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Male Reproductive Health After Childhood, Adolescent, and Young Adult Cancers: A Report From the Children’s Oncology Group

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ABSTRACT

The majority of children, adolescents, and young adults diagnosed with cancer will become long-term survivors. Although cancer therapy is associated with many adverse effects, one of the primary concerns of young male cancer survivors is reproductive health. Future fertility is often the focus of concern; however, it must be recognized that all aspects of male health, including pubertal development, testosterone production, and sexual function, can be impaired by cancer therapy. Although pretreatment strategies to preserve reproductive health have been beneficial to some male patients, many survivors remain at risk for long-term reproductive complications. Understanding risk factors and monitoring the reproductive health of young male survivors are important aspects of follow-up care. The Children’s Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancer (COG-LTFU Guidelines) were created by the COG to provide recommendations for follow-up care of survivors at risk for long-term complications. The male health task force of the COG-LTFU Guidelines, composed of pediatric oncologists, endocrinologists, nurse practitioners, a urologist, and a radiation oncologist, is responsible for updating the COG-LTFU Guidelines every 2 years based on literature review and expert consensus. This review summarizes current task force recommendations for the assessment and management of male reproductive complications after treatment for childhood, adolescent, and young adult cancers. Issues related to male health that are being investigated, but currently not included in the COG-LTFU Guidelines, are also discussed. Ongoing investigation will inform future COG-LTFU Guideline recommendations for follow-up care to improve health and quality of life for male survivors.

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INTRODUCTION

Curative therapy for cancer during childhood, adolescence, and young adulthood can adversely affect all aspects of male reproductive health. The potential for abnormal development, infertility, and sexual dysfunction is a source of significant emotional distress for survivors.1-3 Recognizing treatment-associated risks and educating survivors and providers about potential reproductive complications is a key component of follow-up care. The Children’s Oncology Group (COG) developed clinical practice guidelines to aid the assessment of survivors of childhood and adolescent cancers for long-term complications.4,5 The COG Long-Term Follow-Up Guidelines for Survivors of Pediatric, Adolescent, and Young Adult Cancer (COG-LTFU Guidelines) are evidence-based guidelines indexed by therapeutic exposure, which are updated every 2 years according to task force recommendations derived from literature review and expert consensus.6 In this review, the COG-LTFU Guidelines male health task force presents an overview of male reproductive complications including hypoandrogenism, precocious puberty, reduced fertility, and sexual dysfunction. Risk factors, clinical assessment, and interventions for each of the treatment-associated complications, as put forth in the guidelines, are discussed. In addition, controversial or investigational topics related to male health currently not incorporated in the COG-LTFU Guidelines, but warranting additional consideration, are presented.

HYPOANDROGENISM

Pubertal development and the maintenance of male secondary sexual characteristics depend on adequate production of testosterone by testicular Leydig cells. Inadequate testosterone production—hypoandrogenism—also increases the risk of osteoporosis and metabolic disorders.
associated with chronic disease.\textsuperscript{7,8} Gonadotoxic chemotherapy, testicular radiation, orchietomy, and cranial surgery or radiation involving the hypothalamic-pituitary-gonadal (HPG) axis can result in hypoadrogenism (Table 1). Testicular Leydig cells are relatively resistant to treatment toxicity, compared with testicular germ cells, such that survivors who are azoospermic after gonadotoxic therapy may maintain adequate testosterone production.\textsuperscript{9-11}

**Risk Factors**

Primary hypoadrogenism—testicular failure—can result from treatment with high-dose alkylating agents, testicular irradiation $\geq 20$ Gy, orchietomy, or combinations of these modalities.\textsuperscript{9-11} Treatment-associated risk factors for central hypoadrogenism include surgical disruption of the HPG axis and cranial radiation dose $\geq 30$ Gy.\textsuperscript{15,18,19} Increasing intensity of therapy is associated with increasing risk for hypoadrogenism. Adequate testosterone production is usually maintained after nonmyeloablative doses of alkylating agents and testicular irradiation $< 20$ Gy; however, subclinical Leydig cell insufficiency (low normal testosterone, elevated serum luteinizing hormone [LH]) can be observed after moderate-dose alkylating agent therapy (cumulative cyclophosphamide $\geq 20$ gm/m$^2$)\textsuperscript{11,14} or lower total dose of testicular irradiation ($< 14$ Gy).\textsuperscript{9,13,20-24} Similarly, survivors who undergo unilateral orchietomy and are not exposed to additional gonadotoxic therapy usually maintain adequate testosterone production\textsuperscript{5,26}; however, an increased risk of subclinical Leydig cell insufficiency has been reported in survivors of testicular cancer treated with orchietomy only.\textsuperscript{26} Testicular cancer is associated with hypoadrogenism, independent of treatment,\textsuperscript{16} and pretreatment hypoadrogenism or microlithiasis in the remaining testis is predictive.\textsuperscript{16} Pubertal status is a risk factor for radiation-associated gonadotoxicity. Hypoadrogenism is consistently observed after a testicular radiation dose $\geq 24$ Gy when survivors are treated before puberty\textsuperscript{20,22,23} and not until a testicular dose $\geq 30$ Gy when survivors are treated postpuberty.\textsuperscript{13,20} In contrast, pubertal status is not protective of chemotherapy-associated gonadotoxicity.\textsuperscript{10,11}

It should be noted that the dose of gonadotoxic therapy that impairs testicular function varies among individuals; therefore, any survivor treated with gonadotoxic agents is at risk for hypoadrogenism. In addition, because deterioration in testicular function is associated with normal aging, young men treated with gonadotoxic agents are likely to remain at risk for hypogonadism as they reach older adulthood.\textsuperscript{7,21,24}

**Assessment**

Delayed or arrested puberty is the clinical manifestation of hypoadrogenism in survivors treated before or during pubertal development. Pubertal onset in boys normally occurs between ages 9.5 and 13.5 years, beginning with testicular enlargement (testicular volume $\geq 4$ mL).\textsuperscript{27} For survivors treated with gonadotoxic therapy before the onset of puberty, the COG-LTFU Guidelines recommend annual assessment of pubertal development until sexual maturity using Tanner staging, with testicular volume determined by Prader orchidometer (Table 1). Assessment of puberty may be difficult given that boys who receive gonadotoxic therapy can have testicular volumes smaller than expected for age as a result of testicular germinal aplasia,\textsuperscript{28} and the development of pubic hair can be mediated by adrenal androgens.\textsuperscript{29} Increase in size of the testes beyond 3 mL and scrotal thinning, along with progressive increases in serum testosterone, likely indicate onset of puberty. If puberty does not begin by age 14 years, or puberty does not progress after onset, evaluation by an endocrinologist is recommended.

Young men and adolescents treated with gonadotoxins after completing puberty should be monitored annually for symptoms of androgen deficiency including decreased libido, decreased spontaneous erections, gynecomastia, loss of body hair, reduced muscle bulk, hot flashes/sweating, and reduced testicular volume.\textsuperscript{15,30} Symptoms of hypoadrogenism may be nonspecific, so providers should have a low threshold to evaluate survivors with known treatment-associated risks.

Boys presenting with delayed puberty and those at risk for treatment-associated hypoadrogenism are recommended to have measurement of baseline early-morning serum testosterone and gonadotropin levels at age 14 years. Men who are symptomatic or have treatment-associated risk factors for testosterone deficiency are also evaluated by obtaining early-morning serum testosterone and gonadotropin levels (Table 1). In adults, a low morning testosterone level is considered diagnostic of hypoadrogenism.\textsuperscript{30} Males with primary testicular failure typically have low testosterone and elevated LH, and males with impairment of the HPG axis will have low testosterone and low or inappropriately normal LH. Low serum testosterone levels can be observed in the absence of elevated LH measurements, so LH should not be used to diagnose androgen deficiency in this population.\textsuperscript{7,24} Survivors who are diagnosed with hypoadrogenism should also be evaluated for associated morbidities including low bone mineral density and metabolic syndrome.\textsuperscript{8}

**Treatment**

If screening confirms the diagnosis of hypoadrogenism in an adolescent survivor with delayed or arrested puberty, the decision to begin treatment should be guided by an endocrinologist. Standard treatment for delayed or arrested puberty related to primary testicular failure is administration of increasing doses of testosterone derivatives by either depot intramuscular injection or with transdermal patch or gel.\textsuperscript{28,31} Although testosterone replacement therapy will cause virilization, it has no effect on testicular maturation and can, in fact, inhibit spermatogenesis.

For postpubertal survivors with hypoadrogenism, the goal is to raise serum testosterone levels and sustain them in the midnormal range. Survivors receiving testosterone replacement therapy should be monitored for adverse effects including polycythemia, dyslipidemia, and liver dysfunction; older adults should also be monitored for prostatic hypertrophy. In some clinical settings, pulsatile gonadotropin-releasing hormone (GnRH) delivered via pump is used as an alternative to testosterone replacement therapy in survivors with central hypogonadism and intact pituitary function, resulting in testicular maturation and stimulation of spermatogenesis.\textsuperscript{31,32} Similarly, in cases of central hypogonadism with abnormal pituitary function, human chorionic gonadotropin can be used to stimulate androgen production and recombinant follicle-stimulating hormone (FSH) used to stimulate spermatogenesis.\textsuperscript{31,33}

**Additional Considerations**

The benefit of androgen replacement therapy for survivors with symptoms of androgen deficiency and the diagnosis of subclinical Leydig cell insufficiency remains controversial. Studies have demonstrated an association between clinical manifestations of androgen...
Table 1. Risk Factors for and Assessment and Evaluation of Male Reproductive Complications After Treatment for Childhood, Adolescent, and Young Adult Cancers

<table>
<thead>
<tr>
<th>Complication</th>
<th>Alkylation agents</th>
<th>Risk Factors</th>
<th>Assessment</th>
<th>Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoandrogenism:</td>
<td>• Delayed/arrested puberty</td>
<td>• Higher cumulative doses or combinations of alkylators</td>
<td>• Puberty (onset, tempo)</td>
<td>Endocrine consultation for delayed puberty, persistently abnormal hormone levels, and hormonal replacement for hypogonadal patients</td>
</tr>
<tr>
<td>Low testosterone</td>
<td>• Low testosterone</td>
<td>• Chemotherapy combined with radiation to: abdomen/pelvis, testes, neuroendocrine axis</td>
<td>• Sexual function (erections, nocturnal emissions, libido)</td>
<td></td>
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<tr>
<td></td>
<td>• Busulfan</td>
<td>• Younger age at treatment</td>
<td>• Tanner staging</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Carmustine (BCNU)</td>
<td>• Individual variation in cumulative dose that results in hypoandrogenism</td>
<td>• Testicular volume by Prader orchidometry</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Chlorambucil</td>
<td>• Spermatogenesis is impaired at lower doses compared with testosterone synthesis</td>
<td>• Laboratory:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Cyclophosphamide</td>
<td>• Prepubertal status does not protect against testicular toxicity</td>
<td>• FSH, LH, testosterone (baseline at age 14 years and as clinically indicated in patients with delayed puberty and/or clinical signs and symptoms of testosterone deficiency)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Ifosfamide</td>
<td>• Treatment factors:</td>
<td>• Bone density evaluation in hypogonadal patients</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Lomustine (CCNU)</td>
<td>• Higher cumulative doses or combinations of alkylators</td>
<td>• Hypothalamic pituitary axis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Mechlorethamine</td>
<td>• Chemotherapy combined with radiation to: abdomen/pelvis, testes, neuroendocrine axis</td>
<td>• Hypothalamic pituitary axis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Melphalan</td>
<td>• Younger age at treatment</td>
<td>• Hypothalamic pituitary axis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Procarbazine</td>
<td>• Individual variation in cumulative dose that results in hypoandrogenism</td>
<td>• Hypothalamic pituitary axis</td>
<td></td>
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<tr>
<td></td>
<td>• Thiotepa</td>
<td>• Spermatogenesis is impaired at lower doses compared with testosterone synthesis</td>
<td>• Hypothalamic pituitary axis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Carboplatin</td>
<td>• Prepubertal status does not protect against testicular toxicity</td>
<td>• Hypothalamic pituitary axis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Cisplatin</td>
<td>• Treatment factors:</td>
<td>• Hypothalamic pituitary axis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Dacarbazine (DTIC)</td>
<td>• Higher cumulative doses or combinations of alkylators</td>
<td>• Hypothalamic pituitary axis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Temozolomide</td>
<td>• Chemotherapy combined with radiation to: abdomen/pelvis, testes, neuroendocrine axis</td>
<td>• Hypothalamic pituitary axis</td>
<td></td>
</tr>
<tr>
<td>Radiation:</td>
<td>• 20 Gy: Testes/Pelvis</td>
<td>• Younger age at treatment</td>
<td>• Hypothalamic pituitary axis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Cranial/neuroendocrine axis</td>
<td>• Individual variation in cumulative dose that results in hypoandrogenism</td>
<td>• Hypothalamic pituitary axis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Orbital/eye</td>
<td>• Spermatogenesis is impaired at lower doses compared with testosterone synthesis</td>
<td>• Hypothalamic pituitary axis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Ear/infratemporal</td>
<td>• Prepubertal status does not protect against testicular toxicity</td>
<td>• Hypothalamic pituitary axis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Nasopharyngeal</td>
<td>• Treatment factors:</td>
<td>• Hypothalamic pituitary axis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Waldeyer’s ring</td>
<td>• Higher cumulative doses or combinations of alkylators</td>
<td>• Hypothalamic pituitary axis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Other fields combined with alkylates:</td>
<td>• Chemotherapy combined with radiation to: abdomen/pelvis, testes, neuroendocrine axis</td>
<td>• Hypothalamic pituitary axis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Flank/hemiabdomen</td>
<td>• Younger age at treatment</td>
<td>• Hypothalamic pituitary axis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Whole abdomen</td>
<td>• Individual variation in cumulative dose that results in hypoandrogenism</td>
<td>• Hypothalamic pituitary axis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Inverted Y, TLI</td>
<td>• Spermatogenesis is impaired at lower doses compared with testosterone synthesis</td>
<td>• Hypothalamic pituitary axis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Prostate/bladder</td>
<td>• Prepubertal status does not protect against testicular toxicity</td>
<td>• Hypothalamic pituitary axis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Iliac/inguinal/femoral</td>
<td>• Treatment factors:</td>
<td>• Hypothalamic pituitary axis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• TBI</td>
<td>• Higher cumulative doses or combinations of alkylators</td>
<td>• Hypothalamic pituitary axis</td>
<td></td>
</tr>
<tr>
<td>Surgery:</td>
<td>• Orchiectomy</td>
<td>• Chemotherapy combined with radiation to: abdomen/pelvis, testes, neuroendocrine axis</td>
<td>• Hypothalamic pituitary axis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Hypothalamic pituitary axis</td>
<td>• Younger age at treatment</td>
<td>• Hypothalamic pituitary axis</td>
<td></td>
</tr>
</tbody>
</table>

| Precocious puberty:          | • Pubertal onset before age 9 years                     | • Younger age at treatment                                                    | • Endocrine consultation for accelerated puberty (puberty in boys age < 9 years) |                                                                           |

| Reduced fertility:           | • Oligospermia                                          | • Younger age at treatment                                                    | • Endocrine consultation for accelerated puberty (puberty in boys age < 9 years) |                                                                           |
|                              | • Azospermia                                            | • Younger age at treatment                                                    | • Endocrine consultation for accelerated puberty (puberty in boys age < 9 years) |                                                                           |

| Alkylation agents:           | • Busulfan                                             | • Younger age at treatment                                                    | • Endocrine consultation for accelerated puberty (puberty in boys age < 9 years) |                                                                           |
|                              | • Carmustine (BCNU)                                    | • Younger age at treatment                                                    | • Endocrine consultation for accelerated puberty (puberty in boys age < 9 years) |                                                                           |
|                              | • Chlorambucil                                         | • Younger age at treatment                                                    | • Endocrine consultation for accelerated puberty (puberty in boys age < 9 years) |                                                                           |
|                              | • Cyclophosphamide                                     | • Younger age at treatment                                                    | • Endocrine consultation for accelerated puberty (puberty in boys age < 9 years) |                                                                           |
|                              | • Ifosfamide                                            | • Younger age at treatment                                                    | • Endocrine consultation for accelerated puberty (puberty in boys age < 9 years) |                                                                           |
|                              | • Lomustine (CCNU)                                     | • Younger age at treatment                                                    | • Endocrine consultation for accelerated puberty (puberty in boys age < 9 years) |                                                                           |
|                              | • Mechlorethamine                                      | • Younger age at treatment                                                    | • Endocrine consultation for accelerated puberty (puberty in boys age < 9 years) |                                                                           |
|                              | • Melphalan                                             | • Younger age at treatment                                                    | • Endocrine consultation for accelerated puberty (puberty in boys age < 9 years) |                                                                           |
|                              | • Procarbazine                                          | • Younger age at treatment                                                    | • Endocrine consultation for accelerated puberty (puberty in boys age < 9 years) |                                                                           |
|                              | • Thiotepa                                              | • Younger age at treatment                                                    | • Endocrine consultation for accelerated puberty (puberty in boys age < 9 years) |                                                                           |
|                              | • Carboplatin                                           | • Younger age at treatment                                                    | • Endocrine consultation for accelerated puberty (puberty in boys age < 9 years) |                                                                           |
|                              | • Cisplatin                                             | • Younger age at treatment                                                    | • Endocrine consultation for accelerated puberty (puberty in boys age < 9 years) |                                                                           |
|                              | • Dacarbazine (DTIC)                                    | • Younger age at treatment                                                    | • Endocrine consultation for accelerated puberty (puberty in boys age < 9 years) |                                                                           |
|                              | • Temozolomide                                          | • Younger age at treatment                                                    | • Endocrine consultation for accelerated puberty (puberty in boys age < 9 years) |                                                                           |
| Radiation:                   | • Any testicular dose                                   | • Younger age at treatment                                                    | • Endocrine consultation for accelerated puberty (puberty in boys age < 9 years) |                                                                           |
|                               | • Whole abdomen, inverted Y, pelvic, prostate/bladder/iliac | • Younger age at treatment                                                    | • Endocrine consultation for accelerated puberty (puberty in boys age < 9 years) |                                                                           |
|                               | • Inguinal/femoral                                      | • Younger age at treatment                                                    | • Endocrine consultation for accelerated puberty (puberty in boys age < 9 years) |                                                                           |
|                               | • TBI                                                   | • Younger age at treatment                                                    | • Endocrine consultation for accelerated puberty (puberty in boys age < 9 years) |                                                                           |
|                               | • 30 Gy:                                                | • Younger age at treatment                                                    | • Endocrine consultation for accelerated puberty (puberty in boys age < 9 years) |                                                                           |
|                               | • Cranial                                               | • Younger age at treatment                                                    | • Endocrine consultation for accelerated puberty (puberty in boys age < 9 years) |                                                                           |
|                               | • Orbital/eye                                           | • Younger age at treatment                                                    | • Endocrine consultation for accelerated puberty (puberty in boys age < 9 years) |                                                                           |
|                               | • Ear/infratemporal                                    | • Younger age at treatment                                                    | • Endocrine consultation for accelerated puberty (puberty in boys age < 9 years) |                                                                           |
|                               | • Nasopharyngeal                                       | • Younger age at treatment                                                    | • Endocrine consultation for accelerated puberty (puberty in boys age < 9 years) |                                                                           |
|                               | • Waldeyer’s ring                                      | • Younger age at treatment                                                    | • Endocrine consultation for accelerated puberty (puberty in boys age < 9 years) |                                                                           |
| Surgery:                     | • Orchiectomy                                           | • Younger age at treatment                                                    | • Endocrine consultation for accelerated puberty (puberty in boys age < 9 years) |                                                                           |
|                               | • Hypothalamic pituitary axis                           | • Younger age at treatment                                                    | • Endocrine consultation for accelerated puberty (puberty in boys age < 9 years) |                                                                           |

(continued on following page)
deficiency and Leydig cell insufficiency, but no study to date has shown a measurable improvement with testosterone replacement therapy.\(^7\,^8\,^34\) Furthermore, it is not clear if this clinical entity in young survivors predicts progression to overt Leydig cell failure over time.\(^26\) Recommendations for ongoing screening and therapeutic interventions for survivors with Leydig cell insufficiency will be informed by further investigation.

### PRECOCIOUS PUBERTY

Precocious puberty in boys is defined as pubertal onset before age 9 years.\(^27\) Early onset of puberty results from premature activation of the HPG axis, resulting in the pulsatile secretion of GnRH, which in turn leads to stimulation of the testes by gonadotropins.

### Risk Factors

Any survivor treated with radiation that includes the hypothalamus\(^35\) (Table 1) is at risk for precocious puberty. Males younger at the time of irradiation and those who received doses \(\geq 18\) Gy are at greatest risk.\(^36\)

### Assessment

Increased testicular volume (\(\geq 4\) mL) and other signs of puberty before age 9 years raise concern for precocious puberty. The COG-LTFU Guidelines recommend screening for precocious puberty in any survivor who received cranial radiation that included the hypothalamus (Table 1). Annual screening should include height, height velocity, and Tanner staging. A survivor with early signs of puberty is evaluated with early-morning serum LH, FSH, testosterone, and bone age (Table 1) and then referred to a pediatric endocrinologist. If any neurologic symptoms are present, brain magnetic resonance imaging should be considered to evaluate for other central pathologies associated with precocious puberty.\(^37\,^38\)

### Treatment

The goal of treatment for precocious puberty is to preserve adult height and delay further development of secondary sexual characteristics.\(^39\) Premature testicular stimulation by gonadotropins can be blocked by administering GnRH analogs.\(^40\) Therapeutic options include monthly depot injections of GnRH analogs or yearly implanta-

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**Table 1. Risk Factors for and Assessment and Evaluation of Male Reproductive Complications After Treatment for Childhood, Adolescent, and Young Adult Cancers (continued)**

<table>
<thead>
<tr>
<th>Complication</th>
<th>Therapy</th>
<th>Risk Factors</th>
<th>Assessment</th>
<th>Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejaculatory dysfunction</td>
<td>Surgery: Neurorsurgery: brain-hypothalamus/pituitary, spine</td>
<td>Spinal injury above the sacrum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>Pelvic/gonitourinary surgery</td>
<td>Radiation dose (\geq 55) Gy to penile bulb in adult or (\geq 45) Gy in prepubertal child</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiation: Pelvic, gonitourinary, bladder, cranial, spine</td>
<td>Presacral or retroperitoneal resection or dissection</td>
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<tr>
<td>Host factors: Comorbid medical conditions</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Hypogonadism</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Additional Considerations**

Boys who underwent cranial irradiation and have reduced testicular volume because of treatment-associated testicular germinal cell aplasia are difficult to assess for precocious puberty. For these survivors, monitoring with early-morning serum gonadotropins and testosterone should be considered.

---

**REDUCED FERTILITY**

Male fertility requires the intact function of the testes, HPG axis, and gonitourinary organs. Survivors are at risk for reduced fertility if their treatment impairs the normal function of any component of the male reproductive system. Infertility can be secondary to impaired spermatogenesis from gonadotoxic therapy, gonadotropin deficiency resulting from CNS-directed therapy, or functional abnormalities of the genitourinary organs related to spinal/pelvic surgery or irradiation. The duration of post-treatment azoospermia secondary to gonadotoxic therapy is highly variable, and recovery of spermatogenesis may occur years after therapy.

### Risk Factors

A primary risk factor for reduced fertility is alkylating agent–associated gonadal toxicity. The magnitude of risk is determined by the specific alkylating agent and the cumulative dose. Agents commonly used to treat pediatric malignancies and most often associated with oligo/azoospermia include mechlorethamine, cyclophosphamide, ifosfamide, procarbazine, busulfan, melphalan, and cisplatin (Table 1).\(^11\,^14\,^45\)\(-\)\(^51\) Young male survivors observed in the Childhood Cancer Survivor Study were less likely to sire a pregnancy after treatment with cyclophosphamide (hazard ratio [HR], 0.42; 95% CI, 0.31 to 0.57) or procarbazine (HR, 0.48; 95% CI, 0.26 to 0.87).\(^48\) Although there is individual variation in risk of gonadotoxicity after exposure to alkylating agents, the cumulative dose likely to produce azoosperma has been established for most agents. Cumulative doses of cyclophosphamide \(> 5\) to \(7.5\) \(\text{gm/m}^2\) are associated with abnormal semen parameters, and azoosperma is consistently observed after total cyclophosphamide dose \(> 19\) \(\text{gm/m}^2\), ifosfamide \(> 60\) \(\text{gm/m}^2\), procarbazine \(> 4\) \(\text{gm/m}^2\), busulfan \(> 600\) \(\text{mg/m}^2\), melphalan \(> 140\) \(\text{mg/m}^2\),
and cisplatin > 600 mg/m². Alkylating agents used in combination have an additive effect on gonadotoxicity. Prepubertal status at diagnosis is not protective against alkylating agent germ cell toxicity. Post-treatment azoospermia may be permanent, but recovery of normal spermatogenesis years after treatment is possible.

The testicular germinal epithelium is especially sensitive to radiation. Spermatogenesis can be impaired by direct testicular irradiation, including total-body irradiation, or by scatter from other treatment fields including pelvic, bladder, inguinal/femoral, or abdominal/flank. Impaired spermatogenesis is observed after testicular doses as low as 0.1 Gy, and recovery is unlikely after a single testicular dose exceeding 4 to 6 Gy. The fertility analysis from the Childhood Cancer Survivor Study showed the likelihood of survivors siring a pregnancy decreased after radiation administered to the testes exceeding 7.5 Gy (HR, 0.12; 95% CI, 0.02 to 0.64). Of note, small fractions of testicular radiation over long periods of time seem to be more toxic than an equivalent single-dose exposure.

Evaluation for ejaculatory infertility includes differentiating retrograde ejaculation from anejaculation by analysis of alkalized first morning urine or postejaculatory urine for sperm and fructose. Hormone-mediated azoospermia is diagnosed by measuring serum testosterone and gonadotropins (Table 1).

In addition to semen analysis, testicular volume and serum FSH can be used to assess potential fertility (Table 1). Serum inhibin-B is also a marker for germ cell function; however, the COG-IPTFU Guidelines do not recommend routinely screening with inhibin-B, because its additive value or superiority to other serum markers has not been established. Men with an abnormal semen analysis should be counseled that it is not possible to predict when or whether spermatogenesis will recover, so contraception should be used if pregnancy is not desired.

Survivors with reduced fertility desiring biologic paternity should be referred to an infertility specialist. In the setting of normal testicular function, fertility secondary to central hypogonadism can potentially be restored with hormonal interventions. In vitro fertilization (IVF) and intracytoplasmic sperm injection, an IVF procedure that uses a single sperm to fertilize an oocyte, are available to survivors with cryopreserved semen, oligosper- mia, and ejaculatory dysfunction to restore fertility. Neal et al showed that pregnancy rates after IVF and intracytoplasmic sperm injection were similar in a small cohort of cancer survivor couples compared with couples without a cancer history. Testicular microdissection with sperm extraction (TESE) is a procedure to retrieve sperm from the testicular tissue of survivors with ejaculatory azoospermia who may have reduced but preserved spermatogenesis. Viable sperm retrieval rates of 37% to 60% have been reported using the TESE procedure in the setting of azoospermia after chemotherapy. In a study of 74 chemotherapy-associated azoospermic men, found sperm retrieval with TESE to be less successful after alkylating agent therapy or sarcoma diagnosis.

Additional Considerations

Although interventions to treat reduced fertility are widely available and offer reasonable rates of pregnancy, not all survivors access this technology. Obstacles that have been reported include health care providers’ lack of knowledge about available reproductive technology, financial cost (because fertility treatments are not universally covered by health insurance), and an unwillingness to undergo medical procedures required for fertilization via assisted reproduction. Options for parenthood, other than biologic paternity, include IVF using donor insemination and adoption.

**SEXY DYSFUNCTION**

Sexual dysfunction in the young cancer survivor, broadly defined as the inability to complete sexual intercourse, can be secondary to physical, emotional, and social changes associated with a cancer experience. The process of normal sexual function is complex, and dysfunction can result from diminished desire/interest/opportunity, arousal/erectile difficulty, and emission/ejaculatory/organismic problems. Psychosexual dysfunction can be the result of psychosocial challenges of a cancer experience, including mood disorders, fatigue, altered body image, social isolation, and delayed psychosexual development. Physiologic sexual function depends on the complex interactions of genitourinary organs and associated neurovascular structures, all of which are vulnerable to damage from cancer therapy. Surgery or irradiation of the pelvis or lumbar spine, treatment-associated hormonal insufficiencies, and medical comorbidities are possible etiologies for physiologic sexual dysfunction in cancer survivors. Although considerable research has been done on the prevalence and risk factors for sexual dysfunction in adult cancer survivors, few studies have been specific to childhood and young adult survivor populations. In a study of 1,084 testicular cancer survivors who included older adults, survivors reported a similar prevalence of sexual dysfunction (39%) compared with a normative sample; however, the younger group (age 20 to 39 years) reported more sexual problems than age-matched controls. In a questionnaire study of young male childhood cancer survivors (mean age, 27 years), 32% reported a problem in one or more areas of sexual function.

**Risk Factors**

Cancer diagnosed during adolescence seems to be a risk factor for psychosexual sexual dysfunction. A study of male and female childhood cancer survivors found that survivors treated as adolescents reported more social isolation and delays in achieving sexual milestones compared with both survivors treated at a younger age and the age-matched general population. Childhood brain tumor survivors,
in particular, are reported to be at greater risk for psychosexual dys-
function, related to social isolation and delayed psychosexual develop-
ment. Poor health status was also found to be a risk factor for psychosexual dysfunction in young survivor populations. Risk factors for physiologic sexual dysfunction include prior treatment with pelvic or spinal surgery or irradiation, hormonal deficiency, increasing age, and emotional distress. Erection (ED) is defined as the inability to achieve and maintain an erection sufficient to permit satisfactory sexual intercourse. Ejaculation includes the emission of seminal fluid into the posterior urethra, ejection through the urethral meatus, and rhythmic contraction of the muscles of the pelvic floor, the sensation of orgasm. Ejaculation requires autonomically controlled contraction of the smooth muscles of the vas deferens, seminal vesicle, prostate, pelvic floor, and bladder neck. Survivors are at increased risk for ejaculatory dysfunction (EjD) including failure of emission, retrograde emission into the bladder, orgasmic problems, orgasmic pain, and climacturia. In their study of young adult childhood cancer survivors by Sundberg et al, 10% reported orgasmic difficulty compared with 3% of controls (P = .15). In a Swedish study by Sundberg et al, 8% of sexually active young survivors reported ED compared with 3% of controls (P = .15). Possible treatment-associated etiologies for ED in childhood cancer survivors include pelvic or spinal radiation or surgery (neurovascular), central or primary hypogonadism (hormonal), and psychogenic ED resulting from emotional distress associated with the cancer experience. Survivors with psychosexual dysfunction can be referred for individual counseling with specific attention given to psychosexual development and social support. If ED or EjD is diagnosed, the survivor should be referred to a urologist for evaluation. ED is typically treated using a stepwise approach, including addressing reversible causes such as hypogonadism. First-line therapy includes oral phosphodiesterase type 5 inhibitors, followed by self-injectable penile vasoactive drugs, intraurethral alprostadil, and vacuum-assisted erection devices. For survivors not satisfied with these interventions or survivors who have genitourinary abnormalities related to surgery or irradiation, penile prosthesis may be an option. Depending on the etiology, treatment for EjD may include psychosexual counseling, pharmacotherapy, and possibly surgery.

Additional Considerations
The increased prevalence of sexual dysfunction in the adolescent and young adult survivor population has recently been described. Because all survivors are at risk for psychosexual dysfunction related to their cancer experience, it is recommended that all adolescent and young adult survivors be assessed for sexual dysfunction as part of their follow-up care. The assessment of sexual dysfunction in the childhood cancer survivor includes a thorough psychosexual history, sexual history, medical history, and physical examination including Tanner staging (Table 1). History should be obtained privately and include detailed questions about social relationships, body image, sexual experiences, libido, nocturnal emissions, spontaneous erections, masturbation, orgasm, and quality of ejaculation.

Assessment
Because all survivors are at risk for psychosexual dysfunction related to their cancer experience, it is recommended that all adolescent and young adult survivors be assessed for sexual dysfunction as part of their follow-up care. The assessment of sexual dysfunction in the childhood cancer survivor includes a thorough psychosexual history, sexual history, medical history, and physical examination including Tanner staging (Table 1). History should be obtained privately and include detailed questions about social relationships, body image, sexual experiences, libido, nocturnal emissions, spontaneous erections, masturbation, orgasm, and quality of ejaculation.

Treatment
Survivors with psychosexual dysfunction can be referred for individual counseling with specific attention given to psychosexual development and social support. If ED or EjD is diagnosed, the survivor should be referred to a urologist for evaluation. ED is typically treated using a stepwise approach, including addressing reversible causes such as hypogonadism. First-line therapy includes oral phosphodiesterase type 5 inhibitors, followed by self-injectable penile vasoactive drugs, intraurethral alprostadil, and vacuum-assisted erection devices. For survivors not satisfied with these interventions or survivors who have genitourinary abnormalities related to surgery or irradiation, penile prosthesis may be an option. Depending on the etiology, treatment for EjD may include psychosexual counseling, pharmacotherapy, and possibly surgery.

Pretreatment Preservation of Reproductive Health
Preservation of reproductive health has emerged as a priority for children, adolescents, and young adults diagnosed with cancer. Although not all reproductive complications can be prevented, strategies to minimize long-term issues by addressing reproductive concerns before treatment have improved outcomes for many survivors.

Treatment Modifications
Modifications in the dose and delivery of gonadotoxic therapy commonly used to treat childhood cancer have improved long-term reproductive outcomes. The evolution of the treatment of Hodgkin’s lymphoma (HL) is a paradigm of efforts to reduce the risk of gonadal toxicity by adapting therapy to minimize male exposure to alkylating agents. Pioneering work by Schellong et al employed a nonalkylating agent chemotherapy regimen to treat boys with HL to preserve testicular germ cell function, which has since been adopted in other HL treatment protocols. In a recent COG study for high-risk HL, survival was not compromised when boys received radiotherapy in place of alkylating agents with the aim of preserving future fertility. Modifications in irradiation techniques to reduce dose to healthy tissue has improved long-term reproductive outcomes for survivors requiring treatment to pelvic fields. For example, proton radiotherapy used to treat pediatric pelvic rhabdomyosarcoma resulted in significant dose reduction to normal tissues compared with intensity-modulated radiotherapy. Similarly, refinement of surgical techniques, such as nerve-sparing retroperitoneal surgery, has also been shown to preserve future reproductive capacity without sacrificing cure.

Semen Cryopreservation
In 2006, the American Society of Clinical Oncology expert panel on fertility preservation recommended a discussion of fertility preservation options with all eligible patients before cancer therapy begins as part of the informed consent process. Ideally, semen for cryopreservation should be collected by masturbation from all sexually mature males before the initiation of gonadotoxic therapy. Males with reduced quantity or quality of sperm as a result of age or illness remain eligible for sperm banking, because future fertilization can be achieved from a single sperm using assisted reproductive technology.
sperm quality is not affected by duration of cryopreservation.90 Peripubertal boys should also be considered eligible for semen collection if they report nocturnal emissions, masturbation with ejaculation, or have testicular volume \( \geq 6 \) mL (Tanner stage 3), which roughly correlates with the onset of spermatogenesis.91 If masturbation is not feasible or successful, alternative methods for semen collection including penile vibratory stimulation or intraoperative rectal electroejaculation are available in some clinical settings.92,93 If a semen sample cannot be obtained by these methods, testicular biopsy with TESE can be used to obtain and preserve sperm for future fertility.62

**Investigational Pretreatment Fertility Preservation**

Pretreatment cryopreservation of testicular stem-cell tissue can be considered a fertility preservation option for prepubertal boys who do not yet produce spermatozoa. The success of future fertility using sperm generated from cryopreserved stem cells is not established; therefore, interventions described should be considered investigational. Pilot studies have confirmed that pretreatment testicular biopsy to obtain spermatogonial stem cells for cryopreservation is generally safe for patients and acceptable to parents.94 Although autologous transplantation of cryopreserved testicular stem cells into survivors’ testes seems to be a promising option for future fertility,95-98 the safety and efficacy of this procedure have only been demonstrated in animal models.99 Furthermore, boys with hematopoietic malignancies might not be eligible for this procedure because of the risk for recurrence from reintroducing malignant cells in cryopreserved testicular tissue.100 Grafting cryopreserved spermatogonial stem cells into a host organism (xenograft) or in vitro spermatogenesis from cryopreserved spermatogonial stems might also be future options to preserve fertility for the youngest survivors.101-103

**DISCUSSION**

Semen cryopreservation, hormonal therapy, psychosexual counseling, and assisted reproduction are some of the many interventions available to optimize the long-term reproductive health of young male cancer survivors. The widespread application of these interventions depends, in large part, on the knowledge of the oncology care team about the risk for reproductive complications associated with specific cancer treatments and their comfort with discussing these often sensitive topics with young male patients and their families. The COG-LTFU Guidelines contain information about the reproductive risks associated with current curative cancer therapies. These guidelines are available to clinicians to inform discussion of fertility preservation before instituting therapy and to recommend ongoing evaluations for reproductive health concerns in the setting of follow-up care. Finally, ongoing research to both prevent and treat reproductive complications in males treated for childhood adolescent and young adult cancers is necessary to improve survivors’ health and quality of life.

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