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Review

Evidence-based recommendations on categories for extent of resection in diffuse glioma

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Abstract Surgical resection represents the standard of care in diffuse glioma, and more extensive tumour resection appears to be associated with favourable outcome. Up to now, terminology to describe extent of resection has been inconsistently applied across clinical trials which hampers comparative analysis of cohorts between different studies. Based on a comprehensive literature review, we developed evidence-based expert recommendations on categories for extent of resection. Recommendations are formulated for the categories 'biopsy', 'partial resection', 'subtotal resection', 'near total resection', 'complete resection' and 'supramaximal resection'. Definitions rest on reduction of contrast- and non–contrast-enhancing tumour in glioblastoma, and on reduction of T2/FLAIR-hyperintense tumour in gliomas WHO grade 2 or 3. Both relative reduction of tumour volume (in percentage) as a measurement of surgical efficacy and absolute residual tumour volume (in cm^3) as a measurement of remaining tumour burden are incorporated into the categories for extent of resection. Class of evidence for the proposed categories ranges from class IIB to IV. Limitations of the suggested categories are discussed. The proposed categories on extent of resection offer a framework to standardize

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nomenclature based on previous studies, and will need to be evaluated in prospective, molecularly well-defined cohorts. Our categories may eventually help as a stratification factor for future clinical trials.
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1. Introduction

Diffuse gliomas represent a heterogeneous group of primary central nervous system neoplasms. Such tumours correspond to WHO grades 2–4 (Arabic numerals as per the suggestions of the cIMPACT-NOW update 6) and differ in terms of clinical presentation, treatment and outcome depending on the isocitrate dehydrogenase (IDH) mutation status [1,2]. Recent studies have provided robust evidence that extent of tumour resection respectively postsurgical tumour volumes are associated with further progression and overall survival in diffuse gliomas [3–8]. Quantifying extent of resection is therefore of particular interest in gliomas of WHO grades 2–4. Although IDH-mutant gliomas WHO grade 2 or 3 exhibit a rather prolonged natural history compared with WHO grade 4 glioblastomas, the vast majority of these tumours is life-limiting given that recurrence and progression inevitably occur [9]. However, there is no clear definition of biopsy, partial resection, subtotal resection, near total resection, gross total resection and supramaximal resection with respect to removed or residual tumour volume. Comparative studies between several institutions are therefore limited [10]. Thus, the analysis of the role of surgery across various molecular subgroups of diffuse gliomas is hampered. Given that upcoming classifications rest their definitions on molecular markers rather than on histology alone, the role of surgery will need to be re-assessed in newly defined tumour entities [1,11]. Particularly for investigational purposes, nomenclature for surgical approaches in glioma surgery must therefore be standardized.

Prior studies have frequently defined categories for extent of resection as relative reduction of the preoperative tumour volume in percentage. Although less mature, however, more recent studies claimed that the absolute residual tumour volume might be more relevant than the proportion of removed tumour in terms of prognosis [3,12]. In the present article, we recommend various evidence-based categories for extent of resection in supratentorial diffuse glioma based on recent literature. We aimed to incorporate both removed tumour proportion as well as residual tumour volume into our definitions. Extent of resection in glioblastoma will be discussed separately from resection in gliomas WHO grade 2 or 3, and highest class of evidence is provided [13].

2. Search strategy and selection criteria

A multidisciplinary panel of experts who serve in guideline committees of major neuro-oncological societies from Asia, Europe and North America was formed. References were identified through a search of PubMed using various combinations of the search terms “glioblastoma”, “astrocytoma”, “oligodendroglioma”, “glioma”, “diffuse”, “anaplastic”, “WHO grade II”, “WHO grade III”, “imaging”, “contrast”, “non-contrast”, “resection”, “surgery”, “complete”, “extent”, “volume”, “threshold”, “IDH”, “MGMT”, “survival” and “outcome” from 1990 until August, 2020. Google scholar, authors’ own files, and references from relevant articles were also searched. Only studies published in English language journals were considered. The first and senior author screened for relevance, removed duplicates and circulated information extracted from a preliminary reference list between all authors. The final reference list was then selected by all authors on the basis of originality and relevance to the topics covered in this article. Based on the selected literature, a qualitative synthesis of the literature and recommendations on categories for extent of resection in diffuse glioma were formulated by all authors. Consensus was achieved through repeated circulation of manuscript drafts.

3. Imaging requirements

The intraoperative estimation of the operating neurosurgeon on resection has been shown to be rather inaccurate in both glioblastoma and gliomas WHO grade 2 or 3 [14–16]. Most studies have therefore quantified the extent of resection using postoperative magnetic resonance imaging (MRI) as suggested by the RANO criteria [17]. MRI should be obtained within 48 h after surgery (at latest within 72 h) to reduce the risk of mistakenly considering unspecific contrast enhancement as residual tumour [17]. This is of particular importance in glioblastoma which characteristically shows contrast enhancement. Volumetric image analysis using 3-dimensional measurements should be applied to accurately quantify entire tumour volumes [17]. Although modern imaging segmentation tools enable clinicians to independently quantify tumour volumes with moderate effort and also on retrospective data sets [18], a centralized imaging review using the same image

segmentation method is recommended for multicenter studies to allow standardized comparative analysis between different institutions.

4. Extent of resection in glioblastoma

Glioblastoma is the most common malignant primary brain tumour [19]. Microsurgical tumour resection followed by concomitant radiochemotherapy and maintenance chemotherapy represents the standard of care in such tumours [20].

4.1. Supramaximal resection beyond enhancing tumour borders in glioblastoma

Recent studies have introduced the concept of 'supramaximal resection' including not only the resection of enhancing but also non-enhancing glioblastoma tissue [21–24], especially because comparison of different MRI- and PET-based imaging techniques revealed significant glioblastoma tumour volumes beyond contrast enhancement [25–28]. Analysing data from 876 glioblastoma patients who underwent complete resection of contrast enhancing tumour, Li *et al.* showed that an additional survival benefit was found when ≥53% of the surrounding non-enhancing T2/FLAIR-hyperintense abnormality was resected [29]. In addition, a similar study by Pessina *et al.* suggested that ≥45% of T2/FLAIR-hyperintense abnormality needed to be removed to achieve prognostic relevance [30]. Although prior studies have reported a significant survival advantage for resection beyond contrast enhancement among glioblastoma with IDH mutations [31], more recent studies reported similar effects in additional subsets of IDH wild-type glioma patients [3,32]. Of note, other studies may suggest that higher or lower extents of non-contrast enhancing tissue are needed to achieve prognostic relevance [3,32]. Molinaro *et al.* also reported on absolute tumour volumes and determined that a subset of younger patients with ≤5.4 cm^3 residual non-enhancing, T2/FLAIR-hyperintense tumour had improved outcome when compared with >5.4 cm^3 residual non-enhancing tumour [3]. By contrast, Incekara *et al.* explicitly failed to establish such a connection between residual non-enhancing tumour volume and outcome when considering a more broadly defined IDH wild-type cohort [32]. Collectively, glioblastoma patients in which the complete enhancing and additionally a large proportion of the non-enhancing tumour is removed may benefit in regard of outcome [33]. On a cautionary note, data on definitive cutoff values for the volume of tumour tissue which needs to be removed to convey a prognostic benefit are scarce. Further studies in prospective cohorts are warranted, and such studies must include measures of quality of survival by capturing neurological function and patient-reported outcomes, not only mere survival measured in days or weeks. For now, we propose to denote all approaches with resection beyond contrast enhancing tumour borders into the surrounding non-enhancing T2/FLAIR-hyperintense abnormality as 'supramaximal resection beyond enhancing tumour borders'. Whereas potential cutoffs can only be based on class IV evidence, highest level of evidence that supramaximal resection beyond enhancing tumour borders might be beneficial in terms of survival comes from a prospective cohort reported by Eyüpoglu *et al.* [23] providing class III evidence.

4.2. Complete resection of contrast enhancing tumour in glioblastoma

Gross total resection has historically been defined as complete tumour mass removal. A deeper understanding of the tumour biology and the invasive nature of glioblastoma has shown that such a complete removal is not feasible [7], however, the semantic concept of gross total resection has persisted. Cutoff points for reduction of enhancement in the definition of gross total resection ranged from 90% [30,34], 96% [35], 97% [36], to most frequently 100% (Table 1) [29,31,37–39]. The number of patients in which a high reduction of enhancement was achieved varies substantially across different studies, which might be in part explained by distinct patient cohorts which were analysed. Of note, even small differences in extent of resection within the range of 90–100% may translate into clinical differences [40]. Marko *et al.* [41] and Molinaro *et al.* [3] reported that larger extent of resection particularly within the range of 90–100% were associated with improved outcome in a continuous fashion. Accordingly, Sanai *et al.* reported that glioblastoma patients in which the complete contrast enhancing tumour was removed showed favourable outcome when compared to patients in which only 98% reduction in enhancement was achieved [42]. Similar findings were made in a multicentric study by Müller *et al.* [43] This assumption is also supported by Stummer *et al.* who provided so far the only class IIB evidence, albeit from the pre-temozolomide era and not controlled for MGMT or IDH status, that complete resection of contrast enhancing glioblastoma tissue is associated with improved survival [7]. Based on a large retrospective patient cohort, however, Molinaro *et al.* [3] reported that the association of complete resection of contrast enhancing tumour and favourable outcome is present in patients with and without IDH mutation; and also when IDH-wildtype glioblastoma patients were stratified according to MGMT status.

Data in regard of residual glioblastoma volume and outcome are less mature, but selected studies found that even postoperative contrast enhancement of little more than 1 cm^3 may be associated with inferior outcome [32]. Based on these findings, we assume that outcome between glioblastoma patients may only be rather homogenous and comparable when definition of gross total resection is narrow. We also argue that the term

Table 1
Previous definitions of 'gross total resection' in supratentorial glioblastoma.

Definition: reduction of contrast enhancing tumour (%)	Patients with 'gross total resection'	Cohort and patient inclusion criteria	Reference
≥90–100%	86/832 (10.3%) after new diagnosis	Prospective cohort; newly diagnosed GBM patients	Lamborn *et al.*, 2004 [34]
≥90–100%	60/282 (21.3%) after new diagnosis	Retrospective cohort; newly diagnosed GBM patients which underwent surgery followed by TMZ/RT→TMZ	Pessina *et al.*, 2017 [30]
≥96–100%	52/107 (48.6%) after new diagnosis	Retrospective cohort; GBM patients who underwent surgery after new diagnosis and later re-resection for recurrence	Bloch *et al.*, 2012 [35]
≥97–100%	30/170 (17.7%) at recurrence	Retrospective cohort; GBM patients with tumour re-resection for recurrence	Oppenlander *et al.*, 2014 [36]
100%	125/345 (36.2%) after new diagnosis	Prospective cohort; newly diagnosed GBM patients	Kreth *et al.*, 2013 [37]
100%	268/335 (80.0%) after new diagnosis; including also glioma WHO grade 3	Prospective cohort; newly diagnosed patients with astrocytic tumours WHO grade 3/4 and KPS ≥50 who had open surgery	Beiko *et al.*, 2014 [31]
100%	876/1229 (71.3%) after new diagnosis or at recurrence	Retrospective cohort; GBM patients <80 years who had ≥78% contrast enhancing tumour resection at first diagnosis or recurrence	Li *et al.*, 2016 [29]
100%	40/59 (67.8%) at recurrence	Prospective cohort; GBM patients with recurrence after surgery followed by TMZ/RT→TMZ	Suchorska *et al.*, 2016 [38]
100%	754/1095 (68.9%) after new diagnosis	Retrospective cohort; newly diagnosed GBM patients without deep-seated tumour localization	Al-Holou *et al.*, 2020 [39]

Definitions of 'gross total resection', numbers of patients in which 'gross total resection' was achieved, and patient inclusion criteria are given.
Abbreviations: *KPS*, Karnofsky performance score; *WHO*, World Health Organization.

'gross total resection' in glioblastoma should be replaced by the more precise term 'complete resection of enhancing tumour' (or redefined as such) (Table 2) [17]. Highest class of evidence to support this statement is the class IIB study by Stummer *et al.* [7].

4.3. Near total resection of enhancing tumour in glioblastoma

The concept of 'near total resection' may include patients in which relevantly more than 80% resection (with not more than 5 cm^3 residual tumour volume; the proposed thresholds for subtotal resection, see the next paragraph) but not 100% resection has been achieved. When evaluating the postoperative results in 721 glioblastoma patients, Marko *et al.* found that more than ten percent of their cohort had extent of resection ranging between 95 and 99% [41]. Given that larger extent of resection particularly within the range of 80–100% has been claimed to translate into improved outcome [3], patients who underwent a greater than 95% resection may perform better than patients who only had a less than 95% resection [35,40,42]. On a cautionary note, there are in turn no robust data on whether patients who underwent 95–99% resection also exhibit less favourable outcome when compared to patients with 100% resection. However, the data from Marko *et al.* and Molinaro *et al.* may be interpreted to be in support of such a hypothesis [3,41]. Based on the current data, we therefore assume that a significant proportion of patients match into a category of 95–99% extent of resection. These patients may have a distinct survival curve when compared to patients with 80–94% resection but also to patients with 100% resection. Similar findings were also made when focussing on residual tumour volume, as a rather linear relationship between residual contrast enhancing tumour and outcome has been reported [12,40]. Accordingly, Incekara *et al.* found that glioblastoma patients with 0–1 cm^3 residual contrast enhancing tumour had more

Table 2
Categories for extent of resection in supratentorial glioblastoma.

Category	Extent of resection (glioblastoma)	Class of evidence [13]	Key references (glioblastoma)
Supramaximal resection beyond enhancing tumour borders	Beyond contrast-enhancing tumour borders	III	Li *et al.*, 2016 [29] Eyüpoglu *et al.*, 2016 [23] Pessina *et al.*, 2017 [30] Molinaro *et al.*, 2020 [3]
Complete resection of enhancing tumour	100% contrast-enhancing tumour	IIB	Stummer *et al.*, 2008 [7] Sanai *et al.*, 2011 [42] Marko *et al.*, 2014 [41] Molarino *et al.*, 2020 [3]
Near total resection of enhancing tumour	≥95% contrast-enhancing tumour + ≤1 cm^3 residual contrast-enhancing tumour	IV	Chaichana *et al.*, 2014 [40] Marko *et al.*, 2014 [41] Molarino *et al.*, 2020 [3] Incekara *et al.*, 2020 [32]
Subtotal resection of enhancing tumour	≥80% contrast-enhancing tumour + ≤5 cm^3 residual contrast-enhancing tumour	IV	Sanai *et al.*, 2011 [42] Orringer *et al.*, 2012 [44] Oppenlander *et al.*, 2014 [36] Chaichana *et al.*, 2014 [40] Sales *et al.*, 2019 [46]
Partial resection of enhancing tumour	1–79% contrast-enhancing tumour +/– >5 cm^3 residual contrast-enhancing tumour (for mass effect-related symptoms)	IV (expert opinion)	in analogy to other tumours [48]
Biopsy of enhancing tumour	No reduction of tumour volume and administered for tissue-based diagnosis	IV (expert opinion)	in analogy to other tumours [48]

favourable outcome than patients with 1–5 cm^3 or >5 cm^3 residual tumour [32]. Of note, this finding held true for patients with and without MGMT promotor methylation. We therefore propose that patients with 95–99% extent of resection and ≤1 cm^3 residual contrast-enhancing tumour may be denoted by the term 'near total resection of enhancing tumour'. Highest level of evidence to support these thresholds comes from comes from the the above summarized retrospective studies, all of them representing class IV evidence.

4.4. Subtotal resection of enhancing tumour in glioblastoma

Subtotal resection describes situations in which a significant proportion of the tumour was not removed. Numerous studies have aimed to determine what proportion of contrast enhancing tumour needs to be resected to confer a survival advantage. Sanai *et al.* retrospectively analysed a large cohort of 500 glioblastoma patients and calculated that a minimum of 78% resection needs to be achieved to correspond to a survival benefit [42]. Oppenlander *et al.* [36] also found a threshold of 80% by analysing 170 patients with recurrent glioblastoma. In a study of Orringer *et al.* [44] on newly diagnosed glioblastoma, 80% also seemed to represent a prognostic threshold; however, no definitive statistical analysis was provided. These findings may therefore be consistent with the data from Sanai *et al.* On a cautionary note, some studies have postulated relevantly higher thresholds of 89% [45] or even 98% [12], or relevantly lower thresholds of 70% [40] or even only 40% [3]. However, most recent studies assume that the minimum extent of resection which needs to be achieved for prognostic relevance is 80%, and have provided further evidence to support such a hypothesis [3,4,29]. Prior studies have also aimed to determine maximal residual tumour volumes which still translate into favourable outcome. Chaichana *et al.* [40] and Sales *et al.* [46] reported on a maximal volume of 5 cm^3 residual contrast enhancing tumour among a cohort of 259 and 113 patients who underwent surgical resection for newly diagnosed glioblastoma, respectively. Although some studies may have found somewhat lower thresholds of 2–5 cm^3 residual contrast enhancing tumour [12,47], the threshold of 5 cm^3 was recently confirmed among a large cohort of IDH-wildtype glioblastoma patients with MGMT promotor methylation [32]. Based on these findings, we argue that the term 'subtotal resection of enhancing tumour' should be used in patients in which at least 80% resection of contrast enhancing tumour was achieved and not more than 5 cm^3 residual contrast enhancing tumour is seen. Highest level of evidence to support these thresholds comes from the above summarized studies which all represent class IV evidence.

In our opinion (class IV evidence), patients in which less extent of resection is achieved might be more accurately summarized under the terms 'partial resection of enhancing tumour' (when surgery is administered to improve symptoms attributed to tumour mass effect) or 'biopsy of enhancing tumour' (when surgery is administered for tissue-based diagnosis and no reduction of tumour volume was provided) as it has been proposed for other tumours such as meningioma [48].

5. Extent of resection in gliomas WHO grade 2 or 3

In glioblastoma, the proposed categories for extent of resection are based on removed enhancing and non-enhancing tumour tissue on postoperative MRI. Gliomas WHO grade 2 or 3 often display little or no contrast enhancement [49]. Moreover, the relevance of contrast enhancement might vary across different molecular entities [50]. Cutoff points and definitions of categories for extent of resection may therefore profoundly differ from what has been discussed in glioblastoma [17].

5.1. Supramaximal resection beyond T2/FLAIR-hyperintense tumour in gliomas WHO grade 2 or 3

Selected evidence class IV studies have advocated for a 'supramaximal resection' approach also in glioma WHO grade 2 [51–53]. Such studies were rather vague in defining 'supramaximal resection', but mostly relied their definition on resection beyond FLAIR-hyperintense tumour borders on preoperative MRI [54–56]. The exact volume of non-FLAIR hyperintense tissue which needs to be removed to achieve prognostic relevance as well as a compelling beneficial effect on outcome remains to be elucidated. In addition, only few data for glioma WHO grade 3 are available [56]. Based on class IV evidence, we propose to denote approaches in which resection above FLAIR-hyperintense tumour borders has been provided under the term 'supramaximal resection beyond T2/FLAIR-hyperintense tumour borders'. However, we also conclude that the current literature is too premature to define which amount of tissue bordering to the visible tumour needs to be removed and whether such approaches translate into outcome differences in gliomas WHO grade 2 and 3 [54].

5.2. Complete resection of T2/FLAIR-hyperintense tumour in gliomas WHO grade 2 or 3

Gliomas WHO grade 2 or 3 characteristically present as hyperintense lesions on T2/FLAIR-weighted MRI sequences with or without contrast enhancement. The vast majority of studies has therefore rested their definition of gross total resection on the complete reduction of T2/FLAIR hyperintensity on postoperative MRI [5,57–59]. Also in gliomas WHO grade 2 or 3, even small amounts of residual tumour tissue as displayed by MRI may translate into differences in outcome. Wijnenga *et al.*

Table 3
Categories for extent of resection in supratentorial gliomas WHO grade 2 or 3.

Category	Extent of resection (gliomas WHO grade 2/3)	Class of evidence [[13]]	Key references (gliomas WHO 2/3)
Supramaximal resection beyond T2/FLAIR-hyperintense tumour borders	Beyond T2/FLAIR-hyperintense tumour borders	IV	Duffau *et al.*, 2016 [[53]] Duffau *et al.*, 2019 [[55]] de Leeuw *et al.*, 2019 [[54]]
Complete resection of T2/FLAIR-hyperintense tumour	100% T2/FLAIR-hyperintense tumour	IV	Smith *et al.*, 2008 [[58]] Nuno *et al.*, 2013 [[62]] Wijnenga *et al.*, 2018 [5]
Near total resection of T2/FLAIR-hyperintense tumour	≥90% T2/FLAIR-hyperintense tumour + ≤5 cm^3 residual T2/FLAIR-hyperintense tumour	IV	Keles *et al.*, 2006 [[66]] Smith *et al.*, 2008 [[58]] Wijnenga *et al.*, 2018 [5] Fuji *et al.*, 2018 [6]
Subtotal resection of T2/FLAIR-hyperintense tumour	≥40% T2/FLAIR-hyperintense tumour + ≤25 cm^3 residual T2/FLAIR-hyperintense tumour	IV	Smith *et al.*, 2008 [[58]] Wijnenga *et al.*, 2018 [5] Fuji *et al.*, 2018 [6]
Partial resection of T2/FLAIR-hyperintense tumour	1–39% T2/FLAIR-hyperintense tumour +/– >25 cm^3 residual T2/FLAIR-hyperintense tumour (for mass effect-related symptoms)	IV (expert opinion)	in analogy to other tumours [[48]]
Biopsy of T2/FLAIR-hyperintense tumour	No reduction of tumour volume and administered for tissue-based diagnosis	IV (expert opinion)	in analogy to other tumours [[48]]

analysed 228 patients with glioma WHO grade 2 patients, and showed that residual tumour volume negatively correlated with overall survival in a continuous fashion [5]. Of note, this finding held true among patients with and without IDH mutation. A particular strong favourable effect was seen in patients with no detectable tumour after resection. Similar findings haven been made by other groups [60], and also in glioma WHO grade 3 with and without IDH mutations [31,61–63]. We therefore propose that exclusively gliomas WHO grade 2 and 3 patients in which complete resection of T2/FLAIR-hyperintense tumour was achieved are denoted by the term 'complete resection of T2/FLAIR-hyperintense tumour' (Table 3). Although there might be class II evidence that surgical resection in general is associated with improved survival in gliomas WHO grade 2 and 3 [64,65], the above summarized retrospective studies suggesting distinct outcome after complete resection of T2/FLAIR-hyperintense tumours represent class IV evidence.

5.3. Near total resection of T2/FLAIR-hyperintense tumour in gliomas WHO grade 2 or 3

Not only in glioblastoma but also in gliomas WHO grade 2 and 3, the concept of 'near total resection' has been introduced. This category may include patients in which significantly more than 40% resection (with no more than 25 cm^3 residual tumour volume; the proposed thresholds for subtotal resection, see next paragraph) but less than 100% resection was administered. Given that the 40% cutoff for prognostic relevant subtotal resections is considerably lower than the 80% cutoff which has been postulated in glioblastoma, most studies have also spanned their definition of near total resection broader than it has been proposed in glioblastoma. When evaluating gliomas WHO grade 2 or 3 patients in which a 90–99% reduction of preoperative T2/FLAIR hyperintensity was performed, it has been shown that such patients have a distinct survival curve when compared to patients with <90% resection and also 100% resection [6,58,61]. When focussing on absolute residual tumour, it has been shown that a linear relationship between residual tumour volume and outcome may exist [5,64]. A postoperative volume of ≤5 cm^3 has been used in analogy to near total resection by Smith *et al.* in glioma WHO grade 2 [58], although it has been noted that the prognostic role of residual tumour volumes may depend on molecular markers such as IDH [5]. The study from Keles *et al.* [66] and Fuji *et al.* [6] might be interpreted to support a similar linear relationship between residual tumour and outcome in glioma WHO grade 3. We therefore argue to summarize patients with gliomas WHO grade 2 and 3 in which 90–99% resection and ≤5 cm^3 residual T2/FLAIR-hyperintense tumour is seen under the term 'near total resection of T2/FLAIR-hyperintense tumour'. Highest level of evidence to support these thresholds comes from the above summarized retrospective class IV studies.

5.4. Subtotal resection of T2/FLAIR-hyperintense tumour in gliomas WHO grade 2 or 3

Various studies have aimed to determine what minimal tumour proportion needs to be removed to achieve prognostic relevance in gliomas WHO grade 2 or 3, therefore distinguishing subtotal resection from partial resection. Smith *et al.* performed a volumetric study on 216 patients with glioma WHO grade 2, and patients with ≥41% reduction of preoperative T2/FLAIR hyperintensity were found to live longer [58]. Although no clear rational was provided for the selection of this cutoff, subsequent studies on glioma WHO grade 2 have interpreted the data from Smith *et al.* as cutoff value for minimum extent of resection resulting in prognostic relevance, and have provided further evidence for a threshold of 40% [67,68]. Of note, higher values of 53%–76% have been postulated in glioma WHO grade 3 [6,69]. The discrepancies in thresholds may reflect differences in preoperative tumour volume between glioma WHO grade 2 and 3 [5,6]. Absolute residual tumour volume rather than relative resected tumour proportion might be more relevant in terms of prognosis. Wijnenga *et al.* showed in glioma WHO grade 2 that a postoperative tumour volume of ≤25 cm^3 was the maximal postoperative volume at which resection appeared to be associated with better outcome [5]. Of interest, a residual tumour volume of ≤25 cm^3 as measured on T2/FLAIR-weighted MRI imaging was also the cutoff volume which was found in glioma WHO grade 3 [6]. We acknowledge that some studies have reported on lower thresholds tumour volumes, however, discrepancies may have been caused by different methods for calculating tumour volumes [69]. Based on these retrospective class IV studies, we propose to denote patients with gliomas WHO grade 2 and 3 in which at least 40% resection was achieved and not more than 25 cm^3 residual T2/FLAIR-hyperintense tumour is seen by the term 'subtotal resection of T2/FLAIR-hyperintense tumour'. In our opinion (class IV evidence), patients in which less extent of resection is provided may be summarized under the terms 'partial resection of T2/FLAIR-hyperintense tumour' or 'biopsy of T2/FLAIR-hyperintense tumour'.

6. Discussion

Two different aspects of tumour resection have to be considered in concepts for extent of resection. First, the surgical reduction of tumour burden may be represented through the proportion of tumour removed in relation to the original mass (resected tumour proportion in percentage). A second aspect may acknowledge the absolute postoperative tumour volume which can

eventually be targeted by further therapy beyond surgery (residual volume in cm^3). Although the latter may more accurately depict the biological tumour burden [12], definitions on extent of resection should include both aspects: reduction of tumour volume as a measurement of surgical efficacy, and residual tumour volume as a measurement of remaining tumour burden. Thus, we have incorporated both points into our categories for extent of resection. However, residual tumour volume may turn out more important in future studies from an oncological standpoint. Future prospective studies on diffuse gliomas grade 2–4 should therefore precisely report on the preoperative and postoperative absolute tumour volumes, and such cohorts may deliver further evidence on abandoning the analysis of the proportional tumour removal in favour of measuring residual tumour volumes. This might also contribute to more compelling definitions of the term 'supramaximal resection' in both glioblastoma and gliomas WHO grade 2 and 3.

7. Future perspectives

Molecular markers are increasingly incorporated into the WHO classification, and tumours previously characterized as grade 2 or 3 based on histology may resolve into other entities reclassified as grade 4 tumours due to their poor outcome [70]. IDH wild-type astrocytoma, such a provisional entity likely to resolve partly into grade 4 "glioblastoma", may present with little-to-no contrast enhancement on initial imaging, but nevertheless harbour clinical and molecular features of glioblastoma, and manifest identical outcomes [50,71,72]. It remains to be seen whether our proposed categories and cutoffs may also hold true for glioblastomas being defined by the combination of an IDH wild-type with qualifying molecular features (including TERT promoter mutation, +7/-10 genotype, or EGFR amplification) and gliomas WHO grade 2–4 being defined by the presence of an IDH mutation rather than histology [1]. Our categories for extent of resection need therefore to be prospectively evaluated in molecularly well-defined cohorts and potentially adjusted. We acknowledge that the current level of evidence is overall low. Whereas randomized trials on extent of resection above tumour borders can be pursued in most solid tumours such as breast cancer [73], such studies are hard to design and to ethically justify in neuro-oncological patients (particularly when it comes to leave surgically targetable tumour tissue in situ). The resulting lack of data is accompanied by some degree of uncertainty regarding cutoff values. In addition, some authors have used extent of resection as a categorical rather than a continuous variable to determine prognostic cutoff values. Inherent differences between the two statistical methods need to be considered when interpreting results from such studies.

Importantly, whether it is solely the resection itself that is driving favourable survival or whether less-aggressive gliomas might be more likely to be resected or more responsive to subsequent therapies also remains to be shown [31]. All data favouring higher extent of resection can also be explained by the assumption that non-resectable gliomaglioma has an inherently worse prognosis because of its biology, notably infiltrative growth in critical brain regions. The proof that extent of resection biologically matters still awaits to be delivered. Despite the fact that most malignant gliomas are not suitable to be biologically completely resected, defining extent of resection will help as a stratification factor for clinical trials. Of note, the benefits of surgical resection also include acquisition and analysis of tumour tissue to guide therapy based on molecular markers [74]. Our proposed evidence-based recommendations may offer a framework to standardize nomenclature used in surgery of diffuse glioma, thus improving comparison of outcome data across different institutions or molecular glioma subgroups.

Conflict of interest statement

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References

[1] Louis DN, Wesseling P, Aldape K, et al. cIMPACT-NOW update 6: new entity and diagnostic principle recommendations of the cIMPACT-Utrecht meeting on future CNS tumor classification and grading. Brain Pathol 2020;30(4):844–56.
[2] Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health organization classification of tumors of the central nervous system: a summary. Acta Neuropathol 2016;131(6):803–20.
[3] Molinaro AM, Hervey-Jumper S, Morshed RA, et al. Association of maximal extent of resection of contrast-enhanced and non-contrast-enhanced tumor with survival within molecular subgroups of patients with newly diagnosed glioblastoma. JAMA Oncol 2020;6(4):495–503.
[4] Brown TJ, Brennan MC, Li M, et al. Association of the extent of resection with survival in glioblastoma: a systematic review and meta-analysis. JAMA Oncol 2016;2(11):1460–9.
[5] Wijnenga MMJ, French PJ, Dubbink HJ, et al. The impact of surgery in molecularly defined low-grade glioma: an integrated clinical, radiological, and molecular analysis. Neuro Oncol 2018; 20(1):103–12.
[6] Fujii Y, Muragaki Y, Maruyama T, et al. Threshold of the extent of resection for WHO Grade III gliomas: retrospective volumetric analysis of 122 cases using intraoperative MRI. J Neurosurg 2018; 129(1):1–9.
[7] Stummer W, Reulen HJ, Meinel T, et al. Extent of resection and survival in glioblastoma multiforme: identification of and adjustment for bias. Neurosurgery 2008;62(3):564–76. discussion 564-576.
[8] Vuorinen V, Hinkka S, Farkkila M, Jaaskelainen J. Debulking or biopsy of malignant glioma in elderly people - a randomised study. Acta Neurochir (Wien) 2003;145(1):5–10.
[9] Ostrom QT, Truitt G, Gittleman H, et al. Relative survival after diagnosis with a primary brain or other central nervous system tumor in the National Program of Cancer Registries, 2004 to 2014. Neurooncol Pract 2020;7(3):306–12.
[10] Grasso G. Extent of resection and survival in glioblastoma multiforme. JAMA Oncol 2016;2(11):1508–9.
[11] Weller M, van den Bent M, Preusser M, et al. EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood. Nat Rev Clin Oncol 2021;18(3):170–86.
[12] Grabowski MM, Recinos PF, Nowacki AS, et al. Residual tumor volume versus extent of resection: predictors of survival after surgery for glioblastoma. J Neurosurg 2014;121(5):1115–23.
[13] Brainin M, Barnes M, Baron JC, et al. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces–revised recommendations 2004. Eur J Neurol 2004; 11(9):577–81.
[14] Sezer S, van Amerongen MJ, Delye HHK, Ter Laan M. Accuracy of the neurosurgeons estimation of extent of resection in glioblastoma. Acta Neurochir 2020;162(2):373–8 (Wien).
[15] Buckner JC, Shaw EG, Pugh SL, et al. Radiation plus procarbazine, CCNU, and vincristine in low-grade glioma. N Engl J Med 2016;374(14):1344–55.
[16] Shaw EG, Berkey B, Coons SW, et al. Recurrence following neurosurgeon-determined gross-total resection of adult supratentorial low-grade glioma: results of a prospective clinical trial. J Neurosurg 2008;109(5):835–41.
[17] Vogelbaum MA, Jost S, Aghi MK, et al. Application of novel response/progression measures for surgically delivered therapies for gliomas: response Assessment in Neuro-Oncology (RANO) Working Group. Neurosurgery 2012;70(1):234–43. discussion 243-234.
[18] Chang K, Beers AL, Bai HX, et al. Automatic assessment of glioma burden: a deep learning algorithm for fully automated volumetric and bidimensional measurement. Neuro Oncol 2019; 21(11):1412–22.
[19] Ostrom QT, Cioffi G, Gittleman H, et al. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2012-2016. Neuro Oncol 2019; 21(Suppl 5):v1–100.
[20] Wen PY, Weller M, Lee EQ, et al. Glioblastoma in adults: a society for neuro-oncology (SNO) and European society of neuro-oncology (EANO) consensus review on current management and future directions. Neuro Oncol 2020;22(8):1073–113.
[21] Lasocki A, Gaillard F. Non-contrast-enhancing tumor: a new frontier in glioblastoma research. AJNR Am J Neuroradiol 2019; 40(5):758–65.
[22] Jain R, Poisson LM, Gutman D, et al. Outcome prediction in patients with glioblastoma by using imaging, clinical, and genomic biomarkers: focus on the nonenhancing component of the tumor. Radiology 2014;272(2):484–93.
[23] Eyupoglu IY, Hore N, Merkel A, Buslei R, Buchfelder M, Savaskan N. Supra-complete surgery via dual intraoperative visualization approach (DiVA) prolongs patient survival in glioblastoma. Oncotarget 2016;7(18):25755–68.
[24] Zigiotto L, Annicchiarico L, Corsini F, et al. Effects of supratotal resection in neurocognitive and oncological outcome of high-grade gliomas comparing asleep and awake surgery. J Neuro Oncol 2020;148(1):97–108.
[25] Kickingereder P, Isensee F, Tursunova I, et al. Automated quantitative tumour response assessment of MRI in neuro-oncology with artificial neural networks: a multicentre, retrospective study. Lancet Oncol 2019;20(5):728–40.
[26] Suchorska B, Jansen NL, Linn J, et al. Biological tumor volume in 18FET-PET before radiochemotherapy correlates with survival in GBM. Neurology 2015;84(7):710–9.
[27] Albert NL, Weller M, Suchorska B, 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 Oncol 2016;18(9):1199–208.
[28] Nowosielski M, DiFranco MD, Putzer D, et al. An intra-individual comparison of MRI, [18F]-FET and [18F]-FLT PET in patients with high-grade gliomas. PloS One 2014;9(4):e95830.
[29] Li YM, Suki D, Hess K, Sawaya R. The influence of maximum safe resection of glioblastoma on survival in 1229 patients: can we do better than gross-total resection? J Neurosurg 2016;124(4): 977–88.
[30] Pessina F, Navarria P, Cozzi L, et al. Maximize surgical resection beyond contrast-enhancing boundaries in newly diagnosed glioblastoma multiforme: is it useful and safe? A single institution retrospective experience. J Neuro Oncol 2017;135(1):129–39.
[31] Beiko J, Suki D, Hess KR, et al. IDH1 mutant malignant astrocytomas are more amenable to surgical resection and have a survival benefit associated with maximal surgical resection. Neuro Oncol 2014;16(1):81–91.

[32] Incekara F, Smits M, van der Voort SR, et al. The association between the extent of glioblastoma resection and survival in light of MGMT promoter methylation in 326 patients with newly diagnosed IDH-wildtype glioblastoma. Front Oncol 2020; 10(1087).
[33] Kotrotsou A, Elakkad A, Sun J, et al. Multi-center study finds postoperative residual non-enhancing component of glioblastoma as a new determinant of patient outcome. J Neuro Oncol 2018; 139(1):125–33.
[34] Lamborn KR, Chang SM, Prados MD. Prognostic factors for survival of patients with glioblastoma: recursive partitioning analysis. Neuro Oncol 2004;6(3):227–35.
[35] Bloch O, Han SJ, Cha S, et al. Impact of extent of resection for recurrent glioblastoma on overall survival: clinical article. J Neurosurg 2012;117(6):1032–8.
[36] Oppenlander ME, Wolf AB, Snyder LA, et al. An extent of resection threshold for recurrent glioblastoma and its risk for neurological morbidity. J Neurosurg 2014;120(4):846–53.
[37] Kreth FW, Thon N, Simon M, et al. Gross total but not incomplete resection of glioblastoma prolongs survival in the era of radiochemotherapy. Ann Oncol 2013;24(12):3117–23.
[38] Suchorska B, Weller M, Tabatabai G, et al. Complete resection of contrast-enhancing tumor volume is associated with improved survival in recurrent glioblastoma-results from the DIRECTOR trial. Neuro Oncol 2016;18(4):549–56.
[39] Al-Holou WN, Hodges TR, Everson RG, et al. Perilesional resection of glioblastoma is independently associated with improved outcomes. Neurosurgery 2020;86(1):112–21.
[40] Chaichana KL, Jusue-Torres I, Navarro-Ramirez R, et al. Establishing percent resection and residual volume thresholds affecting survival and recurrence for patients with newly diagnosed intracranial glioblastoma. Neuro Oncol 2014;16(1): 113–22.
[41] Marko NF, Weil RJ, Schroeder JL, Lang FF, Suki D, Sawaya RE. Extent of resection of glioblastoma revisited: personalized survival modeling facilitates more accurate survival prediction and supports a maximum-safe-resection approach to surgery. J Clin Oncol 2014;32(8):774–82.
[42] Sanai N, Polley MY, McDermott MW, Parsa AT, Berger MS. An extent of resection threshold for newly diagnosed glioblastomas. J Neurosurg 2011;115(1):3–8.
[43] Muller DMJ, Robe PA, Ardon H, et al. Quantifying eloquent locations for glioblastoma surgery using resection probability maps. J Neurosurg 2020:1–11.
[44] Orringer D, Lau D, Khatri S, et al. Extent of resection in patients with glioblastoma: limiting factors, perception of resectability, and effect on survival. J Neurosurg 2012;117(5):851–9.
[45] Lacroix M, Abi-Said D, Fourney DR, et al. A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. J Neurosurg 2001;95(2): 190–8.
[46] Sales AHA, Bette S, Barz M, et al. Role of postoperative tumor volume in patients with MGMT-unmethylated glioblastoma. J Neuro Oncol 2019;142(3):529–36.
[47] Bette S, Barz M, Wiestler B, et al. Prognostic value of tumor volume in glioblastoma patients: size also matters for patients with incomplete resection. Ann Surg Oncol 2018;25(2):558–64.
[48] Simpson D. The recurrence of intracranial meningiomas after surgical treatment. J Neurol Neurosurg Psychiatry 1957;20(1):22–39.
[49] van den Bent MJ, Smits M, Kros JM, Chang SM. Diffuse infiltrating oligodendroglioma and astrocytoma. J Clin Oncol 2017; 35(21):2394–401.
[50] Suchorska B, Schuller U, Biczok A, et al. Contrast enhancement is a prognostic factor in IDH1/2 mutant, but not in wild-type WHO grade II/III glioma as confirmed by machine learning. Eur J Cancer 2019;107:15–27.
[51] Yordanova YN, Moritz-Gasser S, Duffau H. Awake surgery for WHO Grade II gliomas within "noneloquent" areas in the left dominant hemisphere: toward a "supratotal" resection. Clinical article. J Neurosurg 2011;115(2):232–9.
[52] Lima GLO, Dezamis E, Corns R, et al. Surgical resection of incidental diffuse gliomas involving eloquent brain areas. Rationale, functional, epileptological and oncological outcomes. Neurochirurgie 2017;63(3):250–8.
[53] Duffau H. Long-term outcomes after supratotal resection of diffuse low-grade gliomas: a consecutive series with 11-year follow-up. Acta Neurochir 2016;158(1):51–8 (Wien).
[54] de Leeuw CN, Vogelbaum MA. Supratotal resection in glioma: a systematic review. Neuro Oncol 2019;21(2):179–88.
[55] Duffau H. Higher-order surgical questions for diffuse low-grade gliomas: supramaximal resection, neuroplasticity, and screening. Neurosurg Clin N Am 2019;30(1):119–28.
[56] Rossi M, Ambrogi F, Gay L, et al. Is supratotal resection achievable in low-grade gliomas? Feasibility, putative factors, safety, and functional outcome. J Neurosurg 2019:1–14.
[57] Choi J, Kim SH, Ahn SS, et al. Extent of resection and molecular pathologic subtype are potent prognostic factors of adult WHO grade II glioma. Sci Rep 2020;10(1):2086.
[58] Smith JS, Chang EF, Lamborn KR, et al. Role of extent of resection in the long-term outcome of low-grade hemispheric gliomas. J Clin Oncol 2008;26(8):1338–45.
[59] Ghinda D, Zhang N, Lu J, Yao CJ, Yuan S, Wu JS. Contribution of combined intraoperative electrophysiological investigation with 3-T intraoperative MRI for awake cerebral glioma surgery: comprehensive review of the clinical implications and radiological outcomes. Neurosurg Focus 2016;40(3):E14.
[60] Kavouridis VK, Boaro A, Dorr J, et al. Contemporary assessment of extent of resection in molecularly defined categories of diffuse low-grade glioma: a volumetric analysis. J Neurosurg 2019:1–11.
[61] Im JH, Hong JB, Kim SH, et al. Recurrence patterns after maximal surgical resection and postoperative radiotherapy in anaplastic gliomas according to the new 2016 WHO classification. Sci Rep 2018;8(1):777.
[62] Nuno M, Birch K, Mukherjee D, Sarmiento JM, Black KL, Patil CG. Survival and prognostic factors of anaplastic gliomas. Neurosurgery 2013;73(3):458–65. quiz 465.
[63] Kawaguchi T, Sonoda Y, Shibahara I, et al. Impact of gross total resection in patients with WHO grade III glioma harboring the IDH 1/2 mutation without the 1p/19q co-deletion. J Neuro Oncol 2016;129(3):505–14.
[64] Roelz R, Strohmaier D, Jabbarli R, et al. Residual tumor volume as best outcome predictor in low grade glioma - a nine-years near-randomized survey of surgery vs. Biopsy. Sci Rep 2016;6:32286.
[65] Jakola AS, Skjulsvik AJ, Myrmel KS, et al. Surgical resection versus watchful waiting in low-grade gliomas. Ann Oncol 2017; 28(8):1942–8.
[66] Keles GE, Chang EF, Lamborn KR, et al. Volumetric extent of resection and residual contrast enhancement on initial surgery as predictors of outcome in adult patients with hemispheric anaplastic astrocytoma. J Neurosurg 2006;105(1):34–40.
[67] Jungk C, Scherer M, Mock A, et al. Prognostic value of the extent of resection in supratentorial WHO grade II astrocytomas stratified for IDH1 mutation status: a single-center volumetric analysis. J Neuro Oncol 2016;129(2):319–28.
[68] Hendriks EJ, Idema S, Hervey-Jumper SL, et al. Preoperative resectability estimates of nonenhancing glioma by neurosurgeons and a resection probability map. Neurosurgery 2019;85(2): E304–13.
[69] Pessina F, Navarria P, Cozzi L, et al. Value of surgical resection in patients with newly diagnosed grade III glioma treated in a multimodal approach: surgery, chemotherapy and radiotherapy. Ann Surg Oncol 2016;23(9):3040–6.
[70] Reuss DE, Kratz A, Sahm F, et al. Adult IDH wild type astrocytomas biologically and clinically resolve into other tumor entities. Acta Neuropathol 2015;130(3):407–17.

[71] Ruda R, Soffietti R. Extent of surgery in low-grade gliomas: an old question in a new context. Neuro Oncol 2018;20(1):6–7.
[72] Tesileanu CMS, Dirven L, Wijnenga MMJ, 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 2020;22(4):515–23.
[73] Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 2002;347(16):1233–41.
[74] Bowden SG, Han SJ. The evolving role of the oncologic neurosurgeon: looking beyond extent of resection in the modern era. Front Oncol 2018;8:406.