Cancer and Male Factor Infertility

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With the increasing success of multimodality anticancer therapy, most men of reproductive age will survive their malignancy. Reproductive function is a principal concern of these men. Health-care providers are shifting the

In 1996, over 400,000 males between the ages of 17 and 50 years were diagnosed with cancer in the United States.[1] Over the past 25 years, there have been increases in the diagnosis of malignancy in men of reproductive age, both in the United States and throughout the world; in particular, a significant increase in the incidence of testicular cancer has been noted.[2,3] Fortunately, with the development of aggressive multimodality therapy, a majority of patients will survive their malignancy.

With the increased success of cancer treatment in young men, the emphasis is shifting toward improving the side effects of therapy. One significant side effect of multimodality therapy in males (as well as females) is damage to reproductive function. Surgery, chemotherapy, and radiation therapy are particularly damaging to the testis. Over the past decade, an increasing number of studies in the oncologic literature have focused on the evaluation and maintenance of reproductive function in young men with cancer.[4,5]

Sexual function and fertility are of principal importance to young men of reproductive age faced with the diagnosis of a cancer. Over 80% of male cancer patients between the ages of 17 and 50 years express concern regarding their fertility potential.[6] However, some studies have indicated that patients’ concern about future fertility may be overrated or underrated by physicians treating them.[7] It is important for clinicians to address fertility issues with patients at diagnosis, both to gather information about the patient’s level of concern and to consider the patient’s wishes when developing the treatment regimen.

Health-care providers involved in the treatment of young men with cancer should evaluate patients’ germ cell function prior to initiating therapy. Knowledge of pretreatment abnormalities in gonadal function will direct care so as to help preserve fertility potential.

New assisted reproductive techniques, including in vitro fertilization and intracytoplasmic sperm injection, allow patients with severe defects in sperm production to father children. Familiarity with these techniques also aids the oncologist in counseling and treating young men.

Pretreatment Abnormalities in Gonadal Function

Certain malignancies are associated with pretreatment abnormalities in sperm production and function, as well as abnormalities in testosterone production and feedback to the hypothalamic-pituitary-gonadal axis. Hodgkin’s disease and germ cell tumors produce nonspecific damage to the seminiferous epithelium, leading to poor seminal parameters and decreased fertility. These pretreatment defects do not appear to be widespread in other malignancies. Despite these abnormalities, the fertility potential of these men is only moderately below that of males without cancer.

Hodgkin’s Disease

Hodgkin’s disease is a lymphoproliferative disorder characterized by circulating malignant cells of poorly defined origin associated with a systemic lymphocytic reaction. Male patients with Hodgkin’s disease demonstrate significant damage to the seminiferous epithelium and the Leydig cell endocrine mechanism early in the disease process. These abnormalities do not appear to be related to disease stage or dominant cell type.[8-12]

Up to 80% of men with Hodgkin’s disease have an abnormal semen analysis at diagnosis (see Table 1 for a review of the literature on these abnormalities). Histologic abnormalities are noted in 90% of testicular biopsy specimens; these range from maturation arrest to complete testicular fibrosis.[9,13,14] A decrease in the number of Sertoli cells, Leydig cell hyperplasia, and Leydig cell aplasia are also noted in biopsy specimens.
Endocrine function is abnormal in most male patients with Hodgkin’s disease.[8,15] These endocrinopathies are manifested by decreased serum testosterone, abnormal stimulatory response to human chorionic gonadotropin (HCG), and an elevation or a decrease in gonadotrophs (with accompanying changes in follicle-stimulating hormone [FSH]/ luteinizing hormone [LH] levels). The mechanism of pretreatment testicular injury in patients with Hodgkin’s disease is not understood. Possible theories include: genetic abnormalities at the germ cell level; germ cell and Leydig cell injury secondary to systemic release of interleukin-6 (IL-6), tumor necrosis factor (TNF), and other cytokines; and negative local effects from resident testicular lymphocytes and macrophages.[16] Additional research is needed to evaluate these pretreatment abnormalities in germ cell function on a genetic and cellular level.

Germ Cell Tumors
Despite the overwhelming success of treatment for patients with germ cell tumors, significant defects in reproductive function are associated with the diagnosis of testicular cancer. An increased worldwide incidence of germ cell tumors also heightens concern over the effects of testicular cancer on reproductive function. Germ cell tumors in males are associated with pretreatment abnormalities in sperm production and function.[17-24] Defects in the hypothalamic-pituitary-gonadal axis also occur.[25]

Table 1 reviews the literature on pretreatment semen analysis in patients with germ cell tumors. Biopsy specimens of the contralateral testis in patients with testicular cancer show defects in the seminiferous epithelium. Significant fibrosis is present in 20% to 60% of patients with germ cell tumors, and Sertoli cell only histology is noted in 8%. Intratubular germ cell neoplasia, formerly known as carcinoma in situ, has been noted in up to 10% of patients with contralateral germ cell tumors.[20,26] While the natural history of intratubular germ cell neoplasia is uncertain, it is estimated that as many as 50% of these patients will ultimately develop clinical germ cell tumors. The mechanism of decreased sperm production and function in patients with germ cell tumors is also poorly understood. Several factors may contribute to abnormal seminal parameters. Unilateral orchiectomy, as well as the stress of diagnosis of a malignancy (see discussion below), may lower sperm numbers and motility by 50%. From 15% to 73% of germ cell neoplasms produce HCG, which may decrease spermatogenesis and Leydig cell function by inhibiting pituitary gonadotrophs.[20] Local tumor effects, including elevation of scrotal temperature and alterations in blood flow, also impair contralateral testicular function. Other theories regarding pretreatment abnormalities in germ cell function include: systemic release of cytokines, alterations in resident leukocyte function, and constitutional effects of malignancy.

Gene deletions in the DNA of primordial germ cells may be responsible for pretreatment abnormalities in patients with germ cell tumors. Subfertile males with idiopathic oligospermia, cryptorchidism, or germ cell tumors have an associated increased incidence of intratubular germ cell neoplasia.[26-29] These three clinical entities may be different manifestations of similar genetic alterations in germ cells.

Other Malignancies
Young men with leukemia, Wilms’ tumor, or sarcoma appear to have normal semen analyses and reproductive function prior to treatment with chemotherapy, surgery, or radiation.[30,31] Ultimate fertility potential seems to be related to testicular injury from the treatment regimen. There is evidence to suggest that advanced stages of malignancy, with accompanying malnutrition and decreasing physical status, have a deleterious effect on gonadal function in both male and female patients.[19,32] The effects of disseminated malignancy on germ cell function are also poorly understood.

Stress
Recent interest has focused on the effects of stress on sperm production and function.[33] A decrease in seminal parameters occurs in individuals with significant life stressors. It is reasonable to conclude that patients with a diagnosis of malignancy, who are undergoing extensive treatment, may be included in this group. It is important that the oncologic health-care provider assist the patient and his family with the associated stress of a malignancy by offering supportive measures and counseling.

Gonadotoxic Effects of Cancer Therapy

Most malignancies in young men are successfully treated by the simultaneous use of surgery, radiation therapy, and chemotherapy to destroy malignant cells. These multimodality therapies often have significant undesirable effects on germ cell function.[34-39] It is important for the clinician to...
understand the effects of each of these modalities on the testis. Careful selection or alteration of treatment modalities may ameliorate these undesirable effects and have a significant impact on the patient’s fertility and quality of life.

**Surgery**

Surgical treatment for cancer has no known direct deleterious effects on testicular function. Surgery may, however, injure the neurovascular mechanisms responsible for erection, seminal emission, and ejaculation, which can prevent the delivery of spermatozoa and result in subfertility.[40,41] Pituitary surgery and adrenal surgery may also interfere with the hypothalamic-pituitary-gonadal axis, causing secondary hypogonadism. Retroperitoneal lymph node dissection, abdominal aneurysm repair, abdominoperineal resection, inguinal surgery, and scrotal surgery may damage the male genital duct system. Surgeons operating in the abdomen, pelvis, inguinal area, or scrotum must be familiar with these neurovascular mechanisms and alter the surgical procedures to preserve them.

**Treatment Alterations to Decrease Potential Damage**

The surgical treatment of nonseminomatous germ cell tumors entails the removal of para-aortic and interaortocaval lymph nodes that are the primary lymphatic drainage of the testis. Surgical lymphadenectomy significantly improves the survival of male patients with germ cell tumors. However, extensive removal of perilymphatic tissue damages the sympathetic ganglion from T12 to L3. These sympathetic nerves are responsible for initiating seminal emission, bladder neck closure, and ejaculation. Complete retroperitoneal lymph node dissection, initially described in the 1950s, resulted in failure of emission and ejaculatory disturbances in up to 100% of patients.

The subsequent development of effective chemotherapy against germ cell malignancies, as well as careful mapping of the testicular lymphatic drainage, has led to a more selective removal of nodal tissue. Modified retroperitoneal lymph node dissection, with delineated templates, preserves sympathetic outflow, resulting in ejaculation in over 75% of men.

Additional modifications of retroperitoneal lymph node dissection to include nerve-sparing operations has led to successful ejaculation in almost 100% of men undergoing this procedure.[42]

Nerve-sparing lymphadenectomy has been successfully performed in patients after chemotherapy.

**Interventions for Permanent Damage**

When irreparable injury to the neurovascular mechanism responsible for sperm delivery has occurred, patients may benefit from other interventions. Patients who have failure of emission, ejaculation, or retrograde ejaculation can be successfully treated with sympathomimetics, electroejaculation, or bladder harvesting of sperm.[43] Sperm may also be directly aspirated from the vas deferens or epididymis for use in assisted reproductive techniques (discussed below). Successful intrauterine insemination, in vitro fertilization, or intracytoplasmic sperm injection can be achieved in up to 70% of patients with ejaculatory dysfunction.[44]

Intracytoplasmic sperm injection induces hyperstimulation of the ovary to produce many eggs, which are harvested by transvaginal aspiration. A solitary sperm is then injected into each egg by means of micromanipulation. After 24 to 24 hours, 8 to 16 cell embryos are transferred to the uterus or fallopian tube for implantation and development.

Surgical injury to the prostate, vas deferens, and seminal vesicles can result in obstruction of the flow of sperm. Microsurgical repair can be performed in patients with vasal or epididymal injury. Damage to or removal of the prostate or seminal vesicles as treatment for sarcoma or other pelvic malignancies is treated with aspiration of sperm from the vas deferens or epididymis with subsequent intracytoplasmic sperm injection or in vitro fertilization.

Injury or removal of the hypothalamus or pituitary results in interruption of the hypothalamic-pituitary-gonadal axis. The loss of FSH/LH results in secondary hypogonadotropic hypogonadism. This can be successfully treated by long-term administration of human menopausal gonadotropin (HMG)/HCG or FSH/LH. The prognosis for fertility in men with secondary hypogonadotropic hypogonadism is excellent.

**Radiation Therapy**

Radiation therapy is a successful adjunct to surgery and chemotherapy in many malignancies involving young men, including Hodgkin’s disease and germ cell tumors. Direct exposure of the testis to ionizing radiation, as well as scatter radiation, inflicts potentially irreversible damage on the cellular DNA of spermatogonia, leading to subfertility. Systemic administration of radioactive iodine-131 or strontium-89 may also adversely affect spermatogenesis.[45] The developing spermatogonia and spermatocytes are exquisitely sensitive to the effects of ionizing radiation.[46] These effects were noted early in the use of x-rays and radiation therapy.[47] Germinal epithelium is more sensitive to ionizing radiation than other rapidly dividing cells. Testicular germ cells appear to be more sensitive to the effects of ionizing radiation (and chemotherapy) than are ovarian follicles.
Injury to spermatocytes and spermatids occurs at low radiation doses. In animals, injury to the seminiferous epithelium has been seen at doses of 10 cGy. In humans, irreversible azoospermia occurs at exposures of greater than 200 cGy.[19,46,48] Recovery of spermatogenesis after radiation is variable and can take from 8 to 30 months.

**Treatment Alterations to Decrease Potential Damage**
Factors that contribute to the gonadotoxic effects of ionizing radiation include the radiation portal utilized and method of delivery. Fractionated doses appear to inflict greater damage than do solitary doses. Small doses may selectively damage germinal epithelium, sparing non-germ cells.

Scatter radiation from abdominal or pelvic fields must be carefully measured at the level of the testis and protective measures taken. Altering radiation portals by adjusting fields and careful coning will decrease the scatter effect on the testis (< 100 cGy) and limit permanent testicular injury. A lead or composite shield should be used to protect the gonad from radiation injury. Imaging studies using ionizing radiation, as well as systemic administration of radioisotopes, should be limited in males of reproductive age.

**Chemotherapy**
Successful treatment of most malignancies requires systemic therapy with single or multiple antineoplastic drugs. Testicular injury occurs both in the acute phase of therapy and as a chronic side effect of antineoplastic therapy. Young men who are receiving chemotherapy have indeterminate periods of azoospermia, decreased libido, and erectile dysfunction.

The gonadotoxic effects of antineoplastic agents are related to the class of agent used, route of administration, dose, frequency of treatment, and use of multiple agents. [35-39,49-51] Table 2 summarizes the testicular damage associated with commonly used chemotherapeutic agents, as well as the potential for and time course of recovery.

Chemotherapeutic agents manifest their cytotoxic effect by interrupting obligatory cell processes involving DNA synthesis and folate metabolism. These effects are multiplied in rapidly dividing malignant cells. The high mitotic rate of germ cells makes the male gonad highly susceptible to the toxic effects of chemotherapy.[52]

Testicular injury, including both injury to the germinal epithelium and, to a lesser extent, the Leydig cells, occurs with most chemotherapeutic regimens. Germ cells are responsible for the development of mature spermatozoa and the continuation of the spermatogenic stem-cell line. Chemotherapeutic agents damage both cell lines, resulting in azoospermia shortly after the onset of treatment; recovery occurs over a variable time period as the stem-cell line regenerates from surviving spermatogonia.[53] The ultimate return of fertility depends on the degree of damage inflicted to the primary spermatogonia.

Complete elimination of spermatogonia can occur after treatment with alkylating agents and results in azoospermia and infertility. Agents that are relatively sparing to the spermatogonia have a more rapid recovery period (see Table 2).

Damage to the Leydig cells, which are responsible for the production of testosterone, is due to direct cytotoxic effects or injury to the hypothalamic-pituitary-testicular axis. Leydig cells have a slow mitotic rate and are relatively spared from the toxic effects of chemotherapy. Testosterone maintains libido, has anabolic effects on bone and skeletal muscle, and is essential for spermatogenesis.

Histopathologic findings in the testis range from mild hypospermatogenesis to germ cell fibrosis and Leydig cell injury. The recovery of germ cells, fertility, and sexual function in men subjected to the damaging effects of chemotherapy is highly variable (see Recovery of Sperm Production and Function below).

**Treatment Alterations to Decrease Potential Damage**
With the successful development of multiagent chemotherapeutic regimens, treatment paradigms have shifted to alternative drug regimens utilizing less gonadotoxic agents. Chemotherapeutic regimens with decreased associated testicular damage and excellent therapeutic efficacy have been developed for several malignancies.[54,34,14,13]

Ongoing trials of antineoplastic drugs, as well as alternate dosing regimens, are presently underway. Prospective studies are essential to develop treatment regimens that will preserve male reproductive function. It is important that oncologists be familiar with these protocols and discuss them with patients prior to initiating therapy.

Reducing the number of treatment cycles, as well as altering the dosing interval, may have a significant effect on fertility. It is important that health-care providers evaluate germ cell, Leydig cell, and pituitary function before and after therapy, to follow recoverability of reproductive function and permit timely intervention if needed.
Recovery of Sperm Production and Function

As outlined above, the ultimate recoverability of sperm production and function after therapy is multifactorial. The potential for recovery depends on the chemotherapeutic agents used, degree of injury to the developing germ cells caused by ionizing radiation, and extent of surgically induced injury to the neurovascular mechanism responsible for sperm delivery. Recovery from the effects of chemotherapy, radiation, and surgery are variable and may take up to 10 years after therapy is completed.

Watchful waiting and observation during this time period is reasonable if the patient is young and does not strongly desire to father children immediately after therapy. With the use of assisted reproductive techniques (see discussion below), patients with severe oligoasthenospermia may initiate pregnancies as early as 6 months after receiving therapy.

The ages of the patient and spouse correlate strongly with fertility potential. Other factors that may influence the timing of pregnancy include: the presence of other offspring, familial support, fear, and stress associated with cancer and cancer treatment.

Cytoprotective Measures

Currently available cytoprotective techniques to limit testicular injury from the damaging effects of cancer and chemotherapy are ineffectual. Inhibition of pituitary control of spermatogenesis by administering gonadotropin-releasing hormone agonists has improved the recovery of spermatogenesis in animal models. The suppression of active spermatogenesis decreases the sensitivity of dividing stem cells to chemical and radiation injury.\(^\text{[33,55,56]}\) These attempts at downregulating germ cell production have not been successful in humans.

Reactive oxygen species are severely injurious to developing germ cells. Research is underway to develop effective antioxidant therapy to protect spermatogenesis in a series of animal models. Administration of the antioxidants N-acetylcysteine and ascorbate before therapy with procarbazine has been effective in preserving spermatogenesis in an animal model. Parallel studies in humans have not been published. The development of new gonadotropin agonists, as well as reactive oxygen scavengers, may, in the future, decrease testicular injury from chemotherapeutic and radiation treatment regimens.

Assisted Reproductive Techniques

Patients with moderate to severe oligoasthenospermia should be referred to reproductive centers to explore the possibility of utilizing assisted reproductive techniques. The past decade has shown tremendous growth in this field. Present reproductive techniques (intrauterine insemination, in vitro fertilization, and intracytoplasmic sperm injection) permit the conception and birth of a child even in cases of severe oligoasthenospermia.\(^\text{[57]}\) A complete overview of assisted reproductive techniques is beyond the scope of this text.

In vitro fertilization or intracytoplasmic sperm injection are often successful in patients with male factor infertility secondary to cancer or cancer therapy, whereas intrauterine insemination can be used in patients with ejaculatory abnormalities. The principle factor in choosing a reproductive technique is the number of total motile sperm available in the ejaculate or harvested specimen. Intrauterine insemination is successful when total motile sperm count exceeds 10 million. In vitro fertilization can be successful with a total motile sperm count of greater than 5 million. Intracytoplasmic sperm injection requires only a few motile sperm (between 10 and 20), which can be directly inserted into the ooplasm. The success rate of intracytoplasmic sperm injection ("take-home baby") in cancer patients is approximately 20% per cycle.

Cryopreservation of Sperm

Patients who have a malignancy should consider cryopreservation of sperm prior to the initiation of therapy, and those who wish to preserve their sperm should be referred to a reproductive center. With present assisted reproductive techniques and improved techniques of cryopreservation, it is possible to bank fertile sperm even from severely oligoasthenospermic patients.\(^\text{[58-60]}\) The only sperm count that is not acceptable for cryopreservation is repetitive azoospermia. Successful pregnancies are possible with sperm obtained from cryopreserved testis biopsy specimens. Cadaveric germ cell harvest with subsequent cryopreservation has also been performed.

Birth Defects

A principle concern among men of reproductive age who are undergoing anticancer therapy is the subsequent possibility of fathering children with significant birth defects. Although chemotherapy
and ionizing radiation cause significant DNA injury, the potential for transmitting genomic defects to offspring is remote, as evidenced by the failure to detect an increase in structural or functional abnormalities among children fathered by men who underwent chemotherapy 1 or more years before conception.[61] No significant increase in major or minor genetic defects has been observed in the offspring of parents who have had cancer or undergone cancer therapy.[58] Since the majority of chemotherapeutic agents injure spermatids and spermatozoa, these cells rapidly lose their function and cannot fertilize an ovum. Cytotoxic abnormalities in sperm DNA prevent the introduction of damaged DNA into the oocyte. It is reasonable to recommend, however, that men delay attempting to father children for 6 months after completing chemotherapy or radiation therapy, to allow regeneration of developing spermatozoa. No increase in genetic defects has been found in cancer patients who have undergone assisted reproductive techniques.[58] Patients should be counseled however, that these techniques have only been effective for the past decade, and data are insufficient to rule out the genetic transmission of a birth defect.

**Summary**

New techniques in multimodality cancer therapy have significantly improved the outlook of young men with cancer. The current emphasis on decreasing the side effects of therapy offers an optimistic view regarding reproductive function in these men. Familiarity with the physiologic mechanisms relating to cancer and male factor infertility will allow health-care providers to incorporate these discoveries into the treatment regimen. Utilization of new assisted reproductive techniques and, possibly in the future, cytoprotective measures should decrease the incidence of infertility in male cancer patients to near zero.

**References:**


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