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Evaluation of RANO response criteria compared to clinician evaluation in WHO grade III anaplastic astrocytoma: implications for clinical trial reporting and patterns of failure

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Abstract

The utility of current response criteria has not been established in anaplastic astrocytoma (AA). We retrospectively reviewed MR images for 20 patients with AA and compared RANO-based approaches to clinician impression described as follow: (1) standard RANO-based criteria met by growth of or development of new enhancing lesion (RANO-C), (2) RANO criteria for progression based on significant FLAIR increase (RANO-F) and (3) clinical progression usually resulting in change of treatment (Clinical). Patterns of failure (POF) were analyzed utilizing all proposed progression MRIs fused with the patients' radiotherapy treatment plan. With an overall median survival of 24.3 months, development of new enhancing lesion was the most common determinant of progression (70 % of patients). Median time to RANO-C, RANO-F and Clinical progression

was 9.2, 9.2 and 11.76 months respectively. RANO-C and RANO-F preceded Clinical in 70 and 55 % of patients, respectively. In six patients (30 %) Clinical was concurrent with RANO-F; four of six also met RANO-C. POF for FLAIR component differed based on time point used to determine progression. FLAIR POF was more often marginal or distant when progression was defined clinically compared to either RANO-C or RANO-F criteria. Central POF based on FLAIR at Clinical determination of progression was associated with significantly poorer OS (9.8 vs. 34.4 months). Clinical progression occurs later than progression determined by RANO-based criteria. Evaluation of POF based on FLAIR signal abnormality at the time of clinical progression suggests central recurrences are associated with worse survival.

Keywords

Anaplastic astrocytoma; RANO; Response assessment; Patterns of failure

Introduction

Anaplastic astrocytoma (AA), accounting for approximately 6–10 % of all gliomas, are the most common type of anaplastic gliomas (WHO grade III), and because of their biological behavior are considered high-grade gliomas (HGG) [1] [2]. Treatment of AA is still controversial and despite the lack of specific randomized trials, most clinicians use the Stupp regimen, adjuvant radiotherapy with concurrent and adjuvant temozolomide, which is based on the glioblastoma (GBM) experience.

Response assessment is important in determining efficacy of therapeutic interventions. Because of differences in imaging characteristics between AA and GBM, however, response assessment in AA can be problematic. Many response evaluation approaches have been developed for gliomas, but none have been specifically established for grade III AA [3]. Response assessment tools developed over time range from 2D WHO criteria (WHO 1979) [4], MacDonald's 2D criteria [5], 1D response evaluation criteria in solid tumors (RECIST) introduced in 2000 [6], to the newest response assessment in neuro-oncology (RANO) 2D criteria published in 2010 as an update of MacDonald's approach [7]. These tools are all tailored primarily for use in GBM patients, where measurements focus on the evaluation of new or enlarging contrast enhancing (CE) lesions. However, compared to the others listed, the RANO criteria incorporates evaluation of the FLAIR signal abnormality as a reaction to the newly described phenomena of pseudoprogression (PsP) and pseudoresponse (PsR), especially seen more commonly with concomitant temozolomide and anti-angiogenic target therapy, respectively.

The majority of grade III tumors are minimally enhancing, thus strict application of the RANO criteria in grade III tumors is not straightforward. For these cases, imaging with T2/FLAIR MRI sequences is established as the modality of choice. Despite the fact that the FLAIR signal is often irregular in shape with ambiguous boundaries leading to substantial interobserver variability [8] attempts have been made to standardize FLAIR response assessment in low grade gliomas (LGG) using modified RANO criteria [9].

Appropriate and timely identification of progression is important not only for each patient, but also for accurate reporting of clinical trials outcomes. In radiotherapy, evaluation of patterns of failure (POF) is a powerful tool for assessing the benefit of various treatment approaches, especially those with modified target volume definitions and dose escalation. Since POF is determined on the image defined by progression, multiple definitions of progression can widely influence these results.

This study compares progression free survival (PFS) time to progression (TTP) as defined by RANO criteria with retrospective clinical impression of PFSTTP and evaluates the utility of RANO-based criteria in grade III AA. We also evaluated the influence of method of progression determination (RANO vs clinical) on POF after radiotherapy using detailed dosimetric data.

Patients and methods

Patients

After approval by the Mayo Clinic Institutional Review Board, medical records for consecutive patients with newly diagnosed AA (WHO grade III) treated at Mayo Clinic, Rochester between April 2004 and May 2010 were retrospectively reviewed. Patients who developed radiographically-proven recurrence after initial surgery followed by fractionated radiotherapy with concurrent temozolomide and adjuvant temozolomide were included in this study. Patients were treated based on standard Stupp regimen. One patient had as part of adjuvant treatment also 5 cycles of carmustine in addition to temozolomide. Patients without available follow-up MRI images, those with brainstem glioma or who were given chemotherapy wafers were excluded. Of 53 pre-identified, 20 patients were eligible for POF analysis.

Definition of progression

Follow-up MRI images were consecutively reviewed for each patient using three criteria for identification of progression: (1) standard RANO-based criteria (RANO-C) most often met by the development of a new or enlargement of an existing CE lesion, (2) RANO criteria for progression based on significant FLAIR increase ignoring changes in CE (RANO-F), and (3) Clinical progression based on oncologist's interpretation of imaging and clinical status (CLINICAL), usually resulting in a change of treatment. Retrospective chart review was performed to determine clinical (CLINICAL) progression based on documentation by the treating neuro-oncologist. In general, CLINICAL progression was the date when treating neurooncologist determined progression to be unequivocal based on the combination of progressive imaging findings and neurologic symptoms resulting in a change in therapy. CLINICAL progression is felt to be consistent with current clinical practice enabling more realistic assessment of usefulness and impact of RANO-based criteria for AA. For each identified time of progression, several subsequent consecutive follow-up MRI examinations were reviewed to ensure true progression versus PsP.

Dosimetric analysis of recurrence

POF was evaluated based on the MRIs identified for progression using RANO-C, RANO-F, and CLINICAL criteria. All MRI scans documenting progression were registered with the original CT scan used for radiotherapy treatment planning (ECLIPSETM treatment planning system, Varian Medical System, Palo Alto, CA, USA). Three to five follow-up MRI image datasets were co-registered to the planning CT for each patient. Two follow-up MRI data sets were mandatory for baseline assessment—MRI with best T1 CE and MRI with best FLAIR signal response. The remaining follow-up MRI studies for progression assessment varied by patient. For some patients, all progression MRIs (RANO-C, RANO-F and CLINICAL) met their respective criteria in one MRI examination leading to a total of 3 MRIs evaluated for that particular patient. However, in some patient cases, progression criteria were met based on separate serial follow-up MRI scans, leading to a total of 5 co-registered MRI datasets.

Recurrence volumes were manually contoured and approved by an experienced Radiation Oncologist. In order to differentiate true FLAIR recurrence from treatment-related changes as well as to be consistent with RANO criteria requirements, we defined a baseline MRI (with the best T1 CE, or T2/FLAIR signal abnormality, respectively) for each patient to serve as a reference image for future comparison. Using Boolean operators, pathologic signal volumes from the baseline MRI were subtracted from volumes defined in the progression MRI, leading to the creation of a recurrence volume representing “true” progression volume. Using dosimetric data from the radiotherapy treatment plan, this recurrence volume was compared against the volume representing 95 % of the prescribed dose to calculate the percentage of the “true” progression volume that received 95 % of prescribed dose (Fig. 1).

The recurrence was subsequently classified into one of four failure patterns as summarized in Table 1 [10]. Recurrence volumes that were not clearly confined within one of the defined isodose regions were assessed using the dose-volume histogram.

Statistical analysis

Statistical analysis was performed using JMP 9 Software (SAS Institute). TTP was assessed among the three criteria using Friedman’s test, and pairwise criteria using a sign test. POF were correlated with survival outcomes using the 1-way ANOVA or Wilcoxon test. Kaplan–Meier estimation was used for survival analysis. Age, sex, performance status, marital status, IDH mutation status, extent of surgery, presence of CE, steroid status and original tumor size were assessed as confounding factors. Cox proportional hazards regression was used for calculating risk ratios. $P < 0.05$ was considered statistically significant.

Results

Characteristics of the 20 identified patients are summarized in Table 2. Gross total resection was obtained in 10 % of patients, 35 % subtotal resection, and 55 % underwent stereotactic biopsy only. All patients received concurrent and adjuvant temozolomide and conformal

external beam radiation (median dose 59.4 Gy, 33 fractions). Median overall survival (OS) was 24.3 months. Twelve (60 %) patients had CE disease at diagnosis.

Definition of progression and PFSTTP

Development of new CE (RANO-C) most frequently determined RANO progression (14 patients, 70 %). Four (20 %) patients were on steroids (1 with decreasing, 1 unchanged and 2 with increasing trend in dosage), all of them were subsequently characterized as marginal progression. At RANO-F progression, the same 4 patients were receiving steroids. Nine (45 %) of patients were steroid dependent at the time of CLINICAL progression (1 with decreasing, 5 unchanged and 3 with increasing trend in dosage). The TTP was significantly different among the 3 criteria ($p < 0.001$, Friedman's test), 9.2 months for both of patients, RANO-C criteria identified progression which led to a change of treatment. Similarly, RANO-F progression preceded CLINICAL progression in 55 % of patients (Sign test, $p = 0.06$, median 4.5 months, IQR = 1.4–9.8 months). In 6 patients (30 %) CLINICAL progression was concurrent with RANO-F progression; 4 patients (20 %) also met RANO-C, so one unique followup MRI met all three progression criteria. Three patients developed CLINICAL progression earlier than RANO-F-based criteria.

Patterns of failure

RANO-C and RANO-F and 11.76 months for CLINICAL assessment. There was no statistical difference between TTP assessed per RANO-C vs. RANO-F criteria (Sign test, $p = 0.45$). The progression was determined at the same time in 13 patients. RANO-C progression preceded CLINICAL progression in 70 % of patients (Sign test, $p < 0.0001$, median 2.9 months, IQR = 1.6–4.5 - months). For the remaining 30 %, RANO-C and CLINICAL progression were concurrent, meaning that for 30 %

POF classification was significantly influenced by the progression MRI used for the evaluation (RANO-C, RANO-F or CLINICAL). Defining the recurrence volume per CE led to a mean recurrence volume encompassed within the 95 % prescribed dose of 98.6 %, SD 3.9 %, which resulted in the majority of recurrences classified as central. For POF based on FLAIR evaluation, the distribution of measured recurrence volumes within the high dose field was more variable, resulting in a median of 83 % (IQR = 62–97), 87 % (IQR = 65–97) and 74 % (IQR = 64–89) for RANO-C MRI, RANO-F and CLINICAL respectively. Corresponding classifications of POF are summarized in Table 3.

Recurrence patterns differed significantly with more peripheral patterns documented based on the CLINICAL MRI compared to the other FLAIR assessments (RANO-C and RANO-F MRI, $p = 0.03$ and 0.008 respectively). In order to evaluate potential effect of delays in radiotherapy or radiotherapy timing on POF, POF evaluation defined as time from the end of RT was also performed (data not shown). There were no statistically significant differences between the times to each types of POF for any of the RANO or CLINICAL progression timepoints. Median time to non-central POF for CLINICAL progression was slightly longer compared to central (9.7 months vs 7.3 months), however the results were not statistically significantly ($p = 0.2$). Central POF based on FLAIR defined on the CLINICAL MRI were associated with both worse OS and time to death after progression compared to non-central

POF (Kaplan–Meier estimation, Log Rank $p = 0.012$ and 0.0012 respectively). Similarly, differences in OS and time to death after progression was significant for IDH mutation status (Kaplan–Meier estimation, Wilcoxon $p = 0.037$ and 0.033 respectively) (Fig. 2). In Cox Proportional Hazards Regression analysis, IDH mutation status ($RR = 0.11$, $p = 0.006$, 95 % CI [0.006, 0.59]) and the grouping of POF as central versus non-central ($RR = 9.2$, $p = 0.0134$, 95 % CI [1.7, 50.7]) remained significantly associated with survival.

Discussion

In our study, we evaluated the utility of RANO criteria in determining progression in grade III AA. The TTP in this series of AA patients was significantly different between RANO criteria and clinical determination of progression. In 20 % of patients, one unique MRI met all proposed criteria for progression. For the remaining patients, TTP was significantly longer when using CLINICAL determination as compared to either RANO-C or RANO-F criteria. There was no significant difference in TTP identified between the RANO-C or RANO-F criteria assessments. PFSTTP based on CLINICAL progression compared to RANO was 2.5 months later (11.76 vs. 9.2 months). This likely corresponds to 1–2 additional MRI examinations to confirmation asymptomatic radiographic progression. Although the clinical significance of this difference is unknown, appropriate determination of progression is increasingly important for evaluation of efficacy of novel treatment strategies [11]. As OS can be influenced by other salvage treatment administered after progression, PFSTTP or progression free survival is increasingly used for evaluating primary treatment efficacy. For GBM, PFSprogression free survival at 6 months has been suggested as a potential surrogate endpoint [12]. Despite the attempts to adjust current RANO criteria for evaluation of T2/FLAIR signal abnormality, especially in LGG cases [9], our data suggests there are limitations of incorporation of RANO criteria to AA which must be accounted for in clinical trials using PFSprogression free survival or TTP as study endpoint.

POF analysis can be used to assess the impact of novel agents on radiotherapy efficacy and new radiotherapy techniques. Generally, gliomas are known to primarily recur centrally after both surgical resection alone and radiotherapy [13]. Because patients with AA do not uniformly have CE disease, we proposed to evaluate the POF based on changes in FLAIR signal in addition to changes in CE. Because FLAIR changes are commonly recognized as an indication of treatment related changes in brain (post-radiation changes), we defined the recurrence volume as the difference in FLAIR signal abnormality in the follow-up MRI associated with progression as compared to the best-response (often post-treatment) image. This is the first study evaluating dosimetric POF for AA based on recurrence volumes defined with FLAIR signal abnormality.

POF when assessed on the MRI determined by either RANO-C or RANO-F criteria were similar. On the other hand, a significant increase in peripheral recurrences (combined in-field and marginal compared to central) was observed when recurrence volumes defined on the CLINICAL MRI were evaluated. Central POF at CLINICAL evaluation is associated with worse overall survival from diagnosis and shorter time to death after progression compared to non-central POF. This does not appear to be related to lead-time bias as there

was no significant difference in time from the end of RT to central versus noncentral failure. The potential of FLAIR signal evaluation for prediction of survival as a biomarker was also reported in a study of 191 patients with recurrent HGG (16 % non-glioblastoma) treated with salvage bevacizumab. Interestingly, the ratio of abnormal T2/FLAIR area to CE area was seen to be prognostic of OS in patients with Grade III tumors but not in patients with glioblastoma [14]. The authors speculated that this may be related to antiedema effect of bevacizumab. Animal models with other anti-VEGFR inhibitors have demonstrated improved survival with reduction of edema [15]. Treatment related reduction of edema may be responsible for survival improvement observed also in our cohort as most patients (60 %) went on the bevacizumab for salvage treatment. Per RANO criteria, increase in corticosteroids alone is not taken into account in determining progression by RANO criteria in the absence of persistent clinical deterioration; however, equivocal radiologic findings associated with clinical decline and increasing steroid dependency can determine progression. This is consistent with our results in that CLINICAL progression patients were more likely to receiving steroids than radiographically determined patients. In addition to determining timing of progression, steroid use may confound subsequent FLAIR evaluation in a POF analysis. By decreasing the peripheral FLAIR abnormality it may be expected that recurrences in patients receiving steroids may be preferentially classified as central recurrences. In our analysis, however, an inverse correlation was found, with more patients being on steroids determined to have a peripheral POF. Since more patients with CLINICAL progression were steroid-dependent at that time of progression, this may be related to the later time point progression was determined as discussed previously. However, more peripheral POF were seen even in RANO determined progression patients receiving steroids so this observation may also reflect underlying biological differences (i.e. increased symptomatic tumor infiltration) associated with more frequent peripheral POF. Larger patient numbers are needed to further evaluate this observation.

Previously, the only factors that have been shown to influence prognosis in patients with AA are age and Karnofsky performance status (KPS). More recently, a total of 1,766 patients with AA were studied using the SEER registry, describing additional factors associated with the hazard of mortality in AA patients, such as type of surgery and marriage status [16]. From molecular genetics predictors, IDH1 mutation is most strongly associated with improved survival [17]. In our study, IDH mutation status was significantly associated with improved survival and survival after progression. Although numbers are small, all of patients with non-central failures in our report were IDH mutant. Central control in these patients suggests that there are biologic differences between these patients and that RT-temozolomide is successful at controlling their disease in high dose RT region. In addition, patients with non-central POF are progressing in regions of sub-therapeutic RT dose so the surviving clones are not necessarily resistant. Our finding that IDH mutant status correlates with non-central POF is also suggestive of biologic differences determining POF. Despite their more favorable prognosis, recent studies suggest IDH mutant tumors have more infiltrative pattern of growth which is consistent with our findings [18].

This small, retrospective study has numerous limitations. The small cohort of investigated patients is the most significant limitation, reflecting the relatively low incidence of AA. Similar trials assessing patients from several centers will be necessary in order to provide

results with higher statistical power. In addition, in clinical practice, such complex dosimetric recurrence evaluation can be challenging and time-consuming. With the advent of more automated contouring tools assessment of MRI images and POF delineation, it will be more clinically feasible to evaluate progression and subsequent recurrence patterns using the suggested subtraction approach. However, based on our data, central FLAIR progression is associated with a significant risk ratio of 9.2 as compared for non-central failures, information which can influence a physician's decision of appropriate salvage and palliative treatment.

In conclusion, early recognition of progression after treatment of gliomas is increasingly important with novel and effective salvage therapy possibilities. It is also important for reporting treatment outcomes, since waiting for OS may not be the best approach for evaluating initial treatment response in gliomas. Unfortunately, evaluation of grade III gliomas possesses many challenges related to the ambiguous imaging patterns. In our analysis of grade III AA investigating several criteria in order to objectively assess response after multimodality treatment, we demonstrated significant differences in identification of progression between RANO criteria and CLINICAL progression. Classical RANO criteria did not differ from the adjusted criteria which included changes in FLAIR signal. Evaluation of POF based on FLAIR signal abnormality at the time of clinical progression suggests central recurrences are associated with worse survival. Our analysis suggests that evaluation of POF at time of CLINICAL progression may be useful for prognosis estimation and for appropriate stratification of patients for subsequent salvage and palliative treatment.

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Fig. 1.

Example of different recurrence volumes (a) for T1 CE in green and (b) for FLAIR signal abnormality in cyan) and its relation to 95 % treatment isodose in red (c). In this case, RANO-C and RANO-F met criteria in same MRI (left side). On the right side, CLINICAL MRI is shown for the same patients demonstrating more peripheral FLAIR failure comparing to central pattern while evaluating RANO MRI

Fig. 2.

a Kaplan–Meier OS estimation. Median survival for central recurrences is 9.8 months compared to 34.4 months for non-central failures on CLINICAL evaluation. b Kaplan–Meier estimation of time to death after CLINICAL progression. Median survival for central recurrences is 3.5 months compared to 12.8 months for non-central failures. c Kaplan–Meier OS estimation. Median survival for IDH mutated is 51.25 months compared to 18.68 months for wild type. d Kaplan–Meier estimation of time to death after CLINICAL progression. Median survival for IDH mutated is 43.8 months compared to 6.75 months for wild type

Table 1

Definition of failure patterns based encompassed within high dose region on volume of recurrence

Failure pattern	Isodose calculation	
Central	V ₉₅ %	95 %
In-field	80 %	V ₉₅ %
Marginal	20 %	V ₉₅ % < 80 %
Distant	V ₉₅ % < 20 %	

Table 2

Patient demographics and tumor characteristics

Patient characteristics	Number of patients (n = 20)
Sex	
Male	11 (55 %)
Female	9 (45 %)
Age (years)	
Mean	54.9
SD	±11.9
Performance status by Karnofsky's scale	
Median	90
Mean	88.5
Radiotherapy dose	
Mean	59.4 Gy in 33 fraction
Cycles of adjuvant temozolomide	
Median/Mean	6/5.8
Tumor size (largest FLAIR diameter)	
Median (mm)	56.1
Range	34.7-101.8
Initial tumor CE	
Enhancement present	12 (60 %)
Extent of resection	
Biopsy	11 (55 %)
Subtotal resection	7 (35 %)
Gross total resection	2 (10 %)
IDH mutation status	
Wild type	16 (80 %)
Mutation (R132H)	4 (20 %)
Married status	
Married	95 %

Table 3

POF by MRI classification of progression

Recurrence	RANO-C T1	RANO-C FLAIR measurement	RANO-F	CLINICAL
Central	18 (95 %)	6 (30 %)	8 (44 %)	3 (15 %)
In-field	1 (5 %)	5 (25 %)	3 (17 %)	5 (25 %)
Marginal	0	9 (45 %)	7 (39 %)	11 (55 %)
Distant	0	0	0	1 (5 %)