Original Article

Pattern of failure in IDH mutated, low grade glioma after radiotherapy – Implications for margin reduction

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ARTICLE INFO

Low grade glioma (LGG) is a group of relatively slow growing primary brain neoplasms, chiefly occurring between 30 and 50 years of age [1]. With recent advances in molecular genetics, it has been found that molecular subtype is a better predictor of prognosis than classical histology [2,3]. The 2016 WHO classification of glioma is based on a genotype-driven classification of diffuse gliomas [4]. The grade 2 gliomas have been subdivided along the presence or absence of a mutation in the *isocytrate dehydrogenase 1* or *2* (*IDH*). The group of tumors with a mutation present in the *IDH* gene (IDHmG) have a relatively favorable prognosis, while group of *IDH* wildtype (IDHwt) tumors have a prognosis more akin to glioblastoma [5,6].

The objective of radiotherapy in low grade glioma is an extended period of local control. The place of postoperative radiotherapy and chemotherapy in grade 2 glioma was established by the results of several multicenter trials [7–9]. After a disease-free interval, a subset of low grade glioma are known to undergo malignant transformation, almost invariably inside or in close proximity to the radiation field.

Improvements in imaging, neurosurgical technique, and the introduction of adjuvant chemotherapy over the past 20 years have increased the prognosis of LGG patients considerably. As such, there has been a shift in focus from achieving disease control towards reducing the late adverse effects of radiotherapy. The use of radiotherapy, especially the large fields applied in the past, has been implicated in the onset of late neurocognitive decline [10]. Recent trials have reduced the GTV-CTV expansion to 10 mm (NRG BN005, NCT03180502) or 5 mm (EORTC 1635, NCT03763422). The current working document of the Dutch Platform for Radiotherapy in Neuro-Oncology advises a margin of 5 mm to be used in clinical care. However, effect of these smaller fields on pattern of failure is not yet known. We sought to assess the safety of a CTV margin reduction to 5 mm using a retrospective analysis of historical treatments of *IDHmt* low grade glioma patients using the 2011 RANO criteria for progressive disease [11].

Methods and materials

Patient population

We reviewed the charts of all patients treated with radiotherapy for histologically confirmed low grade glioma between 1-1-2007 and 31-12-2017 in Erasmus MC. Of the patients exhibiting disease progression, the original planning CT, structure set, and dose object were retrieved. In patients in which the *IDH* status was not known, *IDH* was sequenced from archived material. Finally, a number of cases in which *IDH* status was known from a separate project [12] were found to have disease progression on follow-up. Data from these cases was requested from their treating centers. The study was conducted according to the principles of the Declaration of Helsinki (59th WMA General Assembly, Seoul, October 2008) and in accordance with the local medical research regulations. The study protocol was presented to the local Medical Ethics Committee (MEC-2019-255) and considered not subject to the Medical Research Involving Human Subjects Act.

Event definition

Resection status was defined as either biopsy only, complete resection (if no residual tumor mass was reported on postoperative

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imaging) or partial (if residual tumor mass was present). Follow up MRI's typically included of at least T1 weighed pre- and post-contrast, 2d T2 weighed and FLAIR images. All available MRI's were reviewed. Type of recurrence was defined according to Response Assessment in Neuro Oncology (RANO) criteria as either enhancing (development of a new contrast enhancing lesion) or non-enhancing (an increase of 25% in perpendicular diameter of T2 abnormalities without enhancement). The date of progressive disease (PD_{RANO}) was the date of the first MRI that fulfilled the RANO criteria for recurrence. Time to progression (TTP) was defined as the interval between the last RT fraction and the date of progressive disease according to the RANO criteria. In all centers, it was customary to confirm the diagnosis of recurrence in a multidisciplinary neuro-oncological tumor board before a next intervention was started. The date on which the diagnosis of recurrence was confirmed by the tumor board was defined as "tumor-board progressive disease" (PD_{tb}). In order to avoid transient contrast-enhancing lesions being interpreted as disease recurrence we confirm the presence of these lesions over sequential MRIs between PD_{RANO} until PD_{tb}. Adjuvant chemotherapy was defined as chemotherapy started within 3 months after completion of radiotherapy in absence of disease progression.

Volumetric analysis

The MRI at time of PD_{RANO} was rigidly matched to the original planning CT using MIM (MIM software, version 6.3.9, Cleveland, Ohio). In patients with an enhancing recurrence, the recurrence volume (rTV) was defined as the area of pathological enhancement on T1 series. In patients without an enhancing recurrence, the recurrence volume was defined as the areas of T2 hypo-attenuation that exhibited progression over the preceding 12 months. The volumes were delineated by AMR and JJ (radiation oncologists), and delineations were approved by MvdB (neurologist).

A hypothetical CTV of 5 mm (CTV5mm) was generated by creating a 5 mm expansion of the original GTV, and limiting this to within the original CTV. The overlap between the rTV, the original CTV, the CTV5mm and the original 95% isodose volume was calculated. Recurrence was classified as either central (>95%), inside (>80–95%), edge (>20–80%), or outside ($\leq$20%) of the original CTV. Dose volume histograms (DVH) were generated for all recurrences. The distribution of recurrences with regards to the original CTV and the CTV5mm was compared using a two-way ANOVA. Overall survival and progression free survival were assessed using a Kaplan-Meier analysis. Statistical analysis was done in R (www.r-project.org) and SPSS (IBM Corp., IBM SPSS Statistics for Windows, Version 25.0.0.1, Armonk, New York).

Results

Between 1-5-2007 and 31-12-2017, 113 patients underwent radiotherapy for low grade glioma. A recurrence was diagnosed in 56 patients. Radiotherapy planning and delineation could be retrieved in 49 of these patients. In 35 of these patients a positive *IDH* mutation status was found. Four additional fully documented cases with known *IDH* status and disease recurrence were added from two centers. The final dataset comprised 39 IDHmG patients with known recurrence. Patient characteristics are summarized in Table 1.

Mean age at diagnosis was 42.1 years (95% CI 39.6–45.7). Resection status was gross total resection in 4 patients (10%), partial resection in 23 (59%), biopsy in 11 patients (28%), and unknown in one patient (3%). A 1p/19q deletion was present in 17 patients (44%), absent in 17 patients (44%) and undetermined in 5 patients

Table 1
Patient characteristics.

Age (years)	42.1		(95% CI 39.1 – 45.1)
Sex	Male	26	66.6%
	Female	13	33.3%
Hemisphere	Right	16	41.0%
	Left	19	48.7%
	Both	4	10.3%
Lobe	Frontal	22	56.4%
	Temporal	5	12.8%
	Parietal	4	10.3%
	Occipital	4	10.3%
	Brainstem	1	2.6%
	Overlapping lesion	3	7.7%
Resection status	Biopsy	11	28.2%
	Partial or subtotal resection	23	59.0%
	Gross total resection	4	10.3%
	Unknown	1	2.6%
1p/19q codeletion	Present	17	43.6%
	Absent	17	43.6%
	Undetermined	5	12.8%
Technique	3DCT	25	64.1%
	IMRT	14	35.9%
CTV margin	10 mm	10	25.6%
	15 mm	29	74.4%
CTV volume (cc)	294		(95% CI 252–336)
Adjuvant chemotherapy	None	35	89.7%
	Temozolomide	2	5.1%
	PCV	2	5.1%

(13%). Median interval between surgery and start of radiotherapy was 0.3 years (range 0.2–12.0). All patients were treated to a dose of 50.4 Gy in 28 fractions (ICRU 50). Patients were treated with either 3DCT (64%) or IMRT (36%). GTV-CTV margin was 15 mm in 29 patients (74%), and 10 mm in 10 patients (26%). The mean CTV volume was 294 cc (95% CI 252–336). PTV margin was 5 mm in all patients. Four patients (10%) were treated with adjuvant chemotherapy.

By the time of analysis the median duration of follow-up from end of radiotherapy was 5.0 years (range 1.4–11.4). Median overall survival was 5.6 years (range 1.3–11.4), with 24 patients having died of disease. Median TTP was 2.8 years (range 0.6–9.3). In 21 patients, the date of PD_{RANO} was within 14 days of the date of PD_{tb}. However, in 18 patients the date of PD_{RANO} predated the date PD_{tb} by a median of 0.5 years (range 0.1–3.0). Time intervals and survival are summarized in Fig. 1.

At the time of PD_{RANO} 34 patients developed an enhancing recurrence (87%) and five patients (13%) developed a non-enhancing recurrence. The mean volume of the rTV of enhancing recurrences was 5.2 cc (range 0.1–37.7). The mean volume of the rTV of non-enhancing recurrences was 32.8 cc (range 2.4–140.3). With regards to the original CTV, recurrences were classified as central in 32 (82%), inside in 3 (8%), edge in 1 (2%) and outside in 3 patients (8%). Almost all recurrences (92%) were covered by the 95% isodose line, three (8%) were out-field. Based on the hypothetical CTV5mm, recurrences would have been central in 26 (66%), inside in 4 (10%), edge in 5 (13%), and outside in 4 (10%) patients (Fig. 2). The difference in distribution of recurrence clas was significant (p = 0.005). See Fig. 3 for two examples of recurrences. Owing to the low number of non-enhancing recurrences, we were unable to test whether the distribution of recurrence class differs between enhancing and non-enhancing recurrences. However, the probability of a central recurrence was higher in enhancing recurrences (88%) than in non-enhancing recurrences (40%, p = 0.03, see Supplementary data 1). The mean dose to 98% of the rTV (D98%) was 50.4 Gy in the recurrences classified as central with respect to
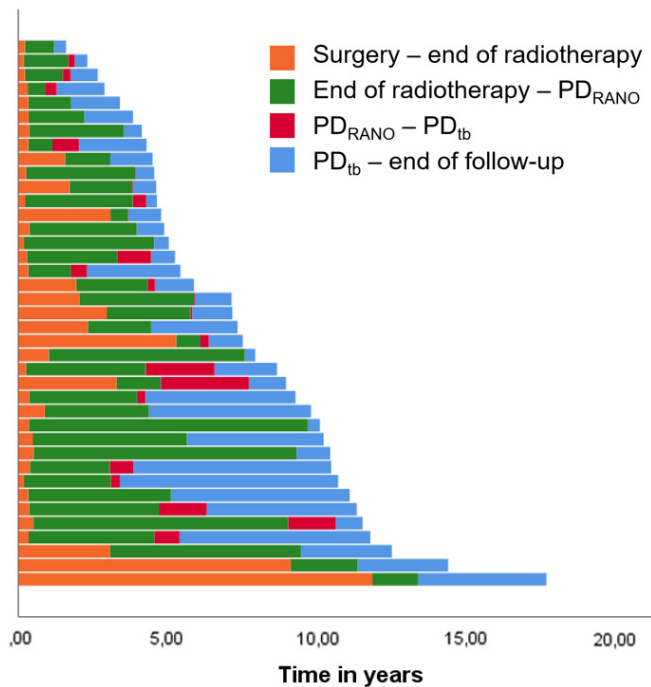
Fig. 1. Waterfall plot of time intervals for all patients from diagnosis until end of follow-up. PD_{RANO} = progressive disease as defined by the RANO criteria. PD_{tb} = progressive disease confirmed by the multidisciplinary tumor board.

the CTV (range 48.4–54.4), 48.8 Gy in the inside category (range 48.6–49.2), 44.1 Gy in the one edge recurrence, and 14.7 Gy (range 1.5–34.4) in the outside category (see Supplementary data 2 and 3).

Discussion

The size of the treatment field has been a point of contention since the introduction of radiotherapy for glioma. Historically, proponents of partial brain techniques argued a smaller treatment field would lead to less adverse effects and potential for dose escalation [13–15], while proponents of whole brain radiotherapy emphasized the risk of out-field failure in light of uncertainties in target localization [16,17]. Following the availability of CT and MRI imaging, the landmark trials in low grade glioma of the 1990s and 2000s all adopted target volumes based on some form of a margin around a lesion visible on imaging of 15 to 20 mm (Table 2). As no prospective data on smaller treatment margins

exists, a CTV margin of 10–15 mm is still standard of care in many centers.

To our knowledge, this study is the first to use a volumetric approach to classify the pattern of recurrence in *IDH* mutated, low grade glioma as defined by the new 2016 WHO classification. Although varying in methodology, for example, a centroid approach [18] or visual methods [19], all known studies investigating pattern of recurrence find the vast majority of failures to occur within high-dose area of the original treatment field (see Table 3). In this study, we find a similar pattern of failure in patients treated between 2007 and 2017 with the dose of 50.4 Gy in 28 fractions regarded as standard, using a GTV-CTV expansion, a PTV margin, and photon therapy planning techniques (3DCT, IMRT) that represented standard of care. The results from the proton therapy cohort presented by Kamran [19], which dates from 2005 to 2015, suggest the pattern of failure in proton beam therapy is comparable.

The cases in our cohort were selected for disease progression, resulting in a median TTP of only 2.8 years after radiotherapy at a median duration of follow-up of 5.0 years. Contrasting this, the median TTP in the entire radiotherapy – only group of EORTC 22033–26033 [20] was 3.8 years at a median duration of follow – up of 4.0 years, reflecting the case selection in this study. It is notable that all but 4 patients treated in this study date from before the introduction of adjuvant chemotherapy. Both PCV and temozolomide chemotherapy are known to inhibit tumor growth [21,22], and the use of chemotherapy is associated with a benefit in PFS in IDHmG [7,9]. As the number of patients that received adjuvant chemotherapy in this study is low, the influence of adjuvant chemotherapy on the pattern of failure is not known.

The definition of disease progression may influence the pattern of failure. As the recurrence volume will increase over time, mostly in a centripetal manner, definition of recurrence at a later time point will lead to an increasing number of failures in the "inside" or "edge" categories. As an additional observation, we found that when retrospectively assessing all imaging, PD_{RANO} was found to predate PD_{tb} almost half of all patients. A similar finding appears in Izquierdo et al [22], reporting an interval between retrospectively assessed RANO – progressive disease and the next intervention of 11 months. New contrast - enhancing lesions after radiotherapy are not uncommon and some represent benign post-treatment changes [23,24]. It is likely that new contrast – enhancing lesion are observed for a time period in follow up, before they are considered indicative of disease recurrence. In this study, the contrast – enhancing lesions that were delineated at PD_{RANO} were identified with the benefit of hindsight. As such, all lesions delineated developed into the actual recurrence confirmed by the tumor board at PD_{tb}.

There are several factors other than the GTV-CTV and tumor size that determine the size of the treatment field. The size of
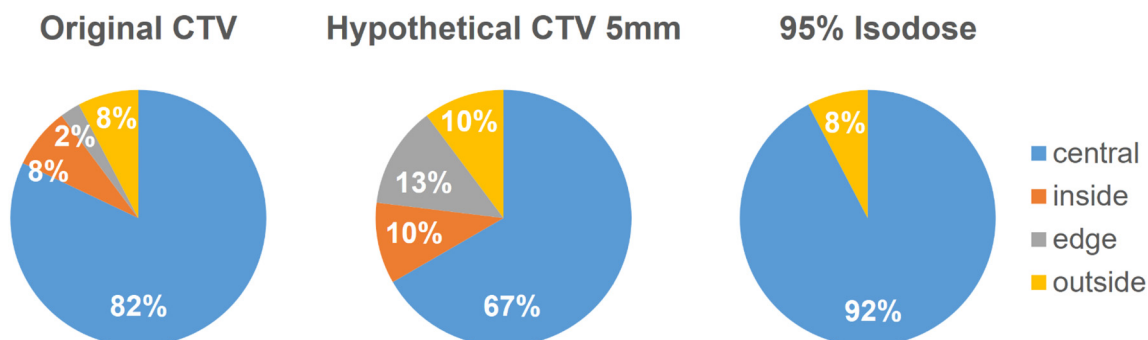

Fig. 2. Classification of recurrences based on original CTV, the hypothetical 5 mm CTV (CTV5mm), and the 95% isodose. The difference in distribution of recurrences with regards to the CTV and the CTV5mm is significant (p = 0.005).
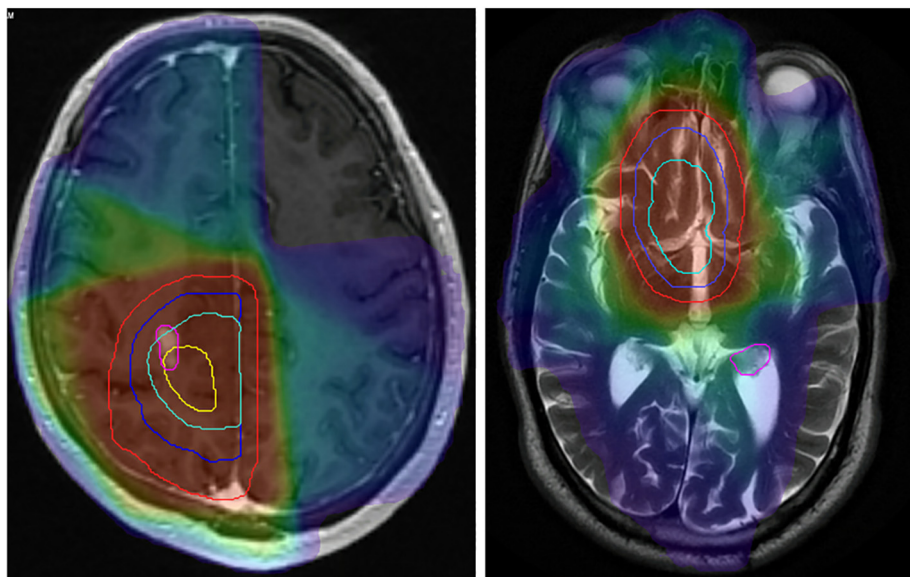
Fig. 3. Two examples of recurrences. The dose distribution and the structure set are superimposed on the MRI at the time of recurrence. The GTV is in yellow, the original CTV is dark blue, the PTV is red. The CTV5mm is in light blue. The rTV is in pink. To the left is a T1 recurrence classified as "central" with regards to the original CTV, "inside" with regards to the CTV5mm, and "in field" with regards to the 95% isodose. To the right is a parahippocampal (and infratentorial) T2 recurrence classified as out-field.

Table 2
Overview of specified treatment margins in selected trials, and published pattern of failure for low grade glioma. Note that ICRU29 definition defined a target volume, and ICRU50 report and on define a CTV and a PTV. See [36] for an illustrated overview.

		Procedure	Target	ICRU definition
Completed trials				
EORTC 22,844 [31]		CT enhancing lesion + 20 mm	Target volume	ICRU29
		CT edema + 10 mm		
EORTC 22,845 [37]		MRI T2 abnormalities + 20 mm	Target volume	ICRU29
RTOG 9802 [9]		MRI T2 abnormalities + 20 mm	Field edge	ICRU29
Intergroup [32]		Lesion on CT or MRI + 20 mm	Target volume	ICRU29
EORTC 22,033–26,033 [20]		MRI T1 enhancement and T2 abnormalities + 15 mm	CTV	ICRU50
Ongoing trials				
NRG BN005	NCT03180502	10 mm	CTV	ICRU50
EORTC 1635	NCT03763422 (QA guideline)	5 mm	CTV	ICRU50

Table 3
Overview of published studies in low grade glioma with pattern of failure data.

	Margin	Number of recurrences	In field	Field edge	Out of field
Pu, 1994 [38]	10–30 mm to target volume	11	100%	0%	0%
Rudoler, 1998 [39]*	20 mm to target volume	16	100%	0%	0%
van den Bent, 2005 [37]	20 mm to target volume	94	90%	5%	4%
Shaw, 2002 [32]	20 mm to target volume	65	92%	3%	5%
Kamran, 2019 [19]	7–15 mm to CTV	41	76%	12%	12%
This study	**10–15 mm to CTV**	**39**	**92%**	**0%**	**8%**

* The study population included 8 cases treated with whole brain radiotherapy.

the GTV is determined in part by the choice of neurosurgical resection, as the resection cavity will be included in addition to residual tumor volume. Larger extent resections have been shown to influence progression-free survival in some series [25,26]. The use of additional imaging modalities, such as PET, may also increase the size of the GTV [27]. Even with the use of modern imaging, the inter – observer variability in GTV delineation is known to be substantial in diffuse glioma [28]. Uncertainty in target identification is normally incorporated in the PTV margin, along with other random and systemic errors in planning and dose delivery, and as such may influence the size of the treatment field [29,30].

In interpreting pattern of failure, in-field failure occurs when insufficient dose was delivered to kill all tumor cells inside the CTV. Contrasting this, edge failure might be interpreted as a result of a geographic miss, occurring when the chosen treatment field failed to encompass the future site of relapse. In low-grade glioma it is known that dose escalation will result in equal survival at best, with a potentially negative impact on quality of life [31,32]. Since an increase in dose using current treatment fields is not opportune, and in light of the improving prognosis of IDHmG patients, it would be interesting to reduce field size while maintaining the current pattern of failure. Future approaches may include individ-

ualized treatment margins based on molecular criteria that define high – and low risk groups [33]. Additionally, incorporating a data driven approach based on recurrence probabilities [34], or an imaging-derived approach based on models of tumor spread [35] may lead to smaller fields with an identical pattern of recurrence. Such an approach would, however, require confirmation in prospective studies with long follow-up.

This study has some limitations, mostly stemming from its retrospective design. It is important to note that the observation of a lower percentage of recurrence volume covered by a retrospectively constructed 5 mm CTV margin should not be interpreted as evidence that smaller margins will lead to increased edge relapse. It can be concluded, however, that not all recurrence volumes are within 5 mm of the GTV. Since no prospective data on treatment margins below 10–15 mm exist in IDHmG, we feel GTV-CTV expansions below 10 mm are to be used cautiously.

Author contribution

JJ wrote the manuscript and conducted the statistical analysis. Volumes were delineated by AMR and JJ, and approved by MvdB. AMR, RN and MvdB supervised the project. All authors contributed to the final version of the manuscript.

An abstract of this work was presented as a poster at ASTRO 2020.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2020.11.019.

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