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Update on Epidemiologic Considerations and Treatment Trends in Testicular Cancer

Solomon L. Woldu, MD and Aditya Bagrodia, MD

University of Texas Southwestern Medical Center, Dallas, TX

Abstract

Purpose of Review: We aim to give an overview of the epidemiology and treatment trends of testicular germ cell tumors (TGCT), with an emphasis on recent trends.

Recent Findings: The incidence of TGCT appears to be increasing, particularly in developed countries, although the reasons are not well understood. There is evidence of racial differences in predisposition to TGCT, with white men having highest risk and men of African or Asian descent having lower risk. In the United States, the incidence of TGCT among Hispanics appears to be rising most quickly. A recent genomic analysis indicates there is no highly penetrant major TGCT susceptibility gene. Incorporation of multi-disciplinary care has led to excellent long-term cure rates, however access to care and insurance remain barriers in young men. Recent treatment trends have centered on maximizing oncologic outcomes while minimizing long-term morbidity.

Summary: Emerging population-level data provides critical insight into the evolving demographics of TGCT, which may allow for elucidation of biologic and environmental determinants of TGCT. Further, identification of socioeconomic barriers to excellent clinical outcomes will allow for targeted interventions to patients with unique demographic and socioeconomic considerations. Treatment trend analyses suggest that the field is moving towards minimizing treatment-related morbidity.

Keywords

testicular cancer; trends; epidemiology; demographics

Introduction

Testicular germ cell tumors (TGCT) are the most common malignancies affecting young men, and the incidence appears to be increasing worldwide. The advent of cisplatin-based chemotherapy, and incorporation of multidisciplinary teams of surgeons, radiologists, oncologists, radiation oncologists, and pathologists has led to dramatic improvements in cure in most cases, yet there are concerns for long-term treatment-related morbidity. Our aim

Corresponding Author: Aditya Bagrodia, MD, Assistant Professor of Urology, Dedman Family Scholar in Clinical Care, Department of Urology, 5323 Harry Hines Blvd, J8.130, Dallas, TX 75390-9110, Office: 214-648-9626, Office fax: 214-648-8786, Clinic: 214-645-8765, Clinic fax: 214-645-8769, Aditya.Bagrodia@UTSouthwestern.edu.

Conflicts of Interest

None

is to review epidemiologic trends in TGCT, explore risk factors, and give a broad overview of treatment patterns.

Epidemiology

TGCT is the most common malignancy affecting young men between 15–44 years of age, and the mean age of diagnosis is 33.(1) In 2018, there will be an estimated 9,310 new cases of TGCT diagnosed in the United States, and approximately 400 men will die of disease.(2) There is substantial variability in the reported incidence of TGCT worldwide. An analysis from the International Agency for Research on Cancer (IARC) indicates age-standardized rates of TGCT varied from less than 1/100,000 person-years in Africa and Asia to over 9/100,000 person-years in Northern and Western Europe.(1)

Rising Incidence

Numerous reports dating back over 50 years have noted an increasing incidence of TGCT worldwide.(3–5) In the United States, the reported incidence has steadily increased to approximately 6.8 per 100,000.(6) Additionally, there appears to be substantial difference in the rising rates between countries, and even within a country (Figure 1A). For instance, the incidence of TGCT in Switzerland between 1974–1987 has remained relatively stable, but there are substantial differences in the incidence in men living in rural (6.8/100,000 person-years) vs. urban (10.7/100,000 person-years) areas. Some of the geographic variability and increasing incidence may be attributable to detection bias, increased patient and physician awareness, increased availability of ultrasounds.(7) Nonetheless, it is unlikely that such biases, which are essentially lead time biases, will substantially impact the overall trends noted. TGCT is a disease that typically affects young men, with few competing causes of mortality. Although more access to care or vigilance might lead to an earlier diagnosis, the overall incidence should remain stable.

Racial Differences

TGCT is a disease that mainly affects White Caucasian men, both in the US and globally. The reported incidence of TGCT in Scandinavia is ten times higher than the rates in Africa and Asia.(8) While such differences can be attributed to environmental causes, there are also substantial difference in the incidence of TGCT among racial groups within a country. In the United States, the highest incidence of TGCT is among Caucasian whites (6.57/100,000 person-years), followed by Hispanics (3.88/100,000 person-years), Asians (1.6/100,000 person-years), and Blacks (1.2/100,000 person-years). Additionally, rates of TGCT appear to be rising most quickly among Hispanics.(9) Woldu and colleagues found that the average age at diagnosis of TGCT was 5 years younger for Hispanic men compared to white men, and they were significantly more like to harbor non-seminomatous vs. seminomatous histology.(10) Reasons for such differences in incidence and trends remain speculative. An allele distribution of TGCT risk loci across races demonstrates that Hispanic men have a distribution of alleles similar to that of higher risk European men compared to lower risk African men.(11) Studies of immigrants from lower to higher rate countries find that the first-generation of migrants do not appear to have an increased rate of TGCT, but subsequent generations do.(12, 13) Ghazarian and colleagues speculate that the rising incidence in

Hispanic men may be due to an increase in 2nd and higher generations of immigrants, whereby a high risk but lower incidence group is being exposed to environmental factor(s) that lead to a more rapid rise in the rate of TGCT.(9)

Mortality

Despite the reported rise of TGCT incidence, mortality rates from TGCT have continued to decline in more highly developed countries for several decades.(1, 14) In the United States, testicular cancer mortality comprises approximately 4% of annual incidence.(2) The advent of cisplatin-based chemotherapy, improvements in surgical techniques, and incorporation of multi-disciplinary care teams has led to this success story. In developed countries the cure rate of stage I disease approaches 100%. (15) Even in metastatic disease, cure rates for good, intermediate, and poor-risk disease are approximately 90%(16), 70%(17), 48%, respectively. (18) There is substantial global variability of mortality rates, which are largely inverse of that seen in the incidence rates. TGCT mortality is highest in low-income countries compared to higher income countries (Figure 1B).(1) Within the United States, a recent analysis of NCDB indicates worse outcomes in racial minorities, and those with lower socioeconomic status and ‘underinsurance.’(19) Such findings highlight the notion that reliable access to care is required to prevent needless mortality in an otherwise healthy population.

Heritability

Familial clustering of TGCT has been noted for decades, in particular for male siblings who have a 4–8 fold higher risk of TGCT.(20–22) Recent genomic studies suggest heritability of TGCT at 49%, and known single nucleotide polymorphisms (SNP) represent only a minority of heritability.(23, 24) Targeted analysis of multiplex TGCT families has identified rare gene mutations, such as *DNAAF1* and related ciliary-microtubule genes, as likely culprits of TGCT in certain cases, however these high-impact mutations are rare.(25) Numerous genome-wide association studies have identified multiple loci associated with TGCT, many of which contain genes which are involved in germ cell development and pluripotency, DNA damage response, mitochondrial function, and kinetochore function.(26–30) These reports combined with epidemiologic evidence has led to speculation of a TGCT susceptibility gene which might be suitable for clinical testing. Recently, Litchfield and colleagues performed germ-line whole-exome sequencing of 919 TGCT cases and compared those to cancer-free controls and found no individual variant or genes that support the notion of a major, high-penetrance TGCT susceptibility gene.(31) Taken together, the development of TGCT is likely a polygenic process with multiple potential loci of susceptibility, combined with environmental exposures and epigenetic modification that lead to disease phenotype.(32)

Treatment Trends

Clinically Localized Disease

Patients with localized disease following radical orchiectomy can be managed in a number of ways. Guidelines-based recommendations for localized seminoma include active surveillance, single-dose carboplatin, or radiation to the retroperitoneum, while localized NSGCT can be managed with surveillance, cisplatin-based chemotherapy (1 cycle of

bleomycin, etoposide, and cisplatin [BEP]), or retroperitoneal lymph node dissection (RPLND). Regardless of the strategy employed, long-term survival approaches 100% as most contemporary data suggests the ability to salvage the estimated 20–30% of patients with occult metastatic disease who recur during surveillance.(15, 33–37) Given high cure rates with all management strategies, significant attention is paid to minimizing long-term effect of adjuvant chemotherapy and radiotherapy in testis cancer survivors, which include cardiovascular disease, secondary malignancies, and various toxicities.(38, 39)

A risk-adapted approach has been advocated to decide management strategies, with adjuvant therapy used in cases of perceived higher risk seminoma (i.e. stromal invasion of the rete testis and/or tumor diameter >4cm).(40, 41) However, these risk factors lack validation.(15) As seminoma has a lower risk of occult metastatic disease than NSGCT, active surveillance is the preferred strategy by most centers. Recent analyses of the National Cancer Database (NCDB) confirms an increasing utilization of surveillance for clinically localized seminoma from 25% in 1998 to over 60% in more recently, and even higher rates of surveillance at TGCT referral centers (Figure 2).(42–44) While use of adjuvant therapies has declined in recent years, the proportion of chemotherapy use has increased significantly compared to radiotherapy, which was the mainstay treatment for decades.(24, 44) This shift followed the publication of trials demonstrating equivalent recurrence-free survival of single-dose carboplatin and radiotherapy, but an improved adverse effect profile with chemotherapy.(45, 46) Further, if patients have relapse after radiotherapy and require chemotherapy, long-term risks including cardiac disease and secondary malignancies, are compounded.

Similar to seminoma, long-term survival approaches 100% with any upfront strategy due to efficacy of salvage therapies. Unlike seminoma, risk of occult disease is higher with NSGCT and a risk-adapted approach is more established. The presence of lymphovascular invasion (LVI) or invasion of the tunica vaginalis are incorporated into the AJCC staging, signifying at least pT2 disease and mark the distinction between clinical stage IA and IB disease. Patients with clinical stage IB disease have a ~50% recurrence rate, compared to an approximately 15% recurrence rate in clinical stage IA disease.(47–49) Embryonal carcinoma predominance has also been reported as marker of occult disease, although the effect is less definitive than LVI.(48, 50) Clinical stage IA NSGCT can be managed with a choice of surveillance, adjuvant chemotherapy, or primary nerve-sparing RPLND though surveillance is the preferred strategy given significant overtreatment rates. There is more controversy for higher risk clinical stage IB NSGCT with respect to adjuvant treatment versus surveillance.(33, 51) Both chemotherapy (BEP) and nerve-sparing RPLND represent viable adjuvant treatment strategies. Although a randomized trial comparing one cycle of BEP vs. RPLND for clinical stage I NSGCT showed superiority of BEP over RPLND,(52) this study has been criticized due to the notion that the RPLND was performed by less skilled surgeons as evidenced by high “in-field” recurrence rates. A single cycle of BEP is the standard for adjuvant chemotherapy based on results from SWENOTECA, demonstrating safety of dose reduction and an attempt to minimize dose related toxicity.(53, 54) Recent analysis of the NCDB indicate that ~75% of men with clinical stage IA NSGCT receive surveillance, compared to ~50% of men with clinical stage IB.(55) Compared to guideline recommendations, this suggests an underutilization of surveillance in clinical stage

IA. In the United States, there appears to be a higher utilization of RPLND and decreased utilization of surveillance at referral centers (Figure 2).(43)

Marker Only Elevation Disease

TGCT is unique with the incorporation of STMs into clinical staging. Although not common, a proportion of patients may have elevated AFP and hCG despite no evidence of distant disease on imaging studies or in the contralateral testicle (clinical stage IS). This situation is very rare for seminoma, and a conservative approach is warranted with repeat of STM measurement and imaging studies.(56) For clinical stage IS NSGCT, treatment recommendations are controversial with suggestions of primary chemotherapy for good-risk disseminated cancer or RPLND.(56, 57) Given the rarity of clinical stage IS disease, analysis of treatment trends is limited to large nationwide databases where there are significant questions about the validity of STM interpretation.(58)

Retroperitoneal Lymph Node Positive Disease

For stage IIA/IIB seminoma, the traditional treatment has been radiotherapy (59, 60) although 3 cycles of BEP or 4 cycles of etoposide and cisplatin (EP) is an alternative option. There are no randomized studies comparing radiotherapy with chemotherapy, a recent meta-analysis by Giannatempo and colleagues indicate that radiotherapy and chemotherapy appear to be equally effective.(61) As expected, chemotherapy was associated with acute toxicity, while long-term toxicity was more frequent in radiotherapy.(61) NCDB analysis indicates decreasing utilization of radiotherapy and increased utilization of chemotherapy, although a clear trend is not indicated. In the last year of analysis (2012), radiotherapy (vs. chemotherapy) was still used in over 70% of clinical stage IIA cases and approximately 50% of stage IIB cases.(62) In an effort to minimize long-term morbidity in TGCT survivors, there are two ongoing prospective clinical trials (SEMS and PRIMETEST) of RPLND for seminoma involving the retroperitoneal lymph nodes.(63)

There is similar controversy regarding treatment of node-positive, marker-negative NSGCT where options include RPLND or primary cisplatin-based chemotherapy (BEPx3 or EPx4). (56, 64) Chemotherapy provides early treatment of possible micrometastatic disease, however RPLND is the only treatment for possible teratoma. There are no randomized trials comparing chemotherapy with RPLND in this setting, though both approaches are associated with high cancer specific survival rates.(65) No nationwide analyses are available to address recent trends in the management of stage II NSGCT, although Memorial Sloan Kettering Cancer Center reports an increasing utilization of primary chemotherapy, in particular for patients with retroperitoneal lymphadenopathy >2cm, outside the primary landing zones, or multifocal disease.(65)

Metastatic Disease

Once TGCT has metastasized to organs beyond the retroperitoneum (cM1 disease) or serum tumor markers are significantly elevated (S2 or S3), cisplatin-based chemotherapy is the mainstay of treatment. Chemotherapy regimens are generally driven by International Germ Cell Cancer Collaborative Group (IGCCCG) categorization of disease into either good, intermediate, or poor-risk.(18, 66) Good-risk disease is typically managed with 3 cycles of

BEP or 4 cycles of EP.(67–71) The standard regimen for Intermediate and poor risk disease is 4 cycles of BEP or alternatively 4 cycles of etoposide, ifosfamide, cisplatin (VIP).(17, 72) In poor-risk cancers, alternative regimens have been proposed and show promise in the first-line setting including paclitaxel, ifosfamide, cisplatin (TIP)(73) though randomized trials are required to demonstrate equivalency or superiority to standard regimens. As an example, addition of high-dose carboplatin chemotherapy and hematopoietic stem-cell rescue did not show improved outcomes for poor-risk TGCT over BEP alone in the first-line setting.(74) Treatment trends for utilization of various chemotherapy regimens based on IGCCCG risk criteria are not reported.

Post-Chemotherapy RPLND

Following chemotherapy for seminoma, an FDG positron-emission tomography (PET) scan is typically recommended to assess >3cm residual disease for viable germ cell tumor.(75) In the event of PET avid disease in the retroperitoneum and normal serum tumor markers following chemotherapy, typical management is post-chemotherapy RPLND (PC-RPLND), salvage chemotherapy, or tumor excision following confirmatory biopsy.(18) Following chemotherapy for NSGCT, PET scan is not typically utilized. Some investigators advocate for the selective use of PC-RPLND based on residual mass size and absence of teratoma in the orchiectomy specimen.(76) This strategy avoids “double therapy” in the majority of patients who have a complete clinical response to chemotherapy alone. Others advocate for PC-RPLND in all patients due the risk of chemotherapy-resistant disease in the retroperitoneum (viable germ cell tumor or teratoma). (65, 77, 78) In the United States, utilization of PC-RPLND appears to be highest at centers of excellence, a finding that may be related to experience with this more complicated surgery (Figure 2).(43)

Sperm Cryopreservation

Testicular cancer is associated with subfertility at baseline(79) and all subsequent treatments are risk factors for further declines in fertility potential. As such, the NCCN recommends discussion of sperm banking (cryopreservation) at the initial work-up of suspected TGCT and recommends sperm banking prior to RPLND, chemotherapy, or radiation treatment.(56) Despite these risks, the reported use of sperm banking is low.(80, 81) Even at high-volume institutions, only 30% of patients received chemotherapy chose to bank sperm.(82) Reasons for low utilization may include logistical concerns, cost, and knowledge of fertility risks associated with testicular cancer treatment. In a recent cost-effectiveness analysis, sperm banking was more cost-effective strategy than other assisted reproductive techniques in those patients interested in paternity. The estimated cost of sperm banking is \$745 in the first year and \$343 for each additional year of cryopreservation.(83)

Conclusion

Epidemiologic studies suggest a rising incidence of TGCT, in particular for developed countries. Additionally, racial variability in incidence and trends suggest a combination of biologic predisposition with environmental exposure is playing a role in the development of TGCT. Although TGCT has largely been shown to have a significant degree of heritability, there does not appear to be a major gene or variant linked with the development of testicular

cancer. Treatment trends indicate an increased understanding of the long-term morbidity associated with adjuvant therapy for localized disease. Despite high cure rates overall, patients with lack of adequate access to care suffer high rates of mortality from TGCT.

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Key Points

- Although there is substantial heterogeneity in reporting and bias in detection across countries, a wide body of literature suggests a rising incidence of testicular germ cell tumor worldwide.
- There does not appear to be a major, high-penetrance gene mutation that confers a substantial risk of testicular germ cell tumor, but TGCT is a highly heritable disease and genome-wide association studies suggest multiple loci of susceptibility.
- Clinically localized testicular cancer can be treated with active surveillance, adjuvant single-dose carboplatin or radiotherapy (seminoma) or adjuvant cisplatin-based chemotherapy or retroperitoneal lymph node dissection (NSGCT). All strategies have long-term survival rates approaching 100%, with high rates of salvage in patients who experience recurrence during surveillance.
- Advanced testicular cancer often requires multi-disciplinary approaches involving chemotherapy and consolidative surgery. There is ongoing debate about the utility of PC-RPLND following complete response to chemotherapy for NSGCT.
- While cure rates for TGCT are high, this requires complex coordination of multi-disciplinary care. Patients with lower socioeconomic status, minorities, and underinsured patients suffer from high rates of mortality.

Figure 1A. Estimated age-standardized rates of incident cases of testicular cancer, worldwide in 2012

Source: GLOBOCAN 2012, Graph production: Cancer Today, (<http://gco.iarc.fr/today>),
 World Health Organization

Figure 1B. Estimated age-standardized rates of deaths due to testicular cancer, worldwide in 2012 (Reprinted with Permission from the International Agency for Research on Cancer)

Source: GLOBOCAN 2012, Graph production: Cancer Today, (<http://gco.iarc.fr/today>), World Health Organization

Figure 2. Testicular cancer treatment patterns stratified by hospital volume. (A) Stage I seminoma, (B) stage I nonseminomatous germ cell tumor, (C) management of stage II to III nonseminomatous germ cell tumor following chemotherapy.

RPLND – retroperitoneal lymph node dissection, PC-RPLND – post-chemotherapy retroperitoneal lymph node dissection

Source: Woldu SL, Matulay JT, Clinton TN, Singla N, Krabbe L-M, Hutchinson RC, et al. Impact of hospital case volume on testicular cancer outcomes and practice patterns. *Urologic Oncology: Seminars and Original Investigations*. 2018;36(1):14.e7-.e5.