Hypogonadism and Infertility in Testicular Cancer Survivors

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Abstract
Testicular cancer is the most common cancer in men in their 20s and 30s, and has been considered a model of a curable neoplasm. The longer life expectancy of testicular cancer survivors makes minimizing the long-term health issues related to hypogonadism particularly important, and because testicular cancer affects men mostly in their reproductive years, infertility can also be a major concern. Hypogonadism, infertility, and testicular cancer have been associated with one another. These associations suggest the existence of common etiologic factors, including improper testicular development during fetal life. The effect of cancer treatment on testosterone, luteinizing hormone, and follicle-stimulating hormone levels, and on fertility and overall paternity rates among testicular cancer survivors, are potentially significant issues. As the biologic mechanisms underlying hypogonadism, infertility, and testicular cancer become clearer, more research is needed to provide clinicians with evidence-based guidelines for the management of testicular cancer survivors. (JNCCN 2012;10:558–563)

Testicular cancer (TC) is the most common cancer of men in their 20s and 30s. TC is considered the model of a curable neoplasm and constitutes one of the greatest success stories in modern medicine since the advent of effective multiagent cisplatin-based chemotherapy more than 30 years ago. An estimated 20% of patients with testicular germ cell tumors will require primary chemotherapy to achieve a cure, and etoposide and cisplatin (EP) or bleomycin, etoposide, and cisplatin (BEP) are the most commonly used treatment regimens. At the completion of treatment, an assessment of response and the need for postchemotherapy surgery (e.g., a retroperitoneal lymph node dissection [RPLND]) is assessed. Radiation therapy is another treatment option for select patients with TC. Radiation therapy, surgery, or chemotherapy can each contribute to hypogonadism, decreased sperm counts, and infertility.

Hypogonadism, or testosterone deficiency, is associated with aging and is more prevalent in men aged 40 to 79 years. When hypogonadism is identified, subsequent treatment can result in relief of sexual symptoms and fertility issues. Testosterone, produced by the Leydig cells, acts upon the Sertoli and peritubular cells in the seminiferous tubule to regulate spermatogenesis. Spermatogenesis is the process through which male primary germ cells undergo division, producing spermatogonia. Primary spermatocytes are derived from the spermato- 
spermatozoa, which develop into mature spermatozoa or sperm cells. This process occurs in the seminiferous tubules, which contain a mixture of germ and Sertoli cells. The main function of the Sertoli cell is to nurture developing sperm cells through the stages of spermatogenesis. Cisplatin-based chemotherapy has severe dose-dependent effects on spermatogenesis, and several mechanisms have been proposed to explain these effects on both spermatogonia and Sertoli cells, which may in turn affect all stages of spermatogenesis; however, the mechanism through which it acts remains somewhat uncertain.

Infertility is a major concern for many TC survivors, because the disease affects men mostly in their reproduc-
tive years.\textsuperscript{11–13} TC has been associated with infertility and genitourinary abnormalities, such as cryptorchidism, hypospadias, and poor semen quality, and TC has been considered a symptom of an underlying entity referred to as testicular dysgenesis syndrome (TDS). Although the association remains in debate, this entity is hypothesized to lead to increased male fertility impairment,\textsuperscript{14,15} with various causal links between the components of TDS fortifying the connection among hypogonadism, infertility, and TC as a manifestation of improper testicular development during fetal life caused by genetic and/or environmental factors.\textsuperscript{1,8,14–16}

The effects of chemotherapy and radiation on testosterone, follicle-stimulating hormone, and luteinizing hormone (LH) levels have been examined in numerous populations of cancer survivors,\textsuperscript{17} and are particularly relevant for men treated for cancer at a young age. The longer life expectancy of many young cancer survivors, including a large cohort of TC survivors, makes it particularly important to minimize the long-term health issues related to hypogonadism, including those that affect fertility. Cytotoxic therapy may influence endocrine testicular function and spermatogenesis, at least temporarily and in some cases permanently,\textsuperscript{12} with cisplatin therapy resulting in temporary azoospermia in most men. Permanent damage is a possibility with doses greater than 400 to 600 mg/m\textsuperscript{2}.\textsuperscript{18} However, recovery of spermatogenesis is reported in a growing percentage of TC survivors.\textsuperscript{18,19} As work in this field advances, the association between TC and preexisting hypogonadism is surfacing as a significant cause of fertility issues in this population.\textsuperscript{17} In many cases, patients with TC present for diagnosis when they are symptomatic and an accurate semen analysis may not be possible. In addition, many of these men are young and have not been concerned about fertility.\textsuperscript{20} Consequently, it is difficult to accurately determine pretreatment fertility status in many patients with TC and whether posttreatment issues with decreased spermatogenesis are the result of an already existing issue that caused or contributed to infertility.\textsuperscript{20,21}

This manuscript reviews the current evidence on hypogonadism and infertility in TC survivors.

**Hypogonadism**

In men, testosterone is primarily synthesized in the Leydig cells of the testicle. This synthesis is regulated by the hypothalamic-pituitary-testicular axis. When serum testosterone levels are low, the hypothalamus releases gonadotropin-releasing hormone (GnRH), which causes the pituitary gland to release LH, which acts on the Leydig cells to stimulate testosterone production. When serum testosterone levels are increased, a negative feedback loop inhibits the release of GnRH and LH. All patients with TC undergo unilateral orchiectomy for diagnosis and treatment. Before orchiectomy, serum testosterone levels are similar to those seen in healthy men. LH may be decreased in the setting of a human chorionic gonadotropin-secreting tumor.\textsuperscript{22} After unilateral orchiectomy, at a median of 5 months of follow-up, serum testosterone levels are usually similar to pre-orchietomy levels, although LH is increased.\textsuperscript{23} The increase in LH is compensatory and maintains the normal serum testosterone levels.

The increased risk of a second contralateral TC in TC survivors is well-documented. A population-based study of more than 29,515 American men diagnosed with TC before 55 years of age showed that 0.6% of patients present with a synchronous contralateral TC and require bilateral orchiectomy. Of the remaining patients who present with a unilateral TC, the 15-year cumulative risk of developing a metachronous TC is 1.9% (95% CI, 1.7–2.1). The median time to diagnosis of a second TC was 63 months (range, 3–233 months).\textsuperscript{24} These patients require a second orchiectomy. The impact of bilateral orchiectomies on sex hormonal status is obvious.

Hormone status as a function of treatment received has been examined in 2 large studies of long-term TC survivors. In the largest study, serum hormone analyses were performed on 1183 Norwegian TC survivors. Patients were grouped according to treatment modality: surgery only, radiotherapy, and chemotherapy (2 groups: cisplatin ≤ 850 mg or > 850 mg). Hypogonadism was defined as a testosterone level less than 8 nmol/L and LH greater than 12 IU/L. With a median follow-up of 11 years, the age-adjusted odds ratio for hypogonadism was 2.0 for surgery only (95% CI, 0.9–4.2), 5.0 for radiotherapy (95% CI, 1.8–7.0), 4.8 for 850 mg or less of cisplatin (95% CI, 2.4–9.5), and 7.9 for greater than 850 mg of cisplatin (95% CI, 3.6–17.4).\textsuperscript{25} A second study from the United Kingdom examined 680 TC survivors also stratified by treatment modality: orchiectomy alone, orchiectomy plus radiotherapy, orchiectomy plus chemotherapy, or orchiectomy plus...
both chemotherapy and radiotherapy. Low testosterone (< 10 nmol/L) was noted in 11%, 15%, 13%, and 34% of patients in these groups, respectively. Increased LH (> 12 IU/L) was shown in 6%, 11%, 10%, and 22% of patients in these groups, respectively. Patients treated with orchiectomy plus chemotherapy or radiotherapy had higher mean LH levels than those treated with orchiectomy alone, but did not have significantly different serum testosterone levels. However, patients treated with orchiectomy plus chemotherapy and radiotherapy had a significantly greater risk of low testosterone levels. Together, these studies show that in patients treated with surgery alone, hypogonadism is uncommon. After chemotherapy, the risk of hypogonadism may be higher and is influenced by treatment intensity.

Hypogonadism in the aging male is associated with multiple complications, including an increased risk of developing osteoporosis, metabolic syndrome, type 2 diabetes, and cardiovascular disease. In addition, hypogonadism is associated with a decreased quality of life. Studies have been performed to determine the clinical significance of hypogonadism in long-term TC survivors. A recent study assessed hormonal and skeletal status in 879 long-term survivors. In 823 unilateral TC survivors at a median follow-up of 96 months, testosterone deficiency was observed in 19.5% and increased LH was seen in 19.1%. Increased serum collagen type 1 cross-linked C-telopeptide (S-CTX) was noted in 44% and osteopenia or osteoporosis in 50.6%. In 56 bilateral TC survivors at a median of 175 months, testosterone deficiency and elevation of LH were noted in 83.9% and 80.4% of patients, respectively. S-CTX was increased in 55.4%, and osteopenia or osteoporosis in 73.2%. However, a study of 64 TC and 51 lymphoma male survivors treated with chemotherapy showed no difference in testosterone, LH, or bone mineral density at a median follow-up of 4.1 years. TC survivors have also been reported to have an increased risk of metabolic syndrome and cardiovascular disease. Metabolic syndrome comprises insulin resistance, hypertension, dyslipidemia, and abdominal obesity. It is associated with cardiovascular morbidity and mortality, and has been described as a late complication among TC survivors. In a study of 589 survivors who had unilateral orchiectomy, the prevalence of metabolic syndrome and hypogonadism was higher in patients who were treated with chemotherapy than in those treated with surgery alone.

In a few studies, hypogonadism in TC survivors has been associated with diminished quality-of-life. In the large United Kingdom study described earlier, low testosterone levels were associated with lower physical, social, and role functioning on the EORTC Qly C-30 scale, and with lower quality-of-life scores related to sexual functioning. In another study of 326 TC survivors, those with elevated LH had higher levels of depression, more sexual problems, and diminished physical well-being. However, several recent studies examining quality of life in long-term survivors of TC indicate that they report high levels of quality of life, approximately the same as the general population. Improved quality of life may be the result of improvements in treatment regimens, resulting in fewer long-term effects and a better understanding of the mechanisms that cause hypogonadism and infertility, which lend themselves to interventions that alter the long-term picture for these survivors.

No evidence-based guidelines exist for practitioners on screening patients with TC for hypogonadism. Obviously, in patients who undergo bilateral orchiectomy, androgen replacement is necessary and associated with an improvement in quality of life. More research is needed to examine hypogonadism in long-term survivors of TC to provide the evidence necessary to guide practitioners caring for this population. If hypogonadism is documented, testosterone replacement can be achieved using transdermal preparations with excellent results. Other modes of testosterone replacement are available, including injectable, oral, transbuccal, and pellet preparations, with associated risks and benefits. Historically, transdermal therapy has been the safest, least invasive, most effective mode with the fewest side effects.

Association Between Fertility and TC
The evidence supporting TDS was reviewed in a 2001 article by Skakkebaek et al. TDS is hypothesized to include poor semen quality, TC, undescended testicles, and hypospadias. However, the complexity of pathogenic and epidemiologic features of each of these disorders make their manifestation dif-
Fertility and Treatment for TC

The effect of cancer treatment on the fertility and overall paternity rates among TC survivors is a potentially significant issue. At diagnosis, an estimated 10% to 35% of men have experienced infertility, and 50% of this population have abnormal semen analyses. The effects of chemotherapy on fertility are divided into those that affect endocrine testicular function and those that have a direct impact on spermatogenesis through damaging the spermatogenic epithelium and Sertoli cells, with the cumulative dose significant for its effect of spermatogenesis, at least temporarily. RPLND may be associated with retrograde ejaculatory dysfunction, which may result in infertility. However, the effect of RPLND on fertility has decreased significantly with the development of nerve-sparing techniques. Improperly delivered radiation therapy may also affect fertility through impairment of spermatogenesis and, in some cases, such as when given for CIS, cause permanent sterility. However, recent studies have shown that improved radiation techniques will lead to a minimal to no effect on fertility in TC survivors.

Most of the studies examining fertility in TC survivors have been performed outside of the United States in European populations. Consequently, the impact of culture and treatment modalities specific to the United States was not considered. In addition, many of these studies used a case-only study design and/or had small sample sizes. Studies exist that report a reduction in overall paternity rates among TC survivors compared with the normal population, identifying cancer treatment–induced azoospermia or oligospermia, dry ejaculation, and/or abnormal function of the remaining testicle as the causal issues. The psychological impact of a cancer diagnosis has also been identified as a contributing factor.

Studies dating back to 2001 suggest that the chances for TC survivors achieving paternity are good, with recovery of spermatogenesis in approximately 50% of patients after 2 years and 80% after 5 years. In fact, a 2010 study reported an overall 85% actuarial paternity rate at 15 years posttreatment. These studies and more dispute the hypothesis that paternity rates are compromised among TC survivors. Several factors must be considered before attributing posttreatment fertility issues to treatment modalities, and although treatment for TC can lead to increased risk for compromised fertility, increasing evidence shows that TC survivors in the United States are no less likely to father children than other men. This finding was reported in the first case control study to systematically assess fertility after treatment for TC conducted in a population of men born in the United States (246 cases, 236 controls). Study participants were enrolled in the U.S. Servicemen's Testicular Tumor Environmental and Endocrine Determinants study between 2002 and 2005. The study subjects were 46 years of age and younger and had at least one serum sample stored, and their diagnoses were limited to classic seminoma or nonseminoma (embryonal, yolk sac, choriocarcinoma, teratomas, and mixed germ cell tumors). All cases were diagnosed at least 5 years before enrolling in the study. Results determined that men with TC expressed greater concern about fertility, had a higher likelihood of undergoing fertility testing, and admitted to having difficulty fathering children. However, TC survivors were no less likely
to father children than controls. The study noted that fertility treatments used to assist study participants in fathering children were not examined and should also be considered.4

Conclusions

Men with TC may have reduced fertility before and after diagnosis, and infertility has been shown to be a risk factor for developing TC. The genetic origins of male infertility and TC combined with the biologic mechanisms underlying TDS have established a possible connection among hypogonadism, male infertility, and TC. This association puts into question the hypothesis that TC survivors have a higher rate of infertility related to treatment. Hypogonadism and fertility cause and effect in TC survivors are difficult to accurately assess unless fertility or endocrine evaluations were performed before diagnosis and treatment.

Evidence shows that with improved treatment modalities, including the nerve-sparing RPLND and more targeted radiation therapy, the risk of infertility is declining. The role of improved reproductive assistance must also be considered when examining improved fertility rates. In addition, cisplatin-based chemotherapy has significantly increased survival in patients with TC, and although toxic effects can persist long after the end of chemotherapy, the effect on fertility and hypogonadism is most likely far less than it was historically thought to be. Evidence has shown that spermatogenesis returns in most cases within 2 to 3 years, and that the infertility and hypogonadism noted in many TC survivors is in many cases caused by preexisting issues.

Further investigation of the biologic mechanisms underlying hypogonadism, fertility, TC, and other genital urinary defects, and any associations among these entities, will contribute to a better understanding of the role treatment modalities play in hypogonadism and infertility in TC survivors. This knowledge will be invaluable in guiding providers and improving the evaluation, management, and follow-up care of these long-term cancer survivors.

References

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