Seminoma Patients Treated at a Minor Oncological Department During 1986-2010: Treatment and Outcome

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Abstract. *Aim: To present results for patients with seminoma treated at our University Clinic. Patients and Methods: All men treated for seminoma in 1986-2010 at the Department of Oncology, University Hospital of North Norway were included (n=232). Treatment was standardized from 2000 as the Swedish and Norwegian Testicular Cancer Project (SWENOTECA) published their first standardised seminoma treatment program (SWENOTECA V). Results: The percentage of patients administered adjuvant radiotherapy (RT) for clinical stage (CS) I decreased gradually from the late 1990s and was abandoned in 2005. Surveillance was the most common management strategy for CS I after 2000. Overall, disease in 1.9% and 11% of patients relapsed after adjuvant RT and surveillance, respectively. There were no relapses after treatment for metastatic disease. Cancer-specific survival was 100%, and overall survival 95% for the total group. Conclusion: The treatment outcome at our University Clinic is excellent with 100% cancer-specific survival, and is essentially a result of the bi-national SWENOTECA network.*

Germ-cell testicular cancer (TC) is the most common type of solid cancer among men aged 15-45 years (1). Norway has one of the highest incidence rates in the world, and in 2010 the incidence was 10.3 per 100,000 person-years (2). About 85% of the patients with seminoma are diagnosed with clinical stage I (CS I) disease (3). Testicular seminomas are highly sensitive to both chemotherapy and radiotherapy (RT), and hold an excellent prognosis, with a 5-year cancer-specific survival of 100% (3, 4). The standard treatment for CS I is currently controversial, and treatment options after orchiectomy may be adjuvant RT, adjuvant carboplatin or surveillance (1).

The Swedish and Norwegian Testicular Cancer Project (SWENOTECA) was initiated in 1981 to provide management programs for staging, treatment and follow-up of germ-cell TC (5). In January 2000, the first program to standardize care for patients with seminoma was published (SWENOTECA V) (3). In Norway, post-orchiectomy treatment and follow-up of patients with TC are centralized to four University Hospitals. The Department of Oncology at the University Hospital of North Norway has participated in the SWENOTECA network since 1985. Our University Clinic covers a large geographical area with a population of 0.5 million. Today, between 30 and 40 men with germ-cell TC are treated at our institution each year. Many oncologists are involved in the treatment and follow-up of patients with TC at our Clinic. However, members of the SWENOTECA working group make sure that all changes in treatment and follow-up are implemented in clinical practice, and are also involved in the treatment of all patients with metastatic disease.

The aim of the present study was to present the results of seminoma treatment with respect to stage, *i.e.* CS I *vs.* metastatic disease, and treatment period, before *vs.* after the SWENOTECA V guidelines.

Patients and Methods

Inclusion of patients. All men treated for testicular seminomas between November 1st 1986 and December 31st 2010 at the Department of Oncology, University Hospital of North Norway were included in this study. Patients with spermatocytic seminomas or extragonadal seminomas were excluded. The regional Data Protection Officer approved the study (approval number PVO 0182).

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Key Words: Seminoma, survival, chemotherapy, radiotherapy, surveillance, carboplatin.

Table I. *Patients' characteristics according to treatment period. Data are presented as number (%), except age at diagnosis, age at follow-up, observation time and tumor size, which are presented as median (range).*

Characteristic	Before SWENOTECA V N=102	After SWENOTECA V N=130	All patients N=232
Age at diagnosis, years	37 (22-72)	38 (24-77)	38 (22-77)
Age at follow-up, years	54 (34-83)	45 (26-83)	50 (26-83)
Observation time, years	17.3 (10.6-26.3)	6.4 (2.3-13.1)	11.3 (2.3-26.3)
Married/cohabitant at diagnosis	66 (69)	86 (67)	152 (68)
Smoking at diagnosis	30 (54)	47 (43)	77 (46)
RMH stage			
Stage I	87 (85)	111 (85.4)	198 (85.3)
Stage II	15 (15)	16 (12.3)	31 (13.4)
Stage III	0	2 (1.5)	2 (0.9)
Stage IV	0	1 (0.8)	1 (0.4)
Tumour size, cm	3.5 (1.0-13)	3.4 (0.6-9.0)	3.4 (0.6-13)
Invasion of rete testis			
Yes	18 (32)	43 (39)	61 (37)
Uncertain	6 (11)	5 (5)	11 (7)
Vascular invasion	15 (22)	22 (19)	37 (20)
Elevated pre-HCG	16 (18)	28 (24)	44 (21)
Bilateral testicular cancer	8 (7.8)	5 (3.8)	13 (5.6)

RMH: Royal Marsden Hospital; HCG: human chorionic gonadotropin. There are missing values for some of the listed variables: married/cohabitant, n=8; smoking, n=66; tumour size, n=21; rete testis invasion, n=66; vascular invasion, n=51; pre-HCG, n=23.

Demographic, histopathological and clinical parameters, in addition to follow-up information, were retrieved from the medical hospital records. Since treatment and follow-up of men with TC in our region has been centralized to our University Hospital, patients living in our health region would have been admitted to our Clinic in cases of suspected relapse. For men who had moved to other health regions, their University Hospital was contacted for information about relapses and potential subsequent treatment. The alive/dead status was verified by searching the National Registry. For the deceased, the cause of death was that given by the certificate of death issued by the local hospital or the patients' general practitioner.

Staging, treatment principles and follow-up 1986-2010. An orchiectomy was, as a routine, the initial treatment. The invasion of *rete testis* in the histological testis specimen was not routinely described prior to the SWENOTECA VII guidelines in 2007 (3). Staging procedures consisted of computed tomography (CT) abdomen/pelvis and X-ray or CT of the lungs. Disease stage was classified according to the Royal Marsden Hospital staging system (3). Tumor markers were preferably analysed prior to the orchiectomy, but at a minimum before the start of additional treatment. Patients with elevated levels of human chorionic gonadotropin (HCG) were included regardless of HCG value if their tumors were described as pure seminomas in the pathology report. Patients with elevated levels of alpha-fetoprotein were considered to harbour non-seminomatous elements, and were classified as non-seminomas. The classification of patients with metastatic disease into prognostic groups was performed retrospectively (6).

Before 2000, men with seminoma stage I, IIA and IIB routinely received RT to the ipsilateral iliac and para-aortic lymph nodes (dog-leg field), as two opposed anterior-posterior fields. The total radiation doses gradually decreased from 36 to 25.2 Gy for CS I, and from 40 to 27 Gy for stage II during the treatment period (7). Men with stage IIC-IV were treated with four cycles of bleomycin, etoposide and cisplatin (BEP) followed by surgery in cases of residual tumour.

In January 2000, SWENOTECA issued a program specifically for treatment and follow-up of patients with seminoma, the SWENOTECA V protocol (3). Men with CS I could choose between RT to a dog-leg field with 25.2 Gy or surveillance. Patients with stage IIA disease were offered 27 Gy to a dog-leg field. Men with stage IIB or more advanced disease received four cycles of etoposide and cisplatin (EP), or four of BEP in cases of very advanced disease. Post-chemotherapy surgery was not recommended.

In 2007, SWENOTECA V was replaced by a new protocol, SWENOTECA VII. Herein, RT in the case of CS I was replaced by either surveillance or one adjuvant carboplatin cycle (dose according to Area Under Curve 7). The preferred treatment was based on the presence of the proposed risk factors i) tumour size >4 cm and ii) invasion of the *rete testis* (8), where patients with both risk factors were recommended carboplatin. For men with stage IIA or more advanced disease, the treatment was as for SWENOTECA V.

Follow-up routines were standardized from 2000 in accordance with the SWENOTECA guidelines. In short, all patients were followed up for a total of 10 years at our Outpatient Clinic, including evaluation of tumor markers and sex hormone levels, clinical examination and CT scans of the abdomen at most follow-ups. During recent years, we have gradually replaced CT scans with MRI during follow-up due to the possible risk for radiation-induced second malignancies after multiple CT scans (9).

Statistics. The observation time was calculated from the date of diagnosis (orchiectomy date in the majority of cases) to the last follow-up date or time of death. Time to relapse was calculated from the date of diagnosis to the date of relapse.

Differences between two groups (prior to *vs.* after SWENOTECA V, or between relapse *vs.* no relapse) were analysed by using

Table II. *Seminoma stage I, treatment and relapses according to treatment period. Data are presented as number (%), except time to relapse, which are presented as median (range). Relapse-free survival, cancer-specific survival and overall survival are presented as percentages.*

Characteristic	Before SWENOTECA V N=87	After SWENOTECA V N=111	All patients N=198
Initial treatment strategy			
RT	83 (96)	23 (21)	106 (53)
Chemotherapy	2 (2)[a]	15 (13)	17 (9)
Surveillance	2 (2)[b]	73 (66)	75 (38)
RT field			
Dog-leg	80 (96)	21 (91)	101 (95)
Other[c]	3 (4)	2 (9)	5 (5)
Total radiotherapy dose			
≤25.2 Gy	22 (26)	22 (96)	44 (42)
27.0 Gy	29 (35)	1 (4)	30 (28)
30.6 Gy	24 (29)	0	24 (23)
36-40 Gy	8 (10)	08 (7)	
Relapses			
After radiotherapy	2 (2.4)	0	2 (1.9)
After chemotherapy	0	0	0
After surveillance	0	8 (11)	8 (10.7)
Time to relapse, months	43 (20-67)	15 (4-93)	18 (4-93)
Relapse localisation			
Retroperitoneum	0	7 (6.3)	7 (3.5)
Mediastinum	1 (1.1)[d]	1 (0.9)	2 (1.0)
Other (temporal region)	1 (1.1)	0	1 (0.5)
Relapse-free survival	98	93	95
Cancer-specific survival	100	100	100

RT, Radiotherapy. There are no missing values. [a]One patient had a retroperitoneal mass which was initially classified as stage II. Biopsy revealed that this was a hematoma, and he received two cycles of bleomycin, etoposide and cisplatin (BEP). Another patient had a tumour in an undescended testis, but no evidence of lymph node metastases, and received three cycles of BEP. [b]One patient had an inguinal lymph node dissection with no signs of malignancy in the pathological specimen. Another patient had a second seminoma stage I and had previously received adjuvant radiotherapy to a dog-leg field, and therefore surveillance was chosen. [c]Four patients received a Y-field, and one received RT to the testis due to testicular-sparing surgery. [d]This patient had a relapse in the mediastinum and the cranium.

Student's *t*-test for continuous variables and by using X^2 for categorical variables. If the X^2 test was invalid due to too many cells with values below the minimum expected count, a non-parametric test was performed (Mann–Whitney *U*-test).

Overall survival curves were calculated by using the Kaplan–Meier method, and the log-rank test was used to evaluate possible differences in overall survival according to disease stage (CS I *vs*. metastatic disease) and according to stage I treatment. All *p*-values are two-sided with a 5% significance limit. The data were analysed using SPSS 21.0 (SPSS Inc., Chicago, IL, USA).

Results

Patients' characteristics. In total 232 men with seminoma were treated at our Institution, out of whom 102 patients (44%) were treated before SWENOTECA V (January 1st 2000). Patients' characteristics according to treatment period are presented in Table I. In total 198 patients (85%) were classified with initial CS I.

A bilateral germ-cell TC was diagnozed in 13 (5.6%) patients, where four (1.7%) cases were synchronous, and nine (3.9%) were metachronous. The median time interval between the first and the second TC diagnosis was 10.8 (range=1.8-16.9) years. Although the absolute percentage of men diagnosed with bilateral TC was higher before than after SWENOTECA V, this difference was not statistically significant (7.8% *vs*. 3.8%, p=0.25).

CS I patients. Treatment: In total, 96% of the patients treated before SWENOTECA V were administered adjuvant RT (Table II). After SWENOTECA V, only 21% of the patients were treated with adjuvant RT, 13% received one adjuvant carboplatin cycle, and 66% were managed by surveillance only.

The percentage of patients administered adjuvant RT decreased gradually from the late 1990s and was abandoned after 2004, while surveillance was the most common management strategy during 2000 until 2010 (Figure 1). Adjuvant carboplatin was increasingly used during the most recent years. The RT portals were dog-leg fields in the majority of cases in both treatment periods (Table II). The total radiation dose was reduced after the introduction of SWENOTECA V in 2000 (p<0.001).

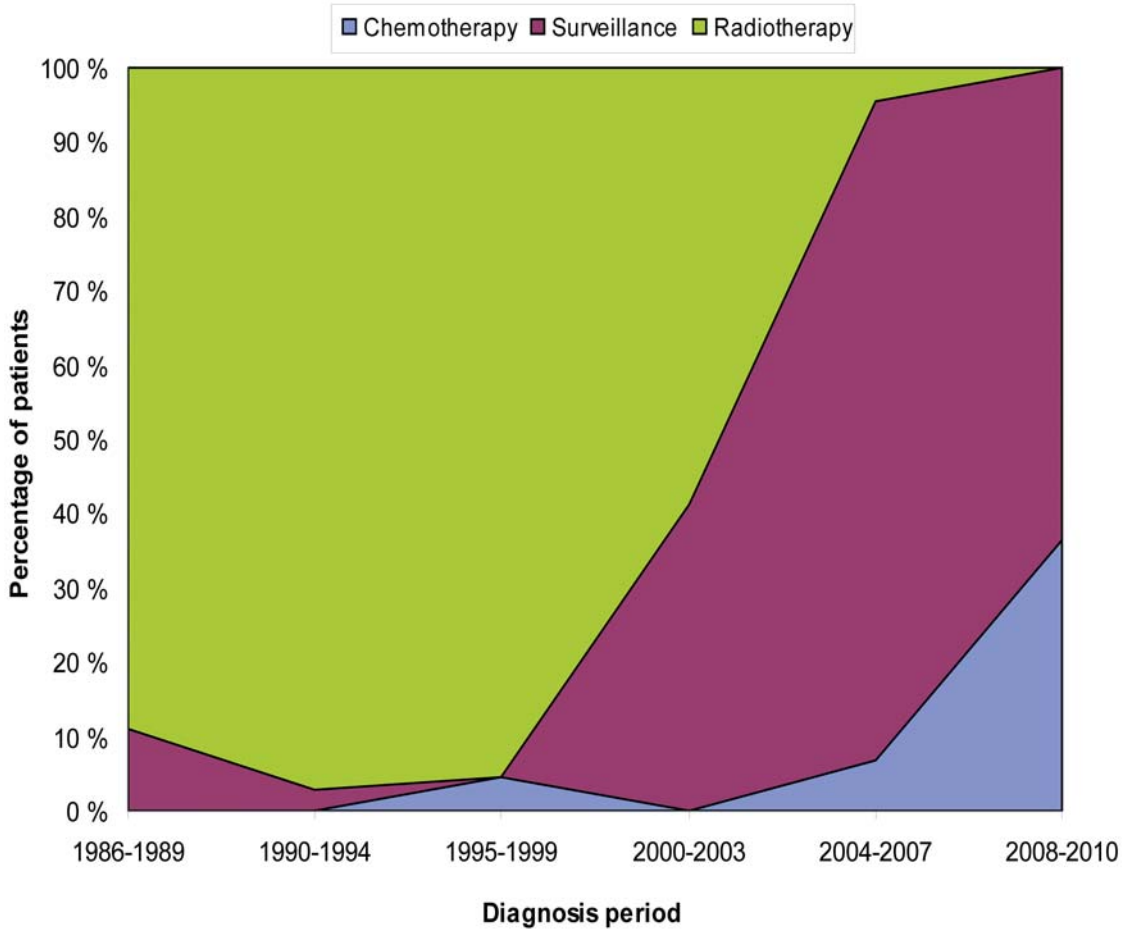

Figure 1. *Changes in the treatment of seminoma clinical stage I over time, from 1986-89 to 2008-10.*

Relapse: Overall 10 relapses were identified at a median of 18 (range=4-93) months after diagnosis. Three of the relapses were diagnosed at later than 24 months of follow-up. After adjuvant RT, only two out of 106 patients experienced relapse (1.9%). One patient had a marker-positive relapse in the mediastinum and cranium 20 months following adjuvant RT, while another patient had a biopsy-proven relapse in the temporal bone 67 months after RT. No relapses after adjuvant chemotherapy were observed. After surveillance, 8 out of 75 patients experienced relapse (11%), of which seven were located in the retroperitoneum, while one relapse diagnosed 93 months after orchiectomy was located in the mediastinum.

All relapses were treated with cisplatin-based chemotherapy, and patients were later rendered disease-free. One patient received additional RT to the temporal region. Invasion of the *rete testis* was present in 12.5% of all patients with relapse *vs*. 34% among patients without relapse (p=0.52). Tumour size was a median of 3.2 (range=0.6-13.0) cm among patients with relapse and 4.0 (range=1.5-7.0) cm among patients without relapse (p=0.55).

Metastatic disease. In total, 34 patients were treated for initial metastatic disease (Table III). Only one patient was retrospectively classified as having an intermediate prognosis, the remaining 33 had good prognostic features. While RT was used in 60% of patients treated before SWENOTECA V, chemotherapy was the standard treatment in the majority of patients treated later (Table III, p=0.036). The total radiation dose was lower after SWENOTECA V than before (p=0.036), and all irradiated patients received infra-diaphragmatic RT. All patients treated with chemotherapy received BEP before SWENOTECA V, while most patients treated later were administered EP (p=0.001).

All patients with stage IIA disease received RT before SWENOTECA V (n=6), whereas later, two received RT and two had chemotherapy. One of the two patients administered chemotherapy had metachronous bilateral TC and had

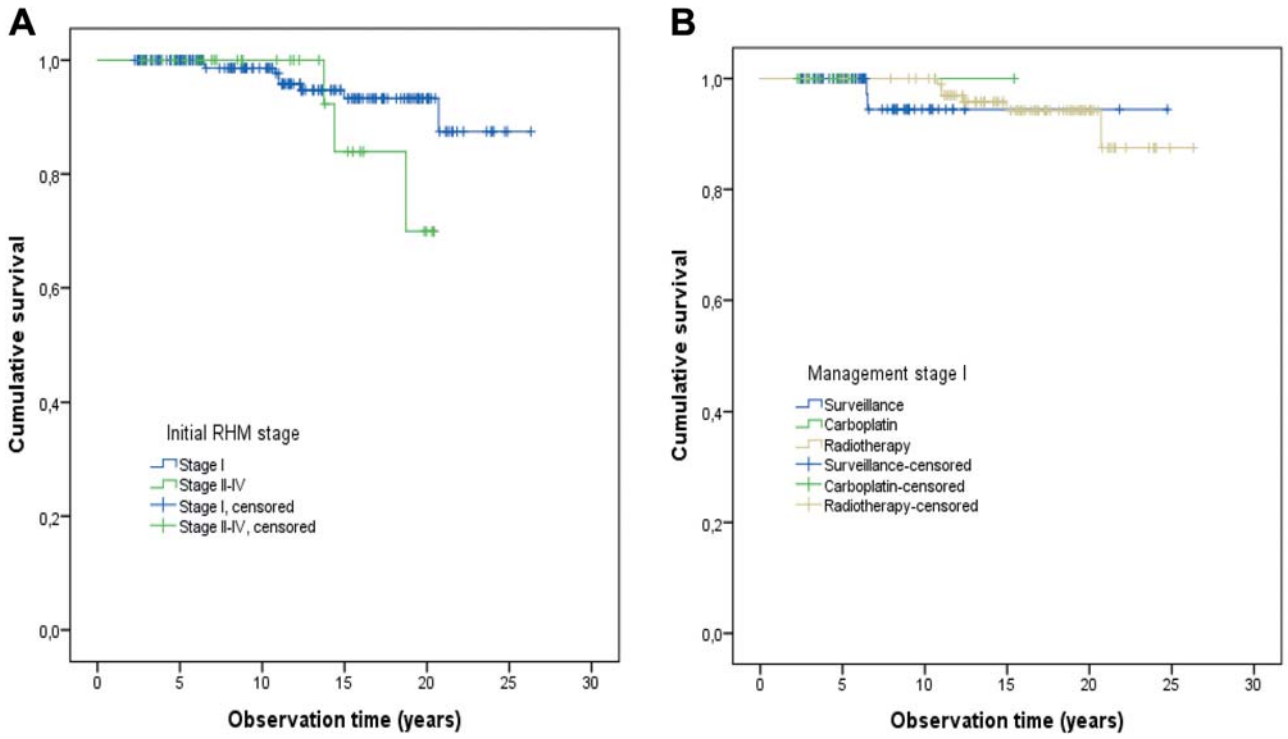

Figure 2. *Overall survival according to disease stage (stage I vs. metastatic disease, p=0.15) (A) and for stage I according to management strategy (radiotherapy, carboplatin and surveillance, p=0.44) (B).*

previously received RT at another institution. The other patient had suspected stage IV disease at diagnosis, which later was disproven.

Prior to SWENOTECA V, two patients with stage IIB received RT and the remaining two received chemotherapy. All patients with stage IIC were administered chemotherapy, and three patients had retroperitoneal lymph node dissection after chemotherapy for stage IIB/C disease. After SWENOTECA V, all patients with stage IIB or more advanced disease received cisplatin-based chemotherapy without additional surgery. The majority of patients received EP. Only three men received four cycles of BEP chemotherapy, out of whom one had intermediate prognosis, the other two were treated prior to 2005.

All patients were rendered disease-free after the primary treatment. There were no relapses among patients with initial metastatic disease.

Survival. There were no deaths as a result of germ-cell cancer or treatment complications, yielding a cancer-specific survival at 100%. Overall survival was 95% in total, and 96% and 91% for CS I and metastatic disease, respectively (Table II and III). Figure 2A presents overall survival according to disease stage, while Figure 2B presents survival for stage I according to treatment.

In total, 11 men (4.7%) had died during follow-up. Four men died as a result of another malignancy, and all were smokers at TC diagnosis. Causes of death are listed in Table IV. Eight of the dead men had previously received RT, one with additional chemotherapy.

Discussion

Treatment of patients with seminoma at our University Clinic has gradually changed over time and in particular after the introduction of the SWENOTECA V seminoma protocol in 2000. Treatment results are excellent with 100% cancer-specific survival.

Strengths of this study include the population-based design and a long observation period, with complete follow-up data for all patients. Since our University Hospital is the only hospital responsible for post-orchiectomy treatment and follow-up in our region, we are able to identify non-compliant patients and make all possible efforts to increase patient compliance by contacting the patient himself and if necessary, the patient's general practitioner. In general, non-compliance is a rather small problem at our University Hospital, representing a strength in the follow-up of these patients. Due to a high number of patients with missing data for *rete testis* invasion and the low number of men with

Table III. *Metastatic seminoma, treatment details according to treatment period. Data are presented as number (%), except relapse-free survival, cancer-specific survival and overall survival, which are presented as percentages.*

Characteristic	Before SWENOTECA V N=15	After SWENOTECA V N=19	All patients N=34
RMH stage			
IIA	6 (40)	4 (21)	10 (29)
IIB	4 (27)	9 (47)	13 (38)
IIC	5 (33)	2 (11)	7 (21)
IID	0	1 (5)	1 (3)
III	0	2 (11)	2 (6)
IV	0	1 (5)	1 (3)
Elevated pre-HCG	3 (23)	6 (35)	9 (30)
Treatment strategy			
RT	8 (53)	2 (11)	10 (29)
Chemotherapy	6 (40)	16 (84)	22 (65)
Combined RT/chemo	1 (7)	1 (5)	2 (6)
RT field			
Dog-leg	8 (89)	2 (67)	10 (83)
Other[a]	1 (11)	1 (33)	2 (17)
Total radiation dose			
27.0 Gy	1 (11)	2 (67)	3 (25)
36.0 Gy	0	1 (1)	1 (8)
39-40 Gy	8 (89)	0	8 (67)
Chemotherapy regimen			
EP	0	14 (82)	14 (58)
BEP	7 (100)	3 (18)	10 (42)
Chemotherapy cycles			
Two	1 (14)	1 (6)[b]	2 (8)
Three	0	1 (6)	1 (4)
Four	6 (86)	15 (88)	21 (88)
Relapse-free survival	100	100	100
Cancer-specific survival	100	100	100
Overall survival	80	100	91

RMH, Royal Marsden Hospital; HCG, human chorionic gonadotropin; RT, radiotherapy; EP, etoposide and cisplatin; BEP, bleomycin, etoposide and cisplatin. Missing values: Elevated HCG, n=4. [a]One patient received RT to a residual para-aortic tumour and one received RT to the columna. [b]One patient with stage IIA terminated chemotherapy after two cycles of EP because of a cerebral insult.

Table IV. *Patients' characteristics and causes of death for 11 men who died during follow-up.*

Diagnosis year	Age at diagnosis, years	Initial stage	Initial treatment	Relapse and treatment	Smoking at diagnosis	Observation time, years	Age at death	Cause of death
1988	52	IIB	Radiotherapy	No	Unknown	18.7	71	Cardiovascular disease
1989	59	I	Radiotherapy	No	No	15.0	73	Pulmonary fibrosis
1991	53	I	Radiotherapy	No	Yes	20.7	74	Lung cancer, radiation pneumonitis
1992	55	IIC	Chemotherapy	No	Yes	13.7	68	Lung cancer
1996	49	IIA	Radiotherapy	No	Yes	14.4	64	Unknown
1996	47	I	Radiotherapy	No	No	12.3	60	Unknown, but severe cardiac failure while alive.
1997	72	I	Radiotherapy	No	No	11.0	83	Subdural hematoma
1999	48	I	Radiotherapy	No	Yes	11.0	59	Accident at sea
1999	40	I	Radiotherapy	Yes, chemotherapy	Yes	10.8	51	Lung cancer
2004	77	I	Surveillance	No	No	6.5	83	Renal failure, pneumonia
2005	50	I	Surveillance	No	Yes	6.5	57	Pancreatic cancer

relapse, it was not possible to evaluate possible risk factors for relapse in CS I.

The incidence of metachronous TC in our patient population was 3.9%, which is in line with results from a large Norwegian study (10), but higher than previous reports from other countries (11-13). This higher incidence of metachronous TC in Norway may, in part, be explained by a low biopsy rate of the contralateral testicle, and infrequent RT when biopsy revealed testicular intraepithelial neoplasia (10). The longest interval between first and second TC in our study was 17 years, corroborating results from previous studies (10-12), and should be taken into account when planning follow-up after treatment.

In line with previous reports, 85% of our patients had CS I disease (3, 14). Of patients administered adjuvant RT, 1.9% experienced relapse, a number which is higher than the 0.8% relapse rate reported in the SWENOTECA study (3), but lower than the 3.6% relapse rate after adjuvant dog-leg RT in the MRC TE10 trial (15). While previous studies have shown that nodal relapse is the most common relapse site after adjuvant RT, the two patients experiencing relapse after adjuvant RT in our study had bone metastases. Although bone metastases from seminoma are a rare entity, they have been reported in 5-25% of relapses following adjuvant RT for stage I seminoma (3, 15, 16).

In line with emerging data regarding the usefulness of adjuvant carboplatin in patients with stage I seminoma, adjuvant carboplatin was increasingly used at our Institution during most recent years. Previous studies have reported relapse rates after adjuvant carboplatin of between 1.4% and 5.0% (3, 4, 17). We did not observe any relapses after carboplatin in our study, but the number of patients was limited. There was an 11% relapse rate among our patients managed with surveillance, which is in line with results from the Spanish Germ Cell Cancer Group (17), but lower than the reported rates in other studies (3, 14, 18, 19). As observed by others, most patients with relapse followed by surveillance had a retroperitoneal relapse (3, 17).

The proposed risk factors for relapse in CS I seminoma (*rete testis* infiltration, tumour size >4 cm) (8) was not associated with risk of relapse in our study, and have not been confirmed in prospective studies (3, 20). However, we had a substantial number of missing data for *rete testis* invasion. There is, nevertheless, at least a negative prognostic value of these risk factors as indicated by a prospective Spanish study (17).

Although adjuvant RT for CS I is effective regarding disease control (4, 21), RT was abandoned after 2004 at our Institution. This treatment strategy is hampered by increasing knowledge regarding serious late-effects and is associated with an increased risk for potential life-threatening morbidity as cardiovascular disease and second malignant neoplasms (21, 22). Given the increasing knowledge about potential serious late-effects after RT combined with long-term excellent cure rates after surveillance (3, 18, 19), the surveillance strategy should be considered the standard management option in compliant patients with CS I seminoma (23) in the absence of the proposed risk factors.

There were no relapses among our patients treated for metastatic disease, and they had a cancer-specific survival of 100%. Contemporary studies have reported relapse rates after infradiaphragmatic RT for stage IIA at 8-17% (3, 14, 24, 25). Standard chemotherapy for stage IIB has yielded excellent results with very low relapse rates at 0-4% (3, 14). For stage IIA and B, controversies regarding the optimal treatment exist, while there is international consensus regarding the use of cisplatin-based combination therapy for patients with stage IIC or more advanced disease (1). We believe that three to four cycles of standard-dose BEP according to the risk group classification should be the standard management for all men with metastatic seminoma unless contraindications to bleomycin exist (14, 26).

The cancer-specific survival was 100% in our study. However, four men died as a result of a non-germ cell cancer, out of whom three had received cytotoxic treatment. No conclusions can be drawn regarding the relationship between treatment and the cause of death in these four men. Nevertheless, avoiding dual therapy is particularly important since the combination of RT and chemotherapy is associated with particularly high risks for both cardiovascular disease and second malignant neoplasms (22), with increased risks of a shortened life expectancy.

In conclusion, outcome for patients with seminoma treated at our minor Oncological Department is excellent and in line with outcomes from larger Institutions. The excellent cure rates are achieved through cooperation within the SWENOTECA network, ensuring standardized and evidence-based care for all men with germ cell cancers (27).

Acknowledgements

We would like to thank the Norwegian Cancer Society for supporting this project.

We would like to thank research nurse Kristin Iren Jensen, and the research secretaries Ann Nyheim and Ingrid Sandstad for valuable help with the database and for help with searching the National Registry.

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Received May 7, 2014
Revised June 14, 2014
Accepted June 16, 2014