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Pubertal development and primary ovarian insufficiency in female survivors of embryonal brain tumors following risk-adapted craniospinal irradiation and adjuvant chemotherapy

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Abstract

Background—Female survivors of central nervous system (CNS) tumors are at an increased risk for gonadal damage and variations in the timing of puberty following radiotherapy and alkylating agent-based chemotherapy.

Procedure—Clinical and laboratory data were obtained from 30 evaluable female patients with newly diagnosed embryonal CNS tumors treated on a prospective protocol (SJMB 96) at St. Jude Children's Research Hospital (SJCRH). Pubertal development was evaluated by Tanner staging. Primary ovarian insufficiency (POI) was determined by Tanner staging and FSH level. Females with Tanner stage 1–2 and FSH >15 mIU/ml, or Tanner stage 3–5, FSH > 25 mIU/ml and FSH greater than LH were defined to have ovarian insufficiency. Recovery of ovarian function was defined as normalization of FSH without therapeutic intervention.

Results—Median length of follow-up post completion of therapy was 7.2 years (4.0 to 10.8 years). The cumulative incidence of pubertal onset was 75.6% by age 13 years. Precocious puberty

was observed in 11.1% and delayed puberty in 11.8%. The cumulative incidence of primary ovarian insufficiency was 82.8%, though recovery was observed in 38.5%.

Conclusions—Treatment for primary CNS embryonal tumors may cause variations in the timing of pubertal development, impacting physical and psychosocial development. Female survivors are at risk for primary ovarian insufficiency, a subset of whom will recover function over time. Further refinement of therapies is needed in order to reduce late ovarian insufficiency.

Keywords

medulloblastoma; puberty; ovarian insufficiency; ovarian dysfunction

Introduction

Embryonal central nervous system (CNS) tumors, including medulloblastoma, primitive neuroectodermal tumor (PNET), and atypical teratoid/ rhabdoid tumor (ATRT), are among the more common malignant brain tumors observed in the pediatric age group [1]. The five-year overall survival (OS) rate of children with non-metastatic medulloblastoma and a gross total resection exceeds 80%, whereas children with high risk disease, including those with metastatic disease, have a five-year OS rate that approaches 70% [2,3]. Patients with supratentorial PNET and ATRT have an inferior outcome compared to children with medulloblastoma [4–6]. Improvements in survival have stimulated research to further refine treatment, with the goal of minimizing the late effects of therapy, including the neurocognitive and neuroendocrine deficits, that may compromise the patients' quality of life [7–10].

Hypothalamic-pituitary-gonadal (HPG) axis damage produced by surgery, radiation therapy (RT), and chemotherapy may cause variations of pubertal timing [11–14]. Delayed puberty in survivors of CNS tumors may be due to gonadotropin deficiency (central or secondary) and/or direct damage to the gonad (primary). The frequency and severity of gonadotropin deficiency usually increases when RT doses to the hypothalamic-pituitary axis exceed 40 Gy [11,15–17]. Lower doses, paradoxically, may cause precocious puberty [18,19].

The risk of primary gonadal dysfunction is more frequent among female CNS tumor survivors [20–22]. Sterilization and loss of hormone production following treatment with alkylating agents and RT are usually concurrent in females because hormone production is closely linked to the presence of ova and maturation of the primary follicle [11].

We undertook this study, as part of the secondary objectives in the protocol in which patients were enrolled, to investigate variations in the timing of pubertal onset and to estimate the cumulative incidence of primary ovarian insufficiency in a cohort of females with CNS embryonal tumors treated with risk-adapted craniospinal irradiation (CSI) followed by high-dose chemotherapy (HDC) with autologous stem cell rescue after maximal surgical resection (St. Jude Medulloblastoma 1996 (SJMB96)).

Patients and Methods

Patients

Previously untreated female patients between three and 21 years of age diagnosed between October 1996 and May 2003 with a primary CNS embryonal tumor were eligible for the clinical trial. Patients were stratified as either average risk (AR) ($< 1.5 \text{ cm}^2$ residual tumor; no metastatic disease) or high risk (HR) ($> 1.5 \text{ cm}^2$ residual disease or metastatic disease) based on postoperative tumor volume and modified Chang staging for metastatic disease [23].

Radiation Therapy and Chemotherapy

All patients received risk-adapted photon RT after maximal surgical resection of their tumor as previously described [2]. Patients with average-risk disease received 23.4 Gy CSI followed by primary site irradiation (55.8 Gy) using a 2-cm clinical target volume (CTV) margin. Similarly, patients stratified to the high-risk arm received primary site irradiation (55.8 Gy) using a 2-cm CTV margin, but the CSI dose ranged from 36 to 39.6 Gy. Additional macroscopic metastatic sites were irradiated to a total dose 50.4 to 54.0 Gy. Treatment was administered using 1.8 Gy fractions per day, five days per week. The hypothalamic and pituitary RT volumes were contoured for each patient based on axial T1-weighted, magnetic-resonance imaging (post-contrast) which was co-registered to the treatment planning computed tomography (CT) image.

HDC was initiated six weeks after completion of RT with a planned cumulative cyclophosphamide dose of $16,000 \text{ mg/m}^2 \pm 10\%$ of planned dose due to variation in body surface area (BSA) as previously reported [2]. Cyclophosphamide dose $11,000 \text{ mg/m}^2$ was used arbitrarily as an upper-limit cut-off in order to capture the majority of patients that received at least > 2 courses of therapy.

Ovarian Radiation Dose

Ovarian RT dose was estimated for 30 patients treated at St. Jude Children's Research Hospital (SJCRH). Fourteen underwent CT planning and median slice thickness was 8 mm (range, 2.5 to 10 mm). Ovarian dose was calculated based on treatment plans developed per Plan UNC (University of North Carolina, Chapel Hill, <http://planunc.radonc.unc.edu>) treatment planning system. The boundaries of the ovarian fossae were defined superiorly by the external iliac vessels, anteriorly and inferiorly by the broad ligament of the uterus, and posteriorly by the internal iliac vessels and ureter. Additional measurements included the distance laterally to the level of the widest bony aspect of the pelvic rim, the distance medially to mid-plane, and the distance posteriorly to the anterior bony edge of the sacrum.

The 16 remaining patients were planned by fluoroscopic imaging, six of whom had CT imaging available for anatomical reference. Magnification was accounted for according to the Focus Film Distance (FFD) [24]. The dose was estimated based upon bony landmarks for ovarian location and the inferior extent of the planned RT field. For patients whom only had CT imaging available as a reference, the dose was estimated based upon identified

location with respect to the inferior aspect of the RT field and depth from the anterior sacrum.

Accurate ovarian estimation was limited by the variability in patient anatomy, daily positioning and bladder distension. CT imaging was inconsistent due to variations in slice thickness and contrast enhancement. Adjustment was not made for dose heterogeneity. Although most ovaries were located in the superior quadrants of the bony pelvis, significant variability in the inferior border of the RT field determined whether the ovaries would be included in the field.

Clinical Data Collection

Demographic and clinical characteristics, including treatment and disease-related data, were obtained from individual patient charts and institutional databases. Institutional Review Board approval was received, and written informed consent was obtained as appropriate from all patients, parents, or legal guardians.

Endocrine Assessment

Following completion of chemotherapy, patients underwent evaluations by a pediatric endocrinologist at regular intervals twice yearly and more frequently as clinically indicated [2,25]. Females diagnosed prior to the age of eight years were evaluable for precocious puberty (presence of Tanner stage II breast development prior to eight years of age). Delayed puberty was defined by lack of breast development (Tanner stage I) at age 13 years.

Patients were excluded from the analysis of pubertal onset if they had evidence of puberty at the time of diagnosis, no documented Tanner stage, had not reached the age defined for delayed puberty, developed progressive disease before the defined age and/or received hormonal therapy prior to evaluation for delayed puberty.

Serially, basal follicle stimulating hormone (FSH) was obtained in all females. The FSH assay is an electro-chemiluminescent assay from Roche Diagnostics (Indianapolis, IN) performed on the Cobas 6000 analyzer. The method was standardized against the 2nd International Reference Preparation, World Health Organization reference standard 78/549. Pediatric ranges from 9–19 years were by Tanner stage. Standard laboratory techniques were utilized and institutional normal ranges defined abnormal results. Primary ovarian insufficiency (POI) was defined by a FSH level > 15 mIU/ml in females of Tanner stage I–II or FSH >25 mIU/ml in addition to FSH>LH in females of Tanner stage III–V, irrespective of the presence or absence of menses. Recovery of ovarian function was defined by the occurrence of unassisted menses, without hormone replacement therapy, and normalization of FSH defined by institutional reference ranges according to age and Tanner stage[25].

Statistical Considerations

Length of follow-up was calculated from the end of primary therapy to the date of last endocrine assessment. Primary ovarian insufficiency (POI) was defined from the end of radiation therapy to the date of the endocrine/laboratory assessment at which the abnormal FSH level was obtained. Death and progressive disease were considered competing events.

Patients with no POI or competing events were censored at the date of the last endocrine assessment. The cumulative incidence of POI was estimated using the methods of Prentice et al [26]. The effect of ovarian RT on the cumulative incidence of POI was evaluated based on the method described by Gray [27]. Patients who remained on hormone replacement therapy (HRT) were censored in evaluating the recovery of ovarian function at the time HRT was started.

Results

Study population

Ninety-four patients were enrolled on the SJMB96 protocol at SJCRH. Thirty of the 33 females were eligible for this analysis. One was excluded due to development of progressive disease less than one year from diagnosis, and two were removed from study less than one year from diagnosis (Figure 1).

Puberty

Of the 30 females, three were pubertal at the time of their tumor diagnosis based on their Tanner stage. The median length of follow up was 7.1 years (range 4.0–10.8). The cumulative incidence of entering puberty in the 27 evaluable females was $75.6\% \pm 9.3\%$ by age 13 years (Figure 2).

Precocious and Delayed Puberty

The occurrence of precocious puberty was assessed in eighteen patients (Table I); two developed precocious puberty (Table II). From the 30 evaluable patients, 12 patients were excluded because diagnosed after the age cut off, i.e. 8 for females and no tanner staging at approximately the age cut-off. The median length of follow up was 7.2 years (range 4.0–10.8). The cumulative incidence of precocious puberty was 11.1%. There were no significant treatment differences among patients who developed and did not develop precocious puberty.

Delayed puberty was evaluable in seventeen patients (Table I). Of the 30 evaluable patients, 13 patients were excluded because pubertal at diagnosis of the brain tumor, no tanner staging at approximately the age cut-off, did not reach the age cut-off i.e. too young to be considered for delayed puberty, progressive disease before the age cut-off, and received some type of hormone therapy prior to the age cut-off. Two had delayed puberty (Table II). POI was not noted in either patient. One patient developed progressive disease and at the time of progression, she did not have evidence of primary ovarian insufficiency. The other patient developed spontaneous menses. The median length of follow up was 7.5 years (range 4.1–9.9). The cumulative incidence of delayed puberty was 11.8%. There were no significant treatment differences among patients who developed and did not develop delayed puberty.

Primary Ovarian Insufficiency

Primary ovarian insufficiency (POI) was evaluable in twenty-nine females (Table I). One patient was excluded due to follow up with an outside endocrinologist. The median length of follow-up was 7.1 years (range, 4.0 to 10.8 years). Twenty-six developed POI, including two

who had coexisting precocious puberty. The cumulative incidence of POI six years after completion of RT was 82.8% (Figure 3). The median age at diagnosis of CNS tumor was 7.1 years (range, 3 to 18 years) among those who did, compared to 5.8 years (range, 4.5 to 7.3 years) among those who did not develop POI ($p=0.47$; HR 1.36).

The median estimated RT doses were 5.6 Gy (range, 0.7 Gy to 30.5 Gy) and 6.1 Gy (range, 0.6 Gy to 31.9 Gy) to the right and left ovaries, respectively. The incidence of ovarian dysfunction was similar among patients who received ovarian RT < 5 Gy compared to those who received ≥ 5 Gy ($p=0.7$; HR 1). There was no significant correlation between dose of CSI or cumulative dose of cyclophosphamide and the incidence of POI.

Six years after completion of RT, among those with POI the incidence of recovery of ovarian function was 38.5%. Three of the ten patients who recovered ovarian function received ≤ 5 Gy ovarian RT (Table I).

Discussion

The impact of CSI, and chemotherapy on pubertal development has not previously been reported among survivors of CNS embryonal tumors who have been followed longitudinally [3]. The SJMB96 study provided the opportunity to perform such a longitudinal analysis on a uniform cohort of females treated with CSI followed by adjuvant cyclophosphamide chemotherapy and stem cell rescue.

The diagnosis of a CNS tumor and exposure to therapies before the onset of puberty may impact the timing of puberty resulting in decreased final height in a population that is already at increased risk for impaired linear growth due to CSI and growth hormone deficiency [28,29]. Data on pubertal development in CNS tumor survivors treated with doses of CSI (>24 Gy) and alkylating agents remain limited as most reports are confined to small, retrospective case series [14,16–19]. Early onset of puberty has been reported in both sexes suggesting that, at higher doses, the CNS of males and females are equally sensitive to the effects of radiation [19]. Xu et al. reported precocious puberty in two of 12 patients (16.6%) treated with CSI (range, 23–39 Gy) versus one of seven (14.2%) patients treated with 18 Gy CSI [14]. Among our cohort, 2 patients (11.1 %) developed precocious puberty, similar to prior studies [14,17,19]. Recently, contemporary studies including the general population of girls have revealed a secular trend towards earlier pubertal timing [30,31]. These contemporary secular trends have led to debate about age of pubertal onset, yet age of menarche has not changed in the decades [30]. Thus, our age cutoff parameters are supported by previous reports despite the recent data from contemporary studies [31]. The ranges of chronological age of pubertal onset in the general population were reported as 8–14.9 years for females [25,32,33]. Seventy-five percent of the females in our cohort entered puberty by age 13 years suggesting the development of abnormal pubertal timing is not clearly a result of therapeutic exposure for CNS tumors. We were unable to confirm the correlation between younger age at time of irradiation and age at onset of puberty as previously reported among CNS tumor survivors treated with CRT (>24 Gy) [19,34], likely due to the small number of cases of precocious puberty.

Chow et al. reported that exposure to alkylating agents was not associated with abnormal timing of menarche among ALL survivors enrolled in the Childhood Cancer Survivor Study. Exposure to CRT increased the risk for early menarche (< 10 years); whereas, CSI was associated with early and late menarche (> 16 years), suggesting that ovarian function was impacted by scatter radiation [35]. Armstrong et al. reported early menarche in survivors of CNS tumors compared with their siblings [36]. CRT dose > 50 Gy, CSI, and diagnosis of CNS tumor at older age (> 10 years) conferred an increased risk of late menarche [36]. Exposure to alkylating agents was not associated with an increased risk of altered timing of menarche [36]. Delayed pubertal development occurred in 11.8% of our cohort and was not clearly associated with either age at treatment or specific therapeutic exposures.

We identified POI in 82.8% of females, including two with coexisting precocious puberty, which has been reported in ALL survivors [18,37]. Using our criteria, some cases of POI might have been missed if patients had co-existent gonadotropin insufficiency and were unable to mount a normal FSH response. The therapy or therapies responsible for ovarian insufficiency remain difficult to discern [38–40]. Stillman et al. reported ovarian failure in five of 35 females diagnosed with ALL who had at least one ovary at the edge of the radiation field (range 0.9–10 Gy) and concluded that irradiation was a risk factor for ovarian failure [41]. Hamre et al. reported elevated basal FSH and/or LH in 16 of 21 girls treated for ALL with CSI (18–24 Gy) and chemotherapy without an alkylating agent, further suggesting CSI as the primary risk factor for ovarian damage [39].

In survivors of CNS tumors, Livesey and Brock reported elevated basal FSH and/or luteinizing hormone (LH) levels in seven of 11 girls (64%) treated with CSI only (median dose to sacral area 32 Gy, range, 29–33 Gy) and in nine of 14 (64%) treated with CSI and chemotherapy that included alkylating agents, suggesting a primary role for CSI in the development of ovarian dysfunction [21]. There is limited data on accurately evaluating the scattered ovarian radiation dosing in the setting of CSI. We attempted to identify potential differences in radiation exposure by estimating ovarian radiation dosing and comparing to prior reports documenting the LD50 to the ovary at < 2 Gy [42]. However, there were no significant differences between patients that received 5 Gy and those that received < 5 Gy. Interestingly, one-third of the patients that had spontaneous ovarian recovery received 5 Gy to the ovaries.

In contrast, Clayton et al. reported ovarian insufficiency in 18 of 21 (85%) females with CNS tumors treated with a combination of alkylating agent chemotherapy, CRT and CSI (estimated ovarian radiation dose – 0.9 to 2.5 Gy). Four with ovarian dysfunction received CRT and alkylating agent chemotherapy without CSI, suggesting that ovarian insufficiency was due to alkylating agent treatment [38]. Likewise, Ahmed et al. reported that four girls who received CSI without chemotherapy had normal ovarian function, further supporting alkylating agent exposure as the predominant risk factor for ovarian insufficiency [20]. We hypothesize that the multi-modality therapy used in this study impacted the risk of ovarian dysfunction rather than exposure to a single agent or modality.

Recovery of ovarian function occurred in 38.5% of our cohort, further corroborating data from Clayton et. al. which revealed recovery of ovarian function following RT and

chemotherapy in four of the 18 patients (22.2%) with ovarian dysfunction [38]. A subset of patients with recovery of ovarian function may still have early menopause [43]. Recent reports have suggested that determination of Anti-Mullerian hormone (AMH) provides a measure of ovarian reserve and may be a better indicator of ovarian dysfunction than FSH. However, the dynamic changes in correlation between AMH and size of the primordial follicle pool throughout pubertal development strongly suggest that AMH is best suited as a marker of ovarian reserve only in women beyond age 25 years [44]. Additionally, longitudinal follow-up has been too short to determine if AMH is superior to FSH as a marker of ovarian damage in the pediatric population [45,46]. POI may be possibly prevented with laparoscopic oophoropexy or proton beam therapy [47]. Currently, newer clinical trials include proton beam therapy and offer fertility consultation prior to starting therapy.

Therapeutic interventions for primary CNS malignancies may impact the timing of pubertal development. Although precocious puberty and delayed puberty are infrequent, the potential impact on linear growth and psychosocial development warrants close follow-up. As long-term follow-up and risk stratifying techniques improve, efforts to identify risk factors for abnormal pubertal development and primary ovarian insufficiency should continue in addition to consideration of fertility preservation techniques prior to starting therapy. Clinicians must be aware that precocious puberty and primary ovarian insufficiency may coexist and recovery of ovarian function may be anticipated in approximately one third of females during their follow-up after treatment with CSI and adjuvant chemotherapy for a CNS malignancy.

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Figure 1. Female survivors of CNS tumors who were evaluable for pubertal development and primary ovarian insufficiency.

Figure 2.
The cumulative incidence of entering puberty by age at onset among females.

Figure 3.
The cumulative incidence of primary ovarian insufficiency among females following radiation therapy.

Table 1

Demographic and treatment characteristics of evaluable patients

	Evaluable for Precocious Puberty (n=18)	Evaluable for Delayed Puberty (n=17)	Evaluable for POI (n=29)		Patients with POI and spontaneous recovery (n=10)
			Non-POI (n=3)	POI (n=26)	Recovered ovarian function (n=10)
Age at diagnosis (years)					
Median (range)	5.0 (3.0–7.5)	7.2 (4.5–13.0)	5.8 (4.5–7.3)	7.1 (3.0–18.0)	8.4 (3.0–12.0)
Age at last endocrine evaluation (years)					
Median (range)	13.7 (9.4–16.9)	15.5 (13.3–22.6)	12.3 (12.3–14.1)	15.7 (9.4–26.8)	16.8 (9.4–21.6)
Diagnosis					
Medulloblastoma	15 (83.3%)	14 (82.4%)	1 (33.3%)	22 (84.6%)	10 (100%)
ATRT	3 (16.7%)	1 (5.9%)	1 (33.3%)	3 (11.5%)	0
PNET	0	2 (11.8%)	1 (33.3%)	1 (3.9%)	0
Race					
White	14 (77.8%)	15 (88.2%)	3 (100%)	20 (76.9%)	8 (80.0%)
Black	2 (11.1%)	2 (11.8%)	0	4 (15.4%)	2 (20.0%)
Hispanic	2 (11.1%)	0	0	2 (7.7%)	0
Ovarian radiation dose (Gy)					
< 5 Gy	8 (44.4%)	8 (47.1%)	1 (33.3%)	15 (57.7%)	7 (70.0%)
5 Gy	10 (55.6%)	9 (52.9%)	2 (66.7%)	11 (42.3%)	3 (30.0%)
Ovarian radiation dose (Gy)					
Median (range)	8.31 (0.65–30.05)	5.60 (0.65–20.80)	7.8 (2.7–18.2)	4.7 (0.58–30.1)	4.6 (0.81–15.6)
Hypothalamic/pituitary radiation dose					
23.4 to < 36 Gy	3 (16.7%)	5 (29.4%)	2 (66.7%)	11 (42.3%)	6 (60.0%)
36 Gy	15 (83.3%)	12 (70.6%)	1 (33.3%)	15 (57.7%)	4 (40.0%)
Hypothalamic/pituitary radiation dose (Gy)					
Median (range)	42.5 (33.2–54.7)	34 (30.2–51.6)	36.9 (33.7–42.1)	40.5 (26.3–54.7)	34.7 (26.3–49.1)
Cumulative cyclophosphamide dose (mg/m²)					
7,000 to < 11,000	1 (5.6%)*	1 (5.9%)**	0	0	0

	Evaluable for Precocious Puberty (n=18)	Evaluable for Delayed Puberty (n=17)	Evaluable for POI (n=29)		Patients with POI and spontaneous recovery (n=10)
			Non-POI (n=3)	POI (n=26)	
11,000 to < 16,300	16 (88.9%)	14 (82.4%)	3 (100%)	24 (92.3%)	9 (90.0%)
Craniospinal radiation dose (Gy)					
23.4 to < 36 Gy	NA	NA	3 (100%)	19 (73.1%)	10 (100%)
36 Gy	NA	NA	0	7 (26.9%)	0

* One patient received < 7000 mg/m² cyclophosphamide and was excluded from analysis.

** Two patients received < 7000 mg/m² cyclophosphamide and were excluded from analysis.

*** Two patients received < 7000 mg/m² cyclophosphamide and were excluded from analysis. NA is defined as Non-Applicable.

Demographic and treatment characteristics of patients who had precocious puberty or delayed puberty

Table II

	Age at diagnosis	Ovarian radiation dose (Gy)	Hypothalamic dose (Gy)	Cumulative cyclophosphamide dose (mg/m ²)	Years from diagnosis to tanner II
Precocious Puberty	3.6	1.1	44.9	16,000	3.5
	3.7	10.8	42.4	12,232	2.5
Delayed Puberty	5.0	19.8	51.6	10,121	11.0
	13.0	7.8	30.2	15,936	1.8