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Survival benefit of postoperative radiation in papillary meningioma: Analysis of the National Cancer Data Base

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ABSTRACT

Aim/Background: Papillary meningioma represents a rare subset of World Health Organization (WHO) Grade III meningioma that portends an overall poor prognosis. There is relatively limited data regarding the benefit of postoperative radiation therapy (PORT). We used the National Cancer Data Base (NCDB) to compare overall survival (OS) outcomes of surgically resected papillary meningioma cases undergoing PORT compared to post-operative observation.

Materials and methods: The NCDB was queried for patients with papillary meningioma, diagnosed between 2004 and 2013, who underwent upfront surgery with or without PORT. Overall survival (OS) was determined using the Kaplan–Meier method. Univariate (UVA) and multivariate (MVA) analyses were performed.

Results: In total, 190 patients were identified; 89 patients underwent PORT, 101 patients were observed. Eleven patients received chemotherapy (6 with PORT, 5 without). 2-Year OS was significantly improved with PORT vs. no PORT (93.0% vs. 74.4%), as was 5-year OS (78.5% vs. 62.5%) (hazard ratio [HR], 0.48; 95% confidence interval [CI], 0.27–0.85; $p = 0.01$). On MVA, patients receiving PORT had improved OS compared to observation (HR, 0.41; 95% CI, 0.22–0.76; $p = 0.005$). On subset analysis by age group, the benefit of PORT vs. no PORT was significant in patients ≤18 years ($n = 13$), with 2-year OS of 85.7% vs. 50.0% (HR, 0.08; 95% CI, 0.01–0.80; $p = 0.032$) and for patients >18 years ($n = 184$), with 2-year OS of 94.7% vs. 76.1% (HR, 0.55; 95% CI, 0.31–1.00; $p = 0.049$), respectively.

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Conclusions: In this large contemporary analysis, PORT was associated with improved survival for both adult and pediatric patients with papillary meningioma. PORT should be considered in those who present with this rare, aggressive tumor.

1. Background & aim

Meningioma is the second most common tumor of the central nervous system (CNS) accounting for 22–35% of CNS masses.[1,2] Malignant meningioma (World Health Organization [WHO] Grade III) represents a rare, aggressive meningioma found in 1–3% of cases. Within the diagnosis of malignant meningioma exists further differentiation into subtypes of papillary and rhabdoid meningioma.[1] Current management includes maximally safe surgical resection, with an attempt at gross total resection (GTR) when feasible. The reported rate of post-operative recurrence in malignant meningioma ranges widely from 20% to greater than 90%.[3–6] Overall survival at 5 years for malignant meningioma ranges from 32 to 64%. These suboptimal outcomes highlight the importance of efforts to promote durable tumor control following surgery.[3,7–9]

Following surgical management in papillary meningioma, the decision to use adjuvant radiotherapy remains questionable. The largest study of malignant meningioma from the University of California, San Francisco (UCSF) included 63 patients.[10] This study suggested that post-operative radiation therapy (PORT) following resection significantly improved survival with no significant difference between GTR and near total resection (NTR). One limitation, however, of the UCSF analysis and other previous studies is that they have rarely separated out papillary meningioma from other malignant meningioma variants in the WHO Grade III category. The largest study exclusively analyzing papillary meningioma was reported by investigators from the University of California, Los Angeles, and included 29 patients of whom 7 received PORT.[11] The results demonstrated an association between improved local control and overall survival with the addition of PORT, irrespective of the extent of resection. However, as the authors concluded, the study was limited by statistical power and was unable to demonstrate a statistically significant benefit with the use of PORT, suggesting the need for larger, prospective trials.

The sizable cancer registry dataset found in the National Cancer Data Base (NCDB) provides tremendous benefits including its large sample sizes, prospective data collection, and generalizability to patients treated outside the context of clinical trials, which may be most beneficial in evaluating treatment patterns and outcomes in rare tumors such as papillary meningioma. Therefore, the purpose of this study was to evaluate patterns of care and outcomes of PORT in pediatric and adult patients with papillary meningioma.

2. Methods and materials

2.1. Data source and patient selection

The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. It is a hospital-based registry that represents 70% of all cancer cases in the US, drawing data from more than 1500 commission-accredited cancer programs. The NCDB contains detailed information on disease stage, RT treatment, and chemotherapy, but does not code for the extent of surgery.[12] Overall survival is coded, but no data is provided on intermediate oncologic endpoints such as local control and progression-free survival. The data used in the study are derived from a de-identified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data.[13]

We identified 243 patients with papillary meningioma diagnosed between 2004 and 2013, with histologic codes based on International Classification of Disease for Oncology [third edition] histology code (ICD-O-3): 9538/3 and known status of radiation. Those included underwent surgical resection upfront; those who underwent biopsy alone were excluded ($n=6$). The dataset was then limited to patients with known follow up and survival outcomes ($n=197$). Next, cases with unknown receipt of adjuvant chemotherapy were excluded ($n=7$).

2.2. Patient demographics and treatment variables

Potentially relevant patient and treatment characteristics were included. Age was analyzed categorically: 0–18 years (pediatric) vs. >18 (adults). Radiation and chemotherapy were analyzed as binary (yes/no). Race was categorized as White, African-American, and all others. Insurance status was defined by the NCDB and included not insured, private insurance/managed care, and government-type (Medicaid, Medicare, other). Patient comorbidities were categorized as 0, 1, or ≥2 according to Charlson-Deyo (CD) comorbidity scores.[14] All patients included in the study underwent an attempt at surgical resection; extent of resection (ex. GTR vs. subtotal resection [STR]) is not defined by the NCDB and could therefore not be accounted for in our analysis. The primary endpoint was overall survival.

Table 1 – Patient and treatment characteristics.

Variables	All patients ($n=190$)		Observation ($n=101$)		PORT ($n=89$)		p
	No.	(%)	No.	(%)	No.	(%)	
Age (years)							0.600
0–18	13	(6.8)	6	(5.9)	7	(7.9)	
>18	177	(93.2)	95	(94.1)	82	(92.1)	
Gender							0.291
Male	99	(52.1)	49	(48.5)	50	(56.2)	
Female	91	(47.9)	52	(51.5)	39	(43.8)	
Race							0.624
White	154	(81.1)	81	(80.2)	73	(82.0)	
African-American	15	(7.9)	10	(9.9)	5	(5.6)	
Other	14	(7.4)	6	(5.9)	8	(9.0)	
Unknown	7	(3.7)	4	(4.0)	3	(3.4)	
Insurance status							0.105
Private	104	(54.7)	48	(47.5)	56	(62.9)	
Government	74	(38.9)	44	(43.6)	30	(33.7)	
Uninsured	10	(5.3)	7	(6.9)	3	(3.4)	
Unknown	2	(1.1)	2	(2.0)	0	(0.0)	
Charlson-Deyo comorbidity score							0.635
0	141	(74.2)	73	(72.3)	68	(76.4)	
1	33	(17.4)	20	(19.8)	13	(14.6)	
2+	16	(8.4)	8	(7.9)	8	(9.0)	
Year of diagnosis							0.250
2004–2006	67	(35.3)	40	(39.6)	27	(30.3)	
2007–2009	63	(33.2)	34	(33.7)	29	(32.6)	
2010–2013	60	(31.6)	27	(26.7)	33	(37.1)	
Chemotherapy							0.924
No	179	(94.2)	95	(94.1)	84	(94.4)	
Yes	11	(5.8)	6	(5.9)	5	(5.6)	
Vital status							N/A
Alive	135	(71.1)	64	(63.4)	71	(79.8)	
Dead	55	(28.9)	37	(36.6)	18	(20.2)	

Abbreviation: PORT, postoperative radiation therapy.

2.3. *Statistical analysis*

All statistical analyses were performed using SPSS V23.0 (SPSS Inc., Chicago, IL). Pearson chi-square tests were used to assess associations between categorical variables and receipt of postoperative radiation. Overall survival interval was calculated from the date of diagnosis to the date of death. Median survival was calculated using the reverse Kaplan–Meier method.[15] Overall survival was first examined using the Kaplan Meier method. Univariate survival analysis (UVA) was performed with the log-rank test and unadjusted Cox proportional hazards models to estimate hazard ratios (HR); HR > 1 corresponded to worse overall survival. Patient and clinical variables were selected a priori. Multivariate Cox regression analysis (MVA) was performed using OS as outcomes with a significance level of $p < 0.05$. Chi-squared heterogeneity (interaction) tests were performed under the assumption of proportional hazards to evaluate whether the survival impact of PORT varied significantly according to age (≤18 vs. >18).[16]

3. Results

A total of 190 patients were evaluated, all of whom received upfront surgical resection. Analysis included both pediatric (≤18 years, $n=13$) and adult (>18 years, $n=177$) patients. Postoperative management included observation ($n=101$) and PORT ($n=89$). Eleven patients received chemotherapy (PORT $n=6$, observation $n=5$).

Median follow up was 56.4 months (range, 1.0–122.2 months). Median population age was 53 years (range, 0–88 years). Patient and treatment characteristics are presented in Table 1. Patients receiving PORT were more likely to be white, male and have private insurance. Use of PORT increased between the 2004–2006 and 2010–2013 cohorts (40.3% to 55%). Of those undergoing observation, CD comorbidity scores were 0 ($n=73$, 72.3%), 1 ($n=20$, 19.8%) and 2+ ($n=8$, 7.8%). For those receiving PORT, CD comorbidity scores were 0 ($n=68$, 76.4%), 1 ($n=13$, 14.6%) and 2+ ($n=8$, 9.0%) (Table 1).

3.1. *Survival outcomes for all patients*

2-Year OS was 93.0% with PORT vs. 74.4% with observation and 5-year OS was 78.5% and 62.5%, respectively (Fig. 1). On UVA, patients receiving PORT had improved OS compared to those receiving observation ($p=0.01$). Patients with government-type insurance had decreased OS compared to patients with private insurance ($p=0.004$).

MVA accounting for age, gender, race, insurance status, comorbidity score, year of diagnosis, and receipt of chemotherapy is shown in Table 2. On MVA, patients receiving PORT had improved OS compared to those who were observed (HR, 0.41; 95% CI, 0.22–0.76; $p=0.005$). MVA also

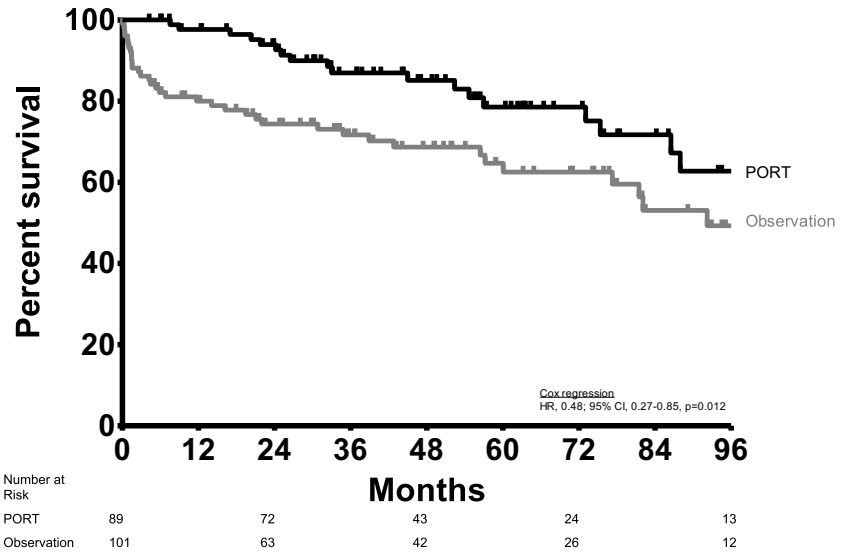

Fig. 1 – Unadjusted Kaplan–Meier curve demonstrating overall survival in papillary meningioma patients undergoing postoperative radiation vs observation.

Table 2 – Univariate and multivariate predictors of overall survival.

Variable	Univariate			Multivariate		
	HR	95% CI	*p*	HR	95% CI	*p*
Postoperative radiotherapy						
No	1			1		
Yes	0.48	0.27–0.85	0.012	0.41	0.22–0.76	0.005
Age (years)						
0–18	1			1		
>18	0.61	0.24–1.52	0.284	0.34	0.12–0.98	0.045
Gender						
Male	1			1		
Female	0.74	0.43–1.27	0.276	0.82	0.45–1.49	0.511
Race						
White	1			1		
African-American	1.64	0.69–3.90	0.264	1.13	0.46–2.79	0.791
Other	1.78	0.70–4.52	0.227	1.68	0.55–5.16	0.362
Unknown	2.12	0.66–6.85	0.210	2.14	0.63–7.26	0.222
Insurance status						
Private	1			1		
Government	2.24	1.30–3.88	0.004	2.35	1.32–4.17	0.004
Uninsured	1.56	0.36–6.67	0.551	1.69	0.33–8.53	0.526
Unknown	–	–	–	–	–	–
Charlson-Deyo comorbidity score						
0	1			1		
1	1.77	0.93–3.36	0.080	2.05	1.01–4.16	0.046
2+	2.28	1.01–5.15	0.049	3.19	1.33–7.63	0.009
Year of Diagnosis continuous	0.96	0.85–1.08	0.497	0.99	0.88–1.12	0.893
Chemotherapy						
No	1			1		
Yes	1.71	0.68–4.30	0.256	1.70	0.63–4.60	0.299

Abbreviations: HR, hazard ratio; CI, confidence interval.

indicated a decreased OS in patients with CD comorbidity score 2+ ($p = 0.009$) and government-type insurance ($p = 0.004$). Race, gender and chemotherapy did not significantly contribute to OS under MVA.

On subset analysis by age group, the benefit of PORT vs. observation was significant in patients ≤18 years ($n = 13$), with 2-year OS of 85.7% vs. 50.0% (HR, 0.08; 95% CI, 0.01–0.80; $p = 0.032$) and for patients >18 years ($n = 184$), with 2-year OS of 94.7% vs. 76.1% (HR, 0.55; 95% CI, 0.31–1.00; $p = 0.049$), respectively (Fig. 2A and B). At 30 months, all patients ≤18 years who had not received RT ($n = 6$) had died. Significant interactions by age were observed, demonstrating greater hazard reductions in association with PORT among patients <18 years old (all interaction $p = 0.015$).

4. Conclusions

Our analysis suggests that there is significant improvement in OS with the addition of PORT when compared to observation following surgery for papillary meningioma. The survival benefit was seen across both pediatric and adult patients on both UVA and MVA accounting for critical factors including age, race, insurance status and CD comorbidity scores.

In the pediatric subset of patients, we saw the most profound benefit in OS with the addition of PORT when compared to post-resection observation. From the pediatric subset of 13 patients, all of the 6 patients who had not received PORT had died by the 30-month follow up point. In contrast, 6 of 7 pediatric patients who received PORT for papillary meningioma were alive at 48 months with observed survival through 96 months of follow-up (Fig. 2B). This subset analysis is limited by small numbers and the retrospective nature of this study overall. However, the absence of long-term survival among pediatric patients who were not treated with RT represents an important hypothesis-generating observation from this analysis.

There is little literature focusing on papillary meningioma as a distinct disease entity from WHO Grade III meningiomas. One systematic review by Fong et al. included 29 patients with papillary meningioma and represents the largest report

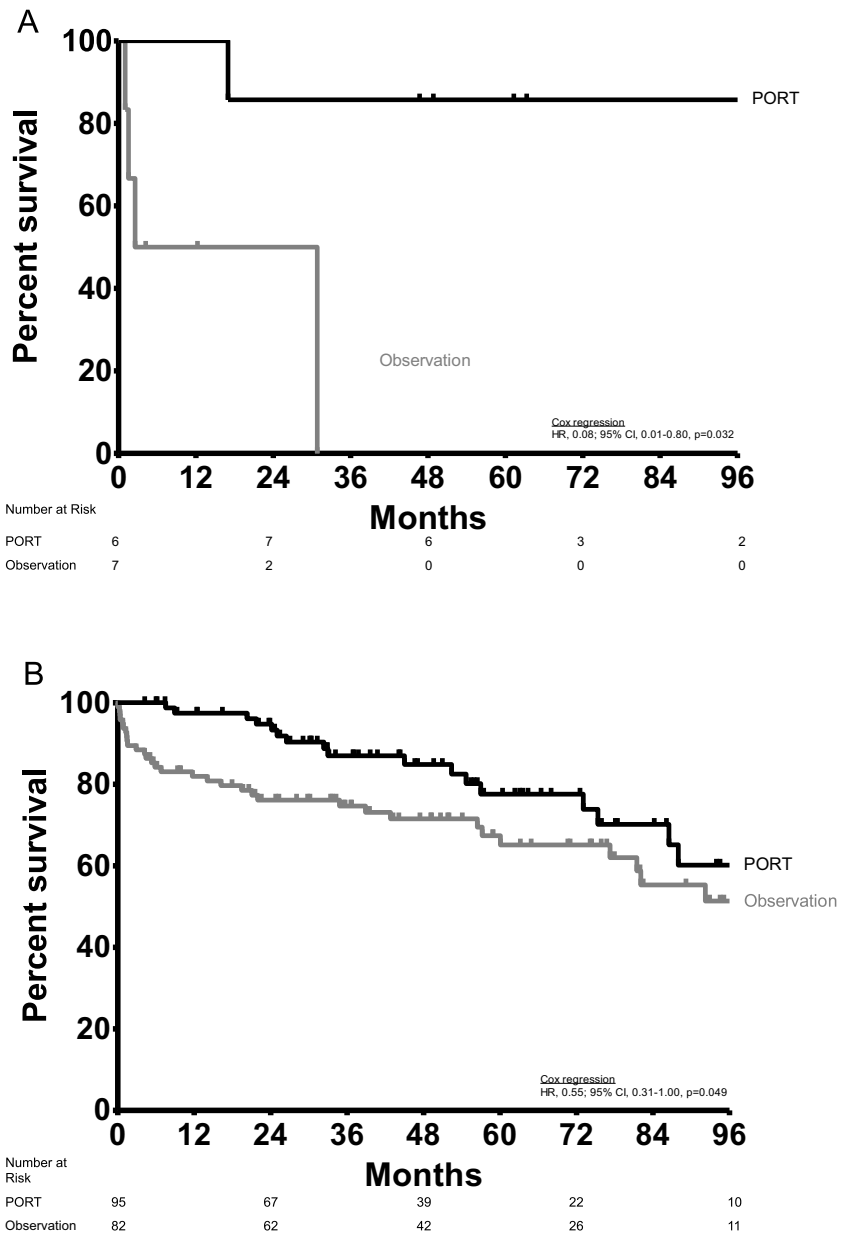

Fig. 2 – Kaplan–Meier curve comparing overall survival in papillary meningioma postoperative radiation vs observation separated by age <18 years (A) and >18 years (B).

of papillary meningioma treatment outcomes prior to our study.[11] Their analysis from 1978 to 2012 included patients primarily derived from case studies and revealed a benefit of STR and GTR in OS for papillary meningioma. Though the data trended toward significance with GTR/STR plus PORT, the study lacked the statistical power to draw firm conclusions. Wang et al. similarly lacked statistical power in their report of 17 papillary meningioma patients who received surgical resection with 9 of 17 receiving PORT.[1]

Overall, there is more data to support PORT in the treatment of WHO Grade III meningioma. Sun et al.[17] published a review of literature summarizing the current management of WHO Grade II and III meningiomas. Seven studies of malignant meningiomas were included. The authors concluded that there was evidence to suggest a treatment algorithm for WHO Grade III meningioma to include a regimen of GTR or NTR with PORT. The largest study included in this review, published by Zhao et al.,[18] included 37 patients with WHO Grade III meningioma and demonstrated improved OS in patients receiving PORT ($p = 0.006$). A complete review of previous Grade III meningioma literature adapted from Sun et al. and Hanft et al. can be reviewed in Table 3.[4,17] It is important to note the rarity of papillary meningioma in the studies that chose to delineate histology. These studies, which may provide the best evidence for PORT in WHO Grade III meningioma, provide somewhat limited evidence for PORT in papillary meningioma given the small representation of this particular histology, again demonstrating the importance of this analysis.

Table 3 – Studies and reviews evaluating management of WHO Grade III meningiomas.

Author	Study period	Patients (*n*)	Papillary[A]	Treatments	Outcomes
Jaaskelainen et al.[19]	1953–1980	9		GTR/STR +/− Adjuvant EBRT	
Milosevic et al.[20]	1966–1990	42		GTR/STR +/− Adjuvant EBRT	28% 5-yr OS
Dziuk et al.[5]	1984–1992	38	3	GTR/STR +/− Adjuvant EBRT	
Durand et al[B][21]	1990–2004	33	1	GTR/STR +/− Adjuvant EBRT	8% 5-yr PFS
Hug et al.[8]	1973–1995	16		Resection + (<60 Gy) vs (>60 Gy)	
Boskos et al.[22]	1999–2006	5		Surgery + RT + Proton Therapy	53% 5-yr OS
Rosenberg et al[B][23]	1981–2006	13	0	Surgery +/− RT; RT vs SRS in recurrent	47% 5-yr OS
Sughrue et al.[10]	22 years, after 1990	34		GTR/STR +/− Adjuvant EBRT	61% 5-yr OS,
Adeberg et al.[24]	1985–2009	23		GTR/STR +/− Adjuvant EBRT	15% 5-yr PFS, 53% 5-yr OS
Pollock et al.[25]	1990–2008	13		Salvage SRS +/− EBRT	27% 5-yr DFS
Wang et al.[1]	2005–2010	17	17	GTR/STR +/− Adjuvant RT	
Choi et al.[26]	1995–2013	42	2	GTR/STR +/− Adjuvant EBRT	79.2% 5-yr OS
Ferraro et al.[27]	2000–2011	4		GTR/STR + SRS	0% 3-yr PFS, 33% 3-yr OS
Fong et al.[11]	Review of Literature	29	29	GTR/STR +/− Adjuvant RT	
Zhao et al.[18]	2001–2011	37		GTR/STR +/− Adjuvant EBRT	12% 5-yr PFS
Present Study	2004–2013	190	190	Surgical Resection +/− PORT	

WHO, World Health Organization, GTR, gross total resection, STR, subtotal resection, SRS, stereotactic radiosurgery, EBRT, external beam radiation therapy, RT, radiation therapy, MVA, multivariate analysis, UVA, univariate analysis, HR, hazard ratio, PFS, progression-free survival, OS, overall survival, NS, non-significant, DFS, disease free survival, PORT, post-operative radiation therapy, RR, relative risk.
A: the number of patients with histology-confirmed papillary meningioma included in the study, if provided.
B: chemotherapy used in study, non-significant benefit.

There are several studies that failed to show significant improvement with PORT, although this may result from the small number of patients in the studies. Rosenberg et al.[23] failed to show significance in OS for WHO Grade III meningioma receiving PORT when compared to post-operative observation or upfront stereotactic radiosurgery (SRS) alone. The study included 13 patients with only four receiving PORT (OS, UVA, $p = 0.1$). Dziuk et al.[5] also trended toward significant OS benefit for PORT for WHO Grade III meningioma, but similarly failed to show significance.

The value of chemotherapy in the treatment of papillary meningioma is still largely unknown and may, therefore, explain why only a small number of patients in this study received adjuvant chemotherapy. Chemotherapeutic agents including hydroxyurea, imatinib, temozolamide, cyclophosphamide and hydroxycarbamide have been used for WHO Grade III meningiomas with no appreciable survival benefit.[5,17,21] Bevacizumab was evaluated in a study of patients receiving surgical resection with or without SRS. The median PFS was 26 weeks and median OS was 15 months.[28] The majority of studies evaluating the role of chemotherapy in the treatment of malignant meningioma come from data in the recurrent setting rather than upfront treatment management.[29–31] When compared to chemotherapy in the upfront setting, the data for chemotherapy in recurrent malignant meningioma was equally ineffective. Very few patients received chemotherapy as a component of upfront therapy in this NCDB dataset ($n = 11$), which limits comment on the efficacy of systemic therapy in this analysis.

The NCDB represents a uniquely vast resource of information on radiation treatment and long-term outcomes. This is particularly crucial for providing data on treatment and outcomes of rare diseases as observed in this study. While this feature of the NCDB allows our study to contribute the largest studied patient population of papillary meningioma, there are inherent limitations. Notably, the NCDB is limited by lack of information related to local or distant disease control, toxicity of therapy, details of radiation treatment planning and cancer-specific survival. While all patients included in our study underwent upfront surgical resection, a prominent limitation for this study is the unknown extent of their resection (GTR vs. STR).

In spite of these limitations, our analysis along with other published studies suggest OS is improved with PORT for papillary meningiomas.

Conflict of interest

None declared.

Financial disclosure

None declared.

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