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Continuing increased risk of second cancer in long-term testicular cancer survivors after treatment in the cisplatin era

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Using complete information on total treatment burden, this population-based study aimed to investigate second cancer (SC) risk in testicular cancer survivors (TCS) treated in the cisplatin era. The Cancer Registry of Norway identified 5,625 1-year TCS diagnosed 1980–2009. Standardized incidence ratios (SIRs) were calculated to evaluate the total and site-specific incidence of SC compared to the general population. Cox regression analyses evaluated the effect of treatment on the risk of SC. After a median observation time of 16.6 years, 572 TCS developed 651 nongerm cell SCs. The SC risk was increased after surgery only (SIR 1.28), with site-specific increased risks of thyroid cancer (SIR 4.95) and melanoma (SIR 1.94). After chemotherapy (CT), we observed 2.0- to 3.7-fold increased risks for cancers of the small intestine, bladder, kidney and lung. There was a 1.6- to 2.1-fold increased risk of SC after ≥2 cycles of cisplatin-based CT. Radiotherapy (RT) was associated with 1.5- to 4.4-fold increased risks for cancers of the stomach, small intestine, liver, pancreas, lung, kidney and bladder. After combined CT and RT, increased risks emerged for hematological malignancies (SIR 3.23). TCS treated in the cisplatin era have an increased risk of developing SC, in particular after treatment with cisplatin-based CT and/or RT.

Introduction

Patients with germ cell testicular cancer (TC) have a 15-year relative survival rate exceeding 98% in Norway.[1] An important factor for the excellent prognosis was the introduction of cisplatin in the late 1970s.[2,3] However, the relative overall survival beyond 20 years after successful TC treatment is continuously decreasing.[4] One explanation is second cancer (SC) development which is a severe and possibly life-threatening late effect after cancer treatment.[5]

Previous studies have demonstrated a 1.7 to 3.5-fold increased risk for both hematological and solid nongerm cell SC in testicular cancer survivors (TCS) compared to age-matched general populations.[6–9] The risk has been associated with both radiotherapy (RT) and chemotherapy (CT), but not with surgery only. The majority of these studies have, however, been based on outdated TC treatment principles. Consequently, there is a lack of studies on SC risk after the introduction of cisplatin.[9–12] Experimental data and animal studies have suggested cisplatin as a carcinogen.[13]

Additional Supporting Information may be found in the online version of this article.

Key words: testicular cancer, second cancer, survivorship, cancer epidemiology, radiotherapy, chemotherapy, surgery, germ cell

Abbreviations: CBCT: cisplatin-based chemotherapy; CRN: Cancer Registry of Norway; CT: chemotherapy; HR: hazard ratio; IQR: interquartile range; RPLND: retroperitoneal lymph node dissection; RT: radiotherapy; SC: second cancer; SIR: standardized incidence ratio; TC: testicular cancer; TCS: testicular cancer survivors

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What's new?

Long-term survival to 15 years among germ cell testicular cancer survivors treated in the cisplatin era, marked by the introduction of cisplatin in the late 1970s, generally has been excellent. Beyond 20 years, however, survival rates decline. In this analysis of data on Norwegian men diagnosed with testicular cancer between 1980 and 2009, an increased overall risk for nongerm cell second cancer was detected among survivors, despite treatment. Risk was elevated in particular beyond 10 years of follow-up after cisplatin-based chemotherapy or radiotherapy. Despite reduced treatment intensity, two or more cycles of cisplatin-based chemotherapy was associated with continuing increased second cancer risk.

Besides, high cumulative cisplatin doses have been linked to an increased leukemia risk.[14,15]

Three recent publications have evaluated SC risk after cisplatin-based chemotherapy (CBCT) in TCS, demonstrating a 40–80% excess risk.[7–9] However, two of these studies lack complete treatment information.[7,9] Rather than calculating standardized incidence ratios (SIRs), Kier *et al.* calculated the cumulative incidence of SC and hazard ratios (HR) by using a control group from the general population matched 10:1 on age at diagnosis.[8] Importantly, this study presented favorable results for the surveillance group, demonstrating no excess risk of SC or reduced survival compared to the control group.

The aim of this population-based study was to investigate the risk of nongerm cell SC among TCS in the cisplatin era, by (*i*) comparing the incidence of SC to that of the general population, and (*ii*) investigating the risks associated with different treatment modalities (surgery, RT, CT and the surveillance strategy).

Methods

Study cohort and design

Men diagnosed with histologically verified germ cell TC from January 1, 1980, to December 31, 2009, were identified through the Cancer Registry of Norway (CRN).[1] Major exclusion criteria included extragonadal germ cell cancer, a prior malignancy, age <16 years at TC diagnosis and death or SC before 12 months follow-up (Supporting Information Fig. S1). Follow-up started 12 months after diagnosis to avoid inclusion of synchronous or treatment-unrelated cancer.

The final study cohort consisted of 5,625 one year survivors of first primary germ cell TC. Detailed information regarding disease stage, histology and primary and subsequent TC treatment was abstracted from medical records and linked with CRN data on subsequent cancer diagnoses, updated through December 31, 2016.

This historical prospective cohort study was approved by the Regional Committee for Medical and Health Research Ethics and the Data Protection Authorities at the University Hospital of North Norway. All eligible TCS still alive have received a study information letter with the possibility to withdraw from participation (passive consent). Twenty-three men (0.38%) declined participation, for reasons undisclosed.

Staging and treatment groups

The clinical staging of TC was based on the Royal Marsden Hospital staging system.[16] Overall, treatment intensity has gradually been reduced during the study period in line with increasing knowledge about efficacy and toxicity (Supporting Information Table S1).[2,17] The number of CT cycles used to treat patients with initially metastatic disease have been reduced over the years from ≥4 to 3 cycles for patients with good prognosis (the majority of patients) and 4 cycles for patients with intermediate and poor prognosis.[2,18] During the study period, the usage of RT for stage I seminoma and primary retroperitoneal lymph node dissection (RPLND) for early stages of nonseminoma was gradually abandoned (Supporting Information Table S1).

The study cohort was categorized into three groups by decade of TC diagnosis. It was further categorized into treatment groups by overall treatment burden: Surgery only (including surveillance, n = 1,394; 25%), CT (n = 2,471; 44%), RT (n = 1,542; 27%) and CT and RT combined (CT + RT; n = 218; 3.9%; Table 1).

Statistical methods

Categorical variables are presented with numbers and percent, while continuous variables are presented with median and interquartile range (IQR), unless otherwise stated.

Participants were followed from the time of their first TC + 1 year, until the development of a nongerm cell SC of interest, death, emigration or December 31, 2016, whichever occurred first. To avoid immortal time bias (a period of follow-up during which, by design, the outcome of interest cannot occur), treatment was analyzed as a time-varying covariate. For instance, a patient accrued person-years of observation time in the surgery only group until the date they received CT or RT.

The crude probability of SC was estimated by the cumulative incidence using the Aalen-Johansen estimator,[19] treating death from any cause as a competing risk.

SIRs were calculated to evaluate the total and site-specific incidence of SC in the TC cohort compared to the general population. A subgroup analysis was performed for those initially designated to surveillance. SIRs were obtained by dividing the observed number of cancers in the cohort by the expected number in a TC-free, male Norwegian population, matched by 5-year age groups and calendar year of follow-up. SIRs were calculated for the total cohort and for different treatment groups, taking the time-varying treatment exposure into account. Results are presented with

Table 1. Patient characteristics according to the decade of first primary TC diagnosis

	Decade of first primary TC diagnosis			
	1980–1989 (*n* = 1,274)	**1990–1999 (*n* = 1,896)**	**2000–2009 (*n* = 2,455)**	**All (*n* = 5,625)**
Treatment, *n* (%)				
Surgery only[1]	244 (19)	359 (19)	791 (32)	1,394 (25)
CT	413 (32)	735 (39)	1,323 (54)	2,471 (44)
RT[2]	518 (41)	729 (38)	295 (12)	1,542 (27)
CT + RT	99 (7.8)	73 (3.9)	46 (1.9)	218 (3.9)
Age at diagnosis, years	31.9 (26.2–39.8)	32.5 (26.7–40.0)	33.8 (27.9–41.4)	32.9 (27.1–40.7)
Seminoma	36.3 (30.1–44.9)	36.4 (30.7–44.4)	37.2 (31.6–44.6)	36.7 (30.8–44.5)
Nonseminoma	27.9 (23.3–33.9)	28.7 (23.9–34.9)	29.6 (24.8–36.4)	28.8 (24.2–35.3)
Age at diagnosis, *n* (%)				
‹20 years	77 (6.0)	82 (4.3)	59 (2.4)	218 (3.9)
20–30 years	468 (37)	671 (35)	764 (31)	1,903 (34)
30–40 years	417 (33)	663 (35)	926 (38)	2,006 (36)
40–50 years	187 (14)	298 (16)	474 (19)	959 (17)
›50 years	125 (10)	182 (10)	232 (10)	539 (9.6)
Histology, *n* (%)				
Seminoma	619 (49)	967 (51)	1,356 (55)	2,942 (52)
Nonseminoma	655 (51)	929 (49)	1,099 (45)	2,683 (48)
Observation time, years	29.3 (24.2–32.2)	20.5 (18.0–23.5)	11.3 (8.8–14.0)	16.6 (10.9–23.8)
Observation time, *n* (%)				
‹10 years	99 (7.8)	132 (7.0)	959 (39)	1,191 (21)
10–19 years	128 (10)	712 (38)	1,496 (61)	2,336 (42)
20–29 years	480 (38)	1,052 (55)	0	1,532 (27)
30–37 years	567 (44)	0	0	567 (10)
Initial disease stage, *n* (%)[3]				
I	798 (63)	1,348 (71)	1829 (74)	3,975 (71)
Mk+/II	325 (25)	359 (19)	440 (18)	1,124 (20)
III	31 (2.4)	43 (2.3)	40 (1.6)	114 (2.0)
IV	120 (9.4)	146 (7.7)	146 (6.0)	412 (7.3)
Cause of first-line CT, *n* (%)				
Adjuvant, CSI	39 (7.6)	199 (25)	639 (47)	877 (32)
Primary metastatic disease	410 (80)	513 (63)	601 (44)	1,524 (57)
Recurrence	63 (12)	96 (12)	129 (9.4)	288 (11)
First CT regimen, *n* (%)				
BEP-20	129 (25)	552 (68)	839 (61)	1,520 (57)
CVB	324 (63)	36 (4.5)	0	360 (13)
EP	6 (1.2)	36 (4.5)	208 (15)	250 (9.3)
Other CBCT[4]	44 (8.6)	118 (15)	21 (1.5)	183 (6.8)
Adjuvant carboplatin	1[5] (0.2)	26 (3.2)	287 (21)	314 (12)
CEB	3 (0.6)	31 (3.8)	8 (0.6)	42 (1.6)
Other[6]	5 (1.0)	9 (1.1)	6 (0.4)	20 (0.7)
CBCT cycles, *n* (%)[7]				
1	8 (1.6)	30 (4.0)	188 (17)	226 (10)
2	27 (5.3)	116 (15)	177 (16)	320 (14)
3	93 (18)	106 (14)	252 (24)	451 (19)
4	289 (57)	351 (47)	381 (35)	1,021 (43)
›4	90 (18)	149 (20)	84 (7.8)	323 (14)

(Continues)

Table 1. Patient characteristics according to the decade of first primary TC diagnosis (Continued)

	Decade of first primary TC diagnosis			
	1980–1989 (*n* = 1,274)	1990–1999 (*n* = 1,896)	2000–2009 (*n* = 2,455)	All (*n* = 5,625)
CBCT containing vinca alkaloids or etoposide, *n* (%)				
Vinca alkaloids	257 (50)	61 (7.6)	0	318 (12)
Etoposide	153 (30)	649 (80)	1,080 (79)	1882 (70)
Both	98 (19)	66 (8.2)	10 (0.7)	174 (6.5)
Other CT	4 (0.8)	32 (4.0)	279 (20)	315 (12)
RT first field, *n* (%)				
L-field[8]	549 (89)	626 (78)	224 (66)	1,399 (80)
Paraaortic	24 (3.9)	147 (18)	99 (29)	270 (15)
Supradiaphragmatic	7 (1.3)	5 (0.6)	1 (0.3)	13 (0.7)
Supra- and infradiaphragmatic[9]	21 (3.4)	0	0	21 (1.2)
RT metastatic[10]	16 (2.6)	24 (3.0)	17 (5.0)	57 (3.2)
RT dose for first field, Gy	36.0 (36.0–40.0)	30.0 (25.2–30.0)	25.2 (25.2–30.0)	30.0 (27.0–36.0)
RT dose for first field[11]				
20–29 Gy	7 (1.1)	309 (38)	208 (60)	524 (30)
30–39 Gy	409 (66)	462 (58)	125 (36)	996 (56)
≥40 Gy	199 (32)	24 (3.0)	10 (2.9)	233 (13)
Total recurrences, *n* (%)	99 (7.8)	166 (8.8)	206 (8.4)	471 (8.4)
Initial surveillance, *n* (%)[12]	75 (5.9)	387 (20)	911 (37)	1,373 (24)
Recurrences in initial surveillance group, *n* (%)[13]	19 (25)	72 (19)	122 (13)	213 (16)

Note: Data are presented as median (IQR), unless otherwise stated.
Abbreviations: BEP-20, bleomycin, etoposide and cisplatin; CBCT, cisplatin-based CT; CEB, carboplatin, etoposide and bleomycin; CSI, clinical stage I; CT + RT, combination of CT and RT; CT, chemotherapy; CVB, cisplatin, vinblastine and bleomycin; EP, etoposide and cisplatin; Gy, grey; IQR, interquartile range; Mk+, marker positive; *n*, number; RT, radiotherapy; TC, testicular cancer.
[1]The surgery only group included men followed with surveillance after orchiectomy (*n* = 1,146; 20%) and men submitted to additional retroperitoneal lymph node dissection without CT or RT (*n* = 248; 4.4%).
[2]There were a total of 10 individuals that received scrotal RT of 16–20 Gy because of carcinoma *in situ* or a new tumor of the remaining testicle who underwent partial orchiectomy. These 10 individuals are not included in the RT group in our analyses.
[3]As described by Peckham *et al*. Combined management of malignant teratoma of the testis.[16]
[4]Of which a total of 139 were dose-escalated CBCT.
[5]Adjuvant carboplatin administered in 2005 because of metachronous TC.
[6]Constitutes the following regimes: carboplatin monotherapy in metastatic setting (*n* = 16), sendoxan/adriamycin (*n* = 1), CAOS (actinomycin D, adriamycin, vincristine, sendoxan; *n* = 2), actinomycin D (*n* = 1).
[7]Number of total CBCT cycles administered. May have received additional CT regimens, but these are not accounted for in this number.
[8]L-field or dogleg-field. Included in this category are also 52 individuals who received RT of groin in addition to L-field and 9 individuals who received a reversed Y-field.
[9]Sixteen of 21 individuals received infradiaphragmatic RT as first RT field and a short while later received supradiaphragmatic RT.
[10]RT toward bone (*n* = 19), CNS (*n* = 16), abdominal residual masses (*n* = 16), intraoperative RT (*n* = 1), skin lesions (*n* = 1) and nonspecified sites (*n* = 4).
[11]Overall, 17 TCS for various reasons received only 1–20 Gy (2, 9 and 6 TCS from first to last decade, respectively). One patient received versions of overlapping infradiaphragmatic fields two times within 3 years. For this, one case the dose presented is an addition of Field 1 and Field 2.
[12]This group consists of all cases with CSI initially intended for surveillance as treatment strategy.
[13]The percentage stated is the amount of recurrences among those initially treated with surveillance.

observed numbers of SC in our database, SIRs and 95% confidence intervals (95% CIs).

The effect of treatment was analyzed in age-adjusted Cox regression models with follow-up time as time scale and the surgery only group as a reference. The proportional hazard assumption for the analysis of treatment groups was judged to be violated using both visual inspection of −log−log survival curves and a significant Schoenfeld test ($p = 0.005$). All analyses were thus performed using a time-dependent Cox model with two-way interaction terms between each treatment and a dummy variable of follow-up time (before/after 10 years). Similar subgroup analyses were performed to evaluate the SC risk in relation to histology and treatment intensity. When we investigated the association between the number of CBCT cycles and risk of SC, men who had subsequently received RT were censored at the start date for their first RT treatment. Likewise, when analyzing effects of the first RT field and abdominal RT dose, individuals who had received CT were censored at the date of administration of CT. Estimates are presented for those with >10 years observation time, starting 1 year from TC diagnosis, unless otherwise specified. Results are presented as HRs with corresponding 95% CIs.

Data were analyzed using Stata statistical software (version MP 14.2; STATA, College Station, TX). A p-value <0.05 was considered significant.

Table 2. SIRs for nongerm cell SC according to treatment group

	Total			Surgery only[1]			CT			RT			CT + RT		
	n[2]	SIR	95% CI	*n*	SIR	95% CI	*n*	SIR	95% CI	*n*	SIR	95% CI	*n*	SIR	95% CI
Total SC	572	**1.58**	**1.45–1.71**	96	**1.28**	**1.05–1.56**	174	**1.62**	**1.39–1.88**	270	**1.64**	**1.46–1.85**	32	**2.14**	**1.51–3.02**
All solid cancers C00–C80	529	**1.44**	**1.32–1.57**	88	1.16	0.94–1.43	161	**1.52**	**1.30–1.77**	252	**1.49**	**1.31–1.68**	28	**1.81**	**1.25–2.63**
Ear, nose and throat C00–14, C31–32	19	1.16	0.74–1.81	3	0.92	0.30–2.85	7	1.44	0.69–3.02	9	7.60	0.62–2.28	0	0	0
Esophagus C15	8	1.50	0.75–3.00	2	1.87	0.47–7.47	4	2.61	0.98–6.94	2	0.80	0.20–3.18	0	0	0
Stomach C16	21	**2.19**	**1.43–3.36**	2	1.05	0.26–4.19	1	0.39	0.06–2.79	12	**2.56**	**1.45–4.51**	6	**12.98**	**5.83–28.90**
Small intestine C17	11	**4.29**	**2.38–7.74**	2	3.74	0.93–14.93	3	**3.73**	**1.20–11.56**	5	**4.43**	**1.84–10.63**	1	**10.48**	**1.48–74.4**
Colorectal C18–20	69	**1.27**	**1.01–1.61**	11	1.01	0.56–1.82	22	1.46	0.96–2.22	34	1.32	0.94–1.84	2	0.86	0.21–3.43
Liver and bile ducts C22, C24	12	**2.11**	**1.20–3.72**	2	1.70	0.42–6.79	1	0.58	0.08–4.13	8	**3.13**	**1.56–6.26**	1	4.49	0.63–31.85
Pancreas C25	28	**2.77**	**1.92–4.02**	4	1.98	0.74–5.27	3	1.09	0.35–3.37	19	**3.90**	**2.46–6.11**	2	**4.54**	**1.14–18.16**
Lung C34	67	**1.54**	**1.21–1.96**	8	0.95	0.48–1.90	23	**2.04**	**1.35–3.07**	32	**1.47**	**1.04–2.08**	4	2.01	0.76–5.37
Skin, malignant melanoma C43[3]	42	**1.49**	**1.07–1.96**	12	**1.94**	**1.10–3.42**	18	**1.86**	**1.17–2.95**	11	0.91	0.50–1.64	1	0.93	0.13–6.63
Skin, other C44	24	1.46	0.98–2.17	3	0.88	0.28–2.72	6	1.39	0.63–3.10	13	1.63	0.94–2.80	2	2.69	0.67–10.77
Soft tissue C47–C49	6	**2.33**	**1.04–5.17**	1	1.80	0.25–12.81	1	1.14	0.16–8.08	3	2.85	0.92–8.84	1	**10.51**	**1.48–74.61**
Prostate C61	122	1.08	0.90–1.29	23	1.02	0.68–1.53	33	1.08	0.78–1.52	63	1.14	0.88–1.46	3	0.64	0.21–1.99
Kidney and upper urinary tract C64–C66	37	**1.94**	**1.41–2.68**	3	0.76	0.25–2.36	13	**2.22**	**1.29–3.83**	19	**2.23**	**1.42–3.50**	2	2.70	0.68–10.80
Bladder C67	57	**2.25**	**1.73–2.91**	4	0.78	0.29–2.09	20	**2.97**	**1.91–4.60**	30	**2.42**	**1.69–3.46**	3	2.66	0.86–8.25
Brain C70–C72, C75.1	28	1.24	0.86–1.80	7	1.42	0.68–2.98	12	1.50	0.85–2.65	9	1.02	0.53–1.96	0	0	0
Thyroid C73[4]	10	**2.81**	**1.51–5.22**	4	**4.95**	**1.86–13.18**	2	1.5	0.36–6.00	3	2.31	0.75–7.16	1	**8.51**	**1.20–60.42**
Malignant neoplasm of other and ill-defined sites C76	10	**2.02**	**1.09–3.75**	1	1.03	0.14–7.30	4	3.30	1.24–8.79	5	1.99	0.83–4.78	0	0	0
All hematological malignancies C81–C85, C88, C90–C93, C95, D45, D46	53	**1.31**	**1.00–1.71**	9	1.05	0.55–2.02	15	1.18	0.71–1.95	24	1.36	0.91–2.02	5	**3.23**	**1.35–7.77**
Lymphoma C81–C85	27	1.31	0.90–1.91	6	1.36	0.61–3.04	5	0.74	0.30–1.77	13	1.50	0.87–2.59	3	**3.96**	**1.28–12.29**
Leukemia C91–C93, C95	15	1.43	0.86–2.38	1	0.46	0.06–3.25	5	1.55	0.65–3.72	7	1.51	0.72–3.18	2	**4.86**	**1.22–19.44**

Notes: Significant results marked with bold. SIRs reported for cancers or groups of cancers with occurrence of ≥5. The following SC were observed in the dataset, but not included in analysis: malignant neoplasm of other and ill-defined digestive organs (C26; *n* = 2), malignant neoplasm of bone and articular cartilage (41, *n* = 3), mesothelioma (C45; *n* = 4), male breast cancer (C50; *n* = 2), penis (C60; *n* = 2) and eye (C69; *n* = 1). Significant results marked with bold. C refers to diagnostic code according to the ICD-10 classification.

Abbreviations: 95% CI, 95% confidence interval; CT + RT, combination of chemotherapy and radiotherapy; CT, chemotherapy; IQR, interquartile range; *n*, number; RT, radiotherapy; SC, nongerm cell second cancer; SIR, standardized incidence ratio.

[1]Includes men treated with surveillance and men treated with retroperitoneal lymph node dissection in addition to orchiectomy.

[2]Observed number in cohort. For total SC, *n* represents total cases diagnosed with SC in the cohort. For site-specific analyses, *n* represents the occurrence of the diagnosis of interest in the cohort.

[3]Overall, median time to melanoma diagnosis was 14.6 years (IQR 7.2–17.8).

[4]Overall, median time to thyroid cancer diagnosis was 5.8 years (IQR 2.5–18.5).

Table 3. SIRs for nongerm cell SC by age at first treatment, follow-up time and attained age at first SC diagnosis, according to treatment group

	Total			Surgery only[1]			CT			RT			CT + RT		
	n[2]	SIR	95% CI	*n*	SIR	95% CI	*n*	SIR	95% CI	*n*	SIR	95% CI	*n*	SIR	95% CI
Total SC	572	**1.58**	**1.45–1.71**	96	**1.28**	**1.05–1.56**	174	**1.62**	**1.39–1.88**	270	**1.64**	**1.46–1.85**	32	**2.14**	**1.51–3.02**
Age at first treatment															
<20 years	7	**2.29**	**1.09–4.80**	0	NA	NA	6	**3.17**	**1.43–7.06**	0	NA	NA	1	**8.00**	**1.13–56.77**
20–30 years	88	**1.95**	**1.58–2.41**	18	**1.69**	**1.06–2.68**	36	**1.76**	**1.27–2.44**	28	**2.27**	**1.56–3.28**	6	**3.75**	**1.69–8.35**
30–40 years	164	**1.65**	**1.41–1.92**	19	0.96	0.62–1.51	53	**1.73**	**1.32–2.27**	84	**1.86**	**1.50–2.30**	8	1.97	0.99–3.94
40–50 years	155	**1.55**	**1.33–1.82**	28	**1.74**	**1.20–2.52**	39	**1.44**	**1.05–1.97**	75	**1.44**	**1.15–1.80**	13	**2.95**	**1.71–5.08**
>50 years	157	**1.39**	**1.19–1.63**	30	1.15	0.81–1.65	40	**1.45**	**1.07–1.98**	83	**1.52**	**1.23–1.88**	4	0.83	0.31–2.21
Follow-up time															
<10 years	141	**1.28**	**1.09–1.51**	43	**1.52**	**1.13–2.05**	48	1.28	0.97–1.70	42	1.03	0.76–1.39	8	**2.38**	**1.19–4.77**
10–20 years	217	**1.58**	**1.39–1.81**	30	1.16	0.81–1.66	56	**1.48**	**1.14–1.92**	122	**1.80**	**1.51–2.15**	9	1.58	0.82–3.04
20–30 years	175	**1.81**	**1.56–2.09**	19	1.10	0.70–1.73	56	**2.11**	**1.62–2.74**	87	**1.81**	**1.46–2.23**	13	**2.59**	**1.50–4.46**
30–37 years	39	**2.12**	**1.55–2.90**	4	1.04	0.39–2.78	14	**2.41**	**1.43–4.08**	19	**2.43**	**1.55–3.81**	2	2.12	0.53–8.47
Attained age at first SC diagnosis															
<40 years	31	**1.65**	**1.16–2.35**	11	**2.16**	**1.19–3.89**	13	1.41	0.82–2.42	6	1.52	0.68–3.38	1	2.28	0.32–16.19
40–60 years	244	**1.59**	**1.40–1.80**	40	1.27	0.93–1.73	91	**1.68**	**1.37–2.07**	98	**1.56**	**1.28–1.90**	15	**2.71**	**1.63–4.49**
60–75 years	236	**1.55**	**1.36–1.76**	37	1.26	0.92–1.74	54	**1.45**	**1.11–1.90**	130	**1.64**	**1.38–1.95**	15	**2.18**	**1.31–3.61**
75–90 years	61	**1.64**	**1.28–2.11**	8	0.87	0.44–1.74	16	**2.27**	**1.39–3.71**	36	**1.91**	**1.38–2.65**	1	0.47	0.07–3.33

Note: Significant results marked with bold.
Abbreviations: 95% CI, 95% confidence interval; CT + RT, combination of chemotherapy and radiotherapy; CT, chemotherapy; *n*, number; RT, radiotherapy; SC, nongerm cell second cancer; SIR, standardized incidence ratio.
[1]Includes men treated with surveillance and men treated with retroperitoneal lymph node dissection in addition to orchiectomy.
[2]Observed number. For total SC, *n* represents total cases diagnosed with SC in the cohort.

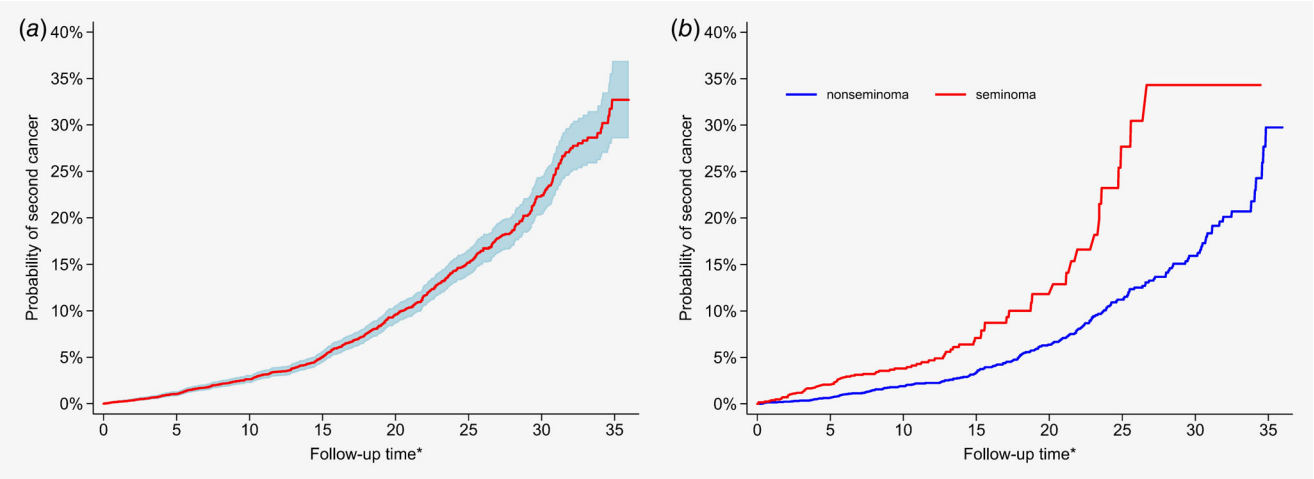

Figure 1. Crude cumulative probability of second cancer by follow up-time. (*a*) All patients (with 95% confidence interval) and (*b*) by histology. In *a*, the red line indicates the probability of second cancer, and the blue area indicates the 95% confidence interval. *years since diagnosis +1 year.

Data availability

The data that support the outcomes of our study are available from the CRN (SC) and a local database (treatment information). Restrictions apply to the availability of these data, which were used under license for our study. Data can be requested by application to the CRN.

Results

Study cohort

Over the decades, the use of surgery only or CT increased, while there was decreasing use of RT or CT + RT (Table 1). Median age at diagnosis was 32.9 years (IQR 27.1–40.7), 36.7 years for seminomas and 28.8 years for nonseminomas. Median observation time for the total cohort was 16.6 years (IQR 10.9–23.8), and 37% had an observation time >20 years.

From 1980–1989 to 2000–2009, the proportion of chemotherapy-treated men receiving adjuvant CT for stage I disease increased from 7.6% to 47%, and the use of the surveillance strategy increased from 5.9% to 37% (Table 1). Of the 1,373 (24%) men subjected to surveillance, 213 (16%) experienced a recurrence.

Overall and site-specific risk of SC in TCS compared to the general population

Overall, 572 TCS (10.2%) developed 651 SCs, with prostate, lung, bladder, melanoma and colon cancer being the most common malignancies (Supporting Information Table S2).

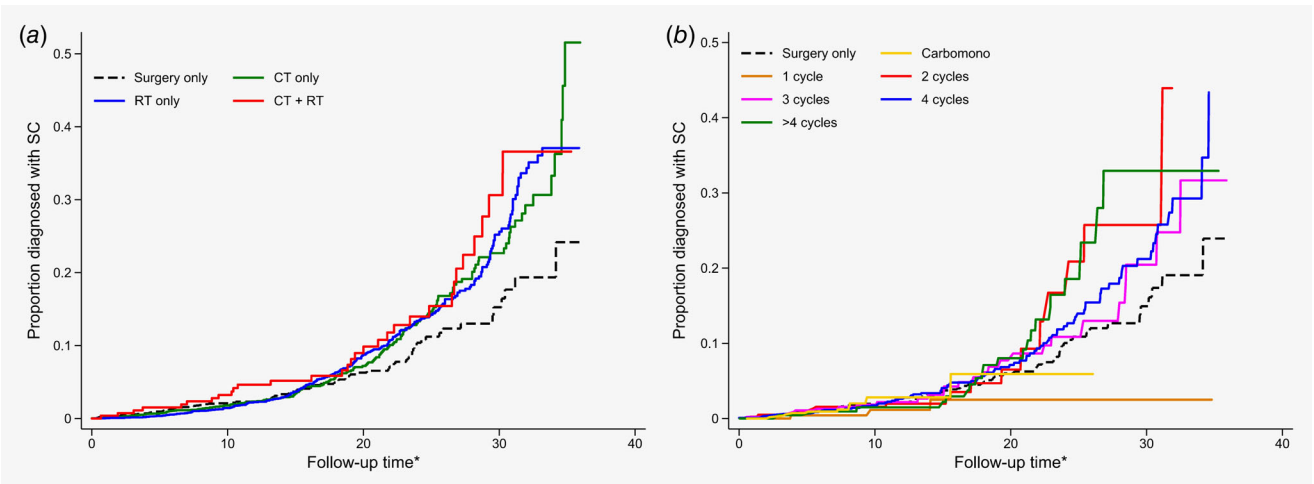

Figure 2. Proportion diagnosed with second cancer by follow-up time, adjusted for age at testicular cancer diagnosis. (*a*) By treatment, (*b*) by number of cisplatin-based chemotherapy cycles and carboplatin monotherapy. *years since diagnosis +1 year. Abbreviations: Carbomono, adjuvant carboplatin monotherapy; CT + RT, combination of CT and RT; CT, chemotherapy; RT, radiotherapy; SC, second cancer.

The crude probability of SC accelerated beyond 15–20 years (2.6% at 10 years and 15.2% at 25 years for the total cohort; Fig. 1*a*).

The TCS had a 58% overall excess risk of developing nongerm cell SC (SIR 1.58, 95% CI 1.45–1.71) compared to the general population. All treatment groups had significantly increased risks, ranging from 28% excess risk after surgery only to twofold increased risk after CT + RT (Table 2).

The overall excess risk of developing a solid cancer was 44%, with significantly elevated risks for cancers of the stomach, small intestine, colon/rectum, liver/bile ducts, pancreas, lung, melanoma, soft tissue, kidney, bladder and thyroid. In addition, the TCS had an overall increased risk of hematological malignancies (SIR 1.31, 95% CI 1.00–1.71).

After surgery only, there were increased risks for melanoma (SIR 1.94, 95% CI 1.10–3.42) and cancer of the thyroid (SIR 4.95, 95% CI 1.86–13.18; Table 2). CT was associated with a significantly 1.9 to 3.7-fold increased risk of cancers of the small intestine, lung, melanoma, kidney and bladder. After RT, the risks were 1.5–4.4 times significantly increased for cancers of the stomach, small intestine, liver and bile ducts, pancreas, lung, kidney and bladder. CT + RT increased the risks for cancers of the stomach, small intestine, pancreas, soft tissue, thyroid, lymphoma and leukemia (Table 2).

Table 4. HRs for total and solid nongerm cell SC according to treatment intensity

	Total SC		Solid SC	
	HR	**95% CI**	**HR**	**95% CI**
CBCT cycles[1]				
Surgery only	1	ref	1	ref
1	0.41	0.07–2.54	0.47	0.07–2.92
2	**1.91**	**1.01–3.59**	**2.19**	**1.16–4.15**
3	1.41	0.83–2.37	1.24	0.70–2.21
4	**1.60**	**1.12–2.30**	**1.73**	**1.19–2.50**
>4	**2.09**	**1.23–3.53**	**2.19**	**1.27–3.78**
Carboplatin[2]	1.17	0.18–7.68	2.54	0.62–10.43
Other[3]	2.21	0.80–6.11	1.77	0.55–5.71
Vinca alkaloids *vs*. etoposide				
Surgery only	1	ref	1	ref
Vinca alkaloids	**1.64**	**1.09–2.48**	**1.82**	**1.19–2.77**
Etoposide	**1.56**	**1.07–2.26**	**1.57**	**1.06–2.32**
Both vinca alkaloids and etoposide	**1.79**	**1.02–3.13**	**1.84**	**1.03–3.29**
Other CT	0.55	0.08–4.02	1.22	0.30–5.03
RT field				
Surgery only	1	ref	1	ref
L-field[4]	**1.66**	**1.23–2.25**	**1.76**	**1.29–2.42**
Paraaortic	1.65	0.95–2.87	1.73	0.97–3.06
Other[5]	**4.40**	**1.07–18.07**	**5.06**	**1.23–20.85**
RT dose for first abdominal RT field				
Surgery only	1	ref	1	ref
20–29 Gy	**1.88**	**1.21–2.90**	**2.01**	**1.28–3.16**
30–39 Gy	**1.71**	**1.25–2.33**	**1.80**	**1.30–2.51**
≥40 Gy	1.42	0.93–2.18	1.50	0.96–2.33

Notes: Significant results marked with bold. Results presented for patients with >10 years observation time. Results for hematological SCs not shown as none were significant.

Abbreviations: 95% CI, 95% confidence interval; CBCT, cisplatin-based chemotherapy; CT, chemotherapy; Gy, grey; HR, hazard ratio; RT, radiotherapy; SC, second cancer.

[1]Number of total CBCT cycles administered. May have received additional CT regimens, but these are not accounted for in this number. A total of 140 TCS received dose-escalated CBCT, of which 1, 27, 12, 35 and 65 men received 1, 2, 3, 4 or >4 cycles, respectively. Then, 13% of those that received dose-escalated CBCT developed SC, compared to 7% in the CT-group overall and 9% in the CT-group when excluding those that received adjuvant CT.

[2]Carboplatin monotherapy, carboplatin in adjuvant setting for stage I seminoma.

[3]Thirty-three CEB (carboplatin, etoposide, bleomycin; of which 32 received 4 cycles and 1 received 2 cycles of CEB), 4 other carboplatin-based CT (3 of which received 4 cycles and 1 received 1 cycle) and 1 actinomycin D.

[4]L-field and variations: The majority received L-field or dogleg-field. Included in this category are also 52 cases who received RT of groin in addition to L-field and 9 cases who received a reverse Y-field.

[5]Eleven supra- and infradiaphragmatic fields, two RT in metastatic setting (bone and abdominal residual tumor).

In TCS initially intended for surveillance, the SIR was 1.34, 95% CI 1.07–1.68, with a significantly increased risk for thyroid cancer (SIR 7.35, 95% CI 3.06–17.66).

Both seminoma and nonseminoma histology were associated with increased risks of SC with SIRs 1.59 (95% CI 1.44–1.76) and 1.55 (95% CI 1.35–1.77), respectively.

Risk of SC by age and follow-up time in TCS compared to the general population

The risk of SC generally declined with increasing age at initial treatment for TC, regardless of which treatment was given. Overall, SIRs ranged from 2.29 (95% CI 1.09–4.80) among patients who initiated treatment before 20 years of age to 1.39 (95% CI 1.19–1.63) among those 50 years or older (Table 3).

The risk of SC generally increased with increasing follow-up time. Overall, SIRs ranged from 1.28 (95% CI 1.09–1.51) among TCS followed less than 10 years to 2.12 (95% CI 1.55–2.90) among patients followed for 30–37 years. Significantly increased risks of SC after CT or RT alone did only emerge with follow-up beyond 10 years, while significantly increased SC risk after surgery was only present with less than 10 years of follow-up.

Overall, SIRs were relatively similar at 1.6 regardless of attained age at first SC diagnosis. Unlike the other treatment groups, the increased SC risk among patients who received surgery only was restricted to SC diagnosed before 40 years of age.

Overall and site-specific risk of SC by histology and treatment group compared to surgery only

The crude cumulative probability of SC at 25 years was 28% (95% CI 18–38%) for seminoma and 11% (95% CI 9.4–13%) for nonseminoma survivors (Fig. 1*b*). SC risk among individuals with seminoma was not significantly increased compared to nonseminoma in age-adjusted analysis (HR 1.14, 95% CI 0.76–1.69).

With surgery only as the reference group, SC risks increased with observation time in all treatment groups (Fig. 2*a*, Supporting Information Table S3), except among the 11 nonseminoma patients treated with RT only when stratifying according to histology (Supporting Information Fig. S2). Risks of solid SCs were significantly increased >10 years of follow-up regardless of treatment group, with HRs ranging from 1.65 to 1.79. The only significantly increased SC risk <10 years of follow-up was for all hematological malignancies after CT + RT (HR 8.73, 95% CI 1.76–43.29).

Compared to the surgery group, we observed a significant 5.1 to 5.3-fold excess risk of bladder cancer after CT or RT, a 7.6-fold excess risk of kidney cancer after RT, and a 24-fold excess risk of cancer of the stomach after combined CT + RT.

SC risk in relation to treatment intensity

The time to development of SC by number of CBCT cycles is illustrated in Figure 2*b*. After >10 years of follow-up, we observed a 1.6 to 2.1-fold excess risk of SC after two or more CBCT cycles compared to surgery only (Table 4). Similar excess risk was found for solid cancer, but not for hematological cancer. No increased SC risk was observed after one CBCT cycle or adjuvant carboplatin, however median observation time was only 9.5 years.

Both the L-field technique and paraaortic RT were associated with 1.6-fold increased risks for SC in comparison to surgery only (Table 4). After paraaortic RT, 9.3% developed SC, of which 0.4% (n = 1) was bladder cancer, compared to 19% developing SC after L-field, of which 1.7% (n = 22) were bladder cancers. SC risks were also increased after RT doses of ≥20 Gy to the first abdominal field.

Discussion

In this national TCS cohort treated since 1980, we found, to the best of our knowledge for the first time, a significantly increased overall risk for nongerm cell SC among TCS treated with surgery only when compared to the general population, with site-specific excess risks of thyroid cancer and melanoma. We also demonstrated that contemporary treatment with CBCT leads to a continuing increased risk of SC, with significantly increased site-specific risk of cancers of the small intestine, lung, melanoma, kidney and bladder. Two or more cycles of CBCT were associated with an excess risk of SC, and CT in combination with RT led to particularly high risks.

The considerable latency from cancer therapy to SC occurrence, as well as the excess risk with increasing follow-up time in our study cohort, is comparable to previous findings,[7–9,20] and underscores the importance of designing studies with sufficient observation time when investigating SC risk in cancer survivors.

Previous publications have reported an excess risk of thyroid cancer after CBCT[7,9] or RT.[20] The elevated risk of thyroid cancer in the surgery only group reported herein, although based on relatively few cases, is a novel finding that needs to be further elucidated in future research. The median time to development of thyroid cancer in our study population was 5.8 years, and our findings may partly be explained by surveillance bias. A few rare inherited syndromes that can cause both thyroid and testicular tumors have been described however,[21] and thyroid cancer can on rare occasions develop from teratomas.[22] It is unknown whether this was the case in our study population.

Excess risk of melanoma in TCS after RT has been reported in previous studies,[20,23,24] but in line with results reported by van den Belt-Dusebout *et al.*,[25] we demonstrated a significant excess risk of melanoma in the surgery only group. However, the number of cases diagnosed with melanoma was low, even though our study includes hitherto the highest number of patients with complete treatment details. Some authors have attributed these findings to increased medical attention during the first years of follow-up.[23] Surveillance bias is a less likely explanation in our cohort due to the long median latency of 14.6 years between diagnosis of TC and melanoma.

Patients with cutaneous melanoma have been found to be at increased risk of developing SC, including testicular and thyroid cancer.[26] There is a genetic link between thyroid cancer and melanoma through a susceptibility to BRAF mutations. A 2014 US

study found a reciprocal twofold increased risk of developing papillary thyroid cancer after cutaneous melanoma or *vice versa*, and a high incidence of BRAF v600e-mutations.[27] In our study population, no patients presented with both thyroid cancer and melanoma.

An association between childhood tumor risk and first-degree family history of solid tumors was recently observed for several solid cancers, including melanomas, even after controlling for probable hereditary cancer syndromes.[28] The increased risk of SC after surgery only, together with the young age at TC diagnosis and the familial risk of developing TC, similarly implies a genetic susceptibility and/or that environmental factors during fetal life or early childhood predispose for both TC and other malignancies.[29–31] The genetic susceptibility for TC is thought to be driven by multiple low-penetrance alleles.[32–34] Additionally, a recent study demonstrated evidence for CHEK2 as a moderate-penetrance susceptibility gene.[35] To this date, however, TC has not been linked to a cancer syndrome that predisposes to other cancers,[32] but our findings suggest that further research within this field should be prioritized. CT-scans during follow-up after treatment for TC have been associated with increased SC risk,[36,37] and might contribute to the excess risk in the surgery only group. Future studies evaluating the impact of follow-up with CT-scans *vs*. MRI should be prioritized.

The increased overall SC risk after surgery alone only before 10 years of follow-up could indicate surveillance bias (Table 3), even though follow-up started 1 year after TC diagnosis. However, in that case, we would also expect increased SC risks after RT or CT before 10 years of follow-up, which was not seen. In summary, we believe that our findings in general are not explained by surveillance bias.

In line with previous publications, we demonstrated a 62% increased risk of SC after treatment with CT in the cisplatin era.[7–9] Bladder cancer was among the most frequent SCs in our study cohort, corroborating previous reports,[7–9,20,25] and we observed a threefold increased risk for bladder cancer after CT when compared to the general population. The risks for cancers of the kidney and upper urinary tract and lung were twofold increased following CT, which is comparable to previous reports.[7–9] There is a possibility that at least some of the cancers diagnosed as soft tissue sarcoma are in fact transformed teratomas,[38,39] but we did not find any increased risk of sarcomas after CBCT as previously reported.[7,9]

Cisplatin is a platinum compound which has been detected in plasma decades after treatment,[40] and in most organs several months after treatment,[41,42] where it remains partly reactive. Despite the lack of long-term data, the accumulation of platinum might be a pathophysiological explanation for the increased risk of SC.[10] In a recent publication by Hjelle *et al*., a reduced risk of SC was found in individuals with larger long-term declines in serum-platinum levels.[43] Importantly, platinum is eliminated through renal clearance, and it has been detected in urine up to 16 years after treatment.[44] An association between CBCT and cancers of the urinary tract is therefore likely.

The 64% excess SC risk following RT confirms the established association between RT and subsequent SC development.[8,9,20,25] The increased risks of cancers of the gastrointestinal tract, pancreas, liver, lung, kidney and bladder after RT compared to the general population reported herein, are in line with previous publications demonstrating that SCs often are localized in relation to previous RT fields.[20,45–48] The excess risk was almost similar after both paraaortic lymph node portal and the more extensive L-field portal, which also includes ipsilateral iliac lymph nodes. The association was, however, not statistically significant after paraaortic RT, probably due to the low number and the shorter follow-up. The absolute numbers suggested that the risk of developing bladder cancer was reduced after paraaortic RT compared to L-field, but statistical analysis was not possible because of low numbers. We could not confirm a linear trend for increasing risk of solid SC with increasing abdominal RT dose, as reported by Groot *et al*.,[9] despite our larger study population.

In our study, combined CT and RT was associated with the highest risks for SC compared to the general population, which is in agreement with previous reports.[49–51] The increased risk of stomach cancer after combination therapy has been previously reported.[25] The risks for all hematological malignancies, lymphoma and leukemia were also increased after CT + RT. Subsequent hematological malignancies generally develop within 10 years following cancer treatment,[14,52] and our results were consistent with this.

To the best of our knowledge, analyses of TCS intended for surveillance after surgery has not been performed previously, and also in this group, we found a significantly increased risk of SC. Kier *et al*. presented favorable results for the surveillance group,[8] however these authors' findings were based on a group that excluded all individuals that relapsed from analyses. There is an ongoing debate as to whether surveillance is superior to adjuvant chemotherapy in the treatment of stage I TC. Of note, we did not observe any increased risk of SC after one cycle of CBCT or carboplatin, but the observation time is still short, and longer follow-up is needed before any conclusions can be drawn.

We found an almost 60% significantly increased risk of SC after both seminomas and nonseminomas compared to the general population, which is in line with the recent Dutch publication.[9] Our remarkably higher 25-year crude probability of all SCs following seminomas of 28%, compared to 12.6% in the Dutch report is interesting. Some of the difference might be explained by the longer median follow-up after seminoma in our study of 16.0 years compared to 13.5 years in the Dutch study.

Strengths of our study are the inclusion of detailed information regarding total treatment burden for the entire study cohort, and the unique quality of the CRN. Based on a distinct personal identification number used in Norway, the CRN receives information from several sources to ensure accuracy, and reporting to this registry is instructed by law.[1] SIRs are easy to understand and interpret, and we considered that

calculation of absolute excess risks (AERs) would not provide more information to the reader. The use of time-dependent Cox-regression implements the important element of observation time in our analyses.

Limitations include the lack of details regarding known risk factors for cancer, for example, smoking, hereditary factors and comorbidities. There is, however, no reason to believe that smoking prevalence among TCS differs from the general population.[53,54]

In conclusion, despite reduced treatment intensity during the last decades, we find a continuing increased risk of SC in TCS treated in the cisplatin era. While treatment-related late effects remain the main culprit, increased SC risks among patients treated with surgery only suggest that genetic and environmental factors are also important. Regardless of cause, improvement of lifestyle behavior, in particular, smoking cessation, reduction of alcohol intake, increased physical activity and a healthy diet may reduce the risk of SC.[55] Promotion and guidance for a healthy lifestyle should thus be implemented to a larger degree during long-term follow-up of all TCS than it is today. Health care professionals must be aware of the SC risk so that proper examination is initiated by the slightest suspicion of a SC to ensure diagnosis at an early stage.

Disclaimer

The study has used data from the Cancer Registry of Norway. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Cancer Registry of Norway is intended nor should be inferred.

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