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Urologic Oncology: Seminars and Original Investigations 34 (2016) 399–406

UROLOGIC ONCOLOGY

Review article

Fertility concerns in men with genitourinary malignancies: Treatment dilemmas, fertility options, and medicolegal considerations

Allison Polland, M.D.[a,*], Boback M. Berookhim, M.D., M.B.A.[b]

[a] *Department of Urology, Icahn School of Medicine at Mount Sinai, New York, NY*
[b] *Department of Urology, Hofstra North Shore-LIJ School of Medicine, Lenox Hill Hospital, New York, NY*

Received 10 September 2015; received in revised form 10 April 2016; accepted 4 May 2016

Abstract

Background: With increasing genitourinary cancer survivorship in patients of reproductive age, fertility preservation has become a greater focus in the management of these patients.

Materials and methods: We performed a review of articles pertaining to male infertility, fertility preservation, and genitourinary cancers. The aim was to review causes of infertility in patients with cancer, current options for fertility preservation, research that may expand preservation options, and ethical as well as medicolegal considerations.

Results: There are multiple causes of infertility in male patients with cancer, including the malignancy itself, and the treatments required to achieve a potential cure. Surgery can affect the normal pathways for erection, emission, and ejaculation. Chemotherapy can have a profound negative effect on spermatogenesis by causing chromosomal aberrations, maturation arrest, mutagenesis, and impaired spermatozoa motility. Radiation can cause cellular apoptosis with resultant reduction in spermatogonial stem cells. There are numerous methods to secure fertility before cancer treatment with the aid of cryopreservation ranging from simple patient-provided semen samples to complex sperm retrieval techniques. Research in the field of spermatogenic stem cells may lead to improved treatment options such as autotransplant of stem cells for repopulation of the testes after cancer treatment.

Conclusions: Early discussion of possible fertility effects in patients undergoing genitourinary cancer treatment is critical in this era of increasing survivorship. Although current cancer treatments can cause infertility, there are well-established options for fertility preservation and current research will likely lead to improved treatment options.

Keywords: Infertility; Cancer; Spermatogenic stem cell transplant; Ethics

1. Introduction

Patients are living longer after genitourinary (GU) cancer diagnosis because of advances in early detection and treatment. Over the past 3 decades, the 5-year relative survival rate for all cancers combined has increased by 20% [1]. In the most recent cancer statistics published in 2016, the 5-year relative survival rate for all patients with cancer is 69% [1]. Survival in GU cancers varies. When considering all types of kidney cancer, the 5-year relative survival rate is 74% [1]. In penile cancer, the 5-year relative survival rate is 73% with significantly lower survival for cancers with regional and distant spread [2]. Bladder cancer 5-year survival rate for all stages is 79% [1]. Some urological cancers have very high survival rates. Testis cancer 5-year survival rate is 97% [1]. Prostate cancer survival has increased greatly with screening and early detection; the 5-year relative survival rate for all stages combined has increased from 68% to 99% [1]. Although many GU cancers, aside from testicular cancer, affect older patients, with screening and with increase in incidental findings on imaging, cancers are being found in younger patients in whom fertility remains a concern. With increasing survivorship in patients of reproductive age, fertility preservation has become a greater focus in the management of these patients. The following is a review of articles pertaining to male infertility, fertility preservation, and GU cancers. We aim to review causes of infertility in patients with cancer, current options for fertility preservation,

* Corresponding author. Tel.: +1-212-241-3071; fax: +1-718-883-6312.
E-mail address: allison.polland@mountsinai.org (A. Polland).

http://dx.doi.org/10.1016/j.urolonc.2016.05.007
1078-1439/

research that may expand preservation options, and ethical as well as medicolegal considerations.

2. Infertility in male patients with GU cancer

There are multiple causes of infertility in male patients with cancer, including the malignancy itself, and the treatments required to achieve a potential cure. Pretreatment fertility status and treatment received are both prognostic factors. Malignancy can influence gonadal function through hormonal alterations and metabolic derangement. Reproductive hormones may be affected in patients with cancer as a result of stress response, direct tumor effect, or in the case of testis cancer via down-regulation of the hypothalamic-pituitary-gonadal axis. Malignancy may also result in malnutrition with deficiencies in vitamins, minerals, and trace elements needed for optimal spermatogenesis. Furthermore, tumor-released cytokines such as interleukins, tumor necrosis factors, and other substances secreted by tumor tissue and the host's response to the tumor can affect spermatozoa function, resulting in low sperm motility [3]. Treatment including surgery, radiation, and chemotherapy can all affect fertility, with chemotherapy having a profound negative effect on spermatogenesis (Table). It is for these reasons that it is important to refer men for sperm banking before treatment.

2.1. Testis cancer

Most GU malignancy fertility concerns pertain to patients with testis cancer given the age of the patient at diagnosis. In testis cancer, reproductive hormones are often affected by the malignancy itself. In healthy men, the hypothalamus produces gonadotropin-releasing hormone that stimulates release of follicle-stimulating hormone and luteinizing hormone from the pituitary. Human chorionic growth hormone, produced by some germ cell tumors such as seminoma and yolk sac tumors, may lead to negative feedback on this axis causing hormonal down-regulation. In addition to the effects of the malignancy on hormonal function, patients with testis cancer may have other factors affecting their fertility. The testicular dysgenesis syndrome is a set of clinical features, including testicular germ cell tumors, cryptorchidism, hypospadias, and infertility, which are thought to have a common cause and may represent a spectrum of disease [4]. Patients with testicular dysgenesis syndrome who develop testicular germ cell tumors may have had a pre-existing defect in spermatogenesis, which puts them at increased risk of infertility before the development of cancer. Additionally, there may be local effects of the tumor likely because of paracrine substances, as spermatogenesis defects have been shown to be highest in testicular tissue close to a tumor [5]. There may also be autoimmune mechanisms at play as testicular cancers disrupt the blood-testis barrier, resulting in antisperm antibodies that have been found in 73% of patients with testicular cancer, compared with 8% in healthy control subjects [6].

The surgical management of testis cancer can profoundly affect fertility. Orchiectomy has been shown to decrease median sperm concentration and total sperm count [7]. Hormonal levels are usually not affected. After unilateral orchiectomy, at a median of 5 months of follow-up, serum testosterone levels are usually similar to preorchiectomy levels, driven by a compensatory increase in luteinizing hormone. Although uncommon, there is a known risk of synchronous or metachronous testis cancer; this may require bilateral orchiectomy with devastating results on hormonal function and fertility [8].

Retroperitoneal lymph node dissection (RPLND) can result in retrograde ejaculation owing to disruption of sympathetic pathways. Advances in surgical techniques, such as nerve-sparing and template dissections, have allowed for the preservation of ejaculatory function [9]. In a recent review of 176 patients who underwent primary RPLND, 97% had antegrade emission. Bilateral nerve sparing resulted in ejaculation in a greater percentage of patients as compared with template non–nerve-sparing dissections, 99% vs. 89%, respectively. Of those patients who attempted to have children, almost three-quarters were successful [10]. Postchemotherapy RPLND is a more

Table
Effect of common chemotherapeutics on male fertility

Drugs	Class	Mechanism of action	Effects on spermatogenesis
Cisplatin, carboplatin	Platinum-based agents	Cross-link DNA, impair DNA synthesis/transcription and function	Spermatogenesis affected with possible chromosomal abberations
Fluorouracil, 6-mercaptopurine, methotrexate, gemcitabine	Antimetabolites	Interfere with DNA transcription	Spermatogenesis affected with possible chromosomal abberations
Vincristine, vinblastine	Vinca alkyloids	Inhibit microtubule polymerization	Spermatogenesis arrest and affects spermatozoa motility
Busulfan, cyclophosphamide, chlorambucil, procarbazine, ifosfamide	Alkylating agents	Alkylation of DNA base pairs, formation of abnormal DNA crossbridges, mispairing of nucleotides	Induces azoospermia with irreversible mutagenic effect on all stages of spermatogenesis
Etoposide, doxorubicin	Topoisomerase inhibitors	Prevent DNA supercoiling and interfere with DNA transcription/replication	Cytotoxic effects with possible chromosomal anomalies