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No Survival Differences among Germ-Cell Cancer Patients from Urban and Rural Areas

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Chemotherapy · Disease management · Surveillance · Testicular cancer

Abstract

Introduction: Germ-cell cancer (GCC) is curable in the majority of men. However, previous reports have described inferior outcomes in men living in rural as compared to urban residential areas. ***Methods:*** We identified all GCC patients treated at two large university hospitals in Zürich and Bern, both in Switzerland, between 2010 and 2020 by retrospective chart review. In 400 patients from Zürich and 274 patients from Bern, details on presentation, diagnosis, treatment, and outcomes were abstracted from medical records. For follow-up, we contacted referring centers or private physicians. Residential region was allocated according to the Federal Statistical Office of Switzerland. ***Results:*** We found no differences in initial presentation (clinical stage I [CSI] versus de novo metastatic), relapse rate in CSI patients, response in metastatic patients (favorable vs. unfavorable), progression-free survival (PFS) or overall survival (OS) between patients from urban as compared to suburban or rural residential areas. PFS at 3 years for CSI patients was 78% (95% confidence interval 72–82%) and OS at 5 years was 98% (95% confidence interval 96–99%). PFS at 3 years for de novo metastatic patients was 74% (95% confidence interval 68–79%) and OS at 5 years was 86% (95% confidence interval 80–90%). ***Conclusion:*** Treatment outcomes in GCC patients were excellent and comparable to international standards at both centers irrespective of the residential area of patients documenting equal access to high-level oncological care at both centers.

Introduction

Germ-cell cancer (GCC) is curable in the majority of men. However, historical as well as recent data point to differences between patients coming from urban as compared to rural areas with more advanced presentations and inferior outcomes in the latter [1, 2]. Since the initial report, access to care has improved through better access to medical information as well as improved awareness of GCC in young men. We aimed to identify access to high-level oncological care at two large university centers in Switzerland in the years 2010–2020 by retrospective chart review.

Materials and Methods

All patients treated for GCC at the university hospitals Zürich (USZ) and Inselspital Bern (Inselspital), both in Switzerland, were identified by from pathology reports, lists of surgical interventions, tumor board documents, and chemotherapy orders during 2010 and 2020. Information on primary tumors, histology, initial presentation and management, treatment responses as well as disease status at

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follow-up was abstracted from medical records. In patients in whom follow-up was performed outside the two universities, referring centers or private physicians were contacted for follow-up information. Residential addresses were allocated to either urban, suburban, or rural areas depending on the classification of the Federal Statistical Office of Switzerland [3]. No written informed consent could be obtained in this retrospective analysis, but according to Swiss Federal Law all captured data were pseudonymized and subsequently entered by several of the authors (D.H., S.H., D.A.) into a central SPSS database (IBM SPSS Statistics, IBM Corp., Chicago, IL, USA, Version 28.0.1.1) at the Inselspital Bern, which could only be accessed by the authors. Plausibility checks and extensive data cleaning was performed by three of the authors (A.L., C.F., and J.B.) prior to analysis to correct entry errors. The database was locked to entries on April 13th, 2023. Data were stored at a secured password-protected database at the Inselspital Bern. The study was conducted according the regulations of the Helsinki Declaration. Ethical approval for the analysis was obtained by the Ethics Committee of the Canton of Berne (BASEC ID 2023-00364).

Primary outcome measure was the presentation at initial diagnosis (clinical stage I [CSI] versus metastatic disease). Secondary outcome measures were the initial prognostic group of metastatic patients according to the classification of the International Germ Cell Cancer Collaborative Group (IGCCCG), the response rate in metastatic patients (favorable vs. unfavorable), the rate of relapses from CSI as well as progression-free survival (PFS) and overall survival (OS) [4].

CSI patients with increasing serum tumor markers alpha-fetoprotein (AFP) or human chorionic gonadotrophin (HCG), but without radiological manifestations were classified as having metastatic disease. Favorable responses were defined either as complete remissions by chemotherapy alone or after surgical resections of all residual tumors with necrosis or teratoma as well as partial remissions with negative tumor markers AFP or HCG in patients with unresectable residual tumors. Unfavorable responses were defined as post-chemotherapy residual tumor resections with vital undifferentiated carcinoma, partial remissions with positive AFP or HCG levels, stable or progressive disease as well as death. Progression was defined as a serological or radiological progression whichever occurred first.

PFS started at the date of diagnosis and ended at the date of documented progression, death, or last follow-up. OS started at the date of diagnosis and ended at the death date or last follow-up. A patient was declared lost to follow-up if we were unable to get information about his follow-up status despite contacting follow-up institutions, or if he did not return to the follow-up institution for further visits. Patients lost to follow-up were censored at the time of their last contact.

Descriptive statistical analyses were performed on relevant parameters. Significance was tested using Pearson χ^2 test of independence and Fisher's exact test for categorical variables as well Mann-Whitney U test for metric variables. PFS and OS probabilities were analyzed using the Kaplan-Meier method. Significance for survival analyses was tested using the log-rank test. Survival probabilities were assessed at three and 5 years to compensate for unequal follow-up. A two-sided p value of <0.05 was considered significant. All tests were performed using the SPSS (IBM SPSS Statistics, IBM Corp., Chicago, IL, USA, Version 28.0.1.1) and STATA (StataCorp LLC, College Station, TX, USA, Version 10.1, 2008) software packages.

Results

During the period 2010 to 2020, 674 GCC patients were identified, 400 patients from the USZ and 274 patients from the Inselspital. Patient characteristics and outcomes are described in Table 1. In the entire cohort of both universities, 360 (53.8%) patients presented with CSI and 309 (46.2%) with metastatic or primary extragonadal disease. In 5 metastatic patients, the IGCCCG stage not determined due to missing information. We did not find any differences at initial presentation, in first-line treatments, response rates, or survival probabilities between the two university hospitals (Table 1; online suppl. Table 1; for all online suppl. material, see https://doi.org/10.1159/000533505; online suppl. Fig. 1). Of the 360 patients who presented with CSI, 78/360 (21.7%) relapsed at a median of 9 months (interquartile range 6–19 months), 47/226 (20.8%) in Zürich and 31/134 (23.1%) in Bern. The majority of patients who relapsed from CSI did so within the good prognosis category according to the ICGCCCG classification. No patient with pure seminoma, and only 11/78 (9%) non-seminoma patients relapsed with intermediate prognosis, none in the poor prognostic group.

The distribution and outcomes of patients according to their residential area are described in Table 2. Again, we did not find clinically relevant differences between the three groups neither in respect to stage at initial diagnosis, treatments (online suppl. Table 2) nor in respect to treatment responses or survival probabilities (Table 2; Fig. 1). The PFS at 3 years was 77% (95% confidence intervals 73–81%) for patients with urban residential addresses as compared to 73% (95% confidence intervals 65–79%) for patients with suburban or rural residential addresses ($p = 0.10$). Although the OS at 5 years was 94% (95% confidence intervals 91–96%) for patients with urban residential addresses and statistically superior compared to 90% (95% confidence intervals 84–94%) for patients with suburban or rural residential addresses ($p = 0.04$), we do not consider this difference clinically meaningful as confidence intervals were marginally overlapping.

Discussion

In our contemporary cohort, we found no clinically relevant differences among patients with urban as opposed to suburban or rural residential addresses. We observed no clinically relevant differences neither in the rate of CSI or the initial IGCCCG stage in metastatic patients, nor in relevant outcomes such as the rate of favorable responses or the probabilities for PFS or OS. Yet, the statistically superior OS probability in favor of patients from urban areas should be monitored prospectively despite being small. This contrasts early reports, which observed an excess mortality among patients living in rural areas even 10 years after the introduction of cisplatin [1]. Many factors may have contributed to this improvement such as better awareness about the high curative potential of GCC among patients and referring physicians, availability and easy access to medical information, open source guidelines, innovations, and centers of excellence through the internet as well as centralization of oncological care for this young group of patients.

Table 1. Patient characteristics and outcomes according to center

	Bern (*N* = 274)	Zurich (*N* = 400)	Overall (*N* = 674)
Age at diagnosis, years, median (range)	35 (17–67)	35 (16–82)	35 (16–82)
Region*, *n* (%)			
Urban	165 (60.2)	305 (76.2)	470 (69.7)
Intermediate	55 (20.1)	73 (18.3)	128 (19)
Rural	54 (19.7)	22 (5.5)	76 (11.3)
Primary site, *n* (%)			
Gonadal	260 (95)	369 (92.2)	629 (93.3)
Retroperitoneal	10 (3.6)	15 (3.8)	25 (3.7)
Mediastinal	2 (0.7)	14 (3.5)	16 (2.4)
Other	2 (0.7)	2 (0.5)	4 (0.6)
Histology, *n* (%)			
Seminoma	119 (43.4)	194 (48.5)	313 (46.4)
Non-seminoma	141 (51.5)	198 (49.5)	339 (50.3)
Mixed tumors/teratoma	14 (5.1)	8 (2)	22 (3.3)
Initial stage number, *n* (%)			
Clinical stage I	134 (48.9)	226 (57.2)	360 (53.8)
Good prognosis±	91 (33.2)	113 (28.6)±	204 (30.5)±
Intermediate prognosis±	23 (8.4)	27 (6.8)±	50 (7.5)±
Poor prognosis±	26 (9.5)	29 (7.3)±	55 (8.2)±
Outcome clinical stage I			
No relapse	103/134 (76.9)	179/226 (79.2)	282/360 (78.3)
Relapse	31/134 (23.1)	47/226 (20.8)	78/360 (21.7)
Best response metastatic patients†, *n* (%)			
Favorable	107/140 (76.4)	134/174 (77)	241/314 (76.8)
Unfavorable	21/140 (15)	24/174 (13.8)	45/314 (14.3)
Unknown	12/140 (8.6)	16/174 (9.2)	28/314 (8.9)
PFS at 3 years, %	77	75	76
95% confidence interval, %	71–81	70–80	72–79
OS at 5 years, %	92	94	93
95% confidence interval, %	87–95	89–96	90–95

PFS, progression-free survival, time from diagnosis until relapse or death. OS, overall survival, time from diagnosis until last follow-up patient was alive. *Region according to "Statistik der Schweizer Städte" from the "Federal Statistical Office of Switzerland." ±Details on prognostic group for 5 metastatic patients in Zurich cohort missing. †Favorable outcome: complete remission, necrosis, or teratoma after retroperitoneal lymphnode dissection, marker negative partial remission; unfavorable outcome: vital tumor after retroperitoneal lymphnode dissection, marker positive partial remission, stable disease, progressive disease, and death.

Table 2. Patient characteristics and outcomes according to residential areas

	Urban (*N* = 470)	Suburban (*N* = 128)	Rural (*N* = 76)
Age, years, median (range)	34 (16–82)	36 (17–69)	38 (18–67)
Initial stage, *n* (%)±			
Stage I	264 (56.2)	65 (50.8)	31 (40.8)
Good prognosis	137 (29.1)±	42 (32.8)	25 (32.9)
Intermediate prognosis	31 (6.6)±	12 (9.4)	7 (9.2)
Poor prognosis	33 (7)±	9 (7)	13 (17.1)
Outcome clinical stage I¥, *n* (%)			
Relapses	57/261 (21.6)¥	15/65 (23.1)	9/31 (29)
No relapses	204/261 (77.3)¥	50/65 (76.9)	22/31 (71)
Best response metastatic patients†, *n* (%)			
Favorable	156/206 (75.7)	49/63 (77.8)	37/45 (82.2)
Unfavorable	28/206 (13.6)	10/63 (15.9)	8/45 (17.8)
Unknown	22/206 (10.7%)	4/63 (6.3%)	–
PFS at 3 years, %	77	72	73
95% confidence interval, %	73–81	63–80	60–82
OS at 3 years, %	94	89	91
95% confidence interval, %	91–96	80–94	80–96

PFS, progression-free survival, time from diagnosis until relapse or death. OS, overall survival, time from diagnosis until last follow-up patient was alive. *Region according to "Statistik der Schweizer Städte" from the "Bundesamt for Statistik Switzerland." ±No prognosis group for 5 metastatic patients in Urban cohort. ¥No PFS data for 3 patients in Urban cohort. †Favorable outcome: complete remission, necrosis, or teratoma after retroperitoneal lymphnode dissection, marker negative partial remission; unfavorable outcome: vital tumor after retroperitoneal lymphnode dissection, marker positive partial remission, stable disease, progressive disease, and death.

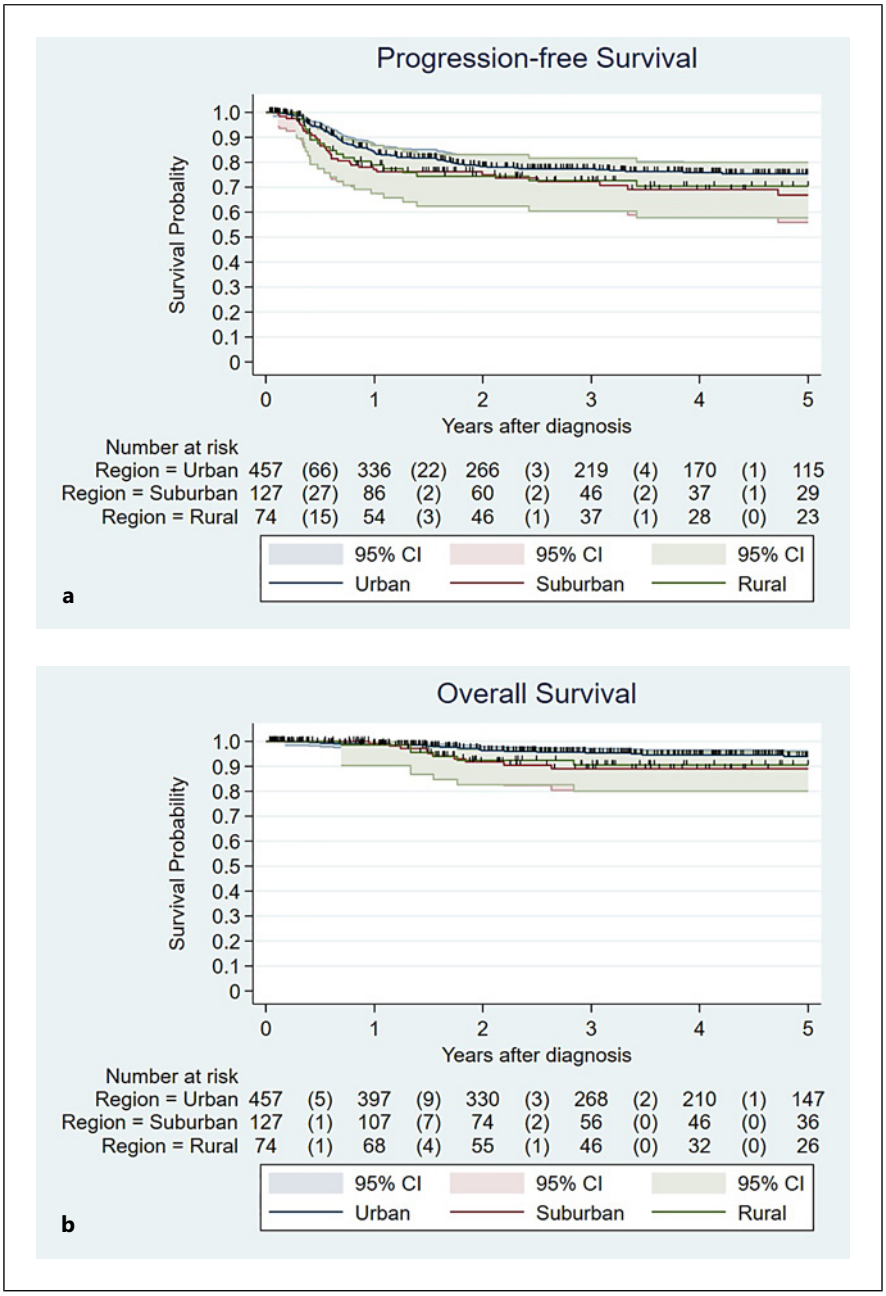

Fig. 1. a, **b** Survival probabilities according to residential area.

Particularly reassuring is that in 360 men initially presenting as CSI, 67/78 (91%) of relapses were identified early and diagnosed within the IGCCCG good prognosis group. This is in line with international reports and confirms the high rate of compliance and the quality of follow-up in the patient cohort studied [5].

Equal access to oncological care is a paramount health care issue. Reports have documented that current guidelines developed at centers of excellence are not always followed in the community [6–8]. In our series at two major referral centers in Switzerland, we found a high rate of compliance with current treatment guidelines, which may have contributed to the excellent survival probabilities observed [9, 10]. Our analysis confirms that if patients are referred to centers of excellence, residential address no longer affects treatment outcome.

There are several biases inherent in the present analysis. We could document and analyze only patients who were referred to and treated at one of the two university hospitals. Due to the lack of adequate epidemiological data, we cannot exclude the possibility that patients who had not been referred had better, the same, or more unfavorable presentations or treatment outcomes irrespective of residential area. In addition, we cannot generalize our results to other centers, other sites in Switzerland or other European countries [2]. To allow a full appreciation of the impact of residential address on presentation and treatment outcome in GCC, comprehensive national registry data such as in Denmark would be

required. Nevertheless, our data contribute to the evidence that once patients are referred to centers of excellence, residential address no longer affects treatment outcomes such as favorable responses or survival probabilities.

Statement of Ethics

The analysis was conducted according to the rules of the World Medical Association Declaration of Helsinki, the Swiss Federal Act on Research Involving Human Beings and obtained permission by the Ethics Committee of the Canton of Berne, Murtenstrasse 31, CH-3010 Bern (BASEC-Nr: 2023-00364). Patient consent was not required in accordance with national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Study idea: Jörg Beyer; design, manuscript draft, and data analysis and statistics: Dennis Hoch and Jörg Beyer; patient treatments/case retrieval: Dennis Hoch, Thomas Hermanns, Anja Lorch, George Thalmann, and Jörg Beyer; data entry: Dennis Hoch, Davide Ardizzone, and Simon Helnwein; data review: Jörg Beyer, Christian Fankhauser, Thomas Hermanns, and Anja Lorch; George Thalmann; manuscript review and approval: all authors.

Data Availability Statement

Due to legal restrictions, source data will not be publicly available. Inquiries can be directed to the corresponding author.

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