Chapter 3
Fertility Preservation in Adult Male Cancer Patients

Robert E. Brannigan, MD

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