



# Differences in future life expectancy of testicular germ-cell tumor patients vs. age-matched male population-based controls

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## Abstract

**Background** It is unknown whether five-year overall survival (OS) differs and to what extent between testicular germ-cell tumor (TGCT) patients and age-matched male population-based controls.

**Materials** We identified newly diagnosed (2004–2014) TGCT patients within Surveillance Epidemiology and End Results database 2004–2019. We compared OS between non-seminoma (NS-TGCT) and seminoma (S-TGCT) patients relative to age-matched male population-based controls based on Social Security Administration Life-Tables. Smoothed cumulative incidence plots displayed cancer-specific mortality (CSM) vs. other-cause mortality (OCM).

**Results** Of all 20,935 TGCT patients, 43% had NS-TGCT and 57% had S-TGCT. Of NS-TGCT patients, 63% were stage I vs. 16% stage II vs. 21% stage III. Of S-TGCT patients, 86% were stage I vs. 8% were stage II vs. 6% stage III. Five-year OS differences between NS-TGCT patients vs age-matched male population-based controls were 97 vs. 99% ( $\Delta = 2\%$ ) for stage I, 96 vs. 99% ( $\Delta = 3\%$ ) for stage II, 76 vs 98% ( $\Delta = 22\%$ ) for stage III. Five-year OS differences between S-TGCT patients vs age-matched male population-based controls were 97 vs. 98% ( $\Delta = 1\%$ ) for stage I, 95 vs. 97% ( $\Delta = 2\%$ ) for stage II, 87 vs. 98% ( $\Delta = 11\%$ ) for stage III. OCM rates ranged from 1 to 3% in NS-TGCT patients and from 2 to 4% in S-TGCT patients.

**Conclusion** The OS difference between NS-TGCT patients vs. age-matched male population-based controls was invariably higher across all stages (2–22%) than for S-TGCT patients (1–11%). Reassuringly, OCM rates were marginal in stage I and stage II patients. Conversely, higher OCM rates were recorded in stage III patients.

**Keywords** SEER program · Testis cancer · Future life expectancy · Germ-cell tumors

## Introduction

Testicular germ-cell tumor (TGCT) is the most common solid malignancy among men aged 20–40 years, enclosing in it two distinct main histological entities: non-seminomas (NS-TGCT) and seminomas (S-TGCT) [1, 2]. Its incidence has risen over the past two decades in Western countries [3]. In 2020, the highest incidence was estimated in western and central Europe (7–11 cases per 100,000), followed by the United States and Canada (5–6 cases per 100,000) [4].

The natural history of TGCT is generally very favorable for stages I and II. Conversely, less favorable survival applies to stage III patients, especially in NS-TGCT rather

than seminoma S-TGCT. Indeed, the five-year overall survival (OS) in NS-TGCT patients ranging from 67 to 96%, and in S-TGCT ranging from 88 to 95% [5, 6]. Epidemiological data describing cancer-specific mortality (CSM), as well as other-cause mortality (OCM) rates of TGCT patients are scarce [7].

Currently, it is unknown whether stage I and II NS-TGCT or S-TGCT diagnosis affects future life expectancy. Moreover, it is also unknown to what extent future life expectancy of stage III NS-TGCT and S-TGCT differs from age-matched male population-based controls according to the United States Social Security Administration (SSA) Life-Tables [8]. Moreover, it is also unknown to what extent future life expectancy of different International Germ Cell Cancer Collaborative Group (IGCCCG) prognostic-risk groups differs

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from age-matched male population-based controls. Additionally, contemporary OCM rates in NS-TGCT as well as S-TGCT patients are unknown.

We addressed these knowledge gaps and tested for differences and quantified their magnitude within the Surveillance Epidemiology and End Results (SEER) database (2004–2019). We hypothesized that no differences exist in stage I and II patients from age-matched male population-based controls. Conversely, we hypothesized that significant differences exist between stage III patients and age-matched male population-based controls. Moreover, we postulated that significant differences exist between different prognostic-risk groups and age-matched male population-based controls. Finally, we hypothesized that OCM rates were marginal at best.

## Materials and methods

### Study population

The SEER database samples 34.6% of the US population in terms of demographic composition and cancer incidence [9]. Within the SEER database from 2004 to 2019, we selected patients  $\geq 18$  years old with newly diagnosed (2004–2014) testis cancer (International Classification of Disease for Oncology [ICD-O-3] site code C62.1 and C62.9) and histologically confirmed S-TGCT (ICD-O histology code 9061-2/3) or NS-TGCT (ICD-O histology code 9065/3, 9070/3, 9071/3, 9080-5/3, 9100-2/3) [2]. We only considered patients treated with orchiectomy with available American Joint Committee on Cancer (AJCC) staging. All autopsy or death certificate-only cases were excluded. Further exclusion criteria consisted of missing follow-up and survival data. Rates of CSM (i.e., death from TGCT) and OCM (i.e., death not attributable to TGCT) were defined according to the SEER mortality code. Owing to the anonymously coded design of the SEER database, study-specific ethics approval was waived by the institutional review board.

### Statistical analyses

For each TGCT patient, we simulated an age-matched male control in a one-to-one fashion, according to previously described methodology [10–15]. Subsequently, the survival of the control population was computed using a Monte Carlo simulation and a Markov chain of natural progression, according to SSA Life-Tables' derived probabilities of survival at five years of follow-up. Therefore, derived five-year OS estimates for each age-matched male stage-specific group control will henceforth be referred to as "age-matched male population-based controls".

Descriptive statistics included frequencies and proportions for categorical variables. Medians and interquartile ranges (IQR) were reported for continuously coded variables.

Kaplan-Meier plots graphically depicted OS of NS-TGCT and S-TGCT patients and of corresponding age-matched male population-based controls in a stage-specific fashion. Subsequently, differences in five-year OS were computed in NS-TGCT and S-TGCT patients relative to age-matched male population-based controls. Finally, smoothed cumulative incidence plots to graphically depicted CSM and OCM rates.

Additionally, we performed subgroup analyses in metastatic NS-TGCT (mNS-CGTT) and in metastatic S-TGCT (mS-TGCT) patients. Here, additional stratification according to IGCCCG prognostic-risk groups (good vs. intermediate vs. poor prognosis mNS-TGCT; good vs. intermediate prognosis mS-TGCT) was applied.

All tests were two-sided, with a significance level set at  $p < 0.05$ . In all statistical analyses, R software environment for statistical computing and graphics (R version 4.1.3, R Foundation for Statistical Computing, Vienna Austria, <http://www.r-project.org/>) was used [16].

## Results

### Characteristics of NS-TGCT and S-TGCT cohorts

Of 20,935 TGCT patients, 9035 (43%) had NS-TGCT while 11,894 (57%) had S-TGCT. Within NS-TGCT patients, the median age was 28 (IQR: 23–35) and the AJCC stage distribution was as follows: stage I 5722 (63%) vs. stage II 1399 (16%) vs. stage III 1,914 (21%). We identified 2469 mNS-TGCT patients that fulfilled IGCCCG prognostic-risk groups criteria, harbored 1260 (51%) good vs. 425 (17%) intermediate vs. 784 (32%) poor prognosis. (Table 1a)

Conversely, within the S-TGCT, the median age was 37 (IQR: 30–45) and the AJCC stage distribution was as follows: stage I 10,204 (85%) vs. stage II 1008 (8%) vs. stage III 682 (6%). We identified 1690 mS-TGCT patients that fulfilled IGCCCG prognostic-risk groups criteria harbored 1531 (91%) good vs. 159 (9%) intermediate prognosis. (Table 1b)

### Overall survival in NS-TGCT and S-TGCT patients versus age-matched male population-based controls

At five years of follow-up, OS differences between NS-TGCT patients vs age-matched male population-based controls ranged from 2 to 22% according to stages (Fig. 1; Table 2). Specifically, the greatest OS difference was

**Table 1** Descriptive characteristics of 20,929 newly diagnosed (2004–2014) with testicular germ-cell tumor (TGCT) patients, 9035 harbored non-seminoma (NS-TGCT) (a) and 11,894 harbored semi-

noma (S-TGCT) (b), within the Surveillance, Epidemiology, and End Results (SEER) database 2004–2019

(a) Non-seminoma testicular germ-cell tumor (NS-TGCT)						
Characteristic	N	Overall, N = 9035 <sup>a</sup>	Stage I N = 5722 (63%) <sup>a</sup>	Stage II N = 1399 (15%) <sup>a</sup>	Stage III N = 1914 (21%) <sup>a</sup>	p-value <sup>b</sup>
Age	9035	28 (23, 35)	28 (24, 35)	27 (23, 34)	27 (23, 35)	0.001
IGCCCG prognostic-risk group	2469					<0.001
Good		1260 (51%)	–	880 (100%)	380 (24%)	
Intermediate		425 (17%)	–	–	425 (27%)	
Poor		784 (32%)	–	–	784 (49%)	
(b) Seminoma testicular germ-cell tumor (S-TGCT)						
Characteristic	N	Overall N = 11,894 <sup>a</sup>	Stage I N = 10,204 (86%) <sup>a</sup>	Stage II N = 1008 (8%) <sup>a</sup>	Stage III N = 682 (6%) <sup>a</sup>	p-value <sup>b</sup>
Age	11,894	37 (30, 45)	37 (30, 45)	38 (31, 46)	39 (32, 47)	<0.001
IGCCCG prognostic-risk group	1690					<0.001
Good		1531 (91%)	–	1008 (100%)	523 (77%)	
Intermediate		159 (9%)	–	–	159 (23%)	

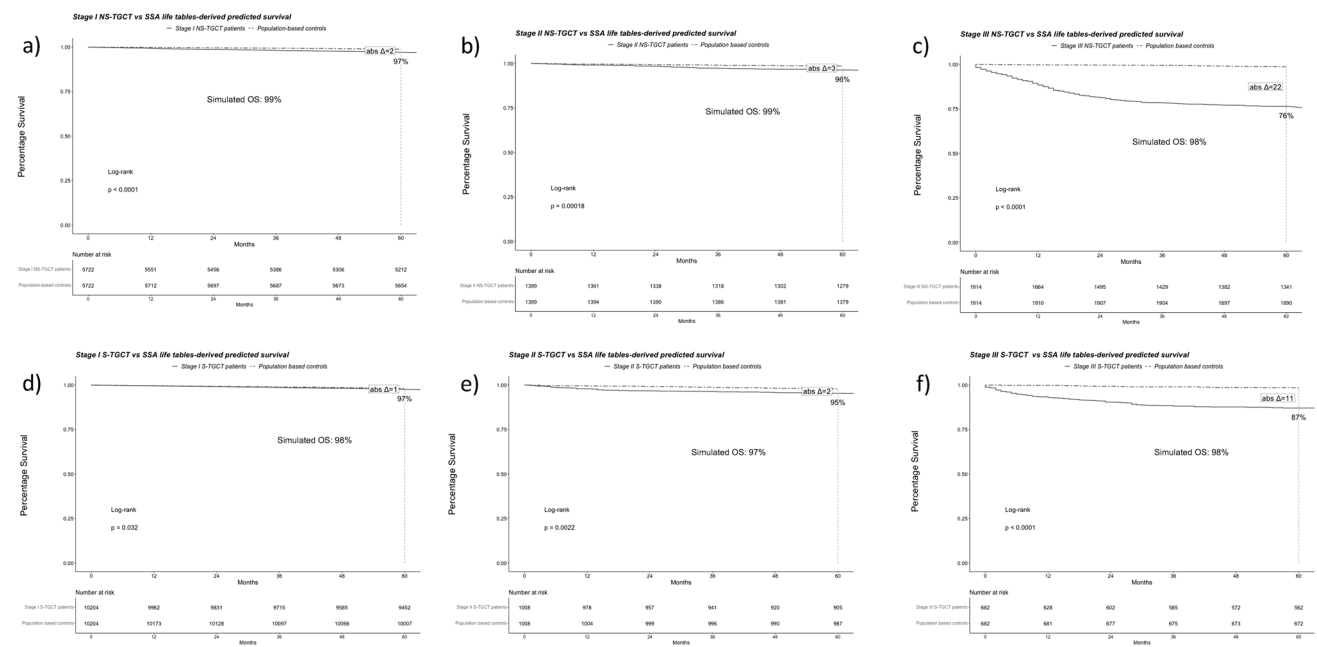
Stratification is made according to American Joint Committee on Cancer (AJCC) stage (I vs II vs III)

Data are shown as medians and interquartile ranges (IQR) for continuously coded variables and frequencies and proportions for categorical variables

IGCCCG International Germ Cell Cancer Collaborative Group

<sup>a</sup>Median (IQR); n (%)

<sup>b</sup>Kruskal-Wallis rank sum test; Pearson's Chi-square test



**Fig. 1** Kaplan-Meier curves comparing five-year overall survival of 20,929 newly diagnosed (2004–2014) testicular germ-cell tumor (TGCT) patients, 9035 harbored nonseminoma (NS-TGCT) (a–c) and 11,894 harbored seminoma (S-TGCT) (d–f) within the Surveil-

lance, Epidemiology, and End Results database 2004–2019 vs their simulated age-matched male population-based controls, according to American Joint Committee on Cancer (AJCC) stage (I vs II vs III). (Legend: abs Δ = absolute difference)

**Table 2** Summary of survival analyses of 20,929 newly diagnosed (2004–2014) with testicular germ-cell tumor (TGCT) patients, 9035 harbored non-seminoma (NS-TGCT) (a) and 11,894 harbored semi-

noma (S-TGCT) (b), within the Surveillance, Epidemiology, and End Results database 2004–2019 according to American Joint Committee on Cancer (AJCC) stage (I vs II vs III)

(a) Non-seminoma testicular germ-cell tumor (NS-TGCT)				
AJCC stage (n, %)	Overall (n = 9035, 100%)	I (n = 5722, 63%)	II (n = 1399, 16%)	III (n = 1914, 21%)
5-year Overall Survival	93%	97%	96%	76%
5-year Overall Survival in controls	99%	99%	99%	98%
Absolute 5-year Overall Survival difference	6%	2%	3%	22%
Cancer-specific mortality	6%	2%	2%	20%
Other-cause mortality	2%	1%	1%	3%
(b) Seminoma testicular germ-cell tumor (S-TGCT)				
AJCC stage (n, %)	Overall (n = 11,894, 100%)	I (n = 10,204, 86%)	II (n = 1008, 9%)	III (n = 682, 6%)
5-year Overall Survival	97%	97%	95%	87%
5-year Overall Survival in controls	98%	98%	97%	98%
Absolute 5-year Overall Survival difference	1%	1%	2%	11%
Cancer-specific mortality	1%	1%	2%	9%
Other-cause mortality	2%	2%	2%	4%

recorded in stage III (76 vs 98%,  $\Delta = 22\%$ ; Fig. 1c), followed by stage II (96 vs 99%,  $\Delta = 3\%$ ; Fig. 1b) and stage I (97 vs 99%,  $\Delta = 2\%$ ; Fig. 1a), in that order.

Conversely, at five years of follow-up, OS differences between S-TGCT patients vs age-matched male population-based controls ranged from 1 to 11% according to stages (Fig. 1; Table 2). Specifically, the greatest OS difference was recorded in stage III (87 vs 98%,  $\Delta = 11\%$ ; Fig. 1f), followed by stage II (95 vs 97%,  $\Delta = 2\%$ ; Fig. 1e) and stage I (97 vs 98%,  $\Delta = 1\%$ ; Fig. 1d), in that order.

### Cancer-specific mortality and other-cause mortality in NS-TGCT and S-TGCT patients

At five years of follow-up, CSM rates in NS-TGCT ranged from 2 to 20%, according to stage (Fig. 2; Table 2). Specifically, the CSM rate was 20% in stage III and 2% in both stage I and stage II. Conversely, at five years of follow-up, CSM rates in S-TGCT ranged from 1 to 9%, according to stage. Specifically, the highest CSM rate was recorded in stage III (9%), followed by stage II (2%) and stage I (1%), in that order.

At five years of follow-up, OCM rates in NS-TGCT ranged from 1 to 3%, according to stage (Fig. 2; Table 2). Specifically, the OCM rates were 3% in stage III and in 1% in both stage I and II. Conversely, OCM rates in S-TGCT ranged from 2 to 4%, according to stage. Specifically, the OCM rates were 4% in stage III and 2% in both stage I and II.

### Subgroup analyses in mNS-TGCT and mS-TGCT patients

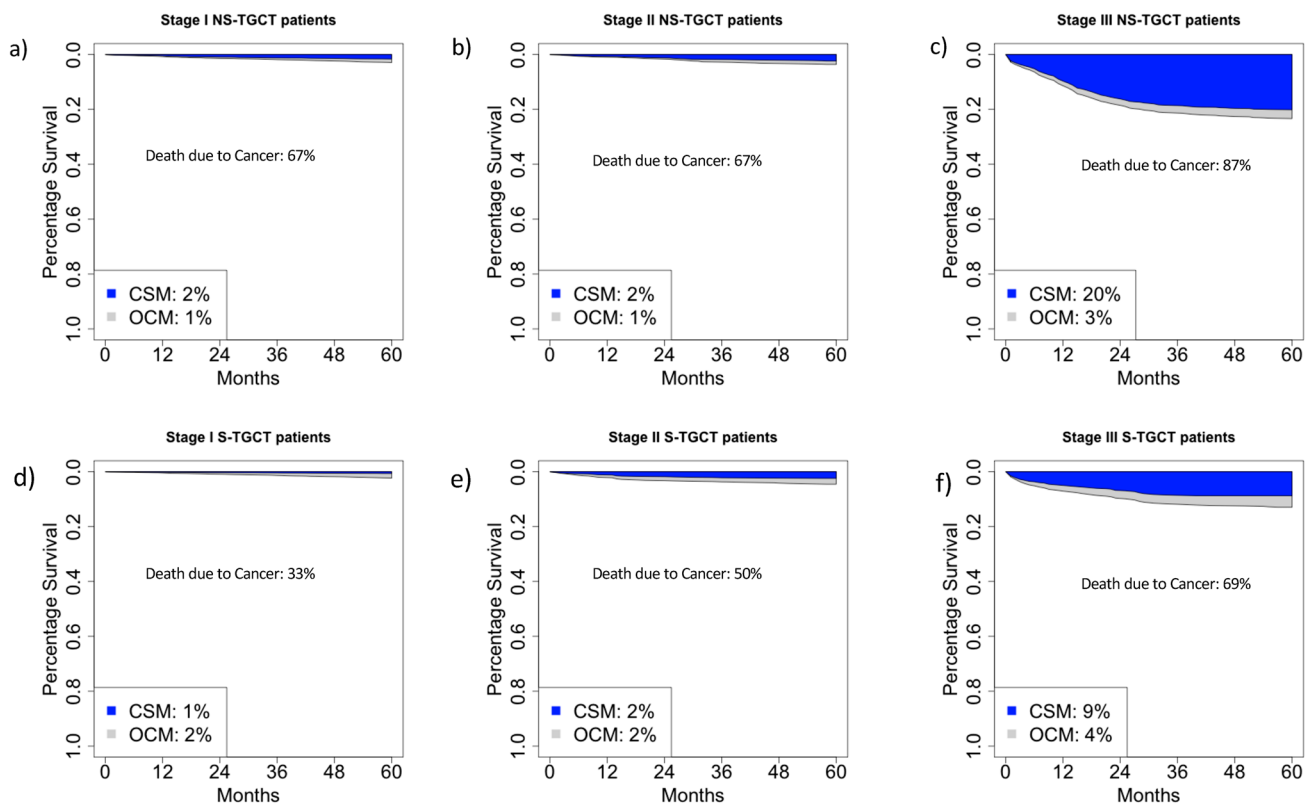
Within mNS-TGCT, the greatest OS difference between IGCCCG prognostic-risk group patients and age-matched male population-based controls was recorded in poor prognosis (65 vs 99%,  $\Delta = 34\%$ ; Fig. 3c), followed by intermediate prognosis (84 vs 99%,  $\Delta = 15\%$ ; Fig. 3b) and good prognosis (93 vs 99%,  $\Delta = 6\%$ ; Fig. 3a), in that order.

Within mS-TGCT, the greatest OS difference between IGCCCG prognostic-risk group patients and age-matched male population-based controls was recorded in intermediate prognosis (78 vs 98%,  $\Delta = 20\%$ ; Fig. 3e), followed by good prognosis (93 vs 97%,  $\Delta = 4\%$ ; Fig. 3d).

At five-years of follow-up, CSM rates in mNS-TGCT ranged from 4 to 31%, according to IGCCCG prognostic-risk groups (Fig. 4; Table 3). Specifically, the CSM rate was 31% in poor prognosis patients, 13% in intermediate prognosis patients and 4% in good prognosis patients.

Conversely, at five-years of follow-up, CSM rates in mS-TGCT ranged from 4 to 18%, according to IGCCCG prognostic-risk groups. Specifically, the CSM rate was 18% in intermediate prognosis patients and 4% in good prognosis patients.

At five-years of follow-up, OCM rates in mNS-TGCT were 2% for good and intermediate patients, while it was 4% for poor prognosis patients. Conversely, at five-years of follow-up, OCM rates in mS-TGCT were 4% in intermediate prognosis patients and 3% in good prognosis patients.



**Fig. 2** Smoothed cumulative incidence plots addressing cancer-specific mortality (CSM) and other-cause mortality (OCM) of 20,929 newly diagnosed (2004–2014) testicular germ-cell tumor (TGCT) patients, 9035 harbored non-seminoma (NS-TGCT) (a–c) and 11,894

harbored seminoma (S-TGCT) (d–f), within the Surveillance, Epidemiology, and End Results database 2004–2019 according to American Joint Committee on Cancer (AJCC) stage (I vs II vs III)

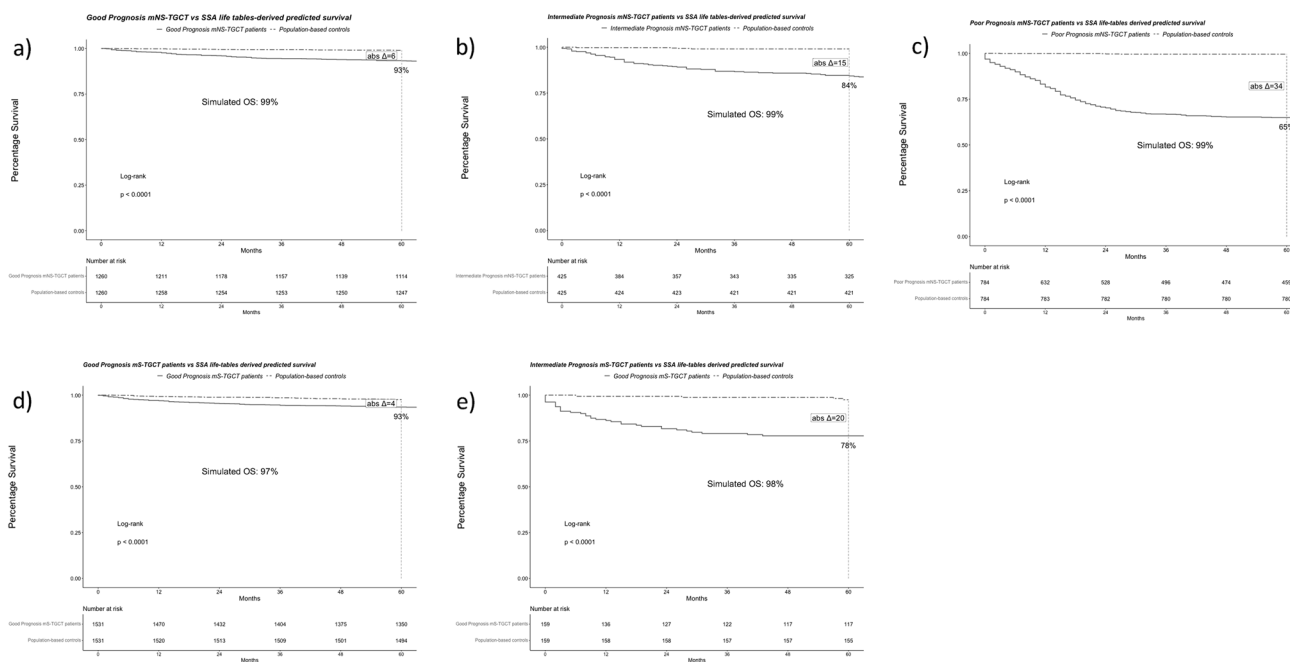
## Discussion

It is unknown whether five-year OS differs and to what extent between TGCT patients and age-matched male population-based controls. Our comprehensive analyses of OS between TGCT patients and age-matched male population-based controls revealed several noteworthy observations.

First, we identified 20,935 TGCT patients who underwent orchiectomy within the SEER database over a period of eleven years (2004–2014). This number is comparable to other publications addressing TGCT within SEER and National Cancer Database (NCDB) [17–19]. TGCT is the most common type of testicular cancer, however, it accounts for less than 2% of adult malignancies [20]. Therefore, single-institution or even multi-institutional databases may suffer of limited numbers of observations. For example, Yamashita et al. relied on a cohort of only 563 patients (1980–2019) diagnosed with testicular cancer from a single high-volume center [21]. Similarly, Nourelidin et al., in a large multi-institutional database identified only 869 patients (2008–2017) diagnosed with testicular cancer [20]. In consequence, only large epidemiological databases such as SEER or NCDB offer the opportunity

to study relatively large cohorts of such a rare entity as TGCT.

Second, in stage I and II marginal OS differences were recorded between NS-TGCT and S-TGCT patients relative to age-matched male population-based controls. Expectedly, the lowest difference was recorded in stage I S-TGCT, followed by stage I NS-TGCT, stage II S-TGCT and stage II NS-TGCT, in that order. These observations are consistent with the notion that stage I and II both NS-TGCT and S-TGCT represent curable diseases [4, 22]. Indeed, our observations validate that notion based on OS differences, that were marginal between S-TGCT stage I patients and age-matched male population-based controls (97 vs. 98%;  $\Delta = 1\%$ ), as well as between NS-TGCT stage I patients and age-matched male population-based controls (97 vs. 99%;  $\Delta = 2\%$ ). Moreover, only marginally higher OS differences were recorded in NS-TGCT and S-TGCT patients relative to corresponding age-matched male population-based controls ( $\Delta = 3\%$  in NS-TGCT and  $\Delta = 2\%$  in S-TGCT). Taken together, these observations indicate that future life expectancy is not affected in stage I and II NS-TGCT and S-TGCT patients, relative to age-matched male population-based controls. The above findings addressing stage I and II



**Fig. 3** Kaplan-Meier curves comparing five-year overall survival of 4159 newly diagnosed (2004–2014) with metastatic testicular germ-cell tumor (mTGCT) patients, 2469 harbored nonseminoma (mNS-TGCT) (a–c) and 1,690 (d, e) seminoma (mS-TGCT), within the Surveillance, Epidemiology, and End Results database 2004–2019 vs

their simulated age-matched male population-based controls, according to International Germ Cell Cancer Collaborative Group (IGCCG) prognostic-risk groups (good vs. intermediate vs. poor for mNS-TGCT; good vs. intermediate for mS-TGCT). (Legend: absΔ = absolute difference)

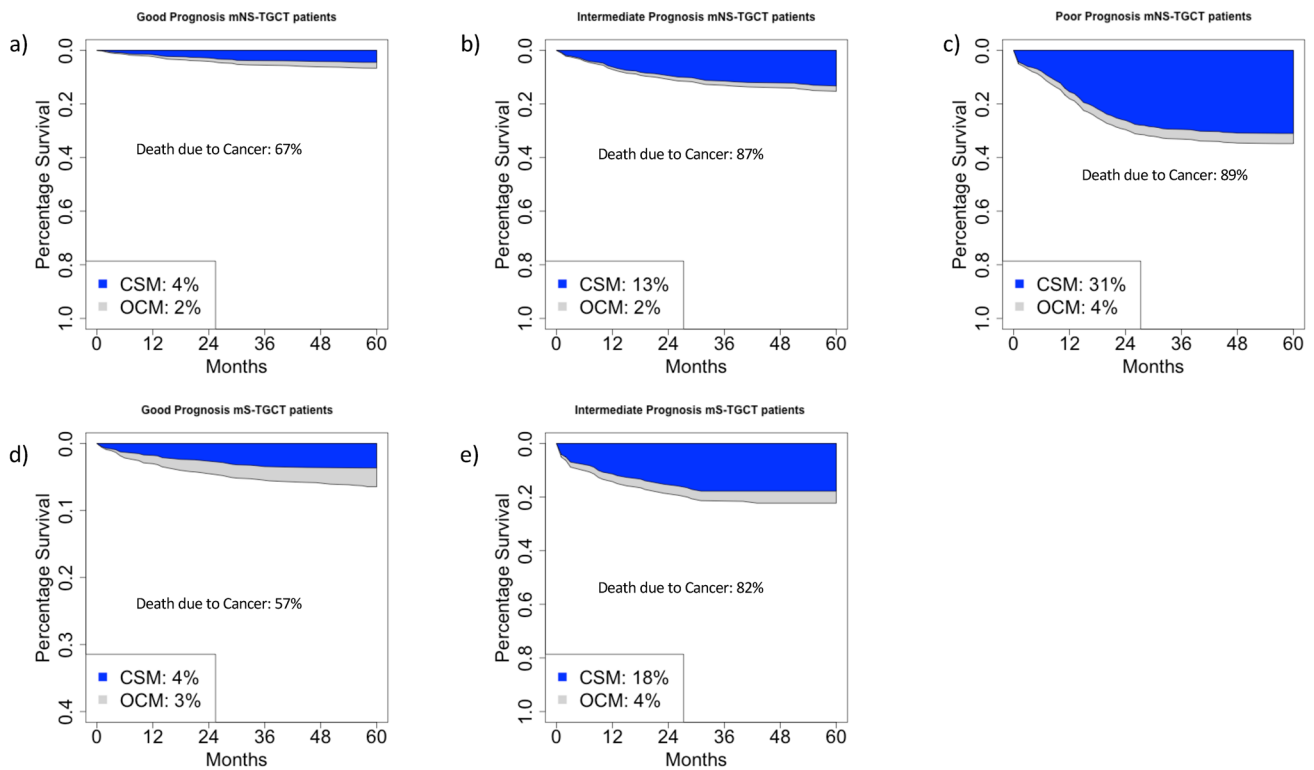
TGCT cannot be directly compared with previous studies, since no such studies exist. However, the observations made in the current study should ideally be validated within an independent external validation cohort from within a different large-scale data repository.

Third, in stage III we recorded higher OS differences in NS-TGCT and S-TGCT patients relative to age-matched male population-based controls. Specifically, the highest difference was recorded between stage III NS-TGCT and age-matched male population-based controls (76 vs. 98%; Δ = 22%), followed by stage III S-TGCT (87 vs. 98; Δ = 11%). Taken together, these observations indicate that future life expectancy is shortened in stage III NS-TGCT relative to age-matched male population-based controls and to a lesser extent to stage III S-TGCT. These observations cannot be directly compared with absolute OS rates from other studies, since no such studies exist.

Fourth, specific subgroup analyses that tabulated mNS-TGCT and mS-TGCT patients according to IGCCG prognostic-risk groups revealed a dose-response effect, where future life expectancy was most reduced in poor, followed by intermediate and good prognosis patients. Specifically, these observations were more pronounced in mNS-TGCT patients (poor 65 vs 99%, Δ = 34%; intermediate 84 vs 99%, Δ = 15%; good 93 vs 99%, Δ = 6%). Despite less pronounced differences in absolute values of

life expectancy detriments, a similar dose-response effect was recorded in mS-TGCT patients (intermediate 78 vs 98%, Δ = 20%; good 93 vs 97%, Δ = 4%). As for the overall analyses, shortened life expectancy is expected in metastatic patients, relative to age-matched male population-based control. Moreover, the magnitude of life expectancy detriment is also expected to be most pronounced in poor IGCCG prognostic-risk group patients, followed by intermediate and good. However, no factual data supporting these expectations were previously reported. In consequence, the current study cannot be directly compared.

Last but not least, we addressed OCM rates in NS-TGCT and S-TGCT patients. We hypothesized that virtually no OCM should be recorded in this young patient population in whom treatment toxicity should be minimal. Indeed, in stage I we recorded an OCM rate of 1% both in NS-TGCT and S-TGCT patients. Additionally, in stage II we recorded an OCM rate of 1% in NS-TGCT patients and 2% in S-TGCT patients. Conversely, higher OCM rates were recorded both in NS-TGCT and S-TGCT stage III patients. Specifically, the OCM rates were 3 and 4% in NS-TGCT and S-TGCT, respectively. These observations regarding OCM are consistent with expected non-existent or at best marginal OCM in stage I and stage II patients. Conversely, higher OCM rates in stage III patients (3% in NS-TGCT and 4% in S-TGCT) are also consistent with



**Fig. 4** Smoothed cumulative incidence plots addressing cancer-specific mortality (CSM) and other-cause mortality (OCM) of 4159 newly diagnosed (2004–2014) with metastatic germ-cell tumor of the testis (mTGCT) patients, 2469 harbored non-seminoma (mNS-TGCT) (a–c) and 1690 harbored seminoma (mS-TGCT) (d, e), within

the Surveillance, Epidemiology, and End Results database 2004–2019 according to International Germ Cell Cancer Collaborative Group (IGCCCG) prognostic-risk groups (good vs. intermediate vs. poor for mNS-TGCT; good vs. intermediate for mS-TGCT)

**Table 3** Summary of survival analyses of 4159 newly diagnosed (2004–2014) with metastatic germ-cell tumor of the testis (mTGCT) patients, 2469 harbored non-seminoma (mNS-TGCT) (a) and 1690 harbored seminoma (mS-TGCT) (b), within the Surveillance, Epide-

miology, and End Results database 2004–2019 according to International Germ Cell Cancer Collaborative Group (IGCCCG) prognostic-risk groups (good vs. intermediate vs. poor for mNS-TGCT; good vs. intermediate for mS-TGCT)

(a) Metastatic non-seminoma germ cell tumor of the testis (mNS-TGCT)				
IGCCCG prognostic-risk group (n, %)	Overall (n = 2469, 100%)	Good (n = 1260, 51%)	Intermediate (n = 425, 17%)	Poor (n = 784, 32%)
5-year Overall Survival	83%	93%	84%	65%
5-year Overall Survival in controls	99%	99%	99%	99%
Absolute 5-year Overall Survival difference	16%	6%	15%	34%
Cancer-specific mortality	14%	4%	13%	31%
Other-cause mortality	3%	2%	2%	4%
(b) Metastatic seminoma germ cell tumor of the testis (mS-TGCT)				
IGCCCG prognostic-risk group (n, %)	Overall (n = 1690, 100%)	Good (n = 1531, 91%)	Intermediate (n = 159, 9%)	
5-year Overall Survival	92%	93%	78%	
5-year Overall Survival in controls	97%	97%	98%	
Absolute 5-year Overall Survival difference	5%	4%	20%	
Cancer-specific mortality	5%	4%	18%	
Other-cause mortality	3%	3%	4%	

expected higher OCM in those individuals that may originate from systemic therapy.

Taken together, despite the younger age at diagnosis future life expectancy of TGCT patients was lower compared to age-matched male population-based controls. Specifically, we recorded a dose-response effect across the different stages, more pronounced in NS-TGCT than in S-TGCT. Indeed, stage I NS-TGCT patients exhibited worse survival relative to age-matched male population-based controls (97 vs 99%;  $\Delta = 2\%$ ) than S-TGCT patients (98 vs 99%;  $\Delta = 1\%$ ). Similar direction, but higher magnitude, even if marginal was recorded in stage II patients. Specifically, NS-TGCT patients exhibited worse survival relative to age-matched population-based controls (96 vs 99%;  $\Delta = 3\%$ ), than S-TGCT patients (97 vs 99%;  $\Delta = 2\%$ ). Moreover, in stage III we recorded the largest difference in future life expectancy. Specifically, stage III NS-TGCT patients exhibited worse survival (76 vs 98%;  $\Delta = 22\%$ ) relative to age-matched male population-based controls than S-TGCT patients (87 vs 98%;  $\Delta = 11\%$ ). Stratification of metastatic patients according to the IGCCCG prognostic-risk group also allowed to identify a dose-response effect. Specifically and expectedly, future life expectancy is most affected in poor, followed by intermediate, and good prognosis, in that order in NS-TGCT patients and to a lesser extent in intermediate and good prognosis in S-TGCT patients. Last but not least, OCM rate is non-existent to marginal in stages I and II NS-TGCT and S-TGCT patients. However, more pronounced OCM rates were recorded in stage III patients. The above results are noteworthy for patient counseling. Indeed, in stage I and stage II, clinicians can reassure patients regarding the low effect of TGCT on future life expectancy after orchiectomy performed. Conversely, in more advanced stage clinicians can encourage patients to undergo post-orchiectomy treatments, such as systemic therapy and/or radiotherapy and/or retroperitoneal lymph node dissection. Additionally, a higher awareness of the disease and its mortality, may be an useful tool to make patients more compliant in attending follow-up visits.

Despite its novelty, our study is not devoid of limitations. First and foremost, our study shares the limitations of all similar studies that were based on the SEER database and relied on a retrospective data design, with potential for selection biases that may apply to prognosis groups in a similar fashion to historical and contemporary multi-institutional retrospective analyses [23, 24]. Second, our findings are applicable to individuals who are identified within the SEER database. Consequently, the observations made within the current study are not generalizable to individuals from outside the United States or even patients who are not comparable to those included in the SEER database. Third, despite a large patient population, the amount of detail is limited. Indeed, only survival rates were available. For example,

no data regarding lymphovascular or stromal invasion that may affect TGCT patients' survival were available. Moreover, the nature of the SEER database did not allow us to address early cancer control outcomes such as relapse rates or metastatic progression rates. Therefore, lack of inclusion of more detailed information and endpoints precludes generalizability of our results. Fourth, baseline comorbidity status of TGCT patients was also not available. However, we partially addressed this limitation by the inclusion of OCM rates in the current analyses. The latter represents a valid surrogate for most significant comorbidities that predispose to mortality. Fifth, the comparison group that consisted of age-matched male controls represented a simulated population in whom OS was defined according to SSA Life-Tables. Although this methodology has been used in various previous publications and is well accepted, it only represents a surrogate for true population controls without the trait of interest, naming TGCT. Moreover, data derived from SSA Life-Tables does not provide a specific cause of death. In consequence, the comparison to the SSA Life Tables only allows for investigating OS. Similarly, further adjustments for patient characteristics other than age could also not be made, since the SSA Life Tables do not provide this type of stratification.

## Conclusion

The OS difference between NS-TGCT patients vs. age-matched male population-based controls was invariably higher across all stages (2–22%) than for S-TGCT patients (1–11%). Reassuringly, OCM rates were marginal in stage I and II patients. Conversely, higher OCM rates were recorded in stage III patients.

**Author contributions** Conceptualization and Methodology: SM, MLP; Acquisition of the data: SM, CCG, AB; Formal analysis: SM, ZT; Investigation and Data Curation: SM, ST, FB; Writing- Original Draft: SM, MLP, RBI, LS; Visualization: FS, VM, GC, CCR, SS, OdC, GM, FKHC, CT, AB, DT, SA, LC; Funding acquisition: N/A; Supervision: NL, PIK; Project administration: PIK.

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**Data availability** All data generated for this analysis were from the SEER database (<https://seer.cancer.gov/data/>). The code for the analyses will be made available upon request.

## Declarations

**Conflict of interest** Shahrokh F. Shariat: Honoraria: Astellas, Astra Zeneca, Bayer, BMS, Cepheid, Ferring, Ipsen, Janssen, Lilly, MSD, Olympus, Pfizer, Pierre Fabre, Richard Wolf, Roche, Sanochemia, Sanofi, Takeda, Urogen. Consulting or Advisory Role: Astellas, Astra Zeneca, Bayer, BMS, Cepheid, Ferring, Ipsen, Janssen, Lilly, MSD,



Olympus, Pfizer, Pierre Fabre, Richard Wolf, Roche, Sanochemia, Sanofi, Takeda, Urogen. Speakers' Bureau: Astellas, Astra Zeneca, Bayer, BMS, Cepheid, Ferring, Ipsen, Janssen, Lilly, MSD, Olympus, Pfizer, Pierre Fabre, Richard Wolf, Roche, Sanochemia, Sanofi, Takeda, Urogen, Movember Foundation. Patents: Method to determine prognosis after therapy for prostate cancer - granted 2002-09-06, Methods to determine prognosis after therapy for bladder cancer - granted 2003-06-19, Prognostic methods for patients with prostatic disease - granted 2004-08-05; Soluble Fas urinary marker for the detection of bladder transitional cell carcinoma - granted 2010-07-20. Our research was conducted without any other potential conflicts of interest.

**Ethics statement** All analyses and their reporting followed the SEER reporting guidelines. Due to the anonymously coded design of the SEER database, study-specific Institutional Review Board ethics approval as not required.


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