Review Article

Current practices in fertility preservation in male cancer patients

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Abstract
The incidence of a cancer diagnosis in children and young adolescents is increasing. With better treatments, the number of young cancer survivors living through reproductive age is increasing. Fertility preservation of these men and women has become essential and needs to be discussed prior to the start of cancer treatment. Here we review the current guidelines for male oncofertility patients and highlight some of the important gonadotoxic effects of chemotherapy, radiotherapy and surgery. Options for fertility preservation are also discussed along with resources that should be made available to all patients.

Key Words: Cancer, fertility, fertility preservation, infertility

INTRODUCTION

It is estimated that one out of every two men will be diagnosed with cancer in his lifetime, of which 4% are under the age of 35.1] Traditionally, the role of cancer treatment has focused on disease cure, however with advances in treatment efficacy and safety; there are a growing number of young adults who are long-term survivors of cancer. Patients under 15 years of age undergoing cancer treatment are projected to have a 75% five-year cancer survival rate.2] Patients between the ages of 15-44 with a diagnosis of cancer are now projected to have a survival rate of 66%.3] It has been estimated that 1 in 700 young adults is a cancer survivor4] and by 2010, 1 in every 250 adults will be a childhood cancer survivor.5] With the increasing incidence of this group of patients, fertility potential has emerged as a core survivorship concern.6]

Fertility can be compromised both with cancer pathophysiology and treatment options.7 While infertility may be reversible for some treatment regimens, persistent infertility may occur in 50-95% of malignancies, therefore a discussion surrounding potential fertility preservation options is paramount.8,9 In addition, the desire for fatherhood later in life, the rise of divorce and second family offspring, and the unexpected death of spouses are factors that have influenced men to have offspring later in life.10 Hence, health care professionals should not assume that older men have completed their families and must address the impact of disease and treatment on their reproductive health. In this review, we present a comprehensive overview of the impact of cancer treatment on male fertility and methods used to ensure adequate fertility preservation.

The effects of cancer therapies on male fertility

It is universally accepted that all cancer treatment options can negatively impact fertility. Normal spermatogenesis and sex hormone production may be disrupted by radiotherapy, chemotherapy, stem cell transplantation, and surgery. While
Mechanism of action
DNA base pair alkylation,
Example(s)
Vincristine, vinblastine
Arrest in spermatogenesis and affects some diseases
Bladder cancer,
Inhibit microtubule polymerization
Fluorouracil,
Sarcomas, germ cell tumors,
Table 1: The impact of common chemotherapeutics on male fertility
<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of action</th>
<th>Example(s)</th>
<th>Some diseases utilizing drugs</th>
<th>Effect on spermatogenesis</th>
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<tbody>
<tr>
<td>Antimetabolites</td>
<td>Interferes with DNA transcription</td>
<td>Fluorouracil, 6-mercaptopurine, methotrexate, gemcitabine Vincristine, vinblastine</td>
<td>Colorectal cancer, HL, NHL, bladder cancer, leukemia HL, NHL, leukemia</td>
<td>Spermatogenesis affected,[21] possible chromosomal aberrations[22]</td>
</tr>
<tr>
<td>Vinca alkyloids</td>
<td>Inhibit microtubule polymerization</td>
<td>Vincristine, vinblastine</td>
<td></td>
<td>Arrest in spermatogenesis and affects spermatozoa motility[23] Vinblastine is cytotoxic to primary spermatocytes[24]</td>
</tr>
<tr>
<td>Alkylating agents</td>
<td>DNA base pair alkylation, formation of abnormal DNA cross-bridges, and mis-pairing of nucleotides</td>
<td>Busulfan, cyclophosphamide, chlorambucil, procarbazine, ifosfamide</td>
<td>Germ cell tumors, sarcomas, HL, NHL</td>
<td>Most toxic class; Induces azoosperma within 90 days[25] Irreversible effect[26] mutagenic in all stages of spermatogenesis; but does not cause aneuploidy[27]</td>
</tr>
<tr>
<td>Topoisomerase Inhibitors</td>
<td>prevents DNA supercoiling and interfere with DNA transcription/replication,</td>
<td>Etoposide, doxorubicin</td>
<td>Sarcomas, germ cell tumors, HL, NHL</td>
<td>Cytotoxic with possible chromosomal anomalies[28]</td>
</tr>
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HL: Hodgkin's lymphoma, NHL: Non-Hodgkin's lymphoma, DNA: Deoxyribonucleic acid

Each of these treatment options has different risks and benefits, patients should receive careful explanations of the impact, they may have on future fertility.[6]

The effects of radiation therapy on male fertility
Radiation therapy has been utilized in the treatment of many cancers including prostate, bladder, penile, testicular, and rectal cancer. Radiotherapy is one of the oldest forms of cancer treatment and its delivery has changed drastically from its inception by decreasing its associated morbidity. For example, radiation delivery has improved drastically in the treatment of prostate cancer. Initial modalities included conventional external beam radiotherapy and have since improved to lessen scatter radiation with 3-dimensional conformal radiotherapy and most recently, intensity-modulated radiotherapy.[11,12] Despite these advances, radiation therapy can still have irreversible effects on testicular function and fertility primarily. Similarly, even with a dose fractionation schedule, semen parameters may be affected.[13] Despite smaller single doses of radiation administered in multiple treatments, some authors have even reported worse semen parameters with fractionated radiation.[14]

The testis is one of the most sensitive organs in the body to radiation because of the rapidly dividing germinal epithelium. Immature spermatogonia are most sensitive to radiation injury, while Leydig cells are more resilient to doses as high as 20 Gy. When Leydig cell damage occurs, testosterone production decreases resulting in a concomitant increase in LH levels.[15] Radiation-induced testicular dysfunction occurs in a dose-dependent fashion.[13] Small doses as low as 0.1 Gy can affect the histological shape and number of spermatogonia, while exposure to 2–3 Gy leads to a significantly altered number of spermatids.[13] Similarly, a dose-dependent relationship is seen with regards to sperm concentration within the ejaculate. Radiation doses less than 0.8 Gy could lead to oligospermia, 0.8–2 Gy could lead to transient azoospermia and doses greater than 2 Gy could lead to irreversible azoospermia.[13] Damage to spermatogenesis could result either from direct radiation to the testis or scatter radiation used in the treatment of cancers below the diaphragm. The testes may receive as much as 18.7% of the administered radiation in pelvic cancers, with rectal cancer being amongst the highest scatter doses to the testes.[16] On average, return to pre-radiation semen parameters can be seen within 10-24 months; however, a prolonged recovery is seen with larger doses of radiation.

While alterations in semen analysis secondary to radiation therapy are proven, the impact of DNA damage from radiation is less concrete. There is an increase in DNA fragmentation in men with testicular carcinoma receiving adjuvant radiation up to 2 years after treatment, but the clinical impact of these results is unclear.[17]

The effects of chemotherapy on male fertility
Chemotherapeutic agents have deleterious effects on spermatogenesis. Similar to radiation therapy, Leydig cells may incur damage following chemotherapy resulting in subsequent hypogonadism.[18] However, with advances in chemotherapy delivery, side effects have been minimized using synergistic agents at lower toxic doses but a risk of infertility is still present. The extent of gonadal damage is largely dependent on the type, the age of the patient, and the extent of the chemotherapeutic agent administered. Table 1 highlights some common chemotherapeutic agents and their effect on spermatogenesis.

Combination chemotherapies
For certain cancers, combination chemotherapies are the
mainstay of treatment; for instance, common regimens include MOPP (mechlorethamine, oncovin/vincristine, procarbazine and prednisone) for Hodgkin’s disease, MVAC (methotrexate, vinblastine, adriamycin and cisplatin) for bladder cancer, and R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) for non-Hodgkin’s lymphoma. MOPP causes azoospermia in 90% of men up to 4 years after their treatment regimen as well as increased rates of aneuploidy.\(^{[29]}\)

The combination of bleomycin, etoposide, and cisplatin (BEP) commonly used in testicular cancer was found to have increased sperm chromosomal anomalies\(^{[30]}\) and sperm aneuploidy was seen with NOVP (novantrone/mitoxantrone, oncovin/vincristine, vinblastine and prednisone) chemotherapy.\(^{[31]}\) The combination of chemotherapy while working synergistically on cancer cells also has a detrimental impact on the rapidly dividing germinal epithelium of the testis and patients must be counseled on the risks of permanent azoospermia following treatment.

**The effects of surgery on male fertility**

As part of many initial cancer treatment protocols, surgery plays an important role in achieving cancer cure. However, like radiation therapy or chemotherapy, surgery has its associated risks with respect to infertility. For aggressive testicular cancer, a retroperitoneal lymphadenectomy may be performed. Such an operation may cause an ejaculation or retrograde ejaculation due to disruption of the lumbar sympathetic plexus and hypogastric plexus.\(^{[32]}\) To best prevent these consequences, modified nerve-sparing procedures are performed with a reported ejaculatory preservation of 50–85% in men.\(^{[33]}\)

Disruption of the genitourinary system is unavoidable in either cystectomy or prostatectomy. Sperm production is not impaired in such procedures, only the genital ducts that transport sperm into the prostatic urethra. In addition, erectile function may be compromised. However, with avoidance of nerve fibers in the neurovascular bundles that innervate the corpora cavernosa, 70% of men who underwent either a “nerve-sparing” radical prostatectomy or radical cystoprostatectomy maintained erectile function.\(^{[34]}\) A discussion with patients surrounding the potential loss of erectile function, and more importantly the permanent loss of fertility, should routinely be done.

**Strategies for Fertility Preservation**

**Onco-fertility: A new paradigm in survivorship**

It has been well documented that there is a reluctance to discuss the effects of cancer therapies on fertility, especially when the patient is a single male in his adolescence or young adulthood.\(^{[35]}\) Over the past decade, there has been substantial advocacy for fertility preservation in this young group of patients. In 2004, the Presidents’ Cancer Panel published a series of guidelines urging all physicians to speak to their patients about the effects of cancer treatment strategies on their reproductive potential. In 2006, the American Society of Clinical Oncology (ASCO) echoed this recommendation with an additional report advocating for an early dialogue regarding fertility preservation during an initial discussion about a new cancer diagnosis; if there is interest, these patients should be referred to a fertility preservation specialist.\(^{[36]}\)

Fortunately, over the last several years, many groups advocating for fertility preservation have emerged. Among them is the Oncofertility Consortium, which is a national, interdisciplinary initiative designed to explore the reproductive future of cancer survivors.\(^{[37]}\) This international network consists of physicians, scientists, and scholars who are providing awareness and resources to all patients battling with cancer and interested in future fertility. Additional national organizations that have been instrumental in shaping the paradigm for fertility preservation include the Livestrong Foundation, Fertile Hope, The American Society for Reproductive Medicine, and The Endocrine Society.

Despite these national initiatives, barriers continue to exist on a daily basis, further advocating for an awareness of fertility preservation at a local level. Reassuringly, a greater number of institutions are developing their own programs to target this concern and provide ample resources for patients and providers. Specific initiatives that have been shown to amplify access to care include creation of a “patient navigator” position or having certain skilled personnel readily available to provide information to patients and families on sperm cryopreservation.\(^{[38]}\) At Northwestern University, we recently demonstrated how a formalized male fertility preservation program led to a 2.4- and 2.7-fold annual increase in the number of men who underwent formal fertility preservation consultation and sperm cryopreservation.\(^{[39]}\) Anecdotally, we have also noticed that we have been referred male cancer patients more consistently across all ages and malignancy subtypes.

**Methods of sperm collection preceding initiation of cancer therapies**

For most patients seeking cryopreservation, the semen sample is collected via masturbation. The patient should be allowed ample time and privacy, and he may collect his sample with a sterile specimen cup. It is important to avoid the use of lubricants as these substances are often spermatotoxic. This is the preferred method as it provides the best quality sperm at the lowest financial cost.\(^{[32]}\) Should no ejaculate be achieved or if the patient has a history of retrograde ejaculation, a post-ejaculate urinalysis should be done to assess for sperm in the urine. If sperm are present in the urine sample, a trial of alpha agonists may be administered to direct ejaculation forwards. If this is unsuccessful, alkalization of the urine followed by urine collection and processing of the post-ejaculate urine specimen can be done to isolate viable sperm.

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Because cytotoxic chemotherapies target rapidly proliferating cells, it has been postulated that altering hypothalamic-pituitary axis with gonadotropin-releasing hormone antagonists may prevent long-term infertility. However, it has been shown that hormonal therapy is not successful when men receive high doses of chemotherapy.\[40,41\] Furthermore, hormonal therapy does not speed up the recovery of spermatogenesis.\[42\]

If the patient is unable to ejaculate, then other techniques can be performed. These include vibratory stimulation and electro-ejaculation in an effort to induce ejaculation.\[32\] For azoospermic men, more invasive surgical techniques for sperm extraction such as microsurgical testicular sperm extraction (microTESE) or microsurgical epididymal sperm aspiration (MESA) are performed prior to cancer therapy. Prior to chemotherapy, patients may be rendered azoospermic as a result of their testicular tumor burden. These men may undergo “Onco-TESE” (Oncological Testicular Sperm Extraction). Schrader et al. first described this procedure using microsurgical dissection and extraction of the seminiferous tubules with selected tubules examined on a wet prep slide under microscopy for viable sperm.\[43\] This technique was shown to yield viable sperm in 6 of 14 men with testicular germ cell tumors and 8 of 17 men with malignant lymphoma.\[44\] In another recent cohort, four out of six men undergoing an onco-TESE had sperm in their testicular tissue and two were able to father a child following IVF with this sperm extracted during onco-TESE.\[44\]

For prepubertal boys, the options for fertility preservation are currently investigatory.\[45\] Research focusing on stem cell transplantation is under review with experimental work on in vitro generation of sperm from harvested spermatogonial stem cells and preservation of immature testicular tissue.\[6,46\]

**Sperm preservation and fertilization methods**

After successful collection, patients have the option of sperm cryopreservation prior to chemotherapy, radiotherapy, and/or surgery that may potentially affect reproductive organs. This induces a “suspended animation state” for storage as long as 15 years.\[34\] Unfortunately, prior literature demonstrating low pregnancy rates with cryopreserved sperm using intrauterine insemination (IUI) has tainted much of clinical decision-making.\[47,48\] With the advent of IVF and intracytoplasmic sperm injection (ICSI), sperm cryopreservation allows achievable pregnancy using testicular or epididymal sperm, or those with less optimal motility and/or morphology.

While these techniques have success rates up to 40%, men may have several reasons for not proceeding with cryopreservation. For example, there may be no time to bank because of many other pressing health issues, or in rare instances there may be no viable sperm for freezing. Moreover, the patient may be on a fertility-friendly protocol and may not be recommended for banking. Finally, survival from cancer may be the focus of care rather than the potential outcomes after treatment. Ultimately, it is the patient’s decision whether to pursue fertility options; however, it remains prudent for the provider to explain the aforementioned collection and preservation options, and provide resources for the patient interested in his future fertility.

**CONCLUSION**

Male factor infertility is a known side effect of cancer therapies. While the precise impact of cancer therapy on fertility is dependent largely on the therapeutic regimen, most cancer treatment modalities will undeniably have a detrimental effect on male reproductive potential. Because men are living longer following a cancer diagnosis due to improved cancer diagnostics and therapeutics, the option for fertility preservation must be discussed at the time of diagnosis. All patients should be thoroughly educated about the impact of treatment on their reproductive capacity and provided with ample resources regarding preserving their future fertility potential. Interested patients should be directed to a specialist in fertility preservation.

**REFERENCES**


