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original reports abstract

Dose-Dependent Effect of Platinum-Based Chemotherapy on the Risk of Metachronous Contralateral Testicular Cancer

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PURPOSE Patients with testicular germ cell tumor (TGCT) are at increased risk of developing a contralateral TGCT (CTGCT). Although some studies suggest that prior treatment with platinum-based chemotherapy affects CTGCT risk, a relationship between CTGCT risk and platinum dose has not previously been assessed. We analyzed the association between the number of platinum-based chemotherapy cycles and CTGCT risk.

PATIENTS AND METHODS The risk of developing a metachronous CTGCT was evaluated in a nationwide cohort of 4,755 patients diagnosed with primary TGCT in the Netherlands between 1989 and 2007. Standardized incidence ratios were computed to compare CTGCT incidence with expected TGCT on the basis of TGCT incidence in the general population. The cumulative incidence of CTGCT was estimated in the presence of death as competing risk. The effect of treatment with platinum-based chemotherapy on CTGCT risk was assessed using multivariable Cox proportional hazards regression models.

RESULTS CTGCT was diagnosed in 136 patients (standardized incidence ratio, 14.6; 95% CI, 12.2 to 17.2). The cumulative incidence increased up to 20 years after primary diagnosis, reaching 3.4% (95% CI, 2.8% to 4.0%) after 20 years of follow up. The risk of developing a CTGCT decreased with age (hazard ratio [HR], 0.93; 95% CI, 0.90 to 0.96), was lower after nonseminomatous germ cell tumor (HR, 0.58; 95% CI, 0.35 to 0.96) and decreased with every additional cycle of chemotherapy ($HR_{per\ cycle}$, 0.74; 95% CI, 0.64 to 0.85).

CONCLUSION Approximately one in every 30 survivors of TGCT will develop a CTGCT, with CTGCT incidence increasing up to 20 years after a primary TGCT. Treatment with platinum-based chemotherapy shows a dose-dependent inverse association with CTGCT risk.

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INTRODUCTION

Patients with a unilateral testicular germ cell tumor (TGCT) are at increased risk of developing a contralateral TGCT (CTGCT).[1-4] The incidence of CTGCT in survivors of TGCT is approximately 12 to 18 times higher compared with general population rates, with a 20-year cumulative incidence between 2% and 5%.[1,2,5,6] This risk remains elevated for 10 to 20 years after the diagnosis of first TGCT.[1,5,7]

A known risk factor for developing a CTGCT is diagnosis of a first TGCT before the age of 30 years.[7-9] The role of prior treatment with chemotherapy, however, is still unclear. Several studies have suggested a decreased risk of CTGCT in patients treated with platinum-based chemotherapy,[1,2,5,10] whereas other studies found no clear effect.[7,11,12] This discrepancy might be a result of differences in duration of follow up, availability of treatment data, and study methodology. So far, well-defined population-based cohort studies with full information on treatment are scarce.

Kleinschmidt et al[13] postulated the hypothesis of a dose-dependent association between chemotherapy and CTGCT risk on the basis of a study in 11 patients with TGCT and contralateral germ cell neoplasia in situ (GCNIS) who were treated with platinum-based chemotherapy. In patients who received two cycles of chemotherapy, subsequent biopsies showed lower rates of GCNIS eradication compared with patients who received three cycles.

This hypothesis was supported by Dieckmann et al,[14] who found a dose-dependent effect of chemotherapy on GCNIS in a series of 96 patients who had been treated with chemotherapy. However, a dose-dependent association between platinum-based chemotherapy and GCNIS eradication has not been investigated in larger cohort studies. Whether such a relationship exists is clinically relevant, as an increasing number of patients with TGCT may receive lower doses of platinum-based chemotherapy now that adjuvant therapy with one or two cycles of

ASSOCIATED CONTENT

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Appendix

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

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CONTEXT

Key Objective

Testicular germ cell tumor (TGCT) has an excellent prognosis, but patients are at increased risk of developing contralateral TGCT (CTGCT). It is unknown whether prior treatment with chemotherapy affects this risk. This population-based cohort study examined the association between platinum-based chemotherapy and CTGCT risk.

Knowledge Generated

We found that approximately one in every 30 survivors of TGCT will develop a CTGCT within 20 years. A Cox proportional hazards regression analysis showed that the risk of developing CTGCT decreases with age, is lower after non-seminomatous germ cell tumor, and decreases with every additional cycle of platinum-based chemotherapy.

Relevance

The more chemotherapy cycles a patient has received, the lower his risk of developing CTGCT. Our findings are useful to inform patients of their specific risk of developing CTGCT. Patients should be made aware that this risk is increased for up to 20 years after diagnosis of the first TGCT.

chemotherapy in high-risk stage I disease is gaining popularity.[15,16]

We studied the incidence of CTGCT in a large population-based cohort of patients with TGCT. The primary aim was to evaluate the association between the number of platinum-based chemotherapy cycles and risk of CTGCT. Secondary aims were to analyze the incidence of CTGCT and the association between primary TGCT histology and CTGCT histology.

PATIENTS AND METHODS

Data Collection

To assess various late effects of TGCT treatment, a multicenter cohort was established including 4,755 survivors of TGCT who were treated for TGCT before age 50 years between 1989 and 2007 in 11 Dutch hospitals. Patients were identified through hospital tumor registries and the population-based Netherlands Cancer Registry. Inclusion and exclusion criteria have been reported elsewhere.[17]

A case-cohort design was used to facilitate efficient collection of detailed treatment data while allowing for the assessment of multiple treatment-associated outcomes. A hospital-stratified subcohort comprising 15% of the base cohort—25% in the coordinating hospitals Netherlands Cancer Institute and University Medical Center Groningen—was randomly selected and consisted of 783 patients with TGCT. For all patients, we retrieved data on relapses, CTGCTs, and vital status through chart review and linkage with the nationwide registry of histo- and cytopathology (PALGA) and the Netherlands Cancer Registry (complete up to January 31, 2018).

For all patients in the cohort who developed a CTGCT and all subcohort members, detailed treatment data were abstracted from medical records, including administered chemotherapy regimens and numbers of cycles for primary treatment as well as relapse treatment. Of note, 1,401 patients—30.7% of all patients in the present cohort—who were diagnosed with primary TGCT before 1996 were also included in a previous study on CTGCT.[2]

Statistical Analysis

The study end point was metachronous CTGCT, defined as any TGCT in the contralateral testicle 2 months or more after diagnosis of the first TGCT. Time at risk started at 2 months after TGCT diagnosis and ended at the date of CTGCT diagnosis, death, emigration, or most recent medical information. Contralateral GCNIS was not considered a CTGCT.

Number of chemotherapy cycles was analyzed both as a continuous and as a categorical variable. To allow a test for trend in categorical analysis, the average number of chemotherapy cycles within each category was used to denote category level. The average number of cycles for all patients with known number of cycles was used for the category denoting patients with an unknown number of cycles. The association between the histology of the primary TGCT and the histology of the CTGCT was assessed using multinomial logistic regression with three possible outcomes: no CTGCT, seminomatous CTGCT, and non-seminomatous CTGCT.

Fisher exact test and Mann-Whitney U test were used for univariable analysis of categorical and continuous variables, respectively. The expected number of CTGCTs was estimated using age-, calendar period–, and site-specific cancer incidence rates for the Dutch male population. Standardized incidence ratios (SIRs), absolute excess risk (expressed per 10,000 person-years), and corresponding 95% CIs were computed using standard methods.[18] Tests for homogeneity and trend of SIRs were performed within collapsed Poisson regression models.

The cumulative incidence of CTGCT was estimated in the presence of death as competing risk. Effects of TGCT treatment on CTGCT risk were assessed in multivariable Cox proportional hazards regression models. Treatment effects were entered in the models as a time-dependent variable, allowing a patient to add person-time to a different treatment category at the date of relapse treatment while accounting for the effects of other covariates where appropriate. Barlow's inverse probability weights were used to adjust the partial likelihood function for the case-cohort design.[18]

Kaplan-Meier survival curves were constructed to compare survival with and without CTGCT. The association between the diagnosis of CTGCT and survival was analyzed in a Cox model, which included age, initial stage, histology of the first TGCT, and treatment with chemotherapy before CTGCT with CTGCT included as a time-dependent variable.

Analyses were performed using STATA (version 11; StataCorp LP, College Station, TX), and $P < .05$ was considered statistically significant.

RESULTS

The cohort was composed of 2,612 patients with seminomatous germ cell tumor (SGCT; 54.9%) and 2,143 with nonseminomatous germ cell tumor (NSGCT; 45.1%; Table 1 and Appendix Table A1, online only). The majority of patients initially presented with stage I disease (65.6%). Median follow up was 17.0 years (interquartile range [IQR], 12.7 to 22.0 years) for the entire cohort and follow up was 20 years or more for 1,636 patients (34.4%).

In total, 161 patients were diagnosed with CTGCT, which was synchronous in 25 patients and metachronous in 136 patients (Appendix Table A2, online only). The median interval between primary TGCT and metachronous CTGCT was 6.1 years (IQR, 3.6 to 9.4 years) and was similar for patients with SGCT and NSGCT ($P = .090$). The interval between primary TGCT and CTGCT was less than 5 years in 41.2%, 5 to 9 years in 38.2%, 10 to 14 years in 15.4%, and 15 to 20 years in 5.2% of CTGCTs. No CTGCTs were diagnosed beyond 20 years of follow up.

SIR for a metachronous CTGCT was 14.6 (95% CI, 12.2 to 17.2) times higher than the expected TGCT incidence on the basis of general population rates (Table 2). SIR decreased with follow-up duration ($P_{trend} < .001$) and higher attained age ($P_{trend} = .019$; Appendix Table A3, online only), and was higher in patients with SGCT (SIR, 22.1) compared with those with NSGCT (SIR, 8.6; $P_{heterogeneity} < .001$).

The 10- and 20-year cumulative incidences of CTGCT were 2.4% (95% CI, 2.0% to 2.9%) and 3.4% (95% CI, 2.8% to 4.0%), respectively (Table 3). The 20-year cumulative incidence was 4.0% (95% CI, 3.3% to 4.9%) after SGCT and 2.6% (95% CI, 1.9% to 3.4%) after NSGCT. Patients diagnosed with a SGCT before age 25 years had the highest 20-year cumulative incidence (8.7%; 95% CI, 4.2% to 15.2%), whereas the 20-year cumulative incidence among patients with NSGCT diagnosed at age 35 years or older was only 1.0% (95% CI, 0.3% to 2.3%). The cumulative incidence did not increase beyond 20 years of follow up (Fig 1).

The 20-year cumulative incidence was 1.7% (95% CI, 1.1% to 2.5%) in patients who had been treated with platinum-based chemotherapy and 4.4% (95% CI, 3.7% to 5.3%) in non–platinum-exposed patients. Time to CTGCT did not differ between patients who were treated with chemotherapy (median interval, 4.9 years; IQR, 3.0 to 6.6 years) compared with non–platinum-exposed patients (median interval, 7.5 years; IQR, 4.6 to 9.7 years; $P = .23$).

In multivariable analysis, the risk of developing a CTGCT decreased with age (hazard ratio [HR], 0.93; 95% CI, 0.90 to 0.96) and was lower after a NSGCT primary (HR, 0.58; 95% CI, 0.35 to 0.96). Using the number of chemotherapy cycles as a continuous predictor, the risk of developing a CTGCT decreased with every additional cycle of chemotherapy (HR, 0.74; 95% CI, 0.64 to 0.85; Fig 2 and Table 4). Patients treated with four cycles of chemotherapy had a much lower risk of CTGCT compared with patients not treated with chemotherapy (HR, 0.18; 95% CI, 0.08 to 0.43; Table 4).

Most CTGCTs (71.3%) were of SGCT histology (Appendix Table A2). Among patients with a SGCT primary, 76.9% of CTGCTs were of SGCT histology, whereas 60% of patients with a NSGCT primary had a CTGCT of SGCT histology. Compared with a patient with a seminoma primary TGCT, having a nonseminoma primary TGCT was associated with a lower risk of both a seminomatous CTCGT (odds ratio, 0.33; 95% CI, 0.20 to 0.56) and a nonseminomatous CTGCT (odds ratio, 0.28; 95% CI, 0.13 to 0.62), and this risk reduction was of a similar magnitude for both histologic CTCGT subtypes ($P_{heterogeneity} = .71$).

The 5- and 10-year overall survival rates in patients with CTGCT were 96.7% (95% CI, 91.5% to 98.8%) and 94.6% (95% CI, 88.3% to 97.6%), respectively. A diagnosis of CTGCT was not associated with increased mortality on the basis of only eight deaths in the CTGCT group.

DISCUSSION

This nationwide cohort study in relatively recently treated patients with detailed treatment information and complete follow up for CTGCT shows that the risk of developing CTGCT decreases with an increase in the number of platinum-based chemotherapy cycles received. Patients with TGCT have an almost 15 times higher risk of developing a CTGCT compared with the risk of developing TGCT in the general population. Approximately one in every 30 survivors of TGCT will develop a CTGCT within 20 years.

The literature on the association between treatment with platinum-based chemotherapy and CTGCT risk is

TABLE 1. Patient Characteristics

Characteristic	Patients With CTGCT[a]	Subcohort	Total Cohort
No. of patients	136	783	4,755
Primary histology			
NSGCT	45 (33.1)	390 (49.8)	2,143 (45.1)
SGCT	91 (66.9)	393 (50.2)	2,612 (54.9)
Median age at primary diagnosis, years (IQR)	29 (33-40)	32 (26-37)	33 (26-40)
Year of primary diagnosis			
1989-1998	55 (40.4)	353 (45.1)	2,141 (45.0)
1999-2007	81 (59.6)	430 (55.9)	2,614 (55.0)
Primary TNM stage			
I	114 (83.8)	518 (66.2)	3,120 (65.6)
II	13 (9.6)	147 (18.8)	947 (19.9)
III	9 (6.6)	118 (15.1)	668 (14.1)
Unknown	0 (0.0)	0 (0.0)	20 (0.4)
Platinum-based chemotherapy cycles	22 (16.2)	293 (37.4)	—
1-2	2 (9.1)	18 (6.1)	—
3	11 (50.0)	86 (29.4)	—
4	6 (27.3)	144 (49.2)	—
> 4	3 (13.6)	38 (13.0)	—
Unknown	0 (0.0)	7 (2.4)	—
Type of platinum-based chemotherapy	22 (16.2)	293 (37.4)	
BEP	22 (100)	266 (90.8)	—
EP	0 (0.0)	6 (2.0)	
VIP	0 (0.0)	5 (1.7)	—
Other[b]	0 (0.0)	16 (5.5)	—
Vital status			
Alive	128 (94.1)	707 (90.3)	4,189 (88.1)
Dead	8 (5.9)	68 (8.7)	533 (11.2)
Lost to follow up/emigrated	0 (0.0)	8 (1.0)	33 (0.7)
Median follow up, years (IQR)	17.9 (13.4-21.7)	17.6 (13.4-22.9)	17.0 (12.7-22.0)

NOTE. Data presented as No. (%) unless otherwise indicated.

Abbreviations: BEP, bleomycin, etoposide, cisplatin; CTGCT, contralateral testicular germ cell tumor; EP, etoposide, cisplatin; IQR, interquartile range; NSGCT, nonseminomatous germ cell tumor; SGCT, seminomatous germ cell tumor; VIP, etoposide, ifosfamide, cisplatin.

[a]Twenty-nine patients with CTGCT are also in the subcohort.

[b]Other chemotherapy regimens: bleomycin, vincristine, cisplatin (n = 4); paclitaxel, bleomycin, etoposide, cisplatin (n = 3); VIP-bleomycin (n = 2); cyclophosphamide, vincristine, carboplatin (n = 2); carboplatin (n = 1); cisplatin, vinblastine, bleomycin (n = 1); cisplatin, vincristine, ifosfamide (n = 1); bleomycin, vincristine, cisplatin, etoposide, ifosfamide, and cisplatin (n = 1); and cisplatin, etoposide, carboplatin (n = 1).

conflicting. Several large studies found no association between receipt of chemotherapy and subsequent CTGCT risk. Fosså et al[5] analyzed SEER Program data, comprising approximately 30,000 patients diagnosed between 1973 and 2001, and found no clear association between initial chemotherapeutic treatment and CTGCT risk. However, data on primary chemotherapy were incomplete and data on treatment received after the initial treatment were lacking completely.

A study in 2,201 Norwegian patients treated between 1953 and 1990 compared the risk of CTGCT between four types of treatment—radiotherapy versus chemotherapy versus radiotherapy with chemotherapy versus surgery or surveillance—and found no significant difference in relative risk between treatment groups.[7] Of note, multivariable analysis was not performed in that study and a large proportion of the patients who were treated with chemotherapy may have received regimens without cisplatin, as this was only introduced in 1978.

TABLE 2. SIR and AER of a Metachronous CTGCT

Variable	Person-Time, Years	CTGCT, No.	SIR (95% CI)	AER (95% CI)
All patients	78,763	136	14.6 (12.2 to 17.2)	16.1 (13.3 to 19.2)
Age at primary diagnosis, years				
< 25	14,522	31	11.0 (7.5 to 15.6)	19.4 (12.6 to 28.4)
25-34	32,220	79	17.1 (13.5 to 21.3)	23.1 (18.0 to 29.1)
≥ 35	32,019	26	13.8 (9.0 to 20.2)	7.5 (4.7 to 11.3)
P_{trend}			.290	
$P_{heterogeneity}$			.096	
Follow up, years				
< 5	22,095	56	19.5 (14.8 to 25.4)	24.0 (17.8 to 31.6)
5-9	21,582	52	17.8 (13.3 to 23.4)	22.7 (16.6 to 30.2)
10-14	17,689	21	9.9 (6.1 to 15.1)	10.7 (6.1 to 16.9)
≥ 15	17,397	7	4.9 (2.0 to 10.2)	3.2 (0.8 to 7.5)
P_{trend}			< .001	
NSGCT	35,964	45	8.6 (6.3 to 11.6)[a]	11.1 (7.7 to 15.3)
Age at primary diagnosis, years				
< 25	12,164	21	8.9 (5.5 to 13.6)	15.3 (8.8 to 24.5)
25-34	16,046	20	8.5 (5.2 to 13.1)	11.0 (6.1 to 17.8)
≥ 35	7,753	4	8.0 (2.2 to 20.4)	4.5 (0.8 to 12.6)
P_{trend}			.817	
$P_{heterogeneity}$			.973	
Follow up, years				
< 5	9,805	14	9.9 (5.4 to 16.6)	12.8 (6.4 to 22.5)
5-9	9,626	19	11.8 (7.1 to 18.4)	18.1 (10.2 to 29.2)
10-14	8,086	9	7.1 (3.2 to 13.4)	9.6 (3.5 to 19.6)
≥ 15	8,447	3	3.3 (0.7 to 9.7)	2.5 (−0.3 to 9.3)
P_{trend}			.020	
SGCT	42,799	91	22.1 (17.8 to 27.1)[a]	20.3 (16.2 to 25.1)
Age at primary diagnosis, years				
< 25	2,359	10	21.3 (10.2 to 39.2)	40.4 (18.3 to 76.0)
25-34	16,175	59	25.9 (19.7 to 33.4)	35.1 (26.4 to 45.6)
≥ 35	24,266	22	15.9 (10.0 to 24.1)	8.5 (5.1 to 13.2)
P_{trend}			.182	
$P_{heterogeneity}$			.130	
Follow up, years				
< 5	12,290	42	29.0 (20.9 to 39.2)	33.0 (23.5 to 45.0)
5-9	11,956	33	25.2 (17.4 to 35.4)	26.5 (17.9 to 37.7)
10-14	9,603	12	14.0 (7.2 to 24.4)	11.6 (5.6 to 20.9)
≥ 15	8,950	4	7.8 (2.1 to 20.1)	3.9 (0.6 to 10.9)
P_{trend}			< .001	

Abbreviations: AER, absolute excess risk; CTGCT, contralateral testicular germ cell tumor; NSGCT, nonseminomatous germ cell tumor; SGCT, seminomatous germ cell tumor; SIR, standardized incidence ratio.

[a]NSGCT primary *v* SGCT primary: $P_{heterogeneity} < .001$.

In contrast, another Norwegian study showed that the cumulative incidence of CTGCT was 50% lower in patients with disseminated TGCT who were treated after 1980 compared with patients with localized TGCT, whereas the cumulative incidence of CTGCT did not differ between initial tumor stages in patients treated in 1953 to 1979.[1]

TABLE 3. Cumulative Incidence of a Metachronous CTGCT

Variable	Patients at Risk, No.		Metachronous CTGCT, No.		Cumulative Incidence, % (95% CI)	
	10 Years	20 Years	10 Years	20 Years	10 Years	20 Years
All patients	4,144	1,549	108	136	2.4 (2.0 to 2.9)	3.4 (2.8 to 4.0)
Age at primary diagnosis, years						
< 25	750	284	20	31	2.5 (1.6 to 3.7)	4.6 (3.1 to 6.4)
25-34	1,667	681	66	79	3.7 (2.9 to 4.7)	4.7 (3.8 to 5.8)
≥ 35	1,727	584	22	26	1.2 (0.8 to 1.8)	1.5 (1.0 to 2.2)
Platinum-based chemotherapy						
Yes	896	341	18	22	1.2 (0.8 to 1.9)	1.7 (1.1 to 2.5)
No	3,248	1,208	90	114	3.3 (2.6 to 4.0)	4.4 (3.7 to 5.3)
NSGCT	1,853	748	33	45	1.7 (1.2 to 2.3)	2.6 (1.9 to 3.4)
Age at primary diagnosis, years						
< 25	627	238	12	21	1.8 (1.0 to 3.0)	3.7 (2.3 to 5.6)
25-34	812	362	18	20	2.1 (1.3 to 3.3)	2.5 (1.6 to 3.8)
≥ 35	414	148	3	4	0.7 (0.2 to 1.8)	1.0 (0.3 to 2.3)
Platinum-based chemotherapy						
Yes	731	277	15	19	1.2 (0.7 to 2.0)	1.8 (1.1 to 2.8)
No	1,122	471	18	26	2.5 (1.5 to 3.8)	3.9 (2.6 to 5.6)
SGCT	2,291	801	75	91	3.0 (2.4 to 3.8)	4.0 (3.2 to 4.9)
Age at primary diagnosis, years						
< 25	123	46	8	10	5.7 (2.7 to 10.4)	8.7 (4.2 to 15.2)
25-34	855	319	48	59	5.2 (3.9 to 6.7)	6.7 (5.2 to 8.6)
≥ 35	1,313	436	19	22	1.4 (0.8 to 2.1)	1.7 (1.1 to 2.5)
Platinum-based chemotherapy						
Yes	165	64	3	3	1.3 (0.4 to 3.5)	—
No	2,126	737	72	88	3.6 (1.8 to 4.4)	4.6 (3.7 to 5.7)

Abbreviations: CTGCT, contralateral testicular germ cell tumor; NSGCT, nonseminomatous germ cell tumor; SGCT, seminomatous germ cell tumor.

The authors concluded that the reduction in CTGCT incidence must have been a result of the introduction of platinum-based chemotherapy for disseminated TGCT in Norway in 1980, although no information about individual treatment was available.

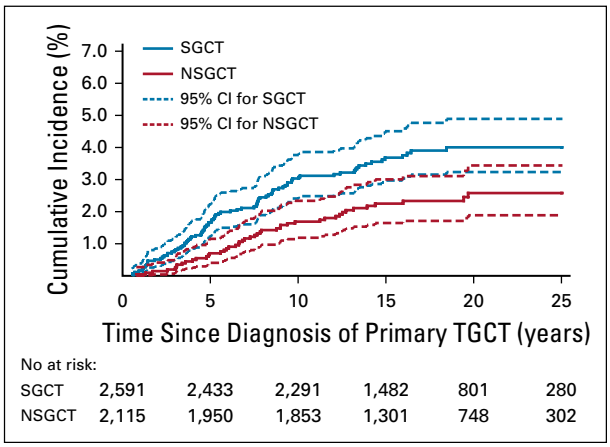

FIG 1. Cumulative incidence of metachronous contralateral testicular germ cell tumor according to primary testicular germ cell tumor (TGCT) histology. NSGCT, nonseminomatous germ cell tumor; SGCT, seminomatous germ cell tumor.

The association between chemotherapy and CTGCT risk was substantiated in a previous study from our group, which had complete data on initial and subsequent treatment.[2] In this study, patients who were treated with platinum-based chemotherapy had a 2.9-fold reduction in CTGCT risk on multivariable Cox proportional hazards regression analysis. These findings suggest that chemotherapy is able to cross the blood-testis barrier.

Several smaller studies have suggested that the association between CTGCT risk and treatment with chemotherapy is dose dependent. Dieckmann et al[14] analyzed the effect of chemotherapy in a study of 228 patients with TGCT with biopsy-proven contralateral GCNIS, of whom 96 patients were subsequently treated with chemotherapy. A malignant event—defined as either GCNIS on rebiopsy or development of CTGCT—occurred in 50% of patients who had received one or two cycles of platinum-based

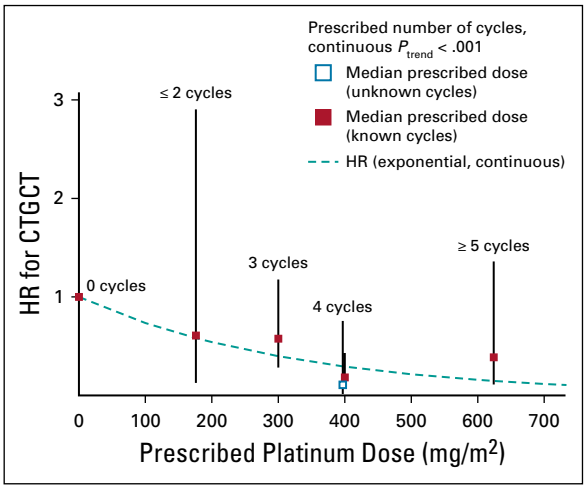

FIG 2. Risk of developing contralateral testicular germ cell tumor (CTGCT) by prescribed platinum dose. Hazard ratios (HRs) for developing CTGCT by prescribed platinum dose compared with no platinum exposure. Red solid squares denote HRs for categories of dose and are plotted at the median prescribed dose (0, 176, 300, 400, 624 mg/m^2) within each category (0, ≤ 2, 3, 4, ≥ 5 cycles, respectively). White square denotes patients with an unknown number of cycles, with the category plotted as the average dose for all patients with known number of cycles (397 mg/m^2). Vertical lines represent the 95% CI. HRs were derived from the Cox proportional hazards regression model with adjustment for age and primary histology (Table 4). Dotted line represents the association of platinum dose with CTGCT risk, with platinum dose fitted as a continuous variable. This dose-response relationship was best described by an exponential model.

TABLE 4. Association of Chemotherapy With CTGCT

Chemotherapy	HR (95% CI)	P
Model 1		
Cycles of platinum-based chemotherapy[a]	0.74 (0.64 to 0.85)	< .001
Model 2		
Cycles of platinum-based chemotherapy[b]		< .001
None	Reference	
1-2[c]	0.61 (0.13 to 2.90)	.534
3	0.58 (0.28 to 1.18)	.131
4	0.18 (0.08 to 0.43)	< .001
> 4[d]	0.39 (0.11 to 1.36)	.139
Unknown[e]	0.11 (0.02 to 0.76)	.025

Abbreviations: CTGCT, contralateral testicular germ cell tumor; HR, hazard ratio.

[a]As a continuous variable, corrected for age and primary histology.

[b]As a categorical variable, corrected for age and primary histology.

[c]Average of 1.76 cycles.

[d]Average of 6.24 cycles.

[e]Average of 3.97 cycles.

chemotherapy. In patients who had received three or more cycles, however, a malignant event occurred in only 24% of cases.

In another series of 61 patients with TGCT with biopsy-proven contralateral GCNIS, the 5-year probability of developing CTGCT was significantly lower for patients who were treated with platinum-based chemotherapy (23%) than it was for nonexposed patients (54%).[19] A dose-dependent association could not be proven because of insufficient statistical power, but the 7.5-year probability of CTGCT was 58% in patients who had received one to three cycles of chemotherapy, whereas this was only 22% in patients who had received four or more cycles. Our population-based cohort study substantiates these previous findings.

Most studies have reported a higher risk of developing CTGCT in patients with a SGCT primary compared with a NSGCT primary[2,5,8,9,20,21]; however, although the risk of CTGCT is influenced by age and treatment, only few studies have adjusted for these variables in their analyses. In reports by Andreassen et al[1] and Schaapveld et al,[2] the effect of primary histology diminished in multivariable analysis, but in the report by Fosså et al,[5] patients with a NSGCT histology had a significantly decreased risk of CTGCT even after correcting for age, initial treatment, and extent of disease. In the current study, we controlled for age and number of chemotherapy cycles and also found a lower risk of CTGCT in patients with a NSGCT primary.

A potential limitation of our study is the lack of information on history of undescended testis, testicular trauma, infertility, testicular atrophy, orchiectomy for nononcologic conditions, or family history. It is unlikely that this lack of information has confounded the observed reduced risk of CTGCT associated with chemotherapy exposure, as these factors do not predict treatment of the primary TGCT. Another potential limitation is the lack of data on ethnicity. Although these data were not collected, the Dutch population is of approximately 90% European, mainly White, descent. Therefore, our findings are not necessarily applicable to other populations.

An important strength of our study is that we have information on all treatment received before CTGCT diagnosis. In studies with data from population-based cancer registries, treatment is often misclassified because data on treatment during follow up are incomplete. The availability of detailed information enabled us to evaluate the effect of platinum-based chemotherapy precisely. Another strength is the nationwide, multicenter, case-cohort design. This makes our study less prone to referral bias, which is an important weakness of single-center series.

The current study gives an accurate and comprehensive estimation of the risk of CTGCT. Our findings are important for clinicians to inform patients of their risk of developing CTGCT. The possibility of developing a CTGCT does not warrant an extension of follow up beyond 5 years, as the

absolute risk of developing CTGCT beyond 5 years of follow up is low. Nevertheless, patients with TGCT should be made aware that they are at increased risk of developing CTGCT for up to 20 years after diagnosis of the first TGCT.

In conclusion, treatment with platinum-based chemotherapy shows a dose-dependent association with lower risk of development of CTGCT. Patients who are diagnosed with SGCT before the age of 25 years have the highest risk of developing a CTGCT. Incidence of CTGCT increases for up to 20 years after diagnosis of first TGCT, resulting in a CTGCT in approximately one in every 30 survivors of TGCT.

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Dose-Dependent Effect of Platinum-Based Chemotherapy on the Risk of Metachronous Contralateral Testicular Cancer

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APPENDIX

TABLE A1. Patient Characteristics by Histology

Characteristic	NSGCT	SGCT
No. of patients	2,143	2,612
Median age, years (IQR)	28 (23-34)	36 (31-43)
Primary TNM stage		
I	1,017 (47.5)	2,103 (80.5)
II	565 (26.4)	382 (14.6)
III	553 (25.8)	115 (4.4)
Unknown	8 (0.4)	12 (0.5)
Vital status		
Alive	1,894 (88.4)	2,295 (87.9)
Dead	230 (10.7)	303 (11.6)
Lost to follow up/emigrated	19 (0.9)	14 (0.5)
Median follow up, years (IQR)	17.4 (12.8-22.5)	16.7 (12.6-21.6)

NOTE. Data presented as No. (%) unless otherwise indicated.

Abbreviations: CTGCT, contralateral testicular germ cell tumor; IQR, interquartile range; NSGCT, nonseminomatous germ cell tumor; SGCT, seminomatous germ cell tumor.

TABLE A2. Characteristics of Patients With a Metachronous CTGCT

Characteristic	NSGCT Primary	SGCT Primary	Total
No. of patients with CTGCT	45	91	136
Primary TNM stage			
I	25 (55.6)	89 (97.8)	114 (83.8)
II	11 (24.4)	2 (2.2)	13 (9.6)
III	9 (20.0)	0	9 (6.6)
Platinum-based chemotherapy	19 (42.2)	3 (3.3)	22 (16.2)
CTGCT histology			
NSGCT	18 (40.0)	21 (23.1)	39 (28.7)
SGCT	27 (60.0)	70 (76.9)	97 (71.3)
Median time to CTGCT, years (IQR)	7.0 (4.8-11.2)	5.2 (3.3-9.1)	6.1 (3.6-9.4)
Vital status			
Alive	42 (93.3)	86 (94.5)	128 (94.1)
Dead	3 (6.7)	5 (5.5)	8 (5.9)

NOTE. Data presented as No. (%) unless otherwise indicated. A previous contralateral biopsy was performed in nine patients with CTGCT. In six patients, germ cell neoplasia in situ was found.

Abbreviations: CTGCT, contralateral testicular germ cell tumor; IQR, interquartile range; NSGCT, nonseminomatous germ cell tumor; SGCT, seminomatous germ cell tumor.

TABLE A3. SIR and AER of a Metachronous CTGCT by Attained Age

Variable	Person-Time, Years	CTGCT, No.	SIR (95% CI)	AER (95% CI)
All patients				
Attained age, years				
< 30	8,649	22	14.5 (9.1 to 22.0)	23.7 (14.2 to 36.8)
30-39	22,846	83	18.9 (15.1 to 23.5)	34.4 (27.0 to 43.1)
40-49	25,385	23	8.7 (5.5 to 13.0)	8.0 (4.7 to 12.5)
≥ 50	21,965	8	10.1 (4.4 to 20.0)	3.3 (1.2 to 6.8)
P_{trend}			.019	
Age at primary diagnosis, years				
< 25				
Attained age				
< 30	6,643	20	17.2 (10.5 to 26.6)	28.4 (16.6 to 44.7)
30-39	5,901	10	7.1 (3.4 to 13.1)	14.6 (5.8 to 28.8)
≥ 40	2,005	1	3.8 (0.1 to 21.0)	3.7 (−1.2 to 26.5)
P_{trend}			.007	
25-34				
Attained age				
< 40	17,021	68	22.2 (17.2 to 28.1)	38.1 (29.2 to 48.8)
40-49	11,956	10	7.3 (3.5 to 13.3)	7.2 (2.9 to 14.2)
≥ 50	3,272	1	5.4 (0.1 to 30.2)	2.5 (−0.5 to 16.5)
P_{trend}			< .001	
≥ 35				
Attained age				
< 40	1,929	7	26.1 (10.5 to 53.8)	34.9 (13.2 to 73.4)
40-49	11,495	12	11.8 (6.1 to 20.6)	9.6 (4.5 to 17.3)
≥ 50	18,620	7	11.6 (4.7 to 24.0)	3.4 (1.2 to 7.4)
P_{trend}			.173	

Abbreviations: AER, absolute excess risk; CTGCT, contralateral testicular germ cell tumor; SIR, standardized incidence ratio.