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

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

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Abstract was presented as a mini-oral at the ESMO virtual congress 2020

Disclaimers: 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.

Context Summary

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

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

Our findings add important knowledge concerning the risk of second testicular cancer. Our results are important and appreciated information for testicular cancer patients and health care personnel involved in testicular cancer treatment.

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.

Methods

Based on the Cancer Registry of Norway, 5620 men were diagnosed with first TC between 1980-2009. Treatment data regarding TC were retrieved from medical records. Cumulative incidences of second TC were estimated, and standardized incidence ratios (SIRs) 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 3.5-4.6), with lower incidence after chemotherapy (3.2%, 95% CI 2.5-4.0) than after surgery only (5.4%, 95% CI 4.2-6.8). The second TC incidence was also lower for those aged ≥30 years (2.8%, 95% CI 2.3-3.4) at first TC diagnosis than those <30 years (6.0%, 95% CI 5.0-7.1). Overall, the second TC risk was 13-fold higher compared with the risk of developing TC in the general male population (SIR 13.1, 95% CI 11.5-15.0). With surgery only as reference, treatment with

chemotherapy significantly reduced the second TC risk (HR 0.55). For each additional CBCT cycle administered, the second TC risk decreased significantly after 3, 4 and >4 cycles (HRs 0.53, 0.41, and 0.21 respectively).

Conclusion

Age at first TC diagnosis, as well as treatment intensity, influenced the second TC risk, with significantly reduced risks after >2 CBCT cycles.

Introduction

After being diagnosed with a primary germ cell testicular cancer (TC), the estimated 15 to 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 to 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 life-long 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 increased risk of developing a second TC.[1-4,12] 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 a 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 either 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 pre-cisplatin era.[3-5]

Andreassen et al investigated the risk for metachronous contralateral TC in 7102 TCS in Norway, treated during 1953-2007.[2] They found a 50% risk reduction for

a second TC in men treated for metastatic compared to 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 treatment details. Furthermore, Fosså et al conducted a large register-based study involving 29151 TCS from the US. 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”.[1]

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 (Supplemental Appendix, Fig S1). 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 5620 TC patients. Details regarding disease stage, histology and TC treatment for first and second TC, including relapse treatment, were retrieved from medical records. Linkage with the CRN updated through December 31, 2018 was done to ensure complete information on 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 1 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=1417; 25%), chemotherapy (CT, n=2450; 44%), RT (n=1543, 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 analysed 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 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% confidence intervals (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 risk factor was investigated in a multivariable Cox regression model which included treatment. Cumulative chemotherapy doses were estimated based on 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 (Supplemental Appendix Table S1) and the dichotomized age variable (p=0.049). 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 analysed using Stata statistical software (version MP 16.1; STATA, College Station, TX). A p-value <0.05 was considered significant.

Results

Characteristics of the Total Study Cohort and the Metachronous TC Sub-Cohort

The total study cohort consisted of 5620 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.

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=0.55), or age at diagnosis of first TC (p=0.10) (Supplemental Appendix, Table S2).

The majority of the second TCs were seminomas (72%) (Supplemental Appendix, Table S3). 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 3.5-4.6) at 20 years (Fig 1A, Table 2). The second TC incidence was lower in those aged ≥30 years at first TC diagnosis (2.8%, 95% CI 2.3-3.4) than in those <30 years (6.0%, 95% CI 5.0-7.1) (Fig 1B). The second TC incidence was also lower after treatment with CT (3.2%, 95% CI 2.5-4.0) and CT+RT at first TC (1.4%, 95% CI 0.4-3.9), than after surgery only (5.4%, 95% CI 4.2-6.8) or RT (4.5%, 95% CI 3.6-5.6) (Fig 1C).

For those aged <30 years at first TC diagnosis, 20-year cumulative incidence after surgery only was 8.0% (95% CI 5.8-10.6) and after CT it was 4.8% (95% CI 3.6-6.3) (Table 2). In comparison, for those aged ≥30 years at first TC diagnosis, the second TC incidence was 3.2% (95% 2.1-4.6) after surgery only and 1.7% (95% CI 1.1-2.7) after CT.

The second TC incidence did not differ according to first TC histology, with estimates of 3.8% (95% CI 3.1-4.6) after seminoma and 4.3% (95% CI 3.5-5.1) 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 11.5-15.0) (Table 3). The risk was

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

Hazard Ratios 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 0.40-0.76) (Table 4). A sensitivity analysis excluding those treated with CT other than CBCT (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 0.79-1.54).

For each additional CBCT cycle administered, the point estimates for second TC risk decreased, with significantly reduced risks after 3 (HR 0.53, 95% CI 0.29-0.97), 4 (HR 0.41, 95% CI 0.25-0.66), and >4 cycles (HR 0.21, 95% CI 0.07-0.66) (Table 4, Fig 2). The hazard of second TC was not significantly different after treatment with adjuvant carboplatin monotherapy (HR 1.22, 95% CI 0.62-2.39). For each increase of 100 mg/m^2 cisplatin, the second TC risk decreased equivalent to the results according to number of CBCT cycles. The effect on second TC risk was weakened for the dose level 101-200 mg/m^2 when carboplatin was included in the analysis of cumulative platinum doses (Supplemental Appendix, Table S1).

The second TC risk was significantly reduced for those ≥30 years at first TC diagnosis (HR 0.47, 95% CI 0.36-0.62). In age-adjusted Cox regression, nonseminoma histology at first TC was associated with decreased risk of second TC (HR 0.73, 95% CI 0.55-0.98). However, compared to seminoma, this association disappeared when treatment at first TC was included in the model (HR 0.97, 95% CI 0.65-1.45) (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 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 >2 CBCT cycles.

The overall second TC cumulative incidence of 4% and total SIR of 13.1 found in this study is in accordance with 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, as well as cumulative cisplatin dose, and the second TC risk. Our results are in line with the study by Brabrand et al, who found significantly reduced second TC risk after ≥4 compared to 1-3 CBCT cycles or no CT in a study of 61 TCS with biopsy-proven GCNIS in the contralateral testicle.[17] We found no risk reduction after 1-2 CBCT cycles, which corroborates results from a prospective study on second TC risk after 1-2 adjuvant CBCT cycles in patients with stage I nonseminoma.[26] In contrast to the results from the randomized trial by Oliver et al comparing adjuvant carboplatin with RT,[32] we found no decrease of second TC risk after treatment with adjuvant carboplatin.

The modulating effect of the blood-testis barrier on the intratubular concentration of cytotoxic drugs,[33,34] possibly in part explain the need for higher cumulative doses of cisplatin before effect on GCNIS and the subsequent second TC risk. However, cisplatin undoubtedly has an effect in 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 number of CBCT cycles and the recovery of spermatogenesis.[36-39] A recent publication by Weibring et al did not find long-term reduction of sperm count after 1 cycle of CBCT.[40] 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 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 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 and second TC in our cohort was 27 years.

A polygenic susceptibility, coupled with fetal and early-life environmental factors, are 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 vs. 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 aged <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 are inconsistent.[1,4,7,13,14] Studies conducted in the pre-cisplatin 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 more often are treated with CBCT than patients with seminoma.

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

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

Important strengths of our study include the consideration of a nation-wide 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 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 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. Even though 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 life-long self-examination is emphasized.

Disclosures

None of the authors have any disclosures to declare.

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Figure Legends

Figure 1

Crude cumulative incidences of metachronous contralateral testicular cancer by follow-up time. A) All patients (with 95% confidence interval), 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% confidence interval.

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

Figure 2

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

Abbreviations: TC, testicular cancer

Figure 1.

Figure 1A)

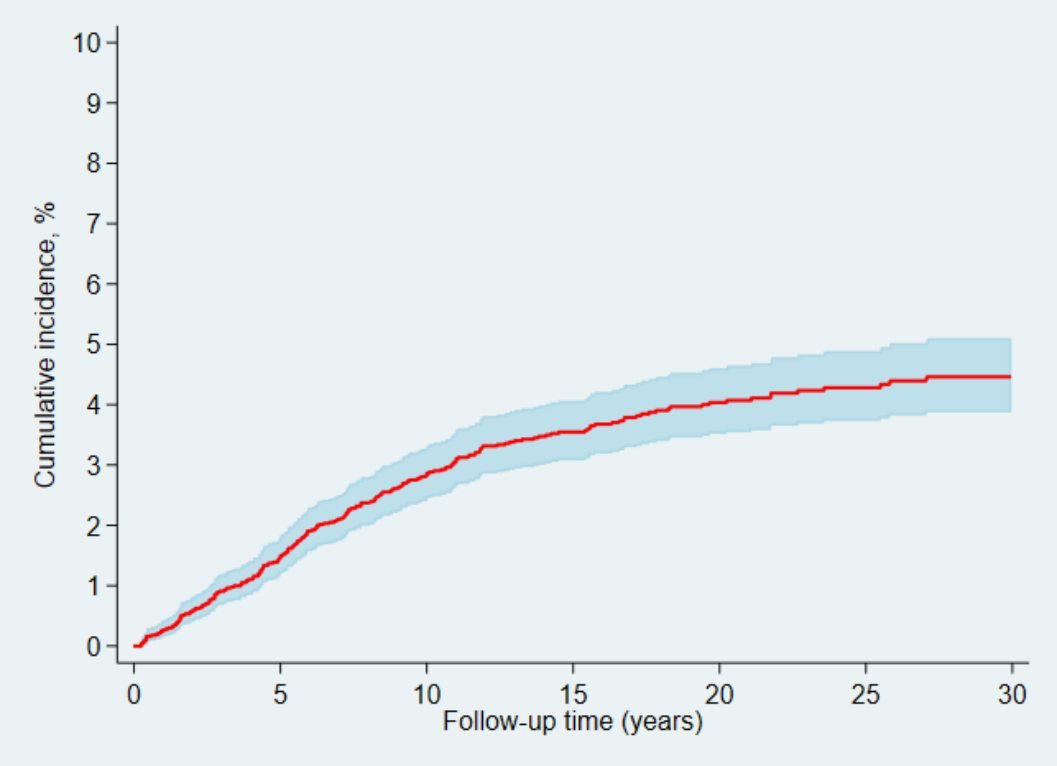


Figure 1B)

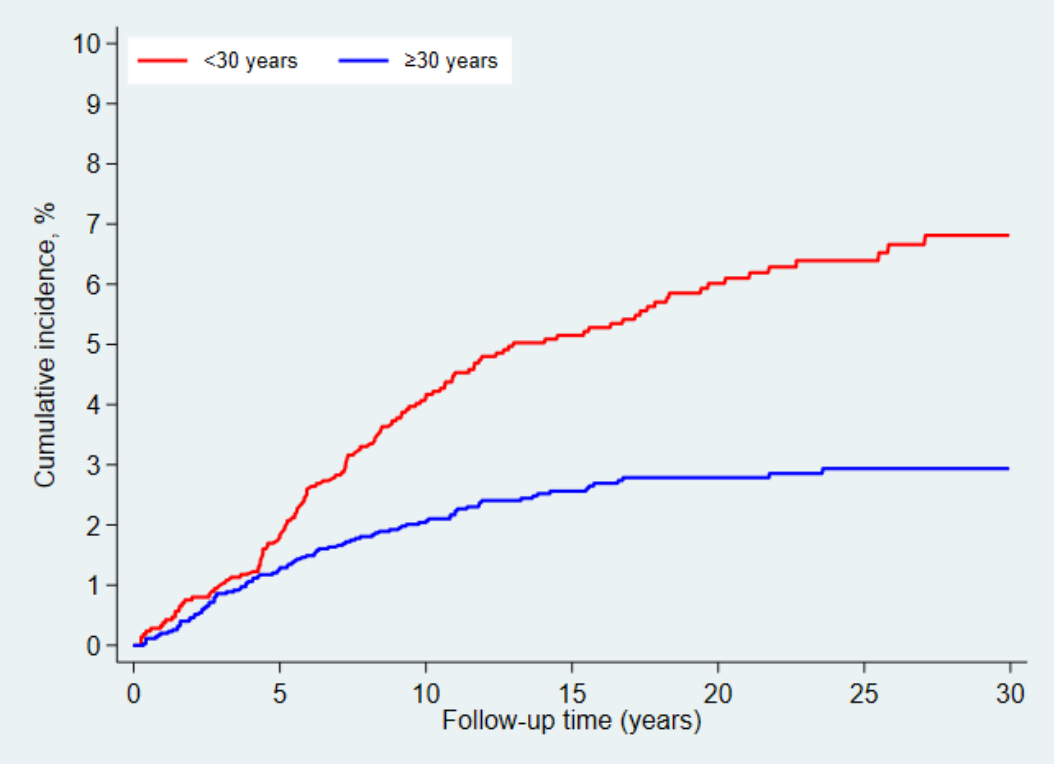


Figure 1C)

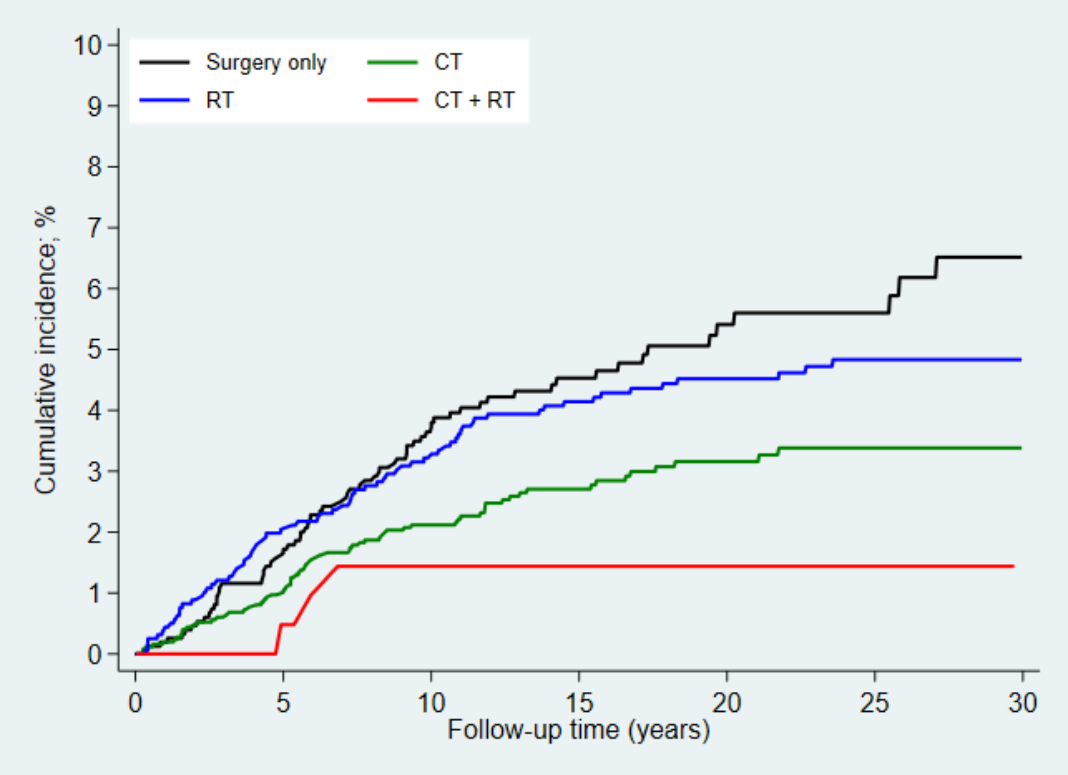


Figure 1D)

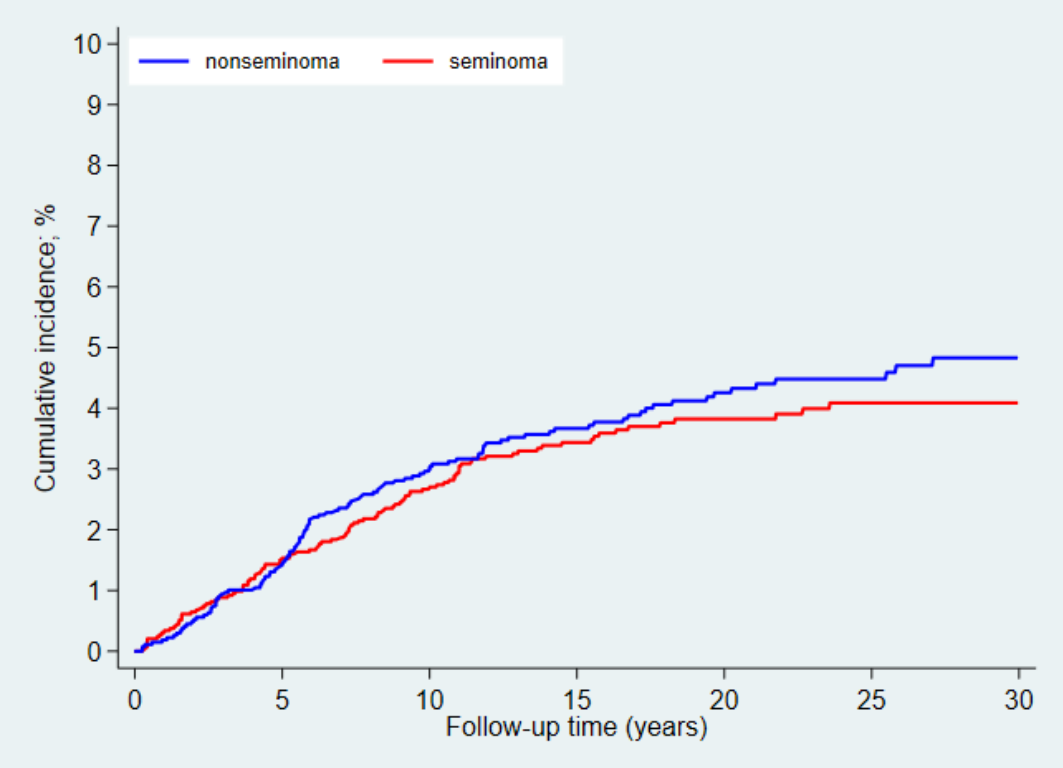
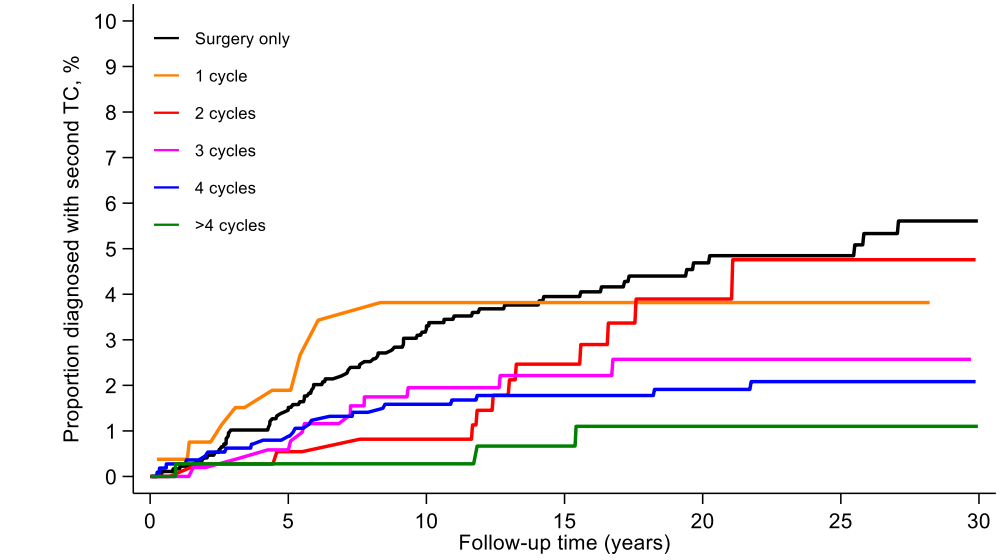


Figure 2.



N at risk:							
Surgery only	2042	1379	1201	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

Abbreviations: TC, testicular cancer.

Table 1. Patient characteristics at first primary TC diagnosis

	Total at risk (n = 5620)	Individuals without second TC (n = 5402)	Individuals developing second TC (n=218)
Decade of first TC diagnosis			
1980-1989	1287 (23)	1228 (23)	59 (27)
1990-1999	1897 (34)	1824 (34)	73 (34)
2000-2009	2436 (43)	2350 (43)	86 (39)
Follow-up, y, median (IQR)*	18.0 (12.0-25.5)	18.5 (12.5-25.8)	6.2 (3.3-10.6)†
Age at diagnosis, y, median (IQR)	33.0 (27.2-40.9)	33.3 (27.3-41.2)	28.7 (24.6-33.5)
Age at diagnosis, dichotomized			
<30 years	2124 (38)	1999 (37)	125 (57)
≥30 years	3496 (62)	3403 (63)	93 (43)
Histology			
Seminoma	2938 (52)	2831 (52)	107 (49)
Nonseminoma	2682 (48)	2571 (48)	111 (51)
Initial disease stage‡			
I	3942 (70)	3766 (70)	176 (80)
Mk+/II	1127 (20)	1097 (20)	30 (14)
III	116 (2.1)	114 (2.1)	2 (1.0)
IV	435 (7.7)	425 (7.9)	10 (4.6)
Treatment§			
Surgery only**	1417 (25)	1345†† (25)	72 (33)
CT	2450 (44)	2379 (44)	71 (32)
RT	1543 (27)	1471 (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	1538 (58)	1502 (58)	36 (49)
Recurrence	279 (10)	273 (11)	6 (8.1)
First CT regimen			
BEP-20	1507 (57)	1464 (57)	43 (58)
CVB	367 (14)	357 (14)	10 (13.5)
EP	241 (9.1)	237 (9.2)	4 (5.4)
Other CBCT‡‡	184 (6.9)	180 (6.9)	4 (5.4)
Adjuvant Carboplatin§§	295 (11)	285 (11)	10 (13.5)
CEB	44 (1.6)	42 (1.6)	2 (2.7)
Other***	22 (0.8)	21 (0.8)	1 (1.4)
No. of CBCT cycles†††			
1	220 (9.5)	210 (9.3)	10 (16)
2	319 (14)	307 (14)	12 (20)
3	439 (19)	427 (19)	12 (20)
4	1028 (44)	1004 (44)	24 (39)
> 4	320 (14)	317 (14)	3 (4.9)
RT first field			
L-field‡‡‡	1388 (79)	1321 (79)	67 (89)
Paraaortal	267 (15)	260 (15)	7 (9.3)
Supradiafragmatic	13 (0.7)	12 (0.7)	1 (1.3)
Supra- and infradiafragmatic§§§	21 (1.2)	21 (1.3)	0
Other****	64 (3.6)	64 (3.8)	0
RT dose for first RT field			
1-20 Gy	13 (0.7)	12 (0.7)	1 (1.3)
20-29Gy	514 (29)	490 (29)	24 (32)
30-39 Gy	986 (56)	943 (56)	43 (57)
≥40 Gy	240 (14)	233 (14)	7 (9.3)

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

Abbreviations: TC, testicular cancer; n, number; y, years; IQR, interquartile range; Mk+, marker positive; CT, chemotherapy; RT, radiotherapy; CT + RT, combination of CT and RT; CS I, clinical stage I; BEP-20, bleomycin, etoposide and cisplatin; CVB, cisplatin, vinblastine and bleomycin; EP, etoposide and cisplatin; CBCT, cisplatin-based CT; CEB, carboplatin, etoposide and bleomycin; no, number; Gy, grey,

* Follow-up until diagnosis of metachronous contralateral TC, death, emigration or December 31st 2018, whichever occurred first.
† The longest time interval between first and second TC was 27.1 years.
‡ As described by Peckham et al.[19]
§ Based on total treatment burden.
** The surgery only group included men followed with surveillance after orchiectomy (n = 1167; 21%) and men who underwent additional retroperitoneal lymph node dissection without CT or RT (n = 250; 4.4%).
†† 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.
‡‡ Of which a total of 141 were dose-escalated CBCT.
§§ 15 of the 295 men initially treated with adjuvant carboplatin were subsequently treated with CBCT, and as a consequence analysed according to total number of cisplatin-based chemotherapy cycles. Also, 1 person had RT in addition to carboplatin. Of the 279 men treated with adjuvant carboplatin monotherapy included in the Cox regression analysis, 273 received 1 cycle and 6 received 2 cycles.
*** Carboplatin monotherapy in metastatic setting (n=17), sendoxan/adriamycin (n=1), CAOS (actinomycin D, adriamycin, vincristine, sendoxan) (n=3), actinomycin D (n=1).
††† May have received additional CT regimes, but these are not accounted for in this number. A total of 334 men received non-CBCT, these are not included here.
‡‡‡ L-field or dogleg-field. Included in this category are also 53 individuals who received RT of groin in addition to L-field and 2 individuals who received a reversed Y-field.
§§§ 16 of 21 individuals received infradiafragmatic RT as first RT-field and a short while later received supradiafragmatic RT.
**** RT towards bone (n=21), CNS (n=21), abdominal residual masses (n=16), intraoperative RT (n=1), skin lesions (n=1), non-specified sites (n=4).

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

* Includes men treated with surveillance and men treated with retroperitoneal lymph node dissection in addition to orchiectomy.

Note: n refers to 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: TC, testicular cancer; n, number; 95% CI, 95% confidence interval; y, years. CT, chemotherapy; RT, radiotherapy; CT + RT, combination of CT and RT.

Table 3. SIRs for metachronous contralateral TC according to treatment, age and histology at first TC and follow-up time

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

Abbreviations: SIRs, standardized incidence ratios; TC, testicular cancer; no, number; 95% CI, 95% confidence interval; CT, chemotherapy; RT, radiotherapy; CT + RT, combination of CT and RT.

* Includes men treated with surveillance and men treated with retroperitoneal lymph node dissection in addition to orchiectomy.

† The longest time interval between first and second TC was 27.1 years.

Table 4. Age-adjusted HRs for metachronous contralateral TC according to treatment groups, treatment intensity, age and histology at first TC.

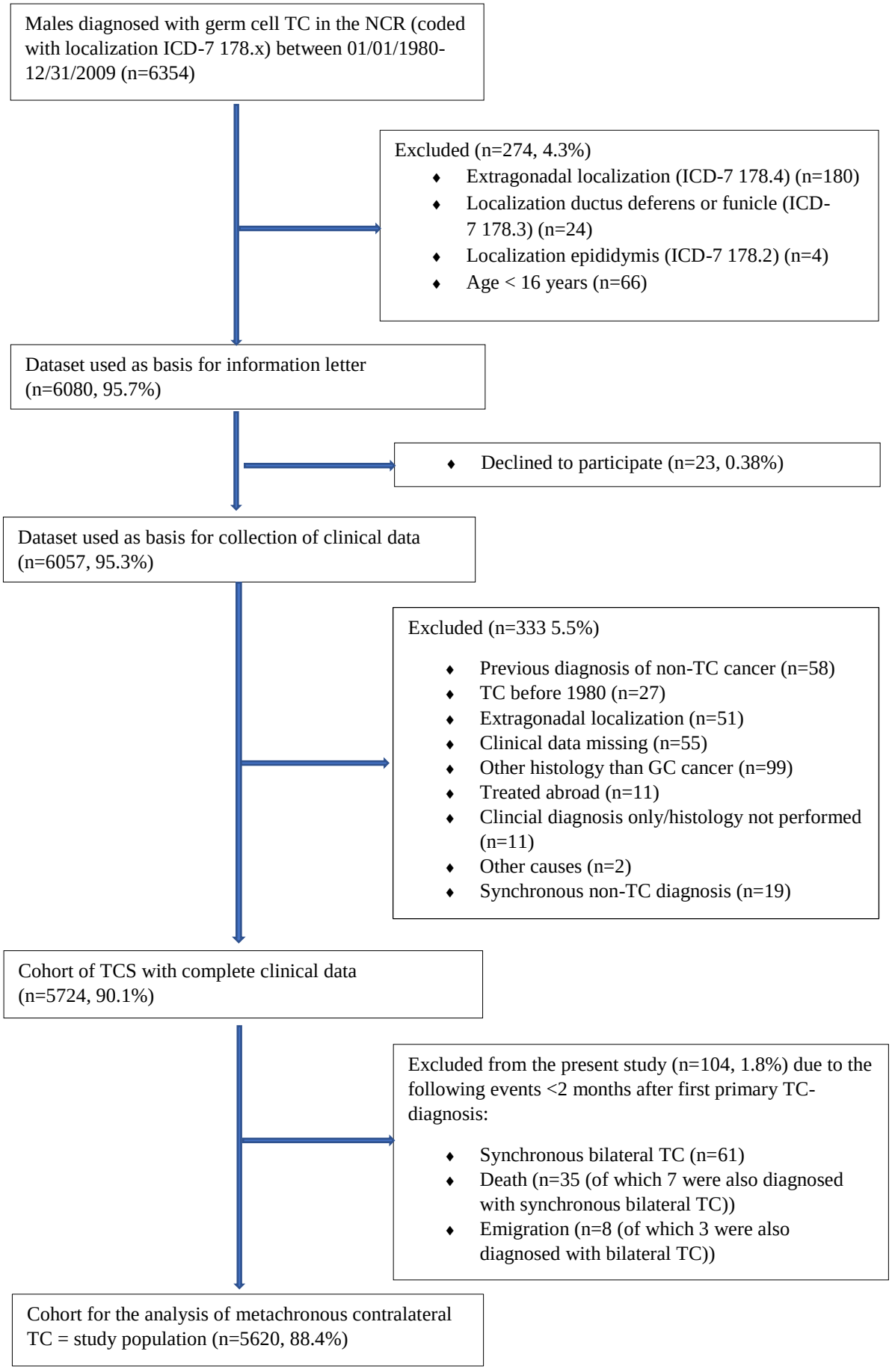
		HR	95% CI	P-value
Treatment				
	Surgery only	1	ref	ref
	CT	**0.55**	**0.40-0.76**	**<0.001**
	RT	1.10	0.79-1.54	0.580
	CT + RT	0.50	0.16-1.57	0.233
No. of CBCT cycles				
	Surgery only	1	ref	ref
	1	1.01	0.52-1.96	0.983
	2	0.74	0.40-1.36	0.332
	3	**0.53**	**0.29-0.97**	**0.040**
	4	**0.41**	**0.25-0.66**	**<0.001**
	>4	**0.21**	**0.07-0.66**	**0.008**
	Carboplatin, adjuvant*	1.22	0.62-2.39	0.565
RT field				
	Surgery only	1	ref	ref
	L-field	1.17	0.78-1.62	0.521
	Paraaortal	0.75	0.34-1.64	0.468
RT dose for first abdominal RT-field				
	Surgery only	1	ref	ref
	20-29 Gy	1.24	0.77-1.98	0.383
	30-39 Gy	1.04	0.70-1.55	0.832
	≥40 Gy	1.17	0.50-2.70	0.721
Age at diagnosis†				
	<30 years	1	ref	ref
	≥30 years	**0.47**	**0.36-0.62**	**<0.001**
Histology				
	Age-adjusted			
	Seminoma	1	ref	ref
	Nonseminoma	**0.73**	**0.55-0.98**	**0.034**
	Multivariable‡			
	Seminoma	1	ref	ref
	Nonseminoma	0.97	0.65-1.45	0.883

* Carboplatin monotherapy, carboplatin in adjuvant setting for stage 1 seminoma.
† Not age adjusted
‡ Adjusted for treatment in addition to age.

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

Abbreviations: HR, hazard ratio; TC, testicular cancer; 95% CI, 95% confidence interval; ref, reference; CT, chemotherapy; RT, radiotherapy; CT + RT, combination of CT and RT; no, number; CBCT, cisplatin-based chemotherapy; Gy, grey

Supplemental Figure S1. Flow Chart Presenting the Study Cohort



Abbreviations: TC, testicular cancer; NCR, the Norwegian Cancer Registry; ICD-7, International Classification of Diseases version 7, GC, germ cell; TCS, testicular cancer survivors.

Supplemental Table S1. Age-adjusted HRs for Metachronous Contralateral TC According to Cumulative Cisplatin, Platinum, and Bleomycin doses at First TC[*]

	HR	95% CI	P-value
Cumulative cisplatin dose, mg/m^2			
Surgery only	1	ref	ref
1-100	1.01	0.52-1.96	0.984
101-200	0.74	0.40-1.36	0.331
201-300	**0.53**	**0.29-0.98**	**0.043**
301-400	**0.43**	**0.27-0.70**	**0.001**
>400	**0.14**	**0.03-0.52**	**0.004**
Carboplatin	1.15	0.62-2.12	0.667
Cumulative total platinum dose, mg/m^{2†}			
Surgery only	1	ref	ref
1-100	1.01	0.52-1.96	0.984
101-200	0.91	0.56-1.47	0.697
201-300	**0.53**	**0.29-0.99**	**0.045**
301-400	**0.46**	**0.29-0.72**	**0.001**
>400	**0.12**	**0.03-0.50**	**0.003**
Cumulative bleomycin dose, IU			
Surgery only	1	ref	ref
1-100 000	0.92	0.50-1.70	0.789
100 001-200 000	0.55	0.26-1.14	0.107
200 001-300 000	**0.46**	**0.30-0.69**	**<0.001**
>300 000	0.29	0.07-1.19	0.086
Chemotherapy without bleomycin	0.84	0.47-1.50	0.550

Note: Significant results marked with bold.

Abbreviations: HR, hazard ratio; TC, testicular cancer; 95% CI, 95% confidence interval; ref, reference

[*] When analysing 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.

[†] 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).

Supplemental Table S2. Time to metachronous contralateral TC according to characteristics at first TC

		Individuals developing metachronous contralateral TC (n=218)
By time since treatment at first TC, years		
	Surgery only*	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: TC, testicular cancer; n; number; CT, chemotherapy; RT, radiotherapy; CT + RT, combination of CT and RT; IQR, interquartile range

* Includes men treated with surveillance and men treated with retroperitoneal lymph node dissection in addition to orchiectomy.

Supplemental Table S3. Patient characteristics at diagnosis of metachronous contralateral TC

		Individuals developing metachronous contralateral TC (n=218)
Histology, second TC		
	Seminoma	157 (72)
	Nonseminoma	58 (27)
	Missing	3 (1.4)
Disease stage, second TC†		
	I	184 (84)
	Mk+/II	16 (7.3)
	III	3 (1.4)
	IV	4 (1.8)
	Missing	11 (5.1)
Treatment, second TC		
	Surgery only	115 (53)
	CT†	71 (33)
	RT	16 (7.3)
	CT + RT	0
	Missing	16 (7.3)

Note: Data are presented as n (%).

Abbreviations: TC, testicular cancer; n; number; Mk+, marker positive; CT, chemotherapy; RT, radiotherapy; CT + RT, combination of CT and RT;