REVIEW

Effect of Chemotherapy on Gonadal Function and Sexual Function of Male Cancer Survivors: A Review Article

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Purpose: The advancement of anti-cancer treatment has increased survival rates among patients, yet putting them in an increased risk for developing side effects. In addition to early side effects, anti-cancer treatments, in particular chemotherapeutic medications can cause long-term side effects; fertility and sexual dysfunction included. The aim of this study was to review existing data on the effects of different chemotherapeutic agents on fertility and sexual function of male cancer survivors who received chemotherapy at different stages of life.

Methods: We searched PubMed/MEDLINE, Scopus, and Google Scholar to detect studies focused on the effect of chemotherapy on the gonadal/testicular function and sexual function of male cancer survivors. We restricted our search to English language publications and manuscript published before the year 2000 were excluded.

Results: It has been well understood that chemotherapy impairs gonadal function in a major number of cancer survivors and gonadal dysfunction is not protected if chemotherapeutic agents are administered before puberty in males. Moreover, the effect of chemotherapy on sexual function is controversial.

Conclusion: While several articles reported the worst effect of chemotherapy on the sexual function of cancer survivors, some studies reported that chemotherapy does not impair sexual function. Higher levels of chemotherapy dose seem to be associated with more gonadal and sexual dysfunction.

Keywords: male; sexual dysfunction; chemotherapy; cancer

INTRODUCTION

The advancement of anti-cancer treatment has increased survival rates among patients, yet putting them at an increased risk for developing side effects. Thanks to the progress in cancer detection and management modalities, the number of cancer survivors is increasingly rising[(1)]. Accordingly, medical centers in the USA have identified around 14.5 million cancer survivors in January 2014; the number will likely increase to about 19 million by January 2024[(2)]. In children and adolescents, the 5-year survival rate for all types of cancer has significantly increased to nearly 82%[(3)].

In addition to early side effects, anti-cancer treatments, in particular chemotherapeutic medications can cause long-term side effects; fertility and sexual dysfunction included[(4,5)]. Adverse effects of chemotherapeutic agents depend on patients' age, treatment agent and dosage and the type of cancer[(6)]. In younger adults with cancer, future fecundity and sexual function is a prominent concern for chemotherapy-receivers which requires prophylactic measures.

Over 3000 men of reproductive ages are receiving chemotherapy in addition to other modalities of cytotoxic cancer treatment[(7)]. The highest incidence of common cancers, namely testicular cancer, Hodgkin's disease, acute lymphocytic leukemia (ALL) and bone and soft tissue sarcoma is identified in 15-45-year-old men [(8)]. Testicular cancer alone is the most common cancer in men aged 25 to 40, a period in which sexual function is a paramount aspect of life[(9)]. In one study, administering chemotherapy in male children was associated with a 46% infertility rate in their adulthood, compared to a rate of 17% in their siblings[(10)].

At the physiologic level, chemotherapeutic agents affect spermatogenesis and hormonal balance. The degree of gonadotoxicity is determined by the dosage of chemotherapeutic agent, stage of spermatogenesis and pre-treatment quality of semen[(11)]. Chemotherapeutic agents target cells with high proliferation rates, hence rapidly-dividing spermatogonia are the most sensitive cells to gonadotoxic effects of chemotherapy while stem cells with lower rates of proliferation are more resistant. Accordingly, the fertility function typically declines to its lowest level during 4th to 6th week after chemotherapy[(12,13)]. Restoration of germ cell damage after treatment cessation is dependent on the type of anti-cancer agent and the severity of gonadal damage. Many chemotherapy agents further destroy gonads by inducing hyalinization and fibrosis of testicular interstitial tissue[(13)].

Sexual dysfunction is another aspect of chemotherapy side effects in male cancer patients. Patients with testicular cancer who received chemotherapy were reported to have reduced libido and sexual arousal, in addition to erection and ejaculation disorders, lower intensity of orgasm and lower volume of semen compared to those

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who underwent orchiectomy alone[14].
Childhood exposure to chemotherapeutic agents was suggested to be safer than exposure during adolescence and pre-puberty period since testes are in the "quiescent stage" in the early years of life. However, recent studies have shown that anti-cancer treatment can execute gonadotoxic effects at all stages of life[15,16]. Childhood cancer survivors are reported to have an increased rate of hypogonadism and impaired spermatogenesis compared to the general population[17,18]. In fact, Sertoli cells which are highly active during infancy, are sensitive targets of chemotherapy[19]. Leyding cells which produce testosterone are considered even more vulnerable than germs cells and sertoli cells in infants and their destruction will lead to hypogonadism in long term survivors[20].
Despite considerable data on the consequences of chemotherapy in adult patients, the literature lacks enough studies on gonadotoxicity of chemotherapy in childhood and the pre-pubertal period and most of the existing data is deduced from adult research. In addition, few studies are available on the exclusive effect of each chemotherapeutic agent on fertility and sexual function since most anti-cancer treatments are administered in combination. Therefore, the classification of anti-cancer agents based on their risk of infertility and sexual dysfunction has remained questionable.
The aim of this study was to systematically review existing data on the effects of different chemotherapeutic agents on fertility and sexual function of male cancer survivors who received chemotherapy at different stages of life.

METHODS

We searched PubMed/MEDLINE, Scopus, and Google Scholar to detect studies focused on the effect of chemotherapy on the gonadal/testicular function and sexual function of male cancer survivors. Studies that reported the effect of chemotherapeutic agents on the general population consisting of both males and females were excluded. Furthermore, studies that investigated gonadal and sexual functions in patients who underwent chemotherapy in combination with other cancer treatments including radiotherapy and surgical approaches were also excluded. We restricted our search to English language publications and manuscripts published before the year 2000 were excluded. The search keywords were as follows: (testicular function OR gonadal function OR sexual function OR sexuality OR sexual dysfunction) AND (chemotherapy) AND (male cancer survivors OR male cancer).
This study was ethically approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences(IR.SBMU.RETECH.REC.1400.062).

Effect of chemotherapy on sexual function of male cancer survivors

A study conducted by Monti et al. in 2003, reported that treatment of germ cell tumor (GCT) with chemotherapy and hematopoietic stem cell support caused sexual dysfunction in 10 of 30 patients (33%) but none of them considered it a major problem. Difficulty in erection was mentioned by 7 patients, difficulty in maintaining an erection was mentioned by 10 (33%), and difficulty achieving orgasm was mentioned by 8 (27%) patients. However, 20 patients declared that they have no problem with their sexual life and 13 patients thought that both disease itself and chemotherapy could cause sexual problems[21]. A study conducted by Chovanec et al. in 2020, reported that germ cell tumor survivors treated with cisplatin-based regimens experienced a low ability to achieve orgasm, orgasmic dysfunction, and a lower level of sexual life quality[21]. Tasdemir et al. reported that testicular cancer survivors treated with 4 cycles of cisplatin, etoposide, and bleomycin (PEB) regimen had a greater risk than control patients in developing erectile dysfunction (ED)[22].
A cross-sectional study conducted by Eeltink et al. reported that survivors of Hodgkin lymphoma (HL) treated on average 4 years with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) did not report any sexual problems. However, one-third of Hodgkin lymphoma survivors who were treated with bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procabazine, and prednisone (BEACOPP) reported experiencing erectile dysfunction. As BEACOPP is used as standard therapy in advanced stage HL, its effect on sexual dysfunction should be noted in daily practice and sexual problem monitoring is recommended in this group of patients. Furthermore, this study failed to show any significant difference in perceived sexual problems between HL survivors and control group[23]. Behringer et al. showed that early stage survivors of HL achieved the same levels of sexual functioning after chemotherapy compared to controls, while advanced stage survivors of HL developed more sexual function [24]. This could be due to the fact that ABVD regimen that is used mainly in early stages of HL is consisted of 1 alkylating agent called dacarbazine, while BEACOPP that is used in higher stages of HL include 2 alkylating agents, namely procabazine and cyclophosphamide. Consistently, Relander et al. reported that male cancer survivors treated with high dose of alkylating agents for childhood cancers experienced sexual dysfunction[25].
While detrimental effects of chemotherapeutic agents on sexual function of male cancer survivors have been understood, it should be noted that some degree of the sexual issues could be due to the stress and concerns related to cancer diagnosis. In fact, activation of stress-related canters causes reduced libido, erection, and ejaculation dysfunction in cancer survivors[26].
Sexuality is a prominent aspect of life. According to Seligman's model, sexuality is composed of 5 distinct layers, namely: sexual identity, sexual orientation, sexual preferences, sex role and sexual performance. Each component of male sexuality can be impaired due to biological or psychological risk factors. However, the larger share of biological factors in particular layers shows the importance of medical conditions and interventions in determining sexual function[27].
Chemotherapy has short and long-term side effects in recipients, with sexual dysfunction being one of the most life-changing among them. Male sex roles encompass various aspects that might be affected by chemotherapy, including: a sense of masculinity, sense attractiveness to the opposite gender, sexual drive, phases of sexual response cycle (arousal, erection, ejaculation and climax) and sexual satisfaction[28].
The risk of sexual impairment in cancer patients who receive chemotherapy is relevant to the dose of cytotoxic agent. Accordingly, two courses of adjuvant chemotherapy with cisplatin, vinblastine and bleomycin, or

bleomycin, etoposide and cisplatin in stage I high risk nonseminomatous germ cell testicular cancer did not lead to significant or permanent sexual dysfunction. However, chemotherapy with a larger number of courses and higher doses increases the risk of sexual disorders in men with testicular cancer at a higher clinical stage[29]. Alkylating agents (cyclophosphamide equivalent dose > 20g/m^2) and platinum-derived agents could lead to sexual dysfunction through damaging testicular tissue which subsequently leads to reduced levels of testosterone[30].

The loss of attractiveness for female partner is another side effect of cancer treatment. According to Gritz et al. who assessed long-term effects of testicular cancer on sexual functioning in married couples, cisplatin-based chemotherapy was associated with a 70% reduction of attractiveness as stated by female partners. However, the patients' own perception of reduced attractiveness was about 60% which is in contrast to the pattern of higher rate of perceived loss of attractiveness by the patients than their partners in other treatment modalities [31].

The effect of chemotherapy on the sexual function of cancer patients who had undergone chemotherapy in their childhood is not well studied. Most children with cancer who were treated by chemotherapy developed secondary sexual characteristics and entered into puberty at a normal age; however, testicular dysfunction and fertility disorders are suggested as potential adverse effects that might occur in their adulthood[6]. Among survivors of pediatric brain tumor who were treated by chemotherapy and other treatment options, growth impairment, growth hormone deficiency and hypogonadism as well as low testicular volume were common [32].

Effect of chemotherapy on fertility of male cancer survivors

Cyclophosphamide

In a study, it has been reported that cyclophosphamide equivalent dose in 214 male childhood cancer survivors (median age 7·7 years [range 0·01–20·3] at diagnosis, 29·0 years [18·4–56·1] at assessment) caused azoospermia in 53 (25%), oligospermia in 59 (28%), and normospermia in 102 (48%) of the participants. Administration of cyclophosphamide equivalent dose was also negatively correlated with sperm concentration[18]. Supportively, males treated with high dose of cyclophosphamide for childhood sarcoma showed azoospermia (10 of 17 patients), oligospermia (5 of 17 patients), abnormal levels of FSH (10 of 14 patients), and elevated gonadotropin-releasing hormone –stimulated LH levels (13 of 14 patients)[16]. Two studies conducted by Yoon et al[33]. and Relander et al.[25], demonstrated that chemotherapy caused impairment of gonadal function (oligospermia and azoospermia) in childhood cancer survivors. Moreover, the level of gonadal function impairment is more severe in patients who received high cyclophosphamide equivalent dose than patients who received low cyclophosphamide equivalent dose. According to a study conducted by Arush et al. male cancer survivors treated with cyclophosphamide for childhood Hodgkin and non-Hodgkin lymphoma showed high rates of azoospermia and oligospermia[34]. A study conducted by Nurmio et al. evaluated the effect of chemotherapy for childhood lymphoblastic leukemia on spermatogonia and future fertility. Authors declared that high dose cyclophosphamide impaired testicular function; however, standard dosage of cyclophosphamide does not deplete spermatogonial stem cell pool and testicular function[35].

Ifosfamide

A study conducted by Longhi et al. demonstrated that fertility is associated with ifosfamide dose and high dose of ifosfamide caused azoospermia in male patients treated for osteosarcoma after 8 years of follow-up [36]. A comparative study between ifosfamide-and cyclophosphamide containing regimen demonstrated that ifosfamide is associated with a lower risk of gonadal dysfunction compared to cyclophosphamide[37].

Cisplatin

A study conducted by Gerl et al. evaluated the effect of cisplatin on gonadal function of germ cell tumor survivors. Based on their results, standard doses of cisplatin-based regimen (< 400mg/m^2) cause no significant deterioration in Leydig cell dysfunction in long term germ cell tumor survivors. However, high cumulative doses of cisplatin based-regimen lead to significant and persistent dysfunction of Leydig cells and abnormal levels of testosterone, FSH, and LH hormones[20]. In contrast, a study conducted by Gaffan et al. demonstrated that fertility of male germ cell tumor survivors is not correlated with cumulative cisplatin dose[38]. A study conducted by Bridoy et al. in 2010, reported that 80% of testicular cancer survivors treated with cisplatin-based regimen had successful paternity at median 12 years' follow-up and number of chemotherapy cycles is significantly associated with paternity. Furthermore, increasing number of cycles is associated with higher levels of FSH hormone but not LH and testosterone levels. Based on the results of this study, decreasing cycles of chemotherapy improves the prospect of paternity in cancer survivors[39]. A study aimed to investigate the factors affecting the post chemotherapy normalization of semen among testicular cancer survivors treated with cisplatin-based regimen. It was concluded that age at diagnosis (< 25 years), number of chemotherapy cycles (< 4 cycles), and level of FSH at the end of chemotherapy (< 18 mIU) were independent factors associated with normalization of semen[40].

Combination therapy

A study conducted by Pectasides et al. in 2004, on testicular cancer patients treated with bleomycin-etoposide-carboplatin combination therapy reported that chemotherapy increased FSH serum level one-year post chemotherapy but it returned to normal level after 18 months. Moreover, this regimen has no effect on LH and Testosterone level and therefore has no major effect on fertility and Leydig cell function[16]. Later, a similar study by Bujan et al., evaluated the effect of chemotherapeutic regimen (bleomycin, etoposide, and cisplatin) on spermatogenesis of patients with testicular germ cell tumor. Based on this study, mean total sperm count returned to a normal levels 12 months after two or fewer cycles of this regimen, but not after more than two cycles of this regimen[41]. Another study reported that chemotherapeutic regimen containing bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, and procarbazine had no effect on male hormones and caused no symptoms of hypogonadism in male Hodgkin cancer survivors[23]. Another study conducted by Rafsanjani et al., evaluated the effect of chemotherapy

on patients with Hodgkin disease. 33 patients received chemotherapy (32 patients received mechlorethamine, vincristine, procarbazine, prednisone (MOPP) / doxorubicin (adriamycin), bleomycin, vinblastine, dacarbazine (ABVD) 6-8 cycles. Based on their results, twenty-seven (81.8%) had azoospermia, 2 had severe oligospermia, 3 had oligospermia, and one had normal sperm count[42]. A study conducted by Ishikawa et al. in 2004 concluded that 5 of 10 patients with testicular cancer who treated with chemotherapy regimen (carboplatin, etoposide, ifosfamide) recovered spermatogenesis. Therefore, all the patients undergoing high-dose chemotherapy do not develop spermatogenesis impairment ad fertility dysfunction[43]. There is some evidence indicating that patients could be recovered from azoospermia to oligospermia and normospermia after more than 10 years[44].

Mechanism of chemotherapeutic damage

Infertility is one of the most concerning adverse effects of chemotherapy in men[45]. Chemotherapeutic agents disrupt testicular function both directly and indirectly. Testes are composed of two compartments: the seminiferous tubules—which contain germ cells and Sertoli cells—and the interstitial tissue—which contains Leydig cells and blood capillaries[46].

The pathophysiology of gonadotoxic effects of chemotherapy is elaborate. Spermatogonial stem cells (SSC), the primary cells in spermatogenesis cycle, are affected by chemotherapy. In prepubertal patients, exposure to alkylating agents is associated with a reduction in SSC pool[47,48]; however, in most cases, the SSC pool is not totally depleted and recovery of spermatogenesis is possible[35,49]. Administration of cyclophosphamide –an alkylating agent- to adult mice reduced the production of glial cell-derived neurotrophic factor, which has a role in SSCs self-renewal and spermatogonia differentiation[50].

Stem cells are known to be more resistant to chemotherapy than differentiating spermatogonia which have higher rate of proliferation[12]. Primate studies show that chemotherapy and radiation in adults lead to an initial depletion of differentiating spermatogonia[51]. The decline of fertility potential to its lowest levels around 4-6 weeks after chemotherapy suggests this gonadotoxic effect[13]. Chemotherapeutic agents that cross blood-testis barrier can damage germ cells directly and by inducing hyalinization and fibrosis of testicular interstitial tissue[11]. Biopsy of the testis after treatment shows a decrease in testis weight or sperm count which demonstrates impaired spermatogenesis[44]. A recent study demonstrated that 6 months of chemotherapy led to severe oligospermia in 67 % and 60 % of testicular cancer and HD patients, respectively; a significant increase in abnormal sperm morphology was also observed[52].

Alkylating agents such as mustine, vincristine, procarbazine and prednisolone are associated with permanent germ cell depletion and Sertoli cell-only testicular feature[44]. Other alkylating agents such as cyclophosphamide and isophosphamide resulted in permanent azoospermia in 80-90%[53]. Newer combinations including mustine, vinblastine, procarbazine and prednisolone also caused azoospermia in 90%[54]. Non-alkylating agents, such as Adriamycin, vincristine, methotrexate and 6-mercaptourine, resulted in azoospermia in 16% of men for up to 11 years after treatment[55]. Nearly 100% of patients who were treated by cisplatin became azoospermic during and immediately after chemotherapy[56,57]. However, multi-drug regimens including cisplatin or carboplatin have a relatively low risk of permanent infertility in testicular cancer[57].

Although non-proliferative Sertoli cells (SCs) and Leydig cells (LCs) are usually resistant, acute exposure to anti-cancer agents leads to their dysfunction [58]. SCs proliferate actively during childhood, which makes them a potential target of childhood anti-cancer treatment[19]. In vivo exposure to chemotherapeutic compounds decreased production of androgen binding protein (ABP) and transferrin, two proteins of SCs involved in the regulation of spermatogenesis[59,60]. SC dysfunction is usually manifested by a rise in the FSH level[61,62]. Pediatric cancer survivors have reduced sperm counts associated with increased FSH levels, which indirectly reflects SC alteration[62,63]. Although LCs have been considered more resistant to chemotherapy than other cell lines, their function can be impaired only at higher doses and result in lower testosterone production[20, 64]. Survivors of pediatric cancer have shown LC dysfunction which presents with a small decline in testosterone levels and a significant increase in LH levels[6]. Delayed puberty might occur, if Leydig cell function is significantly affected[65].

The reversible effects of chemotherapy can be restored over time. Accordingly, each anti-cancer agent has unique rate and duration for sperm recovery based on its mechanism of action[66]. Men who had normal pretreatment sperm count, received carboplatin- rather than cisplatin-based therapy, and were treated with fewer than five cycles of chemotherapy were more likely to recover to a normal sperm count[67]. Moreover, intermittent administration of chemotherapy was associated with higher rates of spermatogenic recovery compared to continuous use[68]. Regarding the type of regimen, 86% of men treated with alkylating agents known as MOPP, had persistent azoospermia, whereas all patients treated with ABVD demonstrated recovery of spermatogenesis[69]. In 82% of patients treated with non-alkylating agents, spermatogenesis recovered after a median time of 19 months, while in patients receiving alkylating agents, recovery occurred in 30% of patients [70].

Although spermatogenesis recovery might happen after chemotherapy, persistent nuclear changes occur in spermatozoa of a majority of cancer survivors[6]. The semen samples of cancer patients, even after a 24-month recovery period were associated with a significant level of sperm DNA and chromatin damages[52,71]. Mutations which occur in stem cell spermatogonia results in permanent damage in spermatogenesis while mutations in later stage spermatogonia, lead to transient spermatogenic damage[72]. The majority of chemotherapeutic compounds cause an increased oxidative stress in testicular tissues and downregulate anti-oxidant enzymes, which leads to the formation of excess reactive oxygen species (ROS). Excessive oxidative stress, may result in DNA damage in germ cells and accumulation of DNA injuries leads to germ cell death[6].

A longitudinal study found increased sperm DNA fragmentation 6 months after the end of chemotherapy in comparison with the baseline in both Hodgkin's disease and testicular cancer patients; this value remained elevated up to 18–24 months[73]. A multicenter prospective study demonstrated that ABVD and CHOP/

MOPP-ABV treatments resulted in increased aneuploidy frequencies three months after the completion of the treatment in lymphoma patients[74]. Interestingly, the integrity of sperm DNA and chromatin seem to be unaffected by chemotherapy in adult survivors of childhood cancer[75,76] while receiving chemotherapy during adolescence might lead to epimutations and to changes in DNA methylation of spermatozoa[77].

The urgency of diagnosis and starting the effective therapy for children has often overshadowed the toxicity of cancer treatments on the gonad[6]. Earlier studies suggested that the childhood period is protected against chemotherapy-induced gonadotoxicity, since childhood was supposed as "quiescent stage" of the testis. However, more recent studies have shown that the testis can be targeted by the deleterious effects of cancer treatments at all stages of life[15,16]. Few studies have focused on the gonadotoxicity of anticancer drugs in adult survivors of childhood cancer compared with adulthood. Since toxic effects of chemotherapy on younger adults is yet not well addressed, many guidelines exist for long-term follow-up of children treated for cancer[6].

Protective approaches

Dose reduction, alternative regimens, and surveillance protocols are suggested to reduce the gonadotoxic effects[78]. Treating cancer patients with weekly fractionated doses rather than a single dose allowed genetic repair and led to reduction of its mutagenicity[68]. Using the first non-alkylating agent-containing combination ABVD for the treatment of HD was one of the first examples for agent substitution[79]. More recent treatments such as the inhibitors of the epidermal growth factor receptor or the vascular endothelial growth factor showed promising outcomes in avoiding the adverse effects of chemotherapy, while their impact on spermatogenesis is yet to be established[66].

Administration of gonadotropin releasing hormone (GnRH) agonists or testosterone prior to cytotoxic therapy would downregulate the pituitary gland by the negative feed-back effect and suppress spermatogenesis, thus rendering the testes less susceptible to chemotherapy[80]. GnRHa initially stimulate gonadotropin secretion but repeated administration of GnRHa suppresses HPG. Several studies on rodents have demonstrated promising outcomes in terms of protection of spermatogenesis when hormonal suppression is commenced before treatment. However, this method has so far failed to show promising results in primates and humans[65].

Administration of special cytoprotective substances prior to receiving chemotherapy may reduce the gonadotoxic effect of several anti-cancer agents. For instance, in Albino rats treated with lipoic acid 1 day prior to ADR treatment, the negative biochemical and morphological changes were reversed enzymatic homeostasis within the testis was maintained and the values for sperm count and sperm motility were increased by 66% and 56%, respectively[81].

Sperm cryopreservation is the safest and most effective method for preserving fertility in young cancer patients prior to chemotherapy[82]. Assisted reproductive techniques (ARTs) particularly intracytoplasmic sperm injection (ICSI), require the least amount of sperm quantity and quality[66]. These technologies helped about 72% and 50% of cancer survivors to become fertile and deliver newborn, respectively[83,84]. However, only less than 18 % of newly diagnosed male cancer patients opted to use this method[84]. Nevertheless, sperm cryopreservation is not available for pre-pubertal patients. Preservation of spermatogonial stem cells for autologous intratesticular stem cell transplantation seems to be the only method for preserving fertility in these boys[85]. Differentiating spermatogonial stem cells in vitro and using the derived spermatids for ICSI could also be an option to restore fertility[86].

It has been well understood that chemotherapy impairs gonadal function in a significant number of cancer survivors. Gonadal dysfunction is not protected when chemotherapeutic agents are administered before puberty in males. Moreover, the effect of chemotherapy on sexual function is controversial. While several articles reported the worst effect of chemotherapy on the sexual function of cancer survivors, some studies reported that chemotherapy does not impair sexual function. Higher levels of chemotherapy dose seem to be associated with more gonadal and sexual dysfunction. However, it should be considered that in cancer survivors not only chemotherapy could damage gonads and cause testicular and sexual dysfunction, but also the psychological impact of cancer diagnosis should be considered.

CONFLICTS OF INTEREST

There are no conflicts of interest declared by the authors.

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