Perspective

A new fertility risk rating system for surgical, radiotherapy, and chemotherapy interventions used in testicular cancer

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Abstract: The vast majority of patients diagnosed with testicular germ cell tumors will survive their disease. This raises the importance of survivorship issues, particularly fertility preservation given that half of patients diagnosed with testicular cancer are under the age of 34. In this perspective, we offer a novel fertility rating system based on the FDA's A/B/C/D/X/N pregnancy risk category system for first line therapies (surgical, chemotherapeutic, and radiation therapies) listed by the National Comprehensive Cancer Network (NCCN). All chemotherapies (bleomycin, carboplatin, cisplatin, etoposide and ifosfamide) have available human data demonstrating a negative impact on fertility yielding category D ratings. Radiation therapy and surgical interventions such as unilateral orchiectomy and retroperitoneal lymph node dissections (RLND) were also designated category D. Despite the clear risk to fertility, the majority of men do not undergo semen cryopreservation (SCP). Future efforts should be made to reduce the barriers to reproductive counseling and fertility preservation for testicular cancer survivors.

Keywords: Testicular cancer; fertility preservation; germ cell tumors; fertility risk; semen cryopreservation (SCP)

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Introduction

The treatment of testicular germ cell tumors represents a success of modern medicine (1). In the 1970s, the cure rate for metastatic testicular cancer went from 10% to 60% with combination chemotherapy. In a recent article, Rajpert-De Meyts *et al.* provide an excellent overview of the current state of knowledge and treatment of testicular germ cell tumors. The authors note that with the surgical, radiotherapy, and chemotherapeutic treatment options available, 99% of patients will have a treatment cure (2).

The treatment success of testicular cancer raises the importance of survivorship issues for these patients. There is a need for continued surveillance for cancer recurrence (3), and monitoring for metabolic syndrome and cardiovascular disease thought to be secondary to low testosterone levels or the delayed effects of chemotherapy such as cisplatin, vincristine, etoposide or bleomycin (3,4). In this perspective, we will focus on how the treatment for germ cell tumors affects future reproductive health, specifically fertility preservation. A new interdisciplinary field, oncofertility, is dedicated to the reproductive needs of cancer patients facing potentially fertility-threatening treatments (5).

Recently, we have proposed a new rating system to grade the male and female fertility risk associated with novel melanoma therapies based on the Food and Drug Administration's (FDA) previously used pregnancy risk stratification system (A/B/C/D/X/N) (6). Although the FDA mandated a labeling change to the pregnancy risk category system in 2014 (7), the new system will be phased in over time for drugs approved prior to June 2015 and the old system will continue to hold clinical relevance in the foreseeable future (6). Testicular cancer predominantly

affects men under the age of 40 and more than 50% of testicular cancer is diagnosed in men 34 years or younger (8). Understanding the fertility risk associated with testicular cancer treatments will enable clinicians to better counsel patients about their future reproductive health.

Methods

The National Comprehensive Cancer Network (NCCN) clinical practice guidelines were used to identify first-line treatments for testicular cancer (9). The male fertility risk for each drug or treatment modality was evaluated based on information available from the FDA, European Medicines Agency, and Health Canada regulatory files, as well as previously published literature. Each treatment was graded based on a novel fertility risk category system based on the FDA's A/B/C/D/X/N pregnancy risk categories (6). Category A is attributed to treatments that have not shown a risk to future fertility in human studies. Category B is assigned to treatments that have not shown evidence of gonadotoxicity in animal studies but do not have available human data. Category C is assigned to treatments in which there is evidence of gonadotoxicity in animal studies but there is no adequate human data. Category D ratings are assigned to treatments with evidence of fertility risk in human studies. Category X ratings are applied to treatments with irreversible fertility risk. Finally, an N designation indicates that there is no available data.

Results

We identified five chemotherapeutic agents, three radiotherapy regimens, and three surgical interventions [unilateral orchiectomy, bilateral orchiectomy and retroperitoneal lymph node dissection (RLND)] in the primary treatment of testicular tumors (*Table S1*). All five chemotherapeutic agents demonstrated a fertility risk in either animal or human studies (category D). For bleomycin, the fertility risk was based on a study evaluating the impact of the bleomycin, etoposide, and cisplatin (BEP) regimen, which caused azoospermia in 20% of patients at 36 months follow-up (10). For cisplatin, the drug's ability to cross the blood-testis barrier causes nearly all patients to become azoospermic during cisplatin therapy (11). While permanent infertility is possible, a study by Namekawa *et al.* showed that the majority (86%) of patients treated for testicular cancer undergoing orchiectomy and cisplatin-based chemotherapy had reappearance of sperm; 54% recovered normospermia with a median time to recovery of 40 months (12). Another study by Lampe *et al.* observed an 80% chance of spermatogenesis at 5 years in 170 patients treated with cisplatin or carboplatin based chemotherapy (13). Finally, the package inserts for both etoposide and ifosfamide report a risk of oligospermia or azoospermia in humans; previously published data has also demonstrated a negative impact on future male fertility after exposure to these agents (10,14).

Radiotherapy and two surgical interventions, unilateral orchiectomy and RLND, also received category D designations. Permanent azoospermia due to radiotherapy is possible in doses as low as 1.2 to 2 gray units (Gy) (15). Avoiding pelvic lymph node dissection has a slightly higher risk of cancer recurrence but tends to impact fertility less severely. For surgical interventions, unilateral orchiectomy leads to a decrease in semen quality and even azoospermia (16,17). Bilateral orchiectomy in the setting of synchronous or metachronous disease in both testicles will render a man infertile (category X). In patients who receive a RLND for germ cell tumors, damage to the sympathetic chain, postganglionic sympathetic fibers, or pelvic plexus damage can result in ejaculatory dysfunction leading to infertility. Current surgical techniques report high rates, upwards of 75% (18), of post-surgical anterograde ejaculation. In the setting of retrograde ejaculation caused by RLND, sympathomimetic or anticholinergic medications can be used to treat retrograde ejaculation. Men can still produce sperm and are candidates for *in-vitro* fertilization after sperm aspiration or testicular sperm extraction.

Discussion

Testicular cancer treatment can have an adverse effect on future fertility. Each of the chemotherapeutic, surgical, and radiation interventions were classified as category D with the exception of bilateral orchiectomy (category X). Although fertility depends on several factors (e.g., age, prior gonadal function), the paternity rate for testicular cancer survivors is 30% lower than expected for age-matched controls (19). It is likely that combination therapies with surgery, radiotherapy, and chemotherapy may further increase the risk of infertility (20). For example, in patients that received no radiation treatment for localized germ cell tumors, infertility was estimated to be less than 20%. However, patients that received localized radiotherapy, either pelvic or testicular, had a much higher risk (>80%) of subfertility after treatment (21). For testicular cancer

survivors, azoospermia is more likely to occur than hypogonadism. Germ cells are more sensitive to toxicity from radiation compared to Leydig cells, which are responsible for testosterone production. The Leydig cells exhibit a lower mitotic rate compared to the germinal epithelium, making them more resistant to damage from cytotoxic therapies (22).

Fertility preservation is a key component of cancer survivorship. Both the American Society for Reproductive Medicine and the American Society of Clinical Oncology recommend counseling on cancer treatments' impact on future fertility, preferably prior to therapy initiation (23,24). Up to 75% of childless cancer patients anticipate the desire for parenting children in the future (25). Simply counseling female cancer patients on fertility preservation and referring to reproductive specialists improves quality of life and reduces regret (26).

In the field of oncofertility, fertility preservation in testicular cancer patients represents a unique opportunity. Unlike female fertility preservation, there is no need for hormonal stimulation for follicle development. The storage of sperm is a fraction of the cost compared to ovarian tissue or egg retrieval. Despite the clear risks to gonadal function, only 25% of patients facing fertility-threatening treatment undergo semen cryopreservation (SCP)—although more than 90% of oncologists agree that SCP should be offered, a significantly smaller proportion explicitly recommend or mention it to eligible male cancer patients (25). Ideally, SCP should be performed prior to any therapy (surgical, radiation, or chemotherapy) to ensure the highest quality semen sample for future use (17,27,28).

Currently, there are several barriers to fertility preservation, including: a lack of physician awareness, a concern for delay in cancer therapy, and cost of sperm preservation. Coverage laws and legal definitions of infertility vary by state; often coverage is only provided for couples unable to conceive after 1 year of unprotected intercourse. Since most patients with testicular cancer need expedited treatment, this delay is untenable. Previous legislative initiatives mandating insurance coverage for fertility preservation in cancer patients have failed to pass (29), but there are ongoing bills attempting to broaden access to care (30). Formal oncofertility programs that encourage collaboration between urologists, oncologists, and reproductive endocrinologists have demonstrated an increase in the rate of SCP for cancer survivors (31). Given the efficacy of the available treatments for patients diagnosed with testicular cancer, a greater emphasis must be placed on survivorship issues with fertility preservation representing one key component for men who have not completed family building.

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Supplementary

Table S1 NCCN recommended therapies for testicular cancer and corresponding fertility risk

Therapy	NCCN indications	Regulatory filings	Previous clinical data	Fertility rating
Chemotherapeutics				
Bleomycin	Seminoma:stage IIA, IIB, IIC, III	FDA: none indicated; Health Canada: effects on fertility not established	Azoospermia possible, but recovery common: (I) In 54 tested patients with germ cell tumors at a median of 36 months post-treatment with BEP, 20% had azoospermia (10); (II) In 45 patients with testicular tumors at 2 years post-treatment with BEP, spermatogenesis recovered in 83%, 80%, and 67% of patients who received 1–2, 3 and 4 cycles, respectively. No recovery in group receiving 5–6 cycles at 2 years, although long-term recovery likely (32)	D
	Nonseminoma: stage IB, IS, IIA, IIB, IIC, IIIA, IIIB, IIIC		Data from Hodgkin's lymphoma: oligospermia possible, but recovery common: (I) In 202 patients at 6 and 12 months post-treatment with adriamycin, bleomycin, vincristine and dacarbazine, sperm concentration and sperm count was significantly decreased. After 24 months, sperm quality returned to pre-treatment values (33)	
Carboplatin	Seminoma: stage IA, IB	FDA: none indicated; Health Canada: single and five daily dose studies led to decreased testicular weights observed in mice (single and 5-day daily dose studies) and dogs (5-day daily dose studies)	Azoospermia possible: (I) In 178 patients with germ cell tumors treated with either cisplatin or carboplatin-based regimens, there was an 80% probability of spermatogenesis at 5 years. In 54 patients treated with carboplatin, there was a higher probability of recovery to oligospermia ($P<0.001$) or normospermia ($P<0.0001$) (13)	D
Cisplatin	Seminoma: stage IIA, IIB, IIC, III	FDA: none indicated; Health Canada: none indicated	Azoospermia possible: (I) In 170 patients with germ cell tumors treated with either cisplatin or carboplatin-based regimens, approximately 50% recover spermatogenesis in 2 years after cisplatin-based chemotherapy, with an 80% chance of recovery at 5 years (13,34)	D
	Nonseminoma: stage IB, IS, IIA, IIB, IIC, IIIA, IIIB, IIIC		Gonadal dysfunction is dose related: (I) In 33 patients with germ cell tumor treated with BEP, decreased sperm production seen in 19% of patients receiving a cumulative cisplatin dose of 400 mg/m^2 and in 47% receiving 600 mg/m^2 (35)	
Etoposide	Seminoma: stage IIA, IIB, IIC, III Nonseminoma: stage IB, IS, IIA, IIB, IIC, IIIA, IIIB, IIIC	FDA: oligospermia, azoospermia, permanent loss of fertility. Sperm counts may normalize years after treatment. Irreversible testicular atrophy in rats treated with IV etoposide for 30 days at 0.5 mg/kg/day; Health Canada: reduced or absent spermatogenesis and reduced testes weight at autopsy in rats and dogs. Subacute toxicity (6.0 mg/kg/day in rats): spermiogenesis decreased or absent. Chronic toxicity (at 1.5 mg/kg in rats): decreased testicular weight and decreased spermiogenesis	Azoospermia possible, but recovery common: (I) In 54 tested patients with germ cell tumors at a median of 36 months post-treatment with BEP, 20% had azoospermia (10); (II) In 45 patients with testicular tumors at 2 years post-treatment with BEP, spermatogenesis recovered in 83%, 80%, and 67% of patients who received 1–2, 3 and 4 cycles, respectively. No recovery in group receiving 5–6 cycles at 2 years, although long-term recovery likely (32)	D
Ifosfamide	Nonseminoma: stage IIIC	FDA: interferes with spermatogenesis. Sterility reported, appears to depend on dose, duration, and gonadal function at start of treatment. Oligospermia, azoospermia also possible. Azoospermia may be reversible. Testicular atrophy possible; Health Canada: risk of infertility, azoospermia, oligospermia. Infertility related to dose, duration, and gonadal function at start of treatment. Infertility possibly reversible. Testicular atrophy possible. Chronic toxicity in rats show decreased spermatogenesis	Data from carboplatin, etoposide, ifosfamide regimen: (I) Azoospermia possible: in 10 patients with testicular cancer treated with a regimen of carboplatin, etoposide and ifosfamide at a mean follow-up of 41 months, 50% were azoospermic (14) Data from osteosarcoma treatment trials: oligospermia, azoospermia possible: (I) In 11 patients treated with high dose ifosfamide (>60 g/m^2) at a mean follow-up of 9.7 years, 17% were azoospermic and 45% were oligospermic (36); (II) In 26 patients with a median follow-up of 9 years, azoospermia seen in 88% of patients receiving MAP (methotrexate, doxorubicin, cisplatin) therapy with ifosfamide *vs*. 50% receiving MAP alone (37)	D
Radiation therapy				
Radiotherapy*	Seminoma: stage IA, IB (20 Gy), IIA (30 Gy), IIB (36 Gy)	N/A	Azoospermia possible. By dose (38): (I) Fractionated dose (39,40): (i) 0.15–0.5 Gy: oligospermia; (ii) >0.6 Gy: azoospermia. Duration varies with dose (<1 Gy, recovery begins within 1 year; 2 Gy, recovery begins after 2 years); (iii) >2.5 Gy: prolonged azoospermia, likely permanent (II) Doses: (i) 0.1–1.2 Gy: adverse effects to spermatogenesis (41); (ii) Doses >2 Gy: risk prolonged or permanent azoospermia (42); (iii) Doses >4 Gy: irreversible damage to spermatogenesis (41); (iv) Doses >20 Gy: leydig cell function affected (42) By delivery method: (I) Fractionated regimens lead to increased gonadal damage (*vs*. single dose) (40); (II) Delivery directly to testicles can lead to irreversible sterility; (III) More accurate dose delivery and protection of gonads allow spermatogenesis recovery in 9–18 months after 1 Gy doses, 30 months after 2–3 Gy doses, 5 years after 4 Gy doses (43) By stage: (I) In 11 patients with stage I and IIA seminomas treated with radical inguinal orchiectomy and radiation treatment at a mean follow-up of 8 years, 56% had normal semen parameters. No cases of azoospermia noted (44)	D
Surgical interventions				
Retroperitoneal lymph node dissection (RPLND)	Nonseminoma: stage IA, IB, IIA, IIB	N/A	Infertility possible due to sympathetic chain, sympathetic nerve, or pelvic plexus damage and ejaculatory dysfunction: (I) In 192 patients with metastatic testicular cancer, anterograde ejaculation was preserved in 11% after modified bilateral template RPLND *vs*. 89% after nerve-sparing technique (45); (II) In 136 patients with metastatic testicular cancer treated with post-chemotherapy RPLND, 79% had anterograde ejaculation after surgery (46); (III) In 81 patients with advanced testicular cancer treated with post-chemotherapy RPLND, 77% reported normal ejaculation after surgery (47)	D
Unilateral orchiectomy	Suspicious testicular mass	N/A	Oligospermia, azoospermia possible: (I) In 35 patients with testicular cancer treated with orchiectomy, 86% had decreased sperm concentration with azoospermia in 3% (48); (II) In 105 patients with stage I nonseminomatous germ cell tumor treated with orchiectomy followed for 10 years, 35% endured permanent infertility as measured by pregnancy rates (48)	D
Bilateral orchiectomy**	Bilateral testicular masses or metachronous disease	N/A		X

Male fertility data and rating for therapies used in testicular cancer. All data is derived from regulatory approval summaries from the FDA, Health Canada, or from clinical trials, as specified. No data was found via regulatory documents from the European Medicines Agency. Fertility risk category system defined as follows. Category A: no risk in controlled human studies, adequate and well-controlled studies have failed to demonstrate a risk to male fertility; category B: no risk in other studies, animal studies have failed to demonstrate a risk to the male reproductive organs and there are no adequate and well-controlled studies in humans of reproductive potential or animal studies have shown an adverse effect to male reproductive organs, but adequate and well-controlled studies in humans of reproductive potential have failed to demonstrate infertility risk; category C: risk not ruled out, animal studies have shown an adverse effect on male reproductive organs and there are no adequate and well-controlled studies in humans of reproductive potential; category D: positive evidence of risk, there is positive evidence of human infertility risk based on adverse reaction data from investigational or marketing experience or studies in humans of reproductive potential; category X: irreversible risk, studies in animals or humans have demonstrated clear, irreversible infertility; category N: no available evidence in preclinical animal or human data (6); *, there are two radiation windows for the treatment of the retroperitoneal lymph nodes for higher-risk seminomas (para-aortic and para-aortic + ipsilateral iliac). **, bilateral orchiectomy is rarely needed in the treatment for testicular cancer, but is performed for metachronous or synchronous disease in a contralateral testicle.

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