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REVIEW ARTICLE

Fertility preservation in men with cancer

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Abstract Due to recent advances in medical technologies, cancer has become more curable and chronic, and post-treatment quality of life, including male fertility, has become an important issue. Cancer itself can affect spermatogenesis through complex interactions, and cancer treatment such as surgery, radiotherapy and chemotherapy, all have certain detrimental effects on spermatogenesis. Currently, sperm cryopreservation before cancer treatment is the mainstay of fertility preservation, and is recommended by numerous guidelines. Although fertility preservation should be discussed with all cancer patients before treatment, it still remains underused. Postpubertal patients who are unable to bank sperm may undergo testicular sperm extraction before treatment. For prepubertal boys, there is no clinically established guideline for fertility preservation. Investigations such as spermatogonial stem cell culture are ongoing, and may lead to clinical options for fertility preservation in the future.

Keywords Cancer · Chemotherapy · Fertility preservation · Male infertility · Radiation

Introduction

During the last decade, the diagnosis and treatment of cancer have developed dramatically. As a result of advances in early detection and treatment, it has become either curable or chronic disease for some men. The prevalence of cancer survivors is increasing [1]. Therefore, post-treatment quality of life, including fertility preservation, has become an important issue.

Infertility is an area of particular concern to young cancer survivors. More than 50 % of men of reproductive age with cancer express a wish to preserve their fertility for the future, and 77 % of them are childless at their diagnosis of cancer [2]. It has also been reported that 70 % of young cancer patients wanted to have a child after chemotherapy [3]. Both the American Society for Reproductive Medicine (ASRM) and the American Society of Clinical Oncology (ASCO) have addressed the issue of potential infertility after cancer [4–6]. They recommend that physicians should discuss the possible impact of cancer and its therapies on fertility, make early referrals of interested patients to reproductive specialists, and address fertility preserving options such as sperm cryopreservation when appropriate. Because it is very difficult to predict which patients will have permanent infertility [7], fertility preserving options are strongly recommended for every cancer patient of reproductive age [4].

The underlying etiology of cancer-related infertility is often multifactorial, including the impact of the cancer itself and the effects of surgical treatment, radiation therapy, and chemotherapy, which could all potentially disrupt normal male fertility. In this review, we focused on the effects of cancer and its treatment on male reproduction. In particular, we emphasized germ cell tumors, Hodgkin's lymphoma and leukemia, which are the commonest malignancies affecting men of reproductive age.

Association between spermatogenesis and cancer

Cancer may affect spermatogenesis through complex interactions. Malnutrition with deficiencies in vitamins,

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minerals, and trace elements will result in impaired spermatogenic failure [8]. Tumor-related fever or hypermetabolism can adversely affects fertility. Autoimmune response promoted by tumors may produce anti-sperm antibodies or release cytokines, either of which can cause impaired spermatogenesis [9]. In addition to the general effects described above, inappropriate endocrine secretions in certain cancers such as Hodgkin's lymphoma and germ cell tumors may affect hypothalamus–pituitary–gonadal (HPG) axis and then result in disturbed spermatogenesis.

Semen characteristics before cancer treatment differ due to the types of malignancy. In the study evaluating 764 male cancer patients prior to cancer treatment, patients with testicular germ cell tumors and extragonadal germ-cell tumors had significantly lower sperm concentration than all other cancer patient groups [10]. One explanation for impaired spermatogenesis in a germ cell tumor is its hormonal effect. The effect of elevated beta-human chorionic gonadotropin (HCG) and alpha-fetoprotein (AFP) might play a partial role in the decline of sperm quality; however, these elevated markers do not totally explain the decrease in spermatogenesis; impaired spermatogenesis is also found in patients without increased tumor markers. It has been described that patients with germ cell tumors have lower inhibin B levels than healthy controls [11], and that declined pre-orchidectomy sperm quality can recover after orchidectomy [12]. However, if an elevated follicle stimulating hormone (FSH) level was found before orchidectomy, no recovery was noted. This indicates that not only the effect of the testicular tumor itself but also a pre-existing gonadal dysfunction, including the contralateral testis, is present [10].

Skakkebaek et al. [13] have hypothesized that the "testicular dysgenesis syndrome" results from disruptions that occur during fetal life, which impair normal testicular development, leading to defective sperm production and higher rates of testicular cancer in the adult. This means that testicular cancer can be found during the examination of male infertility. Indeed, cohort studies in both Europe and the United States suggest that infertility is a risk factor for testicular cancer, and men with male factor infertility were around three times more likely to develop testicular cancer compared with those without [14, 15].

Another explanation for elevated testicular cancer development in infertile male is defects in DNA repair systems. Defects in DNA repair will impair both meiosis and mitosis, which will affect spermatogenesis and increase the risk of carcinogenesis [16–18]. Because up to 25 % of the male genome is involved in reproduction, it is likely that other nonprocreative processes may also be affected by aberrations in fertility [19]. From this point of view, not only testicular cancer, but also other kind of cancers, may be at risk in infertile men. Indeed, Eisenberg et al. [20] analyzed 2,238 infertile men and revealed that azoospermic men had as high as 2.2-fold higher cancer risk, not only for testicular cancer, compared with nonazoospermic men.

Cancer treatment and male infertility

The three main arms of cancer treatment are surgery, radiotherapy, and chemotherapy. Each of these treatments can affect male infertility.

Surgery

Cancer surgery can be one of the iatrogenic causes of infertility, although it is not applicable to all malignancies. Major pelvic surgeries such as prostatectomy, cystectomy, pelvic exenteration, low colon resection, and retroperitoneal lymph node dissection (RPLND) may result in injury to the sympathetic, parasympathetic, or pelvic nerves that can affect ejaculation.

As for orchidectomy, the loss of gonadal tissue results in decreased spermatogenesis. Significant reduction in sperm concentration following unilateral orchidectomy, even developing newly onset azoospermia, has been reported [21, 22]. On the other hand, it has been reported that fertility remains a possibility following unilateral orchidectomy, with a reported rate of 65 % among men with stage I testicular cancer [23].

As described above, RPLND for testicular cancer patients may result in injury to the nerves and thus cause retrograde ejaculation or anejaculation. Bilateral RPLND damages the lumber splanchnic nerves and hypogastric plexus, resulting in the permanent loss of emission and ejaculation [24]. Advances in surgical treatment have allowed sympathetic nerve sparing, and modern series of patients who have undergone nerve-sparing RPLND report preservation of some antegrade ejaculation in 74–96 % of cases [25–29]. However, in certain patients, ejaculation disorder may present after RPLND. Ejaculation disorder is one of the morbidities that can be treated with several therapeutic options. Table 1 summarizes the medical management of retrograde ejaculation. Sympathomimetic agents and/or anticholinergic agents are used to treat retrograde ejaculation, although treatment outcomes are not entirely successful [30–39]. In cases who cannot achieve antegrade ejaculation with medical management, sperm retrieved from urine after ejaculation may be used for intrauterine insemination (IUI) or further assisted reproductive technologies (ART) [40]. Another method to retrieve sperm is massage of seminal vesicles. When the seminal vesicles are massaged with the physician's index finger inserted into the rectum, sperm may be retrieved

Table 1 Medical management of retrograde ejaculation

	n	AE achieved	Article
Sympathomimetic agents			
Ephedrine sulphate	17	3	*30
	6	1	*31
Pseudoephedrine hydrochloride	7	1	*31
	1	0	*32
	4	2	*33
Midodrine	2	2	*34
Phenylpropanolamine	1	1	*35
Synephrine	6	3	*36
Anticholinergic agents			
Imipramine hydrochloride	14	2	*30
	5	0	*31
	7	3	*37
	17	5	*38
Brompheniramine maleate	8	1	*31
Sympathomimetic agents + anticholinergic agents			
Brompheniramine maleate, phenylephedrine hydrochloride	12	4	*31
Chlorpheniramine maleate, phenylpropanolamine, isopropamide iodide	1	0	*39
Others			
Acupuncture + traditional Chinese medicine	25	17	*38

*30 Gilja 1994, *31 Narayan 1982, *32 Reynolds 1998, *33 Hsiao 2012, *34 Jonas 1979, *35 Stewart 1974, *36 Stockamp 1974, *37 Okada 1998, *38 Yuanhui 2002, *39 Virupannavar 1982

AE antegrade ejaculation

from the collection of expressed prostatic secretions, which can be used for ART [37].

Electroejaculation is a more invasive method to achieve antegrade ejaculation in the management of anejaculation [41] or retrograde ejaculation [42], and this procedure may be performed in patients with failed medication therapy, before testicular sperm extraction (TESE) is carried out [33].

Radiotherapy

Radiotherapy remains to be a main treatment for a variety of cancers in reproductive aged men, including testicular cancer and hematological cancer. Because the testes are extremely sensitive to radiation, the gonadotoxic effect of radiotherapy depends on its dosage. While the testes are shielded with lead block during radiation treatment protocols, they are still at risk of radiation toxicity through scatter. In addition to the total doses received, the fractionation or delivery schedule also impacts the degree of damage sustained [43]. A higher dose of radiation delivered over fewer fractions has been shown to result in less damage compared to lower doses administered over a more extended time line, even when equivalent total doses are achieved [44, 45].

The germ cells demonstrate significant sensitivity to radiation compared to other cell types in the testes. Doses of 0.1 Gy have been shown to result in a temporary arrest of spermatogenesis, with a dose of 0.65 Gy resulting in temporary azoospermia [46, 47]. Azoospermia may become permanent with doses in excess of 2 Gy [48]; however, permanent azoospermia with a dose of as low as 1.2 Gy has been described in one study [47].

The time line for the recovery of spermatogenesis is also related to the total dose received. Typically, sperm counts nadir at 6 months and then recover according to the total dose received [49]. Azoospermia is noted for a period of 9–18 months, 30 months, and 5 years following administration of < 1, 2–3, and 4–6 Gy, respectively, while spermatozoa are again noted in the ejaculate at 6 months, 9–18 months, and 4 years with doses of 0.2, 1, and 10 Gy, respectively [43].

In contrast to the germ cells, Leydig cells are shown to be relatively resistant to radiotherapy. However, even if testosterone levels remain normal, elevation of luteinizing hormone (LH) levels may be observed, indicating some degree of Leydig cell injury [50]. Doses of $>$ 20–30 Gy result in hypogonadism, which necessitates androgen replacement therapy [51–53].

In addition to the direct effects on the testes, radiation to the brain can lead to hypopituitarism, disrupting the hypothalamic–pituitary–gonadal (HPG) axis, and causing secondary hypogonadism and infertility [54]. Proper adjustment of the irradiation field, careful coning to prevent radiation scatter, and shielding of the gonads (if appropriate) are mandatory precautions.

Chemotherapy

Chemotherapy plays a central role in treating cancer, especially in patients with advanced testicular cancer or hematologic cancer. Because chemotherapy agents target rapidly proliferating cells, they negatively impact spermatogenesis. Many chemotherapeutic agents cross the blood–testis barrier, damaging germ cells either by reducing their numbers or by causing hyalinization and fibrosis of testicular interstitial tissue [55]. Although conflicting results have been published concerning the degree of gonadal dysfunction induced by anticancer chemotherapeutic agents, the degrees of gonadotoxicity vary depending on the drug, dosage, treatment duration and the method of administration [5].

Table 2 The gonadotoxic risk of common anticancer chemotherapeutic agents

Alkylating agents	High
Platinum analogs	Medium–high
Antibiotics	Low–medium
Antimetabolites	Low
Plant derivatives	Low

The common types of chemotherapeutic agents that induce spermatogenic dysfunction are shown in Table 2. The alkylating agents, which induce apoptosis by impairing DNA synthesis and RNA transcription, are highly gonadotoxic and comprise the highest risk group for resulting in permanent infertility [56]. Among the alkylating agents, chlorambucil, cyclophosphamide, procarbazine and melphalan are known to have the most detrimental effect on spermatogenesis; other alkylating agents known to affect spermatogenesis include carmustine, lomustine, busulfan, ifosfamide [5]. Platinum analogs, which function by causing DNA cross-rink formation, are also at high risk for spermatogenesis, especially in cisplatin [5]. Antibiotics such as adriamycin, bleomycin are at low risk for spermatogenesis, although actinomycin-D has been reported to have possible detrimental effect on spermatogenesis [5]. Antimetabolites including fluorouracil, 6-mecaptopurine, thioguanine, methotrexate and gemcitabine interfere with DNA synthesis and often result in only temporary reductions in sperm counts [5]. Similarly, plant derivatives such as vincristine, vinblastine and etoposide have only a temporary effect on spermatogenesis [5]. Newer agents such as taxans and tyrosine kinase inhibitors have not been fully studied, and should be investigated in the future.

In many cases, chemotherapeutic agents are more frequently used under multi-agent protocols. For example, mustine, vinblastine, procarbazine, prednisolone (MVPP) regimen was a standard therapy for Hodgkin's lymphoma; it induced permanent germ cell depletion, resulting in Sertoli cell-only testicular histologic features, even with limited treatment cycles [57]. Recently, the standard regimen for Hodgkin's lymphoma evolved to adriamycin, bleomycin, vinblastine, dacarbazine (ABVD) regimen. This has resulted in significant improvements in fertility potential, with up to 90 % of patients experiencing normal sperm counts 1 year following completion of therapy [58]. Cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) is a standard regimen for non-Hodgkin's lymphoma. Although all patients are reported to be azoospermic during this regimen, 67 % recovered to have normal sperm counts 5 years post-treatment [59]. As for testicular cancer, cisplatin-based or carboplatin-based regimen [mainly bleomycin, etoposide, cisplatin (BEP)] is used to treat metastatic stages. All patients become azoospermic during and immediately after cisplatin chemotherapy [60]; however, spermatogenic recovery after treatment has been reported. Lampe et al. [61] analyzed data concerning 170 patients with testicular cancers who underwent treatment with either cisplatin-based or carboplatin-based chemotherapy. Although only 64 % of patients who were normospermic before chemotherapy remained normospermic in a median 30 months after completion of the therapy, recovery continued for more than 2 years, with the calculated chance of spermatogenesis at 2 years being 48 % and at 5 years 80 % [61]. They also report that the probability of spermatogenic recovery was higher in patients treated with carboplatin-based regimen, compared with cisplatin-based regimen, and in those treated with fewer than five cycles of chemotherapy [61]. Similarly, Petersen et al. [62] analyzed 55 patients treated with BEP and described that the risk of post-therapeutic azoospermia increased when the cumulative cisplatin dose was > 600 mg/m^2. In contrast, we previously analyzed long-term gonadal function after high-dose chemotherapy (HDC) for testicular cancer. In that study, ten patients with testicular cancer treated with BEP followed by HDC were analyzed. Five of ten patients had positive spermatogenesis after treatment, with two patients fathering children 19 and 44 months after HDC. There was no correlation between the dose of drugs and the fertility status after chemotherapy [63]. It is very difficult to predict which patients will have permanent infertility and which will regain fertility after chemotherapy.

Fertility preservation

Sperm cryopreservation

Currently, sperm cryopreservation is the only effective method of fertility preservation in males treated for cancer [64–71], and sperm cryopreservation before cancer treatment is strongly recommended for cancer patients of reproductive age [4]. Due to recent advances in ART technology and sperm cryopreservation procedures, even men with extremely reduced sperm count and motility are candidates for sperm cryopreservation. It is strongly recommended that sperm be collected before initiation of cancer therapy, because the quality of the sample and sperm DNA integrity may be compromised even after a single treatment session [72, 73].

Numerous guidelines recommend sperm cryopreservation before cancer treatment; however, few practitioners initiate discussions about fertility preservation and few patients choose to preserve their sperm; sperm cryopreservation still remains underused [2, 3, 74–76]. It has been reported that only approximately 20–30 % of young

patients with cancer consider sperm cryopreservation, and only 10–20 % do bank their sperm [77–79]. Although an increase in patients referrals to fertility preservation center has recently been reported [80], some patients may not be informed of the deleterious effects of cancer chemotherapy on spermatogenesis, and may not know about the availability of sperm cryopreservation.

In 2008, Nishiyama et al. surveyed for sperm cryopreservation before chemotherapy in Japanese urological departments. One hundred and four urological departments in Japan were surveyed using questionnaires. Eighty-six percent of the departments answered the questionnaire, and almost 64 % of urological departments "routinely" gave information about fertility preservation to young patients with testicular cancer before chemotherapy, while 25 % did "when appropriate" [81]. In contrast, Watanabe et al. investigated 500 hematologists in Japan for the strategy of fertility preservation before chemotherapy in 2005. Only 31 % of the hematologists answered the questionnaire, and only 37.5 % of them routinely informed patients about the probability of chemotherapy-related infertility before the treatment. Furthermore, almost half of the hematologists who answered the questionnaire were of the opinion that the issue of fertility is not a high priority for the patients requiring cancer treatment [82]. These results reflect that awareness of fertility preservation before gonadotoxic treatment may differ between urologists and hematologists. At the same time, fertility management should be discussed with all cancer patients before treatment, and practitioners who deliver cancer care should be cognizant of the options for fertility preservation, or at least make referral to reproductive specialists.

Bizet et al. [80] comprehensively analyzed cryopreservation activities retrospectively for 1,080 patients referred to the sperm bank for sperm cryopreservation before cancer treatment. In the study, a low utilization rate of cryopreserved spermatozoa (6.3 %) was reported, which was in agreement with previous studies [83–86]. The utilization rate of cryopreserved spermatozoa in Japan has also been reported to be low. Suzuki et al. [87] investigated 163 cryopreserved cases with 3.4 % rate of utilization during 14 years, and Soda et al. [88] reported that the utilization rate was 5.7 % among 88 cryopreserved cases during 5 years. More recently, an article by Taniguchi et al. [89] reported that no utilization was found among 41 cryopreserved cases during 10 years. As shown in these articles, the utilization rate of cryopreserved spermatozoa is not very high; however, considering that it is very difficult to predict the fertility status after cancer treatment, sperm cryopreservation should be taken into account for every cancer patient, because it is the most reliable method of fertility preservation at this moment. Additionally, it has been reported that cancer patients who have undergone sperm cryopreservation might cope better with their cancer management [3, 90].

Patients with azoospermia

Patients who are azoospermic on cancer diagnosis cannot benefit from sperm cryopreservation. For these patients, the only procedure to preserve fertility is TESE. Schrader et al. [91] coined the term oncological TESE (onco-TESE) to describe the process of performing TESE in azoospermic cancer patients prior to gonadotoxic treatment; this was found to be both safe and effective with no complication reported. Especially for patients with testicular cancer, TESE from the testicle with the tumor after orchidectomy as a backbench procedure may be the most feasible option [92–94].

Prepubertal patients

For prepubertal patients, semen cryopreservation is not available, because spermatogenesis does not yet occur. The most promising approach for fertility preservation prior to gonadotoxic therapy among prepubertal patients is the cryopreservation of spermatogonial stem cells (SSCs), followed by autologous transplantation. However, because using tissue from cancer patients holds a potential risk for contamination of the malignant cells, this procedure is still in the research phase and remains experimental [95]. Recently, Sato et al. [96] demonstrated that neonatal mouse spermatogonia can be propagated in vitro into functional spermatids that can produce offspring via microinsemination. Advances in SSC research might lead to future fertility options for male cancer patients.

Conclusion

As cancer survival rates continues to improve, long-term quality of life including male fertility has been an important issue for patients with reproductive age. Although numerous guidelines recommend fertility preservation before cancer treatment, it still remains underused. At present, sperm cryopreservation is the mainstay of fertility preservation for postpubertal men undergoing cancer treatment. Newer investigations such as SSC culture for prepubertal males are ongoing, and it is hoped that with time they will enable us to improve the current fertility preservation strategies.

Conflict of interest The authors have nothing to disclose.

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