Cancer is one of the most common disease states, with approximately 50% of men facing this diagnosis during the course of their lifetime. While the overriding focus for both health care professionals and patients has long been disease cure and survival, a number of factors have led to a significant change in this therapeutic perspective. With marked advances in early disease detection and therapy, patient survival for many cancers has increased dramatically over the last several decades. This, in turn, has provided many patients with the opportunity to live full lives beyond their diagnosis, allowing them to look past their cancer and consider life after treatment. Issues such as post-treatment marriage and parenthood are considered as important as the underlying disease by many patients. As such, measures to preserve sexual and reproductive health in the course of cancer treatment are increasingly important to many patients as they face a malignancy diagnosis.

In addition to improvements in cancer detection and treatment, there has been a growing demographic trend for both men and women to pursue efforts at initiating pregnancy later in life. The reasons for this are many, including initial fulfillment of educational and career goals, marriage at a later age in life, and second families started after divorce or death of a spouse. This shift has also led to a change in the traditional reproductive paradigm. Now, malignancies such as prostate, lung, and colorectal cancer are being seen in patients who may indeed wish to preserve their reproductive potential. It is specifically for these reasons that clinicians must be both vigilant and open-minded when considering the needs of patients who are facing a malignancy diagnosis. A proactive discussion with each patient regarding the possible deleterious impact of their disease state and the associated therapy must be undertaken in order to truly provide patients with comprehensive medical care. Failure to proceed in this fashion will surely lead to missed opportunities for fertility preservation in patients, some of whom may permanently lose their reproductive capability.

The Impact of Cancer on Male Reproductive Health

Cancer as a disease process can have many deleterious effects on male reproduction, even before any therapy has been initiated. These effects include disruption of the hypothalamic-pituitary-gonadal (H-P-G) axis, direct immunological or cytotoxic injury to the germinal epithelium within the testis, systemic processes such as fever and malnutrition, and psychological issues such as anxiety and depression. These pathological changes may individually or collectively lead to fertility impairment, which is sometimes present at the time of diagnosis [1,2].
**Endocrine Effects of Tumors**

Successful spermatogenesis hinges on the normal endocrine function of the hypothalamus, pituitary gland, and testis. The delicate balance maintained by these structures is often disturbed at the time of cancer diagnosis. This is particularly true in patients with testicular cancer whose tumors may produce beta-human chorionic gonadotropin (β-hCG) and alpha-fetoprotein (AFP).

In a series of 15 patients with testicular cancer, Carroll et al. reported that two-thirds had abnormalities in key reproductive hormones. These changes included a decrease in serum follicle-stimulating hormone (FSH) levels and/or elevations in luteinizing hormone (LH) and β-hCG levels [3]. In this series, FSH was decreased in 9 out of 10 patients with impaired semen parameters, and 4 of these 9 patients had elevated β-hCG levels, leading the authors to postulate a possible inhibitory effect of β-hCG on FSH in some patients. Other studies have detected markedly increased FSH levels and decreased testosterone levels in the presence of testicular tumors that produce β-hCG [4]. Larger series are needed to help further define the relationship between these hormones in patients with cancer.

Excessive levels of AFP have also been associated with disruption of spermatogenesis in testicular cancer. Hansen et al. assessed 97 men with seminomatous and non-seminomatous germ cell tumors (NSGCT), and reported an AFP elevation in 38% of these patients [4]. In the subset of men with NSGCT, increased AFP was found on multiple regression analysis to be strongly associated with impaired semen quality.

Estrogen has also been linked to impaired spermatogenesis in men with testicular cancer. Cochran et al. noted that patients with β-hCG–producing tumors exhibited increased estradiol secretion and significantly decreased FSH production, suggesting a possible endocrinopathic pathway leading to diminished sperm production [5]. Aiginger et al. suggested more broadly that increased conversion of steroid precursors to estradiol is a feature of both β-hCG positive and β-hCG negative testicular tumors, leading to inhibition of the H-P-G axis and deleterious effects on spermatogenesis [6].

Much remains to be learned about the complexities of cancer-induced disruption of the H-P-G axis. Over the last several years, the numerous cytokines that are produced by immunological cells and tumor cells alike have garnered increasing interest. In addition to direct injurious effects on germinal epithelium and Leydig cells in the testis, ample evidence suggests that cytokines may also disrupt the central nervous system (CNS) endocrine processes. Cytokine receptors are present in the CNS, and studies by several investigators suggest that some cytokines may cross the blood-brain barrier to activate central kinase systems and disturb normal endocrine pathways [7,8]. Anorexia-cachexia syndrome is an example of such a cancer-related process in which cytokines have been implicated in causing disturbances in food intake and nutrition, ultimately leading to wasting, malnourishment, and death. The cytokines implicated in this process include interleukin 1, interleukin 6, tumor necrosis factor alpha, interferon gamma, leukemia inhibitory factor, and ciliary neurotrophic factor [9].

Anorexia-cachexia syndrome, which is present in 80% of patients with advanced cancer, is relevant to reproductive health in cancer patients in two regards. First, with severe depletion of nutritional reserves, processes such as reproductive function may be detrimentally affected [8].
Second, cytokine-driven CNS endocrinopathic processes such as anorexia-cachexia syndrome should prompt consideration of the existence of similar central cytokine effects on the reproductive function of the hypothalamus and pituitary gland. Further insight into the detrimental endocrine effects of cancer is needed.

**Cytotoxic Autoimmune Response**

A complicated cascade of changes in the immune system occurs in the presence of cancer. While these changes may aid in battling the neoplastic process at hand, secondary detrimental changes may result in reproductive dysfunction. Lymphocytic infiltration is associated with many testicular tumors, particularly seminomas [10]. While there is a paucity of studies examining the impact of testicular inflammation on spermatogenesis in the setting of cancer, several investigators have evaluated the effects of inflammation on spermatogenesis in normal testes.

Using models of experimentally induced orchitis, several different researchers have found that inflammatory cytokines may significantly disturb spermatogenesis. Rival et al. demonstrated a link between interleukin 6 expression, germ cell sloughing, and germ cell apoptosis in a Sprague-Dawley rat model with experimentally induced orchitis [11]. Theas et al. reported increased cytochrome c, caspase 8, and caspase 9 levels with associated germ cell apoptosis also using an experimentally induced orchitis rat model [12].

Reactive oxygen species (ROS) levels may also rise in the setting of testicular lymphocytic infiltrate. Spermatozoa exposure to ROS leads to sperm membrane lipid peroxidation which, in turn, may lead to fertility impairment [13]. Martinez et al. specifically evaluated the impact of several pro-inflammatory cytokines on semen samples from normospermic donors, in particular assessing ROS effects. They found interleukin 8 and tumor necrosis factor-alpha, either alone or in the presence of leukocytes, can lead to sperm plasma membrane lipid peroxidation at levels that could significantly affect sperm function and fertility potential [14].

Cytokine excess may also have direct injurious effects on the testis by disrupting the blood-testis barrier. Guazzieri et al. noted high levels of antisperm antibodies in men with testicular cancer, suggesting violation of the normal blood-testis barrier protecting the germinal epithelium from the immune system [15]. They found a significantly higher percentage of positivity (50%) for serum antisperm antibodies in patients with advanced disease compared with patients with low-stage disease (30%), supporting the hypothesis that autoimmune pathology may play a role in impaired sperm function in testicular cancer patients.

**Systemic Physiological Changes**

Cancer is associated with a host of significant changes in normal physiology and homeostasis. As seen in many patients with chronic disease states, patients with cancer may suffer from a variety of comorbidities, including malnutrition [16] and opportunistic infections [17], which may independently impair reproductive health.

Endocrine changes are commonly associated with a number of cancer types...
The pathophysiology is not entirely understood, but may arise due to inhibitory effects centrally on the hypothalamus and pituitary gland (as discussed earlier) and peripherally via impairment of the testicular Leydig cells. Low testosterone in the setting of cancer may not only impact spermatogenesis, but may also decrease the desire to engage in sexual activity. Anxiety, depression, and decreased overall sense of well-being may also result.

Strasser et al. assessed men with advanced cancer who had not undergone any major intervention or treatment for 2 weeks [21]. They found that 29 out of 45 men (64%) had low free testosterone levels. LH was elevated in these men, suggesting that the low free testosterone levels were caused, at least in part, by primary testicular dysfunction. Interestingly, Strasser et al. acknowledged that central mechanisms may also play a role in their patients’ overall hypogonadism.

Fever, implicated as a systemic effect of cancer leading to impaired spermatogenesis, is also a common finding in patients with Hodgkin’s lymphoma. Marmor et al. evaluated a series of 57 patients with Hodgkin’s disease and found semen abnormalities in 19 (33.3%) [22]. Higher fever temperatures were associated with more severe deficits in sperm production, with severely diminished sperm concentration and even azoospermia seen in some patients. Lower temperatures were associated only with deficits in motility. Of the 19 patients with fever, only 5 had normal semen analyses. In a study by Viviani et al. semen analysis was performed in 92 male patients with Hodgkin’s disease prior to treatment [18]. Sixtyseven percent of these men demonstrated impaired spermatogenesis independent of disease stage.

**Psychological Changes Associated with Cancer**

Patients confronting a diagnosis of cancer often find themselves facing a number of difficult psychological issues. Anxiety and depression are common among male cancer patients, and both have the potential to negatively impact reproductive health. Arai et al. evaluated 85 men with testicular cancer who were disease-free one year or more after treatment [23]. Interestingly, the rates and nature of sexual dysfunction seen in the surveillance patients were similar to those seen in the other treatment groups (surgery, chemotherapy, and radiation therapy). Ejaculatory function was the only exception to this finding, with the surveillance group having better ejaculatory function than the other treatment groups. The highest rates of infertility distress were observed in chemotherapy patients. Aside from ejaculatory function, patients treated with surveillance did not have fewer sexual problems than patients in the other treatment groups [23]. The authors concluded that sexual dysfunction and infertility distress are cancer side effects possibly attributed to psychological problems, which can persist even years after malignancy diagnosis.

**The Impact of Cancer Treatment on Male Reproductive Health**

A number of treatment modalities are utilized in the management of cancer. Surgical therapy, cytotoxic drug therapy, radiation therapy, and stem cell transplantation are commonly used in the treatment of this broad disease state. Each treatment has its own associated risks and benefits, and these effects should be carefully considered and discussed with the patient prior to initiating.
therapy. Specific potential effects of treatment include disruption of the H-P-G axis, direct cytotoxic effects on the germinal epithelium within the testis, impairment of penile erectile function, damage to the sympathetic nervous system driving seminal emission and ejaculation, and injury to the genital ductal system required for normal sperm transport. As highlighted earlier in this chapter, many cancer patients have significantly impaired reproductive potential at the time of diagnosis. With this in mind, when fertility preservation is desired, therapeutic modalities that maximize clinical effectiveness while sparing reproductive potential should be selected.

**Effects of Radiation Therapy**

Radiation therapy has been an important and evolving form of cancer treatment for over 80 years [24]. Radiation is utilized for a variety of cancers, including cancer of the prostate, rectum, bladder, penis, and testis. Over time, the delivery of radiation treatment has improved markedly with a concurrent decrease in associated morbidity. Despite these significant advances, radiation therapy can still have detrimental and irreversible effects on the testis, particularly the germinal epithelium.

Radiation therapy causes germ cell loss in a dose-dependent fashion [25]. Damage may result from direct radiation treatment of the testis or radiation scatter from the treatment of other subdiaphragmatic organs. The testis is one of the most radiosensitive organs in the body, and the most immature cell types are the most sensitive to injury [25]. Very small doses (as low as 0.1 Gy) can affect spermatogonia, leading to histological changes in their number and shape. Exposure to 2–3 Gy of radiation leads to significant spermatocyte damage, with a resultant drop in numbers of spermatids. Doses in the 4–6 Gy range lead to significant decreases in the numbers of spermatozoa, suggesting that doses in this range lead to spermatid injury.

The timeline for radiation injury to be reflected in semen analyses is approximately 60–70 days after exposure. As to its effect on ejaculate sperm concentration, radiation doses less than 0.8 Gy typically lead to oligospermia, doses 0.8–2 Gy often result in transient azoospermia, and exposure to doses greater than 2 Gy may lead to irreversible azoospermia [25].

Factors such as the fractionation schedule and the specific field of treatment determine the ultimate impact of radiation therapy on reproductive health. The larger the dose of radiation, the more precipitous the decline in sperm concentration and the longer the period of time required for recovery of spermatogenesis [25]. Hansen et al. evaluated preand post-radiation treatment semen parameters in 24 patients with seminomas and 24 patients with NSGCT. On Cox regression analysis, recovery of spermatogenesis depended on radiation dose, and use of adjuvant chemotherapy prolonged the patients’ recovery period. Additionally, the return of spermatogenesis was impaired in men with low pretreatment total motile sperm counts and those over 25 years of age [26].

Sperm concentrations usually reach nadir by 4–6 months after the conclusion of radiation therapy. Return to pretreatment levels is typically seen within 10–24 months, with patients who receive higher doses experiencing longer recovery periods. Changes in sperm concentration over time are reflected by accompanying variations in FSH level [27].
Return of spermatogenesis following radiation therapy hinges on the survival and proliferation of surviving type-A spermatogonia. Table 3.1 details the timeline for functional recovery of the human testis after single dose radiation treatment, based on a study by Rowley et al. [28]. Fractionated therapy tends to be associated with longer recovery times than single-dose therapy. Some patients who do ultimately regain spermatogenesis after radiation treatment may exhibit permanently diminished sperm concentration and motility. For these individuals, assisted reproductive techniques are often useful in facilitating achievement of pregnancy.

<table>
<thead>
<tr>
<th>Radiation dosage</th>
<th>Time to complete recovery*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 Gy</td>
<td>9–18 months</td>
</tr>
<tr>
<td>2–3 Gy</td>
<td>30 months</td>
</tr>
<tr>
<td>≥4 Gy</td>
<td>≥5 years</td>
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*return to pre-irradiative sperm concentration

Source: Data from Rowley et al. [28].

Leydig cells are much less likely to sustain functional impairment from radiotherapy than are germinal epithelial cells. However, Rowley et al. demonstrated that even doses of radiation of 0.75 Gy can lead to increases in LH levels [28], suggesting some degree of Leydig cell injury. These authors detected no change in testosterone level at this dose, and LH levels gradually returned to normal within 30 months after radiation exposure [28].

Giwercman et al. evaluated men who had undergone orchiectomy and then proceeded to testicular radiation therapy for carcinoma in situ of the solitary remaining testis. These authors found that impairment in Leydig cell secretory function is generally not observed until radiation exceeds doses of 20 Gy. At this dose, not only do LH levels become elevated, but testosterone levels decline when compared with similar patients who have not undergone radiation therapy to the remaining, solitary testis [29].

External beam radiation therapy for pelvic cancers (such as colorectal, bladder, and prostate cancer) results in testicular exposure to scatter doses of 0.4–18.7% of the administered dose [30,31]. In particular, patients with rectal cancer treated with external beam radiation therapy have the highest doses of radiation reaching the testis. Herman et al. have shown that patients treated with 50 Gy for rectal cancer sustained an 85% increase in serum FSH levels and a 22% decline in serum testosterone levels [31].

Important questions regarding the impact of sperm DNA damage resulting from radiation therapy have yet to be answered. Stahl et al. have shown an increase in DNA fragmentation index in men with testicular carcinoma undergoing adjuvant radiation therapy compared with similar patients not treated with radiation. These transient changes were seen up to 2 years after treatment, but the clinical impact of the increases in sperm DNA fragmentation has yet to be fully clarified [32]. Several small studies suggest that DNA integrity of sperm returns to levels of age-matched controls over time, but additional work is needed to further clarify these findings [33,34]. A number of encouraging studies have shown no increase in congenital anomalies or
other disease states in the offspring of patients treated for cancer (with radiation and/or chemotherapy) when compared with these patients’ cousins and to published figures for the general population [35,36].

**Radiation Therapy for Prostate Cancer**

Prostate cancer, the most common cancer in men, is being increasingly diagnosed at earlier stages and younger ages due to PSA screening. As such, many men facing this diagnosis may still be interested in preserving their reproductive function. A study by Daniell et al. revealed significant differences in hormone levels between men who had received prostate external beam radiation therapy and those who had undergone radical prostatectomy [37]. Three to eight years after completion of treatment, total testosterone levels were 27.3% less, free testosterone levels were 31.6% less, LH levels were 52.7% greater, and FSH levels were 100% greater in men who had undergone external beam radiation therapy compared with men who had undergone radical prostatectomy. No semen analysis comparison is possible as one of the groups underwent radical prostatectomy, but the significant changes in hormone levels, particularly the doubling of FSH, implies a high likelihood of significant disruption of spermatogenesis in the group treated with radiation therapy.

Brachytherapy is an increasingly common modality used to treat low-grade and low-stage prostate cancer. Mydlo et al. assessed semen quality in four young men (age 39–52) treated for prostate cancer with brachytherapy [38]. Assessment of semen parameters 6 months post-treatment revealed no change, and 3 of the 4 men were able to initiate pregnancies after treatment. The fourth patient, who had not yet achieved a pregnancy, was noted to have no change in sperm concentration or motility at the 6-month postoperative time point. Scatter radiation dose with brachytherapy is typically less than 20 cGy. A subsequent study by Grocela et al. found that 3 out of 485 men who continued to be sexually active after prostate brachytherapy achieved pregnancies with their partners. Two pregnancies were carried to term and resulted in the birth of healthy children. The third pregnancy resulted in a first trimester miscarriage. All three men had low ejaculate volume and mildly decreased total sperm count [39]. Although the numbers in these studies are small, the results are encouraging from a fertility preservation standpoint and should prompt a larger study of these patients.

**Radiation Therapy for Testicular Cancer**

Pelvic radiation therapy is a mainstay of treatment for some patients with testicular cancer, particularly those with seminoma. Radiation in these cases is typically delivered to the paraaortic lymph nodes and the iliac lymph nodes ipsilateral to the tumor. In this setting, the testicles receive approximately 0.3–0.5 Gy due to scatter, even if testicular shielding is used [40]. Typically, spermatogenesis will be impaired for a period of 6–8 months, followed by recovery over the next 1–2 years. Despite this improvement, spermatogenesis may never return to the pretreatment baseline levels. Prognostic factors favoring more rapid or complete recovery of spermatogenesis include normal semen parameters prior to therapy and younger age at the time of treatment [41].
In comparing paternity of men with testicular cancer who underwent radiation therapy vs. those who underwent observation, Huyghe et al. found significantly lower paternity in the radiation treatment group [42]. The authors concluded that fertility in patients with testicular cancer declined by 30% after radiation treatment. They also reported that radiation therapy, when compared with chemotherapy and observation, had the most deleterious effects on reproductive potential. Huddart et al. in a study of 680 patients, did not reach similar conclusions. They found that a slightly higher percentage of patients undergoing radiation therapy were successful in conceiving when compared with patients receiving chemotherapy [43]. Given the clear link between even small doses of radiation exposure and impaired testicular function, several authors have recommended the use of protective gonadal shielding to decrease radiation scatter to the remaining testicle [26,27].

**Radiation Therapy for Lymphoma**

Radiation therapy is often used for the treatment of Hodgkin’s lymphoma; as with other disease states, impairment of spermatogenesis occurs in a dose-dependent fashion. Kinsella et al. prospectively followed 17 men with early stage Hodgkin’s disease to assess the impact of low-dose scattered irradiation in men receiving conventional fractionated therapy. In these patients, the testicular dose ranged from 6 to 70 cGy, with follow up ranging from 3 to 7 years after completion of radiation therapy. The authors concluded that if the scattered dose received was between 0.2 and 0.7 Gy, patients may experience a temporary rise in FSH and decline in sperm concentration. Return of normal FSH levels was seen in 12–24 months and resolution of transient oligospermia was observed within 18 months of therapy completion [44].

**Radiation Therapy for Leukemia**

Whole body radiation therapy has been used to achieve myeloablation in many patients prior to stem cell transplantation [45]. Recovery of testicular function (normal FSH, LH, testosterone, and/or sperm concentration) is seen in less than 20% of men undergoing whole body irradiation and subsequent bone marrow transplant [46]. Socie et al. in a large survey of 229 centers of the European Group for Blood and Marrow Transplantation, noted that paternity via natural means after whole body irradiation is a rare event, with only 27 such men being identified from all of the centers surveyed. In 41 pregnancies in female partners of these same male patients, no stillbirths and only 1 miscarriage were observed. The risk for either occurrence in the normal population is approximately 10%, significantly higher than observed for these patients [47].

**Effects of Chemotherapy**

Chemotherapy is a mainstay of treatment for many forms of cancer, and the aim is to kill rapidly proliferating cells. One of the most significant drawbacks for this form of therapy is the destruction of normal, healthy tissue. A large number of chemotherapeutic agents are available, and their effects on male reproductive health are variable. Much has been learned about the impact of various cytotoxic agents since Spitz first described testicular damage in men treated with nitrogen mustard in 1948. In that report, 27 of 30 men having undergone this type of treatment were found at the time of autopsy to be azoospermic [48]. As is the case with radiation therapy, the germinal epithelium is much more sensitive to the effects of chemotherapy than are
Leydig cells. While azoospermia is seen after treatment with a variety of agents, clinical hypogonadism manifest by low serum testosterone levels is less common.

The ultimate impact of chemotherapy hinges on the specific agents used, the dosage of these medications administered, and the age of the patient. The deleterious effects of chemotherapy may act in concert with injury brought about by other forms of therapy, such as radiation therapy. Below is a brief overview of the major classes of chemotherapeutic agents and their impact on male reproductive health.

**Alkylating Agents**

(Includes busulfan, chlorambucil, chlormethine, cyclophosphamide, ifosfamide, and procarbazine)

Alkylating drugs are one of the most toxic classes of chemotherapeutic medications available, with a high risk of inducing post-treatment infertility. These medications disrupt DNA function via several mechanisms, including DNA base pair alkylation, formation of abnormal base cross-bridges, and mispairing of nucleotides. The end result is impaired DNA synthesis and RNA transcription leading to cellular death. These agents cause mutations in all stages of developing germinal epithelium [49].

Byrne et al. reported that severe oligospermia or azoospermia typically develop 90–120 days after alkylating agent therapy, with a significant decrease in male fertility whether or not concurrent radiation therapy was administered [50]. A number of investigators have shown that the deficits in sperm production associated with alkylating agents are often severe and irreversible. Buchanan and colleagues reported that even 4 years after treatment with cyclophosphamide, most patients had not yet regained spermatogenesis. Those patients that did resume sperm production did so at 31 months after treatment [51]. Multi-agent regimens that include procarbazine usually render patients irreversibly infertile, leading investigators such as Bokemeyer and colleagues to recommend alternative agents in its place [52].

**Antimetabolites**

(Includes 5-fluouracil [5-FU], 6-mercaptopurine, gemcitabine, and methotrexate)

The antimetabolites interfere with DNA synthesis and transcription, typically resulting in reversible, transient declines in sperm concentration. Choudhury and colleagues reported that in a rat model, 5-FU induced chromosomal aberrations in spermatogonial cells. A gradual decrease in the transmission of these cytotoxic changes from spermatogonia to sperm was noted over time, with the authors postulating that the damaged spermatogonia are gradually eliminated during the cycle of spermatogenesis [53]. D'Souza et al. reported seminiferous tubule atrophy and marked changes in sperm morphology using a rat model treated with 5-FU [54,55].
Platinum Analogs

(Includes cisplatin and carboplatin)

The platinum analogs cause DNA crosslink formation, and animal studies have shown that spermatogonia and spermatocytes are the most markedly affected cell types [56]. Lampe and colleagues reported on 170 patients with testicular germ cell cancer. Approximately 25% of the men were azoospermic and approximately 25% were oligospermic prior to initiation of therapy [57]. After treatment with platinum-based chemotherapy, recovery of spermatogenesis continued over time, with approximately 50% of men with spermatogenesis at 2 years and 80% of men with spermatogenesis 5 years after completion of therapy. For the subgroup of men with normal sperm concentrations prior to therapy, 64% had normal sperm concentrations at a median of 30 months after completion of platinum-based chemotherapy. These authors found a higher likelihood of recovery of spermatogenesis with carboplatin than with cisplatin therapy.

Vinca Alkaloids

(Includes vinblastine, vincristine, vindesine, and vinorelbine)

The vinca alkaloids, which are derived from the periwinkle plant, exert their antineoplastic effects via inhibition of microtubule formation, which in turn inhibits mitosis. These agents have been implicated in arresting spermatogenesis and in decreasing spermatozoa motility [58]. Other investigators, such as Sjoblom et al. and Aubier et al. have demonstrated that spermatogenesis is relatively resistant to the effects of vinblastine, in contrast to Arnon’s findings [59,60].

Topoisomerase Inhibitor Agents

(Includes doxorubicin, etoposide, and bleomycin)

Topoisomerase-inhibiting agents induce damage in a variety of ways, such as DNA binding, RNA-breaks, and RNA synthesis inhibition. Bleomycin, one such agent, has been shown to cause chromosomal abnormalities in spermatogonia and spermatocytes in an animal study by van Buul et al. [61]. Hou et al. evaluated the effects of doxorubicin in rats of various ages and found that the initiation phase of spermatogenesis is highly susceptible to doxorubicin-induced apoptosis. They discovered that gonocytes and early spermatogonia are most vulnerable to this apoptosis, leading to a decline in the number of germline stem cells [62].

Effects of Surgery

Surgical therapy of cancer can have a wide array of deleterious effects on male reproductive health. Consideration of these effects is imperative during preoperative discussions with patients.

Men suffering from testicular cancer typically sustain a significant loss of overall testicular mass when undergoing orchiectomy, which can impair reproductive health due to lower overall germ cell mass and Leydig cell mass. This may lead to reduced sperm concentration and serum testosterone levels. Some men with testicular cancer may also undergo subsequent
retroperitoneal lymphadenectomy, potentially resulting in anejaculation or retrograde ejaculation as a result of disruption of the lumbar sympathetic plexus and hypogastric plexus. Modified, nervesparing templates for dissection have resulted in preserved ejaculatory function in the majority of these men [63].

Men with bladder or prostate cancer who require extirpative surgery will suffer disruption of the genital ductal system as the prostate gland and seminal vesicles are routinely removed. Patients undergoing these procedures typically still produce sperm normally – it is the transport and delivery of sperm to the prostatic urethra that are disrupted. As a result, normal ejaculatory function, and thus fertility, is destroyed.

While erectile function may be preserved in over 80% of men undergoing radical prostatectomy and radical cystectomy with nerve-sparing techniques [64], recovery of erections may take a year or more and may be incomplete. With the advent of PDE-5 inhibitors and other therapies for erectile dysfunction, this problem is often readily treatable.

Traditional assumptions about a patient’s reproductive aspirations, based on age or other demographic traits, should be carefully considered. Changes in reproductive health are a fairly common outcome of oncological surgery and it is incumbent upon physicians to routinely discuss the potential impact of each procedure on reproductive health prior to initiating surgical therapy.

Effects of Opioids

Pain management is a critical component of cancer therapy. The use of opioids is often chronic and may involve high doses. Opioid-induced suppression of the H-P-G axis is well documented, and the resultant decrease in gonadotropins may lead to declines in libido, erectile function, and spermatogenesis. All of these factors, individually or collectively, may impair fertility. Fortunately, these negative effects are typically reversible with cessation of opiod use [65].

Fertility Preservation in Male Cancer Patients

Over 20,000 patients of childhood and reproductive age are treated with radiation therapy and/or chemotherapy each year [58]. With improving diagnostic and therapeutic modalities, overall survival for most cancers has increased significantly over the last 75 years. For patients under 15 years of age, the 5-year survival rate for cancer is approximately 75% [66], and the survival rate for men aged 15–44 facing a cancer diagnosis is 61% [67]. The prevalence of cancer survivors seeking fertility continues to grow; Bleyer reported that by 2010, one in every 250 adults will be a survivor of childhood cancer [68], and many of these individuals, if not most, will desire parenthood. Furthermore, many men are waiting until later in life to start their first families, and others start second families at an older age due to divorce or death of a spouse. As such, an increasing number of adult male cancer survivors will be pursuing fatherhood post-treatment. The end result of this phenomenon will be an increasing pool of patients striving to achieve parenthood in the wake of fertility impairing cancer treatments.
For patients, a cancer diagnosis is often devastating and overwhelming. The immediate focus is typically on therapy and cure of the underlying disease process. Thus, it is imperative that the treating physicians actively address the issue of fertility preservation as comprehensive care is administered to the patient. This concept was recently recommended by the President’s Cancer Panel; specifically, the panel suggested that all reproductive-age patients and parents of children with cancer be notified in detail of the risks of infertility associated with cancer and cancer treatment [69]. While approaches such as use of donor sperm and adoption are available to facilitate paternity in cancer survivors, many patients express a strong desire to father biological children [70].

A recent study by Zapzalka et al. of American Society of Clinical Oncology (ASCO) members in Minnesota revealed that 100% of oncologists reported discussing fertility issues with their patients [71]. However, Shover et al. surveyed approximately 900 male cancer patients, and only 60% replied that they were informed about fertility issues. Furthermore, only 50% stated they had been notified about sperm banking [70]. Similar observations are anecdotally noted by physicians and patients at many centers, highlighting the significant communication barriers existing between health care providers and patients. The President’s Cancer Panel acknowledged these deficits in effective communication between health care providers and patients. They recommended the use of complete culture- and literacy-sensitive information, both verbally and in writing, regarding fertility preservation options and possible effects of treatments. There is little room for communication breakdown when treating cancer patients. Diagnostic testing and therapeutic procedures in the acute care setting occupy large amounts of time, leaving very little time to address fertility preservation. However, cryopreservation of sperm in advance of cancer treatment is essential, as even one cancer treatment can reduce semen quality and induce sperm DNA damage [72].

**American Society of Clinical Oncology Guidelines**

In 2006, ASCO published recommendations on fertility preservation in cancer patients [73]. The authors of this manuscript acknowledged that application of fertility preservation measures is limited by several factors, including knowledge deficits regarding fertility risks associated with cancer treatments, failure to discuss fertility preserving options prior to treatment, lack of insurance coverage for these procedures, and the investigational status of some of the fertility preservation techniques. The expert panel recommended that oncologists discuss at the earliest opportunity the possible risk of fertility impairment associated with various cancer treatments. For those patients interested in pursuing fertility preservation, the prompt referral of the patient to a qualified specialist in this area was recommended. Finally, the authors advocated the participation of patients in clinical trials to advance the state of knowledge within the field of fertility preservation. Below, several methods available for fertility preservation in men are detailed. A helpful summary algorithm is also provided (Fig. 3.1).
Sperm Cryopreservation

A number of articles from the “pre-in vitro fertilization” (pre-IVF) era highlighted poor outcomes of sperm cryopreservation, with a minority of semen samples provided by cancer patients being adequate to pursue intrauterine insemination [74,75]. As such, this early literature did not advocate pretreatment sperm cryopreservation due to the low resultant pregnancy rates. Unfortunately, these historical outcomes still guide clinical decision making by some health care providers with regard to fertility preservation. With the advent of IVF and intracytoplasmic sperm injection (ICSI), literally just one sperm per oocyte is necessary to achieve possible fertilization and pregnancy. Thus, even men with extremely diminished overall semen quality should be offered sperm cryopreservation, as the above assisted reproductive techniques can often overcome severe deficits in sperm production and function.

Overview of Sperm Collection Techniques

The semen collection process itself is achieved via masturbation. The patient should be provided a sterile specimen collection cup and ample time and privacy to produce the sample. Avoidance of lubricants (such as petroleum jelly and saliva) is critical, as many of these substances are spermatotoxic.

If no ejaculate is expelled on climax, then a post-ejaculate urinalysis should be inspected to assess for retrograde ejaculation. If retrograde ejaculation is observed, alpha agonists may be administered in an effort to convert retrograde to antegrade ejaculation. If this is not successful,
then alkalilization of the urine and subsequent collection and processing of the post-ejaculate urine sample may facilitate isolation of viable sperm.

If the patient is unable to climax, care should be taken to ensure that he has had ample privacy and time. If this difficulty persists, then consideration should be given to vibratory stimulation, electro-ejaculation, or surgical testicular sperm extraction techniques, all of which have a potential role in such patients.

**Testicular Tissue Cryopreservation (ONCO-TESE)**

Azoospermia at the time of attempted sperm cryopreservation was noted in 13.8% of cancer patients by Lass et al. in a 1998 review of their center’s data [72]. When the provided sample reveals azoospermia, surgical testicular sperm extraction prior to cancer treatment is an option [76–79]. Dubbed “Onco-TESE” (Oncological Testicular Sperm Extraction) by Schrader et al. this procedure was successful in yielding sperm retrieval in 6 of 14 men with testicular germ cell tumors and in 8 of 17 patients with malignant lymphoma [79]. Given the possible irreversible damage to germinal epithelium with cancer therapy and the good overall success rates with “Onco-TESE”, Schrader et al. recommend that this procedure be considered as a means of fertility preservation in azoospermic cancer patients.

Figure 3.2 illustrates the Onco-TESE procedure performed on a man with a solitary testis and azoospermia undergoing radical orchiectomy for seminoma. Critical components of this procedure include coordination of laboratory personnel with the operating room staff, availability of an operating microscope, a sterile workbench away from the operating field, and a phase contrast microscope to inspect wet prep slides.
Fig. 3.2 (a) The operating microscope and sterile field where the Onco-TESE will be performed in the foreground. The radical orchietomy is being performed in the background. (b) The radical (continued)
Future Directions in Fertility Preservation in Male Cancer Patients

Many investigational male fertility preserving techniques are undergoing evaluation. Some have been studied more thoroughly than others, and a number offer hope as our understanding of male reproductive physiology grows. Several of these investigational techniques are briefly described below.

Luteinizing hormone releasing hormone (LHRH) agonists have been used to achieve H-P-G axis suppression during chemotherapy. While early animal studies showed some evidence of gonadal protection during chemotherapy, several human studies have been less promising. This approach did not lead to fertility preservation or hasten the return of spermatogenesis in several studies in men [80–83].

Testicular tissue harvesting for autotransplantation has also been considered by several investigators. Effects to date have focused on successful germ cell isolation and cryopreservation [84]. The hope is that after cancer treatment, the harvested germinal epithelium may be transplanted back to the patient with resumption of spermatogenesis. This technique remains investigational, and to date has not been effectively implemented in humans.

Testicular tissue harvesting for transplantation into immunodeficient mice is another investigational technique garnering much attention. Nagano and colleagues have demonstrated that this procedure is technically feasible in these mice with successful ensuing spermatogenesis, pregnancies, and live births. To date, this approach has only been successfully performed in animal models [85,86], but it may hold promise for human application, particularly in prepubescent boys.
Conclusion

Fertility preservation in male cancer patients is an important aspect of comprehensive health care. As cancer diagnostic techniques and treatments improve, a growing number of cancer survivors will continue to look past their malignancy toward issues such as parenthood. In this chapter, we have detailed the numerous ways in which cancer itself and its associated treatments can negatively impact many aspects of normal male reproductive health. This underscores the importance of tailoring a careful discussion with each patient over the potential deleterious impact of their specific disease state and therapy prior to initiating treatment.

At the time of cancer diagnosis, patients and clinicians alike are often overwhelmed by the high volume of urgent tests and procedures that must be accomplished in a timely fashion. This situation sets the stage for a profound breakdown in communication between health care providers and patients with regard to fertility preservation. In retrospect, not only do many patients fail to recall discussions of fertility preservation, they often harbor great disappointment and regret at the perceived oversight in this aspect of their care. Fortunately, with a proactive approach, fertility preservation in men is quite feasible and will help avoid the irreversible and permanent loss of reproductive capacity that accompanies many cancer treatments today.

References