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REVIEW

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Sexual function and fertility preservation in testicular cancer survivors

Shane Davis[1], Labeeqa Khizir[1], Benjamin Lichtbroun[1], Thomas Jang[1], Saum Ghodoussipour[1,*], Danielle Velez[1]

[1]Section of Urologic Oncology, Rutgers Cancer Institute of New Jersey and Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ 08901, USA

***Correspondence**
sg1621@cinj.rutgers.edu
(Saum Ghodoussipour)

Abstract

Testicular cancer is a common cancer among reproductive age men, with the necessary treatment options having varying impacts on fertility and sexual function. Treatment begins with orchiectomy and is often followed by a combination of chemotherapy, radiation, and/or retroperitoneal lymph node dissection, which have different effects on spermatogenesis, gonadotropin levels, and ejaculation. Alkylating agents such as cisplatin are commonly used for testicular cancer and are amongst the most spermatotoxic chemotherapeutic agents. Radiation poses gonadotoxic effects despite gonadal shielding due to a scatter effect. Suprahilar and bilateral retroperitoneal lymph node dissections can cause ejaculatory dysfunction. Options to preserve fertility vary by pubertal status. While the standard recommendation for post pubertal patients is cryopreservation, prepubertal patients rely on experimental protocols for cryopreservation of germ cells with stem cell capabilities, with the hope that these cells will one day be stimulated to produce sperm. These topics are reviewed to give insight into current literature around fertility in testicular cancer survivorship and determine best possible practices in fertility preservation among patients.

Keywords

Testicular cancer; Fertility; Cryopreservation; Fertility preservation; Sexual function; Survivorship

1. Introduction

Testicular cancer (TC) is the most common solid tumor cancer in young men aged 20 to 40 years [1, 2]. Germ cell tumors comprise the majority of testicular cancers and can be designated as either seminoma, non-seminoma, or mixed [3]. TC is treated with a radical orchiectomy and depending on the pathology and stage of the cancer, patients then undergo either surveillance, chemotherapy, radiation, retroperitoneal lymph node dissection, or a combination of these modalities. These treatments provide for a cure rate over 95%, but often at the cost of side effects with lasting impacts on patients [4]. The population that is largely affected by this malignancy is often in their childbearing years [5]. Post-treatment infertility has been a concern largely examined in more than half of testicular cancer survivors [6]. Many survivors feel as though they were inadequately counseled on the impact these treatments can have on their fertility. Studies have shown that only 60% of men who underwent treatments were counseled on fertility consequences prior to beginning treatment, and amongst this group only 51% actually recalled being counseled on cryopreservation [7, 8]. Given that testis cancer often impacts pre-pubertal patients as well, this presents unique challenges for fertility preservation. Currently, the American Society of Clinical Oncology (ASCO) recommends that male cancer patients should be counseled regarding contributing factors for infertility surrounding their diagnosis as early as possible in the treatment process [9]. While cryopreservation is the primary option for post-pubertal patients due to its efficiency and cost effectiveness, this is not currently an option for pre-pubertal patients. In this review, we'll primarily investigate TC treatment options and their impact on fertility and sexual function, along with strategies for fertility preservation in both pre- and post-pubertal patients.

2. Methods

Using PubMed, Google Scholar, and Wiley Online Library, we performed a review of articles between 1966 and 2022. Search terms included a combination of terms including "sexual dysfunction in testicular cancer", "infertility", "orchiectomy", "chemotherapy", "radiotherapy", "cryopreservation", "pre-pubertal fertility preservation" and "post-pubertal fertility preservation". Articles included were original articles published in English. Unpublished works, works not in English, and news articles were not included. Information on clinical trials was collected from clinicaltrials.gov, which was accessed in August 2022.

3. Sexual function

Studies have shown a decrease in nearly every aspect of sexual health in TC survivors, with subsequent loss of quality of life [10]. Given the young age of TC survivors, this can be a devastating consequence with a lifetime of impact. TC survivors are more likely to experience symptoms of sexual dysfunction in the form of erectile dysfunction (ED), decreased libido and poor body image compared to the general population of men [10]. The prevalence of ED among TC survivors is between 12% and 44% regardless of treatment modality [10, 11]. Incidence of decreased libido and ejaculatory disorders have been linked to orchiectomy and chemotherapy [12]. Psychogenic causes, namely through body image, can also play a role in sexual dysfunction among TC survivors after orchiectomy. Sexual function in TC patients relies heavily on the therapies used and their physical and psychogenic effects on sexual function [13].

Of the patients who reported sexual dysfunction after TC treatment, 19% were due to a loss of libido [14]. Chemotherapy appears to have a greater impact on libido with 25% of TC patients who received chemotherapy reporting reduced sexual desire. This is in comparison to 14% and 13% for radiotherapy and RPLND (retroperitoneal lymph node dissection), respectively [15]. Problems related to libido increased significantly during treatment and often did not fully return to baseline following last course of chemotherapy [16, 17]. Stress is common among this population and current neurophysiologic research has demonstrated high stress as a possible cause of sexual inhibition [18]. Post-treatment anxiety and depression is also common among 10%–20% of TC survivors and may be associated with abnormal levels of gonadotropins [10]. High levels of gonadotropins and low testosterone were found in patients treated with platinum based chemotherapy [10]. Patients with abnormally high luteinizing hormone were found to have low sexual desire and dissatisfaction with their sex life [10, 19]. Elevated LH (luteinizing hormone) may persist up to two years following chemotherapy completion [20]. Orgasmic dysfunction differed among treatment modalities with a 28% prevalence among patients undergoing chemotherapy compared to 23% and 22% for radiotherapy and RPLND patients, respectively [21].

Sexual health can greatly impact relationship satisfaction, with nearly 25% of TC patients believing their diagnosis and treatments caused relationship strain [22–24]. One commonly cited reason is decreased sexual frequency, which can be a sensitive indicator for couple distancing and distressed communication [25]. Relationship anxiety that may stem from lower sexual frequency and satisfaction can also arise from body image issues post-orchiectomy [25]. Sixteen percent of TC survivors admit to having significant body image concerns specifically as it relates to the absence of their testicle [26]. This may sway a patient towards choosing a testicular prosthesis after radical orchiectomy [27–30]. Another unwelcome side effect is gynecomastia, which may be found in 11% of TC patients at the time of diagnosis [31]. This may be due to the testicular tumor secreting hCG (human chorionic gonadotropin) or estradiol, although gynecomastia can continue in TC survivors post-treatment, particularly in the presence of hypogonadism and elevated estradiol [10, 15, 29, 32–34].

4. Factors contributing to infertility by therapy

4.1 Orchiectomy

Testicular tumors are generally removed by radical unilateral orchiectomy. While we counsel patients that the majority of men will still be able to father a child after this treatment alone, this may still have an impact on the patient's sexual function and fertility. There is an expected 50% decrease in post-operative sperm concentration within the first few months following surgery, with no change in serum testosterone levels [35, 36]. Studies have shown that 40% of patients are oligozoospermic or azoospermic in the month following orchiectomy, with gradual recovery of spermatogenesis two to three years after surgery [37]. Nine percent of men with previously normal sperm counts will become azoospermic after orchiectomy, without recovery of sperm production [35]. Men with elevated pre-surgical FSH (follicle-stimulating hormone) levels are less likely to have spermatogenesis recovery, as this usually indicates baseline spermatogenic dysfunction [34, 38, 39]. Post-radical orchiectomy patients are also more likely to have elevated LH levels, indicating a predisposition to Leydig cell dysfunction and hypogonadism [36]. In addition to sperm concentration, asthenospermia (motility $<$40%) and teratozoospermia (morphology $<$4%) have been found in 50% of post-orchiectomy patients with TC [40–42].

In order to preserve sperm cell production, partial orchiectomy may be an option for carefully selected patients with a small tumor in a solitary testis, small bilateral tumors, or increased suspicion for a benign tumor [36]. Partial orchiectomy is an effective means of tumor control for prepubertal benign teratomas, with techniques adopted for adult testicular cancer. These patients require closer follow-up to monitor for TC recurrence with routine surveillance ultrasounds and tumor markers [32, 33, 36].

To evaluate fertility of TC patients, Jacobsen *et al.* [43] studied 36 patients and found that 28 patients fathered at least 1 child after orchiectomy, including 19 patients who had not fathered a child prior to being diagnosed with testicular cancer, with median time from orchiectomy to first fatherhood after orchiectomy at 18 months. In terms of testicular endocrine function, men without detectable hCG were found to have an increase in median follicle-stimulating hormone (FSH) from 5.7 IU/L before to 10.0 IU/L after orchiectomy ($p < 0.001$), indicative of spermatogenic dysfunction [35]. Median inhibin B levels were also significantly decreased from 108 pg/L before to 95 pg/L after orchiectomy ($p = 0.003$) [35].

4.2 Chemotherapy

Postoperative chemotherapy can temporarily or permanently impair spermatogenesis and fertility. Alkylating agents, especially cyclophosphamide and ifosfamide, pose the highest risk of azoospermia. Rapidly dividing spermatocytes are particularly sensitive to alkylating agents [44]. The most common chemotherapy regimen used in testicular cancer is bleomycin, etoposide, and cisplatin (BEP). BEP has been

shown to temporarily impair spermatogenesis, with return after 12 months if two or fewer cycles were used. Patients who were treated with greater than 3 courses or with radiotherapy had spermatogenesis return after 24 months from the end of treatment [45]. Because of the risk of underlying DNA damage to sperm from chemotherapy and radiation, it is the recommendation by the American Society of Reproductive Medicine (ASRM) and the American Urological Association (AUA) that conception is not attempted with freshly ejaculated or extracted sperm within 2 years of receiving chemotherapy or radiation [46]. Studies of children with a paternal history of cancer were more likely to have major congenital abnormalities if conceived within 2 years of paternal receipt of chemotherapy/radiation [47].

Spermatogenic side effects of chemotherapy may vary depending on pubertal status, type of chemotherapy, and number of treatment cycles. Alkylating agents carry a risk for azoospermia. Additionally, cumulative doses of platinum-based agents such as cisplatin that are less than or equal to 400–600 mg/m^2 will temporarily damage both spermatogenesis and testicular endocrine function, with more permanent damage conferred at greater doses [48–50]. This temporary damage occurs by causing more injury to rapidly proliferating type B spermatogonia, with minimal damage to type A spermatogonia [51]. Type A spermatogonia are primitive stem cells that undergo active mitosis, and type B spermatogonia are differentiated progenitors that give rise to spermatocytes [52]. Thus, with preservation of the primitive stem cells, sperm counts may be replenished; indeed, this temporary azoospermia typically resolves in 2 years in 50% of cases and in 5 years in 80% of cases [53].

Irreversible loss of spermatogenesis can occur at greater doses due to partial or complete destruction of type A spermatogonia [51]. A large follow-up survey study of 1462 patients showed that paternity was dependent on number of cycles of cisplatin-based chemotherapy. All men receiving 2 cycles, 83% with 3 cycles, and 76% after 4 cycles were able to conceive [54]. Another follow-up survey of 554 men found that high-dose cisplatin with a cumulative dose greater than 850 mg had a paternity rate of 38% compared to 62% in the low-dose cisplatin group that received less than 850 mg/m^2 [55]. It is important to consider the possible impact of chemotherapy on the offspring of cancer patients. These offspring may be at a higher risk of congenital malformations due to the mutagenic nature of treatments received by their parents [56, 57].

4.3 Radiation therapy

Radiation therapy (XRT), despite gonadal shielding, can pose gonadotoxic effects due to scatter radiation [58]. Testicular function is normally affected by XRT in a dose dependent manner. Semen parameters are significantly affected by radiation doses as low as 0.1 Gy [59]. Recovery of spermatogenesis is dependent on radiation dosage. Radiation doses less than 1 Gy can take up to 18 months and less than 4 Gy up to 5 years to recover. Radiation doses exceeding 4 Gy can lead to irreversible damage to spermatogenesis [60]. Leydig cells are more resistant to the gonadotoxic effects of XRT and require on average higher dosages greater than 20 Gy to cause primary hypogonadism [61]. Of note, germinal epithelium of the testis that are exposed to 3–7 week fractionated courses can experience more gonadal damage than with single doses [48]. When radiation is fractionated, cumulative doses that exceed greater than 2.5 Gy can irreversibly impair spermatogenesis [48]. Moreover, prior studies have found that radiotherapy seemed to have a more deleterious effect on fertility compared with chemotherapy alone [62].

Radiation therapy is especially harmful in cells with high replication rates, notably in both cancer cells and normal spermatogonia [63]. It increases sperm DNA damage, which limits replication and persists for 1–2 years following treatment [60]. This radiation induced DNA damage detected in primary spermatocytes continues to be present in mature spermatozoa as well [64]. A study of 96 TC patients found that the proportion of spermatozoa with DNA strand breaks was significantly higher in XRT patients during the first 2 years after therapy [60]. Elevated DNA damage is associated with poor oocyte fertilization, embryo development, implantation, and lower live birth rates [65].

4.4 Retroperitoneal lymph node dissection

Prior to the advent of chemotherapy and accurate cross-sectional imaging, the burden of disease of testicular cancer was great, and a wide surgical resection of retroperitoneal disease was needed to ensure patients with cancer-free survival. As a result, bilateral and suprahilar RPLNDs were routinely performed, with resection of or injury to post-ganglionic sympathetic nerves off the sympathetic chain and subsequent loss of antegrade ejaculatory function in 90% of patients [66, 67]. This has significant repercussions for reproductive age patients, who without forward ejaculation rely on adjunctive measures such as electroejaculation versus sperm extractions from the testis. The loss of forward ejaculation can be diagnosed through post-ejaculate urinalysis, wherein the presence of sperm in the urine is an indicator of retrograde ejaculation [68]. Sperm in the urine may be used for intrauterine insemination versus in vitro fertilization, depending on sperm concentration. While modified templates and meticulous attention to nerve sparing can preserve ejaculatory function, significant risk of nerve damage persists [69].

Electroejaculation (EEJ) uses a waveform generator in a burst or continuous fashion *via* a rectal probe to stimulate the seminal vesicles and sympathetic nerves at the aortic bifurcation and obturator nerves for forward ejaculation. This is typically performed under anesthesia to minimize patient discomfort. Although antegrade ejaculation may be achieved in >85% of patients, it typically requires milking from the urethra into a sterile container. The semen is then prepared for intrauterine insemination [70].

Alternatively, patients may consider testicular sperm extraction. Testicular sperm is not motile, and thus must be used for *in vitro* fertilization with intracytoplasmic sperm injection, a labor-intensive and costly form of assisted reproductive technology. To reduce rates of retrograde ejaculation, modified templates have been proposed which limit suprahilar, inter-

iliac, and contralateral dissection [66, 71–73]. Anatomical mapping studies of retroperitoneal metastases have resulted in modified RPLND that maximize antegrade ejaculation by limiting dissection in areas that have reduced risk of metastatic disease [66, 74–76]. Unilateral dissection leads to loss of antegrade ejaculation in 30% to 50% of patients, contributing to issues of primary hypo-fertility in 25% to 40% of TC patients [77]. In a cohort of 167 TC patients by Donohue *et al.* [78] undergoing prospective nerve-sparing modified unilateral template, the ejaculation rate was 98%.

A study of 341 patients undergoing RPLND found that a right-sided primary testicular tumor (OR 0.4, 95% CI 0.1–1.0, $p = 0.044$) and residual masses $\geq$5 cm (OR 0.1, 95% CI 0.0–0.7, $p = 0.020$) were most likely to be associated with retrograde ejaculation [79]. Another study surveyed 297 testicular cancer survivors for paternity. The paternity rate in patients treated with surgery alone (orchiectomy +/− RPLND) was 59%. In comparison, paternity rates were 68% and 50% in patients treated radiotherapy alone and chemotherapy alone, respectively. Paternity was lowest in patients' post-non-nerve sparing RPLND, versus 62% in patients with nerve sparing RPLND ($p < 0.0001$) [80]. Thus, loss of ejaculation greatly impacts patients' fertility and should be preserved when possible.

5. Strategies of fertility preservation

5.1 Post-pubertal fertility preservation

Sperm cryopreservation has been established as the primary method for fertility preservation in post-pubertal male patients. Prior studies have shown sperm cryopreservation to be not only the most cost-efficient, but also the most productive and robust technique for fertility preservation [81, 82]. Given that cytotoxic treatments including radiation and chemotherapy can lead to testicular failure, freezing of spermatozoa is a suitable solution for fertility preservation in TC patients [83]. Frozen-thawed semen can then be used intrauterine insemination, *in vitro* fertilization, or intracytoplasmic sperm injection [84]. It has been reported that cancer patients who have undergone sperm cryopreservation are also better able to cope with their diagnosis and treatment [85].

Sperm cryopreservation is performed by Andrology laboratories, which are commonly located in reproductive endocrinology or urology practices. Patients who do not have access to these labs may now even take advantage of mail-in kits, such as Overnite Male® (https://hospital.uillinois.edu/primary-and-specialty-care/urology/andrology/over-nite-male-kits), or Fellow® (https://www.meetfellow.com/kit), or Legacy® (https://www.givelegacy.com/). These kits use sperm preservation medium to keep sperm alive for ~24 hours. Thus, patients can ejaculate at home and mail the kit back *via* overnight shipping to a CLIA (Clinical Laboratory Improvement Amendments)-certified lab, where the semen in processed and frozen for future use.

For a majority of neurologically intact, post-pubertal TC patients, ejaculation is considered the most straightforward approach to collection of sperm [86]. However, more invasive means are available for patients who are unable to provide a sample through ejaculation. As noted in the previous section, men may consider electroejaculation as a bridge to intrauterine insemination or *in vitro* fertilization. Men with normal testicular function may undergo percutaneous epididymal sperm aspiration (PESA) or testicular sperm aspiration (TESA), where a small syringe is inserted into the epididymis or testis respectively to retrieve sperm. According to the AUA, 10% of TC patients present with azoospermia secondary to spermatogenic dysfunction, and thus do not have sperm within the ejaculate [87]. For these patients, a microsurgical testicular sperm extraction has the highest likelihood of isolating sperm for cryopreservation. In this surgery, the testis is searched for foci of spermatogenesis, usually in areas with larger and more opaque seminiferous tubules. These tubules are biopsied and sent to the andrology lab for processing. If sperm is recovered, it is cryopreserved in a similar fashion to ejaculated sperm. Prior studies have shown that almost half of men with significantly large volumes of TC still bear areas of spermatogenesis [88]. Additionally, some TC patients with nonobstructive azoospermia have been shown to recover spermatogenesis after treatment and may choose to have surgical testicular sperm extraction (TESE) performed at the time of orchiectomy as a means for fertility preservation [89].

Many techniques are available for the cryopreservation of sperm, including slow freezing and rapid freezing as conventional methods [83]. An alternative method to these freezing techniques is vitrification, which allows for the preservation of spermatozoa without the use of permeable cryoprotectants [90]. Cryopreservation may induce changes that reduce the integrity of sperm plasma membranes and ultimately influence fertilization potential [91, 92], although pregnancy outcomes have not been found to differ between frozen *vs.* thawed sperm [93].

Testicular cancer patients may also experience erectile dysfunction. Options for management include testosterone replacement therapy (TRT) and PDE-5 (Phosphodiesterase-5) inhibitors as first line therapies for ED in hypogonadal and eugonadal patients, respectively. Intracavernosal injection therapy, vacuum erectile devices (VEDs) with constriction bands, intraurethral prostaglandin suppositories and surgical placement of a penile prosthesis are considered for non-responders [94]. Up to 15% of TC survivors experience symptomatic hypogonadism [87]. Testosterone affects nitric oxide synthase release, PDE-5 expression, and cavernosal nerve function—all important factors in maintaining erectile function. Furthermore, PDE-5 inhibitors have been shown to be more efficacious in men with normal serum testosterone levels [95].

PDE-5 inhibitors are a first line therapy for erectile dysfunction. By preventing phosphodiesterase-5 mediated degradation of cGMP (cyclic guanosine monophosphate), PDE-5 inhibitors promote arterial inflow into the corpora cavernosa [96]. VEDs are plastic cylinders that are placed over the penis to create a vacuum, which pulls blood into the penis [96]. They should be used in conjunction with a constriction band at the base of the penis to trap the blood and maintain the erection when the suction is released. Intracavernosal injections are another option for erectile dysfunction patients. Vasoactive substances, which increase arterial inflow into the corpora *via* the cAMP

(cyclic adenosine monophosphate) pathway, are injected into the lateral aspect of the penis through a small gauge needle. These substances may include any combination of alprostadil, papaverine, phentolamine, and/or atropine [97]. An erection typically occurs within 10–15 minutes of the injection [96]. For patients who cannot use injections, alprostadil is also available as an intraurethral gel [98]. Patients who do not respond to first or second line therapies may consider a malleable or inflatable penile prosthesis [96].

5.2 Pre-pubertal fertility preservation

If the testicular cancer patient is pre-pubertal the testicle is unlikely to be producing sperm, thus obtaining ejaculated sperm impossible. Cryopreservation in the prepubertal population depends on the experimental preservation of germ cells with stem cell capability within the cryopreserved tissue. Currently, there are no established methods to use these germ cells for fertility. Subsequent methods for generation of viable sperm such as autologous testicular tissue grafting, spermatogonial stem cells (SSC) transplantation, and *in vitro* spermatogenesis all remain experimental [99, 100]. Of these methods, SSC transplantation is the only one that may reestablish fertility by natural conception and has restored spermatogenesis in non-human primates leading to viable embryos and even offspring [101, 102]. Given the presence of immature germ cell divisions, the prepubertal testis is highly sensitive to radiation and chemotherapy [103]. Leukemic infiltration in the testis of pre-pubertal patients may require direct irradiation of the testicles. This direct irradiation can later cause infertility secondary to oligospermia or azoospermia despite the development of normal secondary sexual characteristics [104]. Fractionation involves using small and incremented doses of radiation therapy over time to overcome the acute toxicity induced by a large single dose. Fractionation has been found to be beneficial for reducing dosage per session, but it also reduces time available for tissue healing and repair [105]. Although susceptibility may vary depending on the treatment, damage to the prepubertal testis can persist well into adulthood after treatment has ended [106]. Moreover, the pharmacological protection of the testis during oncologic treatment is a developing field in male onco-fertility.

Pharmacological agents may be administered collectively with chemotherapy to maintain testicular fertility. Although such strategies are experimental, they may offer non-invasive approaches to preserving fertility in TC patients who cannot leverage sperm cryopreservation [99]. Specifically, the clinical application of granulocyte colony-stimulating factor (G-CSF) may serve a role in male fertility preservation. In preclinical studies, G-CSF conferred a protective role by stimulating spermatogenesis of residual undifferentiated spermatogonia and improving spermatogenic recovery after exposure to high-dose alkylating agents [99]. In addition, antioxidant treatment with melatonin has been proposed to protect against oxidative stress and germline toxicity induced by alkylating agents such as busulfan. Studies in mice showed that melatonin reduces reactive oxygen species and apoptosis of spermatogonia associated with busulfan treatment [107]. These non-invasive approaches are considered experimental.

6. Conclusion

The impact of TC on fertility can be a complex concept. While preservation of fertility is possible for many patients it can be complicated by lack of knowledge surrounding the treatment implications as well as the mental and emotional burden of a cancer diagnosis, as well as lack of access to fertility specialists. In this review, we have highlighted that sexual dysfunction can occur in the treatment of testicular cancer and we discussed that treatment can contribute to long-term infertility and sexual dysfunction regardless of treatment modality. The risk of long-term complications should be considered among treatment options, especially with early-stage disease. All male patients should be offered fertility preservation prior to undergoing oncologic treatment.

ABBREVIATIONS

TC, testicular cancer; ED, erectile dysfunction; RPLND, retroperitoneal lymph node dissection; BEP, bleomycin-etoposide-cisplatin; FSH, follicle stimulating hormone; LH, luteinizing hormone; hCG, human chorionic gonadotropin; XRT, radiation therapy; TRT, testosterone replacement therapy; G-CSF, granulocyte colony-stimulating factor; TESE, testicular sperm extraction; TESA, testicular sperm aspiration; PESA, Percutaneous Epipdymal Sperm Aspiration.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

SD, LK, BL—wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Society A. Cancer treatment & survivorship facts & figures 2019–2021. American Cancer Society Atlanta. 2019.

[2] Huddart RA, Norman A, Moynihan C, Horwich A, Parker C, Nicholls E, *et al*. Fertility, gonadal and sexual function in survivors of testicular cancer. British Journal of Cancer. 2005; 93: 200–207.

[3] Surveillance, Epidemiology and End Results (SEER) Program. 2015. Available at: www.seer.cancer.gov (Accessed: 09 October 2022)

[4] Hanna N, Einhorn LH. Testicular cancer: a reflection on 50 years of discovery. Journal of Clinical Oncology. 2014; 32: 3085–3092.

[5] Carrière P, Baade P, Fritschi L. Population based incidence and age distribution of spermatocytic seminoma. Journal of Urology. 2007; 178: 125–128.

[6] Brodsky MS. Testicular cancer survivors' impressions of the impact of the disease on their lives. Qualitative Health Research. 1995; 5: 78–96.

[7] Schover LR, Brey K, Lichtin A, Lipshultz LI, Jeha S. Knowledge and experience regarding cancer, infertility, and sperm banking in younger male survivors. Journal of Clinical Oncology. 2002; 20: 1880–1889.

[8] Schover LR, Brey K, Lichtin A, Lipshultz LI, Jeha S. Oncologists' attitudes and practices regarding banking sperm before cancer treatment. Journal of Clinical Oncology. 2002; 20: 1890–1897.

[9] Oktay K, Harvey BE, Partridge AH, Quinn GP, Reinecke J, Taylor HS, *et al*. Fertility preservation in patients with cancer: ASCO clinical practice guideline update. Journal of Clinical Oncology. 2018; 36: 1994–2001.

[10] Wiechno P, Demkow T, Kubiak K, Sadowska M, Kamińska J. The quality of life and hormonal disturbances in testicular cancer survivors in cisplatin era. European Urology. 2007; 52: 1448–1455.

[11] Rossen P, Pedersen AF, Zachariae R, von der Maase H. Sexuality and body image in long-term survivors of testicular cancer. European Journal of Cancer. 2012; 48: 571–578.

[12] Kim C, McGlynn KA, McCorkle R, Li Y, Erickson RL, Ma S, *et al*. Sexual functioning among testicular cancer survivors: a case-control study in the U.S. Journal of Psychosomatic Research. 2012; 73: 68–73.

[13] La Vignera S, Cannarella R, Duca Y, Barbagallo F, Burgio G, Compagnone M, *et al*. Hypogonadism and sexual dysfunction in testicular tumor survivors: a systematic review. Frontiers in Endocrinology. 2019; 10: 264.

[14] Jonker-Pool G, Basten JPV, Hoekstra HJ, Driel MFV, Sleijfer DT, Koops HS, *et al*. Sexual functioning after treatment for testicular cancer. Cancer. 1997; 80: 454–464.

[15] Rosendal S, Kristensen E, Giraldi A. Sexual dysfunctions in men treated for testicular cancer—secondary publication. Danish Medical Bulletin. 2008; 55: 211–215.

[16] Arai Y, Kawakita M, Okada Y, Yoshida O. Sexuality and fertility in long-term survivors of testicular cancer. Journal of Clinical Oncology. 1997; 15: 1444–1448.

[17] Lange PH, Narayan P, Vogelzang NJ, Shafer RB, Kennedy BJ, Fraley EE. Return of fertility after treatment for nonseminomatous testicular cancer: changing concepts. Journal of Urology. 1983; 129: 1131–1135.

[18] Bancroft J, Graham CA, Janssen E, Sanders SA. The dual control model: current status and future directions. Journal of Sex Research. 2009; 46: 121–142.

[19] Rastrelli G, Corona G, Maggi M. Testosterone and sexual function in men. Maturitas. 2018; 112: 46-52.

[20] Leitner SP, Bosl GJ, Bajorunas D. Gonadal dysfunction in patients treated for metastatic germ-cell tumors. Journal of Clinical Oncology. 1986; 4: 1500–1505.

[21] Bolen D, Burkhard FC, Mills R, Sonntag RW, Studer UE. Fertility and sexual function following orchiectomy and 2 cycles of chemotherapy for stage I high risk nonseminomatous germ cell cancer. Journal of Urology. 2001; 165: 441–444.

[22] Rieker PP, Edbril SD, Garnick MB. Curative testis cancer therapy: psychosocial sequelae. Journal of Clinical Oncology. 1985; 3: 1117–1126.

[23] Schover LR, von Eschenbach AC. Sexual and marital relationships after treatment for nonseminomatous testicular cancer. Urology. 1985; 25: 251–255.

[24] Schover LR, Gonzales M, von Eschenbach AC. Sexual and marital relationships after radiotherapy for seminoma. Urology. 1986; 27: 117–123.

[25] Gritz ER, Wellisch DK, Siau J, Wang H. Long-term effects of testicular cancer on marital relationships. Psychosomatics. 1990; 31: 301–312.

[26] Sheppard C, Wylie KR. An assessment of sexual difficulties in men after treatment for testicular cancer. Sexual and Relationship Therapy. 2001; 16: 47–58.

[27] Tinkler SD, Howard GCW, Kerr GR. Sexual morbidity following radiotherapy for germ cell tumours of the testis. Radiotherapy and Oncology. 1992; 25: 207–212.

[28] Chapple A, McPherson A. The decision to have a prosthesis: a qualitative study of men with testicular cancer. Psycho-Oncology. 2004; 13: 654–664.

[29] Carpentier MY, Fortenberry JD. Romantic and sexual relationships, body image, and fertility in adolescent and young adult testicular cancer survivors: a review of the literature. Journal of Adolescent Health. 2010; 47: 115–125.

[30] Loh-Doyle J, Ghodoussipour S, Daneshmand S. 105 factors associated with testicular prostheses availability and implantation. The Journal of Sexual Medicine. 2017; 14: e38–e39.

[31] Hassan HC, Cullen IM, Casey RG, Rogers E. Gynaecomastia: an endocrine manifestation of testicular cancer. Andrologia. 2008; 40: 152–157.

[32] Heidenreich A, Weissbach L, Höltl W, Albers P, Kliesch S, Köhrmann KU, *et al*. Organ sparing surgery for malignant germ cell tumor of the testis. The Journal of Urology. 2001; 29: 2161–2165.

[33] Shukla AR, Woodard C, Carr MC, Huff DS, Canning DA, Zderic SA, *et al*. Experience with testis sparing surgery for testicular teratoma. Journal of Urology. 2004; 171: 161–163.

[34] Jacobsen KD, Theodorsen L, Fossa SD. Spermatogenesis after unilateral orchiectomy for testicular cancer in patients following surveillance policy. Journal of Urology. 2001; 165: 93–96.

[35] Petersen PM, Skakkebaek NE, Rorth M, Giwercman A. Semen quality and reproductive hormones before and after orchiectomy in men with testicular cancer. Journal of Urology. 1999; 161: 822–826.

[36] Vakalopoulos I, Dimou P, Anagnostou I, Zeginiadou T. Impact of cancer and cancer treatment on male fertility. Hormones. 2015; 14: 579–589.

[37] Fosså SD, Aabyholm T, Vespestad S, Norman N, Ous S. Semen quality after treatment for testicular cancer. European Urology. 1993; 23: 172–176.

[38] Fosså SD, Theodorsen L, Norman N, Aabyholm T. Recovery of impaired pretreatment spermatogenesis in testicular cancer. Fertility and Sterility. 1990; 54: 493–496.

[39] Moody JA, Ahmed K, Yap T, Minhas S, Shabbir M. Fertility managment in testicular cancer: the need to establish a standardized and evidence-based patient-centric pathway. BJU International. 2019; 123: 160–172.

[40] Fosså SD, Abyholm T, Aakvaag A. Spermatogenesis and hormonal status after orchiectomy for cancer and before supplementary treatment. European Urology. 1984; 10: 173–177.

[41] Hartlapp J, Brensing K, Voss K, Deitenbeck R, Mumperow E. Long-term impairments of the gonadal function after cisplatin-based chemotherapy in 140 patients with testicular cancer. American Society of Clinical Oncology. 1990; 9: 133.

[42] Pectasides D, Pectasides E, Papaxoinis G, Skondra M, Gerostathou M, Karageorgopoulou S, *et al*. Testicular function in poor-risk nonseminomatous germ cell tumors treated with methotrexate, paclitaxel, ifosfamide, and cisplatin combination chemotherapy. Journal of Andrology. 2009; 30: 280–286.

[43] Jacobsen KD, Theodorsen L, Frssa SD. Spermatogenesis after unilateral orchiectomy for testicular cancer in patients following surveillance policy. Journal of Urology. 2001; 165: 93–96.

[44] Abram McBride J, Lipshultz LI. Male fertility preservation. Current Urology Reports. 2018; 19: 49.

[45] Bujan L, Walschaerts M, Moinard N, Hennebicq S, Saias J, Brugnon F, *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. Fertility and Sterility. 2013; 100: 673–680.e2.

[46] Kim ED, Lipshultz LI. Evaluation of the infertile male. Impotence and Infertility. 1999; 113: 97–110.

[47] Stahl O, Boyd HA, Giwercman A, Lindholm M, Jensen A, Kruger Kjaer

S, *et al*. Risk of birth abnormalities in the offspring of men with a history of cancer: a cohort study using danish and swedish national registries. JNCI Journal of the National Cancer Institute. 2011; 103: 398–406.

[48] Blackhall F, DeVita VT, Hellman S, Rosenberg SA. Cancer: Principles and Practice of Oncology. 7th Edn. Elsevier: Philadelphia. 2005.

[49] Colpi GM, Contalbi GF, Nerva F, Sagone P, Piediferro G. Testicular function following chemo-radiotherapy. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2004; 113: S2–S6.

[50] Trottmann M, Becker AJ, Stadler T, Straub J, Soljanik I, Schlenker B, *et al*. Semen quality in men with malignant diseases before and after therapy and the role of cryopreservation. European Urology. 2007; 52: 355–367.

[51] Ostrowski KA, Walsh TJ. Infertility with testicular cancer. Urologic Clinics of North America. 2015; 42: 409–420.

[52] Clermont Y. Renewal of spermatogonia in man. American Journal of Anatomy. 1966; 118: 509–524.

[53] Pont J, Albrecht W, Postner G, Sellner F, Angel K, Höltl W. Adjuvant chemotherapy for high-risk clinical stage I nonseminomatous testicular germ cell cancer: long-term results of a prospective trial. Journal of Clinical Oncology. 1996; 14: 441–448.

[54] Brydøy M, Fosså SD, Klepp O, Bremnes RM, Wist EA, Wentzel-Larsen T, *et al*. Paternity and testicular function among testicular cancer survivors treated with two to four cycles of cisplatin-based chemotherapy. European Urology. 2010; 58: 134–141.

[55] Brydøy M, Fosså SD, Klepp O, Bremnes RM, Wist EA, Wentzel-Larsen T, *et al*. Paternity following treatment for testicular cancer. JNCI: Journal of the National Cancer Institute. 2005; 97: 1580–1588.

[56] Al-Jebari Y. The health of the children in relation to paternal age, cancer, and medication [doctoral thesis]. Lund University. 2021.

[57] Al-Jebari Y, Glimelius I, Berglund Nord C, Cohn-Cedermark G, Ståhl O, Tandstad T, *et al*. Cancer therapy and risk of congenital malformations in children fathered by men treated for testicular germ-cell cancer: a nationwide register study. PLOS Medicine. 2019; 16: e1002816.

[58] Fraass BA, Kinsella TJ, Harrington FS, Glatstein E. Peripheral dose to the testes: the design and clinical use of a practical and effective gonadal shield. International Journal of Radiation Oncology, Biology, Physics. 1985; 11: 609–615.

[59] Howell S, Shalet S. Gonadal damage from chemotherapy and radiotherapy. Endocrinology & Metabolism Clinics of North America. 1998; 27: 927–943.

[60] Ståhl O, Eberhard J, Jepson K, Spano M, Cwikiel M, Cavallin-Ståhl E, *et al*. Sperm DNA integrity in testicular cancer patients. Human Reproduction. 2006; 21: 3199–3205.

[61] Rowley MJ, Leach DR, Warner GA, Heller CG. Effect of graded doses of ionizing radiation on the human testis. Radiation Research. 1974; 59: 665.

[62] Huyghe E, Matsuda T, Daudin M, Chevreau C, Bachaud J, Plante P, *et al*. Fertility after testicular cancer treatments. Cancer. 2004; 100: 732–737.

[63] Gandini L, Sgrò P, Lombardo F, Paoli D, Culasso F, Toselli L, *et al*. Effect of chemo- or radiotherapy on sperm parameters of testicular cancer patients. Human Reproduction. 2006; 21: 2882–2889.

[64] Qu N, Itoh M, Sakabe K. Effects of chemotherapy and radiotherapy on spermatogenesis: the role of testicular immunology. International Journal of Molecular Sciences. 2019; 20: 957.

[65] Robinson L, Gallos ID, Conner SJ, Rajkhowa M, Miller D, Lewis S, *et al*. The effect of sperm DNA fragmentation on miscarriage rates: a systematic review and meta-analysis. Human Reproduction. 2012; 27: 2908–2917.

[66] Donohue JP, Thornhill JA, Foster RS, Rowland RG, Bihrle R. Retroperitoneal lymphadenectomy for clinical stage a testis cancer (1965 to 1989): modifications of technique and impact on ejaculation. Journal of Urology. 1993; 149: 237–243.

[67] Masterson TA, Cary C. The use of modified templates in early and advanced stage nonseminomatous germ cell tumor. Advances in Urology. 2018; 2018: 1–5.

[68] Olooto WE. Diagnostic importance of URINALYSIS in endocrinology—a review. Annals of Biological Sciences. 2013; 1: 23–27.

[69] Ghodoussipour S, Daneshmand S. Surgical strategies for postchemotherapy testis cancer. Translational Andrology and Urology. 2020; 9: S74–S82.

[70] Lipshultz LI, Howards SS, Niederberger CS, Lamb D. Infertility in the male. 5th edn. Cambridge University Press: New York. 2022.

[71] Donohue JP, Zachary JM, Maynard BR. Distribution of nodal metastases in nonseminomatous testis cancer. Journal of Urology. 1982; 128: 315–320.

[72] Eggener SE, Carver BS, Sharp DS, Motzer RJ, Bosl GJ, Sheinfeld J. Incidence of disease outside modified retroperitoneal lymph node dissection templates in clinical stage I or IIA nonseminomatous germ cell testicular cancer. Journal of Urology. 2007; 177: 937–943.

[73] Ray B, Hajdu SI, Whitmore WF. Distribution of retroperitoneal lymph node metastases in testicular germinal tumors. Cancer. 1974; 33: 340–348.

[74] Janetschek G, Reissigl A, Peschel R, Hobisch A, Bartsch G. Laparoscopic retroperitoneal lymph node dissection for clinical stage I nonseminomatous testicular tumor. Urology. 1994; 44: 382–391.

[75] Nelson JB, Chen RN, Bishoff JT, Oh WK, Kantoff PW, Donehower RC, *et al*. Laparoscopic retroperitoneal lymph node dissection for clinical stage I nonseminomatous germ cell testicular tumors. Urology. 1999; 54: 1064–1067.

[76] Weissbach L, Boedefeld E, Horstmann-Dubral B. Surgical treatment of stage-I non-seminomatous germ cell testis tumor. European Urology. 1990; 17: 97–106.

[77] Baniel J, Sella A. Complications of retroperitoneal lymph node dissection in testicular cancer: primary and post-chemotherapy. Seminars in Surgical Oncology. 1999; 17: 263–267.

[78] Donohue JP, Thornhill JA, Foster RS, Rowland RG, Bihrle R. Retroperitoneal lymphadenectomy for clinical stage a testis cancer (1965 to 1989): modifications of technique and impact on ejaculation. Journal of Urology. 1993; 149: 237–243.

[79] Pettus JA, Carver BS, Masterson T, Stasi J, Sheinfeld J. Preservation of ejaculation in patients undergoing nerve-sparing postchemotherapy retroperitoneal lymph node dissection for metastatic testicular cancer. Urology. 2009; 73: 328–331.

[80] Matos E, Škrbinc B, Zakotnik B. Fertility in patients treated for testicular cancer. Journal of Cancer Survivorship. 2010; 4: 274–278.

[81] Agarwal A, Ong C, Durairajanayagam D. Contemporary and future insights into fertility preservation in male cancer patients. Translational Andrology and Urology. 2014; 3: 27.

[82] Gilbert K, Nangia AK, Dupree JM, Smith JF, Mehta A. Fertility preservation for men with testicular cancer: is sperm cryopreservation cost effective in the era of assisted reproductive technology? Urologic Oncology: Seminars and Original Investigations. 2018; 36: 92.e1–92.e9.

[83] Hezavehei M, Sharafi M, Kouchesfahani HM, Henkel R, Agarwal A, Esmaeili V, *et al*. Sperm cryopreservation: a review on current molecular cryobiology and advanced approaches. Reproductive BioMedicine Online. 2018; 37: 327–339.

[84] Agarwal A, Ong C, Durairajanayagam D. Contemporary and future insights into fertility preservation in male cancer patients. Translational Andrology and Urology. 2014; 3: 27–40.

[85] Saito K, Suzuki K, Iwasaki A, Yumura Y, Kubota Y. Sperm cryopreservation before cancer chemotherapy helps in the emotional battle against cancer. Cancer. 2005; 104: 521–524.

[86] Göbel K, Wedell J, Herrmann AM, Wachsmuth L, Pankratz S, Bittner S, *et al*. 4-Aminopyridine ameliorates mobility but not disease course in an animal model of multiple sclerosis. Experimental Neurology. 2013; 248: 62–71.

[87] Stephenson A, Eggener SE, Bass EB, Chelnick DM, Daneshmand S, Feldman D, *et al*. Diagnosis and treatment of early stage testicular cancer: AUA guideline. Journal of Urology. 2019; 202: 272–281.

[88] Moody JA, Ahmed K, Horsfield C, Pedersen MRV, Yap T, Shabbir M. Fertility preservation in testicular cancer—predictors of spermatogenesis. BJU International. 2018; 122: 236–242.

[89] Schrader M, Mller M, Sofikitis N, Straub B, Krause H, Miller K. "Oncotese": testicular sperm extraction in azoospermic cancer patients before chemotherapy—new guidelines? Urology. 2003; 61: 421–425.

[90] Isachenko E, Isachenko V, Katkov II, Dessole S, Nawroth F. Vitrification of mammalian spermatozoa in the absence of cryoprotectants: from past practical difficulties to present success. Reproductive BioMedicine Online. 2003; 6: 191–200.

[91] Di Santo M, Tarozzi N, Nadalini M, Borini A. Human sperm cryopreservation: update on techniques, effect on DNA integrity, and implications

for ART. Advances in Urology. 2012; 2012: 1–12.

[92] Parks JE, Graham JK. Effects of cryopreservation procedures on sperm membranes. Theriogenology. 1992; 38: 209–222.

[93] Liu J, Tsai YL, Katz E, Compton G, Garcia JE, Baramki TA. Outcome of *in-vitro* culture of fresh and frozen-thawed human testicular spermatozoa. Human Reproduction. 1997; 12: 1667–1672.

[94] Randrup E, Baum N, Feibus A. Erectile dysfunction and cardiovascular disease. Postgraduate Medicine. 2015; 127: 166–172.

[95] Zhu J, Zhang W, Ou N, Song Y, Kang J, Liang Z, *et al*. Do testosterone supplements enhance response to phosphodiesterase 5 inhibitors in men with erectile dysfunction and hypogonadism: a systematic review and meta-analysis. Translational Andrology and Urology. 2020; 9: 591–600.

[96] Mobley DF, Khera M, Baum N. Recent advances in the treatment of erectile dysfunction. Postgraduate Medical Journal. 2017; 93: 679–685.

[97] Becher E. Topical alprostadil cream for the treatment of erectile dysfunction. Expert Opinion on Pharmacotherapy. 2004; 5: 623–632.

[98] Khan MA, Raistrick M, Mikhailidis DP, Morgan RJ. MUSE: clinical experience. Current Medical Research and Opinion. 2002; 18: 64–67.

[99] Ntemou E, Alexandri C, Lybaert P, Goossens E, Demeestere I. Oncofertility: pharmacological protection and immature testicular tissue (ITT)-based strategies for prepubertal and adolescent male cancer patients. International Journal of Molecular Sciences. 2019; 20: 5223.

[100] Scarisbrick JJ, Quaglino P, Prince HM, Papadavid E, Hodak E, Bagot M, *et al*. The PROCLIPI international registry of early-stage mycosis fungoides identifies substantial diagnostic delay in most patients. British Journal of Dermatology. 2019; 181: 350–357.

[101] Hermann B, Sukhwani M, Winkler F, Pascarella J, Peters K, Sheng Y, *et al*. Spermatogonial stem cell transplantation into rhesus testes regenerates spermatogenesis producing functional sperm. Cell Stem Cell. 2012; 11: 715–726.

[102] Fayomi AP, Peters K, Sukhwani M, Valli-Pulaski H, Shetty G, Meistrich ML, *et al*. Autologous grafting of cryopreserved prepubertal rhesus testis produces sperm and offspring. Science. 2019; 363: 1314–1319.

[103] Müller J, Skakkebæk NE. Quantification of germ cells and seminiferous tubules by stereological examination of testicles from 50 boys who suffered from sudden death. International Journal of Andrology. 1983; 6: 143–156.

[104] Mitchell G. The rationale for fractionation in radiotherapy. Clinical Journal of Oncology Nursing. 2013; 17: 412–417.

[105] Hussein AA, Tran ND, Smith JF. Fertility preservation for boys and adolescents facing sterilizing medical therapy. Translational Andrology and Urology. 2014; 3: 382–390.

[106] Allen CM, Lopes F, Mitchell RT, Spears N. How does chemotherapy treatment damage the prepubertal testis? Reproduction. 2018; 156: R209–R233.

[107] Zhang X, Xia Q, Wei R, Song H, Mi J, Lin Z, *et al*. Melatonin protects spermatogonia from the stress of chemotherapy and oxidation *via* eliminating reactive oxidative species. Free Radical Biology and Medicine. 2019; 137: 74–86.

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