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 (3). 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 orchietomy, bilateral orchietomy 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 orchietomy 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 orchietomy 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 orchietomy leads to a decrease in semen quality and even azoospermia (16,17). Bilateral orchietomy 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 orchietomy (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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Footnote

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Conflicts of Interest: The authors have no conflicts of interest to declare.


References

30. Relates to insurance coverage of in vitro fertilization and other fertility preservation treatments. Available online: https://www.nysenate.gov/legislation/bills/2015/s7219/amendment/original
**NCCN indications**

- **D** (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 pretreatment values.
- **D**

**Seminoma:** stage IIA, IIB, IIC, III

**Nonseminoma:** stage IIIC

**FDA:** none indicated; **Health Canada:** single and five daily dose studies led to decreased testicular weights observed in mice (single and multiple dose).

**Infertility possible due to sympathetic chain, sympathetic nerve, or pelvic plexus damage and ejaculatory dysfunction:**

- **Seminoma:** stage IA, IB (20 Gy), IIA (30 Gy), III
- **Nonseminoma:** stage IB, IS, IIA, IIB, IIC, IIIA, IIIB, IIIC

**Azoospermia possible.**

- **FDA:** none indicated; **Health Canada:** effects on fertility not established

**Regulatory filings**

**Previous clinical data**

- **Data from Hodgkin's lymphoma:** oligospermia, 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 26 patients with a median follow-up of 9 years, azoospermia seen in 88% of patients receiving MAP (methotrexate, doxorubicin, cisplatin) therapy with ifosfamide**

**(III) In 81 patients with advanced testicular cancer treated with post-chemotherapy RPLND, 77% reported normal ejaculation after surgery (47).**

**(II) In 136 patients with metastatic testicular cancer treated with post-chemotherapy RPLND, 79% had anterograde ejaculation after surgery (46);**

**(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).**

**(I) Fractionated dose (39, 40):**

- 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).

**(II) Delivery directly to testicles can lead to irreversible sterility;**

**(I) Fractionated regimens lead to increased gonadal damage (**i**), with recovery to azoospermia (**ii**), oligospermia (**iii**), or normal semen parameters (**iv**).**

**(ii) Doses >2 Gy: risk prolonged or permanent azoospermia (42);**

**(i) 0.1–1.2 Gy: adverse effects to spermatogenesis (41);**

**(iii) >2.5 Gy: prolonged azoospermia, likely permanent**

**(ii) >0.6 Gy: azoospermia. Duration varies with dose (<1 Gy, recovery begins within 1 year; 2 Gy, recovery begins after 2 years);**

**(i) 0.15–0.5 Gy: oligospermia;**

**(iii) Doses <1 Gy lead to increased gonadal damage (**i**), oligospermia or azoospermia (**ii**), or normal semen parameters (**iii**).**

**(i) Delivery directly to testicles can lead to irreversible sterility;**

**(II) More accurate dose delivery and protection of gonads allow spermatogenesis recovery in 1–18 months after 1 Gy doses, 30 months after 2–3 Gy doses, 5 years after 4 Gy doses (48).**

**By dose:**

- By delivery method:
  - Fractionated regimens lead to increased gonadal damage (i), oligospermia (ii), or normal semen parameters (iii).
  - Delivery directly to testicles can lead to irreversible sterility.
  - More accurate dose delivery and protection of gonads allow spermatogenesis recovery in 5–18 months after 1 Gy doses, 30 months after 2–3 Gy doses, 5 years after 4 Gy doses (48).

**By regimens:**

- 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).

**Cisplatin**

- In 178 patients with germ cell tumors treated with either cisplatin or carboplatin-based regimens, there was an 80% probability of spermatogenesis in 2 years after carboplatin-based chemotherapy, with a 66% chance of recovery at 5 years (15, 34).

- **Data from 170 patients with germ cell tumors treated with either cisplatin or carboplatin-based regimens, approximately 50% recover spermatogenesis in 2 years after carboplatin-based chemotherapy, with an 86% chance of recovery at 5 years (15-34).**

- **Gonadal dysfunction is dose related:**

  - **Data from 2 patients with germ cell tumors treated with BEP, decreased sperm production seen in 15% of patients receiving a cumulative cisplatin dose of 400 mg/m² and 47% receiving 600 mg/m² (36).**

  - **In 3 patients with germ cell tumors treated with BEP, decreased sperm production seen in 15% of patients receiving a cumulative cisplatin dose of 400 mg/m² and 47% receiving 600 mg/m² (36).**

  - **In 45 patients with testicular tumors at 2 years post-treatment with BEP, 20% had azoospermia (19).**

  - **In 44 patients with testicular tumors at 3 years post-treatment with BEP, 20% had azoospermia (19).**

- **Data from 45 patients with testicular tumors at 2 years post-treatment with BEP, spermatogenesis recovered in 65%, 63% and 67% of patients who received 1–3, 4, 5, and 6 cycles, respectively.**

- **Data from 54 patients with germ cell tumors treated with a regimen of carboplatin, etoposide and ifosfamide at a mean follow-up of 8 months, 56% were azoospermic (48).**

- **Data from scrotal cancer treatment trials:**

**Etoposide**

- **Seminoma:** stage IIA, IIB, IIC

**Nonseminoma:** stage IIA, IIB, IIC

**FDA:** oligospermia, azoospermia, permanent loss of fertility. Sperm counts may remain normal years after treatment. Intravascular testicular artery in rat treated with IV etoposide for 14 days at 0.5 mg/kg/m²/day. Health Canada: risk of infertility; azoospermia possible. Testicular atrophy possible; Health Canada: risk of infertility, azoospermia, oligospermia, infertility related to dose, duration, and gonadal function at start of treatment. Infertility possibility reversible.

- **Fractionated dose:**

**Surgical interventions**

- **Data from 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.**

**Data from 18 patients treated with 5–6 cycles at 2 years, although long-term recovery likely (32).**

**Data from 81 patients with advanced testicular cancer treated with a regimen of carboplatin, etoposide and ifosfamide at a mean follow-up of 11 months, 56% were azoospermic (48).**

**Data from scrotal cancer treatment trials:**

- Azospermia possible: in 10 patients with testicular cancer treated with a regimen of carboplatin, etoposide and ifosfamide at a mean follow-up of 8 months, 56% were azoospermic (48).

- **In 26 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).**

- **In 11 patients treated with high dose ifosfamide (>6 g/m²): Doses >4 Gy at a mean follow-up of 8.7 years, 17% were azoospermic and 65% were oligospermic (36).**

- **In 34 patients with a median follow-up of 8 years, azoospermia seen in 69% of patients receiving MAP (methotrexate, doxorubicin, cisplatin) therapy with ifosfamide vs. 56% receiving MAP alone (57).**

- **In 16 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.**

- **By dose:**

**Table S1**

**Fertility rating**

**Suspicious testicular mass**

**Bilateral orchiectomy**

**Surgical interventions**

**Retroperitoneal lymph node dissection (RPLND)**

**Seminoma:** stage I, II, III, IV

**Nonseminoma:** stage I, II, III, IV

**FDA:** none indicated; **Health Canada:** single and five daily dose studies led to decreased testicular weights observed in mice (single and multiple dose).

**Infertility possible due to sympathetic chain, sympathetic nerve, or pelvic plexus damage and ejaculatory dysfunction:**

- **In 160 patients with metastatic testicular cancer, antegrade ejaculation was preserved in 11% after modified scrotal epididymis RPLND vs. 88% after nerve-sparing technique (45).**

- **In 186 patients with metastatic testicular cancer treated with post-chemotherapy RPLND, 75% had antegrade ejaculation after surgery (48).**

- **In 81 patients with advanced testicular cancer treated with post-chemotherapy RPLND, 77% reported normal ejaculation after surgery (45).**

- **Data from Hodgkin's lymphoma:** oligospermia, azoospermia possible:

**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 possibility reversible.**

**Testicular atrophy possible.**

- Chronic toxicity of 1.5 mg/kg in rats, decreased testicular weight and decreased spermatogenesis.

- **Data from 45 patients with testicular tumors at 3 years post-treatment with BEP, spermatogenesis recovered in 65%, 63% and 67% of patients who received 1–3, 4, 5, and 6 cycles, respectively.**

- **Data from 54 patients with germ cell tumors treated with a regimen of carboplatin, etoposide and ifosfamide at a mean follow-up of 41 months, 50% were azoospermic (14).**

**Regulatory filings**

**Previous clinical data**

**Therapy**

**NCCN indications**

**Regulatory filings**

**Fertility rating**
References