Molecular markers associated with pseudoprogression and recurrence pattern in glioblastoma

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Introduction and objectives

Molecular markers have become an integral part of tumour assessment in modern neuro-oncology and guide clinical decisions in gliomas.

This study was conducted to analyse whether isocitrate dehydrogenase (IDH1) mutation, Alpha thalassemia/mental retardation syndrome X-linked (ATRX) mutation and O^6-methyl-guanine methyl transferase (MGMT) gene promoter methylation are associated with pseudoprogression disease (psPD) and pattern of recurrence in GBM patients after concurrent temozolomide (TMZ)-based chemoradiation.

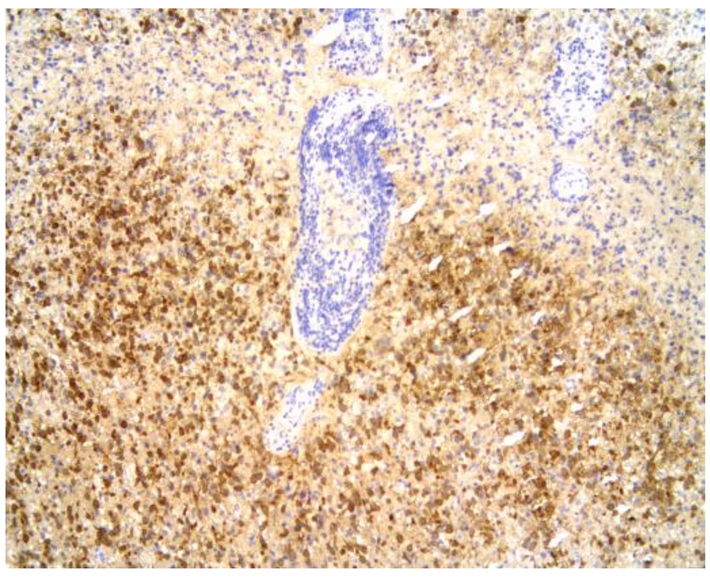


Image 1. Positive for IDH-1 inmunostained.

Methods

A total of 62 GBM patients were included in this retrospective study. All patients were treated following the ESTRO-ACROP guidelines for delineation in GBM, and all of the received concurrent TMZ (daily dose of 75 mg/m^2) and sequential TMZ (150-200 mg/m^2 every 7/28 days until completing 6 cycles).

The first magnetic resonance imaging (MRI) was performed one month after the radiotherapy if no clinical symptoms related to tumor progression were observed. Recent contrast enhancement after total resection or volume increased contrast enhancement after subtotal resection within 3 months was defined as psPD and early real PD. Radiological stabilization within 3 months was defined as stable disease. The radiological enhancement which was stable on subsequent follow-up or pathological confirmed as necrosis was defined as psPD.

Distant recurrence was defined as the radiological enhancement localized outside of the isodose line of 40 Gy in the radiotherapy plan. Otherwise the progression was defined as an inside-radiotherapy recurrence.

Univariate logistic regression was used to evaluate the association between genetic factors and psPD or pattern of recurrence. Log-rank test and K-M were performed for the survival analysis.

Results

Variable	n = 62 (%)
Gender	
Female	22 (64.52%)
Male	40 (35.48%)
Median age (years)	58 ± 12
Resection	
Total	37 (59.68%)
Subtotal	20 (32.26)
Biopsy	5 (8.06%)
Promother of MGMT	
methylation	34 (54.84%)
unmethylation	28 (45.16%)
IDH1	
mutation	8 (12.9%)
wild	54 (87.1%)
ATRX	
mutation	10 (16.13%)
wild	52 (83.67%)
Pseudoprogression	
present	31 (50%)
not present	31 (50%)
Recurrence	
Inside-RT field	34 (79.07%)
Distant	9 (29.93%)
Overall survival (months)	21.04
Progression-free survival (months)	10.68

Table 1. Patients characteristics

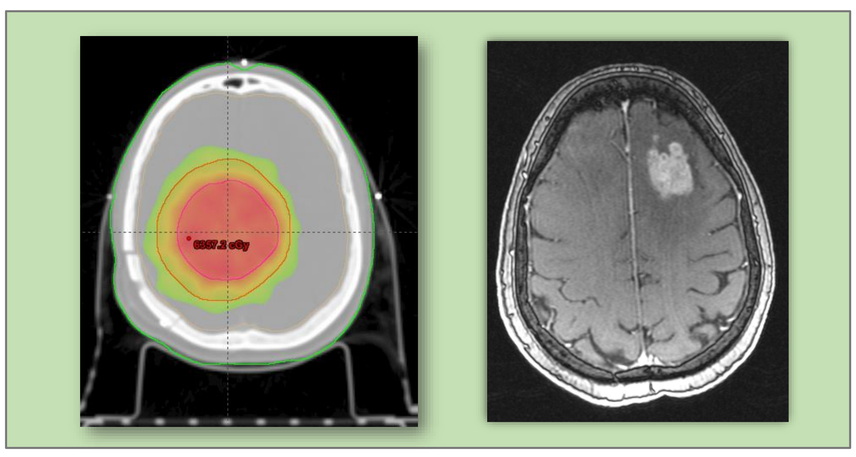
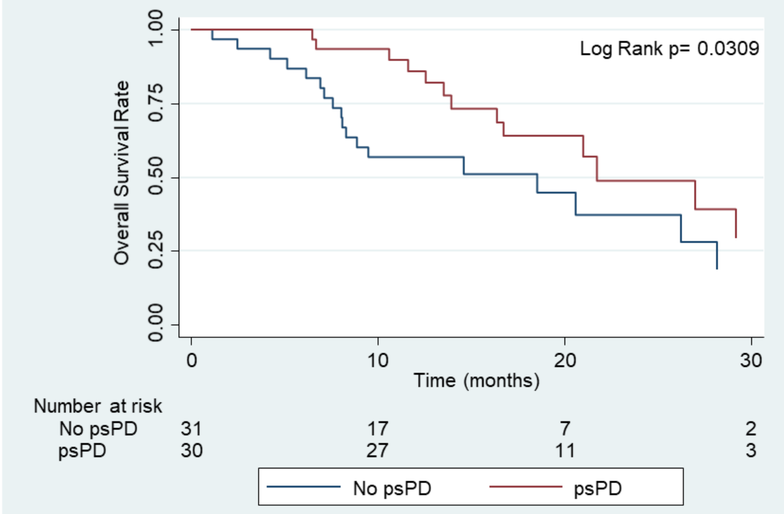
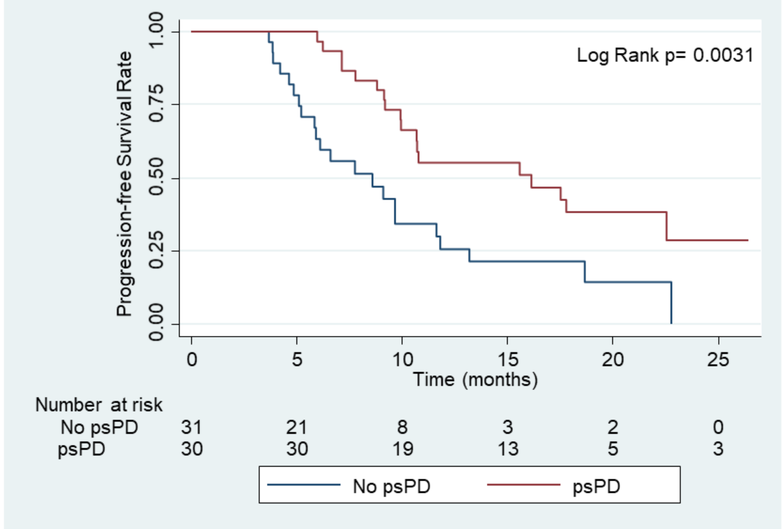


Image 2. Graphic definition of distant recurrence.

Variable	OR (CI 95%)	P
Gender	0.75 (0.26-2.14)	0.596
MGMT methylation	15.16 (3.46-66.45)	**<0.001**
IDH-1 mutation	3.75 (0.68-20.62)	0.129
ATRX mutation	3.02 (0.68-13.44)	0.147

Table 2. Univariate analysis for psPD.





Of the 62 GBM patients, MGMT promoter methylation, IDH1 mutation and ATRX mutation were identified in 34 (54.84%), 8 (12.90%) and 10 (16.13%) patients, respectively. We found a significant association between MGMT promoter methylation and psPD ($p<0.001$), but not between IDH1 or ATRX mutations and psPD. MGMT methylated patients were more likely to show distant recurrence rather than treatment on field or marginal recurrence ($p=0.032$). GBM patients with psPD had a significant longer median overall survival and progression-free survival (21.8 and 16.14 months) than GBM patients with non-psPD (18.6 and 8.6 months).

Conclusions

Our results suggest that MGMT promoter methylation is associated with psPD and pattern of distant recurrence in GBM patients after TMZ-based chemoradiation. Additionally, psPD predicts a longer median survival and progression-free survival.

Bibliography

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2. H. Li, J. et al., Clinical Neurology and Neurosurgery 151 (2016) 31-36

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