Comparison of molecular alteration in glioblastoma tumors from old and young patients

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Abstract #2056

Background: GBM patients (pts.) aged 70 yrs or older have a poorer prognosis than younger pts. IDH1/2 mutations are more prevalent in younger GBM pts. and confer a more favorable prognosis. We compared molecular alterations between younger pts. (YP; 18 =< age <= 45), and older pts. (OP; age > = 70), with additional stratification for wild type IDH1/2 status.

Methods: GBM tumors submitted for tumor profiling between 2009 and Jan 2016 were tested with NextGen sequencing (SEQ), immunohistochemistry (IHC), fluorescent in-situ hybridization (FISH), fragment analysis (FA) and promoter methylation (Me). Retrospective analysis was performed on 375 GBM's (YP = 197, OP = 178). Pediatric tumors were excluded. Chi-square was used for exploratory analyses and significance was defined as p < 0.05. Given the nature of this exploratory study, p values were not adjusted for multiple testing.

Results: Alterations including overexpression of ALK (29% vs. 4.2%), RRM1 (47% vs. 32%) and mutations of ATRX (73% vs. 11%), BRAF (9.3% vs. 1.7%), IDH1 (24% vs. 3%), PDGFRA (7% vs. 0), PTPN11 (6.6% vs. 1%) and TP53 (58% vs. 26%) were significantly more prevalent in YP (N = 197). In contrast, PTEN mutation was significantly more frequent in OP (26% vs. 13%). PTEN loss by IHC was equal between YP and OP (22% vs. 21%). Pts. with known wild type IDH1/2 status were compared between YP and OP (N = 72 and 95). Significantly higher expression of TOPO1 was seen in YP (63% vs. 45%) while MGMT-Me was less common in YP (29% vs. 48%). The differences in ALK IHC (27% vs. 4.5%), mutations of BRAF (12% vs. 1%), PDGFRA (4%, vs. 0), PTPN11 (7% vs. 1%) and TP53% (42% vs. 25%) were significant. cKIT and PDGFRA co-amplifications were seen in 2 out of 3 tumors from OP with wild type IDH1/2 while no cKIT or PDGFRA amplification was seen in YP (0/6). No significant differences were seen in YP vs. OP for EGFRvIII (12% vs. 14%), PD-L1 expression on tumor cells (19% vs. 8.3%) or PD-1 expression on TIL (42% vs. 54%).

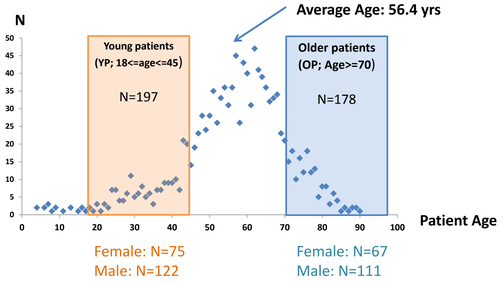
Conclusions: Significant molecular differences were seen between older and younger GBM pts. Alterations seen in OP, including PTEN mutation and cKIT/PDGFRA coamplification were previously associated with recurrent tumors and poor survival, and may underlie the poor prognosis observed in OP. These results suggest and may guide which pts. will benefit from targeted therapies in future studies.

Background

- The prognostic benefit that a younger age confers has been well described in the literature and has been attributed to several factors including: higher pre-treatment KPS, greater likelihood of aggressive surgical resection, increased eligibility for clinical trials and a more robust social support system.
- More recently the age related molecular differences in GBM patients have been highlighted. For instance, IDH 1/2 mutation is more prevalent in younger patients and confers a more favorable prognosis.
- Further, TCGA subtyped GBM into four molecular classes and reported differences in clinic-pathological characteristics including age, as well as clinical course and responses to aggressive therapy.
- The aim of this study is to investigate biomarker data collected for molecular profiles obtained in a CLIA-certified lab on a large cohort of GBM samples and to compare the molecular tumor profiles of younger (18-45 years) patients with elderly patients (>=70 years) to identify molecular alterations specific to different age groups .
- We further studied tumors from the two age groups with confirmed IDH -WT status to investigate age-associated molecular differences independent of the well-known prognostic factor of IDH mutation.

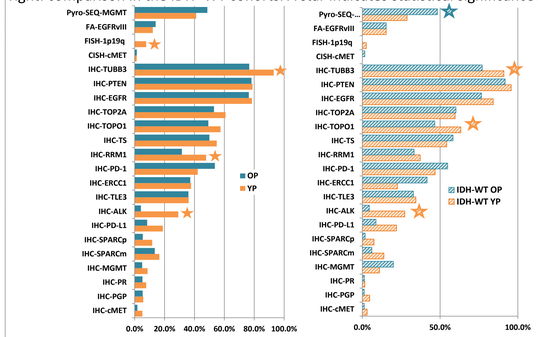
Results

Figure 1: Patient age and gender included in the study



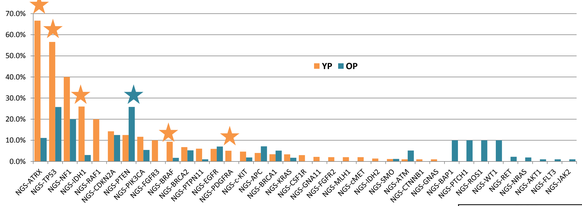
- A total of 375 adult GBM samples comprised the data set, 47% of the samples were collected from OP and 53% from YP.
- Pediatric patients, patients with age between 45 and 70, or those with astrocytomas of grades lower than WHO grade IV, or those with oligodendrogliomas were excluded.
- Specimens were procured at various time points during the disease course.
- Gender is well-balanced in the two age groups.
- Patient treatment history and response were not part of the data collection.

Figure 2: Molecular alterations tested by pyrosequencing, fragment analysis, and in-situ hybridization in the YP and OP cohorts. Left: comparison in the complete YP and OP cohorts; right: comparison in the IDH -WT cohorts. A star indicates statistical significance (p<0.05)



- MGMT promoter methylation is more prevalent in OP when IDH -WT tumors were compared.
- 1p19q co-deletion is seen exclusively in YP tumors.
- Proteins expression of TUBB3 and ALK expression is significantly higher in YP compared to OP.
- RRM1 expression is higher in YP compared to OP while TOPO1 expression is higher in YP when IDH -WT is considered.

Figure 3: Molecular alterations tested by NextGen SEQ in the YP and OP cohorts. A star indicates statistical significance (p<0.05)



ATRX	YP	OP
Wild type (N)	9	9
Mutated (N)	6	1
Protein changes	F2113fs	V1181L
	G1071fs	
	R781X	
	K299fs	
	H865Qx2	

BRAF	YP	OP
Wild type (N)	117	2
Mutated (N)	12	116
Protein Changes	V600E x10	V600E x2
	G460E	
	D594N	

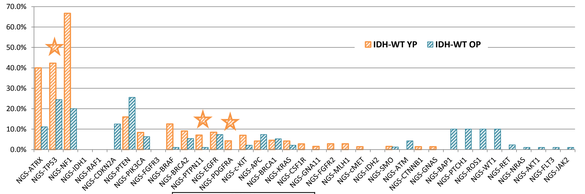
IDH1	YP	OP
Wild type (N)	74	95
Mutated (N)	26	3
Protein Changes	R132Hx23	R132Hx3
	R132S	
	R132G	
	R132C	

PTEN	YP	OP
Wild type (N)	84	69
Mutated (N)	12	24
Protein Changes	R233X	R233X
	T319fs	T319fs x3
	c.1026+2T>C	c.209_209+1del x2
	c.209+1_209+4del4	c.634+1G>A
	I253fs	c.77_79+3delinv2
	K267fs x2	D24fs
	R11X x2	E189fs
	R15S	F299X
	R173C	F241_F242delinsL
	S10R	I203fs
	Y68N	I300fs
		L186V
		L25F
		M198del x3
		N184fs
		Q87X
		R335X x3

PDGFRA	YP	OP
Wild type	94	97
Mutated	5	0
Protein Changes	R841_I843del	R132Hx3
	Y582H	
	D576G	
	D842V	
	D842Y	

- In addition to significantly higher IDH1 mutation rate seen in YP, alterations in TP53, ATRX, BRAF and PDGFRA are also higher in YP.
- PTEN mutations are significantly higher in OP.

Figure 4: Molecular alterations tested by NextGen SEQ in the IDH-WT YP and OP cohorts. A star indicates statistical significance (p<0.05)



PTPN11	YP	OP
Wild type	66	94
Mutated	5	1
Protein Changes	A72T x2	G503V
	A72V	
	D61Y	
	G503V	

- Similar to the comparison in the complete cohorts, TP53 mutation and PDGFRA mutation rates are significantly higher in the YP cohort when only IDH-WT tumors are considered.
- PTPN11 mutation is significantly more frequent in IDH -WT YP cohort.
- In addition to differences described above, PDGFRA co-amplification was observed in 2 out of 3 tumors from OP while no cKIT or PDGFRA amplification was seen in YP (0/6) (p <0.05). All 3 tumors tested were IDH -WT.

Conclusions

- By surveying this large cohort of GBM patients we reported significant molecular differences based on patient age.
- Our data is consistent with previously reported TCGA subtyping of GBM tumors, including a proneural subgroup enriched for TP53, IDH, PDGFRA aberrations associated with younger patient age and a better patient prognosis compared to other subtypes.
- In our study, young patients also showed increased expression of 2 biomarkers, namely ALK and TUBB3, which also have a known role in nervous system development. A significantly higher prevalence of MGMT methylation in OP suggests benefit from TMZ in this patient group.
- Multiplatform tumor profiling has the potential to uncover biomarkers predictive of outcome and potentially yield actionable clinical targets for therapy.
  1. Our results suggest that BRAF, PDGFRA and PTPN11 may be of particular interest for targeted therapy in YP
  2. In contrast, PTEN loss may be a particularly important therapeutic target in OP.
- These observations warrant further investigations in prospective clinical trials.

References

Verhaak, R., TCGA, et. al (2009) "Integrated Genomic Analysis Identifies Clinically Relevant Subtypes of Glioblastoma Characterized by Abnormalities in PDGFRA, IDH1, EGFR, and NF1" Cancer Cell 17, 98–110