

# Long-term Relative Survival after Diagnosis of Testicular Germ Cell Tumor

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## Abstract

**Background:** Long-term relative survival (RS) data for testicular germ cell tumor (TGCT) patients are scarce. We aimed to analyze long-term RS among TGCT patients diagnosed in Norway, between 1953 and 2012.

**Methods:** Data sources were the Cancer Registry of Norway and the Norwegian Cause of Death Registry. TGCT patients diagnosed during 1953 to 2012 were classified by time of diagnosis, histology, age, and disease extent at diagnosis. Estimates for RS were obtained, and a test comparing overall RS was performed. Corresponding data were obtained for men diagnosed with localized malignant melanoma before age 50.

**Results:** A total of 8,736 TGCT patients were included. RS generally continued to decline with increasing follow-up time, particularly beyond 15 to 30 years, unlike in localized malignant melanoma. Although RS was generally higher for seminomas, the continuing decline was more pronounced than for nonseminomas,

even when diagnosed with localized disease. TGCT patients diagnosed before 1980 or after age 40 had lower RS.

**Conclusions:** Although TGCT RS has improved in recent decades, it continues to decline even beyond 30 years of follow-up, regardless of disease extent at diagnosis. The main cause is probably treatment-induced late effects, particularly affecting seminoma patients. The continued use of adjuvant radiotherapy in seminomas until year 2000 is suspected as a culprit.

**Impact:** Long-term TGCT survivors should be closely monitored for the development of late comorbidity. The challenge is to reduce negative consequences of previous and current TGCT treatment on RS while maintaining the excellent cure rates. Further research on causes of long-term morbidity and mortality among TGCT survivors is warranted. *Cancer Epidemiol Biomarkers Prev*; 25(5); 773–9. ©2016 AACR.

## Introduction

The notion that survivors of testicular germ cell tumors (TGCT) have a normal life expectancy is being challenged (1). Despite today's excellent 10-year survival rates of above 95%, TGCT treatment is associated with an increased risk of potentially life-threatening late effects. The most important are second malignant neoplasms and cardiovascular disease, usually manifesting beyond 10 years of follow-up (1–8). Even more alarming are the reports on increased mortality from these and other conditions in TGCT survivors (1–4, 9, 10).

Most TGCT patients are diagnosed before 40 years of age. With long follow-up times, it is highly relevant to not just examine overall survival (OS) but compare it with that of the general population [relative survival (RS); refs. 11, 12]. However, there are no studies directly reporting RS data beyond

20 years of follow-up. The aim of this study was to analyze long-term trends in RS among TGCT patients diagnosed in Norway during 1953 to 2012.

## Materials and Methods

### Data sources

Data were derived from the Cancer Registry of Norway (CRN) and the Norwegian Cause of Death Registry.

The CRN contains compulsorily reported data on all new cancers in Norway since 1953, including information on histopathology and extent of disease at diagnosis. Since 1993, morphology and topography have been coded according to the International Classification of Diseases (ICD) for Oncology, 2nd edition. Before 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 (13).

The Norwegian Cause of Death Registry contains information on causes of death for all inhabitants of Norway since 1951, based on mandatory death certificates. ICD-10 has been used for coding since 1996, whereas ICD-6 to ICD-9 were used during 1951 to 1995.

### Study population

The study population was all men who received a diagnosis of TGCT in Norway from January 1, 1953, until December 31, 2012. Clinical diagnoses of testicular cancer were allowed as 95% are of germ cell origin. Spermatocytic seminomas were excluded from analysis because they are a distinct

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**Note:** Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (<http://cebp.aacrjournals.org/>).

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clinicopathologic entity. Patients diagnosed with extragonadal germ cell tumors were also excluded.

The patients were, if possible, classified by histology (seminoma vs. nonseminoma and mixed cases), disease extent at diagnosis (localized to the testicle vs. metastatic), and age at diagnosis (younger vs. older than 40 years). End of follow-up was December 31, 2013. Patients were followed from diagnosis to death, emigration, or end of follow-up, whichever came first. In bilateral TGCT, follow-up time and classification was determined by the first TGCT diagnosis.

To evaluate and compare the impact of treatment on RS among TGCT patients, we identified all men diagnosed with localized malignant melanoma in Norway before age 50 during the same time frame. In this group, adjuvant treatment has traditionally not been given.

#### Cohorts of diagnosis and TGCT treatment information

Because of the lack of individual treatment information in the CRN, patients were divided into six cohorts by time period of diagnosis from 1953 to 2012. TGCT treatment principles changed considerably during this period, but management remained centralized to Norwegian university hospitals.

**Cohorts 1 (1953–59) and 2 (1960–69).** Retroperitoneal lymph node dissections (RPLND) were seldom performed in this period. X-ray irradiation and gradually betatron high-voltage fractionated radiotherapy was given to para-aortic and ipsilateral iliac lymph nodes with a dose of 35 to 40 Gy in seminoma patients without evidence of metastasis (stage I) and up to 45 Gy in nonseminomas. If lymph node metastases were detected (stages II and III), large abdominal fields received up to 40 Gy, including the mediastinum. In the 1960s, cyclophosphamide or mithramycin was occasionally given to patients with metastases.

**Cohort 3 (1970–79).** Vena cavography, lymphography, and CT improved diagnostic accuracy. CRN data show that radiotherapy was given to 70% to 87% of TGCT patients at the Norwegian Radium Hospital during 1970 to 1979, where about 90% of Norwegian TGCT patients were treated. Although radiation fields remained similar, linear accelerators became available, and nonseminoma patients received doses of up to 50 Gy both in adjuvant and salvage settings. Prophylactic mediastinal irradiation was frequently applied if regional lymph node metastases were found. Most patients with metastases received either mithramycin or combinations of actinomycin D, vincristine, doxorubicin, and cyclophosphamide until the paradigm-shifting introduction of cisplatin-based chemotherapy in Norway in May 1978 (14).

From late 1978, a staging RPLND was increasingly used in nonseminoma patients without clinical or radiologic evidence of metastasis. Patients with retroperitoneal lymph node metastasis at pathology usually received adjuvant cisplatin, etoposide, and bleomycin (CVB; ref. 15), whereas CVB followed by RPLND and/or surgical removal of other residual metastases was considered standard in metastatic disease (stages II–IV) from 1979.

**Cohorts 4 (1980–89) and 5 (1990–99).** Radiotherapy to nonseminomas was, from 1980, mainly given in the palliative setting. Seminoma patients in stage I and low-volume stage II

still received radiotherapy of approximately 30 Gy, with boost to nodal disease. From 1987, the CVB regimen was gradually replaced with the more effective and less toxic bleomycin, etoposide, and cisplatin (BEP) regimen in metastatic nonseminomas and high-volume seminomas (16). From 1995, high-dose chemotherapy with autologous stem cell support was sometimes used after inadequate initial response to chemotherapy or in relapses. From the same year, staging RPLNDs were replaced by surveillance and adjuvant chemotherapy in stage I nonseminoma.

**Cohort 6 (2000–2012).** Adjuvant radiotherapy in stage I seminoma patients remained standard therapy until about 2000. Gradually replaced by surveillance, adjuvant radiotherapy was no longer considered standard in 2007 and has henceforth been an option only in selected patients with low-volume disease (17). One course of adjuvant carboplatin became an option for stage I seminoma. BEP remained standard first-line chemotherapy in metastatic TGCT, and RPLND was routine in patients with retroperitoneal residual tumor. In stage I nonseminoma, most high-risk patients received one BEP adjuvant, whereas most low-risk patients were managed with surveillance (16, 18). MRI was preferred to CT in follow-up to reduce radiation dose.

#### Statistical analysis

To ensure unbiased estimates of long-term RS, the method developed by Perme and colleagues was used (12). Information on population mortality was obtained from national population life tables stratified by gender, age, and year. Overlapping 95% confidence intervals (CI) imply statistically nonsignificant differences ( $P > 0.05$ ). Also, a statistical 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 (19). Subanalyses were performed on 5-year survivors and patients diagnosed with localized disease. As the test assumes a normally distributed test statistic, it will be referred to as a *Z* test in this article.

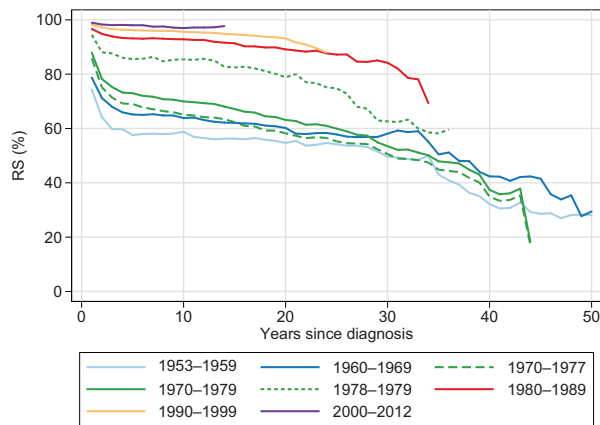
## Results

### RS, all TGCT patients

During 1953 to 2012, 9,173 men received a diagnosis of testicular cancer in Norway. Of these, 198 patients registered with extragonadal germ cell tumors were excluded from analysis, as were 138 patients with histologically verified non-germ cell tumors and 54 with spermatocytic seminomas. Forty-seven patients with identical reported dates of diagnosis and death were also excluded; most were diagnosed postmortem.

Accordingly, 8,736 men were analyzed. At the end of the follow-up, 2,298 deaths had occurred, while 93 had emigrated. The median age at diagnosis across the cohorts was 32 to 36 years, and 260 patients (3.0%) were registered with two cases of TGCT.

RS was significantly reduced among the TGCT patients, regardless of cohort of diagnosis and follow-up time (Fig. 1; Table 1). In the 1953–79 cohorts, point estimates for RS declined markedly the first few years after diagnosis before beginning to level off, probably reflecting mortality from TGCT and treatment complications. With increasing follow-up, RS continued to decline, even at an increased rate beyond 30 years.



**Figure 1.** Point estimates of RS of all testicular germ cell tumor patients by cohort of diagnosis and follow-up time. Interval estimates (95% CI) and persons at risk are given in Table 1. Also shown are point estimates for subcohorts 1970-77 and 1978-79.

In the 1970-79 cohort, point estimates for RS were consistently lower than for the 1960-69 cohort beyond 28 years. We thus analyzed the 1970-77 and 1978-79 subcohorts (Fig. 1). With the latter subcohort representing the transition to cisplatin-based chemotherapy, even lower point estimates were revealed for the former.

In the 1980-2012 cohorts, RS was significantly improved compared with the earlier cohorts regardless of follow-up time. Even so, an accelerated decline in RS was still seen beyond 20 years for the 1990-99 cohort and beyond 30 years for the 1980-89

cohort. RS point estimates were highest in the 2000-2012 cohort, with no visible decline at the current end of follow-up.

**RS by histologic subgroup**

One hundred and twenty six of the 8,736 patients could not be subclassified due to missing or inconclusive histopathology reports. Of the remaining 8,610 patients, 4,730 (55%) had seminoma and 3,880 (45%) nonseminoma. At the end of the follow-up, 1,305 seminoma and 922 nonseminoma patients were deceased. Median age at diagnosis across the cohorts was 36 to 40 years for seminomas and 27 to 30 years for nonseminomas.

Point estimates for RS in nonseminomas were generally inferior to seminomas in all cohorts regardless of follow-up time (Fig. 2, Supplementary Tables S1 and S2). However, with increasing follow-up, these estimates declined more rapidly for seminomas than nonseminomas in all but the 2000-2012 cohort. In the 1980-89 cohort, point estimates for RS in seminomas were even inferior to nonseminomas beyond 15 years.

Results of the Z test supported these findings, showing a statistically significant difference in overall RS, favoring seminomas in all but the 1980-89 cohort (Fig. 2). When analyses were restricted to 5-year survivors, the situation changed with a worse overall RS for seminomas in the 1970-89 cohorts. In the other cohorts, differences were no longer statistically significant.

**RS in localized disease at diagnosis**

A higher percentage of seminomas than nonseminomas were diagnosed with localized disease, on average, 82.0% versus 60.6% of cases where disease extent was known. As expected, restricting

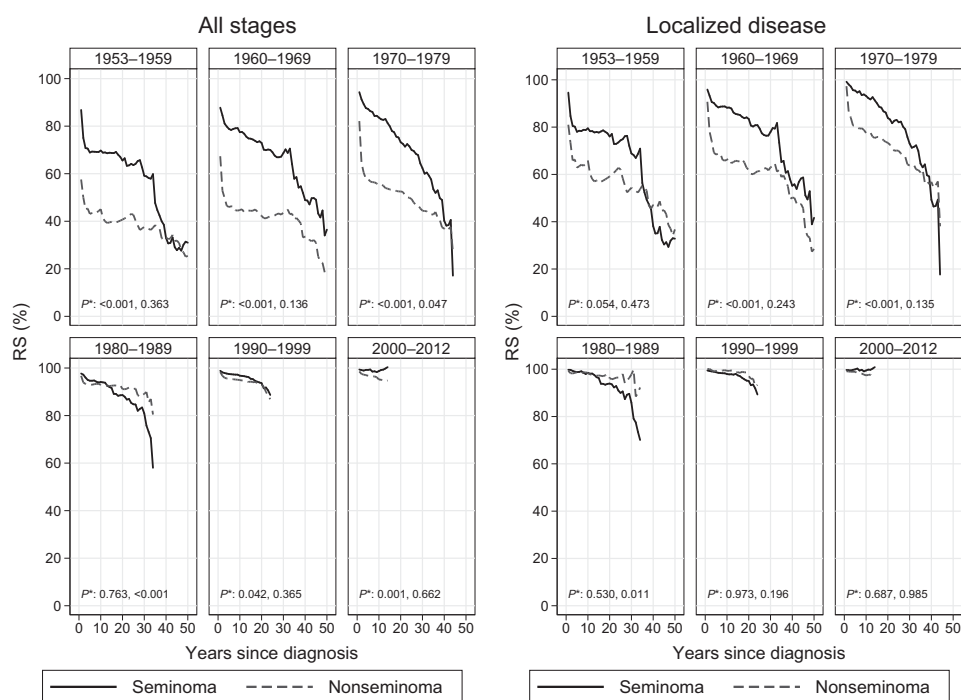
**Table 1.** RS and persons at risk, all testicular germ cell tumor patients, by cohort of diagnosis and follow-up time

Cohort <sup>a</sup>	Follow-up time (years)								
	0	1	5	10	20	30	40	50	
1953-59 (MF: 17.0)	1.0	0.744 (0.693-0.788)	0.576 (0.519-0.629)	0.588 (0.528-0.643)	0.547 (0.474-0.614)	0.497 (0.391-0.593)	0.322 (0.201-0.449)	0.281 (0.148-0.430)	
1960-69 (MF: 21.2)	1.0	0.787 (0.754-0.817)	0.652 (0.612-0.688)	0.638 (0.593-0.680)	0.602 (0.549-0.651)	0.581 (0.515-0.641)	0.424 (0.289-0.552)	0.294 (0.149-0.456)	
1970-79 (MF: 24.5)	1.0	0.879 (0.856-0.899)	0.730 (0.698-0.759)	0.700 (0.665-0.732)	0.632 (0.588-0.672)	0.535 (0.475-0.590)	0.374 (0.260-0.487)		
1980-89 (MF: 27.0)	1.0	0.966 (0.955-0.975)	0.932 (0.914-0.946)	0.928 (0.908-0.945)	0.891 (0.857-0.918)	0.842 (0.773-0.891)			
1990-99 (MF: 17.8)	1.0	0.983 (0.975-0.988)	0.962 (0.951-0.971)	0.956 (0.941-0.967)	0.932 (0.903-0.952)				
2000-12 (MF: 6.6)	1.0	0.989 (0.985-0.993)	0.980 (0.973-0.986)	0.970 (0.957-0.979)					
Persons at risk <sup>c</sup>	1953-59	327 (236, 81)	242 (211, 22)	184 (167, 10)	180 (164, 10)	153 (141, 8)	114 (105, 5)	62 (56, 3)	28 (24, 2)
	1960-69	673 (476, 184)	526 (445, 71)	426 (381, 37)	405 (363, 35)	350 (314, 30)	276 (245, 26)	172 (155, 14)	27 (26, 1)
	1970-79	920 (563, 345)	805 (552, 245)	651 (490, 155)	605 (462, 138)	504 (389, 110)	386 (305, 76)	68 (55, 10)	
	1980-89	1,391 (867, 512)	1,337 (858, 469)	1,265 (834, 425)	1,232 (812, 414)	1,120 (733, 383)	337 (199, 135)		
	1990-99	2,001 (1,399, 490)	1,959 (1,387, 464)	1,890 (1,356, 428)	1,832 (1,320, 412)	623 (468, 152)			
	2000-12	3,424 (2,395, 703)	3,377 (2,375, 679)	2,179 (1,407, 457)	882 (545, 186)				

<sup>a</sup>Cohort of diagnosis, with median follow-up time (MF) in years for each cohort.

<sup>b</sup>Point and interval estimates (95% CI) for RS.

<sup>c</sup>Total number of persons at risk, followed by persons at risk by disease stage at diagnosis, where known (localized, metastatic).



**Figure 2.** Point estimates of RS of all seminoma and nonseminoma patients (left) and localized disease at diagnosis only (right) by cohort of diagnosis and follow-up time. Interval estimates (95% CI) and persons at risk for all patients are given in Supplementary Tables S1 and S2. \*, *P* values, Z test comparing overall RS between seminoma and nonseminoma patients for all above patients and 5-year survivors only, respectively.

RS analyses to these patients led to improved point estimates, mostly in nonseminomas. However, the continuing decline in RS seen for all disease stages combined was still present (Fig. 2). Consequently, point estimates for RS in seminomas became inferior to nonseminomas beyond 15 years in the 1990–99 cohort as well. In contrast, RS among the 3,995 patients diagnosed with localized malignant melanoma seemed to plateau and even increase beyond 15 years (Fig. 3).

Among patients diagnosed with localized TGCT, the Z test remained statistically significant in favor of seminomas for the 1960–79 cohorts, also bordering on significance for the 1953–59 cohort (Fig. 2). Among 5-year survivors, a significant difference in overall RS favoring nonseminomas was still found in the 1980–89 cohort.

#### RS by age at diagnosis

Point estimates for RS were consistently lower among both seminoma and nonseminoma patients diagnosed beyond age 40 compared with those diagnosed at a younger age, all cohorts combined (Fig. 4; Table 2). The Z test was statistically significant, favoring the younger group in both histologies, including 5-year survivors only. Differences in stage distribution between the age groups were minor.

Findings were similar for patients diagnosed with localized TGCT, except that for nonseminomas; the Z test was only statistically significant among 5-year survivors (Fig. 4).

## Discussion

Our principal finding was a continuous decline in long-term RS in TGCT patients diagnosed in Norway between 1953 and 2012, save for seminomas diagnosed after 1999. An accelerated decline was evident beyond 15 to 30 years of follow-up for all applicable cohorts (Fig. 1), particularly so for seminoma patients, even when diagnosed with localized disease (Fig. 2).

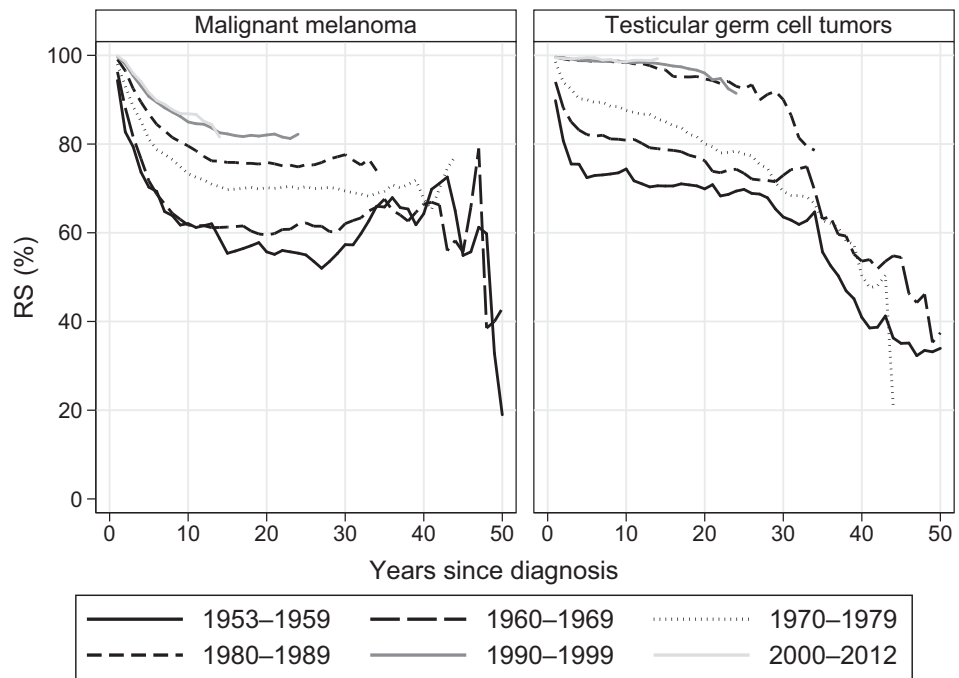
Also, RS was significantly reduced among patients diagnosed beyond age 40 compared with a younger age (Fig. 4). These findings indicate that even beyond 30 years of follow-up, the life expectancy of TGCT survivors continues to decline compared with the general population.

The main cause is probably a continuous development of late effects of TGCT treatment, for which both direct and indirect mechanisms, such as the metabolic syndrome, have been suggested (1–3). Supporting this is the striking difference between RS curves of localized malignant melanoma and TGCT (Fig. 3).

Changes in treatment may contribute to the general improvement in RS from the earliest to the latest cohort of diagnosis. However, advancements in health care are probably also contributing factors, reducing or delaying mortality from treatment-induced morbidities.

In the 1970–77 subcohort, more extensive chemotherapy use in metastatic and relapsing TGCT improved RS the first 10 to 15 years, though perhaps at the cost of combined chemotherapy- and radiotherapy-induced late effects (2, 3).

Spermon and colleagues found inferior 10-year RS among U. S. TGCT patients diagnosed at 50 years or older compared with a younger age, particularly in metastatic disease (20). Our data also support this finding beyond 10 years of follow-up (Fig. 4). In addition, TGCT-specific mortality is reported to increase with increasing age at diagnosis (21, 22). Seminoma patients might be at a particular risk of treatment-associated late toxicity due to increased median age at diagnosis, explaining the more rapid decline in RS (Fig. 2). The inferior point estimates for RS in seminomas diagnosed with localized disease during 1980 to 1999 is most likely due to the continued use of adjuvant radiotherapy in these patients. This is of particular concern as stage I seminoma is the most frequent presentation of TGCT.



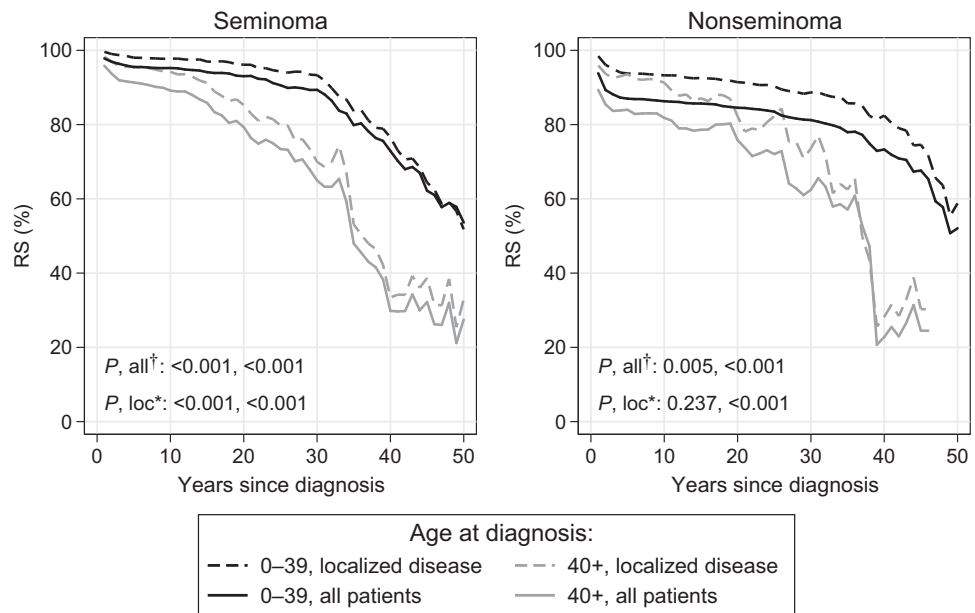
**Figure 3.** Point estimates of RS of male patients diagnosed with localized malignant melanoma before 50 years of age (left) and patients diagnosed with localized testicular germ cell tumors (right), by cohort of diagnosis and follow-up time. Of the 3,995 patients with localized malignant melanoma, 877 were diagnosed before 1980 and 85 before 1960.

Factors not directly related to treatment may also reduce RS. There could be an innate susceptibility for other diseases among TGCT patients, perhaps different from patients with malignant melanoma and even between seminomas and nonseminomas. CT scans traditionally used in the follow-up may have increased the risk of conditions such as second malignant neoplasms (2, 6).

To our knowledge, no other study directly reports RS data for TGCT patients beyond 20 years of follow-up. In 2002, Brenner reported a 20-year RS of 84.1% among U.S. TGCT patients

diagnosed between 1978 and 1998, comparable with our data (23). In 2007, Robinson and colleagues reported up to 20-year RS in 9,892 English TGCT patients, between 1960 and 2004, by histology and decade of diagnosis (24). For reasons unknown, our 20-year RS point estimate was inferior by about 14% for seminomas diagnosed during 1970 to 1979, less so for the other cohorts (about 1%–8%).

Several studies report OS or overall mortality among TGCT patients beyond 20 years of follow-up, data which cannot directly be translated into RS (4, 9, 21, 25–29). Fossa and colleagues



**Figure 4.** Point estimates of RS of all seminoma (left) and nonseminoma patients (right), by age at diagnosis (younger vs. older than 40 years) and follow-up time. Interval estimates (95% CI) and persons at risk are given in Table 2. †, *P* values, *Z* test comparing overall RS between patients diagnosed before or after 40 years for all testicular germ cell tumor patients and 5-year survivors only, respectively. \*, *P* values, *Z* test comparing overall RS between patients diagnosed with localized (loc) testicular germ cell tumors before or after 40 years for all patients and 5-year survivors only, respectively.

**Table 2.** RS and persons at risk, all seminoma and nonseminoma patients, by age at diagnosis (younger vs. older than 40 years) and follow-up time

Histology and age <sup>a</sup>	Follow-up time (years)								
	0	1	5	10	20	30	40	50	
RS <sup>b</sup>	S, <40	1.0	0.978 (0.972–0.983)	0.955 (0.946–0.963)	0.952 (0.942–0.961)	0.930 (0.914–0.944)	0.894 (0.861–0.919)	0.729 (0.656–0.789)	0.536 (0.371–0.676)
	S, >40	1.0	0.958 (0.948–0.967)	0.913 (0.896–0.928)	0.892 (0.865–0.913)	0.793 (0.742–0.835)	0.650 (0.545–0.736)	0.298 (0.146–0.467)	0.275 (0.034–0.610)
	NS, <40	1.0	0.938 (0.929–0.946)	0.870 (0.858–0.881)	0.863 (0.850–0.875)	0.845 (0.829–0.860)	0.812 (0.787–0.835)	0.733 (0.669–0.787)	0.521 (0.352–0.665)
	NS, >40	1.0	0.893 (0.865–0.916)	0.840 (0.803–0.871)	0.818 (0.769–0.858)	0.758 (0.637–0.844)	0.624 (0.403–0.783)	0.228 (0.056–0.468)	
Persons at risk <sup>c</sup>	S, <40	2,736 (2,150, 421)	2,669 (2,135, 370)	2,220 (1,755, 305)	1,757 (1,404, 245)	982 (832, 140)	442 (372, 60)	149 (130, 12)	25 (21, 2)
	S, >40	1,994 (1,505, 381)	1,897 (1,468, 323)	1,456 (1,123, 231)	1,079 (862, 162)	521 (452, 67)	192 (169, 22)	37 (35, 2)	2 (2, 0)
	NS, <40	3,271 (1,868, 1,255)	3,062 (1,835, 1,083)	2,442 (1,451, 852)	1,962 (1,181, 700)	1,072 (644, 426)	427 (277, 148)	112 (97, 13)	27 (26, 1)
	NS, >40	609 (372, 202)	540 (354, 152)	414 (274, 109)	290 (193, 78)	144 (98, 42)	42 (30, 10)	3 (3, 0)	0

<sup>a</sup>Patients are grouped by histology [seminoma (S) vs. nonseminoma (NS)] and by age at diagnosis (younger vs. older than 40 years).

<sup>b</sup>Point and interval estimates (95% CI) for RS.

<sup>c</sup>Total number of persons at risk, followed by persons at risk by disease stage at diagnosis, where known (localized, metastatic).

found significantly reduced OS among 21,629 U.S. TGCT patients diagnosed during 1971 to 2001 with up to 27 years of follow-up, regardless of disease extent (25). OS seemed to decline more rapidly towards the end of the follow-up compared with the reference population. Beard and colleagues reported a significantly increased all-cause mortality among 9,193 U.S. stage I seminoma patients diagnosed during 1973 to 2001, regardless of initial radiotherapy (7,179 patients, ref. 9). Zagars and colleagues found a significantly increased overall standardized mortality ratio among 477 US stage I–II seminoma patients treated with radiotherapy during 1951 to 1999, where the actuarial survival rate at 40 years was 26% (26). Our data support these findings, although Horwich and colleagues did not find a significant increase in overall mortality among 2,543 UK and Norwegian stage I seminoma patients treated during 1960 to 1992 (4). In addition, Capocaccia and colleagues reported favorable annual 25-year conditional RS among U.S. TGCT patients diagnosed during 1985 to 2011, ages 24 to 34 (30).

The most important limitation in our study is the lack of individual treatment information. As such, firm conclusions regarding the impact of different therapeutic strategies on RS cannot be drawn. Particularly, patients treated with surgery alone might not be at increased risk of cardiovascular disease or second malignant neoplasms (2, 6) and are likely to have a higher RS.

It is unknown how many patients relapsed after initial treatment, but most would probably occur within two years of diagnosis. Although pre-TGCT comorbidities were unknown, apart from previously or simultaneously reported other cancers in 92 patients, it is unlikely that the distribution would differ from the reference population. The CRN data quality is considered to be high (11), but minor errors in reporting and coding are likely.

As expected, RS interval estimates became increasingly wide, particularly beyond 40 years of follow-up. Statistically nonsignificant results could be partly due to the relatively few 5-year survivors in the 1950–69 cohorts and because of limited fol-

low-up time in the 1990–2012 cohorts. Also, relatively few nonseminomas were diagnosed after age 40.

In conclusion, long-term RS in TGCT patients generally continues to decline with increasing follow-up time and is likely treatment related. Even though 10-year survival has been improved in patients diagnosed more recently, the unfavorable long-term outcome calls for a continuing relentless effort to reduce the treatment burden without hampering the chance of cure. There should also be a life-long focus on late morbidity in TGCT survivors.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

### Authors' Contributions

**Conception and design:** Ø. Kvammen, A. Solberg, B. Møller, O.H. Klepp, S.D. Fosså, T. Tandstad

**Development of methodology:** T.Å. Myklebust, B. Møller, O.H. Klepp, S.D. Fosså, T. Tandstad

**Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.):** T.Å. Myklebust, O.H. Klepp

**Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis):** Ø. Kvammen, T.Å. Myklebust, A. Solberg, B. Møller, S.D. Fosså, T. Tandstad

**Writing, review, and/or revision of the manuscript:** Ø. Kvammen, T.Å. Myklebust, A. Solberg, B. Møller, O.H. Klepp, S.D. Fosså, T. Tandstad

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**Study supervision:** A. Solberg, O.H. Klepp, T. Tandstad

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