The Association Between Testis Cancer and Semen Abnormalities Before Orchiectomy: A Systematic Review

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Purpose: Testicular germ cell tumors (TGCT) are the most common solid organ malignancy in young men. It is a largely curable disease, so the extent to which it affects quality of life—including male fertility—is important. Abnormal semen analysis is highly predictive of male infertility. We conducted a systematic review of published studies that reported pre-orchietomy semen parameters (as a surrogate for fertility) in TGCT patients to evaluate the association between TGCT and semen abnormalities before orchiectomy.

Methods: We conducted a systematic review of peer-reviewed publications reporting semen parameters before orchiectomy in adult patients diagnosed with TGCT. Further, we assessed the association between TGCT and semen abnormalities that may lead to infertility.

Results: We applied MeSH search terms to four online databases (PubMed, Cochrane Reviews, Web of Science, and Ovid), resulting in 701 potentially relevant citations. After conducting a three-stage screening process, six articles were included in the systematic review. For each study, the participants' data and the study's quality and risk of bias were assessed and described. All studies showed semen abnormalities—including count, motility, and morphology—in men with TGCT prior to orchiectomy.

Conclusions: TGCT is associated with semen abnormalities before orchiectomy. This review shows an increase in abnormal semen parameters among men with TGCT even outside the treatment effects of orchiectomy, radiation, or chemotherapy. To improve long-term quality of life, these findings should be considered when counseling patients on future fertility and sperm banking during discussions about treatment and prognosis for TGCT.

Keywords: germ cell tumor, semen analysis, orchiectomy, fertility, testicular cancer

TESTICULAR GERM CELL TUMORS (TGCT) are the most common solid organ malignancy in young men (ages 15–34), with overall 5-year survival over 95%.¹ It is a highly curable disease, with fertility morbidity either directly from the cancer or from its treatments. As TGCT typically occurs at a young age—and often prior to paternity—patients should be counseled about the extent to which it affects male fertility, as it can contribute to a patient's quality of life. Currently, there are an estimated 1.5 million infertile couples in the United States; male infertility is involved in approximately 47% of these couples and approximately half of the infertile males have abnormal semen parameters.²

While many factors affect fertility, malignancy is clearly a culprit.³ As TGCT arise from germ cells, it has been hy-

pothesized that testicular cancer might cause semen abnormalities that can lead to male infertility.³ Treatment of TGCT in the forms of orchiectomy, chemotherapy, retroperitoneal lymph node dissection, and radiation can also lead to semen abnormality.^{4,5} There are few studies that have examined the association between TGCT and semen abnormalities. Among those, most examined this association after orchiectomy or other TGCT treatment modalities. Subsequently, the relationship between TGCT themselves and semen abnormalities remains unclear. In our systematic review, we have focused on studies that reported semen analysis data in TGCT patients before orchiectomy, as each testis in its normal setting may contribute to half of the reservoir of fertility. Our systematic review results should provide crucial information to elucidate

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any associations between TGCT and semen abnormalities before orchiectomy. We also strove to discover any associations between TGCT and clinical male infertility in pre-orchiectomy patients.

Methods

Before initiating this systematic review, we established the protocol for our study following the recommendations for PRISMA Statements (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).⁶

Search strategy

We undertook an electronic search of four online databases (PubMed, Cochrane Database of Systematic Reviews, Web of Science, and Ovid) through September 2013. We performed a MeSH search with the following search terms indicating testicular germ cell tumor: “testicular neoplasms” or “testis cancer” or “germinoma” or “germ cell tumors,” combined with the following terms to indicate infertility or semen abnormalities: “infertility” or “oligospermia” or “azoospermia” or “astenoazoospermia” or “semen” or “semen analysis.” Duplicate articles were excluded.

Article selection

Inclusion criteria. We included all studies that were (1) published articles in peer-reviewed journals without time limitation, (2) included samples of adult males (18 years of age or older), (3) had a primary exposure of TGCT, and (4) reported semen parameters that were assessed before orchiectomy.

Exclusion criteria. We excluded studies that did not meet the inclusion criteria, unpublished studies, dissertations, abstracts, review articles, studies that examined male infertility or semen abnormalities but not in relationship to TGCT, and studies that included extra-gonadal germ cell tumors as primary exposure. Studies that only discussed semen parameters after orchiectomy, chemotherapy, radiation, or retroperitoneal surgery were also excluded. Studies in languages other than English were excluded.

Screening. Each abstract was independently screened by two of the four primary reviewers (DB, PMP, EB, and KH) to identify those meeting the inclusion/exclusion criteria and was then re-checked by the senior author (HD). The resulting articles were then read in-depth by two of the primary reviewers to examine the pre-orchiectomy data. HD resolved any differences that arose between the two primary reviewers for each article.

Data extraction

We extracted data on the study design, number of patients, and study population. We captured primary outcome data—sperm analysis parameters prior to orchiectomy—from all articles. Abnormal sperm count was defined as <20 million/mL, abnormal sperm motility was defined as <50% of total sperm, and abnormal sperm morphology was defined as >50% of total sperm with abnormal shape. As all six final studies included were reported before the World Health Organization (WHO)-V criteria were released in 2010, we were

unable to apply the more current WHO criteria. Other relevant semen findings were also recorded. Secondary outcome data (infertility findings), when available, were also captured from the qualifying articles.

Data analysis and synthesis

Information abstracted from the qualifying articles is synthesized in Table 1, and includes the number of patients and the primary and secondary findings. The abstracted data were qualitatively combined into a summary of the current understanding of TGCT’s impact on semen parameters and fertility outside of the treatment effects of orchiectomy, radiation, or chemotherapy.

Quality and validity assessment

Each study design, including the number of patients, was analyzed during the abstraction process, and potential bias (e.g., selection bias and information bias) was assessed (Table 2).

Results

Flow of included studies

Based on search results of the target databases using the selected key terms, we initially identified 701 citations and screened their titles and abstracts for inclusion and exclusion criteria. After preliminary screening by junior reviewers, many of the studies were excluded because they used animal models, included female patients, studied other diseases, or were duplicates (Fig. 1). In the second round of screening, titles and abstracts were reviewed by the senior researcher (HD); 96 studies made it to this stage. When reapplying the inclusion and exclusion criteria, an additional 56 articles were excluded because they did not look at the impact of testicular cancer on semen abnormalities, or were case reports or review articles. This left 40 articles for the third screening, a more detailed review of each article’s full text by the two research pairs to confirm inclusion or exclusion. After this round of review, an additional 34 studies were excluded because they did not report pre-orchiectomy semen parameters, were themselves review articles, or reported fertility results without semen analysis. After consensus was reached among the research team, the remaining six studies were included in the systematic review.

Study characteristics

The characteristics of the studies included in this review are detailed in Tables 1 and 2. The six articles reviewed were published between 1983 and 2010. The number of TGCT cases in each study ranged from 6 to 63 males. Semen samples were from patients with TGCT in clinical settings or research centers. The most common semen parameters reported were sperm count, motility, and morphology. Two of the included studies discussed infertility as it relates to abnormal semen analysis. Any data reported on infertility were included in Table 2.

Study quality and bias

To improve the quality of studies selected for this review, case reports were excluded due to their small sample size and

TABLE 1. DESCRIPTIVE STUDIES WITH DATA ON SEMEN FINDINGS IN TESTIS CANCER PATIENTS

<i>Authors (year of publication)</i>	<i>Patients with pre-orchietomy data</i>	<i>Pre-orchietomy sperm count and/or concentration</i>	<i>Pre-orchietomy sperm motility</i>	<i>Pre-orchietomy sperm morphology</i>	<i>Pre-orchietomy infertility evaluation</i>
Jewett MA et al. (1983) ¹⁷	7 cases 101 controls	Total sperm count $\pm$ SD: • Cases: $45.3 \pm 14.8 \times 10^6$ /ejaculate • Controls: $165.2 \pm 12.9 \times 10^6$ /ejaculate	n/a	n/a	n/a
Nijman JM et al. (1985) ¹²	14 cases 59 controls	Mean sperm concentration: • Cases: 13.2×10^6 /mL (range: $0-63 \times 10^6$ /mL) • Controls: 73.8×10^6 /mL (range: $8-185 \times 10^6$ /mL)	Mean: • Cases: 31% (range: 0–70%) • Controls: 50% (range: 10–80%) Progressive motility recorded in 4 patients with median of 12%	Mean: • Cases: 48% (range: 30–58%) • Controls: 58% (range: 32–77%) Morphology recorded in 4 patients with median of 7%	3 of 14 had been under infertility treatment
Kliesch S et al. (1997) ¹¹	6 cases	Median sperm count: • 0.27×10^9 /mL • Azoospermia in 2 patients	Median: • Cases: 66% (range: 0–93%) • Controls: 65% (range: 32–100%)	Median: • Cases: 41% (range: 19–75%) • Controls: 42% (range: 8–65%)	4 of 6 had unexplained infertility before cancer detection
Petersen PM et al. (1999) ³	63 cases 141 controls	Cases: • Median sperm concentration: 15×10^6 /mL (range: $0-128 \times 10^6$ /mL) • Median total sperm count: 29×10^6 /mL (range: $0-589 \times 10^6$ /mL) Controls: • Median sperm concentration: 48×10^6 /mL (range: $0-402 \times 10^6$ /mL) • Median total sperm count: 162×10^6 /mL (range: $0-1253 \times 10^6$ /mL) Median sperm count: 8.6×10^6 /mL	Median: 45%	n/a	n/a
Saint F et al. (2002) ⁷	14 cases	Mean sperm count $\pm$ SD: $15.6 \pm 17.3 \times 10^6$ /mL	Mean normal motility $\pm$ SD: $49.8 \pm 19.6\%$	Mean normal morphology $\pm$ SD: $8.3 \pm 4.6\%$	n/a
Fraietta R et al. (2010) ¹³	31 cases Compared to 67 post-orchietomy cases				

n/a, not available or not applicable; SD, standard deviation.

TABLE 2. CHARACTERISTICS AND BIAS RISK IN INCLUDED STUDIES

Article title, authors, and year	Type of study	Study, patient, and control descriptions	Risk of bias
Exocrine function of testes with germinal testicular tumor. Jewett MA et al. (1983) ¹⁷	Case-control	Semen collected immediately before or soon after therapeutic unilateral orchiectomy from 86 patients with germinal tumors of the testis was analyzed. Pre-orchiectomy data available for 7 cases. 101 normal controls.	Risk of selection bias may exist.
Fertility and hormonal function in patients with a nonseminomatous tumor of the testis. Nijman JM et al. (1985) ¹²	Case-control	54 patients with a unilateral nonseminomatous tumor of the testis. Semen analysis available for 14 pre- and 40 post-orchiectomy patients. 59 fertile men as controls.	Possibly no bias. Other variables controlled.
Semen parameters and testicular pathology in men with testicular cancer and contralateral carcinoma <i>in situ</i> or bilateral testicular malignancies. Kliesch S et al. (1997) ¹¹	Case series	Patients with bilateral testicular tumor, one-sided tumor, and contralateral carcinoma <i>in situ</i> of the testis or testis tumor in single testis. Pre-orchiectomy data available for 6 of 14 patients.	Chances of information bias due to pre-existing infertility.
Semen quality and reproductive hormones before orchiectomy in men with testicular cancer. Petersen PM et al. (1999) ³	Case-control	Out of 83 total, 63 patients with TGCT had pre-orchiectomy semen analysis and 71 had hormonal investigations. 141 randomly selected controls.	None to minimal. Adjusted for variables and confounders.
Dendritic cell infiltration in a patient with seminomatous germ cell tumor of the testis: is there a relationship with infertility and tumor stage? Saint F et al. (2002) ⁷	Case series	30 patients with seminoma underwent orchiectomy at study center, including 14 who underwent spermiography before orchiectomy.	Selection bias may be a problem.
Individual and seminal characteristics of patients with testicular germ cell tumors. Fraietta R et al. (2010) ¹³	Cohort	100 testicular cancer patients referred to infertility clinic for sperm banking. Semen analysis results in men with seminoma and nonseminoma pre- ($n=31$) and post-orchiectomy ($n=67$).	None to minimal. Adjusted for various variables using statistical analysis.

TGCT, testicular germ cell tumor.

poor generalizability. Case-control studies provided the highest level of evidence. Of the final articles reviewed, three were case-control studies and examined pre-orchiectomy semen parameters of men with TGCT as compared with healthy controls or men with other kinds of disease. Two of the studies used a case-series design and the final one was a cohort study. During data abstraction, all studies were evaluated for information bias, selection bias, and confounding. Only three of the reviewed articles had possible bias that should be considered (Table 2).

Description and summary of individual studies

Saint et al. examined the relationship between antigen expression with dendritic cells, histiocytic cells, TGCT, and spermatogenesis.⁷ In 14 patients with TGCT, three serial semen analyses were done before orchiectomy. Median pre-orchiectomy sperm count and motility were lower than normal values (8.6 million/mL and 45%, respectively). The authors did not discuss infertility, nor did they have any control group. The article reported that infiltration of mononuclear cells in the cancerous testis was elevated with testicular

malignant severity changes and suggested that autoimmunity may be a potential mechanism for semen abnormalities in males with TGCT. Similar to other gonadotoxins, including heat and benign systemic disease, cancer may have a harmful effect on sperm production. They concluded that there was an association between TGCT and impaired spermatogenesis that was associated with infiltration of histiocytes.

Petersen et al. compared the semen analysis of 63 TGCT patients pre-orchiectomy with that of 141 controls.³ In evaluating the cases versus the controls, they found significantly lower sperm concentration (15.3 vs. $48.3 \times 10^6/\text{mL}$; $p=0.001$) and total sperm count (29.3 vs. $162.3 \times 10^6/\text{mL}$; $p=0.001$). Motile (66% vs. 65%) and normal morphology (41% vs. 42%) sperms were not significantly different between the two groups ($p>0.05$). Fertility was not evaluated. Previous epidemiologic investigations have found that TGCT patients have high risk of infertility before cancer diagnosis.^{8,9} Petersen et al. confirmed that sperm density (concentration) was lower in men with TGCT than controls, although analyses accounted for year of birth to exclude the cohort effect. They also reviewed seasonal variation as a possible confounder, but ruled it out as those in the control group were

more often seen during the summer and sperm counts have been shown to be lower during summer rather than winter.¹⁰ They believed that the results on motility and morphology of sperm could have been biased, as analyses of sperm motility and morphology are impossible in ejaculates with severe oligo- or azoospermia, which was more frequent in the TGCT patients in this study. They concluded that there was a significant impairment of semen quality pre-orchietomy in TGCT, possibly due to pre-existing spermatogenesis impairment in contralateral testis.

Kliesch et al. evaluated 14 patients who had bilateral testicular tumor, one-sided tumor, or contralateral carcinoma *in situ* of the testis or a testis tumor in a single testis with respect to their fertility.¹¹ Six out of the 14 patients were evaluated before orchietomy; their median sperm count ($0.27 \times 10^6/\text{mL}$), motility (12%), and normal morphology (7%) were lower compared to even 1999 WHO-reported normal values (count of 20,000,000/mL and morphology of 14%). Four of the six patients had infertility before cancer detection. There was no control group. Testicular volumes and serum follicle stimulating hormone levels did correlate with semen parameters that potentially indicate testicular dysfunction in men with testicular cancers. However, they proposed

that patients with unilateral testicular tumors might have the chance to recover spermatogenesis post-orchietomy.

Nijman et al. investigated pre-orchietomy semen analysis and hormonal evaluation in 14 patients with unilateral non-seminomatous testis tumor and 59 controls.¹² The cases had significantly lower mean sperm concentration (13.2 vs. $73.8 \times 10^6/\text{mL}$), motility (31% vs. 50%), and normal morphology (48% vs. 58%) than controls. Three of the 14 patients were evaluated for infertility before orchietomy. Poor semen quality was found both pre- and post-orchietomy; it was not repeated in the same cohort (pre- and post-), so they could not address the effect of orchietomy on semen parameters. They concluded that although spermatogenesis abnormalities present before orchietomy, possible endocrinological factors and dysfunction of the normal remaining testis could contribute to post-orchietomy semen abnormalities.

Fraietta et al. analyzed the data of 100 patients with TGCT and evaluated the patients' sperm quality with respect to histologic type (seminomatous vs. nonseminomatous cancers).¹³ Thirty-one of the patients had pre-orchietomy evaluations. Mean sperm count, motility, and normal morphology were recorded as $15.6 \times 10^6/\text{mL}$, 49%, and 8.3%, respectively. There was no discussion of infertility in these patients.

Possible explanations for these semen derangements are altered function of contralateral testis (atrophy, testicular intratubular germ cell neoplasia),⁴ tumor-associated factors (i.e., hCG, AFP, E2, LH, decreased testosterone level, production of tumor-associated cytokines, anti-sperm antibodies), psychological stresses leading to catecholamine release, increased prolactin, corticotropin-releasing factor, and endogenous opioid hormones.^{14–16} In this study, those with a seminoma presented with a higher number of motile and morphologically normal sperm in their ejaculate than those with a nonseminoma ($p=0.02$). The authors concluded that testicular cancer patients present with lower semen quality even before the initiation of therapy, and thus recommended sperm cryopreservation before any treatment.

Jewett *et al.* completed a case-control study on testicular function in patients with TGCT.¹⁷ They compared the semen analysis of 86 patients with TGCT with 101 controls; seven of the TGCT patients were pre-orchietomy. The mean total sperm count was lower in the seven pre-orchietomy cases than in the controls (45.3 vs. $165.2 \times 10^6/\text{mL}$); motility and morphology were not specifically compared between the pre-orchietomy patients and controls. The authors also reviewed hormonal changes, but did not discuss the issue of fertility. Due to the small number of pre-orchietomy cases, they did not draw separate conclusions for the pre-orchietomy cases, but did discuss that spermatogenesis abnormality in TGCT patients was mostly bilateral and often profound. Unilateral orchietomy would be expected to decrease the reservoir of sperm production by 50%. This again re-emphasizes the recommendation to bank sperm before any treatment for testis cancer.

Discussion

In this systematic literature review, we found six observational studies with pre-orchietomy semen analysis data in patients with TGCT. We focused on pre-orchietomy semen analysis as the findings before orchietomy provide a more nuanced understanding of fertility in TGCT patients. The reviewed studies consisted of three case-controls, one cohort, and two case series, with a combined total of 135 pre-orchietomy patients in these studies. Semen analysis reports consisted primarily of sperm count, motility, and morphology (Fig. 2). In five of the six studies, the mean/median sperm count was below $20 \times 10^6/\text{mL}$ (oligospermia).

In the sixth study, sperm count/mL was not available, but total sperm count was $45.3 \times 10^6/\text{ejaculate}$. In four studies, the mean/median sperm motility was below 50%. Motility was not available in one study and was 66% in the Petersen study.³ Sperm morphology was available in four studies; all of them were <50%. Infertility data were available in only two studies: pre-orchietomy, four of six patients in the Kliesch study¹¹ and three of 14 in the Nijman study,¹² respectively, were infertile. Most notably, all six studies in this review showed that TGCT before orchietomy was associated with semen abnormalities, a surrogate for infertility.

The association between TGCT and abnormal semen analysis after different therapeutic interventions including orchietomy, chemotherapy, radiotherapy, or retroperitoneal surgery is well documented.^{4,5} However, it has been difficult to separate the effects on semen abnormalities and fertility of the cancer itself from that of the different treatment modalities. This systematic review shows that TGCT before orchietomy is associated with semen abnormalities. The results of this review have several implications for clinical practice and future research. There is still no consensus on the timing of sperm banking for patients with TGCT. A study in the United Kingdom found that only 54% of urologists there routinely offered sperm banking before orchietomy.¹⁸ Most studies have recommended sperm banking before adjuvant therapy (chemotherapy or radiation), as these treatments have been shown to be associated with severe semen abnormalities.^{4,5} The sperm retrieved can be used in different assisted reproductive methods for fertility with a high chance of success (pregnancy rate up to 30% per egg collection¹⁹). This review confirms the presence of semen abnormalities before orchietomy in patients with TGCT. With potential decreased fertility after orchietomy and treatment, the routine pre-orchietomy sperm banking recommendation needs to be validated. Future prospective studies should examine the benefit of pre- versus post-orchietomy sperm cryopreservation.

Although the results presented here are valuable, this review has limitations that should be considered. The search was limited to studies published in English and in peer-reviewed journals, which potentially excluded articles that were published in other languages or unpublished data. The data gathered for this review could be distorted by publication bias, which could affect the results of studies that did not find an association and thus were not submitted or accepted

FIG. 2. Pre-orchietomy semen parameters in TGCT patients. *Note.* Not all studies presented their data in the same way, and thus the “sperm counts” portion was excluded for Nijman *et al.* (1985).¹² TGCT, testicular germ cell tumor.

for publication. However, we chose to include only peer-reviewed studies (excluding case reports) in order to assure the validity of the data gathered. The small number of studies available on this topic that were observational studies limits our findings, but at the same time highlights that this issue requires further investigation.

Conclusion

Semen abnormalities are common in patients with TGCT before orchiectomy. Fertility and sperm banking are important issues that should be incorporated into patient counseling and care before any treatment for TGCT. Further research into the magnitude of the impact of TGCT on fertility should be undertaken.

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Author Disclosure Statement

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