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Scientific Article

Modern Radiation Treatment Planning Parameters and Outcomes in Pediatric Tectal Gliomas

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Purpose: Pediatric low-grade tectal gliomas are rare, indolent tumors of the brain stem. We reviewed outcomes of pediatric patients who received a diagnosis of low-grade tectal gliomas and report dosimetric parameters for those receiving radiation therapy (RT).

Methods and Materials: We retrospectively reviewed all pediatric patients (age <18 years) at our institution diagnosed with a low-grade glioma between 1993 and 2020 (n = 288). Twenty-three patients with tectal gliomas were identified. Patients who received RT (n = 8) had detailed dosimetric analyses performed. Doses to critical structures and any resulting toxicities were reviewed. Minimum follow-up was 2 years and complete follow-up was available for all patients.

Results: Twenty-three patients, with a median age of 8.9 years, were included (range, 0.5-16.2 years). At a median follow-up of 7.4 years (range, 2-24 years), all were alive at the end of the study period. Three patients (13%) were treated with upfront RT; none of these patients developed local failure (LF) after a median follow-up of 10.6 years. One patient was treated with upfront chemotherapy with no evidence of progression afterward. Nineteen patients were initially observed after diagnosis and 26% of them (n = 5) experienced local progression. All 5 were treated with salvage RT, with 1 patient requiring further treatment with chemotherapy. Fractionation schedules for patients undergoing upfront or salvage RT included 50.4 Gy in 28 fractions (n = 4), 54 Gy in 30 fractions (n = 2), and 51 Gy in 30 fractions (n = 2). For patients treated after 2007, the gross tumor volume was delineated on a T2 magnetic resonance imaging with an average gross tumor volume-to-planning target volume expansion of 4.5 mm (range, 3-5 mm). Detailed dosimetric parameters were available for all patients treated with RT.

Conclusions: Our review supports the indolent behavior for most tectal gliomas. For the subset of tumors with evidence of progression, modern photon RT results in excellent oncologic outcomes with minimal late effects.

Introduction

Of the 16,000 new pediatric cancers diagnosed annually in the United States, approximately 300 fall under the category of brain stem gliomas. Within this rare subset,

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<5% are tectal gliomas: slow growing tumors of the dorsal midbrain with a prolonged and indolent natural history.[1] Tectal gliomas often present with symptoms of increased intracranial pressure and hydrocephalus, as the tectum abuts the posterior third ventricle and aqueduct of Silvius where tumor growth causes obstruction of the cerebral ventricular system. On magnetic resonance imaging (MRI), tectal gliomas exhibit radiologic characteristics similar to other low-grade gliomas: T1 isointense and T2 hypertense, with little to no contrast enhancement.[2] Classical radiographic appearance is demonstrated in Fig. 1.

Initial management of tectal gliomas often involves cerebrospinal fluid (CSF) diversion, in the form of an endoscopic third ventriculostomy (ETV) or ventriculoperitoneal (VP) shunt.[3] There is no further role for surgical intervention given the eloquent location of the tectum. Biopsies, via endoscopic methods at time of ETV, can be performed for pathologic differentiation of tectal gliomas from other tumors of this region (ie, germ cell tumors and pineal parenchymal tumors). However, given the surgical risks of oculomotor dysfunction, somnolence, mutism, and death, tectal gliomas are most often diagnosed on a clinicoradiologic basis. Once a diagnosis has been established and CSF diversion performed, the best next step in management of these tumors is most often observation. Given the young median age at diagnosis as well as the indolent nature of these tumors, tectal gliomas generally do not require upfront oncologic treatment.[4] Upon progression, often seen as slow interval growth across years, treatment options may include local radiation therapy (RT) or systemic therapy dependent on patient age, tumor extent, physician and parent preference, as well as the presence of genetic risk factors, such as NF1.

At our center, RT has been the preferred treatment for progressive tectal gliomas. During the past 30 years, advances in imaging, stereotactic localization, and delivery techniques have refined our institutional approach. We reviewed all patients who received a diagnosis of tectal gliomas at our institution and describe their clinical presentations, tumor characteristics, management, and outcomes with a special focus on RT dosimetry and long-term toxicity.

Methods and Materials

This retrospective study was approved by our institutional review board. After a detailed review of our low-grade glioma database (n = 288), we identified 23 patients who received a diagnosis tectal gliomas between 1995 and 2023 at our center. Seventeen patients received a diagnosis on a clinicoradiographic basis via MRI, and a biopsy was obtained in the remaining 6 patients. Paper charts and electronic medical records were reviewed. Clinicopathologic features were recorded for each patient, including age at diagnosis, sex, presenting symptoms, radiologic characteristics, therapeutic management, pathologic diagnosis if obtained, follow-up duration, endocrinopathies, neurocognitive dysfunction, and secondary malignancies. Tumor volume was estimated with an ellipsoid volume equation using the 3 largest perpendicular diameters. RT plans were reviewed in detail and doses to critical neural structures were recorded and analyzed.

Eight patients in our cohort received RT. Four patients were treated with stereotactic guidance using volumetric modulated arc therapy (VMAT) between 2008 and 2020. Our institutional protocol has been to delineate the gross tumor volume (GTV) on a high resolution, thin slice T2 MRI (1 mm slice thickness volumetric MR). Given that these tumors are well-defined radiographically and that we use daily stereotactic guidance, we then add an isometric expansion of 3 to 5 mm to create our planning target volume (PTV). Conceptually, this expansion encompasses both a CTV and PTV. For this cohort, our average PTV expansion was 4.5 mm (range, 3-5 mm). VMAT planning for these tectal glioma patients used a 5 arc noncoplanar beam arrangement to create a conformal plan and best spare the organs at risk. Two patients had RT delivered with a 3-dimensional conformal plan (3DCRT); this involved a 4-field beam arrangement with RT delivered with noncoplanar beams. The remaining 2 patients had stereotactic RT using single isocenter cone-based arcs without intensity modulation. For these patients, we obtained paper charts and recreated the RT plans using field and collimator sizes available from the original documents. All organs at risk, including the brain stem,

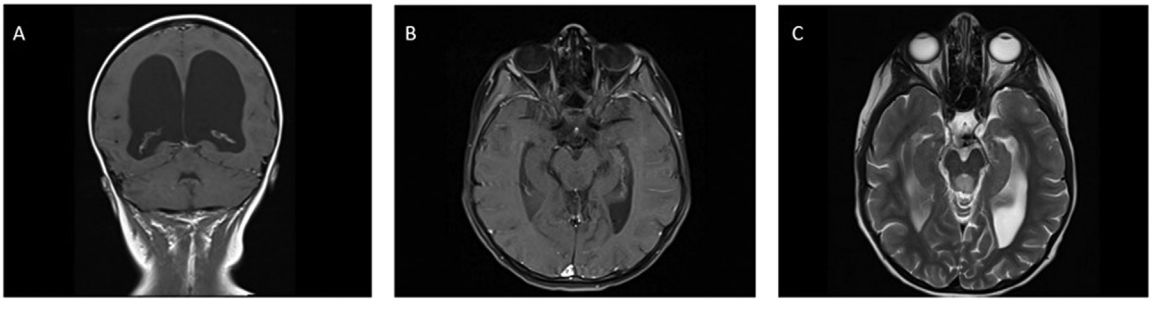

Figure 1 (A) On a coronal T1 sequence magnetic resonance imaging (MRI), an isointense mass can be seen at midline along with resultant hydrocephalus. (B) On an axial T1c sequence MRI, lack of contrast enhancement is noted. (C) On an axial T2 sequence MRI, the mass is clearly visible secondary to its hyperintensity.

pituitary gland, bilateral temporal lobes, cochlea, and hippocampi were contoured and evaluated dosimetrically.

Patients were followed in accordance with standard institutional protocols. MRI of the brain was obtained every 3 months for the first year, every 4 months for years 2 to 3, every 6 months for years 4 to 5, and then yearly thereafter until at least 10 years when follow-up was further reduced with imaging every 2 to 5 years. All patients were evaluated in multidisciplinary pediatric brain tumor clinic. Formal endocrine and neurocognitive testing were performed on an as-needed basis. Neurocognitive data included measurement of verbal and visual spatial intellect, fluid reasoning, attention and working memory, and processing speed with the age appropriate Weschler measure (WISC-4: Weschler Intellectual Scale for Children, fourth edition; WPPSI-4: Wechsler Preschool and Primary Scale for Intelligence, fourth edition; WPPSI-3: Wechsler Preschool and Primary Scale for Intelligence, third edition; WAIS-4: Wechsler Adult Intelligence Scale, fourth edition. Verbal Learning and verbal memory were assessed with the Wide Range Assessment of Memory and Language, second edition (WRAML-2). Basic academic skills within reading and math were assessed with the Wide Range Achievement Test- fifth edition (WRAT-5). Parent report of executive functioning was quantified with the Behavioral Rating Inventory of Executive Functioning-Second Edition (BRIEF-2). The data were collected for clinical purposes and was gathered pre- and postradiation. Raw data within each domain were compared with normative data from same-aged peers and converted to scaled or standard scores. All Weschler indices and WRAT-5 data are represented as standard scores with a mean of 100, and SD of 15; WRAML-2 scores are presented as scaled scores with a mean of 10 and SD of 3. BRIEF-2 data are T scores with a mean of 50, and a SD of 10 (higher scores indicate more problems).

Table 1 Patient characteristics (n = 23)

Characteristic	Value
Age at diagnosis	
Median	8.9 y
Range	6 mo to 16.2 y
Sex	
Male	17 (74%)
Female	6 (26%)
Biopsy	
Yes	7 (30%)
No	16 (70%)
Biopsy result	
Low-grade astrocytoma	6 (86%)
Low-grade neuroepithelial tumor	1 (14%)
Hydrocephalus	
Yes	21 (91%)
No	2 (9%)
Tumor volume, cm^3	
Mean	2.13
Range	0.3-12.3
Contrast enhancement	
Yes	4 (17%)
No	19 (83%)
Initial management	
Observation	19 (83%)
RT	3 (13%)
Chemotherapy	1 (4%)

Abbreviations: RT = radiation therapy.

Results

Patient and tumor charactersitics

Between 1993 and 2020, 23 patients received a diagnosis of a tectal glioma at our institution (Table 1). The median patient age was 8.9 years (range, 0.5-16.2 years). Seventeen patients (74%) were male and 6 patients (26%) were female. Median follow-up for our patient cohort was 7.4 years (range, 2-24 years). On initial presentation, hydrocephalus was noted in 21 patients (91%). Twenty patients (87%) were symptomatic at diagnosis secondary to increased intracranial pressure. The most common symptoms were headache, nausea, and imbalance. In terms of imaging charactersitics, the mean tumor volume was 2.1 cm^3 (range, 0.3-12.3 cm^3). Tumors were hyperintense on T2 MRI in 22 patients (96%) and contrast enhancing in 4 patients (17%). Two lesions had cystic components.

Management and outcomes

After the diagnosis of a tectal glioma was established, surgical management of hydrocephalus was performed in 22 patients (96%); half of these patients had VP shunts placed and half underwent ETV. Patients treated earlier in the study period were more likely to receive a VP shunt, whereas patients diagnosed in later years were generally managed with ETV. One patient received a diagnosis incidentially and no hydrocephalus was seen on imaging. Therefore, this patient was observed with no procedural intervention. Biopsy was performed on 7 patients. Six underwent biopsy at the time of initial diagnosis during ETV and all 6 received a diagnosis of as low-grade astrocytomas. One patient underwent biopsy after tumor progression after RT and pathology revealed a low-grade neuropithelial tumor notable for FGFR1 and PIK3CA pathogenic variants.

After procedural intervention, observation was the intial management strategy in 19 patients (83%). Three patients received RT at the time of diagnosis. One of these patients presented with a large tumor causing severe neurologic symptoms. He was therefore treated at diagnosis, as even slight tumor growth would have likely worsened his clinical condition. The other 2 patients were the first diagnoses of tectal glioma in our cohort; as mentioned previously, observation is the current preferred initial management strategy. Of the 19 patients who were observed, 5 (26%) progressed and received salvage RT. Four of these patients had stable disease after RT; however, one continued to progress and ultimately required salvage chemotherapy consisting of carboplatin and vincristine. The tumor has remained stable after chemotherapy. The median age at the completion of RT was 9.8 years old (range, 4.8-15.5 years). All 23 patients are alive at the time of our analysis with no evidence of recent progression. A summary of our cohort's clinical outcomes can be seen in Table 2.

Radiation dosimetry

Radiation fractionation schedules for the 8 patients receiving radiation treatment included 50.4 Gy in 28 fractions (n = 4), 54 Gy in 30 fractions (n = 2), and 51 Gy in 30 fractions (n = 2). Average dosimetric parameters were obtained from review of all RT plans and are shown in Table 3. A representative VMAT treatment plan and dose distribution is depicted in Fig. 2. A representative 3DCRT treatment plan and dose distribution is depicted in Fig. 3.

Neurocognition, endocrine function, and secondary malignancy risk

Of patients who received RT, 50% underwent both pre- and post-RT neurocognitive evaluations, with one patient having serial evaluations. The patients were between 4 and 12 years of age at the time of testing. All patients who were referred for formal neuropsychological testing were in an at-risk group before radiation. At their pre-RT baseline, defined as time T-1, all patients tested displayed low-average to average cognitive abilities overall (Table 4). Half of the patients had processing speed and verbal learning abilities that were at least one standand deviation below the mean. Patient 1 presented with massive hydrocephalus and impaired cognitive abilities at pre-RT baseline testing. Patients 2 and 3 had baseline developmental and psychiatric diagnoses that preceded both their tectal glioma diagnosis as well as their receipt of RT. These underlying diagnoses included ADHD, developmental delay, and speech disorders. The final patient (patient 4) had processing speed impairments and delayed development at baseline, particularly in the physical, motor, language, and cognitive categories.

Neuropsychological testing was repeated after RT, defined as time T-2 (Table 5). The time interval from RT to post-RT testing was between 4 to 20 months (average, 10.25 months). Three patients demonstrated a significant weakness or impairment in processing speed and verbal learning. Two patients demonstrated perceptual reasoning, visual motor integration, and math calculations skills which were at least a standard deviation below the mean. However, when evaluating for change over time within each individual, most domains remained stable. Two individuals had a 0.5 SD decline in working memory and one had a 1 SD decline in verbal learning across the pre-RT to initial post-RT period. All patients had impaired but stable processing speed when comparing the pre-RT to post-RT testing.

One patient (patient 4) in our cohort underwent serial neuropsychological assessments. Before RT, he had processing speed impairments and delayed development, particularly in physical, motor, language, and cognitive categories. This patient was the youngest patient to be irradiated (age 4) and had the longest RT-to-testing interval at 158 months. Of note, he was treated via 3DCRT. At most recent follow-up, he demonstrated impaired verbal abilities, verbal learning, working memory, and processing speed skills. This represented a significant decline in functioning from the pateint's baseline testing with 1 to 2 SD below the mean seen across multiple parameters.

In terms of endocrine function, 3 patients (13%) were noted to have some dysfunction. The first patient was noted to have premature thelarche 7 years after being diagnosed with a tectal glioma; no RT was administered to this patient. Another patient was noted to have hypotestosteronemia before RT, but no new endocrinopathies developed after treatment. Finally, a third patient developed hypopituitarism, requiring levothyroxine and hydrocortisone replacement, after being treated with stereotactic cone-based arc therapy in 2003. The pituitary gland received a maximum of 11.49 Gy and a mean of 7.22 Gy, which is below the generally accepted threshold of radiation doses known to cause pituitary dysfunction, although no other risk factors were present.[5] No patients in this cohort developed strokes, vasculopathies, or any secondary maligancies to date.

Discussion

Tectal gliomas are rare malignancies, accounting for <5% of pediatric brain stem tumors. Given their proximity to the cerebral ventricular system, they most commonly present with symptomatic hydrocephalus and first line management involves CSF diversion and management of hydrocephalus, most commonly with ETV in

Table 2 Clinical details of patients who received a diagnosis of low-grade tectal glioma

Age/sex at diagnosis	Presenting symptoms	VP shunt or ETV	Tumor features	Result of biopsy	First line treatment	Progression	Time to first progression	Late effects	Time of follow-up	Disease status
16M	Leg weakness, imbalance, slurred speech, swallowing difficulties, hyperreflexia in lower extremities with ankle clonus	VP shunt	1.5 cm, nonenhancing, T2 bright	NA	Observation	No		None	2.1 y	Stable disease
12M	Numbness	ETV	4.1 cm, nonenhancing, T2 bright	Grade 2 astrocytoma	Radiation therapy, 54 Gy in 30 fractions	No		None	2.6 y	Stable disease
4M	Seizures	ETV	1.7 cm, nonenhancing, T2 bright	NA	Observation	Yes, after which received RT to 50.4 Gy in 28 fractions	13 mo	None	3.9 y	Stable disease
5M	Imbalance, falls	ETV	1.7 cm, nonenhancing, T2 bright	Low-grade neuroepithelial tumor	Observation	Yes, multiple relapses	37 mo	None	5.7 y	Stable disease
5M	Imbalance, incontinence	ETV	1.7 cm, nonenhancing, T2 bright	NA	Observation	Yes, after which received RT to 50.4 Gy in 28 fractions	61 mo	None	7.4 y	Stable disease
13M	Double vision, emesis, headaches	ETV	1.4 cm, nonenhancing, T2 bright	NA	Observation	No		None	7.5 y	Stable disease
9M	Imbalance, nausea, visual change	ETV	3.1 cm, nonenhancing, T2 bright	Low-grade astrocytic tumor	Observation	No		None	7.2 y	Stable disease
10M	Headache, nausea, vomiting	ETV	1.5 cm, nonenhancing, T2 bright	NA	Observation	No		None	7.0 y	Stable disease
15F	Headache, nausea, vomiting	VP shunt	1.5 cm, nonenhancing, T2 bright	Pilocytic astrocytoma	Radiation therapy, 54 Gy in 30 fractions	No		None	24.5 y	Stable disease
3M	Imbalance	VP shunt	1.2 cm, nonenhancing, T2 bright	NA	Observation	Yes, after which received RT to 50.4 Gy in 28 fractions	16 months	Extremely low IQ	16.7 y	Stable disease
15F	Papilledema on routine eye examination	ETV	1.6 cm, nonenhancing, T2 bright	NA	Observation	No		None	2.4 y	Stable disease
6 mo, F	Nausea, vomiting	ETV	1.4 cm, contrast enhancing, T2 bright	NA	Observation	No		None	24.0 years	Stable disease
6M	Imbalance, lethargy	VP shunt	4.0 cm, contrast enhancing	NA	Radiation therapy to 51 Gy in 30 fractions	No*		Hypopituitarism	10.6 y	Stable disease
13M	Headaches, nausea	VP shunt	1.4 cm, nonenhancing, T2 bright	NA	Observation	No		None	8.4 y	Stable disease
13F	Headaches, nausea	ETV		NA	Observation	No		None	14.6 y	Stable disease

(*continued on next page*)

Table 2 (*Continued*)

Age/sex at diagnosis	Presenting symptoms	VP shunt or ETV	Tumor features	Result of biopsy	First line treatment	Progression	Time to first progression	Late effects	Time of follow-up	Disease status
			1.4 cm, nonenhancing, T2 bright							
7M	Headaches, nausea, vomiting	VP shunt	1.5 cm, nonenhancing, T2 bright	NA	Observation	No		None	5.0 y	Stable disease
5M	Incidental finding after head trauma	VP shunt	1.9 cm, nonenhancing, T2 bright	Pilocytic astrocytoma	Observation	No		None	6.2 y	Stable disease
9M	Headache, visual changes	ETV	1.8 cm, nonenhancing, T2 bright	NA	Observation	No		None	9.3 y	Stable disease
6 mos, F	Headache, vomiting	VP shunt	1.0 cm, nonenhancing, T2 bright	NA	Observation	No		Bilateral optic nerve hypoplasia	7.5 y	Stable disease
9M	Headaches, seizures	Neither	1.7 cm, nonenhancing, T2 bright	NA	Observation	No		None	7.4 y	Stable disease
10M	Headaches, nausea	VP shunt	1.5 cm, nonenhancing, T2 bright	NA	Observation	No		None	14.3 y	Stable disease
7 mo, M	Increasing head circumference	VP shunt	2.0 cm, contrast enhancing, cystic	Pilocytic astrocytoma	Observation	Yes, after which received RT to 51 Gy in 30 fractions	13 years	None	28.9 y	Stable disease
4F	Imbalance	VP shunt	2.4 cm, contrast enhancing, cystic	Pilocytic astrocytoma	Chemotherapy	No		Hypothyroidism, GH deficiency	15.4 y	Stable disease

Abbreviations: ETV = endoscopic third ventriculostomy; F = female; M = male; NA = not applicable (patient did not undergo biopsy); VP = ventriculoperitoneal.

Table 3 Mean dosimetric variables for all patients treated with radiation therapy for tectal glioma

Organ at risk	Mean dose (range, Gy)	Maximum dose (range, Gy)
Brain stem	31.74 (23.19-44.13)	54.37 (51.74-57.96)
Pituitary	4.73 (0.79-9.86)	7.76 (2.24-12.76)
Right hippocampus	26.08 (11.95-33.73)	51.07 (40.09-57.25)
Left hippocampus	31.80 (17.30-47.51)	51.33 (40.29-57.04)
Right temporal lobe	8.46 (3.60-16.60)	44.00 (35.05-54.34)
Left temporal lobe	10.25 (3.86-19.33)	46.84 (24.68-57.20)
Right cochlea	5.74 (1.91-12.93)	7.23 (2.37-15.60)
Left cochlea	5.45 (1.53-9.05)	6.48 (1.80-10.16)

recent years. Diagnosis can be established radiographically or via an endoscopic or stereotactic biopsy. There is no role for further surgical intervention given the eloquence of the dorsal midbrain, though microsurgical approaches have been described.[6] Although most tectal gliomas have an indolent natural history, a small percentage of tumors exhibit more aggressive behavior and local progression, necessitating the use of regular surveillance imaging. In our cohort only 25% of initially diagnosed tumors progressed, which is less than reported in other series although this could be due to the inclusion of more malignant histologic subtypes in those studies.[4,7] Salvage options include chemotherapy or RT, the choice being most dependent on patient age and parent/physician preference. As shown in our series, modern RT provides durable local control and minimal late effects.

Atomic-bomb survivorship data shows that younger age at the time of irradiation correlates with an increased incidence of neurocognitive deficits.[8-11] However, when considering the effects of curative intent focal cranial irradiation, the data are less clear, as it is difficult to determine the effects of RT versus that of chemotherapy, surgical resection, or the effects of the tumor itself which is often hydrocephalus in tectal gliomas.[12-15] As our understanding of the natural history of low-grade gliomas has developed, along with our experience with oncologic treatment modalities, standard of care has evolved to avoid RT when possible and particularly in younger patients to best protect neurocognitive function in the pediatric population. However, given the less established durability of chemotherapies in pediatric tectal gliomas, and the generally small size of these tumors when becoming symptomatic, consideration of first line RT can be made. Advances in stereotactic guidance and VMAT techniques enable optimal sparing of normal brain and provide excellent outcomes for this patient population. The use of targeted pharmacologic agents for tectal gliomas is quite a challenge given the barriers of obtaining pathologic tissue near the midbrain. However, new techniques in obtaining pathologic information on actionable mutations are rapidly becoming available. One such technique is the utilization of cell-free DNA, genetic material

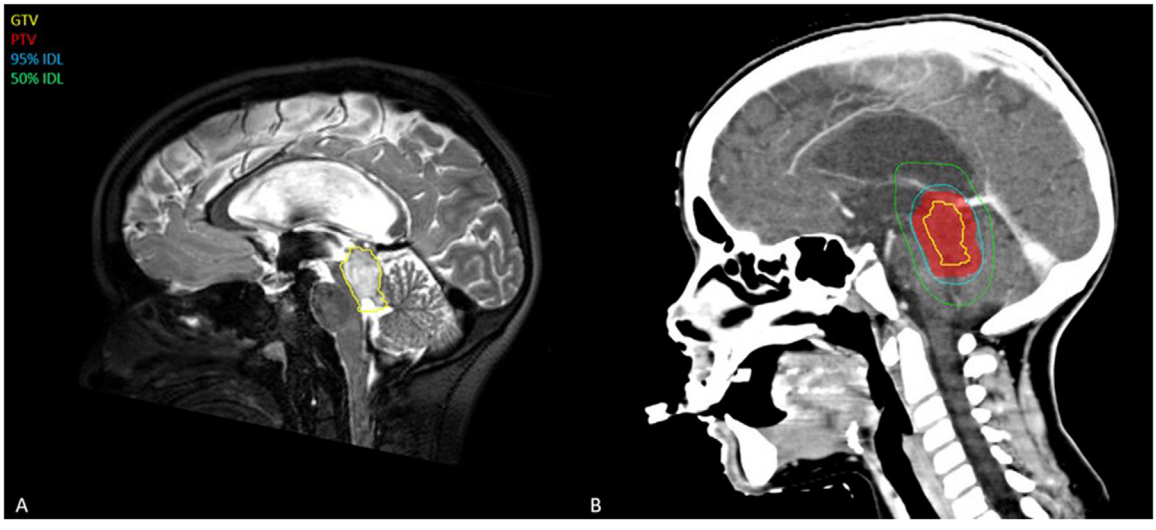

Figure 2 (A) Tumor delineated on the T2 magnetic resonance imaging (yellow = gross tumor volume). (B) Dose distribution of volumetric modulated arc therapy radiation therapy (yellow = gross tumor volume; red = planning target volume; blue = 95% isodose line; green = 50% isodose line).

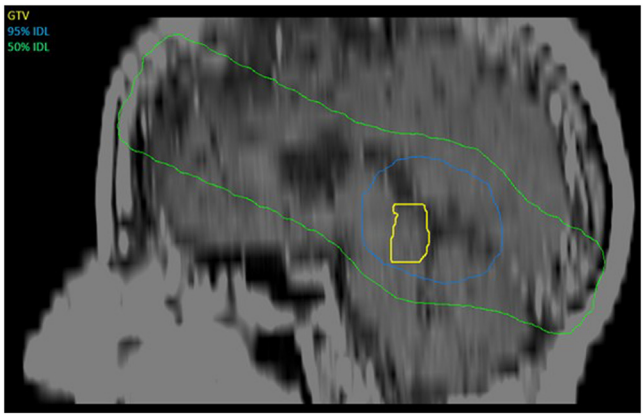

Figure 3 Dose distribution of a 3-dimensional conformal plan delivered with noncoplanar beams (yellow = gross tumor volume; blue = 95% isodose line; green: 50% isodose line). Note the dose is prescribed to the 95% isodose line (IDL).

originating from dying tumor cells. These samples are taken from plasma, CSF, or urine, allowing for liquid biopsies, rather than obtaining true tumor tissue in a location as sensitive as the tectum.[16] Once detected and confirmed as malignant tissue, identification of mutations and initiation of targeted therapies (ie, BRAF, FGFR) is possible, thereby allowing RT to be delayed in this younger pediatric population.[17] However further work and validation of these approaches must be completed, and RT will likely continue to play an important role in the definitive management of this disease. Thus, utilization of advanced image guided RT techniques that enable reduced PTV margins (3-5 mm) and a solid understanding of critical structure dose tolerances is crucial for safe and effective treatment of tectal gliomas.

Given the concern in the oncologic community of RT causing long-term neurocognitive damage, there have been several dosimetric analyses evaluating the relationship between cognition and the receipt of RT. Goda et al prospectively evaluated 48 pediatric patients (median age, 13 years) treated with RT doses of 54 Gy in 30 fractions. On multivariable analysis, age >13 years and mean left hippocampus dose of <30 Gy were predictive of favorable IQ outcomes, consistent with conceptual framework and guidelines of modern pediatric radiation oncology treatments.[18] The relationship between age and receipt of RT is demonstrated in our cohort as well: the patient whose neurocognitive testing demonstrated the highest degree of impairment underwent RT at age 4, although his baseline impairments in development likely played a role as well.[19] In addition, this patient was treated early in our reported experience, without the benefit of intensity modulation which can also improve dosimetric parameters. In another study, Acharya et al evaluated 80 pediatric patients with low-grade gliomas treated with RT to 54 Gy.[20] All patients underwent cognitive testing for a period of 10 years post-RT. In young children (age <12), a significant decline in long-delay recall was associated with hippocampal dose. On multivariable regression, neurocognitive decline was associated with the volume of hippocampus receiving 40 Gy (V40), providing further evidence that radiation injury to the hippocampus

Table 4 Pre-RT cognitive abilities

Patient	Age at T1 (pre-RT)	IQ Measure	VCI	PRI	FRI	WMI	PSI	VL	VLD
1	12 y, 7 mo, 3 d	WISC-4	95	86	94	91	60*	5 †	5 †
2	4 y, 3 mo, 19 d	WPPSI-4	88	106	100	NA	NA	NA	NA
3	7 y, 8 mo, 20 d	WISC-4	100	92	91	107	75 †	7 †	8
4	4 y, 9 mo, 5 d	WPPSI-3	85	85	NA	NA	NA	NA	NA

Abbreviations: FRI = Fluid Reasoning Index; PRI = Perceptual Reasoning Index; PSI = Processing Speed Index; RT = radiation therapy; VCI = Verbal Comprehension Index; VL = Verbal Learning from Wide Range Assessment of Memory and Language, third edition; VLD = Verbal Memory Delayed from Wide Range Assessment of Memory and Language, third edition; WISC-4 = Weschler Intellectual Scale for Children, fourth edition; WMI = Working Memory Index; WPPSI-3 = Wechsler Preschool and Primary Scale for Intelligence, third edition; WPPSI-4 = Wechsler Preschool and Primary Scale for Intelligence, fourth edition.

*At least 2 SD below the mean.

†At least 1 SD below the mean.

VCI, PRI, FRI, WMI, and PSI are all presented as standard scores with a mean of 100, and SD of 15; VL and VLD are presented as scaled scores with a mean of 10 and SD of 3.

Table 5 Post-RT cognitive abilities

Patient	RT date	Age at RT	Time since RT at T2	Age at T2	IQ	VCI	PRI	FRI	WMI	PSI	VL	VLD	VMI	Read	Math	BRI	ECI	CRI
1	2019	12 y, 7 mo	11 mo	14 y, 7 mo	WISC-4	103	84*	105	85*	63†	6*	6*	73*	87	77*	46	44	74‡
2	2019	5 y, 11 mo	1 y, 8 mo	7 y, 9 mo	WISC-4	78*	94	91	70	55†	5†	6	85*	72*	81*	76‡	79‡	56
3	2021	10 y, 10 mo	4 mo	11y, 1m	WISC-4	-	-	85*	100	77*	4†	7*	89	92	100	52	44	62
4	2007	4 y, 9 mo	6 mo	5 y, 7 m (T2)	WPPSI-3	98	79*	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
4			1 y, 9 mo	6 y, 7 mo (T3)	WISC-4	91	88	-	77*	53†	9	5†	NA	NA	NA	NA	NA	NA
4			5 y, 4 mo	10 y, 7 mo (T4)	WISC-4	83	75*	NA	80*	68†	6*	3†	NA	NA	NA	58	NA	69‡
4			13 y, 2 mo	18 y (T5)	WAIS-4	70†	79*	NA	71*	75*	1†	4†	85*	81*	79*	57	62	58

Abbreviations: BRI = Behavior Regulation Index from the Behavioral Rating Inventory of Executive Functioning-Second Edition (BRIEF-2) Parent Report; ECI = Emotional Control Index from the BRIEF-2 Parent Report; Cognitive Regulation Index from the BRIEF-2 Parent Report; FRI = Fluid Reasoning Index; Math = Math Calculation from the Wide Range Achievement Test, fifth edition (WRAT-5); PRI = Perceptual Reasoning Index; PSI = Processing Speed Index; Read = Reading from Wide Range Achievement Test, fifth edition (WRAT-5); RT = radiation therapy; VCI = Verbal Comprehension Index; VL = Verbal Learning from Wide Range Assessment of Memory and Language, second edition (WRAML-2); VLD = Verbal Memory Delayed from Wide Range Assessment of Memory and Language, second edition (WRAML-2). WAIS-4 = Wechsler Adult Intelligence Scale, fourth edition; WISC-4 = Weschler Intellectual Scale for Children, fourth edition; WPPSI-3 = Wechsler Preschool and Primary Scale for Intelligence, third edition; WPPSI-4 = Wechsler Preschool and Primary Scale for Intelligence, fourth edition; WMI = Working Memory Index.

*At least 1 SD below the mean.

†At least 2 SD below the mean.

‡At least 1 standard deviation above the mean, suggesting more difficulties.

All IQ indices and WRAT-5 data are represented as standard scores with a mean of 100, and SD of 15; WRAML-2 scores are presented as scaled scores with a mean of 10 and SD of 3; BRIEF-2 data are T scores with a mean of 50, and a SD of 10 (higher scores indicate more problems).

disrupts learning and that minimizing hippocampal dose represents an important treatment objective that radiation oncologists should adhere to. In our series, the mean doses to the hippocampi were under 30 Gy for most patients treated in the modern era. This was made possible by delineating the tumor on a thin-slice T2 MRI, using stereotactic guidance that enables smaller geometric expansions (average expansion from gross tumor was 4.5 mm), and delivering RT via highly conformal volumetric modulated arc therapy. Given specific tumor presentations, 2 patients treated with this technique had mean hippocampal doses above 30 Gy; one of these individuals did experience a 0.5 SD decline in working memory, at a mean left hippocampal dose of 47.5 Gy.

RT is not the only oncologic treatment modality associated with cognitive impairment. Although the neurologic risks of pediatric neurosurgery are well established, the use of anesthesia in the pediatric population must also be considered.[21] There are several studies demonstrating an association between exposure to anesthesia in early childhood and subsequent neurodevelopmental deficits. However, causation has not been established, and there are likely several variables that need to be further studied.[22,23] Although the role of surgery is quite minimal in the management of tectal low-grade gliomas, chemotherapy is increasingly used as a temporizing measure before definitive RT in small children. Many clinical studies have reported causative associations with leukoencephalopathies, and subsequent neurocognitive deficits after chemotherapy in the pediatric population.[24-26] Similar to the association of different RT techniques with resultant neurocognitive effects, the choice of the chemotherapeutic agent and its dose plays a profound role in the risk of inducing cognitive decline. Therefore, whether RT, chemotherapy, or surgery is used for management of pediatric brain tumors, judicious use of definitive oncologic modalities with toxicity awareness is crucial for favorable long-term patient outcomes. It is important to note that not only do oncologic treatments carry risk of late effects, but also certain tumor presentations do as well. In the previously mentioned study by Acharya et al, the presence of hydrocephalus itself was shown to be associated with long-term neurocognitive difficulty on multivariable analysis. This association has been corroborated in several other studies, highlighting the need for long-term neurocognitive assessment and support for these patients.[13,27,28] Among those who received radiation, all presented with pre-RT cognitive deficits, highlighting the complex dynamics between cognitive function, tumor presentation, and oncologic treatments. Although other studies have demonstrated similar impairments in cognitive function in tectal glioma patients, ours is the first to detail both the pre- and post-RT cognitive evaluations in our radiated cohort.[29]

Other late radiation toxicities reported in the literature include the risk of vasculopathies, strokes, and secondary malignancies. No vasculopathies were seen in our cohort. However, our cohort is small, and follow-up is short at 7.4 years. The risk of such events is quite rare and the rate of vasculopathies after smaller volume modern RT are not clearly established. Therefore, we rely on outcome data from RT delivered with larger-volume less-modern techniques. For example, Moyamoya syndrome develops in ~3% to 4% of patients after cranial RT.[30-32] The risk of late stroke in survivors of pediatric brain tumors treated with RT is approximately 2% at 5 years and 4% at 10 years, with radiation dosing to the circle of Willis being the highest predictor of stroke risk.[33] Vasculopathy incidences have been correlated to the RT dose to the circle of Willis, the diagnosis of neurofibromatosis type 1, and Down syndrome. From a population outcomes standpoint, RT to cranial vasculature and brain parenchyma is not without risk. However, advances in RT during the past 30 years must be considered when providing accurate individual estimates of late effects. No strokes or secondary malignancies were seen in our cohort, although these late effects can take decades to manifest. In terms of reducing the risk of secondary malignancies, many centers have advocated for the universal adoption of protons, as the integral dose conformality of proton plans tend to be dosimetrically superior to those of photons. A large national cancer database study in 2020 explored the comparative risks between proton beam radiation therapy, 3DCRT, and IMRT.[34] In addition, 450,373 patients were identified and 33.5% received 3DCRT, 65.2% received IMRT, and 1.3% received PBRT. In a comparison between IMRT versus 3DCRT, there was no overall difference in the risk of second cancer; however, PBRT had an overall lower risk of secondary malignancies versus IMRT. However, not all studies support this finding. Earlier this year, Upadhyay et al published a meta-analysis of 24 studies comparing photon versus proton CNS radiation and subsequent risk of secondary malignancies in 38,163 children.[35] There was no significant difference in the secondary malignancy incidence between these 2 modalities, with rates of 1.5% with protons and 1.8% with photons. Our data confirm the rarity of these secondary malignancies, although the incidence of such events does not usually significantly increase until >10 years after radiation. We continue to follow our cohort to document the longer-term results of our secondary malignancy rate. Other studies have demonstrated decreased neurocognitive decline with the utilization of proton RT, further highlighting the benefits of this treatment modality.[36,37] Although certainly not unanimously adopted in pediatric radiation therapy, early studies are quite promising; yet questions regarding the magnitude of benefit, patient prioritization, and radiobiology remain.[38] Large, randomized trials will shed further light onto the benefit of protons as the possible standard treatment modality for these low-grade tumors.[39]

The strengths of our analysis include a detailed assessment of a relatively homogenous population of tectal

glioma patients, as all tumors demonstrated low-grade behavior. Other strengths include the ability to perform detailed assessment of a limited number of modern radiation treatment plans and to assess radiation dose to nearby critical structures. Limitations of our analysis include the inherent bias that is present in retrospective analyses, selection bias in the way patients are treated at a single center, and relatively short follow-up precluding long-term assessment of late effects in this patient population. In addition, 3 radiation plans that were no longer available electronically had to be recreated. There are possible slight differences in the dose distribution between the delivered and recreated plans.

Conclusion

Tectal gliomas are a rare subset of pediatric malignancies with limited data available regarding treatment response and outcomes. Although RT has been considered an effective treatment modality, the risk of possible late effects is always a concern. Our study demonstrates that as modern stereotactic guided RT techniques continue to advance and our understanding of dose constraints continues to evolve, the ability to safely treat these tumors with RT has markedly improved. Based on our experience and outcomes in treating tectal gliomas, we conclude that modern RT is an effective treatment modality, providing both favorable oncologic and clinical outcomes.

Disclosures

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.

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