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DISEASE CONTROL AFTER REDUCED VOLUME CONFORMAL AND INTENSITY-MODULATED RADIATION THERAPY FOR CHILDHOOD CRANIOPHARYNGIOMA

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Abstract

PURPOSE—To estimate the rate of disease control after conformal radiation therapy using reduced clinical target volume (CTV) margins and determine factors that predict for tumor progression.

METHODS AND MATERIALS—Eighty-eight children (median age 8.5 years, range 3.2–17.6 years) received conformal or intensity-modulated radiation therapy between 1998 and 2009. This included those prospectively treated from 1998 to 2003 using a 10 mm CTV, defined as the margin surrounding the solid and cystic tumor targeted to receive the prescription dose of 54 Gy. The CTV margin was subsequently reduced after 2003 yielding two groups of patients: those treated with a CTV margin greater than 5 mm (n=26) and those treated with a CTV margin less than or equal to 5 mm (n=62). Disease progression was estimated on the basis of additional variables including sex, race, extent of resection, tumor interventions, target volume margins, and the frequency of weekly surveillance MR imaging during radiation therapy. The median follow-up was 5 years.

RESULTS—There was no difference comparing progression-free survival based on CTV margin (>5mm vs. ≤ 5mm) at 5 years, 88.1 + 6.3% vs. 96.2 + 4.4% (P=0.6386). There was no difference based on the planning target volume (PTV) margin (or combined CTV+PTV). The PTV was systematically reduced from 5 to 3mm during the time period of the study. Factors predictive of superior progression-free survival included Caucasian race (P=0.0175), absent CSF shunting requirement (P=0.0066), and the number of surveillance imaging studies during treatment

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CONFLICT OF INTEREST NOTIFICATION

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(P=0.0216). Patients whose treatment protocol included a higher number of weekly surveillance MR imaging evaluations had a lower rate of tumor progression.

CONCLUSIONS—These results suggest that targeted volume reductions for radiation therapy using smaller margins are feasible and safe but require careful monitoring. We are currently investigating the differences in outcome based on host factors to explain the results.

Keywords

Radiotherapy; Pediatrics; Brain Tumor; Craniopharyngioma; Adaptive Therapy

Introduction

Neurologic, endocrine, and cognitive deficits observed in children treated for craniopharyngioma are known to be associated with tumor extent, surgical morbidity, radiation dose, and irradiated volume (1). Reducing radiation dose and volume may be achieved by reducing the target volume and the implementation of more conformal methods or modalities of irradiation (2).

Because of the rarity of this disease, there have been few systematic applications of focused irradiation attempting to define targeting and the appropriate treatment method. A prospective phase II trial of conformal radiation therapy was conducted from 1997 to 2003. The primary objective was to estimate the local control and patterns of failure for pediatric patients with craniopharyngioma treated with conformal radiation therapy using a 10 mm clinical target volume margin (CTV). The trial demonstrated that event-free survival with a 10 mm CTV margin and 3–5 mm planning target volume (PTV) margin was similar to treatment with conventional radiation therapy (1). With a median follow-up of 28 months, the 3-year event-free survival rate was 85% ± 11%. This study was the first to prospectively define a minimum target volume for this disease. The impact of high-dose irradiation on functional outcomes, specifically cognition, was clearly demonstrated in younger patients and in subsequent investigations evaluating a variety of functional domains (3). These findings and recent advances in radiation therapy, made further reductions in the irradiated volume warranted and feasible.

To that end we investigated further reductions in the targeted volume with the goal to define a new minimum CTV for patients with craniopharyngioma and reduce side effects. In this report we estimate the rate of disease control after conformal radiation therapy using reduced CTV margins and determine factors that might predict for tumor progression.

Methods and Materials

Eighty-eight children (median age 8.5 years, range 3.2–17.6 years) received conformal (n=79) or intensity-modulated (n=9) radiation therapy between 1998 and 2009. This included patients prospectively treated from 1998 to 2003 using a 10 mm CTV margin and those subsequently treated with smaller CTV margins after 2003. For the purpose of this analysis, there were two groups of patients: those treated with a CTV margin greater than 5mm (n=26) and those treated with a CTV margin less than or equal to 5 mm (n=62).

The gross tumor volume (GTV) was defined as the post-operative solid and cystic tumor complex. The CTV included a volumetric expansion of the GTV that was subsequently tailored or reduced at tissue interfaces where tumor invasion or extension was unlikely such as the base of skull. The PTV margin was a 3–5 mm geometric expansion of the CTV. The use of a 3 mm PTV margin was limited to patients who underwent daily localization using cone-beam CT or other image-guided methods.

The prescribed dose was 54 Gy and there were no constraints on normal tissues including the optic chiasm, optic nerves or brainstem. During the time period 1998 to 2003, patients underwent two MR imaging examinations during radiation therapy. These were planned during weeks 3 and 5 of treatment. After 2003, MR imaging was performed at the discretion of the treating physician. A dedicated MR system was installed in the department of radiation oncology in 2005 allowing for more frequent, often weekly, MR imaging. The method of on-treatment MR imaging evaluation included MR imaging, registration of the imaging study to the treatment planning dataset, contouring of a new GTV, and evaluation of target volume coverage by the treating physician. When the contour of the new (on-treatment) GTV was noted to enlarge and approach the previously defined CTV margin, the process of establishing a new CTV and PTV was initiated with the subsequent preparation of a new treatment plan. In most cases, a new plan was initiated within 24 hours.

The primary endpoint for this study was progression-free survival. Progression-free survival was estimated on the basis of additional variables including sex, race, extent of resection, tumor interventions, target volume margins, the use of growth hormone replacement therapy, and the frequency of surveillance MR imaging during radiation therapy. The median follow-up was 5 years for the entire cohort.

Disease control was evaluated using MR imaging performed during regular intervals after enrollment. Patients were considered to have progressive disease if the solid portion of the tumor progressively increased in size by a measurable amount or if the cystic portion of the tumor complex showed unabated progression more than three years after treatment. Limited surgical intervention was allowed including cyst aspiration or drainage and minimal cyst resection.

For factor covariate variables (e.g., Tables 1 and 3), the probabilities of progression-free survival (PFS) were estimated for subgroups of factor by Kaplan-Meier estimation with stratification; and the Log-Rank test was used for comparisons of the subgroups. For continuous covariate variables (e.g., Table 2), the Cox-proportional hazard model was used to estimate the effect of covariate variable, such as D95GTV or D95CTV or D95PTV, on the probability of PFS, for which the odds ratio can be interpreted as that for X vs. X+1, where X is any value of covariate variable. The Cochran-Armitage Trend test was used to test the correlation between the number of MR surveillances and the probability of event of tumor progression (Table 4). All analyses had been done by using SAS statistical analysis package (SAS Institute Inc: SAS for Windows, V 9.1.3, NC, in , 2004).

Results

The primary objective of this study was to estimate the rate of disease control after conformal radiation therapy (including intensity-modulated radiation therapy) using reduced clinical target volume margins and determine factors that would predict for tumor progression.

There was no difference in progression-free survival based on CTV margin: the 5-year progression-free survival rate was 88.1 ± 6.3% for the group treated using a CTV margin >5mm vs. 96.2 ± 4.4% for the group of patients treated using a CTV margin ≤5mm (P=0.6386). There was no difference based on PTV margin or combined CTV+PTV margins. The PTV margin was systematically reduced from 5 to 3 mm during the time period of the study.

Factors predictive of superior progression-free survival included Caucasian race (P=0.0175) and the absent of CSF shunting (P=0.0066) as shown in Table 1. There was no difference in progression-free survival based on sex, extent of resection, number of tumor interventions,

target volume margins or target volume coverage (Table 2), or the use of growth hormone replacement therapy (Table 3). Specifically, the Cox proportional hazards model was used to predict progression-free survival based on target volume coverage (D95%). None of the models were significant. Based on the Kaplan-Meier estimate of progression-free survival, growth hormone replacement therapy was not associated with tumor recurrence.

The frequency of surveillance MR imaging during radiation therapy was associated with progression-free survival (Table 4). By the Cochran-Armitage Trend Test, there was a statistically significant association between MR surveillance studies and progression free survival (p=0.0216). Cyst enlargement that required a change in treatment plan was observed in 22 of 88 cases. Only the cystic component changed during radiation therapy; there was no change in the solid component during radiation therapy.

Discussion

Progression-free and overall-survival rates of 77% and 83% at 10 years and 66% and 79% at 20 years after limited surgery and radiation therapy have been reported from the Royal Marsden Hospital using doses > 50 Gy (4) . These results are considered benchmarks for disease control in the treatment of craniopharyngioma, and the same therapeutic principles are now followed more than 50 years after their initial description. Despite its long-term success in controlling this disease, the side effects of photon irradiation on neurologic, endocrine and cognitive function weigh heavily when recommending irradiation because the long-term prospects for survival for children with this rare brain tumor are excellent. Reducing dose amounts to normal tissue should be a primary goal when radiation therapy is administered.

The progression-free and overall survival rates observed in our series suggest that volume reduction is feasible and safe. Craniopharyngioma is composed of solid and cystic elements and prone to idiosyncratic enlargement during radiation therapy. When limited target volume margins or highly conformal methods of irradiation are used, monitoring for cyst enlargement is critical. Our first prospective series used a relatively large CTV margin of 10 mm. At the time that the trial was designed in 1996 to 1997, the use of MR imaging was considered critical. Imaging was planned only during weeks 3 and 5 because the incidence and time course of cyst enlargement was unknown, and the use of MR imaging required significant resources. As previously reported (1), "nearly one half of the patients experienced cystic enlargement during radiation therapy, including 13 patients who underwent cyst aspiration at least once during radiation therapy and three patients for whom MR imaging demonstrated enough change in the tumor volume to warrant a new treatment plan.” Including the 66 additional patients contributing to this report, and for whom the target volume margins were further reduced, we observed cyst enlargement that required a change in treatment plan in an additional 19 cases for a total of 22 adaptive cases amongst 88 patients. These data suggest that monitoring the tumor is requisite to the appropriate treatment of craniopharyngioma.

Craniopharyngioma is not considered to be an infiltrative tumor and the interface between tumor and normal tissue is usually distinct by neuroimaging. Loss of tissue planes after initial surgery has been noted in specific surgical series (5). Similar conditions exist for radiation therapy planning in patients who undergo extensive surgery; clear identification of the volume at risk might be difficult in these cases, which comprised a substantial proportion in our series. Further reduction in the target volume should be approached systematically and incorporate newer imaging methods and observations made at the time of surgery. The importance of on-going imaging during treatment is associated with improved progression-free survival.

Because of the dynamic nature of the craniopharyngioma cyst and brain shift after tumor resection and the treatment of hydrocephalus, the approach to radiation therapy treatment planning should be systematic and without deadline or urgency. Further, imaging for treatment planning should be proximal to the initiation of treatment, and on-treatment imaging should be provided as a standard – the frequency to be determined by the treating physician and other factors including prior treatment, observation of cyst volume dynamics, and whether the treatment involves irradiation of post-operative solid residual tumor or a solid and cystic tumor complex. Our findings do not account for a variety of improvements in treatment methods that span the era that included improvements in clinical neuro-imaging, image-guided therapy, immobilization, and additional experience. This is a contemporary treatment series since MR registration was used for the initial planning process and evaluation of the pattern of failure for all patients.

Prognostic Factor – CSF shunting

CSF shunting was predictive of disease progression in our series. CSF shunting - a surrogate for severe hydrocephalus - has been shown to predict for disease control in children with craniopharyngioma treated with primary surgery. Data from one of the largest United States series included patients treated primarily with surgery showed that progression-free and overall survival rates were negatively influenced by subtotal resection, tumor size > 5 cm, and the presence of hydrocephalus or CSF shunting (6). It is logical that subtotal resection would affect progression-free survival rates but not overall survival rates in a primary surgery series since patients who have disease progression after primary surgery may be successfully salvaged with radiation therapy. Progression-free survival rates may be impacted by the tumor size, hydrocephalus, and CFS shunting, which may suggest a more extensive and aggressive disease.

The Potential Impact of Growth Hormone Replacement Therapy

Growth hormone (GH) deficiency is common in children with craniopharyngioma prior to irradiation and a certainty in the majority within 12 months of irradiation. GH replacement therapy, initiated within 12 months of irradiation for nearly all of our patients, has many positive attributes (7); however, tumor progression coincident with the use of GH replacement therapy often leaves caregivers and patients wondering about the association of tumor recurrence and GH replacement therapy (8). Indeed, Hofmann et al. (9) described a correlation between the tumor size and cell proliferation indexes and cDNA expression levels of ER-1 and GH receptors. Uchino at al. (10) expressed concern in a small cohort of craniopharyngioma patients that positive immunohistochemical expression of GH receptor in tumor tissue was associated with a high probability of recurrence. These findings address the need to determine the association between hormone status, clinic-pathologic factors and tumor progression. However, we found no statistical association with GH replacement therapy and tumor progression.

Prognostic Factor – Race

Further research is recommended to determine if progression-free survival is inferior in non-Caucasian patients with craniopharyngioma. There were no differences in the extent of surgery, presenting morbidity or the extent of disease progression when comparing patients according to race. One of the non-Caucasian patients died from an opportunistic infection and was censored in the analysis for progression-free survival. The molecular pathogenesis of craniopharyngioma is not understood (11, 12). Angiogenic and hormonal factors and mutations associated with genes involved in ectodermal development have been investigated. These studies showed that expression of PDGFR-alpha and FGF-2 were noted to be significantly higher in tissue specimens taken from patients with recurrent tumors (13). Ki-67 labeling index was significantly higher in patients with tumor progression and the

incidence of post-operative regrowth was higher in patients negative for estrogen and progesterone receptors compared to those who were positive for both receptors (14). Mutated β-catenin (15) and Wnt signaling (16) were associated in the development and natural history of craniopharyngioma.

Tumors such as Ewing sarcoma, that overexpress EWS-FLI1, a known inhibitor of Wnt, have also been associated with racial differences in outcome (17). We suggest that the racial differences in the molecular pathogenesis of craniopharyngioma and their association to the Wnt signaling pathway should be investigated further. In the United States, black children have a significantly lower age-specific and age-adjusted incidence rate of brain and spinal cord tumor (21.7 cases per 100,000 person-years) than whites (26.4 cases per 100,000 person-years). Black children in the United States have a higher incidence of craniopharyngioma than whites. Differences in total incidence or in relative frequencies of particular histological types suggest a substantial contribution of genetic predisposition in etiology (18).

The Potential Benefits of Target Volume Reduction and Proton Therapy

The primary goal of target volume reduction is to minimize the risk of radiation-related complications, most notably cognitive effects. There is less concern for neurological (vision loss and hearing loss) and endocrine effects because their frequency is low or commonly associated with tumor location. Because of morbidity from the tumor and treatment, there is heightened interest in reducing side effects by using more advanced methods of radiation therapy including proton therapy. Proton therapy may be used to reduce the volume receiving the lowest doses and therefore the risk of complications based on the known association between dose to normal brain and cognitive effects (1).

Based on pre-existing morbidity; however, the opportunity to improve outcomes for these patients may be limited. This was highlighted in a report that included 29 children and an assessment of quality of life, mood, and executive functioning after surgery and proton therapy. Overall quality of life self-report was in the normal range; however, the proxy report was lower and nearly half of the responding patients reported depression. (19). In another series, 16 children and young adults were treated using proton therapy and cumulative doses of 50.4–59.4 CGE. Although there were few acute effects, long-term complications included stroke in at least one patient (eleven). Actuarial 5- and 10-year local control rates were 93% and 85% with no observed late effects in the 10 young adults; however, 1 of 5 children developed mental deficiency (20). The patients included in the present report were prospectively followed to determine the association between clinical and treatment factors and neurological, endocrine, cognitive and functional outcomes; however, functional outcomes are not the subject of the current report.

Summary

The CTV margin may be safely reduced without affecting the rate or progression-free survival in children with craniopharyngioma. Monitoring for tumor cyst enlargement during radiation therapy should be integral to the overall treatment plan. The clinical factors of race and CSF shunting are prognostic for progression-free survival and require further investigation.

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Table 1

Factors associated with progression-free survival.

		Estimate ± SE (%)						
Factors	**n**	**Year 1**	**Year 2**	**Year 3**	**Year 5**	**Year 8**	**Year 10**	**p-value***
SEX								
Male	47	100 ± 0.0	97.7 ± 2.4	92.1 ± 4.5	84.2 ± 8.4	84.2 ± 15.0	84.2 ± 19.3	0.1515
Female	41	100 ± 0.0	100 ± 0.0	100 ± 0.0	100 ± 0.0	82.0 ± 13.1	82.0 ± 24.6	
RACE								
White	68	100 ± 0.0	98.4 ± 1.6	98.4 ± 1.7	96.1 ± 3.2	91.9 ± 7.9	91.9 ± 13.0	0.0175 **
Black	19	100 ± 0.0	100 ± 0.0	86.7 ± 8.5	78.0 ± 13.8	0	0	0.0048 ***
Asian	1	100 ± 0.0	100 ± 0.0	No Data	No Data	No Data	No Data	
OMMAYA RESERVOIR								
Yes	47	100 ± 0.0	97.7 ± 2.3	92.4 ± 4.4	89.2 ± 6.0	83.2 ± 12.9	83.2 ± 24.1	0.3371
No	41	100 ± 0.0	100 ± 0.0	100 ± 0.0	96.0 ± 4.4	80.0 ± 16.0	80.0 ± 20.7	
CSF SHUNT								
Yes	28	100 ± 0.0	96.2 ± 3.7	92.0 ± 5.4	82.8 ± 8.6	59.6 ± 16.9	59.6 ± 26.8	0.0066
No	60	100 ± 0.0	100 ± 0.0	97.8 ± 2.2	97.8 ± 2.8	97.8 ± 5.5	97.8 ± 8.3	
SURGERY CLASSIFICATION								
Imaging Diagnosis	4	100 ± 0.0	100 ± 0.0	100 ± 0.0	100 ± 0.0	No Data	No Data	0.4803
Biopsy Attempted	13	100 ± 0.0	91.7 ± 7.6	91.7 ± 8.4	91.7 ± 8.8	61.1 ± 22.0	No Data	
Sub-total Resection	56	100 ± 0.0	100 ± 0.0	95.8 ± 2.9	93.1 ± 4.6	93.1 ± 8.6	93.1 ± 12.2	
Aspiration Only	15	100 ± 0.0	100 ± 0.0	100 ± 0.0	83.3 ± 15.2	62.5 ± 27.1	No Data	
SURGERY EXTENT								
Minimal-None	40	100 ± 0.0	97.2 ± 2.8	93.9 ± 4.5	89.6 ± 6.6	66.6 ± 17.2	66.6 ± 38.5	0.1393
Moderate	17	100 ± 0.0	100 ± 0.0	93.3 ± 6.4	86.2 ± 9.7	86.2 ± 18.5	86.2 ± 32.1	
Extensive	31	100 ± 0.0	100 ± 0.0	100 ± 0.0	100 ± 0.0	100 ± 0.0	100 ± 0.0	
TISSUE DIAGNOSIS								

		Estimate ± SE (%)						
Factors	**n**	**Year 1**	**Year 2**	**Year 3**	**Year 5**	**Year 8**	**Year 10**	**p-value***
Yes	64	100 ± 0.0	98.4 ± 1.7	94.6 ± 3.1	92.3 ± 4.4	83.9 ± 10.6	83.9 ± 16.8	0.6726
No	24	100 ± 0.0	100 ± 0.0	100 ± 0.0	91.7 ± 8.8	78.6 ± 25.7	No Data	
NUMBER OF TUMOR SURGERY PROCEDURES								
≤1	47	100 ± 0.0	100 ± 0.0	100 ± 0.0	96.3 ± 4.0	71.9 ± 19.1	71.9 ± 38.1	0.6868
>1	41	100 ± 0.0	97.4 ± 2.5	91.8 ± 4.6	88.4 ± 6.6	88.4 ± 10.7	88.4 ± 15.1	
NUMBER OF CYST ASPIRATIONS								
≤1	60	100 ± 0.0	100 ± 0.0	97.6 ± 2.4	91.7 ± 5.2	80.2 ± 13.5	80.2 ± 20.6	0.5351
>1	22	100 ± 0.0	100 ± 0.0	95.2 ± 4.5	95.2 ± 5.8	95.2 ± 9.3	95.2 ± 14.7	
NUMBER OF CNS INTERVENTIONS†								
≤2	57	100 ± 0.0	100 ± 0.0	97.4 ± 2.5	94.3 ± 4.5	75.8 ± 15.2	75.8 ± 26.4	0.8888
>2	31	100 ± 0.0	96.8 ± 3.1	93.4 ± 4.5	89.2 ± 7.1	89.2 ± 12.0	89.2 ± 16.9	
CTV Margin								
≤5mm	62	100 ± 0.0	98.2 ± 1.9	96.0 ± 3.0	96.0 ± 4.4	72.0 ± 19.1	72.0 ± 26.9	0.6386
>5mm	26	100 ± 0.0	100 ± 0.0	96.2 ± 3.8	88.1 ± 6.3	83.7 ± 11.9	83.7 ± 19.5	
PTV Margin								
≤3mm	45	100 ± 0.0	97.5 ± 2.6	97.5 ± 3.0	97.5 ± 4.1	97.5 ± 10.9	97.5 ± 10.9	0.2684
>3mm	43	100 ± 0.0	100 ± 0.0	95.1 ± 3.4	89.6 ± 5.4	77.4 ± 11.6	77.4 ± 21.2	
CTV- PTV Margin								
≤8mm	45	100 ± 0.0	97.4 ± 2.7	97.4 ± 3.1	97.4 ± 4.5	97.4 ± 11.0	97.4 ± 11.0	0.3459
>8mm	43	100 ± 0.0	100 ± 0.0	95.2 ± 3.3	89.9 ± 5.1	78.4 ± 11.5	78.4 ± 21.0	

*Log-rank Test for comparing subgroups

**P-value for comparing three subgroups;

***P-value for comparing first two subgroups

†CNS interventions include intracranial surgery and CSF shunt placements

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Table 2

Cox-proportional hazard model of target volume dosimetry and progression-free survival.

Variable	Total (Event)	Estimate (SE)	p-value	Hazard Ratio (95 CI)
D95GTV(Gy)	88(7)	0.313(0.336)	0.3506	1.37(0.71–2.64)
D95CTV(Gy)	88(7)	0.429(0.315)	0.1731	1.54(0.83–2.85)
D95PTV(Gy)	88(7)	0.358(0.297)	0.2276	1.43(0.80–2.56)

Table 3

Association between growth hormone replacement therapy and progression-free survival.

		Progression-Free Survival Estimate ± SE (%)						
Factors	**n**	**Year 1**	**Year 2**	**Year 3**	**Year 5**	**Year 8**	**Year 10**	**p-value***
GH Replacement								
Yes	60	100 ± 0.0	100 ± 0.0	96.2 ± 2.7	91.7 ± 4.4	87.5 ± 10.3	87.5 ± 15.5	0.6986
No	28	100 ± 0.0	95.7 ± 4.4	95.7 ± 4.8	95.7 ± 7.5	63.8 ± 22.2	63.8 ± 38.4	

* Log-rank Test

Table 4

Association between surveillance MR imaging and progression-free survival.

Number of MR Surveillances	% Progression-Free*		Total
	No Progression	Progression	
0–1	9 (81.8%)	2 (18.2%)	11
2–3	23 (85.2%)	4 (14.8%)	27
4–5	38 (97.4%)	1 (2.6%)	39
6–7	11 (100.0%)	0 (0.0%)	11
Total	81 (92.0%)	7 (8.0%)	88

* P=0.0216 (one-sided), P=0.0380 (two-sided) by Cochran-Armitage Trend Test