Radiotherapy and Oncology 156 (2021) 43–48

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

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

J.P.M. Jaspers [a,*], A. Méndez Romero [a], R. Wiggenraad [b], I. Compter [c], D.B.P. Eekers [c], R.M.D. Nout [a], M. van den Bent [d]

[a] Department of Radiotherapy, Erasmus MC Cancer Institute, Erasmus MC University Medical Center, Rotterdam; [b] Department of Radiotherapy, Haaglanden Medisch Centrum, Leidschendam; [c] Department of Radiation Oncology (MAASTRO), GROW – School for Oncology and Developmental Biology, Maastricht University Medical Centre; and [d] Department of Neuro-Oncology/Neurology, Erasmus MC Cancer Institute, Erasmus MC University Medical Center, Rotterdam, the Netherlands

ARTICLE INFO

Article history:
Received 27 July 2020
Received in revised form 26 October 2020
Accepted 16 November 2020
Available online 24 November 2020

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

* Corresponding author at: Department of Radiotherapy, Erasmus MC Cancer Institute, Erasmus MC University Medical Center, Doctor Molewaterplein 40, 3015 GD Rotterdam, the Netherlands.
E-mail address: j.jaspers@erasmusmc.nl (J.P.M. Jaspers).

https://doi.org/10.1016/j.radonc.2020.11.019
0167-8140/

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 (≤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 (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.

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%

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

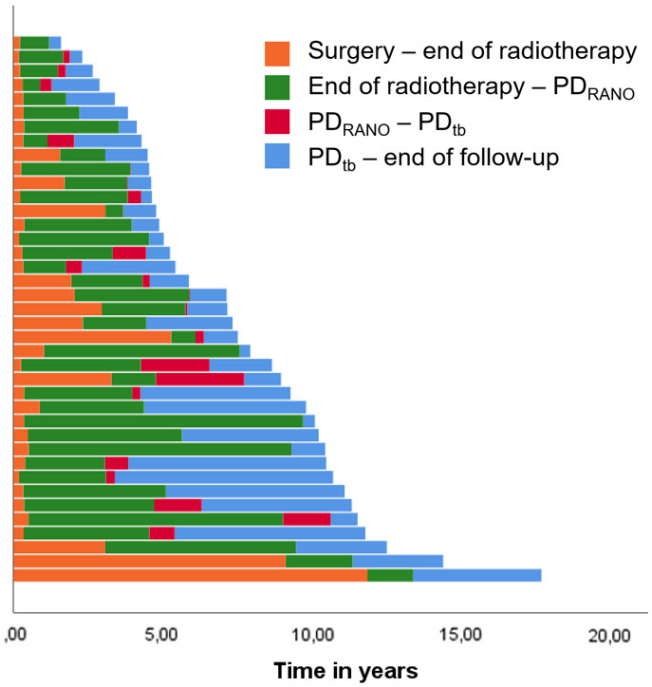

Fig. 1. Waterfall plot of time intervals for all patients from diagnosis until end of follow-up. PD_{RANO} = progressive disease as defined by the RANO criteria. PD_{tb} = progressive disease confirmed by the multidisciplinary tumor board.

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

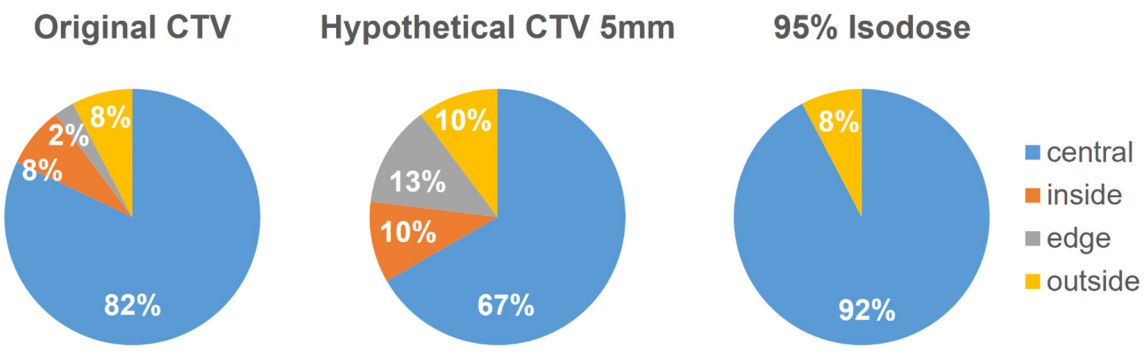

Fig. 2. Classification of recurrences based on original CTV, the hypothetical 5 mm CTV (CTV5mm), and the 95% isodose. The difference in distribution of recurrences with regards to the CTV and the CTV5mm is significant ($p = 0.005$).

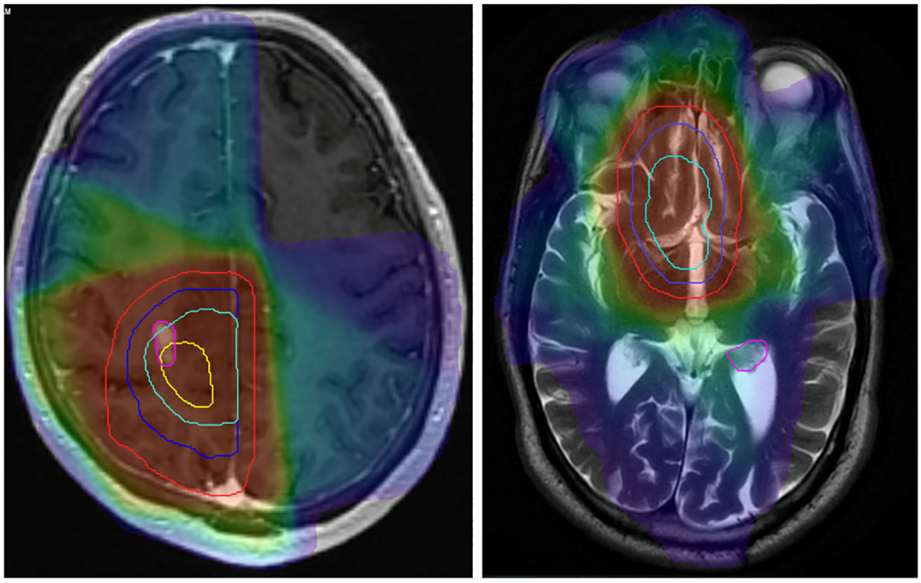

Fig. 3. Two examples of recurrences. The dose distribution and the structure set are superimposed on the MRI at the time of recurrence. The GTV is in yellow, the original CTV is dark blue, the PTV is red. The CTV5mm is in light blue. The rTV is in pink. To the left is a T1 recurrence classified as "central" 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 CT edema + 10 mm	Target volume	ICRU29
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.

References

[1] Forst DA, Nahed BV, Loeffler JS, Batchelor TT. Low-grade gliomas. Oncologist 2014;19:403–13.
[2] Eckel-Passow JE, Lachance DH, Molinaro AM, Walsh KM, Decker PA, Sicotte H, et al. Glioma groups based on 1p/19q, IDH, and TERT promoter mutations in tumors. N Engl J Med 2015;372:2499–508.
[3] Gravendeel LAM, Kouwenhoven MCM, Gevaert O, de Rooi JJ, Stubbs AP, Duijm JE, et al. Intrinsic gene expression profiles of gliomas are a better predictor of survival than histology. Cancer Res 2009;69:9065.
[4] Wesseling P, Capper DWHO. Classification of gliomas. Neuropathol Appl Neurobiol 2016;2018(44):139–50.
[5] Hartmann C, Hentschel B, Wick W, Capper D, Felsberg J, Simon M, et al. Patients with IDH1 wild type anaplastic astrocytomas exhibit worse prognosis than IDH1-mutated glioblastomas, and IDH1 mutation status accounts for the unfavorable prognostic effect of higher age: implications for classification of gliomas. Acta Neuropathol 2010;120:707–18.
[6] Tesileanu CMS, Dirven L, Wijnenga MMJ, Koekkoek JAF, Vincent AJPE, Dubbink HJ, et al. Survival of diffuse astrocytic glioma, IDH1/2 wildtype, with molecular features of glioblastoma, WHO grade IV: a confirmation of the cIMPACT-NOW criteria. Neuro-Oncol 2019;22:515–23.
[7] Buckner JC, Shaw EG, Pugh SL, Chakravarti A, Gilbert MR, Barger GR, et al. Radiation plus procarbazine, CCNU, and vincristine in low-grade glioma. N Engl J Med 2016;374:1344–55.
[8] Fisher BJ, Hu C, Macdonald DR, Lesser GJ, Coons SW, Brachman DG, et al. Phase 2 study of temozolomide-based chemoradiation therapy for high-risk low-grade gliomas: preliminary results of radiation therapy oncology group 0424. Int J Radiat Oncol Biol Phys 2015;91:497–504.
[9] Shaw EG, Wang M, Coons SW, Brachman DG, Buckner JC, Stelzer KJ, et al. Randomized trial of radiation therapy plus procarbazine, lomustine, and vincristine chemotherapy for supratentorial adult low-grade glioma: initial results of RTOG 9802. J Clin Oncol 2012;30:3065–70.
[10] Douw L, Klein M, Fagel SS, van den Heuvel J, Taphoorn MJ, Aaronson NK, et al. Cognitive and radiological effects of radiotherapy in patients with low-grade glioma: long-term follow-up. Lancet Neurol 2009;8:810–8.
[11] van den Bent MJ, Wefel JS, Schiff D, Taphoorn MJ, Jaeckle K, Junck L, et al. Response assessment in neuro-oncology (a report of the RANO group): assessment of outcome in trials of diffuse low-grade gliomas. LancetOncol 2011;12:583–93.
[12] Jaspers J, Mèndez Romero A, Hoogeman MS, van den Bent M, Wiggenraad RGJ, Taphoorn MJB, et al. Evaluation of the hippocampal normal tissue complication model in a prospective cohort of low grade glioma patients—An analysis within the EORTC 22033 clinical trial. Front Oncol 2019;9.
[13] Todd DH. Choice of Volume in the X-ray treatment of supratentorial gliomas. Br J Radiol 1963;36:645–9.
[14] Leibel SA, Sheline GE, Wara WM, Boldrey EB, Nielsen SL. The role of radiation therapy in the treatment of astrocytomas. Cancer 1975;35:1551–7.
[15] Scanlon PW, Taylor WF. Radiotherapy of Intracranial Astrocytomas: Analysis of 417 Cases Treated from 1960 through 1969. Neurosurgery 1979;5:301–8.
[16] Fazekas JT. Treatment of grades I and II brain astrocytomas. the role of radiotherapy. Int J Radiat Oncol Biol Phys 1977;2:661–6.
[17] Salazar OM, Rubin P, McDonald JV, Feldstein ML. Patterns of failure in intracranial astrocytomas after irradiation: analysis of dose and field factors. Am J Roentgenol 1976;126:279–92.
[18] Jakola AS, Bouget D, Reinertsen I, Skjulsvik AJ, Sagberg LM, Bo HK, et al. Spatial distribution of malignant transformation in patients with low-grade glioma. J Neurooncol 2020;146:373–80.
[19] Kamran SC, Dworkin M, Niemierko A, Bussiere M, Oh KS, Loeffler JS, et al. Patterns of failure among patients with low-grade glioma treated with proton radiation therapy. Pract Radiat Oncol 2019;9:e356–61.
[20] Baumert BG, Hegi ME, van den Bent MJ, von Deimling A, Gorlia T, Hoang-Xuan K, et al. Temozolomide chemotherapy versus radiotherapy in high-risk low-grade glioma (EORTC 22033–26033): a randomised, open-label, phase 3 intergroup study. LancetOncol 2016;17:1521–32.
[21] Taal W, van der Rijt CCD, Dinjens WNM, Sillevis Smitt PAE, Wertenbroek AAACM, Bromberg JEC, et al. Treatment of large low-grade oligodendroglial tumors with upfront procarbazine, lomustine, and vincristine chemotherapy with long follow-up: a retrospective cohort study with growth kinetics. J Neurooncol 2015;121:365–72.
[22] Izquierdo C, Alentorn A, Idbaih A, Simó M, Kaloshi G, Ricard D, et al. Long-term impact of temozolomide on 1p/19q-codeleted low-grade glioma growth kinetics. J Neurooncol 2018;136:533–9.
[23] de Wit MC, de Bruin HG, Eijkenboom W, Sillevis Smitt PA, van den Bent MJ. Immediate post-radiotherapy changes in malignant glioma can mimic tumor progression. Neurology 2004;63:535–7.
[24] van West SE, de Bruin HG, van de Langerijt B, Swaak-Kragten AT, van den Bent MJ, Taal W. Incidence of pseudoprogression in low-grade gliomas treated with radiotherapy. Neuro Oncol 2017;19:719–25.
[25] Wijnenga MMJ, French PJ, Dubbink HJ, Dinjens WNM, Atmodimedjo PN, Kros JM, et al. The impact of surgery in molecularly defined low-grade glioma: an integrated clinical, radiological, and molecular analysis. Neuro-Oncol 2017;20:103–12.
[26] Patel T, Bander ED, Venn RA, Powell T, Cederquist GY, Schaefer PM, et al. The role of extent of resection in IDH1 wild-type or mutant low-grade gliomas. Neurosurgery 2018;82:808–14.
[27] Albert NL, Weller M, Suchorska B, Galldiks N, Soffietti R, Kim MM, et al. Response assessment in neuro-oncology working group and European association for neuro-oncology recommendations for the clinical use of PET imaging in gliomas. Neuro-oncology 2016;18:1199–208.
[28] Abrunhosa-Branquinho AN, Bar-Deroma R, Collette S, Clementel E, Liu Y, Hurkmans CW, et al. Radiotherapy quality assurance for the RTOG 0834/EORTC 26053–22054/NCIC CTG CEC.1/CATNON intergroup trial "concurrent and adjuvant temozolomide chemotherapy in newly diagnosed non-1p/19q deleted anaplastic glioma": Individual case review analysis. Radiother Oncol 2018;127:292–8.
[29] van Herk M. Errors and margins in radiotherapy. Semin Radiat Oncol 2004;14:52–64.
[30] Prescribing, Recording, and Reporting Photon-Beam Intensity-Modulated Radiation Therapy (IMRT): Contents Journal of the International Commission on Radiation Units and Measurements. 2016;10:NP-NP.
[31] Karim AB, Maat B, Hatlevoll R, Menten J, Rutten EH, Thomas DG, et al. A randomized trial on dose-response in radiation therapy of low-grade cerebral glioma: European Organization for Research and Treatment of Cancer (EORTC) Study 22844. Int J Radiat Oncol Biol Phys 1996;36:549–56.
[32] Shaw E, Arusell R, Scheithauer B, O'Fallon J, O'Neill B, Dinapoli R, et al. Prospective randomized trial of low- versus high-dose radiation therapy in adults with supratentorial low-grade glioma: initial report of a North Central Cancer Treatment Group/Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group study. J Clin Oncol 2002;20:2267–76.
[33] Geurts M, van den Bent MJ. On high-risk, low-grade glioma: What distinguishes high from low?. Cancer 2019;125:174–6.
[34] Peeken JC, Molina-Romero M, Diehl C, Menze BH, Straube C, Meyer B, et al. Deep learning derived tumor infiltration maps for personalized target definition in Glioblastoma radiotherapy. Radiother Oncol 2019;138:166–72.
[35] Trip AK, Jensen MB, Kallehauge JF, Lukacova S. Individualizing the radiotherapy target volume for glioblastoma using DTI-MRI: a phase 0 study on coverage of recurrences. Acta Oncol 2019;58:1532–5.
[36] Purdy JA. Current ICRU definitions of volumes: limitations and future directions. Semin Radiat Oncol 2004;14:27–40.
[37] van den Bent MJ, Afra D, de Witte O, Ben Hassel M, Schraub S, Hoang-Xuan K, et al. Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomised trial. Lancet 2005;366:985–90.

[38] Pu AT, Sandler HM, Radany EH, Blaivas M, Page MA, Greenberg HS, et al. Low grade gliomas: preliminary analysis of failure patterns among patients treated using 3D conformal external beam irradiation. Int J Radiat Oncol Biol Phys 1995;31:461–6.

[39] Rudoler S, Corn BW, Werner-Wasik M, Flanders A, Preston PE, Tupchong L, et al. Patterns of tumor progression after radiotherapy for low-grade gliomas: analysis from the computed tomography/magnetic resonance imaging era. Am J Clin Oncol 1998;21:23–7.