Urological Survivorship Issues Among Adolescent Boys and Young Men Who Are Cancer Survivors

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ABSTRACT

Background: Urological survivorship issues encompass an area that may potentially be overlooked after treatment of childhood cancer in adolescent boys and young men. Side effects of cancer therapy may include subsequent development of erectile dysfunction (ED), hypogonadism, and infertility in adulthood.

Aim: The purpose of this review is to focus on the etiology and prevalence of the range of sexual and gonadal dysfunction in adolescent boys and young men who are cancer survivors, while discussing current recommendations for evaluation and treatment.

Methods: We performed a literature review of articles evaluating hypogonadism, sexual dysfunction, ED, and infertility in young men cancer survivors.

Outcomes: There is compelling evidence that significant survivorship issues are faced by boys entering adulthood after completing cancer therapy.

Results: Overall, young men cancer survivors are much more likely to report symptoms of sexual dysfunction than the general population of men. These patients can develop ED due to physiologic and psychological changes that take place with diagnosis of a malignancy and subsequent treatment. Primary hypogonadism can arise due to pelvic radiation or chemotherapy, and central hypogonadism may arise from pituitary insufficiency after brain radiation or surgery. Infertility develops from direct damage to the Sertoli cells and germinal epithelium from radiotherapy or chemotherapy. Cancer survivors who are men should therefore be screened for these important urological survivorship issues, although exact surveillance strategies remain unclear.

Conclusions: Urological survivorship issues including ED, hypogonadism, and infertility are common among cancer survivors and result in significant morbidity. Due to the medical complexity of cancer survivorship, the population of adolescent and young adult survivors would benefit from a network of multidisciplinary survivorship experts to aid the transition into adulthood. Improved research efforts may help to clarify risk factors and to develop enhanced strategies for evaluation and treatment. **Sukhu T, Ross S, Coward RM. Urological Survivorship Issues Among Adolescent Boys and Young Men Who Are Cancer Survivors. Sex Med Rev 2018;6:396–409.**

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Key Words: Sexual Dysfunction; Cancer Survivorship; Hypogonadism; Erectile Dysfunction; Infertility

INTRODUCTION

Improvements in the treatment of childhood cancer have had a notably positive impact on survival rates. In fact, more than 80% of children diagnosed with cancer will survive long term.[1] To date, there are over 400,000 survivors of childhood cancer in the United States.[2] Treatment of childhood cancer can result in long-term medical problems, including urological issues such as sexual dysfunction, hypogonadism, and infertility, as well as mental health issues that may also impact these urological problems. As adolescent boys and young men survive their disease, it is important to evaluate for and address these sensitive but important medical issues that can be overlooked in this population.

These patients are often not followed up in an organized manner after their acute treatment is completed. In addition, it is rare to have planned transition of care, thus leaving primary care physicians to address the post-survival sequelae of chemotherapy and radiation treatment. While some physicians may be familiar with common side effects of cancer treatment such as lung and heart disease, many may be unaware of the details of their

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patient's cancer protocols and the complex urological issues that can follow.[3,4] The combination of poor transition options, various protocols, and variable side effects often leave urological problems unaddressed.

Without increased awareness of these complications, the burden of addressing post-cancer urological diseases may unfortunately fall on the patient. While patients are expected to remember discussions of the sequelae of their cancer treatments, it is well established that the stress of a cancer diagnosis, coupled with the mental and physical stress of therapy, most often results in a loss of these detailed discussions. Patients and families often do not remember side effects such as gonadal dysfunction.[5] Additionally, during treatment, the specifics of quality-of-life survivorship sequelae such as sexual health issues may not be sufficiently reviewed by medical providers who are understandably more focused on cancer survival. Lastly, some urological symptoms do not arise until many years after the patient's curative treatment. Young adults must face survivorship issues just as they are transitioning to adulthood and beginning to focus on educational and career goals, establish new relationships, consider children, and focus on financial independence. In some cases, increased focus on these other aspects of life may result in a low importance being placed on dealing with their medical care, and physicians must be the ones to decipher the issues and help prioritize them.[6]

Ideally, these complex patients should have a primary care provider who can coordinate with needed subspecialists in order to provide comprehensive follow-up cancer care. There are models of multidisciplinary care and guidelines in place for long-term follow-up of childhood cancer survivors that can help to elucidate the responsibilities of primary and subspecialty health care providers.[7,8] Multiple studies have focused on the aspect of infertility in this population; however, there is very little emphasis on sexual dysfunction and hypogonadism in boys and young men who are survivors of childhood cancers. In this review, our goal is to focus on the etiology and prevalence of the range of sexual problems, gonadal dysfunction, and infertility in these patients, while discussing current recommendations for evaluation and treatment.

SEXUAL DYSFUNCTION

Etiology

Sexual health has been defined as the physical, emotional, mental, and social well-being in relation to sexuality, which can affect global health of the patient.[9] Despite the relationship between sexual health and overall health, little is known about sexual function in adolescent boys and young men who survive childhood malignancies.[10] As the number of survivors rises, it will be increasingly important to recognize the sexual difficulties these patients confront.

It is clear there are direct associations between curative treatments for cancer and damage to sexual organs, leading to sexual dysfunction and future problems with intimacy and self-esteem.[11,12] Overall, cancer survivors are 3 times more likely to report sexual issues than the general adult population.[13] 2 Common causes of sexual dysfunction in this population are hypogonadism due to gonadal, hypothalamic, or pituitary injury, or direct damage to pelvic nerves and vessels.[14] The effect of hypogonadism can be seen in testicular cancer survivors, where it is clear that low testosterone has a negative effect on the quality of the sexual experience.[15] Men treated for hematologic malignancies with mild Leydig cell dysfunction experience similar effects and are likely to have less sexual activity.[16] In 1 study of 599 survivors who completed standardized tools, 32% of male survivors disclosed a problem in 1 or more areas of sexual function, with these individuals more likely to experience distress linked to sexual difficulties (Table 1).[12]

Types of Sexual Dysfunction

Sexual difficulties for the young men who are survivors can vary. They may experience pain with erections or orgasm, trouble achieving an orgasm, premature ejaculation, or erectile dysfunction (ED).[14] However, ED and premature ejaculation are reportedly the most common sexual problems.[17] Psychosocial factors may also strongly contribute to sexual problems in this population. Studies demonstrate that the diagnosis of a malignancy at a young age can have a negative impact on sexual identity and psychosexual development.[11,18] The fear of being treated differently by peers due to the diagnosis and treatment of cancer can affect psychosexual development and disturb the maturation of normal sexual behaviors such as masturbation, dating, and discussion of sex with peers.[18–20] These sequelae further delay normal relationships typically formed through dating, participation in sexual activity, and marriage.[12,21] Although the majority of young men who are cancer survivors are sexually active, they are less likely than their siblings to have had a sexual experience in the past year.[22] While this could be due to many factors, and attributing this to their cancer diagnosis or treatment is unsubstantiated, it is an interesting finding that should be explored in future studies.

Many cancer survivors develop a negative body image during treatment that persists and prevents development of their sexual identity, thus creating an additional barrier to normal sexual function.[23] When assessing the quality of life and psychosocial well-being of acute lymphoblastic leukemia survivors, treatment of cancer has been shown to result in low physical functioning and emotional well-being compared to the general population.[24] A negative body image may stem from physical features that result from treatment, such as stretch marks and scars. In addition, shortened height or delayed puberty can result from treatment, and may result in poor self-esteem and increased feelings of isolation or being different from peers.[12,25,26] The absence of a sexual identity can delay involvement in physical and emotional intimacy, isolating these patients socially.

Table 1. Summary of Sexual Dysfunction After Pediatric Oncology Treatment

	Etiology	Prevalence	Surveillance	Evaluation	Treatment
Sexual dysfunction	• Hypogonadism, which can also negatively affect the quality of the sexual experience • Damage to pelvic nerves and vessels from surgery or radiation • Direct gonadotoxicity from radiation or chemotherapy	• 32% of Men survivors disclose a problem in 1 or more areas of sexual function[12]	• No formal recommendation exists for the appropriate timing of sexual health evaluation • Survivors with prior radiation to the testes or pelvis, surgery involving the spinal cord or pelvis, or hypogonadism should have a sexual health evaluation	• Gauge sexual function based on sexual arousal, erection quality, ability to obtain an orgasm, satisfaction with sexual intercourse, and any pain symptoms • Utilize tools such as Male Sexual Heath Questionnaire and International Index of Erectile Function	• Formal sex education may alleviate insecurities • More extensive therapy can be provided via physical or psychosocial rehabilitation • Address through a pharmacologic and non-pharmacologic approach • Consider referral to a sexual health expert and involvement of a sexual health counselor or mental health therapist

Evaluation

Young men who are cancer survivors should have an evaluation of sexual health, especially those previously treated with radiation to the testes or pelvis, surgery involving the spinal cord or pelvis, and diagnosed with hypogonadism.[27] Providers should gauge sexual function based on a discussion of sexual arousal, erection quality, ability to obtain an orgasm, satisfaction with sexual intercourse, and pain symptoms.[6] Surveys such as the International Index of Erectile Function (IIEF) are excellent tools and can be utilized as a validated assessment of erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction.[28] Unfortunately, there is no formal recommendation about the appropriate frequency or length of evaluation of sexual health. If evaluation is difficult or if patients prefer, providing formal sex education may help alleviate some of the insecurities these patients experience. In a retrospective review, over 10% of adolescent childhood cancer survivors did not recall receiving any official sex education in the past, so incorporation of this as part of their comprehensive cancer care may be beneficial.[29] More extensive therapy can be provided via physical or psychosocial rehabilitation. Similar to other areas of cancer treatment, it is generally suggested that sexual dysfunction be addressed though a multidisciplinary approach involving both pharmacologic and non-medicinal therapies that specifically target that patient's concerns.[6] Referral to a physician specializing in sexual health may be helpful in complex cases, and a sexual health counselor or mental health therapist can be a highly valuable asset to the treatment team.

ERECTILE DYSFUNCTION

Prevalence

ED is defined as the inability to achieve an erect penis as part of the overall process of male sexual function.[30] The Cross-National Survey on Male Health Issues was a population-based, international survey for men in 6 counties that sought to better understand men's health issues, including ED. Over 32,000 men completed the survey and found a prevalence of ED in 4–6% of men younger than 40 years of age, indicating that ED was a meaningful problem even in the general population of young, healthy men.[31] The prevalence of ED in this study was determined based on a positive response to the question of "difficulty getting or keeping an erection." Unfortunately, ED is more prevalent for young cancer survivors, with a significantly higher relative risk (RR) for ED (RR 2.63, 95% CI 1.40–4.97) based on the IIEF-erectile function (EF) scores of cancer survivors compared to siblings.[22] In the Childhood Cancer Survivor Study cohort, the prevalence of ED was 12.3% (95% CI 10.4–14.3) of survivors and 4.2% (95% CI 2.0–7.9) of siblings, based on IIEF-EF scores lower than 25 out of 30 (Table 2).[22] Generally, ED is not often identified in the population of young men. Because of the sensitive nature of the topic, many patients may feel too ashamed to discuss this problem with health care providers. In fact, the youngest group of patients

Table 2. Summary of Erectile Dysfunction After Pediatric Oncology Treatment

	Etiology	Prevalence	Surveillance	Evaluation	Treatment
Psychogenic ED	• Mental stresses of a cancer diagnosis and treatment can contribute to ED • Survivors are more likely to have mental health disorders • SSRIs can cause sexual dysfunction due to serotonergic activity	• 30% of All patients on anti-depressants describe difficulty achieving arousal or lack of orgasm[37] • 67% of All patients on psychiatric medications report decreased libido and delayed orgasm[36]	• Obtain a sexual history after surgery or radiation involving the spinal cord, lumbosacral nerves, or pelvis	• Inquire about erectile function or utilize validated questionnaires (eg, IIEF-EF) in patients with mental health symptoms	• Address the psychological symptoms first, which may reduce need for invasive medical and surgical treatments • Consider targeted education to promote awareness and understanding of the disease process
Organic ED	• Chemotherapy, especially alkylating agents can cause direct toxicity of nerves and vasculature leading to angiopathy ad ischemia • Radiation >10 Gy to the genitals can lead to Leydig cell damage or toxicity to nerves and blood vessels[22]	• In survivors, the prevalence of ED was 12.3%, based on IIEF-EF scores less than 25 out of 30[22]	• Obtain a sexual history following surgery or radiation similar to psychogenic ED	• Providers can either discuss this issue directly or evaluate with validated questionnaires (eg, IIEF-EF) • Serum hormone testing to evaluate for hypogonadism in those with history of radiation or chemotherapy is often helpful	• PDE5 inhibitors are the first-line treatment • Consider referral to sexual medicine provider for second-line therapies such as vacuum erection devices and intracavernosal injections • Penile prosthesis placement is an option after failing other therapies

ED = erectile dysfunction; IIEF-EF = International Index of Erectile Function-erectile function; PDE5 = phosphodiesterase type 5; SSRI = selective serotonin reuptake inhibitor.

(20−39 years) in the Cross-National Survey on Male Health Issues was negatively associated with seeking treatment for ED ($P < .001$) and more likely to refuse seeking treatment secondary to embarrassment.[31] It is important that providers are not only aware of the possible presence of ED in the young cancer survivor, but also either discuss this issue or screen with validated questionnaires and laboratory testing. In addition, these young men may be aided by a targeted education to promote awareness and understanding of their disease process.

Etiology

The etiology of ED is often multifactorial and may stem from a combination of neurologic, psychological, anatomical, vasculogenic, or endocrine disturbances.[32] For the young man who is a cancer survivor, psychological factors may play a larger role than previously appreciated. The mental stresses of a malignancy diagnosis coupled with the side effects of treatment can impact the ability of the patient to obtain and maintain an erection. Childhood cancer survivors are more likely to have mental health disorders than others, with 17% having symptoms that were somatic or consistent with depression/anxiety.[33] It has been shown that both depression and anxiety are significant psychiatric risk factors and predictors of ED in young men ($P < .001$) based on a correlation between IIEF scores and a validated psychological questionnaire.[34,35] In addition, 20% of these survivors have symptoms of post-traumatic stress disorder as a young adult, which can be triggered by increased anxiety or arousal.[36,37] Compounding the problem, medications such as selective serotonin reuptake inhibitors used to treat depression, anxiety, and post-traumatic stress disorder can actually exacerbate sexual dysfunction in a substantial population due to serotonergic activity.[38] In a multicenter, cross-sectional study, 30% of patients on anti-depressants described difficulty achieving arousal or lack of orgasm, while almost two-thirds reported frequent decreased libido and delayed orgasm.[39] However, only 37% of these patients with sexual dysfunction reported this spontaneously, meaning the provider should lead investigation of these issues. Treating physicians should first address the psychological issues, as correcting these first may avoid more invasive medical and surgical treatments.[40]

The physiological impact of the adverse effects from radiation, chemotherapy, or surgery can significantly influence sexual function.[19] Historically, alkylating agents have been associated with Leydig cell damage and dysfunction, thus leading to primary hypogonadism and low testosterone. Low testosterone is clearly associated with ED, so the assumption has been that the use of alkylating agents may result in ED in this population.[41] However, when performing a retrospective review of boy survivors in the Child Cancer Survivor Study, investigators did not find an association between high-dose alkylating agents and ED.[22] Additionally, they believed this result could not be explained by testosterone supplementation, as they did not find a high rate of use. While more studies are needed, it is still reasonable to evaluate for ED when high-dose chemotherapeutic agents have been used in cancer treatment.

The etiology of ED related to chemotherapy is likely due to direct toxicity of nerves and vasculature, but still remains indeterminate.[42] In addition to alkylating agents, chemotherapeutic agents such as vincristine and cisplatin potentially harm the blood vessels and nerves that facilitate erectile function.[43] A possible mechanism of ED is angiopathy resulting in arteriolar damage and ischemic events, similar to that which leads to Raynaud phenomenon in chemotherapy patients.[44,45] In animal studies, there is evidence of collagen propagation, alteration of the vascular endothelium, and decreased arteriolar diameters in those treated with chemotherapy, which may explain why ED was described more often in non-seminomatous germ cell tumor survivors with Raynaud phenomenon.[43,46]

In the Childhood Cancer Survivor Study cohort, investigators found significant changes in IIEF-EF scores in men who received radiation to the testes as boys with doses as low as 10 Gy.[22] This demonstrates an increased susceptibility to damage relative to men, in whom higher doses (50 Gy) to the penile bulb are required to induce major effects on erectile function.[47] ED is also strongly associated with pelvic or spinal surgery based on IIEF-EF scores of boy survivors of the Childhood Cancer Survivor Study 5 years after treatment. Damage to the neurovascular bundles originating from the pelvic plexus or to the pelvic plexus itself may also contribute to ED.[48] Pelvic surgery more than doubles the risk, surgery involving the spinal cord triples the risk, and prostate surgery is associated with greater than 6 times the RR of ED among survivors, when ED is defined as IIEF-EF scores less than 25.[22]

Treatment

There are multiple treatment options for ED in young men who are cancer survivors and experience psychological or physiologic ED. Phosphodiesterase type 5 (PDE5) inhibitors such as sildenafil and tadalafil are a good first-line treatment option in this population. When evaluating 76 testicular cancer patients with a mean age of 29 years and mean IIEF-EF score of 16, 88% of patients responded to PDE5 inhibitor use with erections sufficient for penetration (increasing the mean IIEF-EF score to 27, indicating normal erectile function), suggesting this is an excellent treatment option in this population.[49] Alternatively, vacuum erection devices with or without a constriction band may be a less expensive option and provide adequate erections. Patients may be treated with intra-urethral suppositories or intracavernosal injections for more severe ED. After treatment with PDE5 inhibitors, these second-line treatment options could be discussed by the primary care physician or oncologist, although referral to a sexual medicine provider for detailed evaluation prior to treatment with these therapies is warranted. Lastly, it would be rare for young men to have medically refractory ED requiring placement of a penile prosthesis, but the 3-piece inflatable prosthesis remains a highly effective and satisfying option in men

who have failed all other therapies. In a study by Wilson and colleagues[50] looking at inflatable implants 10 and 15 years following initial implantation of the prosthesis, they found 98% of patients were satisfied.

HYPOGONADISM

Prevalence

One of the most common survivorship issues young men face after childhood cancer treatment is hypogonadism. This is a clinically complex condition consisting of the inability to produce functional levels of testosterone or sperm, although by convention generally only refers to testosterone production.[51] Clinically, hypogonadism manifests with ED, sexual dysfunction, low libido, fatigue, loss of muscle mass, and eventually osteoporosis.[52] Hypogonadism may be a primary issue due to direct gonadotoxicity after radiation or chemotherapy, or a central issue with pituitary insufficiency after brain radiation or surgery.[6] For boys who survive childhood cancer, hypogonadism is most often due to radiation therapy or chemotherapy affecting the gonads. This effect is seen despite the fact that when compared to Sertoli cells, Leydig cells are typically more resistant to cancer treatments.[5,53] There is an estimated 7-fold increase in the odds that a young man who is a cancer survivor will have hypogonadism, with a prevalence of 23% in a Swedish childhood cancer survivor cohort treated for malignancy prior to 18 years of age, compared to 4.3% in age-matched controls (Table 3).[54]

Hypogonadism Secondary to Radiation

Radiation works by directly inducing breaks in DNA strands, which can lead to apoptosis in the targeted radiation field and any peripheral tissue subjected to scatter.[55] Studies have demonstrated that the timing of long-term endocrine effects secondary to radiation can vary depending on the period of time it takes cells to duplicate.[56] Thus, the consequences of radiation such as hypogonadism can present between 3 months to as long as 10 years after therapy.[57]

Irradiation with doses of 12 Gy can cause subclinical Leydig cell dysfunction, while doses of 24 Gy lead to more substantial Leydig cell damage requiring androgen replacement.[58–60] For the boy or young man undergoing radiotherapy, the testicles are particularly radiosensitive and can sustain significant gonadal dysfunction. For boys who have not reached puberty, testicles irradiated with doses greater than 20 Gy can result in Leydig cell dysfunction. For older post-pubertal boys, slightly higher dosages of 30 Gy can significantly impact Leydig function and increase the risk of hypogonadism.[53] Therefore, it is not surprising that boys who are cancer survivors and receive gonadotoxic radiation in the pre-pubertal and peri-pubertal age ranges may have higher rates of subsequent gonadal failure.

Alternatively, central or hypogonadotropic, hypogonadism can occur following radiation to the brain at high doses or even from neurosurgical procedures. This rarely transpires after exposure of the hypothalamus and pituitary to doses less than 40 Gy, but there is a progressive increased risk after doses above 50 Gy.[61,62] Interestingly, a cross-sectional survey evaluated over 1,100 men who were cancer survivors with a median age of 22 years who were hypogonadal after neurosurgical intervention, and none of the brain tumors were located close to the pituitary gland or the hypothalamus.[54] Therefore, any man with symptoms of hypogonadism who has undergone brain radiation or surgery should be thoroughly evaluated for pituitary insufficiency.

Hypogonadism Secondary to Chemotherapy

Young men with cancer treated with cyclophosphamide or other alkylating agents are at high risk of later developing hypogonadism.[63] Alkylating agents disrupt the function of DNA and lead to cytotoxicity of actively replicating cells, such as those in the peri- and post-pubertal reproductive development time period. However, the exact mechanism of Leydig cell damage is unknown. Chemotherapy may indirectly affect Leydig cells via germinal epithelial damage. There is evidence that germinal cell damage can cause decreased testicular volume and blood flow.[64] Testosterone production by the testicles is directly impacted by reduction in testicular blood flow since it is reliant on testicular venous and arterial testosterone concentration gradients.[65] If there is decreased testicular blood flow, this can reduce stimulatory response to luteinizing hormone (LH). It is also hypothesized that decreased testicular volume and germinal epithelium damage can lead to testicular structural defects or impairment of paracrine control of Leydig cells, further causing poor Leydig cell performance.[66,67]

Although the exact mechanisms for Leydig cell damage remain unclear, it is evident that boys treated with chemotherapy for hematological cancers have a higher rate of gonadal failure. Indeed, in a retrospective review of patients at the National Cancer Center in Korea, 11% of boys who survived childhood lymphoma had complete gonadal failure, with 8% having testosterone levels below 325 ng/dL and a testicular volume of less than 15 mL.[29] The patients were younger than 20 years old when diagnosed with malignancy and more than 2 years had passed since treatment, with an age range of 15–30 years at the time of the study. Young men treated for testicular cancer also experience hypogonadism, with significantly lower testosterone and higher gonadotropin levels following orchiectomy, prior to any other therapy.[15] Aass et al[68] from Norway demonstrated that 16% of patients had low testosterone 2–4 years following treatment with various modalities. A retrospective review of young men who survived testicular cancer in Norway found that at 10 years following chemotherapy, testosterone levels were significantly lower than controls. Within 2 decades, 60% of patients in the treatment group had testosterone levels in the bottom quartile of age-matched controls.[52] It is estimated that up to 75% of testicular cancer survivors have an elevated LH level, while two-thirds have increased follicle stimulating hormone, indicating a high frequency of some degree of gonadal

Table 3. Summary of Hypogonadism After Pediatric Oncology Treatment

	Etiology	Prevalence	Surveillance	Evaluation	Treatment
Secondary (central) hypogonadism	• May occur following radiation exposure of the hypothalamus and pituitary to doses less than 40 Gy • Progressive increased risk for doses above 50 Gy • May also occur following neurosurgical intervention	• Estimated 7-fold increase in the odds that an adolescent cancer survivor will have hypogonadism[52] • Prevalence of 23% in those treated for malignancy prior to 18 y of age[52]	• If exposed to total body radiation, measure Tanner stage and testes volume • Obtain morning testosterone and LH levels in post-pubertal survivors for any signs of hypogonadism or borderline testosterone	• If low testosterone is suspected, obtain morning total testosterone and LH levels in order to determine whether it is primary or secondary (central) hypogonadism • A low testosterone with low LH confirms primary hypogonadism • For central hypogonadism, also obtain serum prolactin, iron saturation studies, and estrogen	• Treatment of central hypogonadism can be accomplished with gonadotropins • Human chorionic gonadotropin is the most physiologic and effective choice for central hypogonadism
Primary hypogonadism	• Testes irradiation with doses of 12 Gy can cause subclinical Leydig cell dysfunction • Doses of 24 Gy can lead to substantial Leydig cell damage requiring androgen replacement[58] • Alkylating agents lead to cytotoxicity of Leydig cells	• 11% of Young men survivors of childhood lymphoma have complete gonadal failure[29] • 13% of Testicular cancer survivors have subnormal testosterone or receive testosterone replacement[15]	• If exposed to testicular radiation, Tanner stage and testes volume should be measured • Obtain morning testosterone and LH levels in post-pubertal survivors for any signs of hypogonadism or borderline testosterone	• If low testosterone is suspected, obtain morning testosterone and LH levels in order to determine whether it is primary or secondary (central) hypogonadism • A low testosterone with high LH confirms primary hypogonadism	• Anastrozole is beneficial for low testosterone and a low testosterone to estrogen ratio • Off-label use of clomiphene citrate can improve low testosterone levels while preserving spermatogenesis • Exogenous testosterone may be required for symptomatic primary hypogonadism, but has a detrimental effect to fertility

LH = luteinizing hormone.

dysfunction in this population.[69,70] A cross-sectional study of 680 long-term survivors of testicular cancer in England who had received any combination of surgery, chemotherapy, or radiation demonstrated that greater than 13% of survivors had either subnormal testosterone or were on testosterone replacement therapy.[15] The considerable risk of hypogonadism in this population suggests that screening for gonadal dysfunction should be routinely included in follow-up for these childhood cancer patients.

Sequelae of Hypogonadism

Gonadal failure has a significant impact on long-term male health. Effects on sexual function, mental health, and increased risk of osteoporosis and metabolic disorders all have a great impact on quality of life and physical well-being. The sequelae of low testosterone put men at risk for cardiac disease by impacting important factors such as body mass index and blood pressure.[15] Greenfield and colleagues[71] found an association between low testosterone levels and increases in fat mass and insulin levels compared to age-matched controls in 13.6% of young men who were cancer survivors. These findings suggest an increased risk of developing metabolic syndrome, which may further impact overall health.[71] It is well established that hypogonadism can lead to poor sexual function, infertility, and mental health issues such as depression.[72,73] European testicular cancer survivors with increased LH levels had significantly more depression symptoms and a decrease in sexual function on validated questionnaires 2 years following treatment. The authors additionally reported that any abnormal gonadotropin in this patient population was associated with a lower level of self-reported physical well-being on linear regression ($P = .028$).[74] Based on these findings, it is not surprising that men successfully treated for acute lymphoblastic leukemia with cyclophosphamide or testicular irradiation had a heightened risk for psychiatric morbidity ($P = .016$) based on responses to the General Health Questionnaire 12, which was designed as a screening tool for psychiatric illness in the general population.[75] A third of the patients in radiation and chemotherapy groups screened positive for possible psychiatric illness, compared to 0 patients in the group that did not receive either type of therapy.[24] Additionally, exposure to either of those treatments lead to approximately a 20% decrease in emotional well-being and 25% decrease in energy/fatigue quality-of-life scores on the RAND-36 questionnaire, which aims to evaluate 8 subscales of long-term health outcomes.[24,76]

Surveillance

While more studies are needed to better understand short- and long-term effects of radiation and chemotherapy treatment effects on the overall health of young men who were cancer survivors, it is clear that screening these patients for androgen deficiency is necessary, especially in the presence of symptoms such as decreased libido and ED, or physical exam findings such as reduced testicular volume or lack of virilization.[54] While there is currently no consensus on how these patients should be evaluated, a group of experts in multiple medical specialties called the International Late Effects of Childhood Cancer Guideline Harmonization Group is working together to provide evidence-based surveillance recommendations for gonadotoxicity in young men who are cancer survivors.[27] Thus far, there has been agreement that cancer survivors who received treatment with potential gonadotoxicity should receive counseling about future health risks, specifically including the risk of testosterone deficiency.

Surveillance recommendations suggest taking a sexual history for survivors who have undergone surgery or radiation involving the spinal cord, sympathetic nerves, or pelvis.[27] Furthermore, they recommend that any survivor who has undergone testicular radiation of 12 Gy or total body radiation should have Tanner stage and testicular volume measured in addition to obtaining an early morning testosterone level in post-pubertal survivors, with a LH level checked for any signs of hypogonadism or borderline testosterone. However, all of these recommendations are solely based on expert opinion likely due to the lack of research concerning hypogonadism in boys who survive childhood cancer.[27] In spite of these recommendations, there continues to be demand for algorithmic surveillance that specifies the duration and frequency of surveillance based on variables such as patient age and treatment protocols.[27] A lack of awareness about this issue may contribute to the dearth of research. This is best demonstrated by the complete absence of these survivors in a listing of groups identified by the Endocrine Society clinical practice guidelines as being high risk for hypogonadism.[54,77] This may change as the medical community becomes more aware of the risk and potential seriousness of hypogonadism and the impact it has on the overall health of these patients.

In addition to a morning total testosterone level, the laboratory evaluation of the hypogonadal man should include assessment of LH in order to determine whether it is primary or secondary hypogonadism. Typically, primary hypogonadism results from direct gonadotoxic effects from chemotherapy, radiation, orchiectomy, or other pelvic surgery. Secondary hypogonadism can result from pituitary or brain radiation. If there is a low LH level and high suspicion for secondary, or hypogonadotropic hypogonadism, providers should consider obtaining additional pituitary studies including serum prolactin levels, iron saturation studies, and estrogen levels to further elucidate the underlying cause.[78,79]

Perhaps the biggest challenge in terms of surveillance and diagnosis of hypogonadism is creating and maintaining treatment algorithms, which remains a significant challenge even in the hypogonadal man without a cancer treatment history. First, the clinical signs of hypogonadism can be an array of vague symptoms such as fatigue or low energy, which may overlap with various other disorders. There is also a natural decrease in testosterone levels with aging that should be considered during evaluation, and, in many cases, no androgen supplementation is

Table 4. Summary of Infertility After Pediatric Oncology Treatment

	Etiology	Prevalence	Surveillance	Evaluation	Treatment
Infertility	• Can be secondary to damage to the testes, male genitalia, or hypothalamic pituitary axis • Small radiation doses of 0.1 Gy can lead to oligospermia • Radiation doses of 2 Gy or greater may lead to azoospermia • Chemotherapy, particularly alkylating agents, can directly impact spermatogenesis and lead to permanent azoospermia or oligospermia	• More than 50% of men childhood cancer survivors will have some degree of spermatogenesis dysfunction[86] • Up to 24% of long-term survivors have azoospermia or severe oligospermia[96] • Cancer survivors are half as likely to have children as their siblings[87]	• Semen analysis is the gold standard screening test • FSH can be used as a screening test in patients who have refused or cannot provide a semen analysis • An FSH greater than 7 mIU/dL is typically associated with severe spermatogenic defects	• Use semen analysis to evaluate for oligospermia or azoospermia • FSH and inhibin B can be used as part of the endocrine evaluation • Workup is generally not performed until at least 2 y after the completion of cancer therapy	• If the patient has an abnormal semen analysis, refer to a male fertility specialist for discussion of reproductive options or sperm retrieval procedures

FSH = follicle stimulating hormone.

necessary for some hypogonadal men who are otherwise asymptomatic. Lastly, while there is a general agreement for treatment in symptomatic men with sexual dysfunction, this too remains a gray zone requiring individualized care plans and a thorough discussion of the risks and benefits of therapy.

Treatment of secondary hypogonadism can be accomplished with gonadotropins, while testicular failure is much more challenging to treat in young men in order to preserve fertility. Young patients and their clinicians need to be keenly aware that testosterone replacement causes infertility, especially in an at-risk population.[80] It has been suggested that a low normal level of testosterone may be a good target in young and asymptomatic men.[77] Anastrozole is an aromatase inhibitor that has proven to be beneficial in patients with low testosterone when associated with a low testosterone to estrogen ratio, by raising testosterone levels.[81] Human chorionic gonadotropin improves many of the clinical signs of hypogonadism and even when combined with testosterone replacement can preserve spermatogenesis.[82,83] Clomiphene citrate, a selective estrogen receptor modulator, has also been shown to improve low testosterone levels while preserving spermatogenesis. This medication remains a good option for young men with hypogonadotropic hypogonadism interested in maintaining fertility, despite not being approved by the Food and Drug Administration for treatment of hypogonadism.[84,85] The downside of these alternative treatments to exogenous testosterone are that they are much less effective in cases of primary hypogonadism, which is more common in cancer survivors.[80] Young patients with primary hypogonadism face a difficult decision of starting testosterone replacement therapy, which can permanently impair fertility vs continuing to struggle with symptoms and less effective alternative treatments.

INFERTILITY

Background

Fertility is a significant issue for cancer survivors transitioning to adulthood and attempting to start families of their own. It is estimated that more than 50% of boys surviving childhood cancer will be diagnosed with some degree of dysfunction of spermatogenesis based on a large St Jude's cohort study evaluating over 1,700 adult survivors (Table 4).[86] In addition, the proportion of pregnancies that result in live birth are significantly lower for the partners of the male survivors than for the partners of the male siblings (RR 0.79, $P = .016$).[87]

Difficulty achieving a pregnancy can certainly affect the quality of life for these patients and their families. Adolescent cancer patients and their parents should be informed about the possible adverse effect of treatment on long-term fertility and material about fertility preservation should be provided. This conversation should cover the cost, success rates, and the option to decline any preservation or consider adoption as a future alternative.[88] Future fertility should be considered in the treatment plan, and providers should strive to limit any gonadotoxic effects, including possibly amending or delaying treatment

algorithms for a brief period to facilitate preservation of sperm or gonadal tissue. The medical team can attempt to expedite the andrology laboratory visit in order to obtain samples in cases where there is urgent or emergent need for chemotherapy induction.[89] If families are given information about fertility risks and methods of fertility preservation initially, studies support an improved quality of life and less regret about therapies pursued.[6] In addition, 77% of young men with cancer without children reported that they desired having children in the future. However, only 60% said that they were counseled on the risk of infertility from treatment, and only 51% of these patients were offered sperm banking at the time. Sadly, only 24% of men in this survey completed sperm banking and cited lack of information about sperm preservation as the common reason for their lack of participation. In fact, the patients who did have a discussion about infertility had significantly higher rates of sperm banking.[90]

Due to all of these factors, both the American Society of Reproductive Medicine and American Society of Clinical Oncology recommend a thorough conversation about the infertility risk and options for preservation prior to cancer therapy.[91,92] Additionally, both societies recommend that these patients be referred to experts on reproduction prior to undergoing treatment. Despite this, 48% of oncologists report that they either have this discussion with less than a quarter of men in this situation or neglect the conversation altogether.[93] This finding does not appear to be from lack of knowledge, as 91% of oncologists agree that sperm banking should be offered to all eligible men at increased risk of infertility due to cancer treatment. Reasons mentioned for not pursuing this conversation included lack of time, overestimation of cost, and lack of convenient facilities.[93]

Etiology

There are different mechanisms through which cancer treatment can affect fertility—either by damage to the testes, male genitalia, or components of the hypothalamic pituitary axis.[6] Due to the rapid proliferation of spermatogonia, these cells are acutely vulnerable to direct damage from radiation and chemotherapy. Even small radiation doses of 0.1 Gy can lead to oligospermia, with doses of 2 Gy or greater leading to azoospermia.[94] Alkylating agents can directly impact spermatogenesis and independently lead to permanent azoospermia with high doses.[95] One of the most common chemotherapeutic agent classes used in children are anthracyclines, which can have a synergistic effect with alkylating agents to cause long-lasting azoospermia.[53,95] At a median of 21 years after treatment, 53% of childhood cancer survivors who received alkylating agent chemotherapy had azoospermia while 28% had oligospermia.[96] For testicular cancer survivors specifically, 24% of survivors may have permanently diminished spermatogenesis in the remaining testicle on biopsies.[97]

The effect of vincristine, Doxorubicin, and cyclophosphamide chemotherapy was evaluated in a study cohort of pediatric sarcoma patients at the Dana Farber Cancer Institute in order to identify risk factors for infertility.[63] Infertility appeared to be largely driven by exposure to chemotherapy rather than orchiectomy in this population. All patients who underwent unilateral orchiectomy received a similar dose of cyclophosphamide to those who did not undergo orchiectomy, and had the same risk of azoospermia (66%). A dose of cyclophosphamide less than 7.5 g/m^2 was associated with a decreased risk of an abnormal sperm count ($P < .01$). All patients who received a dose above 25 g/m^2 were azoospermic while all patients with exposure <7.5 g/m^2 of cyclophosphamide had normal semen analysis. These semen analyses were performed 5 years after therapy, which suggests that the effect of the treatment appears to be long lasting or permanent.[63] When evaluating young men who survived childhood cancer and received chemotherapy with alkylating agents, there was an increased risk per 1 g/m^2 of cyclophosphamide for azoospermia (odds ratio 1.22, 95% CI 1.11−1.34) and oligospermia (odds ratio 1.14, 1.04−1.25).[96]

Evaluation

The primary method for fertility preservation prior to cancer therapy is semen cryo-preservation.[91] The controversial issues surrounding pediatric and adolescent fertility preservation, the numerous barriers that exist for fertility preservation in this population, and the additional methods for sperm retrieval beyond semen cryo-preservation are beyond the scope of this review. However, in the post-cancer treatment setting, the semen analysis remains the hallmark for the infertility evaluation, which is generally not performed until at least 2 years after the completion of all cancer therapy. The International Late Effects of Childhood Cancer Guideline Harmonization Group recommends semen analysis as the gold standard screening test for survivors inquiring about fertility effects after chemotherapy or radiotherapy.[27] Based on level-B evidence, these guidelines also recommend that an endocrine evaluation including an FSH level can be used in patients who have refused or cannot provide a semen analysis. This may uncover issues with spermatogenesis, as FSH levels have been shown to be significantly higher and inhibin levels significantly lower in testicular cancer survivors who have received chemotherapy.[52]

If low testicular volume or elevated FSH is noted during assessment, there is a high likelihood of decreased spermatogenesis. Despite this, interestingly, 1 report demonstrated that 12 sarcoma survivors were found to be azoospermic despite having normal FSH levels and normal testicular volume on physical exam.[63] A cohort of young men who were survivors exposed to chemotherapy 20 years prior demonstrated that a sum testicular volume less than or equal to 20 mL and elevated FSH greater than 10 mIU/mL were present in only half of the azoospermic survivors.[98]

This suggests the possibility that one can still have an abnormal semen analysis regardless of the lack of clinical findings or other laboratory abnormalities. If the patient desiring fertility in the post-cancer treatment setting has an abnormal semen analysis, he would benefit from referral to a male fertility specialist for discussion of reproductive options or sperm retrieval procedures if necessary. If the semen analysis is abnormal 5 years after treatment it can typically be considered irreparable, although there have been reports of improvement of spermatogenesis in patients up to 7 years after cyclophosphamide therapy.[6,99]

CONCLUSION

Hypogonadism, sexual dysfunction, and infertility occur in a significant proportion of men who are survivors of childhood cancer. These issues are typically the result of cancer-related treatment such as chemotherapy, radiotherapy, and surgery. The impact of these treatment side effects can lead to deterioration of physical and mental well-being. Men who are cancer survivors should therefore be screened for hypogonadism, sexual dysfunction, and infertility based on their prior treatments, although there remain controversy and a lack of consensus on surveillance strategies and treatment. As these complex patients transition into adulthood, they deserve a network of multidisciplinary experts and better research efforts by the medical community to clarify risk factors and to develop improved strategies for evaluation and treatment.

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