

Multicenter Database of Patients with Germ-Cell Tumors: A Latin American Cooperative Oncology Group Registry (LACOG 0515)

Diogo A. Bastos,^{1,2} Aline Bobato Lara Gongora,^{1,2} Carlos Dzik,³
Denis Leonardo Jardim,^{1,2} Marina Piva,⁴ Flavio Mavignier Carcano,⁵
Glaucio Bertollo,⁶ Karine Trindade,^{1,7} Mariane Sousa Fontes,⁸ Andrey Soares,^{1,9,10}
Tomas Reinert,¹¹ Rita De Cassia Costamilan,¹² Rodrigo Ughini Villarroel,¹³
Gabriel Watarai,³ Antonia Angeli Gazola,^{14,16} Daniel D Almeida Preto,⁵
Haila Mutti,⁹ Marcela Bonalumi dos Santos,¹⁰ Rodrigo Coutinho Mariano,¹⁵
Monique Binotto,¹¹ Monique Maciel Carvalho,⁷
Veronica Patrícia da Costa Oliveira,⁴ Rafaela Gomes,¹ Taiane F Rebelatto,¹
Fabio A. Schutz,¹⁵ Oren Smaletz,⁹ Andre P. Fay^{1,14,16}

Abstract

LACOG0515 is a multicenter database of patients with germ cell tumors treated in Brazil, with 1,232 patients. The results showed a high rate of adjuvant chemotherapy in clinical stage I. For patients with advanced GCT, although our data demonstrate inferior PFS compared with the International Germ Cell Cancer Collaborative Group and other contemporary series, the survival rates were similar.

Introduction: Germ-cell tumors (GCTs) are the most common malignancy in young men. There is a paucity of data on GCTs in developing countries. LACOG 0515 study aimed to evaluate clinical characteristics and treatment outcomes in patients with GCTs from Brazilian cancer centers. **Materials and Methods:** This is a retrospective cohort study evaluating male patients diagnosed with GCTs from 2000 to 2018 in 13 Brazilian hospitals. We described baseline characteristics, progression-free survival (PFS), and overall survival (OS). **Results:** A total of 1232 patients were included, with a median age of 30 years. Histology was seminoma in 47.1% and non-seminoma GCT (NSGCT) in 52.9%. The primary tumor site was testis in 96.5%. At diagnosis, clinical stage I was present in 68.1% and 34.7% and clinical stages IS/II/III in 31.9% and 65.2% of patients with seminoma and NSGCT, respectively. Following orchiectomy, 55.2% of patients with clinical stage I were managed with surveillance. The 5-year disease-free survival rates among patients with stage I were 98.0% in seminoma and 92.3% in NSGCT, with 5-year OS of 99.6% and 97.6%, respectively. Among patients with advanced disease (IS, II, and III), the 5-year PFS were 88.7% in seminoma and 68.7% in NSGCT, with

¹Latin American Cooperative Oncology Group (LACOG), Porto Alegre, Brazil

²Hospital Sírio-Libanês, São Paulo, Brazil

³Instituto do Câncer do Estado de São Paulo (ICESP), São Paulo, Brazil

⁴Hospital Amaral Carvalho, Jauá, Brazil

⁵Barretos Cancer Hospital, Barretos, Brazil

⁶AFECC – Hospital Santa Rita, Vitória, Brazil

⁷Oncocentro, Fortaleza, Brazil

⁸Grupo Oncoclínicas Botafogo, Rio de Janeiro, Brazil

⁹Hospital Israelita Albert Einstein, São Paulo, Brazil

¹⁰Centro Paulista de Oncologia/Oncoclínicas- São Paulo, São Paulo, Brazil

¹¹Centro de Pesquisa da Serra Gaúcha (CEPESG), Caxias Do Sul, Brazil

¹²IPCEM/UCS - Fundação Universidade de Caxias do Sul - Hospital Geral, Caxias do Sul, Brazil

¹³Hospital São Vicente de Paulo, Passo Fundo, Brazil

¹⁴Hospital São Lucas PUC-RS, Porto Alegre, Brazil

¹⁵Beneficência Portuguesa de São Paulo, São Paulo, Brazil

1558-7673/5 - see front matter © 2022 The Authors. Published by Elsevier Inc.

This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

<https://doi.org/10.1016/j.clgc.2022.11.004>

¹⁶PUC-RS School of Medicine, Porto Alegre, Brazil

Submitted: Sep 6, 2022; Revised: Nov 4, 2022; Accepted: Nov 7, 2022; Epub: xxx

Address for correspondence: Diogo Assed Bastos, Oncology Center, Hospital Sírio Libanês, Rua Dona Adma Jafet, 91, São Paulo 01308-050 Brazil.

E-mail contact: diogoassed@gmail.com

Multicenter Database of Patients with Germ-Cell Tumors

5y-OS of 97.6% and 82.8%, respectively. **Conclusion:** This is the largest Brazilian cohort of GCTs. Our results show a high rate of adjuvant chemotherapy in patients with clinical stage I. Although our data demonstrate slightly inferior PFS compared with the International Germ Cell Cancer Collaborative Group and other contemporary series, the OS rates were similar.

Clinical Genitourinary Cancer, Vol. 000, No.xxx, 1–10 © 2022 The Authors. Published by Elsevier Inc.

This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

Keywords: Developing countries, Germ-cell tumors, Prognostic groups, Testicular cancer

Introduction

Testicular cancer represented 0.4% of new cancer cases globally in 2020, with an age-standardized incidence of 1.8/100,000 men.^{1,2} In Brazil, testicular cancer represents 5% of male malignancies.³ Nevertheless, the incidence of germ cell tumors (GCT) has been increasing, making GCT the most common cancer in young men around the world.^{4,5}

Since the introduction of cisplatin-based treatments in the 1970s, testicular cancer mortality has been decreasing.^{6–8} However, in the early 2000s, mortality was still variable among different regions of the world, with higher rates in Eastern Europe, Latin America, and Asia.^{5,6} In Brazil, an increasing mortality trend has been recorded, with 0.36 deaths/100,000 for the year 2001 and 0.41 deaths /100,000 for the year 2015. This may be explained by the inequality of access to cancer diagnostic and treatment centers in different Brazilian regions and cities and between the private and public health care systems.^{9,10} In 1991, an international collaborative group comprised of clinicians and statisticians from 10 countries was formed, the International Germ Cell Cancer Collaborative Group (IGCCCG), to pool clinical data from a large population with metastatic germ-cell cancer. In 1997, a prognostic factor-based staging system was proposed by this group,¹¹ and since then, the IGCCCG Classification has been widely used not only as a prognostic tool, but also as a guide to treatment selection for patients with advanced GCT.^{12–15} Nevertheless, these prognostic factors are derived mostly from data from high-income countries, and there is a paucity of data regarding outcomes in low and middle-income countries.^{16,17} For this reason, this study aimed to evaluate clinical characteristics and treatment outcomes in patients with GCTs from different Brazilian cancer centers.

Materials and Methods

Study Design and Participants

LACOG 0515 is a retrospective cohort study, which included male patients with histologically proven GCT diagnosed at any stage from 2000 to 2018 in 13 Brazilian hospitals (Supplementary Appendix). Patients with GCT were screened, and those with diagnosis between 2000 and 2018 and with available clinicopathological data (tumor histology) were included in the analysis. The protocol was approved by each Institution's Review Board.

Procedures

Eligible patients had their medical records reviewed and data were registered in an electronic platform for clinical data management (OpenClinica). Data items included baseline characteristics (age,

ECOG PS, comorbidities, tobacco and drug use, family history of testicular cancer and history of cryptorchidism), primary tumor site, TNM staging (AJCC seventh edition), levels of post orchiectomy serum tumor markers (alpha-fetoprotein, lactic dehydrogenase, and human chorionic gonadotropin), IGCCCG risk classification and treatments performed. Primary endpoints were overall survival (OS), defined as the time from diagnosis to death from any cause, disease-free survival (DFS), and progression-free survival (PFS). DFS, defined as the time from orchiectomy to recurrence of disease or death, was estimated for patients with clinical stage (CS) I. PFS, defined as the time from the first cycle of chemotherapy received to the progression of disease or death, was estimated for patients with advanced disease (CS IS, II, or III).

Statistical Analysis

Statistical analyses were performed with information from 1232 patients. Quantitative variables were described by median and range, while categorical variables were described by absolute and relative frequencies. OS, PFS, and DFS were estimated and displayed in graphs using Kaplan-Meier method. Median follow-up was estimated using reverse Kaplan-Meier method. The significance level for claim statistical difference between groups was set at 0.05. All analyses were performed using the SAS statistical software (version 9.4; SAS Institute, Inc. Cary, NC). Since the access to treatment may be different in private and public centers, a separate analysis was performed according to the type of health care coverage - private versus public.

Results

A total of 1315 patients were identified, of which 39 did not meet the minimum available clinicopathological data, and 44 were diagnosed before the year 2000. Therefore, 83 patients were excluded from the analysis, and a total of 1232 patients were analyzed. Baseline characteristics are shown in [Table 1](#). Median age was 30 years (range 12–82 years). Histology was seminoma in 47.1% and non-seminoma GCT (NSGCT) in 52.9%. Patients with NSGCT were younger than those with seminoma (median age: 26 years old [range 12–60] versus 34 years old [range 13–82]). Most patients were white (55.5%), had no comorbidities (74.6%), had ECOG PS 0–1 (83.0%), and had no family history of GCT (78.8%). Personal history of cryptorchidism was present in 6.1% of the patients. The primary tumor site was testis in 96.5%, mediastinum in 1.8%, and retroperitoneum in 1.3%. Pathological staging was T1 or T2 in most patients (79.7%). Most patients with seminoma had clinical stage I (68.1%), while clinical stages IS/II/III

Table 1 Baseline Characteristics of Included Patients

| Information | Seminoma (n = 580) | NSGCT (n = 652) | Total (n = 1232) |
|-------------------------------------|--------------------|-----------------|------------------|
| Median follow-up (95% CI) in mo | 46 (41-48) | 52 (47-57) | 48 (46-50) |
| Median age (range) in y | 34 (13-82) | 26 (12-60) | 30 (12-82) |
| Institution – n (%) | | | |
| Private | 181 (31.2) | 163 (25.0) | 344 (27.9) |
| Public | 399 (68.8) | 489 (75.0) | 888 (72.1) |
| Race/Ethnicity – n (%) | | | |
| White | 303 (52.2) | 381 (58.4) | 684 (55.5) |
| Black | 19 (3.3) | 16 (2.4) | 35 (2.8) |
| Brown | 88 (15.2) | 109 (16.7) | 197 (16.0) |
| Indigenous | 0 (0.0) | 1 (0.2) | 1 (0.1) |
| Asian | 6 (1.0) | 1 (0.2) | 7 (0.6) |
| Hispanic | 11 (1.9) | 3 (0.5) | 14 (1.1) |
| Unknown | 153 (26.4) | 141 (21.6) | 294 (23.9) |
| ECOG PS – n (%) | | | |
| 0 | 407 (70.2) | 389 (59.7) | 796 (64.6) |
| 1 | 92 (15.9) | 135 (20.7) | 227 (18.4) |
| 2 | 8 (1.4) | 36 (5.5) | 44 (3.6) |
| 3 | 3 (0.5) | 13 (2.0) | 16 (1.3) |
| 4 | 2 (0.3) | 5 (0.8) | 7 (0.6) |
| Unknown | 68 (11.7) | 74 (11.3) | 142 (11.5) |
| Comorbidities – n (%) | | | |
| No | 411 (70.9) | 508 (77.9) | 919 (74.6) |
| Yes | 93 (16.0) | 73 (11.2) | 166 (13.5) |
| Unknown | 76 (13.1) | 71 (10.9) | 147 (11.9) |
| Which comorbidity (n = 147) – n (%) | | | |
| Hypertension | 12 (12.9) | 12 (16.4) | 24 (14.5) |
| Diabetes | 2 (2.1) | 2 (2.7) | 4 (2.4) |
| Renal insufficiency | 1 (1.1) | 1 (1.4) | 2 (1.2) |
| Heart failure | 0 (0.0) | 1 (1.4) | 1 (0.6) |
| Other | 65 (69.9) | 50 (68.5) | 115 (69.3) |
| Unknown | 13 (14.0) | 7 (9.6) | 20 (12.0) |
| Tobacco use – n (%) | | | |
| Yes | 98 (16.9) | 111 (17.0) | 209 (17.0) |
| No | 377 (65.0) | 422 (64.7) | 799 (64.8) |
| Unknown | 105 (18.1) | 119 (18.3) | 224 (18.2) |
| Drug use – n (%) | | | |
| No | 416 (71.7) | 461 (70.7) | 877 (71.2) |
| Yes | 18 (3.1) | 35 (5.4) | 53 (4.3) |
| Unknown | 146 (25.2) | 156 (23.9) | 302 (24.5) |
| Which drug (n = 53) – n (%) | | | |
| Marijuana | 8 (44.4) | 20 (57.2) | 28 (52.8) |
| Cocaine | 7 (38.9) | 9 (25.7) | 16 (30.2) |
| Other | 1 (5.6) | 4 (11.4) | 5 (9.4) |
| Unknown | 2 (11.1) | 2 (5.7) | 4 (7.6) |
| Familiar history of GCTs – n (%) | | | |
| Yes | 9 (1.6) | 17 (2.6) | 26 (2.1) |
| No | 456 (78.6) | 527 (80.8) | 983 (78.8) |
| Unknown | 115 (19.8) | 108 (16.6) | 223 (18.1) |
| Cryptorchidism – n (%) | | | |
| Yes | 40 (6.9) | 35 (5.4) | 75 (6.1) |
| No | 405 (69.8) | 487 (74.7) | 892 (72.4) |
| Unknown | 135 (23.3) | 130 (19.9) | 265 (21.5) |

Abbreviation: n = number of patients.

Multicenter Database of Patients with Germ-Cell Tumors

Table 2 Tumor Characteristics by Overall Histology

| Information | Seminoma (n = 580) | NSGCT (n = 652) | Total (n = 1232) |
|-------------------------------------|--------------------|-----------------|------------------|
| Primary tumor site – n (%) | | | |
| Testis | 559 (96.4) | 630 (96.6) | 1189 (96.5) |
| Retroperitoneum | 10 (1.7) | 6 (0.9) | 16 (1.3) |
| Mediastinum | 8 (1.4) | 14 (2.1) | 22 (1.8) |
| Other | 1 (0.2) | 1 (0.2) | 2 (0.2) |
| Unknown | 2 (0.3) | 1 (0.2) | 3 (0.2) |
| T-stage – n (%) | | | |
| Tx | 40 (6.9) | 83 (12.7) | 123 (10.0) |
| T1 | 315 (54.3) | 277 (42.5) | 592 (48.1) |
| T2 | 181 (31.2) | 208 (31.9) | 389 (31.6) |
| T3 | 38 (6.6) | 72 (11.1) | 110 (8.9) |
| T4 | 4 (0.7) | 10 (1.5) | 14 (1.1) |
| Unknown | 2 (0.3) | 2 (0.3) | 4 (0.3) |
| AFP median (IQR) | 1.94 (1.3-3.0) | 19.9 (2.5-350) | 3 (1.6-36) |
| HCG median (IQR) | 1.2 (0.1-3.0) | 4.0 (0.6-183) | 2.36 (0.1-18.8) |
| LDH median (IQR) | 360 (266-518) | 416.5 (295-818) | 383.3 (280-657) |
| IGCCCG risk II-III (IS, II e III) | | | |
| Good | 142 (76.7) | 176 (41.4) | 318 (52.1) |
| Intermediate | 24 (13.0) | 96 (22.6) | 120 (19.7) |
| Poor | 0 (0.0) | 106 (24.9) | 106 (17.4) |
| Unknown | 19 (10.3) | 47 (11.1) | 66 (10.8) |
| Clinical stage at diagnosis – n (%) | | | |
| IS | 10 (1.7) | 22 (3.4) | 32 (2.6) |
| I | 395 (68.1) | 226 (34.7) | 621 (50.4) |
| II | 112 (19.3) | 167 (25.6) | 279 (22.6) |
| III | 63 (10.9) | 236 (36.2) | 299 (24.3) |
| Unknown | 0 (0.0) | 1 (0.1) | 1 (0.1) |

Abbreviations: IQR = interquartile range; n = number of patients.

were more frequent (65.2%) with NSGCT. Tumor characteristics are described in [Table 2](#).

Clinical Stage I

Median follow-up of clinical stage I patients was 47 months (95% CI, 42-49 months). Of 621 patients with clinical stage I, 343 (55.2%) patients were managed with surveillance after orchiectomy. A higher proportion of patients with stage I seminoma (n = 173, 43.8%) received adjuvant treatment compared to patients with stage I NSGCT (n = 69, 30.5%). The most common adjuvant regimens for seminoma were carboplatin (79.8%) and radiation therapy (18.5%). For NSGCT the most frequent treatments were chemotherapy with bleomycin, etoposide, and cisplatin (BEP, 81.2%), etoposide and cisplatin (7.2%), carboplatin monotherapy (2.9%) and retroperitoneal lymph node dissection (RPLND) (7.2%). The characteristics of GCTs clinical stage I are shown in [Table 3](#).

The 5-year DFS rates among patients with clinical stage I were 98.0% in seminoma and 92.3% in NSGCT (P = .0014), with 5-year OS (5y-OS) rates of 99.6% and 97.6% (P = .0224), respectively ([Figure 1](#)). 5y-OS in Stage I NSGCTs according to the type of center health care coverage was 100% in private versus 97.0% in public centers (P = .2127) and in stage I seminoma was 100%

in private versus 99.4% in public centers (P = .4895). Kaplan-Meier curves of DFS and OS for stage I GCTs stratified by center health care coverage are available in the supplementary appendix ([Appendix 1](#)).

Clinical Stage IS, II, and III

Median follow-up of patients with advanced disease (stage IS, II, and III) was 49 months (95% CI, 46-55 months). The distribution of IGCCCG risk was different between seminoma and non-seminoma. Of advanced seminomas, 85.5% were IGCCCG good risk, whereas 53.4% of NSGCT were IGCCCG intermediate or poor risk.

Of 482 patients with advanced disease and treatment modalities information available, systemic treatment with chemotherapy was employed in 434 (90.0%) of advanced disease patients. BEP was the most frequent protocol, accounting for 350 patients (80.6%); varying from 66.7% (12) of patients with intermediate-risk seminoma to 88.4% (152) of patients with intermediate- and poor-risk non-seminoma. Other modalities, such as radiation therapy, RPLND or resection of other sites of disease, were used in less than 10% of patients ([Table 4](#)).

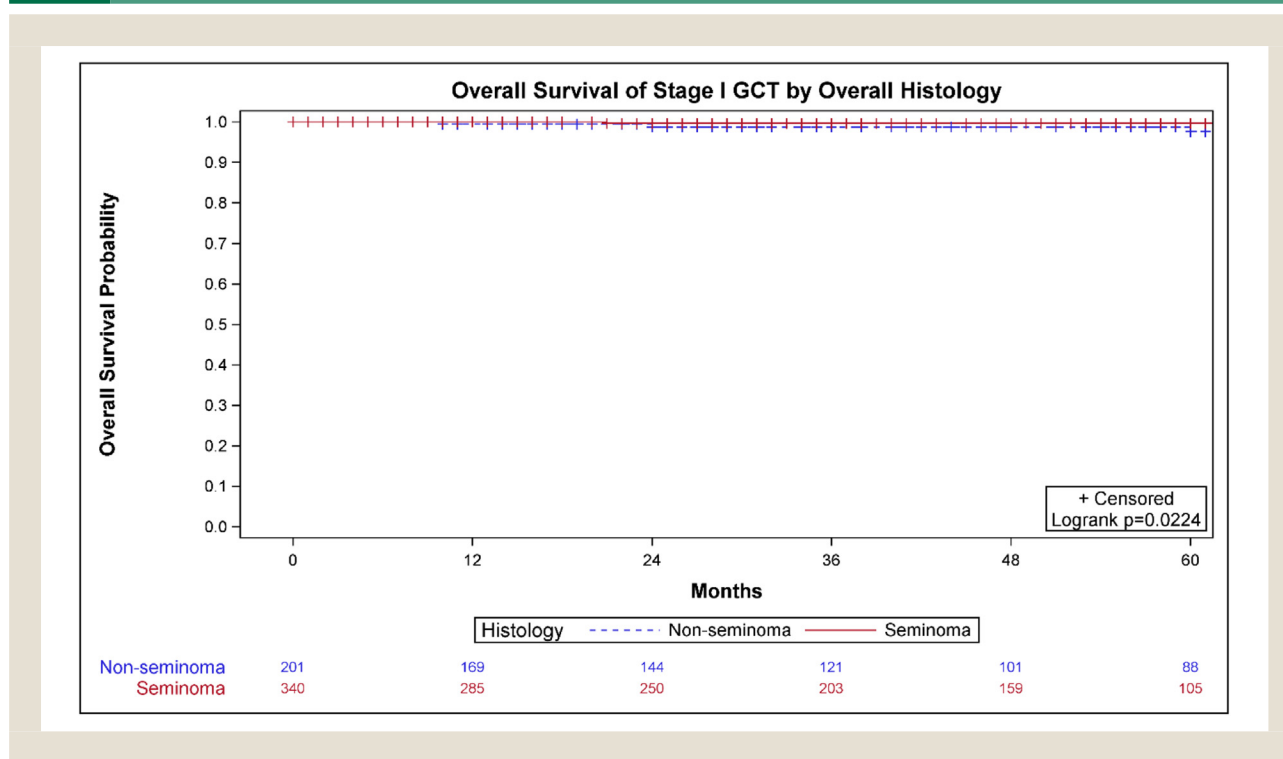
The 5-year PFS (5y-PFS) rates for patients with advanced disease were 88.7% in SGCT and 68.7% in NSGCT (P < .001)

Table 3 Stage I Patients Characteristics by Overall Histology

| Information | Seminoma (n = 395) | NSGCT (n = 226) | Total (n = 621) |
|--|--------------------|-----------------|-----------------|
| Median follow-up (95% CI) in mo | 43 (40-48) | 51 (41-61) | 47 (42-49) |
| AFP median (IQR) | 2 (1.4-3.0) | 3.6 (2.0-41.0) | 2.3 (1.5-3.9) |
| HCG median (IQR) | 1.2 (0.1-3.0) | 2 (0.1-3.3) | 1.2 (0.1-3) |
| LDH median (IQR) | 327 (241-410) | 326 (227-409) | 327 (238-410.5) |
| T stage – n (%) | | | |
| Tx | 11 (2.8) | 12 (5.3) | 23 (3.7) |
| T1 | 247 (62.5) | 147 (65.0) | 394 (63.4) |
| T2 | 120 (30.4) | 55 (24.3) | 175 (28.2) |
| T3 | 16 (4.1) | 10 (4.4) | 26 (4.2) |
| T4 | 1 (0.2) | 1 (0.5) | 2 (0.3) |
| Unknown | 0 (0.0) | 1 (0.5) | 1 (0.2) |
| Management – n (%) | | | |
| Surveillance | 199 (50.4) | 144 (63.7) | 343 (55.2) |
| Adjuvant therapy | 173 (43.8) | 69 (30.5) | 242 (39.0) |
| Unknown | 23 (5.8) | 13 (5.8) | 36 (5.8) |
| Which adjuvant therapy (n = 242) – n (%) | | | |
| BEP | 1 (0.6) | 56 (81.2) | 57 (23.6) |
| EP | 2 (1.1) | 5 (7.2) | 7 (2.9) |
| Carboplatin | 138 (79.8) | 2 (2.9) | 140 (57.8) |
| RPLND | 0 (0.0) | 5 (7.2) | 5 (2.1) |
| RPLND + BEP | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Radiation therapy | 32 (18.5) | 1 (1.5) | 33 (13.6) |

Abbreviations: IQR = interquartile range; n = number of patients.

Figure 1 Kaplan-Meier Curves of overall survival (OS) of stage I GCT, by overall histology.



Multicenter Database of Patients with Germ-Cell Tumors

Table 4 First-Line Systemic Treatment for Advanced Disease (Stage IS/II/III Patients)

| First Line Treatment by Risk | Seminoma | | NSGCT | |
|---|----------------|-----------------------|----------------|-------------------------------|
| | Good (n = 142) | Intermediate (n = 24) | Good (n = 176) | Intermediate + Poor (n = 202) |
| Chemotherapy (Did the patient receive 1st line of chemo?) | | | | |
| Yes | 109 (76.8) | 18 (75.0) | 135 (76.7) | 172 (85.1) |
| No | 15 (10.5) | 2 (8.3) | 25 (14.2) | 6 (3.0) |
| Unknown | 18 (12.7) | 4 (18.7) | 16 (9.1) | 24 (11.9) |
| BEP | 81 (74.3) | 12 (66.7) | 105 (78.4) | 152 (88.4) |
| EP | 26 (23.8) | 5 (27.8) | 27 (20.1) | 8 (4.6) |
| VIP | 1 (0.9) | 0 (0.0) | 2 (1.5) | 10 (5.8) |
| TIP | 1 (0.9) | 1 (5.6) | 0 (0.0) | 2 (1.2) |

Abbreviation: n = number of patients.

(Figure 2A). 5y-OS rate was 97.6% in advanced seminoma and 82.8% in advanced non-seminoma, ($P = .0002$) (Figure 2B). 5y-PFS rates for advanced disease by IGCCC were 84.7% in good risk, 70.3% in intermediate, and 45.5% in poor risk ($P < .001$). 5y-OS rates by IGCCC risk were: 94.3% in good risk, 83.5% in intermediate, and 65.1% in poor risk ($P < .001$) (Figure 3).

For advanced GCTs with good and poor risk, there was no statistical difference in 5y-PFS between public and private centers. For intermediate-risk GCTs, 5y-PFS rates were significantly higher in public versus private centers (72.1% vs. 61.8%, $P = .0332$). No statistical difference was observed in 5y-OS for advanced GCTs in public versus private centers regardless of the risk classification – a 5y-OS for good, intermediate, and poor-risk: 100%, 80.4%, and 60.4% in private centers versus 92.7%, 84.1%, and 66.2% in public centers. The full analysis according to the type of health care coverage – private versus public – is available in the supplementary appendix.

Discussion

The present study showed that the baseline and demographic features of Brazilian patients with GCT are similar to the other cohorts described previously. There were, however, a higher proportion of advanced tumors at diagnosis, especially NSGCT.^{18,19} We hypothesize that the unexpected low proportion of stage I NSGCT may be due to a delay from the clinical diagnosis suspicion by a general practice physician to the treatment performed by a specialist, particularly in public centers, which depend on a referral system (ie, patients must be referred from the basic health care unit/emergency unit to a specialized cancer center). These referrals may take some weeks or a few months.

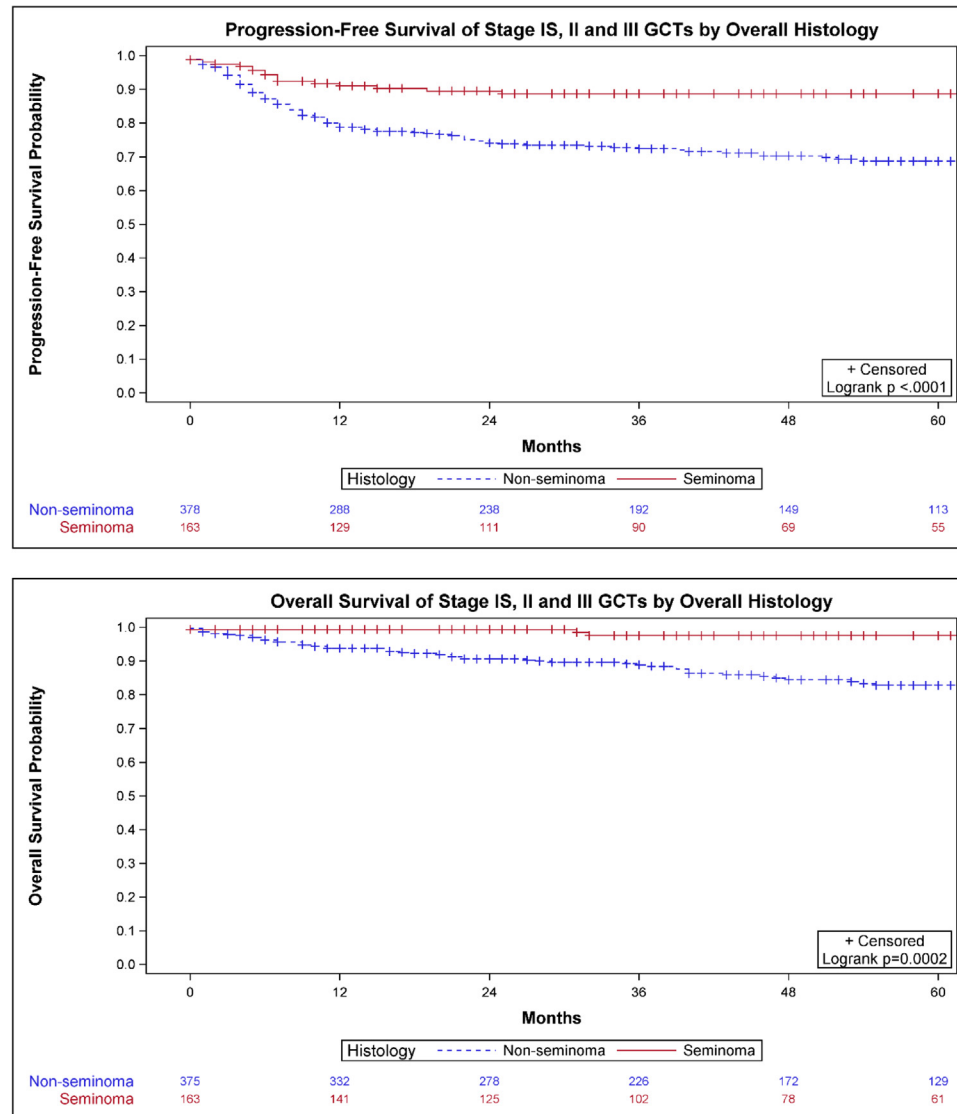
In stage I patients, OS was consistent with other series. Nevertheless, our cohort had a higher proportion of patients receiving adjuvant treatment, particularly patients with seminoma (almost 50%).²⁰⁻²² We hypothesize that this unexpected high proportion of patients receiving adjuvant treatment may be due to the difficulty of maintaining an adequate patient follow-up. Although patients with seminoma CS I of patients already have an excellent prognosis, the employment of adjuvant treatment is still an option if adequate surveillance is a challenge.^{23,24} There is a chance of higher rates of long-term toxicity in this patient population. The impact

of chemotherapy-related complications on survivors needs to be further explored.²⁴

The cohort used to derive the first IGCCCG classification included a great proportion of patients who were not treated with cisplatin and etoposide, which could impact negatively OS rates (5y-OS: 91%, 79%, and 48% in good-, intermediate- and poor-prognosis group, respectively).²⁵ Since the original publication of IGCCCG classification in 1997, an IGCCCG update consortium, with 30 institutions/collaborative groups in Europe, North America and Australia, was formed. The objective was to update survival probabilities and evaluate additional prognostic factors other than the ones defined previously. Patients treated between 1990 and 2013 were analyzed. For NSGCT, the 5y-PFS was similar to the original IGCCCG consortium for the good- and intermediate-prognosis group (90% and 78%, compared to 89% and 75% in the previous data). In the poor-prognosis group, there was an increase in 5y-PFS, from 80% to 89%. OS improved for all risk groups: from 92% to 96%, 80% to 89%, and 48% to 67% in good-, intermediate- and poor-prognosis groups, respectively. Increasing age, the presence of lung metastasis, and a new cutoff of lactate dehydrogenase at 2.5 the upper limit of normal were included as adverse factors in a new validated prognostic model.²⁶ The IGCCCG-Update consortium for seminoma also showed an increase in PFS and OS, when compared to the 1997 series. The PFS in 5 years increased from 82% to 89% and the 5y-OS from 86% to 95% in good prognosis patients, while in intermediate prognosis, 5y PFS went from 67% to 79% and 5y-OS from 72% to 88%.²⁷ This improvement in OS and PFS for both seminoma and NSGCT might be due to several factors: earlier diagnosis, use of cisplatin-etoposide as the first-line standard of care, better salvage strategies, and higher quality of post-chemotherapy surgery for NSGCT, among others.^{26,27}

In our Brazilian cohort, which included 482 patients with advanced disease, we found a 5y-PFS of 84.7%, 70.3%, and 45.5% and 5y-OS of 94.3%, 83.5%, and 65.1% for good-, intermediate- and poor-risk, respectively, which is consistent with the literature and similar to a Danish population-based study evaluating OS rates in 1889 patients who had received first-line BEP regimen. The survival probability in 5 years was 93% for good-risk seminoma, and 94.3%, 83.5%, and 65.1% for good, intermediate- and poor-risk NSGCT. Our OS results are similar to IGCCCG and other contemporary series.^{11,26,28} Our cohort also carried a higher proportion of

Figure 2 Kaplan-Meier Curves for progression-free survival (2A) and overall survival (2B) of stage IS, II, and III GCTs, by overall histology.



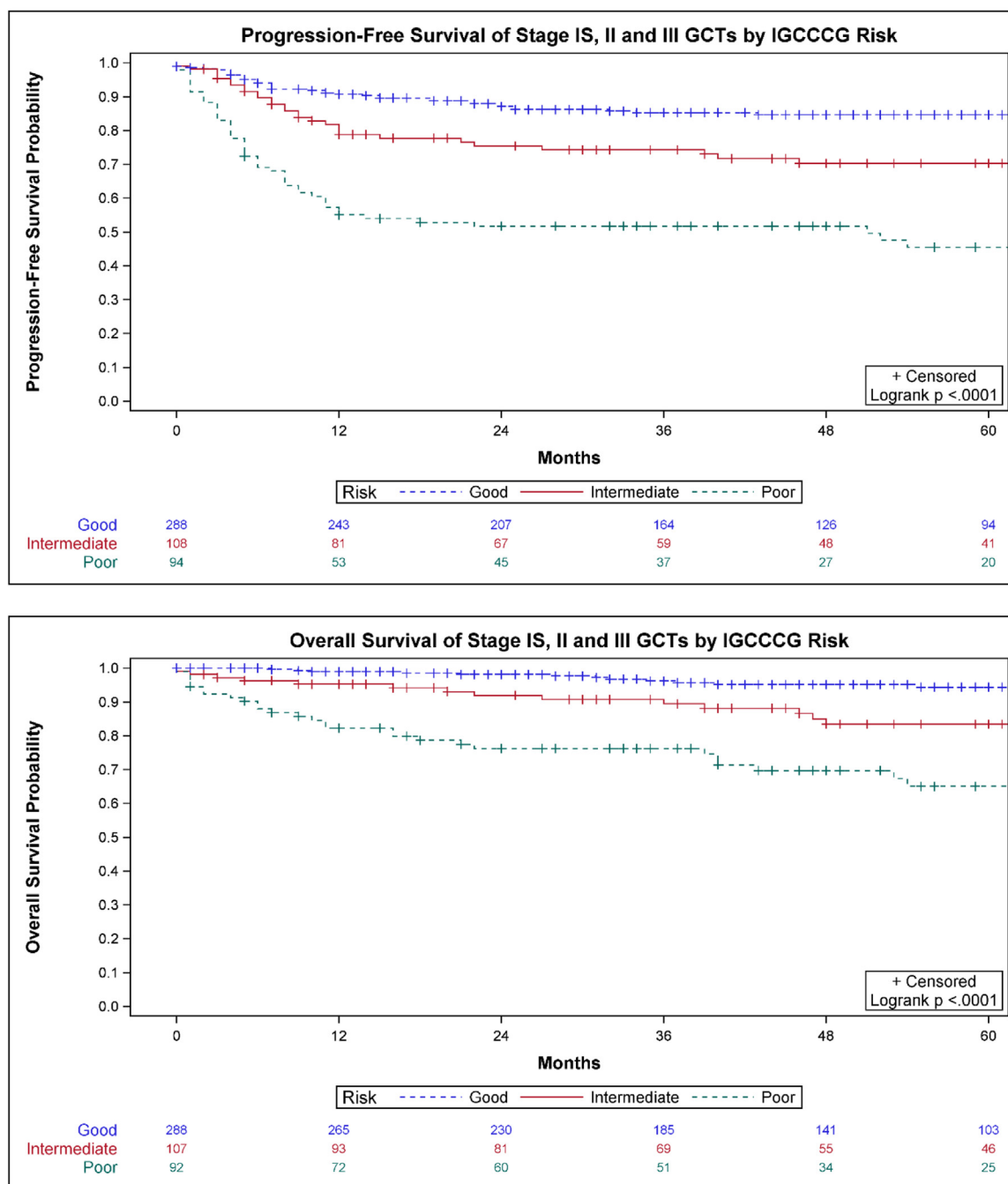
poor-risk disease than the original IGCCCG cohort.¹¹ On the other hand, we had similar proportions of poor prognosis NSGCT to the updated IGCCCG consortium and the Indiana single-institution cohort.^{26,28} A previous single-center Brazilian analysis showed 5y-PFS rates of 83.0%, 70.9%, and 35.1% and 5y-OS of 95.3%, 83.6%, and 62.2% for good-, intermediate- and poor-risk patients, respectively.¹⁷ This single-center analysis had a slightly higher rate of poor-risk patients, compared to ours.

Regarding PFS rates, our results are slightly inferior compared to PFS rates of contemporary series. The inferior PFS in our cohort may reflect limitations in treatment adherence in first-line setting. A Mexican single-center retrospective analysis showed a significant lack of patients' adherence to germ-cell tumor treatment, with a loss to medical follow-up of 58% of the included patients.²⁹ In Brazil,

the lack of adherence to first-line treatments may be due to lower access to specialized oncologic centers after the initial diagnosis.⁹ Challenges in treatment adherence have been observed in low- and middle-income countries, including Brazil, and they might also have contributed to lower PFS rates. Brazil has more than 2000 oncology centers. However, only 11% are exclusively dedicated to the public health care system, assisting 75% of the population.³⁰ Moreover, approximately 40% of the oncology centers are concentrated in state capitals. These barriers may delay the diagnosis and treatment of cancer patients, increasing the rate of advanced disease at diagnosis.³¹ Moreover, the low professional adherence to diagnosis and treatment guidelines may lead to a higher rate of relapse.³² This lack of adherence to the guidelines can be a reality in some Brazilian low-volume centers. Patients with GCTs treated in high-volume centers

Multicenter Database of Patients with Germ-Cell Tumors

Figure 3 Kaplan-Meier Curves for progression-free survival (3A) and overall survival (3B) of advanced germ-cell tumor patients (stage IS, II, and III), by IGCCCG risk (good, intermediate, poor).



have significantly better outcomes than patients treated in low-volume centers.³³ Nevertheless, the centers included in our analysis were mostly high-volume centers for the treatment of GCTs, and this may be one explanation for our similar 5y-OS between private and public centers. This similar OS also demonstrates that the treatments in both types of institutions are effective, even for advanced disease. The lower 5y-PFS rates observed in intermediate-

risk patients in private centers may be justified by the inclusion of fewer patients from private centers.

To our knowledge, this is the largest Latin American multicenter retrospective cohort analyzing epidemiology and outcomes of GCT patients. Therefore, our results might direct Brazil and other Latin American countries to better delineate strategies to improve GCT care. Moreover, our cohort comprised different profiles of

cancer centers: public and private, located in different regions of the country (capitals and non-capital cities), and therefore might reflect more precisely the epidemiological scenario. However, our study has some limitations that should be addressed. First, as a retrospective study, a selection bias may have occurred. In addition, Brazil has important economic and racial disparities when it comes to health care,^{34,35} and some results might be over or underestimated, limiting extrapolation to a specific country region. In the United States, patients of nonwhite race/ethnicity, low socioeconomic status and underinsurance had less access to testicular cancer care and, consequently, poorer outcomes.³⁶ A part of our heterogeneous population may be exposed to the same problems and outcomes.

Conclusions

Our national multicenter retrospective cohort showed a higher proportion of advanced tumors at diagnosis, especially NSGCT, in Brazil. Moreover, a high rate of adjuvant chemotherapy in patients with clinical stage I was demonstrated, which could reflect difficulty of maintaining an adequate patient follow-up. PFS was slightly inferior in our cohort, when compared to IGCCCG and other contemporary series. Nevertheless, OS was very similar to other cohorts. The OS rates suggest that salvage treatments are effective, irrespectively of whether the treatment was performed in a public or private center. Future collaborations with other developing countries around the world may expand the findings and bring opportunities to achieve better outcomes for patients with GCT.

Acknowledgments

We thank all the LACOG sites and investigators for collaborating in this research. We thank SAS software to provide a free license to LACOG. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Contributions of the authors

Concept and design: DAB. Search and collection of the data: all authors. Analysis of data and interpretation: all authors. Statistical analysis: RG. First draft of the manuscript: DAB and ABLG. All authors contributed to the content of the report and reviewed further drafts. All authors reviewed and approved the final report before submission. The authors take full responsibility for the scope, direction, and content of the report. Additional Contributions: SAS.

Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.clgc.2022.11.004](https://doi.org/10.1016/j.clgc.2022.11.004).

References

- International Agency for Research on Cancer. *Global Cancer Observatory. Cancer Fact Sheets. Testis*; 2020.
- Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021 caac.21660. doi:10.3322/caac.21660.
- Instituto Nacional do Câncer. Câncer de Testículo 2021. <https://www.inca.gov.br/tipos-de-cancer/cancer-de-testiculo> Accessed April 1, 2021.
- Cheng L, Albers P, Berney DM, et al. Testicular cancer. *Nat Rev Dis Primer*. 2018;4:29. doi:10.1038/s41572-018-0029-0.
- Znaor A, Lortet-Tieulent J, Jemal A, Bray F. International variations and trends in testicular cancer incidence and mortality. *Eur Urol*. 2014;65:1095–1106. doi:10.1016/j.eururo.2013.11.004.
- Bertuccio P, Malvezzi M, Chatenoud L, et al. Testicular cancer mortality in the Americas, 1980–2003. *Cancer*. 2007;109:776–779. doi:10.1002/ncr.22473.
- Bosetti C, Bertuccio P, Chatenoud L, Negri E, La Vecchia C, Levi F. Trends in mortality from urologic cancers in Europe, 1970–2008. *Eur Urol*. 2011;60:1–15. doi:10.1016/j.eururo.2011.03.047.
- Van Hemelrijck M, Shanmugalingam T, Soultati A, Chowdhury S, Rudman S. Global incidence and outcome of testicular cancer. *Clin Epidemiol*. 2013;417. doi:10.2147/CLEP.S34430.
- da Silva MJS, O'Dwyer G, Osorio-de-Castro CGS. Cancer care in Brazil: structure and geographical distribution. *BMC Cancer*. 2019;19:987. doi:10.1186/s12885-019-6190-3.
- Soares SCM, dos Santos KMR, de Moraes Fernandes FCG, Barbosa IR, de Souza DLB. Testicular cancer mortality in Brazil: trends and predictions until 2030. *BMC Urol*. 2019;19:59. doi:10.1186/s12894-019-0487-z.
- by the International Germ Cell Collaborative Group International germ cell consensus classification: a prognostic factor based staging system for metastatic germ cell cancers. *JCO*. 1997;15:594–603.
- Gilligan T, Lin DW, Aggarwal R, et al. Testicular cancer, Version 2.2020, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2019;17:1529–1554. doi:10.6004/jnccn.2019.0058.
- Oldenburg J, Fosså SD, Nuver J, et al. Testicular seminoma and non-seminoma: esmo clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2013;24 vi125–32. doi:10.1093/annonc/mdt304.
- Laguna MP, Pizzocaro G, Klepp O, Algaba F, Kisbenedek L, Leiva O. EAU guidelines on testicular cancer. *Eur Urol*. 2001;40:102–110. doi:10.1159/000049759.
- Stephenson A, Eggener SE, Bass EB, et al. Diagnosis and treatment of early stage testicular cancer: AUA guideline. *J Urol*. 2019;202:272–281. doi:10.1097/JU.0000000000000318.
- Saju SV, Radhakrishnan V, Ganesan TS, et al. Factors that impact the outcomes in testicular germ cell tumors in low–middle-income countries. *Med Oncol*. 2019;36:28. doi:10.1007/s12032-019-1252-6.
- Vasconcelos VF, Bastos DA, Pereira AAL, et al. Clinical characteristics and treatment outcomes of patients with advanced germ cell tumor treated at a tertiary cancer center in Brazil. *J Glob Oncol*. 2019;1–8. doi:10.1200/JGO.18.00170.
- National Cancer Institute. SEER Cancer Stat Facts: testicular cancer n.d.
- Hanna NH, Einhorn LH. Testicular cancer — discoveries and updates. *N Engl J Med*. 2014;371:2005–2016. doi:10.1056/NEJMra1407550.
- Cohn-Cedermark G, Stahl O, Tandstad T. SWENOTECA. Surveillance vs. adjuvant therapy of clinical stage I testicular tumors - a review and the SWENOTECA experience. *Andrology*. 2015;3:102–110. doi:10.1111/andr.280.
- Cullen M. Surveillance or adjuvant treatments in stage I testis germ-cell tumors. *Ann Oncol*. 2012;23:x342–x348. doi:10.1093/annonc/mds306.
- Tandstad T, Ståhl O, Dahl O, et al. Treatment of stage I seminoma, with one course of adjuvant carboplatin or surveillance, risk-adapted recommendations implementing patient autonomy: a report from the Swedish and Norwegian Testicular Cancer Group (SWENOTECA). *Ann Oncol*. 2016;27:1299–1304. doi:10.1093/annonc/mdw164.
- Feldman DR, Bosl GJ. Treatment of stage I seminoma: is it time to change your practice? *J Hematol Oncol J Hematol Oncol*. 2008;1:22 1756-8722-1–22. doi:10.1186/1756-8722-1-22.
- Hiestler A, Fingerhut A, Niegisch G, et al. Late toxicities and recurrences in patients with clinical stage I nonseminomatous germ cell tumor after one cycle of adjuvant BEP versus primary retroperitoneal lymph node dissection: a 13-years follow-up analysis of a phase III trial cohort. *J Clin Oncol*. 2020;38 5512–5512. doi:10.1200/JCO.2020.38.15_suppl.5512.
- Kier MG, Lauritsen J, Mortensen MS, et al. Prognostic factors and treatment results after bleomycin, etoposide, and cisplatin in germ cell cancer: a population-based study. *Eur Urol*. 2017;71:290–298. doi:10.1016/j.eururo.2016.09.015.
- Gillessen S, Sauvé N, Collette L, et al. Predicting outcomes in men with metastatic nonseminomatous germ cell tumors (NSGCT): results from the IGCCCG update consortium. *J Clin Oncol*. 2021 JCO.20.03296. doi:10.1200/JCO.20.03296.
- Beyer J, Collette L, Sauvé N, et al. Survival and new prognosticators in metastatic seminoma: results from the IGCCCG-update consortium. *J Clin Oncol*. 2021;39:1553–1562. doi:10.1200/JCO.20.03292.
- Albany C, Adra N, Snively AC, et al. Multidisciplinary clinic approach improves overall survival outcomes of patients with metastatic germ-cell tumors. *Ann Oncol*. 2018;29:341–346. doi:10.1093/annonc/mdx731.
- Salazar-Mejia CE, Zayas-Villanueva O, Gutiérrez AG, et al. Clinical characteristics and treatment adherence among men with testicular germ cell tumors: Real-world data from a referral center in Mexico. *J Clin Oncol*. 2020;38 393–393. doi:10.1200/JCO.2020.38.6_suppl.393.
- Nita M, Mussolino F, Vaz P, Riveros B, Tolentino A. Overview of oncology centers structures in both public and private Brazilian health care system. *Value Health*. 2016;19:A24. doi:10.1016/j.jval.2016.03.319.
- Chertack N, Ghandour RA, Singla N, et al. Overcoming sociodemographic factors in the care of patients with testicular cancer at a safety net hospital. *Cancer*. 2020;126:4362–4370. doi:10.1002/ncr.33076.

Multicenter Database of Patients with Germ-Cell Tumors

32. Wymer KM, Pearce SM, Harris KT, Pierorazio PM, Daneshmand S, Eggener SE. Adherence to National Comprehensive Cancer Network® Guidelines for Testicular Cancer. *J Urol*. 2017;197:684–689. doi:10.1016/j.juro.2016.09.073.
33. Woldu SL, Matulay JT, Clinton TN, et al. Impact of hospital case volume on testicular cancer outcomes and practice patterns. *Urol Oncol Semin Orig Investig*. 2018;36:14.e7–14.e15. doi:10.1016/j.urolonc.2017.08.024.
34. Landmann-Szwarcwald C, Macinko J. A panorama of health inequalities in Brazil. *Int J Equity Health*. 2016;15:174 s12939-016-0462-1. doi:10.1186/s12939-016-0462-1.
35. Pavão ALB. Racial discrimination and health in Brazil: evidence from a population-based survey. *Ethn Dis*. 2012;22:353–359.
36. Macleod LC, Cannon SS, Ko O, et al. Disparities in access and regionalization of care in testicular cancer. *Clin Genitourin Cancer*. 2018;16:e785–e793. doi:10.1016/j.clgc.2018.02.014.