

Endocrine Complications in Children Treated for Medulloblastoma or Ependymoma using Radiation Therapy – Outcomes in the Computed Tomography Planning Era

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Abstract

Radiation therapy is an integral part of the treatment of paediatric patients with medulloblastoma and ependymoma. With newer surgical techniques and adjuvant chemotherapy regimens, recurrence-free survival rates have improved dramatically. Unfortunately, improved survival has come at the cost of significant late effects, including endocrine dysfunction. Prior to the 1990s, radiation fields were planned using 2D X-rays, exposing large volumes of healthy tissue to harmful radiation. Over the past two decades, radiation oncologists have increasingly applied 3D computed tomography scans to radiation therapy planning. By shaping target fields more precisely, higher doses of radiation may be delivered directly to the tumour while limiting exposure to healthy tissues and reducing side effects. The objective of this article is to review recent evidence about late endocrine effects among survivors of childhood medulloblastoma and ependymoma who received radiation therapy and to assess whether the introduction of 3D radiation planning techniques has affected the prevalence of these effects. Patients treated for medulloblastoma with current doses of craniospinal radiation continue to be at high risk of growth hormone deficiency and primary hypothyroidism, even when conformal radiation is used to deliver posterior fossa radiation. Patients with ependymoma who are treated with focal radiation alone, however, demonstrate fewer late endocrine effects.

Keywords

Brain tumour, radiation therapy, computed tomography (CT) planning, growth hormone, thyroid hormone, adrenocorticotropin hormone (ACTH), endocrine, paediatrics, late effects, cancer

Disclosure: Stacey L Urbach and Ute Bartels have no conflicts of interest to declare. Normand Laperriere is a consultant and serves on the speaker's bureau and advisory boards for Schering Plough/Merck.

Received: 19 March 2010 **Accepted:** 14 January 2011 **Citation:** *European Oncology & Haematology*, 2011;7(1):48–52 DOI: 10.17925/EOH.2011.07.01.48

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Radiation therapy as a means to improve outcome for a patient suffering from medulloblastoma was first used by Cushing in the 1920s. In 1953 Patterson and Farr reported their success on 27 medulloblastoma patients treated with craniospinal irradiation.¹ As technology has improved, radiation oncologists have developed techniques to deliver higher-energy radiation beams that are more effective at destroying malignant cells. Newer table designs and the advent of the linear accelerator have allowed beams to be delivered from various angles. With the introduction of computed tomography (CT) in 1971, radiologists and radiation oncologists were able to visualise anatomy in 3D. It was not until the 1990s, however, that CT was applied to radiation therapy planning, allowing radiation oncologists to shape their target fields in a more precise manner.² By limiting exposure of the healthy tissues, higher doses of radiation could be delivered to the tumour while reducing side effects.

Radiation therapy is an integral part of the treatment of paediatric patients with medulloblastoma and ependymoma. In general, patients with medulloblastoma are treated with surgical resection followed by radiation given to the craniospinal axis (craniospinal irradiation [CSI]) with an additional boost to the posterior fossa or tumour bed

followed by chemotherapy.³ Implementation of chemotherapy into the treatment of medulloblastoma has increased the chances of cure while allowing irradiation dose reduction.⁴ Despite this, conventional chemotherapy is considered of limited effectiveness in ependymoma. In North America, patients with gross total resected (GTR) M0 ependymoma (except GTR of supratentorial WHO II ependymoma) are currently treated with conformal radiation to the tumour site with or without adjuvant chemotherapy.

With newer surgical techniques and adjuvant chemotherapy regimens, recurrence-free survival rates have exceeded 85% for average-risk medulloblastoma.⁴ Most recent publications report a seven-year overall survival of 81% for ependymoma patients treated with focal irradiation.⁵ Unfortunately, improved survival has come at a cost, especially when whole-brain irradiation is required. Many patients experience significant late side effects, including neurocognitive and endocrine dysfunction.⁶

Radiation oncologists have worked to develop techniques that enhance the delivery of radiation therapy to malignant areas while limiting the exposure of healthy tissues, including the cerebral cortex and hypothalamic pituitary axis. Over the past decade, they have

increasingly used intensity-modulated radiation therapy (IMRT) to treat ependymomas and to deliver the posterior fossa boost to patients with medulloblastoma. IMRT uses 3D planning to shape the radiation beams to fit the dimensions of the tumour. This reduces the dose of radiation delivered to healthy tissues and should therefore lead to a reduction in the side effects experienced by these children. It is hoped that newer modalities like proton beam radiation may further spare childhood brain tumour survivors of late effects and decreased quality of life.⁷

Endocrine Outcomes Prior to the Use of 3D Radiation Planning

There are a number of studies describing the late effects experienced by childhood brain tumour survivors. Many of these studies focus on the most common late effects, namely neurocognitive compromise and endocrine dysfunction.^{6,8-13} These studies have provided invaluable data that have guided the development of newer therapies intended to reduce late effects without adversely affecting survival.

Survivors of childhood brain tumours followed in the Childhood Cancer Survivor Study (CCSS) cohort had a significantly increased risk of endocrine complications, with 43% of patients surviving more than five years from completion of therapy reporting one or more endocrine conditions.⁸ In patients diagnosed between 1970 and 1986 and treated for medulloblastoma or ependymoma with surgery and radiation (with or without chemotherapy), growth hormone (GH) deficiency was found in 39% of medulloblastoma patients and 24% of survivors of ependymoma.⁸ In this same group of patients, hypothyroidism was seen in 30% of the medulloblastoma patients and 12% of the ependymoma survivors.⁸ It is important to keep in mind that data from the CCSS are based on patient report and not derived from prospective surveillance for endocrine dysfunction. Retrospective, self-reported information may underestimate the risk of hormone dysfunction, particularly GH deficiency.

Endocrine Outcomes Since the Use of 3D Radiation Planning

Since 3D radiation treatment planning has only been used for the past two decades, few studies have looked at the endocrine late effects in patients treated with CT-based 3D conformal radiation or IMRT.

In one recent study, Laughton et al. examined the endocrine outcomes in 88 children (75 with medulloblastoma) treated for embryonal brain tumours at St Jude Children's Research Hospital between October 1996 and May 2003.¹⁴ The children were treated as part of the SJMB-96 trial, which included surgical resection followed by CSI and high-dose chemotherapy with autologous stem cell rescue. The radiation dose was given according to risk stratification, with average-risk patients receiving 23.4Gy of CSI, 36Gy of conformal radiation to the posterior fossa and a boost to 55.8Gy at the primary tumour site. High-risk patients received either 36Gy (M0-M1 disease) or 39.6Gy (M2-M3 disease) of CSI followed by conformal radiation therapy to 55.8Gy to the primary tumour site.¹⁴ The authors calculated the mean dose of radiation delivered to the hypothalamus and pituitary gland of all patients. Patients were followed for a median of 5.1 years and were evaluated on a regular basis by an endocrinologist with prospective assessment of endocrine outcomes.¹⁵

The median dose of radiation delivered to the hypothalamus in all patients was 44Gy, with those in the high-risk group receiving

significantly more than the average risk group (50.5 versus 38.6Gy; $p < 0.0001$). Ninety-four per cent of the patients tested were diagnosed with GH deficiency at a median of 1.8 years after radiation therapy (0.9-4.3 years), while 10% of patients developed thyroid-stimulating hormone (TSH) deficiency.¹⁴ The four-year cumulative incidence of GH and TSH deficiency was 93 and 23%, respectively. As expected, patients who received higher doses of radiation to the hypothalamus were more likely to develop TSH deficiency and therefore it was more commonly seen in the high-risk group, with a four-year cumulative incidence of TSH deficiency of 31% compared with 17% among average-risk patients ($p = 0.049$).¹⁴ Primary hypothyroidism was very common. It was diagnosed in 44 patients (51%) with a four-year cumulative incidence of 65%. Hypothyroidism developed at a median of 1.5 years from radiation therapy and was also more likely in the high-risk group (four-year cumulative incidence of 89 versus 54% among average-risk patients; $p = 0.017$).

Seventy-six patients (86%) were tested for integrity of the hypothalamic pituitary adrenal axis using the low-dose (1 μ g) corticotropin stimulation test or the metyrapone test. Adrenocorticotrophic hormone (ACTH) deficiency was diagnosed in 43% of the patients tested, with a four-year cumulative incidence of 38 \pm 6%.¹⁴

The young age of the study patients meant that the authors were not able to consistently evaluate gonadotropin levels.

Endocrine outcomes were studied in a group of patients treated for medulloblastoma and ependymoma at the Hospital for Sick Children and the Princess Margaret Hospital, both in Toronto, from June 2000 to June 2005. These data are currently published in abstract form.¹⁵ During the study time period, 70 children (48 with medulloblastoma and 22 with ependymoma) were treated with radiation at a median age of six years (range one to 17 years). All radiation fields were constructed using CT planning methods. Twenty-four patients received high-dose CSI (median dose of 36Gy with a range of 30.6-39.6Gy) with a median boost dose to the posterior fossa of 18Gy (range 16.2-23.4Gy).¹⁶ The same number of patients received low-dose CSI (median dose 23.4Gy, range 18-23.4Gy) with a median posterior fossa boost of 30.6Gy (range 30.6-36Gy). Twenty-two patients (20 with ependymoma) received only highly conformal RT to the tumour bed using IMRT at a median dose of 54Gy (range 54-59.4Gy).

In this study, children were not evaluated in a consistent prospective fashion, but were referred to an endocrinologist if there were symptoms or biochemical abnormalities that raised concerns about a particular endocrine disorder, such as poor growth or abnormal thyroid function tests. Thyroid function was performed on a regular basis in the neuro-oncology clinic.¹⁵

After a median follow-up period of 5.4 years (range 1.2-8.5 years), 35 children (50%) were diagnosed with an endocrine late effect. The five-year cumulative incidence of endocrine toxicity in children who received CSI was 71% compared with 18% for those children treated with focal radiation alone. In those patients who received CSI, the five-year cumulative incidence was 68% for GH deficiency, 52% for hypothyroidism, and 16% for precocious puberty. No difference was noted in the cumulative incidence of endocrinopathy between children treated with high-dose CSI and those who received low-dose CSI. Only two patients (3%) were diagnosed with ACTH deficiency and three patients (4%) were diagnosed with gonadotropin deficiency.¹⁵

Table 1: Summary of Studies Evaluating Growth Hormone Deficiency After Cranial and Craniospinal Irradiation

Author	Patients Enrolled/ Patients Tested	Malignancy	Proportion with GH Deficiency	Comments
Melin et al., 1998 ¹⁶	35/35	Leukaemia	63%	Patients treated with 18Gy of cranial radiation and routinely evaluated 5 years after therapy
Gurney et al., 2003 ⁸	Medulloblastoma 329/unknown, ependymoma 108/unknown	Medulloblastoma/PNET and ependymoma	Medulloblastoma 39%, ependymoma 24%	Data are based on patient report and are not derived from prospective surveillance for endocrine dysfunction. During this time period, ependymoma was treated with whole-brain radiation or CSI at most institutions
Xu et al., 2004 ¹⁸	7/7	Medulloblastoma	100%	Patients treated with 18Gy of CSI
Laughton et al., 2008 ¹⁴	88/70	Embryonal brain tumours	94%, 4-year CI 93%	Patients assessed for endocrine conditions in a systematic, prospective manner
Bahl et al., 2009 ¹⁵	70/unknown	Medulloblastoma (48), ependymoma (22)	52%, 5-year CI among CSI 68%	Data obtained retrospectively so data on endocrine dysfunction only available if patients had been referred to endocrinologist for evaluation

CI = cumulative incidence; CSI = craniospinal irradiation; GH = growth hormone; PNET = primitive neuroectodermal tumour.

Table 2: Summary of Studies Evaluating Hypothyroidism After Cranial and Craniospinal Irradiation

Author	Patients Enrolled/ Patients Tested	Malignancy	Proportion with Hypothyroidism	Comments
Livesey et al., 1990 ⁷	144/119	Paediatric brain tumour not involving HP axis	41% PH among CSI, 5% PH among cranial radiation, 3.4% TSH deficiency	Patients were not evaluated for endocrine dysfunction in a systematic manner
Chin et al., 1997 ¹⁹	34/34 conventional, 14/14 hyperfractionated	Medulloblastoma and PNET	62% PH with conventional fractionation, 14% PH with hyperfractionated radiation	Patients treated with conventionally fractionated radiation were compared to hyperfractionated (1Gy per fraction twice per day)
Schmiegelow et al., 2003 ²³	71/71	Paediatric brain tumour not involving HP axis	41% PH among CSI, 12% PH among cranial radiation, no cases of TSH deficiency among CSI, 6% TSH deficiency among cranial radiation	Patients treated with cranial radiation (either whole brain or focal) or CSI ± tumour boost
Gurney et al., 2003 ⁸	Medulloblastoma 329/unknown, ependymoma 108/unknown	Medulloblastoma/PNET and ependymoma	Medulloblastoma 30%, ependymoma 12%	Data are based on patient report and are not derived from prospective surveillance for endocrine dysfunction. Primary hypothyroidism not differentiated from TSH deficiency
Xu et al., 2004 ¹⁸	7/7	Medulloblastoma	14% hypothyroidism	Patients treated with 18Gy of craniospinal radiation. Unclear whether this is PH or TSH deficiency
Laughton et al., 2008 ¹⁴	88/87	Embryonal brain tumours	PH: 51% 4-year CI 65% TSH deficiency: 10% 4-year CI 23%	Patients assessed for endocrine conditions in a systematic, prospective manner
Bahl et al., 2009 ¹⁵	70/unknown	Medulloblastoma (48), Ependymoma (22)	33%, 5-year CI among CSI 52% ependymoma (22)	Patients who received cranial radiation were routinely tested for thyroid hormone dysfunction. Authors did not differentiate between primary hypothyroidism and TSH deficiency

CI = cumulative incidence; CSI = craniospinal irradiation; HP = hypothalamic-pituitary; PH = primary hypothyroidism; PNET = primitive neuroectodermal tumour; TSH = thyroid-stimulating hormone.

The relatively low cumulative incidence of endocrinopathies (18%) among patients treated with focal radiation without craniospinal treatment is almost certainly related to the lower dose received by the hypothalamus and pituitary gland as a result of the absence of whole-brain radiation given as part of CSI. In addition, the fact that only the tumour bed was treated in these patients as opposed to the whole posterior fossa as in the medulloblastoma patients may contribute further to the reduced cumulative incidence of endocrinopathies. Ongoing evaluation will document the actual radiation dose delivered to the hypothalamus among the patients in this study.

Growth Hormone Deficiency

The studies on GH deficiency are presented in *Table 1*. Both the research performed at the Hospital for Sick Children and at St Jude demonstrates a very high risk of GH deficiency in patients treated with

CSI.^{14,15} GH deficiency is known to develop after relatively low doses of cranial radiation.¹⁶ It is therefore not surprising that even when conformal radiation is used to deliver the posterior fossa radiation, thereby reducing a portion of the dose delivered to the hypothalamus, patients remain at high risk of GH deficiency. The radiation dose below which patients will not develop GH deficiency is not known. There have even been reports of GH deficiency in patients who received just 12Gy of total-body irradiation as conditioning for bone marrow transplant.¹⁷ Melin et al. described a prevalence of 63% of GH deficiency five years after receiving 18Gy of cranial radiation for therapy for leukemia.¹⁶ Even in the study by Xu et al., where patients with medulloblastoma received a craniospinal dose of only 18Gy, all patients developed GH deficiency.¹⁸ In this study, since the boost doses were not given using conformal radiation it is likely that a large proportion of the posterior fossa dose reached the hypothalamic-pituitary axis. CSI doses used in the studies

Table 3: Summary of Studies Evaluating Adrenocorticotropin Hormone Deficiency After Cranial and Craniospinal Irradiation

Author	Patients Enrolled/ Patients Tested	Malignancy	Proportion with ACTH Deficiency	Comments
Laughton et al., 2008 ¹⁴	88/76	Embryonal brain tumours	43%, 4-year CI 38%	1µg corticotropin test or metyrapone used for evaluation
Bahl et al., 2009 ¹⁵	70/unknown	Medulloblastoma (48), ependymoma (22)	3%	250µg corticotropin test used for evaluation
Livesey et al., 1990 ⁹	144/90	Paediatric brain tumour not involving HP axis	4%	Insulin tolerance test used for evaluation
Rose et al., 2005 ²¹	182/182	Central nervous system tumours	24%	Testing performed in patients referred to endocrinology with slow growth, fatigue or abnormal pubertal timing 1µg corticotropin test and/or metyrapone test
Patterson et al., 2009 ²²	41/41	Paediatric cancer	83% with >40Gy to HP axis, 50% with 30–39Gy to HP axis, 12% with 20–29.9Gy to HP axis, 8% with <20Gy to HP axis	Testing performed in patients referred to endocrinology 1µg corticotropin test

ACTH = adrenocorticotropin hormone; CI = cumulative incidence; HP = hypothalamic–pituitary.

examining outcomes with CT planning – and in current clinical practice – remain above the threshold for development of GH deficiency. It is therefore unlikely that a reduction in GH deficiency will be seen in medulloblastoma patients, even with CT planning. On the other hand, more precise delivery of focal radiation will almost certainly have a large impact on the prevalence of GH deficiency in patients who do not require whole-brain radiation delivered as part of the CSI therapy.

Primary Hypothyroidism

The studies describing primary hypothyroidism are presented in *Table 2*. Primary hypothyroidism is still frequently seen in patients who receive CSI because the thyroid gland is exposed to a portion of the delivered spinal dose. In the studies by Laughton¹⁴ and Bahl,¹⁵ hypothyroidism occurred with a cumulative incidence of 65 and 52%, respectively.

Studies performed prior to the widespread use of CT planning showed similar prevalences of primary hypothyroidism, with some variability depending on how the patients were selected.^{8,19,20} Chin et al.¹⁹ reported a prevalence of 62% of primary hypothyroidism in patients treated with conventionally fractionated CSI for paediatric medulloblastoma. Schmiegelow et al.²⁰ diagnosed 41% of patients treated in the same manner.

In the CCSS cohort, patients who received a radiation dose of 25Gy or higher to the thyroid gland were more than twice as likely to report primary hypothyroidism than those patients who received lower doses.⁸

Xu et al.¹⁸ reported on the endocrine outcomes in seven young children with medulloblastoma who were treated with 18Gy of craniospinal radiation. Only one patient (14%) developed hypothyroidism in the lower dose group compared with 83% of patients from the same institution who received between 23 and 39Gy of CSI.¹⁸ A current ongoing Children's Oncology phase III trial is evaluating the safety of reduced dose of craniospinal radiation (18 versus 23.4Gy) as well as reduced radiation volume to the post fossa for children with average risk medulloblastoma.

Even with the reduced dose to the hypothalamic pituitary axis from cranial boost doses delivered by IMRT, primary hypothyroidism remains a significant risk as long as CSI is required for successful treatment.

Thyroid-stimulating Hormone Deficiency

In their prospective study, Laughton et al. showed a significant risk of TSH deficiency (10% of patients with a four-year cumulative incidence of 23%) see *Table 2*.¹⁴ Livesey et al.⁹ and Schmiegelow et al.²⁰ reported TSH deficiency prevalences of 3.4 and 6%, respectively, in patients treated with radiation for paediatric brain tumour.^{20,21} The relatively higher prevalence seen in the Laughton paper may relate, in part, to the fact that the patients were evaluated in a systematic, prospective manner.

It is important to recognise when comparing these studies that the use of different methods of reporting the data may result in different estimates of endocrine dysfunction. For example, in the Laughton study, the 'prevalence' of TSH deficiency was 10% but the four-year 'cumulative incidence' was 23%. Many of the earlier studies^{9,20} report simple prevalence data, which do not account for differences in the length of follow-up and may underestimate the true risk of endocrinopathy. Careful interpretation of study results taking different methodologies into account seems advisable.

Adrenocorticotropin Hormone Deficiency

The studies describing ACTH deficiency are presented in *Table 3*. There are wide variations in the reported prevalence of ACTH deficiency in the literature. This is likely to be due to the use of different diagnostic tests and selection of patients for evaluation. Most papers report a lower prevalence of central adrenal insufficiency than that reported by Laughton¹⁴ (43% with a four-year cumulative incidence of 38%), with figures ranging from 4% to 24%²¹ of patients treated with radiation for tumours of the central nervous system.

One recent retrospective review described central adrenal insufficiency in patients receiving cranial radiation to the hypothalamic–pituitary axis as part of their treatment.²² The results of the review showed adrenal insufficiency in 83% of cancer survivors who received >40Gy, 50% of patients who received 30–39Gy, 12% of patients who received 20–29.9Gy and 8% of survivors who received <20Gy. This review only included survivors who had undergone hypothalamic–pituitary–adrenal axis testing, and therefore may not be representative of all brain tumour survivors with cranial radiation.

Livesey et al. reported only 4% of patients with ACTH deficiency after a radiation dose of 48Gy to the hypothalamus, using insulin-induced

hypoglycaemia testing for the evaluation of adrenal function.⁹ The method of evaluation with 1µg of corticotropin used by Patterson et al.²² and Laughton et al.¹⁴ resulted in higher percentages of prevalence of central adrenal insufficiency than previously described. Bahl et al. reported only a 3% prevalence of ACTH dysfunction when the standard-dose (250µg) ACTH test was used. These patients were evaluated retrospectively and endocrine assessments were not complete in all patients.¹⁵

Different testing methods and strategies of patient selection make it difficult to draw conclusions about the impact of CT planning on the development of ACTH deficiency in survivors of medulloblastoma and ependymoma. Studies using the 1µg ACTH stimulation test show a higher prevalence of ACTH deficiency than those using the insulin tolerance test or the standard-dose ACTH stimulation test. It is not clear from the literature that patients who fail the low-dose test but pass the 250µg test are at increased risk of symptomatic adrenal insufficiency. This test may therefore detect patients with laboratory abnormalities that do not translate into clinical disease. Another important factor to consider when assessing risk of ACTH deficiency is length of follow-up, as there appears to be a longer delay to the onset of ACTH deficiency compared with GH deficiency and primary hypothyroidism.²³

Hypogonadism

Based on limited data it is difficult to draw conclusions about the impact of 3D radiation therapy planning on the development of luteinising hormone (LH) and follicle-stimulating hormone (FSH) deficiency. Laughton et al. were not able to assess LH and FSH reliably because of the young age of their patients.¹⁴ These values were not consistently measured in the study by Bahl et al. either.¹⁵ Bahl and colleagues reported three patients (4%) with gonadotropin deficiency. Future studies should follow these patients through puberty into young adulthood, when gonadotropin deficiency would become apparent.

Conclusions

Survivors of childhood brain tumours who live more than five years have 10- and 15-year survival estimates of 90 and 85%, respectively. These estimates are significantly lower than those of the age- and

sex-matched US population living during the same time period (survival for 10 years being 99.5% and 99% for 15 years). Eighteen per cent of the mortality seen in these patients was as a result of a medical cause, with death from hormone dysfunction being the most common aetiology.²⁴ These findings underscore the importance of reducing the risk of endocrine dysfunction where possible and understanding which patients are most at risk of developing dysfunction in order to initiate timely hormone replacement and prevent further morbidity.

Current data suggest that reducing the volume of irradiated brain tissue does not appear to have an adverse effect on progression-free survival in patients with ependymoma.²⁵ The use of conformal radiation is associated with a lower cumulative incidence of endocrinopathy. Bahl et al. reported a cumulative incidence of only 18% in survivors of ependymoma treated with focal cranial radiation.¹⁵

In patients treated for medulloblastoma, trials eliminating irradiation, especially in very young children, are associated with a significantly reduced chance of overall survival.^{26,27} An ongoing Children's Oncology Group trial is testing whether it is safe to further reduce radiation dose and volume for patients with average risk medulloblastoma. With current protocols used, children with medulloblastoma are at high risk of GH deficiency and primary hypothyroidism.¹⁴

Patients assessed for endocrinopathies in a prospective, standardised fashion demonstrate high rates of TSH and ACTH deficiency.¹⁵ It is difficult to know which is the most accurate assessment of risk of ACTH deficiency, as many different methods for evaluating the hypothalamic-pituitary-adrenal axis are used in the literature.^{9,15,21}

Even with improved techniques of radiation and dosimetry, children treated for brain tumours remain at risk of endocrine dysfunction. Survivors of childhood brain tumours treated with cranial radiation should receive standardised, serial endocrine assessments. Early identification of hormone deficits and consecutive initiation of effective and safe substitution therapy will prevent further debilitating outcomes of this vulnerable patient population. ■

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