Radiation therapy for pediatric craniopharyngioma

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Object. The treatment of craniopharyngioma is highly controversial. Continued advances in limited surgery and radiation therapy have maintained excellent local disease control while minimizing treatment-related sequelae. Further analyses of outcomes are necessary to characterize the long-term effects of radiation therapy.

Methods. An extensive literature review was performed for all studies including radiation therapy, with or without surgery, for pediatric craniopharyngioma.

Results. The authors identified 32 papers describing radiation therapy for treatment of pediatric craniopharyngioma, with disease control ranging from 44 to 100%. Modern studies report at least 90% disease control with 5-year follow-up. Fifteen studies reported outcomes, demonstrating that more than two-thirds of patients treated with surgery and radiation therapy have favorable outcomes, and this rate is more than 85% in the modern era.

Conclusions. Conservative surgery and radiation therapy results in long-term disease control in pediatric patients with craniopharyngioma that is comparable to results obtained with radical surgery alone. However, children with craniopharyngioma remain vulnerable to late treatment failures and side effects from radiation therapy, including endocrinopathies, vasculopathies, and secondary tumors, which may be detrimental to the quality of life. Long-term follow-up beyond 5–10 years is necessary to assess tumor control relative to functional outcomes. (DOI: 10.3171/2010.1.FOCUS09297)

KEY WORDS • conformal radiation therapy • craniopharyngioma

IN 1932, Harvey Cushing described craniopharyngioma as “the most baffling problem which confronts the neuro-surgeon.”³⁶ In 2 detailed accounts, he described performing frontal craniotomies for cystic fenestration of these lesions, only to have to return for subsequent fenestration and cystic resection due to symptomatic cystic recurrence.^{21,40} The treatment of craniopharyngioma remains equally challenging and controversial in 2010. Although craniopharyngioma is pathologically benign in children, and should be curable by complete surgical removal, the morbidity and mortality associated with such attempts may be avoided by using a multimodality approach.

In 1961, Kramer et al.¹⁸ at the Royal Marsden Hospital became the first group to publish a report on limited surgery and radiation therapy for pediatric craniopharyngioma. They recognized that with fenestration alone, symptomatic regrowth of the cystic portion of the tumor could be expected within 3–6 months.¹⁴ By combining bur-hole aspiration with external-beam radiation therapy to 5000–6550 R, disease control was achieved in all 6 children who were reported to be “alive and well” at follow-up. Long-term disease control and outcomes in this group of patients were updated by Rajan et al.³² in 1993, in an expanded cohort of 77 children also treated with planned limited surgery and radiation. The 10-year

progression-free survival rate was 80% and overall survival was 77%. These results were comparable to major surgical series at that time.

Over the past decade, advances in image guidance and conformal radiation therapy have allowed for precise tumor localization and smaller treatment margins to limit the radiation dose to normal brain. Our preliminary experience with conformal radiation therapy for children with craniopharyngioma, both newly diagnosed and recurrent after prior surgery, showed that the volume of irradiation could be reduced without affecting the expected rate of tumor control. With a median follow-up period of 36.6 months (range 24.4–80 months), the 3-year estimate of progression-free survival was $90.3 \pm 7.3\%$.²⁵ Longitudinal evaluation of IQ in these patients showed a negative correlation between IQ and the volume of normal brain receiving doses in excess of 45 Gy as well as a variety of surgical factors, most notably extent of resection. In this preliminary experience in which conformal radiation therapy was used, the clinical target volume margin surrounding the cystic solid tumor complex was relatively large (10 mm) for a tumor known to lack invasive properties. The clinical target volume margin was subsequently reduced to 5 mm, and with additional follow-up, disease control outcomes parallel those achieved in earlier reports in which conventional radiation therapy was used. Despite these advances in reducing dose to normal tissue, we recognize that these children are vulnerable to

Abbreviation used in this paper: DI = diabetes insipidus.

radiation sequelae that may be delayed in presentation. We have evaluated these patients for other measures, including behavior, to show that good functional outcomes may be achieved, and to show the contribution of factors other than radiation therapy to late effects.⁸

In this review we compare results of combined surgery and radiation therapy for pediatric craniopharyngioma, distinguishing outcomes for pediatric patients separately from adults to account for differences in natural history, which may lead to bias in selecting treatment, reporting tumor- and treatment-related complications, and outcome measures including quality of life.

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We searched the literature for all published reports of radiation therapy for craniopharyngioma. Articles were excluded if specific results for children were not listed in the text. Table 1 summarizes the results of our review, based on series grouped by institution, number of patients, age, and follow-up and disease control, as reported in the original articles. Studies using statistical methods to estimate survival have been identified.

The earliest reports of radiation therapy for pediatric craniopharyngioma are from the Royal Marsden Hospital. Between 1952 and 1954 at that institution, 6 children underwent attempted stereotactic aspiration of cyst contents, followed by radiotherapy consisting of 2 arcs of 180°, delivering 5500 R over 6 weeks. Without the advantages of modern imaging, radiation was aimed at either the sella turcica for uncalcified tumors or at calcifications beyond the sella and presumed to be tumor. All 6 children were alive and free from disease recurrence over a follow-up period of 6 years.¹⁸ During the ensuing decades, 188 patients received conservative surgery followed by external-beam radiation therapy at the Royal Marsden Hospital, 72 of whom were younger than 16 years of age. This represents experiences with one of the largest and most mature patient groups. During this time period, the linear accelerator replaced ⁶⁰Co radiation, allowing for a more predictable and precise method of delivering radiation therapy. Only 8 of these children experienced disease progression, resulting in an estimated progression-free survival rate of 84% when measured beyond 10 years.^{1,33}

In addition to advances in the delivery of radiation with the linear accelerator, CT scans became readily available in the 1970s, as did the operating microscope. Many centers began retrospectively stratifying children into treatment groups for analysis of outcomes. At the University of California, San Francisco, patients who underwent biopsy sampling or cyst resection and radiation had 100% disease control, whereas in more than half of the children undergoing subtotal resection and radiation, the treatment failed.^{19,36,44} Similarly, children treated with conservative surgery and radiation in Boston experienced 95–100% disease control, whereas patients treated with subtotal resection and radiation only achieved 67–83% disease control.^{9,38} Sung⁴² reported 87% disease control with minimal surgery and radiation therapy, and 72% disease control for patients undergoing subtotal surgery

at Columbia. Overall, despite advances in neuroimaging and surgical technique, these results suggested that extensive resection does not improve disease control rates when adjuvant radiation therapy is used.

More modern studies conducted between 1980 and 2000 confirmed that conventional radiation therapy resulted in disease control rates ranging from 79 to 84% at 10 years.^{28,30,41} These series also analyzed many treatment-related factors involving the delivery of radiation therapy. Moon et al.²⁸ analyzed the timing of radiation therapy following surgery and found no significant difference between early and late treatment. Radiation therapy was also found to be highly effective as salvage therapy for patients in whom initial surgery failed.^{25,30,41}

Since 1998, in an effort to reduce the side effects, we have prospectively used conformal and intensity-modulated radiation therapy for the treatment of craniopharyngioma instead of conventional radiation therapy, which in the past included large, parallel, opposed beams. Modern radiation therapy treatment planning involves the use of CT imaging to define the frame of reference and calculate radiation dose. Registration of MR imaging data has further refined target delineation, which is based on the gross tumor volume that includes the entire residual solid and cystic tumor. Relative to the start of treatment, the timing of imaging and the acquired sequences ensures delineation of the proper target and reduces error associated with changes in the tumor over time. Imaging during therapy is critical, because these tumors are known to demonstrate cyst enlargement in response to irradiation. The target for treatment planning comprises the gross tumor volume, defined above, which is then surrounded by the clinical target volume margin to account for subclinical tumor infiltration and uncertainty in interpretation. Our current clinical target volume margin is 5 mm, and may be anatomically constrained at interfaces (for example, bone) where invasion is unlikely. Others have reported applying smaller margins with increasing requirements for stereotactic localization. Finally, the clinical target volume margin is surrounded by a geometrical margin called the planning target volume margin. This margin has been reduced to approximately 3 mm for daily clinical radiotherapy with the advent of linear accelerator on-board imaging systems, which are capable of daily cone-beam CT imaging. As the margins continue to shrink while practitioners gain more experience, it is critical that the images used to define the target have compatible resolution. In our experience, 3D MR imaging using postcontrast T1-weighted, T2-weighted, and postcontrast T2-weighted FLAIR imaging appear to be most useful. The T2-weighted imaging is critical at interfaces involving normal brain, whereas the post-contrast T2-weighted FLAIR imaging is key to defining tumor that interfaces with CSF. Our disease control for patients treated with surgery and radiation therapy is 90 and 85% at 3 and 5 years, respectively.²⁵ Puget et al.³¹ have reported no treatment failures with this approach at a 14-month follow-up.

Patients treated with focused radiation require imaging during treatment to monitor for cyst progression, which may occur early or late during the treatment

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TABLE 1: Literature review of radiation therapy for pediatric craniopharyngioma*

Authors & Year	Pts' Median Age in Yrs (range)	No. of Pts	FU (yrs)	% Disease Control
Kramer et al., 1961	10 (6–14)	6	6	100
Bloom et al., 1990		27	10	96
Rajan & coll, 1993, 1997	<16	72	10	87†
McMurry et al., 1977	<18	6	10	77
Lichter et al., 1977	10 (4–17)	7	6	71
Thomsett et al., 1980	9.2 (1.8–17.2)	7	4.5	82
Richmond et al., 1980	<20			
STR + RT		12	5	44
bx + RT		8	5	100
Onoyama et al., 1977	<25	12	10	77
Thompson et al., 1978	10 (5–18)	5	3.5	60
Shapiro et al., 1979				
STR + RT	7.10	7	9.4	50†
bx + RT	7.93	22	3.3	100†
Cabezudo et al., 1981	<15	9	3	100†
Sung, 1982	<15	14	10	
STR + RT				72
bx + RT				87
Calvo et al., 1983	10 (3–19)	11	6	100
Hoogenhout et al., 1984	<15	12	10	86†
Manaka et al., 1985	<14	21	10	63†
Clayton et al., 1988	9.5 (1–16)	10	6.3	100
Sorva et al., 1988	11 (1–18)	22		
STR + RT			5	100
bx + RT			5	100
Wen et al., 1989	<18	8	5	100
Shillito, 1986		10		
STR + RT	3.45 (11 mos–15 yrs)	6	10	67
bx + RT	11.4 (6–13)	4	10	100
Fischer et al., 1990		27	10	
STR + RT	7.4	4	11	83
bx + RT	9.6	16	10	95
Danoff et al., 1983	8 (3–19)	19		
STR + RT			10	50
bx + RT			10	83
Weiss et al., 1989	10 (3–14)	5	7	80
Regine & coll, 1992, 1993	<16	19	10	75
Hetelekidis et al., 1993		37	4	86
Stripp et al., 2004	8.5 (1.5–24)	18	10	84†
Moon et al., 2005	<20	15	10	80†
Pemberton et al., 2005	<15	28	10	79†
Habrand et al., 1999	7.4 (2–15)	37	10	56†
Puget et al., 2007		22		100
STR + RT (retrospective)	7.5 (4–16)	8	10	100
STR + RT (prospective)	7.9 (2–14)	10	1	100
Lin et al., 2008	9 (2–14)	11	10	100†

(continued)

TABLE 1: Literature review of radiation therapy for pediatric craniopharyngioma* (continued)

Authors & Year	Pts' Median Age in Yrs (range)	No. of Pts	FU (yrs)	% Disease Control
Merchant et al., 2002	7.3 (3–18)	15	6	94
Merchant et al., 2006	7.3 (3–18)	28	3	90†

* The median radiation doses ranged from 50 to 55 Gy. Articles from the same institution are grouped together and designated by shading. Abbreviations: bx = biopsy; coll = colleagues; FU = follow-up; Pts = patients; RT = radiation therapy; STR = subtotal resection.

† Studies that include statistically based survival estimates.

course.³³ Our current protocol includes weekly MR imaging, rapid assessment of changes in the target volume through imaging registration, and development of a new (adaptive) treatment plan when the gross tumor volume intersects with the clinical target volume at any point. Although there is no consensus in the literature on the treatment dose and fractionation schedule, the majority of series limited radiation dose to 50–55.8 Gy in children, delivered in 1.5- to 2.0-cGy fractions, 5 days per week for a period of 6 weeks. Concerns about the maximum dose to the optic chiasm and optic nerves precludes treatment to higher doses.

Side Effects After Radiation Therapy

Treatment-related side effects of radiation therapy have been well described in the literature, and include endocrine, visual, and cognitive sequelae as well as vasculopathy and secondary malignancies. Side effects may occur acutely, but are generally considered to be insidious. Regardless of their timing, they have the ability to affect the quality of life of these children.¹⁶

Visual Outcomes

Visual deterioration occurring during radiation therapy has been well documented, and is usually attributed to cystic progression and/or hydrocephalus.³³ Craniotomy and tumor decompression is sometimes required, but more often cyst aspiration alone reverses vision loss when performed in a timely manner. Aspiration may need to be performed repeatedly. The historical incidence is approximately 14%.³³ In our series, up to 46% of patients required cyst aspiration in the time period immediately before, during, or after radiation therapy.²⁵ Optic neuropathies and/or necrosis may also occur secondary to radiation therapy, and appear to be dose dependent.^{11,13,25,30,32,34,35,41,46} Flickinger et al.¹⁰ reported on 3 children in whom optic neuropathy developed at a radiation dose in excess of 60 Gy. We have not experienced any occurrences of optic neuritis or necrosis when the optic apparatus is treated to 54–55.8 Gy in 1.8-Gy fractions, a consensus dose in the literature.²⁷ We recently reviewed a cohort of 62 children, and found that 38 (61%) had normal vision, 14 (23%) had mildly to moderately impaired vision, and 10 (16%) had severely impaired vision at the start of irradiation. With extended follow-up, none of the patients had clinically significant changes in their vision that were not attributed to tumor progression. Only 5% required craniotomy for decompression when cystic change affected vision early

after radiation therapy, and placement of an Ommaya reservoir was considered not to be feasible.

Endocrine Outcomes

Hypothalamic-pituitary dysfunction may result from the tumor burden alone; however, progressive pituitary dysfunction develops in the months to years following radiation therapy and must be closely monitored.^{11,12,25} With long-term follow-up we have found that up to 70% of children require growth hormone supplementation, 90% require thyroid replacement, 40% require replacement for hypogonadism, and 75% require cortisol supplementation. The incidence of DI after radiotherapy is strictly related to changes in the tumor complex that mechanically impact the pituitary. In general, DI is not considered a common complication of irradiation. The incidence of the more common endocrine deficiencies appears to be dose dependent. At levels higher than 60 Gy it may be as high as 80%, versus 36% incidence at lower doses.³⁴

Cognitive Outcomes

Early attempts to quantify the effects of surgery and adjuvant therapy on cognitive outcomes demonstrated that patients treated with primary radiation for craniopharyngioma had less frontal lobe dysfunction than patients who underwent radical excision.⁴ As radiation treatment has become more conformal, with a reduction in dose to the normal brain, children are tolerating radiation therapy without treatment-related decline.^{9,25,26,28,30,32,35,41} Our results with serial neuropsychometric testing show that overall IQ remains stable through 5 years of follow-up; however, there are factors that predispose some patients to worse outcomes. These characteristics include younger patients (age < 7 years) and those with hydrocephalus treated with shunt insertion, large cystic tumors requiring multiple aspirations, extensive surgery, and DI.²⁵ Jalali et al.¹⁵ also demonstrated that IQ remains stable over a 2-year period, and that age < 15 years was a significant cause of decline, as was dose to the temporal lobe.

Functional Outcomes and Quality of Life

Fifteen articles published during the past 50 years have reported on functional and neurological outcomes following radiation therapy. The first children treated in a combined-modality approach were reported to have a 6% disability rate, with a median follow-up of 12 years.³² With the use of more standardized scales of quality of life and performance status, including the Wen classification

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index, Wechsler IQ and achievement tests, and Health Utility Index, 42–86% of patients treated with surgery and conventional radiation therapy have experienced a favorable functional outcome, defined as limited disability and functional independence, with improved scores in the more modern treatment era (Table 2). With a conversion to conformal radiation therapy, at least 85% of patients have a favorable outcome, as determined by cognitive testing.²⁶

Cerebrovascular Disease

Radiation therapy targeted at the sellar/suprasellar region will unfortunately also include the intracranial carotid arteries and the circle of Willis. Liu et al.²² reported on 6 patients in a series of 20 who developed a vasculopathy on neuroimaging after receiving radiation therapy for craniopharyngioma. Retrospective studies of radiation therapy directed at the sellar/suprasellar region have demonstrated an incidence as high as 21% for cerebrovascular events.¹⁷ The treatment of vasculopathy and moyamoya disease should be approached systematically and cautiously by experienced caregivers, because the risks associated with treatment have been considerable. The relative risk of developing moyamoya has been estimated to increase by 7% for every 100 cGy increase in radiation dose above 5000 cGy. The delay to occurrence is approximately 5–12 years.^{12,45}

Secondary Malignancies

The risk of a radiation-induced secondary malignancy is estimated to be 1.9% at 10 years, and remains a primary concern when managing craniopharyngioma in these children.¹⁶ In the largest single-institution study of 173 patients who were treated with conservative surgery and radiation therapy, no secondary malignancies were reported at a median follow-up of 12 years.³² Of the 626 patients in our literature review, the majority of whom received conventional radiation, there are only 4 reports of secondary malignancies. These were all high-grade glioma, of which the patients subsequently died.^{9,11,38} In the modern treatment era, in which radiation is delivered in a conformal fashion, minimizing the dose to normal tissue, the rate of secondary malignancy may decline. The development of malignant craniopharyngioma after radiation therapy is considered a secondary malignancy by transformation, and it is rare.

Conclusions

We have reviewed the role of radiation therapy in the treatment of pediatric craniopharyngioma at more than 20 major medical centers worldwide over the course of nearly 50 years. When craniopharyngioma is treated using a multidisciplinary approach involving neurosurgeons, neurooncologists, and radiation oncologists, conservative surgery and radiation therapy results in long-term disease control in pediatric craniopharyngioma, and the control is comparable to results obtained with radical surgery alone. However, our results at present are limited to studies with only 5- to 10-year reported

TABLE 2: Literature review of neurological outcomes after radiation therapy for pediatric craniopharyngioma

Authors & Year	% Favorable Functional Outcomes
Kramer et al., 1961	83
Rajan & coll, 1993, 1997	94
Lichter et al., 1977	57
Thomsett et al., 1980	89
Sung, 1982	54
Shillito, 1986	
STR + RT	50
bx + RT	75
Fischer et al., 1990	
STR + RT	67
bx + RT	86
Danoff et al., 1983	79
Weiss et al., 1989	80
Regine & coll, 1992, 1993	42
Pemberton et al., 2005	75
Habrand et al., 1999	66
Puget et al., 2007	
STR + RT (retrospective)	76–80
STR + RT (prospective)	95
Lin et al., 2008	91
Merchant et al., 2002	85

outcomes. At present children with this disease have an average life span of 75 years. Children with craniopharyngioma remain vulnerable to late treatment failures and side effects from radiation therapy including endocrinopathy and vasculopathy, which may have a detrimental impact on quality of life. Long-term follow-up beyond 5–10 years is necessary to assess tumor control relative to functional outcomes.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: TE Merchant. Acquisition of data: TE Merchant, EN Kiehna. Analysis and interpretation of data: TE Merchant, EN Kiehna. Drafting the article: TE Merchant, EN Kiehna. Critically revising the article: TE Merchant, EN Kiehna. Reviewed final version of the manuscript and approved it for submission: TE Merchant, EN Kiehna. Statistical analysis: TE Merchant, EN Kiehna. Administrative/technical/material support: TE Merchant. Study supervision: TE Merchant.

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