



Long term outcomes of Radiotherapy by two different fractionation regimens for IDH negative Glioblastoma in elderly- A Non Randomised Prospective Study

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Abstract

Purpose: To analyze long term outcomes of IDH negative Glioblastoma in elderly treated by two different fractionation regimens. To assess the impact of proportion of necrosis in the index lesion on the long term outcomes

Materials and Methods: A cohort of 14 elderly patients (mean age= 65 years) with Glioblastoma had undergone radiotherapy (Group A, 7: conventional fractionation; Group B, 7: hypofractionation). Patients in Group A had undergone conventional radiotherapy schedule (60Gy in 30 fractions over 6 weeks with concurrent TMZ), while patients in group B had undergone Hypofractionated radiotherapy (35Gy in 10 fractions in the first phase and further RT was based on response). Concurrent chemotherapy with Temozolomide in group B was administered if MGMT promoter methylation was found on methylation specific PCR. We retrospectively reviewed the index post Gado T1W images of all the patients to assess the proportion of necrosis calculated mathematically and termed Tumour Necrotic index (TNI) (defined by ratio of Volume (cc) of Gadolinium enhanced necrotic cavity and solid components of the mass lesion). The data was tabulated on SPSS version 21.0 and various outcomes measures analysed.

Results: Mean age of the group was 65 years, median KPS was 70. Among patients in Group A, 80% had undergone maximal safe resection, while 80% in group B they had undergone only a biopsy (3open:1STB) for histological confirmation. IDH testing by IHC against IDH1-R 132H was negative for all the patients in both groups while one patient in group B had methylated promoter of MGMT. In Group A, there was increased incidence of opportunistic infections, biochemical & metabolic alterations, prolonged overall treatment time of radiotherapy compared to Group B. Only 30% of the patients in Group A completed planned therapy. At a median follow up of 12 months, none of the patients in Group A are alive, whereas OS in Group B is 20% (Logrank, $p= 0.01$). Univariate analysis showed that TNI ratio of <0.3 ($p= 0.03$) and Hypofractionated schedule of radiotherapy (0.01) showed significant impact on overall survival.

Conclusion: We recommend Hypofractionated radiotherapy as the regimen of choice in Elderly patients with IDH negative Glioblastoma. A simple radiological tool- TNI aids in identifying elderly patients with Glioblastoma who will benefit by Hypofractionated radiotherapy.

Introduction

Mutation of an enzyme of the Citric acid cycle, IDH (Isocitrate dehydrogenase) plays a major role in improving the prognosis of patients with Glioblastoma¹ (GB). IDH negative (which are wild type tumours in elderly) tumours are predominantly seen in de-novo and elderly GB². These tumours are known to be large, necrotic and not amenable for maximal safe resection. Adjuvant standard radiotherapy regimen in these patients will invariably lead to increasing need of steroids thereby causing metabolic derangements and infections³. Added to this, these tumours in elderly have worst prognosis- due to the extent of necrosis leading to hypoxia and intrinsic resistance to therapy⁴. IDH can be tested by simple immunohistochemistry technique, with high specificity especially in older patients with Glioblastoma⁵. Along with clinical and surgical indices which aid in decision making in elderly patients with Glioblastoma, we hypothesize that a radiological tool- Tumour Necrotic Index (TNI) can be utilized to identify elderly IDH negative GB patients who may benefit with a short course protracted radiotherapy regimen.

Materials and Methods

Out of the patients treated for Glioblastoma at our institute, between 2014 and 2016, we selected MRI scans of 14 patients with IDH negative Glioblastoma in older patients who had previously undergone radiotherapy either by standard Stupp regimen (in 7) or a more protracted Hypofractionation regimen. The pre operative MRI images of these patients that were previously utilized to co-register with RT planning- CT images were reviewed again to delineate the necrotic and the solid tumour components separately on the Gadolinium enhanced T1 weighted post contrast images, to derive a ratio, termed Tumour-necrotic index. TNI of 0.3 was taken as significant level. Group A consisted of patients who had undergone maximal safe resection and received adjuvant therapy by the standard Stupp regimen. Group B consisted of

patients who underwent RT initially at a dose of 35Gy in 10 fractions (biologically effective to 46Gy) and later received remaining dose to complete 60Gy BED if there was clinical, neurological and radiological response.

Radiotherapy technique:

All patients underwent immobilisation with a 3 clamp thermoplastic mask in neutral neck position. Contrast enhanced CT scans was acquired from vertex to C4 level with 3 mm spacing. This CT was co-registered with Gado enhanced post op/ biopsy MRI scan and GTV contoured as per standard guidelines (post op cavity after total resection/ residual disease+ cavity in case of partial excision). CTV was GTV+3D expansion by 1.5 cm. PTV was CTV +0.5cm 3D expansion. All patients had undergone 3DCRT with a 3 field – non coplanar beam arrangement. IMRT was considered in patients with very large PTV. Group A had received radiotherapy to a dose of 60Gy in 30 fractions, while in patients in group B received RT to dose of 35Gy in 10 fractions (further RT to complete a BED of 60 Gy was based on response to 35Gy). Temozolomide was administered to a dose of 75mg/sqm daily concurrently with RT (excluding the weekends), followed by 150-200mg/sqm for the adjuvant phase. The outcomes of the two groups was compared.

Results

The patient neurological and tumour characteristics are mentioned in Table 1. Performance during RT is listed in table 2 and response assessment at 3months follow up is listed in table 3. Survival curve of OS between the two cohorts is shown in graph 1. Difference in OS based on OTT is shown in graph 2.

Median age of the group was 65 years, median KPS was 70 and weakness/ motor deficit was the main presenting complaint. Patients in Group A had undergone maximal safe resection, while in group B they had undergone only a biopsy (3open:1STB) for histological confirmation. Patients in group A needed steroid support from

the second week of RT. The course of radiation was complicated by opportunistic infections (herpes zoster: 3, gram negative pneumonia: 3, oro-pharyngeal candidiasis: 1). There was grade 2 neutropenia, grade 3 thrombocytopenia, dyselectrolytemia, hyperglycemia and altered liver enzymes in all the patients. Median OTT in group A/B was 50/ 24 days. At a median follow up of 3 months after RT, two patients had progressed in Group A after completion of 3 cycles of TMZ and there was active residual disease on MRI in the other 4 patients. Patients group C had improved KPS/NPS, had radiological response (CR: 2, PR: 5), all patients received the biological effective dose of 60Gy with acceptable toxicity and completed at least 3 cycles of TMZ. At a median follow up of 12 months, OS in group A was 0% vs. 12.5% in Group B. When the OS was compared between the two groups based on OTT, patients with OTT of 6 weeks or less had 12.5% vs. 0% in those with more than 6 weeks (p=0.42).

Table 1: Patient Characteristics

Parameter	Group A	Group B
N	7	7
Median Age	65	65
Presenting complaint	Headache	Motor deficits
Seizure at presentation	Yes	No
KPS post surgery	80	70-80
Surgery	Maximal safe excision	Biopsy (open/STB)
AED	Levetretacetam	Levetretacetam
Steroids before RT	Variable	Yes
Steroids during RT	Yes	Yes
Time to withdraw steroids, post RT	2 weeks	4 weeks
RT dose/ fractionation	60 Gy in 30 fractions	35 Gy/ 10 fractions
Temozolomide	Yes	1/7 Meth MGMT
OTT	50 days	30 days
Hematologic toxicity	Grade 2/3 Leucopenia	Nil
Altered LFT	Raised enzymes	nil
Opportunistic infections	Yes, (Viral/ bacterial)	nil
Improvement in KPS	Dropped by 10 points	Improved to >=70
Radiological response by RANO	Stable/ progressive disease	Partial response
Adjuvant TMZ	3 cycles in 30%	Completion of RT, 3cycles in all

Table 2: Results during RT

	Group A (TNI<0.3)	Group B (TNI>0.3)
Steroid support	From 2 nd week of RT	Continued from post op period
Opportunistic infections	80	80
Herpes zoster	2	1
Gram negative Pneumonia	1	2
Oropharyngeal candidiasis	1	1
Haematological Toxicity	Grade 2	Grade 3
Abnormal LFT, KFT	Present	Present

Table 3: Results at 3 months follow up after RT

	Group A (TNI<0.3)	Group B (TNI>0.3)
Deterioration of KPS	-	2
Deaths	-	2
Active residual disease	2	-
Progressive disease	2	-

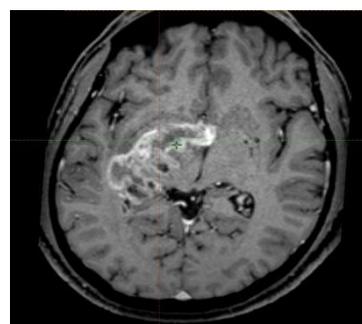


Figure 1: Radiological depiction of TNI <0.3

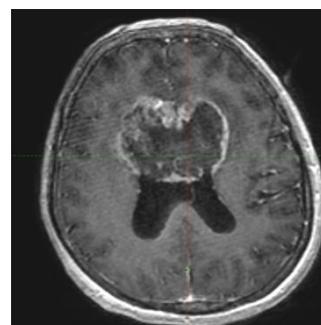


Figure 2: Radiological depiction of TNI >0.3

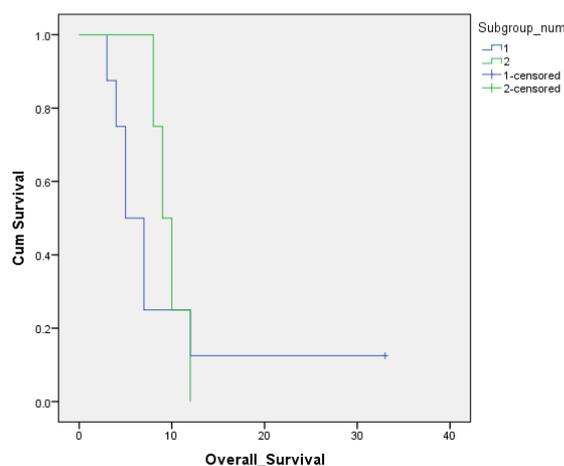


Figure 3: Overall survival difference between the two cohorts

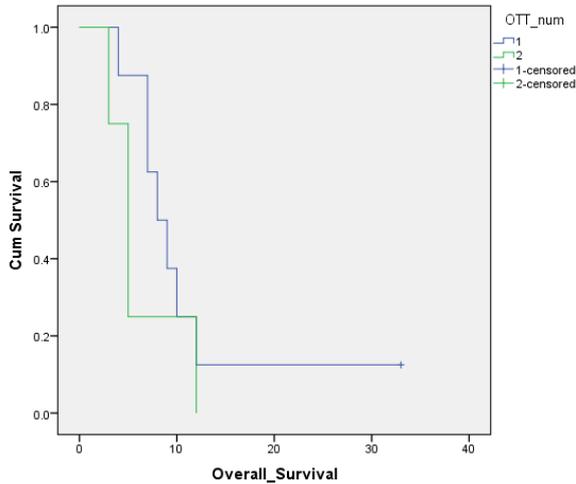


Figure 4: Overall survival difference between the two groups based on OTT

Discussion

Glioblastoma in elderly which are always IDH negative tumours, produce significant necrosis and thereby hypoxia leading to therapy resistance⁹. IDH, an enzyme of the citric acid cycle has been found to render diagnostic and prognostic importance and this when tested by routine IHC is found to be specific in identifying wild type tumours in older patients. Radiological advancements to identify IDH mutant Glioblastoma are not available uniformly and do not add additional information to the clinician to personalize adjuvant therapy⁶. Conventionally fractionated radiotherapy in a setting of sub-optimally excised large hypoxic tumours reduces the radio-therapeutic ratio⁷. Hypofractionated radiotherapy is utilized to address this issue, whenever indicated to reduce the overall treatment time and reduce the radiation related hypoxia complicating the pre-existing hypoxic tumour micro environment⁸. TNI is a simple radiological index, calculated volumetrically through the RT planning software, to quantify relative proportion of necrosis in the tumour. We analysed the outcomes of older patients with IDH negative tumours treated by two different radiotherapy fractionation regimens and also assessed the impact of TNI on overall survival.

We found that in patients with TNI of >0.3 , undergoing the conventional 6 week radiation regimen with Temozolomide had higher adverse

hematologic, biochemical effects, opportunistic infections, longer steroid dependence and prolongation of overall treatment time when compared to those patients who underwent Hypofractionated radiotherapy. Even in patients with TNI <0.3 , Hypofractionated radiotherapy had significant impact on overall survival.

Conclusion

In older patients with IDH negative Glioblastoma, Hypofractionated radiotherapy improves overall survival compared to conventional fractionation. This effect is more pronounced in patients with TNI of <0.3 .

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