Doctoral theses at NTNU, 2022:76

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Doctoral thesis

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Relativ overlevelse og risiko for sekundærkreft etter diagnosen testikulær germinalcellesvulst

Overdødelighet og økt kreftrisiko etter behandling for testikkelkreft

Testikkelkreft er den vanligste kreftsykdommen blant yngre menn med omtrent 300 årlige tilfeller i Norge. I dag blir nesten alle kurert med kirurgi eller moderne cellegiftbehandling, mens strålebehandling nesten ikke brukes lenger.

Dessverre ser man også økt forekomst og dødelighet av alvorlige sykdommer blant overlevere av testikkelkreft. Dette kan for eksempel være andre kreftformer eller hjerte- karsykdommer. Hovedgrunnen er trolig senvirkninger av tidligere cellegift- og strålebehandling.

I mange tilfeller tar det flere tiår fra testikkelkreften ble kurert til disse sykdommene oppstår. Derfor er man bekymret for overlevelsen blant pasienter behandlet for testikkelkreft også på lang sikt, sammenlignet med normalbefolkningen (relativ overlevelse).

Før dette doktorgradsarbeidet var det ikke forsket på relativ overlevelse blant personer med testikkelkreft mer enn 20 år etter diagnosen. Det var også en mangel på detaljert forskning om hvordan de enkelte behandlingsformene ved testikkelkreft påvirker risikoen for å utvikle annen kreftsykdom. Målet med doktorgradsarbeidet var å skaffe mer kunnskap på disse to områdene.

Ved hjelp av registerdata undersøkte vi relativ overlevelse blant ca. 9000 menn som fikk diagnosen testikkelkreft i Norge i tidsrommet 1953-2015. Sammenlignet med normalbefolkningen var den relative overlevelsen stadig fallende med økende oppfølgingstid. Med andre ord så vi en gradvis økende overdødelighet også mer enn 20 år etter diagnosen. Mens hovedårsaken til redusert relativ overlevelse de første fem årene etter påvist testikkelkreft var testikkelkreften i seg selv, ble hovedårsaken etter lengre oppfølgingstid andre kreftformer. Andre mage-tarmsykdommer var også en betydelig årsak, mens hjerte- karsykdommer bare forårsaket en mindre del av overdødeligheten.

Den relative overlevelsen var heldigvis betydelig bedre blant dem som fikk diagnosen testikkelkreft etter 1980, noe som blant annet skyldes at cellegiften cisplatin kom på markedet. Andre viktige grunner er trolig at strålebehandling ble mindre vanlig, stadig bedre medisinsk teknologi og et økende fokus på å unngå overbehandling. Dessverre fant vi en økt forekomst av selvmord blant menn som fikk diagnosen testikkelkreft i 1990 eller senere. Kanskje kan dette skyldes følgetilstander etter behandling.

Vi undersøkte også forekomst av annen kreftsykdom blant ca. 5600 ettårsoverlevere av testikkelkreft påvist i Norge mellom 1980 og 2009. Det spesielle ved vår studie var at vi hadde detaljerte behandlingsdata fra sykehusjournaler for hver enkelt pasient. Vi fant at overlevere av testikkelkreft hadde økt risiko for annen kreftsykdom etter visse former for cellegift og strålebehandling. Noe overraskende fant vi også litt økt kreftrisiko blant dem som hadde blitt behandlet med kirurgi alene. Dette tyder på at også andre faktorer øker kreftrisikoen, som for eksempel arv.

Vår forskning viser dermed at det er en vedvarende overdødelighet og økt kreftrisiko etter behandling for testikkelkreft sammenlignet med normalbefolkningen. Det er viktig at pasienter og leger er klar over at denne risikoen eksisterer også mer enn 20 år etter fullført behandling. Leger bør ved kontrollene ha fokus på å fange opp tegn til både kroppslig og psykisk sykdom. Samtidig håper og tror vi at stadig mer moderne og tilpasset kreftbehandling gradvis reduserer risikoen for senvirkninger ytterligere i fremtiden.

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This thesis is based on three studies subsequently leading to three published research papers. I was first author on the first two papers, and second author on the third paper.

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Last but not least, I would like to thank my family. You mean more to me than I will ever be able to show.

Abbreviations

AFP: Alpha-fetoprotein
BEP: Bleomycin, etoposide, cisplatin
β-hCG: β-subunit of human chorionic gonadotropin
CBCT: Cisplatin-based chemotherapy
CI: Confidence interval
CS: Clinical stage
CT: Computed Tomography
CAD: Coronary artery disease
CNS: Central nervous system
CVB: Cisplatin, vinblastine, bleomycin
CVD: Cardiovascular disease
Gy: Gray
GWAS: Genome-wide association study
HIV: Human immunodeficiency virus
HR: Hazard ratio
IARC: International Agency for Research on Cancer
IGCCCG: International Germ-Cell Consensus Classification Group
IGCN: Intratubular germ cell neoplasia. Also termed carcinoma in situ.
IRT: Infradiaphragmatic radiotherapy
LDH: Lactate dehydrogenase
MI: Myocardial infarction
OS: Overall survival
PA: Para-aortic
PBCT: platinum-based chemotherapy
PFS: Progression-free survival
PLAP: Placental alkaline phosphatase
RPLND: Retroperitoneal lymph node dissection
RR: Relative risk
RS: Relative survival
RT: Radiotherapy
SC: Second cancer, excluding testicular cancer
SEER: Surveillance, Epidemiology, and End Results (US National Cancer Institute)
SRT: Supradiaphragmatic radiotherapy
SIR: Standardized incidence ratio
SMR: Standardized mortality ratio
TC: Testicular cancer
TCS: Testicular cancer survivors
TGCT: Testicular germ cell tumor

Summary in English

Testicular cancer (TC) is the most common cancer among younger men, with about 300 cases yearly in Norway. Almost all TC cases are testicular germ cell tumors, which are classified into seminomas and nonseminomas. An important part of the treatment is removal of the affected testicle, but most patients are cured even if the disease has spread to other parts of the body. The main reason is the chemotherapeutic agent cisplatin, which has been in use since the late 1970s.

However, survivors of TC are at increased risk of serious conditions such as second cancer (SC) and cardiovascular disease. These conditions may appear several decades after TC diagnosis, and contribute to reduced survival compared to the general population (relative survival, RS). The main reason is probably late effects of chemo- and/or radiotherapy, which is therefore taken into consideration during treatment.

Before our studies, there were no RS data for TC survivors followed beyond 20 years of diagnosis. There were also no studies of SC risk using complete information on which TC treatment was given to each patient.

The aims of this thesis were to examine RS and causes of excess risk of death among about 9000 TC patients diagnosed in Norway during 1953-2015, even beyond 20 years of diagnosis (studies I and II). Another aim was to determine SC risk among 5600 one-year survivors of TC diagnosed in Norway during 1980-2009 in Norway using complete treatment information (study III).

In studies I and II we found that, despite improved RS among men diagnosed with TC after 1979, RS continuously declined even beyond 15-30 years of follow-up. The largest decline was seen among patients treated for seminoma. While the TC itself was the main cause of reduced RS during the first five years of follow-up, SC gradually became the most important cause beyond this time. Benign gastrointestinal diseases were another important cause of excess mortality, while cardiovascular disease was a comparatively minor cause. Patients diagnosed with TC in 1990 or later had the highest RS, but there were still excess deaths from several conditions such as some SC forms, suicide and infections.

In study III, we found that TC survivors had increased SC risk after certain forms of chemotherapy and/or radiotherapy. However, there was also a somewhat increased SC risk if they had been treated with surgery alone. This suggests that factors unrelated to treatment, such as genetic causes, contribute to increased SC risk among TC patients and survivors.

Based on the findings in this thesis, TC survivors and their physicians should be aware of the lifetime excess SC risk as well as an increased risk of death from several conditions after a TC diagnosis. This should lead to closer lifetime follow-up and a lower threshold for diagnostics, particularly if chemotherapy or radiotherapy was part of the treatment. Also, further research should focus on reducing the toxicity of treatment while maintaining the excellent prognosis for cure.

Norsk sammendrag

Testikkelkreft (TC) er den vanligste kreftformen blant yngre menn, med omtrent 300 årlige tilfeller i Norge. Nesten alle TC-tilfeller er testikulære germinalcellesvulster, som igjen inndeles i seminomer og nonseminomer. En viktig del av behandlingen er å fjerne den affiserte testikkelen, men de aller fleste blir kurert også hvis sykdommen har spredt seg til andre deler av kroppen. Hovedårsaken er cellegiften cisplatin, som har vært i bruk siden slutten av 70-tallet.

Imidlertid har TC-overlevere økt risiko for å utvikle alvorlige tilstander som ny kreftsykdom (sekundær kreft, SC) og hjerte- karsykdom. Disse tilstandene kan oppstå flere tiår etter TC-diagnosen, og bidra til redusert overlevelse sammenlignet med normalbefolkningen (relativ overlevelse, RS). Hovedgrunnen er trolig senvirkninger av cellegift- og/eller strålebehandling, noe man derfor prøver å ta hensyn til i behandlingen.

Før våre studier fantes det ikke RS-data for TC-overlevere fulgt lenger enn 20 år etter diagnosen. Det fantes heller ikke studier på SC-risiko basert på fullstendig informasjon om hvilken TC-behandling hver enkelt pasient fikk.

Målene med denne avhandlingen var å undersøke RS og årsaker til overdødelighet blant ca. 9000 TC-pasienter diagnostisert i Norge mellom 1953 og 2015, også mer enn 20 år etter diagnosen (studie I og II). Et annet mål var å analysere SC-risiko blant 5600 ettårsoverlevere av TC diagnostisert i Norge mellom 1980 og 2009, basert på fullstendig behandlingsinformasjon (studie III).

I studie I og II fant vi at selv om RS var betydelig høyere blant de som fikk TC-diagnosen etter 1979, fortsatte RS å falle også etter mer enn 15-30 års oppfølging. Det største fallet ble sett blant dem behandlet for seminom. Mens TC i seg selv var hovedårsak til redusert RS de første fem årene etter diagnosen, ble SC gradvis den viktigste årsaken etter denne perioden. Godartede mage-tarmsykdommer var en annen viktig årsak til overdødelighet, mens hjerte- karsykdom til sammenligning var av mindre betydning. Pasienter som fikk TC-diagnosen i 1990 eller senere hadde høyest RS, men hadde fortsatt overdødelighet av flere tilstander som noen former for SC, selvmord og infeksjoner.

I studie III fant vi at overlevere av TC hadde økt risiko for SC etter visse former for cellegift og/eller strålebehandling. Imidlertid fant vi også noe økt risiko for SC blant dem som kun hadde blitt behandlet med kirurgi. Dette tyder på at faktorer som ikke skyldes behandlingen, som for eksempel genetiske årsaker, kan bidra til økt SC-risiko blant TC-pasienter og overlevere.

Basert på funnene i denne avhandlingen bør TC-overlevere og deres leger være oppmerksomme på livslang økt risiko og dødelighet av flere tilstander etter en TC-diagnose. Dette bør føre til tettere livstidsoppfølging og en lavere terskel for utredning, spesielt hvis cellegift eller strålebehandling var del av behandlingen. Det bør også forskes mer for å redusere negative effekter av TC-behandlingen, uten å redusere den utmerkede sannsynligheten for å bli kurert.

List of studies

This PhD thesis was based on the following three studies, leading to three published papers:

Study I:
Kvammen O, Myklebust TA, Solberg A, Moller B, Klepp OH, Fossa SD, Tandstad T. **Long-term Relative Survival after Diagnosis of Testicular Germ Cell Tumor**. *Cancer Epidemiology Biomarkers & Prevention* 2016;**25**: 773-9.[1]

Study II:
Kvammen O, Myklebust TA, Solberg A, Moller B, Klepp OH, Fossa SD, Tandstad T. **Causes of inferior relative survival after testicular germ cell tumor diagnosed 1953-2015: A population-based prospective cohort study**. *PLoS One* 2019;**14**: e0225942.[2]

Study III:
Hellesnes R, Kvammen O, Myklebust TA, Bremnes RM, Karlsdottir A, Negaard HFS, Tandstad T, Wilsgaard T, Fossa SD, Haugnes HS. **Continuing increased risk of second cancer in long-term testicular cancer survivors after treatment in the cisplatin era**. *Int J Cancer* 2019.[3]

1. Background

1.1 Introduction

Testicular cancer (TC), although rare, is the most common cancer in Norwegian males aged 15 to 49 years. About 1% of new cancer cases in Norway are TC; approximately 300 per year.[4]

The treatment of TC can be described as a medical success story.[5] As late as in the early 1970s, about one third of all TC patients were deceased within five years of TC diagnosis in Norway.[6] By contrast, today about 98 % of patients are alive five years after TC diagnosis.[4] An important cause of this dramatic improvement is the introduction of cisplatin-based chemotherapy (CBCT) in the late 1970s.[7] Other contributing factors include improved diagnostic possibilities, focus on multidisciplinary collaboration and the development of guidelines and collaborative groups.[8]

However, there is increasing awareness that TC survivors (TCS) are at increased risk of serious conditions such as non-TC second cancer (SC) and cardiovascular disease (CVD).[9] These conditions can take decades after TC diagnosis to develop, and the main cause is presumably late effects after treatment with chemotherapy and/or radiotherapy (RT). Studies have also shown excess mortality among TCS due to SC, CVD and many other conditions.[9]

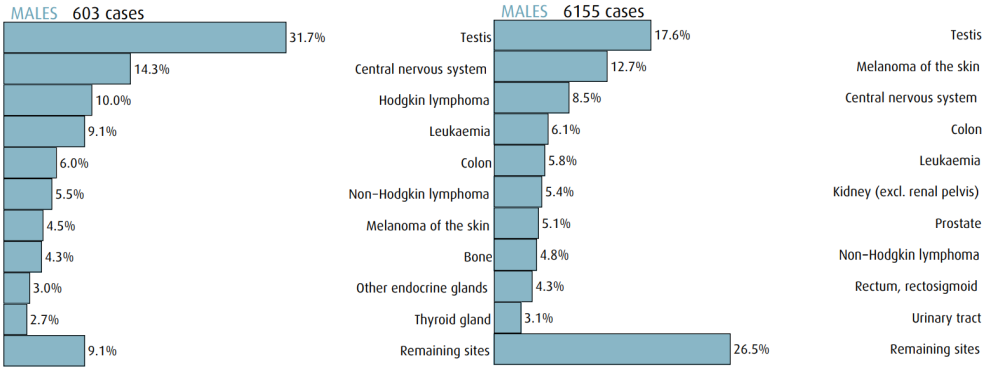
These findings are particularly disturbing because TCS are relatively young at diagnosis, and are expected to live long lives after successful treatment. It is thus important to gain knowledge on the long-term survival among this group of men compared with a reference population such as the general male population (relative survival, RS). It is also important to determine the extent of late effects by the type of TC treatment given.

Prior to the initiation of this PhD thesis, there were no studies examining RS among men who had survived more than 20 years after their TC diagnosis. Also, there was a lack of studies on SC risk where the complete TC treatment given to each patient was considered. The aim of this thesis was to expand the knowledge in these two areas.

1.2 Incidence and prevalence

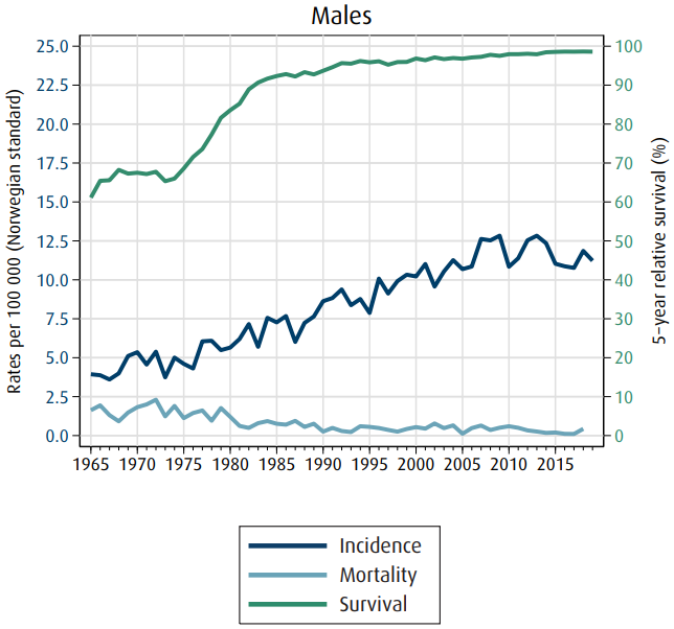
TC is predominantly diagnosed in men younger than 40 years of age. It is the most common cancer diagnosed among males aged between 15 and 49 years in Norway (Figure 1).[4] Even so, it is a relatively rare cancer; about 300 new cases yearly. In 2019, there were almost 35000 new cancer cases in Norway, of which 53.5 % occurred among males.[4]

Figure 1. New cancer cases among males aged 15-24 years (left) and 25-49 years (right) in Norway, 2019[4]



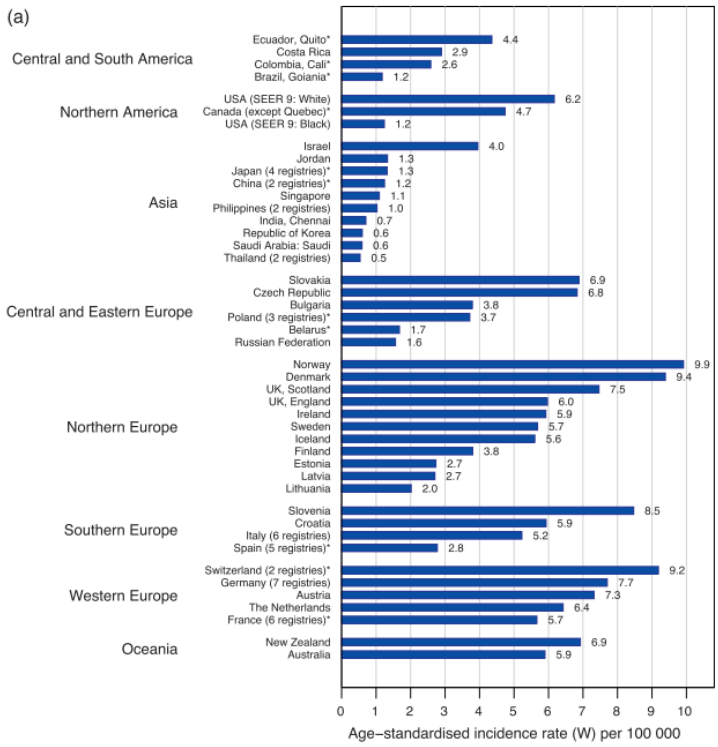
The incidence rate of TC in Norway has risen sharply during the last fifty years, from about 4 / 100.000 in 1965 to about 10-12 / 100.000 in recent years (Figure 2).

Figure 2. Incidence, mortality and survival of testicular cancer in Norway, 1965-2019.[4]



Whereas TC incidence rates vary significantly between regions worldwide, Norway is among countries with the highest incidence rates (Figure 3).[10] The increase seen in Norway is also seen worldwide, although to a varying degree depending on geographical location.[10, 11] TC incidence rates in Asian countries are much lower than in Northern Europe. This is also true for African countries.[12]

Figure 3. Average testicular cancer incidence rates from selected cancer registries, 2000-2004.[10] (used with permission)



As of December 31st, 2019, 8134 men were alive with a TC diagnosis in Norway.[4] This is almost as many as the 9394 men and women alive with a lung cancer diagnosis, even though the incidence of lung cancer in Norway is about ten times higher than TC (about 3000 new cases of lung cancer per year). The reason is the significantly inferior survival of patients with lung cancer.[4, 13]

1.3 Histology and pathogenesis

Histology

TC can be classified into several histological subtypes (Table 1). In about 95% of cases, TC develops from germ cells, which in males normally mature to form sperm cells. These tumors are thus often termed testicular germ cell tumors (TGCT).[14]

Table 1. Simplified classification of testicular tumors.[15]

Germ cell tumors (about 95 % of cases)	Seminoma
	Nonseminoma Embryonal carcinoma, choriocarcinoma, yolk sac tumor (endodermal sinus tumor), teratoma, teratoma with malignant/somatic transformation, mixed germ cell tumor
	Spermatocytic tumor Prepubertal teratoma
Sex cord-stromal tumors	Sertoli cell tumor, Leydig cell tumor, granulosa cell tumor, mixed types, unclassified
Mixed germ cell and stromal tumors	Gonadoblastoma
Adnexal and paratesticular tumors	Adenocarcinoma of rete testis, adenocarcinoma of the epididymis
	Mesothelioma Malignant mesothelioma, adenomatoid tumor
Miscellaneous tumors	Carcinoid, lymphoma, metastatic tumors

TGCT are further classified in two main histologic subtypes: seminoma and nonseminoma. The latter constitutes a subgroup of different histologies which can also include seminoma if other subgroups are present (Table 1).

Seminoma and nonseminoma occur with similar frequency, but while seminomas are usually diagnosed during the fourth decade of life, nonseminomas most often occur during the third decade.[16] In about 88 % of cases, seminomas present with localized (non-metastatic) disease. The corresponding percentage for nonseminomas is about 58 %.[17] Also, seminomas less commonly metastasize to visceral organs.[18]

Spermatocytic tumors are rare TGCT that rarely metastasize and have an excellent prognosis. Previously they were considered to be a form of seminoma. They most often occur in the elderly.[19]

Germ cell tumors may arise outside the testicles, and are then termed extragonadal germ cell tumors.[20, 21] Sometimes in metastatic disease, the primary tumor may have spontaneously regressed or "burned-out".[22]

Non-germ cell tumors comprise less than 5 % of testicular tumors. These include tumors arising from stroma cells of the testicles but also other tumor forms such as lymphomas (Table 1).

Pathogenesis

The pathogenesis of TGCT is complex and not fully understood.[23] It is believed that TGCT mainly develops from premalignant lesions termed intratubular germ cell neoplasia (IGCN), also known as carcinoma in situ. These probably arise due to a failure in the normal maturation of germ cells in the fetus from primordial germ cells into pre-spermatogonia (Figure 4).[23] At puberty, when IGCN cells begin to proliferate due to hormonal changes, they progress from IGCN towards invasive TGCT.

Figure 4. Normal spermatogenesis (left) and occurrence of TGCT (right).[23] Used with permission.

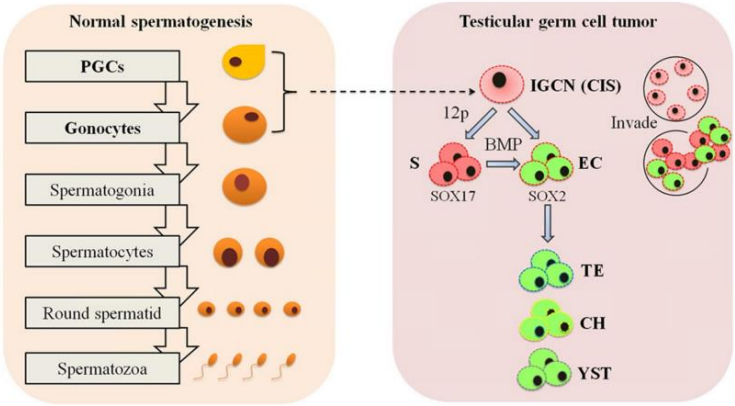


Fig. 1 Model of normal spermatogenesis and occurrence of TGCTs. Spermatogenesis is a tightly regulated process of the continuous supply of spermatozoa. Differentiation of primordial germ cells (PGCs) into gonocytes, self-renewal and differentiation of spermatogonial stem cells, and subsequent commitment to meiotic spermatocytes and haploid round/elongating spermatids are the key events of spermatogenesis. Under pathological conditions, gonocytes that fail to undergo correct spermatogenic differentiation, but develop into intratubular germ cell neoplasia (IGCN) or carcinoma in situ (CIS) represent the precursor cells for TGCTs during early stage of germline development. CIS can further progress into invasive seminoma (S) and (or then) nonseminoma, including undifferentiated EC, as well as differentiated teratoma (TE), choriocarcinoma (CH) and yolk sac tumor (YST)

TGCT development is thought to be modified by some combination of genetic, environmental and hormonal factors.[12]

A large 2002 study showed that TC is strongly associated with genetic factors.[24] In more recent years, several genome-wide association studies (GWAS) have been performed.[12] Several areas of the genome with multiple low- or moderate penetrance alleles and risk loci have been associated with TGCT development.[25] TGCT has so far not been linked to a cancer syndrome that predisposes to other cancers.[26]

Suspected environmental factors include viral infections,[27] physical trauma, pesticides, heavy metals and radiation.[12] Several compounds, including some pesticides, seem to have hormone mimicking properties.[12]

Epigenetics is a very recent field of investigation which aims to integrate genetic and environmental factors on TGCT risk. The focus is the inheritance of genetic factors that do not rely on changes of the genetic code, but rather to what degree these genes are expressed in the body.[12]

Several risk factors for developing TGCT are known. Having a brother with TGCT increases one's risk up to tenfold compared to the general male population. The son of a father with TGCT has a 4- to 6-fold increased risk.[12]

In the US, TC is significantly more frequent among white males compared to African Americans (approximately 6.9 vs 1.2 / 100.000).[10, 28]

Conditions that increase the risk of TC include cryptorchidism and hypospadia.[12, 43, 29] Because these conditions arise in fetal life and increase in incidence along with infertility, it has been hypothesized that they may comprise a testicular dysgenesis syndrome with a common etiology.[30]

A man with a previous TGCT diagnosis has a significantly increased risk of developing a contralateral TGCT compared to the general population. In one large study, the risk of a contralateral TC was 12.4-fold increased, and 1.9 % of the study population with TC developed a contralateral TC after 15 years.[31] A recent study by Hellesnes et al. showed that the overall 20-year incidence of a second primary TC was 4.0 % among Norwegian TCS.[32]

1.4 Diagnosis and staging

Diagnosis

The most common presentation of TC is a growing, painless lump in the testicle of a young man.[33] In some cases there is swelling of the scrotum and/or testicular pain. If the TC is metastatic, there may be additional symptoms and signs depending on disease extent. A few examples are back pain due to spread to retroperitoneal lymph nodes, or hemoptysis due to lung metastases. In rare cases, the patient may present with gynecomastia due to hormonal changes.[34]

If TC is suspected, urgent diagnosis is mandatory. Initial diagnostics include an ultrasound of the testicles followed by orchiectomy for histological examination. Also, a whole-body CT scan is urgently performed to determine if there are metastases, preferably before orchiectomy.

Serum tumor markers are highly useful in the diagnosis, treatment and follow-up of TGCT. The most common are the β-subunit of human chorionic gonadotropin (β-hCG), alpha-fetoprotein (AFP) and lactate dehydrogenase (LDH).[35]

β-hCG is always secreted by choriocarcinomas, in about 40-60 % of embryonic carcinomas and about 10-30% of seminomas. Its half-life in serum is about 18 to 36 hours.

AFP is secreted by 90 % of yolk-sac tumors and sometimes embryonic carcinoma, but not by choriocarcinoma or by pure seminoma. Its half-life is about 5 days.

Elevated levels of LDH occur in 40-60 % of TGCT patients, but is nonspecific. The LDH isoenzyme LD-1 is correlated to the extent of TC, but is not regularly measured.[36] Another tumor marker not regularly measured in Norway is placental alkaline phosphatase (PLAP).

Measurements of tumor markers are commonly repeated during or after TGCT treatment to determine the effect of treatment and to assist in detecting any relapses as soon as possible.

Research is ongoing to identify new and more accurate tumor markers. In particular, the marker miR-371a-3p is promising, but is not yet in routine clinical use.[35]

Staging

In Norway, TC has traditionally been staged according to the Royal Marsden staging system.[37] In this system, the disease is classified into four clinical stages (CS) by disease extent (Table 2).

Table 2. The Royal Marsden staging system.[37]

Clinical staging according to Royal Marsden, modified	
CS I	No evidence of metastases
CS Mk+	Tumour markers AFP/ß-hCG persistently elevated (not declining according to half-life), but no macroscopic metastatic disease demonstrated
CS II	Metastatic disease restricted to abdominal nodes: A Maximal transverse diameter <2 cm B Maximal transverse diameter 2–5 cm C Maximal transverse diameter >5–10 cm D Maximal transverse diameter >10 cm
CS III	Supradiaphragmatic node involvement For abdominal lymph-nodes: 0 No metastases; A-D According to CS II.
CS IV	Extra-lymphatic metastases For abdominal lymph-nodes: 0 No metastases; A-D According to CS II. H+ Liver metastases, Br+ Brain metastases, Bo+ Bone metastases

In CS1 TGCT, repeated staging with imaging and tumor markers has been incorporated to determine the true disease stage as accurately as possible.

Patients with metastatic TGCT are also classified into prognostic groups for five-year survival using the International Germ-Cell Consensus Classification Group (IGCCCG) prognostic staging system.[38] The original classification from 1997 was recently updated.[39, 40] The prognosis is based on a combination of disease extent, histology, and levels of tumor markers (Table 3). Notably, no patients with seminoma are in the “poor prognosis” group.

Table 3. Prognostic staging system for testicular germ cell tumors.[37]

Prognostic risk group classification according to IGCCCG

Nonseminoma	Seminoma
Good prognosis	
Primary site: Testis or retroperitoneum **and** No non-pulmonary visceral metastases (for example liver, bone, brain) **and all** good markers ß-hCG < 5000 IU/L (1000 µg/L) **and** AFP < 1000 µg/L **and** LDH < 1.5 x ULN	Any primary site **and** No non-pulmonary visceral metastases (for example liver, bone, brain) **and** any ß-hCG, any LDH and normal AFP *LDH > 2.5 x ULN may imply a worse prognosis within the good prognosis group*
Intermediate prognosis	
Primary site: Testis or retroperitoneum **and** No non-pulmonary visceral metastases (for example liver, bone, brain) **and any** intermediate markers ß-hCG ≥ 5000 IU/L and ≤ 50000 IU/L **or** AFP ≥ 1000 and ≤ 10000 µg/L **or** LDH ≥ 1.5 x ULN ≤ 10 x ULN	Non-pulmonary visceral metastases (for example liver, bone, brain)
Poor prognosis	
Mediastinal primary **or** Non-pulmonary visceral metastases (for example liver, bone, brain) **or any** poor markers ß-hCG > 50000 IU/L) **or** AFP > 10000 µg/L **or** LDH > 10 x ULN	No seminoma with poor prognosis

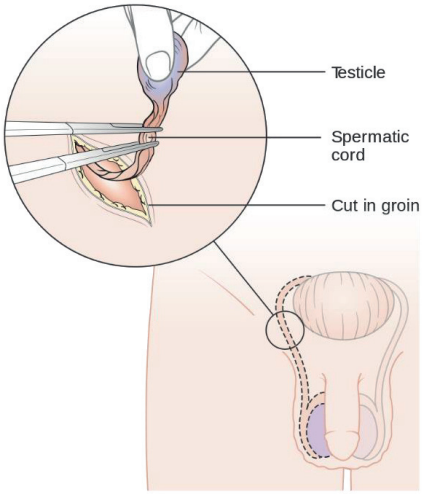
In CS1 disease, the most important prognostic factors for relapse are tumor invasion into small blood- and lymphatic vessels[41-44] (nonseminoma) or stromal invasion in the rete testis (seminoma). In seminoma, a tumor size >4 cm is also associated with a higher risk of relapse.[45, 46]

1.5 Treatment options

Orchiectomy

Orchiectomy is the surgical removal of the affected testicle. This procedure remains the cornerstone of local TC treatment, and is the first line of treatment in nearly all cases of TC. In addition to providing histological confirmation of the diagnosis, orchiectomy is curative in true CS1 TC (Figure 5).

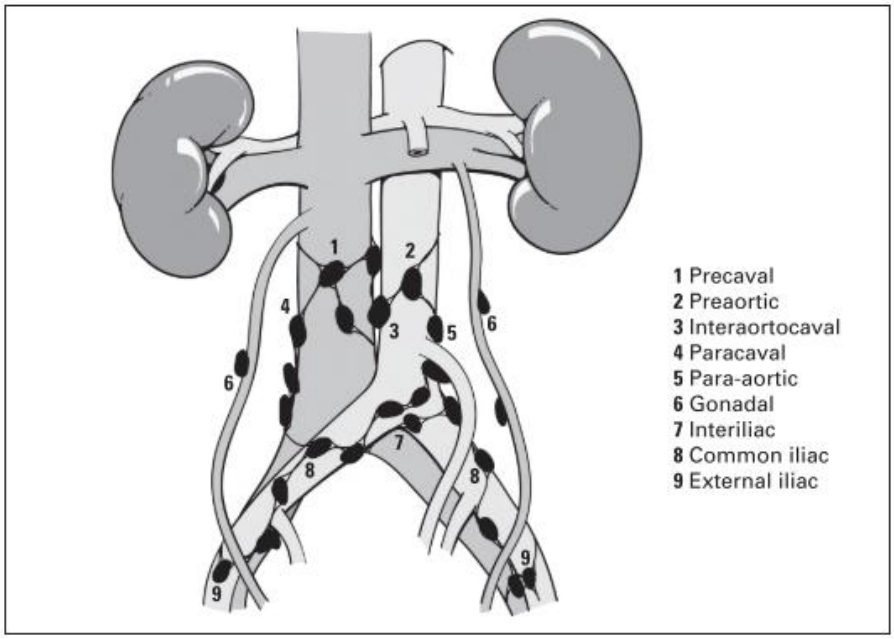
Figure 5. Inguinal orchiectomy. This file is licensed under the Creative Commons Attribution-Share Alike 4.0 International license. Cancer Research UK / Wikimedia Commons.



Retroperitoneal lymph node dissection

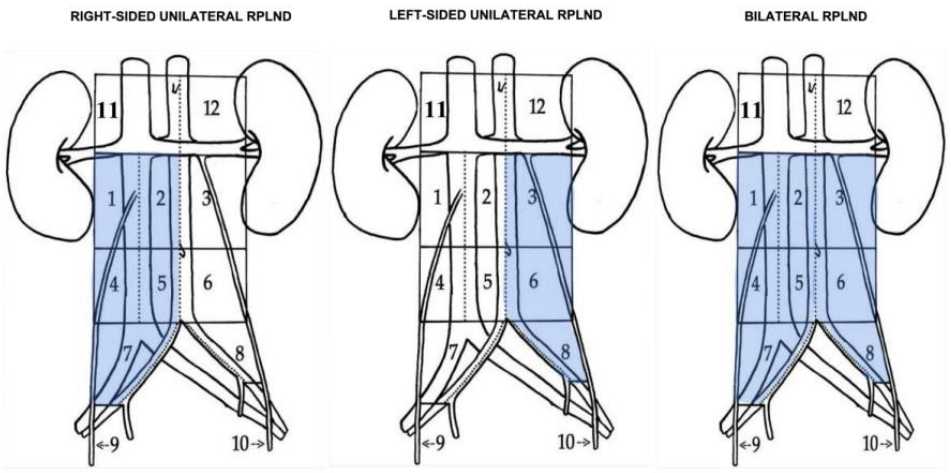
Retroperitonal lymph node dissection (RPLND) is the surgical removal of lymph nodes located in the retroperitoneum along the large vessels in the abdomen and pelvis (Figure 6).

Figure 6. Anatomic retroperitoneal nodal regions.[47] Used with permission.



RPLND is of value because the metastatic spread of TC usually follows a predictive anatomical route to these retroperitoneal lymph nodes.[47] The procedure can be unilateral or bilateral (Figure 7).

Figure 7. Areas of retroperitoneal lymph node dissection.[37] Numbers refer to lymph node regions.



RPLND has been used extensively in CS1 nonseminoma to establish an accurate pathological staging of the retroperitoneum. Moreover, the procedure can be curative in early-stage metastatic disease. After chemotherapy for metastatic nonseminoma, any remaining lesion (>1 cm) should be removed surgically. In rare cases, surgery is performed on seminoma patients with lesions >3 cm after chemotherapy.

The most common complications after an RPLND are lymphatic leakage and retrograde ejaculation, the latter leading to infertility.[48]

Radiotherapy

High-energy radiation has been used to treat cancer for more than a century.[49] During this time, several methods of delivering external beam RT have been developed, some of which are no longer in use. At the Norwegian Radium Hospital in Oslo, Norway, RT was given by X-ray machines prior to 1955, from 1955 to 1969 by Betatron particle accelerator and since about 1970 by linear particle accelerators.[50]

Linear accelerators can deliver high-energy photons, or gamma radiation, which damages DNA mostly through indirect ionization of water.[51] This forms free radicals which then react with DNA. The resulting DNA damage leads to cell death or impaired cell division. Linear accelerators have also benefited from advances in technology, physics and biology, which has led to more accurate and safe treatment.

Seminomas are highly sensitive to radiation. RT has thus been commonly used to treat seminomas, with excellent rates of cure in CS1. Even in CS3, RT has the potential for cure, with reported survival of about 60%.[52] Nonseminomas are less sensitive to radiation, and thus require higher radiation doses.

Typical infradiaphragmatic RT (IRT) fields were variants on L-fields, which included the lumbar and ipsilateral iliac lymph node regions (Figure 8). Until about 1980, the anterior field also included the inguinal region in selected patients and was then called a dog leg field (Figure 9). L-fields were gradually replaced by smaller para-aortic (PA) fields in the mid-2000s (Figure 9). Before 1980, supradiaphragmatic RT (SRT) was frequently given as prophylaxis to the mediastinum if lymph node metastases were detected.

Figure 8. L-field. Images used with permission from Olbjørn H. Klepp.

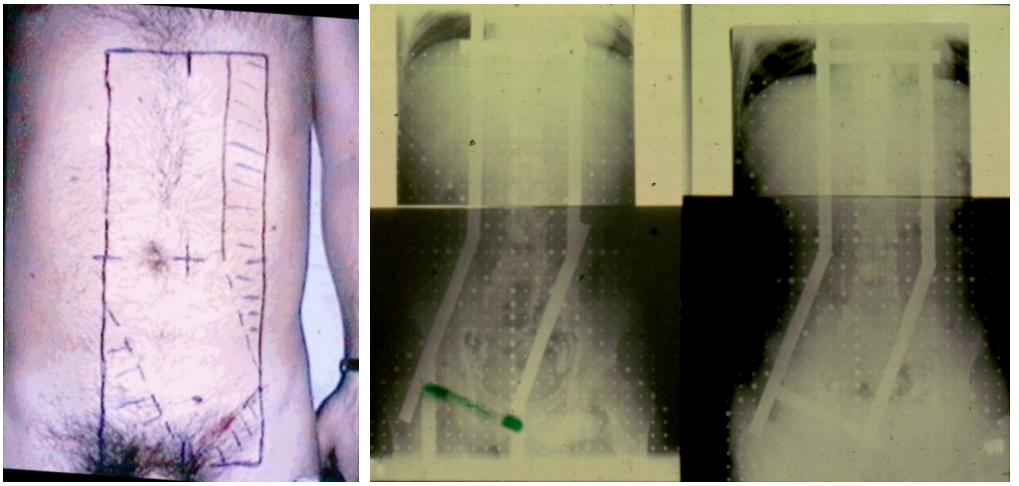
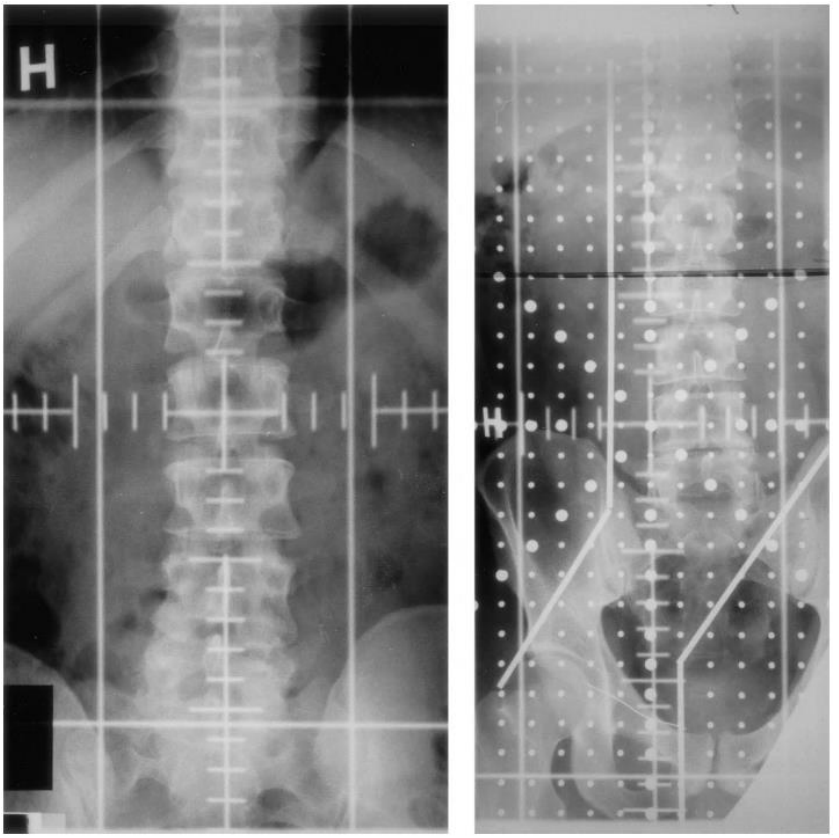


Figure 9. Para-aortic field (left) and dog leg field (right).[53] Used with permission.



In most cancers, RT remains an important treatment modality.[49] While fractionated external beam RT was commonly used to treat TGCT until 10-15 years ago, it has since been substituted by

adjuvant chemotherapy or surveillance, especially in CS1 seminoma. In Norway, adjuvant or curative RT was given to nonseminoma patients until 1980 and to seminoma patients until the early 2000s. Increasing evidence of serious RT late effects as well as effective adjuvant and salvage chemotherapy regimens led to this change of practice.

Acute and long-term RT side effects depend on radiation dose and irradiated volume. Acute effects are usually transient, predictable, and often caused by tissue inflammation. Long-term effects are largely related to tissue fibrosis.

Chemotherapy

In 1960, the first successful trial of combination chemotherapy for TC was published.[54] Dactinomycin, chlorambucil and methotrexate had response rates of about 50-70%, including 10-20% complete responses.[55, 56]

In the early 1970s, vinblastine, bleomycin and mithramycin showed effect on TC.[57-59] In the mid-1970s, bleomycin and vinblastine in combination was shown to induce complete responses in almost 40 % of cases.[60] During 1974 to 1978, Norwegian TC patients received a combination of adriamycin, cyclophosphamide, actinomycin-D and medroxyprogesterone acetate (CAOS regimen, also called VACAM)[61, 62] which led to partial responses in 73 % and complete responses in one third of patients.

In 1974, cisplatin monotherapy showed promising results in TC.[63] Einhorn et al. published results of combined treatment with cisplatin, vinblastine and bleomycin (CVB*)* in 1977,[7] with a 100 % response rate, including 74 % complete responses. CVB thus became the standard treatment of metastatic TC from the late 1970s.

In 1983, Peckham et al. reported encouraging results on the combination of bleomycin, etoposide and cisplatin (BEP) as first line treatment of metastatic TC.[64] Four years later, a study comparing BEP and CVB showed that BEP had better efficacy and lower toxicity.[65] BEP became the standard regimen in the treatment of metastatic TC in 1987.

Due to the chemo-sensitivity of TC, several studies were performed through the 1990s and 2000s to determine whether chemotherapy could be useful also in the adjuvant setting.[66-71] The standard adjuvant regimen in the 2000s were two courses of BEP. Relapse rates after this regimen were low, although there was a lack of data on long-term toxicity.[67] After reports on low relapse rates after one course of adjuvant BEP, this gradually became the new standard adjuvant regimen in nonseminoma patients in the late 2000s.[72] One course of adjuvant carboplatin became an option for seminoma patients.[73]

Different chemotherapy regimens are associated with varying degrees of short-term side effects such as nausea, diarrhea and hair loss, but also long-term effects. For cisplatin, these include peripheral neuropathy, ototoxicity, hypogonadism, infertility, renal toxicity, SC, CVD and pulmonary toxicity. [74]

1.6 Treatment principles in Norway, 1953-2020

In Norway, TC treatment is centralized to the university hospitals. Between 1956 and 1977, 68 % of TC patients diagnosed in Norway received their primary treatment at the Norwegian Radium Hospital in Oslo, Norway.[75] In the 1970s, about 90% of the patients diagnosed in Norway were treated there.[1]

The Swedish and Norwegian Testicular Cancer Group (SWENOTECA) was founded in 1981 and has provided comprehensive evidence-based TC management programs and study protocols. The current management program is SWENOTECA X.[37]

Table 4 shows a summary of TC treatment principles in Norway from 1953 until 2020. It should be noted that the approach to TGCT treatment has differed somewhat in different parts of the world.[76]

Table 4. General treatment principles for testicular germ cell tumor patients diagnosed in Norway.[1]

Time of diagnosis	Localized disease (CS1[a])	Metastatic disease (CS1 Mk+, CS2-4)
1953-1969	X-ray irradiation and gradually Betatron RT (1955-1969)[62] was given adjuvant to para-aortic and ipsilateral lymph nodes, sometimes also to the inguinal region. Doses were 35-40 Gy among seminoma patients and up to 50 Gy in nonseminoma patients.	RPLND rarely performed. In stage II or III disease, large abdominal fields received up to 40 Gy, also including the mediastinum. In the 1960s, patients with metastases also occasionally received chemotherapy with cyclophosphamide or mithramycin, and/or palliative limited field RT
1970-1979	Diagnostic accuracy improved by vena cavography, lymphography and CT. RT fields remained similar, but linear accelerators became available from 1970.[62] Nonseminoma patients received RT doses of up to 50 Gy both in adjuvant and salvage settings. From late 1978, a staging RPLND was more often used in nonseminoma patients without evidence of metastatic disease. If lymph node metastases were found at pathology, they usually received adjuvant CVB.[43]	If regional lymph node metastases were detected, prophylactic mediastinal irradiation was frequently applied. Before May 1978, most patients with metastases received mithramycin or combinations of actinomycin D, vincristine, doxorubicin and cyclophosphamide (CAOS or VACAM during 1974-78).[61] From May 1978, patients with stage II-IV disease received three or four courses of CVB followed by RPLND and/or removal of other residual metastases. Bleomycin was omitted if there was high risk of pulmonary toxicity.
1980-1989	Seminomas: adjuvant abdominal RT (L-field), dose gradually reduced to 30 Gy or less.[77] The Norwegian Radium Hospital offered RT to PA fields from 1989.[53] Nonseminomas: staging RPLND followed by adjuvant chemotherapy if metastases were detected.[78] From 1989, inclusion in a surveillance programme.	1980 to 86: CVB. Seminoma patients with advanced stage II disease received post-chemo RT (30 Gy) with boost to nodal disease. RT to non-seminoma patients usually only in the palliative setting. Prophylactic mediastinal irradiation discontinued.[62] From 1987: Transition to the BEP-regimen, three or four courses. Bleomycin omitted if high risk of pulmonary toxicity. Nerve-sparing RPLND from 1989.[78]
1990-1999	Seminomas: Adjuvant RT as above. Nonseminomas: Surveillance or 1-2 cycles of adjuvant CBCT[43, 67, 79] 1 BEP became the norm in the mid-90s.[80]	The BEP-regimen remained standard first-line therapy. Dose-escalation to ifosfamide-containing regimens. High-dose chemotherapy with autologous stem cell support available from 1995. Post-chemotherapy residual masses in nonseminoma patients were resected.
2000-2019	Seminomas: the usage of adjuvant RT was reduced from year 2000 and no longer considered as standard from 2007. Replaced with one course of adjuvant carboplatin or surveillance.[73, 81] Non-seminomas: Patients are offered surveillance or one adjuvant BEP, depending on prognostic factors.[72]	BEP remains standard first-line therapy; three cycles for patients with good prognosis, otherwise four. Stage II seminoma patients received RT until about year 2000. Decrease in usage of abdominal RT for stage II seminomas after year 2000, but still an option in stage 2A disease.

[a] Clinical stage as defined in the Royal Marsden Hospital staging system

BEP, cisplatin, etoposide, bleomycin; CT, computer tomography; CVB, cisplatin, vinblastine, bleomycin; Gy, Gray; RPLND, retroperitoneal lymph node dissection; RT, radiotherapy; TGCT, testicular germ cell tumor.

The challenge of TC treatment during the last decades has been to reduce the burden of treatment to minimize the extent of late toxicities while preserving the excellent cure rates. Chemotherapy has largely replaced RT.

In virtually all cases today, treatment is initiated with the intention of cure. Adjuvant chemotherapy is less toxic than treatment for metastatic disease, mainly because fewer courses of chemotherapy are given. However, with adjuvant treatment there is also the risk of overtreatment of patients already cured by surgery. Prognostic factors may help to select patients eligible for adjuvant treatment.

After orchiectomy, surveillance is an option in all patients with CS1 disease. The advantage of surveillance is that overtreatment is avoided. Surveillance is a viable strategy because there is effective treatment in the event of a relapse.

SWENOTECA guidelines recommend hospital follow-up for five to ten years after successful TGCT treatment.[37] The rationale for follow-up is to detect any TGCT relapses, contralateral TC as well as late effects of treatment.

1.7 Survival, mortality and morbidity after diagnosis of testicular germ cell tumor

Survival

A long-term survivor of cancer in general[82] or of TC in particular[5, 9] can be defined as an individual who is disease-free five years or more after primary treatment. Long-term survival is not synonymous with cure as late relapses can occur.[83]

Overall survival (OS) is the proportion of individuals alive after a fixed duration of time. It is considered the definitive end point in cancer clinical trials.[84] OS is unbiased, unambiguous, and easily measured. A disadvantage of OS is that it is not specific enough to provide information on survival associated solely with a cancer diagnosis,[85] since OS is also affected by death from other causes. Progression-free survival (PFS) is a common surrogate end point for OS.

5-year OS data for IGCCCG prognostic groups were recently updated,[39, 40] showing substantially improved OS among TC patients compared to the original 1997 data (Table 5).[38]

Table 5: 5-year overall survival and progression-free survival by International Germ-Cell Consensus Classification Group prognostic group. Data published 1997 → 2021.[38-40]

	Good prognosis	Intermediate	Poor
Seminoma	OS: 86 % → 95 % PFS: 82 % → 89 %	OS: 72 % → 88 % PFS: 67 % → 79 %	
Nonseminoma	OS: 92 % → 96 % PFS: 89 % → 90 %	OS: 80 % → 89 % PFS: 75 % → 78 %	OS: 48 % → 67 % PFS: 41 % → 54 %

OS, overall survival; PFS, progression-free survival.

OS data beyond 20 years of follow-up have been analyzed in several studies.[86, 87 31, 88-92] The largest study by Fosså et al.[31] showed significantly reduced OS among 21.648 US TCS followed for up to 27 years. OS was lower than in the general population, and seemed to decline more rapidly towards the end of follow-up.

Relative survival (RS) is the ratio of an observed OS rate in a study population compared to a reference population.[93] Ideally, one would want a cancer-free reference population, but this is difficult to obtain. Therefore, life expectancy tables are often used, and one assumes that deaths of a specific cancer comprise a negligible proportion of all deaths in the reference population.

RS is typically used in the analysis of cancer registry data. An RS point estimate of 1 (100%) implies equal survival between the populations. An advantage of RS is that relative trends exclusively reflect changes in "net survival" related to the cancer of interest.[94] The point estimates are usually accompanied by interval estimates (confidence intervals, CIs) and sometimes p-values to quantify the uncertainty of the estimate.

Five-year RS among TC patients, with the general male population of the same age as reference, has improved dramatically since the early 1970s. Today, it is 98.6 % in Norway, and even with distant metastases at diagnosis it is about 87-89 %.[4] Until the late 1970s, however, 5-year RS among patients with distant metastases was less than 50 % (Table 6).[6]

Table 6. Five-year relative survival of testicular cancer by primary site, stage and period of diagnosis, 1956-2000.[6]

				Relative survival (%)								
ICD10	Site	Stage	n 1996 -2000	1956-1960	1961-1965	1966-1970	1971-1975	1976-1980	1981-1985	1986-1990	1991-1995	1996-2000
		Total	**1183**	**60.2**	**62.1**	**67.7**	**66.9**	**82.0**	**93.0**	**94.6**	**95.8**	**96.0**
		Localized	676	76.2	81.8	83.2	87.9	94.7	98.1	98.4	99.3	98.6
C62	Testis	Regional	177	72.9	64.0	77.4	74.2	84.4	95.9	96.2	96.2	98.3
		Distant	160	9.4	15.8	21.0	22.4	43.9	75.2	75.5	75.9	81.0
		Unknown	170	90.2	60.7	72.4	38.6	91.3	53.3	86.2	87.1	97.2

Fifteen-year RS data are currently also excellent in Norway regardless of age at diagnosis, possibly with an exception for patients older than 55 years.[4] Overall, the most recent 15-year RS data published by the Cancer Registry of Norway (CRN) was 98.1 %.[4]

Twenty-year RS data were previously analyzed in two studies.[95, 96] Brenner found a declining 20-year RS of 84.1% among US TCS diagnosed 1978-1998.[95] Robinson et al. analyzed data for English TCS by decade of diagnosis between 1960 and 2004, without an obvious decline in RS at end of follow-up.[96]

Beyond 20 years of follow-up, there were no published RS data for TC patients prior to this PhD thesis.

Mortality and morbidity

An increasing number of studies demonstrate that TGCT patients and TCS have excess mortality and/or morbidity from a variety of causes. These causes can be grouped into four categories:

- TC itself
- non-TC SC
- CVD
- other / remaining causes

The studies vary regarding study population size, reference population, time period of diagnosis, geographical location, histology, follow-up time, disease stage and treatment.

TGCT treatment may cause a broad spectrum of acute, long-term and late effects, ranging from mild to severe. While both acute and long-term effects appear during treatment, long-term effects generally persist during follow-up. Late effects are subclinical or absent until months to years after treatment has been completed.[5, 82]

To quantify the late effects of TGCT and its treatment, Kerns et al. evaluated the cumulative burden of morbidity (CBM) among 1214 1-year TCS who received CBCT.[97] A CBM score encompassed the most common adverse health outcomes. After a median follow-up time of 4.2 years, about one in five TCS had a CBM score of high, very high or severe.

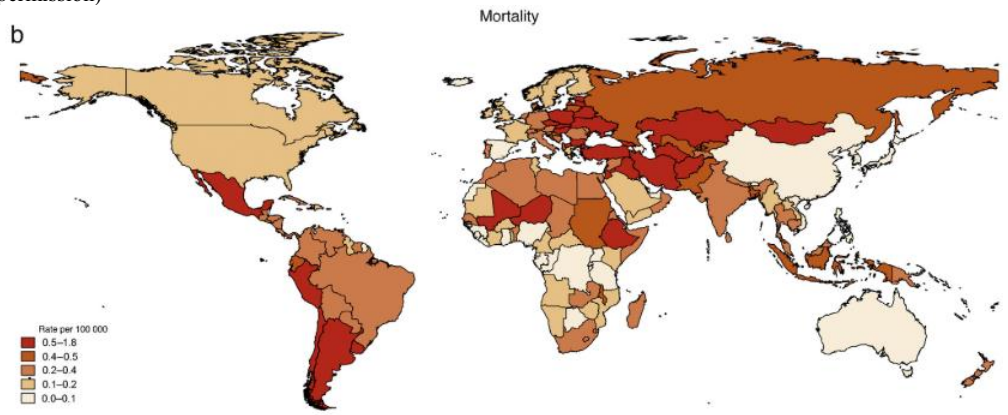
It is important to determine the morbidity and mortality resulting from a particular TGCT treatment. There is a lack of studies based on complete individual TC treatment information, including chemotherapy- or RT doses. The main reason is that most studies are based on cancer registry data in which only the type of primary treatment is reliably registered, if at all. In studies without complete treatment data, it is more difficult to draw conclusions regarding the effects of a specific treatment or treatment combination. The focus on morbidity in this thesis will be on selected, serious conditions that are usually not transient and that may even lead to death.

When comparing the risk of disease or death in a study population to that of a reference population, several statistical terms are relevant. The standardized incidence ratio (SIR) is perhaps the most common, and the point estimate is calculated by dividing the number of observed cases of a disease in the study population by the expected number of cases in the reference population.[98] The standardized mortality ratio (SMR) is calculated similarly but pertains to mortality. SIRs and SMRs are estimates of relative risk (RR).[99] The hazard ratio (HR) is used in Cox regression, and is interpreted similarly as RR.[98]

1.8 Testicular cancer-specific mortality

Despite the generally excellent prognosis with regards to 5-year RS, there are still young men who succumb to TC every year. During 2009-2017, there were 76 TC deaths in Norway. Worldwide, more than ten thousand deaths from TC occurred in 2012 (Figure 10).[10]

Figure 10. International variations in estimates of national age-standardized testicular cancer mortality.[10] (used with permission)

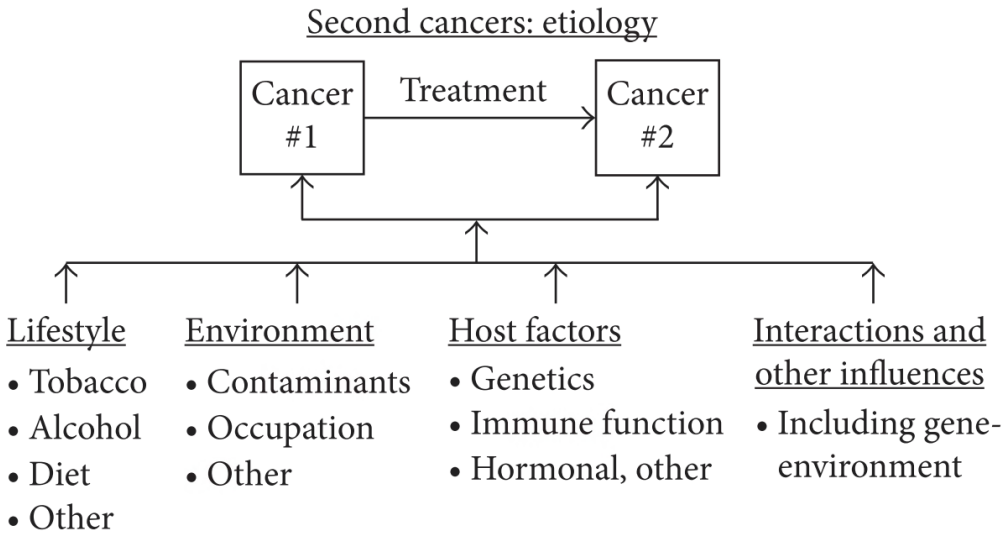


In most countries there has been a decrease in mortality during the last decades.[11]

1.9 Second cancer risk among testicular cancer survivors

The risk of SC is thought to be modulated by a variety of factors, including previous cancer treatment (Figure 11).[9]

Figure 11. Etiology of second cancers.[9] (used with permission)



Any TGCT treatment

In most studies of TCS, the SIR or RR for any SC was significantly elevated; between 1.3 and 3.5 compared to the general population.[50, 75, 86, 96, 100-110] The risk of leukemia was elevated about threefold.[105, 111, 112] While solid SC often manifested several decades after successful TC treatment, leukemia more often appeared after about 5 to 10 years.[112] Solid SC risk has been found to be elevated for at least 35 years after TGCT diagnosis.[109]

Travis et al. found a strong age dependence regarding SC risk.[109] A 20-year-old treated for seminoma or nonseminoma had an about threefold increased risk of SC compared to a patient treated at age 40.

Elevated site-specific SC risks among TCS have been reported for most organs (Table 7).[50, 103, 104, 106, 107, 109]

Table 7. Selected point estimates of relative risk of non-testicular second cancer. All provided point estimates are statistically significant.

Study	**Wanderås 1997[50]** N=2006 (1-yr) S=any P=1952-1990 F=mean 12.5 D=Norwegian Radium Hospital T=any	**Travis 2005[109]** N=40576 (1-yr) S=any P=1943-2001 F=mean 11.3 D=14 registries from Europe and US T=any	**Van den Belt-Dusebout 2007[104]** N=2707 (5-yr) S=any P=1965-1995 F=median 17.6 D=registries in the Netherlands T=any	**Richiardi 2007[103]** N=29511 S=any P=1943-2000 F=median 8.3 D= 13 non-US registries T=any	**Groot 2018[106]** N=5848 (1-yr) S=any P=1976-1995 F=median 14.1 D=registries, Netherlands T=any	**Zhang 2019[107]** N=8788 S=any P=1980-2015 F= median 11 D: Swedish registries T=any
All cancer sites*	1.65	-	1.7	1.65	-	1.30
All sites (solid only)*	-	1.41	1.7	-	1.8	-
Supradiaphragmatic	-	-	-	-	3.9	-
Infradiaphragmatic	-	-	-	-	2.4	-
Digestive tract	1.81 (- esophagus / small intestine)	-	1.9	-	2.1	-
- Esophagus		1.44	-	1.79	-	NS
- Stomach	2.24	2.16	2.7	2.37	2.3	NS

- Small intestine	-	2.60	-	NS	5.2	NS
- Colon	NS	1.36	NS	1.45	1.8	1.33
- Rectum and/or anus	NS	1.46	-		NS	
- Pancreas	NS	2.30	4.0	2.56	4.0	NS
- Liver / biliary	4.04	NS	-	2.01 (biliary)	-	NS
Lung / bronchi	2.31	1.19	NS	1.33	1.5	NS
- Pleura	-	2.80	-	-	-	-
Genitourinary tract	NS	-	2.0	-	3.0	-
- Prostate	NS	NS	NS	NS	NS	1.16
- Kidney	NS	1.42	2.2	2.05	2.1	2.19
- Bladder	2.04	1.93	3.9	2.12	4.3	1.78
Melanoma	2.68	1.48	2.9	1.62	2.1	NS
Skin, other	-	-	-	2.26	2.0	1.52 (squamous)
Brain, CNS	NS	NS	-	NS	NS	-
Thyroid	-	2.17	-	2.86	4.6	2.64
Bone	-	NS	-	NS	-	-
Connective tissue	8.8	2.65	NS	2.63	4.7	2.60
Lymphoma	NS	-	NS	1.65 (NHL)	-	1.87 (NHL)
Leukemia	NS	-	NS	3.62 (myeloid)	-	1.99
*, excluding TC; -, no data provided; 1-yr, one-year survivors; D, data source; P, time period of TGCT diagnosis; F, follow-up time in years; N, study population size; NHL, non-Hodgkins lymphoma; NS, not statistically significant; S, stage and histology; T, TGCT treatment; CNS, central nervous system						

Surgery

In TCS who were treated with surgery only, almost no data have pointed to increased overall solid SC risk.[50, 100, 104, 110, 113] Fung et al. did report an overall excess SC SIR, but only within the first year after TC diagnosis.[110] In some studies, the surgery group has been used as the reference group for selected analyses between treatment groups.[104, 106, 114]

A few studies have shown excess risks of kidney cancer,[110] soft tissue sarcoma,[106] melanoma[104] and acute myeloid leukemia after surgery only.[111]

Radiotherapy

Studies have shown a 1.4- to 2.0-fold elevated overall risk of solid SC after RT (Table 8),[50, 86, 102, 104, 106, 109, 114-117] and about threefold elevated risks of leukemia.[111, 112]

Table 8. Selected point estimates of relative risk of non-testicular second cancer after radiotherapy. All provided point estimates are statistically significant.

Study	**Wanderås 1997[50]** N=1194 (1-yr) S=any P=1952-1990 F=mean 15.9, until end of 1992 D=Norwegian Radium Hospital T=RT	**Travis 2005[109]** N=<9551 (10-yr) S=any P=1943-2001 F=mean 11.3 D=14 registries from Europe and US T=RT	**Van den Belt-Dusebout 2007[104]** N=1304 (5-yr) S=any P=1965-1995 F=median 17.6 D=registries in the Netherlands T=RT	**Horwich 2014[86]** N=2543 (1-yr) S=CS1 seminoma P=1960-1992 F=median 21.8 D=UK / Norway T=RT	**Kier 2016[114]** N=787 S=any P=1984-2007 F=median 14.4, until end of 2012 D=Denmark T=RT	**Groot 2018[106]** N=2230 (1-yr) S=any P=1976-1995 F=median 14.1 D=registries, Netherlands T=RT, 105 also chemo
All cancer sites*	1.58	-	1.7	1.53	1.8	-
All sites (solid only)*	-	2.0	1.8	-	-	1.91
Supradiaphragmatic	-	-	-	-	-	1.43
Infradiaphragmatic	-	2.7	-	1.62	-	2.64

Digestive tract	1.70(-esophagus / small intestine)	-	2.1	-	-	2.44
- Esophagus		-	-	-	NS	NS
- Stomach	2.46	4.1	2.9	1.93	9.8	3.48
- Small intestine	-	-	-	1.9	-	NS
- Colon	-	1.9	NS	1.32	NS	NS
- Rectum and/or anus	-	1.8	-			NS
- Pancreas	-	3.8	5.5	3.14	4.1	5.7
- Liver / biliary	-	-	-	NS	-	-
Lung / bronchi	2.19	1.4	NS	NS	NS	NS
- Pleura	-	4.4	-	-	-	-
Genitourinary tract	-		2.1	-	NS	-
- Prostate	-	1.4	NS	1.33	2.0	NS
- Kidney	-	2.8	2.3	NS	NS	2.26
- Bladder	2.10	2.7	4.2	2.46	2.4	4.50
Melanoma	NS	1.6	NS	NS	NS	2.05
Skin, other	-	-	-	-	-	2.69
Brain, CNS	-	-	-	-	NS	NS
Thyroid	-	3.1	-	-	-	4.73
Bone	-	-	-	-	-	-
Connective tissue	9.22	5.1	-	NS	NS	4.48
Leukemia	-	-	-	NS	NS	-
*, excluding TC; -, no data provided; 1-yr, one-year survivors; CNS, central nervous system; CS, clinical stage; D, data source; P, time period of TGCT diagnosis; F, follow-up time in years; N, study population size; NHL, non-Hodgkins lymphoma; NS, not statistically significant; RT, radiotherapy; S, stage and histology; T, TGCT treatment						

There seems to be a positive relationship between RT dose and SC risk.[104, 106, 108, 118, 119] One study showed that the HR for SC increased from 2.3 to 3.2 when the RT dose was increased from 26-35 Gy to 40-50 Gy, compared with surgery alone.[104]

After IRT, SC risk has been found to be highest in organs located within the infradiaphragmatic radiation field.[106, 109] PA fields have been associated with lower SC risk than dogleg fields.[106] SRT has not similarly been associated with excess supradiaphragmatic SC risk.[106]

Chemotherapy

Several studies have analyzed SC risks among TCS treated before and after CBCT became widely available in the late 1970s.[50, 104, 109, 113] In a study of 4607 10-year TCS diagnosed 1943-2001 and treated with chemotherapy, the RR for SC was 1.8.[109] In contrast, other studies showed no elevated overall SC risk.[50, 104]

Because CBCT remains a cornerstone of TGCT treatment, it is of particular interest to determine SC risks associated with this form of treatment. Prior to this PhD thesis there was a lack of studies of SC risk among TCS treated in the cisplatin era using complete individual treatment information.

Some recent studies have evaluated solid SC risks among TCS treated with CBCT.[106, 110, 114] Complete individual treatment information was not available in two studies.[106, 110] Across these studies, overall SC risks were 1.4- to 2.3-fold elevated after CBCT. All studies also showed increased site-specific risks (Table 9).

Table 9. Selected point estimates of relative risk of non-testicular second cancer after chemotherapy. All provided point estimates are statistically significant.

Study	**Fung 2013**[110] N=6013 S=nonseminoma P=1980-2002 F=median 7.3 D=SEER database, US T=chemotherapy	**Kier 2016**[114] N=1862 S=any P=1984-2007 F=median 14.4 D=Denmark T=BEP	**Groot 2018**[106] N=2202 (1-yr) S=any P=1976-1995 F=median 14.1 D=registries, the Netherlands T=CBCT
All cancer sites*	-	1.7	-
All sites (solid only)*	1.43	-	2.25
Supradiaphragmatic	-	-	2.24
Infradiaphragmatic	-	-	3.03
Digestive tract	-	-	2.77
- Esophagus	NS	3.4	NS
- Stomach	NS	NS	NS
- Small intestine	NS	-	11.01
- Colon	NS	NS	2.46
- Rectum and/or anus	NS		2.85
- Pancreas	NS	NS	3.61
- Liver / biliary	NS	NS	-
Lung / bronchi	NS	1.9	2.08
Genitourinary tract	-	NS	3.74
- Prostate	NS	NS	NS
- Kidney	3.37	NS	NS
- Bladder	NS	2.0	6.35
Melanoma	-	NS	2.15
Skin, other	-	-	NS
Brain, CNS	NS	NS	NS
Thyroid	4.40	-	5.83
Bone	-	-	-
Connective tissue	7.49	4.9	6.01
Leukemia	-	6.3 (myeloid)	-

*, excluding TC; -, no data provided; 1-yr, one-year survivors; BEP, bleomycin/etoposide/cisplatin; CBCT, cisplatin-based chemotherapy; CS, clinical stage; D, data source; P, time period of TGCT diagnosis; F, follow-up time in years; N, study population size; NHL, non-Hodgkins lymphoma; NS, not statistically significant; S, stage and histology; T, TGCT treatment

Groot et al. found that patients who received CBCT had a HR of 2.40 for SC compared to those who did not.[106] Also, there was a dose-response relationship between CBCT and solid SC risk.

Regarding leukemia, several studies have shown increased risk following CBCT.[112, 114, 120, 121] As with RT, the risk seems to be dose-dependent.[9, 112, 121]

Adjuvant carboplatin has not been associated with increased SC risk.[122]

Combined treatment

Many TCS have received both RT and chemotherapy. Older studies gave conflicting results on whether these TCS were at significantly higher risk of SC than after either modality alone,[123] although one study showed a 3.5-fold elevated SC risk.[50] More recently, Kier et al. found a 3.7-fold increased HR after more than one line of treatment compared to the control group, but based on only 86 patients.[114] This could also include second-line chemotherapy. In one study, RT in addition to chemotherapy increased the SC risk from 8.0% to 13.9% at 20 years of follow-up.[104]

1.10 Second cancer mortality among testicular cancer survivors

Any treatment

Most studies have shown elevated overall SC SMRs compared to the reference population, ranging from 1.2 to 5.8.[86, 87, 89, 114, 124-127] Unlike for SC risk, relatively few previous studies have provided site-specific cancer SMRs, at least until recent years (Table 10).

Table 10. Selected point estimates of non-testicular second cancer mortality (standardized mortality ratios or hazard ratios). All provided point estimates are statistically significant.

Study	**Fosså 2004[125]** N=3378 S=any P=1962-1997 F=41960 PY D=Norway T=any	**Beard 2013[87]** N=7179 S=seminoma, CS1 P=1973-2001 F=median 12.7 RT D=SEER data (US) T=RT. Also, no RT in 2014 patients	**Kier 2016[114]** N=1862 S=any P=1984-2007 F=median 14.4 D=Denmark T=any	**Groot 2020[126]** N=6042 S=any P=1976-2006 F=median 17.6 D: 13 Dutch hospitals T=any
All cancer sites*	2.0	1.89 (1.46 if no RT)	NS (surveillance), 1.6 (BEP), 2.1 (RT), 5.8 (MTOL)	1.9 2.67 (chemo vs no chemo)
Infradiaphragmatic	-	1.79 (in-field)	-	-
Digestive tract	-	-	-	2.4
- Esophagus	-	-	-	NS
- Stomach	3.0	-	-	2.8
- Colon	-	-	-	NS
- Rectum and/or anus	-	-	-	3.2
- Pancreas	3.0	3.19	-	3.9
Lung / bronchi	1.7	1.35	-	1.3**
- Kidney	-	-	-	3.0
- Bladder	-	-	-	4.0
Melanoma	-	-	-	NS
Connective tissue	-	-	-	7.2
Lymphoma	-	-	-	NS
Leukemia	-	-	-	3.6

*, excluding TC; **, reported with a 95 % CI ranging from 1.0; -, no data provided; 1-yr, one-year survivors; BEP, bleomycin/etoposide/cisplatin; CBCT, cisplatin-based chemotherapy; CS, clinical stage; CT, chemotherapy; D, data source; P, time period of TGCT diagnosis; F, follow-up time in years; MTOL, more than one line of treatment; N, study population size; NHL, non-Hodgkins lymphoma; NS, not statistically significant; PY, person years; RT, radiotherapy; S, stage and histology; SEER, Surveillance, Epidemiology and End Results; T, TGCT treatment

Radiotherapy

SC mortality among stage I/II seminoma patients has been well studied.[86, 87, 89, 117, 124, 128] Many of these patients received RT, and most studies have shown elevated overall SC SMRs ranging between 1.5 and 3.4. Regarding site-specific SMRs after IRT, a study showed an elevated SMR for in-field SC of about 1.8 and for pancreatic cancer of 3.4.[87] Another study showed elevated SMRs for bladder cancer (3.8) and leukemia (5.5).[128] In a study also including patients with metastatic TGCT, SC caused excess mortality by 2.1 times after RT, compared to age-matched controls.[114] Groot et al. recently found that a PA field >26 Gy was associated with a HR for SC mortality of 2.68 vs no RT, and similarly 2.64 for a dogleg field >26 Gy. There was no excess mortality after lower radiation doses or SRT.[126]

Chemotherapy and combined treatment

In contrast to RT, SC mortality after initial chemotherapy alone has been analyzed in relatively few studies. Kier et al.[114] found an SC SMR of 1.6 after BEP and 5.8 times after more than one line of

treatment (Table 10). A recent study by Groot et al. also showed an about 2.5-fold elevated HR for SC death after CBCT compared with no chemotherapy.[126]

1.11 Cardiovascular disease risk among testicular cancer survivors

CVD is a major cause of morbidity and mortality across the world. Several definitions exist, but those used by Haugnes et al.[129] will be used here:

- Coronary artery disease (CAD) includes myocardial infarction (MI) and angina pectoris.
- CVD includes thromboembolic events, stroke, peripheral atherosclerotic disease and CAD.

There are several modifiable risk factors for CVD such as hypertension, obesity, dyslipidemia including elevated cholesterol, age, smoking, impaired glucose tolerance and inactivity. Worldwide, the two most important risk factors for MI are smoking and abnormal lipids, accounting for about two thirds of the attributable risk.[130] Elevated C-reactive protein may also predict CAD.[131, 132]

Some risk factors for CVD and diabetes 2 occur together more often than by chance alone. The metabolic syndrome is a clustering of hypertension, insulin resistance, elevated triglyceride levels, low high-density lipoprotein cholesterol levels, and obesity.[133]

Persons with the metabolic syndrome have twice the risk of developing CVD over the coming 5-10 years compared with healthy individuals, and a 5-fold increased risk of type 2 diabetes.[133] While physical activity may reduce the risk of metabolic syndrome, smoking may increase the risk.[134] Haugnes et al. found that TGCT patients treated with chemotherapy had increased odds for metabolic syndrome.[134] Huddart et al. found that more patients in the RT group had an increased cholesterol levels or were being treated with lipid-lowering medication than in the surveillance group.[135]

Short-term risks

CVD can develop decades after successful TGCT treatment, but it can also occur acutely during treatment.[136] Until 2015, data on early vascular toxicity among TC patients was based on case series and anecdotal reports.[137-140] In 2010, Dieckmann et al. reported twenty-five cases of major early CVD events associated with chemotherapy for testicular cancer.[136] Of these, twenty were MI. Coronary angiography was indicative of thromboembolic rather than atherosclerotic origin.[136] The reported incidence rates of thromboembolic events during CBCT for metastatic TC range between 8 and 18 %.[141-143]

A recent study by Lauritsen et al. showed that patients treated with BEP had a more than 20-fold increased HR of venous thromboembolism compared with the normal population.[144] This risk was no longer significantly elevated beyond 10 years. The same study showed a more than sixfold increased HR of MI, an almost fivefold increased risk of CAD and a sixfold increased HR of cerebrovascular accidents during the first year after start of BEP.

A few years ago, the aim of a Norwegian multicenter study was to determine whether high intensity exercise during CBCT for TGCT would be beneficial. This study had to be aborted due to an unexpected increased amount of acute CVD events.[145]

Long-term risks

Several studies have examined long-term CVD / CAD risk among TC patients and TCS.[104, 132, 135, 136, 146, 147] Excess CVD risks have ranged from either not significantly increased to 7.1-fold higher, depending on treatment.

IRT for TGCT has been associated with increased CAD risk in some studies,[132, 135] but not all.[104, 129, 144, 147] With surgery alone as reference, mediastinal irradiation was more consistently associated with an about threefold increased risk of MI, CVD and heart failure.[104, 147]

The RR of CVD after chemotherapy was 1.4 to 7.1-fold higher than within the general population or TCS managed with surgery only / surveillance.[9, 104, 132, 135, 146-148] Ranging from years to decades after TC diagnosis, TCS given CBCT had a 2- to 5.6-fold higher CAD risk than the general population or TCS who received surgery only.[5, 129, 132, 135, 136]

After combined RT and chemotherapy, the risk of CVD seemed to be greater than following RT or chemotherapy alone.[104, 132, 135, 147]

1.12 Cardiovascular disease mortality among testicular cancer survivors

Any treatment

Long-term CVD mortality among TC patients and TCS has been analyzed in several studies. When disregarding the form of TGCT treatment given, borderline elevated SMRs of 1.2-1.3 have been shown (Table 11).[125, 126, 149]

Table 11. Selected point estimates of cardiovascular and overall non-cancer mortality (standardized mortality ratios or hazard ratios). All provided point estimates are statistically significant.

Study	**Fosså 2004**[125] N=3378 S=any P=1962-1997 F=41960 PY D=Norway T=any	**Zagars 2004**[89] S=seminoma, CS1-2 P=1951-1999 F=median 13.3 D=MDACC, Texas T=RT	**Fosså 2007**[149] N=38907 (1-yr) S=any P=1943-2002 F=median 10 D: 14 cancer registries in US / Europe T=8802 surgery, 12454 RT, 4586 chemotherapy	**Fung 2015**[148] N=15006 S=nonseminoma P=1980-2010 F=median 6.5-7.9 D: SEER data, US T=8097 surgery, 6909 chemotherapy, no RT	**Groot 2020**[126] N=6042 S=any P=1976-2006 F=median 17.6 D: 13 Dutch hospitals T=1450 surgery, 2255 RT, 2337 chemotherapy	**Lauritsen 2020**[144] N=5185 S=any P=1984-07 F=median 15.8 D=Danish TC database T=3332 surveillance, 780 RT, 1819 BEP, 295 MTOL
Non-cancer SMR	-	-	**1.06**	**1.60** if chemo, NS if surgery	**1.2**	-
CVD, any treatment	**1.2**	-	**1.23** (if diagnosed with TC <35 yrs)	-	**1.3*** Non-seminoma: **1.5** **2.1** (chemo vs no chemo)	-
CVD, surgery	-	-	NS	NS	-	NS
CVD, RT	-	-	**1.70** (if RT ≥1975 and diagnosed with TC <35 yrs)	-	-	NS
CVD, chemo	-	-	**1.34** (if T ≥1975)	**1.36** (5.31 first yr, NS >1 yr)	-	**1.44** (**7.4** first yr)
CVD, combined treatment	-	-	**2.06** (if T ≥1975)	-	-	-
Heart / cardiac disease, any treatment	-	-	**1.19** (if diagnosed with TC <35 yrs)	-	**1.4***, MI **1.4*** Non-seminoma: IHD **1.9**, MI **2.1**	-
Heart / cardiac disease, RT	-	**1.61**. NS <15 yrs, **1.95** >15 yrs	-	-	NS	-
Heart / cardiac disease, chemo	-	-	-	NS	HR **2.05** vs no chemo	-
Cerebrovascular disease	-	-	-	**2.40** (chemo)	-	-
*, reported with a 95 % CI ranging from 1.0 ; -, no data provided; 1-yr, one-year survivors; BEP, bleomycin/etoposide/cisplatin; CBCT, cisplatin-based chemotherapy; chemo, chemotherapy; CS, clinical stage; D,						

data source; HR, hazard ratio; P, time period of TGCT diagnosis; F, follow-up time in years; MDACC, MD Anderson Cancer Center; MI, myocardial infarction; N, study population size; NHL, non-Hodgkins lymphoma; NS, not statistically significant; PY, person years; RT, radiotherapy; S, stage and histology; T, TGCT treatment; TC, testicular cancer

Radiotherapy

CVD SMRs among TCS treated with RT have ranged from significantly lower,[86] not significantly elevated[87, 114, 144] to 1.70 in patients <35 years at TGCT diagnosis (Table 11).[148, 149]

A few studies have shown elevated cardiac SMRs of 1.6-2.3,[89, 124] for which there seemed to be an association with SRT. Zagars et al. found that the cardiac SMR was 2.39 among those who received prophylactic mediastinal irradiation, otherwise not statistically significant.[89] Hanks et al. reported that 8 of 10 patients who died of cardiac disease had received SRT.[124] This association could not be confirmed in a more recent study.[126]

Chemotherapy

Among TCS given chemotherapy, studies have shown an overall CVD SMR of about 1.4 in patients treated after 1975 (Table 11).[148, 149] However, when restricting analyses to CVD mortality during the first year after chemotherapy, SMRs were elevated five- to sevenfold.[144, 148] Fung et al. did not find excess CVD mortality after one year.[148]

Combined treatment

There is some evidence that the combination of chemotherapy and RT leads to increased CVD mortality, as reported by Fosså et al. (Table 11).[149] Kier et al. did not find excess CVD mortality after more than one line of treatment, but these patients did not necessarily receive RT.[114]

1.13 Other causes of mortality among testicular cancer survivors

Several studies have shown excess mortality among TCS due to a variety of non-malignant, non-CVD causes (Table 12). The most notable are non-malignant gastrointestinal disorders, respiratory disease, infections and suicide.

Non-malignant gastrointestinal disorders

In 2004, Fosså et al. unexpectedly found an SMR of 2.1 for non-malignant gastrointestinal diseases among TCS treated in Norway.[125] In a subsequent larger international study, an SMR of 1.44 was found (Table 12).[149] Subgroup analyses revealed increased SMRs for ulcers and other digestive diseases, predominantly vascular intestinal disorders. More recent studies did not show excess mortality,[114, 126] except in a subgroup who received more than one line of treatment.[114]

Table 12. Selected point estimates for non-cancer, non-cardiovascular disease mortality. All presented point estimates are statistically significant.

Study	**Fosså 2007[149]** N=38907 (1-yr) S=any P=1943-2002 F=median 10 D=14 registries in US / Europe T=8802 surgery, 12454 RT, 4586 chemo	**Fung 2015[148]** N=15006 S=nonseminoma P=1980-2010 F=median 6.5-7.9 D=SEER data, US T=8097 surgery, 6909 chemo, no RT	**Kier 2016[114]** N=5190 S=any P=1984-2007 F=median 14.4 D=Denmark T=3335 surveillance, 787 RT, 1862 BEP, 304 MTOL	**Groot 2020[126]** N=6042 S=any P=1976-2006 F=median 17.6 D=13 Dutch hospitals T=1450 surgery, 2255 RT, 2337 chemo	**Alanee 2012[150], Gunnes 2017[151]**
Infectious diseases	**1.28**. T ≥1975: **1.45** (surgery), NS (RT), **2.48** (chemo)	-	NS (surveillance), NS (RT), **3.1** (BEP)	NS	-

- Septicemia	-	NS (surgery), **7.14** (chemo)	-	-	-
- Intestinal	**9.1**	-	-	-	-
- HIV	**1.34**	+parasitic: NS	-	-	-
- pneumonia	**1.27**	+influenza: NS (surgery), **3.05** (chemo)	-	**2.4**	-
Endocrine	NS. **1.56** (nonseminoma)		-	-	-
- diabetes mellitus	NS	NS	NS	-	-
Digestive system	**1.44**. T ≥1975: NS (surgery), **1.61** (RT), NS (chemo)	-	NS. **13.5** (MTOL)	NS	-
- ulcers	**1.67** (**1.79** if age ≥35)	-	-	-	-
- liver	NS	NS	-	-	-
- other	**2.11**	-	-	-	-
Respiratory diseases	NS. **2.66** (chemo ≥1975)	-	NS	NS	-
- chronic lower	NS	NS	-	NS	-
- other	**1.94**	-	-	-	-
Genitourinary	NS	-	NS	**3.0**	-
Alzheimer's disease	-	NS	-	-	-
External causes (accidents, suicide)	NS	NS	NS	NS	Suicide: **1.2**[150], **2.9**[151]
Benign neoplasms, or unknown behaviour	-	**4.03** (surgery), **10.62** (chemo)	-	-	-
Ill-defined conditions	-	NS (surgery), **4.31** (chemo)	-	-	-

*, excluding TC; -, no data provided; 1-yr, one-year survivors; BEP, bleomycin/etoposide/cisplatin; CBCT, cisplatin-based chemotherapy; chemo, chemotherapy; CS, clinical stage; D, data source; F, follow-up time in years; MTOL, more than one line of treatment; N, study population size; NHL, non-Hodgkins lymphoma; NS, not statistically significant; P, time period of TGCT diagnosis; PY, person years; S, stage and histology; SEER, Surveillance, Epidemiology and End results; T, TGCT treatment; TC, testicular cancer

Respiratory disease

Fosså et al. found that among TCS who received initial chemotherapy in 1975 or later, mortality from all respiratory diseases was significantly increased (SMR 2.66). There was also excess mortality from a subgroup of respiratory diseases comprising pulmonary fibrosis, pneumoconiosis and aspiration pneumonia (Table 12).[149]

Infections

Fosså et al. found an overall SMR of 1.28 for infections (Table 12).[149] Excess mortality was particularly elevated among TCS who received chemotherapy, a finding which has since been replicated in other studies.[114, 148]

Suicide or accidental deaths

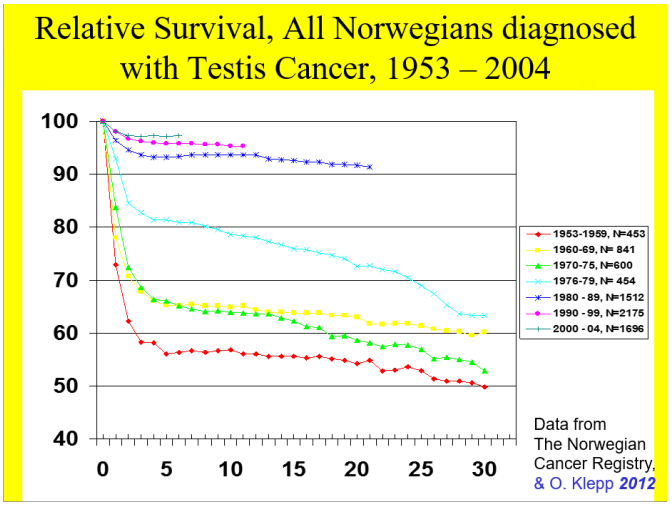
Increased suicide risk has been reported among US TCS,[87, 150, 152] but until 2017 the same had not been found in Norway.[151, 153]

Younger patients seem to be at particular risk. Alanee et al. found an overall suicide risk of 1.2 among US TCS, and 1.5 if diagnosed <30 years of age.[150] Gunnes et al. reported that Norwegian TCS born 1965-85 and diagnosed before the age of 25, had a suicide HR of 2.9.[151]

2. Aims of the thesis

At the 2012 Oncological Forum in Norway, professor emeritus Olbjørn Harald Klepp presented worrying new preliminary data on the long-term RS of TGCT patients diagnosed in Norway compared to the general male population (Figure 12).

Figure 12. Preliminary relative survival data among testicular cancer patients diagnosed in Norway, as presented at the 2012 Oncological Forum in Norway by professor emeritus Olbjørn H. Klepp (used with permission). Survival in the general male population is always 100 %.



Arising from these data, the over-arching research questions of this PhD thesis became: How is the long-term RS among men diagnosed with TCGT in Norway, and what are the reasons behind the findings?

More specifically, the aims of this PhD thesis were

- To evaluate long-term RS among TCS diagnosed in Norway.
- To evaluate causes of excess mortality among TCS diagnosed in Norway.
- To evaluate long-term SC risk among TCS diagnosed in Norway using complete treatment information.

3. Materials and methods

3.1 Data sources

The Cancer Registry of Norway

All three studies included patient data registered in The Cancer Registry of Norway (CRN). This registry contains prospectively collected and compulsory reported data on all new cancer cases in Norway since 1953. Histopathology reports were collected if available. Additionally, some data on initial disease extent as well as the intended primary treatment were collected. CRN data quality was in a 2009 study considered to be high,[154] although information regarding treatment and follow-up are incomplete. Complete RT data have been registered in the CRN since 1997.

Morphology and topography were coded according to the International Classification of Diseases (ICD) for Oncology, 2nd edition since 1993. Prior to 1970, in-house coding systems were used. Between 1970 and 1993, morphology was coded according to the Manual of Tumor Nomenclature and Coding, whereas topography was coded according to ICD-7.[154]

The Norwegian Cause of Death Registry

Study I and II included data from the Norwegian Cause of Death Registry (NCDR). This registry contains information on cause of death for all deceased inhabitants of Norway since 1951, derived from mandatory death certificates. Causes of death were recorded using the ICD-6 to ICD-9 coding systems until 1996, afterwards the ICD-10 was used. Data quality is considered to be high.[155]

Statistics Norway

Statistics Norway is the national statistical institute of Norway, and the main provider of official statistics. Data for the generation of population life tables required for RS analyses in studies I and II were obtained from here.

Medical records

In study III, individual data on treatment and disease stage were obtained from Norwegian hospital medical records. Previously collected SWENOTECA data were used if available.

3.2 Statistics and study design

Study I

All deaths in the study population during the study period were obtained from the NCDR. To ensure unbiased estimates of RS, the method developed by Pohar-Perme et al. was used.[156] The reference group was the general male population in Norway, for which national population life tables were obtained. These were stratified by gender, five-year age groups and calendar year. Overlapping 95 % CIs between two groups would imply statistically non-significant differences between point estimates.

In addition, a test for comparing overall RS between two groups across a given follow-up time was performed, comparing TGCT patients by histology and age at diagnosis.[157] Because this test did not have an official name, but assumed a normal distribution, it was termed a Z test in study I.

The software used was Stata version 13, copyright StataCorp LLC.

Study II

Study population deaths and their cause, as well as deaths in the reference population, were obtained from the NCDR. The reference group constituted the general male population in Norway, as described for study I.

SMRs were calculated for most causes of death as defined in the NCDR shortlist.[2] This is based on the 2012 version of the European Shortlist for Causes of Death.[158] SMRs were also calculated by the three larger categories of non-TC death: SC, CVD and other causes including unknown. RS for all patients was calculated similarly as for study I, but stratified by cause of death category (TC, SC, CVD and other causes).

The software used was Stata/MP version 15.1, copyright StataCorp LLC.

Study III

To avoid immortal time bias (a period of follow-up during which, by design, the outcome of interest cannot occur),[159] treatment was analyzed as a time-varying covariate.

The crude probability of SC was estimated by the cumulative incidence using the Aalen-Johansen estimator.[160] Death from any cause was treated as a competing risk.

SIRs were calculated to evaluate the total and site-specific incidence of SC in the study population with the general male population in Norway as reference, matched by 5-year age groups and calendar year of follow-up. SIRs were calculated for all included TCS as well as the different treatment groups, for which the time-varying treatment exposure was taken into account.

The effect of treatment was analyzed using age-adjusted Cox regression models with follow-up time as the time scale and the surgery only group as reference.

The software used was Stata/MP version 14.2, copyright StataCorp LLC. A p-value <0.05 was considered statistically significant.

Study design

All three studies were historical population-based prospective cohort studies. Although these are registry studies, the CRN and NCDR collect data prospectively.

3.3 Ethics

Studies I and II did not require institutional review board approval because the analyses were based on deidentified registry data obtained by application.

Study III was approved by the Regional Committee for Medical and Health Research Ethics and the Data Protection Authorities at the University Hospital of North Norway. All eligible TCS still alive were sent a study information letter with the possibility to withdraw from participation (passive consent).

4. Summary of studies

4.1 Study I: "Long-term Relative Survival after Diagnosis of Testicular Germ Cell Tumor"

Background

Despite today's excellent prognosis for cure among TGCT patients, several studies have shown increased incidence and mortality of several conditions such as SC and CVD. These conditions often manifest several decades after successful TGCT treatment. Because most patients diagnosed with TGCT are younger than 40 years and are expected to live for decades more, their RS compared to the general male population has become a particular concern. Prior to this study there were no published studies on RS beyond 20 years of follow-up.

Aim

To analyze long-term RS among TGCT patients diagnosed in Norway during 1953 to 2012.

Methods

Data sources were the CRN and the NCDR. Clinical diagnoses of TGCT were allowed, but spermatocytic tumors and extragonadal germ cell tumors were excluded. Patients were classified by histology (seminoma vs nonseminoma), disease extent at diagnosis (localized to the testis vs

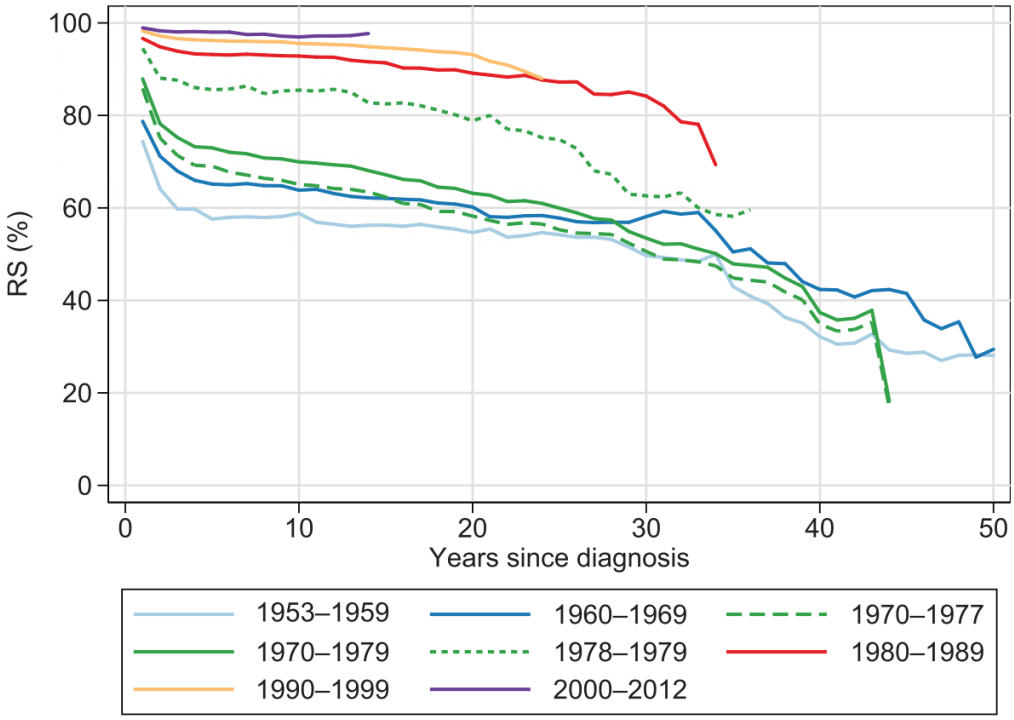
metastatic) and age at diagnosis (younger vs older than 40 years). They were also classified into six cohorts by decade of diagnosis. The first cohort comprised TGCT patients diagnosed 1953-59, the last 2000-2012. Patients diagnosed with localized melanoma <50 years during 1953-2012 were included for comparative purposes. Follow-up was until December 31st, 2013. RS was analyzed for all patients.

Results

Of the 8737 included TCGT patients, 4730 had seminoma and 3880 nonseminoma. Median follow-up ranged from 6.6 to 27.0 years by cohort of diagnosis. Median age at diagnosis was 36 to 40 years among seminoma patients and 27 to 30 years among patients with nonseminoma. About 82% and 61% of seminoma and nonseminoma patients were diagnosed with localized disease, respectively. By the end of follow-up, 2298 deaths had occurred.

RS, all patients: Overall, RS point estimates were highest in the 2000-2012 cohort of diagnosis, and lowest in the 1953-1959 cohort (Figure 13).

Figure 13. Relative survival point estimates for all testicular germ cell tumor patients by cohort of diagnosis and follow-up time. Survival in the general male population is always 100 %.[1]



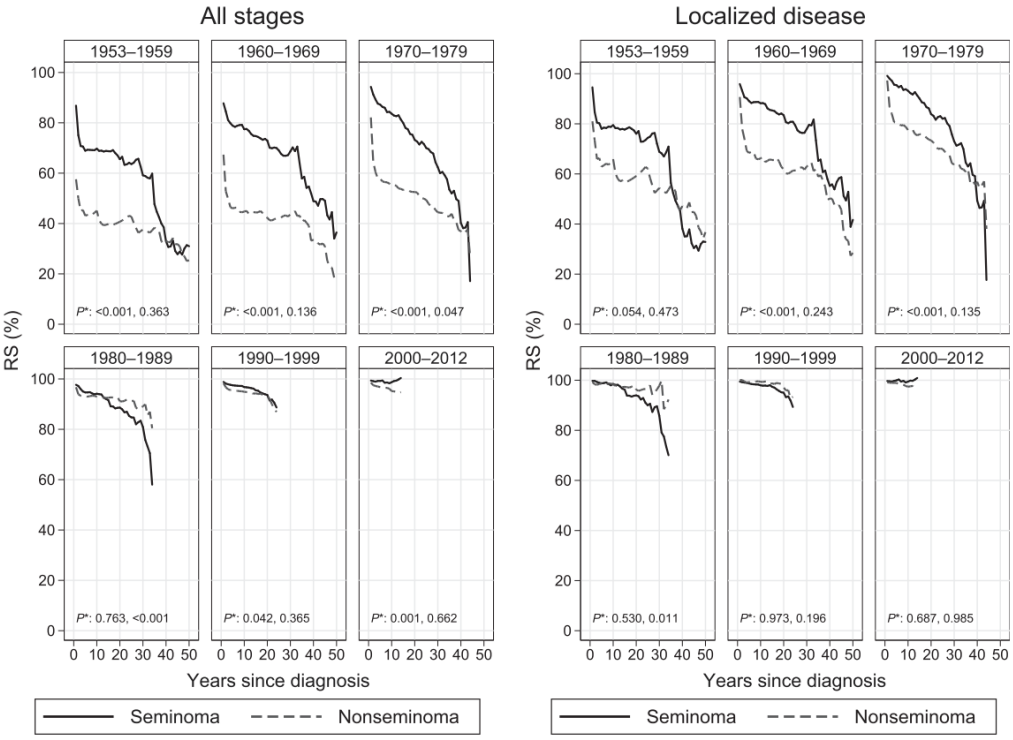
RS was significantly reduced among the TGCT patients compared to the general Norwegian male population, regardless of cohort of diagnosis and follow-up time. RS generally continued to decline with increasing follow-up time.

In the 1953-1979 cohorts, RS was reduced markedly during the first few years of follow-up before beginning to level off. An accelerated decline in RS was seen beyond 15-30 years of follow-up depending on cohort of diagnosis.

RS by histology: RS point estimates continued to decline with follow-up, except among seminoma patients diagnosed after 1999 (Figure 14). Point estimates for nonseminoma patients were generally inferior to seminoma patients regardless of follow-up time. Overall RS across the entire follow-up

period was statistically significantly superior among seminoma patients in all but the 1980-89 cohort.

Figure 14. Relative survival point estimates for all seminoma and nonseminoma patients (left) and localized disease at diagnosis only (right) by cohort of diagnosis and follow-up time.[1]



*, P-values, Z test comparing overall RS between seminoma and nonseminoma patients for all above patients and 5-year survivors only, respectively.

However, with increasing follow-up time, RS estimates declined more rapidly for seminoma patients than non-seminoma patients diagnosed <2000. Among 5-year TCS, overall RS was inferior for seminoma patients in the 1970-89 cohorts. In the other cohorts, overall RS was no longer statistically significantly different between seminoma and nonseminoma patients (Figure 14).

RS in localized TGCT: Although RS point estimates were improved among these patients, the continuing decline in RS with follow-up was still present (Figure 14). Overall RS remained statistically significantly superior for seminoma patients in the 1960-79 cohorts and for nonseminoma patients in the 1980-89 cohort (Figure 14).

This continuing decline in RS differed from the RS of 3995 patients diagnosed with localized melanoma before age 50, where such a long-term decline in RS was not seen beyond 10 years of follow-up.

RS by age at TGCT diagnosis: Overall RS was significantly inferior for patients diagnosed with TGCT after age 40 compared to those who were younger, regardless of TGCT histology. This was also true among 5-year survivors, including 5-year survivors of localized TGCT only. Differences in stage distribution between the two age categories were minor.

Conclusions

Despite the excellent prognosis for cure during the last few decades with generally improved RS, long-term RS continues to decline with increasing follow-up time. The main cause for this is likely treatment-induced late effects. In particular, the reduced long-term RS among patients diagnosed with localized seminoma during 1980 to 1999 could be due to the continued use of adjuvant RT in these patients as opposed to nonseminoma patients.

TGCT survivors should be closely monitored for the development of late comorbidities. Treatment regimens should be further optimized to reduce the risk of late effects but maintain the excellent cure rates. Further study of causes of long-term morbidity and mortality among TGCT patients is warranted.

4.2 Study II: "Causes of Inferior Relative Survival after Testicular Germ Cell Tumor Diagnosed 1953-2015: A population-based Prospective Cohort Study"

Background

TGCT patients and survivors have excess mortality compared to the general male population due to a variety of conditions, including SC and CVD. RS generally continues to decline with increasing follow-up, even beyond 25 years. The separate impact of deaths by TC, SC, CVD and other causes on RS has been scarcely studied, however.

Aim

To analyze causes of excess mortality among TGCT patients and TCS diagnosed in Norway during 1953-2015, and to examine the impact of these causes on RS.

Methods

Data sources were the CRN and the NCDR. Only TGCT cases confirmed by histopathological reports were allowed. Spermatocytic tumors and extragonadal germ cell tumors were excluded. Patients were followed until December 31st, 2015, death or emigration, whichever occurred first. They were, if data were available, classified by histology (seminoma vs nonseminoma), and by disease extent at diagnosis (localized to the testis vs metastatic). Furthermore, they were classified into three cohorts by time period of diagnosis: 1953-79, 1980-89 and 1990-2015.

SMRs were calculated by cause of death except those of TC. RS was calculated for all TGCT patients by histology, disease extent at diagnosis, follow-up time and cause of death category (TC, non-TC SC, CVD and other causes).

Results

Of 9541 included TCGT patients, 5278 had seminoma and 4126 nonseminoma. Median follow-up time was 23.5 years for patients diagnosed <1980, 28.9 years when diagnosed in the 1980s and 10.0 years for patients diagnosed in 1990 or later. In 79 % of seminoma patients and 60 % of nonseminoma patients, the disease was localized at diagnosis.

At the end of follow-up, 816 TC and 1508 non-TC deaths had occurred. Compared to the reference population, there were 402 non-TC excess deaths in the study population, resulting in an overall non-TC SMR of 1.36 (95 % CI 1.30-1.44).

TC mortality: During the first five years after diagnosis, 80 % of study population deaths were caused by TC, during which time 90 % of all TC deaths occurred. TC deaths were more common among patients diagnosed before 1980, among nonseminoma patients and in metastatic disease at diagnosis.

SC mortality: SC caused 262 (65 %) of excess non-TC deaths (Table 13). The overall SC SMR was 1.84 (95 % CI, 1.74-2.06), ranging from 1.39 (95 % CI, 1.08-1.35) among TCS diagnosed >1989 to 2.00 (95 % CI, 1.79-2.23) among TCS diagnosed <1980.

Table 13. Selected second cancer standardized mortality ratio point estimates for all testicular germ cell tumor patients by cohort of diagnosis. Statistically significant results are highlighted in bold. More detailed SMR data stratified by histology and disease extent at diagnosis (with 95 % confidence intervals) can be found in Supplementary Table S3 of study II.[2]

Cause of death[a]	Cohort of diagnosis								
	1953-1979			1980-1989			1990-2015		
	O	SMR	SMR by follow-up time[b]	O	SMR	SMR by follow-up time	O	SMR	SMR by follow-up time
Testicular cancer	617			76			123		
All non-TC causes	901	**1.42**	A(**1.34**),B(**1.42**) C(**1.46**),D(**1.41**)	319	**1.36**	A(**1.26**),B(**1.38**) C(**1.51**),D(**1.39**)	288	**1.21**	A(**1.21**),D(**1.17**)
All non-TC second cancers	342	**2.00**	A(**1.70**),B(**2.12**) C(**2.05**),D(**2.03**)	135	**1.90**	A(**1.57**),B(**1.94**) C(**2.26**),D(**1.90**)	98	**1.39**	A(**1.27**),B(**1.77**) D(**1.45**)
MN, lip, oral cavity, pharynx	3	0.99		5	**3.44**	A(**5.79**),D(**2.96**)	2	1.44	
MN, esophagus	7	1.99	C(**2.74**)	1	0.55		5	**2.61**	B(**7.64**),D(**3.30**)
MN, stomach	31	**2.62**	B(**4.29**),C(**2.64**) D(**2.89**)	13	**3.98**	A(**4.78**),C(**4.65**) D(**4.52**)	5	1.90	B(**5.23**),D(**2.58**)
MN, colorectal, anus	44	**1.95**	C(**2.25**),D(**2.89**)	11	1.17	C(**2.36**)	6	0.65	
MN, liver, intra-hepatic bile ducts	11	**5.68**	B(**8.92**),C(**6.22**) D(**5.93**)	1	0.91		2	1.34	
MN, pancreas	28	**2.97**	B(**4.11**),C(**3.50**) D(**3.10**)	18	**4.31**	B(**6.45**),C(**3.96**) D(**4.35**)	8	1.85	
MN, trachea, bronchus, lung	47	1.25	A(**2.02**)	32	**1.89**	A(**1.82**),B(**2.30**) D(**1.96**)	14	0.87	
Melanoma	10	**2.53**	B(**5.53**),D(**2.63**)	3	1.18		6	2.00	
MN, prostate	39	**1.46**	A(**2.43**),C(**1.53**) D(**1.42**)	7	0.83		9	1.30	
MN, kidney	13	**2.64**	C(**3.29**),D(**2.76**)	1	0.46		2	0.91	
MN, bladder	18	**2.71**	A(**4.03**),B(**2.96**) C(**2.32**),D(**2.64**)	10	**4.74**	B(**3.44**),C(**10.3**) D(**5.10**)	4	2.32	B(**4.73**)
MN, brain and CNS	9	**2.06**	B(**3.41**)	2	0.67		8	**1.98**	A(**2.46**),D(**2.39**)
Hodgkin, lymphoma	6	1.32		1	0.44		2	0.97	
Leukemia	8	1.60		3	1.59		6	**3.47**	A(**3.83**),D(**3.04**)
MN, other lymphoid / hematopoietic tissue[c]	9	**1.89**	A(**3.91**),D(**2.16**)	2	1.65		1	0.71	
MN, other (no TC deaths)	59	**3.50**	A(**2.31**),B(**3.08**) C(**4.20**),D(**3.55**)	24	**3.68**	A(**2.35**),B(**4.39**) C(**4.78**),D(**3.37**)	17	**2.72**	A(**2.43**),B(**3.83**) D(**2.63**)

CI, confidence interval; O, observed deaths in the study population; MN, malignant neoplasm; SMR, standardized mortality ratio; TC, testicular cancer. [a] For details, see Supplementary Table S1 in study II.[2] [b] Subgroups with statistically significant SMRs pertaining to follow-up time, given in parentheses: A, <16 years follow-up only; B, 16-<26 years follow-up only; C, ≥26 years follow-up only; D, >5 years follow-up only.

Overall, gastrointestinal and non-TC genitourinary cancer caused 38 % and 15 % of excess SC deaths, respectively. Cancers of the stomach, pancreas and bladder caused 34 % of all excess SC deaths. SMRs for the "other malignant neoplasms" group of cancers were about threefold elevated. This group included sarcomas, for which SMRs were not specifically calculated.

TCS diagnosed before 1980 had elevated SMRs between 1.46 and 5.68 for most cancer forms including brain/central nervous system (CNS) and prostate cancer, but not lymphoma or leukemia. For most cancer forms, SMRs were also elevated beyond 26 years of follow-up (Table 13). The

SMR for esophageal cancer became elevated beyond 26 years of follow-up, and for lung cancer it was elevated among TCS with less than 16 years of follow-up.

TCS diagnosed in the 1980s had about fourfold elevated SMRs for cancers of the bladder, pancreas, stomach and lip/oral cavity/pharynx. There was also an about twofold elevated SMR for lung cancer. For most of these cancer forms, the SMRs were elevated beyond 26 years of follow-up Also, the SMR for cancer of the large intestine became elevated after this time. The subgroup of patients diagnosed with localized nonseminoma did not have an overall excess SC SMR, but it was twofold increased among patients diagnosed with localized seminoma or with metastatic TGCT.[2]

TCS diagnosed in 1990 or later had a twofold elevated SMR for brain/CNS cancer and about threefold elevated SMRs for esophageal cancer and leukemia. Also, SMRs for stomach and bladder cancer became about fivefold elevated beyond 16 years of follow-up. The overall SC SMR was elevated at 1.5 among patients diagnosed with localized seminoma and 2.2 among patients diagnosed with metastatic nonseminoma. It was not significantly elevated among patients with localized nonseminoma or metastatic seminoma.[2]

CVD mortality: CVD caused 35 (9 %) of excess non-TC deaths (Table 14). About nine of ten excess CVD deaths occurred in patients diagnosed with metastatic TGCT.

Table 14. Selected cardiovascular disease standardized mortality ratio point estimates for all testicular germ cell tumor patients by cohort of diagnosis. Statistically significant results are highlighted in bold. More detailed SMR data stratified by histology and disease extent at diagnosis (with 95 % confidence intervals) can be found in Supplementary Table S3 of study II.[2]

Cause of death	Cohort of diagnosis								
	1953-1979			1980-1989			1990-2015		
	O	SMR	SMR by follow-up time[a]	O	SMR	SMR by follow-up time	O	SMR	SMR by follow-up time
Cardiovascular disease	300	**1.12**	D(**1.14**)	81	1.07		59	0.96	
Ischemic heart diseases	169	1.06		52	1.21		30	0.92	
Acute MI	119	1.06		39	1.34	A(**1.51**)	18	0.84	
Non-ischemic heart diseases	50	**1.59**	B(**1.86**),C(**1.55**) D(**1.59**)	16	1.42		13	1.25	
Cerebrovascular disease	44	0.88		5	0.37		13	1.20	
Other circulatory diseases	37	**1.39**	D(**1.40**)	8	1.02		3	0.45	

CI, confidence interval; MI, myocardial infarction; MN, malignant neoplasm; O, observed deaths in the study population; SMR, standardized mortality ratio; TC, testicular cancer. [a] Subgroups with statistically significant SMRs pertaining to follow-up time, given in parentheses: A, <16 years follow-up only; B, 16-<26 years follow-up only; C, ≥26 years follow-up only; D, >5 years follow-up only.

Among TCS diagnosed before 1980, the CVD SMR was 1.12 (95 % CI, 1.00-1.26), increasing to 1.88 among patients with metastatic TGCT at diagnosis. The SMR for non-ischemic heart diseases was 1.59, also significant beyond 26 years of follow-up. For the subgroup of other circulatory diseases (including pulmonary embolism, aortic diseases, hypertensive disorders and rheumatic heart disease) the SMR was 1.39.

TCS diagnosed in the 1980s had an SMR for MI of 1.5 with less than 16 years of follow-up, or if they had been diagnosed with localized seminoma.[2] TCS diagnosed with metastatic seminoma had an about fivefold elevated SMR for non-ischemic heart diseases.

Among TCS diagnosed >1989, the only significant CVD SMR was among patients diagnosed with metastatic nonseminoma with less than 16 years of follow-up.[2]

Other cause mortality: Deaths by non-cancer and non-CVD causes were responsible for 105 (26%) of excess non-TC deaths (Table 15). Digestive and genitourinary diseases caused 58% of excess deaths in this category.

Table 15. Selected standardized mortality ratio point estimates for non-malignant, non-cardiovascular disease causes for all testicular germ cell tumor patients by cohort of diagnosis. Statistically significant results are highlighted in bold. More detailed SMR data stratified by histology and disease extent at diagnosis (with 95 % confidence intervals) can be found in Supplementary Table S3 of study II.[2]

Cause of death	Cohort of diagnosis								
	1953-1979			1980-1989			1990-2015		
	O	SMR	SMR by follow-up time[a]	O	SMR	SMR by follow-up time	O	SMR	SMR by follow-up time
All non-cancer, non-CVD causes	259	**1.34**	A(**1.53**),C(**1.32**) D(**1.24**)	103	1.19	D(**1.24**)	131	**1.23**	A(**1.25**)
Infectious / parasitic	8	1.12		6	1.82		10	**3.06**	A(**3.64**),D(**2.47**)
Endocrine, nutr., metab.[b]	15	1.50	B(**2.66**)	10	**2.06**	D(**1.99**)	3	0.54	
Nervous system, senses	15	1.07		3	0.45		13	**1.72**	A(**2.08**)
Alzheimer's disease	2	0.73		0	0		4	**3.85**	A(**5.68**),D(**4.64**)
Respiratory system diseases	44	0.88		14	0.89		10	0.74	
Other respiratory[c]	3	0.77	A(**4.87**)	5	**3.35**	A(**6.80**),B(**4.63**) D(**3.48**)	1	0.71	
Digestive system diseases	50	**2.83**	B(**3.20**),C(**3.26**) D(**2.88**)	19	**2.51**	B(**3.44**),D(**2.64**)	9	1.21	
Jejunal and stomach ulcers	11	**3.78**	B(**6.09**),C(**3.23**) D(**3.31**)	1	1.30		2	3.32	
Cirrhosis, fibrosis, hep.[d]	5	1.02		8	**2.57**	A(**2.83**),D(**2.91**)	3	0.96	
Other digestive diseases	34	**3.64**	B(**3.95**),C(**4.20**) D(**3.82**)	10	**2.98**	B(**4.40**),D(**2.89**)	4	1.24	
Genitourinary diseases	21	**2.31**	C(**2.70**),D(**2.50**)	2	0.87		7	**3.76**	A(**5.18**),D(**2.70**)
External causes of death	36	0.94		27	1.14		58	**1.47**	A(**1.33**),B(**2.48**) D(**1.49**)
Accidents	25	0.90		17	1.15		35	**1.46**	B(**2.59**),D(**1.53**)
Suicide	10	1.02		10	1.23		22	**1.54**	

O, observed deaths in the study population; MN, malignant neoplasm; SMR, standardized mortality ratio; TC, testicular cancer. [a] Subgroups with statistically significant SMRs pertaining to follow-up time, given in parentheses: A, <16 years follow-up only; B, 16-<26 years follow-up only; C, ≥26 years follow-up only; D, >5 years follow-up only. [b] Endocrine, nutritional and metabolic diseases. [c] Subgroup including upper respiratory tract conditions but also unspecified acute lower respiratory tract infections and pneumonitis of various cases. [d] Chronic hepatitis

Among TCS diagnosed before 1980, there was a threefold excess mortality from digestive system diseases, including ulcers of the jejunum and stomach. These findings were also significant beyond 26 years of follow-up (Table 15). SMR for genitourinary diseases was about twofold elevated, as were the "other respiratory diseases" subgroup with less than 16 years of follow-up as well as endocrine / nutritional diseases between 16 and 26 years of follow-up.

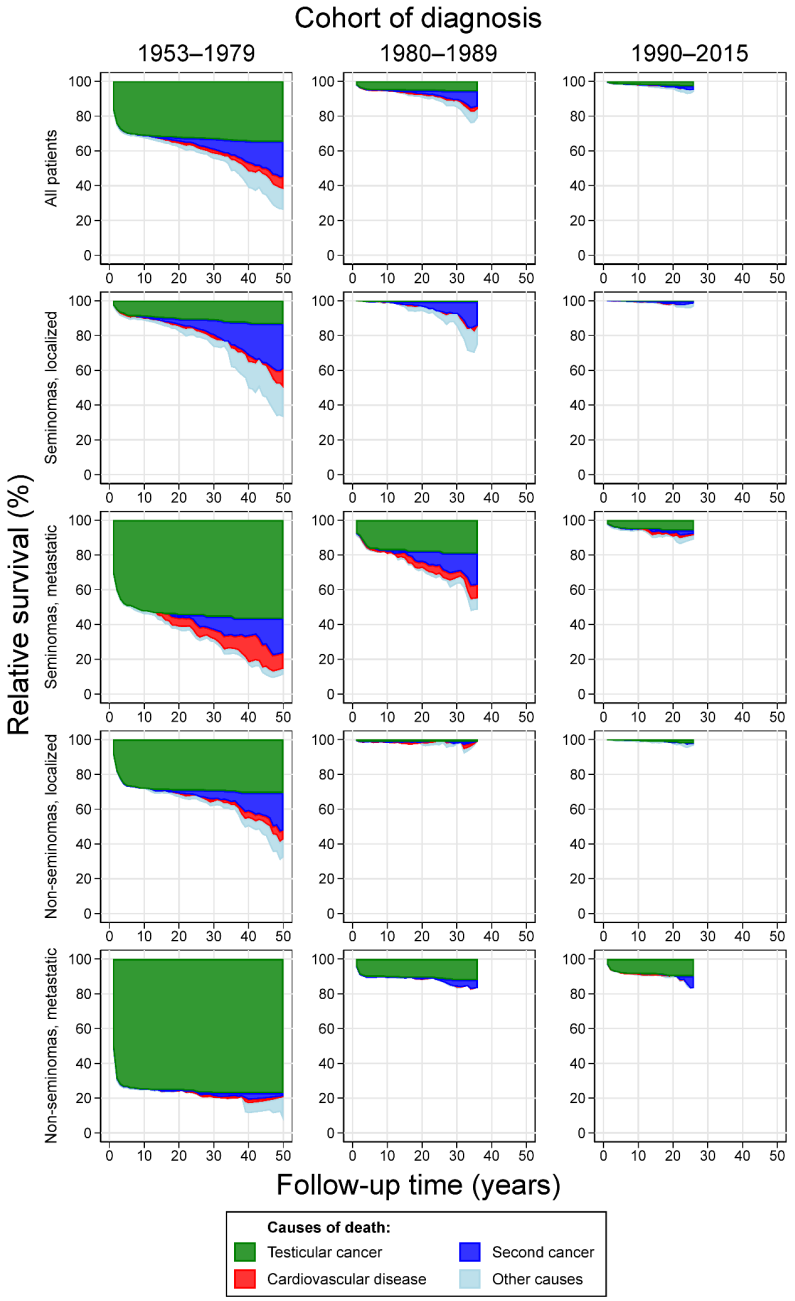
TCS diagnosed in the 1980s had excess SMRs for digestive system diseases including liver disease, the subgroup of "other respiratory diseases" as well as endocrine / nutritional diseases.

Among TCS diagnosed in 1990 or later, there was an almost fourfold elevated SMR for genitourinary diseases. Also, there was an SMR of 1.5 for deaths due to accidents or suicide. Furthermore, the SMR for infection was increased threefold and nervous system disorders almost twofold. Among the latter, the SMR for Alzheimer's disease was almost fourfold elevated.

Mortality among 5-year TGCT survivors: In general, when restricting SMR analyses to 5-year TGCT survivors, only minor changes in SMRs were seen compared to those of the entire study population (Tables 13-15). For TCS diagnosed after 1989, SMRs for suicide and nervous system diseases were no longer significantly elevated. Conversely, the SMR for stomach cancer became elevated (2.58).

RS by cause of death category: RS improved significantly from the first to the last cohort of diagnosis, but generally continued to decline with increasing follow-up time (Figure 15). During the first five years after diagnosis, TC was the main cause of reduced RS. Beyond this time, non-TC causes of death gradually became dominant, and the most important cause was SC. TCS diagnosed with localized seminoma after 1979 had elevated non-TC SMRs as opposed to nonseminoma patients, contributing to inferior RS in this group of patients.

Figure 15. Point estimates for relative survival among testicular germ cell tumor patients diagnosed in Norway, by histology and disease extent at diagnosis, with cause of death category. Survival in the reference population is always 100 %.[2]



Conclusions

TC remains the main cause of reduced RS among TGCT patients during the first five years after TGCT diagnosis, even though the prognosis has improved significantly since 1980. Beyond five years of follow-up, malignant and non-malignant conditions of the gastrointestinal and genitourinary organs are among the main causes of excess mortality and a continuing decline in long-term RS. CVD is a comparatively minor cause. Most excess long-term deaths are probably related to chemotherapy and/or RT, although innate or genetic causes cannot be ruled out. Elevated non-TC SMRs among TCS diagnosed with localized seminoma after 1979 could be due to the contemporary use of RT in these patients. Excess mortality among patients diagnosed after 1989, including suicide, is a particular concern. Continuing optimization of treatment and follow-up schemes is required, as well as research on identifying subgroups of TGCT patients at particular risk of excess mortality.

4.3 Study III: "Continuing Increased Risk of Second Cancer in Long-term Testicular Cancer Survivors after Treatment in the Cisplatin Era"

Background

TGCT patients have a 15-year RS rate of 98 % in Norway, but RS continuously declines beyond 20 years of follow-up. One explanation is SC, for which previous studies have shown a 1.7 to 3.5-fold increased risk compared to the general population. This risk has been associated with chemo- and/or RT but not surgery alone. However, there is a lack of studies on SC risk after the introduction of cisplatin in the late 1970s. Also, there is a lack of studies based on complete individual treatment information.

Aim

To investigate the risk of non-germ cell SC among TCS treated in the cisplatin era, by 1) comparing the incidence of SC to that of the general population and 2) investigating SC risk according to treatment modality (surgery, RT, chemotherapy and the surveillance strategy).

Methods

Men older than 16 years diagnosed with histologically verified TGCT in Norway during 1980-2009 were identified through the CRN. Follow-up started 12 months after TGCT diagnosis and ended at time of death, emigration or end of 2016. Information on disease stage, histology and treatment was abstracted from medical records. SIRs for SC by treatment modality compared with the general population as well as HRs by treatment intensity compared with surgery alone were calculated.

Results

Study cohort: Of the included 5625 one-year survivors of first primary TGCT, 2942 (52 %) had seminoma and 2683 nonseminoma. Of these, 4435 patients were followed for 10 years or more. CS1 disease was initially diagnosed in 71% of patients. Median age at diagnosis was 36.7 years for seminoma patients and 28.8 years for patients with nonseminoma. Median follow-up time was 16.6 years. Overall, 25 % of patients were treated with surgery only, 44 % with chemotherapy, 27 % with RT and 3.9 % with both chemotherapy and RT.

During the study period, the proportion of men receiving adjuvant chemotherapy in CS1 disease increased from 7.6 to 47%, while surveillance usage increased from 5.9 to 37%.

SC risk among TCS compared with the general population: In total, 572 TCS developed one or more non-germ cell SC. The crude cumulative probability of SC accelerated beyond 15-20 years of follow-up, to 15.2% at 25 years.

The overall SIR of developing a solid SC or hematological malignancy was 1.44 (95 % CI, 1.32-1.57) or 1.31 (95 % CI, 1.00-1.71), respectively (Table 16).

Table 16. Selected point estimates for second cancer standardized incidence ratios among 1-year testicular cancer survivors.[3]

Cancer SIRs (O=observed cases)	Treatment modality				
	Total	Surgery only	Chemotherapy	RT	Chemo + RT
Total SC	**1.58** (O=572)	**1.28** (O=96)	**1.62** (O=174)	**1.64** (O=270)	**2.14** (O=32)
All solid cancers	**1.44** (O=529)	1.16 (O=88)	**1.52** (O=161)	**1.49** (O=252)	**1.81** (O=28)
Ear, nose, throat	1.16 (O=19)	0.92 (O=3)	1.44 (O=7)	7.60 (O=9)	(O=0)
Esophagus	1.50 (O=8)	1.87 (O=2)	2.61 (O=4)	0.80 (O=2)	(O=0)
Stomach	**2.19** (O=21)	1.05 (O=2)	0.39 (O=1)	**2.56** (O=12)	**12.98** (O=6)
Small intestine	**4.29** (O=11)	3.74 (O=2)	**3.73** (O=3)	**4.43** (O=5)	**10.48** (O=1)
Colorectal	**1.27** (O=69)	1.01 (O=11)	1.46 (O=22)	1.32 (O=34)	0.86 (O=2)
Liver and bile ducts	**2.11** (O=12)	1.70 (O=2)	0.58 (O=1)	**3.13** (O=8)	4.49 (O=1)
Pancreas	**2.77** (O=28)	1.98 (O=4)	1.09 (O=3)	**3.90** (O=19)	**4.54** (O=2)
Lung, trachea, bronchi	**1.54** (O=67)	0.95 (O=8)	**2.04** (O=23)	**1.47** (O=32)	2.01 (O=4)
Melanoma	**1.49** (O=42)	**1.94** (O=12)	**1.86** (O=18)	0.91 (O=11)	0.93 (O=1)
Skin, other	1.46 (O=24)	0.88 (O=3)	1.39 (O=6)	1.63 (O=13)	2.69 (O=2)
Soft tissue	**2.33** (O=6)	1.80 (O=1)	1.14 (O=1)	2.85 (O=3)	**10.51** (O=1)
Prostate	1.08 (O=122)	1.02 (O=23)	1.08 (O=33)	1.14 (O=63)	0.64 (O=3)
Kidney, upper urinary	**1.94** (O=37)	0.76 (O=3)	**2.22** (O=13)	**2.23** (O=19)	2.70 (O=2)
Bladder	**2.25** (O=57)	0.78 (O=4)	**2.97** (O=20)	**2.42** (O=30)	2.66 (O=3)
Brain	1.24 (O=28)	1.42 (O=7)	1.50 (O=12)	1.02 (O=9)	(O=0)
Thyroid	**2.81** (O=10)	**4.95** (O=4)	1.5 (O=2)	2.31 (O=3)	**8.51** (O=1)
Other, ill-defined	**2.02** (O=10)	1.03 (O=1)	3.30 (O=4)	1.99 (O=5)	(O=0)
All hematological	**1.31** (O=53)	1.05 (O=9)	1.18 (O=15)	1.36 (O=24)	**3.23** (O=5)
Lymphoma	1.31 (O=27)	1.36 (O=6)	0.74 (O=5)	1.50 (O=13)	**3.96** (O=3)
Leukemia	1.43 (O=15)	0.46 (O=1)	1.55 (O=5)	1.51 (O=7)	**4.86** (O=2)

Chemo, chemotherapy; RT, radiotherapy; SIR, standardized incidence ratio

SC SIRs were 1.6-fold increased after chemotherapy or RT, and 2.14-fold increased if the patient had received both modalities. Site-specific excess mortality from cancers of the small intestine, lung, kidney and bladder occurred after either modality. After RT alone, there was also excess risk of stomach and liver cancer, while chemotherapy alone was associated with excess risk of melanoma and pancreatic cancer. Among patients who received both modalities, excess risk of hematological malignancies, cancers of the thyroid, soft tissue, stomach and small intestine emerged.

The risk of SC was also increased after surgery only (SIR: 1.28), with increased site-specific risks of thyroid cancer and melanoma. Among TCS intended for surveillance, the SC SIR was 1.34, with significantly increased risk of thyroid cancer.

SC risks by age at first TGCT treatment, follow-up time and attained age at first SC diagnosis: The SIRs generally declined with increasing age at first treatment, but increased with increasing follow-up time (Table 17). Overall, SC SIRs were relatively similar at 1.6 regardless of attained age at first SC diagnosis. Unlike for the other treatment groups, the increased SC risk after surgery alone was only seen when the SC was diagnosed <40 years of age.

Table 17. Selected standardized incidence ratio point estimates by age at first treatment, follow-up time and age at first second cancer diagnosis. Statistically significant results are shown in bold.[3]

		SIR				
		Total	Surgery only[1]	Chemo	RT	Chemo + RT
Age at first treatment (y)	<20	**2.29** (O=7)	(O=0)	**3.17** (O=6)	(O=0)	**8.00** (O=1)
	20-30	**1.95** (O=88)	**1.69** (O=18)	**1.76** (O=36)	**2.27** (O=28)	**3.75** (O=6)
	30-40	**1.65** (O=164)	0.96 (O=19)	**1.73** (O=53)	**1.86** (O=88)	1.97 (O=8)

	40-50	**1.55** (O=155)	**1.74** (O=28)	**1.44** (O=39)	**1.44** (O=75)	**2.95** (O=13)
	>50	**1.39** (O=157)	1.15 (O=30)	**1.45** (O=40)	**1.52** (O=83)	0.83 (O=4)
Follow-up time (y)	<10	**1.28** (O=141)	**1.52** (O=43)	1.28 (O=48)	1.03 (O=42)	**2.38** (O=8)
	10-20	**1.58** (O=217)	1.16 (O=30)	**1.48** (O=56)	**1.80** (O=122)	1.58 (O=9)
	20-30	**1.81** (O=175)	1.10 (O=19)	**2.11** (O=56)	**1.81** (O=87)	**2.59** (O=13)
	30-37	**2.12** (O=39)	1.04 (O=4)	**2.41** (O=14)	**2.43** (O=19)	2.12 (O=2)
Age at first SC diagnosis (y)	<40	**1.65** (O=31)	**2.16** (O=11)	1.41 (O=13)	1.52 (O=6)	2.28 (O=1)
	40-60	**1.59** (O=244)	1.27 (O=40)	**1.68** (O=91)	**1.56** (O=98)	**2.71** (O=15)
	60-75	**1.55** (O=236)	1.26 (O=37)	**1.45** (O=54)	**1.64** (O=130)	**2.18** (O=15)
	75-90	**1.64** (O=61)	0.87 (O=8)	**2.27** (O=16)	**1.91** (O=36)	0.47 (O=1)

Chemo, chemotherapy; O, observed cases; RT, radiotherapy; SIR, standardized incidence ratio; y, years

SC risks by histology and treatment group compared to surgery only: The crude cumulative probability of SC at 25 years were 28% and 11% for survivors of seminoma and nonseminoma, respectively. These were not significantly different after correcting for age. Compared to surgery only, SC generally increased with observation time in all treatment groups.

Among 10-year TCS compared with surgery only, there was a 5-fold excess risk of bladder cancer after chemotherapy or RT, a 7.6-fold excess risk of kidney cancer after RT and a 24-fold excess risk of stomach cancer after combined chemo- and RT.

SC risks by treatment intensity: Among 10-year TCS who had received ≥2 cycles of CBCT, there was a 1.6- to 2.1-fold increased SC risk compared to surgery only (Table 18). A similar risk was seen for solid SC, but not for hematological malignancies.

Table 18. Selected point estimates for second cancer hazard ratios by treatment intensity among 10-year testicular cancer survivors with more than 10 years of observation time.[3]

		HR	
		Total SC	Solid SC
CBCT cycles	Surgery only	1 (ref)	1 (ref)
	1	0.41	0.47
	2	**1.91**	**2.19**
	3	1.41	1.24
	4	**1.60**	**1.73**
	>4	**2.09**	**2.19**
	Carboplatin	1.17	2.54
	Other	2.21	1.77
RT field	Surgery only	1	1
	L-field	**1.66**	**1.76**
	Para-aortic	1.65	1.73
	Other	**4.40**	**5.06**
RT dose for first abdominal RT field	Surgery only	1	1
	20-29 Gy	**1.88**	**2.01**
	30-39 Gy	**1.71**	**1.80**
	≥40 Gy	1.42	1.50

CBCT, cisplatin-based chemotherapy; Gy, Gray; HR, hazard ratio; ref, reference category; RT, radiotherapy; SC, second cancer

Both the L-field and PA RT techniques were associated with a 1.7-fold increased SC risk, although not significantly so for the latter. SC risks were also increased 1.7- to 1.8-fold after RT doses of 20-39 Gy to the first abdominal field, but there was no linear trend between radiation dose and SC risk.

Conclusions

While increased SC risks were seen after CBCT and/or RT, there was also a smaller but significantly increased SC risk among TCS treated with surgery only, with site-specific increased risks of thyroid cancer and melanoma. Treatment with CBCT led to a significantly increased site-specific risk of cancers of the small intestine, lung, melanoma, kidney or bladder. Two or more cycles of CBCT led to increased SC risk. CT and RT combined were associated with particularly high risk. In addition to form of treatment, genetic and environmental factors may be of importance for SC risk. Promotion and guidance for a healthy lifestyle should be emphasized. Health care professionals must be aware of the increased SC risks among TCS.

5. Discussion

5.1 Summary of main findings

This PhD thesis has given valuable new insight regarding RS and SC risk among TGCT patients diagnosed in Norway. Study I provided the first published RS data beyond 20 years of follow-up, confirming the preliminary data presented by Olbjørn H. Klepp (Figure 12). Study II was the first to examine the impact of different causes of death on long-term RS. With access to full treatment history, study III provided the most detailed analysis of SC risks available for TGCT patients diagnosed in the cisplatin era.

Novel findings included a continuing decline in RS among men diagnosed with TGCT, even beyond 30 years of follow-up.[1] This long-term decline was most pronounced among seminoma patients. The most important long-term cause was SC, with elevated SMRs even beyond 26 years of follow-up as well as among 5-year survivors. Excess mortality from cancers of the prostate, kidney, CNS, esophagus, large intestine and liver had not been found previously, nor had excess mortality from nervous system disorders including Alzheimer's disease.[2]

Excess overall SC risk after surgery only and among TCS intended for surveillance were also novel findings, with site-specific risks of melanoma and thyroid cancer.[3]

5.2 Testicular cancer-specific mortality

The inferior TC-specific survival among TGCT patients diagnosed before 1980 can largely be explained by comparatively less effective treatment regimens, subsequently leading to lower cure rates (Figure 15). Of particular importance is CBCT which became available in Norway in May, 1978.

Even among TGCT patients diagnosed with localized disease before 1980, there was a significant number of TC-specific deaths during the first five years of follow-up (Figure 15). This is unexpected in true localized disease. A likely explanation is a relative lack of diagnostic accuracy. For instance, CT scanners were not available during the first part of this time period. Thus, some patients may have been understaged.

The improved TC-specific survival among TGCT patients diagnosed in 1980 or later mirrors the reported increases in PFS during the last decades (Table 5). This trend is probably mainly due to the introduction of CBCT. Increased emphasis on standardized diagnosis, optimized treatment and

follow-up are also important factors.[8] Advances in general health care and living standards likely have contributed to increased OS, although it would probably have less impact on RS as the same advances would be expected to benefit the reference population.

TGCT patients are at the highest risk of relapse within two years of treatment.[83] Rates are highly dependent upon stage and treatment.[46] In study III we found a total relapse rate of 8.6 %, and 16 % among patients intended for surveillance. Late TGCT relapses are defined as occurring two or more years after successful treatment, with reported frequencies of 1-6 % across studies.[83] The most frequent area of relapse is the retroperitoneum.

Some patients may have died due to a metachronous TC, for which we did not differentiate in study II. Recently, Hellesnes et al. reported a decreasing risk of metachronous TC by number of CBCT cycles, statistically significant after two or more cycles.[32] A recent Dutch study showed similar results.[161] CBCT may therefore also have contributed to reduced mortality from metachronous TC.

5.3 Second cancer risk and mortality

Overall second cancer risk and mortality

A twofold elevated SC SMR among TCS diagnosed before 1980 was in line with previous reports, which had shorter median follow-up times (Table 10).

Among TCS diagnosed in 1980 or later, our finding of 58 % excess SC risk was in agreement with previous reports (Table 7). Also, this finding correlated with elevated overall SC SMRs of 1.39-1.90 in study II, depending on cohort of diagnosis. Kier et al.[114], Groot et al.[126] (Table 10) and Sung et al.[127] reported comparable overall SC SMRs, although our study II lacked treatment data.

Hellesnes et al. very recently examined causes of death among 5707 TCS diagnosed in Norway during 1980-2009, using complete individual TGCT treatment information.[162] The median follow-up time was 18.7 years. An overall SC SMR of 1.53 (95 % CI, 1.35-1.73) was found (Table 19). SMRs were elevated after platinum-based chemotherapy (PBCT) (1.43, 95 % CI 1.12-1.83), RT (1.59, 95 % CI, 1.34-1.89) and combined treatment (3.24, 95 % CI 2.17-4.83) but not surgery alone. These findings strongly suggest that chemo- and RT are important factors for SC mortality.

Table 19. Selected standardized mortality ratio point estimates for overall and site-specific second cancer by treatment group among patients diagnosed with testicular germ cell tumor in Norway, 1980-2009. Statistically significant results are given in bold. Adapted and abbreviated.[162]

Cause of death	Total		Surgery		PBCT		RT		PBCT + RT	
	n	SMR	n	SMR	n	SMR	n	SMR	n	SMR
Total non-TC second cancer	257	**1.53**	39	1.13	64	**1.43**	130	**1.59**	24	**3.24**
Lip, oral cavity, pharynx	9	**3.89**	0	0	4	**6.78**	5	**4.28**	0	0
Esophagus	7	**2.29**	3	**4.83**	3	**3.72**	1	0.66	0	0
Stomach	18	**2.92**	3	2.45	1	0.69	10	**3.15**	4	**12.9**
Colon, rectum, anus	29	1.31	3	0.66	10	1.73	15	1.38	1	1.01
Liver and intrahepatic bile ducts	5	1.75	1	1.67	0	0	4	**3.02**	0	0
Pancreas	33	**3.20**	5	2.40	3	1.10	22	**4.36**	3	**6.86**
Trachea, bronchus, lung	49	1.26	3	0.39	17	**1.69**	25	1.28	4	2.30
Melanoma	8	1.38	3	2.52	1	0.59	3	1.12	1	4.43
Prostate	14	0.78	1	0.26	3	0.79	7	0.74	3	**3.27**
Kidney	5	1.26	2	2.53	1	1.03	2	0.99	0	0
Bladder	16	**4.17**	1	1.23	5	**6.33**	10	**4.91**	0	0
Brain and central nervous system	10	1.32	3	1.89	5	2.07	2	0.61	0	0
Lymphoma	5	1.12	3	**3.45**	0	0	1	0.43	1	4.83
Leukemia	8	**2.09**	0	0	3	**3.26**	4	2.04	1	5.74

PBCT, platinum-based chemotherapy; RT, radiotherapy; SMR, standardized mortality ratio; TC, testicular cancer

The increase in SC risk with younger age at TGCT diagnosis correlated with previous findings by Travis et al.[109] Hellesnes et al. recently reported a similar finding pertaining to mortality.[162] This is perhaps not so surprising since cancer risk and mortality increases with age in the general population as well, thus requiring a proportionally higher number of excess cases among TCS of the same age to similarly affect SIRs or SMRs.

There have been concerns that ionizing radiation exposure from diagnostic imaging increases the risk of SC,[163] although studies on TC patients have yielded conflicting results.[164, 165] A recent study showed that patients on surveillance were at no excess SC risk when followed on a program including five CT scans.[114] SWENOTECA recommends MRI as opposed to CT scans during follow-up to avoid exposing patients to this potential risk.[37]

A possible general explanation for excess SC mortality is that survival of SC may be inferior to that of a comparable primary cancer.[166] Prior treatment for TC may limit subsequent SC treatment options. For instance, prior RT for TC could limit the ability to perform surgery or deliver adequate radiation doses to the SC.[167-169] Also, response to SC treatment may be inferior to that of a primary cancer.[170-172]

Schairer et al.[173] studied 29356 TC patients registered in the US SEER (Surveillance, Epidemiology and End Results) program during 1973-2002. The authors found that mortality from SC following TC was similar to that of matched first cancers. The exceptions were some tumors in the RT field, or lung cancer, among TC patients diagnosed during 1973-1979. It was hypothesized that bone marrow suppression due to previous irradiation could limit dosing of subsequent chemotherapy.[173]

Overall second cancer risk by TGCT treatment

SC risk after surgery: Our novel finding of 28 % excess SC risk indicates that factors other than chemo- or RT, such as genetic or environmental factors, play a significant role in SC development among TCS. Surveillance bias was thought to be of negligible importance, possibly with the exception of thyroid cancer risk. The subject of surveillance bias will be discussed further in section 5.7.

Another possible reason why excess SC risk after surgery has not been reported previously is that the surgery group is sometimes used as the reference group in HR calculations.[103, 105, 113] These studies would thus be unable to detect any excess SC risk in the surgery group. Kier et al.[114] reported favorable results for the surveillance group, but their analysis excluded relapses.

SC risk after chemotherapy: A 62 % increased SC risk among patients who received CBCT was in line with previous publications (Table 9).

Treatment with two or more CBCT cycles led to increased SC risk, in line with Groot et al. who found that platinum dose was linearly associated with gastrointestinal cancer risk[106] and SC mortality.[126] While we did not find excess SC risk after one CBCT cycle or carboplatin, a longer observation time is desired to draw firm conclusions.

According to the International Agency for Research on Cancer (IARC), etoposide alone or in combination with cisplatin and bleomycin are classified as carcinogenic in humans. Cisplatin alone is classified as probably carcinogenic in humans, while bleomycin alone is possibly carcinogenic.[174] The causal association between cisplatin and solid cancer development is not clear, although cisplatin-DNA adducts may be of importance.[106] Cisplatin is detectable in the blood stream for several decades after administration.[175] This may partly explain the excess SC risks seen after CBCT.

SC risk after radiotherapy: After RT, we found a 63 % excess SC risk. As demonstrated in other studies, excess SCs were often localized to previous RT fields (Table 8). This is not unexpected as

ionizing radiation is a known carcinogen.[166] PA fields were not associated with significantly elevated SC risk, which could be due to the relatively low number of cases and the shorter follow-up time. We could not confirm a linear trend for increasing risk of solid SC with increasing abdominal RT dose, as reported by Groot et al.[106]

SC risk after combined treatment: Combined RT and chemotherapy were associated with the highest SC risks compared with the general population, as seen in other studies.[50, 114]

Thyroid cancer and melanoma

Excess risks of thyroid cancer and melanoma have been reported after CBCT[106, 110] and RT.[109] After surgery, only excess melanoma risk has been reported.[104]

Despite finding increased risks of thyroid cancer, we could not detect excess mortality, possibly due to few cases or to successful thyroid cancer treatment.[2] Excess mortality from melanoma was also reported previously,[106] but was not found in the recent study by Hellesnes et al. (Table 19).[162]

Patients with cutaneous melanoma seem to be at increased risk of SC, including testicular and thyroid cancer.[176] There is also a genetic link between melanoma and thyroid cancer through BRAF mutations. A study showed a reciprocal twofold increased risk of papillary thyroid cancer after cutaneous melanoma and vice versa.[177] Also, the study population had a high incidence of BRAF v600e-mutations. In study III, there were no cases of both thyroid cancer and melanoma.

An association between tumor risk in childhood and first-degree family history of solid cancers including melanomas was observed recently, even after taking hereditary cancer syndromes into account.[178] This indicates that genetic and/or environmental factors predispose for both TC and other malignancies. Further genetic research within this field should be prioritized.

Non-testicular genitourinary cancers

Among the most frequent excess SCs found in study III were those of the urinary tract, with a two- to threefold excess risk of kidney and bladder cancer after both chemo- or RT (Table 16).[3] Of these, bladder cancer risk has been the most consistently elevated across other studies (Tables 7-9). Fung et al. did not detect excess risk, but median follow-up time was short (Table 9).[110]

Bladder cancer was also one of few cancer forms where excess mortality was found within all cohorts of diagnosis, including among patients diagnosed with localized seminoma before 1990.[2] Excess mortality for kidney cancer was only found among patients diagnosed before 1980 (Table 15).

While excess bladder cancer mortality was previously found by Horwich et al.,[128] excess kidney cancer mortality was a novel finding. In a more recent study, Groot et al. reported excess mortality for both bladder and kidney cancers.[126] Hellesnes et al. very recently found excess mortality from bladder cancer after both chemo- or RT, but not from kidney cancer (Table 19).[162]

Another novel finding was excess mortality for prostate cancer among patients diagnosed before 1980, including patients with localized seminoma.[2] Although we did not find excess prostate cancer risk in patients diagnosed in the 1980s or later, some studies have shown excess prostate cancer risk.[107, 109] Hellesnes et al. recently reported excess prostate cancer mortality after combined treatment with PBCT and RT (Table 19).[162]

Nephrotoxicity is a well-known complication of cisplatin treatment.[74] Studies have shown that several structures in the kidney may be damaged, depending on dose.[5] Fosså et al. found reduced long-term renal function among TCS.[179] One study showed a 23 % incidence of chronic renal failure 1 year after CBCT.[180] Because platinum is mainly eliminated through renal clearance,[181] the apparent association between CBCT and tumors of the urinary tract is plausible.

Travis et al. estimated radiation doses to different organs after RT for TGCT for different forms of IRT as well as mediastinal RT (Table 20).[109] The bladder received large RT doses in L-fields and dogleg fields, but not PA-fields. While the prostate received less than half the RT dose compared to the bladder, even blocked kidneys received moderate doses also in PA fields.[109] While RT was in routine use among seminoma patients until the early- to mid-2000s, it was not routinely used among nonseminoma patients diagnosed after 1980.

Table 20. Estimated dose to selected organs after radiation therapy for testicular cancer (used with permission).[109]

	Avg total dose received by organ or site, Gy			
	Infradiaphragmatic radiotherapy			
	Para-aortic and iliac fields			
Organ	50 Gy	30 Gy	Para-aortic field only, 20 Gy	Chest radiotherapy, mediastinal field, 30 Gy
Esophagus				
Total	1.6	1.0	0.4	21.5
Lower third	4.5	2.7	1.1	27.9†
Stomach	24.7	14.8	10.0	1.7
Small intestine	22.5	13.5	4.7	0.2
Colon‡	2.8–50	1.7–30	0.5–9.4	0.2
Rectum	38.8	22.8	0.2	0.1
Liver	15.9	9.5	7.0	2.3
Gallbladder and ducts	8.0	4.8	7.3	0.7
Pancreas	28.0	16.8	12.9	1.2
Lung	1.1	0.6	0.3	11.9§
Prostate	7.1	4.3	0.1	0.05
Kidneys				
Total‖	7.0	4.2	5.7	0.8
Medial sections	10.2	6.1	9.5	0.9
Bladder	17.0	10.2	0.2	0.06
Thyroid	0.09	0.06	0.03	15.5¶

*Radiation doses to target organs were estimated with methods as described by Stovall et al. *(21)*. Treatment simulation was based on standard anterior–posterior (AP)/posterior–anterior para-aortic and iliac fields (total administered doses of 50 Gy and 30 Gy) or para-aortic fields only (20 Gy) *(22)*. Mediastinal radiotherapy included the left supraclavicular fossa *(20)*. Although representative fields during the study period are shown above, radiation doses for individual patients are not available but likely fall within the range of values presented. Gy = gray.

†Average doses to the upper and middle third of the esophagus are 8.4 and 28.3 Gy, respectively.

‡The range represents doses to different segments of the colon (ascending, transverse, descending, and sigmoid).

§Average doses to the medial and lateral parts of the lung are 16.8 and 1.2 Gy, respectively.

‖For para-aortic and iliac fields, doses are listed for the unblocked kidney. Doses to the blocked kidney are 6.0 Gy and 3.6 Gy for treatment doses of 50 Gy and 30 Gy, respectively.

¶Average doses to the left and right lobes of the thyroid are 25.2 and 5.7 Gy, respectively.

Thus, RT may well be responsible for excess mortality from non-TC genitourinary cancers. Due to the high median age at diagnosis and the relatively good prognosis for patients with prostate cancer, longer follow-up is likely needed to identify any excess mortality.

Gastrointestinal cancers

In agreement with other studies (Tables 10 and 19), we found excess mortality due to several gastrointestinal cancers depending on cohort of diagnosis (Table 13).

In particular, we found elevated SMRs for stomach cancer across all cohorts of diagnosis, including among patients diagnosed with localized TGCT before 1980 and localized seminoma before 1990. Similarly, SMRs for pancreatic cancer were elevated among TCS diagnosed before 1990, including among those diagnosed with localized seminoma.[2]

Findings of excess mortality correlated well with our findings of excess risks after RT only or in combination with chemotherapy. These results were in line with previous publications.[86, 106, 109, 110, 114, 116]

The stomach and pancreas received high radiation doses with IRT (Table 20).[109] Thus, one explanation for these findings could be late effects of RT. Supporting this hypothesis are recent findings by Hellesnes et al. of excess mortality from stomach and pancreatic cancers after RT with or without PBCT, but not after PBCT alone (Table 19).[162]

A novel finding was excess mortality from esophageal cancer, including among TCS diagnosed in 1990 or later.[2] Although Groot et al. did not find excess mortality,[126] our finding was recently reproduced by Hellesnes et al. after surgery only or PBCT (Table 19).[162]

A few previous studies have shown elevated risks for esophageal cancer (Tables 7 and 9).[103, 109, 114] Notably, Kier et al. found excess risk after chemotherapy but not RT (Tables 8 and 9).[114]

Patients given IRT received relatively low radiation doses to the esophagus.[109] In mediastinal radiation it was the organ that received the highest dose, but this was no longer standard treatment after the early 1980s.[109] Thus, it is more likely that treatment-induced excess mortality from esophageal cancer is chemotherapy-induced. Also, the recent finding by Hellenes et al. of excess esophageal cancer mortality after surgery alone is intriguing.[162]

In study II we found excess mortality from cancers of the large intestine among TCS diagnosed before 1980, and among TCS diagnosed in the 1980s beyond 26 years of follow-up. These were novel findings, later confirmed by Groot et al. who reported excess mortality of rectum and/or anal cancer (Table 10).[126] Hellesnes et al. did not find excess mortality from cancers of the large intestine, possibly due to also including patients diagnosed after the 1980s.[162] We did not specifically report on the mortality of small intestine cancer.

In study III we found elevated risks for both cancers of the small and large intestine. This correlated well with findings by Groot et al.[106] and other studies (Tables 7 to 9), although Fung et al. and Kier et al. did not find elevated risk for cancers of the large intestine (Tables 8 and 9).[110, 114]

Our finding of excess mortality from liver cancer was novel, although there is always the possibility of misclassification of metastases as a primary tumor. Also, this finding was based on relatively few cases.[2] Hellesnes et al. recently found excess mortality from liver cancer after RT (Table 19), which is in agreement with our findings both pertaining to mortality and risk.[162]

Central nervous system cancers

Excess brain/CNS cancer mortality was another novel finding, although we did not detect excess risk. The number of cases were few and there is the possibility of misclassification of metastatic disease as a primary tumor.

Hematological cancers

In study III, excess leukemia risk was only found among TCS who had received both chemotherapy and RT. In study II we found excess mortality of leukemia among TCS diagnosed after 1990, including among 5-year survivors.

Excess mortality from leukemia has also been shown in other studies (Table 10). With a mean follow-up time of 10 years, Horwich et al. reported an increased SMR among CS1 seminoma patients who had received IRT.[128] Groot et al. also found excess mortality due to leukemia.[126] Hellesnes et al. recently reported a threefold excess mortality from lymphoma after surgery alone, and a threefold excess mortality from leukemia after PBCT (Table 19).[162]

The bone marrow is inherently sensitive to mutagenic chemotherapy agents.[170] It has been postulated that agents with differing mechanisms of action, such as cisplatin (direct binding to DNA) and etoposide (inhibition of DNA-topoisomerase II), may have a synergistic effect in leukemogenesis.[182] However, emerging data suggest that some hematologic malignancies evolve from a germ cell precursor.[183] This might explain the recent finding of excess lymphoma risk after surgery alone, although the finding was based on few cases.[162]

Cancers of the respiratory system

In study II we found an almost twofold elevated SMR for cancers of the lung, trachea or bronchus among TCS diagnosed in the 1980s, comparable to findings by Fosså et al.[125] and recently Hellesnes et al. after PBCT (Table 19).[162]

In study III we similarly found an about 50% increased risk of lung cancer in patients receiving chemotherapy and/or RT. Other studies have also shown elevated risks (Tables 7-9).

Cigarette smoking might be a confounding factor. Because we did not have smoking data, we cannot say whether any differences in smoking habits between the study and reference populations would have affected these results.

Connective tissue cancers

Travis et al. reported a fourfold increased risk of connective tissue cancers,[109] which was in line with our findings in study III.

We did not analyze mortality of sarcomas in study II, although we noted several deaths by sarcoma in the study population. Groot et al.[126] found excess mortality from connective tissue cancers, as did Hellesnes et al. (Table 19).[162]

Some cancers diagnosed as soft tissue sarcoma might be transformed teratomas.[184]

5.4 Cardiovascular disease mortality

Cardiovascular mortality, TGCT diagnosed <1980

Among TGCT patients diagnosed prior to 1980, CVD SMRs in other studies were generally slightly or not significantly elevated (Table 11). In study II, we similarly found a borderline significant CVD SMR among TGCT patients diagnosed 1953-79. The SMR remained elevated among 5-year TCS, suggesting that acute treatment-induced CVD events were not the primary cause of excess CVD mortality in this population. Our data instead pointed to non-ischemic heart disease developing more than a decade after TGCT diagnosis, as a 59 % excess mortality was detected both for all TGCT patients and 5-year TCS.

The increased SMR among TGCT patients diagnosed with metastatic seminoma during the same time frame, with an even higher SMR of 2.08 among 5-year TCS, indicates that treatment burden is an important factor in long-term CVD mortality.

Cardiovascular mortality, TGCT diagnosed 1980 and later

For patients diagnosed during 1980-89, we found excess mortality of MI among patients followed for <16 years (SMR: 1.51). Two studies showed a five- to sevenfold elevated CVD SMR during the first year after chemotherapy in 1980 or later.[144, 148] Fung et al. did not find excess CVD mortality after one year.[148] Hellesnes et al. recently found excess mortality from non-cardiac, non-cerebrovascular circulatory disease among patients who received both PBCT and RT (Table 21).[162]

Table 21. Selected standardized mortality ratios for cardiovascular disease and other non-malignant causes by treatment group among patients diagnosed with testicular germ cell tumor in Norway, 1980-2009. Statistically significant results are given in bold. Adapted and abbreviated.[162]

Cause of death	Total		Surgery		PBCT		RT		PBCT + RT	
	n	SMR	n	SMR	n	SMR	n	SMR	n	SMR
Non-cancer deaths, total	408	1.15	70	0.92	120	**1.23**	193	**1.17**	25	**1.55**
Cardiovascular disease	151	1.01	28	0.89	42	1.18	71	0.94	10	1.29
Ischemic heart diseases	90	1.12	20	1.22	22	1.16	45	1.10	3	0.70
Other heart diseases	31	1.37	5	1.03	9	1.76	11	0.96	6	**5.30**
Cerebrovascular diseases	17	0.65	1	0.18	6	1.04	9	0.67	1	0.73
Other circulatory diseases	13	0.85	2	0.63	5	1.45	6	0.76	0	0

Infectious and parasitic diseases	15	**2.35**	5	3.73	4	2.49	6	1.91	0	0
Endocrine and metabolic diseases	12	1.13	2	0.91	0	0	9	1.76	1	2.16
Mental and behavioural disorders	18	1.00	3	0.79	2	0.38	12	1.47	1	1.34
Diseases of the nervous system	20	1.16	5	1.38	6	1.27	8	0.98	1	1.40
Diseases of the respiratory system	33	0.96	2	0.27	10	1.29	18	1.02	3	1.78
Diseases of the digestive system	32	**1.89**	4	1.15	6	1.31	20	**2.46**	2	2.68
Diseases of the genitourinary system	7	1.55	2	1.96	3	**3.29**	1	0.42	1	4.07
External causes	85	**1.25**	14	**0.87**	35	1.34	32	1.36	4	1.79
Accidents	51	1.22	9	0.91	19	1.22	21	1.41	2	1.41
Suicide	33	1.38	4	0.70	16	**1.65**	11	1.41	2	2.73

PBCT, Platinum-based chemotherapy; RT, radiotherapy; SMR, standardized mortality ratio

Fung et al. reported excess mortality from cerebrovascular disease[148], but neither we nor Hellesnes et al.[162] could reproduce this finding. This could be due to relatively few cases in our study population.

Study II did not specifically focus on acute CVD mortality, and we did not calculate SMRs for shorter follow-up times after TGCT diagnosis than 16 years. However, in the 1980-89 cohort there was one CVD death within one year of follow-up, and ten after five years. In the 1990-2015 cohort, six CVD deaths occurred during the first year of follow-up.[2] Regardless of any statistical significance, because fatal CVD events are rare in a population as young as TGCT patients, it is fair to assume that at least some of these CVD deaths could be due to TGCT or its treatment.

Radiation-induced heart disease comprises a wide range of disorders, most commonly coronary artery atherosclerosis and valve disease.[185] Radiation-induced DNA damage may lead to long-term effects such as stromal change with collagen deposition and neoangiogenesis causing organ dysfunction.[186] Moreover, in patients with Hodgkin's lymphoma given mediastinal irradiation, CVD risks have been reported to increase three- to sevenfold.[135] Heart disease is also among the main long term hazards after RT for breast cancer.[187]

Among TCS given chemotherapy, several hypotheses for the development of CVD exist:[9]

- The direct vascular (blood vessel) damage hypothesis, which proposes that CBCT causes direct damage to the vascular endothelium. This may occur through inflammation, contraction of blood vessels and promotion of blood clotting.
- The indirect hypothesis states that CBCT leads to increased frequency of CVD risk factors such as hyperlipidemia, hypertension, diabetes, insulin resistance, and metabolic syndrome.
- The multiple-hit hypothesis, stating that the synergetic effect of orchiectomy-derived subclinical hypogonadism, chemotherapy-induced vascular injury, chemotherapy-related disturbance of metabolic homeostasis, and other TC treatment-related toxicities increases CVD risk among TCS.

A sign of vascular damage is Raynaud phenomenon, affecting 25-61% of TCS (Figure 16).[113, 188-191]

Figure 16. Raynaud phenomenon. Wikipedia

In general, the onset of symptoms begin within 4 to 12 months after chemotherapy, and about 25 % of TCS have these symptoms beyond 20 years after treatment.[192] Bleomycin is strongly associated with the development of Raynaud phenomenon.[193] Vinblastine and cisplatin may also contribute.[189-191]

There are no indications that the TC diagnosis itself leads to increased CAD risk.[129] On the other hand, a cancer diagnosis is itself associated with a 4- to 7-fold increased risk of venous thrombosis.[194]

Although up to sevenfold excess CVD risk has been reported among TGCT patients, overall excess CVD mortality after a TGCT diagnosis seems to be relatively minor compared to that of SC. The reason is most likely that diagnostic and therapeutic options for preventing CVD-induced mortality is under continuous development, benefiting TGCT survivors and the general population alike.

5.5 Other causes of excess mortality

Non-malignant gastrointestinal diseases

Our finding of excess mortality from benign gastrointestinal diseases was also reported previously by Fosså et al. and Kier et al. (Table 12). Fosså et al. found excess mortality of digestive diseases after RT but not chemotherapy.[149] Similarly, Hellesnes et al. recently found excess mortality from digestive system disorders after RT but not PBCT (Table 21).[162] These findings indicate that CBCT may be a less important factor than RT regarding mortality from non-malignant gastrointestinal disease.

RT induces radiation enteritis, which can be augmented by chemotherapy.[195, 196] Abdominal RT affects intestinal blood vessels, which after several years can lead to tissue necrosis, perforation of the intestine and hemorrhage.[149] Also, postradiation fibrosis may lead to dysfunction of the bowel, liver and pancreas.[197] RT has been shown to increase diabetes risk among TCS compared to surgery only.[198]

The major late morbidity following gastric irradiation is ulceration.[195] Several studies published in the 80s and 90s showed increased risk of peptic ulceration among TCS after RT, with a reported incidence of about 6-8 %.[128, 199-201]

Cisplatin causes a wide range of gastrointestinal toxicities and oxidative damage to intestinal cells.[202] Data on cisplatin-induced late gastrointestinal toxicity are more sparse.

Suicide and death from external causes

In line with the results of a Norwegian study published in 2017[151] and recently by Hellesnes et al.,[162] our finding of about 50 % excess suicide risk among TGCT patients diagnosed in Norway in 1990 or later is disturbing.

Some evidence suggests increased prevalence of anxiety disorder[203] and fatigue[204] among TC patients. In a 2016 study, increased prevalence of depression and reduced health-related quality of life was also shown,[205] although other studies indicate that health-related quality of life in TCS is similar to the general population.[34] These findings could partly explain the increased suicide risk, as could changes in coding practices.

One could also speculate that today's society with increasing social demands can affect suicide rates. Perceived loss of masculinity and control during or after TC treatment may lead to psychological distress.[150]

Infections

In study II, we found excess mortality from infections among TGCT patients diagnosed in 1990 or later. Fosså et al. and Fung et al. previously reported excess mortality from infections (Table 12).[148, 149] Fung et al. reported a sevenfold excess risk of septicemia after chemotherapy, but not after surgery alone.[148] Hellesnes et al. very recently found excess mortality from infections after surgery alone, but not RT or chemotherapy (Table 21).[162]

Chemotherapy-induced immunodeficiency, catheters of various types, and tumor growth reducing the efficacy of normal protective organ barriers are underlying mechanisms of increased infection risk and severity. Infection is also a feared complication after surgery in general.

Nervous system disorders

In study II, increased mortality of nervous system disorders including Alzheimer's disease was a novel finding, although based on few cases. Several studies have shown an inverse relationship between cancer and dementia, although it is not possible to rule out surveillance bias (section 5.7).[206] Comorbidity data were not available, so we were not able to rule out for instance Down syndrome as a possible confounding factor.[207] Whether chemotherapy can cause cognitive dysfunction ("chemo brain") in breast cancer patients is a topic of controversy.[208] Studies on cognitive performance among TCS given chemotherapy have also yielded conflicting results.[209]

Respiratory disease

We found excess mortality from a group of respiratory disorders comprising unspecified acute lower respiratory infections, pneumoconiosis and pneumonitis of various causes (Table 15).[2] Fosså et al. previously reported a similar finding among patients given chemotherapy after 1975 (Table 12).[149]

Bleomycin is inactivated by the enzyme bleomycin hydrolase, which is present in most tissues. However, this enzyme does not exist in the lungs and the skin, explaining that bleomycin toxicity primarily occurs in these organs.[129] The drug may cause pneumonitis, in some cases progressing to pulmonary fibrosis which may be life-threatening. Our finding may thus partly be explained by bleomycin-induced toxicity. We did not quantify the number of deaths due to each condition in our study.

5.6 Relative survival

Relative survival up to 20 years of follow-up

The treatment of TGCT has truly become the model of a curable neoplasm, even being considered among the top five accomplishments in cancer medicine during the last five decades.[8] In agreement with CRN data (Table 6), we found significant improvements in short-term RS during this time frame (Figure 13). Even though we used slightly modified inclusion criteria, it was expected that our 5- and 15-year RS data would be similar to the CRN data because the study populations were largely the same.

The marked decline in RS during the first five years after TGCT diagnosis was most pronounced among patients diagnosed prior to 1980 (Figure 13). In study I we hypothesized that this was due to TGCT-specific mortality or complications of treatment. The subsequent analyses of mortality data in study II supported this hypothesis.

There has been a lack of published data on the impact of different causes of death on RS. The most detailed previous study examining the impact of different causes of death in TGCT patients was published in 2014 by Gandaglia et al.[210] These were not RS data, but 15-year mortality data due to TC, other-cancer and non-cancer causes among 31330 TGCT patients diagnosed between 1973 and 2009. Of particular interest was that non-cancer related mortality was generally responsible for

more deaths than SC at 15 years of follow-up, even among patients diagnosed with TGCT in 1990 or later. The median follow-up was fairly short at 7.7 years.

Our 20-year RS point estimates were in line with the 20-year RS data published by Brenner,[95] and about 1-8 % inferior to the findings of Robinson et al.[96] For seminoma patients diagnosed in the 1970s, we found an approximately 14% inferior RS in study I. Unlike our data, Robinson et al. did not find a decline in RS by follow-up time. The reason for this could be a shorter median follow-up than in our studies.

Changes in treatment principles most likely contributed to the general improvement in RS in the later cohorts of diagnosis. However, improved health care was probably also of importance, preventing or delaying mortality from treatment-induced morbidities. Conversely, the same improvements probably contributed to improved survival in the general population as well.

Relative survival beyond 20 years of follow-up

Prior to our studies, no RS data beyond 20 years of follow-up among TCS had been published. Several studies had provided OS data beyond 20 years of follow-up, but these cannot be directly converted into RS data. Thus, our findings in studies I and II represent worrying new knowledge. Even though the probability of cure has improved significantly after 1980, the RS of TCS continues to decline even beyond 20 years of follow-up. Further follow-up time is needed to determine long-term RS among patients diagnosed in the last few decades.

Most likely, the main cause of the continuous decline in RS is the gradual development of late treatment-related morbidity and mortality, particularly following RT and/or chemotherapy.[5] Supporting this is the striking difference in RS curves between localized melanoma and localized TGCT showed in study I. In contrast to localized TGCT, patients with localized melanoma did traditionally not receive adjuvant RT or chemotherapy.

Many of the previously discussed late effects of chemotherapy for TGCT occur with increasing frequency in the elderly general population, including CVD, SC, renal function decline, cognitive complaints and ultimately decreased survival. This can be considered signs of early aging among TCS. In recent years, it has been hypothesized that chemotherapy induces cellular senescence as manifested by this early ageing phenotype, possibly via systemic low-grade inflammation.[209]

There may be other factors affecting RS that are not directly related to treatment, such as genetic factors. Supporting this is the finding in study III of excess SC risk after surgery only.

Relative survival by histology

Given the superior 5-year RS among seminoma patients over nonseminoma patients shown in study I and II (Figures 14 and 15, respectively), the more rapid decline in long-term RS for seminomas was remarkable. The RS in different groups should, however, be compared with caution. In part, the differences may be explained by differences in seminoma and nonseminoma treatment, especially the continued use of RT in CS1 and CS2 seminoma into the 2000s. By contrast, adjuvant RT was omitted in nonseminoma treatment after 1980. The observed inferior long-term RS among seminoma patients during this time period could thus be attributed to late effects of RT. Stage at diagnosis could be a confounding factor, although this is less likely since the same trend was seen among TCS diagnosed with localized disease.

TGCT-specific mortality has been found to increase with increasing age at diagnosis.[88, 211] It is possible that seminoma patients are more susceptible to treatment-induced toxicity, due to their higher median age at diagnosis. As an example, bleomycin is often omitted if chemotherapy is required among TGCT patients over 50 years of age. Similarly, a higher age at SC diagnosis could prevent effective SC treatment, ultimately leading to reduced RS.

Another possibility is that TGCT have genetic susceptibilities for several conditions that differ between seminoma and nonseminoma patients. Since TGCT susceptibility may be innate, it could also be hypothesized that the disease becomes more treatment resistant over time due to an innate genetic instability.

Nevertheless, these data strongly suggest that long-term follow-up should be particularly vigilant among seminoma patients.

Relative survival by age at TGCT diagnosis

Related to the above is our finding that RS was significantly inferior among patients diagnosed with TGCT after 40 years of age.[1] Our analyses were stratified by histology, and the same trend was found both for seminoma and nonseminoma patients. A possible source of error in our estimates could be differences in TGCT stage distribution between age groups. This difference was minor and likely not of significance.

Spermon et al. similarly found inferior 10-year RS among US TGCT patients diagnosed at 50 years or older, but with a shorter follow-up time.[212] Gandaglia et al. reported that 15-year overall mortality was increased among patients diagnosed with TGCT at age 34 or older.[210]

Our finding that that a younger age at TGCT diagnosis increased the SIRs for SC (Table 17), although in agreement with Travis et al.,[109] could seem counterintuitive to the above. Hellesnes et al. recently observed a higher SC SMR among patients diagnosed with TGCT before 20 years of age compared to patients diagnosed in their 30s, 40s or 50s.[162] We did not examine the impact of different causes of excess mortality on RS by age at TGCT diagnosis, but it is still likely that a higher age is associated with excess risk of serious late effects after TGCT treatment, with inferior RS as a result.

Relative survival by disease stage at diagnosis

Prior to our study II, there were no studies directly comparing the RS of TGCT patients diagnosed with localized disease with overall TGCT RS.

The consistently superior RS point estimates among patients diagnosed with localized disease when compared to all stages combined, was mainly due to fewer TC deaths. A reduced overall treatment burden among patients with TGCT was also a likely explanation. The most striking example of this was the RS for seminoma and nonseminoma patients diagnosed in the 1980s. In study II, we found that seminoma patients diagnosed with localized disease in the 1980s had a significantly elevated non-TC SMR of 1.39, while this was not significantly elevated among nonseminoma patients. Most likely, the cause was the continued use of adjuvant RT among seminoma patients during this period, while RT was abandoned for nonseminoma patients.

Another factor that may improve RS in localized disease is that patients who are diagnosed with a localized TC may be more conscious of their own health than are patients who are first diagnosed with metastatic disease.

5.7 Methodological considerations

Relative or overall survival

In studies I and II, it was decided to exclusively report RS data and not OS data. TCS are relatively unique with regards to long-term cancer survival, especially among cancer survivors diagnosed with metastatic disease. Because the median age at diagnosis is less than 40 years, and nearly all patients are cured, TCS usually live several decades after diagnosis. The mortality among 40-year-olds is

very low in the general population, increasing the likelihood that an early study population death could be in excess from what would be expected.

With increasing follow-up time, mortality increases in the general population as well due to increased age and comorbidity. According to Statistics Norway, the contemporary death rates are 84 / 100.000 among Norwegian men aged 35-39 years, while it is almost fourteen times higher (1170 / 100.000) among those aged 65-69 years.[213] A weakness of only reporting OS in long-term TCS is that it does not take this into account. This was the main reason for choosing RS as the primary measure of survival.

Relative survival analyses

In studies I and II, we used the method for calculating RS proposed by Pohar Perme et al.[156] This method provides an unbiased estimate of "net survival", but may cause estimate instability especially for long-term survival and small data.[85] It is now generally agreed that the method by Pohar Perme et al. is the preferred method of RS analysis.[214] Regarding the Z test used in study I, an improved log-rank type test has since become available.[215]

Multiple comparisons correction

In study II, we decided to not adjust for multiple comparisons. There are both advantages and disadvantages to this approach. The principal argument for performing multiple comparisons correction is to reduce the chance of false positive results. If one considers twenty statistically significant SMR analyses with a chosen significance level of <5%, one of these (1/20 = 5%) could be expected to be false positive. A false positive would mean that the statistical test shows a significantly superior or inferior SMR when, in fact, there is no excess mortality compared to the general population.

The risk of such type I errors (Table 22) is a common problem in clinical research, especially with multiple comparisons.

Table 22. Type I and II errors

	Truth		
Test result		Positive	Negative
	Positive	True positive	Type I error
	Negative	Type II error	True negative

There are different ways to adjust for multiple comparisons in the analysis, such as the Bonferroni correction.[216]

The main disadvantage of multiple comparisons correction is that it increases the likelihood of type II errors, which in this case is to incorrectly retain the null hypothesis of no difference in mortality when there actually is one (Table 22). Depending on the situation, one might debate which type of error is the most important to avoid. Several statisticians are of the general opinion that corrections should be avoided, particularly in exploratory studies.[217, 218]

Due to the exploratory nature of our studies, we believe that it was the right decision to not perform such corrections. The risk of reporting more false positive findings (which can later be explored in further studies) does not outweigh the risk of reporting more false negatives in this case.

Validity of data sources

The analyses in any study can only be as accurate as the data they are based on. Accordingly, data quality in the registries is crucial.

The completeness of the CRN during 2001-2005 was 98.8%, and the validity was 93.8% when compared to morphologic verification. Validity was reduced with increasing age at diagnosis.[154, 219] A study of European registries showed that, during 1998-2002, Norway had the eight highest percentage of morphologically verified cases of 32 countries. This suggests a relatively high validity.[220]

There have been some concerns regarding the data quality of the NCDR,[155, 221] regarding logical and content errors in death certificates. In an international study, the NCDR was shown to be one of many registries with a significant proportion of codes that are non-specific or cannot represent the underlying cause of death.[222]

The registered cause of death depends on correct reporting on the death certificates. The filling in of the death certificates by the treating physicians represent a possible source of error. For instance, a cerebral hemorrage may be secondary to thrombocytopenia, which may be secondary to TGCT treatment. If the death certificate was completed correctly, he would receive TGCT as the cause of death. However, if the cause of death was reported to be cerebral hemorrage with the additional information of TGCT, the cause of death would be registered as the cerebral hemorrage (source: written personal communication with the NCDR).

It is impossible to know the extent of misclassification in our study population, but there is no reason to believe that errors in reporting or registration were more common among TC patients and TCS than in the general population.

Surveillance bias

In research, the term bias refers to any trend or deviation from the truth in data collection, data analysis, interpretation and publication which can cause false conclusions.[223]

Surveillance bias is also known as detection bias. It can occur if some subjects are monitored more closely than others, for instance with more frequent check-ups or more diagnostic tests. This can lead to an outcome being diagnosed more frequently in the closely monitored.[224] Surveillance bias is potentially present in study II and III because a patient diagnosed with cancer is followed more closely than the general age-matched population, at least the first five to ten years after TGCT diagnosis.

In studies I and II, we included patients from the time of TGCT diagnosis. This was necessary to provide the most complete estimate of RS across the entire follow-up period, but also as to not infer a particular mechanism behind excess deaths (for instance, treatment induced as opposed to hereditary).

In study II, we investigated the extent of surveillance bias by performing separate statistical analyses on 5-year survivors only. Because the median time to diagnosis for most conditions was long, it was as expected that most SMRs did not change significantly when the analyses were restricted to 5-year survivors.

There were a few SMRs that were no longer significantly elevated among 5-year TCS, in particular the increased frequency of suicide among patients diagnosed in 1990 or later. However, this was not surprising as the median time to death of suicide among all TCS diagnosed >1989 was 7.1 years, and there were relatively few cases. Also, the point estimate of 1.5 remained unchanged. Overall, we conclude that the impact of surveillance bias on our results in study II are negligible.

There was a considerable latency from cancer therapy to the occurrence of SC in study III. The median latency between diagnosis of TC and melanoma was 14.6 years, making surveillance bias a less likely explanation of excess risks among TCS treated with surgery. However, the median time

to development of thyroid cancer was 5.8 years, and it is possible that our findings regarding thyroid cancer risk are in part attributable to surveillance bias.

Immortal time bias and the Aalen-Johansen estimator

In study III, treatment was analyzed as a time-varying covariate to avoid immortal time bias.[159] As an example, a patient accrued person years of observation time in the surgery only group until the date they received chemotherapy or RT. It could be argued that the average number of person years accrued after surgery was closer to TGCT diagnosis than that of chemotherapy or RT, and that fewer late effects could thus be expected in the surgery group. However, there are no good alternatives to this approach short of delaying the start time of follow-up.

The crude probability of SC in study III was estimated by the cumulative incidence using the Aalen-Johansen estimator. This method incorporates competing risks and can be regarded as a counterpart to the Kaplan Meier method in which other causes of death are censored. It is considered the most realistic estimate for SC risk in our study population.[225]

5.8 Study strengths and limitations

All studies included TGCT patients and survivors diagnosed in Norway across a wide time frame and regardless of treatment center, disease stage at diagnosis, treatment given and follow-up time (the exception to the latter is study III where patients followed <1 year were excluded).

The advantage of such population-based studies is a high external validity, with results generalizable to the total population of interest. Also, the population-based approach minimizes selection bias associated with hospital or clinical series.[111]

The long follow-up times enabled us to draw more firm conclusions regarding the long-term outcome of patients treated for TGCT.

A complete individual TCGT treatment history is a definitive strength of study III. Inclusion of these data enabled valid results regarding the impact of each treatment modality on SC risk.

It follows that the main limitation in studies I and II were lack of individual, complete treatment information, making it difficult to conclude regarding the effect of specific treatment modalities on mortality. However, because general treatment principles within a specific time period were known, we believe time period of diagnosis to be an acceptable proxy when viewed together with disease stage and histology. Notably, many studies on TGCT mortality and morbidity only include treatment data on primary treatment. For instance, a patient who initially received RT could also have received chemotherapy at a later date. This would mask the true effect of RT on morbidity or mortality.

A limitation shared by all three studies is the lack of data on comorbidities and smoking, which most likely would affect survival and SC risk. One example is our finding of excess mortality of Alzheimer's disease, discussed above. Men with Down syndrome have increased risks of both TGCT and several other conditions e.g. Alzheimer's disease.[207] Groot et al. also recently reported an HR for SC death of 1.8 among patients who smoked at TGCT diagnosis vs those who did not. For CVD death it was 3.35.[126]

However, as the median age of TGCT patients is <40 years, the frequency of comorbidity is expected to be low. Moreover, studies indicate that the proportion of smokers among TCS is not significantly different from that of the general population.[132, 226]

In study II, several of the SMR estimates were calculated based on relatively small numbers of cases. One should be cautious to draw firm conclusions in these cases, and the results should be regarded as hypothesis-generating in need of confirmation in subsequent studies.

Power calculations to determine study population size needed to answer a specific research question would have no purpose in our studies. Our studies were exploratory in nature with many outcomes of interest. There was no way of expanding the study sample because all eligible patients diagnosed in Norway at the time were included.

In study II, we did not have any data on recurrence of the primary testicular cancer under observation. As such we could not say whether late TC deaths were due to recurrence of the primary TGCT or a subsequent contralateral TC.

In study I, patients with a clinical diagnosis of TGCT were included. The rationale for this was the expectation that about 95 % of these would be TGCT. Although it likely led to the inclusion of patients with a non-germ cell testicular tumor, we considered these cases to have negligible impact on the analyses.

5.9 Implementation of new knowledge

The findings in this thesis should have implications for the follow-up of TGCT patients and survivors. Routine hospital follow-up after successful TGCT treatment is usually ended after 5 to 10 years, but our studies confirm that an excess of many potentially lethal conditions continue to appear well after this time frame. Primary health care professionals should be aware of this risk and have a lower threshold of referring the patient to further examinations should suspicions arise.

It is important that the patient is made aware that there is a long-term excess risk of serious disease, but that the benefits of TGCT treatment still clearly outweigh the risks overall. Monitoring of several cardiovascular risk factors is already implemented in SWENOTECA guidelines, and written information regarding long-term follow-up is provided to the patient at end of hospital follow-up.[37] The patient should have a low threshold of consulting his primary doctor if any unexplained symptoms arise. Also, psychosocial aspects should not be overlooked during follow-up.

Of course, it is also important with balanced information. Although there is an excess long-term risk of death in historical data for radio- and/or chemotherapy-treated patients in particular, findings so far also indicate that patients treated for TGCT today may fare significantly better. For instance, since routine RT has not been given to TGCT patients since the mid-2000s, one can hope that this will translate into improved long-term RS in the future. New studies will have to be performed to confirm or refute this.

Awareness of late effects is increasing not only for survivors of TC. Reflecting this, the Norwegian Directorate of Health published a report on late effects of cancer treatment in 2017 which was updated in 2020.[227] Hopefully, this report will also contribute to the further spreading of knowledge on this important topic.

5.10 Suggestions for further studies

It would be of great interest to examine the patients in study II further, specifically to stratify by age as was done in study I. This was omitted as the scope would otherwise be too big. It would also be of great interest to repeat RS analyses for TGCT patients diagnosed in Norway after 1990 in perhaps 10 years, to see if the decline in RS continues also for this group of patients. One can of course hope that this is not the cause.

Hellesnes et al. recently provided new insight on the impact of treatment on excess mortality among TGCT patients diagnosed in Norway during 1980-2009, mitigating one shortcoming of studies I-II.[162]

Genetic studies are ongoing, but further GWAS studies should be performed to discover more candidate genes associated with excess disease risk and possibly to introduce novel treatment options. It is possible that gene profiles can predict responses to chemotherapy and prognosis, tailoring the treatment regimen for the individual patient.

Further research should also focus on optimizing treatment regimens, reducing risk of long-term toxicity while preserving the excellent cure rates. More research on suicide among young cancer survivors is also important.

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7. Papers, studies I-III

PAPER I

PAPER II

PLOS ONE

RESEARCH ARTICLE

Causes of inferior relative survival after testicular germ cell tumor diagnosed 1953–2015: A population-based prospective cohort study

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Abstract

Background

Testicular germ cell tumor (TGCT) patients and survivors have excess mortality compared to the general male population, but relative survival (RS) has been scarcely studied. We investigated causes of excess mortality and their impact on RS among men diagnosed with TGCT in Norway, 1953–2015.

Methods and findings

Using registry data (n = 9541), standardized mortality ratios (SMRs) and RS were calculated. By December 31st, 2015, 816 testicular cancer (TC) and 1508 non-TC deaths had occurred (non-TC SMR: 1.36). Within five years of TGCT diagnosis, 80% were TC deaths. Non-TC second cancer (SC) caused 65% of excess non-TC deaths, of which 34% from gastric, pancreatic or bladder cancer. SC SMRs remained elevated ≥26 years of follow-up. In localized TGCT diagnosed >1979, SC SMRs were only elevated after seminoma. Cardiovascular disease caused 9% and other causes 26% of excess non-TC deaths, of which 58% from gastrointestinal and genitourinary disorders. RS continuously declined with follow-up. TGCT patients diagnosed >1989 had superior five-year TC-specific RS (98.3%), lower non-TC SMR (1.21), but elevated SMRs for several SCs, infections, Alzheimer's disease, genitourinary disease and suicide. A limitation was lack of individual treatment data.

Conclusions

RS declines mainly from TC deaths <5 years after TGCT diagnosis. Later, excess SC mortality becomes particularly important, reducing RS even ≥26 years. Radiotherapy; standard

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Abbreviations: CI, confidence interval; CRN, Cancer Registry of Norway; CVD, cardiovascular disease; NCDR, Norwegian Cause of Death Registry; OC, other causes; RS, relative survival; SC, second cancer; SMR, standardized mortality ratio; TC, testicular cancer; TCS, testicular cancer survivors; TGCT, testicular germ cell tumor.

adjuvant seminoma treatment 1980–2007, is likely an important contributor, as are chemotherapy and possibly innate susceptibilities. Vigilant long-term follow-up, including psychosocial aspects, is important. Further research should focus on identifying survivor risk groups and optimizing treatment.

Introduction

Despite today's excellent cure rates for testicular germ cell tumor (TGCT), more than ten thousand men died from testicular cancer (TC) worldwide in 2012 [1]. Among TCGT survivors (TCS), excess mortality is also a concern. We previously reported a continuing decline in relative survival (RS) among men diagnosed with TGCT in Norway compared to the general male population, even beyond 25 years of follow-up [2].

TGCT treatment is associated with potentially life-threatening late effects such as second cancer (SC) and cardiovascular disease (CVD), which can manifest decades after chemo- or radiotherapy [3]. Indeed, several studies show excess mortality from these and other conditions among TCS [4–6]. However, to what extent such findings impact RS compared to the general male population is less clear.

We analyzed causes of excess mortality among TGCT patients diagnosed in Norway, 1953–2015, and examined the impact of these causes on RS.

Methods

Data sources

Data were obtained from the Cancer Registry of Norway (CRN) and the Norwegian Cause of Death Registry (NCDR). The study did not require institutional review board approval.

The CRN comprises data on all new cancers reported in Norway since 1953, collected prospectively. Data quality is considered to be high [7], but treatment and clinical follow-up data are incomplete. The NCDR contains cause of death information on all Norwegian inhabitants since 1951. Causes of death were recorded using the ICD-6 to ICD-9 coding systems until 1996, then ICD-10 (S1 Table).

Study population

We included all men diagnosed with histologically verified TGCT in Norway from January 1st, 1953 until December 31st, 2015, except extragonadal germ cell tumors and spermatocytic tumors [8, 9]. Because of incomplete individual treatment data, general treatment principles at the year of diagnosis were used as a proxy (Table 1).

Patients were classified into cohorts by time period of diagnosis: 1953–1979, 1980–1989 and 1990–2015. They were further classified as either seminoma, nonseminoma or unspecified TGCT. Disease extent at diagnosis was classified by CRN variables as either localized, metastatic or unknown [10]. Nonmetastatic tumors with direct micro- or macroscopic growth into neighboring tissues were classified as localized.

Follow-up was from the time of first TGCT diagnosis until death, emigration or December 31st, 2015, whichever occurred first.

Table 1. General treatment principles for testicular germ cell tumor patients diagnosed in Norway.

Time of diagnosis	Localized disease	Metastatic disease
1953–1979	Nearly all patients received adjuvant abdominal RT to para-aortic and ipsilateral iliac lymph nodes (up to 40 and 50 Gy in seminomas and nonseminomas, respectively).	Before 1971: Large abdominal RT fields in stage II or III disease[a]. Mediastinal irradiation and/or palliative limited field RT. Chemotherapy rarely used; mainly monotherapy with cyclophosphamide or mithramycin. RPLND rarely performed. 1971 until summer of 1978: Monotherapy or combinations of cyclophosphamide, actinomycin D, doxorubicin, vincristine, or bleomycin/ vinblastine, methotrexate, mithramycin. From summer of 1978: CVB, three or four courses. Bleomycin omitted if high risk of pulmonary toxicity.
1980–1989	Prophylactic mediastinal irradiation discontinued. Seminomas: adjuvant abdominal RT, dose usually 30 Gy or less. Nonseminomas: staging RPLND or, from 1989, inclusion in a surveillance program.	1980 to 86: CVB. Seminoma patients with advanced stage II disease received post-chemo RT to residual masses until 1986. RT to nonseminoma patients usually only in the palliative setting. From 1987: Transition to the BEP-regimen, three or four courses. Bleomycin omitted if high risk of pulmonary toxicity.
1990–2015	Seminomas: the usage of adjuvant RT was reduced from year 2000 and no longer considered as standard from 2007. Replaced with one course of adjuvant carboplatin. Nonseminomas: From 1995, staging RPLNDs were replaced by surveillance and adjuvant BEP.	The BEP-regimen remained standard first-line therapy. Dose-escalation to ifosfamide-containing regimens. High-dose chemotherapy with autologous stem cell support available from 1995. Stage II seminoma patients received prophylactic mediastinal RT until about year 2000. Decrease in usage of abdominal RT for stage II seminomas after year 2000, but still an option in stage 2A disease.

[a] Stage as defined in the Royal Marsden Hospital staging system [9]

BEP, cisplatin, etoposide, bleomycin; CVB, cisplatin, vinblastine, bleomycin; Gy, Gray; RPLND, retroperitoneal lymph node dissection; RT, radiotherapy; TGCT, testicular germ cell tumor.

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Statistical analysis

In this population-based prospective cohort study, cause of death was the principal outcome parameter. Date and underlying cause of death were obtained from the NCDR for all deceased patients. Deaths were classified using the NCDR shortlist (S1 Table) by reported cause: TC, SC excluding TC, CVD and other causes including unknown (OC).

RS was computed using the method developed by Pohar Perme et al [11]. Standardized mortality ratios (SMRs) with 95% confidence intervals (CIs) were computed for all non-TC causes of death. NCDR mortality data for the general male Norwegian population, matched on 5-year age groups and calendar year, constituted the reference population. Four follow-up time subintervals were defined: <16 years, 16–<26 years, ≥ 26 years and ≥ 5 years, the latter to assess the impact of surveillance bias.

Multiple comparisons correction was not performed due to the explorative nature of the study [12, 13]. Patients with partially missing data were not included in the respective subgroup analyses. The software used was Stata/MP version 15.1, copyright 1985–2017 StataCorp LLC.

Results

Patient characteristics and overall mortality

In total, 9541 patients were included, of whom 5278 were diagnosed with seminoma, 4126 with nonseminoma, and 47 with an unspecified TGCT (Table 2). Overall, 79% of seminomas and 60% of nonseminomas were localized at diagnosis. Disease extent was unknown in 457 patients. Median age at diagnosis was 38 and 29 years for seminoma and nonseminoma patients, respectively. Median follow-up times were 23.5 years for TGCT patients diagnosed <1980, 28.9 years when diagnosed in the 1980s and 10.0 years when diagnosed >1989.

Table 2. Persons at risk, cumulative deaths and relative survival by follow-up time.

	Cohort of diagnosis	Follow-up time (years)										Total deaths at end of follow-up
		0	1	5	10	20	25	30	35	40	50	
Persons at risk (SL, SM) (NL, NM)	1953–1979	1866 (827, 236) (439, 333)	1540 (795, 162) (399, 160)	1253 (721, 115) (313, 84)	1181 (686, 102) (298, 78)	1000 (576, 74) (265, 71)	895 (510, 58) (249, 65)	771 (428, 49) (225, 56)	626 (331, 36) (201, 48)	348 (189, 17) (116, 17)	68 (32, 4) (29, 1)	
	1980–1989	1360 (530, 137) (328, 357)	1325 (527, 124) (325, 341)	1260 (510, 110) (320, 315)	1225 (493, 105) (313, 309)	1115 (434, 88) (295, 295)	1040 (389, 79) (285, 284)	547 (196, 48) (133, 168)	58 (14, 2) (20, 22)			
	1990–2015	6315 (2805, 471) (1754, 821)	5956 (2638, 436) (1658, 762)	4605 (1936, 346) (1264, 611)	3166 (1285, 247) (877, 446)	932 (416, 79) (294, 152)	135 (53, 13) (48, 21)					
Cumulative deaths (TC, SC) (CVD, OC)	1953–1979	0	325 (299, 2) (2, 22)	609 (550, 9) (14, 36)	678 (573, 22) (34, 49)	859 (593, 79) (98, 89)	962 (593, 120) (134, 110)	1086 (603, 173) (176, 134)	1228 (611, 230) (218, 169)	1356 (615, 283) (259, 199)	1492 (616, 335) (294, 247)	1518 (617, 342) (300, 259)
	1980–1989	0	35 (27, 5) (1, 2)	95 (67, 10) (10, 8)	125 (69, 18) (20, 18)	227 (71, 57) (50, 49)	298 (73, 85) (65, 75)	359 (76, 115) (74, 94)	395 (76, 135) (81, 103)			395 (76, 135) (81, 103)
	1990–2015	0	69 (41, 11) (6, 11)	189 (101, 21) (7, 50)	272 (110, 46) (35, 81)	381 (122, 84) (56, 119)	411 (123, 98) (59, 131)					411 (123, 98) (59, 131)
Relative survival, % (95% CI)	1953–1979	100	83.0 (81.2–84.6)	69.0 (66.8–71.2)	67.2 (64.7–69.6)	61.9 (58.9–64.8)	59.2 (55.8–62.4)	55.4 (51.2–59.3)	48.4 (42.4–54.1)	38.7 (32.6–44.8)	26.3 (18.3–34.9)	
	1980–1989	100	97.8 (96.8–98.5)	94.5 (92.9–95.8)	94.2 (92.2–95.7)	90.5 (87.1–93.1)	88.4 (84.5–91.4)	85.0 (79.4–89.1)				
	1990–2015	100	99.1 (98.8–99.3)	97.9 (97.3–98.3)	97.2 (96.4–97.8)	95.4 (93.3–96.9)	92.8 (88.9–95.4)					

NL or NM, nonseminoma, localized or metastatic at diagnosis; SL or SM, seminoma, localized or metastatic at diagnosis; TC, testicular cancer; SC, second cancer (excluding TC); CVD, cardiovascular disease; OC, other causes; CI, confidence interval. Cumulative deaths by histology and disease extent at diagnosis are given in S2 Table.

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At end of follow-up, 2324 deaths had occurred. Of these, 816 were due to TC, 575 to SC, 440 to CVD and 493 to OC including 56 deaths of unknown cause (Table 2, S2 Table). Bilateral TC was registered in 2.9% of patients, and 102 patients had emigrated. The overall non-TC SMR was 1.36, 95% CI 1.30–1.44.

Testicular cancer mortality

During the first five years after TGCT diagnosis, 718 of 893 deaths (80%) were caused by TC. About 90% of TC deaths occurred within five years of follow-up. TC deaths were more common in patients diagnosed <1980, among nonseminoma patients and in patients with metastatic TGCT at diagnosis (Table 2, S2 Table).

Second cancer mortality, excluding testicular cancer

The overall SC SMR was 1.84 (95% CI 1.74–2.06), causing 262 (65%) of 402 excess non-TC deaths. Median time to SC death was 24.2 years after TGCT diagnosis (25^{th}–75^{th} percentile 14.5–32.5 years).

SC SMRs ranged from 1.39 among TCS diagnosed >1989 to 2.00 among TCS diagnosed <1980 (Table 3). In general, SC SMRs increased with follow-up and were higher among TCS with metastatic TGCT at diagnosis. TCS diagnosed with localized seminoma >1979 had elevated SC SMRs, while those with localized nonseminoma did not (S3 Table).

Gastrointestinal and non-TC genitourinary cancer caused 38% and 15% of excess SC deaths, respectively. Gastric, pancreatic and bladder cancer caused 34% of excess SC deaths combined, with SMRs of 2.62–2.97 in TCS diagnosed <1980 and 3.98–4.74 among those diagnosed in the 1980s. For gastric and bladder cancers, SMRs were also elevated ≥16 years of follow-up among TGCT patients diagnosed >1989 (Table 3).

SMRs were generally threefold elevated in the "other malignant neoplasms" group. This group comprises several cancer forms, for which separate SMRs were not calculated (S1 Table). However, about half of deaths in this group were due to either sarcoma or cancer of unknown origin.

TCS diagnosed <1980 also had elevated SMRs for cancer of the large intestine, liver or intrahepatic bile ducts, prostate and central nervous system, melanoma, certain hematological malignancies, and esophageal cancer (the latter ≥26 years of follow-up only). Additionally, there was an about twofold risk of death from cancer of the lung, trachea or bronchus <16 years of follow-up.

TCS diagnosed in the 1980s had an SMR of 1.89 for cancer of the lung, trachea or bronchus. The SMR for cancer of the lip, oral cavity or pharynx was 3.44. ≥26 years of follow-up, there was an about twofold risk of death from cancer of the large intestine.

Among TCS diagnosed >1989, the SMRs for leukemia, esophageal and central nervous system cancer were 3.47, 2.61 and 1.98, respectively.

Cardiovascular disease mortality

The CVD SMR for all TCS was borderline significant at 1.09 (95% CI 0.99–1.22), causing 35 (9%) of excess non-TC deaths. Median time to CVD death was 21.4 years (25^{th}–75^{th} percentile 12.2–32.4 years). Thirty-one (89%) of the excess CVD deaths, mostly non-ischemic heart diseases, occurred among TCS initially diagnosed with metastatic TGCT.

Among TCS diagnosed <1980, the overall CVD SMR was 1.12, and 1.88 for TCS diagnosed with metastatic seminoma. The SMR for non-ischemic heart diseases was 1.59 (Table 3 and S3 Table).

TCS diagnosed in the 1980s had a 50% increased risk of death from acute myocardial infarction <16 years of follow-up, as had TCS diagnosed with localized seminoma (S3 Table). TCS diagnosed with metastatic seminoma had an about fivefold risk of death from non-ischemic heart diseases.

The only significant finding in TCS diagnosed >1989 was among TCS diagnosed with metastatic nonseminoma with <16 years of follow-up, where the CVD SMR was 2.23 (S3 Table). Five of seven deaths were due to heart diseases.

Other cause mortality

The OC SMR for all TGCT patients was 1.27 (95% CI 1.17–1.39), causing 105 (26%) of 402 excess non-TC deaths. Of these, 18 (17%) were of unknown cause (Table 3, S3 Table). Median time to OC death was 19.1 years (25^{th}–75^{th} percentile 7.7–31.0 years).

Table 3. Standardized mortality ratios for selected causes of death among testicular germ cell tumor patients diagnosed in Norway.

Cause of death	Cohort of diagnosis									Code[a]
	1953–1979			1980–1989			1990–2015			
	O	SMR (95% CI)	SMR by follow-up time[b]	O	SMR (95% CI)	SMR by follow-up time	O	SMR (95% CI)	SMR by follow-up time	
Testicular cancer	617			76			123			
All non-TC causes	901	**1.42** (1.33–1.52)	A(**1.34**),B(**1.42**),C(**1.46**),D(**1.41**)	319	**1.36** (1.22–1.52)	A(**1.26**),B(**1.38**),C(**1.51**),D(**1.39**)	288	**1.21** (1.08–1.35)	A(**1.21**),D(**1.17**)	
All non-TC second cancers	342	**2.00** (1.79–2.23)	A(**1.70**),B(**2.12**),C(**2.05**),D(**2.03**)	135	**1.90** (1.61–2.25)	A(**1.57**),B(**1.94**),C(**2.26**),D(**1.90**)	98	**1.39** (1.15–1.70)	A(**1.27**),B(**1.77**),D(**1.45**)	2.1-TC
MN, lip, oral cavity, pharynx	3	0.99 (0.31–4.87)		5	**3.44** (1.45–10.27)	A(**5.79**),D(**2.96**)	2	1.44 (0.31–14.42)		2.1.1
MN, esophagus	7	1.99 (0.97–4.77)	C(**2.74**)	1	0.55 (–)		5	**2.61** (1.10–7.77)	B(**7.64**),D(**3.30**)	2.1.2
MN, stomach	31	**2.62** (1.86–3.81)	B(**4.29**),C(**2.64**),D(**2.89**)	13	**3.98** (2.36–7.26)	A(**4.78**),C(**4.65**),D(**4.52**)	5	1.90 (0.80–5.66)	B(**5.23**),D(**2.58**)	2.1.3
MN, colorectal, anus	44	**1.95** (1.46–2.66)	C(**2.25**),D(**2.89**)	11	1.17 (0.67–2.24)	C(**2.36**)	6	0.65 (0.30–1.71)		2.1.4
MN, liver, intrahepatic ducts	11	**5.68** (3.21–11.07)	B(**8.92**),C(**6.22**),D(**5.93**)	1	0.91 (–)		2	1.34 (0.29–13.48)		2.1.5
MN, pancreas	28	**2.97** (2.08–4.41)	B(**4.11**),C(**3.50**),D(**3.10**)	18	**4.31** (2.75–7.13)	B(**6.45**),C(**3.96**),D(**4.35**)	8	1.85 (0.95–4.16)		2.1.6
MN, trachea, bronchus, lung	47	1.25 (0.94–1.69)	A(**2.02**)	32	**1.89** (1.35–2.72)	A(**1.82**),B(**2.30**),D(**1.96**)	14	0.87 (0.53–1.55)		2.1.8
Melanoma	10	**2.53** (1.39–5.11)	B(**5.53**),D(**2.63**)	3	1.18 (0.37–5.80)		6	2.00 (0.91–5.26)		2.1.9
MN, prostate	39	**1.46** (1.08–2.04)	A(**2.43**),C(**1.53**),D(**1.42**)	7	0.83 (0.40–1.99)		9	1.30 (0.69–2.78)		2.1.14
MN, kidney	13	**2.64** (1.57–4.83)	C(**3.29**),D(**2.76**)	1	0.46 (–)		2	0.91 (0.20–9.09)		2.1.15
MN, bladder	18	**2.71** (1.73–4.48)	A(**4.03**),B(**2.96**),C(**2.32**),D(**2.64**)	10	**4.74** (2.60–9.55)	B(**3.44**),C(**10.31**),D(**5.10**)	4	2.32 (0.87–8.33)	B(**4.73**)	2.1.16
MN, brain and CNS	9	**2.06** (1.09–4.37)	B(**3.41**)	2	0.67 (0.14–6.73)		8	**1.98** (1.01–4.45)	A(**2.46**),D(**2.39**)	2.1.17
Hodgkin disease, lymphoma	6	1.32 (0.60–3.47)		1	0.44 (–)		2	0.97 (0.21–9.71)		2.1.19
Leukemia	8	1.60 (0.82–3.60)		3	1.59 (0.50–7.84)		6	**3.47** (1.59–9.15)	A(**3.83**),D(**3.04**)	2.1.20
MN, other lymph./ hematol.[c]	9	**1.89** (1.00–4.00)	A(**3.91**),D(**2.16**)	2	1.65 (0.26–12.1)		1	0.71 (–)		2.1.21
MN, other (no TC deaths)	59	**3.50** (2.73–4.57)	A(**2.31**),B(**3.08**),C(**4.20**),D(**3.55**)	24	**3.68** (2.50–5.65)	A(**2.35**),B(**4.39**),C(**4.78**),D(**3.37**)	17	**2.72** (1.72–4.57)	A(**2.43**),B(**3.83**),D(**2.63**)	2.1.22
Cardiovascular disease	300	**1.12** (1.00–1.26)	D(**1.14**)	81	1.07 (0.85–1.34)		59	0.96 (0.75–1.26)		7.
Ischemic heart diseases	169	1.06 (0.91–1.24)		52	1.21 (0.92–1.60)		30	0.92 (0.65–1.34)		7.1
Acute myocardial infarction	119	1.06 (0.89–1.28)		39	1.34 (0.99–1.87)	A(**1.51**)	18	0.84 (0.54–1.40)		7.1.1
Non-ischemic heart diseases	50	**1.59** (1.20–2.13)	B(**1.86**),C(**1.55**),D(**1.59**)	16	1.42 (0.87–2.46)		13	1.25 (0.74–2.31)		7.2
Cerebrovascular diseases	44	0.88 (0.66–1.20)		5	0.37 (0.16–1.09)		13	1.20 (0.71–2.21)		7.3
Other circulatory diseases	37	**1.39** (1.02–1.96)	D(**1.40**)	8	1.02 (0.51–2.30)		3	0.45 (0.14–2.17)		7.4

(*Continued*)

Table 3. (Continued)

Cause of death	Cohort of diagnosis									Code[a]
	1953–1979			1980–1989			1990–2015			
	O	SMR (95% CI)	SMR by follow-up time[b]	O	SMR (95% CI)	SMR by follow-up time	O	SMR (95% CI)	SMR by follow-up time	
Other or unknown causes	259	**1.34** (1.18–1.51)	A(**1.53**),C(**1.32**),D(**1.24**)	103	1.19 (0.98–1.45)	D(**1.24**)	131	**1.23** (1.04–1.46)	A(**1.25**)	
Infectious / parasitic diseases	8	1.12 (0.57–2.52)		6	1.82 (0.83–4.79)		10	**3.06** (1.69–6.18)	A(**3.64**),D(**2.47**)	1.
Endocrine, nutr., metab.[d]	15	1.50 (0.92–2.62)	B(**2.66**)	10	**2.06** (1.13–4.19)	D(**1.99**)	3	0.54 (0.17–2.64)		4.
Nervous system, sense organs	15	1.07 (0.66–1.87)		3	0.45 (0.14–2.22)		13	**1.72** (1.02–3.14)	A(**2.08**)	6.
Alzheimer's disease	2	0.73 (0.16–7.26)		0	0 (–)		4	**3.85** (1.46–13.57)	A: **5.68**, D(**4.64**)	6.2
Respiratory system diseases	44	0.88 (0.66–1.20)		14	0.89 (0.55–1.56)		10	0.74 (0.41–1.50)		8.
Other respiratory diseases[e]	3	0.77 (0.24–3.79), 3	A(**4.87**)	5	**3.35** (1.41–10.00)	A(**6.80**),B(**4.63**),D(**3.48**)	1	0.71 (–)		8.4
Digestive system diseases	50	**2.83** (2.16–3.78)	B(**3.20**),C(**3.26**),D(**2.88**)	19	**2.51** (1.62–4.11)	B(**3.44**),D(**2.64**)	9	1.21 (0.64–2.57)		9.
Ulcers, stomach–jejunum	11	**3.78** (2.13–7.38)	B(**6.09**),C(**3.23**),D(**3.31**)	1	1.30 (–)		2	3.32 (0.71–33.43)		9.1
Cirrhosis, fibrosis, c. hep[f]	5	1.02 (0.43–3.03)		8	**2.57** (1.31–5.77)	A(**2.83**),D(**2.91**)	3	0.96 (0.30–4.74)		9.2
Other digestive diseases	34	**3.64** (2.62–5.20)	B(**3.95**),C(**4.20**),D(**3.82**)	10	**2.98** (1.62–6.05)	B(**4.40**),D(**2.89**)	4	1.24 (0.47–4.47)		9.3
Genitourinary diseases	21	**2.31** (1.54–3.64)	C(**2.70**),D(**2.50**)	2	0.87 (0.19–8.69)		7	**3.76** (1.82–8.99)	A(**5.18**),D(**2.70**)	12.
External causes	36	0.94 (0.68–1.33)		27	1.14 (0.79–1.70)		58	**1.47** (1.15–1.93)	A(**1.33**),B(**2.48**),D(**1.49**)	17.
Accidents	25	0.90 (0.62–1.38)		17	1.15 (0.73–1.93)		35	**1.46** (1.06–2.07)	B(**2.59**),D(**1.53**)	17.1
Suicide	10	1.02 (0.56–2.08)		10	1.23 (0.68–2.49)		22	**1.54** (1.03–2.42)		17.2

Causes of death are classified according to S1 Table. Statistically significant results (P = <0.05) are highlighted in bold.

CI, confidence interval; O, observed deaths in the study population; MN, malignant neoplasm; SMR, standardized mortality ratio; TC, testicular cancer.

[a] Code for cause of death as defined in S1 Table.

[b] Subgroups with statistically significant SMRs pertaining to follow-up time, given in parentheses: A, <16 years follow-up only; B, 16-<26 years follow-up only; C, ≥26 years follow-up only; D, ≥5 years follow-up only. SMRs for additional conditions with 95% CI by follow-up, histology and disease extent at diagnosis are given in S3 Table.

[c] Other malignant neoplasms of lymphoid and hematopoietic tissue.

[d] Endocrine, nutritional and metabolic diseases.

[e] Excluding influenza (code 8.1), pneumonia (code 8.2) and chronic lower respiratory diseases (code 8.3).

[f] Chronic hepatitis.

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Digestive and genitourinary diseases caused 58% of excess deaths in the OC category. SMRs for digestive diseases were increased about threefold in TCS diagnosed <1990 (Table 3). Thirteen of 45 excess deaths by digestive diseases were due to ulcers or chronic liver disease, while intestinal disorders caused most of the remaining excess deaths.

Among TCS diagnosed <1980, the SMR for genitourinary diseases was 2.31. TCS diagnosed in the 1980s had a twofold risk of death from endocrine, nutritional and/or metabolic

diseases and a threefold risk of death from a subgroup of respiratory disorders not including pneumonia and chronic lower respiratory disorders (S1 Table).

TCS diagnosed >1989 had elevated SMRs for genitourinary diseases (3.76) including diseases of the kidney and ureter (3.18), infections (3.06) and nervous system / sense organ diseases (1.72) including Alzheimer's disease (3.85). Elevated SMRs for suicide (1.54) and accidents (1.46) were found, elevated also among nonseminoma patients with metastases at diagnosis (S3 Table). Median time to suicide among TCS diagnosed >1989 was 7.1 years (25^{th}–75^{th} percentile 2.8–12.7 years), and the median age at suicide was 40.1 years (25^{th}–75^{th} percentile 34.0–50.0 years).

Mortality among five-year TGCT survivors

In general, restricting SMR analyses to the 7111 five-year TCS caused only minor changes in SMRs from those of the entire study population (Table 3, S3 Table). Notable exceptions were that the SMRs for suicide and nervous system diseases in TCS diagnosed >1989 were no longer significantly elevated. This was also true for central nervous system cancer in TCS diagnosed <1980. Conversely, the SMR for stomach cancer became significantly elevated for five-year TCS diagnosed >1989, bladder cancer for TCS diagnosed <1980, as did the OC SMR among TCS diagnosed in the 1980s.

Relative survival by cause of death category, all TGCT patients

RS among TGCT patients generally declined with increasing follow-up time (Fig 1, Table 2). While TC deaths were the main cause of reduced RS during the first five years of follow-up, non-TC causes gradually became dominant beyond this time, with elevated SMRs among TCS increasing with follow-up even ≥26 years. Overall, SC was the prime non-TC contributor to reduced RS (Fig 1, Table 3). Patients diagnosed with localized seminoma >1979 had increased overall non-TC SC SMRs, while patients with localized nonseminoma did not, contributing to the inferior RS point estimates for this patient group.

Both short- and long-term RS improved significantly from TGCT patients diagnosed <1980 to patients diagnosed in the 1980s. Five-year RS increased from 69.0 to 94.5%, while 25-year RS increased from 59.2 to 88.4%. Further increases in RS point estimates were seen among TGCT patients diagnosed >1989 (Fig 1, Table 2). Five-year TC-specific RS increased from 70.1% (95% CI 68.0–72.1%) among patients diagnosed <1980 to 95.0% (95% CI 93.7–96.1%) in the 1980s and 98.3% (95% CI 97.9–98.6%) >1989.

Discussion

The primary objective of this study was to give an overview of causes of excess mortality and their impact on RS among men diagnosed with TGCT in Norway, 1953–2015, compared with the general Norwegian male population.

TC was, unsurprisingly, the main cause of declining RS during the first five years after diagnosis. Non-TC SC became the prime contributor to the continuing decline in RS beyond this time, particularly due to excess mortality from gastrointestinal and non-TC genitourinary cancer. Similarly, non-malignant digestive and genitourinary diseases were important contributors to excess OC mortality. CVD was a comparatively minor contributor, with most excess deaths occurring among TCS diagnosed with metastatic TGCT.

Other notable findings included the elevated non-TC SMRs among seminoma patients diagnosed with localized disease >1979, and the elevated SMR for suicide in patients diagnosed >1989.

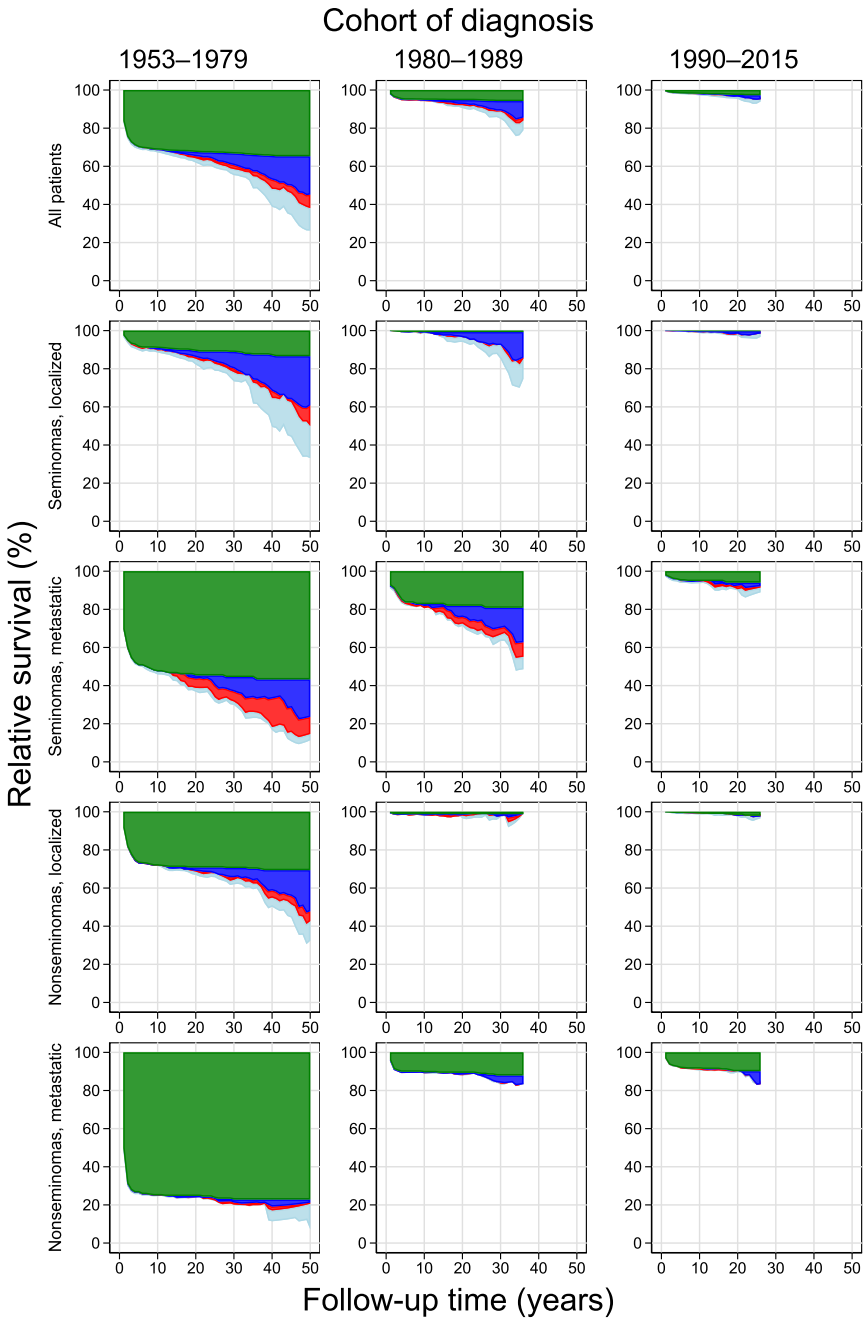
Cohort of diagnosis
1953–1979
1980–1989
1990–2015
All patients
Seminomas, localized
Seminomas, metastatic
Nonseminomas, localized
Nonseminomas, metastatic
Relative survival (%)
Follow-up time (years)

Fig 1. Point estimates for relative survival among testicular germ cell patients diagnosed in Norway, by histology and disease extent at diagnosis, with cause of death category. Survival in the reference population is always 100%.

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Increased SMRs for central nervous system cancer and nervous / sensory system diseases including Alzheimer's disease, were novel findings, though based on few cases. Many studies have shown an inverse relationship between cancer and dementia, although bias cannot be ruled out [14]. Prostate cancer excess mortality among TCS diagnosed <1980 was also a novel finding, though consistent with excess risks previously reported [15, 16]. Patients with a previous genitourinary cancer are perhaps more likely to be screened for prostate cancer, thus increasing detection.

To our knowledge, this is the first study to examine the impact of any cause of excess mortality on RS among TGCT patients. Study strengths are the inclusion of almost ten thousand patients diagnosed both in the pre- and post-cisplatin era regardless of disease extent and histology, inclusion of all causes of death, and the long follow-up times, all using high quality data sources. We believe our study has high external validity.

Several studies have reported long-term cause-specific mortality data among TC patients (S4 Table). Most of these studies are registry based and lack complete treatment data.

Mortality after radiotherapy

Radiation-induced DNA damage may lead to long-term effects such as stromal change with collagen deposition and neoangiogenesis causing organ dysfunction [17]. An increased SC risk within radiation fields with a dose-response relationship has been reported among TCS [18]. Increased mortality from SC, CVD, gastrointestinal diseases and infections has also been reported after radiotherapy (S4 Table). Zagars et al reported an SC SMR of 1.91 and a CVD SMR of 1.61 beyond 15 years of follow-up among stage I-II seminoma patients. Prophylactic mediastinal irradiation was the only factor correlated with survival in univariate analysis [19].

In Norway, most patients diagnosed in the pre-cisplatin era received infradiaphragmatic radiotherapy. Adjuvant radiotherapy was omitted in nonseminoma patients from 1980, whereas stage I seminoma patients continued to receive adjuvant irradiation to the paraaortic lymph nodes until about year 2007. Stage II seminoma patients received prophylactic mediastinal radiotherapy until about year 2000 (Table 1).

Thus, our findings suggest that infradiaphragmatic radiotherapy is a strong contributor to declining long-term RS by excess mortality from SC and OC in TCS diagnosed <1980, as well as in patients with localized seminoma. Mediastinal radiotherapy may likewise explain the excess CVD mortality among patients with metastatic seminoma diagnosed <1980, or the excess lung cancer mortality among corresponding patients diagnosed in the 1980s.

Mortality after chemotherapy

Cisplatin-based chemotherapy regimens are associated with a wide range of toxicities and late effects, including nephrotoxicity, CVD and SC [20–22]. Such treatment might increase the CVD risk directly through vascular damage, or indirectly through modifying CVD risk factors, such as obesity, hypercholesteremia and hypertension [23]. Cisplatin can be detected in the blood and urine for decades after treatment, and serum levels have been positively correlated to SC risk [21, 24]. Cisplatin and etoposide have been linked to excess leukemia risk, often manifesting earlier than solid cancers [25]. Bleomycin can cause life-threatening pulmonary toxicity [20].

Several studies have analyzed long-term mortality among TGCT patients who received chemotherapy (S4 Table). Kier et al [26] reported a 1.6 times risk of SC death among Danish

patients diagnosed between 1984 and 2008. Fung et al [5] reported a CVD SMR of 1.36 among nonseminoma patients diagnosed between 1980 and 2010.

Combined radio- and chemotherapy yields a higher risk of non-TC death than either treatment alone. Conversely, patients having undergone initial surgery only seem to be at lower risk [26]. Our findings of excess mortality from CVD, SC, respiratory and genitourinary diseases could thus partly be chemotherapy-related.

Treatment-independent mortality

SC has been reported to be more common among seminoma patients [15, 16, 27], who are approximately ten years older than nonseminoma patients at diagnosis, possibly causing a reduced long-term tolerance to treatment [28]. Moreover, previous TCGT treatment may hamper the possibility to provide effective SC treatment [29]. Repeated CT scans could be associated with elevated SC risks [30].

TC development occurs by an interaction between polygenetic, environmental and hormonal causes [31]. TGCT patients might genetically be more susceptible to developing life-threatening diseases such as cancer. A recent study on TC patients diagnosed 1980–2009 in Norway with complete treatment information, found increased SC risk even after surgery only [32].

Increased suicide risk has been reported among US TCS [33–35]. In a recent Norwegian study, TCS born between 1965 and 1985, diagnosed before age 25, had a suicide hazard ratio of 2.9 [36].

Some evidence suggests increased prevalence of anxiety disorder [37] and fatigue [38] among TC patients. In a 2016 study, increased prevalence of depression and reduced health-related quality of life was also found [39], though other studies indicate that health-related quality of life in TCS is similar to the general population [40]. These findings could partly explain the increased suicide risk, as could changes in coding practices.

Conversely, general health care advances during the last decades have probably improved survival in the study population as well.

Study limitations

Incomplete CRN treatment and relapse data makes the long-term effects of a particular treatment difficult to assess.

Potential differences in comorbidity and smoking habits, for which we had no data, could affect SMRs and RS [41]. For instance, men with Down's syndrome have increased risks for both TC and several other conditions such as Alzheimer's disease [42]. With an overall median age of <40 years at diagnosis, we nevertheless expect little pre-TGCT comorbidity, and smoking habits were likely similar in the reference population [43].

TC deaths were not excluded from the NCDR reference population data, which could have led to a slight underestimation of overall SC SMRs. SMR and RS subgroup comparisons should be interpreted with caution due to potential differences in age distribution, follow-up time and reference population mortality rate. The decision to not perform multiple comparisons correction increases the risk of type I errors. Several SMRs are based on a relatively low number of cases, but there was no way of expanding the study sample as all eligible patients were included.

Surveillance bias must be considered, particularly during the first five years of follow-up. It is possible, for instance, that a patient that has previously been diagnosed with cancer is more likely to have any subsequent condition detected due to more vigorous follow-up. This could ultimately have an impact on survival. We included TGCT patients followed for <5 years in

the analyses as to not infer a particular mechanism behind excess deaths (i.e., treatment-induced as opposed to genetic or other conditions), but also to provide the most complete estimate of RS across the entire follow-up period from time of TGCT diagnosis.

To investigate the extent of surveillance bias, we performed separate SMR analyses on five-year TCS only (Table 3, S3 Table). Because of the long MTD for most conditions, it was as expected that most SMRs did not significantly change for analyses restricted to five-year survivors. A few SMRs were no longer significantly elevated, perhaps most notably the important finding of increased suicide risk among TCS diagnosed >1989. As the MTD was 7.1 years and the number of cases was limited, such a result was not unexpected. The SMR point estimate of 1.54 remained unchanged. We conclude that the overall impact of surveillance bias on our results is negligible.

Conclusions

Despite the improved prognosis for cure, death by TC remains the main cause of excess mortality the first five years of follow-up among TGCT patients diagnosed in Norway. TCS also remain at increased long-term risk of death by SC in particular, negatively impacting RS even beyond 25 years of follow-up. Malignant and non-malignant diseases of the gastrointestinal and genitourinary organs are among the main long-term causes of excess mortality, while CVD is a comparatively minor cause. Late effects of radio- and chemotherapy are the main culprits. The elevated non-TC SMRs among seminoma patients diagnosed in the 1980s could be due to radiotherapy given in early-stage disease.

RS point estimates are highest among patients diagnosed >1989, but follow-up time is also the shortest. Excess mortality among these patients, including suicide, is a concern. Continuing optimization of TGCT treatment and appropriate follow-up schemes are thus required, covering psychosocial health as well. Particular focus should be on the follow-up of patients previously treated with radio- and/or chemotherapy. Further research should also be directed towards identifying subgroups of TGCT patients and survivors at particular risk of excess mortality.

Supporting information

S1 Table. Extended EU shortlist for causes of death, in use by the Norwegian Cause of Death Registry.
(DOCX)

S2 Table. Cumulative deaths by cause of death, histology, disease extent at diagnosis and follow-up time.
(DOCX)

S3 Table. Standardized mortality ratios for selected causes of death among testicular germ cell tumor patients diagnosed in Norway.
(DOCX)

S4 Table. Summary of selected publications reporting long-term cause-specific mortality data among testicular cancer patients.
(DOCX)

S5 Table. STROBE checklist.
(DOC)

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S1 Table. Extended European shortlist for causes of death, in use by the Norwegian Cause of Death Registry.

Code	Description	ICD-10	ICD-9	ICD-8	ICD-6/7
1.	Infectious and parasitic diseases	A00-B99	001-139	000-136	001-138, 571
1.1	Tuberculosis	A15-A19, B90	010-018, 137	010-019	001-019
1.2	AIDS (HIV-disease)	B20-B24	042-044 (279.1)	-	-
1.3	Viral hepatitis	B15-B19, B94.2	070	070	092
1.4	Other infectious and parasitic diseases	A00-A09, A20-B09, B25-B89, B91-B94.1, B94.8-B99	001-009, 020-041, 045-066, 071-136, 138-139	000-009, 020-068, 071-136	020-091, 093-138, 571
2.	Neoplasms	C00-D48	140-239	140-239	140-239
2.1*	Malignant neoplasms	C00-C97	140-208	140-209	140-207
2.1.1	Malignant neoplasm of lip, oral cavity, pharynx	C00-C14	140-149	140-149	140-148
2.1.2	Malignant neoplasm of esophagus	C15	150	150	150
2.1.3	Malignant neoplasm of stomach	C16	151	151	151
2.1.4	Malignant neoplasm of colon, rectum and anus	C18-C21	153-154	153-154	153-154
2.1.5	Malignant neoplasm of liver and intrahepatic bile ducts	C22	155	155, 197.8	155-156
2.1.6	Malignant neoplasm of pancreas	C25	157	157	157
2.1.7	Malignant neoplasm of larynx	C32	161	161	161
2.1.8	Malignant neoplasm of trachea, bronchus, lung	C33-C34	162	162	162-163
2.1.9	Malignant melanoma of skin	C43	172	172	190
2.1.10	Malignant neoplasm of breast	C50	174-175	174	170
2.1.11	Malignant neoplasm of cervix uteri	C53	180	180	171
2.1.12	Malignant neoplasm of other and unspecified parts of uterus	C54-C55	179, 182	182	172, 174
2.1.13	Malignant neoplasm of ovary	C56	183.0	183.0	175
2.1.14	Malignant neoplasm of prostate	C61	185	185	177
2.1.15	Malignant neoplasm of kidney	C64	189.0	189.0	180
2.1.16	Malignant neoplasm of bladder	C67	188	188	181
2.1.17	Malignant neoplasm of brain and central nervous system	C70-C72	191-192	191-192	193.0-193.2
2.1.18	Malignant neoplasm of thyroid	C73	193	193	194
2.1.19	Hodgkin disease and lymphomas	C81-C86	200-201	200-201	201-202
2.1.20	Leukemia	C91-C95	204-208	204-208	204

2.1.21	Other malignant neoplasms of lymphoid and hematopoietic tissue	C88, C90, C96	202-203	202-203	200, 203, 205, 206, 207
2.1.22[a]	Other malignant neoplasms	C17, C23-C24, C26-C31, C37-C41, C44-C49, C51-C52, C57-C60, **C62**-C63, C65-C66, C68-C69, C74-C80, C97	152, 156, 158-160, 163-171, 173, 181, 183.2-184, **186**-187, 189.1-190, 194-199	152, 156, 158-160, 163-171, 173, 181, 183.1-184, **186**-187, 189.1-190, 194-197.7, 197.9-199	152, 158-160, 164-165, 173, 176, **178**-179, 191-192, 193.3-193.9, 195-199
2.2	Non-malignant neoplasms (benign and uncertain)	D00-D48	209-239	210-239	210-239
3.	Diseases of the blood and blood forming organs and certain disorders involving the immune mechanism	D50-D89	280-289	280-289	290-299
4.	Endocrine, nutritional and metabolic diseases	E00-E89	240-279	240-279	250-289
4.1	Diabetes mellitus	E10-E14	250	250	260
4.2	Other endocrine, nutritional and metabolic diseases	E00-E07, E15-E89	240-246, 251-279	240-246, 251-279	250-254, 270-289
5.	Mental and behavioral disorders	F01-F99	290-319	290-315	300-326
5.1	Dementia	F01, F03	290	290	304-305
5.2	Alcohol abuse (including alcoholic psychosis)	F10*	291, 303	291, 303	307, 322
5.3	Drug dependence, toxicomania	F11*-F16*, F18*-F19*	304-305	304-305	323
5.4	Other mental and behavioral disorders	F04-F09, F17*, F20-F99	292-302, 306-319	292-302, 306-315	300-306, 308-321, 324-326
6.	Diseases of the nervous system and the sense organs	G00-H95	320-389	320-389	340-398
6.1	Parkinson's disease	G20	332.0	342	350
6.2	Alzheimer's disease	G30	331.0	-	-
6.3	Other diseases of the nervous system and the sense organs	G00-G12, G14, G21-G25, G31-H95	320-330, 331.1-331.9, 332.1-389	320-341, 343-389	340-345, 351-398
7.	Diseases of the circulatory system	I00-I99	390-459	390-444.1, 444.3-458, 782.4	330-334, 400-468, 782.4
7.1	Ischemic heart diseases	I20-I25	410-414	410-414	420, 422.1
7.1.1	Acute myocardial infarction	I21-I22	410-411	410-411	420.1

7.1.2	Other ischemic heart diseases	I20, I23-I25	412-414	412-414	420.0, 420.2, 422.1
7.2	Other heart diseases	I30-I51	420-429	420-429	430-434
7.3	Cerebrovascular diseases	I60-I69	430-438	430-438	330-334
7.4	Other diseases of the circulatory system	I00-I15, I26-I28, I70-I99	390-405, 415-417, 440-459	390-404, 440-444.1, 444.3-458, 782.4	400-416, 421, 422.0, 422.2, 440-468, 782.4
8.	Diseases of the respiratory system	J00-J99	460-519	460-519	470-527, 240, 241
8.1	Influenza	J09-J11	487	470-474	480-493
8.2	Pneumonia	J12-J18	480-486	480-486	490-493
8.3	Chronic lower respiratory diseases	J40-J47	490-494, 496	491-493, 518	241, 501, 502, 526, 527.1
8.3.1	Asthma	J45-J46	493	493	241
8.3.2	Other chronic lower respiratory diseases	J40-J44, J47	490-492, 494, 496	491-492, 518	501, 502, 526, 527.1
8.4	Other diseases of the respiratory system	J00-J06, J20-J39, J60-J99	460-478, 495, 500-519	460-466, 490, 500-517, 519	240, 470-475, 500, 510-525, 527.0, 527.2
9.	Diseases of the digestive system	K00-K92	520-579	520-577, 444.2	530-570, 572-587
9.1	Ulcer of stomach, duodenum and jejunum	K25-K28	531-534	531-534	540-542
9.2	Cirrhosis, fibrosis and chronic hepatitis	K70, K73-K74	571	571	581
9.3	Other diseases of the digestive system	K00-K22, K29-K66, K71-K72, K75-K92	520-530, 535-570, 572-579	520-530, 535-570, 572-577, 444.2	530-539, 543-570, 572-580, 582-587
10.	Diseases of the skin and subcutaneous tissue	L00-L99	680-709	680-709	690-716
11.	Diseases of the musculoskeletal system / connective tissue	M00-M99	710-739	710-738	720-749
11.1	Rheumatoid arthritis and osteoarthrosis	M05-M06, M15-M19	714-715	712-713	722-723
11.2	Other diseases of the musculoskeletal system / connective tissue	M00-M02, M08-M13, M20-M99	710-712, 716-739	710-711, 714-738	720-721, 724-749
12.	Diseases of the genitourinary system	N00-N99	580-629	580-629, 792	590-637, 792
12.1	Diseases of kidney and ureter	N00-N29	580-594	580-594	590-604
12.2	Other diseases of the genitourinary system	N30-N99	595-629	595-629, 792	605-637, 792
13.	Complications of pregnancy, childbirth and puerperium	O00-O99	630-676	630-678	640-689

14.	Certain conditions originating in the perinatal period	P00-P96	760-779	760-779	760-777
15.	Congenital malformations and chromosomal abnormalities	Q00-Q99	740-759	740-759	750-759
16.	Symptoms, signs, ill-defined causes	R00-R99	780-799	780-782.3, 782.5-791, 793-796	780-782.3, 782.5-791, 793-795
16.1	Sudden infant death syndrome	R95	798.0	-	-
16.2	Unknown and unspecified causes	R96-R99	798.1-9, 799.0,2-3,5-9	796-796	795
16.3	Other symptoms, signs, ill-defined causes	R00-R94	780-797, 799.1, 799.4	780-782.3, 782.5-791, 793-794	240, 242-245, 780-782.3, 782.5-791, 793-794
17.	External causes of morbidity and mortality	V01-Y89	E800-E999	E800-E999	E800-E999
17.1	Accidents	V01-X59, Y85-Y86	E800-E929	E800-E929, E940-E946	E800-E936, E960-E962
17.1.1	Transport accidents	V01-V99, Y85	E800-E845, E929.0-1	E800-E845, E940-E941	E800-E866
17.1.2	Accidental falls	W00-W19	E880-E888	E880-E887	E900-E904
17.1.3	Drowning and accidental submersion	W65-W74	E910	E910	E929
17.1.4	Accidental poisoning	X40-X49	E850-E869	E850-E877	E870-E895
17.1.5	Other accidents	W20-W64, W75-X39, X50-X59, Y86	E870-E879, E890-E909, E911-E928, E929.2-9	E890-E909, E911-E929, E942-E946	E910-E928, E930-E936, E960-E962
17.2	Suicide and intentional self-harm	X60-X84, Y87.0	E950-E959	E950-E959	E963, E970-E979
17.3	Homicide, assault	X85-Y09, Y87.1	E960-E969	E960-E969	E980-E983, E964
17.4	Events of undetermined intent	Y10-Y34, Y87.2	E980-E989	E980-E989	-
17.5	Other external causes of injury and poisoning	Y35-Y84, Y88-Y89	E930-E949, E970-E978, E990-E999	E930-E936, E943-E949, E970-E978, E990-E999	E940-E959, E965, E984, E990-E999

ICD: International Classification of Diseases

From reference year 2006, ICD-10 codes from F10 to F19 having the 4th digit coded '0' (acute intoxication) are recoded to ICD-10 codes X41, X42, X44, X45, X46 or X49 with the 4th digit coded '9', according to the 2006 update of the ICD-10 classification. The table is an extension of the European Shortlist for Causes of Death, May 2012 [1].

[a] The highlighted ICD-codes under code 2.1.22 were used in this study to identify deaths by testicular cancer, and to exclude from analyses as appropriate.

References, S1 Table

1. Eurostat. European Shortlist of Causes of Death, May 2012. Available from: http://ec.europa.eu/eurostat/ramon/nomenclatures/index.cfm?TargetUrl=LST_NOM_DTL&StrNom=COD_2012&StrLanguageCode=EN&IntPcKey=&StrLayoutCode=HIERARCHIC.

S2 Table. Cumulative deaths by cause of death, histology, disease extent at diagnosis and follow-up time.

	Cohort of diagnosis	Follow-up time (years)										Total deaths at end of follow-up
		0	1	5	10	20	25	30	35	40	50	
Cumulative TC deaths (SL, SM) (NL, NM)	1953–1979	0	299 (20, 71) (36, 165)	550 (69, 115) (116, 239)	573 (73, 122) (122, 244)	593 (84, 126) (126, 245)	593 (86, 127) (126, 248)	603 (87, 127) (127, 250)	611 (93, 127) (128, 250)	615 (94, 128) (130, 250)	616 (95, 128) (130, 250)	617 (95, 128) (131, 250)
	1980–1989	0	27 (1, 10) (2, 14)	67 (4, 22) (4, 36)	69 (4, 23) (4, 37)	71 (4, 24) (4, 38)	73 (4, 24) (4, 40)	76 (4, 25) (4, 42)	76 (4, 25) (4, 42)			76 (4, 25) (4, 42)
	1990–2015	0	41 (1, 10) (6, 24)	101 (4, 21) (11, 63)	110 (6, 22) (13, 65)	122 (6, 23) (17, 69)	123 (6, 23) (18, 69)					123 (6, 23) (18, 69)
Cumulative SC deaths (SL, SM) (NL, NM)	1953–1979	0	2 (1, 0) (0, 1)	9 (4, 0) (3, 2)	22 (17, 0) (3, 2)	79 (52, 7) (14, 5)	120 (78, 14) (22, 5)	173 (112, 19) (32, 9)	230 (152, 24) (42, 11)	283 (186, 25) (57, 14)	335 (214, 29) (75, 14)	342 (216, 30) (78, 15)
	1980–1989	0	5 (1, 1) (1, 2)	10 (4, 1) (2, 3)	18 (8, 3) (4, 3)	57 (31, 11) (7, 7)	85 (51, 15) (8, 10)	115 (62, 19) (13, 20)	135 (75, 22) (14, 22)			135 (75, 22) (14, 22)
	1990–2015	0	11 (8, 1) (0, 1)	21 (16, 3) (0, 1)	46 (30, 5) (5, 2)	84 (50, 10) (12, 5)	98 (56, 11) (13, 11)					98 (56, 11) (13, 11)
Cumulative CVD deaths (SL, SM) (NL, NM)	1953–1979	0	2 (2, 0) (0, 0)	14 (14, 0) (0, 0)	34 (25, 4) (4, 0)	98 (60, 18) (14, 3)	134 (84, 24) (17, 5)	176 (113, 26) (26, 7)	218 (140, 31) (32, 10)	259 (164, 39) (39, 12)	294 (188, 39) (49, 12)	300 (190, 39) (51, 12)
	1980–1989	0	1 (1, 0) (0, 0)	10 (5, 2) (1, 0)	20 (10, 4) (3, 1)	50 (24, 9) (9, 5)	65 (32, 12) (12, 6)	74 (37, 12) (13, 9)	81 (41, 14) (14, 9)			81 (41, 14) (14, 9)
	1990–2015	0	6 (4, 0) (1, 1)	7 (10, 2) (2, 3)	35 (18, 4) (3, 6)	56 (31, 8) (6, 7)	59 (32, 8) (7, 7)					59 (32, 8) (7, 7)
Cumulative OC deaths (SL, SM) (NL, NM)	1953–1979	0	22 (9, 3) (4, 6)	36 (18, 6) (5, 7)	49 (24, 8) (9, 7)	89 (53, 12) (16, 7)	110 (67, 14) (20, 8)	134 (85, 15) (24, 9)	169 (107, 17) (31, 12)	199 (127, 17) (36, 17)	247 (158, 19) (49, 19)	259 (166, 19) (53, 19)
	1980–1989	0	2 (0, 2) (0, 0)	8 (4, 2) (0, 2)	18 (10, 2) (2, 4)	49 (27, 5) (9, 8)	75 (42, 7) (15, 11)	94 (53, 9) (17, 14)	103 (58, 12) (18, 14)			103 (58, 12) (18, 14)
	1990–2015	0	11 (4, 3) (3, 0)	50 (19, 7) (16, 4)	81 (33, 9) (23, 9)	119 (47, 14) (30, 14)	131 (56, 14) (32, 15)					131 (56, 14) (32, 15)

CI, confidence interval; NL or NM, non-seminoma, localized or metastatic at diagnosis; SL or SM, seminoma, localized or metastatic at diagnosis; TC, testicular cancer; SC, second cancer (excluding TC); CVD, cardiovascular disease; OC, other causes

S3 Table. Standardized mortality ratios for selected causes of death among testicular germ cell tumor patients diagnosed in Norway.

Cause of death	Cohort of diagnosis									Code[a]
	1953–1979			1980–1989			1990–2015			
	O	SMR (95% CI)	SMR by subcategory[b], O	O	SMR (95% CI)	SMR by subcategory, O	O	SMR (95% CI)	SMR by subcategory, O	
Testicular cancer	617			76			123			
All non-TC causes	901	**1.42** (1.33–1.52)	A: **1.34** (1.16–1.55), 194 B: **1.42** (1.23–1.64), 200 C: **1.46** (1.34–1.60), 507 D: **1.41** (1.32–1.52), 842	319	**1.36** (1.22–1.52)	A: **1.26** (1.06–1.50), 117 B: **1.38** (1.15–1.67), 120 C: **1.51** (1.22–1.88), 82 D: **1.39** (1.24–1.57), 291	288	**1.21** (1.08–1.35)	A: **1.21** (1.07–1.38), 231 B: 1.18 (0.91–1.54), 57 D: **1.17** (1.02–1.34), 200	All-TC
Seminomas, localized	572	**1.34** (1.23–1.46)	A: **1.24** (1.04–1.48),120 B: **1.26** (1.06–1.51), 124 C: **1.42** (1.27–1.59), 328 D: **1.33** (1.22–1.45), 536	174	**1.39** (1.20–1.62)	A: **1.27** (1.01–1.60), 65 B: **1.42** (1.10–1.84), 66 C: **1.58** (1.18–2.15), 43 D: **1.45** (1.23–1.70), 161	144	**1.17** (1.00–1.38)	A: 1.15 (0.97–1.39), 112 B: 1.26 (0.89–1.83), 32 D: 1.13 (0.93–1.38), 99	
Seminomas, metastatic	88	**1.82** (1.43–2.29)	A: **1.75** (1.21–2.58), 26 B: **2.54** (1.67–3.88), 30 C: **1.47** (1.04–2.06), 32 D: **1.86** (1.45–2.38), 82	48	**1.79** (1.36–2.37)	A: **1.58** (1.03–2.49), 19 B: **1.95** (1.20–3.29), 17 C: **1.99** (1.14–3.63), 12 D: **1.86** (1.38–2.50), 43	33	1.36 (0.98–1.94)	A: **1.48** (1.03–2.19), 29 B: 0.86 (0.34–2.82), 4 D: 1.22 (0.82–1.88), 21	
Non-seminomas, localized	182	**1.49** (1.28–1.73)	A: 1.28 (0.87–1.92), 31 B: **1.53** (1.09–2.19), 36 C: **1.54** (1.28–1.86), 115 D: **1.50** (1.29–1.75), 174	46	1.05 (0.78–1.42)	A: 1.17 (0.75–1.88), 19 B: 0.97 (0.58–1.70), 16 C: 1.00 (0.57–1.90), 11 D: 1.08 (0.80–1.49), 43	52	1.06 (0.82–1.38)	A: 1.16 (0.87–1.57), 43 B: 0.75 (0.42–1.46), 9 D: 0.96 (0.70–1.34), 34	
Non-seminomas, metastatic	46	**1.99** (1.38–2.82)	A: **2.51** (1.40–4.69), 14 B: 1.24 (0.59–2.87), 7 C: **2.10** (1.34–3.25), 25 D: **1.73** (1.19–2.48), 37	45	1.32 (0.98–1.79)	A: 1.05 (0.60–2.00), 12 B: 1.42 (0,89–2.34), 19 C: 1.49 (0,89–2.64), 14 D: 1.27 (0.94–1.76), 40	33	**1.55** (1.04–2.33)	A: 1,41 (0,91–2,28), 22 B: 1,93 (0,92–4,13), 11 D: 1.58 (1.00–2.54), 25	
All non-TC second cancers	342	**2.00** (1.79–2.23)	A: **1.70** (1.32–2.22), 55 B: **2.12** (1.71–2.66), 82 C: **2.05** (1.78–2.36), 205 D: **2.03** (1.82–2.27), 333	135	**1.90** (1.61–2.25)	A: **1.57** (1.15–2.20), 38 B: **1.94** (1.50–2.56), 55 C: **2.26** (1.69–3.08), 42 D: **1.90** (1.61–2.27), 125	98	**1.39** (1.15–1.70)	A: **1.27** (1.01–1.62), 69 B: **1.77** (1.24–2.60), 29 D: **1.45** (1.17–1.82), 77	2.1-TC
Seminomas, localized	216	**1.89** (1.65–2.16)	A: **1.75** (1.31–2.41), 39 B: **1.71** (1.29–2.30), 46 C: **2.01** (1.68–2.41), 131 D: **1.94** (1.69–2.23), 212	75	**1.95** (1.56–2.45)	A: **1.66** (1.11–2.57), 23 B: **2.01** (1.43–2.90), 31 C: **2.28** (1.51–3.59), 21 D: **2.01** (1.60–2.55), 71	56	**1.46** (1.13–1.91)	A: **1.40** (1.04–1.92), 41 B: **1.65** (1.00–2.89), 15 D: **1.39** (1.03–1.91), 40	
Seminomas, metastatic	30	**2.27** (1.61–3.25)	A: 0.57 (0.12–5.50), 2 B: **4.55** (2.68–8.07), 15 C: **2.03** (1.22–3.52), 13	22	**2.55** (1.72–3.87)	A: 1.74 (0.79–4.50), 6 B: **3.54** (1.96–6.86), 11 C: **2.39** (1.06–6.57), 5	11	1.39 (0.78–2.70)	A: 1.44 (0.76–3.04), 9 B: 1.20 (0.26–11.60), 2 D: 1.36 (0.70–3.02), 8	

			D: **2.44** (1.72–3.51), 30			D: **2.71** (1.81–4.18), 21				
Non-seminomas, localized	78	**2.31** (1.85–2.91)	A: 1.66 (0.83–3.74), 8 B: **2.89** (1.80–4.88), 18 C: **2.29** (1.76–3.02), 52 D: **2.30** (1.83–2.90), 75	14	1.10 (0.67–1.90)	A: 1.28 (0.53–3.79), 5 B: 0.58 (0.18–2.84), 3 C: 1.64 (0.75–4.22), 6 D: 1.00 (0.59–1.83), 12	13	1.02 (0.61–1.81)	A: 0.89 (0.47–1.95), 8 B: 1.31 (0.56–3.78), 5 D: 1.31 (0.78–2.35), 13	
Non-seminomas, metastatic	15	**2.21** (1.29–3.95)	A: **3.98** (1.59–12.01), 5 B: 1.81 (0.56–8.53), 3 C: 1.81 (0.88–4.22), 7 D: **2.02** (1.15–3.72), 13	22	**2.18** (1.45–3.39)	A: 1.61 (0.59–5.8), 4 B: **2.17** (1.13–4.61), 9 C: **2.61** (1.39–5.46), 9 D: **1.97** (1.28–3.16), 19	11	**2.12** (1.18–4.11)	A: 1.12 (0.41–4.10), 4 B: **4.34** (2.05–10.27), 7 D: **2.43** (1.32–4.88), 10	
MN, lip, oral cavity, pharynx	3	0.99 (0.31–4.87)	A: 0 (–), 0 B: 2.39 (0.51–23.92), 2 C: 0.64 (–), 1 D: 1.03 (0.32–5.08), 3	5	**3.44** (1.45–10.27)	A: **5.79** (1.81–28.41), 3 B: 3.37 (0.73–33.88), 2 C: 0 (–), 0 D: **2.96** (1.11–10.64), 4 SL: **3.85** (1.20–18.91), 3 NM: **9.07** (1.93–91.14), 2	2	1.44 (0.31–14.42)	A: 1.86 (0.40–18.72), 2 B: 0 (–), 0 D: **1.89** (0.41–19.03), 2	2.1.1
MN, esophagus	7	1.99 (0.97–4.77)	C: **2.74** (1.26–7.21), 4 D: 2.05 (1.00–4.92), 7	1	0.55	D: 0.58 (–), 1	5	**2.61** (1.10–7.77)	B: **7.64** (2.88–27.35), 4 D: **3.30** (1.40–9.82), 5 NL: **6.37** (1.40–62.25), 2	2.1.2
MN, stomach	31	**2.62** (1.86–3.81)	B: **4.29** (2.54–7.85), 13 C: **2.64** (1.56–4.84), 13 D: **2.89** (2.05–4.20), 31 SL: **2.10** (1.33–3.51), 17 NL: **4.15** (2.19–8.82), 9 NM: **8.33** (2.50–41.32), 3	13	**3.98** (2.36–7.26)	A: **4.78** (2.33–11.4), 7 C: **4.65** (1.47–22.68), 3 D: **4.52** (2.68–8.27), 13 SL: **4.42** (2.26–9.84), 8 SM: **9.48** (3.61–32.95), 4	5	1.90 (0.80–5.66)	B: **5.23** (1.64–25.67), 3 D: **2.58** (1.09–7.71), 5	2.1.3
MN, colorectal, anus	44	**1.95** (1.46–2.66)	C: **2.25** (1.59–3.27), 31 D: **2.02** (1.51–2.76), 44 SL: **1.92** (1.35–2.83), 29 NL: **2.94** (1.73–5.37), 13	11	1.17 (0.67–2.24)	C: **2.36** (1.09–6.14), 6 D: 1.26 (0.72–2.42), 11	6	0.65 (0.30–1.71)	D: 0.85 (0.39–2.23), 6	2.1.4
MN, liver, intrahepatic ducts	11	**5.68** (3.21–11.07)	B: **8.92** (2.79–43.83), 3 C: **6.22** (3.18–13.93), 8 D: **5.93** (3.35–11.55), 11 SL: **6.30** (3.22–14.10), 8 NL: **4.96** (1.06–49.70), 2	1	0.91	D: 0.94 (–), 1	2	1.34 (0.29–13.48)	D: 0.82 (–), 1	2.1.5
MN, pancreas	28	**2.97** (2,08–4,41)	B: **4.11** (2.18–8.71), 9 C: **3.50** (2.26–5.71), 19 D: **3.10** (2.16–4.60), 28	18	**4.31** (2.75–7.13)	B: **6.45** (3.64–12.55), 11 C: **3.96** (1.67–11.83), 5 D: **4.35** (2.74–7.32), 17	8	1.85 (0.95–4.16)	D: 1.77 (0.81–4.66), 6	2.1.6

			SL: **3.04** (1.97–4.95), 19 SM: **5.44** (2.01–19.62), 4			SL: **4.01** (2.12–8.49), 9 SM: **7.90** (2.94–28.13), 4 NM: **6.58** (2.48–23.38), 4				
MN, trachea, bronchus, lung	47	1.25 (0.94–1.69)	A: **2.02** (1.19–3.71), 13 D: 1.26 (0.95–1.71), 46	32	**1.89** (1.35–2.72)	A: **1.82** (1.00–3.67), 10 B: **2.30** (1.43–3.92), 16 D: **1.96** (1.40–2.85), 31 SL: **2.17** (1.42–3.48), 20 SM: **2.80** (1.28–7.23), 6	14	0.87 (0.53–1.55)	D: 0.97 (0.56–1.82), 12	2.1.8
Melanoma	10	**2.53** (1.39–5.11)	B: **5.53** (2.34–16.45), 5 D: **2.63** (1.44–5.32), 10 SL: **2.41** (1.10–6.34), 6 SM: **6.41** (1.37–63.71), 2	3	1.18 (0.37–5.80)	D: 1.27 (0.40–6.25), 3	6	2.00 (0.91–5.26)	D: 2.21 (0.93–6.61), 5	2.1.9
MN, prostate	39	**1.46** (1.08–2.04)	A: **2.43** (1.19–5.76), 7 C: **1.53** (1.07–2.25), 29 D: **1.42** (1.04–2.00), 39 SL: **1.47** (1.02–2.20), 27	7	0.83 (0.40–1.99)	D: 0.63 (0.26–1.88), 5	9	1.30 (0.69–2.78)	D: 2.25 (0.70–11.08), 3	2.1.14
MN, kidney	13	**2.64** (1.57–4.83)	C: **3.29** (1.75–6.95), 9 D: **2.76** (1.63–5.04), 13 SM: **5.22** (1.16–50.00), 2 NL: **5.16** (2.16–15.39), 5	1	0.46	D: 0.49 (–),1	2	0.91 (0.20–9.09)	D: 0.59 (–), 1	2.1.15
MN, bladder	18	**2.71** (1.73–4.48)	A: **4.03** (1.52–14.35), 4 B: **2.96** (1.11–10.63), 4 C: **2.32** (1.28–4.70), 10 D: **2.64** (1.67–4.44), 17 SL: **2.84** (1.67–5.19), 13 NL: **3.30** (1.26–11.56), 4	10	**4.74** (2.60–9.55)	B: **3.44** (1.10–16.43), 3 C: **10.31** (4.66–27.32), 6 D: **5.10** (2.80–10.29), 10 SL: **5.71** (2.80–13.52), 7 NM: **13.83** (4.20–67.81), 3	4	2.32 (0.87–8.33)	B: **4.73** (1.01–47.50), 2 D: 2.25 (0.70–11. 08), 3	2.1.16
MN, brain and CNS	9	**2.06** (1.09–4.37)	B: **3.41** (1.29–12.24), 4 D: 1.93 (0.98–4.33), 8 NL: **3.99** (1.49–14.35), 4	2	0.67 (0.14–6.73)	D: 0.74 (0.16–7.41), 2	8	**1.98** (1.01–4.45)	A: **2.46** (1.26–5.52), 8 D: **2.39** (1.16–5.75), 7 NL: **3.64** (1.93–7.73), 9	2.1.17
MN, thyroid	0	0 (–)		0	0 (–)		0	0 (–)		2.1.18
Hodgkin disease, lymphoma	6	1.32 (0.60–3.47)	D: 1.36 (0.62–3.59), 6 SM: **5.66** (1.20–56.57), 2	1	0.44	D: 0.46 (–), 1	2	0.97 (0.21–9.71)	D: 0.66 (–), 1	2.1.19
Leukemia	8	1.60 (0.82–3.60)	D: 1.71 (0.87–3.85), 7	3	1.59 (0.50–7.84)	D: 1.76 (0.55–8.65), 3	6	**3.47** (1.59–9.15)	A: **3.83** (1.62–11.39), 5 D: **3.04** (1.14–10.90), 4 SL: **4.21** (1.59–15.03), 4	2.1.20
MN, other lymph./hematol.[c]	9	**1.89** (1.00–4.00)	A: **3.91** (1.47–14.03), 4	2	1.65 (0.26–12.1)	D: 0.68 (–), 1	1	0.71	D: 0 (–), 0	2.1.21

			D: **1.76** (0.90–3.95), 8 SL: **2.16** (1.05–5.19), 7							
MN, other (no TC deaths)	59	**3.50** (2.73–4.57)	A: **2.31** (1.23–4.89), 9 B: **3.08** (1.78–5.81), 12 C: **4.20** (3.07–5.89), 38 D: **3.55** (2.75–4.67), 56 SL: **2.58** (1.81–3.81), 29 SM: **6.90** (3.73–14.14), 9 NL: **5.71** (3.68–9.30), 19	24	**3.68** (2.50–5.65)	A: **2.35** (1.07–6.23), 6 B: **4.39** (2.47–8.57), 11 C: **4.78** (2.32–11.50), 7 D: **3.37** (2.21–5.40), 20 SL: **3.13** (1.76–6.12), 11 SM: **6.30** (2.67–18.36), 5 NM: **5.34** (2.27–15.66), 5	17	**2.72** (1.72–4.57)	A: **2.43** (1.41–4.56), 12 B: **3.83** (1.61–11.45), 5 D: **2.63** (1.53–4.95), 12 SL: **2.98** (1.63–6.04), 10	2.1.22
Cardiovascular disease	300	**1.12** (1.00–1.26)	A: 1.03 (0.81–1.32), 68 B: 1.15 (0.92–1.46), 75 C: 1.15 (0.99–1.35), 157 D: **1.14** (1.01–1.28), 286	81	1.07 (0.85–1.34)	A: 1.26 (0.94–1.72), 43 B: 0.93 (0.63–1.41), 25 C: 0.86 (0.51–1.58), 13 D: 1.07 (0.84–1.37), 71	59	0.96 (0.75–1.26)	A: 1.08 (0.83–1.44), 53 B: 0.48 (0.22–1.27), 6 D: 0.94 (0.70–1.30), 42	7.
Seminomas, localized	190	1.03 (0.90–1.19)	A: 0.93 (0.69–1.28), 42 B: 1.04 (0.79–1.40), 48 C: 1.08 (0.89–1.32), 100 D: 1.02 (0.88–1.18), 172	41	0.96 (0.70–1.32)	A: 1.04 (0.70–1.63), 21 B: 0.87 (0.52–1.57), 13 C: 0.90 (0.43–2.18), 7 D: 0.97 (0.70–1.38), 36	32	0.98 (0.70–1.41)	A: 1.11 (0.78–1.62), 29 B: 0.46 (0.14–2.25), 3 D: 0.94 (0.62–1.47), 22	
Seminomas, metastatic	39	**1.88** (1.33–2.66)	A: **1.90** (1.17–3.27), 13 B: **2.22** (1.19–4.36), 12 C: 1.65 (0.96–2.91), 14 D: **2.08** (1.45–2.99), 39	14	1.51 (0.89–2.70)	A: 1.86 (0.98–3.89), 9 B: 1.10 (0.34–5.26), 3 C: 1.18 (0.26–10.71), 2 D: 1.56 (0.88–2.94), 12	8	1.25 (0.65–2.67)	A: 1.34 (0.68–3.04), 7 B: 0.83 (–), 1 D: 1.31 (0.62–3.27), 6	
Non-seminomas, localized	51	1.05 (0.80–1.39)	A: 0.98 (0.50–2.07), 10 B: 0.88 (0.46–1.85), 9 C: 1.14 (0.81–1.63), 32 D: 1.10 (0.84–1.46), 51	14	1.07 (0.62–1.95)	A: 1.72 (0.86–3.71), 9 B: 0.62 (0.18–3.10), 3 C: 0.66 (0.16–5.78), 2 D: 1.10 (0.62–2.06), 13	7	0.59 (0.28–1.47)	A: 0.69 (0.30–1.87), 6 B: 0.32 (–), 1 D: 0.57 (0.23–1.74), 5	
Non-seminomas, metastatic	12	1.42 (0.75–2.79)	A: 0.94 (0.20–9.01), 2 B: 1.33 (0.43–5.98), 3 C: 1.72 (0.71–4.49), 7 D: 1.53 (0.80–3.02), 12	9	1 (0.52–2.14)	A: 0.68 (0.14–6.79), 2 B: 1.34 (0.54–4.09), 5 C: 0.86 (0.18–8.60), 2 D: 1.07 (0.55–2.30), 9	7	1.50 (0.64–3.92)	A: **2.23** (1.00–5.61), 7 B: 0 (–), 0 D: 1.07 (0.35–4.14), 4	
Ischemic heart diseases	169	1.06 (0.91–1.24)	D: 1.08 (0.92–1.26), 160 SM: **1.74** (1.13–2.73), 22	52	1.21 (0.92–1.60)	D: 1.20 (0.90–1.63), 44	30	0.92 (0.65–1.34)	D: 0.94 (0.63–1.48), 22	7.1
Acute myocardial infarction	119	1.06 (0.89–1.28)	D: 1.10 (0.92–1.33), 114 SM: **2.01** (1.25–3.33), 18	39	1.34 (0.99–1.87)	A: **1.51** (1.02–2.34), 23 D: 1.26 (0.90–1.84), 31 SL: **1.48** (1.01–2.27), 24	18	0.84 (0.54–1.40)	D: 0.73 (0.41–1.43), 11	7.1.1
Non-ischemic heart diseases	50	**1.59** (1.20–2.13)	B: **1.86** (1.02–3.77), 10 C: **1.55** (1.12–2.21), 35	16	1.42 (0.87–2.46)	D: 1.43 (0.86–2.53), 15 SM: **4.96** (2.25–12.86), 6	13	1.25 (0.74–2.31)	D: 1.02 (0.52–2.31), 8	7.2

			D: **1.59** (1.21–2.14), 49 SL: **1.43** (1.01–2.09), 31 SM: **2.59** (1.12–6.99), 6 NM: **4.63** (1.69–14.80), 5							
Cerebrovascular diseases	44	0.88 (0.66–1.20)	D: 0.90 (0.67–1.23), 42	5	0.37 (0.16–1.09)	D: 0.42 (0.18–1.23), 5	13	1.20 (0.71–2.21)	D: 1.13 (0.60–2.41), 9	7.3
Other circulatory diseases	37	**1.39** (1.02–1.96)	D: **1.40** (1.01–1.99), 35 SM: **3.94** (1.96–8.87), 8	8	1.02 (0.51–2.30)	D: 0.99 (0.48–2.39), 7	3	0.45 (0.14–2.17)	D: 0.59 (0.19–2.90), 3	7.4
Other or unknown causes	259	**1.34** (1.18–1.51)	A: **1.53** (1.22–1.95), 71 B: 1.15 (0.86–1.57), 43 C: **1.32** (1.13–1.55), 145 D: **1.24** (1.09–1.41), 223	103	1.19 (0.98–1.45)	A: 1.04 (0.77–1.46), 36 B: 1.27 (0.93–1.77), 40 C: 1.31 (0.90–1.95), 27 D: **1.24** (1.02–1.52), 95	131	**1.23** (1.04–1.46)	A: **1.25** (1.04–1.51), 109 B: 1.12 (0.75–1.75), 22 D: 1.11 (0.90–1.38), 81	All-2.1-7-TC
Seminomas, localized	166	**1.30** (1.12–1.52)	A: 1.34 (0.98–1.86), 39 B: 1.20 (0.84–1.75), 30 C: **1.33** (1.10–1.61), 97 D: **1.24** (1.06–1.45), 148	58	**1.33** (1.03–1.73)	A: 1.22 (0.82–1.89), 21 B: 1.37 (0.89–2.18), 22 C: 1.47 (0.91–2.50), 15 D: **1.40** (1.07–1.84), 54	56	1.09 (0.85–1.43)	A: 1.01 (0.76–1.38), 42 B: 1.42 (0.85–2.54), 14 D: 1.05 (0.77–1.47), 37	
Seminomas, metastatic	19	1.31 (0.82–2.18)	A: **2.44** (1.33–4.86), 11 B: 0.97 (0.31–4.45), 3 C: 0.73 (0.30–2.10), 5 D: 1.01 (0.58–1.85), 13	12	1.35 (0.77–2.51)	A: 1.06 (0.41–3.63), 4 B: 1.04 (0.32–5.06), 3 C: 2.23 (0.87–6.82), 5 D: 1.29 (0.71–2.57), 10	14	1.42 (0.85–2.55)	A: 1.61 (0.93–3.01), 13 B: 0.56 (–), 1 D: 1.03 (0.50–2.44), 7	
Non-seminomas, localized	53	**1.33** (1.02–1.76)	A: 1.42 (0.84–2.59), 13 B: 1.28 (0.68–2.70), 9 C: 1.31 (0.92–1.90), 31 D: 1.30 (0.98–1.74), 48	18	1.01 (0.64–1.67)	A: 0,70 (0,30–2,06), 5 B: 1.54 (0.83–3.14), 10 C: 0.70 (0.21–3.49), 3 D: 1.13 (0.71–1.89), 18	32	1.30 (0.94–1.85)	A: 1.49 (1.06–2.17), 29 B: 0.58 (0.20–2.61), 3 D: 0.96 (0.61–1.60), 16	
Non-seminomas, metastatic	19	**2.39** (1.51–3.89)	A: **3.20** (1.49–7.89), 7 B: 0.57 (–), 1 C: **2.75** (1.54–5.10), 11 D: **1.69** (1.00–2.98), 12	14	0.93 (0.56–1.65)	A: 1.01 (0.46–2.65), 6 B: 0.91 (0.39–2.66), 5 C: 0.82 (0.25–4.06), 3 D: 0.90 (0.52–1.69), 12	15	1.32 (0.78–2.34)	A: 1.25 (0.70–2.44), 11 B: 1.56 (0.51–6.01), 4 D: 1.38 (0.75–2.76), 11	
Infectious / parasitic diseases	8	1.12 (0.57– 2.52)	D: 0.89 (0.41– 2.35), 6	6	1.82 (0.83–4.79)	D: 1.62 (0.68–4.83), 5 SM: **5.84** (1.23–58.57), 2	10	**3.06** (1.69–6.18)	A: **3.64** (1.94–7.68), 9 D: **2.47** (1.14–6.44), 6 NL: **4.84** (1.50–23.71), 3	1.
Viral hepatitis	0	0 (–)	D: 0 (–), 0	1	22.86 (–)	D: 22.86 (–), 1	3	**32.49** (10.19–159.5)	A: **43.56** (13.67–213.7), 3 D: **26.69** (5.76–267.7), 2 SL: **40.03** (8.64–400.9), 2	1.3
Other infectious diseases[d]	7	1.32 (0.64–3.18)	D: 0.97 (0.41–2.89), 5	3	1.40 (0.44–6.84)	D: 1.43 (0.45–7.02), 3	5	**2.38** (1.00–7.10)	A: **2.74** (1.03–9.87), 4 D: 1.75 (0.55–8.56), 3	1.4
Non-MN, benign / uncertain	8	**2.62** (1.34–5.88)	C: **3.06** (1.40–8.05), 6	2	2.28 (0.49–22.85)	D: 2.43 (0.52–24.37), 2	1	1.39 (–0)	D: 1.79 (–), 1	2.2

			D: **2.74** (1.40–6.15), 8							
Endocrine, nutr., metab.[e]	15	1.50 (0.92–2.62)	B: **2.66** (1.12–7.93), 5 D: 1.57 (0.96–2.73), 15	10	**2.06** (1.13–4.19)	D: **1.99** (1.05–4.22), 9 SL: **2.37** (1.08–6.23), 6 SM: **5.63** (1.74–27.48), 3	3	0.54 (0.17–2.64)	D: 0.49 (0.11–4.88), 2	4.
Diabetes mellitus	12	1.51 (0.88–2.84)	D: 1.58 (0.91–2.96), 12	6	1.63 (0.75–4.30)	D: 1.75 (0.80–4.61), 6 SM: **4.83** (1.04–47.53), 2	1	0.25 (–)	D: 0.33 (–), 1	4.1
Other	3	1.73 (0.54–8.50)	B: **6.79** (1.46–68.13) D: 1.77 (0.55–8.70), 3	4	**4.17** (1.57–15.01)	A: **8.38** (1.80–84.23), 2 B: **4.74** (1.02–47.50), 2 D: **3.23** (1.01–15.88), 3	2	1.88 (0.40–18.90)	D: 1.23 (–), 1	4.2
Mental, behavioral disorders	6	0.49 (0.23–1.28), 6	D: 0.50 (0.23–1.31), 6	6	0.75 (0.34–1.97)	D: 0.69 (0.29–2.04), 5	11	1.21 (0.68–2.36)	D: 0.86 (0.36–2.57), 5	5.
Nervous system, sense organs	15	1.07 (0.66–1.87)	D: 1.12 (0.69–1.95), 15	3	0.45 (0.14–2.22)	D: 0.16 (–), 1	13	**1.72** (1.02–3.14)	A: **2.08** (1.21–3.90), 12 D: 1.58 (0.93–8.86), 9 SL: **2.02** (1.04–4.51), 8	6.
Alzheimer's disease	2	0.73 (0.16–7.26)	D: 0.73 (0.16–7.26), 2	0	0 (–)	D: 0 (–), 0	4	**3.85** (1.46–13.57)	A: **5.68** (2.18–19.81), 4 D: **4.64** (1.76–16.36), 4 SL: **5.43** (1.74–25.76), 3	6.2
Respiratory system diseases	44	0.88 (0.66–1.20)	D: 0.88 (0.65–1.20), 42	14	0.89 (0.55–1.56)	D: 0.97 (0.59–1.69), 14	10	0.74 (0.41–1.50)	D: 0.38 (0.14–1.37), 4	8.
Pneumonia	18	0.93 (0.59–1.53)	D: 0.98 (0.62–1.62), 18	5	1.08 (0.47–3.04)	D: 1.22 (0.54–3.45), 5	4	1.20 (0.44–4.34)	D: 0.80 (0.17–8.08), 2	8.2
Chronic lower respiratory	23	0.91 (0.61–1.41)	D: 0.89 (0.59–1.40), 22	4	0.44 (0.17–1.57)	D: 0.47 (0.18–1.67), 4	4	0.50 (0.19–1,79)	D: 0.16 (–), 1	8.3
Other respiratory diseases[f]	3	0.77 (0.24–3.79)	A: **4.87** (1.06–48.11), 2 D: 0.53 (0.11–5.29), 2	5	**3.35** (1.41–10.00)	A: **6.80** (1.46–67.74), 2 B: **4.63** (1.45–22.63), 3 D: **3.48** (1.46–10.4), 5 SL: **3.50** (1.08–17.23), 3 NM: **11.90** (2.65–112.0), 3	1	0.71 (–)	D: 0 (–), 0	8.4
Digestive system diseases	50	**2.83** (2.16–3.78)	B: **3.20** (1.89–5.87), 13 C: **3.26** (2.31–4.73), 31 D: **2.88** (2.19–3.88), 48 SL: **2.89** (2.09–4.12), 34 NL: **2.86** (1.57–5.75), 10 NM: **5.64** (2.05–20.39), 4	19	**2.51** (1.62–4.11)	B: **3.44** (1.88–7.00), 10 D: **2.64** (1.68–4.38), 18 SL: **3.01** (1.73–5.68), 12 NL: **2.78** (1.03–10.00), 4	9	1.21 (0.64–2.57)	D: 1.26 (0.61–3.04), 7 SL: **1.98** (1.01–4.45), 8	9.
Ulcers, stomach–jejunum	11	**3.78** (2.13–7.38)	B: **6.09** (2.29–21.84), 4 C: **3.23** (1.36–9.64), 5 D: **3.31** (1.75–7.03), 9 SL: **3.45** (1.67–8.31), 7 NL: **7.80** (2.89–28.14), 4	1	1.21	D: 1.44 (–), 1	2	3.32 (0.71–33.43)	D: 4.41 (0.94–44.31), 2 SL: **6.06** (1.30–60.91), 2	9.1

Cirrhosis, fibrosis, c. hep.[g]	5	1.02 (0.43–3.03)	D: 1.07 (0.45–3.21), 5	8	**2.57** (1.31–5.77)	A: **2.83** (1.06–10.13), 4 D: **2.91** (1.49–6.53), 8 NL: **6.40** (2.41–22.78), 4	3	0.96 (0.30–4.74)	D: 0.88 (0.19–8.87), 2	9.2
Other digestive diseases	34	**3.64** (2.62–5.20)	B: **3.95** (1.91–9.51), 7 C: **4.20** (2.86–6.40), 25 D: **3.82** (2.74–5.45), 34 SL: **3.60** (2.42–5.59), 23 NL: **3.42** (1.56–8.92), 6 NM: **12.56** (4.30–47.14), 4	10	**2.98** (1.62–6.05)	B: **4.40** (1.99–11.68), 6 D: **2.89** (1.53–6.15), 9 SL: **3.73** (1.80–8.98), 7	4	1.24 (0.47–4.47)	D: 1.20 (0.38–5.92), 3	9.3
Skin, subcutaneous diseases	1	2.93 (–)	D: 2.93 (–), 1	0	0 (–)	D: 0 (–), 0	0	0 (–)	D: 0 (–), 0	10.
Musculoskeletal, connective[h]	1	0.49 (–)	D: 0.51 (–), 1	0	0 (–)	D: 0 (–), 0	0	0 (–)	D: 0 (–), 0	11.
Genitourinary diseases	21	**2.31** (1.54–3.64)	C: **2.70** (1.69–4.58), 16 D: **2.50** (1.66–3.94), 21 SL: **2.55** (1.61–4.29), 16	2	0.87 (0.19–8.69)	D: 0.93 (0.20–9.37), 2	7	**3.76** (1.82–8.99)	A: **5.18** (2.52–12.33), 7 D: **2.70** (1.01–9.68), 4 SL: **4.20** (1.59–14.73), 4 NL: **5.61** (1.19–53.83), 2	12.
Kidney and ureter	18	**3.04** (1.96–5.00)	C: **3.64** (2.20–6.46), 14 D: **3.29** (2.11–5.40), 18 SL: **3.16** (1.89–5.71), 13	1	0.65 (–)	D: 0.69 (–), 1	4	**3.18** (1.20–11.30)	A: **4.37** (1.65–15.46), 4 D: **2.99** (0.94–14.61), 3 SL: **4.60** (1.47–21.89), 3	12.1
Other	3	1.01 (0.32–4.89)	D: 1.09 (0.34–5.28), 3	1	1.44 (–)	D: 1.59 (–), 1	3	**5.68** (1.76–27.80)	A: **7.96** (2.47–38.86), 3 D: 2.37 (–), 1 NL: **18.50** (3.87–175.0), 2	12.2
Congenital, chromosomal	3	**4.94** (1.55–24.27)	D: **6.24** (1.96–30.61), 3 SL: **6.30** (1.36–62.99), 2	0	0 (–)	D: 0 (–), 0	1	1.62 (–)	D: 0 (–), 0	15.
Symptoms, signs, ill-defined	43	**1.89** (1.41–2.58)	A: **3.64** (2.52–5.44), 27 D: 0.97 (0.64–1.55), 20 SM: **3.99** (1.87–9.84), 7 NM: **10.43** (4.93–24.43), 8	7	0.97 (0.47–2.32)	D: 1.10 (0.53–2.64), 7	6	0.85 (0.39–2.24)	D: 1.17 (0.54–3.08), 6	16.
External causes	36	0.94 (0.68–1.33)	D: 0.92 (0.65–1.34), 30	27	1.14 (0.79–1.70)	D: 1.27 (0.86–1.95), 24	58	**1.47** (1.15–1.93)	A: **1.33** (1.01–1.81), 46 B: **2.48** (1.43–4.66), 12 D: **1.49** (1.08–2.10), 36 NM: **2.42** (1.43–4.42), 13	17.
Accidents	25	0.90 (0.62–1.38)	D: 0.89 (0.59–1.41), 21	17	1.15 (0.73–1.93)	D: 1.25 (0.77–2.18), 15	35	**1.46** (1.06–2.07)	B: **2.59** (1.33–5.79), 8 D: **1.53** (1.03–2.38), 23 NM: **2.18** (1.06–5.24), 7	17.1
Suicide	10	1.02 (0.56–2.08)	D: 1.02 (0.56–2.08), 8	10	1.23 (0.68–2.49)	D: 1.23 (0.68–2.49), 9	22	**1.54** (1.03–2.42)	D: 1.54 (0.90–2.78), 13	17.2

									NM: **2.99** (1.37–7.86), 6	

Causes of death are classified according to S1 Table. Statistically significant results (P = <0.05) are highlighted in **bold**.

CI, confidence interval; O, observed deaths in the study population; MN, malignant neoplasm; SMR, standardized mortality ratio; TC, testicular cancer.

[a] Code for cause of death as defined in S1 Table.

[b] Selected subgroups with SMRs pertaining to follow-up time, histology and disease extent at TGCT diagnosis, given in parentheses with 95% CI: A, <16 years follow-up only; B, 16-<26 years follow-up only; C, ≥26 years follow-up only; D, ≥5 years follow-up only; SL: seminoma, localized; SM: seminoma, metastatic; NL: nonseminoma, localized; NM: nonseminoma, metastatic.

[c] Other malignant neoplasms of lymphoid and hematopoietic tissue.

[d] Not including tuberculosis (group 1.1) and acquired immunodeficiency syndrome (AIDS, code 1.2).

[e] Endocrine, nutritional and metabolic diseases.

[f] Not including influenza (group 8.1).

[g] Chronic hepatitis.

[h] Musculoskeletal and connective tissue diseases.

S4 Table. Summary of selected publications reporting long-term cause-specific mortality data among testicular cancer patients.

Publication	# of patients, histology and stage at diagnosis	Time and location of diagnosis	Follow-up time	Initial treatment (# of patients)	Selected standardized mortality ratios (95 % CI), and/or other selected findings
Hanks et al, 1992 [1]	387, seminoma, stage I-II	1973 to 1974, US	1990 (mail survey)	- Infradiaphragmatic RT (387) - Supradiaphragmatic RT (161)	- SC: 3.4 (no CI, P = <0.001) - Cardiac death: 2.3 (no CI, P = <0.001) - Non-cancer death: 3.1 (no CI, P = <0.01) - Other findings: eight of 10 patients dead of cardiac disease had received supradiaphragmatic RT
Horwich 1994 [2]	859, seminoma, stage I	1961 to 1985, UK	End of 1989. 8459 person years.	Infradiaphragmatic RT (859)	- SC, overall: 0.90 (0.58 to 1.40). Bladder cancer: 3.80 (1.33 to 10.87). Leukemia: 5.45 (1.99 to 14.9)
Fosså 2004 [3]	3378, malignant germ cell tumor, any stage. Age <56 years at diagnosis, censored at 60 years	1962 to 1997, CRN data, Norway	End of 1997. 41 960 person years.	Any, but no individual treatment data	- SC, overall: 2.0 (1.7 to 2.4). Stomach cancer 3.0 (1.6 to 5.0). Pancreatic cancer 2.9 (1.? to 5.4). Lung cancer 1.7 (1.1 to 2.6) - CVD: overall 1.2 (1.0 to 1.5), myocardial infarction 1.1 (0.9 to 1.4) - OC: GI disorders 2.1 (1.1 to 3.5). Accidents, poisoning, suicide 0.8 (0.6 to 1.2)
Zagars 2004 [4]	453, seminoma, stage I-II	1951 to 99, MD Anderson Cancer Center, Texas	Median 13.3 years, range = 1.4 to 42.8 years	- Abdominal RT (453) - PMI (71)	- All causes: 1.59 (1.30 to 1.93). SC: 1.91 (1.14 to 2.98). CVD: 1.61 (1.21 to 2.24). Significant beyond 15 years of follow-up only - CVD: overall 1.61 (1.21 to 2.24). Findings were significant beyond 15 years of follow-up only - Other findings: Actuarial survival rates at 10-20-30-40 years were 93-79-59-26%. PMI the only factor correlated with survival in univariate analysis
Hem 2004 [5]	Unknown, any histology and stage	1960 to 99, CRN data, Norway	59 858 person years (TC patients)	Any, but no individual treatment data	- Suicide: 1.08 (0.62 to 1.76) among TC patients - Several cancer forms were included in the study
Fosså 2007 [6]	38 907, TGCT, any stage. Only survivors of at least one year	1943 to 2002, 14 registries in US/Europe including Norway (1953 to 1999)	Median 10 years, range = 1 to 55 years	- Surgery (8802) - RT (12454) - CT (4586) - RT + CT (777) - Other / unspecified (459)	- Non-cancer, overall: 1.06 (1.02 to 1.10) - CVD, overall: 0.98 (0.94 to 1.04), of which hypertensive disorders 1.39 (1.01 to 1.89). CVD by initial treatment >1975: Surgery 0.91 (0.76 to 1.10), CT 1.44 (1.06 to 1.91), RT 0.95 (0.84 to 1.08), CT+RT 2.06 (1.27 to 3.14). - OC: Infections 1.28 (1.12 to 1.47), of which intestinal 9.10 (4.73 to 16.00). Digestive diseases 1.44 (1.26 to 1.64). Respiratory diseases 1.15 (0.99 to 1.34). Genitourinary diseases 1.27 (0.96 to 1.6). Endocrine/metabolic disorders 1.17 (0.95 to 1.44). Suicide 0.99 (0.83 to 1.18)
Schairer 2007 [7]	29 356, any histology except spermatocytic tumors, any stage.	1973 to 2002 (SEER, US)	End of 2002	Any. Initial treatment data only for the 621 patients who developed a SC	- Reporting hazard rate ratios of second cancers in TC patients relative to first cancers for a matched sample. All-cause mortality not significantly increased. - Among patients diagnosed during 1973 to 1979, increased cancer-specific and all-cause mortality for second cancers in the RT field
Robinson 2007 [8]	9892 (5555 seminoma, 3733 non-seminoma), any stage	1960 to 2004 (UK)	End of 2004. 104 622 person-years	Any, but no individual treatment data	- Overall SMRs decreasing with later decade of diagnosis, from 8.62 to 1.69 in seminomas and from 56.76 to 8.50 in non-seminomas. - Relative survival data with up to 20 years of follow-up
Powles 2008 [9]	199, seminoma, stage I	1986 to 2007 (UK)	Median 9 years, 1841 person years	Carboplatin (199)	-All-cause mortality 0.89 (0.36 to 1.83) -CVD 1.44 (0.39 to 3.69)
Alanee 2012 [10]	23 381, any histology and stage	1995 to 2008, SEER, US	End of 2008. 126 762 person years	Any. RT (8153)	-Suicide, overall 1.21 (1.08 to 2.14). Patients aged <30 years at diagnosis: 1.53 (1.09 to 2.09)
Beard 2013 [11]	9193, seminoma, stage I. Age 15 to 70 years at diagnosis	1973 to 2001, SEER, US	Median 12.7 years if RT, 10.9 years if not. 121 037 person years	- RT (7179) - Surgery (2014)	- SC: overall 1.81 (1.61 to 2.03). If RT: 1.89 (1.67 to 2.14). Pancreatic cancer 2.54 (1.12 to 5.92) if no initial RT, 3.35 (2.32 to 4.84) if initial RT - CVD: overall 0.91 (0.80 to 1.05). If RT: 0.89 (0.76 to 1.04) - OC: suicide 1.45 (1.06 to 1.98), infection 2.32 (1.80 to 3.00), COPD 0.93 (0.63 to 1.38)
Horwich 2014 [12]	2543, seminoma, stage I	1960 to 1992, 12 cancer centers (11 UK, 1 Norway)	Median 21.8 years, 51 151 person years	- Abdominal RT (2543). - Mediastinum / neck-RT (25)	- Overall: 1.06 (0.98 to 1.14) - SC, non-TC: 1.46 (1.30 to 1.65), of which abdominopelvic 1.62 (1.43 to 1.83) - CVD: overall 0.80 (0.70 to 0.92)

					- OC: overall 0.85 (0.72 to 1.00)
Gandaglia 2014 [13]	31 330. Between 1990 and 2009: 16151 seminoma and 11324 nonseminoma, any stage	1973 to 2009, SEER, US	Median 92.0 months	Any. - Orchiectomy (19480) - RT (11850)	- SMRs not reported - At 15 years of follow-up, cancer-specific mortality was 1.2%, other-cancer mortality was 1.1%, non-cancer mortality was 2.9%. Mortality was higher in patients with distant disease at diagnosis, as well as higher age.
Fung 2015 [14]	15006, non-seminoma, any stage	1980 to 2010, SEER, US	Median 7.9 years / 81 227 person years (surgery), 6.5 years / 60 065 person years (CT)	Either initial CT (6909) or initial surgery alone (8097) without RT.	-Non-cancer, surgery only 0.96 (0.84 to 1.11), CT only 1.60 (1.40 to 1.82) -CVD, surgery only 0.81 (0.60 to 1.07). -CVD, CT only 1.36 (1.03 to 1.78), of which patients diagnosed 2000 to 2010 1.97 (1.13 to 3.20). Cerebrovascular diseases 2.40 (1.15 to 4.42) -CVD during first year of diagnosis: 5.31 (2.65 to 9.51) -OC after initial CT: septicemia 7.14 (3.41 to 13.14). Pneumonia / influenza 3.05 (1.12 to 6.65). Symptoms/signs/ill-defined conditions 4.31 (2.36 to 7.23) -OC regardless of initial treatment: increased SMRs from benign neoplasms and those of unknown behavior -Other findings: increased CVD mortality with extent of disease and increasing age at TC diagnosis
Kier 2016 [15]	2804, seminoma, any stage. 2386, non-seminoma, any stage.	1984-2007, Denmark	Median 14.4 years, until December 31st, 2012	- Surveillance (2985) - BEP (1432) - RT (588) - MTOL (86)	Risk for death from all causes, including GCC, was increased 2 times after BEP, 1.3 times after RT, 16 times after MTOL and reduced after surveillance (HR, 0.9). Second malignant neoplasms caused excess mortality by 1.6 times after BEP, by 2.1 times after RT, and by 5.8 times after MTOL
Gunnes 2017 [16]	738, any histology and stage. Other cancer patients also included.	Born during 1965 to 1985. Diagnosed with TC before age 25, Norway	Through 2008	Any, but no individual treatment data	- A hazard ratio for suicide of 2.9, 95% CI = 1.3 to 6.4 was found for TC survivors. - Other cancers with a particularly elevated suicide risk was CNS tumors, leukemia and bone/soft tissue sarcomas.
Patel 2017 [17]	16 463, seminoma, stage I-II	1998-2013, SEER, US	Median 99.5 months	- No RT (7337) - RT (9 126)	RT associated with reduced overall- and cancer-specific survival among stage IA patients due to an almost twofold risk of SC
Zhang 2019 [18]	4879, seminoma, any stage. 3717, nonseminoma, any stage.	1980-2015, Swedish Cancer Registry data	Median 11 years	Any	- SMRs not reported - Survival at 30 years of follow-up was approximately 80% for TC patients without SC and 40% for patients with SC.

BEP, bleomycin, etoposide, cisplatin; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; CRN, Cancer Registry of Norway; CVD, cardiovascular disease; CT, chemotherapy; GCC, germ cell cancer; MTOL, more than one line of treatment; OC, other causes of death (not SC or CVD); PMI, prophylactic mediastinal irradiation; RT, radiotherapy; SC, second cancer; SEER, Surveillance, Epidemiology, and End Results; SMR, standardized mortality ratio; TC, testicular cancer; TGCT, testicular germ cell tumor; UK, United Kingdom; US, United States.

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PAPER III

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

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

Introduction

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

Previous studies have demonstrated a 1.7 to 3.5-fold increased risk for both hematological and solid nongerm cell SC in testicular cancer survivors (TCS) compared to age-matched general populations.[6–9] The risk has been associated with both radiotherapy (RT) and chemotherapy (CT), but not with surgery only. The

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

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

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

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What's new?

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

majority of these studies have, however, been based on outdated TC treatment principles. Consequently, there is a lack of studies on SC risk after the introduction of cisplatin.[9–12] Experimental data and animal studies have suggested cisplatin as a carcinogen.[13] Besides, high cumulative cisplatin doses have been linked to an increased leukemia risk.[14,15]

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

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

Methods

Study cohort and design

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

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

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

Staging and treatment groups

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

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

Statistical methods

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

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

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

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

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

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

(Continues)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

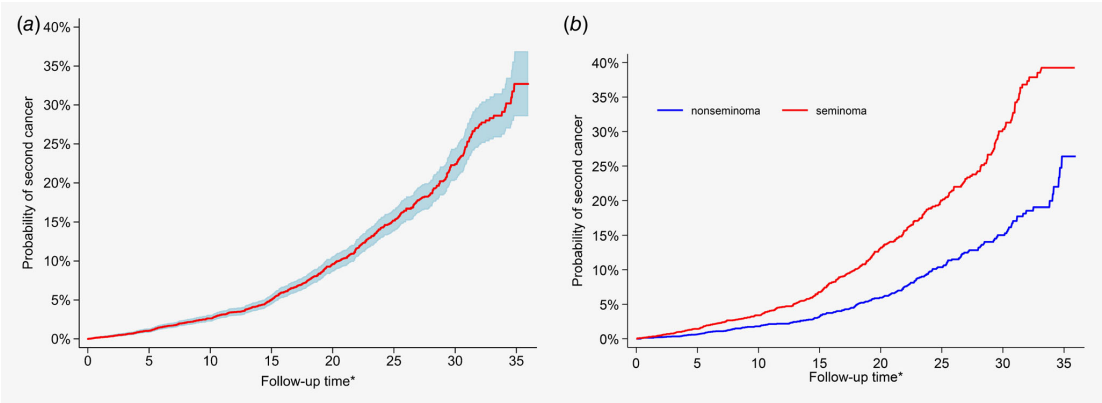

Figure 1. Crude cumulative probability of second cancer by follow up-time. (*a*) All patients (with 95% confidence interval) and (*b*) by histology. In *a*, the red line indicates the probability of second cancer, and the blue area indicates the 95% confidence interval. *years since diagnosis +1 year. [Correction added on 1 May 2020, after first online publication: Figure 1b was incorrect due to a mathematical error and has been replaced in this version.]

Data availability

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

Results

Study cohort

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

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

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

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

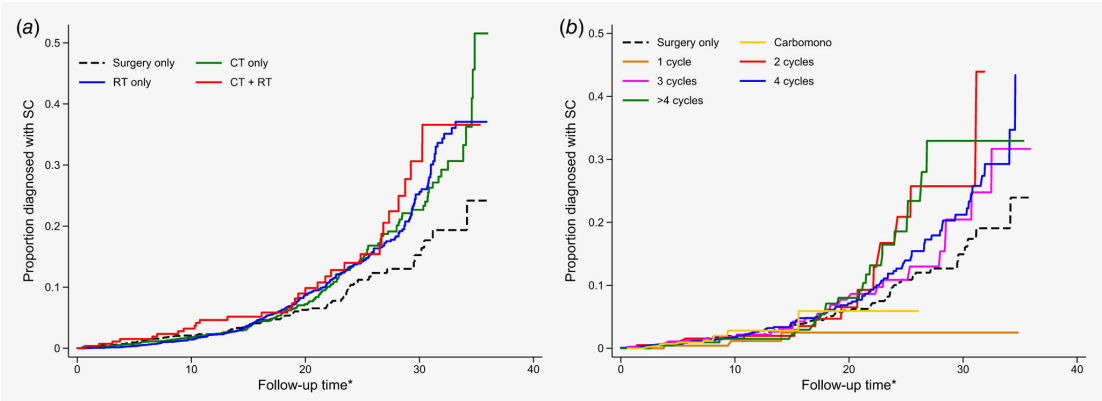

Figure 2. Proportion diagnosed with second cancer by follow-up time, adjusted for age at testicular cancer diagnosis. (*a*) By treatment, (*b*) by number of cisplatin-based chemotherapy cycles and carboplatin monotherapy. *years since diagnosis +1 year. Abbreviations: Carbomono, adjuvant carboplatin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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The crude cumulative probability of SC at 25 years was 20% (95% CI 18–22%) for seminoma and 10% (95% CI 8.7–12%) for nonseminoma survivors (Fig. 1*b*). SC risk among individuals with seminoma was significantly increased compared to nonseminoma in age-adjusted analysis (HR 1.20, 95% CI 1.01–1.44). [Correction added on 1 May 2020, after first online publication: The values in the preceding paragraph have been corrected.]

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

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

SC risk in relation to treatment intensity

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

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

Discussion

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

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

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

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

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

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

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

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

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

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

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

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

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

We found an almost 60% significantly increased risk of SC after both seminomas and nonseminomas compared to the general population, which is in line with the recent Dutch publication.[9] Our remarkably higher 25-year crude probability of all SCs following seminomas of 20%, compared to 12.6% in the Dutch report is interesting. [Correction added on 1 May 2002, after first online publication: 28% has been changed to 20% in the preceding sentence.] Some of the difference might be explained by the longer median follow-up after seminoma in our study of 16.0 years compared to 13.5 years in the Dutch study.

Strengths of our study are the inclusion of detailed information regarding total treatment burden for the entire study cohort, and the unique quality of the CRN. Based on a distinct personal identification number used in Norway, the CRN receives information from several sources to ensure accuracy, and reporting to

this registry is instructed by law.[1] SIRs are easy to understand and interpret, and we considered that calculation of absolute excess risks (AERs) would not provide more information to the reader. The use of time-dependent Cox-regression implements the important element of observation time in our analyses.

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

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

Disclaimer

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

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Supplemental appendix Table 1. General treatment principles for TC patients in Norway by decade of diagnosis

Decade	Localized disease	Metastatic disease
1980 to 1989	Seminomas: adjuvant RT towards paraaortal and ipsilateral iliacal lymph nodes by the L-field technique.[1] The target dose was gradually reduced from 36-40 Gy to 25.2-27 Gy.[1, 2] One institution offered RT restricted to the para-aortic area only from 1989.[3] Nonseminomas: staging RPLND followed by adjuvant chemotherapy if metastases were histologically verified.[4]	Majority of cases treated with CT. CVB standard CT-regimen up until 1987 when BEP became standard treatment.[5] Some treated according to experimental regimens within research protocols.[6-11] Generally ≥4 cycles administered. Seminoma patients received post-chemo RT to residual masses until 1986. Residual masses after CT in nonseminoma patients were resected, primarily as a RPLND. RT was a treatment option if residual masses persisted after CT and/or surgery. Nerve-sparing RPLND from 1989.[4]
1990 to 1999	Seminomas: adjuvant RT continued as above, target dose usually <30 Gy. Nonseminomas: After 1990, primary RPLND was abandoned, and stage 1 patients were instead offered surveillance or 1-2 cycles of adjuvant CBCT.[12-14]	The BEP-regimen remains standard first-line therapy in metastatic disease. High-dose chemotherapy with autologous stem cell support available from 1995. Some treated according to experimental regimens within research protocols.[6-11] Residual masses after CT in nonseminoma patients were resected, primarily as a RPLND
2000 to 2009	Seminomas: From 2000, RT was gradually abandoned in stage I, and patients were increasingly offered surveillance or adjuvant carboplatin.[15, 16] Nonseminomas: patients are offered surveillance or one adjuvant cycle of BEP.[17] Follow-up: By the end of the study-period recommendation to use MRI-scan because of the concern about increased second cancer risk after multiple CT-scans.[18, 19]	The number of CT cycles have been reduced to 3 cycles for patients with good prognosis (the majority of patients) and 4 cycles for patients with intermediate and poor prognosis.[11, 20] Seminoma patients offered EP instead of BEP. Decrease in usage of RT for seminomas, but still an option in stage IIA disease.

TC: testicular cancer; RT: radiotherapy; RPLND: retroperitoneal lymph node dissection; CT: chemotherapy; CVB: cisplatin, vinblastine, bleomycin; BEP: cisplatin, etoposide, bleomycin; Gy: Grey; CBCT: cisplatin-based CT; MRI: magnetic resonance imaging.

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Supplemental appendix Table 2. Presentation of numbers of first and subsequent non-germ cell SC in the study cohort according to diagnostic code

Diagnostic code ICD-10	First	Second	Third	Fourth	SUM
C00-C14 Ear, nose, throat	14	1	0	0	15
C15 Esophagus	8	0	0	0	8
C16 Stomach	20	1	0	0	21
C17 Small intestine	8	3	0	0	11
C18 Colon	35	6	0	0	41
C19 Rectosigmoid junction	4	0	0	0	4
C20 Rectum	24	2	0	0	26
C22 Liver and intrahepatic bile ducts	6	0	0	0	6
C24 Extrahepatic bile ducts	6	0	0	0	6
C25 Pancreas	25	3	0	0	28
C26 Ill-defined digestive organs	1	1	0	0	2
C31 Accessory sinuses	1	0	0	0	1
C32 Larynx	3	1	0	0	4
C34 Bronchus and lung	65	3	1	0	69
C41 Bone and articular cartilage	2	0	1	0	3
C43 Malignant melanoma of skin	38	6	1	0	45
C44 Other malignant neoplasms of skin	22	2	1	0	25
C45 Mesothelioma	4	0	0	0	4
C47 Peripheral nerves and autnomic nervous system	1	0	0	1	2
C48 Retroperitoneum and peritoneum	2	0	0	0	2
C49 Other connective and soft tissue	2	0	0	0	2
C50 Breast	2	0	0	0	2
C60 Penis	2	0	0	0	2
C61 Prostate	107	11	2	2	122
C64 Kidney	23	4	0	0	27
C65 Renal pelvis	2	1	0	0	3
C66 Ureter	4	3	2	0	9
C67 Bladder	49	7	1	0	57
C68 Other and unspecified urinary organs	0	1	0	0	1
C69 Eye	1	0	0	0	1
C70 Meninges	4	0	0	0	4
C71 Brain	12	0	0	0	12
C72 Spinal cord, cranial nerves and other parts of CNS	3	0	0	0	3
C75.1 Pituitary gland	9	0	0	0	9
C73 Thyroid	10	0	0	0	10
C76 Other and ill-defined sites	8	2	0	0	10
C81 Hodgkin lymphoma	7	0	0	0	7
C82 Follicular lymphoma	8	0	1	1	10
C83 Non-follicular lymphoma	6	1	1	0	8
C85 Non-Hodgkin lymphoma, unspecified	2	1	0	0	3
C88 Malignant immunoproliferative diseases	1	0	0	0	1
C90 Multiple myeloma	3	1	0	0	4
C91 Lymphoid leukaemia	5	0	0	0	5
C92 Myeloid leukaemia	6	1	1	0	8
C93 Monocytic leukaemia	1	0	0	0	1
C95 Leukaemia, unspecified	1	0	0	0	1
D45 Polycytemia vera	1	0	0	0	1
D46 Myelodysplastic syndrome	4	1	0	0	5
SUM	**572**	**64**	**12**	**4**	**651**

Note: Data are presented as numbers. Thirteen cases are registered with identical ICD-10 diagnoses twice, and as a result, the sum in this table does not add up to the numbers presented in table 2 for certain diagnoses. Median time between first and second diagnosis: 2.04 years (IQR 4.75); median time between second and third diagnosis: 1.54 years (IQR 4.05); median time between third and fourth diagnosis: 0.33 years (IQR 0.34).

SC: non-germ cell second cancer; CNS: central nervous system; ICD-10: international classification of diseases; IQR: interquartile range.

Supplemental Table 3. HRs for non-germ cell SC according to treatment group: age-adjusted time-dependent Cox

	Surgery only[1]		CT		RT		CT + RT	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Total SC[2]								
>10 y obs	1	ref	**1.57**	**1.13-2.16**	**1.71**	**1.27-2.31**	**1.71**	**1.06-2.78**
>15 y obs[3]	1	ref	**1.78**	**1.23-2.60**	**1.83**	**1.29-2.62**	**1.85**	**1.07-3.19**
>20 y obs	1	ref	**1.96**	**1.22-3.14**	**1.78**	**1.13-2.80**	**2.08**	**1.13-4.00**
All solid cancers C00-C80	1	ref	**1.65**	**1.18-2.31**	**1.77**	**1.29-2.42**	**1.79**	**1.09-2.95**
Ear, nose and throat C00-14, C31-32	1	ref	1.16	0.28-4.91	0.84	0.21-3.36	NA	NA
Esophagus C15	1	ref	0.98	0.16-5.94	0.35	0.05-2.47	NA	NA
Stomach C16	1	ref	0.78	0.05-12.57	4.19	0.54-32.50	**24.25**	**2.89-203.41**
Small intestine C17	1	ref	0.92	0.15-5.51	0.70	0.13-3.88	1.72	0.15-19.22
Colorectal C18-20	1	ref	2.31	0.85-6.28	2.10	0.81-5.41	0.66	0.08-5.63
Liver and bile ducts C22, C24	1	ref	0.29	0.03-3.25	1.42	0.29-6.95	NA	NA
Pancreas C25	1	ref	0.64	0.09-4.52	2.75	0.63-11.99	3.47	0.49-24.77
Lung C34[4]	1	ref	2.16	0.87-5.39	1.59	0.65-3.89	1.80	0.45-7.25
Skin, malignant melanoma C43	1	ref	1.06	0.41-2.75	0.56	0.21-1.48	0.63	0.08-5.10
Skin, other C44	1	ref	0.80	0.11-5.70	1.25	0.26-6.05	3.76	0.52-27.14
Soft tissue C47-49	1	ref	0.55	0.03-8.89	1.43	0.14-14.32	NA	NA
Prostate C61	1	ref	1.27	0.65-2.50	1.56	0.85-2.85	0.81	0.23-2.86
Kidney and upper urinary tract C64-C66[5]	1	ref	6.03	0.77-47.15	**7.58**	**1.01-56.94**	7.88	0.71-87.27
Bladder C67	1	ref	**5.07**	**1.16-22.09**	**5.33**	**1.27-22.43**	5.10	0.85-30.68
Brain C70-72, C75.1	1	ref	4.01	0.49-32.63	2.77	0.33-23.14	NA	NA
Thyroid C73	1	ref	0.59	0.04-9.43	0.92	0.08-10.39	NA	NA
Malignant neoplasm of other and ill-defined sites C76	1	ref	2.50	0.28-22.44	1.69	0.20-14.62	NA	NA
All haematological malignancies[6] C81-85, C88, C90-93, C95, D45, D46	1	ref	0.92	0.33-2.59	1.13	0.44-2.87	1.30	0.26-6.49
Lymphoma C81-85	1	ref	0.60	0.12-2.98	1.27	0.34-4.75	2.76	0.46-16.64
Leukaemia C91-93, C95	1	ref	1.83	0.19-17.63	1.64	0.18-14.87	NA	NA

Note: HRs reported for cancers or groups of cancers (of defined sites) with occurrence of ≥5. Please refer to the supplemental appendix Table 2 for details. Results presented only for >10 year observation time. Significant results marked with bold. C refers to diagnostic code according to the ICD-10 classification.

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

[2] Of the total n of 4199 with > 10 y obs time, 431 cases developed SC. Of the total n of 2974 with > 15 y obs, 340 cases developed SC. Of the total n of 1876 with > 20 y obs time, 213 cases developed SC.

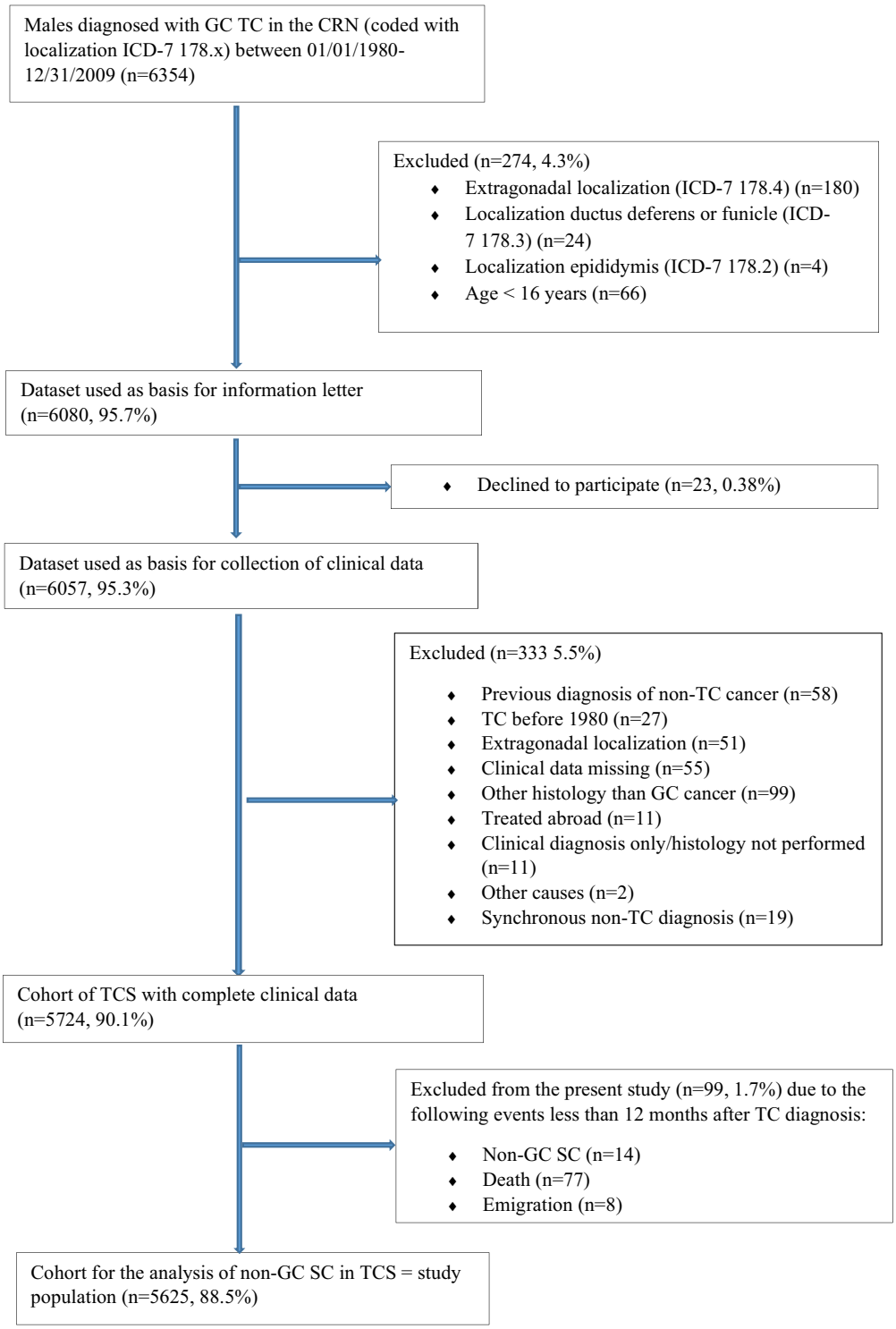
[3] Analyses with >15 and >20 years done with time-dependent Cox model and a dummy variable of follow-up time (before/after 15 or 20 years).

[4] All of which were localized in the bronchi

[5] The morphology of C64 was diverse. We chose to analyze kidney and upper urinary tract together.

[6] No haematological malignancies occurred before 12 months observation time in eligible participants.

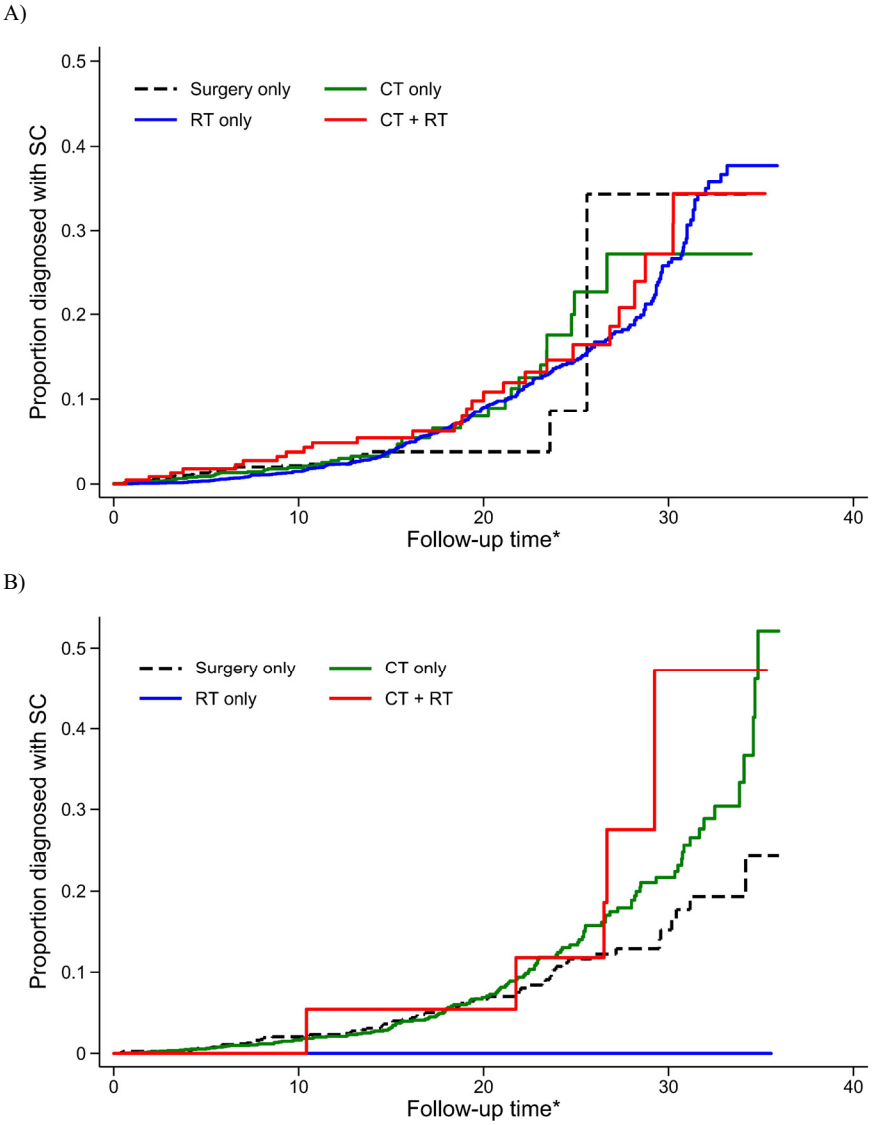
Abbreviations: HR, hazard ratio; SC, second cancer; CT, chemotherapy; RT, radiotherapy; CT + RT, combination of chemotherapy and radiotherapy; 95% CI, 95% confidence interval; y, years; obs, observation, NA, not available because of too few events.



Supplemental appendix Figure 1. Flow chart presenting the study cohort

Abbreviations: GC: germ cell; TC: testicular cancer; CRN: Cancer Registry of Norway; ICD-7: International Classification of Diseases version 7; SC: second cancer; TCS: testicular cancer survivors.

Supplemental Appendix Figure 2. Proportion diagnosed with second cancer after seminoma or nonseminoma by follow-up time, adjusted for age at testicular cancer diagnosis



Supplemental Appendix Figure 2. Proportion diagnosed with second cancer after seminoma or nonseminoma by follow up-time, adjusted for age at testicular cancer diagnosis. A) Seminoma, B) Nonseminoma.

*years since diagnosis + 1 year

Abbreviations: SC: second cancer; CT: chemotherapy; RT: radiotherapy; CT + RT: combination of CT and RT.