original reports

Metachronous Contralateral Testicular Cancer the Cisplatin Era: A Population-Based Cohort Study

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abstract

PURPOSE It is hypothesized that cisplatin-based chemotherapy (CBCT) reduces the occurrence of metachronous contralateral (second) germ cell testicular cancer (TC). However, studies including treatment details are lacking. The aim of this study was to assess the second TC risk, emphasizing the impact of previous TC treatment.

PATIENTS AND METHODS Based on the Cancer Registry of Norway, 5,620 men were diagnosed with first TC between 1980 and 2009. Treatment data regarding TC were retrieved from medical records. Cumulative incidences of second TC were estimated, and standardized incidence ratios were calculated. The effect of treatment intensity was investigated using Cox proportional hazard regression.

RESULTS Median follow-up was 18.0 years, during which 218 men were diagnosed with a second TC after median 6.2 years. Overall, the 20-year crude cumulative incidence was 4.0% (95% CI, 3.5 to 4.6), with lower incidence after chemotherapy (CT) (3.2%; 95% CI, 2.5 to 4.0) than after surgery only (5.4%; 95% CI, 4.2 to 6.8). The second TC incidence was also lower for those age ≥ 30 years (2.8%; 95% CI, 2.3 to 3.4) at first TC diagnosis than those age < 30 years (6.0%; 95% CI, 5.0 to 7.1). Overall, the second TC risk was 13-fold higher compared with the risk of developing TC in the general male population (standardized incidence ratio, 13.1; 95% CI, 11.5 to 15.0). With surgery only as reference, treatment with CT significantly reduced the second TC risk (hazard ratio [HR], 0.55). For each additional CBCT cycle administered, the second TC risk decreased significantly after three, four, and more than four cycles (HRs, 0.53, 0.41, and 0.21, respectively).

CONCLUSION Age at first TC diagnosis and treatment intensity influenced the second TC risk, with significantly reduced risks after more than two CBCT cycles.

J Clin Oncol 39:308-318. © 2020 by American Society of Clinical Oncology

INTRODUCTION

After being diagnosed with a primary germ cell testicular cancer (TC), the estimated 15-20–year cumulative incidence of a metachronous contralateral (second) TC is 1.9%-3.9%.[1-4] Standardized incidence ratios (SIRs), comparing the incidence of second TC with the incidence of TC in the general population, range from 12.4 to 35.7.[1-7] Treatment of the second TC will usually involve a surgical castration, leading to infertility and lifelong dependency of testosterone substitution.[8,9] From personal experience, many testicular cancer survivors (TCS) with unilateral disease fear losing their remaining testicle.

Shared etiological factors for the first and second TC, hypothesized to cause the testicular dysgenesis syndrome, represent a likely explanation for the increased incidence of a second TC.[10,11] Young age at diagnosis of the first TC is associated with the increased risk of developing a second TC.[1-4,12] The results are, however, inconclusive regarding the effect of first TC histology and subsequent second TC risk.[1,4,7,13,14]

The introduction of cisplatin in the late 1970s led to dramatically improved survival of patients with metastatic TC.[15,16] Cisplatin-based chemotherapy (CBCT) is hypothesized to reduce or delay the incidence of a metachronous contralateral TC. However, the existing literature lacks TC treatment details, if based on public registries,[1,2] involves populations screened for germ cell neoplasia in situ (GCNIS),[12,17] or includes patients treated in the precisplatin era.[3-5]

Andreassen et al[2] investigated the risk for metachronous contralateral TC in 7,102 TCS in Norway treated during 1953-2007. They found a 50% risk reduction for a second TC in men treated for metastatic compared with localized disease only for those treated after 1980, implying that this risk reduction was related to the introduction of CBCT. They emphasized that the greatest limitation of their study was the lack of TC

ASSOCIATED CONTENT

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Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on October 21, 2020 and published at ascopubs.org/journal/jco on December 23, 2020: DOI https://doi.org/10.1200/JCO.20.02713

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CONTEXT

Key Objective

Does cisplatin-based chemotherapy (CBCT) reduce the risk of a metachronous contralateral (second) testicular cancer (TC)?

Knowledge Generated

The overall 20-year cumulative incidence of second TC in a population-based cohort was 4%. Treatment with CBCT significantly reduced the second TC risk, with a stronger risk reduction for each additional CBCT cycle administered. Older age at diagnosis of first TC also reduced the risk.

Relevance

Our findings add important knowledge concerning the risk of second TC. Our results are important and appreciated information for patients with TC and healthcare personnel involved in TC treatment.

treatment details. Furthermore, Fosså et al[1] conducted a large register-based study involving 29,515 TCS from the United States. They concluded that a potential dose-response relationship between cisplatin and eradication of germ cell carcinoma in situ should be investigated in future clinical studies.

The aim of this population-based study was to assess the risk of developing a metachronous contralateral TC, with emphasis on the impact of previous TC treatment including CBCT, in a national cohort with complete data on TC treatment.

PATIENTS AND METHODS

Study Cohort and Design

The Cancer Registry of Norway (CRN) identified men diagnosed with histologically verified primary germ cell TC from January 1, 1980, to December 31, 2009.[18] Major exclusion criteria included age < 16 years at TC diagnosis, a prior malignancy, extragonadal germ cell cancer, and synchronous contralateral TC or death within 2 months of follow-up (Appendix Fig A1, online only). Metachronous TC was defined as a second germ cell TC diagnosed > 2 months after the primary TC.

After exclusions, this historical prospective cohort study consisted of 5,620 patients with TC. Details regarding disease stage, histology, and TC treatment for first and second TCs, including relapse treatment, were retrieved from medical records. Linkage with the CRN updated through December 31, 2018, was done to ensure complete information on the incidence of second TC.

The 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. Passive consent from all eligible men still alive was obtained through a study information letter with the possibility to withdraw from participation, after which 23 (0.38%) men declined participation.

Staging, Treatment, and Treatment Groups

TC was staged according to the Royal Marsden Hospital staging system.[19] During the study period, the treatment principles for TC changed as previously described.[20] Adjuvant radiotherapy (RT) for stage I seminoma has gradually been abandoned, and the number of CBCT cycles applied for metastatic disease has been reduced. The use of a risk-adapted surveillance strategy or one cycle of adjuvant CBCT (nonseminoma) or carboplatin (seminoma) for stage I disease has been implemented as recommended by the Swedish and Norwegian Testicular Cancer Group (SWENOTECA).[21]

Based on total treatment burden for the first TC, the cohort was divided into four treatment groups: surgery only (including surveillance n = 1,417; 25%), chemotherapy (CT, n = 2,450; 44%), RT (n = 1,543, 27%), and both CT and RT (CT + RT, n = 210; 3.7%) (Table 1).

Statistical Methods

Continuous variables were presented with median and interquartile range (IQR), and categorical variables were presented with numbers and percent.

Follow-up was calculated from 2 months after diagnosis of the first TC until a diagnosis of a second TC, death, emigration, or December 31, 2018, whichever occurred first. Treatment was analyzed as a time-varying covariate, achieved by splitting follow-up time at exact treatment dates for each treatment modality, to avoid immortal time bias. The K-sample median test was used to test differences in median time to second TC among those developing a second TC, presented with two-sided *P*-values.

The crude cumulative incidence of metachronous contralateral TC was estimated using the Aalen-Johansen estimator,[22] with death of any cause as a competing risk. To compare the incidence of metachronous contralateral TC to the incidence of TC in the general population, SIRs were calculated. The estimates were obtained by dividing the number of metachronous contralateral TCs in the cohort to the expected number of metachronous contralateral

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TABLE 1. Patient Characteristics at First Primary TC Diagnosis

Characteristic	Total at Risk (N = 5,620)	Individuals Without Second TC (n = 5,402)	Individuals Developing Second TC (n = 218)
Decade of first TC diagnosis			
1980-1989	1,287 (23)	1,228 (23)	59 (27)
1990-1999	1,897 (34)	1,824 (34)	73 (34)
2000-2009	2,436 (43)	2,350 (43)	86 (39)
Follow-up, years, median (IQR)[a]	18.0 (12.0-25.5)	18.5 (12.5-25.8)	6.2 (3.3-10.6)[b]
Age at diagnosis, years, median (IQR)	33.0 (27.2-40.9)	33.3 (27.3-41.2)	28.7 (24.6-33.5)
Age at diagnosis, dichotomized, years			
< 30	2,124 (38)	1,999 (37)	125 (57)
≥ 30	3,496 (62)	3,403 (63)	93 (43)
Histology			
Seminoma	2,938 (52)	2,831 (52)	107 (49)
Nonseminoma	2,682 (48)	2,571 (48)	111 (51)
Initial disease stage[c]			
I	3,942 (70)	3,766 (70)	176 (80)
Mk+/II	1,127 (20)	1,097 (20)	30 (14)
III	116 (2.1)	114 (2.1)	2 (1.0)
IV	435 (7.7)	425 (7.9)	10 (4.6)
Treatment[d]			
Surgery only[e]	1,417 (25)	1,345[f] (25)	72 (33)
CT	2,450 (44)	2,379 (44)	71 (32)
RT	1,543 (27)	1,471 (27)	72 (33)
CT + RT	210 (3.7)	207 (3.8)	3 (1.4)
Cause of first-line CT			
Adjuvant, CS I	843 (32)	811 (31)	32 (43)
Primary metastatic disease	1,538 (58)	1,502 (58)	36 (49)
Recurrence	279 (10)	273 (11)	6 (8.1)
First CT regimen			
BEP-20	1,507 (57)	1,464 (57)	43 (58)
CVB	367 (14)	357 (14)	10 (13.5)
EP	241 (9.1)	237 (9.2)	4 (5.4)
Other CBCT[g]	184 (6.9)	180 (6.9)	4 (5.4)
Adjuvant carboplatin[h]	295 (11)	285 (11)	10 (13.5)
CEB	44 (1.6)	42 (1.6)	2 (2.7)
Other[i]	22 (0.8)	21 (0.8)	1 (1.4)
No. of CBCT cycles[j]			
1	220 (9.5)	210 (9.3)	10 (16)
2	319 (14)	307 (14)	12 (20)
3	439 (19)	427 (19)	12 (20)
4	1,028 (44)	1,004 (44)	24 (39)
> 4	320 (14)	317 (14)	3 (4.9)
RT first field			
L-Field[k]	1,388 (79)	1,321 (79)	67 (89)
Para-aortal	267 (15)	260 (15)	7 (9.3)

(continued on following page)

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TABLE 1. Patient Characteristics at First Primary TC Diagnosis (continued)

Characteristic	Total at Risk (N = 5,620)	Individuals Without Second TC (n = 5,402)	Individuals Developing Second TC (n = 218)
Supradiaphragmatic	13 (0.7)	12 (0.7)	1 (1.3)
Supra- and infradiaphragmatic[l]	21 (1.2)	21 (1.3)	0
Other[m]	64 (3.6)	64 (3.8)	0
RT dose for first RT field, Gy			
1-20	13 (0.7)	12 (0.7)	1 (1.3)
20-29	514 (29)	490 (29)	24 (32)
30-39	986 (56)	943 (56)	43 (57)
≥ 40	240 (14)	233 (14)	7 (9.3)

NOTE. Data are presented as n (%), unless otherwise stated.

Abbreviations: BEP-20, bleomycin, etoposide, and cisplatin; CBCT, cisplatin-based chemotherapy; CEB, carboplatin, etoposide, and bleomycin; CS I, clinical stage I; CT, chemotherapy; CT + RT, combination of CT and RT; CVB, cisplatin, vinblastine, and bleomycin; EP, etoposide and cisplatin; Gy, gray; IQR, interquartile range; Mk+, marker positive; RT, radiotherapy; TC, testicular cancer.

[a]Follow-up until diagnosis of metachronous contralateral TC, death, emigration, or December 31, 2018, whichever occurred first.

[b]The longest time interval between first TC and second TC was 27.1 years.

[c]As described by Peckham et al.[19]

[d]Based on total treatment burden.

[e]The surgery-only group included men followed with surveillance after orchiectomy (n = 1,167; 21%) and men who underwent additional retroperitoneal lymph node dissection without CT or RT (n = 250; 4.4%).

[f]Two men included in the surgery-only group were diagnosed with clinical stage IV. One refused treatment, and the other was no candidate for treatment. They both died shortly (but > 2 months) after diagnosis.

[g]Of which a total of 141 were dose-escalated CBCT.

[h]Fifteen of the 295 men initially treated with adjuvant carboplatin were subsequently treated with CBCT and, as a consequence, analyzed according to the total number of CBCT cycles. Also, one person had RT in addition to carboplatin. Of the 279 men treated with adjuvant carboplatin monotherapy included in the Cox regression analysis, 273 received one cycle and 6 received two cycles.

[i]Carboplatin monotherapy in metastatic setting (n = 17), cyclophosphamide/adriamycin (n = 1), CAOS (actinomycin D, adriamycin, vincristine, cyclophosphamide) (n = 3), actinomycin D (n = 1).

[j]May have received additional CT regimes, but these are not accounted for in this number. A total of 334 men received non-CBCT, which are not included here.

[k]L-Field or dogleg-field. Also included in this category are 53 individuals who received RT of groin in addition to L-field and two individuals who received a reversed Y-field.

[l]Sixteen of 21 individuals received infradiaphragmatic RT as first RT-field and a short while later received supradiaphragmatic RT.

[m]RT toward bone (n = 21), CNS (n = 21), abdominal residual masses (n = 16), intraoperative RT (n = 1), skin lesions (n = 1), nonspecified sites (n = 4).

TC, given the incidence of TC in a comparable Norwegian male population, matched by 5-year age groups and calendar year of follow-up. Cumulative incidences and SIRs with respective 95% CIs were calculated for the whole cohort and stratified according to treatment groups, age at diagnosis, follow-up time, and histology.

The effect of treatment and histology on the second TC risk were evaluated using Cox proportional hazard regression models with time since diagnosis as time scale, the surgery-only group as reference, and adjusting for age at diagnosis.[20] Additionally, histology as a risk factor was investigated in a multivariable Cox regression model which included treatment. Cumulative CT doses were estimated based on the CT regimen and number of CT cycles. The Cox regression model was also used to evaluate the effect of age at diagnosis (dichotomized). A nonsignificant Schoenfeld test showed that the proportional hazard assumption was met for all analyses, except for cumulative doses (Appendix Table A1, online only) and the dichotomized age variable ($P = .049$). For the latter, the proportional hazard assumption was judged to be met by visual inspection of a log-log survival plot. The results are presented as hazard ratios (HRs) with corresponding 95% CIs and *P*-values.

Data were analyzed using Stata statistical software (version MP 16.1; STATA, College Station, TX). A *P*-value $< .05$ was considered significant.

RESULTS

Characteristics of the Total Study Cohort and the Metachronous TC Subcohort

The total study cohort consisted of 5,620 men with a median follow-up time of 18 years (IQR, 12.0-25.5) (Table 1). Median age at diagnosis was 33 years, 38% were < 30 years, and 70% were diagnosed with stage I disease at first TC. Overall, 25% were treated with surgery only, and 44% were treated with CT at first TC.

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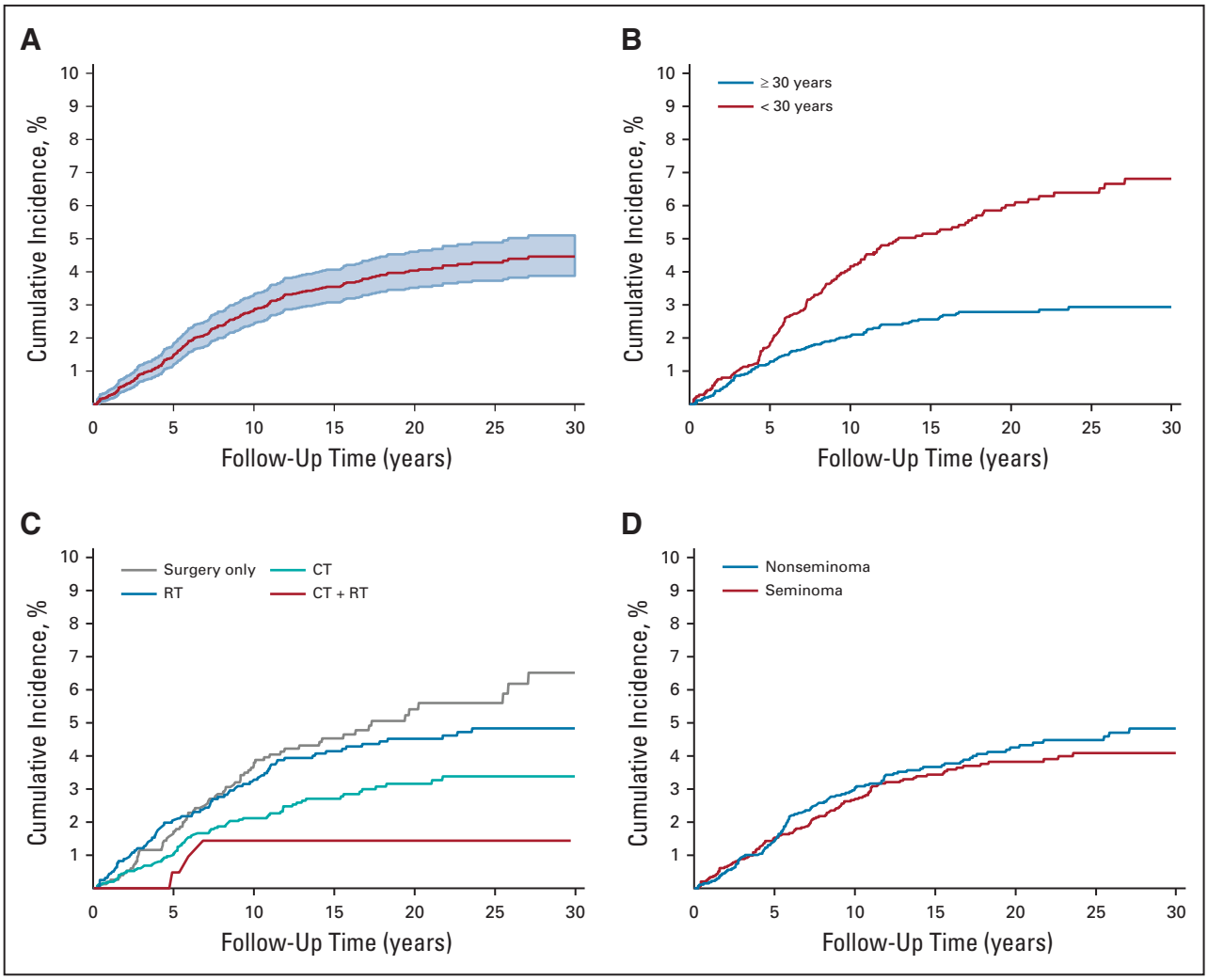

FIG 1. Crude cumulative incidences of metachronous contralateral TC by follow-up time. (A) All patients (with 95% CI), (B) by age at first TC, dichotomized (C) by treatment groups at first TC, and (D) by histology at first TC. In (A), the red line indicates the incidence of metachronous contralateral TC, and the blue area indicates the 95% CI. CT, chemotherapy; CT + RT, combination of CT and RT; RT, radiotherapy; TC, testicular cancer.

Overall, 218 (3.9%) men developed a metachronous contralateral TC after median 6.2 years (IQR, 3.3-10.6) (Table 1). Among these 218 men, median age at first TC diagnosis was 28.7 years, 57% were < 30 years at diagnosis of first TC, and seminoma (49%) and nonseminoma (51%) histology of the first TC was equally distributed. Furthermore, 80% were diagnosed with clinical stage I at first TC, and as treatment for first TC, 33% had surgery only and 32% received CT. Median time to second TC did not differ according to treatment ($P = .55$) or age at diagnosis of first TC ($P = .10$) (Appendix Table A2, online only).

The majority of the second TCs were seminomas (72%) (Appendix Table A3, online only). At diagnosis of the second TC, 84% had stage I disease and 53% were treated with surgery only.

Cumulative Incidences of Second TC

The overall crude cumulative second TC incidence was 4.0% (95% CI, 3.5 to 4.6) at 20 years (Fig 1A, Table 2). The second TC incidence was lower in those age ≥ 30 years at first TC diagnosis (2.8%; 95% CI, 2.3 to 3.4) than in those age < 30 years (6.0%; 95% CI, 5.0 to 7.1) (Fig 1B). The second TC incidence was also lower after treatment with CT (3.2%; 95% CI, 2.5 to 4.0) and CT + RT at first TC (1.4%; 95% CI, 0.4 to 3.9) than after surgery only (5.4%; 95% CI, 4.2 to 6.8) or RT (4.5%; 95% CI, 3.6 to 5.6) (Fig 1C).

For those age < 30 years at first TC diagnosis, 20-year cumulative incidence after surgery only was 8.0% (95% CI, 5.8 to 10.6), and after CT, it was 4.8% (95% CI, 3.6 to 6.3) (Table 2). In comparison, for those age ≥ 30 years at first TC diagnosis, the second TC incidence was 3.2% (95% CI,

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TABLE 2. Cumulative Incidences of Metachronous Contralateral TC According to Treatment, Age, and Histology at First TC and Specified Follow-up Time

	< 5 years			< 10 years			< 15 years			< 20 years		
Variable	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Total	82	1.5	1.2 to 1.8	157	2.8	2.4 to 3.3	192	3.5	3.1 to 4.1	209	4.0	3.5 to 4.6
Age at diagnosis, years												
< 30	38	1.8	1.3 to 2.4	86	4.1	3.3 to 5.0	106	5.2	4.3 to 6.2	118	6.0	5.0 to 7.1
≥ 30	44	1.3	0.9 to 1.7	71	2.0	1.6 to 2.6	86	2.6	2.1 to 3.1	91	2.8	2.3 to 3.4
Treatment, all patients												
Surgery only[a]	24	1.6	1.1 to 2.4	52	3.6	2.8 to 4.7	62	4.5	3.5 to 5.7	68	5.4	4.2 to 6.8
CT	25	1.0	0.7 to 1.5	52	2.1	1.6 to 2.7	63	2.7	2.1 to 3.4	69	3.2	2.5 to 4.0
RT	32	2.0	1.4 to 2.8	50	3.2	2.4 to 4.2	64	4.1	3.2 to 5.2	69	4.5	3.6 to 5.6
CT + RT	1	0.5	0.1 to 2.5	3	1.4	0.4 to 3.9	3	1.4	0.4 to 3.9	3	1.4	0.4 to 3.9
Treatment, age < 30 years												
Surgery only[a]	11	1.8	1.0 to 3.1	28	4.7	3.2 to 6.6	36	6.3	4.5 to 8.5	42	8.0	5.8 to 10.6
CT	18	1.6	1.0 to 2.5	40	3.6	2.6 to 4.8	46	4.2	3.1 to 5.6	50	4.8	3.6 to 6.3
RT	9	2.5	1.2 to 4.6	16	4.5	2.7 to 7.0	22	6.3	4.0 to 9.1	24	6.9	4.6 to 10.0
CT + RT	0	0	0	2	2.9	0.6 to 9.1	2	2.9	0.6 to 9.1	2	2.9	0.6 to 9.1
Treatment, age ≥ 30 years												
Surgery only[a]	13	1.5	0.9 to 2.5	24	2.9	1.9 to 4.2	26	3.2	2.1 to 4.6	26	3.2	2.1 to 4.6
CT	7	0.5	0.2 to 1.0	12	0.9	0.5 to 1.5	17	1.4	0.9 to 2.2	19	1.7	1.1 to 2.7
RT	23	1.9	1.2 to 2.8	34	2.8	2.0 to 3.9	42	3.5	2.6 to 4.7	45	3.8	2.8 to 5.0
CT + RT	1	0.7	0.1 to 3.6	1	0.7	0.1 to 3.6	1	0.7	0.1 to 3.6	1	0.7	0.1 to 3.6
Histology, all patients												
Seminoma	44	1.5	1.1 to 2.0	78	2.7	2.1 to 3.3	97	3.4	2.8 to 4.2	104	3.8	3.1 to 4.6
Nonseminoma	38	1.4	1.0 to 1.9	79	3.0	2.4 to 3.7	95	3.7	3.0 to 4.4	105	4.3	3.5 to 5.1
Histology, age < 30 years												
Seminoma	13	2.1	1.2 to 3.4	26	4.2	2.8 to 5.9	35	5.8	4.1 to 7.9	38	6.6	4.7 to 8.8
Nonseminoma	25	1.7	1.1 to 2.4	60	4.0	3.1 to 5.1	71	4.9	3.8 to 6.1	80	5.8	4.6 to 7.1
Histology, age ≥ 30 years												
Seminoma	31	1.3	0.9 to 1.9	52	2.3	1.7 to 2.9	62	2.8	2.2 to 3.5	66	3.1	2.4 to 3.9
Nonseminoma	13	1.1	0.6 to 1.8	19	1.6	1.0 to 2.5	24	2.1	1.4 to 3.1	25	2.3	1.5 to 3.3

NOTE. n refers to the cumulative number of men developing metachronous contralateral TC up until specified follow-up time. Age refers to age at diagnosis of first TC, dichotomized on < 30 or ≥ 30 years.

Abbreviations: CT, chemotherapy; CT + RT, combination of CT and RT; RT, radiotherapy; TC, testicular cancer.

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

2.1 to 4.6) after surgery only and 1.7% (95% CI, 1.1 to 2.7) after CT.

The second TC incidence did not differ according to first TC histology, with estimates of 3.8% (95% CI, 3.1 to 4.6) after seminoma and 4.3% (95% CI, 3.5 to 5.1) after nonseminoma (Fig 1D).

Risk of Second TC in Relation to the General Population

Overall, the second TC risk was 13-fold higher compared with the risk of developing TC in the general population (SIR, 13.1; 95% CI, 11.5 to 15.0) (Table 3). The risk was lower after treatment with CT (SIR, 9.1; 95% CI, 7.2 to 11.5) and CT + RT (SIR, 8.6; 95% CI, 2.8 to 26.7) at first TC than after surgery only (SIR, 16.3; 95% CI, 12.9 to 20.5) and RT (SIR, 17.7; 95% CI, 14.1 to 22.3). SIRs decreased with increasing age at diagnosis and was highest for those age 20-30 years (SIR, 14.0; 95% CI, 11.7 to 16.8.). The risk for a second TC was the highest within the first 5 years of follow-up after diagnosis of the first TC (SIR, 17.0; 95% CI, 13.7 to 21.2) and decreased with increasing follow-up time.

HRs for Second TC

With surgery only as the reference group, the second TC risk was significantly lower after treatment with CT at first TC (HR, 0.55; 95% CI, 0.40 to 0.76) (Table 4). A sensitivity analysis excluding those treated with CT other than CBCT

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TABLE 3. SIRs for Metachronous Contralateral TC According to Treatment, Age, and Histology at First TC and Follow-up Time

Variable	No. of Events	SIR	95% CI
Total	218	13.1	11.5 to 15.0
Treatment, first TC			
Surgery only[a]	72	16.3	12.9 to 20.5
CT	71	9.1	7.2 to 11.5
RT	72	17.7	14.1 to 22.3
CT + RT	3	8.6	2.8 to 26.7
Age, dichotomized, years			
< 30	125	13.4	11.2 to 15.9
≥ 30	93	12.8	10.4 to 15.7
Age at diagnosis, years			
16-20	9	8.5	4.4 to 16.4
20-30	116	14.0	11.7 to 16.8
30-40	76	13.6	10.9 to 17.0
40-50	14	10.3	6.1 to 17.4
> 50	3	9.6	3.1 to 29.6
Histology			
Seminoma	107	14.7	12.2 to 17.8
Nonseminoma	111	11.9	9.9 to 14.3
Follow-up time, years			
< 5	82	17.0	13.7 to 21.2
5-10	75	15.5	12.3 to 19.4
10-15	35	10.4	7.4 to 14.4
15-20	17	8.7	5.4 to 13.9
> 20[b]	9	5.6	2.9 to 10.7

Abbreviations: CT, chemotherapy; CT + RT, combination of CT and RT; RT, radiotherapy; SIR, standardized incidence ratio; TC, testicular cancer.

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

[b]The longest time interval between first TC and second TC was 27.1 years.

(carboplatin-based, n = 332; other CT, n = 2) was performed with no significant change of results (data not shown). Treatment with RT did not affect the second TC risk (HR, 1.10; 95% CI, 0.79 to 1.54).

For each additional CBCT cycle administered, the point estimates for second TC risk decreased, with significantly reduced risks after three (HR, 0.53; 95% CI, 0.29 to 0.97), four (HR, 0.41; 95% CI, 0.25 to 0.66), and more than four cycles (HR, 0.21; 95% CI, 0.07 to 0.66) (Table 4, Fig 2). The hazard of second TC was not significantly different after treatment with adjuvant carboplatin monotherapy (HR, 1.22; 95% CI, 0.62 to 2.39). For each increase of 100 mg/m^2 cisplatin, the second TC risk decreased equivalent to the results according to the number of CBCT cycles. The effect on second TC risk was weakened for the dose level of 101-200 mg/m^2 when carboplatin was included in the analysis of cumulative platinum doses (Appendix Table A1).

The second TC risk was significantly reduced for those age ≥ 30 years at first TC diagnosis (HR, 0.47; 95% CI, 0.36 to 0.62). In age-adjusted Cox regression, nonseminoma histology at first TC was associated with a decreased risk of second TC (HR, 0.73; 95% CI, 0.55 to 0.98). However, compared with seminoma, this association disappeared when treatment at first TC was included in the model (HR, 0.97; 95% CI, 0.65 to 1.45) (Table 4).

DISCUSSION

In this population-based study, the overall 20-year cumulative incidence of a metachronous TC was 4.0% in a well-described cohort with complete information on total treatment burden and a long follow-up time. We demonstrated, to the best of our knowledge for the first time, that the risk of a metachronous contralateral TC decreased with each additional CBCT cycle administered, with significantly reduced risks after more than two CBCT cycles.

The overall second TC cumulative incidence of 4% and total SIR of 13.1 found in this study are in accordance with the existing literature.[1-7] We found a reduced second TC risk after treatment with CT at first TC, and our results lend strong support to the hypothesis that cisplatin reduces the second TC risk.[1-3,5] Treatment with RT has not been considered to affect the TC incidence,[3,4,12] and our results are in agreement with this. Adjuvant infradiaphragmatic RT after seminoma results in a total dose of 0.09-0.32 Gy of scattered radiation to the remaining testicle, which is probably insufficient for eradication of GCNIS if present.[23]

GCNIS is the precursor of germ cell TC.[24] If left untreated for 5 years, 50% of patients with GCNIS will develop an invasive cancer.[25] There has not been a tradition to screen for GCNIS in Norway during the study period as it has only been performed in selected high-risk patients.[17,26,27] Metastatic TC is highly sensitive to cisplatin. However, cisplatin seems to have a modest but possibly dose-dependent effect on eradication of GCNIS.[17,25,28-31] In the present study, we found a strong association between the number of CBCT cycles, cumulative cisplatin dose, and the second TC risk. Our results are in line with the study by Brabrand et al,[17] who found significantly reduced second TC risk after more than four compared with one to three CBCT cycles or no CT in a study of 61 TCS with biopsy-proven GCNIS in the contralateral testicle. We found no risk reduction after one to two CBCT cycles, which corroborates results from a prospective study on second TC risk after one to two adjuvant CBCT cycles in patients with stage I nonseminoma.[26] In contrast to the results from the randomized trial by Oliver et al[32] comparing adjuvant carboplatin with RT, we found no decrease of second TC risk after treatment with adjuvant carboplatin.

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TABLE 4. Age-Adjusted HRs for Metachronous Contralateral TC According to Treatment Groups, Treatment Intensity, Age, and Histology at First TC

Variable	HR	95% CI	P
Treatment			
Surgery only	1	Ref	Ref
CT	**0.55**	**0.40 to 0.76**	**< .001**
RT	1.10	0.79 to 1.54	.580
CT + RT	0.50	0.16 to 1.57	.233
No. of CBCT cycles			
Surgery only	1	Ref	Ref
1	1.01	0.52 to 1.96	.983
2	0.74	0.40 to 1.36	.332
3	**0.53**	**0.29 to 0.97**	**.040**
4	**0.41**	**0.25 to 0.66**	**< .001**
> 4	**0.21**	**0.07 to 0.66**	**.008**
Carboplatin, adjuvant[a]	1.22	0.62 to 2.39	.565
RT field			
Surgery only	1	Ref	Ref
L-Field	1.17	0.78 to 1.62	.521
Para-aortal	0.75	0.34 to 1.64	.468
RT dose for first abdominal RT-field, Gy			
Surgery only	1	Ref	Ref
20-29	1.24	0.77 to 1.98	.383
30-39	1.04	0.70 to 1.55	.832
≥ 40	1.17	0.50 to 2.70	.721
Age at diagnosis,[b] years			
< 30	1	Ref	Ref
≥ 30	**0.47**	**0.36 to 0.62**	**< .001**
Histology			
Age-adjusted			
Seminoma	1	Ref	Ref
Nonseminoma	**0.73**	**0.55 to 0.98**	**.034**
Multivariable[c]			
Seminoma	1	Ref	Ref
Nonseminoma	0.97	0.65 to 1.45	.883

NOTE. Significant results marked with bold. Age refers to age at diagnosis of first TC, dichotomized on < 30 or ≥ 30 years.

Abbreviations: CBCT, cisplatin-based chemotherapy; CT, chemotherapy; CT + RT, combination of CT and RT; Gy, gray; HR, hazard ratio; Ref, reference; RT, radiotherapy; TC, testicular cancer.

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

[b]Not age adjusted.

[c]Adjusted for treatment in addition to age.

The modulating effect of the blood-testis barrier on the intratubular concentration of cytotoxic drugs,[33,34] possibly in part, explains the need for higher cumulative doses of cisplatin before effect on GCNIS and the subsequent second TC risk. However, cisplatin undoubtedly has an effect on the testis, demonstrated by the decrease of sperm concentration and quality and the changes of sperm DNA following CBCT.[35-37] Furthermore, there seems to be a relationship between the number of CBCT cycles and the recovery of spermatogenesis.[36-39] A recent publication by Weibring et al[40] did not find a long-term reduction of sperm count after one cycle of CBCT. On the other hand, three or more cycles of CBCT may lead to long-term or permanent impairment of sperm function.[36-38]

It has been suggested that cisplatin delays rather than reduces the development of a second TC.[29,31] In accordance with Schaapveld et al,[3] our results do not lend support to this hypothesis. On the contrary, we found that there was a longer median time interval between first TC and second TC after surgery only (7.0 years) than after CT (5.8 years), although not statistically significant. The overall latency of 6.2 years between first TC and second TC agrees with previous studies.[1-3] In the present study, with a very long follow-up time of median 18 years, 72% of second TCs developed within 10 years of follow-up. This is in line with the report of a plateau in incidence after 15-20 years.[3,4] However, second TCs may occur late,[41] and the longest time interval between first TC and second TC in our cohort was 27 years.

A polygenic susceptibility, coupled with fetal and early-life environmental factors, is involved in TC development.[10,11,42-45] The shared prenatal predisposition of the first and second TC probably accounts for the increased risk of metachronous contralateral TC, and the increased risk in younger versus older men is in turn presumably explained by this.[1,46] Young age at TC diagnosis has been established as an important risk factor for developing metachronous contralateral TC,[1-4,12,13,47] and our results are in complete agreement with this. In our study, median age at diagnosis of first TC was 4.6 years younger in men who later developed a second TC than men with unilateral TC. Furthermore, men age < 30 years at first TC had more than twice as high 20-year cumulative second TC incidence than those 30 years or older at first TC diagnosis.

The current knowledge regarding histology and the risk of metachronous contralateral TC is inconsistent.[1,4,7,13,14] Studies conducted in the precisplatin era found a higher risk for metachronous contralateral TC after nonseminoma than after seminoma.[4,14] In the cisplatin era, some studies concluded with the opposite,[7,13] supporting an effect of CBCT.[1] We found no association between first TC histology and the risk of a second TC when adjusting for age and treatment, which is in line with Andreassen et al.[2] Our results suggest that the differences found in histology[1,4,7,13,14] are in fact caused by the effect of CBCT, as patients with nonseminoma

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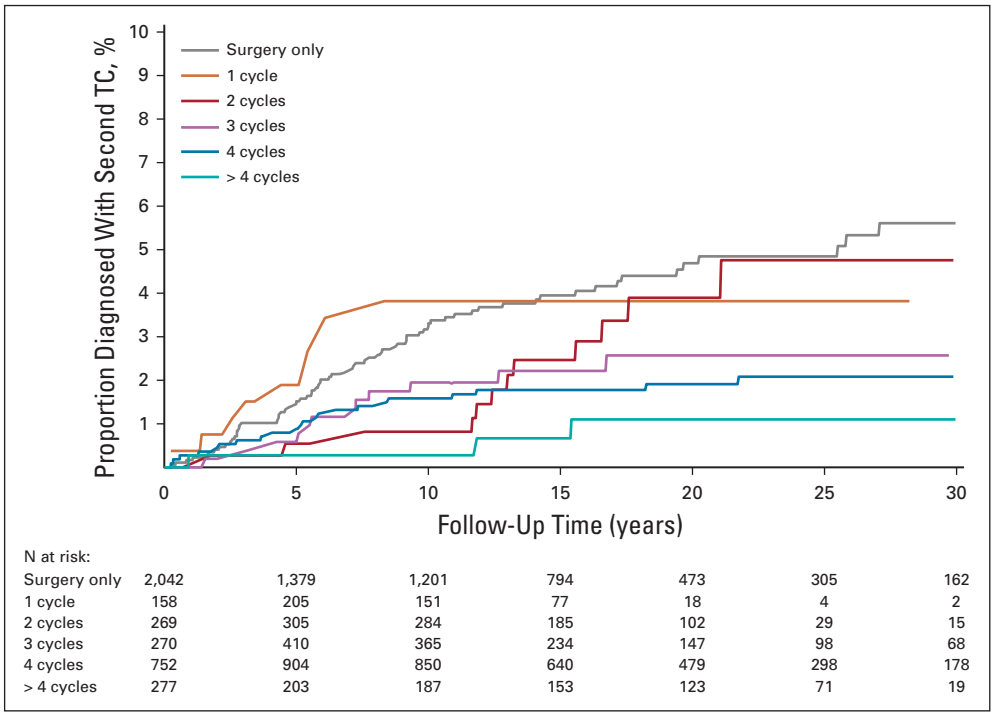

N at risk:							
Surgery only	2,042	1,379	1,201	794	473	305	162
1 cycle	158	205	151	77	18	4	2
2 cycles	269	305	284	185	102	29	15
3 cycles	270	410	365	234	147	98	68
4 cycles	752	904	850	640	479	298	178
> 4 cycles	277	203	187	153	123	71	19

FIG 2. Proportion diagnosed with metachronous contralateral TC by follow-up time and the number of cisplatin-based chemotherapy cycles, adjusted for age at TC diagnosis. The risk table presents the crude number of individuals by follow-up time. TC, testicular cancer.

are more often treated with CBCT than patients with seminoma.

In a recent review by Zequi et al,[48] 60.4% of metachronous contralateral TCs had a seminoma histology. This is in line with the present study in which 72% of the second TCs were seminomas. The abundancy of seminoma histology of second TCs is probably caused by age.[18]

In our study, the majority (84%) of second TCs were diagnosed as clinical stage I, and this correlates with the results published in the review by Zequi et al[48] (73.3% in stage I). Our even higher proportion diagnosed in stage I might be a result of robust follow-up procedures, centralized treatment of TC in Norway, and the risk-adapted biopsy strategy of the contralateral testicle.[27,49]

Important strengths of our study include the consideration of a nationwide cohort, the completeness of cancer incidence rates of the CRN,[18] and the complete information on treatment burden in a large and unselected study cohort with a long follow-up time. The risk-adapted treatment strategy in clinical stage I disease recommended by SWENOTECA has made it possible to compare adjuvant CT with the surveillance strategy.[21]

The lack of information regarding GCNIS and risk factors for TC, such as family history of TC, history of cryptorchidism, or infertility, are potential limitations. Tissue samples available for genetic analyses could have been of particular interest.

In conclusion, we found a strong association between the number of CBCT cycles and the subsequent risk of a metachronous contralateral TC. Patients with metastatic unilateral TC might appreciate information on the significant risk reduction of second TC after treatment with CT. Although most second TCs develop within 10 years after diagnosis of the first TC, they may develop after more than 20 years. It is important that TCS are aware of this risk and that the importance of regular lifelong self-examination is emphasized.

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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.

PRIOR PRESENTATION

Presented in part at the ESMO Virtual Congress 2020, Science Weekend, September 19-21, 2020.

SUPPORT

Supported by grants from Helse Nord RHF (grant no. SPF1230-15).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.20.02713.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Metachronous Contralateral Testicular Cancer in the Cisplatin Era: A Population-Based Cohort Study

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APPENDIX

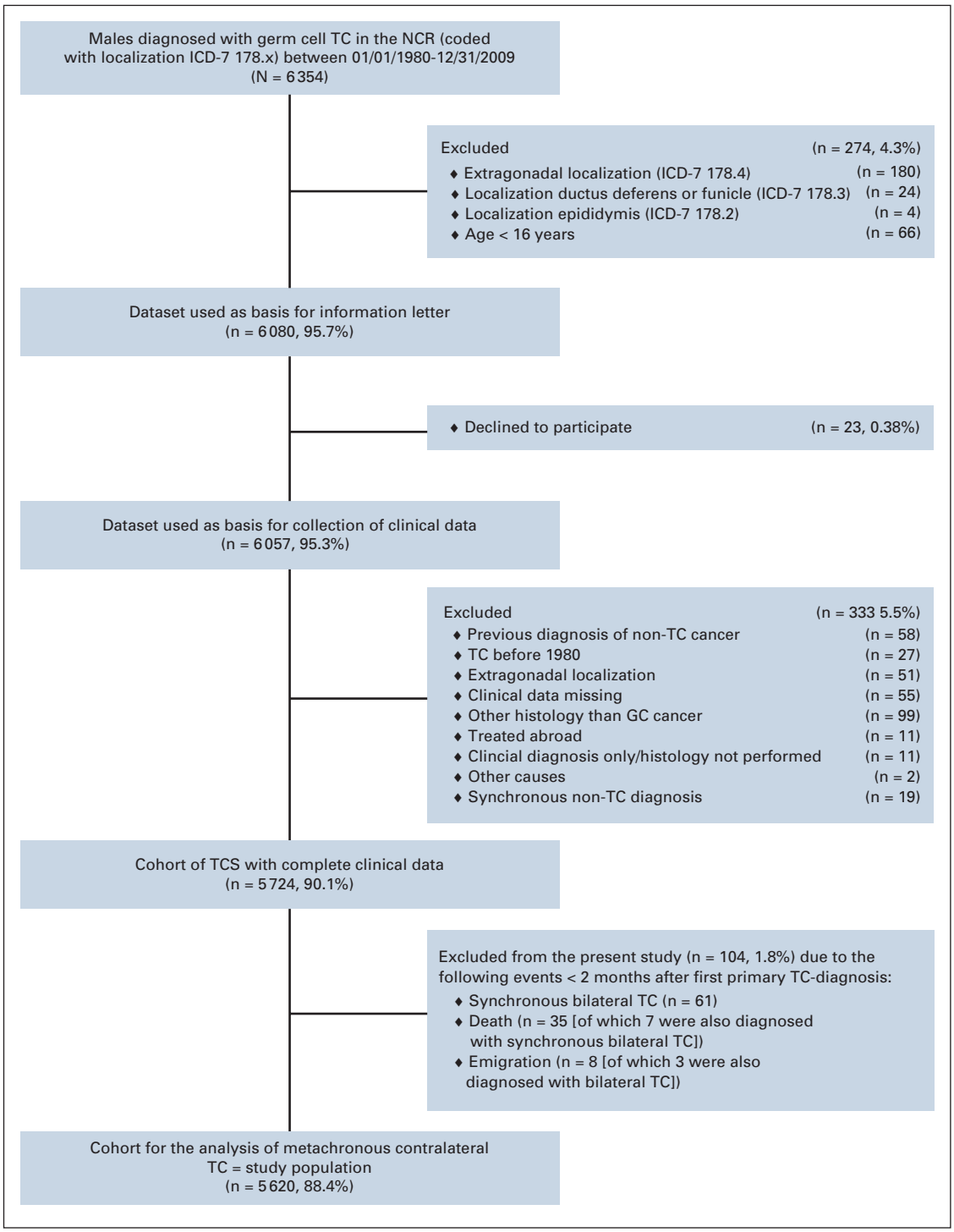

FIG A1. Flowchart presenting the study cohort. GC, germ cell; ICD-7, International Classification of Diseases Version 7; NCR, the Norwegian Cancer Registry; TC, testicular cancer; TCS, testicular cancer survivors.

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TABLE A1. Age-Adjusted HRs for Metachronous Contralateral TC According to Cumulative Cisplatin, Platinum, and Bleomycin Doses at First TC[a]

Chemotherapy Dose	HR	95% CI	*P*
Cumulative cisplatin dose, mg/m^2			
Surgery only	1	Reference	Reference
1-100	1.01	0.52 to 1.96	.984
101-200	0.74	0.40 to 1.36	.331
201-300	**0.53**	**0.29 to 0.98**	**.043**
301-400	**0.43**	**0.27 to 0.70**	**.001**
> 400	**0.14**	**0.03 to 0.52**	**.004**
Carboplatin	1.15	0.62 to 2.12	.667
Cumulative total platinum dose, mg/m^2[b]			
Surgery only	1	Reference	Reference
1-100	1.01	0.52 to 1.96	.984
101-200	0.91	0.56 to 1.47	.697
201-300	**0.53**	**0.29 to 0.99**	**.045**
301-400	**0.46**	**0.29 to 0.72**	**.001**
> 400	**0.12**	**0.03 to 0.50**	**.003**
Cumulative bleomycin dose, IU			
Surgery only	1	Reference	Reference
1-100,000	0.92	0.50 to 1.70	.789
100,001-200,000	0.55	0.26 to 1.14	.107
200,001-300,000	**0.46**	**0.30 to 0.69**	**<.001**
> 300,000	0.29	0.07 to 1.19	.086
Chemotherapy without bleomycin	0.84	0.47 to 1.50	.550

NOTE. Significant results marked with bold.

Abbreviations: HR, hazard ratio; TC, testicular cancer.

[a]When analyzing the effect of cumulative doses, the proportional hazard assumption was violated for some treatment groups. We fitted new models with an interaction effect between follow-up time and the selected treatment groups and compared model fit using BIC. In all cases, the best fit was provided by the simple model without interaction effects, and hence, the results from these are presented.

[b]Cumulative total platinum doses contain cumulative doses of cisplatin and/or carboplatin. For carboplatin, the corresponding cisplatin-equivalent doses were estimated by dividing the carboplatin doses by four (Ozols Cancer Treat Rev. 1985).

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TABLE A2. Time to Metachronous Contralateral TC According to Characteristics at First TC

Characteristic	Individuals Developing Metachronous Contralateral TC (n = 218)
By time since treatment at first TC, years	
Surgery only[a]	7.0 (4.3-10.0)
CT	5.8 (3.2-10.9)
RT	6.5 (2.7-10.7)
CT + RT	5.9 (4.9-6.2)
By age at first TC, dichotomized, years	
< 30 years	7.2 (4.4-10.9)
≥ 30 years	5.3 (2.6-9.3)
By histology at first TC, years	
Seminoma	6.7 (3.2-10.5)
Nonseminoma	5.9 (4.1-10.9)

NOTE. Data are presented as median (IQR).
Abbreviations: CT, chemotherapy; CT + RT, combination of CT and RT; IQR, interquartile range; RT, radiotherapy; TC, testicular cancer.
[a]Includes men treated with surveillance and men treated with retroperitoneal lymph node dissection in addition to orchiectomy.

TABLE A3. Patient Characteristics at Diagnosis of Metachronous Contralateral TC

Characteristic	Individuals Developing Metachronous Contralateral TC (n = 218)
Histology, second TC	
Seminoma	157 (72)
Nonseminoma	58 (27)
Missing	3 (1.4)
Disease stage, second TC[a]	
I	184 (84)
Mk+ and II	16 (7.3)
III	3 (1.4)
IV	4 (1.8)
Missing	11 (5.1)
Treatment, second TC	
Surgery only	115 (53)
CT[b]	71 (33)
RT	16 (7.3)
CT + RT	0
Missing	16 (7.3)

NOTE. Data are presented as n (%).
Abbreviations: CT, chemotherapy; CT + RT, combination of CT and RT; Mk+, marker positive; RT, radiotherapy; TC, testicular cancer.
[a]As described by Peckham et al.[19]
[b]Of which one had disseminated synchronous nongerm cell SC (C34) treated with CT. A few of these cases were originally treated with surveillance but received CT at relapse.

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