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CLINICAL STUDY

Disease Control after Radiotherapy for Adult Craniopharyngioma: Clinical Outcomes from a Large Single-Institution Series

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Abstract

Purpose To report disease control and treatment-related side effects among adult patients with craniopharyngioma treated with radiotherapy.

Methods We performed a single-institution review of adult patients (> 21 years old) with craniopharyngioma treated with radiotherapy either definitively or postoperatively for gross residual disease. We report disease control, survival, and radiotherapy-related side effects.

Results A total of 49 adult patients with craniopharyngioma were included, 27 of whom were treated at initial presentation and 22 for recurrent disease following initial surgery and observation. Overall, 77% received radiotherapy postoperatively (either after primary surgery or surgery for recurrence). With a median clinical and radiographic follow-up of 4.2 (range, 0.4–21.6) years and 3.0 (range, 0–21.5) years, the 5- and 10-year local control rates were 100 and 94%, respectively. The 5- and 10-year overall survival rates were 80 and 66%, respectively. Eleven percent of patients experienced grade 2 vision deterioration and 18% suffered grade 2 endocrinopathies following radiotherapy.

Conclusions Radiotherapy provides excellent disease control with acceptable toxicity among adult patients with craniopharyngioma. These data support the use of fractionated radiotherapy in adult patients with recurrent or gross residual disease after surgery. For inoperable patients or those with moderate or high surgical risk to neurologic and/or vascular structures, we advocate for limited surgical resection and postoperative radiotherapy to balance optimal tumor control with tumor- and treatment-related morbidity.

Keywords Radiation therapy · Cancer outcomes · Central nervous system tumors · Benign tumors · Radiotherapy toxicity

Introduction

Craniopharyngioma is a benign epithelial tumor of the suprasellar region which occurs along the path of the hypophyseal-pharyngeal duct. Craniopharyngiomas are believed to arise from remnants of squamous cell rests within Rathke's pouch. They are rare tumors affecting approximately 1 in 1.3 million people and, although they have a bimodal age distribution (5–15 years and 65–74 years), they occur across the age spectrum. Despite their "benign" designation, due to their location relative to critical neurologic and neurovascular structures (such as the optic apparatus, pituitary gland, hypothalamus, Circle of Willis, and brainstem) they are responsible for significant tumor- and treatment-associated morbidity and mortality. While the management of pediatric craniopharyngioma occupies much of the research landscape, its incidence in the adult population is higher overall, and the burden of tumor- and treatment-related morbidity in adults can be similarly devastating with vision deficits, endocrinopathies, diabetes insipidus, metabolic consequences, hypothalamic injury, and decline in functional status and quality of life [1]. Surgical resection remains the mainstay of diagnosis and initial management of craniopharyngioma; however, increasing evidence supports the role of minimal resection/surgical decompression followed

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by postoperative radiotherapy (RT) [2]. This is particularly relevant when complete surgical resection is expected to result in injury to the hypothalamic–pituitary–adrenal axis or optic apparatus. Especially in the adult population where the late effects of radiotherapy (such as radiation-induced malignant neoplasms, cerebrovascular accidents, and neurocognitive decline) are less impactful than in the pediatric and young adult populations, radiotherapy as a component of craniopharyngioma management offers high disease-control rates and low rates of significant morbidity. Nevertheless, owing to remnants of historical standards cautioning the use of radiotherapy, a lack of distinction between the risks of radiotherapy side effects in adults compared with children, and a general lack of standardization of craniopharyngioma treatment, widespread adoption of a combined-modality approach has been slow. Herein, we describe our clinical experience at the University of Florida utilizing radiotherapy in the management of adult craniopharyngioma. We describe our outcomes with respect to local disease control, overall survival, and treatment-related complications. The current study represents one of the largest series of adult patients treated with radiotherapy for craniopharyngioma.

Methods

We retrospectively reviewed the medical records of 49 consecutive adult patients treated with radiotherapy for craniopharyngioma between 1985 and 2020. Patients provided informed consent to be enrolled on an institutional review board-approved outcomes tracking protocol (IRB201802930). Patients younger than 22 years old at the time of radiotherapy were excluded. No patient received prior radiotherapy. Forty-eight of the 49 patients had pathologic confirmation of craniopharyngioma and 1 patient had a radiographic diagnosis only. The date of diagnosis was the date of the first confirmatory imaging study identifying the craniopharyngioma. Patient and disease characteristics are detailed in Table 1. Treatment details are described in Table 2.

Table 1 Patient and disease characteristics ($N=49$)

Characteristic	Value
Sex	
Male	25 (51%)
Female	24 (49%)
Age at diagnosis, median	45 (range, 17–72) years
Age at radiotherapy, median	46 (range, 22–73) years
Tumor histology (N = 48)	
Adamantinomatous	41 (85%) patients
Papillary	7 (15%) patients
Tumor type	
Cyst dominant tumor	31(63%) patients
Solid dominant tumor	18 (37%) patients
Disease at time of radiotherapy	
Primary	27 (55%) patients
Recurrent	22 (45%) patients
Clinical follow-up, median	4.2 (range, 0.4–21.6) years
Radiographic follow-up, median	3.0 (range, 0–21.5) years

Table 2 Treatment details (N = 49)

Characteristic	Value
Number of surgeries prior to RT	
0	1 (2%) patient
1	32 (65%) patients
2	12 (27%) patients
≥ 3	3 (6%) patients
Timing of radiotherapy	
Post-op at presentation	26 (53%) patients
Definitive RT at presentation	1 (2%) patient
Post-op at recurrence	12 (25%) patients
Definitive RT at recurrence	10 (20%) patients
Radiation dose, median	54 GyRBE (range, 50.4–61.2)
Radiation modality	
2D or 3D CRT	27 (55%) patients
Intensity-modulated radiation therapy	7 (14%) patients
Proton beam therapy	15 (31%) patients

RT, radiotherapy; *Gy*, Gray; *RBE*, relative biological effectiveness; *2D*, two-dimensional; *3D CRT*, three-dimensional conformal radiation therapy

Radiotherapy treatment

Prior to 1996, patients ($n=10$) were treated with three-field 2-dimensional radiotherapy delivered with right and left laterals and an anterior–posterior field. After 1996, patients were simulated using a 3-dimensional computed tomography (CT) scan ($n=39$, 80%). Patients were immobilized using a thermoplastic mask and most used a bite piece. Target volumes were typically generated as follows: The gross tumor volume (GTV) included the tumor resection bed and gross residual tumor. The clinical target volume (CTV) was generated by adding a 5- to 10-mm expansion to the GTV. Since 2012, the CTV expansion has been limited to 2–3 mm into uninvolved brain parenchyma or barriers of tumor spread. The planning target volume (PTV) was generated by adding a 3- to 5-mm isotropic expansion to the CTV. In the early 3-dimensional-conformal radiotherapy era (mid/late 1990s), target volumes included the GTV with a 10- to 15-mm PTV expansion (and no CTV expansion). Since ~ 2012,

target delineation was informed by the co-registration of contrast-enhanced, pre- and postoperative magnetic resonance imaging (MRI) to the radiation planning CT scan. Our median total prescription dose was 54 GyRBE (range, 50.4–61.2 GyRBE). One patient was treated to a dose above 55.8 Gy while all others received doses between 50.4 Gy and 55.8 Gy. The patient who received a higher dose was treated early in this series (in 1987) and received 61.2 Gy in 1.8-Gy fractions. Although this dose was not uncommon for the era, it is an outlier for this cohort. Additionally, 12 photon patients received twice-daily (BID) fractionation with 1.2 Gy per fraction. The range of doses for patients treated BID was 50.4–55.2 Gy given at the discretion of the treating physician. BID fractionation was selected due to physician concerns about the risk of optic pathway injury. Our current standard dose is 54 Gy delivered in 1.8 Gy fractions. Twenty-seven patients (55%) underwent imaging during radiotherapy to assess for solid or cystic tumor changes requiring intervention and/or treatment replanning. Sixteen patients completed weekly MRI evaluation of the target volume during radiotherapy. These patients underwent imaging on a 0.23 T open bore MRI without contrast (Philips Panorama MR Scanner, USA). Two patients underwent on-treatment diagnostic MRIs and nine patients had daily CBCT imaging to evaluate the tumor during radiotherapy. Twenty-two patients had no radiographic tumor assessment during RT. Over the latter years of this study period, proton radiotherapy has become the predominant modality used for treatment of adult craniopharyngiomas at the University of Florida. Patients seen in our Jacksonville clinic are offered proton radiotherapy and patients seen in our Gainesville clinic are referred for protons based on age ($\leq$40 years old) or patient preference. Otherwise, they are treated with intensity-modulated radiotherapy (IMRT)/volumetric modulated arc therapy (VMAT). Of note, all patients with pediatric craniopharyngioma ($\leq$21 years old) are treated with proton radiotherapy.

Patient Follow-up

Patients underwent follow-up clinical examination and imaging 1–3 months after completing radiotherapy. Clinical and imaging follow-up was recommended at 3- to 6-month intervals until 2–3 years following radiotherapy, at which time clinical and imaging follow-up could be extended based on tumor control at the discretion of the treating physician. Post-radiotherapy ophthalmology and endocrinology follow-up examinations were recommended. Three patients in our series died within 6 months of completing radiotherapy, 2 of whom died of disease or surgical complications after developing post-RT cystic enlargement (see section below, "Transient Cyst Enlargement during and after Radiotherapy"). A third died of unknown causes 6 months after completing radiotherapy. His tumor showed regression on imaging 6 weeks prior to his death. These patients were excluded from the late radiotherapy toxicity analysis.

Radiographic tumor assessment

Two patients treated prior to 1986 underwent CT imaging for tumor assessment. All other patients underwent MRI surveillance for the assessment of local disease control. Formal criteria have recently been established to define local craniopharyngioma progression and treatment failure following radiotherapy. The following two sets of criteria were applied to the patients in this series: The Pediatric Brain Tumor Consortium (see PBTC-039 Trial) criteria defines progression at 6–12 months after radiotherapy as a $\geq$25% increase in the product of the greatest perpendicular diameters of the solid component and $\geq$0.4 cm increase in each of at least two dimensions of the solid component. Twelve months after completing radiotherapy, progression is defined as a $\geq$25% increase in the product of the greatest perpendicular diameters of the solid component or $\geq$0.4 cm increase in each of at least two dimensions of the solid component. Cyst enlargement according to PBTC guidelines is determined 12 months after completing radiotherapy and defined by a continued increase in the cystic component on two serial MRI scans performed at least 4 weeks apart, or accumulation of the cyst following one or more cyst aspirations) [3]. The second set of criteria, established by St. Jude Children's Research Hospital (Memphis, TN), defines progression as progressive, measurable growth of the solid portion of the tumor or the cystic portion of the tumor complex more than 3 years after treatment [4]. For local control calculations, disease progression by either PBTC or St. Jude criteria were considered a treatment failure.

Statistical analysis

SAS version 9.4 and JMP Pro version 16.1.0 were utilized for statistical analysis (SAS Institute, Cary, NC). Basic descriptive statistics are provided for this series. Medians rather than means estimate the center of a continuous distribution to avoid the impact of outliers. The Kaplan–Meier product limit estimator was utilized to estimate overall survival. The cumulative incidence method with intercurrent death treated as a competing risk was instead utilized to assess local control and cause-specific survival.

Results

Forty-nine adult patients with craniopharyngioma were treated with radiotherapy and were included in this study. The median age at diagnosis was 45 years old (range,

17–72). The median age at the time of radiotherapy was 46 years old (range, 22–73). The most common presenting symptoms were vision changes and headaches, which affected most patients. Patients' presenting symptoms are shown in Table 3. All patients had gross disease at the time of radiotherapy. Of the 48 patients with pathologic confirmation of craniopharyngioma, 41 (85%) had adamantinomatous subtype and 7 (15%) had papillary subtype. Among the 7 patients with papillary craniopharyngioma, only 2 were diagnosed in the era of BRAF mutation testing (after 2014). Both of these patients had BRAF V600E mutations. One patient was treated with definitive radiotherapy after radiographic diagnosis of craniopharyngioma (partially solid and cystic suprasellar mass with dystrophic calcifications). She was a 25 year old woman who presented with amenorrhea due to hyperprolactinemia and low gonadotropin levels. After consulting with multiple neurosurgeons and radiation oncologists, and considering treatment options including radical surgery, subtotal resection and postoperative RT, or definitive RT, she elected to receive definitive proton RT. Three years after RT, she has had significant tumor regression and has experienced no late RT-related complications. Just over half of the patients (55%) received radiotherapy treatment after their initial presentation, while 44% received radiotherapy for recurrent disease following initial surgery and observation. Nearly half of the patients treated for recurrence received only salvage radiotherapy (without surgical salvage at the time of recurrence). Of the 22 patients treated with radiotherapy for recurrent disease, the median interval to recurrence from initial surgery to the time of imaging recurrence was 21 (range, 2–174) months.

Table 3 Patient presenting symptoms (N = 49)

Presenting sign/Symptom	Number of patients (%)
Vision changes	33 (67)
Headaches	26 (53)
Endocrinopathy	16 (33)
Nausea/vomiting	10 (20)
Cognitive/memory changes	8 (16)
Hydrocephalus	4 (8)
Photophobia	4 (8)
Personality changes	3 (6)
Other	
Taste/smell changes	1 (2)
Seizure	1 (2)
Fatigue/generalized weakness	1 (2)

Local control and survival outcomes

With a median clinical follow-up of 4.2 (range, 0.4–21.6) years and a median radiographic follow-up of 3.0 (range, 0–21.5) years, the 5-year actuarial local control rate was 100%. There was one local failure in our cohort following radiotherapy, which occurred 73 months after definitive radiotherapy for treatment of recurrent disease. The 5-year cause-specific survival and overall survival rates were 96% (95% CI, 85–99%) and 80% (95% CI, 65–90%), respectively. Among the 12 patients in our series with tumor control 10 years after RT and long-term clinical and radiographic follow-up (range, 11–21.6 years), no late recurrences occurred.

Transient cyst enlargement during and after radiotherapy

Of the 27 patients with imaging surveillance during radiotherapy to assess for tumor changes, only 1 (4%) had changes requiring a modification in the radiotherapy treatment plan due to changes in the target volume. After receiving 18 Gy, this patient underwent an MRI which revealed multicystic enlargement of his craniopharyngioma. The treatment plan was modified to account for these changes and treatment was completed to a total of 54 Gy. The 3-month post-treatment MRI showed an interval decrease in the cystic tumor components.

Six patients (12%) experienced cyst enlargement on their first post-radiotherapy MRI. The mean interval from RT completion to cyst enlargement was 1.7 (range, 1–3) months. Due to the time interval from radiotherapy, these were not considered radiotherapy-related treatment failures but rather cases of the transient cystic pseudoprogression commonly observed in the year following surgery and radiotherapy. Three of the six patients had moderate/severe symptoms due to cyst expansion, all 3 of whom experienced acute vision deterioration with fatigue ($n = 2$) or cognitive changes, headaches, nausea ($n = 1$). These three patients underwent a second craniotomy with cyst decompression and tumor debulking. One of these patients died 4 months after surgery from complications of panhypopituitarism. A second died of postoperative complications from salvage surgery. The third patient underwent a near-total tumor resection and remained free of disease progression until his non-tumor-related death 14 years later.

Three additional patients with postradiotherapy cyst expansion were asymptomatic ($n = 2$) or had mild symptoms (headaches, $n = 1$) despite increased mass effect due to cyst enlargement. All three patients underwent close clinical and radiographic follow-up every 1–3 months, and subsequent imaging showed dramatic regression with cyst collapse and minimal or no residual solid or cystic tumor at the most

recent radiographic follow-up (Fig. 1). The time from treatment completion to radiographic cyst shrinkage in these patients was 2–7 months.

Radiotherapy treatment-related toxicity

Excluding three patients with inadequate clinical follow-up (< 6 months) or who died within 6 months of completing radiotherapy, 46 patients were included in the treatment-related toxicity analysis. Among these patients, the median clinical follow-up was 5.0 (range, 0.5–21.6) years. Two patients (4%) experienced ≥ grade 3 treatment-related toxicity. There were no grade 5 complications attributable to radiotherapy. The first of these was a 29-year-old woman who had a right thalamic stroke 29 months after radiotherapy. This left her debilitated and requiring significant care (Eastern Cooperative Oncology Group performance status 3).

The second patient experienced grade 3 memory impairment, which developed at age 63 years, 17 years after completing radiotherapy. Although not definitively attributable to radiotherapy or surgery, they cannot be excluded as a cause.

Five patients (11%) developed new or progressive visual field or visual acuity deficits (grade 2). There were no cases of blindness following radiotherapy (unilateral or bilateral). One patient developed acquired nystagmus (grade 2) 4 years after completing radiotherapy, which was attributed to radiotherapy versus chronic use of anxiolytic medications.

Among the 33 patients with intact pituitary function at the time of diagnosis and prior to surgery, 22 patients (67%) developed immediate postoperative pituitary dysfunction or panhypopituitarism. Eleven patients had normal pituitary function after surgery and prior to radiotherapy. Among these 11 patients, with a median follow-up of 84 (range, 3–257) months after radiation, 2 (18%) developed hypopituitarism (grade 2) attributable to surgery and radiotherapy.

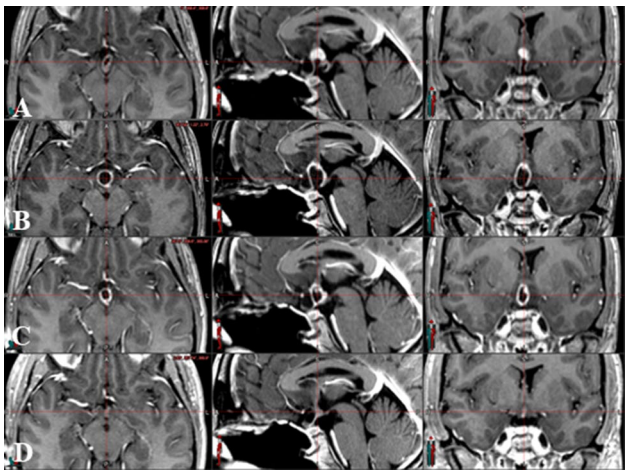

Fig. 1 Postradiotherapy transient cyst expansion is shown for a 37-year-old patient with papillary craniopharyngioma after subtotal resection and postoperative radiotherapy. Residual tumor is identified by red crosshairs. (**A**) Postoperative, preradiotherapy magnetic resonance image (MRI) with residual cystic tumor with enhancing cyst walls. (**B**) Three-month postradiotherapy MRI shows transient cyst expansion. The patient remained asymptomatic and continued close follow-up. (**C**) Five-month postradiotherapy MRI shows spontaneous cyst regression. (**D**) Forty-two-month postradiotherapy MRI shows minimal residual enhancing tissue with no residual cyst

Discussion

Craniopharyngioma is a histologically benign tumor, but its consequences as well as its treatment can be devastating, resulting in high rates of vision impairment, endocrinopathies, hypothalamic syndromes, and reduced quality of life [1]. While much of the interest in craniopharyngioma is in the pediatric population, its incidence is greatest among adults who are at risk of similar consequences from the disease and treatment [4, 5]. Gross total resection provides excellent disease control; however, without careful patient selection, patients may experience unnecessary surgical complications [5–7]. Incomplete resection, on the other hand, leads to high rates of local recurrence resulting in additional operations with increased morbidity due to recurrent tumor and/or salvage treatments [7, 8]. A systematic review by Akinduro et al. of adult craniopharyngioma patients demonstrated a tumor control benefit with gross tumor resection but increased risk of pituitary (twofold increase) and hypothalamic (threefold increase) complications compared to subtotal resection [6]. Numerous studies have indicated no compromise in overall or cause-specific survival with salvage radiotherapy as compared to adjuvant (that is, immediate postoperative) radiotherapy [9–12]. However, the risks associated with recurrent tumors and surgical salvage can be avoided with early radiotherapy [5, 7, 13]. Moon et al. compared cohorts of adult and pediatric craniopharyngioma patients treated with adjuvant (immediate postoperative) or salvage radiotherapy (with or without salvage surgery) [14]. They observed no overall survival or progression-free survival differences between the patients treated with adjuvant radiotherapy versus salvage therapy; however, patients in the adjuvant radiotherapy cohort had lower rates of diabetes insipidus, visual acuity loss, and visual field deficits. Muller et al. longitudinally followed 102 childhood craniopharyngioma survivors and confirmed that tumor relapse or progression had a negative impact on long-term quality of life [14].

Limited surgical resection combined with postoperative radiotherapy provides disease control comparable to gross total resection—balancing the benefits of surgical debulking/

decompression with the risks of surgical morbidity [2, 8, 15, 16]. Although the addition of radiotherapy after limited surgical resection carries the risk of radiotherapy toxicity compared to surgery alone, in adults the risks of severe radiation-related treatment complications are low [10, 17].

Our series reports the outcomes of adult craniopharyngioma patients with gross residual tumor treated with radiotherapy. Of the patients in our series, 45% were treated for recurrent disease. We achieved 5- and 10-year actuarial local control rates of 100 and 94%, respectively. Our disease control rates are consistent with the post-radiotherapy 5- and 10-year local control rates of 95.3 and 92.1%, respectively, reported by Harrabi et al. [12]. Table 4 reviews the largest series reporting outcomes for adult patients treated with radiotherapy for craniopharyngioma.

Vision impairment is the most common presenting symptom of craniopharyngioma and is a source of significant morbidity and reduced quality of life. While postoperative radiotherapy carries the risk of vision impairment, in adult patients the risk appears reasonably low [18, 19]. In our series, 11% of patients had vision deterioration (grade 2). No instances of unilateral or bilateral blindness occurred. This rate of vision damage is comparable to the 7% rate of radiotherapy-related vision dysfunction reported by Masson-Cote et al. in their adult craniopharyngioma series and the 6% rate of radiation-induced optic neuropathy reported by Astradsson et al. in a prospective cohort [10, 17].

Endocrinopathies are another source of morbidity for craniopharygioma patients. More than 1/3 of adult patients present with hypothalamic-pituitary dysfunction, and more than half will experience hypopituitarism and/or hypothalamic dysfunction as a result of tumor resection [6, 19, 20]. Subtotal resection lessens the risk of hypopituitarism and permanent diabetes insipidus [6]. The addition of radiotherapy to subtotal resection in adults adds a relatively small risk of further pituitary dysfunction with a very-low risk of hypothalamic injury or diabetes insipidus. Eighteen percent of patients in our series developed a new endocrinopathy after radiation. This compares to a 20% rate of new endocrinopathies in the series reported by Masson-Cote et al. [10]. Both Astradsson et al. and Harrabi et al. reported no new cases of pituitary deficits following radiotherapy in their series [12, 17].

With advances in radiotherapy techniques (i.e., IMRT, proton beam RT), the risks of radiation-related complications may be lessened by reducing the dose to nearby critical structures, including the brainstem, hippocampi, dentate gyrus, carotid arteries, and anterior circle of Willis [21, 22]. Proton RT uses charged particles to reduce the integral radiation dose to normal surrounding tissues while delivering highly conformal treatment (see Supplemental Fig. 2). Early outcomes with proton therapy in adults and pediatric patients with craniopharyngioma are very promising for disease control and treatment toxicity [21, 23], although comparative data between the two treatment modalities are limited [24]. Our cohort contains patients treated with both proton and photon radiotherapy (31% and 69%, respectively). Nevertheless, due to the relatively small numbers of events (both treatment failures and toxicity), no statistical comparisons can be made between these modalities. Additionally, a significant difference in length of follow-up between the two cohorts (median follow-up of 3.3 years for proton and 7.1 years for photon patients) limits the ability to make meaningful comparisons. Of the 2 grade 3/4 complications in our entire group, 1 was in the photon cohort and 1 was in the proton cohort. Three patients in the photon cohort developed new post-RT endocrine deficits compared to four patients in the proton cohort. There were five patients (16%) in the photon cohort with post-RT vision deficits compared to 0 in the proton cohort. It must be emphasized that there are confounding factors that may account for these apparent visual toxicity differences.

Altogether, these data argue for a balanced approach to the management of adult craniopharyngioma, weighing the risks of aggressive surgical resection with those of postoperative radiotherapy. In patients with moderate and

Table 4 Literature review of studies on adult craniopharyngioma treated with radiotherapy

Series	Years	Total patients (Adult patients)	Median age (range), yrs	Median clinical FU, yrs	Local control at 10 yrs	Progression-free survival at 10 yrs (%)	Overall survival at 10 yrs (%)
Masson-Cote et al., 2013 [10]	1980–2009	53 (53 > 21 yo)	53 (22–76)	5.3[a]	NA	88	70
Pemberton et al., 2005 [11]	1976–2002	87 (59 > 15 yo)	NA	10.9[b]	NA	78	86
Harrabi et al., 2014 [12]	1989–2012	55 (47 ≥ 18 yo)	37 (6–70)	10.7[c]	92%	NA	83
Rutenberg et al., current series	1985–2021	49 (49 > 21 yo)	46 (22–73)	4.2[a]	94%	94	66

FU, follow up; *yrs*, years; *yo*, years old; *NA*, not available

[a]From date of completion of radiotherapy

[b]From date of first surgery

[c]From date of primary diagnosis

high surgical risk of neurovascular, endocrine, or optic pathway injury, patients are better served by conservative, subtotal resection followed by postoperative radiotherapy. Advances in targeted agents for particular tumor types will provide additional treatment options for management of this disease, as evidenced by early data from the Alliance A071601 trial investigating the efficacy of BRAF/MEK inhibition on papillary craniopharyngiomas (NCT03224767) [25].

An important observation in this series is the incidence of cystic tumor enlargement during or after radiotherapy. Cystic changes during radiotherapy necessitating treatment plan modifications are well-described [26, 27]. In our cohort, among the 26 patients with on-treatment imaging to assess for tumor changes, only 1 patient required treatment replanning during radiation, which may reflect biologic behavior or the generous CTV and PTV treatment margins of the era. Postradiotherapy transient cyst enlargement is also well documented, typically occurring within 6 months of treatment. In pediatric series, the rate of postradiotherapy cyst expansion ranges from 11 to 60% [24, 27, 27, 28]. In nearly all cases, spontaneous resolution and cyst regression occur without intervention. There are minimal data detailing this phenomenon in adults [21]. In our series, 12% of patients (6 of the 49) experienced postradiotherapy cyst expansion within 3 months of completing treatment. Three patients with postradiotherapy cyst expansion were symptomatic and underwent salvage craniotomy for cyst fenestration/tumor debulking. Two of these patients died from complications after surgery. The third patient underwent redo craniotomy with subtotal resection and lived another 14 years without disease recurrence. Three additional patients with asymptomatic cyst enlargement were closely monitored and had subsequent tumor regression (complete or near-complete solid and cystic tumor response) without requiring intervention (Fig. 1). Masson-Cote et al. reported that 9% of their adult patients required cyst aspiration within 6 months of completing radiotherapy (the total number of cases of cyst expansion was not reported). After simple cyst drainage, all of the tumors in their series remained controlled without additional interventions necessary [10]. While early intervention in the case of symptom development or mass effect on critical structures may be necessary, the risks associated with overly aggressive intervention should be balanced with the need for decompression. These cases should not be treated as radiotherapy failures, but should be managed with the minimum intervention necessary to prevent permanent injury by mass effect of the cyst, such as endoscopic cyst fenestration or ommaya placement. As evidenced in our cohort, craniotomy and debulking of the solid component of the tumor carries serious risk and may be unnecessary. If given time, most of these cases result in ultimate cyst regression [27, 27].

Limitations

The current study suffers from the weaknesses inherent to any retrospective review. Due to the rarity of this disease and despite this being one of the larger RT outcomes studies, we are limited by patient numbers. Additionally, the study spans a long treatment interval (35 years) during which time diagnostic imaging, surgical techniques, and RT techniques evolved.

Conclusions

Our data indicate excellent local disease control and reasonably low risks of multimodality toxicity in adult patients with craniopharyngioma. Our findings support the use of fractionated radiation for recurrent disease or gross residual disease after surgery. In cases of moderate or high surgical risk to neurologic, endocrine, or vascular structures, we advocate for limited surgical resection and postoperative radiotherapy as a means of balancing optimal tumor control with tumor- and treatment-associated morbidity.

Data Availability Statement

The authors agree to share anonymized data upon reasonable request by researchers.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11060-022-03983-z.

Author Contributions MR: conceptualization, methodology, formal analysis, investigation, writing—original draft; AH: investigation, writing—review and editing; DI: investigation, writing—review and editing; SH: investigation, writing—review and editing; DR: investigation, writing—review and editing; PF: investigation, writing—review and editing; CM: methodology, formal analysis, data curation, writing—review and editing; DT: investigation, writing—review and editing; RA: investigation, writing—review and editing.

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Declarations

Conflict of interests The authors report no conflict of interests.

Ethics approval This retrospective study was approved by the University of Florida Institutional Review Board.

Previous Presentations A subset of this patient cohort (14 patients) has been previously published: Rutenberg MS, Rotondo RL, Rao D, et al. Clinical outcomes following proton therapy for adult craniopharyngioma: a single-institution cohort study. *J Neurooncol*. Apr 2020;147(2):387–395. https://doi.org/10.1007/s11060-020-03432-9. https://pubmed.ncbi.nlm.nih.gov/32086697/.

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