 50-99%: 36.7 100%: 60	<50%: 14.6	3 categories: *P*=0.008	NR	NR
Albers (1995)	90	0	4 categories: 0-25% 26-50% 51-75% 76-100%	>50%: 49.4 0-25%: 43.3 26-50%: 17.8 51-75%: 14.4 76-100%: 24.4 >50%: 38.9	>50%: 42.5 0-25%: 15.4 26-50%: 25.0 51-75%: 30.8 76-100%: 50.0 >50%: 42.9	≤50%: 18.2	4 categories: NS	NR	NR
Other categories									
Sturgeon (2011)	371	0	Pure EC	Pure: 15.1%	NR	NR	NR	Cox prop. hazards model	HR 1.74 (1.10-2.74) *P*=0.02
Sweeney (2000)	292	0	Predominant vs. not predominant	Predominant: 42.8	46.4	18.6	*P*<0.0001	NR	NR
Sogani (1998)	105	0	Predominance	24.8	46	19	*P*=0.0072	Cox prop. hazards model	OR 2.6 *P*=0.016
Ondrus (1994)	80	0	Major EC vs. minor EC	Major EC: 51.3 Minor EC: 30.0	58.5	20.8	*P*=0.096	NR	NR

EC = Embryonal carcinoma; RFR = relapse-free rate; HR = hazard ratio; NR = not reported; NS = not significant; RR = relative risk; OR = odds ratio; LVI = lymphovascular invasion

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Supplementary File 1. Search strategy (Pubmed)

1. "testicular neoplasms"[Mesh] OR testic*[tiab] OR testis*[tiab] OR testes*[tiab] OR paratestic*[tiab] OR paratestis*[tiab] OR paratestes*[tiab]
2. "Neoplasms"[Mesh] OR neoplasm* [tiab] OR tumor* [tiab] OR tumour* [tiab] OR cancer* [tiab] OR malign* [tiab] OR oncolog* [tiab] OR carcinom* [tiab] OR lymphoma* [tiab]
3. "Neoplasms , Germ Cell and Embryonal"[Mesh] OR germ cell*[tiab]
4. nonseminom*[tiab] OR non seminom*[tiab] OR nongerminom*[tiab] OR non germinom*[tiab] OR NSGCT[tiab] OR NGGCT[tiab] OR "Nonseminomatous germ cell tumor" [Supplementary Concept]
5. stage 1[tiab] OR stage 1A[tiab] OR stage 1B[tiab] OR stage 1S[tiab] OR stage I[tiab] OR stage IA[tiab] OR stage IB[tiab] OR stage IS[tiab] OR stadium 1[tiab] OR stadium 1A[tiab] OR stadium 1B[tiab] OR stadium 1S[tiab] OR stadium I[tiab] OR stadium IA[tiab] OR stadium IB[tiab] OR stadium IS[tiab]
6. (clinical stage [tiab] OR clinical stadium[tiab]) AND (CS I[tiab] OR CS IA[tiab] OR CS IB[tiab] OR CS IS[tiab])
7. #1 AND #2 AND #3
8. #7 OR #4
9. #5 OR #6
10. #8 AND #9

Figure S1. Funnel plot for (A) LVI presence, (B) EC presence, (C) EC >50%

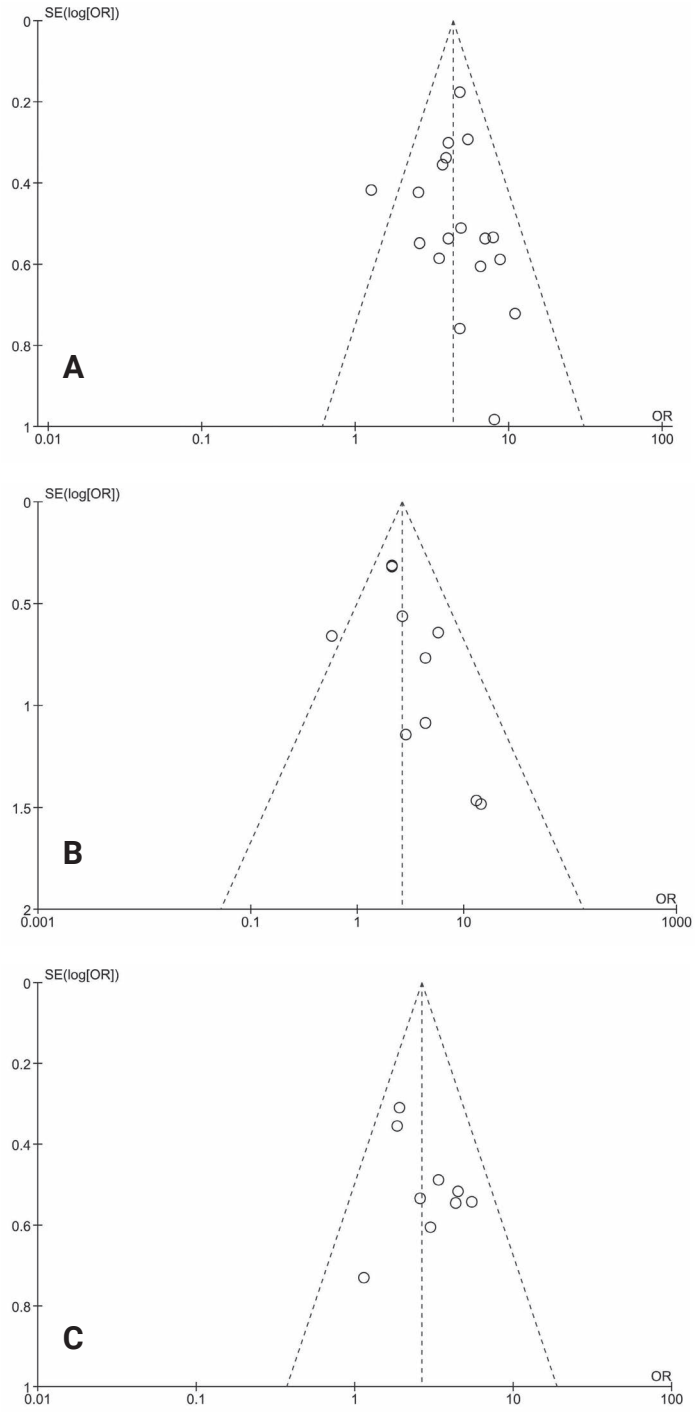

Table S1. Risk of bias assessment (QUIPS)

Study	Domain 1: Study Participation	Domain 2: Study Attrition	Domain 3: Prognostic Factor Measurement	Domain 4: Outcome Measurement	Domain 5: Study Confounding	Domain 6: Statistical Analysis and Reporting	Overall Risk of Bias
Gilbert (2015)	Moderate	Moderate	Moderate	High	Moderate	Moderate	High
Li (2015)	High	Low	Low	Low	Low	Low	High
Kollmannsberger (2015)	High	Low	Moderate	Moderate	High	Moderate	High
Daugaard (2014)	Low	Moderate	Moderate	Low	Low	Low	Moderate
Keskin (2011)	Moderate	High	Moderate	Low	High	Moderate	High
Nicolai (2011)	Moderate	Moderate	Low	Low	Moderate	Low	Moderate
Sturgeon (2010)	Moderate	Low	Moderate	Low	Moderate	Moderate	Moderate
Kollmannsberger (2010)	Low	Moderate	Moderate	Low	Moderate	Moderate	Moderate
Albers (2003)	Low	Low	Low	Moderate	Moderate	Low	Moderate
Atsu (2003)	High	Moderate	Moderate	Moderate/High	Moderate	High	High
Daugaard (2003)	Low	Moderate	High	Low	Moderate	High	High
Spermon (2002)	High	Low	Low	Moderate	High	High	High
Alexandre (2001)	Low	Moderate	Low	Low	Low	Moderate	Moderate
Roeleveld (2001)	Moderate	Low	Low	Low	Low	Moderate	Moderate
Sweeney (2000)	Moderate	Moderate	Low	Low	Moderate	Low	Moderate
Colls (1999)	High	Moderate	High	Moderate	High	Moderate	High
Sogani (1998)	Moderate	Low	Low	Low	Moderate	High	High

Table S1. Risk of bias assessment (QUIPS) *(continued)*

Study	Domain 1: Study Participation	Domain 2: Study Attrition	Domain 3: Prognostic Factor Measurement	Domain 4: Outcome Measurement	Domain 5: Study Confounding	Domain 6: Statistical Analysis and Reporting	Overall Risk of Bias
Maher (1998)	Moderate	Low	Low	Low	High	High	High
Albers (1997)	Moderate	High	Low	Low	Moderate	Low	High
Albers (1995)	Low	Moderate	Low	Low	High	High	High
Gels (1995)	Moderate	Moderate	Moderate	Low	Low	Low	Moderate
Nicolai (1995)	Moderate	Low	High	Low	High	High	High
Tekgül (1995)	Moderate	Low	Moderate	Low	High	High	High
Moul (1994)	High	Moderate	Low	High	Moderate	Moderate	High
Ondrus (1994)	Moderate	Low	Moderate	Low	High	High	High
Read (1992)	Moderate	Low	Low	Moderate	Low	Low	Moderate
Sturgeon (1992)	Moderate	Low	Moderate	Low	Moderate	Moderate	Moderate
Rørth (1991)	Low	Low	Low	Low	Moderate	High	High
Klepp (1990)	Low	Moderate	Moderate	Low	Moderate	Low	Moderate
Wishnow (1989)	Moderate	Low	Low	Low	Moderate	High	High
Dunphy (1988)	Moderate	Low	Low	Low	Moderate	Moderate	Moderate
Fung (1988)	Moderate	Low	Low	Low	Moderate	Moderate	Moderate
Thompson (1988)	High	Low	Moderate	Low	Moderate	High	High
Freedman (1987)	Moderate	Low	Low	Moderate	Low	Moderate	Moderate
Hoskin (1986)	Low	Low	Low	Low	Moderate	Moderate	Moderate

3

Chapter

Sentinel node biopsy in clinical stage I testicular cancer enables early detection of occult metastatic disease

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Abstract

Objectives

To report the long-term results of the sentinel node (SN) approach in patients with clinical stage I testicular tumors in our facility.

Patients and Method

We conducted an analysis of 27 consecutive patients suspected of clinical stage I testicular germ cell tumor (TGCT) and treated with a SN procedure at our tertiary referral center. SNs were identified using lymphoscintigraphy with or without single–photo-emission computed tomography with CT (SPECT/CT). Patients underwent laparoscopic retroperitoneal SN excision with inguinal orchiectomy. Patients with a tumor-positive SN underwent adjuvant treatment. Follow-up was conducted according to then-current guidelines.

Results

In two patients, no SNs were visualized on scintigraphy. In the remaining 25 patients, a median (range) of 3 (1-4) SNs per patient were removed. Two patients showed no malignancy on histopathological examination of the testis. Of the 23 patients diagnosed with TGCT (16 seminomas, 7 non-seminomas), three (13.0%) had occult metastatic disease. All 23 patients were without evidence of disease at a median (range) follow-up of 63.9 (29.0 – 143.4) months.

Conclusion

The SN procedure allows early identification of patients with occult metastatic disease in clinical stage I TGCT, enabling early treatment.

Introduction

The majority of patients with testicular germ cell tumor (TGCT) present in clinical stage I (CS I) [1]. The predominant management for CS I disease in Europe is inguinal orchiectomy followed by active surveillance (AS) [2]. However, a substantial number of CS I patients have occult metastatic disease at time of presentation, mostly in the retroperitoneal lymph nodes, and will relapse under AS. This is the case in approximately 15-20% of seminomas and 30% of non-seminomatous germ cell tumors (NSGCT) [2–4]. Risk-adapted strategies, based on risk prognosticators, have been developed to anticipate occult metastatic disease and to decide about adjuvant treatment strategies [5–8]. Nevertheless, considerable over- and undertreatment still exists [2].

A major limitation to diagnose occult metastatic disease is the inability of standard imaging techniques to detect microscopic nodal tumor spread. TGCTs have a strong tendency for lymphatic dissemination [8–10]. The SN concept is based on the assumption of a sequential dissemination of metastases through the lymphatic system: from tumor to first-echelon lymph nodes (SNs) and subsequently to other regional nodes (higher-echelon nodes). The hypothesis underlying the SN procedure is that patients without metastases in the SNs have no metastases in the rest of the lymphatic basin. SN procedures are routinely used in several types of cancer, such as breast cancer, penile cancer and melanoma [11].

The feasibility of the SN procedure in TGCT has already been established in several smaller series [12–15], including a prospective study from our institution [15]. Here we report the long-term results of this approach, with additional data from a patient registry.

Patients and Methods

The first 10 patients were included in a feasibility study (study number M00LMT), with appropriate institutional ethics approval. Subsequent patients were included in a patient registry to expand the safety data. The feasibility study received ethical approval and patients signed informed consent. All patients with CS I testicular tumors referred to The Netherlands Cancer Institute between September 2001 and February 2015 were asked to participate.

Lymphoscintigraphy procedure

After local anesthesia by means of a funicular block with Lidocaine 2%, a single dose of ^{99m}Tc-nanocolloid (Amersham Cygne, Eindhoven, the Netherlands) was injected with a fine needle into the affected testicular parenchyma. The mean (range) administered dose was 78.9 (54.0-109.8) MBq in a volume of 0.10 – 0.20 mL.

Immediately after injection, anterior and lateral dynamic images were obtained with a dual-head gamma camera to visualize the lymphatic flow and identify early draining lymph nodes. After the dynamic scan, static planar images were acquired to differentiate SNs from higher-echelon

nodes. Two hours after tracer injection, additional planar images were acquired to identify slower draining SNs and unexpected drainage patterns. In patients treated from 2006 onwards (patients 6-25) additional single-photo-emission computed tomography with computed tomography (SPECT/CT) scan was made in the same session.

The first node(s) in each nodal basin appearing on early planar imaging were considered to be the SN(s). Nodes appearing later in the same basin were considered to be higher-echelon nodes. An additional first node in another basin was also considered to be an SN.

Surgical procedure

The surgical procedure was performed by one of four urological surgeons. Each surgeon had > 10 years' experience in laparoscopic retroperitoneal surgery. Laparoscopic sentinel node excision and open inguinal orchiectomy were performed in the same surgical setting, within six hours after injection of the radioactive tracer. SNs were intra-operatively localized using a laparoscopic gamma probe. In addition, a portable gamma camera (Sentinella, Oncovision) was used in a number of patients (patients 10 and 12-22).

After resection of the SNs, the gamma probe and gamma camera were used to make sure that no relevant nodes were overlooked and left behind. A remaining radioactive node at the side of an SN was considered to be part of a cluster of SNs and was resected. If no clear distinction between first- and second-echelon nodes could be made, all potential SNs were resected. After removal of the SN(s), an open inguinal orchiectomy was performed.

Resected lymph nodes were fixed in formalin, bisected, paraffin-embedded and cut at a minimum of six levels at 50 – 150 µm intervals. They were then pathologically examined, which included haematoxylin and eosin staining, and immunohistochemistry staining.

Follow-up

Any next step in the management of the patient was discussed at a multidisciplinary board meeting, consisting of a urologist, medical oncologist, pathologist, radiation oncologist, nuclear medicine physician and radiologist. Follow-up was carried out according to the then-current European Association of Urology (EAU) guidelines and did not differ from that of patients with CS I TGCTs treated with active surveillance [16]. Follow-up included clinical examination, measurement of serum tumor markers (alpha-fetoprotein, human chorionic gonadotropin and lactate dehydrogenase), abdominal/thoracic computed tomography (CT) scanning, or chest X-rays. Tumor markers were measured every month in the first year, every two months in the second year, every three to four months in the third year and biannually in the fourth and fifth year. CT imaging and chest X-rays were performed at least biannually in the first and second year, and yearly thereafter. After five years, the follow-up was at the discretion of the clinician, but patients were encouraged to participate for at least 10 years. Follow-up duration was measured as time between surgery and last follow-up visit.

Results

Between September 2001 and February 2015, 27 consecutive patients with CS I testicular tumors were included. The median (range) age was 33.1 (20.8-52.4). Sixteen patients (59.3%) had a left-sided tumor and 11 (40.7%) had a right-sided tumor. Study results are shown in Table 1.

Six patients (22.2%) had a history of contralateral testicular tumor. Two of these patients (patients 3 and 25) had had stage I NSGCT and had been treated with active surveillance after orchiectomy. Two patients (patients 13 and 14) had had stage I seminoma and had been treated with adjuvant radiotherapy. In both patients, the radiation field did not include the localization of the SN of their current testicular tumor. One patient (patient 10, stage Is) had received three cycles of bleomycin, etoposide, cisplatin (BEP) and one patient (patient 22, stage I) had been treated with a modified-template laparoscopic retroperitoneal lymph node dissection (RPLND), not including the site of the SN of his current tumor.

In two patients an SN was not shown on scintigraphy. One of these patients showed immediate flow of the radiocolloid on the dynamic scan, with high accumulation in the liver, suggesting venous drainage from a hyperemic tumor. Because the urologist expected to be able to find the SN intra-operatively with the gamma probe, a laparoscopic procedure was initiated; however, no SN was found and a laparoscopic modified-template lymph node dissection was performed. All excised lymph nodes were free of microscopic disease and the patient showed no evidence of disease after 10 years of follow-up. The second patient showed no lymphatic flow of the radiocolloid at all; therefore, laparoscopic SN detection was not deemed feasible and he was treated with orchiectomy only. This patient was lost to follow-up after 33 months without evidence of disease. Both patients were excluded from further analysis.

The remaining 25 patients showed one or more SN(s) on scintigraphy and/or SPECT/CT (Figure 1), and underwent laparoscopic SN resection with synchronous inguinal orchiectomy. Patient characteristics and study results are presented in Table 1. A median (range) of 3 (1 - 4) SNs per patient were removed and histologically examined. In the 15 patients with a left-sided tumor, a total of 37 SNs were removed from the left para-aortic (34 nodes), pre-aortic (one node) interaortocaval (one node) and inguinal (one node, patient with history of orchidopexy) regions. In the 10 patients with a right-sided tumor, a total of 26 SNs were removed from the interaortocaval (19 nodes), right paracaval (four nodes), precaval (one node), left para-aortic (one node) and pre-iliac (one node) regions. The distribution of resected SNs is shown in Figure 2. In addition to the 63 definite SNs, 19 higher-echelon nodes were resected in 11 patients and histologically examined. In seven of these patients (14 nodes) these nodes were merely resected in the same surgical specimen as the SNs. In four patients (five nodes) the nodes were resected because it could not be determined whether they were SNs or higher-echelon nodes; thus, a total of 82 lymph nodes were resected and histologically examined (median of 3 per patient, range 1 – 6).

Table 1 Study results

Patient	Age (yrs)	Tumor side	S-stage	pT-stage	Pathology	Risk factors	No. of resected SNs	SN meta	Adjuvant treatment	Lymph node recurrence	Follow-up (months)
1	44.6	Left	0	N/A	Benign Leydig cell	N/A	2	-	-	-	99.4
2	26.4	Left	1	1	SGCT	> 4 cm	3	-	-	-	143.4
3	33.2	Left	1	1	NSGCT	> 4 cm; EC > 50%; RTI	4	+	BEP x4	-	121.1
4	48.6	Left	0	1	SGCT	RTI	1	-	-	-	89.7
5	44.0	Right	1	N/A	Infarction	N/A	1	-	-	-	3.0
6	46.4	Left	0	1	SGCT	None	1	-	-	-	59.5
7	25.9	Right	1	1	SGCT	> 4 cm; RTI	2	-	-	-	113.6
8	30.9	Right	0	2	SGCT	LVI	2	-	-	-	63.9
9	30.6	Left	1	1	SGCT	> 4 cm	2	-	-	-	119.3
10	33.1	Right	1	2	NSGCT	RTI; LVI	3	-	-	-	100.1
11	40.3	Left	0	1	SGCT	> 4 cm	1	-	Carbo x1	-	62.8
12	47.6	Right	0	3	SGCT	RTI; LVI	3	+	CEB x4	-	88.7
13	46.8	Right	0	1	SGCT	RTI	2	-	-	-	62.0
14	35.1	Left	0	1	SGCT	None	4	-	-	-	71.5
15	25.5	Left	1	2	NSGCT	LVI	3	-	-	-	66.1
16	32.6	Right	1	1	NSGCT	None	3	-	-	-	62.2

Table 1 Study results *(continued)*

Patient	Age (yrs)	Tumor side	S-stage	pT-stage	Pathology	Risk factors	No. of resected SNs	SN meta	Adjuvant treatment	Lymph node recurrence	Follow-up (months)
17	52.4	Left	0	1	SGCT	None	2	-	-	-	65.4
18	42.2	Right	0	1	SGCT	RTI	2	-	-	-	66.1
19	27.8	Left	0	1	NSGCT	EC > 50%; RTI	3	-	-	-	60.2
20	32.4	Left	0	1	NSGCT	None	3	-	-	-	58.3
21	32.5	Right	0	1	NSGCT	> 4 cm; EC > 50%	4	-	-	-	60.4
22	30.7	Left	0	1	SGCT	None	3	-	-	-	58.5
23	39.1	Right	0	1	SGCT	> 4 cm; RTI	4	-	-	-	55.3
24	35.1	Left	0	1	SGCT	None	3	-	-	-	29.0
25	32.7	Left	0	1	SGCT	RTI	2	+	Carbo x2	-	30.9

RTI = rete testis invasion. LVI = lymphovascular invasion. EC = embryonal carcinoma. SN = sentinel node. Meta = metastasis. N/A = not applicable. SGCT = seminoma germ cell tumor. NSGCT = nonseminomatous germ cell tumor. BEP x4 = 4 cycles of bleomycin, etoposide, cisplatin. Carbo x1 = 1 cycle of carboplatin. CEB x4 = 4 cycles of carboplatin, etoposide, bleomycin. + = positive. - = negative.

Figure 1. Lymphoscintigraphy with planar (left) and SPECT/CT (middle and right) images of a single sentinel node in the left para-aortic region.

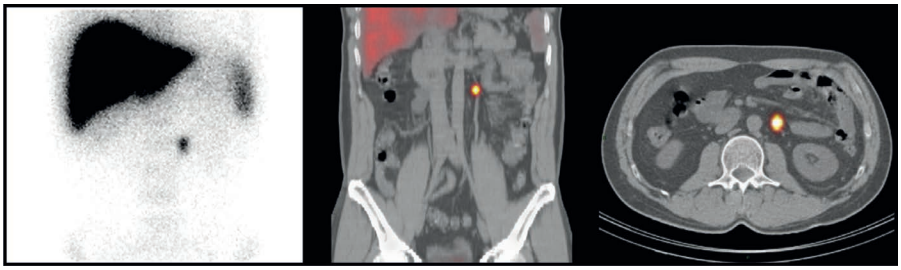
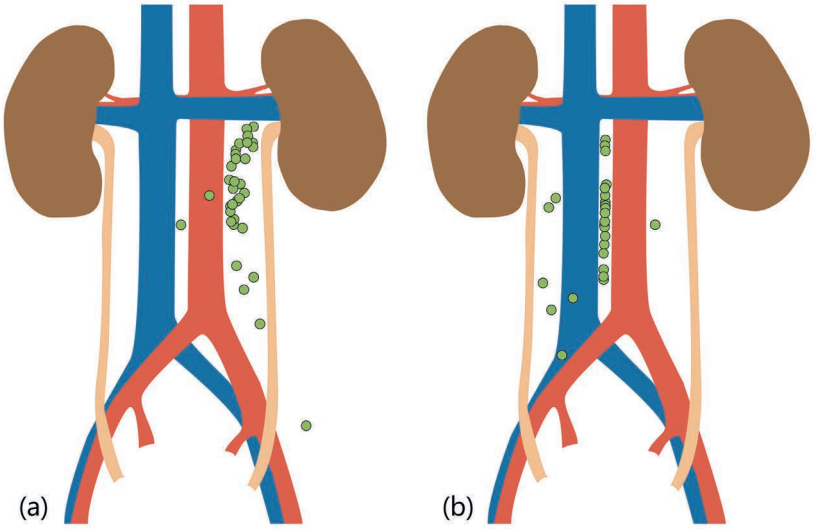


Figure 2. Fusion image of sentinel node localizations of left-sided (a) and right-sided (b) testicular tumor



Pathological examination of the testicular specimen showed seminoma in 16 patients (64.0%) and non-seminoma in 7 patients (28.0%). In two patients (8.0%), pathology showed no malignancy: one patient had a benign Leydig cell tumor and another patient showed infarction without any signs of malignancy. The primary tumor was radically resected in all patients except one (patient 12). This patient had spermatic cord invasion of the tumor (T3 tumor) with tumor cells in the surgical margin. Of the 23 patients with TGCT, three (13.0%) showed occult metastases in a total of six SNs.

All patients with a positive SN received adjuvant systemic treatment with either four cycles of BEP, four cycles of carboplatin, etoposide, bleomycin (CEB; microscopically irradical resection of primary tumor), or two cycles of carboplatin. One patient without occult metastatic disease received one cycle of carboplatin at his own request.

Three Clavien-Dindo grade I complications were reported. Two patients had postoperative pain for which they received additional analgesic medication. One patient had urinary retention after removal of his Foley catheter for which he was in-and-out-catheterized twice. No other complications were noted.

All 23 patients with TGCTs were without evidence of disease at a median (range) follow-up of 63.9 (29.0 – 143.4) months.

Discussion

We report the long-term results of a series of patients undergoing a laparoscopic SN procedure for testicular tumor in CS I. Thirteen percent (3/23) of patients with TGCT showed occult metastatic disease in at least one SN. No patient relapsed after a median follow-up of 63.9 months.

This study shows that an SN procedure enables early identification of patients with occult metastatic disease in CS I TGCT. With no false-negative procedures, no serious complications or side effects so far, the procedure is safe and well tolerated.

The prognosis of CS I TGCT is very favorable and cancer-specific survival rates as high as 100% have been reported [17–19]; however, there is no international consensus how to best manage these patients. In contrast to US guidelines, RPLND is not recommended for clinical stage I patients in Europe [2,20]. European guidelines currently recommend active surveillance for most patients, as it minimizes morbidity associated with lymphadenectomy [21,22]; however, up to 20% of patients with seminomas and 30% of patients with NSGCTs have occult metastatic disease and will relapse during active surveillance [2,3,23]. In case of relapse, patients are treated with three to four cycles of BEP or radiotherapy. These treatment regimens cause serious short- and long-term side effects. For example, patients with TGCTs treated with chemotherapy have a 1.5 – 1.9-fold higher chance of cardiovascular disease and a 2.1-fold higher chance of a secondary malignancy [24,25]. Because of these late effects, the relative survival of patients with localized disease keeps declining even beyond 30 years of follow-up [26].

To overcome this problem, a risk-adapted strategy, in which only high-risk patients are treated with adjuvant chemotherapy, has been advocated in European guidelines [2].

Patients with a seminoma > 4 cm and rete testis invasion have a 5-year risk of relapsing of 31.5%, compared to 12.2% in patients without risk factors [5]. This means that using this risk-adapted strategy, 68.5% of high-risk patients unnecessarily receive adjuvant chemotherapy, while 12.2% of low-risk patients may need adjuvant treatment, but do not receive it.

Patients with NSGCTs with lymphovascular invasion have a 48% chance of developing metastatic disease, whereas patients without lymphovascular invasion have a 14-22% chance of relapsing [6–8,23,27]. As with seminoma, approximately 52% of patients with high-risk

NSGCT receive adjuvant treatment without any benefit, while 14-22% of low-risk patients are undertreated. These rates of over- and under-treatment show that there is room for improvement in the selection of patients who need adjuvant therapy.

With an SN approach, candidates for adjuvant treatment for seminoma and non-seminoma could be identified based on objective histopathological findings; however, it is unknown how to best manage patients with occult metastatic disease in their SN. Our study did not involve performing a complete RPLND; therefore, the SN approach for testicular cancer is currently a non-validated diagnostic procedure. Several management strategies can be discussed and would require confirmation in clinical trials.

Considering the microscopic nature of the disease stage, one option would be to regard SN-positive patients as having high-risk stage I disease which may be treated adequately with a lower dose of adjuvant treatment: one cycle of carboplatin for patients with seminomas and one cycle of BEP for patients with NSGCTs [2,28]. Adjuvant treatment at this early stage might prevent relapse in SN-positive patients, thereby avoiding the necessity of multiple cycles of chemotherapy and reducing short- and long-term side-effects [29,30].

Alternatively, patients who had removal of early nodal disease in their SN may be candidates for active surveillance, while those with negative SN may benefit from a potential reduction of follow-up visits and costly investigations. Since no relapses were observed in patients without tumor-positive SNs, the need for intensive follow-up protocols in this group may be reduced and retroperitoneal imaging might no longer be necessary. This requires a larger study, however, with additional RPLND to confirm absence of further nodal involvement. False-negative SN procedures (patients who relapse in the retroperitoneum after a tumor-negative SN procedure) may be the limiting factor of this technique. Despite the fact that no false-negative procedures were observed in the present series, much larger studies are needed to determine precisely the risk of false-negative procedures.

No serious complications occurred in the present series, although the safety of the procedure has to be investigated within a larger study population. It is unlikely, however, that side effects would differ from what is generally known from recent primary laparoscopic RPLND series (postoperative complication rate 0-9.8%) [31]. In a large series by Nicolai et al., only 8 / 221 patients (3.6%) who underwent laparoscopic RPLND had a complication with Clavien-Dindo grade >2 [32]. Nevertheless, patients with a suspicion of TGCT but without evidence of TGCT on testicular pathology (two patients in our series) have been unnecessarily subjected to an invasive procedure.

The SN approach is well established for several other malignancies, but there is very little literature on the use in TGCT. The feasibility of the procedure was first demonstrated in 2002 by Tanis et al. [12]. Two studies have described follow-up results of this approach. Satoh et al. reported on a series of 22 patients with CS I testicular tumors of whom two had a tumor-

positive SN and were treated with two cycles of BEP without relapse at 31 and 29 months follow-up; however, two patients without metastases on histopathological examination showed relapse at 10 and 20 months of follow-up [14]. The authors attributed this to an intra-operative detection error and an aberrant route of lymphatic dissemination [14]. This study from 2005 used preoperative planar lymphoscintigraphy with intra-operative gamma probe detection, but no SPECT/CT imaging. SPECT/CT enables more exact preoperative localization of the SNs, making it easier to find the SNs and potentially decreasing the false-negative rate. In a case series of ten patients by Brouwer et al., one patient with seminoma had a positive SN and was treated with four cycles of CEB. During a median (range) follow-up of 21 (2-50) months, no patient relapsed [15]. Results in our updated series are in line with this early report from our institution.

In five patients with TGCT, follow-up was <5 years and the minimum duration of follow-up was 29.0 months. As the chance of relapse after two years of negative follow-up is <6%, we believe that follow-up duration in the present study was sufficient [33,34].

The inconsistency in adjuvant chemotherapy courses for node-positive patients can be explained by the limited experience with the SN procedure in TGCTs. As the exact significance of an occult metastasis is still unclear, the best treatment approach is still undetermined; therefore, throughout the duration of the study, oncologists preferred different chemotherapy regimens. The present study was, however, focused on the long-term outcome of SN-negative disease.

The relatively long period needed to include this number of patients and the high proportion of patients with a history of contralateral TGCTs is attributable to the referral system of our institute. The Netherlands Cancer Institute is a tertiary referral center and mostly treats large-volume disease. In addition, orchiectomies are often performed at diagnosis in the referring hospitals.

The next step in the development of this procedure is to investigate whether patients with a negative SN have no risk of relapsing, with a larger sample size and in a prospective study design. To achieve this goal, we have initiated a prospective clinical trial (www.clinicaltrials.gov identifier: NCT03448822).

We concluded that the SN procedure seems feasible and safe for CS I TGCT, and enables detection of microscopic lymph node invasion at an early stage. This approach could potentially lead to less intensive follow-up protocols in node-negative patients and reduced systemic treatment of microscopic disease. Larger prospective studies are needed to further substantiate these findings.

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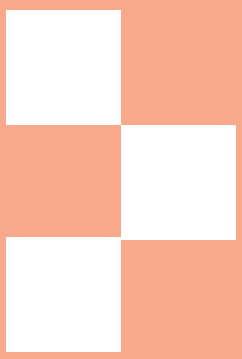
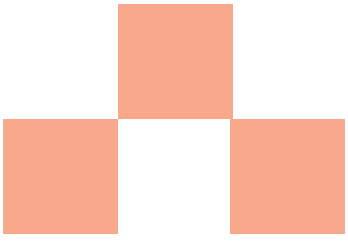
Part 2



Surgical resection of postchemotherapy residual tumors



4

Chapter

Clinical outcome of postchemotherapy retroperitoneal lymph node dissection in metastatic nonseminomatous germ cell tumor: A systematic review

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Abstract

Background

Postchemotherapy retroperitoneal lymph node dissection (PC-RPLND) is an important element of the management of patients with residual tumor after chemotherapy for disseminated nonseminomatous germ cell tumor (NSGCT). This is a challenging procedure and the outcome varies widely between institutions. There is much debate concerning the anatomical extent of the dissection and the literature is conflicting regarding the outcome of this procedure.

Objective

In this systematic review we aim to summarize the literature on the relapse rate of PC-RPLND.

Materials and Methods

We performed a search of the literature of the PubMed/MEDLINE and Embase databases, in accordance with the PRISMA guidelines. Studies reporting on the relapse rate of PC-RPLND in NSGCT patients with residual tumor were eligible for inclusion. We calculated the weighted average relapse rates of included studies and assessed the risk of bias using the Newcastle-Ottawa scale.

Results

A total of 33 studies, reporting on 2,379 patients undergoing open PC-RPLND (O-RPLND) and 463 patients undergoing minimally invasive PC-RPLND (MI-RPLND) were included. The weighted average relapse rates were 11.4% for O-RPLND, and 3.0% for MI-RPLND. The rates of retroperitoneal relapse were 4.6% and 1.7% after O-RPLND and MI-RPLND, respectively. For O-RPLND specifically, the average retroperitoneal relapse rate was 3.1% after modified dissection and 6.1% after bilateral dissection.

Conclusions

We conclude that modified template dissection is oncologically safe in carefully selected patients. Minimally invasive procedures are feasible but long-term data on the oncological outcome are still lacking. PC-RPLND is a complex and challenging procedure, and patients should be treated at high-volume expert centers.

Introduction

Postchemotherapy retroperitoneal lymph node dissection (PC-RPLND) plays an important role in the management of metastatic nonseminomatous germ cell tumor (NSGCT) [1]. Up to 40% of patients demonstrate residual retroperitoneal tumor after completion of primary chemotherapy [2]. These tumors contain viable cancer in 10-20% and teratoma in 30-40% of patients [1]. Resection of the residual tumor is a vital aspect of optimal patient care [2,3].

The anatomical extent of PC-RPLND has been a matter of debate for many years. Full bilateral open PC-RPLND (O-RPLND) used to be the standard approach in all patients [4,5]. Nowadays, the application of modified templates is widely accepted in selected patients, since it reduces morbidity without impairing oncological efficacy [1,6–8]. In addition, laparoscopic (L-RPLND) and robot-assisted (RA-RPLND) techniques are evolving [9–11]. For example, bilateral template RA-RPLND without patient repositioning is feasible [12,13] and Aufderklamm et al. have reported L-RPLND with vessel wall reconstruction in patients with residual tumor infiltrating the great vessels [14]. In a recent series of 30 patients by Li et al., none of the patients had retroperitoneal relapse after RA-RPLND [15]. This suggests that the minimally invasive approach doesn't compromise oncological safety. As robotic surgical techniques keep evolving, the indication of RA-RPLND will expand even further.

The majority of studies on PC-RPLND are from high-volume centers [16,17]. It is debatable whether these large series reflect the outcome of PC-RPLND in general, since most PC-RPLNDs are performed by intermediate- or low-volume surgeons [16,18]. Therefore, a systematic review of the literature is necessary to give a more comprehensive overview of the clinical outcome of PC-RPLND. In the present study, we have systematically reviewed the current literature on the relapse rate of PC-RPLND.

Methods

Search strategy and eligibility criteria

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [19]. The review protocol has been published in the PROSPERO database (registration number: 142872).

A systematic literature search using the PubMed/MEDLINE and Embase databases was performed on July 1, 2019. An information specialist was involved in the design of the search strategy (Supplementary File 1).

Two reviewers (J.B. and R.H.) independently screened all articles for eligibility based on the following inclusion criteria: (1) studies including patients with metastatic NSGCT undergoing PC-RPLND; (2) studies reporting relapse rates; (3) studies reporting data from institutional (single or multicenter) series. Studies on primary RPLND, repeat RPLND, desperation/salvage

RPLND, patients with pure seminoma, or patients with non-germ cell tumor were excluded. Review articles, case reports, feasibility studies, conference abstracts, editorials, comments, studies not in the English language and studies published before 1998 were also excluded. If two studies reported on the same patient cohort, we selected the study with the longest follow-up time. If two studies had some overlap in patients, but not exactly the same patient cohort, both studies were included.

Data extraction and outcome measures

Data were extracted by one reviewer (R.H.) and checked for accuracy by a second reviewer (J.B.). The primary outcome measure was relapse rate during follow-up. The secondary outcome measure was the rate of peri-operative complications. Using Microsoft Excel 2010, we calculated the weighted average relapse rates by dividing the total number of relapses by the total number of included patients. We also evaluated the association between relapse rate and annual study sample size.

Quality assessment

Two reviewers (J.B. and R.H.) independently assessed the risk of bias, using the Newcastle-Ottawa scale for three domains: selection of the study groups, comparability of the groups and outcome (Supplementary Table 2) [20]. Disagreement was resolved by discussion, with R.M. acting as an independent arbiter, if necessary.

Results

A total of 145 studies were selected for full-text screening, of which 33 studies were included in the final synthesis (Figure 1) [1,5-9,15,17,21-45]. Twenty studies reported on O-RPLND [1,5-8,17,21,22,24,25,27-36], ten studies reported on MI-RPLND [9,37–45], and three studies reported on both techniques [15,23,26]. All studies were retrospective in nature, and most were single-center cohorts. Two studies were multi-center cohort studies [1,27]. Studies were heterogeneous in regard to patient selection criteria (e.g. age, IGCCCG prognosis, tumor characteristics), population size (range 12–432), treatment period (1980–2018) and median length of follow-up (range 12–125 months) (Supplementary Table 1). The majority of studies were from European (n = 15) or Northern American (n = 10) centers.

Open PC-RPLND

The weighted mean relapse rate was 11.5% (Table 1). The distribution of the relapse locations was reported in 21 studies [1,5-8,17,21-27,29-36]. The retroperitoneum was the most common site of relapse, with an average rate of 4.6%. Other common sites of relapse were the chest and lungs. The median time to relapse ranged from 6.1 months to 15 months, but this is based on only four studies [7,17,29,31].

The largest series in our study is from the Memorial Sloan-Kettering Cancer Center [30]. Between 1989 and 2006, 695 patients were treated with PC-RPLND. Whether a full bilateral or modified

template dissection was performed was left to the discretion of the surgeon. Patients with viable cancer on retroperitoneal histology were excluded from the study. Of the 432 patients included in the analysis, 30 patients (6.9%) relapsed, with only eight retroperitoneal relapses (1.9%).

Figure 2 shows the association between reported procedures per year and retroperitoneal relapse in O-RPLND. The combined retroperitoneal relapse rate for the five smallest series [22–24,26,34] was 1.5 times higher compared to the five largest series (6.7% vs. 4.4%) [6,29,30,33,35]. For studies from centers reporting 10 or fewer procedures per year, the relapse rate varied widely and the two largest centers had a relapse rate of only 1.9% and 3.4% [6,30].

Six studies discussed the results of unilateral dissection separately (Table 1) [1,5,7,26,34,35]. In these series, 18 of 287 patients (6.3%) developed a relapse, which was a retroperitoneal relapse in nine patients (3.1%).

Perhaps the most influential study on modified template PC-RPLND is the series by Heidenreich et al. [1]. In this study, patients with a residual tumor <5 cm in the primary landing zone were treated with a unilateral dissection. Three out of 98 patients (3.1%) relapsed. In one patient the relapse was inside the modified surgical field. The other two patients relapsed outside the anatomical boundaries of a full bilateral PC-RPLND. Thus, none of the patients were treated with a modified dissection while they should have been treated with a bilateral dissection.

In the series by Busch et al., twenty-four patients were treated with an open procedure, of which five patients underwent a modified template dissection [26]. A retroperitoneal relapse occurred in two of five patients (40.0%). This was located inside the boundaries of a modified template in one patient (20.0%). The location of the other relapse was unknown.

Cho et al. reported the long-term outcome of 100 patients treated with a modified-template dissection [7]. After a median follow-up of over 10 years, seven patients relapsed, with all relapses outside the boundaries of a bilateral dissection. Thus, none of the patients would have benefitted from a more extensive dissection.

In the study by Tanaka et al., one patient had a retroperitoneal relapse, outside the boundaries of a modified template dissection, but within the boundaries of a bilateral dissection [34]. This patient would have benefitted from a bilateral approach.

The outcome of bilateral template dissection was analyzed in eleven studies (Table 1) [1,5, 8,22–24,26,32–35]. Overall, 82 of 560 patients experienced a relapse (14.6%) and relapse location was reported in all cases. Thirty-four patients had a retroperitoneal relapse (6.1%).

Figure 1. PRISMA diagram

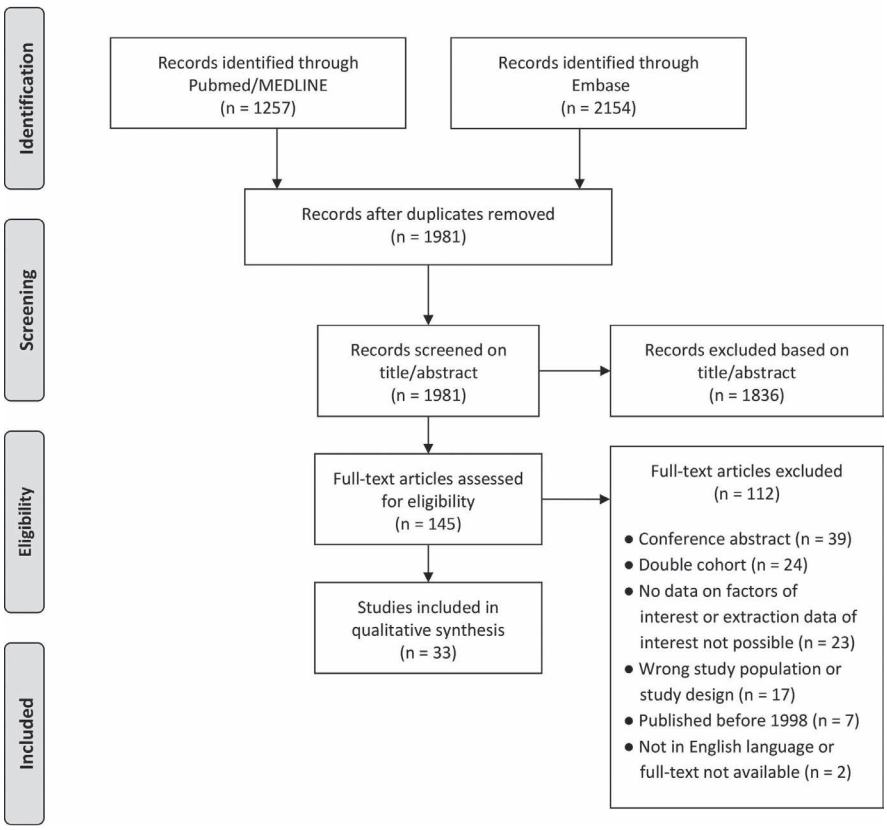

Figure 2. Association between reported procedures per year and retroperitoneal relapse in O-RPLND

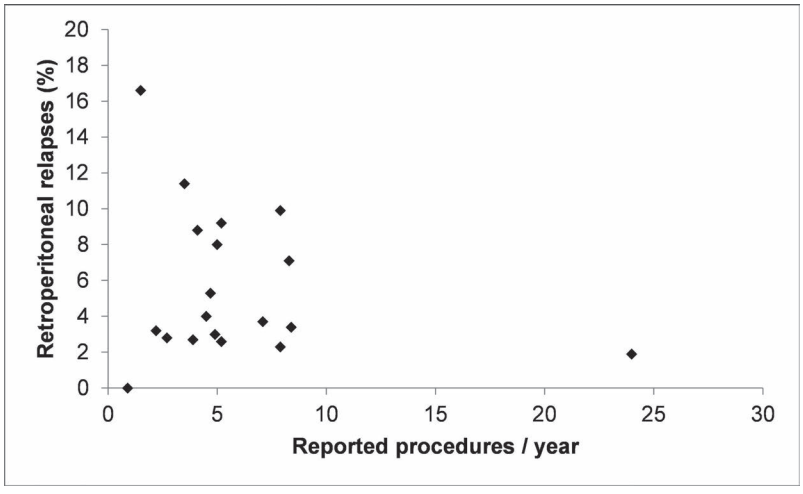

Table 1. Relapse following open PC-RPLND

First author (year)	Treatment period	Number of patients	Relapses, n (%)	Retroperitoneal relapses, n (%)
Studies reporting on unilateral dissection				
Cho (2017)	1991 – 2004	100	7 (7.0)	3 (3.7)
Busch (2012)*	1999 – 2010	5	2 (40.0)	2 (40.0)
Heidenreich (2009)*	1999 – 2007	98	3 (3.1)	3 (3.1)
Tanaka (2006)	1992 – 2005	25	3 (12.0)	1 (4.0)
Oldenburg (2003)	1990 – 2000	50	3 (6.0)	0
Rabbani (1998)	1985 – 1995	9	0	0
Subtotal		**287**	**18 (6.3)**	**9 (3.1)**
Studies reporting on bilateral dissection				
Ariffin (2017)	2002 – 2015	36	2 (5.6)	1 (2.8)
Nakamura (2016)†	2009 – 2013	14	0	0
Singh (2016)	2003 – 2012	35	7 (20.0)	4 (11.4)
Busch (2012)*	1999 – 2010	13	1 (7.7)	1 (7.7)
Miki (2009)†	1994 – 2008	78	2 (2.6)	2 (2.6)
Heidenreich (2009)*	1999 – 2007	54	5 (9.3)	5 (9.3)
Spiess (2007)	1980 – 2003	198	45 (22.7)	14 (7.1)
Ehrlich (2006)	1996 – 2005	50	9 (18.0)	4 (8.0)
Tanaka (2006)	1992 – 2005	6	0	0
Oldenburg (2003)	1990 – 2000	37	2 (5.4)	2 (5.4)
Rabbani (1998)	1985 – 1995	39	9 (23.1)	1 (2.6)
Subtotal		**560**	**82 (14.6)**	**34 (6.1)**
Studies reporting no distinction between templates				
Li (2019)	2007 – 2018	63	12 (19.0)	NM
Schmidt (2018)	1993 – 2013	109	13 (13.4)	10 (9.2)
Considine (2016)§	1996 – 2011	78	9 (13.6)	2 (3.0)

Table 1. Relapse following open PC-RPLND *(continued)*

First author (year)	Treatment period	Number of patients	Relapses, n (%)	Retroperitoneal relapses, n (%)
Vallier (2014)	2007 – 2013	59	8 (13.6)	2 (3.4)
Ekenel (2012)‡	1991 – 2010	94	8 (8.5)	5 (5.3)
Winter (2012)* |	1995 – 2011	339	45 (13.3)	10 (2.9)
Luz (2010)	1994 – 2008	73	7 (9.6)	NM
Flechon (2010)	1992 – 2010	151	28 (18.5)	15 (9.9)
Carver (2010)	1989 – 2006	432	30 (6.9)	8 (1.9)
Williams (2009)	1993 – 2006	57	5 (8.8)	5 (8.8)
Ozen (2001)‡	1980 – 1998	75	5 (6.7)	2 (2.7)
Rabbani (1998)	1985 – 1995	2	1 (50.0)	1 (50.0)
Subtotal		**1,532**	**171 (11.2)**	**60 (4.3)**
Total		**2,379**	**271 (11.4)**	**103 (4.6)**

NM = not mentioned
*, †, ‡ = overlap in patients
§ = follow-up data available for 66 patients
| = follow-up data available for 307 patients

Minimally invasive PC-RPLND

Studies on MI-RPLND had a smaller sample size and shorter follow-up period. Therefore, we have combined the studies on laparoscopic and robot-assisted procedures. The reported relapse rates ranged from 0% to 10.5%, with a weighted mean rate of 3.0% (Table 2) [9,15,23,26,37-45]. Eight relapses were in the retroperitoneal area (1.7%) and median follow-up time was relatively short (range: 13-59 months).

Eleven studies analyzed the outcome of 326 patients undergoing a unilateral dissection (Table 2). In these series, seven relapses were reported (2.1%) of which six were in the retroperitoneum (1.8%) [26,39,40].

The study with the highest volume was the series by Steiner et al. [39]. A total of 100 patients were treated between 1993 and 2010. A laparoscopic unilateral dissection was used until 2004, after which all patients were treated with a laparoscopic bilateral nerve-sparing procedure. The study cohort was relatively favorable: all patients had stage II disease at initial staging, the mean size of residual tumor was 1.4 cm and 51 patients had residual disease <1 cm. Histology of the retroperitoneal specimen showed necrosis or fibrosis in 60 patients, teratoma in 38 patients and active cancer in only 2 patients, who were both treated with adjuvant chemotherapy. One

patient who was treated with a left-sided unilateral dissection had a relapse, which was located posterior of the inferior caval vein [39].

Another large volume study was the series by Nicolai et al. [37]. Between 2011 and 2015, 67 unilateral L-RPLNDs were performed. Patients were eligible if they had no history of retroperitoneal surgery, unilateral disease from the start, normalized tumor markers, and a residual lesion between 10 and 50 mm. Patients with a residual lesion >50 mm suggestive of teratoma were also included. The median residual tumor size was 27 mm. None of the patients relapsed after a median follow-up of 21 months [37].

Six studies, reporting on 86 patients, analyzed the outcome of bilateral MI-RPLND (Table 2) [9,23,26,38–40]. Two retroperitoneal relapses were described (2.3%).

An in-field relapse was reported in two MI-RPLND studies. Aufderklamm et al. described a series of 29 patients, of which 19 patients were treated with a unilateral dissection [40]. Two patients (10.5%) relapsed after a unilateral dissection, both inside the surgical field. Busch et al. reported an in-field relapse in three out of 46 patients (6.5%) [26]. Two of these patients were treated with a unilateral dissection, and one patient with a bilateral dissection.

Table 2. Relapse following minimally invasive PC-RPLND

First author (year)	Treatment period	Number of patients	Relapses, n (%)	Retroperitoneal relapses, n (%)
Studies reporting on unilateral dissection				
Nicolai (2016)	2011 - 2015	67	0	0
Nakamura (2016)	1998 - 2013	2	0	0
Kamel (2016)*	2011 - 2015	6	0	0
Gaya (2015)	2004 - 2008	15	0	0
Sharma (2015)*	2006 -2011	9	0	0
Steiner (2013)	1993 - 2010	71	1 (1.4)	1 (1.4)
Aufderklamm (2013)	2002 - 2009	19	2 (10.5)	2 (10.5)
Busch (2012)	1999 - 2010	32	3 (9.4)†	2 (6.3)
Arai (2012)	2002 - 2010	20	0	0
Calestroupat (2009)	2002 - 2006	26	0	0
Albqami (2005)	1995 - 2004	59	1 (1.7)	1 (1.7)
Subtotal		**326**	**7 (2.1)**	**6 (1.8)**

Table 2. Relapse following minimally invasive PC-RPLND *(continued)*

First author (year)	Treatment period	Number of patients	Relapses, n (%)	Retroperitoneal relapses, n (%)
Studies reporting on bilateral dissection				
Nakamura (2016)	1998 - 2013	12	0	0
Kamel (2016)	2011 - 2015	3	0	0
Sharma (2015)*	2006 - 2011	10	0	0
Steiner (2013)	1993 - 2010	29	0	0
Aufderklamm (2013)	2009 - NM	20	2 (10.0)	1 (5.0)
Busch (2012)	1999 - 2010	12	1 (8.3)	1 (8.3)
Subtotal		**86**	**3 (3.5)**	**2 (2.3)**
Studies reporting no distinction between templates				
Kamel (2016)	2011 - 2015	3	0	0
Busch (2012)	1999 - 2010	2	0	0
Permpongkosol (2007)	1966 - 2005	16	1 (6.3)	0
Subtotal		**51**	**4 (7.8)**	**0**
Total		**463**	**14 (3.0)**	**8 (1.7)**

* = robot-assisted procedures
† = one location unknown

Open versus minimally invasive surgery

Only three studies compared MI-RPLND with O-RPLND [15,23,26]. Busch et al. retrospectively compared the outcome of 46 patients treated with L-RPLND, with 21 patients treated with O-RPLND [26]. There were three relapses in the open surgery group (14.3%), all in the retroperitoneal area. In the minimally invasive group, four patients relapsed (8.7%), of which three (6.5%) in the retroperitoneum. The groups, however, were not really comparable as the median size of residual tumor in the minimally invasive group was smaller (2.2 cm vs. 6.8 cm). Li et al. compared 30 RA-RPLNDs and 63 O-RPLNDs performed by a single surgeon [15]. Patients undergoing RA-RPLND had favorable IGCCCG prognosis and smaller retroperitoneal masses, compared to O-RPLND, but a substantial number of patients had elevated markers at surgery (RA-RPLND: 23.3%; O-RPLND: 29%). Twelve patients (19%) relapsed following O-RPLND and three patients (10%) relapsed after RA-RPLND. All relapses after RA-RPLND were at distant sites and two of the three patients who relapsed had undergone desperation RPLND with viable cancer in the retroperitoneal specimen. In the other study that compared open surgery with minimally invasive surgery, no relapses were found in either group [23].

Postoperative complications

Fourteen studies on O-RPLND reported on the presence or absence of postoperative complications [1,15,17,21-24,26,27,29,31-33,36]. The average complication rate was 21.8%, with the majority of complications graded as Clavien-Dindo Grade I or II [46]. Two Grade V complications were reported. In the study by Heidenreich et al., one patient in the bilateral group developed an aorto-duodenal fistula and died due to massive postoperative bleeding [1]. Flechon et al. reported one death due to an intra-abdominal bleeding 10 days after surgery [29].

Thirteen studies reported on the presence or absence of postoperative complications following MI-RPLND [9,15,23,26,37-45]. The average complication rate for minimally invasive PC-RPLND was lower, compared to O-RPLND (15.9%). The majority of complications were Grade I or II, and no Grade V complication was reported.

The rate of conversion to an open procedure was reported in all series and ranged from 0% to 13.3% [9,15,23,26,37-45]. No conversion was recorded in four studies [23,40,41,44]. The average conversion rate was 4.3% (Supplementary Table 1) with uncontainable blood loss as the most common cause [9,15,26,37,39,42,43,45].

Discussion

Resection of the retroperitoneal residual tumor is an important part of the treatment of metastatic NSGCT, since these lesions can contain viable cancer or teratoma in up to 40% of patients [2,47,48]. Completeness of the surgical resection is a strong predictor of progression-free survival and overall survival [7,29,49,50].

Although centralization of such complex surgical procedures is preferred, most RPLNDs are still performed by low-volume surgeons. According to case log data from urologists seeking recertification with the American Board of Urologists, the median annual number or RPLNDs per surgeon in the USA between 2003 and 2013 was only one procedure [16]. Of the 290 urologists that performed at least one RPLND, 75% logged only one procedure and three urologists logged 23% of all RPLNDs [16]. This is further substantiated by Yu et al., who showed that more than half of RPLNDs in the USA are performed at hospitals with ≤2 procedures per year [51]. In the UK, the median number of RPLNDs per surgeon is six [18]. Groeben et al. analyzed German hospital billing data covering 2006-2015 and found that the majority of RPLNDs (43.7%) were performed in a low-volume center (<4 cases annually) [52]. Although there was a modest trend towards centralization and the number of low- and intermediate volume centers declined over the years, only 18.3% of all 382 RPLNDs in 2015 were performed in a high-volume center (>10 cases annually).

Several studies have demonstrated that patient outcome is better in large-volume hospitals [51,53,54]. Woldu et al. analyzed testicular cancer data from the American National Cancer Database [54]. The 5-year overall survival of stage II NSGCT was 98% in high-volume institutions,

but only 78% in low-volume centers. Compared to high-volume hospitals, the hazard ratio (HR) of overall mortality was significantly higher in low-volume centers (HR 1.83, P<0.001) [54]. In the study by Yu et al., the risk of a respiratory complication after RPLND was significantly lower in high-volume centers, compared to low-volume centers (4.2% vs. 7.2%) [51]. The overall risk of complication was also lower in high-volume centers (22.5% vs. 27.0%) but the difference was not statistically significant. Our results suggest the same trend, since relapse risk was clearly lower in the two centers with the highest annual volume. These findings need to be interpreted with caution, as a statistical analysis was not appropriate in our study, but they show that PC-RPLND should only be performed in experienced large-volume referral centers.

The debate about the optimal anatomical extent of PC-RPLND continues. While a modified resection is considered oncologically safe in selected patients, some centers prefer a full bilateral resection in all patients. Others regard the resection of the residual mass only as oncologically equivalent [21]. The potential benefits of a less extensive dissection are: fewer complications, shorter operative times, reduced fluid requirements, and preservation of antegrade ejaculation [23]. Our literature study confirms that a modified template dissection is oncologically safe. However, this is mostly based on single center retrospective studies and the results vary widely between institutions.

In addition to the expertise of the surgeon, accurate staging and patient selection are important drivers for success. As the debate on the benefit and safety of a more limited dissection is still ongoing, there are currently no universally accepted selection criteria for a modified approach. The Heidenreich criteria are probably most often used [1]. According to these criteria, a unilateral dissection is suitable in patients with a residual tumor <5 cm in the primary landing zone. In patients with a lesion in the inter-aortocaval region, a bilateral dissection is warranted. These criteria have been externally validated in a cohort of 59 patients and did not misclassify a single patient [6].

A study from the Memorial Sloan-Kettering Cancer Center analyzed the incidence of retroperitoneal disease outside the boundaries of five different modified templates [4]. A total of 269 patients who underwent surgery between 1989 and 2003, and had viable cancer or teratoma in their retroperitoneum were included. Most patients (76%) were treated with a bilateral dissection. Histopathological analysis and reporting were done for each nodal region individually and these findings were compared to five modified templates described in the literature. Depending on the template, the incidence of extra-template disease was 7% to 32%. The modified template from the Memorial Sloan-Kettering Cancer Center was the most extensive template and had the lowest incidence of extra-template disease (7%). It should be noted that 28% of patients in the study had a residual tumor >5 cm and 16% had elevated tumor markers at the time of surgery. This makes the findings less applicable to general practice, since careful selection of patients who can be safely treated with a modified dissection is an important driver of success. Nevertheless, this study shows that a more extensive dissection leads to a lower risk of retroperitoneal relapse.

The studies on unilateral PC-RPLND employed slightly different templates. Busch et al. used the anatomical boundaries as defined by Heidenreich et al [1,26]. For right-sided tumors, this included the precaval, paracaval, retrocaval, and interaortocaval regions, including the area lateral to the common iliac vessels with the crossing of the ureter as the caudal boundary and the renal vessels as the cranial boundary. The left-sided template included the para-aortic and retroaortic regions with the crossing of the ureter over the iliac artery as the caudal boundary. The preaortic region was included down to the inferior mesenteric artery (IMA). The modified templates used by Tanaka et al. were more extensive [34]. Their right-sided template also included the preaortic region between the renal vessels and the IMA. Similarly, the left-sided template included the interaortocaval region between the renal vessels and IMA. The caudal border of both modified templates was the bifurcation of the common iliac artery.

Although the feasibility of MI-RPLND has been established in several studies, the data on the oncological safety are not yet mature enough to draw firm conclusions. The results from the three largest series suggest that the procedure is safe in expert hands [37,39,44]. A minimally invasive approach has substantial benefits, such as reduction of blood loss, shorter hospitalization time, and less need of postoperative analgesics [37,39]. In a recent systematic review on MI-RPLND by Tselos et al., the average rate of antegrade ejaculation was 95.5%, the incidence of a major complication was 4% and mean postoperative stay was 1.3 days [55]. Most studies describe a unilateral approach, but bilateral RA-RPLND is feasible with only single docking [13].

One of the strengths of our study is the systematic approach. Our methodology is in line with the PRISMA guidelines, the search strategy was developed in consultation with an information specialist, and the risk of bias of included studies was assessed.

Our findings, however, are limited by the heterogeneity of included studies and by the fact that most studies were of retrospective nature. Many studies had a small sample size and were of poor methodological quality. In addition, we are limited by the likely publication bias in the literature on PC-RPLND. There are many more (large and small) centers where this procedure is performed, but their results have not yet been published or were not eligible for inclusion in the present review. This risk of bias makes our results less universally applicable.

Further work needs to be done to answer some of the open questions. For example, prospective studies randomizing between modified and bilateral template dissection would greatly add to the ongoing debate on PC-RPLND.

Conclusions

A modified template dissection is oncologically safe, but accurate patient selection is important. Long-term data on the oncological outcome of MI-RPLND are still lacking. To ensure optimal clinical outcome and long-term survival, patients should be treated at high-volume expert centers.

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Supplementary Table 1. Characteristics of included studies

First author (year)	Treatment period	Country	Number of patients	Study inclusion criteria	PC-RPLND inclusion criteria	Median age (range)	IGCCCG prognosis, n (%)	Median size residual tumor, cm	Type of resection, n	Histology retroperitoneal specimen, n (%)	Median follow up in months (range)	Conversion to open, n (%)
Studies reporting on open surgery												
Li (2019)	2007 – 2018	USA	63	Pts. who underwent PC-RPLND for residual tumor, no prior RPLND	NM	26 (IQR 22-33)	Good: 38 (60.3) Intermediate: 7 (11.1) Poor: 18 (28.6)	NM	Bilateral template: 56 Unilateral modified: 7	Necrosis/fibrosis: 16 (25.4) Teratoma: 36 (57.1) Viable cancer: 11 (17.4)	33.4 (1-115)	N/A
Schmidt (2018)	1993 – 2013	Denmark	109	NSGCT patients of a consecutive cohort with residual disease following cisplatin-based chemotherapy	NM	27.1 (15.3-64.4)	Good: 59 (54) Intermediate: 29 (27) Poor: 20 (18) Missing: 1 (1)	NM	Residual mass resection	Necrosis/fibrosis: 35 (32) Teratoma: 63 (58) Viable cancer: 7 (6) Teratoma and viable cancer: 3 (3) Other: 1 (1)	124 (10-377)	N/A
Ariffin (2017)	2002 – 2015	Ireland	36	Pts. who underwent PC-RPLND for metastatic NSGCT at a tertiary referral university teaching hospital between 2002 and 2015	NM	Mean: 31.3 (19-41)	NM	NM	Bilateral template	Necrosis/fibrosis: 6 (16.7) Teratoma: 26 (72.2) Viable cancer: 4 (11.1)	Mean: 35 (1-144)	N/A
Cho (2017)*	1991 – 2004	USA	100	Metastatic NSGCT with residual disease limited to the primary landing zone on CT and normal serum tumor markers	NM	27 (21-31)	Good: 98 (98) Intermediate: 0 (0) Poor: 2 (2)	NM	Modified template	Necrosis/fibrosis: 36 (36) Teratoma: 62 (62) Viable cancer: 2 (2)	125 (NM)	N/A
Considine (2016)	1996 – 2011	Ireland	78; 5 (6.4%) seminoma	Pts. who underwent RPLND for metastatic testis cancer of all histological subtypes with residual disease after neo-adjuvant primary chemotherapy	NM	Mean: 28.5 (±7.5)	NM	NM	Unilateral: 36 Bilateral: 23 NM: 19	Necrosis/fibrosis: 37 (47.4) Teratoma: 32 (41.1) Viable cancer: 9 (11.5)	100 (11-207) (n=66)	N/A
Nakamura (2016)†	1998 – 2013	Japan	14	Stage IIA/B NSGCT with residual disease after induction or salvage chemotherapy and normalization of tumor markers	NM	29.5 (18-42)	Good: 10 (71.4) Intermediate: 3 (21.5) Missing: 1 (7.1)	16.5 (6-32) mm	Bilateral template	Necrosis/fibrosis: 7 (50.0) Teratoma: 4 (28.6) Viable cancer: 3 (21.4)	70 (NM)	N/A

Supplementary Table 1. Characteristics of included studies *(continued)*

First author (year)	Treatment period	Country	Number of patients	Study inclusion criteria	PC-RPLND inclusion criteria	Median age (range)	IGCCCG prognosis, n (%)	Median size residual tumor, cm	Type of resection, n	Histology retroperitoneal specimen, n (%)	Median follow up in months (range)	Conversion to open, n (%)
Singh (2016)	2003 – 2012	India	35; 4 (11.4%) seminoma	GCT pts. with residual masses after chemotherapy, normalized tumor markers, no previous RPLND and complete follow-up	NM	Mean: 26.8 (16-50)	Good: 14 (40) Intermediate: 10 (28.5) Poor: 11 (31.4)	Mean: 5.4 (1.2-14.6)	Bilateral template	Necrosis/fibrosis: 17 (48.5) Teratoma: 12 (34.2) Viable cancer: 6 (17.1)	33 (9-60)	N/A
Vallier (2014)	2007 – 2013	Germany	59	NSGCT pts. who underwent PC-RPLND for residual masses	NM	Mean: 31.7 (NM)	Good: 28 (47.5) Intermediate: 18 (30.5) Poor: 13 (22)	37.5 (5-150) mm	Unilateral: 17 Bilateral: 42	Necrosis/fibrosis: 24 (40.7) Teratoma: 28 (47.5) Viable cancer: 6 (10.2) Malignant transformation teratoma: 1 (1.7)	54 (NM)	N/A
Ekenel (2012)§	1991 – 2010	Turkey	94; 24 (26.4%) seminoma	NM	NM	25.5 (17-51)	Good: 56 (63.6) Intermediate: 22 (25) Poor: 10 (11.4)	32.5 (10-130) mm	Residual mass resection	Necrosis/fibrosis: 25 (27.5) Teratoma: 47 (51.6) Viable cancer: 19 (20.9)	60.25 (2.7-334.8)	N/A
Busch (2012)‡	1999 – 2010	Germany	21; 6 (28.5%) seminoma	NM	NM	28.0 (22.0-34.0)	Good: 8 (38.1) Intermediate: 1 (4.8) Poor: 8 (38.1) Missing: 4 (19.0)	6.8 (2.5-7.6)	Unilateral: 5 Bilateral: 13 NM: 3	Necrosis/fibrosis: 10 (47.6) Teratoma: 5 (23.8) Viable cancer:5 (23.8) Missing: 1 (4.8)	54.5 (22.0-87.7)	N/A
Winter (2012)‡	1995 – 2011	Germany	339; 39 (12%) seminoma	GCT pts. who underwent open RPLND in 9 GTCSG centers with complete data survey and follow-up	NM	31 (14-67)	Good: 147 (43) Intermediate and poor: 192 (56)	Mean: 5.6 (±4.8)	Unilateral and bilateral template	NM	36 (0-192)	N/A
Luz (2010)	1994 – 2008	Canada	73	NSGCT with normal postchemotherapy tumor markers and no prior surgical attempts to resect retroperitoneal tumors	NM	Mean: 30.6 (16-58)	Good: 56 (76.7) Intermediate: 10 (13.7) Poor: 7 (9.6)	Mean: 4.0 (±2.6)	Modified: 2 Bilateral: 67 Extended: 4	Necrosis/fibrosis: 27 (37.0) Teratoma: 30 (41.1) Viable cancer: 16 (21.9)	47 (NM)	N/A

Supplementary Table 1. Characteristics of included studies *(continued)*

First author (year)	Treatment period	Country	Number of patients	Study inclusion criteria	PC-RPLND inclusion criteria	Median age (range)	IGCCCG prognosis, n (%)	Median size residual tumor, cm	Type of resection, n	Histology retroperitoneal specimen, n (%)	Median follow up in months (range)	Conversion to open, n (%)
Flechon (2010)	1992 – 2010	France	151	NSGCT pts. with initial retroperitoneal involvement treated with platinum-based chemotherapy and residual masses	NM	27.3 (15-67)	Good: 62 (41) Intermediate: 48 (32) Poor: 30 (20) Missing: 11 (7)	40 (8-240) mm	Unilateral: 44 Bilateral: 107	Necrosis/fibrosis: 62 (41) Teratoma: 73 (48) Viable cancer: 13 (9) Malignant transformation teratoma: 3 (2)	77 (1.3-186.5)	N/A
Carver (2010)	1989 – 2006	USA	432	Pts. who underwent PC-RPLND for NSGCT with residual fibrosis or teratoma and known retroperitoneal nodal size	NM	30 (24-36)	Good: 330 (76) Intermediate: 50 (12) Poor: 49 (11)	1.4 (0.6-3.0)	Modified and bilateral template Based on discretion of the surgeon	Necrosis/fibrosis: 248 (57) Teratoma: 184 (43)	3.2 yrs (NM)	N/A
Williams (2009)	1993 – 2006	USA	57; 15 (26%) stage I	Pts. with orchiectomy specimens >30% embryonal carcinoma with complete medical records	Pts. were offered PC-RPLND if residual disease was suspected	Mean: 28 (NM)	NM	NM	NM	NM	Mean: 4.2 yrs (NM)	N/A
Miki (2009)†	1994 – 2008	Japan	78; 19 (24%) seminoma	Pts. with advanced GCT with residual disease and normalized tumor markers who underwent nerve-sparing procedure	NM	32 (18-50)	Good: 46 (59) Intermediate: 23 (29) Poor: 9 (12)	22 (5-90) mm	Bilateral template	Necrosis/fibrosis: 43 (55) Teratoma: 26 (33) Viable cancer: 9 (12)	42 (1-138)	N/A

Supplementary Table 1. Characteristics of included studies *(continued)*

First author (year)	Treatment period	Country	Number of patients	Study inclusion criteria	PC-RPLND inclusion criteria	Median age (range)	IGCCCG prognosis, n (%)	Median size residual tumor, cm	Type of resection, n	Histology retroperitoneal specimen, n (%)	Median follow up in months (range)	Conversion to open, n (%)
Heidenreich (2009)‡	1999 – 2007	Germany	152	Patient who underwent PC-RPLND for residual masses after primary chemotherapy for metastatic NSGCT and normalized or plateauing tumor markers	NM	Total: Mean: 32.3 (16-67) Modified: Mean: 32.9 (18-55) Bilateral: Mean: 31.8 (16-67)	Total: Good: 83 (58.4) Intermediate: 38 (26.8) Poor: 31 (21.8) Modified: Good: 57 (58.1) Intermediate: 26 (26.5) Poor: 15 (15.3) Bilateral: Good: 26 (48.1) Intermediate: 12 (22.2) Poor: 16 (29.6)	Total: Mean: 6.1 (0.5-30.0) Modified: Mean: 4.5 (0.5-10.0) Bilateral: Mean: 10.9 (1.5-30.0)	Modified: 98 Bilateral: 54 Modified template if prechemotherapy location of the residual mass corresponded to the primary landing zone of the tumor bearing testicle and the residual mass ≤5 cm in diameter	Modified: Necrosis/fibrosis: 54 (55.1) Teratoma: 30 (30.6) Viable cancer: 14 (14.2) Bilateral: Necrosis/fibrosis: 30 (55.5) Teratoma: 15 (27.8) Viable cancer: 9 (16.7)	Mean: 39 (6-105)	N/A
Spiess (2007)	1980 – 2003	USA	198	Primary testicular cancer pts. with stage ≥ II, normalized tumor markers after chemotherapy and complete medical charts	NM	28 (15.1-55.1)	NM	3.5 (1.6-21)	Bilateral template	Necrosis/fibrosis: 86 (43.4) Teratoma: 79 (39.9) Viable cancer: 33 (16.7)	41 (6-250)	N/A
Ehrlich (2006)	1996 – 2005	Israel	50	NM	Pts. with advanced NSGCT with residual mass ≥1 cm and normal tumor markers after cisplatin-based chemotherapy	29 (18-52)	NM	NM	Bilateral template	Necrosis/fibrosis: 19 (38) Teratoma: 28 (56) Viable cancer: 3 (6)	53 (NM)	N/A

Supplementary Table 1. Characteristics of included studies *(continued)*

First author (year)	Treatment period	Country	Number of patients	Study inclusion criteria	PC-RPLND inclusion criteria	Median age (range)	IGCCCG prognosis, n (%)	Median size residual tumor, cm	Type of resection, n	Histology retroperitoneal specimen, n (%)	Median follow up in months (range)	Conversion to open, n (%)
Tanaka (2006)	1992 – 2005	Japan	31[!]; 1 (3.2%) seminoma	Pts. with testicular cancer who underwent RPLND	NM	Mean: 31.8 (16-52)	Good: 6 (35.3) Intermediate: 8 (47.1) Poor: 3 (17.6) (n=17)	NM	Modified: 25 Bilateral: 6 Modified dissection if area included the pre- and post chemotherapy extension; bilateral dissection in pts. with extensive disease	With prior chemotherapy (n=29): No viable cells: 15 (51.7) Teratoma: 11 (37.9) Viable cancer: 3 (10.4) Without prior chemotherapy (n=2): Seminoma: 1 (50.0) No metastasis: 1 (50.0)	34.0 (2-153)	N/A
Oldenburg (2003)	1990 – 2000	Norway	87	Metastatic NSGCT pts. with pre- and postchemotherapy residual mass ≤20 mm and RPLND performed within 3 months after induction chemotherapy	Routine RPLND independently of tumor marker	28 (15-56)	Good: 66 (76) Intermediate: 12 (14) Poor: 9 (10)	10 (0-20) mm	Unilateral: 50 Bilateral: 37 Unilateral RPLND in pts. with minimal residual tumors	Necrosis/fibrosis: 58 (67) Teratoma: 23 (26) Viable cancer: 6 (7)	80 (15-148)	N/A
Ozen (2001)§	1980 – 1998	Turkey	75; 14 (18.7%) seminoma	NM	Residual nodes >2 cm in NSGCT and >4 cm in seminomas with normalized tumor markers	28 (18-60)	NM	NM	Residual mass resection	Necrosis/fibrosis: 25 (33.3) Teratoma: 34 (45.3) Viable cancer: 16 (21.3)	Mean: 37.4 (3-127)	N/A

Supplementary Table 1. Characteristics of included studies *(continued)*

First author (year)	Treatment period	Country	Number of patients	Study inclusion criteria	PC-RPLND inclusion criteria	Median age (range)	IGCCCG prognosis, n (%)	Median size residual tumor, cm	Type of resection, n	Histology retroperitoneal specimen, n (%)	Median follow up in months (range)	Conversion to open, n (%)
Rabbani (1998)	1985 – 1995	Canada	50	Stage II and III NSGCT with residual disease after cisplatin-based chemotherapy	NM	28 (16-48)	NM	NM	Modified: 9 Bilateral: 39 Residual mass resection: 2	Bilateral template (39 pts. with 28 residual masses): No residual disease: 11 Necrosis/fibrosis: 13 (46) Teratoma: 10 (36) Viable cancer: 5 (18) Unilateral/residual mass (11 pts. with 16 residual masses): Necrosis/fibrosis: 6 (37.5) Teratoma: 8 (50) Viable cancer: 2 (12.5%	56 (1-140)	N/A
Studies reporting on minimally invasive surgery												
Li (2019)	2013 – 2018	USA	30	Pts. who underwent PC-RPLND for residual tumor, no prior RPLND	NM	30 (IQR 26-36)	Good: 25 (83.3) Intermediate: 4 (13.3) Poor: 1 (3.3)	NM	Bilateral: 13 (43.3) Unilateral modified: 17 (56.7)	Necrosis/fibrosis: 10 (33.3) Teratoma: 15 (50) Viable cancer: 11 (16.7)	15.1 (1-51)	3 (10.0)
Nicolai (2016)	2011 – 2015	Italy	67	NM	No prior RP surgery, unilateral disease, lesion 10-50 mm, normalized markers, <30% encasement of residual mass in inferior vena cava and/or aorta	Mean: 27.5 (17-45)	Good: 62 (92.5) Intermediate: 3 (4.5) Poor: 2 (3.0)	27 (15-31) mm	Unilateral template	Necrosis/fibrosis: 14 (20.9) Teratoma: 51 (76.1) Viable cancer: 2 (3.0)	21 (10-30)	3 (4.5)
Nakamura (2016)	2009 – 2013	Japan	14	Stage IIA/B NSGCT with residual disease after induction or salvage chemotherapy and normalization of tumor markers	NM	32.5 (19-56)	Good: 13 (92.9) Intermediate: 1 (7.1)	19 (5-25) mm	Unilateral: 12 Bilateral: 2	Necrosis/fibrosis: 7 (50.0) Teratoma: 7 (50.0)	36 (NM)	0

Supplementary Table 1. Characteristics of included studies *(continued)*

First author (year)	Treatment period	Country	Number of patients	Study inclusion criteria	PC-RPLND inclusion criteria	Median age (range)	IGCCCG prognosis, n (%)	Median size residual tumor, cm	Type of resection, n	Histology retroperitoneal specimen, n (%)	Median follow up in months (range)	Conversion to open, n (%)
Kamel (2016)	2011 – 2015	USA	12; 3 (25%) seminoma	Pts. who underwent robot assisted PC-RPLND	NSGCT: normal tumor markers and residual mass ≥1 cm and to consolidate chemotherapy. Seminoma: residual mass ≥3 cm	Mean: 37.8 (20-55)	NSGCT: Good: 6 (66.7) Intermediate: 2 (22.2) Poor: 1 (11.1) Seminoma: Good: 3 (100%)	NM	Residual mass resection: 3 Modified: 6 Bilateral: 3 Robotic: 12	Necrosis/fibrosis: 5 (45.5) Teratoma: 5 (45.5) Viable cancer: 1 (9.0)	31 (5-39) (n=10)	1 (8.3)
Gaya (2015)	2004 – 2008	Spain	15; 1 (6.7%) seminoma	NM	NM	31.5 (18-47)	NM	NM	Unilateral template	Necrosis/fibrosis: 6 (40.0) Teratoma: 8 (53.3) Seminoma: 1 (6.7)	Mean: 28.9 (1-79)	2 (13.3)
Sharma (2015)	2006 – 2011	USA	19	All pts. treated with minimally invasive PC-RPLND	No prior abdominal surgery, prechemo tumor <5 cm, residual tumor <5 cm, no organ/vascular invasion	32 (28-39)	Good: 17 (90) Intermediate: 1 (5) Poor: 1 (5)	2.1 (1.7-3)	Modified: 9 Bilateral: 10 Laparoscopic: 14 Robotic: 5	Necrosis/fibrosis: 11 (58) Teratoma: 8 (42) Viable cancer: 0	24 (5-76)	2 (10.5)
Steiner (2013)	1993 – 2010	Austria	100	All pts. who underwent L-RPLND for residual tumor	No bulky disease	Mean: 29.6 (11.4-52.0)	NM	Mean: 1.4 (0.3-10)	Unilateral: 71 Bilateral: 29	Necrosis/fibrosis: 60 (60) Teratoma: 38 (38) Viable cancer: 2 (2)	59 (1-222)	1 (1.0)
Aufderklamm (2013)	Unilateral: 2002 – 2009 Bilateral: 2009 – NM	Germany	39	GCT pts. without relapsing cancer or late recurrence	Stage ≥IIA with normalized tumor markers post chemotherapy and residual masses >1cm	Unilateral: Mean: 30.8 (±8.43) Bilateral: Mean: 31.5 (±11.01) Total: Mean: 31.2 (18-62)	NM	Unilateral: Mean: 2.28 (±0.72) Bilateral: Mean: 2.3 (±0.75)	Unilateral: 19 Bilateral: 20	Unilateral: No residual disease: 1 (5.3) Necrosis/fibrosis: 7 (36.8) Teratoma: 8 (42.1) Viable cancer: 3 (15.8) Bilateral: No residual disease: 1 (5) Necrosis/fibrosis: 11 (55) Teratoma: 7 (35) Viable cancer: 1 (5)	Unilateral: 24 (4-38) Bilateral: 13 (3-37)	0
Busch (2012)	1999 – 2010	Germany	46; 2 (4.3%) seminoma	NM	NM	32.0 (26.5-37.5)	Good: 29 (63) Intermediate: 9 (19.6) Poor: 6 (13.0) Missing: 2 (4.3)	2.2 (1.5-3.9)	Unilateral: 32 Bilateral: 12 Lumpectomy: 2	Necrosis/fibrosis: 28 (60.9) Teratoma: 12 (26.1) Viable cancer: 10 (21.7) Missing: 1 (2.2)	30.1 (12.1-47.1)	3 (6.5)
Arai (2012)	2002 – 2010	Japan	20	NM	Pre-chemotherapy mass <5 cm	27 (18-49)	NM	1.0 (0.5-4.2)	Unilateral template	Necrosis/fibrosis: 16 (80) Teratoma: 2 (10) Viable cancer: 2 (10)	45 (24-112)	0

Supplementary Table 1. Characteristics of included studies *(continued)*

First author (year)	Treatment period	Country	Number of patients	Study inclusion criteria	PC-RPLND inclusion criteria	Median age (range)	IGCCCG prognosis, n (%)	Median size residual tumor, cm	Type of resection, n	Histology retroperitoneal specimen, n (%)	Median follow up in months (range)	Conversion to open, n (%)
Calestroupat (2009)	2002 – 2006	France	26	Pts. with residual masses post chemotherapy and negative or plateauing markers	NM	Mean: 31 (26-34)	NM	3.4 (2-6)	Unilateral template	Necrosis/fibrosis: 14 (54) Teratoma: 9 (35) Viable cancer: 3 (12)	Mean: 27 (14-36)	3 (11.5)
Permpongkosol (2007)	1996 – 2005	USA	16; 2 (12.5%) seminoma	Pts. who underwent laparoscopic PC-RPLND	Residual mass or prechemotherapy mass >3.0 cm	Mean: 34±10.4 (16-5)	NM	Mean: 2.4 (1-5)	Modified: 14 Bilateral: 2	Necrosis/fibrosis: 6 (37.5) Teratoma: 5 (31.3) Viable cancer: 5 (31.3)	Mean: 30.7 (4-108)	2 (12.5)
Albqami (2005)	1995 – 2004	Austria	59; 1 (1.7%) seminoma	Stage II NSGCT who underwent laparoscopic PC-RPLND	NM	Mean: 29.2 (15-56)	NM	NM	Unilateral template	No residual disease: 36 (61.0) Teratoma: 21 (35.6) Viable cancer: 2 (3.4)	Mean: 53 (10-89)	0

GCT = germ cell tumor
NSGCT = nonseminomatous germ cell tumor
IGCCCG = International Germ Cell Cancer Collaborative Group
GTCSG = German Testicular Cancer Study Group
RP = retroperitoneal
PC-RPLND = postchemotherapy retroperitoneal lymph node dissection
NM = not mentioned
N/A = not applicable
*, †, ‡, § = overlap in patients
|| = two patients without prior chemotherapy

Supplementary Table 2. Quality assessment of included studies based on Newcastle-Ottawa scale

First author (year)	Selection	Comparability	Outcome	Total stars
Studies reporting on open surgery				
Schmidt (2018)	***	N/A	***	6
Ariffin (2017)	***	N/A	**	5
Cho (2017)	**	N/A	*	3
Considine (2016)	***	N/A	***	6
Singh (2016)	***	N/A	**	5
Vallier (2014)	***	N/A	**	5
Ekenel (2012)	***	N/A	**	5
Winter (2012)	***	N/A	***	6
Luz (2010)	**	N/A	**	4
Flechon (2010)	***	N/A	**	5
Carver (2010)	***	N/A	**	5
Wiliams (2009)	***	N/A	***	6
Miki (2009)	**	N/A	**	4
Heidenreich (2009)	***	N/A	**	5
Spiess (2007)	***	N/A	**	5
Ehrlich (2006)	***	N/A	**	5
Tanaka (2006)	**	N/A	**	4
Oldenburg (2003)	***	N/A	**	5
Ozen (2001)	***	N/A	***	6
Rabbani (1998)	***	N/A	**	5
Studies reporting on minimally invasive surgery				
Nicolai (2016)	***	N/A	*	4
Kamel (2016)	**	N/A	***	5
Gaya (2015)	**	N/A	**	4
Sharma (2015)	***	N/A	***	6
Steiner (2013)	***	N/A	**	5
Aufderklamm (2013)	***	N/A	*	4
Arai (2012)	**	N/A	**	4
Calestroupat (2009)	***	N/A	***	6
Permpongkosol (2007)	**	N/A	***	5
Albqami (2005)	***	N/A	**	5
Studies reporting on both open and minimally invasive surgery				
Li (2019)	***	N/A	*	4
Nakamura (2016)	***	N/A	*	4
Busch (2012)	**	N/A	**	4

N/A = not applicable

Supplementary File 1

PubMed search strategy:

Population (#1): (testicular cancer*[Title/Abstract]) OR testicular neoplasm*[Title/Abstract]) OR testicular tumor*[Title/Abstract]) OR testicular tumour*[Title/Abstract]) OR testis cancer*[Title/Abstract]) OR testis neoplasm*[Title/Abstract]) OR testis tumor*[Title/Abstract]) OR testis tumour*[Title/Abstract]) OR cancer of testis[Title/Abstract]) OR cancer of the testis[Title/Abstract]) OR cancer of the testes[Title/Abstract]) OR testicular germ cell tumor*[Title/Abstract]) OR testicular germ cell tumour*[Title/Abstract]) OR TGCT[Title/Abstract]) OR nonseminomatous germ cell tumor*[Title/Abstract]) OR nonseminomatous germ cell tumour*[Title/Abstract]) OR non seminomatous germ cell tumor*[Title/Abstract]) OR non seminomatous germ cell tumour*[Title/Abstract]) OR nonseminoma germ cell tumor*[Title/Abstract]) OR nonseminoma germ cell tumour*[Title/Abstract]) OR non seminoma germ cell tumor*[Title/Abstract]) OR non seminoma germ cell tumour*[Title/Abstract]) OR NSGCT[Title/Abstract])) OR ((("Testicular Neoplasms"[Mesh]) OR "Testicular Germ Cell Tumor" [Supplementary Concept]) OR "Nonseminomatous germ cell tumor" [Supplementary Concept])

Intervention/Comparison (#2): ("Lymph Node Excision"[Mesh]) OR lymph node dissection*[Title/Abstract]) OR RPLND[Title/Abstract]) OR lymphadenectomy[Title/Abstract]) OR retroperitoneal lymph node dissection[Title/Abstract]) OR PCRPLND[Title/Abstract]) OR LRPLND[Title/Abstract]) OR RRPLND[Title/Abstract]) OR ORPLND[Title/Abstract]) OR RARPLND[Title/Abstract]) OR residual tumor resection*[Title/Abstract]) OR residual tumour resection*[Title/Abstract]) OR residual mass resection*[Title/Abstract])

Outcome (#3): ("Recurrence"[Mesh]) OR "Neoplasm Recurrence, Local"[Mesh]) OR "Incidence"[Mesh]) OR "Intraoperative Complications"[Mesh]) OR "Postoperative Complications"[Mesh]) OR "Treatment Outcome"[Mesh]) OR relaps*[Title/Abstract]) OR relapse rate*[Title/Abstract]) OR rate of relapse[Title/Abstract]) OR recurrence*[Title/Abstract]) OR recurrence rate*[Title/Abstract]) OR rate of recurrence[Title/Abstract]) OR recurrent*[Title/Abstract]) OR recrudescen*[Title/Abstract]) OR recurrence free survival rate*[Title/Abstract]) OR local neoplasm recurrence*[Title/Abstract]) OR locoregional neoplasm recurrence*[Title/Abstract]) OR incidence*[Title/Abstract]) OR recurrence risk[Title/Abstract]) OR recurrent disease[Title/Abstract]) OR complication*[Title/Abstract]) OR adverse event*[Title/Abstract]) OR outcome*[Title/Abstract])

#1 AND #2 AND #3

5

Chapter

Retroperitoneal relapse of testicular cancer after postchemotherapy residual mass resection versus template-based retroperitoneal lymph node dissection

Submitted

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Abstract

Background

The anatomical extent of postchemotherapy retroperitoneal lymph node dissection (PC-RPLND) in patients with advanced germ cell tumor (GCT) has been a matter of debate for many years. Although template-based PC-RPLND is recommended by current guidelines, some centers perform residual mass resection (RMR). The results of this approach need to be presented.

Purpose

To compare the oncological outcome of RMR with a contemporaneous cohort of patients treated with template-based PC-RPLND (TBR).

Methods

Retrospective analysis of all patients who underwent open or minimally invasive RMR or PC-RPLND in three tertiary referral centers in the Netherlands between 2001 and 2018.

Results

A total of 301 patients were included (TBR: 85; RMR: 216). Of these, 245 patients (TBR: 76; RMR: 169) had complete resection, no grade 5 complication and >1 year follow-up. Thirteen patients (5.3%) relapsed in the retroperitoneum: ten patients (5.9%) in the RMR group and three (3.9%) in the TBR group (P=0.759). The five-year cumulative incidence of retroperitoneal relapse was 4.2% (95% CI 1.9-8.1) in the RMR group, versus 3.0% (95% CI 16 0.6-9.3) in the TBR group (P=0.286).

Conclusion

The rate of retroperitoneal relapse in our study is higher in patients treated with 18 RMR, compared to template-based PC-RPLND, although the difference is small

Introduction

In approximately 40% of patients with nonseminomatous germ cell tumor (NSGCT), residual tumor mass remains after treatment with first-line chemotherapy [1]. Surgical resection of the residual tumor mass is indicated if the mass is larger than 1 cm in diameter [2]. The rationale for this procedure is that persistent lymph nodes contain vital cancer in 6-10% and teratoma in up to 50% of patients [3,4].

The anatomical extent of this procedure has been debated for many years. Bilateral template-based retroperitoneal lymph node dissection (RPLND) used to be the standard approach in all patients. Nowadays, modified template RPLND is widely accepted in selected patients [4,5]. More recently, laparoscopic and robot-assisted approaches are gaining acceptance [6–8].

Although template-based resection is advocated by current guidelines, some centers regard the resection of the residual mass only as oncologically equivalent [9,10]. This non-template-based approach has been standard of care at the Netherlands Cancer Institute (NKI) and the Radboud University Medical Center (RUMC) for many years. In this study, we present the results of residual mass resection (RMR) and compare this with a series of patients treated with template-based RPLND at one of these two centers and at the University Medical Center Utrecht (UMCU).

Patients and methods

The standard policy at all centers is that patients with a residual mass >1 cm after chemotherapy and normalization of tumor markers are scheduled for retroperitoneal lymph node dissection. At the UMCU, patients undergo a template-based resection (TBR). Whether a unilateral or bilateral template is applied depends on the location and extent of the residual tumor and of the original extent of the tumor before chemotherapy. At the RUMC and NKI, complete removal of the residual mass and enlarged lymph nodes identified on postchemotherapy imaging or during surgery, is performed (RMR). However, the tumor location prior to chemotherapy is taken into account and lymph nodes that were enlarged prior to chemotherapy are also resected, but no template resection of clinically and radiologically unsuspicious lymph nodes is done. At the NKI, patients with a small residual tumor (<5cm) at a favorable location are predominantly treated with a minimally invasive procedure (i.e. robot-assisted). In all, 45 men who have been treated with a robot-assisted procedure between January 2007 and April 2019 were also included in a previous report from our group [8].

After internal review board approval, we performed a retrospective analysis of the medical records of all consecutive patients who underwent resection of residual tumor between 2001 and 2018. All patients were treated with chemotherapy for disseminated testicular germ cell tumor (TGCT) according to international guidelines: three to four cycles of bleomycin, etoposide and cisplatin (BEP) combination therapy, or four cycles of etoposide and cisplatin (EP). Patients with a history of

retroperitoneal tumor resection (re-do resection); history of retroperitoneal radiotherapy; salvage, desperation (i.e. elevated tumor markers) or palliative indication were excluded.

Post-operative 90-day complications were collected from the hospital complication registries. This information was supplemented with complications reported in the medical records but not entered in the complication registry. Complications were ranked according to the Clavien Dindo classification [11].

For categorical variables, differences between the two groups were analyzed using the Fisher's exact test. For continuous variables, the Mann Whitney-U test was used. Kaplan Meier curves were constructed to compare overall and retroperitoneal relapse between TBR and RMR. Analyses were performed using SPSS (version 25, IBM Corp.). Statistical significance was considered if $P<0.05$.

Results

A total of 334 patients underwent PC-RPLND during the study period. Thirty-three patients were excluded from our analysis because of: a history of previous RPLND (n=13), salvage/palliative RPLND (n=14), missing operative report (n=3), no tissue was resected (n=2) or history of radiotherapy (n=1). The remaining 301 patients were included in the analysis.

Patient characteristics

The patient and tumor characteristics are shown in Table 1. Eighty-five patients (28.2%) underwent TBR and 216 patients (71.8%) underwent RMR. Sixty-nine patients (22.9%) underwent a minimally-invasive procedure, all in the RMR group (Supplementary Tables 1 and 2).

The majority of patients had a residual tumor ≤5 cm (74.4%). Seven patients had a tumor <1 cm (2.3%; RMR: 6; TBR: 1). Median residual tumor size was significantly smaller in the RMR group (2.7 cm), compared to the TBR group (3.3 cm, $P=0.034$). IGCCCG risk category and Royal Marsden stage prior to chemotherapy did not differ between the two groups.

Intra- and post-operative outcome

The median operative time was shorter in the RMR group (145 mins), compared to the TBR group (271 mins; $P<0.001$). This was also the case if only open procedures were taken into account (TBR: 271 mins; open RMR: 155 mins; $P<0.001$). We found no significant difference in other intraoperative outcome measures between the two groups (Table 2).

The rate of postoperative complications Clavien-Dindo grade ≥2 was higher in the TBR group 88 (23.5%), compared to the RMR group (11.6%; $P=0.012$). RMR was also associated with fewer 89 complications if we only took the open procedures into account, although the difference was 90 not significant (TBR: 23.5%; RMR: 15.1%; $P=0.115$). Three patients (TBR: 1; RMR 2) died of 91 complications related to the surgery (grade 5 complication).

Table 1. Patient characteristics

	Overall	TBR	RMR	P-value
Number of patients	301	85	216	
Median age at surgery, (IQR)	29 (24-36)	28 (23-34)	30 (24-36)	0.133
Extragonadal primary, ***n*** (%)	18 (6.0)	8 (9.4)	10 (4.6)	0.173
Testicular tumor side, ***n*** (%)				0.225
Left	155 (54.8)	37 (48.1)	118 (57.3)	
Right	127 (44.9)	39 (50.6)	88 (42.7)	
Missing	1 (0.4)	1 (1.3)	0	
Primary histology, ***n*** (%)				0.172
NSGCT	276 (91.7)	75 (88.2)	201 (93.1)	
Seminoma	25 (8.3)	10 (11.8)	15 (6.9)	
Initial Royal Marsden Stage				0.907
Stage 2a	50 (16.6)	11 (12.9)	39 (18.1)	
Stage 2b	73 (24.3)	22 (25.9)	51 (23.6)	
Stage 2c	72 (23.9)	25 (29.4)	47 (21.8)	
Stage 3	29 (9.6)	5 (5.9)	23 (10.8)	
Stage 4	71 (23.6)	20 (23.5)	52 (24.5)	
Missing	6 (2.0)	2 (2.4)	4 (1.9)	
IGCCCG prognostic group, ***n*** (%)				0.941
Good	175 (58.1)	48 (56.5)	127 (58.8)	
Intermediate	77 (25.6)	26 (30.6)	51 (23.6)	
Poor	41 (13.6)	10 (11.8)	31 (14.4)	
Missing	8 (2.7)	1 (1.2)	7 (3.2)	
Salvage chemotherapy, ***n*** (%)	24 (8.0)	12 (14.1)	12 (5.6)	0.018
Median residual tumor size at surgery, ***cm*** (IQR)	2.9 (1.7-5.1)	3.3 (1.9-6.3)	2.7 (1.6-5.0)	0.034
Residual tumor size at surgery, ***n*** (%)				0.069
<2 cm	94 (31.2)	22 (25.9)	72 (33.3)	
2-5 cm	130 (43.2)	37 (43.5)	93 (43.1)	
5.1-10 cm	56 (18.6)	17 (20.0)	39 (18.1)	
>10 cm	20 (6.6)	9 (10.6)	11 (5.1)	
Missing	1 (0.3)	0	1 (0.5)	

IQR = interquartile range; NSGCT = nonseminomatous germ cell tumor; TBR = template-based retroperitoneal lymph node dissection; RMR = residual mass resection

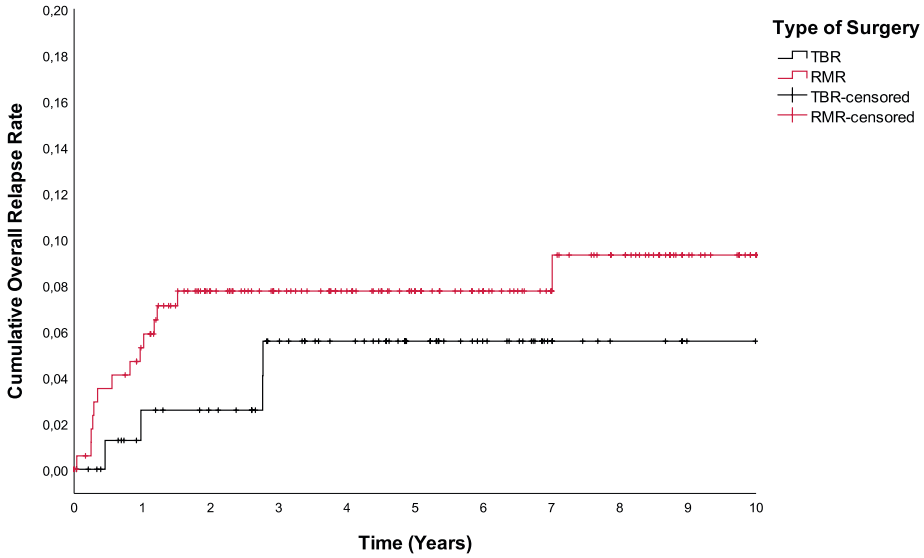
Table 2. Operative and follow-up outcome

	Overall	TBR	RMR	P-value
Minimally invasive procedure, *n* (%)	69 (22.9)	0	69 (31.9)	
Median operative time, mins (IQR)	168 (115-250)	271 (201-348)	145 (105-212)	<0.001
Median blood loss, cc (IQR)	358 (100-924)	275 (100-775)	400 (100-1,000)	0.684
Intraoperative complications, *n* (%)	84 (27.9)	24 (28.2)	60 (27.8)	1.00
Aorta injury	19 (6.3)	5 (5.9)	14 (6.5)	
IVC injury	23 (7.6)	9 (10.6)	14 (6.5)	
Iliac artery injury	7 (2.3)	2 (2.4)	5 (2.3)	
Iliac vein injury	2 (0.7)	2 (2.4)	0	
Renal artery injury	5 (1.7)	1 (1.2)	4 (1.9)	
Renal vein injury	13 (4.3)	6 (7.1)	7 (3.2)	
Splenal injury	4 (1.3)	0	4 (1.9)	
Tumor rupture	11 (3.7)	1 (1.2)	10 (4.6)	
Kidney/ureter injury	5 (1.7)	1 (1.2)	4 (1.9)	
Median hospital stay, days (IQR)	5 (3-7)	7 (5-9)	4 (3-5)	<0.001
30-day postoperative complications Clavien-Dindo Grade ≥2, *n* (%)	45 (15.0)	20 (23.5)	25 (11.6)	0.012
Grade 2	29 (9.6)	14 (16.5)	15 (6.9)	
Grade 3a	9 (3.0)	2 (2.4)	7 (3.2)	
Grade 3b	6 (2.0)	2 (2.4)	4 (1.9)	
Grade 4a	4 (1.3)	3 (3.5)	1 (0.5)	
Grade 4b	0	0	0	
Grade 5	3 (1.0)	1 (1.2)	2 (0.9)	
Missing	1 (0.3)	0	1 (0.5)	
Histology, *n* (%)				0.423
Necrosis/fibrosis	109 (36.2)	30 (35.3)	79 (36.6)	
Teratoma	164 (54.5)	44 (51.8)	120 (55.6)	
Viable cancer	28 (9.3)	11 (12.9)	17 (7.9)	
Relapse*, *n* (%)	20 (8.2)	5 (6.6)	15 (8.9)	0.623
Retroperitoneal relapse*, *n* (%)	13 (5.3)	3 (3.9)	10 (5.9)	0.759
Death of disease*, *n* (%)	6 (2.4)	2 (2.6)	4 (3.7)	0.650

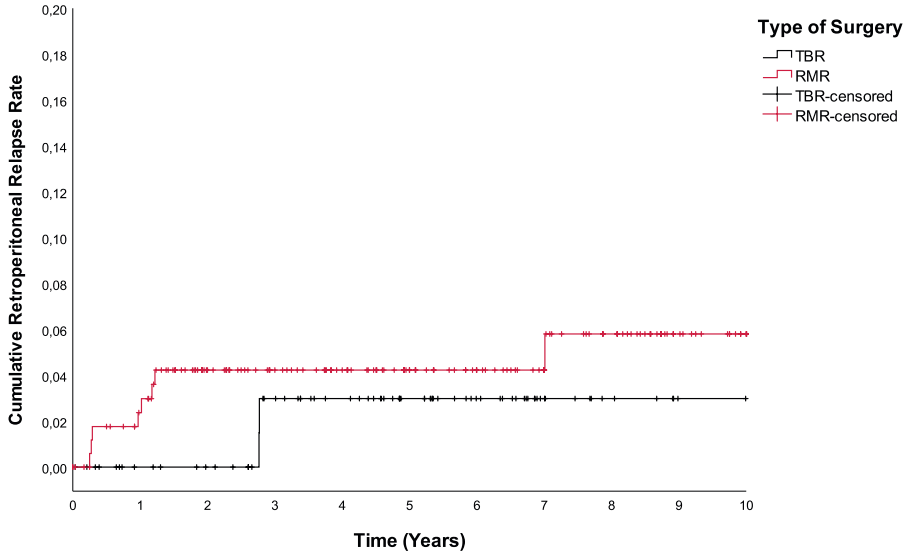
IVC = inferior vena cava; IQR = interquartile range; TBR = template-based retroperitoneal lymph node dissection; RMR = residual mass resection

* Based on 245 patients (template: 76; RMR: 169) with complete resection, no grade 5 complication and >1 year follow-up or relapse <1 year.

Figure 1. Kaplan-Meier curves for overall and retroperitoneal relapse



A. Estimated cumulative overall relapse rate for the entire cohort (P=0.286)



B. Estimated cumulative retroperitoneal relapse rate for the entire cohort (P=0.350)
TBR = template-based resection; RMR = residual mass resection

Follow-up

The retroperitoneal specimen contained viable cancer in 28 patients (9.3%; Table 2). This was 95 GCT in 19 patients and malignant transformation of teratoma in nine patients (3.0%).

During surgery, the surgeon regarded the resection as incomplete in 19 patients (8.8%) because the tumor was too extensive or because of an intraoperative complication. These were all patients undergoing open RMR. Five patients with incomplete resection were treated with redo resection. Of these, one patient received additional chemotherapy and another patient received additional radiotherapy. Two patients with progression of disease after incomplete resection died of disease. The patients with an intraoperatively determined incomplete resection were excluded from the relapse analyses.

In addition to the patients with an intraoperatively determined incomplete resection, there was one laparoscopic RMR patient in whom the first postoperative CT-scan showed that the residual tumor of interest was not resected. This patient underwent redo resection.

In total, 245 patients (TBR: 76; RMR: 169) had complete resection, no grade 5 complication, and >1 year follow-up. Twenty of these patients suffered from relapse (8.2%; Supplementary Table 3), which was a retroperitoneal relapse in 13 patients (5.3%). All patients with a retroperitoneal relapse had a relapse in the surgical field of the initial dissection.

Nine patients with a retroperitoneal relapse underwent a redo resection. In all, 15 patients underwent redo resection, either for incomplete resection or relapse (TBR: 1 [1.4%] RMR: 14 [6.5%]).

The five-year cumulative incidence of retroperitoneal relapse was 4.2% (95% CI 1.9-8.1) in the RMR group, versus 3.0% (95% CI 0.6-9.3) in the TBR group (P=0.286; Figure 1). In addition to the three patients with a grade 5 complication, six patients died of disease (3.1%; TBR: 2.4%; RMR: 3.6%). Four out of 13 patients with retroperitoneal relapse died of disease (30.8%). All four patients had also metastases beyond the retroperitoneum. Out of the remaining 232 patients without retroperitoneal relapse, two died of disease (0.9%).

Discussion

In the present study, we reviewed our experience with RMR and compared this with a contemporaneous cohort of patients treated with TBR. We found higher overall and retroperitoneal relapse rates in patients treated with RMR, although the differences were small.

Reducing treatment-associated morbidity is important in patients with postchemotherapy residual disease, since they are relatively young and long-term survival is expected in most cases [12]. The retroperitoneal specimen contains only necrosis in approximately half of NSGCT patients, which means that surgical resection is without oncological benefit in these cases [4,13]. Since relatively more patients are presenting with low-stage disease and chemotherapy

is applied more often in patients with low-volume retroperitoneal metastases [14,15], benign histology is encountered more often, as this is especially common in patients with small residual tumors [13].

These factors have led to the adoption of less morbid surgical approaches. Nowadays, there is general consensus that the resection template can be limited in patients with a small unilateral residual tumor [2,4]. However, Carver et al. showed that the total number of lymph nodes resected and analyzed is a predictor of disease recurrence after PC-RPLND [16]. The authors examined a cohort of 432 patients with either fibrosis or teratoma in the retroperitoneal specimen; patients with viable GCT were excluded since they were treated with adjuvant chemotherapy. The study showed that patients with 10 nodes resected had a predicted 2-year relapse free probability of 90%, which increased up to 97% when 50 nodes were resected [16]. Another study by Carver et al. examined the incidence of extra-template retroperitoneal disease in five different modified templates [17]. Depending on the template used, 7-32% of patients had teratoma or viable GCT outside the boundaries of a modified template. It should be noted that the latter study also included patients with a residual tumor >5 cm or elevated tumor markers at time of surgery, who would not have qualified for a modified template resection. Nevertheless, 36 out of 154 patients with a residual tumor <5cm (24%) had retroperitoneal disease outside the Testicular Tumor Study Group modified template [17,18]. Both studies show that a more extensive resection leads to fewer retroperitoneal relapses.

A recent systematic review of 23 studies on 2,379 patients found an average retroperitoneal relapse rate after open PC-RPLND of 4.6% [19]. This was higher in patients undergoing a bilateral dissection (6.1%), compared to a unilateral dissection (3.1%), which may be because patients undergoing a unilateral dissection generally have a smaller residual tumor. The retroperitoneal relapse rate in our template group is in line with these findings, but the relapse rate in our RMR group is slightly higher than what has been reported in the literature.

There are only few studies describing the results of RMR. In a retrospective series of 75 patients undergoing RMR, two patients (2.7%) relapsed in the retroperitoneum [20]. A subsequent report from the same institution, which had some overlap in patients, found that 5/94 patients (5.3%) relapsed in the retroperitoneum [21]. In the largest series on RMR so far, Schmidt et al. described the results of 109 patients treated with RMR [9]. The tumor was partly unresectable in 12 patients (11%), most of whom underwent debulking/desperation surgery. Of the 97 patients without evidence of disease after surgery, seven patients (7%) relapsed in the retroperitoneum, which is comparable with the relapse rate in our RMR group. In the study by Schmidt et al., none of the patients died of relapsing GCT, but one patient died of an out-field late relapse with somatic transformation [9].

The relatively low annual number of cases per hospital in our study implies that centralization of RPLND care still has a long way to go. This is in line with studies from the USA and Germany [22–24]. Studies on logistical, health care system related and other barriers to centralization of TGCT care in various countries are desperately needed.

Our findings have to be seen in light of some limitations. First, this was a retrospective observational study. This may have introduced selection bias, although we included all eligible patients. The retrospective nature made it sometimes challenging to classify procedures as either RMR or TBR. Especially RMR of bulky disease can equal a full bilateral template resection. Second, the number of resected lymph nodes was not systematically recorded. This is an important parameter since it reflects the actual extent of the dissection and would have enabled us to compare the extent of our dissection with those in other studies.

An important strength of our study is its multicenter design. Most studies on RPLND are single-center or single-surgeon series, which are prone to referral bias and not widely applicable. In addition, the three centers in our study are among the largest centers for RPLND in the Netherlands. Another strength is the relatively large number of patients included in our study. Approximately 5,500 patients were diagnosed with NSGCT in the Netherlands between 2001 and 2018, of which an estimated 450 eventually needed PC-RPLND. Thus, this series constitutes approximately two-thirds of all procedures during the study period.

We also included patients who were treated with a minimally invasive resection. Since retroperitoneal relapse is the primary endpoint, it should not matter whether patients were treated with an open or minimally invasive procedure, provided the approach and extent of the resection is the same. Excluding all minimally invasive procedures would have introduced bias, since these are only patients with a relatively small residual tumor.

Our study identified two important benefits of RMR. RMR was associated with a shorter operative time and lower rate of postoperative complications, compared to template surgery. Although it should be noted that the procedures were performed by different surgeons in different centers, it is in line with expectations that a more limited dissection leads to shorter operative time and fewer complications.

However, these benefits should be seen in light of a slightly higher risk of retroperitoneal relapse. Although based on a small number of cases, 30% of patients with retroperitoneal relapse died of disease.

All cases with an intraoperatively determined incomplete resection were in the RMR group. These patients were excluded from the follow-up analyses. Including these patients (intention to-treat analysis) would lead to worse outcomes for the RMR group. The retroperitoneal relapse/progression rate would be 8.1% (15/186), versus 3.9% after TBR. The percentage of patients who died of disease would be 3.2% (6/186), versus 2.4% after TBR.

To the best of our knowledge, this is the first study that has compared both approaches in two contemporaneous cohorts. We found that the risk of retroperitoneal relapse is higher in RMR, compared to TBR. However, the differences were small.

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Supplementary Table 1. Patient characteristics for open and minimally-invasive surgery separately

	Overall	TBR	O-RMR	MI-RMR
Number of patients	301	85	147	69
Median age at surgery, (IQR)	29 (24-36)	28 (23-34)	31 (24-38)	29 (23-34)
Extragonadal primary, *n* (%)	18 (6.0)	8 (9.4)	10 (6.8)	0
Testicular tumor side, *n* (%)				
Left	155 (54.8)	37 (48.1)	71 (51.8)	47 (68.1)
Right	127 (44.9)	39 (50.6)	66 (48.2)	22 (31.9)
Missing	1 (0.4)	1 (1.3)	0	0
Primary histology, *n* (%)				
NSGCT	276 (91.7)	75 (88.2)	133 (90.5)	68 (98.6)
Seminoma	25 (8.3)	10 (11.8)	14 (9.5)	1 (1.4)
Initial Royal Marsden Stage				
Stage 2a	50 (16.6)	11 (12.9)	17 (11.6)	22 (31.9)
Stage 2b	73 (24.3)	22 (25.9)	33 (22.4)	18 (26.1)
Stage 2c	72 (23.9)	25 (29.4)	43 (29.3)	4 (5.8)
Stage 3	29 (9.6)	5 (5.9)	11 (7.5)	12 (17.4)
Stage 4	71 (23.6)	20 (23.5)	39 (26.5)	13 (18.8)
Missing	6 (2.0)	2 (2.4)	4 (2.7)	0
IGCCCG risk category, *n* (%)				
Good	175 (58.1)	48 (56.5)	72 (49.0)	55 (79.7)
Intermediate	77 (25.6)	26 (30.6)	41 (27.9)	10 (14.5)
Poor	41 (13.6)	10 (11.8)	28 (19.0)	3 (4.3)
Missing	8 (2.7)	1 (1.2)	6 (4.1)	1 (1.4)
Salvage chemotherapy, *n* (%)	24 (8.0)	12 (14.1)	9 (6.1)	3 (4.3)
Median residual tumor size at surgery, *cm* (IQR)	2.9 (1.7-5.1)	3.3 (1.9-6.3)	3.6 (1.9-6.1)	2.0 (1.5-2.8)
Residual tumor size at surgery, *n* (%)				
<2 cm	94 (31.2)	22 (25.9)	39 (26.5)	33 (47.8)
2-5 cm	130 (43.2)	37 (43.5)	57 (38.8)	36 (52.2)
5.1-10 cm	56 (18.6)	17 (20.0)	39 (26.5)	0
>10 cm	20 (6.6)	9 (10.6)	11 (7.5)	0
Missing	1 (0.3)	0	1 (0.7)	0

TBR = template-based retroperitoneal lymph node dissection; O-RMR = open residual mass resection; MI-RMR = minimally invasive residual mass resection

Supplementary Table 2. Operative results for open and minimally-invasive surgery separately

	Overall	TBR	O-RMR	MI-RMR
Median operative time, mins (IQR)	168 (115-250)	271 (201-348)	155 (112-243)	134 (98-185)
Median blood loss, cc (IQR)	358 (100-924)	275 (100-775)	500 (144-1,025)	75 (21-388)
Intraoperative complications, ***n*** (%)	84 (27.9)	24 (28.2)	49 (33.3)	11 (15.9)
Aorta injury	19 (6.3)	5 (5.9)	13 (8.8)	1 (1.4)
IVC injury	23 (7.6)	9 (10.6)	13 (8.8)	1 (1.4)
Iliac artery injury	7 (2.3)	2 (2.4)	5 (3.4)	0
Iliac vein injury	2 (0.7)	2 (2.4)	0	0
Renal artery injury	5 (1.7)	1 (1.2)	4 (2.7)	0
Renal vein injury	13 (4.3)	6 (7.1)	7 (4.8)	0
Splenic injury	4 (1.3)	0	3 (2.0)	1 (1.4)
Tumor rupture	11 (3.7)	1 (1.2)	5 (3.4)	5 (7.2)
Kidney/ureter injury	5 (1.7)	1 (1.2)	4 (2.7)	0
Median hospital stay, days (IQR)	5 (3-7)	7 (5-9)	5 (4-6)	2 (1-3)
30-day postoperative complications Clavien-Dindo Grade ≥2, ***n*** (%)	45 (15.0)	20 (23.5)	22 (15.1)	3 (4.3)
Grade 2	29 (9.6)	14 (16.5)	14 (9.5)	1 (1.4)
Grade 3a	9 (3.0)	2 (2.4)	6 (4.1)	1 (1.4)
Grade 3b	6 (2.0)	2 (2.4)	3 (2.0)	1 (1.4)
Grade 4a	4 (1.3)	3 (3.5)	1 (0.7)	0
Grade 4b	0	0	0	0
Grade 5	3 (1.0)	1 (1.2)	2 (1.4)	0
Missing	1 (0.3)	0	1 (0.7)	0
Histology, ***n*** (%)				
Necrosis/fibrosis	109 (36.2)	30 (35.3)	56 (38.1)	23 (33.3)
Teratoma	164 (54.5)	44 (51.8)	77 (52.4)	43 (62.3)
Viable cancer	28 (9.3)	11 (12.9)	14 (9.5)	3 (4.3)
Relapse*, ***n*** (%)	20 (8.2)	5 (6.6)	11 (10.4)	4 (6.3)
Retroperitoneal relapse*, ***n*** (%)	13 (5.3)	3 (3.9)	7 (6.6)	3 (4.8)
Death of disease*, ***n*** (%)	6 (2.4)	2 (2.6)	3 (2.8)	1 (1.6)

TBR = template-based retroperitoneal lymph node dissection; O-RMR = open residual mass resection; MI-RMR = minimally invasive residual mass resection

Supplementary Table 3. Characteristics of patients with relapse/progression of disease

No.	Primary histology	Initial Royal Marsden stage	IGCCCG risk classification	Residual tumor size in RP, *cm*	Location residual tumor	Type of surgery	Histopathology RP	Additional treatment	Time between surgery and relapse	Location of relapse	Treatment of RP relapse	Status	Follow-up duration, *years*
Patients treated with template-based resection													
1	NSGCT	2b	Good	1.8	RP	Open	Mature teratoma	1x VIP*	170 months	RP, brain, lung, liver, spleen	Salvage CT	DOD	N/A
2	NSGCT	2c	Intermediate	10.4	RP	Open	Mature teratoma	None	33 months	RP, liver	Salvage CT and RT	DOD	N/A
3	Seminoma	2c	Good	2.4	RP	Open	Viable cancer	None	13 months	Lung and liver	Salvage CT and RT	NED	7
4	NSGCT	4	Good	1.4	RP, lung	Open	Viable cancer	None	5 months	Lung	Salvage CT and resection	NED	8
5	NSGCT	3	Good	1.7	RP, mediastinal	Open	Teratoma	Thoracic resection	33 months	RP	Redo RPLND	NED	6.8

Supplementary Table 3. Characteristics of patients with relapse/progression of disease *(continued)*

No.	Primary histology	Initial Royal Marsden stage	IGCCCG risk classification	Residual tumor size in RP, *cm*	Location residual tumor	Type of surgery	Histopathology RP	Additional treatment	Time between surgery and relapse	Location of relapse	Treatment of RP relapse	Status	Follow-up duration, *years*
Patients treated with residual mass resection													
6	NSGCT	2c	Poor	5.7	RP	Open	Mature teratoma	None	18 months	Marker-only at first, later pelvic nodes	Salvage CT and pelvic resection	NED	8
7	NSGCT	4	Poor	13.0	RP, liver	Open	Mature teratoma	None	3 months	Marker-only	Salvage CT	NED	4
8	NSGCT	3	Intermediate	8.0	RP, mediastinum, supraclavicular	Open	Mature teratoma	Selective neck dissection	14 months	RP	Redo RPLND	NED	11
9	NSGCT	2a	Intermediate	14.5	RP	Open	Adenocarcinoma ex teratoma	4x capecitabine	6 months	Peritoneum	Palliative CT	DOD	N/A
10	NSGCT	4	Good	10.0	RP, lung, mediastinum	Open	Mature teratoma	Multiple resections of lung and mediastinal mets	1 year: lung and mediastinum 11 years: supraclavicular 12: years: RP	Lung, supraclavicular, RP	RPLND	DOD	N/A

Supplementary Table 3. Characteristics of patients with relapse/progression of disease *(continued)*

No.	Primary histology	Initial Royal Marsden stage	IGCCCG risk classification	Residual tumor size in RP, *cm*	Location residual tumor	Type of surgery	Histopathology RP	Additional treatment	Time between surgery and relapse	Location of relapse	Treatment of RP relapse	Status	Follow-up duration, *years*
11	NSGCT	2c	Intermediate	14.6	RP, retrocrural	Open	Malignant transformation ex teratoma	None	3 months	Lung, mediastinum, liver, RP	Palliative CT	DOD	N/A
12	NSGCT	3	Unknown	5.0	RP, mediastinum, supraclavicular	Open	Teratoma	Resection supraclavicular node	14 months: RP 19 months: mediastinum and RP	RP	2x redo RPLND and resection mediastinal node	NED	3.3
13	NSGCT	2a	Good	1.4	RP	Open	Teratoma	None	84 months	RP	Redo RPLND	NED	8.7
14	Seminoma	3	Good	5.8	RP	Open	Viable cancer	None	4 months	Retrocrural	Salvage CT	NED	7.0
15	NSGCT	2a	Good	3.1	RP	Open	Teratoma	None	11.7 months	RP	Redo RPLND	NED	9.8
16	Seminoma	2c	Good	2.4	RP	Open	Viable cancer	None	3.5 months	RP	Salvage CT	NED	1.8
17	NSGCT	4	Intermediate	2.5	RP, mediastinum	Minimally invasive	Teratoma	None	2 weeks	Brain	Resection, salvage CT	DOD	N/A

Supplementary Table 3. Characteristics of patients with relapse/progression of disease *(continued)*

No.	Primary histology	Initial Royal Marsden stage	IGCCCG risk classification	Residual tumor size in RP, *cm*	Location residual tumor	Type of surgery	Histopathology RP	Additional treatment	Time between surgery and relapse	Location of relapse	Treatment of RP relapse	Status	Follow-up duration, *years*
18	NSGCT	2a	Good	1.5	RP	Minimally invasive	Teratoma	None	14 years	RP	Redo RPLND	NED	15.6
19	NSGCT	2a	Good	1.6	RP	Minimally invasive	Teratoma	None	12.2 months	RP	Redo RPLND	NED	11.1
20	NSGCT	2b	Good	1.0	RP	Minimally invasive	Necrosis/ fibrosis	None	3 months	RP	Redo RPLND, salvage CT	NED	6.9

RP = retroperitoneum; RMR = residual mass resection; IGCCCG = International Germ Cell Cancer Collaborative Group; NSGCT = nonseminomatous germ cell tumor; RPLND = retroperitoneal lymph node dissection; CT = chemotherapy; RT = radiotherapy; DOD = death of disease

* This patient received additional chemotherapy because histopathology showed vital cancer at first but mature teratoma without vital cancer on revision.

6

Chapter

Additional surgical procedures and perioperative morbidity in postchemotherapy retroperitoneal lymph node dissection for metastatic testicular cancer in two intermediate volume hospitals

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Abstract

Purpose

To evaluate the perioperative morbidity of PC-RPLND in two intermediate volume centers and to identify predictors of high morbidity.

Methods

Retrospective analysis of 124 patients treated with open PC-RPLND at two tertiary referral centers between 2001 and 2018. Perioperative morbidity was determined by analyzing additional surgical procedures, intra-operative blood loss, and postoperative complications.

Results

An additional procedure was necessary in 33 patients (26.6%). The risk was higher in patients with IGCCCG intermediate/poor prognosis (OR 3.56; 95% CI 1.33-9.52) and residual tumor size >5 cm (OR 3.53; 95% CI 1.39-8.93). Blood loss was higher in patients with IGCCCG intermediate/poor prognosis (β=0.177; P=0.029), large residual tumor (β=0.570; p<0.001), an additional intervention (β=0.342; p<0.001) and teratoma on retroperitoneal histology (β=-0.19; P=0.014). Thirty-one patients had a postoperative complication Clavien-Dindo Grade ≥2 (25.0%). Complication risk was highest in patients undergoing an additional intervention (OR 3.46; 95% CI 1.03-11.60; P=0.044).

Conclusions

The rate of additional interventions in our series is comparable to what has been reported in high-volume centers. IGCCCG intermediate/poor prognosis patients with high-volume disease and patients undergoing an additional surgical procedure can be classified as high-risk patients.

Introduction

Post-chemotherapy retroperitoneal lymph node dissection (PC-RPLND) is an important component of the treatment of disseminated germ cell tumor (GCT) [1–4]. It is a technically challenging procedure and is associated with significant treatment-related morbidity [5, 6]. In up to 30% of procedures, an additional surgical intervention is necessary during the procedure (e.g. nephrectomy or vascular reconstruction) [5, 7–9]. However, the identification of patients that are at increased risk of an additional procedure is primarily based on preoperative imaging.

Previous publications about the outcome of RPLND are mainly from high volume centers and these reports make the case for further centralization [10–12]. It is debatable whether these large series reflect the outcome of the procedure in general. After all, most patients are not treated in one of the leading centers of the world. For example, the median annual number of RPLNDs per urologist in the USA is only one [13]. Between 2003 and 2013, 75% of urologists performed one RPLND, while three urologists logged 23% of all procedures. These findings are confirmed by Yu et al., who showed that 51.6% of RPLNDs in the USA were performed at hospitals with ≤2 procedures annually [14]. In their analysis of German hospital billing data covering 2006-2015, Groeben et al. found that 44% of RPLNDs were performed in a low volume center (<4 cases annually) [15]. Although there was a modest trend towards centralization, still only 18% of all RPLNDs in 2015 were performed in a high volume institution (>10 cases annually). Thus, although most publications about PC-RPLND concern the outcomes in high volume centers, the overall majority of patients are treated in a low volume center.

In smaller countries, such as The Netherlands, the low incidence of testicular cancer prevents the establishment of very high volume centers. Since 2017, the quality standards of the Dutch urological society state that a center offering RPLND should perform at least 10 procedures annually [16].

Although it has been shown that the overall complication risk of RPLND is significantly lower in hospitals with a higher volume [14], reports from low and intermediate volume centers are still scarce. These reports are important to give a true view on the morbidity of PC-RPLND.

In the present study, we evaluate the perioperative morbidity of PC-RPLND in two intermediate volume centers. Our primary aim is to analyze whether the perioperative morbidity is comparable to what has been reported in the literature. Our secondary aim is to investigate whether there are any risk factors that can be used to better identify patients with a high risk of perioperative morbidity.

Materials and Methods

We performed a retrospective analysis of the medical records of all patients who were treated with open PC-RPLND in two tertiary referral centers between 2001 and 2018. In both centers, surgery was indicated in case of retroperitoneal residual tumor >1 cm after at least three cycles of cisplatin-based combination chemotherapy (bleomycin, etosposide, cisplatin). All patients who were treated with open PC-RPLND for gonadal or extragonadal GCT between 2001 and 2018 were included in our analysis. Exclusion criteria were incomplete data, prior retroperitoneal radiotherapy, prior RPLND (re-do RPLND), elevated tumor markers at time of surgery (desperation RPLND) and a minimally-invasive procedure. Patients who were previously treated with salvage chemotherapy but had normal tumor markers at the time of surgery were also eligible for inclusion. Institutional review board approval was obtained from both centers.

During the period covered by our analysis, patients with a small tumor (<5 cm) that was not adjacent to the large vessels were mainly treated with a minimally-invasive procedure at the Netherlands Cancer Institute (NCI). These patients were excluded from the present analysis.

All patients at the University Medical Center Utrecht (UMCU) underwent a template-based RPLND. In case of a residual tumor <5 cm in the primary landing zone, a modified template was applied. In right-sided modified template dissection, the right ureter and the aorta were the lateral and medial boundaries, respectively. The renal vein was the cranial boundary and the crossing of the ureter over the common iliac vessels was the caudal boundary. In left-sided dissection, the lateral, cranial and caudal boundaries were represented by the ureter, the renal vein, and the crossing of the ureter over the common iliac vessels, respectively.

At the NCI, complete removal of the residual mass and all enlarged lymph nodes identified on imaging and during surgery were resected, but no template resection of clinically and radiologically unsuspicious lymph nodes was done. The tumor localization prior to chemotherapy is taken into account.

An additional procedure was defined as any surgical intervention that was performed in the same surgical session as the PC-RPLND.

Complications that occurred during the 30-day postoperative period were categorized according to the Clavien-Dindo classification of surgical complications [17]. In case of multiple complications in one patient, all complications were registered but only the highest grade was used for the statistical analysis of risk factors.

The available abdominal computed tomography (CT) scans prior to chemotherapy and prior to surgery were re-analyzed by one of two independent radiologists (J.V. and J.U.). They measured the tumor mass in three dimensions (axial, coronal, and sagittal) and examined whether the additional interventions could be predicted on the basis of these scans.

Variables significant at the P<0.10 level in univariate logistic regression analysis were considered for inclusion in the multivariate logistic regression analysis. Multiple regression analysis was performed to analyze the association between intra-operative blood loss as a continuous variable and relevant predictor variables. We corrected for type of surgery (template-based RPLND vs. residual mass resection [RMR]) and primary histology. All tests were two-tailed and ***p***-value <0.05 was considered significant. SPSS version 22 (IBM Corp., USA) was used for statistical analysis.

Results

A total of 148 open PC-RPLNDs were identified between 2001 and 2018. Twenty-four patients were excluded because of a history of prior RPLND (n=11), elevated tumor markers (n=10), missing operative report (n=2), or history of retroperitoneal radiotherapy (n=1). The remaining 124 patients (seminoma n=17; nonseminomatous germ cell tumor [NSGCT] n=107) were included in the present analysis (Table 1).

Eleven surgeons performed at least one of the procedures. Five surgeons had a volume of more than ten procedures and performed a combined total of 106 procedures. The remaining 16 procedures were divided among six surgeons.

Seventy-two patients were treated with template-based surgery and 52 patients with residual mass resection. Fifteen patients (12.1%) had received salvage chemotherapy prior to surgery. The median residual tumor size was larger in the RMR group (6.1 cm), compared to the RPLND group (3.9 cm; ***p***=0.010). Patients in the RMR group had more often International Germ Cell Cancer Collaborative Group (IGCCCG) intermediate/poor prognosis (63.5%), compared to patients in the RPLND group (47.2%).

A total of 33 patients (26.6%) required 46 additional surgical procedures (Table 1). Most common interventions were nephrectomy (n=9; 7.3%) and inferior vena cava (IVC) resection/reconstruction (n=8; 6.5%). Less common interventions were: partial bowel resection, renal artery resection (each n=3; 2.4%), partial liver resection (n=2; 1.6%), adrenalectomy, superior mesenteric artery reconstruction, and segmental ureter resection with ureteroureterostomy (each n=1, 0.8%). Assistance of a vascular surgeon was required in 20 cases (16.1%). An additional procedure was performed in 16/72 patients undergoing template RPLND (22.2%) and 17/52 patients undergoing residual mass resection (32.7%).

In all, 29 of 46 additional interventions (63.0%) were performed to achieve an adequate resection and 17 interventions (37.0%) were the consequence of an intraoperative complication. These complications were lesions of the iliac artery (n=6), aorta (n=4), renal artery (n=3), renal vein (n=2), IVC (n=1) and superior mesenteric artery (n=1). The tumor was adjacent to the site of additional intervention in all cases, which suggests that a preoperative CT scan is sufficient to identify patients in whom an additional intervention is likely to be necessary.

Table 1. Patient Characteristics and Operative Outcome

	Overall	Template RPLND	RMR	P-value
Patients, no.	124	72	52	
Median age at surgery, years (IQR)	29.8 (24.4-37.5)	28.5 (24.4-35.0)	32.3 (24.5-40.1)	0.104
Retroperitoneal primary, no. (%)	14 (11.3)	9 (12.5)	5 (9.6)	0.776
Histologic subtype primary tumor, no. (%)				0.792
Non-seminoma	107 (86.3)	63 (87.5)	44 (84.6)	
Seminoma	17 (13.7)	9 (12.5)	8 (15.4)	
IGCCCG risk classification, no. (%)				0.120
Good	56 (42.2)	37 (51.4)	19 (36.5)	
Intermediate	43 (34.7)	24 (33.3)	19 (36.5)	
Poor	24 (19.4)	10 (13.9)	14 (26.9)	
Missing	1 (0.8)	1 (1.4)	0	
Median diameter residual tumor, cm (IQR)	4.7 (2.9-8.0)	3.9 (2.4-6.9)	6.1 (3.9-8.8)	0.010
≤ 5 cm	67 (54.0)	46 (63.9)	21 (40.4)	
> 5-10 cm	38 (30.6)	16 (22.2)	22 (42.3)	
> 10 cm	19 (15.3)	10 (13.9)	9 (17.3)	
Median operative time, mins (IQR)	248 (178-343)	275 (202-356)	217 (139-330)	0.009
With additional procedure	360 (264-433)	409 (350-465)	280 (141-362)	
Without additional procedure	233 (173-297)	245 (193-300)	184 (135-289)	
Median blood loss, ml (IQR)	890 (400-2,080)	500 (250-1,372)	1,265 (570-3,000)	0.001
With additional procedure	2,008 (800-3,315)	1,800 (1,050-3,500)	2,015 (650-3,230)	
Without additional procedure	700 (325-1,505)	400 (190-600)	1,100 (535-2,143)	
Additional surgical procedures, pts. (%)	33 (26.6)	16 (22.2)	17 (32.7)	0.220
Nephrectomy	9 (7.3)	6 (8.3)	3 (5.8)	0.733
IVC resection/ reconstruction	8 (6.5)	2 (2.8)	6 (11.5)	0.068
Aorta reconstruction	6 (4.8)	4 (5.6)	2 (3.8)	1.00

Table 1. Patient Characteristics and Operative Outcome *(continued)*

	Overall	Template RPLND	RMR	P-value
Iliac artery reconstruction	7 (5.6)	2 (2.8)	5 (9.6)	0.129
Renal vein reconstruction	5 (4.0)	4 (5.6)	1 (1.9)	0.398
Median postoperative stay, days (IQR)	7 (5-9)	7 (6-9)	7 (5-8)	0.084
Patients with postoperative complications ≥ Grade 2 (%)	31 (25.0)	19 (26.4)	12 (23.1)	0.834
Clavien-Dindo Grade 2	24 (19.4)	12 (16.7)	12 (23.1)	0.812
Clavien-Dindo Grade 3a	4 (3.2)	3 (4.2)	1 (1.9)	0.641
Clavien-Dindo Grade 3b	5 (4.0)	4 (5.6)	1 (1.9)	0.402
Clavien-Dindo Grade 4a	3 (2.4)	2 (2.8)	1 (1.9)	1.00
Clavien-Dindo Grade 5	2 (1.6)	1 (1.4)	1 (1.9)	1.00
Histology lymphadenectomy specimen, no. (%)				0.936
Teratoma	62 (50.0)	36 (50.0)	26 (50.0)	
Fibrosis / necrosis	46 (37.1)	26 (36.1)	20 (38.5)	
Viable cancer	16 (12.9)	10 (13.9)	6 (11.5)	

IGCCCG = International Germ Cell Cancer Group; IVC = inferior vena cava; IQR = interquartile range; RMR = residual mass resection; RPLND = retroperitoneal lymph node dissection

The necessity of an additional surgical procedure was significantly associated with IGCCCG intermediate/poor prognosis and residual tumor size >5 cm (Table 2). Pure seminoma on primary histology and type of surgery were not significantly associated with an additional intervention. On multivariate analysis, intermediate/poor risk category (OR 3.56; 95% CI 1.33-9.52; p=0.011) and tumor size >5 cm (OR 3.53; 95% CI 1.39-8.93; p=0.008) were significant predictors of an additional intervention. Taking only the 107 patients with NSGCT into account, tumor size >5 cm was still a significant predictor (OR 3.38; 95% CI 1.23-9.27; p=0.018) but intermediate/poor prognosis became borderline insignificant (OR 2.72; 95% CI 0.93-7.97; p=0.068; Supplementary Table 1).

Multiple regression analysis found that tumor regression and viable cancer on retroperitoneal histology were not significantly correlated with blood loss. Retroperitoneal primary, type of surgery, teratoma on retroperitoneal histology, additional intervention, IGCCCG prognosis and residual tumor size were included in the model. IGCCCG intermediate/poor prognosis (β=0.177; p=0.029), residual tumor size (β=0.570; p<0.001), necessity of an additional intervention

(β=0.342; p<0.001) and teratoma on retroperitoneal histology (β=-0.190; p=0.014) were significantly correlated with blood loss (adjusted R^2=0.438; p<0.001).

A total of 38 postoperative complications Clavien-Dindo Grade ≥2 were identified in 31 patients (25.0%; Supplementary Table 2). A reoperation (Grade 3b) was necessary in three patients (3.2%). One patient underwent a hemicolectomy for colon ischemia. Another patient had a perforation of the small intestine, which was repaired during explorative laparotomy. The third patient had metabolic instability with unknown cause for which he underwent explorative laparotomy without an additional intraoperative intervention.

The risk of a severe complication (Grade ≥3) was higher in patients with an additional intervention (24.2%) compared to patients without an additional intervention (6.6%, p=0.011) and this was borderline significant when corrected for residual tumor size (OR 3.46; 95% CI 1.03-11.60; p=0.044; Supplementary Table 3). Tumor regression was not associated with an additional intervention or postoperative complication.

Two patients (1.6%) died from a postoperative complication (Grade 5). One patient had IGCCCG poor prognosis and a 10 cm large residual tumor in the left para-aortal region. The day after surgery, he developed hematochezia but exploratory laparotomy showed no sign of intestinal ischemia. A week later, the patient became hemodynamically unstable and a bleeding of the left renal artery was diagnosed, which was sutured during a subsequent surgical procedure. Unfortunately, the patient developed necrotizing pancreatitis with abdominal bleeding of unknown origin and had to undergo seven more exploratory laparotomies with resection of necrotic tissue. One month after PC-RPLND, a new aortic bleeding developed, for which an endovascular stent was placed by a vascular surgeon. Twenty-three days later, however, the patient became hemodynamically unstable again and CT-imaging showed an aortic bleeding proximally to the stent. There were no more therapeutic options and the patient died the same day.

The second patient had intermediate prognosis and a 25 cm large residual tumor. He had persistent chylous ascites for which he underwent multiple abdominal drainages. Forty-six days after surgery, a peritoneovenous shunt was placed. After three months, the leaking lymph vessels were ligated during laparotomy. During this procedure, the aorta had to be reconstructed by a vascular surgeon because of an intraoperative avulsion. After surgery, he developed an aortic bleeding of which he died.

After a median follow-up of 60.2 months (IQR 28.0-93.8), 9 patients (7.3%) had disease recurrence or progression. This was a retroperitoneal relapse in five patients (4.0%; template: 2/72 patients, RMR: 3/52 patients). All retroperitoneal relapses were inside the surgical field, except for one patient in the RMR group. The patients with retroperitoneal relapse were treated with salvage chemotherapy (n=1), palliative chemotherapy (n=1), chemotherapy with radiotherapy (n=1) or surgery (n=2). The four patients with relapse outside the retroperitoneum

were all treated with chemotherapy. One patient also received radiotherapy and another patient underwent pelvic node resection in addition to his chemotherapeutic treatment.

Five patients (4.0%) died of disease. Four of these had a retroperitoneal relapse and one had tumor recurrence in the peritoneum. The cause of death was unknown in two patients. Together with the two patients who died of a postoperative complication, nine patients in our cohort died. Follow-up was <12 months in 14 patients. Among the remaining 110 patients, overall survival was 91.8% (template: 93.9%; RMR: 88.6%) and cancer-specific survival was 93.6% (template: 95.5%; RMR: 90.9%).

Table 2. Predictors of Additional Surgical Procedures

	Univariate		Multivariate	
	OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**
Age	0.99 (0.95-1.03)	0.640		
Left-sided primary	0.67 (2.88-1.58)	0.361		
Retroperitoneal primary	1.63 (0.50-5.27)	0.426		
Seminoma primary	1.62 (0.55-4.79)	0.395	1.47 (0.46-4.75)	0.521
IGCCCG intermediate / poor prognosis	**4.44 (1.75-11.27)**	**0.001**	**3.56 (1.33-9.52)**	**0.011**
Tumor regression	1.01 (0.99-1.04)	0.188		
Residual tumor size >5 cm	**4.69 (1.95-11.27)**	**<0.001**	**3.53 (1.39-8.93)**	**0.008**
Residual mass resection*	1.70 (0.76-3.79)	0.195	1.09 (0.45-2.66)	0.852
Histology RPLND specimen		0.761		
Necrosis / fibrosis	Reference			
Viable cancer	0.76 (0.21-2.78)	0.680		
Teratoma	0.73 (0.31-1.72)	0.470		

* Compared to template-based surgery
IGCCCG = International Germ Cell Cancer Group; OR = odds ratio; RMR = residual mass resection; RPLND = retroperitoneal lymph node dissection; CI = confidence interval

Discussion

The rate of an additional intervention in our study is comparable to what has been reported in other series, which ranges between 13% and 38% [11, 12, 18–21]. As in our study, nephrectomy and IVC interventions are the most commonly performed additional procedures [7, 11, 12, 18–20]. Cary et al. reported the results of 755 patients of the Indiana University, which is one of the largest series to date [11]. From 2003 to 2011, the annual rate of additional procedures ranged between 17% and 30%. A nephrectomy was necessary in 7.3% of patients. In a series of 85 patients who were treated by a single surgeon between 2004 and 2010, 28 patients (33%) required adjuvant surgery [19]. This was a vascular procedure in 13 patients (15%) and a nephrectomy in 12 patients (14%). In a multicenter analysis of 339 PC-RPLNDs by the German Testicular Cancer Study Group, the rates of IVC intervention and nephrectomy were 10% and 9%, respectively [20].

The results from these institutional series are similar to what has been found in nationwide studies. Wells et al. evaluated audit data for all RPLNDs in the UK between March 2012 and February 2013 and found that the rates of synchronous nephrectomy and vascular reconstruction were 11.1% and 5%, respectively [22]. Not all RPLNDs were in the post-chemotherapy setting (72.2%), but only 5.6% of procedures were primary RPLNDs. Macleod et al. analyzed the insurance data of 206 patients undergoing PC-RPLND in the USA [23]. Overall, 19% of patients underwent an adjunctive procedure, of which nephrectomy (10%) and vascular reconstruction (8%) were the most common interventions. Thus, the rate of an additional intervention in our series is similar to what has been reported by large institutional series and nationwide cohort studies.

Postoperative complication rates reported in the literature vary widely and are primarily based on single-center series. Several high volume centers have reported rates between 3% and 12% [6, 11, 12, 18, 24]. However, several population-based studies have found much higher complication rates than what has been reported in series from high volume institutions. The study by Wells et al. showed that in only 73.5% of all RPLNDs in the UK no complication was recorded [22]. In a nationwide sample of all RPLNDs in the USA between 2001 and 2008, the overall rate of complication was 24.8% [14]. According to a population-based analysis of all PC-RPLNDs in Norway and Sweden between 2007 and 2014, a complication occurred in 25% of patients treated with unilateral PC-RPLND and 45% of bilateral PC-RPLND [25]. A Clavien-Dindo Grade ≥3b complication occurred after 2.2% of unilateral procedures and 9.2% of bilateral procedures. This shows that the complication rate in our cohort is equal to what has been reported in nationwide cohort studies.

Although based on only two cases, the rate of Grade 5 complications in our cohort (1.6%) is higher than what has been reported in comparative studies. In a series of 152 patients by Heidenreich et al, one patient (0.7%) died due to massive postoperative bleeding caused by an aorto-duodenal fistula [18]. Fléchon et al. reported one death due to an intra-abdominal bleeding in a cohort of 151 patients (0.7%) [3].

Patient outcome after complex cancer surgery is correlated with hospital volume [26, 27]. For testicular malignancies specifically, the recent literature is scarce. Woldu et al. found an association between hospital volume and survival in patients with non-localized NSGCT [28]. The authors analyzed data from the National Cancer Database (USA) for patients treated for testicular germ cell tumor (TGCT) in the years 2004-2014. Compared to the highest volume hospitals, the hazard ratios for overall mortality were 1.28, 1.45, 1.48, and 1.83 for high-intermediate, intermediate, low-intermediate, and low volume hospitals, respectively. For RPLND specifically, Yu et al. showed that the overall complication risk was significantly lower in hospitals with a higher volume [14]. This shows that centralization of RPLND is important to improve patient outcome. Although the most optimal annual number of procedures has yet to be determined, the current cutoff value of ten procedures per year in The Netherlands is relatively low.

Several reports have shown a strong association between residual tumor size and additional interventions, similar to our findings [7, 11, 20]. In the series by Cary et al., residual tumor size >10 cm was the strongest predictor of an additional procedure (OR 7.2; 95% CI 2.6-19.5) [11]. In an earlier study by the same authors, 31.9% of patients with a residual tumor size >10 cm had to undergo nephrectomy [7]. A recent study from the University Hospital of Dusseldorf found a higher rate of additional interventions in patients undergoing a bilateral PC-RPLND (43%), compared to a unilateral PC-RPLND (23%; p=0.006) [9]. Nephrectomy was indicated in 12% of bilateral procedures but only in 3% of unilateral procedures (p=0.03). This difference can be most likely attributed to the difference in tumor size, since the decision whether to perform a unilateral or bilateral procedure was based on the size and location of the residual tumor, with 5 cm as a cut-off value [9].

The correlation between IGCCCG intermediate/poor prognosis and an additional intervention has been described previously by Winter et al. [20]. The authors found that the probability of an IVC intervention increased with tumor size ≥5 cm and worse IGCCCG risk category. Our study shows that these risk factors also apply to non-vascular additional procedures. The association between pre-chemotherapy risk category and additional (vascular) procedures can be explained by the fact that IGCCCG prognosis group can be regarded as a measure of tumor burden. Another possibility is a more severe desmoplastic reaction in patients treated with more cycles of chemotherapy.

In addition to these patient and tumor characteristics, the indication of an additional intervention is also dependent on the PC-RPLND setting. The risk of an additional procedure is higher in patients who were treated with salvage chemotherapy [29]. Since only 15/124 patients in our cohort were treated with salvage chemotherapy and this parameter was highly correlated with IGCCCG prognosis, we did not include this parameter in our analysis.

Whether complete resection of all residual tumor outside the retroperitoneal nodes is always indicated is up for debate. Recent studies have shown that a more extensive resection does not always lead to a better outcome. Nini et al. reported on a series of 14 patients with nodal and bone involvement undergoing PC-RPLND with simultaneous partial or complete bone resection [30]. All four patients with vital cancer had disease progression, irrespective of the extent of the

bone resection, and three out of four died. Among the six patients with teratoma, both patients that were treated with partial bone resection had disease progression and died, whereas the four treated with a complete resection have been cured. This suggests that a more extensive bone resection was only beneficial in patients with teratoma but not in patients with vital cancer [30]. This is in line with a study by Nestler et al., who analyzed the tumor histology in resected organs in a cohort of 235 patients undergoing PC-RPLND with an additional resection [31]. Most common interventions were nephrectomy (n=74), IVC resection (n=66) and partial liver resection (n=48). Histopathological analysis of the resected organs showed necrosis in 40% of patients, which implies that the additional resection was oncologically unnecessary in these cases.

We have identified clinical predictors that are useful for the risk classification of PC-RPLND patients. Patients with intermediate or poor prognosis, high volume disease, or patients undergoing an additional surgical procedure can be classified as high risk patients. Although a complete diagnostic workup is necessary in all patients, extra attention is warranted in high risk patients. Evaluation of possible tumor ingrowth in adjacent organs is of particular importance in these patients. All tumors were adjacent to the site of additional intervention in our series. This shows that a preoperative CT scan is sufficient to identify patients in which an additional intervention is necessary.

Our study is subject to certain limitations. First, a substantial portion of patients was treated with RMR instead of template-based RPLND. RMR is not standard of care and may be associated with a higher risk of retroperitoneal relapse. Although we corrected for the type of surgery in our analysis, this makes our results less generalizable. Second, its retrospective nature can lead to bias and underreporting of perioperative morbidity. We believe that the underreporting of complications is low, as we only included complications Grade ≥2, which are generally well reported. Third, patients at the NCI who had small volume residual disease (<5 cm) were not included in this study, since they were treated with a minimally-invasive procedure. This may have introduced selection bias and overestimated the relapse rate, mortality rate and rate of additional interventions and complications. It also prevents a solid comparison between both surgical approaches, since the patient cohorts differed significantly. Fourth, PC-RPLND is performed at a lower frequency in our centers, compared to other larger series. Both centers, however, are two of the largest centers for PC-RPLND in The Netherlands. In addition to the treatment of low volume disease with a minimally-invasive procedure, the low frequency of this procedure can be explained by the low number of TGCT patients in our country (~800 new TGCT patients annually). Nevertheless, the outcomes of this study could spur the discussion on further centralization of PC-RPLND.

A key strength of our study is that a radiologist re-analyzed the CT scans prior to chemotherapy and surgery. This assured uniformity in method of tumor measurement and calculation of tumor regression. Another strength was the long median follow-up (>5 years), since almost all patients had their post-surgery follow-up at one of the participating centers.

Conclusions

In conclusion, the rate of additional interventions and postoperative complications in our series is comparable to what has been reported in other reports. IGCCCG intermediate/poor risk patients with high-volume disease can be classified as high-risk patients. To optimize outcome, extra attention to possible tumor ingrowth and precautionary measures (e.g. assistance from a vascular surgeon, postoperative stay at intensive care unit) is warranted in these patients. The preoperative CT scan is sufficient to identify patients in which an additional intervention is necessary.

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Supplementary Table 1. Predictors of Additional Surgical Procedures in NSGCT Patients

	Univariate		Multivariate	
	OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**
Age	0.99 (0.94-1.04)	0.750		
Left-sided primary	0.68 (0.27-1.72)	0.409		
Retroperitoneal primary	1.81 (0.49-6.75)	0.386		
IGCCCG intermediate / poor prognosis	**3.97 (1.45-10.90)**	**0.004**	2.72 (0.93-7.97)	0.068
Tumor regression	1.01 (0.99-1.03)	0.333		
Residual tumor size >5 cm	**4.66 (1.81-12.02)**	**0.001**	**3.38 (1.23-9.27)**	**0.018**
Residual mass resection*	1.80 (0.74-4.33)	0.192	1.14 (0.43-3.01)	0.797
Histology RPLND specimen		0.874		
Necrosis / fibrosis	Reference			
Viable cancer	1.07 (0.27-4.28)	0.927		
Teratoma	0.81 (0.31-2.15)	0.674		

IGCCCG = International Germ Cell Cancer Collaborative Group; RPLND = retroperitoneal lymph node dissection; OR = odds ratio; CI = confidence interval

Supplementary Table 2. Overview of types of complications

Type of complications	**Treatment**	**Overall**	**Template RPLND**	**RMR**
Clavien-Dindo Grade 2		**24 (19.4)**	**12 (16.7)**	**12 (23.1)**
Infection	Antibiotics	14 (11.3)	8 (11.1)	6 (11.5)
Chylous leakage	Minimal chain diet	3 (2.4)	2 (2.8)	1 (1.9)
Ileus	Enema / readmittance	2 (1.6)	-	2 (3.8)
Anemia	Blood transfusion	2 (1.6)	-	2 (3.8)
High blood pressure	Medication	1 (0.8)	-	1 (1.9)
Pain	PCEA	2 (1.6)	2 (2.8)	-
Clavien-Dindo Grade 3a		**4 (3.2)**	**3 (4.2)**	**1 (1.9)**
Chylous leakage	Percutaneous drainage	2 (1.6)	1 (1.4)	1 (1.9)
Renal artery thrombosis	Thrombectomy	1 (0.8)	1 (1.4)	-
Atrial fibrillation	Cardioversion	1 (0.8)	1 (1.4)	-
Clavien-Dindo Grade 3b		**5 (4.0)**	**4 (5.6)**	**1 (1.9)**
Intestinal perforation / ischemia	Laparotomy	2 (1.6)	1 (1.4)	1 (1.9)
Hydronephrosis	Double pigtail stent	1 (0.8)	1 (1.4)	-

Supplementary Table 2. Overview of types of complications *(continued)*

Type of complications	Treatment	Overall	Template RPLND	RMR
Metabolic instability, unknown cause	Laparotomy	1 (0.8)	1 (1.4)	-
Compartment syndrome	Fasciotomy	1 (0.8)	1 (1.4)	-
Clavien-Dindo Grade 4a		**3 (2.4)**	**2 (2.8)**	**1 (1.9)**
Tubular necrosis	Continuous hemofiltration, ICU	1 (0.8)	1 (1.4)	-
Cardiac arrest	Resuscitation, ICU	1 (0.8)	1 (1.4)	-
Retroperitoneal fluid collection with septic shock	Drainage, ICU	1 (0.8)	-	1 (1.9)
Clavien-Dindo Grade 5		**2 (1.6)**	**1 (1.4)**	**1 (1.9)**
Postoperative bleeding	Surgery	2 (1.6)	1 (1.4)	1 (1.9)

PCEA = Patient-controlled epidural analgesia; ICU = Intensive care unit; RMR = residual mass resection; RPLND = retroperitoneal lymph node dissection

Supplementary Table 3. Predictors of a Complication Clavien-Dindo Grade ≥III

	Univariate		Multivariate	
	OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**
Age	1.05 (0.99-1.10)	0.087		
Retroperitoneal primary	2.43 (0.59-10.06)	0.248		
Seminoma primary	1.04 (0.21-5.14)	0.958		
IGCCCG intermediate / poor prognosis	2.24 (0.66-7.57)	0.179		
Tumor regression	1.02 (0.99-1.05)	0.243		
Residual tumor size >5 cm	3.30 (0.97-11.17)	0.055	2.26 (0.62-8.25)	0.218
Residual mass resection*	1.31 (0.41-4.18)	0.640		
Additional intervention	**4.48 (1.42-14.13)**	**0.011**	**3.46 (1.03-11.60)**	**0.044**
Histology RPLND specimen		0.520		
Necrosis / fibrosis	Reference			
Viable cancer	0.80 (0.15-4.30)			
Teratoma	0.50 (0.15-1.68)			

* Compared to template-based surgery
IGCCCG = International Germ Cell Cancer Group; OR = odds ratio; RMR = residual mass resection; RPLND = retroperitoneal lymph node dissection; CI = confidence interval

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Chapter

Clinical outcome of robot-assisted residual mass resection in metastatic nonseminomatous germ cell tumor

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Abstract

Purpose

To evaluate the outcome of robot-assisted residual mass resection (RA-RMR) in nonseminomatous germ cell tumor (NSGCT) patients with residual tumor following chemotherapy.

Patients and Methods

Retrospective medical chart analysis of all patients with NSGCT undergoing RA-RMR at two tertiary referral centers between January 2007 and April 2019. Patients were considered for RA-RMR in case of a residual tumor between 10 and 50 mm at cross-sectional computed tomography (CT) imaging located ventrally or laterally from the aorta or vena cava, with normalized tumor markers following completion of chemotherapy, and no history of retroperitoneal surgery.

Results

A total of 45 patients were included in the analysis. The Royal Marsden stage before chemotherapy was IIA in 13 (28.9%), IIB in 16 (35.6%), IIC in 3 (6.7%) and IV in 13 patients (28.9%). The median residual tumor size was 1.9 cm (interquartile range [IQR] 1.4-2.8; range 1.0-5.0). Five procedures (11.1%) were converted to an open procedure due to a vascular injury (n=2), technical difficulty (n=2) or tumor debris leakage (n=1). A postoperative adverse event occurred in two patients (4.4%). Histopathology showed teratoma, necrosis and viable cancer in 29 (64.4%), 14 (31.1%), and 2 patients (4.4%), respectively. After a median follow-up of 41 months (IQR 22-70), one patient (2.2%) relapsed in the retroperitoneum. The one- and 2-year recurrence-free survival rate was 98%.

Conclusion

RA-RMR is an appropriate treatment option in selected patients, potentially providing excellent cure rates with minimal morbidity. Long-term outcome data are needed to further support this strategy and determine inclusion and exclusion criteria.

Introduction

Approximately one-third of patients who undergo cisplatin-based combination chemotherapy for disseminated nonseminomatous germ cell tumor (NSGCT) have significant residual retroperitoneal disease [1, 2]. Histopathological analysis after postchemotherapy retroperitoneal lymph node dissection (PC-RPLND) shows fibrosis or necrosis in 40-50%, teratoma in 30-40%, and viable cancer in 10-20% of cases [3, 4]. Since there are currently no validated methods to reliably predict the histology of a residual mass, PC-RPLND remains important in all patients with significant residual disease in NSGCT [5].

There is a debate concerning the anatomical extent of PC-RPLND. Historically, bilateral template-based retroperitoneal lymph node dissection was the standard approach in all patients undergoing PC-RPLND [5]. Heidenreich et al. showed that a modified template decreases morbidity and does not compromise oncological outcome in selected patients [4]. Although a template-based procedure is the standard approach, several centers consider residual mass resection as oncologically equivalent [6, 7].

More recently, the minimally invasive approach is gaining recognition in the postchemotherapy setting. Two large series have shown excellent oncological outcomes after laparoscopic PC-RPLND [8, 9], but high volume series on robot-assisted PC-RPLND (RA-PC-RPLND) are still lacking [10]. In the largest series to date, none of the 30 patients undergoing RA-PC-RPLND had retroperitoneal relapse [11]. These promising initial results and the continuous evolvement of surgical techniques and technology suggest that robotic surgery may replace open PC-RPLND in selected patients. On the condition that oncological safety is warranted, this may provide significant benefit to patients. After all, the morbidity of open PC-RPLND is high, while histopathology of the retroperitoneal specimen shows fibrosis or necrosis in a large proportion of patients [3, 4, 12, 13].

Current reports on minimally invasive PC-RPLND mainly concern template-based surgery. We hypothesized that, in selected patients, oncological control can be achieved by robot-assisted residual mass resection (RA-RMR). In this study, we retrospectively evaluated the results of this approach in two tertiary referral centers.

Patients and Methods

Study Design

After institutional review board approval, we retrospectively reviewed the medical charts for all NSGCT patients who underwent postchemotherapy RA-RMR in two tertiary referral centers between January 2007 and April 2019.

Work-up prior to surgery included abdominopelvic computed tomography (CT) scanning and measurement of serum tumor markers (α-fetoprotein, human chorionic gonadotropin and

lactate dehydrogenase). All treatment options were discussed by a multidisciplinary panel consisting of a urological oncologist, medical oncologist, radiologist, radiation oncologist and genitourinary pathologist. Patients were considered for RA-RMR in case of one or two residual tumors between 10 and 50 mm at cross-sectional CT imaging located ventrally or laterally from the aorta or vena cava, with normalized tumor markers following completion of chemotherapy, and no history of retroperitoneal surgery.

Surgical Technique

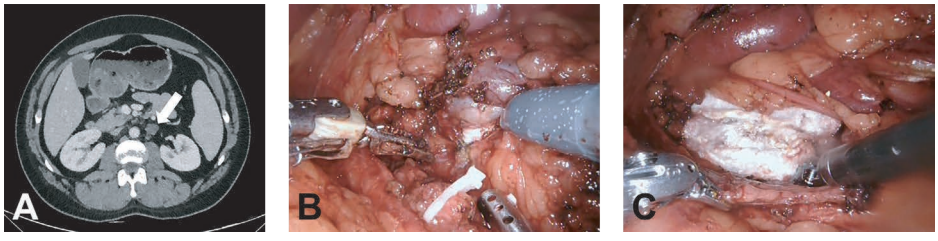
Patients were positioned in the flank position contralateral of the residual tumor. Exact port placement depended on the location of the residual tumor and the surgeon's preference. In general, a four-port diamond-shaped method was used. The camera port was placed in the paramedian line 3-4 cm cranial to the umbilicus and three additional ports were placed in the upper quadrant, lower quadrant and flank, including an assistant port. In some cases, a fifth port was placed subcostally in the midline.

The surgical resection was not template-based, with the individual extent of the resection adhering to the location of the metastases prior to chemotherapy and the location of the residual tumor (Figure 1). Any mass in addition to the lesion defined on presurgical CT suspicious for residual tumor that was noticed during surgery was resected as well as lymph nodes in the vicinity and the remnant testicular vessels.

Follow-up

Follow-up was performed according to current guidelines of the European Society for Medical Oncology. In general, this consisted of monthly clinical examinations and evaluations of serum tumor markers in the first year. After the first year, the frequency of follow-up was gradually reduced every year. Abdominal/thoracic CT scanning was done at least three times (after 6, 12 and 24 months).

Figure 1. Computerized Tomography Scan and Intraoperative Images of Patient Undergoing RA-RMR



This patient had a residual tumor (short axis 1.3 cm) in the left para-aortal region. Histopathology showed a 3 cm large teratoma. (A) Axial abdominal CT scan after chemotherapy with a residual tumor in the left para-aortal region (arrow). (B) Intra-operative image with the tumor still in situ. (C) Intra-operative image after the tumor has been resected and a Surgicel has been placed in the retroperitoneum. In images (B) and (C) it is clear that the surrounding nodes and fat are not resected.

Results

Out of a total of 208 RPLNDs, 67 RA-RMRs were performed. Twenty-two patients were excluded from the current analysis because (a) they were not treated with chemotherapy prior to surgery (n=15), (b) the operative report was missing (n=2), (c) tumor markers were elevated at time of surgery (n=2), (d) no NSGCT primary (n=2) or (e) history of prior RPLND (n=1). The remaining 45 patients were included in the analysis (Table 1).

In 71% of patients, the residual tumor was located in the left para-aortal region. Thirty-eight patients (84.4%) had a solitary tumor on preoperative imaging. Five patients (11.1%) had two nodes and one patient (2.2%) had five nodes. The median tumor size was 1.9 cm (interquartile range [IQR] 1.4-2.8; range 1.0-5.0).

Adverse Events

An intra-operative adverse event was recorded in five patients (11.1%; Table 1). Two vascular injuries occurred: one renal artery injury and one inferior mesenteric artery injury. Both events required conversion to an open procedure. In two patients, debris leaked from the residual tumor, which required conversion to an open procedure in one case. The fifth patient had a splenic injury, most likely due to excessive traction. No bleeding was observed and the injury was coagulated with a bipolar coagulator.

In addition to the three patients who required a conversion due to an intra-operative adverse event, two patients required conversion to an open procedure due to technical difficulties. One patient had a retro-aortic node adhesive to the surrounding tissue which could not be resected during robotic surgery. The node was successfully resected after conversion. The second patient had two residual tumors: one para-aortic node and one node adjacent to the left common iliac vein. The surgeon was able to resect the para-aortic node during the robot-assisted procedure, but resection of the para-iliacal tumor was unsuccessful. After midline laparotomy, the para-iliacal tumor (sized 4 x 3 x 2.5 cm) was successfully resected. Palpation of the para-aortal region revealed two additional small nodes which were resected and were confirmed to contain teratoma at histopathology.

Two patients (4%) had a postoperative adverse event Clavien-Dindo grade ≥2. One patient was readmitted 22 days after surgery for a 9 cm large lymphocele with urinary tract obstruction and secondary pyelonephritis. He was treated with intravenous antibiotics (grade 2 complication). The second patient too was readmitted with a lymphocele six days after surgery (four days after hospital discharge). A drain was placed and a medium-chain triglyceride diet was prescribed (grade 3a).

Table 1. Patient characteristics and outcome

Number of patients	45
Median age at surgery, *years (IQR)*	29 (23-36)
Primary tumor side, *n (%)*	
Left	32 (71.1)
Right	13 (28.9)
Royal Marsden stage prior to chemo, *n (%)*	
IIA	13 (28.9)
IIB	16 (35.6)
IIC	3 (6.7)
IV	13 (28.9)
IGCCCG prognosis category	
Good	38 (84.4)
Intermediate	6 (13.3)
Poor	1 (2.2)
Cycles of platinum-based chemotherapy, *n (%)*	
3 cycles	24 (53.3)
4 cycles	14 (31.1)
>4 cycles	1 (2.2)
Unknown	6 (13.3)
Median residual tumor size, *cm (IQR)*	1.9 (1.4-2.8)
Residual tumor location, *n (%)*	
Para-aortic	32 (71.1)
Para-caval	3 (6.7)
Interaortocaval	10 (22.2)
Median operative time, *mins (IQR)*	134 (100-174)
Median intraoperative blood loss, *ml (IQR)*	50 (5-110)
Intraoperative adverse events, *n (%)*	5 (11.1)
Vascular lesion	2 (4.4)
Debris leakage	2 (4.4)
Spleen lesion	1 (2.2)
Conversions to open surgery, *n (%)*	5 (11.1)
Technical difficulty	2 (4.4)
Vascular lesion	2 (4.4)
Debris leakage	1 (2.2)
Postoperative complication, *n (%)*	2 (4.4)
Clavien-Dindo Grade 2	1 (2.2)
Clavien-Dindo Grade 3a	1 (2.2)
Median length of hospitalization, *days (range)*	2 (1-3)
Retroperitoneal histology, *n (%)*	
Necrosis / fibrosis	14 (31.1)
Teratoma	29 (64.4)
Viable cancer	2 (4.4)
Median length of follow-up, *months (IQR)*	41 (22-70)
Relapse, *n (%)*	1 (2.2)
Survival status, *n (%)*	
No evidence of disease	43 (95.6)
Died of other causes	2 (4.4)

IGCCCG = International Germ Cell Cancer Collaboration Group; IQR = interquartile range

Histology

The median number of resected nodes was three (IQR 1-6). The retroperitoneal specimen showed teratoma, necrosis and viable cancer in 29 (64%), 14 (31%), and 2 patients (4%), respectively. Since the amount of viable cancer was <10% in both patients, they were not treated with additional chemotherapy.

Follow-up

The median follow-up of the entire cohort was 41 months (IQR 22-70). Follow-up was shorter than 1 year in three patients, who preferred to have their follow-up visits at the referring hospital. Based on only one patient with disease progression, the 1- and 2-year relapse-free survival rates were 98%.

One patient had disease progression with elevated tumor markers. The CT-scan of this patient, prior to RA-RMR, showed a 1.5 cm large residual tumor cranial to the left renal vessels. The CT-scan 3 months after surgery showed a 2.9 cm large para-aortic node at the same location, which suggests that the residual tumor was overlooked during surgery and not adequately resected. In addition, a 2.9 cm large node in the interaortocaval region was found. A CT-scan prior to chemotherapy had shown minimal growth of small interaortocaval nodes, but there was no residual tumor visible in the interaortocaval region after completion of chemotherapy. Subsequent treatment with salvage chemotherapy and open RPLND was successful and he had no evidence of disease after 83 months of follow-up.

None of the patients died of disease but two patients died of other causes. One patient died 11 months after surgery due to acute leukemia. Another patient died of renal cell carcinoma, more than 4 years after surgery.

Discussion

We report the perioperative and oncologic outcomes in a series of 45 selected NSGCT patients undergoing RA-RMR. Two patients (4.4%) had a postoperative complication Clavien-Dindo grade ≥2 with short admission time and one patient (2.2%) had disease progression in the retroperitoneum. After a median follow-up of more than 3 years, none of the patients had evidence of disease.

Patients with a residual tumor after chemotherapy for disseminated NSGCT form a unique group of cancer patients. They are relatively young and long-term survival is expected in most cases [14]. Although surgical resection of viable cancer is important, histopathological examination of the retroperitoneal specimen shows necrosis in most patients [4, 15]. In addition, the presentation of patients with testicular cancer is changing. The proportion of patients initially presenting with low-stage disease is increasing and systemic chemotherapy is applied more often in patients with low-volume retroperitoneal metastases [16, 17]. Non-cancer histology is especially common in patients with a small residual lesion [15]. These aspects highlight the

increasing importance of the reduction of treatment-associated morbidity and shift the focus of testicular germ cell tumor (TGCT) treatment to a more patient-tailored approach.

Maintaining oncological efficacy is an important prerequisite for the adoption of a minimally invasive approach and several series on minimally invasive PC-RPLND have shown promising results (Supplementary Table 1) [7–9, 11, 18–20]. Steiner et al. reported on 100 patients that were treated with a unilateral (n=71) or bilateral (n=29) laparoscopic template dissection [9]. Patient characteristics were relatively favorable, since the largest tumor diameter was <1 cm in 51/100 patients. Only one relapse (outside the surgical field) was observed after a mean follow-up of >5 years.

Another key study is a series of 67 patients by Nicolai et al. [8]. Contrary to the series by Steiner et al., only patients with a clinically significant residual tumor (1-5 cm) were eligible. Although the median follow-up was only 21 months, none of the patients relapsed. These promising findings are supported by a recent systematic review, which found a weighted average retroperitoneal relapse rate of minimally invasive PC-RPLND of only 1.7% [10].

For RA-PC-RPLND specifically, the data on oncological safety are not yet mature enough to draw firm conclusions [10, 21]. In the largest cohort to date, Li et al. retrospectively analyzed the outcome of 30 patients undergoing template-based RA-PC-RPLND and compared this with a cohort of patients treated with open resection [11]. None of the patients in the robot-assisted group relapsed in the retroperitoneum.

Several studies have shown that completeness of the residual tumor resection is an important factor in oncological outcome [22, 23]. Fléchon et al. reported the results of 151 patients treated with open PC-RPLND between 1992 and 2002 with the aim to determine whether conformity to the recommendations of the Memorial Sloan Kettering Cancer Center (MSKCC) and completeness of the resection are associated with oncological outcome [22]. Of the 70 patients with a complete resection according to the MSKCC recommendations, only two patients (2.9%) had a retroperitoneal relapse. In the group of 58 patients with a complete resection, but not according to the MSKCC recommendations, three patients (5.2%) had a retroperitoneal relapse. If patients with an incomplete resection are also considered, thirteen out of 81 patients with a compliant but incomplete resection or with a non-compliant complete or incomplete resection relapsed in the retroperitoneum (16%). This corresponded to an event-free survival probability at 10 years of 72%, compared to 85% for patients with compliant and complete resection. It should be noted that the initial tumor was ≥5 cm in fourteen out of fifteen patients with retroperitoneal relapse. In our series, none of the patients had a residual tumor >5 cm. Nevertheless, this study shows that conformity to the guidelines and completeness of the resection might have an effect on oncological outcome [22].

In another large series of patients undergoing open RMR, seven out of 97 patients with macroscopically complete resection (7%) suffered from retroperitoneal relapse [6]. As with the

study by Fléchon et al., patient characteristics were relatively worse compared to our cohort, since more than half of patients had a residual tumor >4 cm. Both studies showed that RMR may not be an appropriate approach in patients with large residual tumors.

In a randomized comparison of chemotherapeutic regimens, complete resection was mandatory without stating the extent of the template [24]. Four out of 100 patients with normalized tumor markers and nonviable histology of residual tumor (4%) relapsed. In the group with normalized tumor markers and viable histology of residual tumor, four out of eleven patients (36%) relapsed. In our series, RA-RMR was only considered in those cases where complete resection of the residual lesion was considered possible.

The literature on minimally invasive RMR is scarce. Öztürk et al. described the results of laparoscopic RMR in a series of 89 patients treated between 2005 and 2015 [7]. Eight patients (9%) of the entire cohort relapsed, or four out of 75 procedures that were completed laparoscopically (5%). This relatively high relapse rate may be explained by the substantial number of patients with vital cancer in the retroperitoneum: 16% versus 4.4% in our cohort. In addition, three of the relapsed patients had interaortocaval tumor spread and two had contralateral tumor spread, which would have justified a bilateral dissection according to the Heidenreich criteria [4]. In a series of 12 patients undergoing RA-PC-RPLND by Kamel et al., three patients were treated with RA-RMR [20]. None relapsed after a follow-up of 5, 22, and 30 months.

In our cohort, one patient had tumor progression. This was partly due to an incomplete resection, but also due to a retroperitoneal relapse in the interaortocaval region outside the surgical field. If this patient would have been treated with a template-based approach, this probably would have been a left-sided modified template, since interaortocaval dissemination is highly unusual in patients with a left-sided primary tumor [25] and the para-aortic residual tumor was only 1.5 cm. This approach would not have prevented the interaortocaval relapse.

An important benefit of minimally invasive surgery is the improved perioperative outcome, compared to open surgery [8, 9, 26–28]. Robot-assisted surgery has additional benefits such as 360° movement of instruments, ability of three dimensional vision, better surgeon ergonomics, and accuracy and stability in confined spaces [21, 29]. The only major complication in our series was a lymphocele requiring drainage. This is in contrast with several population-based studies on open RPLND, which have reported average complication rates of ~25% [30, 31].

The duration of follow-up in the present study is relatively long, but it is not long enough to safely rule out any future retroperitoneal relapses. Although rare, relapse after complete remission following chemotherapy is possible even beyond 5 years of follow-up [2, 32, 33].

Several studies have shown that patient outcome after complex cancer surgery is correlated with hospital volume [10, 31, 34]. In patients with advanced TGCT, higher hospital volume is associated with improved survival outcomes [35] and high volume hospitals have fewer

post-operative complications and more routine home discharges after RPLND [31]. Therefore, patients with advanced TGCT should be managed at high volume expert centers. Our study is subject to certain limitations. The major limitation is its retrospective design. There were no strict predefined inclusion and exclusion criteria, which may have introduced bias in patient selection. In addition, postoperative antegrade ejaculation was not routinely recorded, which is an important aspect of retroperitoneal surgery.

It is unlikely that all open procedures will be replaced by a minimally invasive approach. In case of a large residual tumor, infiltration or encasement of the large vessels, retro-aortic or retro-caval tumor location, or if an additional surgical intervention (e.g. nephrectomy) is indicated, open surgery may still be the preferred approach. At the same time, the criteria for a minimally invasive procedure are dynamic instead of fixed. Surgical techniques, surgeon experience and technological innovations keep evolving, which will expand the indication of the minimally invasive approach. For example, the feasibility of a bilateral template dissection without patient repositioning has already been shown [36] and Aufderklamm et al. have reported laparoscopic PC-RPLND with vascular reconstruction in patients with a residual tumor infiltrating the large vessels [37]. Rapidly developing robot-assisted techniques will expand the indication even further.

RMR has been the standard management for postchemotherapy resection at our institute since 1979. Not all residual tumor patients are suitable for RMR instead of template dissection. According to the Heidenreich criteria, patients with contralateral tumor spread, residual tumor >5 cm or interaortocaval location should undergo a bilateral instead of unilateral template dissection [4]. Thus, they are also not eligible for RMR.

In addition, patients with multiple enlarged nodes postchemotherapy may have an increased risk of microscopic residual teratoma or vital cancer elsewhere in the retroperitoneum and are preferably treated with a template based procedure. It is also conceivable that the extent of the tumor prior to chemotherapy plays an important role. Pre-chemotherapy retroperitoneal nodal size and presence of visceral metastases are associated with relapse after PC-RPLND [3]. Patients with supradiaphragmatic node involvement or multiple tumors prior to chemotherapy may also have an increased risk of residual tumor beyond what is visible on postchemotherapy CT-scans.

In summary, RA-RMR may be an appropriate treatment option in patients with a single tumor in the primary landing zone which has not extended beyond 5 cm in diameter since initial diagnosis. However, further studies are necessary to establish the inclusion and exclusion criteria for a more limited dissection.

RA-RMR encompasses two developments: RMR instead of template resection and robot-assisted surgery instead of open surgery. It is important to bear in mind that there are currently no high-volume long-term data on either development. Since RA-RMR is a more limited

approach than conventional PC-RPLND, sufficient follow-up is especially important. At the very least, patients should be considered as if they have been treated with a template-based PC-RPLND and thus followed for five years. However, it could be the case that patients need to be followed for a longer period of time (e.g. up to 10 years) because they underwent a more limited resection. This is an important topic for further research.

Conclusion

RA-RMR may be an appropriate treatment option in selected patients, potentially providing excellent cure rates with minimal morbidity at intermediate follow-up. Long-term outcome data are needed to further support this strategy and determine inclusion and exclusion criteria.

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Supplementary Table 1. Summary of Outcomes of Minimally Invasive PC-RPLND in Other Reports

Study	Procedure	Inclusion criteria	No. of patients	Residual tumor size	Conversion, *n* (%)	Postoperative complications, *n* (%)	RP histology, *n* (%)	RP relapse, *n* (%)	Median follow-up
Li et al. (2019) [11]	RA	NM	30*	<1 cm: 7 pts. (26%) >5 cm: 4 pts. (13%)	3 (10): inadequate visualization in 2 pts., vascular injury in 1 pt.	6 (20): wound infection in 2 pts.; delirium tremens; chylous ascites; pneumothorax; colon perforation	Necrosis: 10 (33.3) Teratoma: 15 (50) Vital cancer: 11 (16.7)	None†	15 months
Öztürk et al. (2019) [7]	Lap.	Residual tumor <5 cm and not posterior to large vessels	89	Median 2.0 cm (range 0.5-7.0)	14 (15.7): technical difficulty in 7 pts., patient-related factors in 4 pts., ureter injury, aortic injury, IVC injury	9 (12)	Necrosis: 33 (37) Teratoma: 42 (47) Vital cancer: 14 (16)	7 (7.9)‡	91 months
Overs et al. (2018) [18]	RA	NSGCT: residual tumor >1 cm SGCT: residual tumor >3 cm	11	Median 2.0 cm (range 1.25-4.0)	None	1 (9): chylous ascites	Necrosis: 3 (27) Teratoma: 8 (73) Vital cancer: 0	None	4 months‖

Supplementary Table 1. Summary of Outcomes of Minimally Invasive PC-RPLND in Other Reports (continued)

Study	Procedure	Inclusion criteria	No. of patients	Residual tumor size	Conversion, *n* (%)	Postoperative complications, *n* (%)	RP histology, *n* (%)	RP relapse, *n* (%)	Median follow-up
Singh et al. (2017) [19]	RA	Normal markers, single residual tumor at landing zone <6 cm, or multiple tumors over IVC and aorta <5 cm, no organ involvement	13	Stage 2a: 7 pts. Stage 2b: 5 pts. Stage 2c: 1 pt.	None	4 (31): chylous ascites	Necrosis: 10 (77) Teratoma: 3 (23) Vital cancer: 0	None	23 months
Kamel et al. (2016) [20]	RA	NSGCT: normal markers, residual tumor ≥1 cm SGCT: residual tumor ≥3 cm / tumor <3 cm PET/CT positive	12§	≥5 cm: 10 pts. (83%)	1 (8): inferior mesenteric artery injury	None	Necrosis: 5 (45.5) Teratoma: 5 (45.5) Vital cancer: 1 (9)	None	31 months
Nicolai et al. (2016) [8]	Lap.	No previous RP surgery, unilateral disease since the beginning, residual tumor 1-5 cm, marker normalization, encasement of IVC/aorta <30% of circumference	67	Median: 2.7 cm <1 cm: 1 pt. (1.5%)	3 (4.5): extensive fibrosis involving IVC/ aorta in 2 pts., renal vein injury in 1 pt.	3 (4.5): retrograde ejaculation; blood transfusion; percutaneous drainage of lymphocele	Necrosis: 14 (20.9) Teratoma: 51 (76.1) Vital cancer: 2 (3.0)	None	21 months

Supplementary Table 1. Summary of Outcomes of Minimally Invasive PC-RPLND in Other Reports (continued)

Study	Procedure	Inclusion criteria	No. of patients	Residual tumor size	Conversion, *n* (%)	Postoperative complications, *n* (%)	RP histology, *n* (%)	RP relapse, *n* (%)	Median follow-up
Steiner et al. (2013) [9]	Lap.	No bulky disease	100	Mean: 1.4 cm <1 cm: 51 pts. (51%)	1 (1): vena cava injury	2 (2): fenestration of lymphocele and peritoneal venous shunt for chylous ascites	Necrosis: 60 (60) Teratoma: 38 (38) Vital cancer: 2 (2)	One patient, outside the surgical field	59 months
Steiner et al. (2013) [9]	Lap.	No bulky disease	100	Mean: 1.4 cm <1 cm: 51 pts. (51%)	1 (1): vena cava injury	2 (2): fenestration of lymphocele and peritoneal venous shunt for chylous ascites	Necrosis: 60 (60) Teratoma: 38 (38) Vital cancer: 2 (2)	One patient, outside the surgical field	59 months

IVC = inferior vena cava; Lap. = laparoscopic; NM = not mentioned; PET/CT = positron emission tomography / computed tomography; RA = robot-assisted; RP = retroperitoneum

* Including 7 patients (26%) with elevated markers at time of surgery.

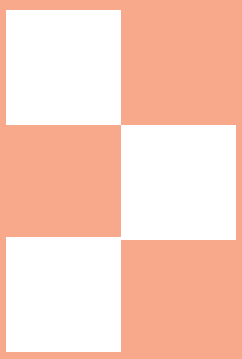
† Three patients relapsed at distant sites. Two of these had undergone desperation surgery with viable cancer in the retroperitoneum. The other patient had pulmonary metastases after pulmonary lobectomy and neck dissection in conjunction with PC-RPLND.

‡ Seven out of 8 relapses were in the retroperitoneum (author communication).

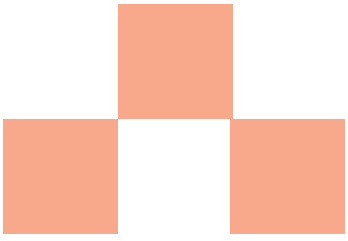
§ Including 3 patients with a seminoma primary.

| Long-term follow-up available for 6 patients. None of these patients had recurrence after 24 months of follow-up.

Part 3



Contralateral testicular germ cell tumor



8

Chapter

Dose-dependent effect of platinum-based chemotherapy on the risk of metachronous contralateral testicular cancer

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Abstract

Purpose

Patients with testicular germ cell tumor (TGCT) are at increased risk of developing a contralateral testicular germ cell tumor (CTGCT). Although some studies suggest that prior treatment with platinum-based chemotherapy affects CTGCT risk, a relationship between CTGCT risk and platinum dose has not previously been assessed. We analyzed the association between the number of platinum-based chemotherapy cycles and CTGCT risk.

Patients and Methods

The risk of developing a metachronous CTGCT was evaluated in a nationwide cohort of 4,755 patients diagnosed with primary TGCT in the Netherlands between 1989 and 2007. Standardized incidence ratios (SIRs) were computed to compare CTGCT incidence with expected TGCT based on TGCT incidence in the general population. The cumulative incidence of CTGCT was estimated in the presence of death as competing risk. The effect of treatment with platinum-based chemotherapy on CTGCT risk was assessed using multivariable Cox proportional hazards regression models.

Results

CTGCT was diagnosed in 136 patients (SIR 14.6; 95% CI 12.2 to 17.2). The cumulative incidence increased up to 20 years after primary diagnosis, reaching 3.4% (95% CI 2.8% to 4.0%) after 20 years of follow-up. The risk of developing a CTGCT decreased with age (hazard ratio [HR] 0.93; 95% CI 0.90 to 0.96), was lower after nonseminomatous germ cell tumor (HR 0.58; 95% CI 0.35 to 0.96) and decreased with every additional cycle of chemotherapy ($HR_{per\ cycle}$ 0.74; 95% CI 0.64 to 0.85).

Conclusion

Approximately one in every 30 TGCT survivors will develop a CTGCT, with CTGCT incidence increasing up to 20 years after a primary TGCT. Treatment with platinum-based chemotherapy shows a dose-dependent inverse association with CTGCT risk.

Introduction

Patients with a unilateral testicular germ cell tumor (TGCT) are at increased risk of developing a contralateral testicular germ cell tumor (CTGCT) [1–4]. The incidence of CTGCT in survivors of TGCT is approximately 12 to 18 times higher compared with general population rates, with a 20-year cumulative incidence between 2% and 5% [1,2,5,6]. This risk remains elevated for 10 to 20 years after the diagnosis of first TGCT [1,5,7].

A known risk factor for developing a CTGCT is diagnosis of a first TGCT before the age of 30 years [7–9]. The role of prior treatment with chemotherapy, however, is still unclear. Several studies have suggested a decreased risk of CTGCT in patients treated with platinum-based chemotherapy [1,2,5,10], while other studies found no clear effect [7,11,12]. This discrepancy might be a result of differences in duration of follow-up, availability of treatment data, and study methodology. So far, well-defined population-based cohort studies with full information on treatment are scarce.

Kleinschmidt et al. postulated the hypothesis of a dose-dependent association between chemotherapy and CTGCT risk on the basis of a study in 11 patients with TGCT and contralateral germ cell neoplasia in situ (GCNIS) who were treated with platinum-based chemotherapy [13]. In patients who received two cycles of chemotherapy, subsequent biopsies showed lower rates of GCNIS eradication, compared with patients who received three cycles.

This hypothesis was supported by Dieckmann et al., who found a dose-dependent effect of chemotherapy on GCNIS in a series of 96 patients who had been treated with chemotherapy [14]. However, a dose-dependent association between platinum-based chemotherapy and GCNIS eradication has not been investigated in larger cohort studies. Whether such a relationship exists is clinically relevant, as an increasing number of TGCT patients may receive lower doses of platinum-based chemotherapy now adjuvant therapy with one or two cycles of chemotherapy in high-risk stage I disease is gaining popularity [15,16].

We studied the incidence of CTGCT in a large population-based cohort of patients with TGCT. The primary aim was to evaluate the association between the number of platinum-based chemotherapy cycles and risk of CTGCT. Secondary aims were to analyze the incidence of CTGCT and the association between primary TGCT histology and CTGCT histology.

Patients & Methods

Data Collection

To assess various late effects of TGCT treatment, a multicenter cohort was established including 4,755 survivors of TGCT who were treated for TGCT before age 50 years between 1989 and 2007 in 11 Dutch hospitals. Patients were identified through hospital tumor registries and the population-based Netherlands Cancer Registry. Inclusion and exclusion criteria have been reported elsewhere [17].

A case-cohort design was used to facilitate efficient collection of detailed treatment data while allowing for the assessment of multiple treatment-associated outcomes. A hospital-stratified subcohort comprising 15% of the base cohort (25% in the coordinating hospitals Netherlands Cancer Institute and University Medical Center Groningen) was randomly selected and consisted of 783 patients with TGCT. For all patients, we retrieved data on relapses, CTGCTs, and vital status through chart review and linkage with the nationwide registry of histo- and cytopathology (PALGA) and the Netherlands Cancer Registry (complete up to 31 January 2018).

For all patients in the cohort who developed a CTGCT and all subcohort members, detailed treatment data were abstracted from medical records, including administered chemotherapy regimens and numbers of cycles for primary treatment as well as relapse treatment. Of note, 1,401 patients (30.7% of all patients in the present cohort) who were diagnosed with primary TGCT prior to 1996, were also included in a previous study on CTGCT [2].

Statistical Analysis

The study end point was metachronous CTGCT, defined as any TGCT in the contralateral testicle 2 months or more after diagnosis of the first TGCT. Time at risk started at 2 months after TGCT diagnosis and ended at date of CTGCT diagnosis, death, emigration, or most recent medical information. Contralateral GCNIS was not considered a CTGCT.

Number of chemotherapy cycles was analyzed both as a continuous and as a categorical variable. To allow a test for trend in categorical analysis, the average number of chemotherapy cycles within each category was used to denote category level. The average number of cycles for all patients with known number of cycles was used for the category denoting patients with an unknown number of cycles. The association between the histology of the primary TGCT and the histology of the CTGCT was assessed using multinomial logistic regression with three possible outcomes: no CTGCT, seminomatous CTGCT and nonseminomatous CTGCT.

The Fishers Exact test and Mann-Whitney U test were used for univariate analysis of categorical and continuous variables, respectively. The expected number of CTGCT was estimated using age-, calendar period-, and site-specific cancer incidence rates for the Dutch male population. Standardized incidence ratios (SIRs), absolute excess risk (expressed per 10,000 person-years), and corresponding 95% CIs were computed using standard methods [18]. Tests for homogeneity and trend of SIRs were performed within collapsed Poisson regression models.

The cumulative incidence of CTGCT was estimated in the presence of death as competing risk. Effects of TGCT treatment on CTGCT risk were assessed in multivariable Cox proportional hazard regression models. Treatment effects were entered in the models as a time-dependent variable, allowing a patient to add person-time to a different treatment category at the date of relapse treatment while accounting for the effects of other covariates where appropriate. Barlow's inverse probability weights were used to adjust the partial likelihood function for the case-cohort design [18].

Kaplan-Meier survival curves were constructed to compare survival with and without CTGCT. The association between the diagnosis of CTGCT and survival was analyzed in a Cox model, which included age, initial stage, histology of the first TGCT, and treatment with chemotherapy before CTGCT with CTGCT included as a time-dependent variable.

Analyses were performed using STATA statistical software (version 11; StataCorp LP, College Station, TX, USA) and $p<0.05$ was considered statistically significant.

Results

The cohort was composed of 2,612 patients with seminomatous germ cell tumor (SGCT; 54.9%) and 2,143 with nonseminomatous germ cell tumor (NSGCT; 45.1%, Table 1 and Supplementary Table 1). The majority of patients initially presented with stage I disease (65.6%). Median follow-up was 17.0 years (interquartile range [IQR] 12.7 to 22.0 years) for the entire cohort and follow-up was 20 years or more for 1,636 patients (34.4%).

In total, 161 patients were diagnosed with CTGCT, which was synchronous in 25 patients and metachronous in 136 patients (Supplementary Table 2). The median interval between primary TGCT and metachronous CTGCT was 6.1 years (IQR 3.6 to 9.4 years) and was similar for patients with SGCT and NSGCT ($p=0.090$). The interval between primary TGCT and CTGCT was less than 5 years in 41.2%, 5 to 9 years in 38.2%, 10 to 14 years in 15.4% and 15 to 20 years in 5.2% of CTGCTs. No CTGCTs were diagnosed beyond 20 years of follow-up.

SIR for a metachronous CTGCT was 14.6 (95% CI 12.2 to 17.2) times higher than the expected TGCT incidence on the basis of general population rates (Table 2). SIR decreased with follow-up duration (P_{trend} <0.001) and higher attained age (P_{trend} = 0.019; Supplementary Table 3), and was higher in patients with SGCT (SIR 22.1), compared with those with NSGCT (SIR 8.6; $P_{heterogeneity}$ <0.001).

The 10- and 20-year cumulative incidences of CTGCT were 2.4% (95% CI 2.0% to 2.9%) and 3.4% (95% CI 2.8% to 4.0%), respectively (Table 3). The 20-year cumulative incidence was 4.0% (95% CI 3.3% to 4.9%) after SGCT and 2.6% (95% CI 1.9% to 3.4%) after NSGCT. Patients diagnosed with a SGCT before 25 years of age had the highest 20-year cumulative incidence (8.7%; 95% CI 4.2% to 15.2%), whereas the 20-year cumulative incidence among patients with NSGCT diagnosed at age 35 years or older was only 1.0% (95% CI 0.3% to 2.3%). The cumulative incidence did not increase beyond 20 years of follow-up (Figure 1).

Table 1. Patient characteristics

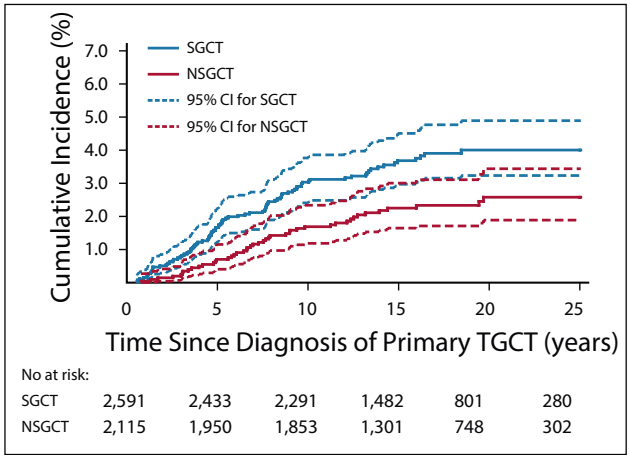
	Patients with CTGCT*	Subcohort	Total cohort
Patients, n (%)	136	783	4,755
Primary histology, n (%)			
NSGCT	45 (33.1)	390 (49.8)	2,143 (45.1)
SGCT	91 (66.9)	393 (50.2)	2,612 (54.9)
Median age at primary diagnosis, years (IQR)	29 (33-40)	32 (26-37)	33 (26-40)
Year of primary diagnosis			
1989-1998	55 (40.4)	353 (45.1)	2,141 (45.0)
1999-2007	81 (59.6)	430 (55.9)	2,614 (55.0)
Primary TNM stage, n (%)			
Stage I	114 (83.8)	518 (66.2)	3,120 (65.6)
Stage II	13 (9.6)	147 (18.8)	947 (19.9)
Stage III	9 (6.6)	118 (15.1)	668 (14.1)
Unknown	0	0	20 (0.4)
Platinum-based chemotherapy, n (%)	22 (16.2)	293 (37.4)	-
1-2 cycles	2 (9.1)	18 (6.1)	-
3 cycles	11 (50.0)	86 (29.4)	-
4 cycles	6 (27.3)	144 (49.2)	-
>4 cycles	3 (13.6)	38 (13.0)	-
Unknown	0	7 (2.4)	-
Type of platinum-based chemotherapy, n (%)	22 (16.2)	293 (37.4)	-
BEP	22 (100)	266 (90.8)	-
EP	0	6 (2.0)	-
VIP	0	5 (1.7)	-
Other †	0	16 (5.5)	-
Vital status, n (%)			
Alive	128 (94.1)	707 (90.3)	4,189 (88.1)
Dead	8 (5.9)	68 (8.7)	533 (11.2)
Lost to follow-up / emigrated	0	8 (1.0)	33 (0.7)
Median follow-up, years (IQR)	17.9 (13.4-21.7)	17.6 (13.4-22.9)	17.0 (12.7-22.0)

* 29 patients with CTGCT are also in the subcohort

† Other chemotherapy regimens: bleomycin, vincristine, cisplatin (n=4); paclitaxel, bleomycin, etoposide, cisplatin (n=3); VIP-bleomycin (n=2); cyclophosphamide, vincristine, carboplatin (n=2); carboplatin (n=1); cisplatin, vinblastine, bleomycin (n=1); cisplatin, vincristine, ifosfamide (n=1); bleomycin, vincristine, cisplatin, etoposide, ifosfamide and cisplatin (n=1); cisplatin, etoposide, carboplatin (n=1)

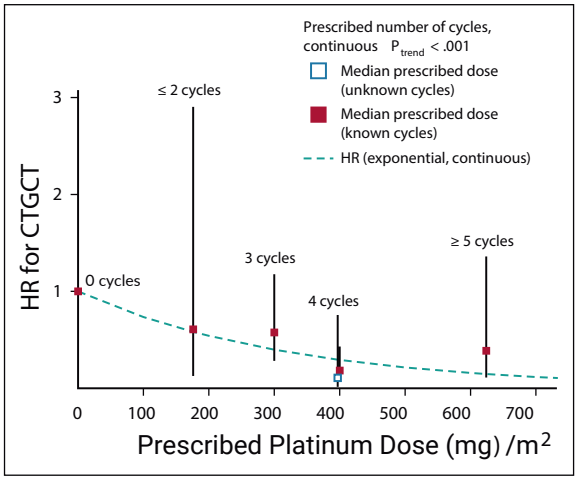
BEP = bleomycin, etoposide, cisplatin; CTGCT = contralateral testicular germ cell tumor; EP = etoposide, cisplatin; IQR = interquartile range; NSGCT = nonseminomatous germ cell tumor; SGCT = seminomatous germ cell tumor; VIP = etoposide, ifosfamide, cisplatin

Figure 1. Cumulative incidence of metachronous CTGCT according to primary TGCT histology



CI = confidence interval; CTGCT = contralateral testicular germ cell tumor; TGCT = testicular germ cell tumor; NSGCT = nonseminomatous germ cell tumor; SGCT = seminomatous germ cell tumor

Figure 2. Risk of developing CTGCT by prescribed platinum dose



Hazard ratios (HRs) for developing CTGCT by prescribed platinum dose compared with no platinum exposure. The black solid squares denote HRs for categories of dose and are plotted at the median prescribed dose (0, 176, 300, 400, 624 mg/m^2) within each category (0, ≤2, 3, 4, ≥5 cycles, respectively). The white square denotes patients with an unknown number of cycles, with the category plotted as the average dose for all patients with known number of cycles (397 mg/m^2). Vertical lines represent the 95% confidence intervals. The HRs were derived from the Cox-regression model with adjustment for age and primary histology (Table 4). The dotted line represents the association of platinum dose with CTGCT risk with platinum dose fitted as a continuous variable. This dose-response relationship was best described by an exponential model

CTGCT = contralateral testicular germ cell tumor; HR = hazard ratio

Table 2. SIR and AER of a metachronous CTGCT

	Person-time, *years*	CTGCT, *n*	SIR (95% CI)	AER (95% CI)
All patients	78,763	136	14.6 (12.2-17.2)	16.1 (13.3-19.2)
Age at primary diagnosis				
<25	14,522	31	11.0 (7.5-15.6)	19.4 (12.6-28.4)
25-34	32,220	79	17.1 (13.5-21.3)	23.1 (18.0-29.1)
≥35	32,019	26	13.8 (9.0-20.2)	7.5 (4.7-11.3)
P_{trend}			0.290	
$P_{heterogeneity}$			0.096	
Follow-up				
<5 years	22,095	56	19.5 (14.8-25.4)	24.0 (17.8-31.6)
5-9 years	21,582	52	17.8 (13.3-23.4)	22.7 (16.6-30.2)
10-14 years	17,689	21	9.9 (6.1-15.1)	10.7 (6.1-16.9)
≥15 years	17,397	7	4.9 (2.0-10.2)	3.2 (0.8-7.5)
P_{trend}			<0.001	
NSGCT	35,964	45	8.6 (6.3-11.6)*	11.1 (7.7-15.3)
Age at primary diagnosis				
<25	12,164	21	8.9 (5.5-13.6)	15.3 (8.8-24.5)
25-34	16,046	20	8.5 (5.2-13.1)	11.0 (6.1-17.8)
≥35	7,753	4	8.0 (2.2-20.4)	4.5 (0.8-12.6)
P_{trend}			0.817	
$P_{heterogeneity}$			0.973	
Follow-up				
<5 years	9,805	14	9.9 (5.4-16.6)	12.8 (6.4-22.5)
5-9 years	9,626	19	11.8 (7.1-18.4)	18.1 (10.2-29.2)
10-14 years	8,086	9	7.1 (3.2-13.4)	9.6 (3.5-19.6)
≥15 years	8,447	3	3.3 (0.7-9.7)	2.5 (-0.3-9.3)
P_{trend}			0.020	
SGCT	42,799	91	22.1 (17.8-27.1)*	20.3 (16.2-25.1)
Age at primary diagnosis				
<25	2,359	10	21.3 (10.2-39.2)	40.4 (18.3-76.0)
25-34	16,175	59	25.9 (19.7-33.4)	35.1 (26.4-45.6)
≥35	24,266	22	15.9 (10.0-24.1)	8.5 (5.1-13.2)
P_{trend}			0.182	
$P_{heterogeneity}$			0.130	
Follow-up				
<5 years	12,290	42	29.0 (20.9-39.2)	33.0 (23.5-45.0)
5-9 years	11,956	33	25.2 (17.4-35.4)	26.5 (17.9-37.7)
10-14 years	9,603	12	14.0 (7.2-24.4)	11.6 (5.6-20.9)
≥15 years	8,950	4	7.8 (2.1-20.1)	3.9 (0.6-10.9)
P_{trend}			<0.001	

* NSGCT primary vs. SGCT primary: $P_{heterogeneity}$ <0.001
AER = absolute excess risk; CI = confidence interval; CTGCT = contralateral testicular germ cell tumor; NSGCT = nonseminomatous germ cell tumor; SGCT = seminomatous germ cell tumor; SIR = standardized incidence ratio

Table 3. Cumulative incidence of a metachronous CTGCT

	Patients at risk, *n*		Metachronous CTGCT, *n*		Cumulative incidence, % (95% CI)	
	10 years	20 years	10 years	20 years	10 years	20 years
All patients	4,144	1,549	108	136	2.4 (2.0-2.9)	3.4 (2.8-4.0)
Age at primary diagnosis						
<25	750	284	20	31	2.5 (1.6-3.7)	4.6 (3.1-6.4)
25-34	1,667	681	66	79	3.7 (2.9-4.7)	4.7 (3.8-5.8)
≥35	1,727	584	22	26	1.2 (0.8-1.8)	1.5 (1.0-2.2)
Platinum-based chemotherapy						
Yes	896	341	18	22	1.2 (0.8-1.9)	1.7 (1.1-2.5)
No	3,248	1,208	90	114	3.3 (2.6-4.0)	4.4 (3.7-5.3)
NSGCT	1,853	748	33	45	1.7 (1.2-2.3)	2.6 (1.9-3.4)
Age at primary diagnosis						
<25	627	238	12	21	1.8 (1.0-3.0)	3.7 (2.3-5.6)
25-34	812	362	18	20	2.1 (1.3-3.3)	2.5 (1.6-3.8)
≥35	414	148	3	4	0.7 (0.2-1.8)	1.0 (0.3-2.3)
Platinum-based chemotherapy						
Yes	731	277	15	19	1.2 (0.7-2.0)	1.8 (1.1-2.8)
No	1,122	471	18	26	2.5 (1.5-3.8)	3.9 (2.6-5.6)
SGCT	2,291	801	75	91	3.0 (2.4-3.8)	4.0 (3.2-4.9)
Age at primary diagnosis						
<25	123	46	8	10	5.7 (2.7-10.4)	8.7 (4.2-15.2)
25-34	855	319	48	59	5.2 (3.9-6.7)	6.7 (5.2-8.6)
≥35	1,313	436	19	22	1.4 (0.8-2.1)	1.7 (1.1-2.5)
Platinum-based chemotherapy						
Yes	165	64	3	3	1.3 (0.4-3.5)	-
No	2,126	737	72	88	3.6 (1.8-4.4)	4.6 (3.7-5.7)

CI = confidence interval; CTGCT = contralateral testicular germ cell tumor; NSGCT = nonseminomatous germ cell tumor; SGCT = seminomatous germ cell tumor

The 20-year cumulative incidence was 1.7% (95% CI 1.1% to 2.5%) in patients who had been treated with platinum-based chemotherapy and 4.4% (95% CI 3.7% to 5.3%) in non-platinum-exposed patients. The time to CTGCT did not differ between patients treated with chemotherapy (median interval 4.9 years; IQR 3.0 to 6.6 years) compared with non-platinum-exposed patients (median interval 7.5 years; IQR 4.6 to 9.7 years; ***p***=0.23).

In multivariable analysis, the risk of developing a CTGCT decreased with age (hazard ratio [HR] 0.93; 95% CI 0.90 to 0.96) and was lower after a NSGCT primary (HR 0.58; 95% CI 0.35 to 0.96). Using the number of chemotherapy cycles as a continuous predictor, the risk of developing a CTGCT decreased with every additional cycle of chemotherapy (HR 0.74; 95% CI 0.64 to 0.85; Figure 2; Table 4). Patients treated with four cycles of chemotherapy had a much lower risk of CTGCT, compared with patients not treated with chemotherapy (HR 0.18; 95% CI 0.08 to 0.43; Table 4).

Table 4. Association of chemotherapy with CTGCT

	HR (95% CI)	**P-value**
Model 1		
Cycles of platinum-based chemotherapy*, *n*	0.74 (0.64-0.85)	<0.001
Model 2		
Cycles of platinum-based chemotherapy†, *n*		<0.001
None	Reference	
1-2 cycles‡	0.61 (0.13-2.90)	0.534
3 cycles	0.58 (0.28-1.18)	0.131
4 cycles	0.18 (0.08-0.43)	<0.001
>4 cycles§	0.39 (0.11-1.36)	0.139
Unknown‖	0.11 (0.02-0.76)	0.025

* As a continuous variable, corrected for age and primary histology
† As a categorical variable, corrected for age and primary histology
‡ Average of 1.76 cycles
§ Average of 6.24 cycles
‖ Average of 3.97 cycles
CI = confidence interval; CTGCT = contralateral testicular germ cell tumor; HR = hazard ratio

Most CTGCTs (71.3%) were of SGCT histology (Supplementary Table 2). Among patients with a SGCT primary, 76.9% of CTGCTs were of SGCT histology, whereas 60% of patients with a NSGCT primary had a CTGCT of SGCT histology. Compared with a patient with a seminoma primary TGCT, having a nonseminoma primary TGCT was associated with a lower risk of both a seminomatous CTCGT (odds ratio [OR] 0.33; 95%CI 0.20 to 0.56) and a nonseminomatous CTGCT (OR 0.28, 95% CI 0.13 to 0.62) and this risk reduction was of a similar magnitude for both histological CTCGT subtypes ($P_{heterogeneity}$ = 0.71).

The 5- and 10-years overall survival rates in patients with CTGCT were 96.7% (95% CI 91.5% to 98.8%) and 94.6% (95% CI 88.3% to 97.6%), respectively. A diagnosis of CTGCT was not associated with increased mortality on the basis of only eight deaths in the CTGCT group.

Discussion

This nationwide cohort study in relatively recently treated patients with detailed treatment information and complete follow-up for CTGCT shows that the risk of developing CTGCT decreases with an increase in the number of platinum-based chemotherapy cycles received. Patients with TGCT have an almost 15 times higher risk of developing a CTGCT, compared with the risk of developing TGCT in the general population. Approximately one in every 30 survivors of TGCT will develop a CTGCT within 20 years.

The literature on the association between treatment with platinum-based chemotherapy and CTGCT risk is conflicting. Several large studies found no association between receipt of chemotherapy and subsequent CTGCT risk. Fosså et al. analyzed Surveillance, Epidemiology and End Results (SEER) Program data, comprising approximately 30,000 patients diagnosed between 1973 and 2001, and found no clear association between initial chemotherapeutic treatment and CTGCT risk [5]. However, data on primary chemotherapy were incomplete and data on treatment received after the initial treatment were lacking completely.

A study in 2,201 Norwegian patients treated between 1953 and 1990 compared the risk of CTGCT between four types of treatment (radiotherapy versus chemotherapy versus radiotherapy with chemotherapy versus surgery or surveillance) and found no significant difference in relative risk between the treatment groups [7]. Of note, multivariable analysis was not performed in that study and a large proportion of the patients treated with chemotherapy may have received regimens without cisplatin, as this was only introduced in 1978.

In contrast, another Norwegian study showed that the cumulative incidence of CTGCT was 50% lower in patients with disseminated TGCT who were treated after 1980 compared with patients with localized TGCT, whereas the cumulative incidence of CTGCT did not differ between initial tumor stages in patients treated in 1953 to 1979 [1]. The authors concluded that the reduction in CTGCT incidence must have been a result of the introduction of platinum-based chemotherapy for disseminated TGCT in Norway in 1980, although no information about individual treatment was available.

The association between chemotherapy and CTGCT risk was substantiated in a previous study from our group, which had complete data on initial and subsequent treatment [2]. In this study, patients who were treated with platinum-based chemotherapy had a 2.9-fold reduction in CTGCT risk on multivariable Cox proportional hazards regression analysis. These findings suggest that chemotherapy is able to cross the blood-testis barrier.

Several smaller studies have suggested that the association between CTGCT risk and treatment with chemotherapy is dose-dependent. Dieckmann et al. analyzed the effect of chemotherapy in a study of 228 patients with TGCT with biopsy-proven contralateral GCNIS, of whom 96 patients were subsequently treated with chemotherapy [14]. A malignant event (defined as either GCNIS on re-biopsy or development of CTGCT) occurred in 50% of patients who had received one or two cycles of platinum-based chemotherapy. In patients who had received three or more cycles, however, a malignant event occurred in only 24% of cases.

In another series of 61 patients with TGCT with biopsy-proven contralateral GCNIS, the 5-year probability of developing CTGCT was significantly lower for patients treated with platinum-based chemotherapy (23%) than for nonexposed patients (54%) [19]. A dose-dependent association could not be proven due to insufficient statistical power, but the 7.5-years probability of CTGCT was 58% in patients who had received one to three cycles of chemotherapy, while this was only 22% in patients who had received four or more cycles. Our population-based cohort study substantiates these previous findings.

Most studies have reported a higher risk of developing CTGCT in patients with a SGCT primary compared with a NSGCT primary [2,5,8,9,20,21]; however, although the risk of CTGCT is influenced by age and treatment, only few studies have adjusted for these variables in their analyses. In the reports by Andreassen et al. and Schaapveld et al., the effect of primary histology diminished in multivariable analysis, but in the report by Fosså et al., patients with a NSGCT histology had a significantly decreased risk of CTGCT even after correcting for age, initial treatment, and extent of disease [1,2,5]. In the current study, we controlled for age and number of chemotherapy cycles and also found a lower risk of CTGCT in patients with a NSGCT primary.

A potential limitation of our study is the lack of information on history of undescended testis, testicular trauma, infertility, testicular atrophy, orchiectomy for nononcological conditions, or family history. It is unlikely that this lack of information has confounded the observed reduced risk of CTGCT associated with chemotherapy exposure, as these factors do not predict treatment of the primary TGCT. Another potential limitation is the lack of data on ethnicity. Although these data were not collected, the Dutch population is for approximately 90% of European, mainly White, descent. Therefore, our findings are not necessarily applicable to other populations.

An important strength of our study is that we have information on all treatment received before CTGCT diagnosis. In studies with data from population-based cancer registries, treatment is often misclassified because data on treatment during follow-up are incomplete. The availability of detailed information enabled us to evaluate the effect of platinum-based chemotherapy precisely. Another strength is the nationwide, multicenter, case-cohort design. This makes our study less prone to referral bias, which is an important weakness of single-center series.

The current study gives an accurate and comprehensive estimation of the risk of CTGCT. Our findings are important for clinicians to inform patients of their risk of developing CTGCT.

The possibility of developing a CTGCT does not warrant an extension of follow-up beyond 5 years, as the absolute risk of developing CTGCT beyond 5 years of follow-up is low. Nevertheless, patients with TGCT should be made aware that they are at increased risk of developing CTGCT for up to 20 years after diagnosis of the first TGCT.

In conclusion, treatment with platinum-based chemotherapy shows a dose-dependent association with lower risk of development of CTGCT. Patients who are diagnosed with SGCT before the age of 25 have the highest risk of developing a CTGCT. Incidence of CTGCT increases for up to 20 years after diagnosis of first TGCT, resulting in a CTGCT in approximately one in every 30 survivors of TGCT.

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Supplementary Table 1. Patient characteristics by histology

	NSGCT	SGCT
Patients, n (%)	2,143	2,612
Median age, years (IQR)	28 (23-34)	36 (31-43)
Primary TNM stage, n (%)		
Stage I	1,017 (47.5)	2,103 (80.5)
Stage II	565 (26.4)	382 (14.6)
Stage III	553 (25.8)	115 (4.4)
Unknown	8 (0.4)	12 (0.5)
Vital status, n (%)		
Alive	1,894 (88.4)	2,295 (87.9)
Dead	230 (10.7)	303 (11.6)
Lost to follow-up / emigrated	19 (0.9)	14 (0.5)
Median follow-up, years (IQR)	17.4 (12.8-22.5)	16.7 (12.6-21.6)

CTGCT = contralateral testicular germ cell tumor; IQR = interquartile range; NSGCT = nonseminomatous germ cell tumor; SGCT = seminomatous germ cell tumor

Supplementary Table 2. Characteristics of patients with a metachronous CTGCT

	NSGCT primary	SGCT primary	Total
CTGCT, n (%)	45	91	136
Primary TNM stage, n (%)			
Stage I	25 (55.6)	89 (97.8)	114 (83.8)
Stage II	11 (24.4)	2 (2.2)	13 (9.6)
Stage III	9 (20.0)	0	9 (6.6)
Platinum-based chemotherapy, n (%)	19 (42.2)	3 (3.3)	22 (16.2)
CTGCT histology, n (%)			
NSGCT	18 (40.0)	21 (23.1)	39 (28.7)
SGCT	27 (60.0)	70 (76.9)	97 (71.3)
Median time to CTGCT, years (IQR)	7.0 (4.8-11.2)	5.2 (3.3-9.1)	6.1 (3.6-9.4)
Vital status, n (%)			
Alive	42 (93.3)	86 (94.5)	128 (94.1)
Dead	3 (6.7)	5 (5.5)	8 (5.9)

Note: A previous contralateral biopsy was performed in nine patients with CTGCT. In six patients, germ cell neoplasia in situ (GCNIS) was found.
CTGCT = contralateral testicular germ cell tumor; IQR = interquartile range; NSGCT = nonseminomatous germ cell tumor; SGCT = seminomatous germ cell tumor

Supplementary Table 3. SIR and AER of a metachronous CTGCT by attained age

	Person-time, *years*	CTGCT, *n*	SIR (95% CI)	AER (95% CI)
All patients				
Attained age				
<30	8,649	22	14.5 (9.1-22.0)	23.7 (14.2-36.8)
30-39	22,846	83	18.9 (15.1-23.5)	34.4 (27.0-43.1)
40-49	25,385	23	8.7 (5.5-13.0)	8.0 (4.7-12.5)
≥50	21,965	8	10.1 (4.4-20.0)	3.3 (1.2-6.8)
P_{trend}			0.019	
Age at primary diagnosis				
<25 years				
Attained age				
<30	6,643	20	17.2 (10.5-26.6)	28.4 (16.6-44.7)
30-39	5,901	10	7.1 (3.4-13.1)	14.6 (5.8-28.8)
≥40	2,005	1	3.8 (0.1-21.0)	3.7 (-1.2-26.5)
P_{trend}			0.007	
25-34 years				
Attained age				
<40	17,021	68	22.2 (17.2-28.1)	38.1 (29.2-48.8)
40-49	11,956	10	7.3 (3.5-13.3)	7.2 (2.9-14.2)
≥50	3,272	1	5.4 (0.1-30.2)	2.5 (-0.5-16.5)
P_{trend}			<0.001	
≥ 35 years				
Attained age				
<40	1,929	7	26.1 (10.5-53.8)	34.9 (13.2-73.4)
40-49	11,495	12	11.8 (6.1-20.6)	9.6 (4.5-17.3)
≥50	18,620	7	11.6 (4.7-24.0)	3.4 (1.2-7.4)
P_{trend}			0.173	

CTGCT = contralateral testicular germ cell tumor; SIR = standardized incidence ratio; CI = confidence interval; AER = absolute excess risk

8a

Chapter

Does testicular seminoma involve a higher predisposition than nonseminoma to develop contralateral testicular tumors?

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Comment by K-P Dieckmann

To the editor

Blok et al [1] provide sound evidence for a dose-dependent reduction of the risk of contralateral tumors in patients with testicular germ cell tumors (GCTs) by cisplatin-based chemotherapy, which is an effect that has been hypothesized since decades.

Nonetheless, two of their secondary results need further consideration: first, the higher risk of bilateral tumors in patients with seminoma (in relation to nonseminoma); second, the reported zero risk of contralateral GCT (CGCT) after intervals of more than 20 years.

With respect to the first point, the authors report a higher absolute excess risk for CGCT in primary seminoma than in nonseminoma (absolute excess risk 20.3 v 11.1, $p < .01$). However, this finding is strikingly inconsistent with another finding in their report, the significantly increased risk of CGCT in patients younger than 25 years. It is basic knowledge that patients with nonseminoma are usually several years younger than their seminoma counterparts, which is also documented in the present study. So, the biological link between the two findings (greater predisposition of seminoma and predisposition of young age) is missing.

Furthermore, it is undisputed that all testicular GCT arise from the precursor lesion germ cell neoplasia in situ (GCNis) and contralateral testicular biopsies have shown the presence of contralateral GCNis in around 5%-6% of patients with unilateral GCT [2]. This figure correlates well with the prevalence of clinically detected CGCT as found in the present report and by others. Of note, all the major contralateral biopsy studies in patients with testicular GCT revealed only two relevant risk factors for the presence of GCNis (and thus for the development of CGCT): young age and testicular atrophy [3-5]. Histology of the primary tumor was not a significant factor in any of the studies. In fact, Ruf et al. observed a rate of 4.8% contralateral GCNis in patients with seminoma and 5.3% in patients without seminomas in a sample of 780 patients [6]. Two other studies comprising 1,956 and 2,318 patients reported slightly higher frequencies of GCNis in nonseminomatous primaries than in seminomas, respectively, although the differences were not significant, statistically [3,4]. These findings in contralateral GCNis represent the biologic bottom line for the development of second testicular tumors, and these data are clearly at odds with the purported predisposition of seminoma to develop CGCT.

The key to understanding this discrepancy between basic knowledge (equal prevalence of contralateral GCNis in seminoma and nonseminoma) and clinical findings (bilateral tumors more frequent in seminoma) probably lies in the main result of the study, that is, the protective effect of cisplatin-based chemotherapy regarding the development of CGCT. Patients with nonseminoma are younger than patients with seminoma, usually have higher clinical stages, and thus receive chemotherapy in a much higher proportion than patients with seminoma. Accordingly, the chemotherapy employed in many of these patients probably prevents the development of CGCTs. Noteworthily, the multivariable statistical analysis employed in the

study showed seminoma histology to be an independent factor for the development of CGCT. However, that result should at least be cautioned since it lacks a plausible biological explanation.

Second and briefly, there is sufficient evidence for the continuing risk of CGCT even after an interval of 20 years. We reported three such cases with intervals of 36, 25, and 21 years, respectively, and identified 22 additional cases in the literature [7]. The longest interval reported so far is 40 years. So, the risk of a CGCT does probably persist lifelong.

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8b

Chapter

Reply to K.P. Dieckmann

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Michael Schaapveld
Joost M. Blok

Reply to K.-P. Dieckmann

We thank Dr Dieckmann for his letter [1] in response to our recently published article [2]. Our study showed a higher absolute excess risk for developing a contralateral testicular germ cell tumor (CTGCT) in primary seminoma compared with primary nonseminoma [2]. This is in line with the main result of our study, namely, that receipt of platinum-based chemotherapy is associated with a dose-dependent decrease in the risk of developing a CTGCT, and the fact that platinum-based chemotherapy is offered in a higher proportion to patients with nonseminoma, to which Dr Dieckmann also alludes [1]. Our multivariable (cause-specific) analysis, however, also suggested that seminoma histology was associated independently with the development of CTGCT, mainly because of a somewhat higher risk of CTGCT in patients with chemotherapy-naive seminoma. This was also to some extent reflected by the 10-year cumulative incidence of CTGCT in patients without chemotherapy-naive seminoma, which was 2.5% compared with 3.6% in patients with chemotherapy-naive seminoma. We agree that this finding should be treated with some caution, as a biological explanation is not clear. Contralateral testicular biopsies are infrequently performed in the Netherlands, so we have no information on the presence of contralateral germ cell neoplasia in situ (GCNis) before treatment. Nonetheless, the 20-year cumulative incidence of CTGCT in chemotherapy-naive patients (3.9% in patients with nonseminoma v 4.6% in patients with seminoma) agrees well with a 5%-6% prevalence of GCNis in contralateral testicular biopsies of patients with unilateral testicular germ cell tumor. The distribution of the tumor histology of the CTGCT did not differ in patients with chemotherapy-naive nonseminoma (77.3% seminoma) compared with patients with chemotherapy-naive seminoma (76.9% seminoma, $p = 0.97$). In contrast, the CTGCT among chemotherapytreated patients with nonseminoma was predominantly of nonseminoma histology (63.2%) and CTGCT histology differed significantly between patients with chemotherapy-naive and chemotherapy-treated nonseminoma. The overrepresentation of seminoma CTGCT among patients with a nonseminoma germ cell tumor primary is interesting. As stated by Dieckmann,[1] it is known that patients with nonseminoma are usually several years younger than their seminoma counterparts. Could our data show that when our patients with nonseminoma age, they do tend to develop more often CTGCT with a seminoma origin as do their peers in the general population, while GCNis with nonseminoma delineation does develop into CTGCT less often? As yet it is actually unclear what proportion of contralateral GCNis would develop into CTGCT when left untreated. Cases of GCNis without progression to germ cell neoplasia after more than 10 years have been reported [3]. In addition, the number of actual CTGCT events in our study is also much larger than the number of contralateral GCNis (39) in the study of Ruf et al, [4] allowing (more) stable estimation of at least CTGCT risk in our cohort.

Regarding the Dr Dieckmann's second point, [1] we agree that CTGCT may occur more than 20 years after an index testicular cancer. Nonetheless, although in our study 1,636 patients had a follow-up of more than 20 years, we identified no such case. However, in a previous study, we indeed did observe that two of 39 CTGCTs among 1,675 patients with seminoma occurred more than 20 years after the index seminoma, with one CTCGT diagnosed 23.9 years after the index tumor [5]. In that study, among patients with nonseminoma none of the CTGCT occurred at an interval >20 years. Thus, although CTGCT may occur more than 20 years after a primary germ cell tumor, this at least appears to be a rare event.

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9

Chapter

General discussion and future perspectives

General discussion and future perspectives

The research presented in this thesis focuses on the treatment of testicular germ cell tumor (TGCT). The aim was to contribute to the improvement of:

1. The early identification of microscopic metastases (Part 1)
2. The outcome of surgical resection of postchemotherapy residual tumors (Part 2)
3. The knowledge of incidence of contralateral testicular cancer (Part 3)

Identification of microscopic metastases

The early identification of microscopic metastases is particularly important in TGCT since up to 30% of CS I patients who are treated with surveillance suffer from relapse. These patients had microscopic metastases in their lymph nodes at the time of first presentation, undetectable by current imaging protocols [1–3].

Patients who relapse are treated with three or four cycles of bleomycin, etoposide, cisplatin combination chemotherapy (BEP). In case of seminomatous germ cell tumor (SGCT), radiotherapy is also an option. Both treatment regimens are associated with serious short- and long-term side effects. Common short-term side effects of the BEP regimen are transient neutropenia, thrombocytopenia, neutropenic fever, pneumonitis, Raynaud's phenomenon and thromboembolic events (e.g. myocardial infarction and pulmonary embolism) [4,5].

Long-term side effects include secondary malignant neoplasms (SMN), cardiovascular disease (CVD), pulmonary damage, neuropathy, metabolic syndrome and worse cognitive function [6–8]. Patients treated with cisplatin-based chemotherapy have a 1.5 to 2-fold increased risk of SMN, including cancer of the lung, bladder, kidney and small intestine [6,9–12]. A Dutch cohort study found a 25-year cumulative incidence of SMN of 10.3%, with evidence for a dose-dependent relationship between chemotherapy and second cancers [10,13,14]. Possible explanations for the increased risk include a direct toxic effect of chemotherapy, malignant transformation of residual teratoma or unhealthy lifestyles of patients treated with chemotherapy [6,15]. Another possible mechanism is the storage of platinum, since active compounds of cisplatin have been detected in plasma for up to 20 years and in urine for up to 16 years after treatment completion [16,17].

After radiotherapy, patients have an approximately 1.5-fold increased risk of SMN, mainly cancer of the stomach, bladder, pancreas and prostate [6,11,12]. This risk is also dose-dependent, with an 8% increased risk of infradiaphragmatic cancer for each additional radiation dose increase of 1 Gy [10].

Cardiovascular disease is another possible late adverse effect of treatment with chemotherapy. Multiple studies found an increased risk of CVD after platinum-containing chemotherapy,

although these studies also included patients with outdated chemotherapy regimens (e.g. cisplatin, vinblastine, bleomycin combination chemotherapy) [18–20]. A recent study with data from the Danish Testicular Cancer database compared the outcomes of 5,185 TGCT patients with 51,850 men without TGCT and found that CVD risk is comparable to the general population after one year of treatment, but that after 10 years, patients have an increasing risk of myocardial infarction and CVD-associated death [21].

The association between radiotherapy and CVD is not entirely clear, although an association between mediastinal radiotherapy and CVD has been shown [6,18].

As a consequence of these late effects, patients treated with chemotherapy or radiotherapy have a higher risk of dying from non-TGCT causes, compared to the general population, and the relative survival of TGCT survivors continues to decline even beyond 30 years of follow-up [22,23].

The young age at diagnosis, high survival rate and long life-expectancy of TGCT patients have shifted the focus to minimization of treatment-related morbidity. This includes minimization of long-term toxicities caused by salvage therapy. Early identification of patients who will suffer from relapse enables treatment at the earliest possible moment with adjuvant therapy, instead of salvage treatment at the moment of relapse. Since there is evidence that the long-term side effects are dose-dependent, it is likely that this will reduce treatment-related morbidity [18].

Therefore, in recent years, the risk-adapted approach has gained recognition in CS I TGCT [24,25]. Patients with a high risk of microscopic metastases (thus a high risk of relapse) can be treated with adjuvant treatment. The identification of high-risk patients is currently based on histopathological features of the primary tumor specimen. Risk factors for SGCT are primary tumor size and invasion of the rete testis [26]. Patients with both risk factors have a relapse rate of ~30%, compared to 6% in patients without risk factors [25,27].

Adjuvant treatment for SGCT consist of one cycle of carboplatin chemotherapy. A prospective trial found that in high risk patients the relapse risk was 9.3% after adjuvant carboplatin, compared to 15.5% after surveillance [27]. Patients who relapse following adjuvant treatment with carboplatin can still be successfully treated with BEP chemotherapy [28]. Adjuvant radiotherapy is equally effective, yet associated with the development of second primary neoplasms and therefore only indicated if chemotherapy is not suitable [29,30].

In **Chapter 2** we systematically reviewed the literature on the two main histopathological risk factors in NSGCT: lymphovascular invasion (LVI) and presence of embryonal carcinoma (EC). Our meta-analysis confirmed that presence of LVI is the strongest predictor of microscopic metastases: 47.5% of patients with LVI have microscopic metastases and will relapse under surveillance [31]. Patients with LVI are four times more likely to harbor microscopic metastases,

compared to patients without LVI. EC is an additionally useful risk factor, but there is no agreement about the definition to be used (presence / absence vs. <50% / ≥50%).

For NSGCT, adjuvant treatment is based on one cycle of BEP. This reduces the relapse rate of patients with LVI to approximately 3%, suggesting that more than 90% of relapses are prevented by adjuvant chemotherapy [32,33].

The risk-adapted strategy reduces relapses and consequently decreases the number of patients needing toxic salvage therapy. Therefore, this approach is gaining popularity and included in the current European guidelines [34,35]. However, there is still some controversy. First, the risk-adapted strategy introduces overtreatment. After all, the fact that ~50% of high risk NSGCT patients will relapse under surveillance, indicates that ~50% of high-risk patients will not relapse under surveillance. Treating all high-risk patients leads to an overtreatment of half of high-risk patients. In case of SGCT, overtreatment is even higher: ~70% of high-risk patients will not relapse under surveillance. Second, the long-term side effects of adjuvant treatment are still unknown, since this is a relatively novel concept. However, there are side-effects of chemotherapy regardless of dose [29]. Third, long-term survival is expected in most cases of, irrespective of treatment strategy [36–39].

In an effort to base the selection of high-risk patients on the true presence of microscopic metastases, the sentinel node procedure for TGCT was developed at the Netherlands Cancer Institute. In this experimental procedure, the sentinel lymph nodes are resected and histopathologically examined. **Chapter 3** describes the outcome of this procedure in CS I TGCT. We found that the sentinel node procedure is feasible for the identification of microscopic metastases. None of the patients with a negative sentinel node had evidence of disease after a median follow-up of more than five years, although based on only 23 patients.

As suggested by our study, it is likely that the relapse rate in sentinel node negative patients is small. In this group, the number of follow-up visits may be reduced. It is even conceivable that retroperitoneal imaging can be omitted altogether in sentinel node negative patients. However, false-negative sentinel node procedures (patients who relapse in the retroperitoneum after a tumor-negative SN procedure) are the limiting factor for this approach and larger studies are necessary to confirm these hypotheses.

It is unknown how patients with a positive sentinel node should be best managed. One option would be to consider patients with a positive sentinel node as having high risk CS I disease and treat them with adjuvant chemotherapy. It should be noted that only the sentinel lymph nodes were resected and no complete retroperitoneal lymph node dissection (RPLND) was performed. Another option would be to manage these patients with surveillance.

We had initiated a multicenter prospective observational study to investigate the false negative rate of sentinel node biopsy (www.clinicaltrials.gov identifier: NCT03448822). Our prospect was

to include 87 CS I TGCT patients. However, this study unfortunately had to be terminated due to a lack of funding and poor enrollment.

Future perspectives

Both methods of identifying microscopic metastases (risk-stratification based on histopathological risk factors of the primary tumor or sentinel node resection) have their disadvantages. Risk stratification based on histopathological features of the primary tumor will always be a "game of chance". It is not based on the true presence or absence of microscopic metastases. This issue may be solved by the sentinel node procedure, but this entails an invasive procedure with non-negligible morbidity in a patient group in which ~70% will never relapse, and with excellent survival rates even after relapse. Current serum tumor markers (AFP, HCG, LDH) have no benefit in the early identification of patients with microscopic metastases since these markers will not be elevated (yet). Functional imaging modalities (i.e. FDG-PET) also have no benefit in diagnosing microscopic metastases and are only indicated in SGCT with retroperitoneal tumor larger than 3 cm [35].

Therefore, there is a clinical need for novel biomarkers with improved sensitivity and specificity. Recent developments have recognized microRNAs (miRNAs) as a great promise in the clinical management of TGCT [40,41]. MiRNAs are small single-stranded non-coding RNA molecules with a role in post-transciptional gene regulation [40]. They play a role in biological processes such as cell differentiation, tumor development and apoptosis and can be detected in blood serum [41].

Two clusters of miRNAs, miR-371-3 and miR-367-3p, seem to be the most promising biomarkers for TGCT. In particular miR-371a-3p is the most consistent marker with the highest sensitivity and specificity [40,42]. Multiple studies have shown that miR-371a-3p outperforms the classic tumor markers (HCG, AFP, LDH) for the primary detection of TGCT [43–46]. In a prospective study of 616 TGCT patients and 258 healthy controls by Dieckmann et al., miR-371a-3p showed a sensitivity, specificity and area-under-the-curve of 90%, 94% and 0.97, respectively [46]. In contrast, the sensitivity of the three classic markers combined was ~60% [40,46]. MiR-371a-3p was also expressed by TGCTs smaller than 10 mm and serum levels were correlated with clinical stage and primary tumor size, but it was not expressed by teratoma [46].

However, the initial diagnosis of TGCT is almost never difficult and microRNAs are unlikely to solve a clinical dilemma in this setting. A more promising feature of the miR-371-3 cluster is the potential for detecting metastatic disease. In the same study by Dieckmann et al., miR-371a-3p was significantly associated with clinical stage and response to treatment in a prospective study in 188 patients [46]. Patients with relapse had higher median levels, compared to controls, and levels dropped upon remission.

Although these initial data are promising, the clinical significance of elevated miRNA levels in CS I patients is not clear yet. So far, no large prospective trials evaluating the prognostic value

of miRNA levels have been published. A recent study in 151 CS I TGCT patients on surveillance (101 with SGCT and 50 with NSGCT) found no significant association between relapse and postorchiectomy miR-371a-3p levels or percent decline [47]. This suggests that miR-371a-3p is not a reliable marker to guide adjuvant treatment. However, some findings suggested that miR-371a-3p may be an early relapse maker: postorchiectomy levels rose as the drawing date approached relapse, conventional markers (HCG, AFP) were normal in 62% of relapses while miR-371a-3p was elevated in 94% of relapses, and the magnitude of miR-371a-3p elevation was correlated with disease burden [47].

Future studies are necessary to determine the threshold serum values, whether treatment is indicated in the case of high microRNAs with normal classic tumor markers and absence of relapse on imaging, and whether serial measurement of miRNAs is able to predict metastases before imaging or classic tumor markers. If this turns out be the case, this would have multiple advantages for TGCT management. First, reliable detection of microscopic metastatic disease enables treatment at the earliest possible moment. Perhaps these patients can be salvaged with regimens typically used in the adjuvant setting (e.g. one cycle of carboplatin in SGCT and one cycle of BEP in NSGCT). This would have substantial benefits in terms of short- and long-term morbidity. Second, early detection of relapse could result in better oncological outcomes. Third, miRNAs could reduce the intensity of follow-up protocols. They may, for example, lower the need for routine imaging studies, which would reduce radiation exposure and costs [48].

Before this is the case, we should rely on the current biomarkers for microscopic metastases in CS I TGCT (i.e. LVI and EC in NSGCT, tumor size and rete testis invasion in SGCT). Adjuvant treatment reduces macroscopic relapses and decreases the number of patients requiring toxic salvage therapy and should be offered to all high-risk patients.

Surgical resection of postchemotherapy residual tumors

Approximately one-third of patients who undergo cisplatin-based combination chemotherapy for metastatic nonseminomatous germ cell tumor (NSGCT) have significant residual retroperitoneal disease [49,50]. Histopathological analysis after postchemotherapy retroperitoneal lymph node dissection (PC-RPLND) for residual tumor in NSGCT patients shows fibrosis or necrosis in 40-50%, teratoma in 30-40%, and viable cancer in 10-20% of cases [51,52]. There are currently no validated methods to reliably predict the histology of a residual tumor. Therefore, PC-RPLND remains important in all patients with a significant residual tumor (> 1 cm) [53].

In **chapter 4**, we systematically reviewed the literature on the outcome of PC-RPLND in NSGCT. We found a weighted retroperitoneal relapse rate of 4.6% and 1.7% for open and minimally invasive resection, respectively. In the open procedures, the average retroperitoneal relapse rate was 3.1% after modified dissection and 6.1% after bilateral dissection. The higher relapse rates after open vs. minimally invasive and bilateral vs. modified dissection is likely due to selection bias.

Anatomical extent of PC-RPLND

There is an ongoing debate concerning the anatomical extent of PC-RPLND. The decision on the extent of the resection is in essence a balance between surgery-related morbidity and risk of retroperitoneal relapse.

Reducing treatment-associated morbidity is important in patients with postchemotherapy residual tumor, since they are relatively young and long-term survival is expected in most cases [22]. As stated before, histopathological examination of the retroperitoneal specimen shows necrosis only in approximately half of patients, which means that surgical resection is without oncological benefit in these cases [52,54]. Since relatively more patients are presenting with low-stage disease and chemotherapy is applied more often in patients with low-volume retroperitoneal metastases [55,56], it is likely that benign histology will be encountered more often, because this is especially common in patients with small residual tumors [54].

Over the years, these factors have led to the adoption of less morbid surgical approaches. Historically, all patients were treated with a full bilateral template resection [53]. Nowadays, there is general consensus that the resection template can be limited in patients with a small unilateral residual tumor [57]. Heidenreich et al. showed that a unilateral modified template resection is appropriate in the case of unilateral retroperitoneal disease in the primary landing zone of the affected testis (pre- and postchemotherapy) and the postchemotherapy residual mass is smaller than 5 cm [52]. A bilateral resection is recommended in the case of contralateral spread, inter-aortocaval location, or a residual mass >5 cm.

In **chapter 5** we compared the outcome of template-based resection (TBR) to residual mass resection (RMR). We found a higher retroperitoneal relapse rate after RMR (5.9%), compared to

TBR (3.9%), which was also reflected in a higher five-year cumulative incidence of retroperitoneal relapse (RMR: 4.2%, TBR: 3.0%). In addition, a higher proportion of patients in the RMR group required a redo-resection for incomplete resection (6.5%), compared to the TBR group (1.5%). Four out of thirteen patients with retroperitoneal relapse died of disease (~30%).

These findings show that RMR is a less appropriate technique, compared to TBR. The goal of PC-RPLND is to resect all residual retroperitoneal metastases, macroscopic and microscopic, to prevent future tumor growth. The higher rate of retroperitoneal relapse and higher rate of redo-resection suggest that resection of the residual tumor only is less sufficient. These findings are in line with previous studies, which have shown that a more extensive resection decreases the risk of retroperitoneal relapse and that completeness of resection is a strong predictor of progression-free survival and overall survival [58–62]. In addition, the current EAU guidelines advise against RMR (lumpectomy) [35]. Thus, it is necessary to also resect macroscopically healthy tissue to decrease the relapse risk.

Although our study showed that RMR in all patients is not an appropriate approach, there may still be an indication for RMR in a selected group of patients. After all, patients with a single retroperitoneal tumor have no benefit of a more extensive resection. Future studies are necessary to identify this group of patients. A possible approach for such a study would be to perform RMR followed by TBR in the same surgical setting. Separate histopathological analysis of the surgical specimen can reveal which patients had vital cancer or teratoma outside the surgical field of RMR.

Additional procedures

PC-RPLND is an extensive procedure with serious peri-operative morbidity. In **chapter 6** we described the morbidity of this procedure in a cohort of two intermediate-volume hospitals. An additional surgical procedure was necessary in 27% of patients. The most common interventions were nephrectomy (7.3%) and inferior vena cava (IVC) resection/reconstruction (6.5%). The assistance of a vascular surgeon was necessary in 16% of procedures. The majority of interventions was necessary to achieve adequate tumor resection (63%) but a substantial portion was due to an intraoperative complication (37%, e.g. vascular lesion).

A quarter of patients had a postoperative complication Clavien-Dindo Grade ≥II [63]. The risk of postoperative complication was higher in patients undergoing an additional intervention (odds ratio 3.46; 95% confidence interval 1.03-11.60).

An interesting finding is that the rate of additional interventions in our series is comparable to what has been reported in high-volume centers [52,64–67]. This suggests that whether an additional procedure is necessary depends mainly on patient and tumor characteristics, and to a lesser degree on surgical volume. This is in line with the finding that two-thirds of additional procedures were necessary to achieve adequate tumor resection.

Accurately predicting the morbidity of PC-RPLND is of clinical importance, since it is an important aspect of decision making and patient counseling. It also enables the surgeon to take the necessary preparations (e.g. schedule more operating time, notify vascular surgeon to either stand-by or scrub in from the start of the procedure). Especially with the increasing acceptance of minimally invasive procedures, this can be a deciding factor between an open or minimally invasive approach. After all, a major intraoperative complication during a robot-assisted procedure can be difficult to deal with. If a complication can't be repaired robotically, the unsterile surgeon needs precious time to undock the robot and return to the operating table for a laparotomy [68].

We found that International Germ Cell Cancer Collaborative Group (IGCCCG) intermediate/poor prognostic group and residual tumor size larger than 5 cm were associated with additional surgical intervention on multivariable analysis. This is in line with several previous studies [65,66,69]. The exact nature of the role of IGCCCG prognosis (which is determined prior to chemotherapy) is not yet clear. It is possible that IGCCCG can be seen as a proxy of tumor aggressiveness and a more aggressive tumor is more likely to invade surrounding structures, increasing the risk of postchemotherapy residual tumor in these areas. Another possible explanation is a more severe desmoplastic reaction in patients treated with more cycles of chemotherapy. After all, intermediate and poor risk patients are generally treated with four cycles of cisplatin-based chemotherapy instead of three [35]. Whether the higher risk of an additional procedure is due to worse tumor characteristics or extra chemotherapy cycles remains unclear.

In our study, all tumors were adjacent to the site of additional intervention. A recent study found that degree of circumferential involvement of the great vessels is the single independent predictor of major vascular surgery (vena cava or aortic replacement/reconstruction) [70]. Other clinical characteristics (e.g. IGCCCG prognostic group and residual tumor size) were not significant on multivariate analysis. Another study found that the presence of aorta-tumor contact angle ≥64° or cava-tumor contact angle ≥98° are predictive of major vascular surgery (caval or aortic replacement/reconstruction) [71]. These recent findings suggests that a preoperative CT scan may be sufficient to identify patients in whom an additional intervention is necessary.

It is possible that a preoperative CT scan is already sufficient to predict the necessity of an additional intervention in most cases. Other prognosticators, such as IGCCCG group and residual tumor size, can alert the surgeon to pay extra attention to the preoperative images and may play a role in case of doubt.

Resection of adjacent visceral or vascular organs is not always of oncological benefit. A recent study (presented as an abstract) analyzed the tumor histology in resected organs in a cohort of 235 patients undergoing PC-RPLND with an additional resection [72]. The resected organs contained necrosis only in 40% of cases which means that the additional resection was without oncological benefit in these patients.

Minimally invasive PC-RPLND

The minimally invasive approach is gaining recognition in the postchemotherapy setting. The main advantages are reduction of morbidity, shorter hospital stay and improved cosmetic outcome. Additional advantages of robot-assisted surgery are 360° movement of instruments, ability of three dimensional vision, better surgeon ergonomics, and accuracy and stability in confined spaces [68,73,74]. The main criticisms concerns oncological outcome, difficulty to repair major intraoperative vascular complications and increased costs in the case of robotic surgery [68].

Although multiple large series have shown excellent oncological outcomes after laparoscopic PC-RPLND, high volume series on robot-assisted PC-RPLND are still lacking [75,76]. In **chapter 7** we evaluated the outcomes of RA-RMR in 45 patients and showed that none of the patients had evidence of disease after a median follow-up of 3 years. However, five procedures had to be converted to an open procedure due to an intraoperative complication or technical difficulty. We concluded that the minimal invasive approach is an appropriate treatment option in selected patients.

Future perspectives

Promising initial results and the continuous evolvement of surgical techniques suggest that minimally invasive surgery may replace open PC-RPLND in selected patients. The most important condition for the acceptance of minimally invasive techniques, is the warranty of oncological safety. Therefore, minimally invasive PC-RPLND should adhere to the same principles of open PC-RPLND in indication and extent. The data on minimally invasive PC-RPLND are not yet mature enough to draw firm conclusions regarding the oncological safety. This is especially the case in case of robot-assisted surgery; the current studies are too small with too short follow-up time.

However, it is unlikely that all open procedures will be replaced by minimally invasive surgery. Open surgery still is the preferred approach in case of high risk of an intraoperative complication (e.g. infiltration or casement of the large vessels) or if an additional surgical intervention is indicated. An important disadvantage of robot assisted surgery is the distance between the surgeon and the patient. This makes repairing a major vascular complication challenging, as the unsterile surgeon needs costly time to undock the robot, scrub and return to the operating table for a laparotomy [68].

On the contrary, the criteria for a minimally invasive procedure are dynamic instead of fixed. The continuous evolvement of surgical techniques, surgeons' experience and technological innovations will expand the indication of the minimally invasive approach even further. For example, the feasibility of laparoscopic PC-RPLND with vascular reconstruction in patients with a residual tumor infiltrating the large vessels has been shown, as well as bilateral template dissection without patient repositioning [77,78]. For the postchemotherapy setting, the decision between a minimally invasive or open procedure depends on the patient and tumor

characteristics, but to a great extent also on the capabilities of the urologist. The safety of a minimally invasive resection of more challenging residual masses will depend to a great extent on the development of new robotic techniques for major vascular surgery.

It is feasible that the improved perioperative outcome of minimally invasive RPLND will expand its indication also in the primary setting for patients with clinical stage IIA or IIB. There is an ongoing debate regarding the best management for these patients with low volume metastatic disease. As stated before, the high survival rates of testicular cancer shift the focus to reduction of treatment-related toxicity. In a way, there is a compromise between toxicity of chemotherapy and morbidity of RPLND [79,80]. The minimally invasive approach lowers the morbidity of RPLND, which favors primary RPLND instead of toxic chemotherapy.

Primary RPLND already plays an important role in marker-negative CS IIA/B. According to the EAU guidelines, these patients should be treated with either nerve-sparing RPLND or follow-up for 6 weeks [35]. A recent analysis from Indiana University found that 81% of patients with marker negative pathological stage II disease were cured with RPLND alone [81].

In the same way, minimally invasive primary RPLND can play an increasing role in the case of relapse after surveillance for clinical stage I disease. In a retrospective study in selected patients with stage II relapse after surveillance for stage I NSGCT, 73% of cases were successfully treated with RPLND alone [82]. Patients who received only RPLND had tumor marker stage S0 or S1. Serum tumor marker elevation on relapse was the only factor associated with requiring further therapy after RPLND: 18% of S0 patients needed additional treatment after RPLND, compared to 53% of S1 patients [82]. This suggests that RPLND can be considered for CS I patients who relapse in the retroperitoneum with negative or mildly elevated markers, since it prevents the toxicity of chemotherapy in a substantial portion of patients.

RPLND may also play an increasing role in CS IIA/B SGCT patients. Currently, its indication is limited, as these patients are primarily treated with chemotherapy or radiotherapy [35]. Data is limited to small case series (<20 patients) but two prospective studies are underway to evaluate the efficacy of primary RPLND for CS II SGCT. The SEMS (Surgery in Early Metastatic Seminoma) trial was a multicenter phase II trial in patients with pure testicular SGCT, either stage I with an isolated relapse <3 cm or stage 2 with a maximum of 2 retroperitoneal lymph nodes no larger than 3 cm [83]. Tumor markers were required to be normal. A total of 55 patients were included and all were treated with open RPLND. The 2-year recurrence-free survival was 82% and overall survival was 100%. All patients with relapse were successfully treated with chemotherapy or additional surgery.

The PRIMETEST trial included CS II patients with <5 cm retroperitoneal metastases and CS I patients with relapse after adjuvant chemotherapy [84]. Patients are treated with open or robot-assisted RPLND and the study aims to include 30 patients. A planned interim analysis of 22 patients found that 5 out of 22 patients (23%) developed a relapse, which was out-of-field

in 4 out of 5 cases. All patients with relapse were successfully treated with chemotherapy or radiotherapy.

Although we have to wait for the final results, these outcomes suggest that there is a role of primary RPLND in CS II/A SGCT. If these preliminary results hold up in the final analyses, the benefit will be that a substantial portion of patients can be treated without chemotherapy or radiotherapy. This has significant short- and long-term benefits.

A clinical dilemma is the treatment of marker negative CS IIA (i.e. retroperitoneal tumor smaller than 2 cm). Deciding on the appropriate treatment can be challenging in these cases, since 40% of patients have no viable GCT or teratoma while there is no biomarker that can reliably predict the nature of the retroperitoneal tumor [85]. In case of viable GCT, chemotherapy or radiotherapy is the appropriate option; in case of teratoma, surgery is the preferred option. In addition, these tumors could be inflammatory, infectious or related to another malignancy (e.g. lymphoma) [86]. Current guidelines suggest an observation period for six to eight weeks and advise that treatment should only be initiated if the diagnosis is clear (i.e. biopsy, tumor growth or marker rise) [35]. There is a clear need for biomarkers that can distinguish between viable GCT, teratoma and necrosis / fibrosis.

MicroRNAs may have the potential to solve this unmet need. In an analysis of 12 CS I and 12 CS II patients with SGCT and NSGCT undergoing primary RPLND, miR-371a-3p levels were correlated with the presence or absence of GCT [87]. The sensitivity (100%) and specificity (92%) were high, and area-under-the-curve of the ROC was 0.96 for distinguishing viable GCT from pure teratoma or benign histology. MiR-371a-3p levels were also elevated in case of retroperitoneal viable GCT without elevated classic tumor markers [87]. Similar findings were found in another study of 41 patients with moderate risk for GCT metastasis (CS IB NSGCT, CS I suspicious of relapse or postchemotherapy with low makers) [88]. None of the patients had elevated markers or bulky tumor on imaging and miR-371a-3p was elevated in 11 out of 12 patients with confirmed relapse (sensitivity 92%). MicroRNA assessment outperformed CT imaging and tumor marker assessment with an area-under-the-curve of the ROC of 0.89.

Further studies are necessary to confirm the role of microRNAs in this particular setting. If microRNAs are indeed useful to predict the presence or absence of vital GCT, this has the potential to alter the treatment algorithm of marker negative CS IIA patients. Patients with high microRNA levels for vital GCT may undergo salvage treatment, whereas patients with normal levels may be treated with surveillance. Patients with normal levels but growing lesions can be treated with surgery, since they are suspect of teratoma. In case of a stable or shrinking lesion, no salvage treatment is necessary and these patients can be treated with surveillance.

It has been suggested that the level of microRNA correlates with tumor burden [47]. If this can be validated in other studies, this also has the potential to alter the treatment algorithm for metastatic disease. Perhaps patients with low volume metastases and low microRNA levels

can be sufficiently treated with local therapy (surgery or radiotherapy), while patients with high volume and high microRNA levels still undergo systemic chemotherapy [48].

Another unmet need in TGCT care is the assessment of residual tumor after treatment with systemic chemotherapy. As stated before, PC-RPLND is without oncological benefit in approximately 50% of patients, since they have only necrosis or fibrosis in their retroperitoneal specimen. The role of functional imaging modalities (i.e. FDG-PET) is limited to SGCT patients with a residual tumor >3 cm [35]. In this setting, the negative predictive value of FDG-PET is high (~90%), but the positive predictive value is low (~30%) and current guidelines warn against using FDG-PET as a single parameter to drive clinical decisions [35,89,90]. Reliable biomarkers that can distinguish clinically relevant tumor (i.e. viable GCT or teratoma) from clinically non-relevant tumor (i.e. necrosis or fibrosis) are needed.

Several efforts have been made to develop imaging techniques that can predict the histology of residual tumors. For example, an exploratory trial is being conducted to assess the usefulness of the new radiotracer Gallium-68 in several cancer types including testicular cancer (NCT04459273) [91].

Another example is the field of radiomics. This emerging field in radiology uses machine learning to extract quantitative data from medical images in order to create characteristic profiles of tumors [91]. The data can be used for decision support. One retrospective study in eighty NSGCT patients undergoing PC-RPLND found that a machine learning classifier was able to distinguish benign from malignant tumor with an accuracy of 0.81 (sensitivity 88%, specificity 72%) [92].

Another promising area to predict the histology of residual tumor, are, again, microRNAs. In addition to the prediction of retroperitoneal histology of chemotherapy-naïve marker negative CS IIA patients, microRNAs may be able to identify patients with residual tumor after chemotherapy that benefit from additional treatment.

In a retrospective study of patients undergoing PC-RPLND, patients harboring necrosis or teratoma showed decreasing serum levels of miR-371a-3p after chemotherapy, whereas those with viable GCT showed little change [93]. Out of several other microRNAs, miR-371a-3p demonstrated the best accuracy to distinguish viable GCT from necrosis and teratoma (AUC 0.874). In a subgroup of 39 patients with residual tumor smaller than 3 cm, sensitivity, specificity and negative predictive value was 100%, 54% and 100%, respectively. This suggest that low levels of miR-371a-3p indicates absence of viable GCT in the retroperitoneum [93].

The low levels of miR-371a-3p in teratoma can create a clinical dilemma, since PC-RPLND is also indicated in these patients. Fortunately, multiple efforts are underway to identify specific markers for teratoma. In a recent study in 48 patients treated with PC-RPLND, the combination of miR-371a-3p and miR-375-5 was able to distinguish viable GCT and teratoma from necrosis/fibrosis, with a sensitivity, specificity and AUC of 94%, 94% and 0.94, respectively [94].

It is encouraging to see that studies evaluating the role of microRNAs are being initiated. For example, the prospective S1823 clinical trial (NCT04435756) is currently accruing early and advanced stage TGCT patients across North America with the goal to validate the clinical usefulness of miR-371a-3p in predicting tumor relapse [86]. At the UMC Utrecht, we established the Germ Cell Tumour Biobank (bioGCT) in 2019 to prospectively collect patient samples and data with the objective of identifying and validating novel biomarkers in TGCT.

Centralization of retroperitoneal lymph node dissection

The annual number of RPLND procedures is decreasing [95,96]. In Germany, the RPLND caseload (including primary RPLND) has reduced by 38.7% in the years 2006 to 2015 [96]. This is partly due to the diminishing role of primary RPLND in the last decades [96]. Current EAU guidelines recommend surveillance or adjuvant chemotherapy in CS I TGCT patients and primary RPLND is only recommended in the highly selected subgroup of pT2-pT4 NSGCT patients with contraindication to adjuvant chemotherapy and unwilling to accept surveillance [35]. Also, in the PC-RPLND setting, there is a shift towards surveillance in patients with residual tumors <1 cm.

Another reason for the decreasing incidence of PC-RPLND is the increasing acceptance of adjuvant chemotherapy in CS I. After all, fewer patients suffering from retroperitoneal relapse likely equals fewer patients needing PC-RPLND.

Due to the complexity of the procedure and the decreasing caseload, centralization of RPLND is important. However, most procedures are still performed by low-volume surgeons. Case log data from urologists seeking recertification with the American Board of Urologists shows that the median annual number or RPLNDs per surgeon in the USA between 2003 and 2013 was only one procedure. Of the urologists that performed at least one RPLND, 75% logged only one procedure and three urologists logged 23% of all RPLNDs [97]. Additional data shows that more than half of RPLNDs in the USA are performed at hospitals with ≤2 procedures per year [98].

In the UK, the median number of RPLNDs per surgeon is six [99]. In Germany, 43% of RPLNDS between 2006 and 2015 were performed at a low-volume center (<4 cases annually) [96]. Although there was a modest trend towards centralization and the number of low- and intermediate volume centers declined over the years, only 18% of all 382 RPLNDs in 2015 were performed in a high-volume center (>10 cases annually).

RPLND is an extensive, challenging and potentially morbid procedure with a long learning curve. To improve perioperative outcome, urologic surgeons performing these procedures should have sufficient training and experience. The centralization of RPLND care is important to improve national outcome measures.

Also in the Netherlands, there is still room for improvement. Currently, there are at least five centers performing PC-RPLND but these are not actively recorded by the Dutch Urological

Society (Nederlandse Vereniging voor Urologie, NVU). The 2017 quality standards of the NVU state that a center offering RPLND should perform at least ten procedures annually [100]. In light of the potential case load and the relatively short distance between the various centers, this minimum number of annual procedures is rather low. There are 800 patients diagnosed with TGCT in The Netherlands each year. Assuming that 20% has to be treated with chemotherapy and in 30% of those have postchemotherapy residual tumor, approximately 50 patients require PC-RPLND annually. To improve outcome, these patients should be centralized in only two or three centers. A first step would be recording the number of RPLNDs per center and per urologist in a case log system.

Contralateral testicular cancer

In **chapter 8** we evaluated the long-term risk of contralateral testicular germ cell tumor (CTGCT). We found that the patients with TGCT have an almost 15 times higher risk of developing a CTGCT, compared to the general population. Approximately one in every 30 patients will develop a CTGCT within 20 years. Furthermore, we found that the risk of developing CTGCT decreases with an increasing number of platinum-based chemotherapy cycles received. The 20-year cumulative incidence was highest in patients who were diagnosed with SGCT at age <25 years (8.7%) and lowest in patients who were diagnosed with a NSGCT at age ≥35 years (1.0%).

Earlier studies have shown conflicting results regarding the association between chemotherapy treatment and CTGCT risk. Some studies found no association between the two, although those studies had either incomplete data on primary treatment, no data on subsequent treatment or performed no multivariable analysis [101,102].

Frankly, our study was published simultaneously with another large study on cisplatin and CTGCT [103]. This study in 5,620 Norwegian men found comparable risk and incidence rates, and also found an association between treatment intensity and CTGCT. The risk of developing CTGCT was significantly reduced after more than two cisplatin-based chemotherapy cycles. Other significant predictors were age and primary histology: CTGCT risk was higher in patients aged <30 years and patients with SGCT primary. These results are in line with our findings.

Our findings are useful in daily clinical practice. Patients should be accurately informed about their increased risk of CTGCT, preferably according to age at primary diagnosis, primary histology and initial treatment. The risk of developing a CTGCT does not warrant an extension of follow-up beyond 5 years in all patients, since the absolute risk in the entire population is low and testicular tumor can be found with self-examination. The lower risk of CTGCT after chemotherapy also does not warrant expanding the indication of adjuvant chemotherapy, since the absolute reduction in cumulative incidence is very low (2-4%) and treatment with 1-2 cycles of chemotherapy probably does not affect the risk of developing CTGCT. Nevertheless, it is important that patients are aware of their increased risk of developing CTGCT and the importance of self-examination way beyond their final follow-up visit.

There remains a controversy whether or not SGCT patients have a higher risk of CTGCT, compared to NSGCT patients. This is also addressed in the letter by Professor Dieckmann **(chapter 8a)** and our reply **(chapter 8b)**. Our multivariable analysis showed that SGCT histology was an independent predictor of development of CTGCT. In addition, the 10- and 20-year cumulative incidences were higher in chemotherapy-naïve SGCT patients, compared to chemotherapy-naïve NSGCT patients. However, there is no biological explanation and other studies on contralateral biopsies have found a higher incidence of germ cell neoplasia in situ (GCNIS) in patients with a NSGCT primary [104,105]. It is possible that the higher risk of CTGCT after SGCT is actually a reflection of treatment with chemotherapy, which is applied more

in NSGCT patients (especially during the treatment period of our study). The role of primary histology in CTGCT risk is an interesting area for further work. Our study provides evidence that cisplatin is able to cross the blood-testis barrier. This is substantiated by earlier findings of decreased sperm concentration and quality and changes in sperm DNA following cisplatin-based chemotherapy [103,106,107]. Therefore, a likely mechanism of the lower incidence of CTGCT after chemotherapy is that cisplatin is able to eradicate germ cell neoplasia in situ (GCNIS), the precursor of invasive TGCT. According to our and other studies, a certain dosage threshold of cisplatin needs to be met.

Future perspectives

A possible explanation for the higher risk of developing CTGCT, compared to the general population, is the testicular dysgenesis syndrome. The precise mechanism of TGCT (and CTGCT) development remains to be elucidated. Future studies on the etiological factors are necessary.

The role of contralateral biopsy in patients with TGCT is still a matter of controversy [108]. Current guidelines do not recommend routine biopsy in all patients but advice discussing the risks and benefits with the patient in case of high risk of contralateral GCNIS [35,109]. Patients considered high risk are those younger than 40 years old, with testicular volume smaller than 12 mL and/or a history of cryptorchidism. If contralateral GCNIS is found, radiotherapy can be offered but this will result in infertility and risk of Leydig cell insufficiency in case of solitary testis [35].

The prevalence of contralateral GCNIS is approximately 5%, but there is debate regarding its clinical relevance [108]. Approximately 50% of GCNIS cases will progress to invasive TGCT within 5 years, but there is no agreement whether all cases will do so in the long term [105]. In addition, patients with negative biopsy can still develop TGCT [110]. The higher prevalence of GCNIS in younger patients has led to the hypothesis that there is a continuously degradation process of GCNIS [108,111]. Tumor degradation and burned-out tumors are well-known phenomena in TGCT and it is conceivable that this is also possible in case of GCNIS. Nevertheless, it is important to diagnose contralateral GCNIS before progression to invasive TGCT, since GCNIS can be treated with preservation of the testicle [108].

The risk of CTGCT does not warrant expanding follow-up protocols in all patients. But a greater knowledge on the risk factors for CTGCT may be beneficial. New predictive models (combining clinical, histopathological and biomarker parameters) could help to identify patients who are at high-risk of harboring contralateral GCNIS. Combined with a better understanding of the clinical relevance of GCNIS, a more specific subgroup of patients that would benefit from contralateral biopsy and subsequent treatment could be identified.

Summary of future perspectives

Novel biomarkers

MicroRNAs have the potential to solve several clinical dilemmas in TGCT care: the identification of microscopic metastases in CS I, prediction of the histology of the retroperitoneal tumor in CS IIA/B, and prediction of histology of the residual tumor in patients treated with chemotherapy. In addition, novel biomarkers may lead to a subdivision between low-volume and high-volume metastatic disease, in which the first group may be treated with local instead of systemic treatment (e.g. RPLND). Several hurdles have to be taken before biomarkers can be adopted in daily clinical practice, including validation in large prospective trials, consensus on cut-off values and standardization of testing methods.

RPLND

There will be an increasing acceptance of minimally invasive techniques. This will expand the indication for RPLND. Patients with low-volume metastatic disease may be treated with RPLND, in order to prevent chemotherapy-related toxicity. The same could be the case for CS I patients suffering from relapse. Several studies on primary RPLND for CS II SGCT are underway. If these have favorable results, RPLND will become more accepted in SGCT patients. The evolvement of technological innovations, surgeons' experience and (vascular) surgical techniques will make minimally invasive surgery also possible in more challenging cases. New imaging techniques and biomarkers will be able to better identify patients who could benefit from RPLND in CS II and in the postchemotherapy setting. And finally, registration and centralization of RPLND is necessary to improve patient outcome.

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10

Chapter

Summary

Nederlandse samenvatting

Summary

Testicular germ cell tumor (TGCT) is introduced in **chapter 1**, describing the epidemiology, etiology, diagnosis and disease management.

Chapter 2 systematically reviews the literature on the two main histopathological risk factors for relapse in clinical stage I (CS I) nonseminomatous germ cell tumor (NSGCT): lymphovascular invasion (LVI) and embryonal carcinoma (EC). In the included studies on active surveillance, the percentages of patients with relapse were between 17.1% and 36.3%. In the studies on primary retroperitoneal lymph node dissection (P-RPLND), percentages of pathological stage II disease varied between 18.6% and 41.3%. Twenty-four studies were included in one of the meta-analyses. The pooled rates of occult metastases were 47.5% for LVI-positive and 16.9% for LVI-negative histopathology. This resulted in an odds ratio (OR) of 4.33. Pooled rates of occult metastases for EC presence and EC absence were 33.2% and 16.2%, respectively (OR 2.49). This was 40.0% for EC more than 50% and 20.0% for EC less than 50% (OR 2.62).

Our findings show that LVI in the primary tumor is the strongest histopathological predictor for relapse in CS I NSGCT. The prognostic value of EC is also high, but there is no consensus on a threshold value. Our research suggests that the mere presence of EC is already sufficient for the classification of EC. Here described risk factors can be used to inform patients of their relapse risk and identify patients who would benefit from closer surveillance or adjuvant treatment.

To base the selection of patients at high risk of relapse on the true presence of microscopic metastases, the sentinel node (SN) procedure for CS I TGCT was developed at the Netherlands Cancer Institute. We retrospectively analyzed the results of this procedure in 27 consecutive patients in **chapter 3**. SNs were identified prior to orchiectomy, using lymphoscintigraphy with single-photon-emission computed tomography with CT (SPECT/CT). After visualization of the SN, patients underwent laparoscopic retroperitoneal resection of the SN with inguinal orchiectomy.

In two patients, no SNs were visualized on SPECT/CT. In the remaining 25 patients, a median of 3 SNs were resected. Two patients had no malignancy on histopathological examination of the testis. The remaining 23 patients were diagnosed with either NSGCT (7 patients) or seminomatous germ cell tumor (SGCT; 16 patients). Three of these patients (13.0%) had microscopic metastases in their retroperitoneal SNs and were treated with additional chemotherapy. After a median follow-up of more than five years, none of the patients had evidence of disease. This study shows that the SN procedure is feasible in patients with CS I TGCT. Our findings suggest that patients with a negative SN can be managed with surveillance.

In **chapter 4** we systematically review the literature on the relapse rate in NSGCT after postchemotherapy retroperitoneal lymph node dissection (PC-RPLND). We stratified between open and minimally-invasive techniques. The weighted average relapse rates were 11.4% after

open PC-RPLND, compared to 3.0% after minimally-invasive PC-RPLND. The retroperitoneal relapse rates were 4.6% after open PC-RPLND and 1.7% after minimally-invasive PC-RPLND. The higher relapse rates after an open procedure are most likely due to selection bias. Patients treated with a minimally-invasive procedure were more likely to have smaller tumors.

We further stratified the open procedures into bilateral and unilateral dissections. The average retroperitoneal relapse rate after a bilateral dissection was 6.1%, compared to 3.1% after a unilateral dissection. Again, this difference was likely due to selection bias. However, an important takeaway is that, based on this literature review, a unilateral dissection seems to be feasible in appropriately selected patients.

We also took postoperative complication risk into account. The average reported complication rate for open PC-RPLND was 21.8%. After minimally-invasive PC-RPLND, the complication rate was lower (15.9%). In both cases, the majority of complications were graded as Clavien-Dindo Grade I or II.

There is a debate concerning the anatomical template of PC-RPLND. In **chapter 5** we retrospectively compared the outcome of two approaches: template-based resection (TBR) and residual mass resection (RMR). TBR is the most widely used technique and consists of resecting the residual tumor and all lymph nodes in a certain anatomical template, including the non-suspicious nodes. In RMR, only the residual tumor and macroscopically suspicious nodes are resected. Lymph nodes that were enlarged prior to chemotherapy are also resected, but no template resection of unsuspicious lymph nodes is done.

A total of 301 patients treated in three centers (TBR: 85; RMR: 216) were included in the study. For most analyses, we excluded patients with incomplete resection, grade V complication or less than one year follow-up. Based on 245 patients (TBR: 76; RMR: 169), the absolute rate of retroperitoneal relapse was 5.3% (13 patients). The retroperitoneal relapse rate was higher in the RMR group (5.9%), compared to the TBR group (3.9%). The five-year cumulative incidence of retroperitoneal relapse was also higher in the RMR group (4.2%), compared to the TBR group (3.0%).

A redo resection was necessary in 15 patients, either for incomplete resection or relapse. Fourteen out of fifteen patients that had to undergo a redo resection were previously treated with RMR. This corresponds to a redo percentage of 6.5% after RMR. Four out of thirteen patients with a retroperitoneal relapse died of disease (31%). These results show that RMR is an inappropriate technique as it is associated with higher percentages of redo procedures and retroperitoneal relapse.

PC-RPLND is a challenging procedure with a high risk of intra- and postoperative complications. A substantial proportion of patients need an additional surgical intervention during PC-RPLND (e.g. nephrectomy or vascular repair). In **chapter 6** we retrospectively analyzed the morbidity

of PC-RPLND in a cohort of 124 patients treated in two intermediate-volume hospitals. In 33 patients (27%), a total of 46 additional procedures were necessary. Most common interventions were nephrectomy and vena cava resection or reconstruction. The assistance of a vascular surgeon was necessary in 20 procedures (16%). Risk factors for an additional procedure were International Germ Cell Cancer Collaborative Group (IGCCCG) intermediate or poor prognostic group (OR 3.56) and residual tumor size larger than 5 cm (OR 3.53).

A postoperative complication Clavien-Dindo grade II or higher was recorded in 31 patients (25%). On multivariate analysis, the only significant risk factor for postoperative complication was the necessity of an intraoperative additional intervention (OR 3.46).

Our study showed that patients with IGCCCG intermediate/poor prognosis and high-volume disease can be classified as high-risk patients. In these patients, extra attention to possible tumor ingrowth and precautionary measures (such as assistance from a vascular surgeon) are advised.

Chapter 7 evaluates the outcome of robot-assisted RMR. A total of 45 patients with a median residual tumor size of 1.9 cm were included. A conversion to an open procedure was necessary in five patients (11%). Two patients had a postoperative complication (4.4%). Histopathological analysis of the specimen showed teratoma in 29 patients (64%), necrosis in 14 patients (31%) and viable tumor in 2 patients (4%). After a median follow-up of 41 months, one patient suffered from retroperitoneal relapse (2%). These results suggest that robot-assisted RMR is an appropriate treatment option in carefully selected patients, although long-term data is necessary to support this hypothesis.

In **chapter 8** we evaluated the risk of developing metachronous contralateral TGCT (CTGCT) in a cohort of 4,755 patients with TGCT. Standardized incidence ratios (SIRs) were computed to compare CTGCT incidence with what would have been expected on the basis of TGCT incidence in the general population. We found a SIR of 14.6, which means that patients with TGCT have an almost 15 times higher risk of developing CTGCT, compared to the general population. The cumulative incidence increased for up to 20 years after the primary diagnosis and reached 3.4% for the entire cohort. Patients who are diagnosed with a SGCT before the age of 25 years have the highest risk (SIR 40.4; 20-year cumulative incidence 8.7%).

Furthermore, we analyzed risk factors for developing CTGCT using Cox-proportional hazards model. We found that CTGCT risk decreased with age at primary diagnosis (hazard ratio [HR] 0.93), was lower after NSGCT compared to SGCT (HR 0.58) and decreased with every additional cycle of chemotherapy (HR 0.74). Our study showed that approximately one in every 30 patients with TGCT will develop a CTGCT and that the incidence increases for up to 20 years after a primary TGCT. Treatment with platinum-based chemotherapy decreases the risk of developing CTGCT.

Chapter 9 provides a reflection on the findings of our research, places our results in a broader perspective and postulates future perspectives.

Samenvatting

In **hoofdstuk 1** wordt de epidemiologie, etiologie, diagnose en behandeling van testistumoren behandeld.

Hoofdstuk 2 beschrijft een literatuuronderzoek naar de twee belangrijkste histopathologische risicofactoren voor een recidief in klinisch stadium I (KS I) nonseminoma testis: lymfovasculaire invasie (LVI) en embryonaal carcinoom (EC). In de geïncludeerde studies over "actief volgen" liggen de recidiefpercentages tussen de 17,1% en 36,3%. In studies over primaire retroperitoneale lymfeklierdissectie (P-RPLKD), liggen de percentages van pathologisch stadium II tussen 18,6% en 41,3%. Wij includeerden vierentwintig studies in een van de meta-analyses. De gecombineerde percentages van occulte uitzaaiingen waren 47,5% voor LVI-positieve en 16,9% voor LVI-negatieve histopathologie. Dit resulteerde in een odds ratio (OR) van 4,33. De gecombineerde percentages van occulte uitzaaiingen voor EC-aanwezigheid en EC-afwezigheid waren 33,2% en 16,2%, respectievelijk (OR 2,49). Dit was 40% voor EC meer dan 50% en 20,0% voor EC minder dan 50% (OR 2,62).

Onze bevindingen tonen aan dat LVI in de primaire tumor de sterkste histopathologische voorspeller voor recidief van KS I nonseminoma testis is. De voorspellende waarde van EC is ook hoog, maar er is geen overeenkomst over een drempelwaarde. Ons onderzoek suggereert dat louter het vaststellen van de aanwezigheid van EC al voldoende is voor de classificatie van EC. De beschreven risicofactoren kunnen gebruikt worden om patiënten voor te lichten over hun kans op het ontwikkelen van een recidief en om patiënten te selecteren die baat hebben bij strikter actief volgen of aanvullende behandeling.

Om de selectie van patiënten met hoog een risico op een recidief te baseren op de daadwerkelijke aanwezigheid van microscopische uitzaaiingen, is de schildwachtklierprocedure voor KS I testistumor ontwikkeld in het Nederlands Kanker Instituut. **Hoofdstuk 3** beschrijft een retrospectieve analyse van de resultaten van deze procedure bij 27 opeenvolgende patiënten. Schildwachtklieren (SWKs) werden voorafgaand aan de orchidectomie geïdentificeerd met behulp van lymphoscintigrafie met ***single photon emission computed tomography with CT (SPECT/CT)***. Nadat de SWK in beeld was gebracht ondergingen patiënten een retroperitoneale resectie van SWK met inguinale orchidectomie.

Bij twee patiënten werden geen SWKs in beeld gebracht op de SPECT/CT. Bij de overige 25 patiënten werd een mediaan aantal van 3 SWKs gereseceerd. Bij twee patiënten werd geen maligniteit in het histopathologisch preparaat van de testis aangetroffen. De overige 23 patiënten werden gediagnosticeerd met ofwel nonseminoma testis (7 patiënten), ofwel seminoma testis (16 patiënten). Drie van deze patiënten (13,0%) hadden microscopische uitzaaiingen in hun retroperitoneale lymfeklieren en werden behandeld met aanvullende chemotherapie. Geen van de patiënten had een recidief na een mediane follow-up duur van meer dan vijf jaar. Deze studie laat zien dat de schildwachtklierprocedure mogelijk is bij patiënten met KS I testistumor. Onze bevindingen suggereren dat patiënten met een negatieve SWK als behandeling actief gevolgd kunnen worden.

Hoofdstuk 4 beslaat een literatuuronderzoek naar het recidiefpercentage na postchemotherapie retroperitoneale lymfeklierdissectie (PC-RPLKD) voor nonseminoma testis. We maakten onderscheid tussen open en minimaal-invasieve procedures. De gewogen gemiddelde recidiefpercentages waren 11,4% na open PC-RPLKD, tegen 3,0% na minimaal-invasieve PC-RPLKD. De retroperitoneale recidiefpercentages waren 4,6% na open PC-RPLKD en 1,7% na minimaal invasieve PC-RPLKD. De hogere recidiefpercentages na een open procedure worden waarschijnlijk veroorzaakt door selectiebias. Patiënten die behandeld worden met een minimaal invasieve procedure hebben namelijk vaker een kleinere tumor.

We maakten verder nog onderscheid tussen bilaterale en unilaterale dissecties. Het gemiddelde retroperitoneaal recidiefpercentage na een bilaterale dissectie was 6,1%, tegen 3,1% na een unilaterale dissectie. Ook hier werd het verschil waarschijnlijk veroorzaakt door selectiebias. Echter, een belangrijke conclusie is dat, gebaseerd op ons literatuuronderzoek, een unilaterale dissectie geschikt is voor bepaalde patiënten.

We keken in deze studie ook naar het risico op een postoperatieve complicatie. Het gemiddelde complicatierisico voor open PC-RPLKD was 21,8%. Dit risico was lager na een minimaal invasieve PC-RPLKD (15,9%). Voor beide groepen gold dat het vooral Clavien-Dindo Graad I of II complicaties betrof.

Er bestaat discussie over de anatomische grenzen van PC-RPLKD. In **hoofdstuk 5** vergelijken we retrospectief de uitkomsten van twee operatietechnieken: template-gebaseerde resectie (TBR) en restmassa resectie (RMR). TBR is de meest toegepaste techniek en bestaat uit het verwijderen van de restmassa en alle lymfeklieren in een bepaald anatomisch template, inclusief de niet-verdachte lymfeklieren. Bij RMR worden alleen de restmassa en macroscopisch verdachte klieren gereseceerd. Lymfeklieren die voorafgaand aan chemotherapie vergroot waren worden ook gereseceerd, maar er wordt geen template resectie van niet-verdachte klieren verricht.

In totaal werden 301 patiënten (TBR: 85; RMR: 216), die in een van drie centra waren behandeld, geïncludeerd in de studie. Voor de meeste analyses werden patiënten geëxcludeerd als er sprake was van een incomplete resectie, graad V complicatie of follow-up minder dan een jaar. Op basis van 245 patiënten (TBR: 76; RMR: 169) was het absolute risico op een retroperitoneaal recidief 5,3% (13 patiënten). Het risico op een retroperitoneaal recidief was hoger in de RMR groep (5,9%), dan in de TBR groep (3,9%). De vijfjaars cumulatieve incidentie van retroperitoneaal recidief was ook hoger in de RMR groep (4,2%), dan in de TBR groep (3,0%).

Vijftien patiënten moesten een tweede resectie ondergaan, vanwege een incomplete resectie of een recidief. Veertien van de vijftien patiënten die een tweede resectie moesten ondergaan waren eerder behandeld met RMR. Dit komt overeen met een percentage van 6,5% na RMR. Vier van de dertien patiënten met een retroperitoneaal recidief overleden als gevolg van hun ziekte (31%). Deze resultaten laten zien dat RMR een inadequate techniek is, aangezien het is geassocieerd met een hoger percentage patiënten dat een tweede ingreep moet ondergaan en een hoger percentage patiënten met een retroperitoneaal recidief.

PC-RPLKD is een uitdagende procedure met een hoog risico op intra- en postoperatieve complicaties. Een substantieel deel van de patiënten moet een aanvullende chirurgische ingreep ondergaan tijdens PC-RPLKD (bijvoorbeeld nefrectomie of herstel van vaatletsel). In **hoofdstuk 6** hebben we retrospectief de morbiditeit van PC-RPLKD in een cohort van 124 patiënten in twee ziekenhuizen van gemiddelde grootte onderzocht. Er waren 46 aanvullende ingrepen nodig bij 33 patiënten (27%). De meest voorkomende interventies waren nefrectomie en resectie of herstel van de vena cava. De assistentie van een vaatchirurg was nodig bij 20 procedures (16%). Risicofactoren voor een aanvullende ingreep waren een gemiddelde of slechte prognose volgens de International Germ Cell Cancer Collaborative Group (IGCCCG) classificatie (OR 3,56) en een restmassa groter dan 5 cm (OR 3,53).

Een postoperatieve complicatie graad II of hoger volgens de Clavien-Dindo classificatie werd bij 31 patiënten (25%) vastgelegd. Na multivariate analyse was de noodzaak voor een aanvullende chirurgische ingreep de enige significante risicofactor voor een postoperatieve complicatie (OR 3,46).

Onze studie toonde aan dan patiënten met gemiddelde of slechte prognose volgens de IGCCCG-classificatie en grote tumoren kunnen worden geclassificeerd als hoogrisicopatiënten. Bij deze patiënten adviseren we om extra aandacht te besteden aan mogelijke ingroei van de tumor en voorzorgsmaatregelen te treffen (zoals assistentie van een vaatchirurg).

Hoofdstuk 7 beslaat de uitkomsten van robotgeassisteerde RMR. Er werden 45 patiënten met een mediane restmassa van 1,9 cm geïncludeerd. Conversie naar een open procedure was nodig bij vijf patiënten (11%). Bij twee patiënten (4.4%) was sprake van een postoperatieve complicatie. Bij histopathologisch onderzoek van het preparaat werd bij 29 patiënten (64%) teratoom, bij 14 patiënten (31%) necrose en bij 2 patiënten (4%) vitaal tumorweefsel gevonden. Na een mediane follow-up van 41 maanden, werd bij één patiënt (2%) een retropertioneaal recidief gediagnosticeerd. Deze resultaten suggereren dat robotgeassisteerde RMR een geschikte behandeloptie is bij zorgvuldig geselecteerde patiënten, hoewel er meer studies met langere follow-up nodig zijn om deze hypothese te ondersteunen.

In **hoofdstuk 8** hebben we in een cohort van 4.755 patiënten met testistumor gekeken naar het risico op het ontwikkelen van testistumor in de contralaterale testis (contralaterale testistumor; CLTT). Gestandaardiseerde incidentieratio's (SIRs) werden berekend om de incidentie van CLTT te vergelijken met wat we zouden verwachten op basis van de incidentie van testistumoren in de algehele populatie. We vonden een SIR van 14,6, wat betekent dat patiënten met testistumor een bijna 15 keer hoger risico hebben op het ontwikkelen van CLTT, in vergelijking met de algehele populatie. De cumulatieve incidentie blijft stijgen tot en met 20 jaar na de initiële diagnose, tot 3,4% voor het hele cohort. Patiënten die werden gediagnosticeerd met seminoma testis voor de leeftijd van 25 jaar hebben het grootste risico (SIR 40,4; 20-jaars cumulatieve incidentie 8,7%).

Bovendien hebben we door middel van een Cox-proportional hazards model onderzocht welke risicofactoren er zijn voor het ontwikkelen van CLTT. We vonden dat het risico op CLTT afnam met de leeftijd ten tijde van de initiële diagnose (hazard ratio [HR] 0,93). Daarnaast was het risico lager na nonseminoma testis, in vergelijking met seminoma testis (HR 0,58) en daalde dit risico met iedere aanvullende cyclus chemotherapie (HR 0,74). Onze studie toonde aan dat ongeveer één op de dertig patiënten met testistumor een CLTT zal ontwikkelen en dat de incidentie hiervan toeneemt tot en met 20 jaar na diagnose van de primaire testistumor. Behandeling met chemotherapie op basis van cisplatinum zorgt voor een lager risico op het ontwikkelen van CLTT.

In **hoofdstuk 9** reflecteren we op de bevindingen van onze onderzoeken, worden de resultaten in een bredere context geplaatst en worden mogelijkheden voor de toekomst aangedragen.

Appendices

List of abbreviations

AFP	α-fetoprotein
AS	active surveillance
ASR	age-standardized incidence rate
BEP	bleomycin, etoposide, cisplatin combination chemotherapy
CEB	carboplatin, etoposide, bleomycin
CI	confidence interval
CS I	clinical stage I
CT	computed tomography
CTGCT	contralateral testicular germ cell tumor
CVD	cardiovascular disease
DOD	death of disease
EC	embryonal carcinoma
EP	etoposide and cisplatin
EAU	European Association of Urology
ESMO	European Society for Medical Oncology
FDG-PET	fluorodeoxyglucose-positron emission tomography
GCNIS	germ cell neoplasia in situ
GCT	germ cell tumor
GTCSG	German Testicular Cancer Study Group
HR	hazard ratio
HCG	human choriogonadotropin
IGCCCG	International Germ Cell Cancer Collaborative Group
IMA	inferior mesenteric artery
IQR	interquartile range
IVC	inferior vena cava
L-RPLND	laparoscopic retroperitoneal lymph node dissection
LDH	lactate dehydrogenase
LR	late relapse
LVI	lymphovascular invasion
miRNAs	microRNAs
MI-RPLND	minimally invasive postchemotherapy retroperitoneal lymph node dissection
MOOSE	Meta-analysis Of Observational Studies in Epidemiology
MRI	magnetic resonance imaging
MSKCC	Memorial Sloan Kettering Cancer Center
NCI	Netherlands Cancer Institute
NM	not mentioned
NPV	negative predictive value
NSGCT	nonseminomatous germ cell tumor
NVU	Nederlandse Vereniging voor Urologie

N/A	not applicable
O-RMR	open residual mass resection
O-RPLND	open postchemotherapy retroperitoneal lymph node dissection
OR	odds ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
P-RPLND	primary retroperitoneal lymph node dissection
PC-RPLND	postchemotherapy retroperitoneal lymph node dissection
PPV	positive predictive value
QUIPS	Quality in Prognosis Studies
RA-PC-RPLND	robot-assisted postchemotherapy retroperitoneal lymph node dissection
RA-RMR	robot-assisted residual mass resection
RA-RPLND	robot-assisted retroperitoneal lymph node dissection
RMR	residual mass resection
RP	retroperitoneal
RR	relative risk
RT	radiotherapy
RTI	rete testis invasion
RUMC	Radboud University Medical Centre
SEMS	Surgery in Early Metastatic Seminoma
SGCT	seminomatous germ cell tumor
SIR	standardized incidence ratio
SMN	secondary malignant neoplasms
SN	sentinel node
SPECT/CT	single-photo-emission computed tomography with computed tomography
SWENOTECA	Swedish and Norwegian Testicular Cancer Groups
TBR	template-based resection
TGCT	testicular germ cell tumor
ULN	upper limit of normal range
UMCU	University Medical Center Utrecht
VI	vascular invasion
VLR	very late relapse

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2021 **Publiekslezing Zaadbalkanker, UMC Utrecht (online)**
Zaadbalkanker: Wie krijgt het?

2020 **Utrechtse Refereeravond Urologie, Utrecht**
Laat recidief na testistumor: Resultaten van een landelijk testistumorcohort

ASCO Genitourinary Cancers Symposium, San Francisco
Incidence and risk factors for contralateral testicular tumor (poster presentation)

35th Annual European Association of Urology Congress, Amsterdam (online)

- Incidence of metachronous contralateral testicular germ cell tumour and association with chemotherapy (poster presentation)
- Lymphovascular invasion and presence of embryonal carcinoma as risk factors for occult metastatic disease in clinical stage I nonseminomatous germ cell tumour: A systematic review and meta-analysis (poster presentation)
- Association between age and histopathology of testicular tumour: Higher risk of benign pathology in older patients? (poster presentation)

Annual Meeting of the American Urological Association, Washington DC (online)

- Lymphovascular invasion and presence of embryonal carcinoma as risk factors for occult metastases in clinical stage I nonseminomatous germ cell tumor: A systematic review and meta-analysis (poster presentation)
- Incidence of metachronous contralateral testicular cancer and association with chemotherapy (poster presentation)

2019 **34th Annual European Association of Urology Congress, Barcelona**
Laparoscopic residual mass resection as an alternative to template-based postchemotherapy retroperitoneal lymph node dissection (poster presentation)

Voorjaarsvergadering Nederlandse Vereniging voor Urologie, Rotterdam
Schildwachtklierprocedure bij testistumor: SENATOR studie

Najaarsvergadering Nederlandse Vereniging voor Urologie, Nieuwegein
De incidentie en risicofactoren van een contralaterale testistumor

9e Dutch Uro-Oncology Studygroup (DUOS) Symposium, Utrecht
Dose-depended chemotherapy effect on the risk of metachronous contralateral testicular cancer

2018 **ASCO Genitourinary Cancers Symposium, San Francisco**
Sentinel node biopsy in clinical stage I testicular cancer (oral presentation)

10th European Multidisciplinary Congress on Urological Cancers (EMUC), Amsterdam
Post-chemotherapy residual mass resection in testicular cancer (poster presentation)

7th Meeting of the EAU section of Urological Imaging, Amsterdam
Sentinel lymph node biopsy in clinical stage I testicular cancer (oral presentation)

Utrechtse Refereeravond Urologie, Utrecht
Schildwachtklierprocedure bij klinisch stadium I testistumor: SENATOR studie

Najaarsvergadering Nederlandse Vereniging voor Urologie, Nieuwegein
Risicofactoren voor additionele chirurgische ingrepen en postoperatieve complicaties bij retroperitoneale lymfeklierdissectie voor gemetastaseerde testistumor en risicofactoren voor intra-operatief vaatletsel bij retroperitoneale lymfeklierdissectie voor gemetastaseerde testistumor

2017 **Najaarsvergadering Nederlandse Vereniging voor Urologie, Nieuwegein**
Schildwachtklierprocedure bij klinisch stadium I testistumor

7e Dutch Uro-Oncology Studygroup (DUOS) Symposium, Utrecht
Sentinel node procedure bij stadium I testistumor

Curriculum vitae

Joost Blok was born on the 30th of October 1990 in Dagenham, the United Kingdom, and grew up in Eindhoven and Waalre.

After graduating from Gymnasium at the Augustinianum in Eindhoven, he attended medical school at Utrecht University. During his student years, he was an active member of several student associations.

As part of his medical training he went abroad to Tygerberg Hospital, South Africa for an elective in Paediatrics. His first steps in scientific research were in the field of andrology under the supervision of drs. M.T.W.T. Lock.

After receiving his medical degree in 2016, he started working as a PhD Candidate at the Department of Oncological Urology at the University Medical Center Utrecht and the Department of Urology at the Netherlands Cancer Institute, under the supervision of prof. dr. J.L.H.R. Bosch, prof. dr. S. Horenblas and dr. R.P. Meijer. In addition to his research, he set up a biobank for germ cell tumors at the UMC Utrecht (bioGCT), was a mentor to refugee doctors as part of the Stichting voor Vluchteling Studenten UAF program, and participated in the SMO Promovendi program, which resulted in a publication on technological innovation in healthcare.

In August 2020, Joost started working as a resident not in training at the urology department of the Elisabeth-TweeSteden Hospital in Tilburg (program director dr. J.H. van Roijen). He currently works as a surgical resident in training at the Franciscus Gasthuis & Vlietland Hospital in Rotterdam (program directors dr. T.M.A.L. Klem and dr. M.M. Poelman) as part of his urology training at the University Medical Center Utrecht (program director prof. dr. L.M.O. de Kort).

He currently lives in Rotterdam with Steffi.