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Sexual and Reproductive Consequences of Testicular Cancer

Learning Objective: At the conclusion of this continuing medical education activity, the participant will be able to appropriately counsel patients with testicular cancer about their future fertility potential and discuss pretreatment fertility preservation strategies, educate patients on the risks of testosterone deficiency and sexual side effects of testicular cancer therapies and discuss management options for testicular cancer survivors who have testosterone deficiency or infertility.

This AUA Update aligns with the American Board of Urology Module on Impotence, Infertility and Andrology. Additional information on this topic can be found in the AUA Core Curriculum sections on Oncology–Testis and Sexual Medicine and Andrology.

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INTRODUCTION

Testicular cancer can have a significant impact on a man's health, especially with regard to sexual and reproductive function. Both the disease process itself and the associated treatments can have deleterious effects (see table). This Update focuses on the sexual and reproductive impact of testicular cancer and its treatments.

Testicular dysgenesis syndrome. Testicular dysgenesis syndrome refers to the theory that abnormal fetal development of the testis can lead to a constellation of urological issues later in life including testicular cancer, infertility, hypospadias and cryptorchidism (fig. 1). This theory was developed by Wohlfahrt-Veje and colleagues in part because these conditions are all risk factors for one another and commonly occur together.[1] For example, men with a history of cryptorchidism are more likely to have infertility, hypospadias and testicular cancer. This theory could also explain why men with testicular cancer commonly have testosterone deficiency (testosterone <300 ng/dl with symptoms) and impaired spermatogenesis in the contralateral testicle.[1,2] One proposed etiology for testicular dysgenesis syndrome is maternal exposure to endocrine disruptors during fetal testicular development. This exposure can lead to a disruption of fetal germ cell differentiation, persistent gonocytes and ultimately testicular carcinoma *in situ*.[1,2] Animal studies support a role for endocrine disruptors in most of these conditions, although the data in testicular cancer are lacking.[1] **It is estimated that pre-orchiectomy, approximately 20% of patients with testicular cancer have irreversible testosterone deficiency due to testicular dysgenesis.[3]**

Testicular cancer and impaired testicular function. While any malignancy and its associated therapy can potentially impact a man's fertility, sexual function and testosterone production, there are unique considerations in testicular cancer.[4,5] **Despite the fact that testicular cancer has a lower lifetime incidence than other malignancies at 0.4% in the United States, it has a disproportionately higher incidence in young men and therefore a greater potential to affect their current and future fertility.[6]** A multidecade longitudinal study in Norway demonstrated that 22% of testicular cancer survivors required assisted reproductive technologies in order to conceive and that the median time to conception following their cancer diagnosis was increased at 6.6 years.[7]

The impact of testicular cancer on fertility occurs even prior to the initiation of therapy. Several meta-analyses have shown that men with a diagnosis of testicular cancer have decreased semen parameters compared to otherwise healthy men and even compared to men with other malignancies.[5] **Furthermore, Baker et al demonstrated that regardless of semen parameters, men with testicular cancer were less likely to father children prior to their diagnosis compared to healthy controls with an OR of 0.67 and a 95% CI of 0.42–1.06.[4]** While the cause is likely multifactorial, proposed explanations include alterations in hormone levels, impaired testicular maturation, testicular damage, mitochondrial dysfunction and possible autoimmune effects.[8–10] Biopsy specimens of nonmalignant contralateral testes in men with testicular cancer corroborate these findings, demonstrating hypospermatogenesis and potential alterations in the hormonal milieu.[9]

Similarly, men with testicular cancer are at increased risk for low testosterone levels prior to intervention. One contemporary study demonstrated that 5% of men had testosterone deficiency prior to orchiectomy, and this increased to 16% when assessed at 1-month post-orchiectomy, though the threshold for testosterone deficiency in in this population was lower (<231 ng/dl).[11] These data show that even prior to treatment, a significant percentage of men have low or borderline testosterone levels, which supports the notion of an inherent testicular abnormality. The increase in the percentages of patients affected by testosterone deficiency after orchiectomy suggests that testicular tissue loss further compounds this issue.

To complicate matters, the current treatment modalities for testicular cancer can negatively impact male fertility, testosterone production and sexual function (fig. 2).[8,12] Surgical therapy (orchiectomy), radiation therapy, chemotherapy and retroperitoneal lymph node dissection (RPLND) will each be reviewed below.

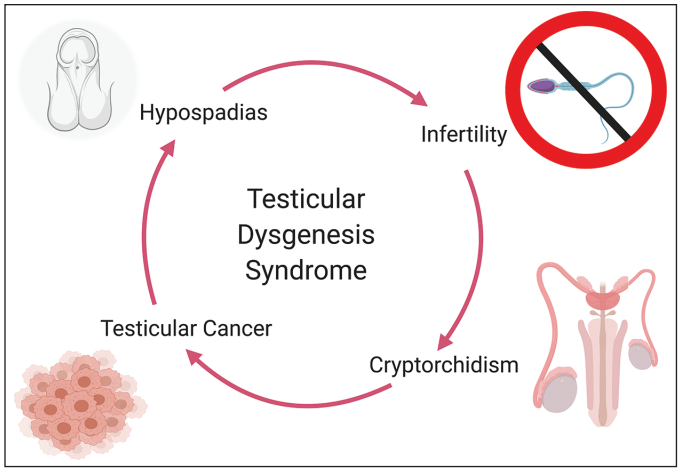

Figure 1. Testicular dysgenesis syndrome. Created with BioRender.com.

CLINICAL CONSIDERATIONS AT TIME OF TESTICULAR CANCER DIAGNOSIS

Testosterone and luteinizing hormone levels should be established at baseline (pre-orchiectomy). If this is not done, these levels should at a minimum be obtained post-orchiectomy and prior to definitive therapy given the high prevalence of low testosterone among these patients.

The new American Urological Association and American Society for Reproductive Medicine guidelines on the diagnosis

ABBREVIATIONS: bleomycin, etoposide, eisplatin (BEP), erectile dysfunction (ED), electroejaculation (EEJ), human chorionic gonadotropin (hCG), microdissection testicular sperm extraction (mTESE), post ejaculate urinalysis (PEU), retro peritoneal lymph node dissection (RPLND)

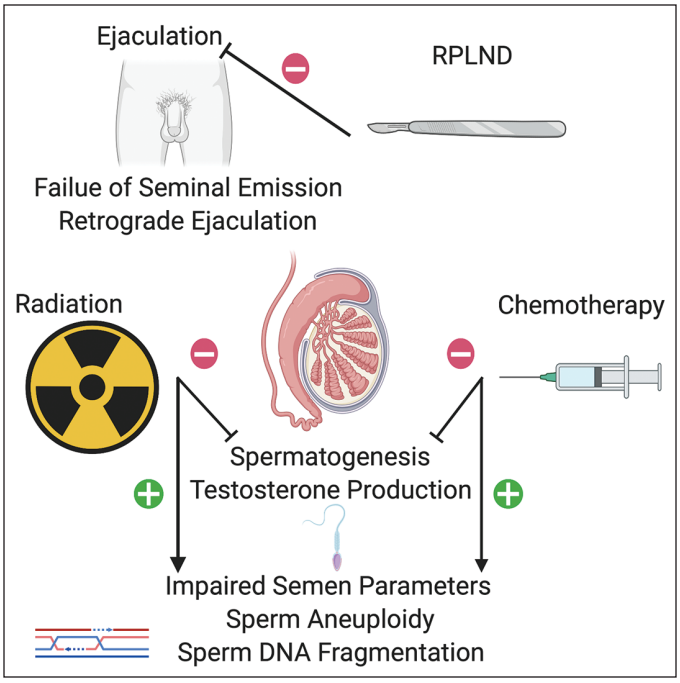

Figure 2. Effects of testicular cancer therapy on fertility and sexual function. Created with BioRender.com.

and treatment of infertility in men advocate for clinicians to discuss the effects of gonadotoxic therapies on sperm production and encourage men to cryopreserve sperm prior to starting potentially gonadotoxic therapy.[13,14] This sentiment is also echoed in the American Urological Association guidelines for the diagnosis and treatment of early stage testicular cancer.[15] Given the combination of inherent subfertility and the negative effects of all potential treatment modalities, having these discussions is of paramount importance.

Optimally, postpubertal men should be allowed several days to produce 1 or more semen samples for cryopreservation in order to optimize their future fertility potential.[14] Problems with sexual stimulation, ejaculation and sperm production (ie nonobstructive azoospermia) may require more invasive methods of sperm retrieval like electroejaculation (EEJ) or microdissection testicular sperm extraction (mTESE) to facilitate fertility preservation measures.[16] Allowing for men to bank sperm pretreatment not only maximizes the patient's fertility potential, but also may prevent the need for additional procedures and might facilitate biological paternity should the germ cells all be destroyed as a result of the cancer treatment.

ADVERSE EFFECTS OF TESTICULAR CANCER TREATMENTS

Orchiectomy. While patients with testicular cancer often have worse pretreatment semen parameters than healthy controls, orchiectomy can further exacerbate this difference. Petersen et al found that in 35 men undergoing orchiectomy, the median sperm concentration decreased from 17 million/ml presurgery to 7 million/ml postsurgery.[17] These results were corroborated in a more contemporary setting showing a decrease in sperm concentration from 26.7 million/ml prior to orchiectomy to 16.6 million/ml post-orchiectomy. These differences tended to be more pronounced in the cases of nonseminomatous germ cell tumors.[18] Orchiectomy can also result in decreased Leydig cell mass, resulting in testosterone deficiency and increasing the likelihood of sexual dysfunction.

Radiation therapy. Radiation directly to the testis can result in oligospermia, azoospermia and even hypergonadotropic hypogonadism depending on the dose and fractionation.[19] **While testicular shielding during abdominal and pelvic radiation can significantly decrease the amount of scatter radiation, the remaining testicle can still experience up to 0.115 Gy (0.28% of the treatment dose).**[20] Increasing the fractionation may actually lead to an increased total dose of radiation to the testicle due to an increase in scatter, as seen in studies of patients with pelvic radiation for Hodgkin's lymphoma.[21]

Testicular doses as low as 0.1 Gy can cause transient seminal changes, typically resulting in oligospermia as the rapidly dividing spermatocytes are the most radiosensitive cells in the testis.[19,22,23] Doses above 0.35 Gy can cause azoospermia with variable reversibility.[19,23] As doses increase above 1 Gy, the chances of reversibility decrease and the recovery time for spermatogenesis increases from 9–18 months to 10–30 months.[19,23] **Doses greater than 4 Gy are more likely to result in permanent azoospermia with recovery taking greater than 5 years or more among those men experiencing return of spermatogenesis.**[19,22,23] Leydig cells are more resistant to the deleterious effects of radiation therapy and typically require doses higher than 20–30 Gy (depending on age and pubertal status) to disrupt their ability to produce testosterone.[19,22,24,25] A contemporary study demonstrated that men exposed to radiation, compared to men who underwent surveillance, had an increased risk of testosterone deficiency at 6 and 12 months posttreatment (OR 10, 95% CI 2.1–47 and OR 3.9, 95% CI 1.1–14, respectively).[26]

Radiation therapy for seminomas to the para-aortic region (with or without ipsilateral iliac node inclusions, based on stage) ranges from 20–36 Gy.[27] With appropriate shielding the risk of permanent infertility and endocrine dysfunction is low, based on overall testicular exposure.[20] Radiation therapy for men with germ cell neoplasia *in situ* directly to the testicle, however, is often between 18 and 20 Gy; this is not only likely to cause irreversible azoospermia but can also cause permanent hypogonadism.[19,22,24,25,28] Nearly all patients receiving 20 Gy directly to the testicle, and about half of patients receiving 16 Gy, will require lifelong testosterone replacement.[29]

Erectile dysfunction (ED) is also a possible sequela of radiation therapy due to internal scatter. Even a very small radiation dosage to the corpora cavernosa can contribute to ED, with doses as low as 0.1 Gy commonly resulting in substantial and consequential endothelial damage.[30]

Chemotherapy. Chemotherapeutic agents' effects on spermatogenesis and testosterone synthesis vary substantially by drug class. Traditional first line chemotherapeutic agents for testicular cancer, such as bleomycin and etoposide, have a low overall risk of causing permanent infertility.[22,31–33] **Chemotherapies such as cisplatin and carboplatin ("alkylating-like" agents) have a higher risk of causing permanent azoospermia.**[34] Finally, alkylating agents such as ifosfamide and cyclophosphamide, which are typically reserved for second line and salvage chemotherapy, are associated with the highest risk of causing permanent infertility among this group of treatments.[34,35]

The overall impact on fertility associated with the use of standard first line agents depends on the dosage administered. One or 2 cycles of carboplatin, or the regimen bleomycin/etoposide/cisplatin (BEP), in the post-orchiectomy setting typically causes a transient decline in total motile sperm count that recovers by 12 months and rarely results in irreversible azoospermia.[36–38] **Three or 4 cycles of BEP, however, can cause delayed recovery of spermatogenesis (up to 2 years) with permanent azoospermia occurring in up to 10% of patients.**[34,37,38] Similarly, studies found that men exposed to 3–4 cycles of BEP had a higher testosterone deficiency risk compared to men only exposed to 1–2 cycles of standard chemotherapy at 6 and 12 months posttreatment (OR 22, 95% CI 4.4–118 and OR 5.8, 95% CI 1.5–22, respectively).[29]

Retroperitoneal lymph node dissection. Traditionally (prior to *in vitro* fertilization), nonnerve-sparing RPLND had the greatest treatment effect on male fertility.[39] **If the surgeon did not spare at least 1 postganglionic sympathetic lumbar nerve during the procedure, the patient would ultimately have some degree of aspermia (ie lack of release of semen from the penis during ejaculation).**[40] Modified surgical techniques, in both open and minimally invasive surgery, were created to spare these nerves.[40,41] However, nerve-sparing RPLNDs may not be possible in certain settings (ie post-chemotherapy or cancer recurrence).[40,41] While there are no data suggesting that injury to these nerves directly impacts spermatogenesis, the alterations in ejaculatory physiology could ultimately require assisted reproductive technologies.

Posttreatment fertility options. For men who are undergoing RPLND, clinicians should discuss the possibility of ejaculatory dysfunction prior to the procedure, as numerous post-RPLND procedures may be needed to recover sperm (fig. 3).[14] If men develop aspermia, then clinicians should obtain a post-ejaculate urinalysis (PEU) to assess for retrograde ejaculation.[14] Retrograde ejaculation in this setting can be treated with alpha agonist therapy, which is successful in up to 50% of men. If this fails, sperm can be retrieved from the urine after PEU.[42] **Unfortunately, most men undergoing nonnerve-sparing RPLND will experience a complete failure of seminal emission as opposed to retrograde ejaculation, which results in no sperm seen on PEU.**[42] Men with failure of emission are unlikely to respond to alpha agonist therapy. They will, however, have sperm in the semen up to 75% of the time when undergoing EEJ; of the men who fail EEJ, 43% will have sperm on mTESE.[42] If appropriate based on the patient's fertility goals, these treatment efforts can be delayed because neurological recovery of antegrade ejaculation can take up to 1–2 years.[14]

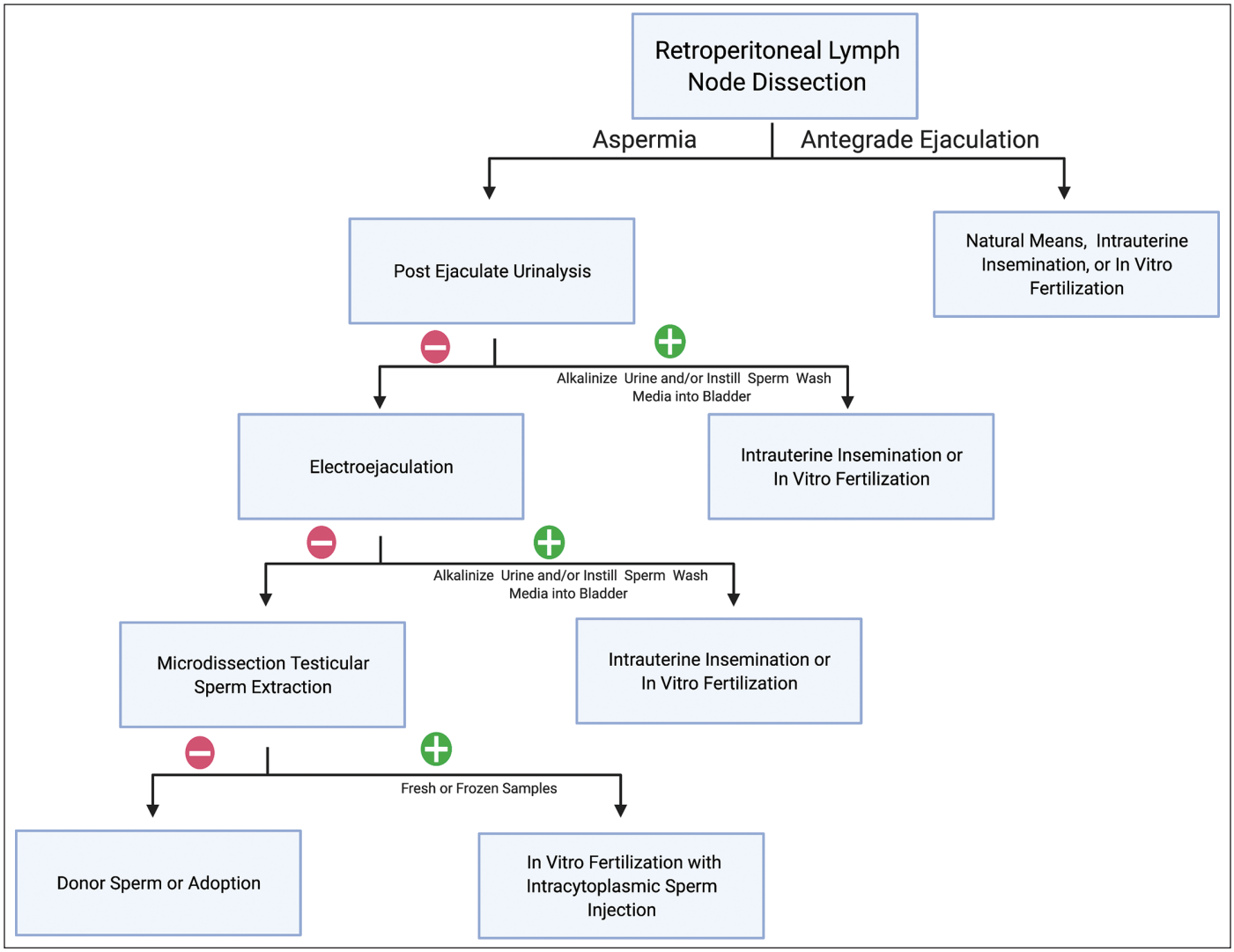

Figure 3. Algorithm to manage fertility after retroperitoneal lymph node dissection. Created with BioRender.com.

Patients who undergo radiation treatment or receive cytotoxic chemotherapy should also wait at least 12 months before attempting to conceive.[14] There is a concern that these treatments can cause transient mutagenic effects to spermatozoa, which in turn could lead to deleterious mutations in the patient's offspring.[43] Despite this concern, a large retrospective study with long-term followup found no difference in the risk of cytogenic abnormalities in children whose father was treated with chemotherapy or radiation compared to children of men not treated with these gonadotoxic agents.[44] While sperm aneuploidy rates vary by treatment modality, nonazoospermic men often see a return to pretreatment sperm aneuploidy rates after 2 years.[45] **Despite the risk of increased rate of sperm aneuploidy for up to 12 months after completion of therapy, clinical data do not suggest that there is a significant risk in offspring born with mutations over the lifetime of cancer survivors.[44]**

In men who remain azoospermic 1 year after treatment, total chemotherapeutic and radiation dosing needs to be considered.[14] Dosage of therapy affects recovery time; in some cases men may want to defer definitive sperm extraction with mTESE until at least 2 years after treatment.[14,19,23,34,37,38] **A recent meta-analysis demonstrated a sperm recovery rate of 40% in all azoospermic men undergoing mTESE after receiving gonadotoxic therapy for any type of malignancy.[14]** Smaller series specific to testis cancer have indicated that sperm retrieval rates may be even higher.[46]

Ultimately, it is the provider's responsibility to appropriately inform patients of the risks, benefits and timing of sperm extraction in the posttreatment setting. Ideally, the need to surgically extract sperm in the post-gonadotoxic therapy setting can be obviated by appropriate patient counseling and successful fertility preservation measures in the pretreatment setting.

Posttreatment testosterone deficiency. As discussed above, testosterone deficiency is a common sequela among men treated for testicular cancer. Exogenous testosterone therapy should be avoided in those men desiring future fertility as this can suppress intratesticular testosterone production and spermatogenesis, and therefore exacerbate fertility concerns. Alternative therapies such as clomiphene citrate, human chorionic gonadotropin (hCG) and anastrozole are better choices that can be used in an "off-label" fashion, as they support endogenous testosterone production and do not have a negative impact on fertility.[2] There are certain limitations to these alternative therapies. For example, men are not ideal candidates for clomiphene citrate or hCG if their luteinizing hormone is elevated, since those patients will likely have a very limited response in terms of increased testosterone production. Similarly, men with normal estradiol levels are not optimal candidates for anastrozole, which blocks the conversion of testosterone to estradiol. If exogenous testosterone therapy is needed, it can be combined with hCG in an effort to maintain some degree of intratesticular testosterone production.

Posttreatment sexual dysfunction. Unlike infertility and testosterone deficiency, sexual dysfunction in the setting of testicular cancer has not been as rigorously studied. This is due to a number of factors including the heterogeneity of treatment modalities, use of unvalidated questionnaires, low patient response rates and a lack of control groups. Among the existing studies in the literature, however, a systematic review found high rates of sexual dysfunction among survivors of testicular cancer when compared to controls. Ejaculatory dysfunction was the most common sexual symptom among survivors, followed by ED and reduced or absent orgasm. [47] A case-control study by Kim et al provided further insight into sexual dysfunction in men with a history of testicular cancer by comparing 246 testicular cancer patients with 236 age-matched and race-matched controls.[48] The cases were at least 5 years post-diagnosis with a median of 14 years' duration, and they all completed the Brief Male Sexual Function Inventory. Patients were more likely to have ED (OR 1.72, 95% CI 1.11–2.64) and impaired ejaculation (OR 2.27, 95% CI 1.32–3.91) and to endorse that sexual dysfunction was a problem for them (OR 2.36, 95% CI 1.43–3.90). Patients should therefore be counseled on all of these complications prior to testicular cancer treatment.

Similar to testosterone deficiency, the data suggest that the more treatment men receive for testicular cancer, the greater the risk of an adverse effect of sexual function. In the aforementioned case-control study, men were analyzed based on whether they were treated with surgery alone, chemotherapy or radiation therapy. Interestingly, the incidence of sexual dysfunction was not significantly different when comparing the surgical groups to controls. However, radiation therapy was associated with an increased risk of ED (OR 1.77, 95% CI 1.01–3.13), and these men were more likely to consider sexual dysfunction to be a problem (OR 1.96, 95% CI 1.03–3.74). Patients receiving chemotherapy fared the worst, with higher rates of both delayed ejaculation (OR 4.81, 95% CI 2.25–10.29) and problematic sexual dysfunction (OR 3.20, 95% CI 1.55–6.59).[48]

With regard to ED, there are several proposed mechanisms regarding its association with testicular cancer. One is that men with testicular cancer can have testosterone deficiency, as discussed previously. At very low levels of testosterone, men can experience ED. This was demonstrated in a study of 400 healthy men 20–50 years old who received 16 weeks of androgen deprivation therapy. Study subjects were randomized to simultaneously receive either testosterone gel (in concentrations of 1.25 gm, 2.5 gm, 5 gm or 10 gm) or a placebo gel daily. The study revealed a link between ED and testosterone, but only at subphysiological levels of testosterone. A decline in erectile function was seen in the men on placebo or on the lowest testosterone dose (1.25 gm daily), but the men on 2.5–10 g daily dosages did not experience a change in their erections ($p > 0.05$).[49] Thus, testosterone deficiency alone, especially in severe cases, can contribute to ED.

Psychogenic ED may play a role in these men, given the inherent stress and anxiety associated with a cancer diagnosis. These men can experience fear of the cancer, its treatment and recurrence risk. With testicular cancer in particular, body image issues and a sense of emasculation sometimes arise in patients after undergoing an orchiectomy. Many clinical features of psychogenic ED can be used to help to distinguish it from organic ED. For example, psychogenic ED is commonly characterized by intermittency of function, in which case a man might have normal nocturnal erections and normal erectile function with masturbation but poor-quality erections during sexual activity with a partner. Tal et al specifically evaluated psychogenic ED in 76 men with testicular cancer and a mean age of 29 years.[50] The subjects exhibited a delay in seeking treatment, with

a mean time of 12 months posttreatment to time to ED consultation. While 26% of the men had testosterone deficiency as a possible contributory factor, the authors concluded that most of these men had psychogenic ED. Functionally, 84% of the men reported loss of sustaining capability, and all had normal penile duplex Doppler ultrasound, signifying normal vascular function. The vast majority of these men (88%) responded to phosphodiesterase 5 inhibitors. Thus, while the etiology of ED in these men was predominately psychogenic, the authors asserted that there is a role for medical therapy. Furthermore the treatment of ED in these men should follow a standard clinical care algorithm, as with any general ED patient.

CONCLUSIONS

Testicular cancer can affect a broad array of male health conditions including fertility, ejaculatory and erectile function. Not only does the pathology have direct effects on normal male physiology, but the therapies for testicular cancer are also intimately linked to similar clinical consequences. Chemotherapy, radiation, and surgery all have different effects on fertility and sexual function, and it is paramount for practicing urologists to understand these nuances to counsel their patients appropriately.

DID YOU KNOW?

- Men with testicular cancer often have reduced fertility potential prior to any therapy being administered.
- Clinicians should encourage sperm cryopreservation prior to initiating therapy for testicular cancer.
- Men with testicular cancer are at an increased risk for testosterone deficiency prior to any treatment being administered.
- The risk of testosterone deficiency increases with increased exposure to chemotherapeutic agents.
- After receiving cytotoxic therapy, men should delay attempts at conceiving a pregnancy for at least 12 months (unless using sperm cryopreserved prior to treatment).

Table. Overview of effects of testicular cancer and associated treatments on fertility, erectile function and serum testosterone levels

	Pretreatment and after Orchiectomy	Chemotherapy	Radiation	Retroperitoneal Lymph Node Dissection
Fertility	Reduced semen parameters, reduced fecundity, more likely to need assisted reproductive technology secondary to hormone alterations, impaired testicular maturation, testicular damage, mitochondrial dysfunction and possible autoimmune effects	Varies by drug class but ranges from no effect to transient azoospermia to permanent azoospermia in up to 10% of patients treated with 3–4 cycles of BEP. Men requiring second line chemotherapy with alkylating agents are at an even higher risk for permanent azoospermia depending on the regimen	Low doses can cause transient azoospermia with doses >4 Gy commonly causing permanent azoospermia	Can cause aspermia in men if no postganglionic sympathetic lumbar nerves are spared. PEU, EEJ or mTESE to retrieve sperm
Erectile function	Can have reduced erections secondary to alterations in testosterone levels	Can have ED mediated by testosterone deficiency	Scatter can cause endothelial damage affecting erections	Not typically affected
Serum testosterone levels	Can have testosterone deficiency secondary to testicular dysgenesis syndrome in up to 20% of patients	Elevated risk of testosterone deficiency immediately after treatment. While some slowly recover over time, the risk persists beyond 12 months	Leydig cell damage can occur at higher doses requiring lifelong testosterone replacement in men with >20 Gy exposure	Not typically affected

REFERENCES

1. Wohlfahrt-Veje C, Main KM and Skakkebaek NE: Testicular dysgenesis syndrome: foetal origin of adult reproductive problems. Clin Endocrinol (Oxf) 2009; **1:** 459.
2. Mulhall JP, Trost LW, Brannigan RE et al: Evaluation and management of testosterone deficiency: AUA guideline. J Urol 2018; **200:** 423.
3. Fosså SD, Oldenburg J and Dahl AA: Short- and long-term morbidity after treatment for testicular cancer. BJU Int 2009; **104:** 1418.
4. Baker JA, Buck GM, Vena JE et al: Fertility patterns prior to testicular cancer diagnosis. Cancer Causes Control 2005; **16:** 295.
5. Williams DH, Karpman E, Sander JC et al: Pretreatment semen parameters in men with cancer. J Urol 2009; **181:** 736.
6. DeSantis CE, Lin CC, Mariotto AB et al: Cancer treatment and survivorship statistics, 2014. CA Cancer J Clin 2014; **64:** 252.
7. Brydøy M, Fosså SD, Klepp O et al: Paternity following treatment for testicular cancer. J Natl Cancer Inst 2005; **97:** 1580.
8. Ostrowski KA and Walsh TJ: Infertility with testicular cancer. Urol Clin North Am 2015; **42:** 409.
9. Dieckmann K-P, Linke J, Pichlmeier U et al: Spermatogenesis in the contralateral testis of patients with testicular germ cell cancer: histological evaluation of testicular biopsies and a comparison with healthy males. BJU Int 2007; **99:** 1079.
10. Dias TR, Agarwal A, Pushparaj PN et al: New insights on the mechanisms affecting fertility in men with non-seminoma testicular cancer before cancer therapy. World J Mens Health 2020; **38:** 198.
11. Wiechno PJ, Kowalska M, Kucharz J et al: Dynamics of hormonal disorders following unilateral orchiectomy for a testicular tumor. Med Oncol 2017; **34:** 84.
12. Ping P, Gu B-H, Li P et al: Fertility outcome of patients with testicular tumor: before and after treatment. Asian J Androl 2014; **16:** 107.
13. Schlegel PN, Sigman M, Collura B et al: Diagnosis and treatment of infertility in men: AUA/ASRM guideline part I. J Urol 2021; **205:** 36.
14. Schlegel PN, Sigman M, Collura B et al: Diagnosis and treatment of infertility in men: AUA/ASRM guideline part II. J Urol 2021; **205:** 44.
15. Stephenson A, Eggener SE, Bass EB et al: Diagnosis and treatment of early stage testicular cancer: AUA guideline. J Urol 2019; **202:** 272.
16. Berookhim BM and Mulhall JP: Outcomes of operative sperm retrieval strategies for fertility preservation among males scheduled to undergo cancer treatment. Fertil Steril 2014; **101:** 805.
17. Petersen PM, Skakkebaek NE, Rørth M et al: Semen quality and reproductive hormones before and after orchiectomy in men with testicular cancer. J Urol 1999; **161:** 822.
18. Liguori G, Trombetta C, Bucci S et al: Semen quality before and after orchiectomy in men with testicular cancer. Arch Ital Urol Androl 2008; **80:** 99.
19. De Felice F, Marchetti C, Marampon F et al: Radiation effects on male fertility. Andrology 2019; **7:** 2.
20. Singhal MK, Kapoor A, Singh D et al: Scattered radiation to gonads: role of testicular shielding for para-aortic and homolateral illiac nodal radiotherapy. J Egypt Natl Canc Inst 2014; **26:** 99.
21. Speiser B, Rubin P and Casarett G: Aspermia following lower truncal irradiation in Hodgkin's disease. Cancer 1973; **32:** 692.
22. Parekh NV, Lundy SD and Vij SC: Fertility considerations in men with testicular cancer. Transl Androl Urol, suppl., 2020; **9:** S14.
23. Biedka M, Kuźba-Kryszak T, Nowikiewicz T et al: Fertility impairment in radiotherapy. Contemp Oncol (Pozn) 2016; **20:** 199.
24. Shalet SM, Tsatsoulis A, Whitehead E et al: Vulnerability of the human Leydig cell to radiation damage is dependent upon age. J Endocrinol 1989; **120:** 161.
25. Rowley MJ, Leach DR, Warner GA et al: Effect of graded doses of ionizing radiation on the human testis. Radiat Res 1974; **59:** 665.
26. Eberhard J, Ståhl O, Cwikiel M et al: Risk factors for post-treatment hypogonadism in testicular cancer patients. Eur J Endocrinol 2008; **158:** 561.
27. Gilligan T, Lin DW, Aggarwal R et al: Testicular cancer, version 2.2020, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2019; **17:** 1529.
28. Stephenson AJ, Scardino PT, Eastham JA et al: Postoperative nomogram predicting the 10-year probability of prostate cancer recurrence after radical prostatectomy. J Clin Oncol 2005; **23:** 7005.
29. La Vignera S, Cannarella R, Duca Y et al: Hypogonadism and sexual dysfunction in testicular tumor survivors: a systematic review. Front Endocrinol (Lausanne) 2019; **10:** 264.
30. Wiedermann JG, Marboe C, Amols H et al: Intracoronary irradiation markedly reduces neointimal proliferation after balloon angioplasty in swine: persistent benefit at 6-month follow-up. J Am Coll Cardiol 1995; **25:** 1451.
31. Lee SJ, Schover LR, Partridge AH et al: American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. J Clin Oncol 2006; **24:** 2917.
32. Levine J, Canada A and Stern CJ: Fertility preservation in adolescents and young adults with cancer. J Clin Oncol 2010; **28:** 4831.
33. Giwercman A and Petersen PM: Cancer and male infertility. Baillieres Best Pract Res Clin Endocrinol Metab 2000; **14:** 453.
34. Abram McBride J and Lipshultz LI: Male fertility preservation. Curr Urol Rep 2018; **19:** 49.
35. Green DM, Liu W, Kutteh WH et al: Cumulative alkylating agent exposure and semen parameters in adult survivors of childhood cancer: a report from the St Jude Lifetime Cohort Study. Lancet Oncol 2014; **15:** 1215.
36. Weibring K, Nord C, Ståhl O et al: Sperm count in Swedish clinical stage I testicular cancer patients following adjuvant treatment. Ann Oncol 2019; **30:** 604.
37. Bujan L, Walschaerts M, Moinard N et al: Impact of chemotherapy and radiotherapy for testicular germ cell tumors on spermatogenesis and sperm DNA: a multicenter prospective study from the CECOS network. Fertil Steril 2013; **100:** 673.

38. Isaksson S, Eberhard J, Ståhl O et al: Inhibin B concentration is predictive for long-term azoospermia in men treated for testicular cancer. Andrology 2014; **2:** 252.
39. Matos E, Skrbinc B and Zakotnik B: Fertility in patients treated for testicular cancer. J Cancer Surviv 2010; **4:** 274.
40. Masterson TA, Cary C, Rice KR et al: The evolution and technique of nerve-sparing retroperitoneal lymphadenectomy. Urol Clin North Am 2015; **42:** 311.
41. Abdul-Muhsin HM, L'esperance JO, Fischer K et al: Robot-assisted retroperitoneal lymph node dissection in testicular cancer. J Surg Oncol 2015; **112:** 736.
42. Hsiao W, Deveci S and Mulhall JP: Outcomes of the management of post-chemotherapy retroperitoneal lymph node dissection-associated anejaculation. BJU Int 2012; **110:** 1196.
43. Meistrich ML: Risks of genetic damage in offspring conceived using spermatozoa produced during chemotherapy or radiotherapy. Andrology 2020; **8:** 545.
44. Signorello LB, Mulvihill JJ, Green DM et al: Congenital anomalies in the children of cancer survivors: a report from the childhood cancer survivor study. J Clin Oncol 2012; **30:** 239.
45. Martinez G, Walschaerts M, Le Mitouard M et al: Impact of Hodgkin or non-Hodgkin lymphoma and their treatments on sperm aneuploidy: a prospective study by the French CECOS network. Fertil Steril 2017; **107:** 341.
46. Meseguer M, Garrido N, Remohí J et al: Testicular sperm extraction (TESE) and ICSI in patients with permanent azoospermia after chemotherapy. Hum Reprod 2003; **18:** 1281.
47. Nazareth I, Lewin J and King M: Sexual dysfunction after treatment for testicular cancer: a systematic review. J Psychosom Res 2001; **51:** 735.
48. Kim C, McGlynn KA, McCorkle R et al: Sexual functioning among testicular cancer survivors: a case-control study in the U.S. J Psychosom Res 2012; **73:** 68.
49. Finkelstein JS, Lee H, Burnett-Bowie S-AM et al: Gonadal steroids and body composition, strength, and sexual function in men. N Engl J Med 2013; **369:** 1011.
50. Tal R, Stember DS, Logmanieh N et al: Erectile dysfunction in men treated for testicular cancer. BJU Int 2014; **113:** 907.

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1. A 23-year-old man is seen 1 year after retroperitoneal lymph node dissection for a stage I nonseminomatous germ cell tumor. His postoperative axial imaging is negative, as are his tumor markers. He is interested in paternity but reports that since his surgery, he is no longer able to release semen from the tip of his penis during ejaculation. The next step is
   a. serum follicle-stimulating hormone level
   b. post-ejaculate urinalysis
   c. electroejaculation
   d. microsurgical testicular sperm extraction

2. A 26-year-old man is trying to decide between chemotherapy and radiation for his stage IIa seminoma. He is currently 6 weeks status post-orchiectomy with normal tumor markers. He is currently married, and until his diagnosis, he was actively trying for a pregnancy. He remains interested in family building. He should be counseled to
   a. proceed immediately with therapy. You can continue trying to conceive; however, treating your cancer cannot wait.
   b. consider sperm banking prior to therapy. Regardless of if you bank sperm, you can continue trying to conceive while undergoing therapy.
   c. consider sperm banking prior to therapy. Do not try to conceive during therapy or for the 12 months following.
   d. proceed immediately with therapy. Do not try to conceive during therapy or for the 12 months following.

3. Five years after orchiectomy and BEP × 4 for intermediate risk nonseminomatous germ cell tumor, a 28-year-old man remains with no evidence of disease recurrence (NED). He presents to your office regarding his fertility as he desires biological children. He has 2 semen analyses that reveal normal volume azoospermia with normal pH. His hormonal workup is also normal. The next step is
   a. electroejaculation
   b. donor sperm for use in intrauterine insemination
   c. microdissection testicular sperm extraction for use in *in vitro* fertilization
   d. adoption

4. What conditions are associated with testicular dysgenesis syndrome?
   a. cryptorchidism, hypospadias, testicular cancer, testicular torsion
   b. cryptorchidism, hypospadias, infertility, testicular cancer
   c. testosterone deficiency, testicular torsion, hypospadias, erectile dysfunction
   d. testosterone deficiency, infertility, testicular torsion, hypospadias

5. A 20-year-old man is status-post orchiectomy for testicular cancer and has elected surveillance. He does not have children but is engaged to be married and desires future children. He has multiple testosterone deficiency symptoms such as fatigue, low energy, muscle loss and irritability. His early morning testosterone levels are 251 ng/dl and 239 ng/dl on a repeat lab. A medication he could be offered is
   a. finasteride
   b. clomiphene citrate
   c. depot leuprolide acetate
   d. intramuscular testosterone