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Risk of second primary malignancies of adolescent and young adult patients with germ cell cancer: A US population-based analysis

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A B S T R A C T

Purpose: Germ cell cancer (GCC) is a group of neoplasms with heterogeneity. Predominant in young adults, GCC potentially mitigates a high number of productive years of life lost. Indeed, long-term side effects have arisen as a problem in GCC survivors, especially in adolescent and young adult (AYA) subgroup. The objective of this study is to delineate survival and second primary malignancies (SPMs) in AYA patients with GCC.

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ᵠ Informed consent: Access to the SEER database was authorized through the SEER web site, without specific ethical or review board approvals.

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Methods: We used US population-based Surveillance, Epidemiology and End Results (SEER) 18 Regs Custom Data (1976-2016 varying) and SEER 9 Regs Research Data, November 2019 Sub (1975-2017) for survival analysis and SPM analysis, respectively.
Results: Overall, 5-, 10- and 20-year overall survival rates for AYA patients with GCC were 93%, 91.3%, and 86.9%, respectively. Compared with the general population, a significantly higher risk of SPMs was observed in multiple sites, especially stomach, (standardized incidence ratio [SIR] = 2.94), pancreas (SIR = 3.72), intrahepatic bile duct (SIR = 3.12), soft tissue including heart (SIR = 4.65), leukemia (SIR = 3.70), and testis (SIR = 562.18). The excess risks to develop leukemia were even higher in those with primary mediastinal GCC (SIR = 69.50, $P < 0.05$, 95% confidence interval = 30.00-136.94). Multivariate analysis indicated age of diagnosis, primary site, race, receipt of radiotherapy, and histological subtype independently correlated with risk of SPMs.
Conclusion: The present study provides risk factors of SPM in AYA patients with GCC, which could facilitate the individualization of long-term surveillance in this population.

ARTICLE INFO

Keywords: Germ cell cancer; Second primary malignancy; Adolescent and young adult; Seminoma; Risk factor

Introduction

Germ cell cancer (GCC) is a group of neoplasms usually arising in the gonads (testes or more rarely in the ovaries) and other sites along the midline.[1] Despite of the rarity, incidence of GCC has doubled worldwide over the past 4 decades.[2] According to the National Cancer Institute's Adolescent and Young Adult Oncology Progress Review Group, the range of age 15 to 39 seems more reasonable to define the adolescents and young adult (AYA) population.[3] AYA population represent a population wherein GCC account for a significant proportion of the overall malignancies that occur. Indeed, testicular GCC is one of the most frequent solid tumors among adolescent and young adults.[4] Hence, GCC potentially mitigate a high number of productive years of life lost.

The proceeding 40 years have witnessed the rapid evolvement of multidisciplinary management as well as the prognosis of GCC patients. Surgery and radiotherapy along with chemotherapy have collaboratively made GCC a curative disease in the vast majority of patients. For patients with metastatic disease, standard therapy composed of 3 or 4 cycles of cisplatin, etoposide, and bleomycin (BEP) in good-risk population, or 4 cycles of BEP in intermediate- or poor-risk population per the criteria from the International Germ Cell Cancer Consensus Group have been firmly established.[5,6] For patients fail to achieve a complete remission or experience relapse, salvage regimens such as paclitaxel-ifosfamide-cisplatin (TIP) resulted in a 63% durable complete remission rate and a 2-year progression-free survival rate of 65%.[7,8]

Despite of the effort for optimal approaches and effective regimens, a plethora of short- and long-term side effects including cardiovascular disease and second primary malignancies (SPMs) remains an unresolved problem[9-13] for GCC survivors. Given the curability of GCC and the early onset of this disease, SPMs could be a more prominent problem for AYA patients as they have longer interaction of external factors compared with their older counterparts, and individual predisposition such as the immunodysfunction. Thus, identifying the risk factors of SPMs, evaluating the individual risk, and optimizing the follow-up schedule may assist in improving the surveillance program.

Because of the relative rarity of GCC and the favorable patient outcome, clinical data from large database could bring the insight into the SPM. Thus, we utilize the National Cancer

Institute Surveillance, Epidemiology and End Results (SEER) Program database to assess the clinical data of AYA patients with GCC in recent decades, identify the predictors of patient outcome, and evaluate risk of second malignancies in this population.

Materials and methods

Based on the US population-based SEER 18 Regs Custom Data (with additional treatment fields), November 2018 Sub (1976-2016 varying), we selected GCC patients aged 15-39 years, diagnosed with ICD-O-3 Hist/behav, malignant 9061/3—9102/3 from January 1975 to December 2016 for survival analysis (Fig S1). To evaluate SPM, we selected GCC patients from the US population-based SEER 9 Regs Research Data, Nov 2019 Sub (1975-2017) for SMR Patients diagnosed with ICD-O-3 Hist/behav, malignant 9061/3—9102/3 from January 1975 to December 2017 were included and cases diagnosed during an autopsy and lost to follow-up were excluded. SPM was defined as a metachronous malignancy developing at least 2 months after GCC diagnosis. With the multiple primary standardized incidence ratio (MP-SIR) session of the SEER stat software version 8.3.6 for statistical analysis; calculated with the standard rates provided by SEER*Stat, SIR and 95% confidence interval (CI) for SPM were used to evaluate the risk for SPMs. Absolute excess risk (AER) is reported as the number of excess events per 10,000 person-years, which is an absolute measure of the subsequent cancer in the study group. Age at diagnosis, sex, race, histological type, year of diagnosis, primary site, receipt of radiation therapy (None/Unknown or Beam radiation or other), receipt of chemotherapy, survival months, and vital status were collected. Access to the SEER database was authorized through the SEER web site, without specific ethical or review board approvals.

Statistical analysis

Pearson's Chi-square test was used to compare the differences in patient characteristics. The Kaplan-Meier method was utilized to calculate survival curves and compared using log-rank tests in univariate analysis. Multivariate survival analysis was performed by Cox proportional hazards regression. Logistic regression was employed to analyze the risk factors for SPM. Statistical analysis was conducted in SPSS 22.0 (SPSS Inc, Chicago, IL). A 2 tailed P value <0.05 was considered statistically significant.

Results

Study group and patient characteristics

A total of 63,558 patients were initially identified and among them, 61,277 patients had GCC as their first malignancy. After excluding female patients and patients with age less than 15 or older than 39, we included 39,565 AYA GCC patients with survival data available for further analysis (Supplement Figure 1). With respect to the primary site, gonad was the most commonly seen (n = 37630), followed by mediastinum (n = 890), brain (n = 213), and retroperitoneum (n = 186). There were 18,048 and 21,517 patients with seminoma and nonseminoma, respectively. Different patient characteristics were observed between seminoma group and nonseminoma group (Table 1). Non-seminoma was more commonly observed in younger patients aged 15-29 years while seminoma are more likely to occur in patients aged 30-39 years (<0.001). SPMs were seen in 6.5% of patients with seminoma and 4.7% of nonseminoma. Additionally, among patients with nonseminoma, those with terotoma were most likely to develop SPMs (7.3%), followed by embryonal carcinoma (6.3%).

Table 1
Patient demographics and clinical characteristics

Characteristics	Seminoma, n (%)	Nonseminoma, n (%)	*P* value
Primary tumor site			<0.001
Gonad	17767 (98.4)	19863 (92.3)	
Mediastinum	214 (1.2)	676 (3.1)	
Retroperitoneum	36 (0.2)	150 (0.7)	
Brain	1 (<0.1)	212 (1.0)	
other	30 (0.2)	616 (2.9)	
Race			0.002
White	16293 (90.3)	19566 (90.9)	
Black	527 (2.9)	518 (2.4)	
American Indian/AK Native, Asian/Pacific Islander	939 (5.2)	1146 (5.3)	
NA	289 (1.6)	287 (1.3)	
Age at diagnosis			<0.001
15-29	6680 (37.0)	14498 (67.4)	
30-39	11368 (63.0)	7019 (32.6)	
Year of diagnosis			<0.001
1976-1985	1493 (8.3)	2219 (10.3)	
1986-1995	2814 (15.6)	3004 (14.0)	
1996-2005	5666 (31.4)	6106 (28.4)	
2006-2016	8075 (44.7)	10188 (47.3)	
Stage			<0.001
Localized	10389 (57.6)	8443 (39.2)	
Regional	1821 (10.1)	3140 (14.6)	
Distant	515 (2.9)	2824 (13.1)	
NA	5323 (29.5)	7110 (33.0)	
Number of second malignancy			<0.001
1	16879 (93.5)	20507 (95.3)	
2	1056 (5.9)	929 (4.3)	
3 or more	113 (0.6)	81 (0.4)	
Chemotherapy			<0.001
Yes	3076 (17.0)	10977 (51.0)	
No/Unknown	14972 (83.0)	10540 (49.0)	
Radiotherapy			<0.001
Yes	9011 (49.9)	1218 (5.7)	
No/Unknown	9037 (50.1)	20299 (94.3)	

Survival of AYA patients with GCC

Overall, 5-, 10- and 20-year overall survival rates for the entire AYA cohort were 93%, 91.3%, and 86.9%, respectively. The survival data for different races, histological types, and multiple malignancies were presented in Fig. 1. Univariate analysis identified predictors for death of any cause and included them into multivariate analysis. Independent parameters with statistical significance were histological types ($P < 0.001$), primary site ($P < 0.001$), SPM ($P < 0.001$), age of diagnosis ($P < 0.001$), race ($P < 0.001$), receipt of radiation ($P < 0.001$), and chemotherapy ($P < 0.001$). After adjusting for other independent indicators, SPM (hazard ratio [HR] = 1.78, 95%CI = 1.59-2.00, $P < <0.001$) was associated with adverse prognosis.

Observed risk of SPM as compared with the general population

Overall, 1605 patients with second cancers were identified, with an SIR of 5.67 (95% CI: 5.39-5.95, $P < 0.05$), and an AER of 39.34/10,000 person-years. Compared with the general population, a significantly higher risk of malignancy was observed in the multiple sites, especially stomach (SIR = 2.94, $P < 0.05$, 95%CI = 1.82-4.50), pancreas (SIR = 3.72, $P < 0.05$, 95%CI = 2.90-4.71), intrahepatic bile duct (SIR = 3.12, $P < 0.05$, 95%CI = 1.35-6.15), soft tissue including heart

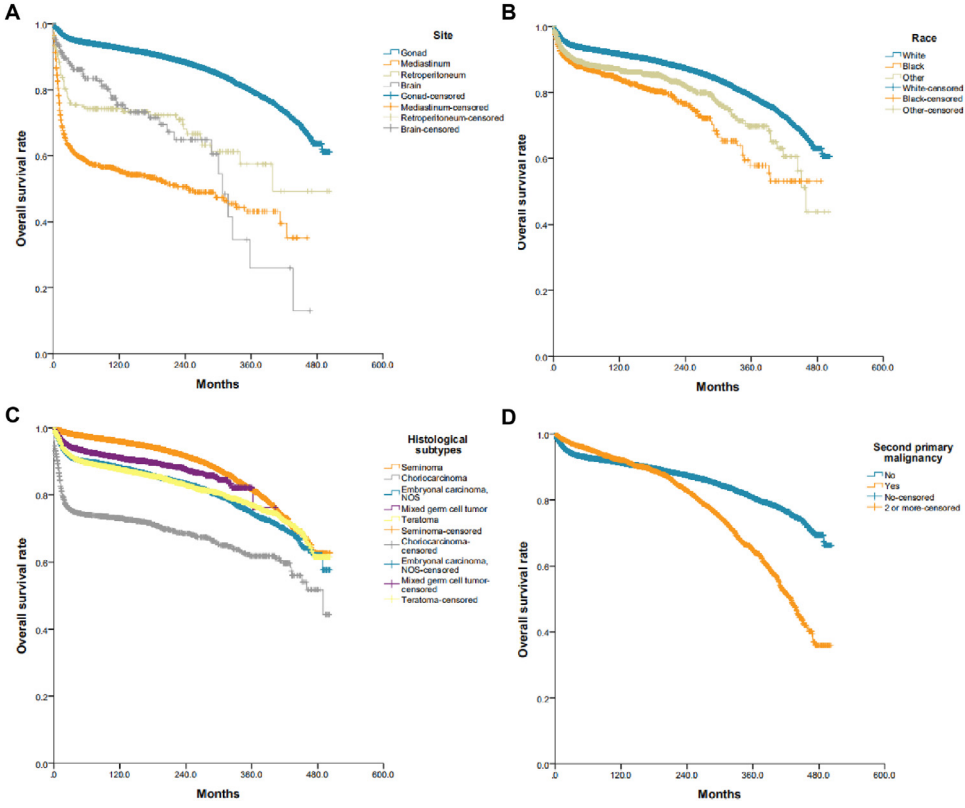

Fig. 1. Kaplan-Meier curve of overall survival stratified by different primary site (A); stratified by race (B); stratified by pathological subtypes (C); stratified by number of total malignancies (D).

(SIR = 4.65, $P < 0.05$, 95%CI = 2.66-7.55), leukemia (SIR = 3.70, $P < 0.05$, 95%CI = 2.68-4.99), and testis (SIR = 562.18, $P < 0.05$, 95%CI = 524.01-602.39). More specifically, among leukemia, incidence of myeloid leukemia (SIR = 5.88, $P < 0.05$, 95%CI = 3.97-8.40) was most significantly increased among GCC AYA. The excess risk was significantly elevated in those with primary mediastinal GCC, with an SIR of 66.03, ($P < 0.05$, 95%CI = 56.42-76.80, AER = 369.18/10,000 person-years). Similarly, the risks for a subsequent lymphoma (SIR = 30.80, $P < 0.05$, 95%CI = 8.39-78.86), and leukemia (SIR = 69.50, $P < 0.05$, 95%CI = 30.00-136.94) were even higher in those with primary mediastinal GCC.

Risk factors for developing SPM

Univariate analysis was performed and identified age, site, race, chemotherapy, radiotherapy and histological subtype were correlated with incidence of SPM. Multivariate analysis revealed age, site, race, radiotherapy, and histological subtype were the 5 independent indicators for SPM risk (Table 2). Compared with seminoma, patients with nonseminoma were more likely to experience a second primary malignancy (odds ratio [OR] = 1.152, 95%CI = 1.024-1.296, $P = 0.019$). Individuals with primary mediastinal GCC have a higher probability of developing multiple malignancies than those with gonad-originated GCC (OR = 2.825, 95%CI = 1.184-6.743, $P = 0.019$). While no elevated risk of multiple primary tumors was observed in patients with previous exposure to

Table 2
Multivariate analysis of risk factors for multiple primary malignancies

Characteristics	OR	95%CI	*P* value
Pathological subtypes			
Seminoma	1.000	-	-
Nonseminoma	1.152	1.024-1.296	0.019
Primary site			
Brain	1.000	-	-
Gonad	2.636	1.157-6.008	0.021
Mediastinum	2.825	1.184-6.743	0.019
Retroperitoneum	3.502	1.292-9.497	0.014
Race			
Other (American Indian/AK Native, Asian/Pacific Islander)	1.000	-	-
White	1.262	1.017-1.565	0.034
Black	1.061	0.745-1.511	0.744
Age of diagnosis	0.947	0.809-1.108	0.494
35-39	1.000	-	-
15-19	0.581	0.468-0.723	<0.001
20-24	0.716	0.621-0.826	<0.001
25-29	0.778	0.688-0.881	<0.001
30-34	0.846	0.751-0.953	0.006
Receipt of radiotherapy			
No	1.000	-	-
Yes	2.068	1.843-2.32	p<0.001
Receipt of chemotherapy			
No	1.000	-	-
Yes	1.007	0.904-1.121	0.906

Abbreviations: CI, confidence interval; OR, odds ratio.

chemotherapy, receipt of radiotherapy was associated with a higher frequency of second malignancy (OR = 2.068, 95%CI = 1.843-2.32, $P < 0.001$).

Discussion

In this population-based study, we focused on AYA patients with GCC, and revealed risk factors of SPM. In addition to indicators such as age of diagnosis, histological types, and anatomic location,[14-17] we also find ethnicity and SPMs associated with prognosis, indicating an ethical diversity in prognosis.

Since 1970s, improvement of diagnostic and treatment advances has resulted in improved patient outcome in the area of GCC. With the significantly improved long-term survival, long-term side effects have been raised as a problem, especially for patients diagnosed at a young age. Previously, risk of SPM has been investigated in patients with GCC suggesting younger age of diagnosis, site of disease, receipt of radiotherapy as risk factors. During the past decades, although radiotherapy conferred substantial benefit in the adjuvant setting of clinical stage I seminoma patients, the increased risk of second primary cancer has been aware of.[12] Given the possibility of increased late-onset toxicity associated with radiotherapy, adjuvant radiotherapy is not recommended as a routine practice for stage I testicular seminoma.[10,18] A report published in 2005 investigated second cancers among testicular cancer patients based on data collected from 14 population-based cancer registries, including the SEER Program, demonstrating an excess risk of a second solid tumor (relative risk [RR] = 1.9) among 10-year survivors with testicular cancer at age 35 years. Further, radiotherapy alone (RR = 2.0) and chemotherapy alone (RR = 1.8) and both (RR = 2.9) were significantly associated with increased risk of subsequent solid cancers.[19] Similarly, the present study indicated age of diagnosis, primary site, and receipt of radiotherapy independently correlated with SPMs in AYA subgroup. Besides, we also delineated the significant difference in SPM risk among different pathological subtypes and races. Recently, according

to the recent establishment of The European Society for Medical Oncology (ESMO) consensus conference, patients with low-risk nonseminoma are recommended for surveillance in order to manage the balance between survival benefit and late side effects.[20] It is expected that the advances in the radiotherapy, less intensified cytotoxic agents, optimization of, surgery, and individualized surveillance would decrease the risk of late side effects including SPM in this patient population.

Jörg T et al analyzed the data of extragonadal GCC patients from 11 European and American cancer centers in early 21th century and suggested primary mediastinal site as a risk factor for a subsequent primary hematologic disorder.[11] A previous report also revealed significantly elevated risks for secondary acute myeloid leukemia (excess absolute risk = 7.2) and acute lymphoblastic leukemia (excess absolute risk = 1.3).[21] Likely, our study demonstrated a significantly excess risk of hematological disorder in AYA patients with GCC, with the excess risks to develop myeloid leukemia substantially higher. These observations of early onset of subsequent primary hematologic malignancies indicated a clonal relationship to primary mediastinal GCC. Actually, biological correlation of chromosome abnormality i(12p) has been identified within leukemic blasts in some cases. An aggressive developing nature of the secondary hematologic neoplasia in patients with extragonadal GCC was also reported in previous studies, with a median overall survival of 5 months following diagnosis of hematologic neoplasia in primary mediastinal nonseminomatous GCC patients.[11] Series biomarker in combination with risk factor assessment may facilitate early identification of second hematological disorder as well as more favorable outcome. Nevertheless, the rarity of this population pose a challenge on biomarker investigation, which should be pursued with collaborate effort.[22]

Second testicular cancer is another commonly observed neoplasm in patients with testicular GCC,[23,24] with a reported prevalence of 4.4%-8.1% of germ cell neoplasia in situ in the contralateral testis.[25-29] Risk factors for contralateral germ cell neoplasia in situ have been identified including younger than 40 years, testicular atrophy and testicular microlithiasis and infertility, and thus biopsies of the contralateral testis at the time of orchiectomy are recommended by The European Society for Medical Oncology consensus conference in high-risk population.[30] Our data confirm the excess probability of secondary testicular cancer and further address the attention on high-risk AYA population for SPM after treatment of GCC.

The limitations in this study should be taken into consideration. First, absent data of disease stage, migration of patients, underestimation of radiotherapy, and chemotherapy may cause bias in the analysis of the risk factors of SPM. Second, some recurrences may have been categorized as SPMs. Additionally, with the evolvement of the treatment paradigm, the lack of radiation dose and fields, regimens of chemotherapy and surgical detail limit the generalizability and validity of our findings.[31]

Conclusion

The current study provides data for predictors of SPM in AYA patients with GCC. In our analysis, SPMs significantly impact patient outcome. Moreover, factors such as histological types, race, primary site, age of diagnosis and receipt of radiotherapy were correlated with risk of SPMs. Notably, the excess risks to develop leukemia were substantially higher in those with primary mediastinal GCC, which indicated a possible environmental or genetic correlation. Hopefully, investigations of the biological underpinnings of these SPMs and the optimization of follow-up schedule will facilitate an understanding of how to prevent or diagnose SPM earlier.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.currproblcancer.2020.100641.

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