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

Ragnhild Hellesnes1,2, Øivind Kvammen3,4, Tor Å. Myklebust5,6, Roy M. Brennes1,2, Ása Karlsdottir7, Helene F.S. Negaard8, Torgrim Tandstad8,9, Tom Wilsgaard10, Sophie D. Foss6,8,11 and Hege S. Haugnes1,2

1Department of Oncology, University Hospital of North Norway, Tromsø, Norway  
2Department of Clinical Medicine, UiT The Arctic University, Tromsø, Norway  
3Department of Oncology, Ålesund Hospital, Ålesund, Norway  
4Department of Clinical and Molecular Medicine, The Norwegian University of Science and Technology, Trondheim, Norway  
5Department of Research and Innovation, Møre and Romsdal Hospital Trust, Ålesund, Norway  
6Department of Registration, Cancer Registry of Norway, Oslo, Norway  
7Department of Oncology, Haukeland University Hospital, Bergen, Norway  
8Department of Oncology, Oslo University Hospital, Oslo, Norway  
9The Cancer Clinic, St. Olav’s University Hospital, Trondheim, Norway  
10Department of Community Medicine, UiT The Arctic University, Tromsø, Norway  
11Institute of Clinical Medicine, University of Oslo, Oslo, Norway

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

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
Conflict of interest: The authors declare no potential conflicts of interest.
Grant sponsor: Helse Nord Regional Health Trust, Tromsø, Norway; Grant number: SPF1230-15
This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.
DOI: 10.1002/ijc.32704
History: Received 1 Mar 2019; Accepted 10 Sep 2019; Online 9 Oct 2019
Correspondence to: Øivind Kvammen, E-mail: oivind.kvammen@helse-mr.no

Int. J. Cancer: 147, 21–32 (2020) © 2019 The Authors. International Journal of Cancer published by John Wiley & Sons Ltd on behalf of UICC
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.

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). 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. Overall, treatment intensity has gradually been reduced during the study period in line with increasing knowledge about efficacy and toxicity (Supporting Information Table S1). 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. 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, 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
| 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           |                  |                  |                  |            |
| Seminoma                          | 31.9 (26.2–39.8) | 32.5 (26.7–40.0) | 33.8 (27.9–41.4) | 32.9 (27.1–40.7) |
| Nonseminoma                       | 36.3 (30.1–44.9) | 36.4 (30.7–44.4) | 37.2 (31.6–44.6) | 36.7 (30.8–44.5) |
| 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           |                  |                  |                  |            |
| <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)       | 1,829 (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 (30.0–40.0) | 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 (19) | 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 orchietomy (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 orchietomy. 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 S2. SIRs for nongerm cell SC according to treatment group

| Treatment Group | Total | CT | RT |
|-----------------|-------|----|----|
| Surgery only    | 195  | 96 | 99 |
| Total SC        | 572  | 21 | 33 |
| All solid cancers C00–C80 | 444 | 17 | 27 |
| Ear, nose and throat C01–C04 | 84 | 3 | 51 |
| Stomach C16     | 20   | 6  | 14 |
| Colon and rectum C18-20 | 47 | 2 | 45 |
| Liver and biliary tract C22, C24 | 22 | 1 | 21 |
| Lung C34        | 53   | 19 | 34 |
| Skin, malignant melanoma C433 | 61 | 22 | 39 |
| Skin, other C44  | 13   | 3  | 10 |
| Soft tissue C47–C49 | 6  | 2  | 4  |
| Prostate C61    | 122  | 43 | 79 |
| Bladder C67     | 57   | 22 | 35 |
| Brain C70–C72, C75.1 | 10 | 5  | 5  |
| Malignant neoplasm of other and ill-defined digestive organs C26 | 2  | 1  | 1  |
| Malignant neoplasm of bone and articular cartilage C41 | 3  | 1  | 2  |
| Mesothelioma C45 | 4  | 2  | 2  |
| Male breast cancer C50 | 1  | 1  | 0  |
| Penis C60       | 1    | 1  | 0  |
| Other sites C90–C93, C95, D45, D46 | 10 | 2 | 8  |
| Lymphoma C81–C85 | 3  | 1  | 2  |
| Multiple myeloma C90–C92 | 5  | 2  | 3  |

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 cancer.

Notes: Significant results marked with bold. SIRs reported for cancers or groups of cancers with occurrence of ≥5. The following SCs were observed in the dataset, but not included in analysis: malignant neoplasm of bone and articular cartilage (C41), mesothelioma (C45), male breast cancer (C50), male breast cancer (C50), and malignant neoplasm of other and ill-defined digestive organs (C26; n = 2), malignant neoplasm of bone and articular cartilage (C41; n = 3), mesothelioma (C45; n = 4), male breast cancer (C50; n = 1). Significant results marked with bold refer to diagnosis according to the ICD-10 classification. Abbreviations: SIR, standardized incidence ratio; CI, 95% confidence interval; CT + RT, combination of chemotherapy and radiotherapy; CT, chemotherapy; IQR, interquartile range; n, number. RT, radiotherapy; SC, nongerm cell cancer.

1 Includes men treated with surveillance and men treated with retroperitoneal lymph node dissection in addition to orchiectomy.
2 Overall, median time to melanoma diagnosis was 14.6 years (IQR 7.2–17.8).
3 Overall, median time to thyroid cancer diagnosis was 5.8 years (IQR 2.5–18.5).
4 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.
5 The following SCs were excluded from the analysis: malignant neoplasm of bone and articular cartilage (C41; n = 3), mesothelioma (C45; n = 4), male breast cancer (C50; n = 1). Significant results marked with bold refer to diagnosis according to the ICD-10 classification. Abbreviations: SIR, standardized incidence ratio; CI, 95% confidence interval; CT + RT, combination of chemotherapy and radiotherapy; CT, chemotherapy; IQR, interquartile range; n, number. RT, radiotherapy; SC, nongerm cell cancer.

**Abbreviations:** 95% CI, 95% confidence interval; CT, chemotherapy; IQR, interquartile range; RT, radiotherapy; SC, nongerm cell cancer.

**Notes:** Significant results marked with bold. SIRs reported for cancers or groups of cancers with occurrence of ≥5. The following SCs were observed in the dataset, but not included in analysis: malignant neoplasm of bone and articular cartilage (C41), mesothelioma (C45), male breast cancer (C50), male breast cancer (C50), and malignant neoplasm of other and ill-defined digestive organs (C26; n = 2), malignant neoplasm of bone and articular cartilage (C41; n = 3), mesothelioma (C45; n = 4), male breast cancer (C50; n = 1). Significant results marked with bold refer to diagnosis according to the ICD-10 classification. Abbreviations: SIR, standardized incidence ratio; CI, 95% confidence interval; CT + RT, combination of chemotherapy and radiotherapy; CT, chemotherapy; IQR, interquartile range; n, number. RT, radiotherapy; SC, nongerm cell cancer.
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                 |
|------------------|------------------------|-------------------|-------------------------|-------------------------|-------------------------|
|                  | $n$ | 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 |
| 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 |
| 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 |
| 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 |
| >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 |
| 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 |
| 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 |
| 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 |
| 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 |
| 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 |
| 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 |
| 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 |
| 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 |

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.
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 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. [Correction added on 1 May 2020, after first online publication: Figure 1b was incorrect due to a mathematical error and has been replaced in this version.]

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. 1a).

The TCS had a 58% overall excess risk of developing non-germ 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 non-germ cell SC according to treatment intensity

|                         | Total SC |         | Solid SC |         |
|-------------------------|----------|---------|----------|---------|
|                         | HR       | 95% CI  | HR       | 95% CI  |
| CBCT cycles1            |          |         |          |         |
| 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 |
| Carboplatin7            | 1.17     | 0.18–7.68 | 2.54     | 0.62–10.43 |
| Other3                  | 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-field4                | 1.66     | 1.23–2.25 | 1.76     | 1.29–2.42 |
| Paraaoortic             | 1.65     | 0.95–2.87 | 1.73     | 0.97–3.06 |
| Other5                  | 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 II 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).

Int. J. Cancer: 147, 21–32 (2020) © 2019 The Authors. International Journal of Cancer published by John Wiley & Sons Ltd on behalf of UICC
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 20% (95% CI 18–22%) for seminoma and 10% (95% CI 8.7–12%) for nonseminoma survivors (Fig. 1b). SC risk among individuals with seminoma was significantly increased compared to nonseminoma in age-adjusted analysis (HR 1.20, 95% CI 1.01–1.44) [Correction added on 1 May 2020, after first online publication: The values in the preceding paragraph have been corrected.]

With surgery only as the reference group, SC risks increased with observation time in all treatment groups (Fig. 2a, Supporting Information Table S3), except among the 11 nonseminoma patients treated with CT 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 2b. 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, 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 or RT. 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 tumours have been described however, and thyroid cancer can on rare occasions develop from teratomas. 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, but in line with results reported by van den Belt-Dusebout et al., 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. 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. 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. 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. 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. The genetic susceptibility for TC is thought to be driven by multiple low-penetrance alleles. Additionally, a recent study demonstrated evidence for CHEK2 as a moderate-penetrance susceptibility gene. To this date, however, TC has not been linked to a cancer syndrome that predisposes to other cancers, 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, 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. Bladder cancer was among the most frequent SCs in our study cohort, corroborating previous reports, 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. There is a possibility that at least some of the cancers diagnosed as soft tissue sarcoma are in fact transformed teratomas, but we did not find any increased risk of sarcomas after CBCT as previously reported.

Cisplatin is a platinum compound which has been detected in plasma decades after treatment, and in most organs several months after treatment, 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. 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. Importantly, platinum is eliminated through renal clearance, and it has been detected in urine up to 16 years after treatment. 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. 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. 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. 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. The increased risk of stomach cancer after combination therapy has been previously reported. 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, 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, 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. Our remarkably higher 25-year crude probability of all SCs following seminomas of 20%, compared to 12.6% in the Dutch population, 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.
this registry is instructed by law. 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.

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. 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.
radiation during surveillance for stage I testicular cancer using computerized tomography. J Urol 2009;181:627–32. discussion 32–3.

38. Bosl GJ, Motzer RJ. Testicular germ-cell cancer. N Engl J Med 1997;337:242–53.

39. Motzer RJ, Amsterdam A, Prieto V, et al. Teratoma with malignant transformation: diverse malignant histologies arising in men with germ cell tumors. J Urol 1999;159:133–8.

40. Hjelle LV, Gundersen PO, Oldenburg J, et al. Long-term platinum retention after platinum-based chemotherapy in testicular cancer survivors: a 20-year follow-up study. Anticancer Res 2015;35:1619–25.

41. Tothill P, Klys HS, Matheson LM, et al. The long-term retention of platinum in human tissues following the administration of cisplatin or carboplatin for cancer chemotherapy. Eur J Cancer 1992;28a:1358–61.

42. Poirier MC, Reed E, Litterst CL, et al. Persistence of platinum-ammine-DNA adducts in gonads and kidneys of rats and multiple tissues from cancer patients. Cancer Res 1992;52:149–53.

43. Hjelle LV, Gundersen POM, Hellesnes R, et al. Long-term serum platinum changes and their association with cisplatin-related late effects in testicular cancer survivors. Acta Oncol 2018;57:1392–400.

44. Gerl A, Schierl R. Urinary excretion of platinum in chemotherapy-treated long-term survivors of testicular cancer. Acta Oncol 2000;39:519–22.

45. Hauptmann M, Fossa SD, Stovall M, et al. Increased stomach cancer risk following radiotherapy for testicular cancer. Br J Cancer 2015;112:44–51.

46. Hauptmann M, Borge Johannesen T, Gilbert ES, et al. Increased pancreatic cancer risk following radiotherapy for testicular cancer. Br J Cancer 2016;115:901–8.

47. Gilbert ES, Curtis RE, Hauptmann M, et al. Stomach cancer following Hodgkin lymphoma, testicular cancer and cervical cancer: a pooled analysis of three international studies with a focus on radiation effects. Radiat Res 2017;187:186–95.

48. van den Belt-Dusebout AW, Aleman BM, Besseling G, et al. Roles of radiation dose and chemotherapy in the etiology of stomach cancer as a second malignancy. Int J Radiat Oncol Biol Phys 2009;75:1420–9.

49. Gilbert ES, Stovall M, Gospodarowicz M, et al. Lung cancer after treatment for Hodgkin’s disease: focus on radiation effects. Radiat Res 2003;159:161–73.

50. Travis LB, Curtis RE, Glimelius B, et al. Bladder and kidney cancer following cyclophosphamide therapy for non-Hodgkin’s lymphoma. J Natl Cancer Inst 1995;87:524–30.

51. Travis LB, Gospodarowicz M, Curtis RE, et al. Lung cancer following chemotherapy and radiotherapy for Hodgkin’s disease. J Natl Cancer Inst 2002;94:182–92.

52. Howard R, Gilbert E, Lynch CF, et al. Risk of leukemia among survivors of testicular cancer: a population-based study of 42,722 patients. Ann Epidemiol 2008;18:416–21.

53. Haugnes HS, Wethal T, Aass N, et al. Cardiovascular risk factors and morbidity in long-term survivors of testicular cancer: a 20-year follow-up study. J Clin Oncol 2010;28:4649–57.

54. Shinn EH, Swartz RJ, Thornton BB, et al. Testis cancer survivors’ health behaviors: comparison with age-matched relative and demographically matched population controls. J Clin Oncol 2010;28:2374–9.

55. Ligibel J. Lifestyle factors in cancer survivorship. J Clin Oncol 2012;30:3697–704.