Implications of cancer on male fertility

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Abstract

Modern cancer treatments have resulted in remarkable improvements in the survival rates of young cancer patients. Consequently, conserving the fertility of cancer survivors has become a main focus of researchers involved in the fields of oncology treatment and infertility. We will review the contemporary data on the two most common malignancies affecting the reproductive age group, as well as the consequences of treatment protocols on fertility and strategies to mitigate these hazards. The efficacy of cryopreservation in conjunction with assisted reproductive technologies will be analyzed. Finally, current research on the welfare of offspring of cancer survivors will be reviewed.

Key words: cancer, male fertility, cytotoxic therapy, cryopreservation, future offspring.

Overview

The American Cancer Society estimated the incidence of testis cancer and Hodgkin's disease (HD) in the United States would be over 8,000 new cases for each disease in 2008 [1, 2]. Due to the improving long term survival rates of these and other cancers among the reproductive age group, cancer and its impact on male fertility has gained more attention.

Survival rates have increased substantially due to advancements in modern modalities of cancer management. Consequently goals of cancer treatment have expanded beyond improving survival and recurrence rates to include maximization of fertility potential and offspring welfare. Moreover, according to research, over 50% of cancer surviving men desire to preserve their future fertility especially that over three quarters of this group remains childless upon discovering their cancer [3].

This review provides a current and comprehensive overview of the effects of cancer and cancer management on male reproduction. Gonadotoxic damage by the three arms of cancer treatment (surgery, chemotherapy and radiotherapy) along with the effects of the disease itself on male fertility will be analyzed. We address the contemporary measures to preserve future fertility with special emphasis to sperm cryopreservation. Finally, we review the latest studies on the detrimental effect of cancer therapy on sperm DNA in attempt to infer the potential risk of harm to future offspring of cancer survivors.

Malignancy and male reproduction

Cancer causes a general disturbance in all body functions including fertility. The global effect of malignancy on fertility may be mediated by cancer-induced

metabolic, endocrine and nutritional alterations. Tumors may release cytokines leading to the injury of both endocrine and exocrine compartments of the testes, or promote an autoimmune response hindering sperm motility [4, 5]. Other features of tumor-related hypermetabolism such as fever also negatively affect sperm motility and density [6].

Stress caused by cancer or its treatment may also indirectly affect spermatogenesis by altering levels of reproductive hormones. Some testicular tumors secrete β-human chorionic gonadotropin (β-HCG) which indirectly inhibits gonadotropin release through its negative feed-back on the anterior pituitary [7, 8].

A properly functional reproductive system, from normal testicular development to ultimate spermatogenetic quality, requires a combination of essential vitamins, minerals and trace elements. Malnutrition associated with malignancy deprives the body of these crucial elements with negative reproductive consequences [9].

Fertility in genitourinary cancer and Hodgkin's disease patients

Testicular cancer and Hodgkin's disease represent the two most common cancers affecting men within the reproductive age group. Moreover, their uniqueness among all other tumors derives from their direct local adverse effects on the germinal epithelium.

Although, the number of newly diagnosed cases of testicular cancer in the U.S.A. will reach about 8,090 in 2008, the mortality rate linked to this disease has diminished to less than 1 in 5000 aided by advancements in modern cancer therapy [2]. Testicular tumors cause significant disturbance of spermatogenesis by a variety of mechanisms such as destruction of adjacent normal spermatogenic tissue, local secretion of β-HCG and other paracrine factors as well as alterations of local testicular environment by elevating scrotal temperature and disturbing blood flow. Post-orchiectomy pathology demonstrates the severity of impairment of spermatogenesis to be highest in tissues adjacent to the tumor [10]. Furthermore, these effects are not exclusive to the involved testicle and can also involve the contralateral testis [4].

Skakkekbaek and others proposed the testicular dysgenesis syndrome (TDS) theory which presents a pathogenetic link between testicular tumors and infertility. This theory suggests that in-utero exposure to stressors and hormonal disruptors during testicular embryological development alters the normal development and function of the Sertoli cells which are responsible for the normal differentiation of primordial germ cells. Ultimately, infertility, testicular cancer or both can be the result [11].

Fortunately, death rates due to HD have also followed testicular cancers by showing a significant decline with a more than 60% since the early 1970's [2]. Nonetheless, the fertility of 70% of HD patients will remain adversely affected by this disease. Abnormalities in semen parameters vary to include single parameter defects (24%), combined defects (26%), oligoasthenoteratozoospermia (13%) or azoospermia (8%) [12]. While the exact mechanism for impaired spermatogenesis is not known, a variety of detrimental factors have been proposed to include the systemic release of cytokines which injure both the seminiferous tubules and Leydig cells, genetic abnormalities at the germ cell level and local negative effects of intra-testicular lymphatic tissue [4].

In the past, prostate cancer was traditionally not considered a significant threat to male fertility. However, with aggressive early detection of this disease and in an era where many men choose to father children at an older age, fertility has become an emerging issue in decision-making for patients with this diagnosis. Radical prostatectomy (including cystoprostatectomy for bladder cancer) creates complete surgical sterility. Radiation and cryotherapy reduce semen volume, both through destruction of tissue that creates the majority of semen contents, and may obstruct ejaculatory ducts. In addition, prostate radiation affects semen parameters by its direct access to mature semen stored in the nearby seminal vesicles. External beam radiation affects semen at all stages-testicular, epididymal, and seminal vesicle.

Male fertility after cancer treatment

Surgery for testicular cancer

While organ sparing testicular surgery holds promise for select patients as described later in the review, radical orchiectomy remains the mainstay treatment for testicular tumors due to excellent long term survival and low recurrence rates. After orchiectomy, patients will have a 50% decrease in sperm concentration during the first few months post-operatively and up to 10% will be azoospermic [13]. Up to 5% of men with testicular cancer will develop a metachronous cancer in the contralateral testis which may necessitate a contralateral orchiectomy in the future [14].

In conjunction with radical orchiectomy, retroperitoneal lymph node dissection (RPLND) is a standard of care especially for many non-seminomatous germ cell tumors to improve survival rates and reduce recurrence of testicular tumors. Before the era of modified nerve-sparing dissecting templates, classic RPLND included bilaterally excising all retroperitoneal lymph nodes extending from nerve level T12 to L3, resulting in inevitable damage to adjacent sympathetic ganglia that controlled emission and ejaculation culminating in ejaculatory dysfunction in almost all patients [4].

Chemotherapeutic agents

The type and dosage of the chemotherapeutic agent used, pretreatment semen quality and the developmental stage of the germ cells are all factors that determine the extent of gonadotoxicity caused by different chemotherapeutic combinations [15]. Gonadotoxicity to the earliest stages of the spermatogenic cycle causes permanent impairment to spermatogenesis [16].

Platinum based regimens such as bleomycin, etoposide and cisplatin (BEP) are the standard care for metastatic germ cell tumors, but can cause transient or permanent azoospermia. After following up a large series of testicular patients whom were subjected to cytotoxic measures for 3 years, fertility among this group significantly declined by almost 30% compared to their pre-treatment fertility [17]. It takes a period of at least two years after cessation of therapy for spermatogenesis to recover, ultimately recovering in 80% of the patients within 8 years [18, 19]. Spermon and his group observed a decrease in ejaculatory volume with a significant increase in levels of DNA fragmentation when they compared pre and post-treatment semen samples of 22 patients who had received bleomycin, etoposide and cisplatin on a 5-day regimen for advanced stages of testis cancer [20].

Combination drug regimens have continuously evolved during the past decades. Earlier combinations for HD treatment contained alkylating agents such as mustine in MOPP (mustine, vincristine, procarbazine and prednisolone), cyclophosphamide and iphosphamide. Later alkylating agents proved to cause permanent azoospermia in almost all cases [18, 21]. Measuring levels of follicle stimulating hormone (FSH) as a marker for testicular dysfunction caused by different chemotherapeutic agents, high dose alkylating chemotherapy before bone marrow transplantation caused a significant rise in FSH levels in 88% of the patients [22].

Ionizing radiation

Despite the detrimental side effects of radiation on spermatogenesis, it still remains a chief modality of treatment for seminoma and HD. Testicular damage depends on the dosage and method of exposure to radiation. Disturbance of spermatogenesis starts at doses of 0.1-1.2 Gy with irreversible damage at doses above 4 Gy [23]. In contrast to spermatogenesis, testosterone levels may stay undisturbed with doses below 30 Gy due to the higher resistance of Leydig cells [24]. Patients being treated for retroperitoneal lymph node metastasis in testicular cancer or HD, receive fractionated doses of radiation, which can result in higher levels of spermatocytic damage than single dose irradiation [25]. Damage can be either by direct irradiation or more commonly by radiation scattered during treatment of adjacent tissues. Although shielding of the gonads may reduce exposure to scattered radiation by 2-5 fold, significant gonadal damage may still be unavoidable. Gonads typically received 2-3 Gy with an inverted Y field used for the treatment of HD [26]. Spermatogenic recovery following this type of irradiation may be delayed for more than 2 years [27]. Despite recovery of normal parameters, fertility rates were significantly altered, suggesting that the harmful effect of radiation extended beyond basic parameters. Patients exposed to ionizing radiation showed high levels of sperm DNA fragmentation which persisted 1-2 years after treatment [23]. Combined radiotherapy and chemotherapy had an even more detrimental effect in contrast to using chemotherapy as a solo treatment [17].

Strategies to conserve male fertility

After reviewing the harmful side effects of the different modalities of cancer treatment, it becomes easy to conclude that cancer treatment acts as a double edged sword, having undesirable effects on a man's fertility as a byproduct of its therapeutic effect. Therefore, improving survival of cancer patients has been paralleled by equal efforts to minimize harmful side effects, including gonadotoxicity. Evolving strategies seek to minimize the fertility impacts of the standard surgical, chemotherapy and radiation regimens.

Organ sparing surgery

Testicular tissue sparing surgery in select patients has been gaining favor as a means to preserve both endocrine and exocrine function. According to the German Testicular Cancer Study Group, criteria for adopting such a technique included the presence of bilateral testicular tumors or a unilateral tumor in a solitary testis, provided that strict guidelines were regarded. Heidenreich specified these guidelines for organ confined tumors less than 2 cm with treatment considerations to include cold ischemia, multiple negative biopsies from the tumor bed, adjuvant local irradiation postoperatively to avoid local recurrence especially in the presence of CIS, and rigorous follow-up. He reported a 99% disease free survival after 7 years of follow up [28]. A small series of partial orchiectomies for pre-pubertal benign teratomas showed no evidence of post-operative testicular atrophy during the first year of follow-up and no recurrences after a mean of 7 year follow-up [29]. Recommendations following a post- partial orchiectomy pathology of a testicular malignancy, involve a subsequent radical orchiectomy in cases of seminoma provided both testes were present or in any case of nonseminomatous germ cell

testicular cancer (NSGCT) with consideration for sperm harvest within the same procedure in cases that fail to provide a positive semen sample prior to surgery [30]. Failure to identify sperm from the excised testis may justify a concurrent contralateral testicular biopsy prior to initiating adjuvant gonadotoxic therapy [30].

Finally, there is some interest in prostate sparing surgery for bladder cancer, although this remains controversial from a standpoint of both disease control and unproven effect on sexual function and fertility. Focal therapy for prostate cancer may offer preservation of fertility, but its ability to do so and impact on cancer control remain unvalidated at present.

Nerve-sparing surgery

Retroperitoneal lymph node dissection templates have experienced a series of modifications during the past years aiming to preserve the neurovascular mechanism responsible emission and ejaculation. Using the nerve sparing modified template, the frequency of these complications has markedly diminished with fewer than 5% of patients experiencing anejaculation after right-sided nerve sparing dissection. In appropriately selected patients, this had no detrimental effect on relapse rates [19]. Ultimately, the incidence of this is reduced when a modified, less extensive, template is used, and is even further reduced by nerve-sparing lymphadenectomy.

Non-alkylating chemotherapeutic regimens

The appearance of the first non-alkylating agent containing combination ABVD (adriamycin, bleomycin, vinblastine and decarbazine) was a breakthrough chemotherapeutic regimen for the treatment of HD, with a sperm recovery rate of 90% 1-5 years post-treatment and improving the 5 year recurrence free survival by 10% over standard MOPP regimens [31, 32]. Comparing alkylating agents to nonalkylating agents, FSH rose in 60% of those receiving alkylating agent chemotherapy in contrast to only 8% of patients receiving nonalkylating agents [33]. Contemporary clinical trials have focused on dose reduction, alternative regimens, and surveillance protocols to reduce the drug-related toxicity without compromising cure rates [34]. These choices are tailored according to pretreatment clinical criteria such as tumor pathology, primary tumor extension, metastatic sites and serum tumor marker levels [35]. Newer lines of therapy such as inhibitors of the epidermal growth factor receptor or the vascular endothelial growth factor hold promise to avoid the adverse affects of current conventional cytotoxic therapy, although the exact impact on spermatogenesis remains to be established.

Gonadal protection

Modern radiation technologies with more accurate dose delivery and gonadal protection to prevent radiation scatter may minimize the time required for spermatogenetic recovery following radiotherapy. With the help of these strategies, complete recovery of spermatogenesis was documented after 9-18 months of treatment with doses equal to or less than 1 Gy, after 30 months with doses ranging between 2 and 3 Gy but doses above 4 Gy required more than a 5 year interval [18]. The "clamshell" system for gonadal protection reduced the overall testicular dose of scattered external radiation over older lead block style systems [36]. The use of brachytherapy for prostate cancer has significantly diminished the amount of scattered radiation reaching the surrounding tissues compared to conventional external beam radiation [37]. With the advent of the "Calypso 4D localization system" that monitors prostate motion during external beam radiotherapy delivery, radiation doses can be accurately targeted at the prostate. This real time adaptive radiation technology significantly decreases the amount of radiation scatter while improving outcomes of treatment [38]. A combination of chemotherapy with limited field irradiation may also replace the use of extensive radiation fields, reducing gonadotoxicity [39]. Also, both radiologists and urologists should limit the use of diagnostic imaging in males within the reproductive period to minimize spermatogenic impairment [4].

Preserving fertility in the era of cryopreservation

Cytoprotective strategies have been a focus of intense research during the past decades. The main idea was creating an artificial state of spermatogenetic abeyance within the testes by using either gonadotropin releasing hormone (GnRH) agonists or testosterone through their negative feed-back effect on the pituitary. Theoretically by suppressing active spermatogenesis before cytotoxic therapy, this would mimic the state of insensitivity of the pre-pubescent testis to gonadal toxicity [40]. However, this technique remains effective in animal models only and has not been proven successful in humans [41-43].

At the present time, pretreatment sperm cryopreservation is the most effective method for preserving fertility in young cancer patients. A recent comparison between fertilization and pregnancy rates using cryopreserved vs. fresh sperm for ICSI showed no difference [44]. Almost 50% of cancer patients were able to conceive using their cryopreserved sperm [45-47]. Testicular sperm extraction and cryopreservation in cancer patients (Onco-TESE) is another option for fertility preser-

vation in patient with pre-treatment azoospermia. With Onco-TESE, sperm retrieval was possible in nearly half the cases of testicular cancer and malignant lymphoma with azoospermia without delaying post-operative adjuvant therapy [48]. Schrader believed this technique to be superior to conventional TESE after chemotherapy by avoiding the extraction of sperm with DNA anomalies due to chemotherapy [48]. Figure 1 summarizes the strategy for sperm procurement and cryopreservation.

A recent study achieved excellent results in terms of preserving the architecture, viability and function of the major testicular components after cryopreserving immature testicular tissue from prepubertal boys about to face cytotoxic therapy [49]. This preserved tissue would be the crucial reserve for future fertility. Cryobanking under special conditions successfully maintained spermatogonia, Sertoli cells and stromal components in mice [50]. A potential method for the maturation of immature testicular tissue after future thawing was introduced when animal studies succeeded in male germ cell transplantation and *in-vitro* maturation [51, 52]. The potential implications of these studies on fertility in prepubertal cancer patients remain to be determined.

Unfortunately, sperm cryopreservation remains underutilized for a variety of reasons [36, 53]. Failure of adequate counseling about cryopreservation prior to cancer treatment suggests that many oncologists may be unfamiliar with current preservation options [53]. According to Goodwin, pediatric oncologists in the USA reported that finding proper facilities and specialists for fertility preservation was difficult [54]. Only 60% of young cancer survivors recalled being counseled about their fertility before therapy while only 51% were offered sperm banking [3, 55]. General health status and disease prognosis were other determining factors for counseling. Patients with poorer prognosis were less likely to be counseled about preserving their fertility [53]. Lack of time for counseling was the common obstacle that prevented almost half of the oncologists from offering sperm banking to the majority of their patients [55]. Others related the problem to the lack of proper guidelines due to unresolved medical, legal and ethical issues [56]. In 2003, the British Fertility Society issued guidelines stating that sperm banking is an option for all pubertal male cancer patients that carried a medium to high risk of fertility impairment [57]. The American Society of Clinical Oncology (ASCO) recommendations state that all patients on the verge of receiving treatment for cancer are entitled to a thorough disclosure of their risks of future infertility in addition to a comprehensive discussion of all available options of fertility preservation that should be considered antecedent to treatment [32].

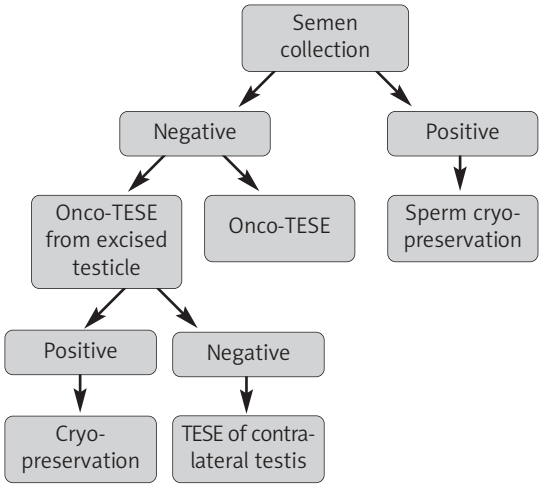

Figure 1. Fertility preservation options in cancer patients within reproductive age

Health implications to offspring of cancer survivors

Damage to the genetic material of sperm due to cancer treatments represents a theoretical risk to the health of offspring of cancer survivors. Research has documented that cancer together with cytotoxic therapy have a negative effect on the DNA integrity of sperm of cancer patients. Using different assays for sperm DNA integrity assessment, testicular cancer and HD patients were found to have increased DNA damage and low DNA compaction when compared to controls [58]. In an assisted reproduction program, the percentage of spermatozoa with fragmented DNA from cancer patients before treatment reached over 34% as opposed to 10.8% in donors [59]. Post-cancer treatment studies have demonstrated single gene mutations and chromosomal translocations in spermatogonia following cytotoxic treatment [60]. This became the obvious rationale behind postponing conception for a washout period of at least two to four spermatogenic cycles post therapy [16]. Newer studies that documented sperm aneuploidy after chemotherapy suggested longer periods of contraception reaching 18 months [61]. Bypassing natural mechanisms of sperm selection using assisted reproductive technologies (ARTs), especially intracytoplasmic sperm injection (ICSI), raises the concern of using DNA damaged sperm of cancer survivors.

Fortunately, studies have failed to detect any significant increase in structural or functional abnormalities among children fathered by men who had a course of cytotoxic therapy one or more years prior to conception [62-64]. Offspring of these patients revealed birth outcomes resembling that of the general population with regards to birth weight, sex ratios and major birth defects [64, 65]. Despite these promising provisional results, large

long term epidemiological studies of offspring of cancer patients remain to be performed.

In conclusion, the substantial improvement in survival rates of cancers affecting the reproductive age population, especially testicular cancer and HD, has raised an equivalent concern regarding the future quality of life of these cancer survivors. Conception has become an important priority to over half of these young patients [3]. Current research on the adverse effects of cancer and subsequent therapy on male fertility has awakened a new concern regarding the potential hazards of transferring damaged genetic material to offspring. Despite several studies that deny a significant difference in congenital anomalies between children born to cancer-survivors and the general population, larger population studies are crucial to obtain a definitive conclusion.

In the end, it still remains incumbent on the health care provider to adequately counsel these patients with available information regarding their fertility after cancer and cancer treatment, fertility preservation options with emphasis on cryo-preservation and contemporary data on potential risks to their future offspring.

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