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Institutional Patterns of Care of Diffuse Intrinsic Pontine Glioma

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Abstract

Background and Aim: Despite recent advances, the outcomes of diffuse intrinsic pontine glioma (DIPG) remain dismal. This is a retrospective study to understand the pattern of care and its impact on DIPG patients diagnosed over 5 years in a single institute. **Subjects and Methods:** DIPGs diagnosed between 2015 and 2019 were retrospectively reviewed to understand the demographics, clinical features, patterns of care, and outcomes. The usage of steroids and response to treatment were analyzed as per the available records and criteria. The re-irradiation cohort was propensity matched with patients with a progression-free survival (PFS) >6 months treated with supportive care alone based on PFS and age as a continuous variable. Survival analysis was performed using the Kaplan–Meier method, and Cox regression model was used to identify any potential prognostic factors. **Results:** One hundred and eighty-four patients were identified with demographic profiles similar to western population-based data in the literature. Of them, 42.4% were residents from outside the state of the institution. About 75.2% of patients completed their first radiotherapy treatment, of which only 5% and 6% had worsening clinical symptoms and persistent need for steroids 1 month posttreatment. On multivariate analysis, Lansky performance status <60 (P = 0.028) and cranial nerve IX and X (P = 0.026) involvement were associated with poor survival outcomes while receiving radiotherapy with better survival (P < 0.001). In the cohort of patients receiving radiotherapy, only re-irradiation (reRT) was associated with improved survival (P = 0.002). **Conclusion:** Many patient families still do not choose radiotherapy treatment, although it has a consistent and significant positive association with survival and steroid usage. reRT further improves outcomes in the selective cohorts. Involvement of cranial nerves IX and X needs improved care.

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Full Text

Diffuse intrinsic pontine glioma (DIPG) is a brain stem glioma, commonly presenting in the middle-age child group[1], [2],[3] with dismal survival outcomes. Given its critical location and the morbidity associated with surgery, these tumors have traditionally been diagnosed as per clinical and radiological criteria. The presentation of symptoms is usually acute in onset (less than 6 months), with a classical triad of cerebellar signs, long-tract signs, and cranial nerve palsies, where at least two of the three should be present at diagnosis.[4] Radiologically, on magnetic resonance imaging (MRI), these tumors should have diffuse T1-hypointense and T2-hyperintense lesion involving at least 50%–67% of pons with >180° encasement of the basilar artery. It may extend to the midbrain or cerebellar peduncles or medulla with or without small areas of ring enhancement.[1],[2],[3],[5]

The role of stereotactic biopsy for these tumors has been evolving, with some studies showing a comparable rate of complications and morbidity as other brain locations.[6],[7] This has led to a better understanding of the molecular background of these tumors. The discovery of K27-mutant histone in almost 80% of DIPGs has led to the reclassification of these tumors into H3K27-mutant diffuse midline glioma in the recent World Health Organization (WHO) 2016 and WHO 2021 classification of central nervous system (CNS) tumors.[8],[9],[10],[11] In the absence of any known successful targeted therapy, biopsy and molecular diagnostics are still not routinely employed in most clinical practices.

Currently, focal radiotherapy (RT) has stood the test of time and remains the standard treatment of choice. Radiation to the tumor along with a margin of 1–2 cm to a total dose of 54–60 Gy at 1.8-2 Gy per fraction given daily over 5–6 weeks, which is essentially palliative in nature, has been known to provide transient improvement in symptoms with a survival benefit.[3],[12],[13] Numerous clinical trials and studies have tested chemotherapeutic, targeted agents and altered fractionation RT schedules in various permutations and combinations, demonstrating no additional benefit.[14–19] Most of these patients progress within 6–9 months of treatment with limited treatment options available at progression and are managed with supportive care comprising mainly corticosteroids. In a select group of patients, re-irradiation may provide symptomatic relief with some benefits and acceptable toxicity.[11],[20],[21],[22],[23] The purpose of this study was to understand the demographic profile, clinical features, patterns of care, and outcomes for the DIPG kids presenting at our institute over the last 5 years.

Subjects and Methods

This is a retrospective pattern of care study approved by the Institutional Ethics Committee (IEC Project No. 900597) which functions with the Declaration of Helsinki.

Identification of patient population

An initial screening through our institutional prospectively maintained neuro-oncology database was performed with the keywords "DIPG," "brainstem glioma," "astrocytoma," "posterior fossa mass," "diffuse midline glioma," and "pontine glioma" with age <18 at diagnosis; a total of 500 search results were obtained between 2015 and 2019. To ensure that only typical DIPG patients were identified, the electronic records were thoroughly screened to identify patients as per the clinical and radiological criteria and reviewed by a team of neuro-oncologist and neuro-radiologist.[5] Atypical features such as age >18 years or duration of symptoms more than 6 months were also excluded. A total of 184 subjects were identified as eligible and were included for further study analysis.

Data collection

Information regarding demography, clinical presentation, cranial nerve involvement, imaging features, and treatment details was collected from the electronic records for the selected cohort. Based on available follow-up data on electronic records, the clinical response to treatment and steroid usage was objectively coded as per the criteria previously described.[22] Briefly, very good response (VGR) was defined as complete/near-complete resolution of all neurological signs/symptoms, good response (GR) as partial response in all symptoms, fair response (FR) as partial/complete response in some but not all symptoms, stable response (SR) as no change in any symptom's severity, and clinical worsening (CW) as further clinical deterioration. Steroid response criteria were defined as completely off (CO) (completely weaning off steroids), partially off (PO) (decrease in dosage/frequency or both), and persistent need (PN) (PN of the same dose per day/unable to taper).

A group of patients who underwent re-irradiation (reRT group) were identified. The criteria followed at our institution for patients to receive re-irradiation have been described previously. Briefly, they were patients with initial progression-free survival (PFS) >6 months and no disseminated disease at progression.[22] To determine the impact of re-irradiation, a comparable subgroup (C-group) of patients was identified from the remaining cohort with similar characteristics of PFS >6 months and with no disseminated disease at progression.

Statistical analysis

All statistical analyses were done on R studio version 4.0.0 using the ''survival" package and Statistical Package for Social Sciences (SPSS·) version 25.0 (IBM Corp., Armonk, NY). The demographic details, clinical features, histopathologic features, and treatment details were analyzed for the cohort using descriptive statistics. Survival analysis was limited to the subjects with available follow-up and treatment details. Overall survival (OS) was calculated from the date of diagnosis till death or the last documented follow-up. PFS was defined as the interval from diagnosis to documented clinical or radiological recurrence/progression or death/last documented follow-up. The date of diagnosis was estimated from the date of the baseline magnetic resonance imaging (MRI) confirming the diagnosis. The survival outcomes were analyzed using

the product-limit method of Kaplan–Meier.

Univariate analysis of relevant patient-, disease-, and treatment-related factors such as age, gender, duration of symptoms, performance status, cranial nerve involvement, place of RT, RT versus supportive care alone at diagnosis, and chemotherapy and re-RT versus supportive care at progression was done. Factors which were significant on univariate analysis were entered into multivariate analysis using the Cox regression model to identify any potential prognostic factors. A P value <0.05 was considered statistically significant.

Match-pair analysis

The patients in the reRT and C-groups were matched for PFS and age as a continuous variable. Logistic regression was used to estimate the propensity scores for each group. The size of the calliper was set at 0.25 of the standard deviation of the logit of the estimated propensity score. A simple nearest-neighbor matching algorithm was used to achieve the best covariate balance after matching. Units outside the area of common support were disregarded to further improve the balance of the covariates.

Results

Patient characteristics and demographics

The baseline general characteristics of the 184 patients identified as eligible are summarized in [Table 1]. There were 53.8% males with a median age at presentation of 8 years (interquartile range [IQR] 6–11 years), while 52.2% were of 6–12 years of age. Only a minority of the patients (9.8%) were from the district of our hospital; the remaining 47.8% were from the rest of the state, whereas 42.4% were from the rest of the country. The median time from the onset of symptoms to diagnosis was 30 days, with a median Lansky Performance Status (LPS) at presentation of 70. The most commonly observed clinical feature was cranial nerve involvement, where VI and VII nerves were the commonest. All three classical clinical criteria and three radiological criteria were present in 83 (45.1%) and 146 (79.3%) patients, respectively. Histologic diagnosis was available in 20 subjects, with high-grade glioma being the most common. All biopsies were done before reporting to our institution, where three of the available four samples were confirmed to have H3K27 mutation.{Table 1}

Patterns of care

Treatment and outcome details were available for 161 patients. A total of 121 (75.2%) received RT, of which 50.4% were at our institution while the rest preferred their nearby centers for logistic convenience. There was no significant difference in referral to the local hospital versus treatment at our center by location of their residence (hospital district/rest of the state/rest of the country). The RT dose received was 54 Gy (median), of which 22 received some form of chemotherapy – either concurrent, adjuvant, or salvage. The most commonly prescribed chemotherapeutic agent was temozolomide [Table 1]. Surgical intervention for raised intracranial pressure in the form of ventriculoperitoneal shunting (VP shunt) was done for four patients. Modality of best supportive care or medical decompressive therapy was provided in 40 (24.8%) patients who did not receive RT, had poor neurological status/progression (seven), or based on parent's preference (33). There was again no difference in the selection of radiation treatment versus best supportive care by location of their residence or gender.

Outcomes of the whole cohort

The response to treatment and usage of steroids 4–6 weeks post-RT was available in 101 and 84 patients and is summarized in [Table 1]. The majority of the patients showed VGR (n = 43; 42.6%) and only 5% (n = 5) had CW. Similarly, 38% (n = 32) were CO steroids and 6% (n = 5) patients had a PN.

Information on the exact instances of disease progression was available only in 77 patients, of which 51.6% received no further tumor-directed therapy, 8.1% went ahead with salvage chemotherapy, and 40.3% went ahead with received salvage re-irradiation (of which 20 patients were previously described).[8] The survival data were available for all 161 patients. The median PFS and OS were 6.6 months (95% confidence interval [CI] 5.5–7.7 months, standard error [SE] 0.54) and 9.4 months (95% CI 6.5–12.5, SE 1.4), respectively, for the whole cohort. The OS at 12 and 24 months was 46.6% and 7.2%, respectively. On multivariate analysis, patient-related factors such as LPS <60 (hazard ratio [HR] 1.66, 95% CI 1.05–2.63; P = 0.028) and cranial nerve IX and X (HR 1.77, 95% CI 1.06–2.92; P = 0.026) involvement at diagnosis were associated with poor survival outcomes, as illustrated in [Figure 1]. A highly significant survival advantage was seen in patients receiving RT treatment when compared to those receiving best supportive care alone (HR 39.01, 95% CI 18.3–82.9; log-rank P <<0.0) and could not be captured on the forest plot due to the skewed HR and CIs [Figure 1]. There was no prognostic significance associated with age, duration of symptoms, age dichotomized by the median, gender, duration of treatment, and additional chemotherapy treatment.{Figure 1}

RT cohort

In the cohort of the patients who received RT, on univariate analysis, the clinical response groups (P = 0.0), steroid response groups (P = 0.004), reRT (P = 0.0), and involvement of cranial nerves IX and X (P = 0.018) were significantly associated with OS, of which only cranial nerve IX, X involvement (HR 2.26, 95% CI 1.2–4.2; P = 0.01) and reRT (HR 3.3, 95% CI 1.7–6; P < 0.0) retained their impact on multivariate analysis. Further, we clubbed the clinical response groups as three modified clinical response groups, that is, improved (VGR + GR), stable (SR + FR), and progression (CW), and the two modified steroid response groups as improved (CO + PO) and progressive (PN), based on similarity in OS [Supplementary Table 1] and is proposed for future validation. On rerunning the analysis, the modified clinical (P = 0.00) and steroid (P = 0.002) responses were significant on univariate analysis. On multivariate analysis, only reRT (HR 2.7, 95% CI 1.4–5.4; P = 0.002) remained a significant factor.[INLINE:1]

Re-irradiation

In the selective cohort of propensity-matched subgroup comparing 77 patients (reRT group: 25 vs. C-group: 52), the median age was 8 (IQR: 6–10) years and 9 (IQR 6.5–14) years in C-group and reRT group, respectively. The median follow-up was 26.2 months (95% CI 11.7–40.5). The mean (±standard deviation [SD]) PFS for C-group and reRT group was 10.7 ± 4 and 11.4 ± 5.9, respectively (P = 0.55), while the OS was 12.1 ± 4 and 19.1 ± 6.9 months, respectively (P = 0.0001). In the reRT group, the median time from progression to death was 209 (IQR 150–288) days, compared to 19 (IQR 0–43 days) days in C-group (P = 0.0001). At 2 years, the survival probability in the two cohorts (reRT vs. C-group) was noted to be 21.8% and 0%, respectively. A statistically significant OS improvement was demonstrated using the log-rank test between the two groups (HR 0.456, 95% CI 0.244–0.851; P = 0.014) [Figure 2].{Figure 2}

Discussion

Our retrospective audit describes a large institutional experience of patterns of care in patients diagnosed with DIPG in conventional times. Although a hospital-based registry, it represents a varied population from far-off regions of the country. The demographic profile of the cohort was similar to population-based registry data reports from western countries.[3],[13],[24],[25] This consistency is generally not seen in other brain tumors, especially in adults reported previously from this part of the world.[26],[27]

The median time from the onset of symptoms to diagnosis in our cohort was 30 days, which was marginally shorter than the duration of symptoms reported by the Canadian Paediatric Brain Tumour Consortium (CPTBC) registry and European reports.[3],[13],[24] Cranial nerve involvement followed by cerebellar symptoms was the most common symptom at presentation, with the majority presenting with abducens or facial nerve palsy as reported previously.[3],[24]

Although DIPG has been diagnosed clinicoradiologically, recent developments regarding the feasibility of safe stereotactic biopsy at certain centers and the identification of molecular markers have emerged.[6],[7] However, the practice of regular stereotactic biopsy is still not routinely done. Being a high-throughput center with a large number of patients awaiting treatment at all times, these procedures are not favored due to logistic challenges and perception of lack of benefit for the individual patient in present times.

The counseling of caregivers regarding the disease, treatment options, and prognosis remains an integral part of the holistic approach to manage these pediatric patients. The use of medical decompressive therapy alone as a treatment modality was found to be much higher in our population compared to the reports in western literature.[3],[24] This may be due to the logistic challenges faced by families to stay back for 5 weeks of palliative treatment and associated social and financial constraints. A large numbers of families are not natives from nearby area to the RT center. Also, RT center with pediatric RT facility may not be easily available nearby to most patient families.[28–30] The patients who received no RT (n = 40) rapidly progressed with a poor survival period of 1.7 months, while patients receiving upfront focal RT had a median PFS and OS of 6.2 and 9.5 months, respectively, similar to previous studies.[3],[24]

The common practice of using steroids as a part of supportive care comes with the challenges of steroid dependency and other related adverse effects.[31] RT has been established to reduce steroid dependency in the primary setting.[20],[32] In our study, the steroid weaning rates were CO 38% and PO 55%. Also, the clinical response and steroid usage post-RT were positive predictors of OS and the modified groups also retained significant association. Patients with clinical response to treatment and reduced steroid dependence showed good disease biology, which could have resulted in better survival outcomes. Similar findings were demonstrated in our reRT cohort previously.[22]

The glossopharyngeal nerve (IX) and the vagus nerve (X) supply the pharyngeal musculature and the larynx, respectively, and palsy affects the speech and swallowing function, making these children more prone to aspiration pneumonia. This

could be the probable hypothesis for the negative impact on survival outcomes in our patients. We need to strengthen the care for these kids more effectively in our system.

The treatment options at progression in DIPG are limited, with a majority being managed with the best supportive care alone. The role of reRT in the salvage setting has been explored in multiple studies.[20],[21],[22],[23] A recent meta-analysis with a 90-patient cohort suggested a median OS of 16.4 months from initial diagnosis. The median OS of the re-irradiation cohort in our study was 17.8 months. In the PS-matched subgroups, reRT versus Group C showed a better 2-year survival probability of 21.8% and 0%, respectively. This matched cohort analysis is similar to the retrospective match cohort analysis performed by the Société Internationale d'Oncologie Pédiatrique/International Society of Paediatric Oncology -Diffuse intrinsic pontine glioma (SIOP-DIPG) group,[9] which showed a survival benefit of reRT in DIPG patients. These patients had an interval of at least 3 months between the initial course of RT and reRT. The study demonstrated a survival benefit (13.7 vs. 10.3 months, P = 0.04) in favor of reRT with no grade 4–5 toxicity. At our institute, reRT was primarily offered to patients with a longer initial PFS of around 6 months; so, a cohort of patients with PFS of more than 6 months was chosen for comparison. These findings are suggestive that re-irradiation can be offered as a treatment modality at progression essentially to alleviate symptoms. It provided a survival benefit in a select group of patients with longer PFS with acceptable toxicity.[20–22] In an ideal scenario, these findings need to be replicated in a prospective, randomized manner, but it may remain unfeasible owing to challenges in treating these rare tumors.

This is a fairly large series of DIPG patient outcomes and patterns of care from a single institution. The retrospective design of this study makes it susceptible to the expected biases and confounders as any other similar study. The radiological response data, quality of life (QOL), and toxicity details are also lacking. The use of PS matching based on age and PFS criteria may reduce potential bias for reRT comparison, but data remain retrospective and nonrandomized.

Conclusion

DIPG remains a challenging tumor in children. With this fairly large series, we notice that in our country, many patient families still do not choose RT treatment, although it has a consistent and significant positive association with survival and steroid usage. reRT further improves outcomes in the selective cohorts. It may be noted that involvement of cranial nerves IX and X impacts poorly the outcomes and improved associated care may help change it.

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Conflicts of interest

There are no conflicts of interest.

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Figure 1: Forest plot to show th

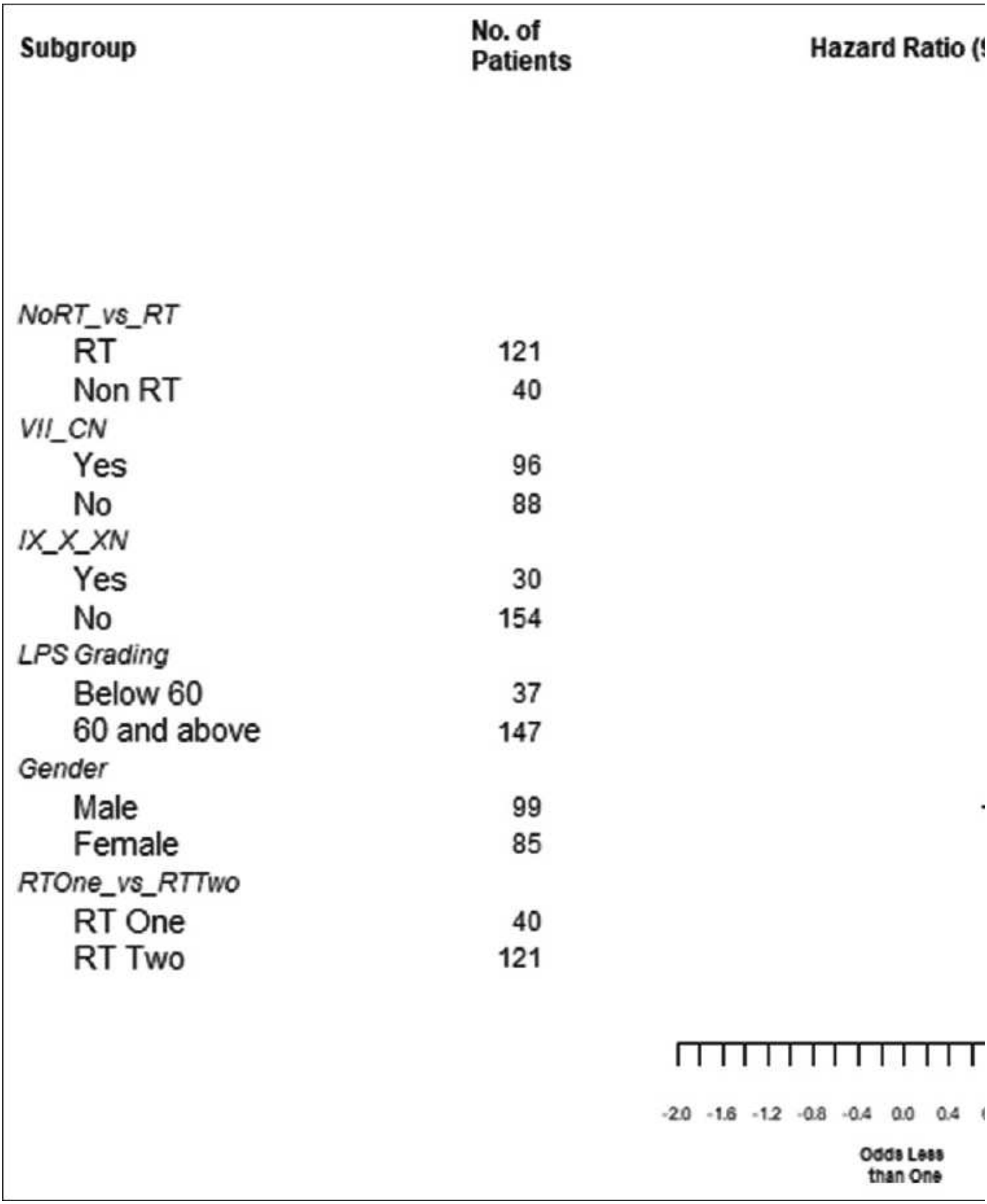

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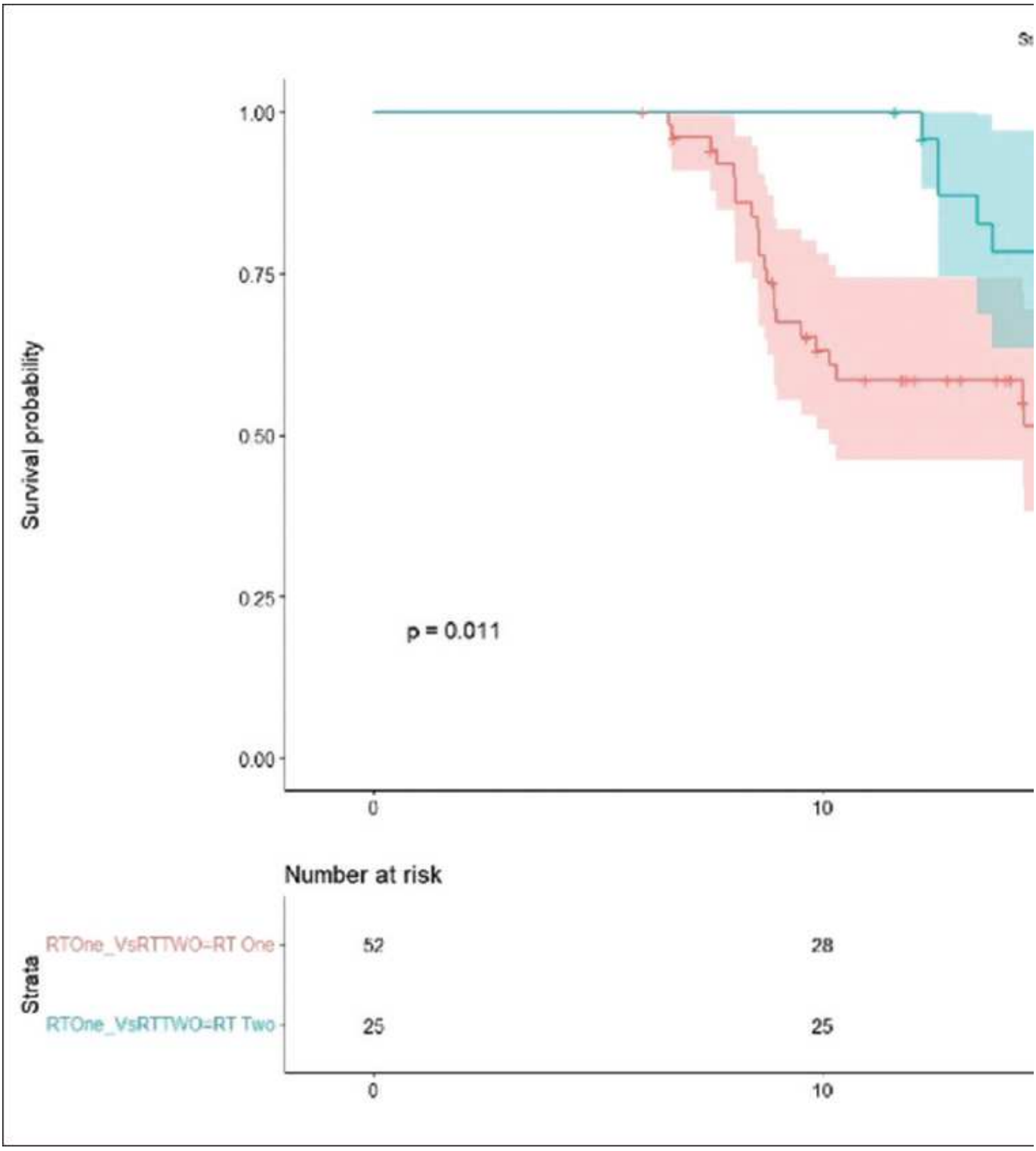
Figure 2: Comparison of survival between re-irradiation



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Close

Table 1: General characteristics of the entire cohort

Demographic profile (*n*=184)	*n*	%
Age (years)		
1-3	8	4.3
3-6	49	26.6
6-12	96	52.2
>12	31	16.8
Gender		
Male	99	53.8
Female	85	46.2
Residence		
Patients within the district	18	9.8
Within the state	87	47.3
Outside the state	79	42.9
Clinical characteristics		
Duration of symptoms		
1 month	120	65.2
1-3 months	52	28.3
3-6 months	12	6.5
LPS		
<60	37	20.1
≥60	144	79.9
Clinical criteria		
Cerebellar signs +	148	
Long tract signs +	124	
Cranial nerves +	168	
Cranial nerve involved		
VI	96	
VII	96	
VIII	5	
IX/X	30	
Clinical criteria		
3/3	83	45.1
2/3	86	46.7
1/3	15	8.2
Radiological criteria		
All three criteria	146	79.3
Histology (n=20)		
High-grade glioma	16	80
Low-grade glioma	3	15
Necrotic tissue	1	5
Patterns of care		
Index radiation	121	75.2
No treatment/best supportive care	40	24.8
EBRT technique (*n*=97)		
Conventional	24	24.7
3DCRT	55	56.7
IMRT	18	18.6
Systemic treatment		
Chemotherapy (*n*=22)		

Concurrent and adjuvant	6	
Adjuvant	10	
Salvage	5	
Concurrent	1	
Chemotherapeutic drugs/regimen		
TMZ	13	
COMBAT	10	
CET	1	
Valproic acid	5	
VP shunt	4	
Clinical response		
VGR	44	43.6
GR	28	27.8
FR	16	15.8
SR	08	7.9
PD	05	4.9
Steroid response		
CO	33	39.3
PO	46	54.7
PN	5	6
Treatment at progression		
Supportive only	32	51.6
Salvage re-irradiation	25	40.3
Chemotherapy	5	8.1

CO=completely off, FR=fair response, GR=good response, LPS=Lansky Performance Status, PD=progressive disease, PN=persistent need, PO=partially off, SR=stable response, VGR=very good response, VP=ventriculoperitoneal, IMRT=Intensity-modulated radiation therapy, EBRT=External beam radiation therapy, 3DCRT=Three-dimensional conformal radiation therapy, TMZ=Temozolomide, COMBAT=Combined Oral Metronomic Biodifferentiating Antiangiogenic Treatment: temozolomide, etoposide, celecoxib, vitamin D, fenofibrate and retinoic acid. CET=Celecoxib, etoposide, temozolomide