

Original Article

Initial surveillance in men with marker negative clinical stage IIA non-seminomatous germ cell tumours

Axel Gerdtsson^{1,3} , Helene F. S. Negaard⁵, Bjarne Almås⁷ , Anna Grenabo Bergdahl^{9,10}, Gabriella Cohn-Cedermark^{2,11}, Ingrid Glimelius¹³, Dag Halvorsen¹⁴, Hege Sagstuen Haugnes^{16,17}, Annika Hedlund¹⁸, Martin Hellström¹⁹, Göran Holmberg¹⁰, Ása Karlsdóttir⁸, Anders Kjellman^{1,12}, Signe Melsen Larsen⁶, Anna Thor^{1,12}, Rolf Wahlqvist⁶, Olof Ståhl^{4,20} and Torgrim Tandstad^{15,21}

¹Department of Clinical Science, Intervention and Technology, Division of Urology, ²Department of Oncology-Pathology, Karolinska Institutet, Stockholm, ³Department of Urology, Skåne University Hospital, Malmö, ⁴Department of Oncology, Skåne University Hospital, Lund, Sweden, ⁵Department of Oncology, ⁶Department of Urology, Oslo University Hospital, Oslo, ⁷Department of Urology, ⁸Department of Oncology, Haukeland University Hospital, Bergen, Norway, ⁹Department of Urology, Institute of Clinical Science, Sahlgrenska Academy, University of Gothenburg, Gothenburg, ¹⁰Department of Urology, Region Västra Götaland, Sahlgrenska University Hospital, Gothenburg, ¹¹Department of Pelvic Cancer, Genitourinary Oncology Unit, ¹²Department of Urology, Pelvic Cancer, Karolinska University Hospital, Stockholm, ¹³Department of Immunology, Genetics and Pathology, Cancer Precision Medicine, Uppsala University, Uppsala, Sweden, ¹⁴Department of Urology, ¹⁵The Cancer Clinic, St. Olavs University Hospital, Trondheim, ¹⁶Department of Oncology, University Hospital of North Norway, ¹⁷Department of Clinical Medicine, UiT- The Arctic University of Norway, Tromsø, Norway, ¹⁸Department of Oncology, Sahlgrenska University Hospital, Gothenburg, ¹⁹Department of Radiation Sciences, Oncology, Umeå University, Umeå, ²⁰Department of Clinical Sciences, Lund University, Lund, Sweden, and ²¹Department of Clinical and Molecular Medicine, The Norwegian University of Science and Technology, Trondheim, Norway

O.S. and T.T. contributed equally as last author.

Objectives

To assess whether extended surveillance with repeated computed tomography (CT) scans for patients with clinical stage IIA (CS IIA; <2 cm abdominal node involvement) and negative markers (Mk–) non-seminomatous germ cell tumours (NSGCTs) can identify those with true CS I. To assess the rate of benign lymph nodes, teratoma, and viable cancer in retroperitoneal lymph node dissection (RPLND) histopathology for patients with CS IIA Mk– NSGCT.

Patients and methods

Observational prospective population-based study of patients diagnosed 2008–2019 with CS IIA Mk– NSGCT in the Swedish and Norwegian Testicular Cancer Group (SWENOTECA) registry. Patients were managed with surveillance, with CT scans, and tumour markers every sixth week for a maximum of 18 weeks. Patients with radiological regression were treated as CS I, if progression with chemotherapy, and remaining CS IIA Mk– disease with RPLND. The end-point was the number and percentage of patients down-staged to CS I on surveillance and rate of RPLND histopathology presented as benign, teratoma, or viable cancer.

Results

Overall, 126 patients with CS IIA Mk– NSGCT were included but 41 received therapy upfront. After surveillance for a median (range) of 6 (6–18) weeks, 23/85 (27%) patients were in true CS I and four (5%) progressed. Of the remaining 58 patients with lasting CS IIA Mk– NSGCT, 16 received chemotherapy and 42 underwent RPLND. The RPLND histopathology revealed benign lymph nodes in 11 (26%), teratoma in two (6%), and viable cancer in 29 (70%) patients.

Conclusions

Surveillance with repeated CT scans can identify patients in true CS I, thus avoiding overtreatment. The RPLND histopathology in patients with CS IIA Mk– NSGCT had a high rate of cancer and a low rate of teratoma.

Keywords

chemotherapy, germ cell tumour, non-seminoma, retroperitoneal lymph node dissection, testicular cancer

Introduction

Testicular non-seminomatous germ cell tumours (NSGCTs) with limited retroperitoneal lymphadenopathy, <2 cm in maximum transverse diameter classified as clinical stage (CS) IIA, constitutes a specific clinical challenge [1]. In the setting of marker-positive disease (Mk+) the retroperitoneal lymphadenopathy is considered malignant, and the patient is treated accordingly [2,3]. The challenge remains for the marker-negative patients (Mk-), in whom the moderately enlarged lymph nodes might harbour teratoma, cancer, or benign tissue. Therefore, the European Association of Urology recommends primary retroperitoneal lymph node dissection (RPLND) or initial surveillance followed by a CT scan after 6 weeks [3]. In CS IIA Mk- NSGCT, the prognosis is excellent with nearly a 100% cure rate after chemotherapy and post-chemotherapy RPLND (PC-RPLND), if ≥ 10 mm residual retroperitoneal disease after chemotherapy, or primary RPLND and adjuvant chemotherapy if viable cancer in the resected lymph nodes [3–9]. However, both treatment options are excessive therapy for patients that have benign lymph nodes and are in true CS I. For CS I patients, these treatment options should be avoided, as treatments are associated with acute and long-term side-effects and mortality [10,11].

Since 2012, the Swedish and Norwegian Testicular Cancer Group (SWENOTECA) management programme recommends a CT scan every 6 weeks for patients with CS IIA Mk- NSGCT until therapy decision (maximum 18 weeks) [12,13]. The aim of this strategy is to reduce overtreatment for patients with true CS I.

This is the first study focusing on patients with CS IIA Mk- NSGCT in a population-based setting. The primary aim was to assess if an extended surveillance period and repeated CT scans could identify patients in true CS I, thus avoiding overtreatment. The secondary aims were to assess the rate of benign lymph nodes (pathological stage I, true CS I), teratoma, and germ cell cancer (GCC) in primary RPLND histopathology. Finally, we aimed to present recurrence and mortality rates for patients with CS IIA Mk- NSGCT, as well as perioperative data including complication rates.

Patients and Methods

Patients

All patients diagnosed with CS IIA Mk- NSGCT during 2008–2019 in Sweden and Norway were identified in the population-based SWENOTECA registry. The registry consists of male patients aged ≥ 16 years, diagnosed with a primary GCT in the testis, mediastinum, or retroperitoneum. Patients in this study were managed according to the SWENOTECA IV and VIII guidelines

[12,14]. We included patients that were classified as modified Royal Marsden CS IIA [15] at the initial staging CT scan or at the definitive staging CT scan (6–8 weeks after orchidectomy for patients with initial CS I). CS I in the modified Royal Marsden classification is disease limited to the testicle, CS II is metastatic disease in a retroperitoneal lymph node (A = <20 mm, B = 20–49 mm, C = 50–100 mm, D = >100 mm), CS III is supradiaphragmatic lymph node metastasis, and CS IV is extra-lymphatic metastasis [15]. To make the outcome applicable for clinicians who do not routinely perform a second staging CT scan for patients with initial CS I, the results are presented separately for patients with initial CS I disease (progressing to CS IIA on the definitive staging CT scan) and those with initial CS IIA Mk- (at initial staging CT scan). The definition of Mk- is normal levels of alpha fetoprotein (AFP) and β -hCG after orchidectomy, regardless of pre-orchidectomy marker levels. The maximum transverse diameter measured on CT scan of the largest retroperitoneal lymph node was used to categorise the patients as CS IIA (retroperitoneal lymph nodes <2 cm).

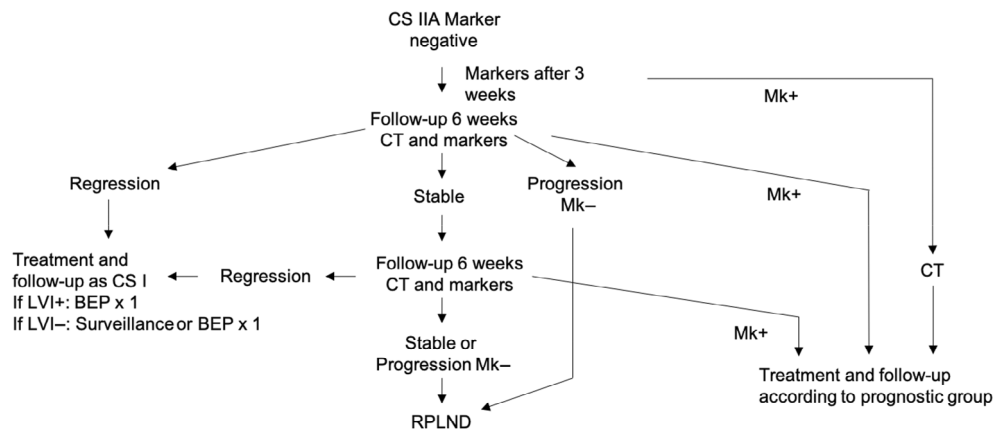
Surveillance Protocol and Primary Therapy

Surveillance included tumour marker monitoring (AFP and β -hCG) and repeated CT scans up to 12 weeks further, as outlined in Fig. 1. Between 1995 and 2012 (SWENOTECA IV) [14] primary RPLND and chemotherapy were regarded as equal alternatives, whereas primary RPLND was the preferred treatment modality in the subsequent guideline SWENOTECA VIII [12] (2012–2020), even though primary chemotherapy was an alternative, as per the discretion of the treating physician. The recommended template was a modified unilateral nerve-sparing RPLND. Adjuvant chemotherapy with two courses of bleomycin, etoposide and cisplatin (BEP), was recommended for patients with confirmed GCC in the RPLND specimen.

During surveillance, patients with radiological signs of progressive disease and/or rising tumour markers received chemotherapy. The standard primary chemotherapy regimen for metastatic disease was three courses of BEP. PC-RPLND was recommended for patients with residual tumour ≥ 10 mm in maximum transverse diameter.

Patients with spontaneous radiological regression and normal tumour markers during the observation period were considered to be in true CS I and treated accordingly. The decision to recommend adjuvant chemotherapy for patients in CS I was risk adapted and based on presence or absence of histopathological lymphovascular invasion (LVI+ or LVI-) of the tumour cells in the orchidectomy specimen. Adjuvant treatment, with one course of BEP, was recommended in case of LVI+ and optional for LVI- [16].

Fig. 1 Surveillance plan for patients with CS IIA Mk⁻ NSGCT [11]. The patients were monitored with tumour markers and CT scan every sixth week.



All patients were followed according to SWENOTECA guidelines for 5–10 years after therapy, until death or 31 December 2021, whichever came first.

Data Collection and Statistical Analyses

Clinical data: such as modified Royal Marsden CS [15], number of CT scans and CT scan results, fluorodeoxyglucose positron emission tomography (FDG-PET)/CT scan results, histopathology from the orchidectomy specimen, LVI status, and number and type of chemotherapy courses, recurrence, and mortality were collected from the SWENOTECA registry and chart reviews. Information on areas dissected at RPLND, histopathology for each area, lymph node yield and surgical complications according to the Clavien–Dindo classification were noted by the surgeon in a case report form, as was operating time, perioperative blood loss, and length of hospital stay.

Outcome measurements for the primary aim: number and rate of patients in true CS I after surveillance are presented using descriptive statistics.

Outcome measurements for the secondary aim: descriptive statistics are used to present RPLND histopathology (benign, teratoma, or cancer). Follow-up time was calculated from date of orchidectomy to last date of follow-up. Recurrence and mortality during follow-up are presented as exact numbers and percentages. LVI, embryonal carcinoma, or teratoma in the orchidectomy specimen and lymph node size were tested as predictors of the finding of viable cancer in the resected lymph nodes with univariate logistic regression.

All statistics were calculated using the Statistical Package for the Social Sciences (SPSS®), version 27 (IBM Corp., Armonk, NY, USA).

This study was approved by the regional Ethics Committee. Patients in Norway signed an informed consent to be included in the SWENOTECA database. In Sweden the

principle of opt-out was practiced. Patients were informed of the database and automatically included in the SWENOTECA database unless they explicitly chose not to be included.

Results

In total, 126 patients were diagnosed with CS IIA Mk⁻ NSGCT during the study period, with a median (interquartile range [IQR]) follow-up of 63 (42–100) months. Of those, 58 patients had no evidence of metastatic disease at initial CT scan (CS I) but progressed to CS IIA Mk⁻ at the definitive CT scan 6 weeks later (Fig. 2).

Clinical Stage I Progressing to CS IIA Mk⁻

Of the 58 patients with initial CS I that progressed to CS IIA Mk⁻ NSGCT, 28 patients were put on surveillance. During surveillance, seven of 28 (25%) patients were down-staged to CS I, 18/28 (64%) had lasting CS IIA Mk⁻ disease, and three of 28 (11%) progressed (Fig. 2). The outcomes for the non-surveillance patients can be found in Table 1.

Two of the seven patients that were down-staged to CS I on surveillance, chose to receive adjuvant therapy with one course of BEP (both were LVI⁻) and the remaining five patients chose surveillance (one LVI⁺, four LVI⁻). All seven CS I patients were alive and without recurrences during the median (IQR) follow-up of 61 (55–63) months (Table 1).

The three patients that progressed while on surveillance, were treated with three courses of BEP, resulting in complete remission, and all were alive and without recurrence during follow-up.

Of the 18/28 (64%) patients with lasting CS IIA Mk⁻ disease, nine received primary chemotherapy and nine underwent primary RPLND. The median (IQR) time from orchidectomy to RPLND was 18 (14–23) weeks. Viable cancer was found in six of nine of the RPLNDs, and the remaining patients had benign lymph nodes (Table 3). There were no recurrences

Fig. 2 Outcomes of the 126 patients with CS IIA Mk- NSGCT. The patients were diagnosed either at initial CT scan (68 patients) or, if CS I at diagnosis, on the definitive staging CT scan 6 weeks later (58). Approximately half of these patients (28/58 [48%]) with initial CS I were put on surveillance after the second staging compared to 84% (57/68) in the initial CS IIA Mk- group. A total of 41 patients were treated up-front with either chemotherapy or RPLND. The remaining were put on surveillance. During surveillance, 23 patients were downgraded to CS I and four patients progressed (two patients to CS IVA [lung metastasis], one developed inguinal metastasis, and one progressed to CS IIB Mk+). The remaining 58 patients were treated with either chemotherapy or surgery.

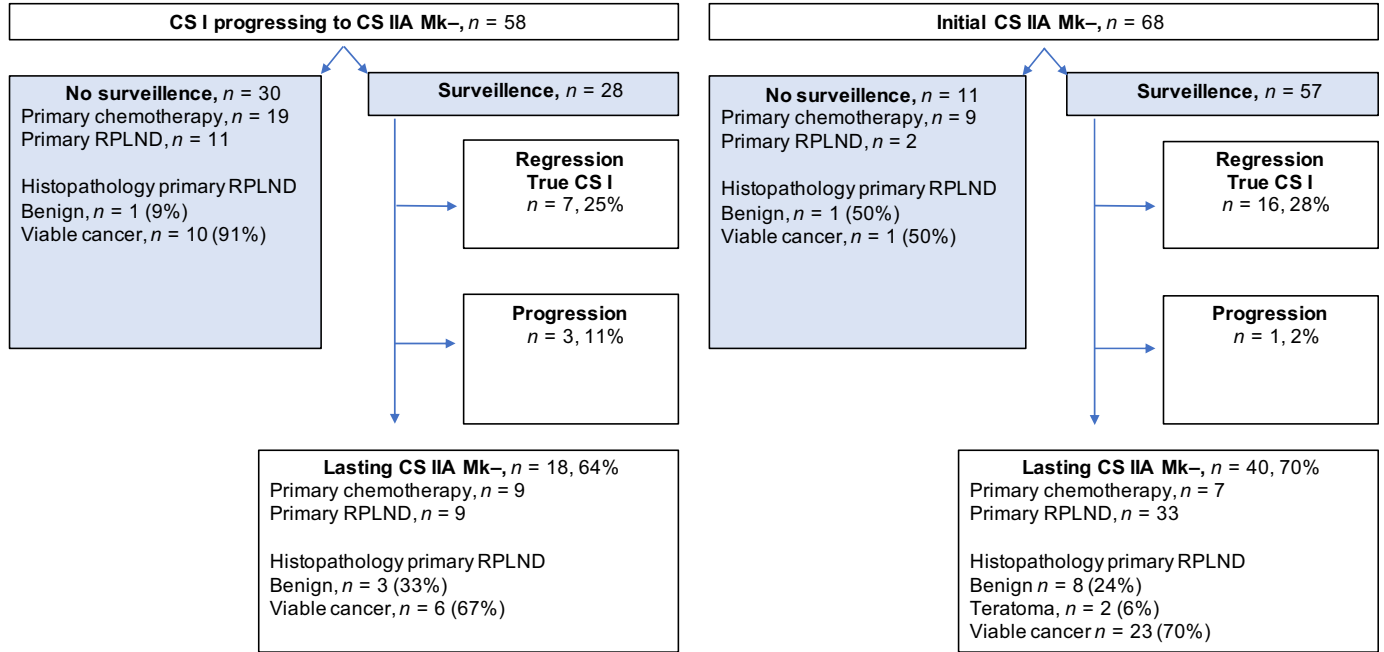


Table 1 Patients in CS I progressing to CS IIA Mk-.

Variable	No surveillance (n = 30)		Surveillance (n = 28)*		
	Chemotherapy	RPLND	True CS I	Chemotherapy†	RPLND‡
Patients, n	19	11	7	9	9
Age, years, median (IQR)	32 (25–42)	29 (23–40)	39 (27–45)	24 (22–35)	33 (25–40)
Mk+ before orchidectomy, n/N (%)	6/19 (32)	3/11	7/7	2/9	3/9
Number of surveillance CT scans, n/N					
1			4/7	9/9	5/9
2			2/7		3/9
3			1/7		1/9
Testicle histopathology, n/N (%)					
Embryonal carcinoma only	10/18 (56)	6/11		5/9	3/9
Mixed germ cell tumour	7/18 (39)	5/11	7/7	4/9	6/9
Teratoma only	1/18 (5)				
Teratoma in orchidectomy specimen§, n/N (%)	3/18 (17)	2/11	6/7	1/9	
LVI, n/N (%)	14/18 (78)	8/11	1/7	6/9	6/9
Lymph node size at therapy, mm, median (IQR)	15 (11–18)	14 (12–17)	–	20 (12–23)	13 (12–19)
Time from orchidectomy to therapy, weeks, median (IQR)	7 (6–8)	10 (8–11)	14	16 (13–19)	18 (14–23)
Overall mortality rate, n/N (%)	0/19	0/11	0/7	0/9	1/9
Cancer-specific mortality rate, n/N (%)	0/19	0/11	0/7	0/9	0/9
Recurrence rate, n/N (%)	1/19¶	0/11	0/7	0/9	0/9
Follow-up, months, median (IQR)	55 (30–97)	46 (41–64)	61 (55–63)	69 (30–102)	64 (49–126)

Patient characteristics at time of therapy for initial CS I patients that progressed to CS IIA Mk- disease at secondary CT scan. The patients are stratified by surveillance or no surveillance and type of therapy. The rate of patients treated with chemotherapy before and after 2012 changed from 75% to 59%. *The three patients that progressed on surveillance are not included in the table. †The chemotherapy regimen was three courses of BEP (n = eight) except for one patient that received two courses of cisplatin, etoposide, ifosfamide (PEI; n = one). PC-RPLND was performed in two patients due to residual lymph nodes of ≥10 mm after chemotherapy. The patient treated with two PEI courses had benign lymph nodes in the PC-RPLND histopathology and the other patient had teratoma. ‡The six patients with viable cancer in RPLND histopathology received two courses of BEP (four patients) or three courses of BEP (two). §Teratoma solely in orchidectomy specimen or in combination with other subtypes. ¶The patient was treated at diagnosis with chemotherapy (three courses of BEP) and developed a recurrence 15 months later treated with RPLND (primary neuroectodermal tumour) and chemotherapy.

during the median (IQR) follow-up of 64 (49–126) months, but one patient died of a non-testicular cancer-related cause (Table 1).

In total, nine of 28 patients put on surveillance and with lasting CS IIA Mk– disease were treated with chemotherapy. The median (IQR) time from orchidectomy until start of chemotherapy was 16 (13–19) weeks. Compared to patients treated with RPLND, patients treated with chemotherapy had fewer surveillance CT scans, and larger lymph node sizes at time of treatment (Table 1). There were no recurrences following primary chemotherapy (median [IQR] follow-up of 69 [30–102] months).

Initial CS IIA Mk– NSGCT

Out of 68 patients diagnosed with CS IIA Mk– disease, a total of 57 patients were put on surveillance. Outcomes for the non-surveillance patients can be found in Table 2. While on surveillance, 16/57 (28%) were down-staged to CS I, 40/57 (70%) had lasting CS IIA Mk– disease, and one of the 57 (2%) progressed.

The 16 patients that were down-staged to CS I were treated with one course of BEP (four LVI+, one LVI–) or chose surveillance (one LVI+, 10 LVI–). Recurrence was seen in three of 16 of the patients (all had LVI– disease at diagnosis, managed by surveillance) after a median (IQR) follow-up of 63 (43–75) months (Table 2). The recurrences were treated as per the SWENOTECA guidelines and the patients were without further recurrence at follow-up.

Patients with lasting CS IIA Mk– disease were treated with either chemotherapy (seven of 40) or RPLND (33/40). Viable cancer was found in RPLND histopathology in 23/33 (70%), teratoma in two of 33 (6%), and benign lymph nodes in eight of 33 (24%). None of the investigated variables (LVI, embryonal carcinoma or teratoma in the orchidectomy specimen, or lymph node size) were predictive of a malignant RPLND specimen on univariate regression analysis. The median (IQR) lymph node size in patients with benign lymph nodes at time of RPLND was 15 (13–18) mm and for patients with cancer was 16 (12–19) mm. In total, 22 of the 23 patients with viable cancer in the RPLND specimen received adjuvant chemotherapy (Table 3). During follow-up

Table 2 Patients with initial CS IIA Mk– NSGCT.

Variable	No surveillance (n = 11)		Surveillance (n = 57) ^a		
	Chemotherapy	RPLND	True CS I	Chemotherapy ^b	RPLND
Patients, n	9	2	16	7	33
Age, years, median (IQR)	34 (29–41)	36	31 (26–37)	30 (28–33)	31 (25–38)
Mk+ before orchidectomy, n/N (%)	4/9	1/2	10/16 (63)	3/7	18/33 (62)
Number of surveillance CT scans, n/N (%)					
1			4/16 (25)	5/7	12/33 (36)
2			8/16 (50)	2/7	17/33 (52)
3			3/16 (20)		4/33 (12)
5			1/16 (6)		
Testicle histopathology, n/N (%)					
Embryonal carcinoma only	6/8	1/2	5/16 (31)	2/7	7/33 (22)
Mixed germ cell tumour	2/8	1/2	10/16 (63)	5/7	25/33 (69)
Teratoma only			1/16 (6)		3/33 (9) ^c
Teratoma in orchidectomy specimen ^d , n/N (%)	2/8		7/16 (44)	3/7	18/33 (55)
LVI, n/N (%)	5/8	2/2	5/15 (33)	4/7	16/30 (53)
Lymph node size at therapy, mm, median (IQR)	17 (15–19)	15	17 (12–22)	17 (14–31)	15 (13–19)
Time from orchidectomy to therapy, weeks, median (IQR)	4 (3–7)	6	17 (12–22)	8 (5–17)	16 (10–25)
Overall mortality rate, n/N (%)	0/9	1/2	0/16	0/7	1/33
Cancer-specific mortality rate, n/N (%)	0/9	1/2 ^{††}	0/16	0/7	0/33
Recurrence rate, n/N (%)	1/9 ^{†††}	1/2 ^{††}	3/16 ^{**}	0/7	0/33
Follow-up, months, median (IQR)	114 (22–126)	19	63 (43–75)	107 (67–121)	64 (40–102)

Patient characteristics at time of therapy for patients with initial CS IIA Mk– NSGCT stratified on 'surveillance' or 'no surveillance' and 'type of therapy'. The rate of patients treated with chemotherapy before and after 2012 changed from 100% to 60%. All variables are presented as exact numbers with percentage in parenthesis except for age, lymph node size and time from orchidectomy to therapy presented as median (IQR). *The patient that progressed on surveillance is not included in the table. [†]Seven patients with lasting CS IIA Mk– were treated with chemotherapy (three to four courses of BEP). Two of the seven were also treated with PC-RPLND due to residual tumour size > 10 mm and the histopathology showed teratoma in one of the patients and fibrosis/necrosis in the other. [‡]Adjuvant therapy was given to 22/23 patients with viable cancer in the RPLND histopathology. Four patients received one course of BEP, 17 patients received two courses of BEP, and one patient received three courses of BEP. [§]The three patients with teratoma only in the orchidectomy specimen had the following RPLND histopathology; benign lymph nodes, seminoma, and mixed GCT (embryonal carcinoma and teratoma). [¶]Teratoma solely in orchidectomy specimen or in combination with other subtypes. ^{**}During follow-up, three of the patients had a retroperitoneal recurrence at 3, 4 and 14 months after orchidectomy. They were all LVI– and had not received adjuvant BEP initially. At time of recurrence, two were treated with RPLND (teratoma) and one received chemotherapy (two courses of BEP and one course BEP-ifosfamide) followed by PC-RPLND (teratoma). ^{††}Primarily treated with four courses of BEP and had a retroperitoneal recurrence 21 months later. Treated with RPLND (teratoma) at relapse. ^{†††}Primarily treated with RPLND and adjuvant three courses of cisplatin, etoposide, ifosfamide (PEI) and had a retroperitoneal recurrence 11 months later. Treated with high-dose chemotherapy followed by salvage PC-RPLND at relapse and later died from disease.

Table 3 Outcomes for the 42 surveillance patients that underwent primary RPLND for CS IIA Mk– disease during 2008–2019 in Sweden and Norway.

Variable	Initial CS I (n = 9)	Initial CS IIA Mk– (n = 33)
Unilateral RPLND, n/N (%)	1/9	10/32 (31)
Modified unilateral RPLND, n/N (%)	5/9	16/32 (50)
Bilateral RPLND, n/N (%)	3/9	6/32 (19)
Operating time, min, median (IQR)	150 (123–183)	161 (133–180)
Blood loss, mL, median (IQR)	100 (75–600)	196 (100–313)
Perioperative complication, n	1/9	1/33 (3)
Lymph node yield, n, median (IQR)	15 (10–26)	21 (10–26)
Postoperative nights in the hospital, n, median (IQR)	6 (5–10)	7 (5–8)
RPLND histopathology, n/N (%)		
Benign	3/9	8/33 (24)
Teratoma	–	2/33 (6)
Embryonal carcinoma	4/9	15/33 (45)
Seminoma	1/9	6/33 (18)
Mixed GCT	1/9	2/33 (6)
Any postoperative complication, n/N (%)	4/9	4/33 (12)
≥Clavien–Dindo IIIa, n	2/9	2/33 (6)
Retrograde ejaculation, n	4/9	3/33 (10)

Outcomes for the 42 surveillance patients that underwent primary RPLND for CS IIA Mk– disease during 2008–2019 in Sweden and Norway. The patients were classified as either initial CS I or initial CS IIA Mk– based on the initial CT scan. All variables are presented as exact numbers with percentage in parenthesis except for lymph node yield, operating time and preoperative bleeding that are presented as median (IQR).

at a median (IQR) 64 (40–102) months there were no recurrences, but one patient died from metastatic kidney cancer (Table 2).

Seven of the 40 patients with persistent CS IIA Mk– NSGCT were treated with chemotherapy. With a median (IQR) follow-up of 107 (67–121) months, all patients were alive and without recurrences (Table 2).

In total, 12 patients had a FDG-PET/CT performed and a positive scan was seen in nine of them. Six of the 12 patients underwent RPLND (five with positive and one with negative FDG-PET/CT scans) resulting in benign lymph nodes in four and GCT in two patients.

Discussion

The Surveillance Strategy

This is the first study to describe a surveillance strategy for patients with CS IIA Mk– NSGCT in a population-based cohort. Surveillance resulted in down-staging to CS I for 27% of the patients (initial CS I 25%, initial CS IIA Mk– 28%) making them candidates for avoiding treatment with RPLND or chemotherapy. However, the uncertainty for patients on surveillance with delayed initiation of potential therapy and

concurrent risk of progression might be negative from a quality-of-life perspective. Furthermore, surveillance carries a risk of progression to non-regional metastatic disease. Nevertheless, in this study only four of 85 patients (5%) progressed during observation, two of which progressed outside of the retroperitoneum. Although the surveillance strategy significantly delayed the initiation of systemic treatment, all patients were cured and were without recurrences at last follow-up following standard chemotherapy.

Primary RPLND Histopathology

Only two patients (none in initial CS I group and two of 33 [6%] in the initial CS IIA Mk– group) that underwent primary RPLND, had teratoma in the retroperitoneal lymph nodes, whereas 67% in the initial CS I group and 70% in the initial CS IIA Mk– group had viable cancer. Hence, despite the current belief that retroperitoneal lymph nodes in patients with CS IIA Mk– disease most likely contain benign or teratoma elements, this study in fact demonstrated a high likelihood of finding GCC in the retroperitoneal lymph nodes.

The rate of GCC in histopathology found in this study is in line with published data on patients with CS IIA Mk– NSGCT that can be extrapolated from studies involving patients with limited stage NSGCT undergoing primary RPLND. In these studies, 67–70% of the patients with normalised markers following orchidectomy had pathological lymph nodes in RPLND histopathology, mostly consisting of viable cancer [2,6,8].

Almost 70% of the patients with viable cancer in the retroperitoneal lymph nodes had GCC differentiated as embryonal carcinoma. Embryonal carcinoma does not always produce tumour markers [17], and the need for new biomarkers or radiomics to monitor this group of patients is urgently needed. MicroRNA-371a-3p might be clinically useful in this setting, with its high sensitivity and specificity for viable GCC [18,19]. Furthermore, LVI+ predicts the risk of metastatic spread in patients with CS I [7,20,21]. Although few in number, LVI status does not seem to predict the presence of viable GCC in patients with CS IIA Mk– disease in this study. However, the results should be interpreted in the light of the small number of patients.

Ideally, one would wish that improved diagnostics will reduce the burden of overtreatment, both from chemotherapy and surgery. Histopathological confirmation by guided percutaneous biopsy is an attractive option but remains a challenge due to the inherent technical difficulties in accessing a 10–20 mm sized lymph node in the retroperitoneum, as well as the risk of intratumoral heterogeneity. The FDG-PET/CT, sporadically utilised in this study, has not been found to be of significant value in NSGCT diagnostics due to its low specificity [22,23]. In the current SWENOTECA X guideline, FDG-

PET/CT is mandatory, and hopefully results from this guideline will give data to answer if FDG-PET/CT is clinically useful in this setting.

Outcome after Surveillance

None in the surveillance group treated with RPLND or chemotherapy had a recurrence, and none died from testicular cancer. Three patients that were down-staged to CS I during surveillance recurred, which is in line with the expected recurrence rate in CS I disease managed by surveillance.

Considering the low recurrence rate after all treatment modalities, our results do not resolve the issue regarding the optimal treatment strategy for CS IIA Mk– NSGCT. A primary RPLND strategy will reveal benign lymph nodes in 30% of the patients, and the remaining patients will need adjuvant chemotherapy (according to the SWENOTECA guidelines) to decrease the risk of recurrence and are thus at risk of long-term consequences of both chemotherapy and RPLND [8]. Patients with viable cancer in the RPLND histopathology have a reported recurrence rate of 30% without adjuvant chemotherapy [24,25]. However, the use of adjuvant therapy varies between countries [26]. The use of two adjuvant courses of BEP reduces the recurrence rate to 2% [9,27,28]. Perhaps one course of BEP, highly effective as adjuvant treatment in CS I [16], can be equally effective in the post-RPLND adjuvant setting. The treatment recommendation with three courses of BEP could also be justified since as many as 70% had viable cancer. However, the increasing knowledge of adverse health outcomes following cisplatin-based chemotherapy consistently indicates a dose dependency, and one course of adjuvant BEP has a lower risk of long-term toxicity compared to three courses of chemotherapy [11,29,30].

A weakness of our study is the lack of adherence to the SWENOTECA guidelines after 2012. Even though the guidelines recommended RPLND for patients with persistent CS IIA Mk– disease, some patients received chemotherapy. This study includes a case mix of patients before and after 2012. Patients selected for chemotherapy had a larger median lymph node size, and the lymph nodes had during surveillance more often progressed in size within the limit of CS IIA, which indicated a greater likelihood of progressing to viable GCC. These factors might explain the observed protocol deviations. Another limitation is the lack of a central pathology and imaging review. However, the patients have been discussed at local/regional/national multidisciplinary tumour boards.

Conclusion

The surveillance strategy was successful in identifying both patients with more advanced disease and patients with true CS I disease. An initial surveillance period does not influence

survival and has the potential to spare true CS I patients from overtreatment. Most patients that undergo RPLND due to persistent CS IIA Mk– NSGCT have cancer, predominately embryonal carcinoma, in the retroperitoneal lymph nodes, supporting both chemotherapy and RPLND as the primary treatment modality. Outcome after therapy with either chemotherapy or RPLND is excellent. Initial treatment with RPLND will reduce the total burden of chemotherapy in this group of patients but comes with the potentially adverse effects of RPLND treatment.

Disclosure of Interests

The authors have no conflict of interest to disclose.

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Correspondence: Axel Gerdtsen, Jan Waldenströms gata 5, 21421 Malmö, Sweden.

e-mail: axel.gerdtsen@ki.se

Abbreviations: AFP, alpha fetoprotein; BEP, bleomycin, etoposide, cisplatin; CS, clinical stage; FDG-PET, fluorodeoxyglucose positron emission tomography; GCC, germ cell cancer; GCT, germ cell tumour; IQR, interquartile range; LVI(+)(–), lymphovascular invasion (present) (absent); Mk(+)(–), marker (positive) (negative); NSGCT, non-seminomatous GCT; (PC-)RPLND, (post-chemotherapy) retroperitoneal lymph node dissection; SWENOTECA, Swedish and Norwegian Testicular Cancer Group.