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National trends in management of adult myxopapillary ependymomas

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Abstract

Myxopapillary ependymomas (MPE) are WHO Grade I ependymomas that annually occur in 0.05–0.08 per 100,000 people. Surgical resection is the recommended first line therapy. Due to the rarity of the disease, there is a relatively poor understanding of the use of radiotherapy (RT) in managing this disease. The National Cancer Database (NCDB) was analyzed for patterns of care for adult MPE diagnosed between 2002 and 2016. Of 753 qualifying cases, the majority of patients underwent resection (n = 617, 81.9%). A relatively small portion received RT (n = 103, 13.3%) with most receiving RT post-operatively (n = 98, 95.1%). The likelihood of patients to undergo resection and RT was associated with patient age at diagnosis ($p = 0.002$), tumor size ($p < 0.001$), and race ($p = 0.017$). Chemotherapy was not widely utilized (0.27% of patients). One limitation of our analysis is that there was no data on progression free survival (PFS), an important outcome given the high survival rate in this disease. Surgery remains the primary means to manage adult MPE. For spinal MPE, it is understood that gross total resection (GTR) should be attempted whenever possible as GTR has been associated with improved PFS in several studies. The impact of RT on overall survival (OS) is indeterminate given the 1.6% death rate in the cohort. Analyses of the impact of RT on PFS in a larger database would be beneficial for determining an algorithm for post-operative and definitive RT in this disease entity.

Keywords

Myxopapillary ependymomas; Radiotherapy; NCDB; Spine

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

1. Introduction

In the United States, ependymomas (EPN) account for 1.7% of all primary central nervous system (CNS) tumors with an annual incidence of about 0.43 patients per 100,000 population and a respective 5-year and 10-year relative survival rate of 84.8% and 79.5% [1]. They occur in three main anatomic compartments of the CNS: supratentorial (ST), posterior fossa (PF), and the spinal cord [2]. Historically, they were subdivided into three histology-based grades to help predict disease progression and direct treatment options. The World Health Organization (WHO) Grade I tumors include subependymomas (SE) and myxopapillary ependymomas (MPE), while the WHO Grade II and III EPN capture conventional EPN. However, upon analyzing multiple intracranial EPN cohorts, the disease classification as WHO II and III indicated a broad variation in applicability due to their poor definitions [3,4]. These grades thereby lack reliable associations between tumor grade and patient outcomes and may result in controversial risk-stratifications [3,5]. Thus, the 2015 global EPN consensus conference decided that treatment decisions for EPN should not be based only on histological traits, especially in regards those characterized as WHO Grade II and III [3].

EPN can be further subdivided into nine molecular subgroups with WHO Grade I SE occurring in any anatomic CNS compartment [3]. In the spine, the two other subtypes are MPE and WHO Grade II/III EPN. In the ST region, the subtypes also include ST-EPN-RELA and ST-EPN-YAP1, which are respectively characterized by the fusion of the C11ORF95-RELA genes and the oncogene YAP1 [5,6]. The two other subtypes in the PF are grouped as PF-EPN-A or PF-EPN-B with the former having poorer patient outcomes and a higher recurrence rate due to the difficultly in completely resecting the tumor in this region [7]. In 2015, the global EPN consensus conference concluded that in addition to histological traits, molecular profiling should be used in future clinical trials, as these molecular sub-classifications can improve risk-stratification and aid in treatment decisions [3].

MPE has a reported annual occurrence of 0.05–0.08 per 100,000 persons, and is usually seen in the spine, the conus medullaris, and cauda equina [4,8]. The clinical presentation of this disease include chronic lower back pain, sacral pain that potentially expands from the spinal nerve into the leg extensors and the bottom of the feet or to the buttocks, probable weakness of the leg, impotence, and potential dysfunction of the bladder and/or bowel sphincters [4].

The general standard of care for patients with EPN consist of surgical resection and adjuvant radiation therapy (RT), especially after subtotal resection in cases of WHO Grade III (anaplastic) EPN and of extensive residual disease [3]. However, the role of RT and chemotherapy in MPEs remain controversial. Recent studies have reported on trends in treatment modalities delivered to patients with high-grade intracranial and spinal EPN and their associated overall survival (OS) [9,10]. One study identified an enhanced OS for children (2–18 years) with high grade intracranial EPN treated with an adjuvant RT dose >5400 cGy, while another study indicated a significant association between the administration of adjuvant RT in patients diagnosed with WHO Grade III EPN and the facility distance. To further encapsulate the patterns of care and OS of patients with EPN, this study will analyze the effect of RT on patients with WHO Grade I spinal EPN through

the use of the National Cancer Database (NCDB). Additionally, we intend to identify the role of chemotherapy in patient outcomes for this population.

2. Methods

The NCDB is hospital-based registry that was established in 1988 through the joint sponsorship of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society [11]. It consists of about 70% of all newly diagnosed cancer cases within the US, having derived its data from facilities accredited by the CoC with varying hospital environments. Although the NCDB only captures patients that receive some form of cancer care from a CoC accredited facility (i.e. diagnosis or treatment), it provides de-identified information on sociodemographic, disease staging, treatment courses, and OS.

Data was derived from the NCDB for patients diagnosed between 2002 and 2016 with MPE based on the International Classification of Diseases for Oncology (ICD-O-3) 9394 code, yielding 2,893 patients. As illustrated in Fig. 1, the exclusion criteria include the following: patients with missing or inconsistent surgical procedure information (1,745 patients), missing RT information (7 patients), improperly coded or missing WHO grades (305 patients), extra-spinal disease (18 patients) and an age of ≤ 18 (65 patients). The final sample population consisted of 753 patients. The demographic, clinical, and treatment variables evaluated were age, sex, race, education, comorbidity score, insurance status, income, facility type, facility regional location, facility's urban or rural designation, year of diagnosis, tumor size, extent of surgery, RT modality, radiation dose, and receipt of chemotherapy.

The demographics, clinical, and treatment variables were evaluated for general significance via univariate analyses. Multivariate analyses were not performed due to the limited sample size of the cohort. Points of significance for binary and continuous variables were respectively obtained from the Fisher's extract test and Wilcoxon rank-sum test. Patient populations that comprised of ≤ 20 patients were reported as asterisks (*) for further de-identification purposes. A p-value ≤ 0.05 served as the basis for statistical significance. Statistical analysis was performed using Strata version 15.1 (Strata Corporation, College Station, TX).

3. Results

Of the 753 qualifying patient cases, the patients were mostly male (n = 409, 54.3%) with a median age at diagnosis of 43 years (n = 753, range = 32–56 years). A majority of the patients were Caucasian (n = 625, 83.0%), followed by Latino/Hispanic (n = 53, 7.0%) and African American (n = 30, 4.0%). Most patients had an income ≥ $48 K (n = 494, 65.7%), were geographically located in metropolitan areas (n = 628, 83.4%), and had less than a high school education (n = 466, 61.9%). Patients primarily had private insurance (n = 522, 69.3%), followed by Medicare (n = 105, 13.9%) and Medicaid (n = 70, 9.3%). About 69.2% (n = 521) of the patients had a reported tumor size with median of 25 mm (range = 15–43 mm). Most patients had no comorbidities (n = 633, 84.1%).

Although many patients had missing facility type information (n = 323, 42.9%), those with known facility types were noted to have obtained their treatment in academic/research programs (n = 204, 27.1%), comprehensive community cancer programs (n = 138. 18.3%), or integrated network cancer programs (n = 69, 9.2%). Some also had unknown facility locations, but of those with known locations, 25.4%, 20.3% and 11.4% had respectively received treatment in the Central, East/Atlantic and West region of the United States.

Tables 1A, 1B, and 2 include information on the demographics, clinical, and treatment characteristics based on whether patients received adjuvant RT. The majority of patients underwent surgical resection (n = 617, 81.9%). Overall, a relatively small portion of patients received RT (n = 103, 13.7%), with most patients receiving RT post-surgical resection (n = 98, 95.1%). The median RT dose among these patients was 50.4 Gy (range, 25–72 Gy). The predominant RT modality was external beam radiation therapy (EBRT). Chemotherapy was not a widely utilized treatment option as only 0.27% of patients were reported to receive chemotherapy. The likelihood of patients to undergo adjuvant RT and surgical resection was significantly affected by race ($p = 0.017$), age at diagnosis ($p = 0.002$), and tumor size ($p < 0.001$). Race, younger age, and larger tumor size were associated with increased likelihood to receive adjuvant RT.

4. Discussion

MPE is a rare subtype of EPN in which the standard of care remains unclear [8,12,13]. Through the analysis of the NCDB, our study identified current treatment practices with an emphasis on the role of RT. *Bates et al* conducted similar analyses regarding the effects of demographic, clinical and treatment variables on the OS of patients with MPE through the use of the Surveillance, Epidemiology and End Results (SEER) database [8]. Unlike *Bates et al* where they found a poor use of RT among patients ≤ 30 years (12.3%, $p = 0.03$), our data indicated a significant lack of RT administration in older patients with a reported median age of 44 years at diagnosis (n = 641, range = 33–56 years) when compared to the median age of patients undergoing RT at 36 years (n = 98, range = 26–52 years, $p = 0.002$) [8]. The uncommon use of RT in the older patient population in our study may be secondary to non-RT recipients having no comorbidities (n = 535, 83.5%) and proceeding with surgery as the prime means of treatment (n = 641, 85.1%).

The tumor size of these patients could be a contributing factor to the lack of RT administration. Patients who did not have RT had a smaller tumor size (mean = 2.3 cm) than patients who proceeded with RT (mean = 3.9 cm, $p < 0.001$). Our study was supported by published literature that tumor size significantly affected a patient's likelihood to receive RT [8,14]. The common use of RT in patients with a larger tumor size may be due to an increased risk associated with resecting these tumors in such a critical anatomical location, as well as the increased likelihood of failing to achieve GTR [8,13,15].

Although our study indicated a higher percentage of patients in the metropolitan area that received RT (81.6%) than *Bates et al* (16.5%), our study did not find a significant association between the overall residence of patients and RT administration ($p = 0.54$) [8]. The observed decline in patients in the metropolitan area receiving RT may be due to conflicting literature

on whether adjuvant RT contributes to improved survival (with RT, n = 80, 81.6%, without RT, n = 536, 83.6%). Some studies recommend the use of RT despite the extent of surgery because an increased progression-free-survival (PFS) and local control (LC) was observed in both pediatric and adult patients [12,16-19]. Others encourage the use adjuvant RT after STR, while a number demonstrate no statistically significant benefit with adjuvant RT administration regardless of surgery in terms of limiting tumor progression [13-15,20-28].

Our analysis further indicated that race significantly impacted the likelihood of RT delivery among patients ($p = 0.017$). The utilization of RT appears to decline in Caucasians, African-Americans, and Asian/Pacific Islanders, whereas an 8.2% increase of RT usage was found in the Hispanic/Latino population. A minimal increase was also found in other and unknown populations. However, due to the limited distribution of MPE patients amongst ethnicities, we are unable to determine the significance of this observed trend. This limitation also affected our evaluation of the prominent occurrence of MPE in Caucasian patients (n = 613, 82.9%). Such limitation may be a result of the NCDB consisting of hospital-based data, which accounts for 30% of the 5,000 US hospitals based on the CoC accreditation of these facilities and the proportion of patients that sought cancer care in these facilities [11]. Such hospital-based data further impacts the ability of NCDB to equally represent all ethnicities, typically capturing only 65% of cancers in Caucasian, African-American, and Asian ethnicities and 50% of cancers in Hispanic ethnicities.

For RT administration, a median RT dose of 50.4 Gy (range = 25–72 Gy) over 28 fractions was determined and is concurrent with the standard of care for EPN [8,12,13,17,19,20,29]. Some studies recommended the use of an adjuvant RT dose of ≥ 50.4 Gy as this dose is associated with a higher OS and PFS than with <50.4 Gy, while a number encourage the use of >45 Gy or an RT dose range of 45–54 Gy [12,25,27,29-32]. A few found no significant benefit to high RT doses [18,20,21,23,28]. These conflicting findings may be skewed due to either a poor sample size or the unequal distribution of EPN between grades and ages. This current study and published literature highlight how ideal RT utilization and dosing for the treatment of EPN remains controversial. This should all be in context of the known side effects of RT including but not limited to gliosis, fibrosis, and radiation myelopathy [23,33].

Our study supports the prevailing notion that GTR is the primary goal of treatment in the management of MPE. If such a resection is not possible, STR with adjuvant RT is recommended. Several studies have indicated an association with GTR and better patient outcomes, which are typically measured in PFS or LC, when compared to STR with or without RT [8,13,14,20,22,23,25-28,32,34]. For GTR, the resection of the encapsulated, intact tumor is recommended over piecemeal, as the former has been shown to have lower recurrence incidents [13,22]. Nonetheless, patients who proceeded with GTR, whether encapsulated or piecemeal, were shown to have better mean survival than patients with STR (GTR mean = 19 years v. STR mean = 14 years) [22]. Technological advancements in diagnostic imaging, microsurgery and electrophysiological cord monitoring (e.g. somatosensory- and motor- evoked potential) have also contributed to a decline in morbidity and mortality rates in the resection of intramedullary spinal tumors, resulting in increased preferential use of GTR [23,33]. Complications due to surgery should remain heavily weighed upon recommendation. These complications include neurological deficits,

pulmonary embolism, lowered Franklin grade, wound infections, leakage of cerebrospinal fluid, development of cysts and syrinx, paraplegia, kyphosis and scoliosis [14,33].

5. Potential study limitations

This study was limited by the paucity of adult patients with histologically confirmed MPE in the NCDB. For this reason, the sample size was not robust enough to yield significant data on OS. Additionally, the study was limited by the poor data on utilization of alternative therapies to surgical resection and RT, such as chemotherapy. The NCDB is unable to differentiate between patients who received a STR versus a GTR in spinal cases, which is a possible confounder of the likelihood of RT being offered to a particular patient. While the NCDB is a strong tool for evaluating OS, it does not have the capability to report on PFS as the database only account for newly diagnosed cancer cases. This is a big weakness for a population with such high survival rates, but for which re-resection may impact patient morbidity. Furthermore, as the NCDB provides no information beyond Charlson-Deyo comorbidity score on overall patient health (i.e. Karnofsky Performance Status), its ability to assess true equipoise among MPE patients facing surgery with or without adjuvant RT is limited.

6. Future studies

Although this study comprise of one of the largest cohorts of adult patients diagnosed with MPE, future aims included a multi-institutional collaboration between CoC and non-CoC accredited facilities to aggregate a more robust patient population with complete clinical data. This would allow for the conduction of a more comprehensive analysis and limit the possible over- or under-representation of certain sociodemographic groups. This analysis should also be expanded to include the pediatric population.

7. Conclusion

The patterns of care for the treatment of adult MPE listed in the NCDB are reported in this study, with a particular interest in the utilization of RT. NCDB analysis supported GTR as the primary treatment goal, but also acknowledged the role for STR combined with RT in presumed unresectable cases. A discrepancy was noted in the treatment of different ethnic groups with patients of Latino/Hispanic ethnicity showing a significantly higher utilization of RT compared to all other ethnic groups. Additional studies are indicated to determine the efficacy of RT in prolonging PFS and OS in patients following STR, GTR, or as stand-alone treatment in patients with MPE.

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Abbreviations:

CNS	Central Nervous System
CoC	Commission on Cancer
EBRT	External Beam Radiation Therapy
EPN	Ependymomas
GTR	Gross total resection
ICD-O-3	International Classification of Diseases for Oncology
MPE	Myxopapillary Ependymomas
NCDB	National Cancer Database
OS	Overall Survival
PF	Posterior Fossa
PFS	Progression Free Survival
RT	Radiation Therapy
SE	Subependymomas
SEER	Surveillance, Epidemiology and End Results
ST	Supratentorial
STR	Subtotal resection
WHO	World Health Organization

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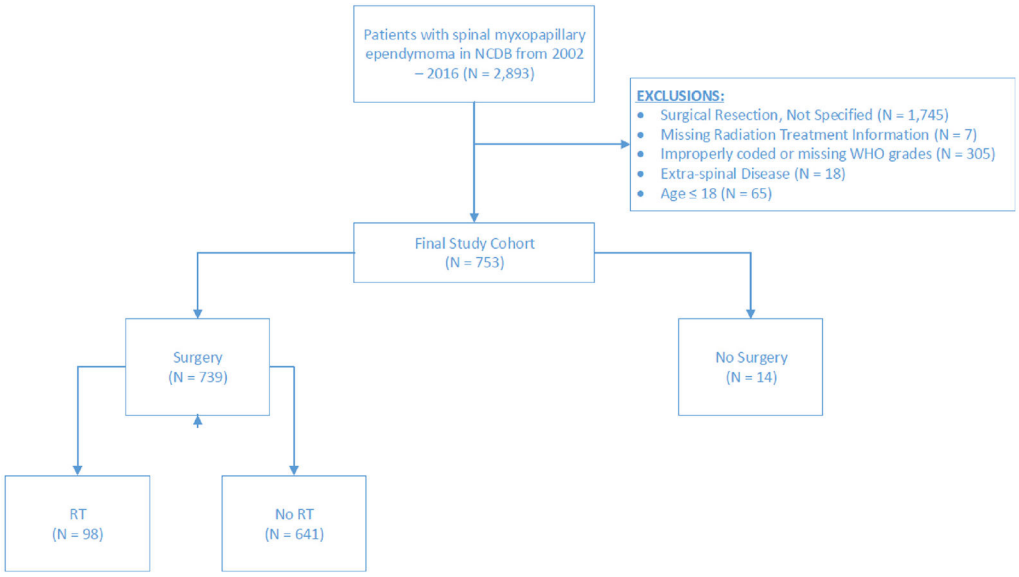

Fig. 1.
Exclusion and Inclusion Criteria for NCDB Analyses of Adult MPE Patients.

Table 1A

Percent and P-value of Adult Myxopapillary Ependymoma Patient Characteristics based on Receipt of Adjuvant Radiation Therapy.

	No Radiation Therapy			Radiation Therapy			
	N	**Column %**	**Row %**	**N**	**Column %**	**Row %**	**P-value**
Sex							0.91
Male	347	54.1%	86.5%	54	55.1%	13.5%	
Race							0.017
Caucasian	535	83.5%	87.3%	78	79.6%	12.7%	
Black	27	4.2%	93.1%	*	*	*	
Asian/Pacific Islander	*	*	*	*	*	*	
Hispanic/Latino	39	6.1%	73.6%	*	14.3%	26.4%	
Other	*	*	*	*	*	*	
Unknown	*	*	*	*	*	8	
Comorbidities							0.56
0	535	83.5%	86.2%	86	87.8%	13.8%	
1	78	12.2%	88.6%	*	10.2%	11.4%	
≥2	28	4.4%	93.3%	*	2.0%	6.7%	
Insurance							0.38
Not Insured	22	3.4%	81.5%	*	*	*	
Private Insurance	449	70.0%	87.4%	65	66.3%	12.6%	
Medicaid	59	9.2%	85.5%	*	*	*	
Medicare	90	14.0%	89.1%	*	*	*	
Other Government	*	*	*	*	*	*	
Unknown	*	*	*	*	*	*	
Education							0.58
≥13% High School Graduates	245	38.3%	87.8%	34	34.7%	12.2%	
Income							0.91
≥48 K	424	66.3%	86.9%	64	65.3%	13.1%	
Population							0.54
Non-Metropolitan	91	14.2%	85.0%	*	*	*	
Metropolitan	536	83.6%	87.0%	80	81.6%	13.0%	

	No Radiation Therapy			Radiation Therapy			
	N	**Column %**	**Row %**	**N**	**Column %**	**Row %**	**P-value**
Unknown	*	*	*	*	*	*	
Facility Type							0.18
Community Cancer Program	*	*	*	*	*	*	
Comprehensive Community Cancer Program	128	20.0%	93.4%	*	*	*	
Academic/Research Program	171	26.7%	86.8%	26	26.5%	13.2%	
Integrated Network Cancer Program	60	9.4%	89.6%	*	*	*	
Unknown	266	41.5%	83.4%	53	54.1%	16.6%	
Facility Location							0.051
East/Atlantic	140	21.8%	94.0%	*	*	*	
Central	159	24.8%	85.9%	26	26.5%	14.1%	
West	76	11.9%	88.4%	*	*	*	
Other	266	41.5%	83.4%	53	54.1%	16.6%	
Extent of Surgery							
No Surgery	*	*	*	*	*	*	
Surgery	641	85.1%	86.7%	98	13.0%	13.3%	Surgery

Patient populations of ≤20 patients were reported with asterisks (*) for de-identification purposes. The p-values was obtained through the Fisher's extract test.

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Table 1B

Median and Range of Adult Myxopapillary Ependymoma Patient Characteristics based on Receipt of Adjuvant Radiation Therapy.

	No Radiation Therapy			Radiation Therapy			P-value
	N	Median	Range	N	Median	Range	
Age	641	44	33–56	98	36	26–52	0.002
Tumor size (mm)	448	23	15–40	63	39	20–64	<0.001
Greater Circle distance (mi)	640	15.85	7.55–37.2	98	16.25	6.3–39.7	0.83

Patient populations of ≤20 patients were reported with asterisks (*) for de-identification purposes. The p-values were obtained from the Wilcoxon rank-sum test.

Table 2

Adjuvant Radiation Therapy Administration in Adult Myxopapillary Ependymoma.

Extent of Radiation Treatment	N	Column %		
None	650	86.3%		
External Beam	89	11.8%		
SRS	*	*		
	Median	**Mean**	**Standard Deviation**	**Range**
RT Regional Dose (Gy)	50.4	48.94	6.97	25–72
Radiation Ended (Days)	42	42.88	9.06	7–106
Number of RT to this Volume	28	28.87	4.92	5–56

Patient populations of ≤20 patients were reported with asterisks (*) for de-identification purposes.

SRS – stereotactic radiosurgery.

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