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Review

Fertility in childhood cancer survivors following cranial irradiation for primary central nervous system and skull base tumors

Tamara Z. Vern-Gross, Julie A. Bradley, Ronny L. Rotondo, Daniel J. Indelicato *

Department of Radiation Oncology, University of Florida, Jacksonville, FL, United States

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ABSTRACT

Recent advances in pediatric cancer treatment have improved disease control and survival outcomes for childhood cancers survivors, including those treated for primary central nervous system and skull base malignancies. Future research in this population will focus on identifying risk factors for infertility, novel screening techniques and recommendations, and quality-of-life outcomes improvement. The purpose of this review is to define the infertility complications observed in pediatric cancer survivors who receive cranial irradiation for central nervous system and skull base malignancies.

In the United States, there were approximately 379,000 cancer survivors of child and adolescent cancer as of January 2010 [1]. With advances in multimodality therapy, 5-year survival rates have increased to about 83% [2,3] and children with primary central nervous system (CNS) malignancies represent approximately 14% of long-term survivors. Cancer survivors are at increased risk for post-treatment toxicities and chronic conditions compromising neurologic/neurosensory, cardiovascular, pulmonary, endocrinologic, or reproductive function [4]. Infertility is a major treatment-related toxicity, which is the result of a disease or dysfunction of the reproductive tract preventing conception of a child or the ability to carry a pregnancy to delivery [4]. Failed conception after at least 1 year of unprotected intercourse should prompt evaluation, unless physical findings and medical history dictate earlier intervention [5,6]. Childhood cancer survivors with CNS and skull base tumors may be less likely to conceive [7,8]. Successful fertility requires functional testes, ovaries, and genitourinary organs as well as a functional hypothalamic–pituitary–gonadal (HPG) axis, all of which can be affected by the initial tumor involvement, treatment, and the psychogenic effects of therapy. Risk of infertility depends on direct effects of treatments received: surgical, chemotherapeutic, and radiotherapeutic [9,10]. This review specifically summarizes frequently unidentified fertility concerns and outcomes of cancer survivors who have received cranial irradiation.

* Corresponding author at: Department of Radiation Oncology, University of Florida College of Medicine, 2015 North Jefferson St., Jacksonville, FL 32206, United States.

E-mail address: dindelicato@floridaproton.org (D.J. Indelicato).

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Frequency of infertility following childhood cancer treatment

The Childhood Cancer Survivor Study (CCSS) reported outcomes of young male and female survivors treated for various malignancies, identifying risk factors for procreating. The relative risk (RR) for female survivors of becoming pregnant was 0.81 (95% CI, 0.73–0.90) [7]. After adjustment for confounding factors, the likelihood of pregnancy was decreased for hypothalamic–pituitary doses above 30 Gy (RR, 0.61; 95% CI, 0.44–0.83; $P = 0.002$). Male participants were less likely to sire a pregnancy (hazard ratio, 0.56; 95% CI, 0.49–0.63) [11] yet no effect on fertility after pituitary irradiation was observed after adjusting for confounding factors in males (RR, 0.25; 95% CI, 0.06–1.13; $P = 0.72$). Results from the CCSS cohort demonstrated that 64% of survivors with self-reported clinical infertility eventually conceived after 1 or more years of failed attempts at conception [5]. Infertility and pregnancy outcomes may be underestimated because there are no standards for laboratory study parameters to define infertility, patient desire, number of pregnancy attempts, time to conception, or successful utilization of infertility treatments [5].

The German Childhood Cancer Registry reported 1110 female and male childhood cancer survivors treated with cranial irradiation, chemotherapy, or both [12]. Depending on the pituitary irradiation dose, survivors reported fewer pregnancies with their partners, higher rates of infertility and permanent amenorrhea (Table 1) [12]. Those who had received cranial radiotherapy had a significantly shorter time to pregnancy than survivors exposed to pelvic radiotherapy or alkylating agents; this finding may be due to selection bias of a good prognosis group that received low-dose radiotherapy [5]. Higher cranial doses may produce

Table 1
Assessments of reproductive health in females treated for primary central nervous system and skull base tumors.

	Prepubertal	Pubertal	Postpubertal
History	– Complete history pertaining to visit – Any signs of pubertal onset – Psychosocial assessment – Medications	– Complete history pertaining to visit – Pubertal onset, temp – Menstrual cycle patterns (regular/irregular, primary vs secondary amenorrhea) – Sexual activity – Function (dryness, dyspareunia, libido) – Contraception/pregnancy – Psychosocial assessment – Medications	– Complete history pertaining to visit – Pubertal onset, temp – Menstrual cycle patterns (regular/irregular, primary vs secondary amenorrhea) – Sexual activity – Function (dryness, dyspareunia, libido) – Contraception – Pregnancy (low-birth weight, premature labor, spontaneous abortions, etc) – Psychosocial assessment – Medications
Physical examination	– Annual physical examination (sooner if clinically indicated) – Height/weight – Tanner staging	– Annual physical examination (sooner if clinically indicated) – Height/weight – Tanner staging	– Annual physical examination (sooner if clinically indicated) – Height/weight
Screening	At diagnosis – Obtain baseline sexual hormone studies prior to initiation of treatment in children diagnosed with CNS and skull base tumors (prolactin, LH, FSH, testosterone, estradiol, and GnRH stimulation test) – AMH At follow-up – Repeat LH, FSH, estradiol, GnRH Stimulation test, and AMH only as clinically indicated if evidence of accelerated growth and signs or early pubertal development – X-ray for bone age as clinically indicated in the setting of accelerated growth and early pubertal development	At diagnosis – Obtain baseline sexual hormone studies prior to initiation of treatment in children diagnosed with CNS and skull base tumors (prolactin, LH, FSH, testosterone, estradiol, and GnRH Stimulation test) – AMH At follow-up – Repeat LH, FSH, estradiol, GnRH stimulation test, and AMH at 13 years of age – Repeat LH, FSH, estradiol, GnRH Stimulation test, and AMH sooner or as clinically indicated if delayed puberty, irregular menses, primary or secondary menses, or clinical signs of secondary estrogen deficiency	At diagnosis – Obtain baseline sexual hormone studies prior to initiation of treatment in children diagnosed with CNS and skull base tumors (prolactin, LH, FSH, testosterone, estradiol, and GnRH Stimulation test) – AMH At follow-up – Repeat LH, FSH, estradiol, GnRH stimulation test, testosterone, and AMH at 13 years of age – Repeat LH, FSH, estradiol, GnRH Stimulation test, testosterone, and AMH sooner or as clinically indicated if delayed puberty, irregular menses, primary or secondary menses, or clinical signs of secondary estrogen deficiency. – Consider bone mineral density in patients diagnosed with hypogonadism
Precocious puberty	Tumor-related factors Tumor Involvement of the hypothalamus or pituitary glands Treatment-related factors Radiotherapy CSI Cranial, skull base, orbit/eye Nasopharynx Risk factor Cranial irradiation dose $\geqslant$18 Gy	Not applicable	Not applicable
Hypogonadism	Not applicable	Treatment-related factors Chemotherapy Alkylating agents, heavy metals, and nonclassical alkylators Radiotherapy CSI (any ovarian dose) Cranial ($\geqslant$30 Gy) Skull base, orbit/eye Nasopharynx Spine (lumbar, sacral, whole) Surgery Injury to HP axis	Treatment-related factors Chemotherapy Alkylating agents, heavy metals, and nonclassical alkylators Radiotherapy CSI Cranial ($\geqslant$30 Gy) Skull base, orbit/eye Nasopharynx Spine (lumbar, sacral, whole) Surgery Injury to HP axis

Table 1 (*continued*)

	Prepubertal	Pubertal	Postpubertal
		Risk factors Chemotherapy Higher cumulative doses or combination of alkylators Busulfan >600 m^2 Cyclophosphamide >7.5 g/m^2 Radiotherapy Older age at gonadal irradiation Pubertal gonadal dose ⩾5 Gy Prepubertal gonadal dose ⩾10 Gy	Risk factors Chemotherapy Higher cumulative doses or combination of alkylators Busulfan >600 m^2 Cyclophosphamide >7.5 g/m^2 Radiotherapy Older age at gonadal irradiation Pubertal gonadal dose ⩾ 5 Gy Prepubertal gonadal dose ⩾ 10 Gy
Sexual dysfunction	Not applicable	Treatment-related factors Radiotherapy Spinal tumor (lumbar and sacral) Surgery Neurosurgery (spinal cord injury) Psychosocial Effects of physical differences, diagnosis, and treatment Risk factors – Tumor or metastatic foci involving spinal cord or cauda equine – Hypogonadism – Multiple adverse outcomes from primary tumor treatment-related side effects	Treatment-related factors Radiotherapy Spinal tumor (lumbar and sacral) Surgery Neurosurgery (spinal cord injury) Psychosocial Effects of physical differences, diagnosis, and treatment Risk factors – Tumor or metastatic foci involving spinal cord or cauda equine – Hypogonadism – Multiple adverse outcomes from primary tumor treatment-related side effects
Referral	Endocrine consultation for accelerated puberty (age <8 years)	Gynecology – Referral for hypogonadism Endocrinology – Referral for abnormal hormonal levels – Delayed puberty Reproductive endocrinology – Infertility – Evaluation and consultation on assisted reproduction or gestational surrogates Psychological consultation – Identify optimal coping strategies with emotional difficulties	Gynecology – Referral for hypogonadism Endocrinology – Referral for abnormal hormonal levels – Delayed puberty Reproductive endocrinology – Infertility – Evaluation and consultation on assisted – reproduction or gestational surrogates Psychological consultation – Identify optimal coping strategies with – emotional difficulties

Abbreviations: FSH, follicle-stimulating hormone; LH, luteinizing hormone; AMH, Anti-Müllerian hormone; GnRH, gonadotropin releasing hormone; CSI, craniospinal irradiation; HP axis, hypothalamic–pituitary axis.
Note: adapted from Greenfield et al. [13], Metzger et al. [15], Kenney et al. [25], Izard et al. [34], Byrne et al. [70], Cooke [71], Gupta [72], Kiserud [73], and Kumanov [74].

neurologic impairment making partner selection challenging, and survivors less likely to attempt conception [5]. Various risk-based guidelines facilitate appropriate evaluation after completion of primary pediatric cancer treatment such as the Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancer (COG-LTFU Guidelines) [13]. Personalized follow-up care provides a strategy for prevention and surveillance of late effects based on risks associated with cancer therapy, genetic predisposition, lifestyle factors, and co-morbidities [14].

Unique female and male considerations

- Female survivors may have decreased ovarian reserve from direct effects of chemotherapy or radiation, indirect effects from injury to the HPG axis [15] resulting in amenorrhea, or functional abnormalities related to pelvic surgery or radiotherapy [16,17]. Ovaries contain a finite number of oocytes within primordial follicles that begin to form at approximately 18 weeks of gestation and enter arrest in meiosis. Hormonal disruption or depletion of the ovarian follicular pool can cause a decrease in ovarian steroid secretion, leading to absent menarche, ultimately resulting in premature ovarian failure and/or menopause [18,19]. Reduced ovarian function is associated with osteoporosis and increased risk of cardiovascular disease, and infertility [20,21].
- Male survivors may have impaired spermatogenesis from the effects of gonadotoxic chemotherapy or radiation on gametes as well as gonadotropin deficiency from CNS-directed radiotherapy causing central hypogonadism [22]. Functional abnormalities related to spine or pelvic surgery or radiotherapy may result in erectile or ejaculatory dysfunction [16,17]. Pubertal development and maintenance of secondary sexual characteristics depends on appropriate production of testosterone by testicular Leydig cells. Although these cells are relatively resistant to treatment toxicity, gonadotoxic chemotherapy, testicular radiation, cranial surgery, and radiation involving the HPG axis can result in testosterone deficiency, increasing risk of osteoporosis and metabolic disorders [13,23–25].

The direct effects of radiotherapy on gonadal function

- The vast number of follicles in a prepubertal ovary provides more resilience to toxic reproductive effects of radiotherapy than in a more mature ovary [26]. Although postnatal cells are mitotically inactive, they remain vulnerable to direct effects of radiotherapy, giving rise to primary ovarian failure. Radiotherapy affects gonadal function in patients who receive total-body irradiation for bone marrow transplantation and craniospinal radiotherapy for certain CNS tumors [27,28]. Radiotherapy for abdominal neoplasms may directly impact ovaries or significantly reduce uterine volume and injure the endometrium [29], increasing the risk of low-birth-weight children or miscarriages [30]. Signorello et al. [29] reported on the risk of stillbirth and neonatal death in 1657 participants of the Childhood Cancer Survivor Study. Uterine and ovarian irradiation significantly increased the risk of stillbirth and neonatal death at doses above 10 Gy (RR, 9.1; 95% CI, 3.4–24.6). Irradiation in girls prior to menarche with doses between 2.50 and 9.99 Gy resulted in stillbirth or neonatal death of 4 (8%) or 49 offspring (RR, 5.8; 95% CI, 1.2–28.2); and when treated to doses above 10 Gy, there was an increased risk of stillbirth or neonatal death to 5 (23%) deaths per 23 offspring (RR, 19.0; 95% CI, 5.6–65.2) [30]. The exact mechanism associated with increased risk of stillbirth or neonatal death requires further investigation. It is unclear whether uterine damage from radiotherapy or an increased risk of placental or umbilical-cord anomalies contributes to the adverse fetal and neonatal outcomes. A Scandinavian series evaluated the effects of radiotherapy on uterine volume in 100 childhood cancer survivors. Assessments with serial transvaginal sonography revealed significantly reduced uterine volume in nulliparous patients following direct uterine irradiation ($n = 12$; median, 12 mL; range 1–52 mL) compared with those treated with chemotherapy alone ($n = 37$; 47 mL; range, 22–88 mL); radiotherapy superior to the diaphragm ($n = 17$; 40 mL; range, 24–61); or radiotherapy below the diaphragm without direct uterine involvement ($n = 13$; 34 mL; range, 8–77 mL) ($P < 0.02$ in all comparisons) [29]. Risk of primary ovarian failure and infertility increases with higher doses of pelvic and abdominal RT, reported as high as 70–100%; smaller doses can cause more impairment in advancing age [7,10,31,32]. Direct effects on ovaries can be demonstrated at doses <2 Gy, destroying approximately 50% of immature oocytes [7,10]. CCSS reported a dose–response relationship for decreased risk of pregnancy with increasing dose of ovarian/uterine radiotherapy exposure in female cancer survivors. Fertility was noted in 52% of females following RT doses of 0.001–2.5 Gy; in 5.1% following doses of 2.51–5 Gy; and 3.3% after doses of 5.01–10 Gy. The relative risk of pregnancy was 0.56 (95% CI, 0.37–0.85) for exposure of 5–10 Gy and decreased to 0.18 (95% CI, 0.13–.26) after doses greater than 10 Gy [7].
- Spermatogenesis can be impaired when the testes are exposed to radiation doses as low as 0.1–0.2 Gy, with doses >4 Gy resulting in permanent azoospermia [33]. Leydig cells are more resistant to radiation. As a result, hypoandrogenism commonly develops following prepubertal testicular radiation doses of $\geqslant$24 Gy and $\geqslant$30 Gy for postpubertal males [34]. Because of variability in dose tolerance, spermatogenesis is often compromised following testicular irradiation, while puberty and testosterone levels are unaffected.

Central gonadotrophin dysfunction following cranial irradiation

The hypothalamic–pituitary-axis (HPA) can be compromised by single or combined therapy, placing these children at high risk of developing endocrine abnormalities [35]. Such abnormalities include thyroid disease, growth delay, obesity, and abnormal pubertal regulation. Direct injury to the HPA can decrease circulating gonadotropins, FSH and LH, which are produced by the pituitary gland and regulated by gonadotropin-releasing hormone (GnRH). Gonadotropin dysregulation is not as immediate as other hormonal deficiencies of the HPA after cranial irradiation, but can be evident within the first 2 years [36].

The HPA was evaluated in 35 patients with optic glioma with no progression of their puberty at a pubertal age; they had reached adult height following cranial irradiation [37]. The hypothalamic–pituitary dose was 49 ± 1 Gy. Pubertal status was based on LH and FSH response to GnRH in addition to age-appropriate estradiol and testosterone levels. Pubertal disruption was identified in 15 (43%) patients and precocious puberty in 8 (23%) patients [37]; delayed puberty ($n = 4$), lack of pubertal development ($n = 3$), primary amenorrhea ($n = 4$), and irregular menses ($n = 4$).

- Pregnancy in female patients who develop gonadal dysfunction depends on hypothalamic–pituitary reserve, extent of initial tumor involvement, and surgical injury. In the setting of central hypogonadism, GnRH may facilitate normalization of

menstruation and ovarian function, allowing for a successful pregnancy; if decreased levels of LH persist, this may result in an attenuated LH surge, which is a key component to menstruation. Shorter luteal phases can portend emerging ovarian failure and have been associated with pregnancy loss [38,39].

- The hypothalamic–pituitary–testicular axis is influenced by the secretion of testicular hormones, including Inhibin B and testosterone. Produced by Leydig cells, testosterone is an essential component of spermatogenesis, which is initiated by secretion of LH. Together, FSH and testosterone promote Sertoli cells to further support the process of spermatogenesis, while ongoing stimulatory and inhibitory pathways communicate with the h ypothalamic–pituitary–testicular axis. Disruption of this pathway can impair spermatogenesis and testosterone production [39], resulting in hypoandrogenism and compromised fertility.

Precocious puberty

In most populations, achievement of pubertal milestones is normally distributed, with a standard deviation of 1 year. The mean age of pubertal onset is approximately 10.5 and 11.5 years of age for girls and boys, respectively. Secondary sexual characteristics that develop before 8 years of age in a girl (Tanner stage B2) or 9 years in a boy (Tanner stage G2 and/or testicular volume $\geqslant$4 mL) suggest underlying precocious puberty requiring evaluation and treatment. These parameters are selected as 2.5–3 standard deviations below the mean age of onset of puberty [40–42]. Central precocious puberty (CPP) is premature stimulation of the hypothalamic GnRH pulse generator that secretes pulsatile gonadotropin, stimulating ovaries and testes by gonadotropins. CPP can be triggered by tumor involvement, surgical, and/or radiotherapeutic factors. In females, breast development (thelarche) suggests early pubertal development; signs of pubarche are not indicative of HPG activation and may present as inappropriate early biological maturation alongside psychological immaturity [43]. Screening for CPP should include an annual exam with Tanner staging, height, height velocity [44], bone age radiographs, as well as endocrine evaluations: baseline estradiol (girls), testosterone (males), and LH/FSH in response to acute GnRH stimulation.

CPP has been reported more commonly in girls following cranial radiotherapy for treatment of acute lymphoblastic leukemia, observed after doses of 18–24 Gy [45,46]. Early puberty may affect predominantly irradiated girls, but has also been documented in irradiated males [47,48]. Ogilvy-Stuart et al. reported that age at irradiation was the only characteristic significantly associated with age at the onset of puberty in children with CNS tumors who received cranial irradiation [47]. The estimated age at the onset of puberty was approximately 0.7 years earlier in girls than boys at each age of irradiation. Lower therapeutic doses affected pubertal development in girls; higher doses of 25–47.5 Gy impacted both sexes [47,49], with the highest doses leading to gonadotropin deficiency [50,51]. The mechanism for this sexual dichotomy is unclear but has been ascribed to differences in interactions between CNS and hypothalamic function.

Treatments are initiated to preserve adult height, delay menarche in females, and prevent or arrest further development of secondary sexual characteristics [52]. In both sexes, GnRH agonists are able to desensitize the gonadotrophs, which in turn reduce LH release and arrest gonadal stimulation [53]. Development of an underlying gonadotropin deficiency has been reported in patients treated for precocious puberty following cranial irradiation [54]. Once age appropriate, failure of pubertal progression despite discontinuation of hormonal therapy should prompt evaluation with a GnRH-stimulation test.

Central hypogonadism

Central hypogonadism often presents as pubertal delay or arrested maturation after direct injury to the HPG before or during pubertal development. Unlike CPP, central hypogonadism is more commonly seen following higher doses of radiation of approximately 40–50 Gy; it has been documented after doses as low as 30 Gy [38]. Several series have reported clinical outcomes related to endocrinopathies following cranial irradiation [55,56].

Merchant et al. described late effects following conformal RT in 78 children treated for low-grade glioma [56]. At a mean age of 9.7 ± 4 years, 12% had evidence of precocious puberty prior to RT. Of 50 evaluable patients, sex hormone replacement therapy (HRT) was required for six, eight, and 11 children at baseline, 12 months, and 24 months respectively. One patient required sex HRT within 24 months of irradiation (Table 2). Multiple endocrinopathies were evident in these patients, with the 10-year incidence of GH required in 48.9%; thyroid hormone, 64%; glucocorticoid, 19.2%; GnRH analog therapy, 34.2%. These findings underscore the importance of earlier evaluation and management in these patients because of the high risk of synchronous endocrinopathies.

An Indiana University study reported endocrine outcomes of 31 children treated for brain tumors following proton beam therapy (PBT) (53.8 ± 2.7 Gy(RBE); n = 19) or PBT + conventional RT (57.87 ± 2.3 Gy(RBE); n = 12) [55]. Although children treated with PBT + conventional RT received higher doses of radiation, no significant differences were noted in the incidence of endocrine deficiencies, but endocrine hormonal complication were seen earlier (at 0.33 ± 0.11 years) in children treated with PBT + conventional RT compared to children treated with PBT only (1.17 ± 0.4 years), P < .01). Because the risk of developing hormonal abnormalities was high in this patient population due to pre-treatment surgical procedures (n = 28) and chemotherapy (n = 22), future prospective studies evaluating the benefit of PBT alone are warranted.

Management of central hypogonadism

A combination of gonadotropin with or without *in vitro* fertilization (IVF) is commonly utilized to facilitate a successful pregnancy and birth in survivors who develop disruption of the HPG axis. Outcomes depend on the extent of injury to the hypothalamus and pituitary glands, in addition to ovarian or testicular insult from chemotherapy and/or pelvic RT [57]. Analysis of pregnancy outcomes from the Childhood Cancer Survivor Studies revealed that survivors of CNS tumors, including those that received craniospinal irradiation (CSI) were at higher risk of miscarriage compared to those treated for other tumor types [58,59].

Female and male aspect

- Female survivors treated for CNS and skull base tumors are at risk of infertility, osteoporosis, early menopause, and depression [22,60–62]. Pregnancy outcomes from CCSS reported by Green et al. indicated that the risk of pregnancy was decreased with hypothalamic/pituitary radiation doses >30 Gy (RR, 0.61; 95% CI, 0.44–0.83 P = .002) compared to $\leqslant$10 Gy (RR 1.00) or 10.00–30.00 Gy (RR, 0.85; 95% CI, 0.72–1.01 P = .67) [59]. Replacement therapy is dependent on whether the patient was prepubertal at the time of treatment or developed HPA injury after menarche [63,64]. Estrogen and progesterone may be replaced using oral or transdermal preparations in the form of oral contraceptives. In addition, the thecal cells produce ovarian androgens under the trigger of LH, which promote initiation of primordial follicle growth and development. Androgen

Table 2
Recommended assessment of reproductive health in males undergoing treatment for primary central nervous system and skull base tumors.

	Prepubertal	Pubertal	Postpubertal
History	– Complete history pertaining to visit – Any signs of pubertal onset – Psychosocial assessment – Medications	– Complete history pertaining to visit – Pubertal onset – Sexual activity – Function (erectile function, completion of intercourse, libido) – Contraception – Psychosocial assessment – Medications	– Complete history pertaining to visit – Pubertal onset – Sexual activity – Function (erectile function, completion of intercourse, libido) – Contraception – Successful conception – Psychosocial assessment – Medications
Physical examination	– Annual physical examination (sooner if clinically indicated) – Height/weight – Tanner staging – Testicular volume measured by Prader orchidometer	– Annual physical examination (sooner if clinically indicated) – Height/weight – Tanner staging – Testicular volume measured by Prader orchidometer	– Annual physical examination (sooner if clinically indicated) – Height/weight
Screening	At diagnosis – Obtain baseline sexual hormone studies prior to initiation of treatment in children diagnosed with CNS and skull base tumors (prolactin, LH, FSH, testosterone, and GnRH stimulation test)	At diagnosis – Obtain baseline sexual hormone studies prior to initiation of treatment in children diagnosed with CNS and skull base tumors (prolactin, LH, FSH, testosterone, and GnRH stimulation test) – Semen analysis as requested by patient	At diagnosis – Obtain baseline sexual hormone studies prior to initiation of treatment in children diagnosed with CNS and skull base tumors (prolactin, LH, FSH, testosterone, and GnRH stimulation test) – Semen analysis as requested by patient
	At follow-up – Repeat LH, FSH and GnRH stimulation test only as clinically indicated if evidence of accelerated growth and signs or early pubertal development – X-ray for bone age as clinically indicated in the setting of accelerated growth and early pubertal development	At follow-up – Repeat LH, FSH, GnRH stimulation test and testosterone at 14 years of age – Repeat LH, FSH, GnRH stimulation test, and testosterone sooner or as clinically indicated if delayed puberty and/or clinical signs of testosterone deficiency – Semen analysis as clinically indicated	At follow-up – Repeat LH, FSH, GnRH stimulation test and testosterone at 14 years of age – Repeat LH, FSH, GnRH stimulation test, and testosterone sooner or as clinically indicated if delayed puberty and/or clinical signs of testosterone deficiency – Semen analysis as clinically indicated
Precocious Puberty	Tumor-related factors Tumor involvement of the hypothalamus or pituitary glands Treatment-related factors Radiotherapy CSI Cranial, skull base, orbit/eye Nasopharynx Risk factor Cranial irradiation dose $\geqslant$18 Gy	Not applicable	Not applicable
Hypogonadism	Not applicable	Treatment-related factors Chemotherapy Alkylating agents, heavy metals, and non-classical alkylators Radiotherapy CSI (any ovarian dose) Cranial ($\geqslant$30 Gy) Skull base, orbit/eye Nasopharynx Spine (lumbar, sacral, whole) Surgery Injury to HP axis Risk factors Chemotherapy Higher cumulative doses or combination of alkylators Busulfan >600 m^2 Cyclophosphamide >7.5 g/m^2	Treatment-related factors Chemotherapy Alkylating agents, heavy metals, and non-classical alkylators Radiotherapy CSI Cranial ($\geqslant$30 Gy) Skull base, orbit/eye Nasopharynx Spine (lumbar, sacral, whole) Surgery Injury to HP axis Risk factors Chemotherapy Higher cumulative doses or combination of alkylators Busulfan >600 m^2 Cyclophosphamide >7.5 g/m^2

Table 2 (*continued*)

	Prepubertal	Pubertal	Postpubertal
		Radiotherapy Gonadal radiotherapy affecting testosterone Pubertal gonadal dose ⩾24 Gy Prepubertal gonadal dose ⩾30 Gy	Radiotherapy Gonadal radiotherapy affecting testosterone Pubertal gonadal dose ⩾24 Gy Prepubertal gonadal dose ⩾30 Gy
Reduced fertility	Treatment-related factors Chemotherapy Alkylating agents, heavy metals, and non-classical alkylators Temozolamide Radiotherapy CSI (any ovarian dose) Cranial (⩾30 Gy) Skull base, orbit/eye Nasopharynx Spine (lumbar, sacral, whole) Any testicular dose Surgery Injury to HP axis Risk factors Chemotherapy Higher cumulative doses or combination of alkylators Busulfan >600 m^2 Cyclophosphamide >7.5 g/m^2 MOPP ⩾3 cycles Ifosfamide ⩾60 mg/m^2 Radiotherapy Testicular irradiation 1–3 Gy, azoospermia may be reversible 4 Gy, azoospermia may not be reversible	Treatment-related factors Chemotherapy Alkylating agents, heavy metals, and non-classical alkylators Temozolamide Radiotherapy CSI (any ovarian dose) Cranial (⩾30 Gy) Skull base, orbit/eye Nasopharynx Spine (lumbar, sacral, whole) Any testicular dose Surgery Injury to HP axis Risk factors Chemotherapy Higher cumulative doses or combination of alkylators Busulfan >600 m^2 Cyclophosphamide >7.5 g/m^2 MOPP ⩾3 cycles Ifosfamide ⩾60 mg/m^2 Radiotherapy Testicular irradiation 1–3 Gy, azoospermia may be reversible 4 Gy, azoospermia may not be reversible	Treatment-related factors Chemotherapy Alkylating agents, heavy metals, and non-classical alkylators Temozolamide Radiotherapy CSI (any ovarian dose) Cranial (⩾30 Gy) Skull base, orbit/eye Nasopharynx Spine (lumbar, sacral, whole) Any testicular dose Surgery Injury to HP axis Risk factors Chemotherapy Higher cumulative doses or combination of alkylators Busulfan >600 m^2 Cyclophosphamide >7.5 g/m^2 MOPP ⩾3 cycles Ifosfamide ⩾60 mg/m^2 Radiotherapy Testicular irradiation 1–3 Gy, azoospermia may be reversible 4 Gy, azoospermia may not be reversible
Sexual dysfunction	Not applicable	Treatment-related factors Radiotherapy Spinal tumor (lumbar and sacral) Surgery Neurosurgery (spinal cord injury) Psychosocial Effects of physical differences, diagnosis, and treatment Risk factors – Tumor or metastatic foci involving spinal cord or cauda equina – Hypogonadism – Multiple adverse outcomes from primary tumor treatment-related side effects	Treatment-related factors Radiotherapy Spinal tumor (lumbar and sacral) Surgery Neurosurgery (spinal cord injury) Psychosocial Effects of physical differences, diagnosis, and treatment Risk factors – Tumor or metastatic foci involving spinal cord or cauda equina – Hypogonadism – Multiple adverse outcomes from primary tumor treatment-related side effects
Referral	Endocrine consultation for accelerated puberty (age <9 years)	Endocrinology – Referral for abnormal hormonal levels; delayed puberty Reproductive endocrinology – Infertility – Evaluation and consultation on assisted reproduction or gestational surrogates Psychological consultation – Identify optimal coping strategies with emotional difficulties	Endocrinology – Referral for abnormal hormonal levels; delayed puberty Reproductive endocrinology – Infertility – Evaluation and consultation on assisted reproduction or gestational surrogates Psychological consultation – Identify optimal coping strategies with emotional difficulties

Abbreviations: CNS, central nervous system; FSH, follicle-stimulating hormone; LH, luteinizing hormone; AMH, Anti-Müllerian hormone; GnRH, gonadotropin-releasing hormone; CSI, craniospinal irradiation; HP axis, hypothalamic–pituitary axis; MOPP, mustargen, oncovin, procarbazine, and prednisone.

insufficiency has been associated with inadequate follicular development, suggesting a potential role for androgen supplementation to increase follicular recruitment and assist with successful reproduction; further research is necessary for the role in this population [61,65,66].

- Male survivors who develop severe hypogonadism are at risk of infertility, osteoporosis, metabolic syndrome, type II diabetes, cardiovascular disease, and depression [22,60,62]. Green et al. reported male CCSS fertility outcomes [11]. The RR following hypothalamic/pituitary radiation doses of 0 Gy were 0.72 (95% CI, 0.45–0.86 $P < .001$); >0–40 Gy, 0.50 (95% CI, 0.43–0.58 $P < .001$), and >40 Gy, 0.31 (95% CI, 0.19–0.50 $P < .001$). Accounting for potential contributing factors, RR of fertility for a participant who had an Alkylating Agent Dose score of 0, a hypothalamic/pituitary radiation dose of 0 Gy, and a testes radiation dose of 0 Gy was 0.91 (95% CI, 0.73–1.14; $P = .41$). The RR for fertility for a participant who had an Alkylating Agent Dose (AAD) score of 1, a hypothalamic/pituitary radiation dose of 0 Gy, and a testes radiation dose of 0 Gy was 0.52 (95% CI, 0.42–0.60; $P = .001$). Treatment of central hypogonadism is encouraged to avoid morbidities of low bone mineral densities and metabolic syndrome. Testosterone supplementation or pulsatile gonadotropin-releasing hormone by infusion pump has been effective in facilitating testicular maturation and stimulating spermatogenesis in males diagnosed with central hypogonadism and intact pituitary function [67]. In men with abnormal pituitary function, human chorionic gonadotropin can stimulate androgen production and recombinant FSH [68].

Evaluation of gonadal dysfunction

The number of cancer survivors diagnosed with gonadal dysfunction may be underrepresented. Most published series are based on blood sampling only, without a restricted time for blood draws, even though hormonal secretion varies throughout the day in both females and males. Pfitzer et al. shared their longitudinal experience of 144 survivors treated for brain tumors at two German Pediatric Oncology Centers [69]. In females, infertility was defined as patients >13 years of age fulfilling one or more of the following criteria: follicle-stimulating hormone (FSH) $\geqslant$15 IU/L, luteinizing hormone (LH) $\geqslant$15 IU/L, or amenorrhea [69]. In males, infertility was defined as testicular volume <5 mL at age 14 years, <8 mL at age 15 years, <10 mL at age 16 years, or <12 mL at age 17 years [69]. Of those $\geqslant$13 years of age who received cranial doses $\geqslant$30 Gy, 11 of 65 females reported amenorrhea 6 years after diagnosis (range, 1–10 years); 5 developed regular menstrual cycles without hormone replacement therapy. Overall, when signs of infertility were evident at time points between 1 and 12 years after chemo-radiotherapy, FSH levels normalized 1–7 years after being elevated, reflecting either pituitary atrophy or recovery from fertility impairment [69]. Patients with abnormal hormone levels or clinical evidence of early or delayed pubertal development required referral to an endocrinologist.

Female and male considerations

- Identifying an accurate and reliable way to measure ovarian function has challenged clinicians because of variable plasma concentrations of FSH and LH. Females at risk of developing precocious puberty or central hypogonadism should undergo regular screening to identify gonadotropin deficiencies, resulting in early, delayed or arrested puberty (Table 1). Baseline LH, FSH, and estradiol levels as well as history of irregular menses, primary/secondary amenorrhea, and clinical signs/symptoms of estrogen deficiency should be evaluated in patients who present with pubertal abnormalities [13,15]. In prepubertal females, annual evaluations should include onset and transition of puberty, menstrual history, and Tanner staging until sexual maturity has been achieved [13,15]. Once a survivor has reached puberty or age 13 years, baseline LH, FSH, and estradiol levels should be obtained. In postpubertal females, complete menstrual and pregnancy histories should also be acquired in annual visits in addition to any sexual dysfunction. Although menarche may be spontaneous in many women, infertility is commonly observed, especially in those treated at the time of pubertal development [70].
- In males, annual assessment of pubertal development should include evaluation of sexual maturity by Tanner staging with testicular volume measured by Prader orchidometer (Table 2) [25]. Testosterone levels in men are subject to diurnal variation, with evening levels 20% lower than morning levels in those with normal gonadal function [71,72]. Suspicion of hypoandrogenism should prompt measurement of baseline early-morning serum testosterone and gonadotropin levels at age 14 years. Unlike males with primary testicular failure who may present with low levels of testosterone and LH, males with central hypogonadism will often have low levels of testosterone and normal levels of LH [73]. Serum Inhibin B has been used as a marker of germ cell function. It has not been shown to be superior to the more established biomarkers, and is not routinely recommended for screening [74].

Utility of Anti-Müllerian hormone (AMH) in predicting gonadal toxicity

Despite the availability of hormone replacement therapy, limitations of current laboratory studies for a timely and accurate diagnosis of hypogonadism may prevent a confirmatory diagnosis, delaying appropriate treatments and interventions. Anti-Müllerian hormone (AMH) has recently been investigated as a potential biomarker to identify gonadal deficiency following cancer treatment.

Female and male considerations

- Measurement of serum biomarkers is currently limited to anticipated pubertal development or when it is delayed. Although menstrual irregularities have historically been measured by gonadotropin and estradiol levels, a single level of AMH may be a more accurate first-line measurement. Unlike FSH and estradiol, AMH is produced by granulosa cells (present at birth) of immature ovarian follicles prior to the preovulatory stage [75] and can be used as a potential biomarker to evaluate prepubertal girls. AMH peaks within the second decade of life, decreases with age, and is undetectable following the start of menopause [9,76,77].Serum concentrations of AMH do not fluctuate during the menstrual cycle and it can be used to assess ovarian reserve at any time of the cycle in postpubertal girls [75,78–80].

  Measuring AMH levels is useful in several populations. Oligoamenorrheic women with polycystic ovarian syndrome (PCOS) generate high levels of AMH due to the large number of antral follicles, whereas amenorrheic women, as a result of primary ovarian failure, will have low levels of AMH [54,81]. Women with hyperprolactinemia or hypogonadotropic hypogonadism may demonstrate normal circulating concentrations of AMH with low levels of FSH [80,82]. Although reduced levels of AMH can be expected from the follicle pool, suppression of the growing follicle pool may not impact AMH production in females who develop central hypogonadism [54]. While ovarian dysfunction is necessary to demonstrate reduced levels of AMH, one prospective series demonstrated that gonadotropin

suppression with a GnRH agonist in maturing girls may cause a decline in AMH levels, suggesting AMH is somewhat gonadotropin dependent [83].

AMH has recently become a useful biomarker for ovarian reserve and primary ovarian insufficiency in female survivors of childhood cancer, and recently been investigated in females following treatment for breast and hematologic malignancies [10,75,80]. In prepubertal girls, it is well known that levels of AMH fall rapidly with the onset of chemotherapy with recovery dependent on the level of toxicity of the treatment, whereas other reproductive hormones would fail to demonstrate these various fluctuations [80,84]. In children treated for posterior fossa tumors, Inhibin B and AMH levels indicated primary radiation-induced gonadotropin deficiency in patients with normal plasma gonadotropin levels [85]. Although some patients received craniospinal radiotherapy, it was unclear whether AMH was useful in detecting gonadal deficiencies in patients with CNS tumors, warranting further investigation. Because of the variability of current hormonal assessments, obtaining AMH alongside traditional markers or independently as a biomarker of hypogonadism in both pre- and postpubertal females may help facilitate early diagnosis so that necessary interventions occur and fertility education is available. AMH produced by testicular Sertoli cells reaches high levels in late infancy and declines with the onset of male puberty [39,85,86]. It serves more as a marker of Sertoli cell number and function and is most useful in detecting the presence of testes in several congenital conditions [86]. The role of AMH as a biomarker in detecting pubertal delay in males has not been defined.

Quality of life and health outcomes following cranial irradiation

Psychosocial implications of failing to transition through puberty with peers can be challenging and oftentimes unavoidable. Prepubertal girls can fail to progress into puberty, resulting in primary amenorrhea. Delayed onset of puberty may affect the appearance of secondary sexual characteristics, linear growth, psychosexual development, and fertility [87,88]. Secondary amenorrhea is a primary concern of postpubertal females. Concerns for threatened reproductive vitality have been described in adolescents and young adults, resulting in significant reductions in quality of life [89,90]. Increased risk of late effects impairing both physiological and psychosocial function merely underscores the importance of addressing fertility concerns and providing ongoing education for children and young adults throughout survivorship [91].

Conserving reproductive health is critical among children, adolescents, and young adults from the time of diagnosis through adulthood. At Stanford University Medical Center (Palo Alto, CA), most parents of cancer patients expressed concern regarding fertility-related side effects of treatment, regardless of the treatments received [92]. Decisions around preservation are often complicated by emotional, biologic, psychosocial, and ethical principles, requiring guidance from a multidisciplinary team [93–95]. Communication barriers prevent patients and parents from being fully informed of treatment-related toxicities and the prospects for fertility preservation. Such hurdles include lack of provider knowledge, patient reluctance to undergo medical procedures, financial cost, and a desire to avoid treatment delay. A large cross-sectional survey initiated by the Pediatric Oncology Group demonstrated inconsistencies in clinical guidelines for fertility-preservation referral. Gender disparities were prominent, with 93% of centers offering sperm cryopreservation and only 10% offering ova cryopreservation [96,97]. Köhler et al. reported practice patterns of pediatric oncologists toward fertility preservation in adolescent cancer patients: only 46% of oncologists refer male pubertal cancer patients to a fertility specialist prior to cancer treatment >50% of the time; only 12% refer female pubertal cancer patients [97]. Gender disparities persist as a result of limited available reproductive options and biologic differences. Males have demonstrated ongoing success of sperm cryopreservation and subsequent intracytoplasmic sperm injection (ICSI/IVF), whereas adolescent girls have rarely been offered ovarian transposition, mature oocyte cryopreservation, and embryo cryopreservation. In addition to potential ethical and legal considerations regarding consent and donor sperm, concern for treatment delay highlights a unique barrier for female cancer patients. Oocyte cryopreservation or emergency IVF may require approximately 2–3 weeks for menstrual cycle synchronization, ovarian stimulation, and oocyte retrieval; however, in the setting of aggressive malignancies, immediate initiation of therapy may overrule [97].

Future directions

Future prospective studies should focus standardizing and improving the evaluation and management of gonadal dysfunction in order to improve accuracy and consistency in identifying survivors at risk of infertility. Compared to other modern radiotherapeutic techniques such as 3D conformal radiotherapy and intensity-modulated radiotherapy (IMRT), proton therapy (PT) provides additional sparing of normal tissue, including testicular doses in pediatric pelvic rhabdomyosarcoma and hypothalamic doses in children treated for common pediatric brain tumors [98,99]. PT can reduce the RR of primary ovarian failure, highlighting its ability to minimize disruption of the HPG axis [100]. Dosimetric advantage has been highlighted among various CNS malignancies, particularly when treating posterior fossa tumors [99–102]. St. Clair et al. described dosimetric differences between conventional RT, IMRT, and PT in the treatment of medulloblastoma [101]. Compared to other modalities, PT was superior in reducing radiation dose to the cochlea, pituitary, hypothalamus, temporomandibular joint, parotid, pharynx, and structures beyond the vertebral body. In a recent study, children diagnosed with standard risk medulloblastoma were treated in either proton ($n = 45$) or photon cohorts ($n = 60$) [102]. Although 5-year overall survival (OS) and disease-free survival were similar for both cohorts, the proton cohort had reduced hypothyroidism (23% vs 69%) and sex hormone deficiency (3% vs 21%) compared to photon cohort. Future prospective studies designed to reduce the integral dose to the HPG axis, comparing outcomes with current radiotherapeutic techniques and investigation of new biomarkers are warranted.

Conclusions

Infertility in childhood cancer survivors is influenced by the extent of chemotherapy, radiation, surgery. Fertility concerns and outcomes of survivors who have received cranial irradiation are often overlooked and underreported. Further prospective trials are needed to evaluate quality-of-life outcomes and potential biomarkers that can identify central hypogonadism in prepubertal and postpubertal females and males following cranial irradiation. Clinical trials will also help standardize how we evaluate and treat this population, facilitate more personalized treatment plans, and provide more consistent infertility counseling. Abnormal pubertal development, infertility, and sexual dysfunction are sources of potential health risks and cause considerable emotional distress in this population. Identifying treatment-related risk factors early in follow-up care, providing improved fertility education at the time of diagnosis, and creating innovative strategies to facilitate

earlier intervention will allow further optimization of care and improved quality of life in childhood cancer survivors who had received cranial irradiation.

Conflict of interest statement

The authors have do not have conflicts of interest to disclose.

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