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CLINICAL STUDY

Patterns of care and treatment outcomes of patients with Craniopharyngioma in the national cancer database

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Abstract To investigate the patterns of care and outcomes in patients with craniopharyngioma in the National Cancer Data Base (NCDB). This study included 697 patients (166 pediatric and 531 adult cases) treated for craniopharyngioma between 2004 and 2012 in the NCDB. Adjuvant radiotherapy (RT) was defined if within 6 months of surgery. Limited surgery (LS) was defined as biopsy or subtotal resection. Proportional-hazards models were used to evaluate associations between covariates and overall survival (OS). A time-dependent analysis of RT was performed to account for early deaths after surgery. Median follow-up was 46 months. Overall, 21% of patients received adjuvant RT. Of patients with known surgical extent (n = 195), 71% had LS. Utilization of adjuvant RT increased from 18% in 2004–2007 to 24% in 2008–2012. Patterns of care regarding adjuvant RT or LS were not significantly different between adult and pediatric patients. Tumor size, low comorbidity, and LS were associated with increased utilization of adjuvant RT. The 5-year OS among patients treated with LS, LS+RT, and gross total resection were 75, 85, and 82% (p = 0.02). On multivariate analysis of the 195 patients with known surgical extent, LS+RT was associated with improved OS compared to LS (HR 0.22, 95% CI 0.05–0.99, p = 0.04), but was not significant when early deaths (<2 months from surgery) were removed to adjust for immortal-time bias. Medical practice regarding surgical approach and adjuvant RT are similar for pediatric and adult craniopharyngiomas. Immortal-time bias may confound assessment of OS for adjuvant RT. Prospective studies comparing adjuvant RT versus observation after LS are warranted.

Keywords Craniopharyngioma · National Cancer Database (NCDB) · Radiation · Patterns of care · Surgery

Introduction

In the United States, craniopharyngiomas represent 1–3% of all primary intracranial tumors and 5–10% of pediatric brain tumors, with an incidence of approximately 350 new cases reported annually [1, 2]. Historically, craniopharyngioma has been treated with primary surgery with the goal of gross total resection (GTR). However, radical surgery can be challenging due to the close proximity of tumor to vital structures [3–5] and treatment-related morbidity including neurocognitive, pituitary, and hypothalamic dysfunction are commonly seen in patients treated with aggressive surgery [6, 7]. As a result, less invasive surgical approaches have gained acceptance in recent years, especially for pediatric patients [8]. In patients for whom GTR is not achievable without excess morbidity, a limited surgery (LS), which may include biopsy or subtotal resection (STR), followed by adjuvant radiation (LS+RT) is a reasonable treatment

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strategy [9]. Retrospective studies demonstrate that adjuvant radiation improves local control after limited surgery while reducing long-term sequelae, but it is not clear that adjuvant radiation improves survival [7, 10–13]. Indeed, several retrospective studies of adult craniopharyngiomas have reported equivalent survival between adjuvant and salvage RT after STR, and therefore routine use of adjuvant RT remains controversial, especially in adults [14, 15]. A survey of 102 adult and pediatric neurosurgeons in 2013 [16] showed that following STR, 18% never recommended RT, 41% recommended it in ≤50% of cases, and 35% always recommend RT. Following biopsy, 56% always recommend RT and 71% recommended RT in ≥90% of cases. There are no published randomized trials that compare adjuvant RT with salvage RT at the time of recurrence in patients receiving LS. Additionally, many previous studies included patients treated over several decades, which makes it difficult to generalize to patients treated with more modern techniques of surgery or RT.

The objective of the current study is to evaluate the recent pattern of care regarding the use of adjuvant RT and aggressive surgery and their outcomes for adult and pediatric patients with craniopharyngioma in the National Cancer Data Base (NCDB) after 2004.

Methods and materials

Data source and study population

The NCDB is a joint project of the American Cancer Society and the Commission on Cancer of the American College of Surgeons. The American College of Surgeons has executed a Business Associate Agreement that includes a data use agreement with each of its Commission on Cancer accredited hospitals. The NCDB, established in 1989, is a nationwide, facility-based, comprehensive clinical surveillance resource oncology data set that currently captures 70% of all newly diagnosed malignancies in the United States (US) annually. Data elements are collected and submitted to the NCDB from commission-accredited oncology registries using standardized coding and data item definitions, including details not available from Surveillance, Epidemiology, and End Results (SEER) registry, such as RT dose/technique, chemotherapy use/timing, and comorbidity. Deidentified data for pediatric (age ≤18) and adult (age >18) patients with histologically confirmed craniopharyngioma (histology code 9350-9352) were obtained from the NCDB participant user file. This study was exempted by the institutional review board.

The NCDB included 881 patients treated for craniopharyngioma from 2004 to 2012. Patients who had no survival data (n = 86), who did not have surgical confirmation (n = 87), or who lacked information on the status of adjuvant RT (n = 11) were excluded. A total of 697 remaining patients were analyzed. The following data were collected: demographic information, treatment, overall survival (OS), and surgical acute toxicity data which included length of inpatient admission after surgery and frequency of 30-day readmission after surgery. In the NCDB, medical comorbidities were defined using the Charlson/Deyo score [17] and were scored as 0, 1, or ≥2, not including patient's primary malignancy. In NCDB, the Charlson/Deyo score is a summary value of ten reported ICD-9-CM secondary diagnosis codes. A score of 1 indicates a secondary diagnosis of myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver disease, or diabetes. A score of 2 or above indicates multiple secondary diagnoses; or a secondary diagnosis of diabetes with chronic complications, renal disease, moderate or severe liver disease, AIDS, hemiplegia or paraplegia. The comorbidity score was calculated based on diagnosed conditions in the 1 year prior to diagnosis. The histology subtype was coded as adamantinomatous, papillary, or not otherwise specified. Tumor size was reported as the largest extent in a single dimension. Extent of surgery was only routinely coded for patients diagnosed after 2009 in the NCDB. For those with known surgical extent, treatment strategy was organized into: (1) limited surgery (LS, either biopsy or STR) followed by observation, (2) LS followed by adjuvant RT (LS+RT), and (3) GTR. Adjuvant RT was defined if RT was started ≤6 months after surgery while salvage RT was defined if thereafter. Patients in the LS group included those who received salvage RT.

The radiation dose and the equivalent dose in 2 Gy fractions (EQD2) was also collected. An alpha/beta ratio of 3 was used as a reasonable estimate for this benign histology. The equation used to calculate the EQD2 dose is $EDQ2 = D \times (d+3)/5$, where D is the total dose in Gy and d is the dose per fraction in Gy.

Statistical analysis

The χ^2 test and Fisher's exact test were used to evaluate patterns of care and other contingency tables, as appropriate. Logistic regression was used to determine odds ratios (OR). OS rates were determined using the Kaplan–Meier method and were compared between groups using log-rank statistics. The Cox proportional hazards model was used to determine significant contributors to OS and to estimate hazard ratios (HRs) as well as associated 95% confidence intervals (CIs). A multivariate proportional hazards model (MVA) on the subset of patients with LS versus LS+RT was performed using a forward stepwise procedure.

Significance was considered at a value of $p < 0.05$ and all statistical tests were two-sided. To assess for the possibility of immortal time bias, the survival analyses were repeated with patients dying or lost to follow-up at 1, 2, and 3 months removed from the data, and the new models were assessed for differences in statistical significance. Statistical analyses were performed with the Statistical Package for Social Sciences, version 22 (IBM SPSS Statistics, Chicago, IL, USA).

Results

Patient and tumor characteristics

The mean patient age was 40 years (range 0–90), and included 166 pediatric (≤18 years old) and 531 adult patients. The age distribution was bimodal, with peaks occurring at 9 and 59 years. The median follow-up time was 46 months (range 0.1–127 months). Patient, tumor, and treatment characteristics for adult and pediatric craniopharyngioma patients were described in Table 1. Pediatric patients had longer follow-up, larger tumor, lower comorbidity, and more adamantinomatous histology (all $p < 0.01$). In addition, papillary histology was not reported among pediatric patients.

Treatment

Since surgical extent was only recorded in the NCDB after 2009, only 195 patients had available information on surgical extent: 77 (39%) received biopsy, 61 (31%) received STR, and 57 (29%) received GTR. Among all patients, 522 (75%) did not receive any RT, 148 (21%) received adjuvant RT, and 27 (4%) received salvage RT. Adjuvant RT was delivered at a median time of 2.2 months (range, 0–6) after diagnosis. Salvage RT was delivered at a median time of 7.4 months (range, 6–23.5) after diagnosis. Of those received RT, 112 patients received X-ray external beam radiotherapy (EBRT), 13 received radiosurgery, four received proton therapy, and 46 with unknown RT technique. The median radiation dose in patients receiving conventional fractionation was 5400 cGy (range: 2700–5940): one patient received 2700 cGy at 180 cGy per fraction and another received 3780 cGy at 140 cGy per fraction, while the remaining patients received 4500–5940 cGy. The mean EQD2 dose was 4893 cGy (range of 2240–6313). Other parameters of RT are described in Supplement Table E1.

Patterns of care

As seen in Table 1, no significant differences in patterns of surgical or RT practices were identified between pediatric and adult patients. Additional patterns of care data are depicted in Fig. 1. The Charlson/Deyo comorbidity was the only factor associated with the extent of surgery. Biopsy alone was performed in 59% of patients with Charlson/Deyo score ≥1 as compared to only 33% for those with Charlson/Deyo score of 0 ($p < 0.01$). The proportion of patients receiving adjuvant RT increased from 18% in 2004–2007 to 24% in 2008–2012. Patients treated with adjuvant RT versus observation had similar age, race, insurance, education, income, metropolitan area population, and histology. Patients receiving adjuvant RT were more likely to have larger tumor size (OR 1.96 for >3 cm vs. ≤3 cm, 95% CI 1.26–3.05, $p < 0.01$), male sex (OR 0.67 for female vs. male sex, 95% CI 0.46–0.97, $p = 0.03$), treatment after 2008 (OR 1.48 for 2008–2012 treatment vs. 2004–2007, 95% CI 1.48–2.13, $p = 0.04$), lower Charlson/Deyo comorbidity index (OR 0.32 for score 1 vs. score 0, 95% CI 0.17–0.65, $p < 0.01$), and limited extent of surgery (OR 0.31 for GTR vs. Bx, 95% CI 0.12–0.84, $p = 0.02$). Likewise, patients with Charlson/Deyo score ≥1 were less likely to have adjuvant RT than those with Charlson/Deyo of 0 (11 vs. 24%, respectively, $p < 0.01$). A full table patterns of care and odds ratios (OR) for receiving adjuvant radiation or gross total resection are in Supplement Tables E2 and E3.

Overall survival

Among all patients, the 3 and 5 year actuarial rates of OS were 85 and 79% respectively. A total of 138 deaths occurred in the follow-up period. The median time to death was 13.8 months (range 0.07–119 months). The 5-year actuarial OS in adult patients was 75 and 89% in pediatric patients ($p < 0.01$). Treatment strategy (LS+RT vs. LS), age, race, insurance status, median income of patient's zip code, and Charlson/Deyo comorbidity score were significantly associated with OS on univariate analysis (Table 2). On multivariate analysis of the 195 patients with known surgical extent, only the treatment strategy remained statistically significant. In particular, LS+RT was associated with significantly improved OS compared to LS (HR 0.22, 95% CI 0.05–0.99, $p = 0.04$). The 5 year OS rates of LS, LS+RT, and GTR were 75, 85 and 82%, respectively ($p = 0.02$). Kaplan–Meier survival curves of selected groups of patients based on patient, tumor, and treatment factors are shown in Fig. 2. The 5 year OS rates of patients treated with adjuvant RT versus salvage RT were 87 and 74% ($p = 0.38$) as seen in Fig. 3a. No statistically significant correlation between radiation dose or EQD2 dose and overall survival was identified. However, an optimum cut-point EQD2 dose of >5000 cGy was associated with a trend toward significantly improved survival ($p = 0.051$) as seen in Supplement Figure E4.

Table 1 Patient characteristics

	All patients		Adult (>18)		Pediatric (≤18)		p
	n	%	n	%	n	%	
No. of patients	697	–	531	–	166	–	
Follow-up (median and range)	46 months (0.1–127)		42 months (0.1–125)		58 months (0.1–127)		**<0.01**
Tumor size (mean and range)	3.0 cm (0.3–15)		2.8 cm (0.3–11)		3.5 cm (1.4–15)		
≤3cm	260	57%	221	64%	39	34%	
>3cm	199	43%	123	36%	76	66%	**<0.01**
Sex							
Male	365	52%	268	50%	97	58%	
Female	332	48%	263	50%	69	42%	ns
Race							
White	505	73%	381	73%	124	80%	
Nonwhite	170	24%	138	27%	32	20%	ns
Treatment year							
2004–2007	345	49%	258	49%	87	52%	
2008–2012	352	51%	273	51%	79	48%	ns
Insurance							
Private	379	58%	279	57%	100	63%	
Government	230	35%	176	36%	54	34%	
Uninsured	42	6%	38	8%	4	3%	ns
Education of zip code							
≥21% without high school education	145	23%	115	22%	30	18%	
<21% without high school education	492	77%	410	78%	82	82%	ns
Median income of zip code							
<$38,000 median income	137	20%	112	21%	25	15%	
≥$38,000 median income	553	80%	413	79%	140	85%	ns
Metropolitan population							
≥250,000	511	76%	391	76%	120	76%	
<250,000	158	24%	121	24%	37	24%	ns
Charlson/Deyo comorbidity							
0	547	78%	398	75%	149	90%	
1	114	16%	99	19%	15	9%	
≥2	36	5%	34	6%	2	1%	**<0.01**
Histology subtype							
Unspecified	429	–	313	–	116	–	
Adamantinomatous	201	75%	151	69%	50	100%	
Papillary	67	25%	67	31%	0	0%	**<0.01**
Extent of surgery							
Unknown	502	–	379	–	123	–	
Biopsy (Bx)	77	39%	59	39%	18	42%	
Subtotal Resection (STR)	61	31%	47	31%	14	33%	
Gross Total Resection (GTR)	57	29%	46	30%	11	26%	ns
Radiation (RT)							
No radiation	522	75%	405	76%	117	71%	
Adjuvant radiation (≤6 months)	148	21%	106	20%	42	25%	
Salvage radiation (>6 months)	27	4%	20	4%	7	4%	ns
Surgery and RT combination							
Biopsy only	51	26%	41	27%	10	23%	
STR only	33	17%	25	16%	8	19%	
GTR only	49	25%	39	26%	10	23%	

Table 1 (continued)

	All patients		Adult (>18)		Pediatric (≤18)		p
	n	%	n	%	n	%	
Biopsy and adjuvant RT	21	11%	16	11%	5	12%	
STR and adjuvant RT	24	12%	19	13%	5	12%	
GTR and adjuvant RT	6	3%	6	4%	0	0%	
Biopsy and salvage RT	5	3%	2	1%	3	7%	
STR and salvage RT	4	2%	3	2%	1	2%	
GTR and salvage RT	2	1%	1	1%	1	2%	ns
Initial treatment strategy							
Limited surgery (LS) and observation	93	48%	71	47%	22	51%	
LS and adjuvant RT	45	23%	35	23%	10	23%	
GTR with or without adjuvant RT	57	29%	46	30%	11	26%	ns

p-values in bold denote statistically significant associations

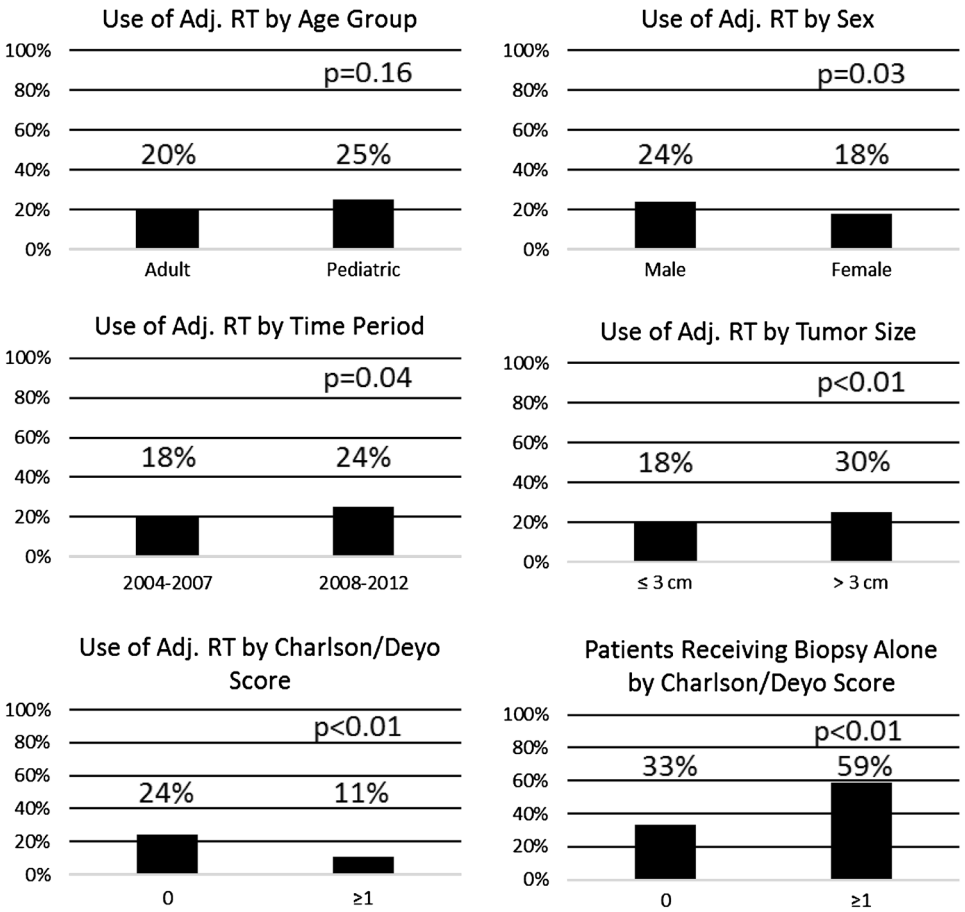

Fig. 1 Comparison of patterns of care among subgroups of patients

Assessing for immortal time bias

LS+RT was still significantly associated with improved OS (p = 0.03) compared to limited surgery alone after the seven patients who died (or lost to follow up) before 1 month after surgery were removed from the analysis. However, when the 11 patients who died (or lost to follow up) before 2 months or the 13 patients who died (or lost to follow up) before 3 months after surgery were removed, LS+RT was no longer statistically correlated with improved OS (p = 0.09 and p = 0.14, respectively).

Table 2 Univariate analysis of factors associated with overall survival

	Univariate analysis	
	HR (95% CI)	p
Treatment strategy		
Limited surgery (LS)	Reference	–
Limited Surg. + Adj. RT (LS+RT)	0.19 (0.05–0.83)	**0.03**
Gross total resection (GTR)	0.51 (0.22–1.20)	0.12
Age		
>18 years	Reference	–
≤18 years	0.33 (0.19–0.57)	**<0.01**
Sex		
Male	Reference	–
Female	1.10 (0.79–1.54)	0.56
Race		
White	Reference	–
Nonwhite	2.12 (1.54–3.05)	**<0.01**
Insurance		
Private	Reference	–
Government	4.02 (2.76–5.85)	**<0.01**
Uninsured	2.83 (1.42–5.65)	**<0.01**
Education of zip code		
≥21% without high school education	Reference	–
<21% without high school education	0.79 (0.53–1.18)	0.26
Median income of zip code		
<$38,000 median income	Reference	–
≥$38,000 median income	0.64 (0.43–0.94)	**0.02**
Metropolitan population		
≥250,000	Reference	–
<250,000	1.07 (0.72–1.59)	0.75
Charlson/Deyo comorbidity		
0	Reference	–
1	3.17 (2.18–4.60)	**<0.01**
≥2	3.62 (2.08–6.30)	**<0.01**
Histology		
Adamantinomatous	Reference	–
Papillary	1.139 (0.614–2.112)	0.68
Unspecified	1.026 (0.696–1.513)	0.89
Tumor size	1.009 (0.998–1.020)	0.11

p-values in bold denote statistically significant associations

Toxicity

Acute toxicity based on the extent of surgery was evaluated using time to discharge after surgery and rate of readmission within 30 days as endpoints. The time to discharge after surgery was evaluated based on the extent of surgery (for 122 patients with available information): stratified by LS versus GTR (for ≤3 cm tumor) versus GTR (for >3 cm tumor). As seen in Fig. 3b, there was no statistical difference in the time to discharge between these surgical strategies (p = 0.72). Of the 195 patients with coded readmission data, 8% (11 of 138) of patients with LS versus 7% (4 of 57) of patients with GTR were readmitted within 30 days of surgery (p = 0.85).

Discussion

This study evaluated surgical and RT practices among 697 adult and pediatric craniopharyngioma patients in the NCDB from 2004 to 2012. Practice patterns were similar between adult and pediatric patients. Patients with higher Charlson/Deyo comorbidity scores were less likely to receive adjuvant RT and more likely to undergo biopsy alone. Furthermore, there was a modest increase in the utilization of adjuvant RT after 2008. Although adjuvant RT after LS was associated with increased OS as compared to LS alone, the observed OS benefit could be confounded by selection bias or immortal time bias.

Our study showed no significant difference in the pattern of surgical or RT practices between pediatric and adult craniopharyngioma patients. This finding is consistent with previous studies from the Surveillance Epidemiology and End Results (SEER) database [18, 19]. However, this reported pattern of care is in contrast to the prevailing recommendations in the literature. Published series from several high-volume pediatric centers advocated LS followed by adjuvant RT instead of GTR, especially in cases where there is a higher risk of post-operative morbidity with radical resection [11, 20–22]. In addition, systematic reviews by both Kiehna et al. and Clark et al. recommended STR + RT for the pediatric population given the similar rates of tumor control when compared to GTR with lower long-term morbidity [7, 23]. In comparison to the pediatric population, a paper reviewing recent literature on the management of adult craniopharyngioma preferred treatment with GTR alone followed by observation instead of LS and adjuvant RT [24]. Despite the dichotomy between much of the literature on the preferred treatment for pediatric and adult craniopharyngioma, the modern management for pediatric versus adult patients appear to be very similar in this large hospital-based registry of the United States. This may reflect a lack of adequate high-level evidence to support the role of less aggressive surgery and adjuvant RT as stratified by age.

Our study observed a slight increase in the use of adjuvant RT in the treatment of craniopharyngioma after 2008, which may reflect an emerging trend. From 2004 to 2007, 18% of patients received adjuvant RT compared to 24% from 2008 to 12. Similarly, a survey of pediatric neurosurgeons regarding their patterns of care reported a preference for STR followed by adjuvant RT, with 59% of neurosurgeons stating they recommend STR + RT in over half of their cases [16]. This follows a growing consensus among

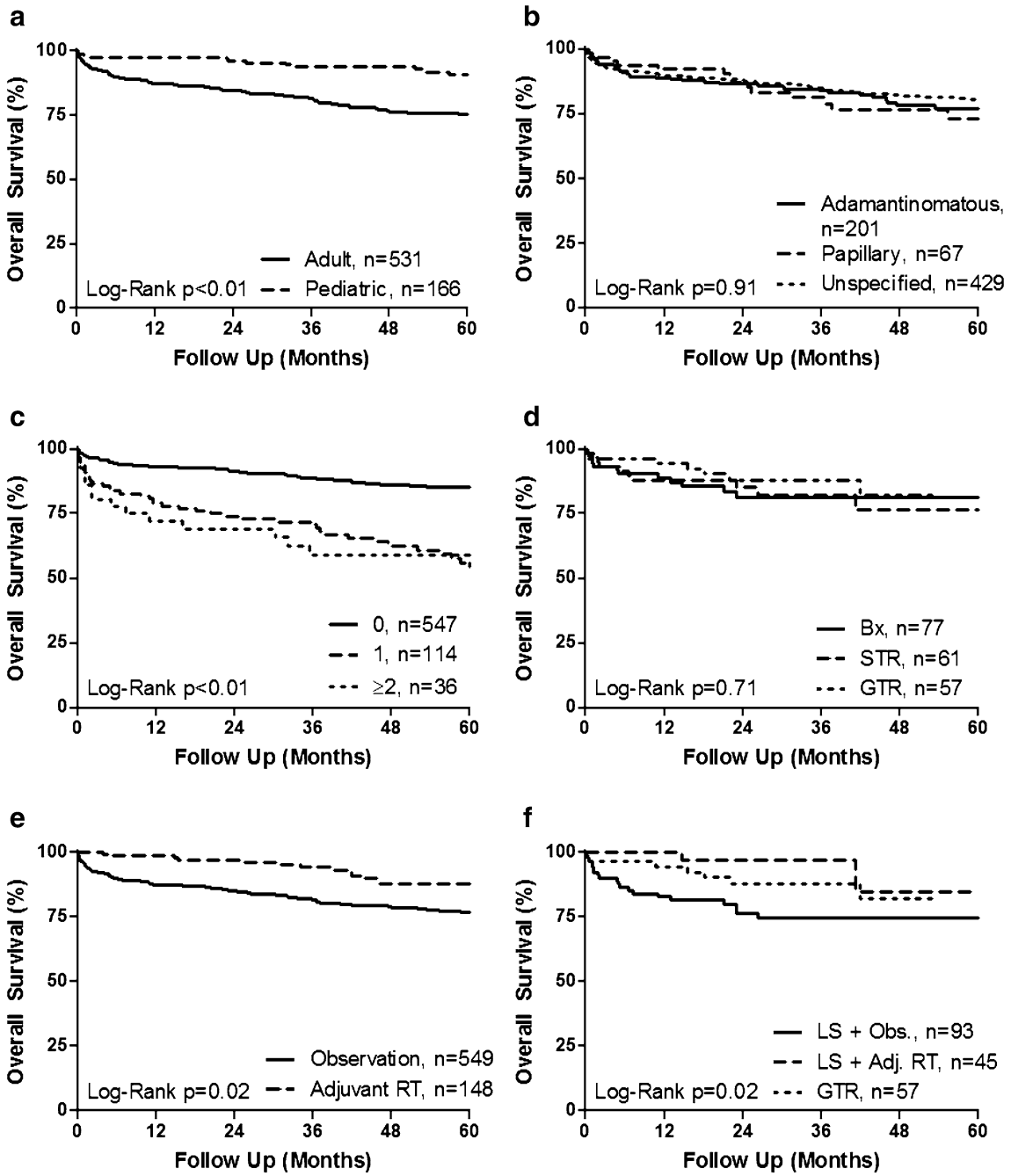

Fig. 2 Comparison of Kaplan–Meier estimates of clinical outcomes by **a** adult versus pediatric patients, **b** pathology subtypes, **c** Charlson/Deyo comorbidity score, **d** extent of surgery, **e** radiation therapy, **f** treatment strategy

several retrospective studies supporting the use of adjuvant RT in the initial management of craniopharyngioma. For example, a retrospective study by Yang et al. found similar tumor control rates between GTR and STR + RT, and favored conservative surgery with adjuvant RT given the improved morbidity outcomes [12]. Similarly, Schoenfeld et al. found no statistical difference in survival outcomes between GTR and STR + RT and showed less post-treatment morbidity for STR + RT [10]. These retrospective data may explain the increasing trend of utilization of adjuvant RT.

Similar to previous retrospective studies [7, 8, 16, 17, 23–29], this study also observed an improved OS for adjuvant RT after LS as compared to observation after LS or GTR. However, this data should be interpreted cautiously. While MVA adjusts for certain confounding variables,

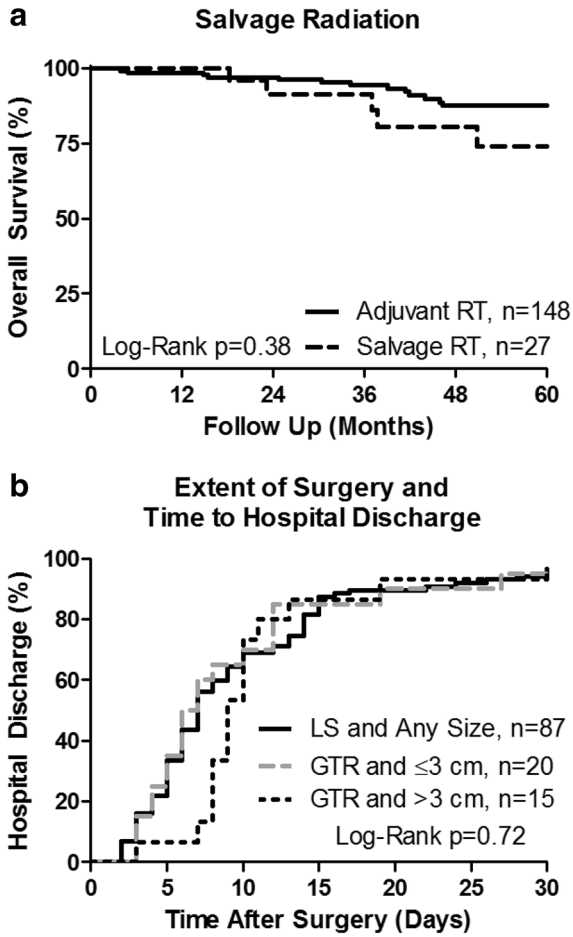

Fig. 3 Comparison of Kaplan–Meier estimates of clinical outcomes and hospitalization duration, **a** comparison of survival after adjuvant and salvage radiation, **b** time to hospital discharge after limited surgery or gross total resection

there are likely selection biases that are not taken into account. In addition, our study found that when patients who died or were lost to follow-up within 2–3 months from diagnosis were removed using a "landmark" adjustment, the OS benefit of adjuvant RT was no longer significant. This demonstrates that immortal time bias may play a significant confounding effect on previous retrospective studies. For example, a review of the Kaplan–Meier curves of previous studies reporting a survival benefit with adjuvant RT demonstrates a pattern of early deaths in the LS group [10, 18]. However, beyond OS, other retrospective studies have shown that adjuvant RT may improve local control (LC) and quality of life (QOL). KRANIOPHARYNGEOM 2000, a nonrandomized observational study of pediatric patients, reported that the use of adjuvant RT was associated with an 88% reduction in recurrence/progression [30]. Muller et al. retrospectively analyzed more than 300 pediatric craniopharyngioma patients and found significantly worse QOL outcomes with GTR compared to those receiving adjuvant RT [31]. Merchant et al. also reported that extensive surgery resulted in poorer quality of life and an average loss of 9.8 IQ points while limited surgery followed by radiation resulted in an average loss of 1.25 IQ points [11]. Thus, prospective randomized studies with LC and QOL analyses are necessary to conclusively evaluate the benefit of adjuvant RT. KRANIOPHARYNGEOM 2007 [32] is an ongoing prospective randomized study comparing adjuvant RT versus observation for pediatric craniopharyngiomas after incomplete resection which will hopefully provide valuable insights to guide future practice.

There are several limitations to our study. LC and QOL were not coded in the NCDB, therefore the impact of adjuvant RT on these important endpoints could not be assessed. For a non-malignant tumor such as craniopharyngioma, LC and QOL may be more relevant than OS. Due to the retrospective design, selection bias may have a significant confounding effect on OS. Although MVA was used to adjust for potential confounders, there may be other unknown confounders that would explain the OS difference. Furthermore, extent of surgery was only routinely coded for patients treated after 2009, which limited the number of patients that could be evaluated for the impact of treatment strategy. Although EQD2 dose >5000 cGy is associated with a trend toward improved OS in the study, this may be due selection bias and that some patients who received lower dose might not have completed the intended RT course. The NCDB also de-identifies case data by treating institution and provider; and the data use agreement does not allow linking of case data to individual institutions or providers. Therefore, no conclusions can be drawn regarding patterns of care according to institution and training of neurosurgeons using NCDB data. Indeed, surgical expertise may be a reason for limited surgical resection for many patients in the data, and future research using Medicare-linked databases may allow for more granular patterns of care analysis based on individual providers. Nevertheless, the NCDB data shows that the question of adjuvant RT versus observation after incomplete resection is applicable to approximately 70% of both pediatric and adult patients, and that retrospective data have significant design flaws and limitations to guide clinical practice. Thus, a prospective randomized study to examine the role of adjuvant RT after incomplete resection for both pediatric and adult craniopharyngiomas should be supported.

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responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

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Compliance with ethical standards.

Conflict of interest The authors report no conflicts of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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