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RESEARCH

Long-term outcomes after adjuvant radiotherapy in adult spinal ependymomas: a multicenter study by the trod Neuro-Oncology research group (07 – 005)

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Abstract

Purpose The optimal adjuvant treatment strategy for spinal ependymomas (SEs) is controversial, especially in patients with adverse risk factors. The efficacy of adjuvant radiotherapy (RT) and its prognostic factors remain understudied.

Methods This retrospective, multicenter study analyzed 45 adult patients (≥18 years) with histologically proven SE (WHO Grade 2 and 3) treated with RT between 1998 and 2024. Patients with Grade 1 tumors or surgery-to-RT intervals exceeding 6 months were excluded. Clinical outcomes were estimated using the Kaplan-Meier method, and prognostic factors were identified using multivariate Cox regression analysis.

Results In the Grade 2 cohort ($n=37$; median follow-up: 7.9 years), gross total resection (GTR) was achieved in 43.2% of patients. Extent of resection served as the primary determinant of disease control: zero local failures occurred in the GTR group (100% 10-year local control (LC) and disease-free survival (DFS), whereas 41.2% of non-GTR patients experienced local failure (5- and 10-year DFS: 63.9% and 54.7%, respectively; $p=0.006$). Despite superior local control with GTR, overall survival remained statistically similar between resection groups (10-year OS: 88.9% for GTR vs. 74.3% for non-GTR; $p=0.70$). In non-GTR patients without initial dissemination, a surgery-to-RT interval exceeding 1.5 months was identified as the sole independent predictor of early recurrence (HR: 13.3 and 15.9 for DFS and PFS, $p=0.04$ for both). Additionally, younger age and baseline spinal dissemination were independent adverse prognostic factors for progression and mortality. For Grade 3 tumors, the 5-year LC, progression-free survival, and OS rates were 56.3%, 41.7%, and 75.0%, respectively, with a 62.5% progression rate. Although GTR achieved complete LC in Grade 3 tumors, distant metastasis remained a primary pattern of failure, occurring in 60% of progressive cases. For patients with initial spinal dissemination, the progression rate was 60% with a median OS of 15.2 months.

Conclusion While GTR remains the gold standard for long-term prognosis, adjuvant RT provides effective LC in Grade 2 SE patients with residual disease. Early adjuvant RT (within 1.5 months post-surgery) is a critical management strategy for non-GTR cases. Grade 3 histology and initial spinal dissemination remain significant indicators of poor long-term survival.

Keywords Spinal ependymoma · Adjuvant radiotherapy · Long-term outcomes · Subtotal resection

Introduction

Spinal ependymomas (SEs) are relatively uncommon tumors, representing approximately 2–8% of all central nervous system tumors and 5–10% of all spinal tumors [1]. While ependymomas are predominantly intracranial in pediatric populations, 50–60% of adult ependymomas arise in the intraspinal compartment [2]. Despite histopathological similarities to intracranial variants, SEs exhibit distinct molecular profiles and clinical behaviors, leading to their unique categorization in the 2021 World Health Organization (WHO) Classification of Tumors of the Central Nervous

Extended author information available on the last page of the article

System [3, 4]. This classification identifies three histomorphologic grades: Grade 1 (subependymoma), Grade 2 (classic and myxopapillary), and Grade 3 (anaplastic).

SEs, especially in low grades, generally demonstrate favorable prognoses, with 5-year and 10-year survival rates exceeding 90% and 75%, respectively [5, 6]. However, these tumors carry inherent risks of recurrence and leptomeningeal dissemination, which significantly impair neurofunctional outcomes and increase morbidity [7].

Management of SEs poses a unique challenge due to the rarity of tumor and the lack of prospective data. Although microsurgery remains the main therapeutic approach, the use of adjuvant radiotherapy (ART) is subject to ongoing debate. ART is typically omitted if a gross total resection (GTR) is achieved. However, ART is indicated for Grade 2 tumors following subtotal resection (STR) and all Grade 3 cases [8, 9]. The utilization of ART in adult populations remains significantly lower compared to pediatric and adolescent cohorts [10]. Furthermore, several retrospective analyses have questioned the necessity of ART, suggesting that it may not only provide limited survival benefit in certain cases but could also lead to severe radiation-induced neurological dysfunction [9, 11]. Given the limited data on ART's long-term efficacy, this multicenter retrospective study evaluates survival outcomes, prognostic factors for recurrence, and relapse patterns in adult SE patients who received ART.

Materials and methods

Study design and ethical approval

This study was designed as a retrospective, multicenter study conducted by Neuro-Oncology Research Group of Turkish Society for Radiation Oncology (Trial Number: TROD 07 − 005). The study protocol was approved by the Institutional Review Board (No:2024 − 1897). This study adhered to the principles of the Declaration of Helsinki. Due to its retrospective design, the requirement for informed consent was waived, and all patient information was fully anonymized before data analysis. The study outcomes were reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [12].

Patient selection and variables

Adult patients (aged ≥18 years) with histologically proven SE who received ART between January 1998, and December 2024 were included. Patients with Grade 1 ependymoma, surgery-RT interval exceeding 6 months, and lacking long-term follow-up were excluded.

Comprehensive clinicopathological data, including epidemiological characteristics, tumor features, treatment modalities, and clinical outcomes, were retrospectively collected. Histopathological grading and classification were updated to reflect the 2021 WHO criteria, specifically reclassifying myxopapillary ependymomas as Grade 2 [4]. Molecular profiling was not performed, as it was not part of the routine diagnostic protocol at the participating centers during the study period. Tumor size was defined as the maximum unidimensional tumor diameter (cm) recorded on preoperative MRI, based on official radiology reports.

The extent of resection (EOR) was determined based on a combination of operative reports and postoperative magnetic resonance imaging (MRI) findings. EOR was categorized as GTR, STR, or biopsy. To enhance statistical robustness, STR and biopsy were collectively analyzed as the non-GTR group.

Treatment-related side effects were evaluated during RT and during routine post-treatment follow-up visits. Acute and late side effects were graded according to the Common Terminology Criteria for Adverse Events (CTCAE, version 5.0) [13].

Disease progression was monitored through regular follow-up imaging. The site of failure was determined by comparing the location of the recurrence with the initial tumor bed and was categorized as local (within the primary surgical site), distant spinal (elsewhere in the spinal axis), or intracranial. Treatment response and disease progression were evaluated on serial MRI scans based on adapted Response Assessment in Neuro-Oncology (RANO 2.0) criteria, using the first post-radiotherapy scan as the baseline [14].

Endpoints

Survival-related outcomes were explored using Local Control (LC), Disease-Free Survival (DFS), Progression-Free Survival (PFS), and Overall Survival (OS). LC was defined as the time from the date of surgery to the detection of local recurrence or the last follow-up. DFS was calculated from the date of surgery to the date of disease progression (local or distant) or death from SE; PFS was calculated from the date of surgery to the date of any disease progression (local or distant) or death from any cause; and OS was measured from the date of diagnosis to the date of death or last contact, with all outcomes measured to whichever event occurred first. Follow-up duration was defined as the time interval from the date of primary surgery to the date of the last documented clinical contact or death.

Table 1 Clinical and treatment characteristics of grade 2 spinal ependymoma patients

Variables	All Patients ($n=37$)	GTR ($n=16$)	Non-GTR[α] ($n=17$)	p value[β]
Age (median)	40.8	46.9	41.0	0.2
<45	22 (59.5%)	8 (50.0%)	11 (64.7%)	0.4
≥45	15 (40.5%)	8 (50.0%)	6 (35.3%)	
Sex				0.6
Female	18 (48.6%)	9 (56.3%)	8 (47.1%)	
Male	19 (51.4%)	7 (43.8%)	9 (52.9%)	
KPS (median)	90	90	90	0.7
<90	10 (27.0%)	3 (18.8%)	6 (35.3%)	
≥90	22 (59.5%)	9 (56.3%)	10 (58.8%)	
Unknown	5 (13.5%)	4 (25.0%)	1 (5.9%)	
Major symptom				0.8
Back pain	11 (29.7%)	4 (25.0%)	5 (29.4%)	
Paresthesia	10 (27.0%)	4 (25.0%)	6 (35.3%)	
Extremity weakness	7 (18.9%)	3 (18.8%)	3 (17.6%)	
Extremity pain	5 (13.5%)	3 (18.8%)	1 (5.9%)	
Abnormal gait	2 (5.4%)	1 (6.3%)	1 (5.9%)	
Urinary dysfunction	1 (5.4%)	0	1 (5.9%)	
Tumor Size (median)	2.0 cm	1.9 cm	3.7 cm	**0.003**
<2 cm	16 (43.2%)	12 (80.0%)	2 (16.7%)	**0.001**
≥2 cm	13 (35.1%)	3 (20.0%)	10 (83.3%)	
Localization				0.3
Cervical	14 (37.8%)	6 (37.5%)	8 (47.1%)	
Thoracal	12 (32.4%)	4 (25.0%)	6 (35.3%)	
Lumbar	10 (27.0%)	6 (37.5%)	2 (11.8%)	
Sacral	1 (2.7%)	0	1 (5.9%)	
Spinal Dissemination				
Yes	4 (10.8%)	0	0	
No	33 (89.2%)	16 (100%)	17 (100%)	
Resection Status				
GTR	16 (43.2%)	16 (100%)		
STR	19 (51.4%)	0	15 (88.2%)	
Biopsy	2 (6.7%)	0	2 (11.8%)	
RT Field				
Local	33 (89.2%)	16 (100%)	17 (100%)	
CSI + Local Boost	4 (10.8%)			
RT Dose (median)	50 (44.0–60.0)	50	50	0.6
<50 Gy	15 (40.5%)	7 (43.8%)	6 (35.3%)	
≥50 Gy	22 (59.5%)	9 (56.3%)	11 (64.7%)	
RT Technique				0.2
2D-RT	7 (18.9%)	5 (31.3%)	1 (5.9%)	
3D-RT	16 (43.2%)	4 (25.0%)	10 (83.3%)	
IMRT	9 (24.3%)	5 (31.3%)	4 (23.5%)	
VMAT	5 (13.5%)	2 (12.5%)	2 (11.8%)	
Surgery-RT Interval (median)	1.64 months	1.9 months	1.5 months	0.8
Recurrence				**0.04**
Yes	10 (27.0%)	1 (6.3%)	7 (41.2%)	
No	27 (73.0%)	15 (93.8%)	10 (58.8%)	
Recurrence Pattern				
Local	8 (21.6%)		7 (100%)	
Cranial	0			
Distant Spinal	1 (2.7%)	1 (100%)		
Cranial + Distant Spinal	1 (2.7%)			
Local+ Cranial + Distant Spinal	0			

Table 1 (continued)

Variables	All Patients ($n=37$)	GTR ($n=16$)	Non-GTR[α] ($n=17$)	p value[β]
Treatment Pattern at Recurrence				
Surgery	3 (30.0%)		3 (42.9%)	
RT	1 (10.0%)		1 (14.3%)	
Surgery + RT	1 (10.0%)	1 (100%)		
ChT	2 (20.0%)		1 (14.3%)	
Surgery + RT + ChT	1 (10.0%)		1 (14.3%)	
Surgery + ChT	1 (10.0%)		1 (14.3%)	
No treatment	0			
Unknown	1 (10.0%)			
Status at Last Follow-up				0.6
Alive without Disease	12 (75.0)	12 (75%)	4 (23.5%)	
Alive with Disease	10 (27.0%)		9 (52.9%)	
Exitus	11 (29.7%)	4 (25.0%)	4 (23.5%)	
Follow-up Time (median)	7.9 years	8.0 years	7.1 years	0.8

[α] Non-GTR includes patients who underwent STR or biopsy. Patients with initial spinal dissemination were excluded

[β] Comparative analysis of GTR vs. Non-GTR. Bolded p-values indicate statistical significance ($p < 0.05$). Statistical significance was evaluated using the Mann–Whitney U test for continuous variables (age, tumor size, and surgery-to-RT interval). For categorical variables, Pearson's chi-square test or Fisher's exact test was utilized as appropriate based on cell counts

Abb: ChT, Chemotherapy; GTR, Gross-total Resection; STR, Subtotal Resection; RT, Radiotherapy; 2D-RT, 2-Dimensional Radiotherapy; 3D-RT, 3-Dimensional Radiotherapy; IMRT, Intensity-Modulated Radiotherapy; VMAT, Volumetric-Arc Radiotherapy

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics software, version 31.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize the patient, tumor, and treatment characteristics. Continuous variables are presented as mean or median (range), and categorical variables are expressed as frequencies and percentages. Survival rates and curves were estimated using the Kaplan-Meier method. The log-rank test was employed to compare survival distributions between subgroups. Univariate analysis of prognostic factors for recurrence and local failure was conducted using univariate logistic regression and Cox proportional hazard models. Variables with a significance level of $p < 0.2$ in the univariable analyses and potential prognostic factors for survival were included in the multivariable models. Odds ratios (OR) and hazard ratios (HR) with 95% confidence intervals (CIs) were calculated. Variables with zero events in one category (e.g., GTR group) were excluded from the multivariate Cox regression to avoid model instability due to "complete separation". A p-value of less than 0.05 was considered statistically significant for all tests.

Results

Results for grade 2 spinal ependymoma

A total of 37 patients with WHO Grade 2 SE were included; clinical and treatment characteristics are summarized in Table 1. GTR was achieved in 16 (43.2%) patients, and 21 (56.8%) in non-GTR. The median total RT dose was 50.0 Gy (44.0–60.0 Gy). Focal RT was administered to 33 patients (89.2%), while 4 (10.8%) received craniospinal irradiation (CSI) with a focal boost. Modern techniques (intensity-modulated RT [IMRT] / volumetric-modulated RT [VMAT]) were utilized in 37.8% of patients. The median interval between surgery and RT was 1.64 months (1.0–5.9 months).

Outcomes of adjuvant radiotherapy

The median follow-up was 7.9 years. For the entire Grade 2 cohort, the median DFS and PFS were 266.7 and 139.1 months, respectively. **(**Table 2**)** The estimated 5-year and 10-year DFS rates were 76.2% and 71.7%, respectively. Recurrence occurred in 10 patients (27.0%), with a median time to progression of 54.8 months. The clinical data and treatment patterns of patients who experienced disease recurrence are summarized in Supplementary Table 1. Local recurrence was the primary cause of first failure, observed in 8 patients (21.6%), yielding 5-year and 10-year LC rates of 78.3% and 73.7%, respectively.

Table 2 Survival outcomes of spinal ependymoma patients stratified by histological grade, extent of resection, and baseline dissemination status

Grade 2 Cohort	*n*	Event	Median (month)	5-year Survival %, (95% CI)	10-year Survival %, (95% CI)	*p*-value[β]
LC						**0.006**
GTR + RT	16	0	NR	100.0	100.0	
Non-GTR + RT[α]	17	7	266.7	63.9 (62.4–65.4)	54.7 (53.1–56.3)	
All G2 Patients	37	8	266.7	78.3 (77.4–79.2)	73.7 (72.7–74.7)	
DFS						**0.05**
GTR + RT	16	1	NR	100.0	100.0	
Non-GTR + RT[α]	17	7	266.7	63.9 (62.4–65.4)	54.7 (53.1–56.3)	
All G2 Patients	37	10	266.7	76.2 (75.3–77.1)	71.7 (70.7–72.7)	
PFS						0.26
GTR + RT	16	4	139.1	100.0	88.9 (87.7–90.1)	
Non-GTR + RT[α]	17	8	78.8	56.8 (55.2–58.4)	48.7 (47.1–50.3)	
All G2 Patients	37	15	139.1	70.4 (69.4–71.4)	62.1 (61.0–63.2)	
OS						0.7
GTR + RT	16	4	341.7	100.0	88.9 (87.7–90.1)	
Non-GTR + RT[α]	17	4	389.8	83.6 (82.4–84.8)	74.3 (72.8–75.8)	
All G2 Patients	37	11	341.7	87.2 (86.5–87.9)	73.8 (72.8–74.8)	
				2-year Survival %, (95% CI)	5-year Survival %, (95% CI)	
Grade 3 Cohort	8					
LC		3	NR	75.0 (73.2–76.8)	56.3 (54.0–58.6)	
PFS		5	59.6	75.0 (73.2–76.8)	41.7 (39.3–44.1)	
OS		3	NR	75.0 (73.2–76.8)	75.0 (73.2–76.8)	
Spinal Dissemination Cohort	5					
PFS		4	14.1	40.0 (37.5–42.5)	-	
OS		4	15.2	40.0 (37.5–42.5)	-	

Survival rates were estimated using the Kaplan–Meier method, with 95% confidence intervals shown in parentheses. Survival rates are presented at 5- and 10-year intervals for Grade 2 tumors, whereas 2- and 5-year intervals are reported for Grade 3 tumors and spinal dissemination cohort due to the aggressive clinical course and limited follow-up beyond 5 years in these high risk subgroups. Bolded p-values indicate statistical significance ($p < 0.05$)

[α] Non-GTR includes patients who underwent subtotal resection or biopsy. Patients with initial spinal dissemination were excluded

[β1] p values were calculated for comparison of GTR and non-GTR cohorts. Group comparisons were performed using the log-rank test

Abb: DFS, Disease Free Survival; GTR, Gross-total Resection; LC, Local Control; PFS, Progression Free Survival; RT, Radiotherapy; OS, Overall Survival

Univariate analysis identified age < 45 years and non-GTR as significant predictors of overall recurrence and local failure. In multivariate logistic regression, each decade of increasing age was independently associated with a decreased risk of recurrence (OR = 0.32, 95%CI:0.15–0.72, p = 0.006). Notably, EOR was excluded from multivariate models due to 'complete separation' (zero events in the GTR group), establishing it as the absolute clinical determinant of disease control.

The estimated 5-year and 10-year PFS rates were 70.4% and 62.1%, respectively. For PFS, multivariate Cox regression identified male sex (HR = 6.4, 95%CI:1.6–25.4, $p = 0.009$) and baseline spinal dissemination (HR = 4.8, 95%CI:1.1–21.3, $p = 0.041$) as independent adverse prognostic factors. Non-GTR demonstrated a strong trend toward reduced PFS (HR = 3.6, $p = 0.06$).

The median OS was 341.7 months, with 5-year and 10-year rates of 87.2% and 73.8%, respectively. In the multivariate model, independent predictors of increased mortality were a pre-treatment Karnofsky Performance Status (KPS) [15] less than 90 (OR = 38.3, $p = 0.02$), baseline spinal dissemination (OR = 66.6, $p = 0.04$), and male sex (OR = 26.6, $p = 0.03$).

Comparative analysis of GTR versus non-GTR

A comparative analysis was performed between the GTR ($n = 16$) and non-GTR ($n = 17$) groups, excluding patients with initial spinal dissemination ($n = 4$) to ensure accurate evaluation. The patient demographics and clinical characteristics according to EOR status are summarized in Table 1. Tumor size was the primary determinant for achieving GTR, being significantly smaller in the GTR group (median 1.9 cm vs. 3.7 cm; $p = 0.003$). Conversely, tumor localization and other baseline factors did not significantly influence the resection status.

Clinical outcomes varied significantly depending on the EOR. **(**Table 2 and Fig. 1a-b-c**)** No local failures occurred in the GTR group (0/16, 0%). In contrast, 7 of 17 non-GTR patients (41.2%) experienced local failure ($p=0.001$; OR = 23.6, 95%CI:1.22–458.7). Only one recurrence occurred in patients underwent GTR during follow-up; this recurrence developed at the 150th month and was a distant spinal recurrence. Consequently, the 5-year and 10-year LC and DFS rates were 100% for the GTR group, compared to 63.9% (5-year) and 54.7% (10-year) for the non-GTR group ($p=0.006$ for LC; $p=0.05$ for DFS). Although patients who underwent GTR demonstrated numerically higher 5-year and 10-year PFS rates than those in the non-GTR group (100% vs. 56.8% at 5 years and 88.9% vs. 48.7% at 10 years, respectively), this clinical advantage did not reach statistical significance ($p=0.26$). Despite these marked differences in disease control, the 5 and 10-year OS rates remained statistically similar between the cohorts ($p=0.70$, 100% and 88.9% for GTR, 83.6% and 74.3% for non-GTR, respectively).

Subgroup analysis of non-GTR patients without initial dissemination

To evaluate the impact of ART in the setting of residual disease, an analysis was conducted on 17 non-GTR patients without initial spinal dissemination. Notably, all recurrences in this subgroup were local. For this cohort, the 5- and 10-year LC/DFS rates were 63.9% and 54.7%, while the PFS rates were 56.8% and 48.7% (median:78.8 months), respectively. The 5- and 10-year OS rates were 83.6% and 74.3%.

Univariate analysis identified the timing of ART and age as critical variables. A surgery-to-RT interval of < 1.5 months was associated with superior DFS ($p=0.05$) and PFS ($p=0.01$). Specifically, the 5-year DFS rates were 85.7% for the < 1.5-month interval versus 40% for the > 1.5-month interval, respectively. **(**Fig. 1d**)** Similarly, the 5-year PFS rates were 71.4% and 20%, respectively. Age also emerged as a considerable factor; patients younger than 45 years had a recurrence rate of 54.5% (6/11) compared to 16.7% (1/6) in those aged 45 years and older ($p=0.2$). Although this difference did not reach statistical significance, it indicated a more than twofold increase in the risk

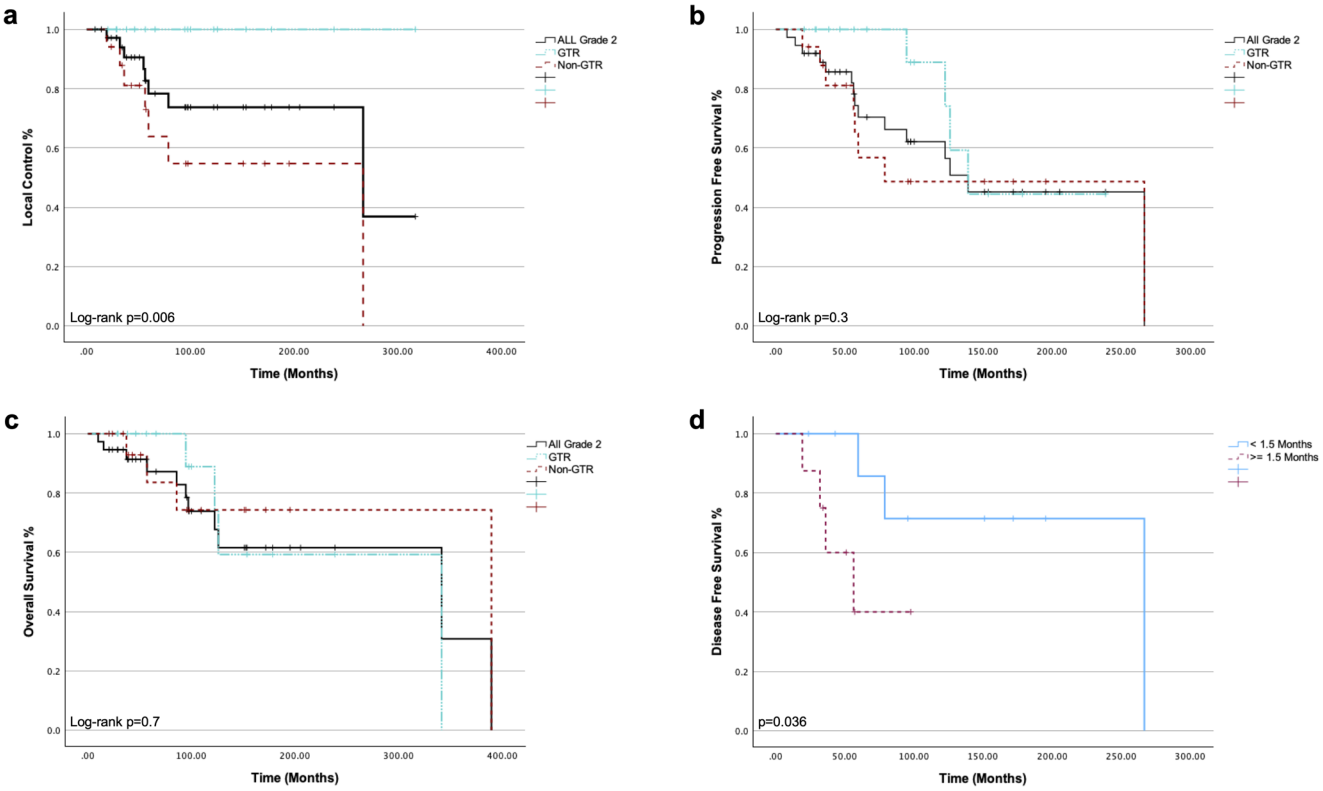

Fig. 1 Kaplan–Meier survival curves for Grade 2 spinal ependymoma patients. (**a**), (**b**), and (**c**) illustrate outcomes stratified by the extent of resection (GTR vs. non-GTR) and p-values from log-rank test. (**a**) LC demonstrating a significant therapeutic advantage for GTR ($p=0.006$); (**b**) PFS ($p=0.3$); and (**c**) OS ($p=0.7$). (**d**) Displays a subgroup analysis of non-GTR patients without initial spinal dissemination, showing a significant DFS benefit for a surgery-to-RT interval of < 1.5 months compared to ≥ 1.5 months ($p=0.036$). p-value from Cox proportional hazard regression. Crosses (+) indicate censored observations

Table 3 The results of cox multivariate analysis for grade 2 Non-GTR cohort

Variables	DFS		PFS	
	HR (95% CI)	p value	HR (95% CI)	p value
Age		0.8		0.4
<45	1.6 (0.06–41.8)		3.5 (0.3–50.2)	
≥45	Ref		Ref	
KPS		0.4		0.2
<90	4.9 (0.2-165.7)		5.5 (0.4–77.1)	
≥90	Ref		Ref	
Surgery-RT Interval		**0.04**		**0.04**
<1.5 m	**13.3 (1.2-149.3)**		**15.9 (1.1-227.9)**	
≥1.5 m	**Ref**		**Ref**	

Non-GTR includes patients who underwent subtotal resection or biopsy. Patients with initial spinal dissemination were excluded. Bolded p-values indicate statistical significance (p <0.05)

Abb: DFS, Disease-Free Survival; GTR, Gross-total Resection; HR, Hazard Ratio; KPS, Karnofsky Performance Score; PFS, Progression-Free Survival

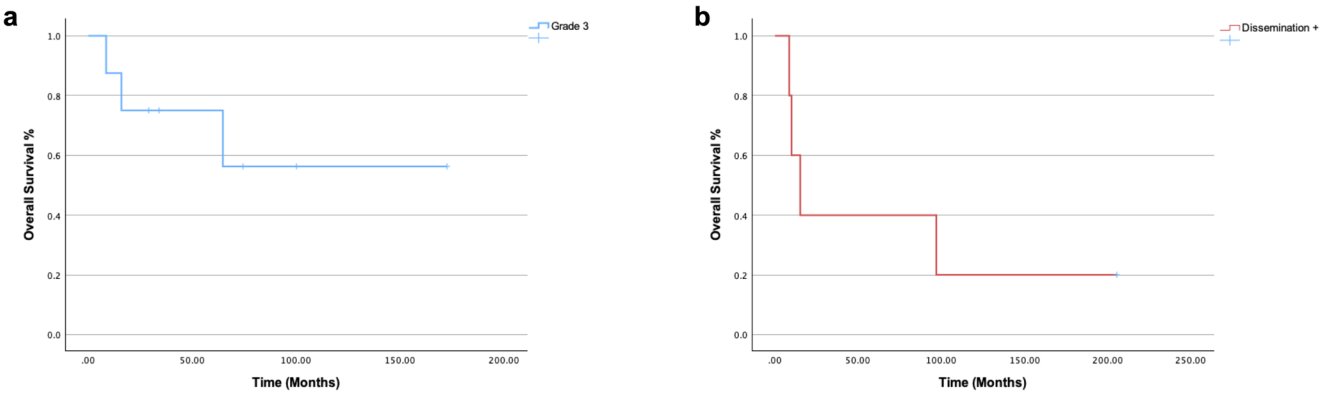

Fig. 2 Kaplan–Meier overall survival (OS) curves for high-risk spinal ependymoma subgroups. (**a**) Overall survival of the WHO Grade 3 anaplastic spinal ependymoma cohort ($n=8$), demonstrating a 5-year OS rate of 56.3%; (**b**) OS of patients presenting with initial spinal dissemination at diagnosis ($n=5$), showing a steep decline in survival with a median OS of 15.2 months. Crosses (+) indicate censored observations

of recurrence in younger patients. This observation is consistent with the finding that the risk of treatment failure decreases significantly with each increasing decade of life (OR = 0.3, $p=0.04$). In multivariate analysis, the surgery-to-RT interval remained the sole independent prognostic factor for DFS and PFS; an interval exceeding 1.5 months was associated with a significantly higher risk of early progression (HR = 13.3, $p=0.04$ for DFS; HR = 15.9, $p=0.04$ for PFS) (Table 3).

When evaluating the impact of total radiation therapy dose on tumor control in this cohort, the median RT dose was 50 Gy. **(**Table 1**)** Local recurrence occurred in 33.3% (2/6) of patients receiving < 50 Gy compared to 45.5% (5/11) in those receiving ≥ 50 Gy ($p=0.6$). Despite this numerical difference in local recurrence rates, log-rank analysis revealed no statistically significant difference in DFS between the two dose cohorts ($p=0.9$). When analyzing the impact of RT technique on LC, local failure occurred in 100% (1/1) of patients treated with 2D-RT, 30.0% (3/10) with 3D-CRT, 75.0% (3/4) with IMRT, and 0.0% (0/2) with VMAT. Statistical analysis revealed that radiation therapy technique had no significant impact on either LC or DFS ($p=0.2$ and $p=0.09$, respectively).

Results for anaplastic spinal ependymoma

Eight patients with WHO Grade 3 anaplastic SE were identified, and their clinical details are summarized in Supplementary Table 2. The median age was 37 years, with a 75% male predominance. Tumors were localized to the cervical (67.5%) and thoracic (32.5%) segments, and one patient presented with initial spinal dissemination.

GTR was achieved in 50% of patients. All patients received ART (median:50 Gy) via focal RT (75%) or CSI (25%), while 37.5% ($n=3$) also received adjuvant chemotherapy.

Over a median follow-up of 49.1 months, 62.5% (5/8) of patients experienced recurrence or progression. The 5-year LC, PFS, and OS rates were 56.3% (median: NR), 41.7% (median: 59.6 months), and 75.0% (median: NR), respectively. **(**Fig. 2a**)** Notably, no local failures occurred following GTR, highlighting the critical role of EOR in managing

Grade 3 tumors. However, the risk of distant failure persisted for this aggressive histology, among the 5 progressive cases, distant metastasis was observed in 3 patients (60%).

Results for patients with spinal dissemination

The incidence of spinal dissemination at the time of diagnosis was 10.8% (4/37) for Grade 2 and 12.5% (1/8) for Grade 3 patients. This subgroup ($n=5$) was predominantly young (mean age:29.6 years) and male (80%). All patients received CSI with a median dose of 37.8 Gy.

The clinical outcomes for this cohort were poor; 60% of patients experienced disease progression, with a median PFS and OS of 14.1 and 15.2 months, respectively. At the time of analysis, four of these patients (80%) had died, while one remained alive with disease at a follow-up of 17.1 years. **(**Fig. 2b**)**

Radiation related side effects

Acute radiation-related side effects were observed in 14 patients (31%), the majority of which ($n=12$) were Grade 1 or 2 according to CTCAE v5.0. The most frequently observed acute side effects were localized pain which was observed in five patients (11%). The remaining acute side effects are detailed in Supplementary Table 3. Grade 3 acute side effects occurred in two patients (4.4%): one patient developed acute radiation myelitis, and another experienced leukopenia and thrombocytopenia.

Radiation-related late side effects were documented in five patients (11%), with no Grade 3 or 4 late events recorded. Specifically, one patient who underwent two courses of focal RT experienced Grade 2 myelopathy, one patient who received 36 Gy CSI exhibited Lhermitte's sign, two patients experienced extremity hypoesthesia and dysesthesia, and the remaining patient had peripheral neuropathy following a single course of focal RT.

Statistical analysis revealed no significant association between RT technique and the incidence of acute or late side effects ($p>0.05$). However, a clear numerical trend toward decreased acute side effects was observed with advancing modalities, dropping from 37.5% (3/8) with 2D-RT and 41.2% (7/17) with 3D-CRT to 27.3% (3/11) with IMRT and 11.1% (1/9) with VMAT. Due to the very low number of late side effects ($n=5$), a meaningful comparative analysis regarding radiation techniques could not be performed for late side effects.

Discussion

The management of SEs presents a significant clinical challenge, requiring a careful balance between achieving oncological control and preserving neuro-functional integrity. Due to the rarity of these neoplasms, prospective randomized trials are lacking, leaving the definitive role of ART, even in cases of STR, a subject of ongoing controversy. In this retrospective multicenter study of 45 patients, we report the long-term outcomes following postoperative RT with a median follow-up of 7.9 years for Grade 2 disease and identified key prognostic factors influencing recurrence and survival. While WHO Grade 2 tumors are generally associated with a favorable prognosis, our findings underscore the EOR as the key determinant of both LC and DFS. In contrast, the presence of residual disease significantly compromises the oncological outcomes. Furthermore, both the timing of ART and patient age emerged as important prognostic factors, with a prolonged surgery-to-RT interval (≥ 1.5 months) and younger age associated with an increased risk of treatment failure.

The primary therapeutic objective in the management of SEs remains maximal safe surgical resection, which aims to achieve optimal oncological control while preserving critical neurofunctional integrity. GTR is the most significant determinant of survival [9, 11, 16–23]. A meta-analysis of 407 patients with SE from 23 studies revealed that the pooled risk of progression after GTR was only 2%, and the mean time to progression was 17.5 years after GTR [21]. Generally, large surgical series report excellent long-term prognosis, with 5- and 10-year PFS and OS rates consistently exceeding 90.0% [18, 19, 24–26]. Notably, GTR followed by RT achieved an absolute 100% LC rate (16/16 patients) in our cohort, consequently yielding 5- and 10-year DFS rates of 100%. However, in contemporary practice, ART is generally withheld following GTR for WHO Grade 2 tumors because of exceptionally low recurrence rates and excellent long-term outcomes. Consequently, the routine administration of ART in the post-GTR setting provides negligible therapeutic benefit while exposing patients to the unnecessary risk of radiation-induced side effects, such as myelopathy. Instead, RT should be strategically reserved as a salvage modality for disease relapse. This strategy is further supported by Kotecha et al., who disclosed that salvage RT significantly extends post-recurrence relapse-free survival compared to salvage surgery alone [7].

Despite the clear advantages of GTR in achieving superior disease control, our results and those of several studies suggest that it may not offer a statistically significant contribution to OS compared with STR followed by ART (STR + ART) [20, 21, 23, 25]. Therefore, achieving GTR should not compromise the patient's neurological function.

STR combined with ART can yield comparable long-term OS outcomes, and maintaining the patient's functional status should remain the primary surgical objective when GTR poses a high risk of morbidity.

STR is a critical independent risk factor for treatment failure, consistently resulting in significantly higher recurrence rates and diminished PFS compared to GTR [19, 21–23, 26–28]. Recurrence rates following STR range from 50 to 70% in the absence of adjuvant therapy. Correspondingly, oncological control is profoundly compromised in these patients; while GTR provides excellent long-term results, the 5-year PFS for STR patients without adjuvant treatment can fall as low as 40–50%. While the EANO (European Association of Neuro-Oncology) guidelines advocate for routine ART after STR, its therapeutic benefit remains debated due to conflicting retrospective evidence [8]. Pronounced study heterogeneity—including small cohorts, disparate follow-up durations, and mixed tumor grades—limits definitive clinical conclusions. Furthermore, the low incidence of STR and inconsistent administration of ART across surgical series confound efficacy evaluation. Nonetheless, in a systematic review of 348 patients (including 80 STR patients), Oh et al. reported that ART increased 5-year PFS from 45.1% to 65.3%, representing a 20.2% improvement [19]. More compellingly, median PFS doubled from 48 months in patients without RT to 96 months in those receiving adjuvant treatment. In another study evaluating RT efficacy after STR in Grade 2 patients, 10-year PFS rates were 77.1% versus 68.2%, and 10-year LC rates were 85.7% versus 50.0% for STR plus RT versus STR alone, respectively [27]. In our cohort, RT following STR yielded a median survival of 78.8 months, a 5-year PFS of 56.8%, and a recurrence rate of 42.9%. While these results align with the trends reported by Oh et al. and other studies, they appear notably lower than those described by Savoor et al. This discrepancy likely reflects prognostic differences between cohorts; specifically, the median age in the study of Savoor et al. was 57 years, whereas the median age in our STR cohort was only 41 years. Our analysis confirmed that younger age is a significant risk factor for disease recurrence.

Our findings also provide important insight by identifying the surgery-to-RT interval as a key prognostic factor. Specifically, an interval exceeding 1.5 months was the sole independent predictor of early treatment failure in the non-GTR cohort (HR = 13.3, $p = 0.04$). Patients who initiated RT within this 1.5-month window demonstrated significantly superior DFS ($p = 0.05$) and PFS ($p = 0.01$) than those with delayed intervention. These results suggest that the therapeutic efficacy of ART is highly time-dependent, underscoring that early clinical intervention - ideally within the first six weeks postoperatively – is crucial to optimizing disease control in the setting of residual disease. In addition to our clinical variables, evidence from previous studies suggests that molecular and immunohistochemical markers including high Ki-67 proliferation index, *MYCN* amplification, and vimentin positivity provide essential prognostic stratification for identifying aggressive tumor phenotypes and predicting shortened PFS [18, 26, 29].

In our non-GTR group without initial spinal dissemination, all recurrences were local, indicating that the RT dose may be critical for achieving LC. However, higher radiation doses (> 50 Gy) were not associated with a statistically significant improvement in local control within our cohort. This is consistent with the results reported by Oh et al., who similarly found no significant advantage for doses above 50 Gy [19]. In contrast, Weber et al. showed that doses of 50.4 Gy or higher could be beneficial, though this effect was limited to myxopapillary ependymomas [20]. While it is recognized that doses exceeding 54 Gy enhance LC in cranial ependymomas, such high doses cannot be safely applied to the spinal cord due to the risk of radiation-induced myelopathy [30]. Furthermore, Ehret et al. reported an 84% LC rate using stereotactic body radiotherapy (SBRT), suggesting that higher biological effective dose values might improve outcomes [31]. Nevertheless, the technical application of SBRT in this region remains a significant challenge. Although SBRT appears to be safe and effective, very narrow treatment margins are required for this technique compared to conventional fractionation techniques. Additional research is needed to clarify the potential negative effects of reduced margins on tumor control.

In our subgroup analysis evaluating RT techniques in non-GTR patients, no statistically significant differences were observed regarding LC or DFS. This lack of oncological impact across technical eras can be explained by fundamental radiotherapeutic principles. In SE, prescribed target dose is strictly constrained by the radiation tolerance of the adjacent normal spinal cord, typically limited at 45–54 Gy. Because total prescribed doses cannot be escalated even with highly conformal modalities such as IMRT or VMAT, target coverage and total effective tumor dose remain virtually identical across 2D-RT, 3D-CRT, and intensity-modulated techniques. To the best of our knowledge, there is no study in the literature evaluating the impact of different focal radiation therapy techniques on oncological outcomes in spinal ependymoma patients. In line with our findings, intrinsic disease control and survival rates appear unlikely to be substantially altered by the choice of radiation technique.

Metastatic SE poses a significant clinical challenge and is associated with dismal prognosis. This presentation is a critical independent negative prognostic factor; in the study cohort, patients with initial dissemination had a median OS of only 15.2 months and a median PFS of 14.1 months. While CSI is the standard treatment approach for these

cases, outcomes remain suboptimal compared with localized disease. The risk of dissemination and rapid progression is significantly increased in patients with anaplastic histology or those had *MYCN* amplification [29, 32]. These findings emphasize that while LC is often achievable with surgery and RT, systemic dissemination drastically alters long-term survival.

WHO Grade 3 anaplastic SE is a rare and aggressive histological subtype, accounting for approximately 7.3% of all spinal ependymal tumors [33]. In our cohort, eight anaplastic cases were identified, with a median age of 37 years and a marked male predominance (75%). Compared with Grade 2 tumors, anaplastic variants exhibit a significantly more aggressive clinical course; we reported a 5-year PFS of only 41.7% and a 5-year OS of 56.3%. This poor prognosis is consistent with broader literature, where Grade 3 histology is recognized as a critical independent negative prognostic factor for survival. While GTR remains the most important determinant of LC - with no local failures observed following GTR in the study - distant failure remains a persistent risk due to the infiltrative nature and biological behavior of these tumors. Consequently, the high recurrence rate of 62.5% observed in this study underscores the necessity of aggressive management, typically combining maximal surgery with ART to optimize outcomes. Novel therapies targeting molecular changes are therefore needed to improve dismal outcomes.

The majority of SEs have an indolent nature, and patients have a long survival. In our cohort, RT was generally well tolerated, with acute side effects being predominantly mild-to-moderate and severe (Grade 3) acute events occurring only rarely. Literature reports indicate that acute side effects occur in approximately 10–68% of patients, primarily manifesting as Grade 1–2 skin erythema, nausea, and occasionally manageable hematological issues such as anemia or neutropenia [20, 28]. Late radiation-related side effects in our series were similarly acceptable, with major events being confined to high-risk clinical scenarios such as craniospinal irradiation or re-irradiation. Importantly, no Grade 3 or 4 late side effects were recorded. These findings are consistent with the existing literature, which indicates that the risk of serious (Grade 3–4) late side effects are typically below 1% with the application of modern RT techniques [27]. However, encompassing a span of nearly 25 years allowed our series to evaluate the impact of evolving RT techniques on side effect outcomes. While statistical significance was not reached—likely due to subgroup sample sizes—a distinct numerical decrease in acute side effect rates was observed with advancing modalities. This clear trend highlights how modern conformal techniques (IMRT and VMAT) effectively protect surrounding normal tissues, ultimately leading to a superior safety profile during spinal irradiation. Specifically, highly conformal techniques such as VMAT deliver these safety advantages by providing superior dose homogeneity and a steeper dose fall-off outside the target volume.

Our study had several limitations, including its retrospective, non-comparative, and multicenter design, which led to variations in treatment and follow-up protocols. The relatively small sample size and lack of objective neurofunctional assessments, such as the McCormick Grade [34], further restricts our conclusions. Additionally, the absence of molecular profiling limits our understanding of the survival outcomes. Moreover, given the low number of events, the risk of statistical overfitting in our multivariable analysis cannot be completely excluded; consequently, these findings should be interpreted with caution and validated in larger prospective cohorts. Nevertheless, the study is strengthened by its long follow-up period and detailed characterization of recurrences among high-risk patients.

Conclusion

In conclusion, our findings underscore that while EOR remains the primary determinant of oncological control in adult spinal ependymomas, adjuvant RT is a vital intervention to optimize local control in patients with residual disease. Crucially, minimizing the surgery-to-RT interval—specifically initiating ART within 1.5 months—significantly improves LC and PFS in non-GTR cases. Additionally, younger age and baseline spinal dissemination were identified as significant adverse prognostic factors for recurrence. Grade 3 tumors exhibiting a distinctly aggressive clinical course. These results advocate for timely, risk-stratified adjuvant interventions to maximize long-term oncological control in high-risk patients while maintaining a manageable side effect profile. The decision to use ART should be individualized, incorporating clinical risk factors and molecular characteristics.

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Data availability The datasets generated and analyzed in the current study are available from the corresponding author upon reasonable request.

Declarations

Ethical approval This study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Gazi University (No:2024 − 1897).

Consent to participate Informed consent was not required because of the retrospective design of the study.

Competing interests The authors declare no competing interests.

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