Recurrent glioblastoma in the era of molecular diagnostics: practice variation and practical implications

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Chapter 3

Practice variation in re-resection for recurrent glioblastoma: a nationwide survey among Dutch neuro-oncology specialists

Neuro-Oncology Practice. 2023;10(4):360-69.

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ABSTRACT

Background. Despite current best treatment options, a glioblastoma almost inevitably recurs after primary treatment. However, in the absence of clear evidence, current guidelines on recurrent glioblastoma are not well defined. Re-resection is one of the possible treatment modalities, though it can be challenging to identify those patients who will benefit. Therefore, treatment decisions are made based on multidisciplinary discussions. This study aimed to investigate the current practice variation between neuro-oncology specialists.

Methods. In this nationwide study among Dutch neuro-oncology specialists, we surveyed possible practice variation. Via an online survey, four anonymized recurrent glioblastoma cases were presented to neurosurgeons, neuro-oncologists, medical oncologists, and radiation oncologists in the Netherlands using a standardised questionnaire on whether and why they would recommend a re-resection or not. The results were used to provide a qualitative analysis of the current practice in the Netherlands.

Results. The survey was filled out by 56 respondents, of which 15 (27%) neurosurgeons, 26 (46%) neuro-oncologists, 2 (4%) medical oncologists, and 13 (23%) radiation oncologists. In two of the four cases, there appeared to be clinical equipoise. Overall, neurosurgeons tended to recommend re-resection more frequently compared to the other specialists. Neurosurgeons and radiation oncologists showed opposite recommendations in two cases.

Conclusions. This study showed that re-resection of recurrent glioblastoma is subject to practice variation both between and within neuro-oncology specialties. In the absence of unambiguous guidelines, we observed a relationship between preferred practice and specialty. Reduction of this practice variation is of importance; to achieve this, adequate prospective studies are essential.

Keywords. Glioblastoma, recurrence, re-resection, practice variation, survey

INTRODUCTION

Glioblastoma is a devastating primary malignant brain tumor with a median survival of 15 months. Despite current best treatment options the tumor inevitably recurs [1, 2]. International guidelines on the diagnosis and treatment of diffuse gliomas in adulthood do not provide well defined standard-of-care treatments for patients with a recurrent glioblastoma [3]. According to these guidelines, re-resection remains an option for about 20-30% of the patients, typically patients with symptomatic but circumscribed lesions and symptomatic patients with progression exceeding six months after initial surgery. In general, there is little discussion that re-resection can improve overall survival, provided that patient and tumor specific factors such as Karnofsky Performance Status (KPS), extent of resection and radiological findings are on the favourable end of the spectrum [4-9]. A consensus on re-resection has been shown difficult to obtain and patients discussed in multidisciplinary meetings still depend on expert opinions. It is exactly this deliberation, however, together with treatment specific and future specific factors, that makes the decision whether or not to perform a re-resection everything but straightforward and even controversial instead. And although some patients with a recurrent glioblastoma could benefit from a re-resection, for a larger group an optimal treatment paradigm remains not clear. What do different neuro-oncology specialists recommend in those cases? What are decisive factors and which considerations are taken into account when recommending re-resection in specific cases of recurrent glioblastoma?

This study aimed to investigate the current practice variation between neuro-oncology specialists by surveying their recommendations in four different cases. Given the lack of support in international guidelines, the results of this study might offer new insights in areas of consensus and controversy regarding re-resection for recurrent glioblastoma, and contribute to more consensus in the treatment of these patients.

MATERIALS AND METHODS

Study design

In the Netherlands, there are fourteen neurosurgical centers and seventeen radiotherapy centers, including seven academic hospitals, that treat patients with glioblastoma. Patients are referred to these centers from smaller, regional hospitals that do not have the expertise or the optimal neurosurgical facilities. To assess possible practice variation in re-resection for patients with a recurrent glioblastoma,

four cases were presented to practicing neurosurgeons, neuro-oncologists (i.e. neurologists with neuro-oncology expertise), radiation oncologists and medical oncologists throughout the Netherlands (selection process described below). The cases were selected based both on their representativeness and variability with respect to patient characteristics (such as age and clinical performance), radiological findings and the course over time (especially the time between initial surgery and recurrence). The first case is an example of a resectable tumor with considerable risks of post-operative neurological deficits in a patient who is in a good clinical condition and for whom adjuvant/other treatment options are available. The second case illustrates a diffuse, multifocal recurrence in a young patient, with very limited adjuvant treatment options. Third, we show a case of a small, asymptomatic, and late recurrence in a patient for whom reasonable adjuvant/other treatment options are available. Finally, the fourth case describes an early and multifocal recurrence in a young patient with a preference not to have surgery. All four patients had already died at moment of selection, and family was not consulted to ask for consent in order to avoid increasing their emotional burden. Furthermore, we anonymized the images and added fictitious, non-relevant patient characteristics to create four illustrative but anonymous vignettes. All images shown in the cases were T1-weighted MRI images after contrast administration. Relevant T2-features are described as well. The vignettes of the cases can be found in *Figure 2-5*.

Survey design and distribution

Respondents were contacted with an online survey: for every case we asked whether the respondent would recommend a re-resection [yes/no]. Following questions were asked for the considerations taken into account and subsequently for decisive factors (Supplementary *Table 1)*. The decisive factors that were asked for were subdivided in patient, tumor characteristics, treatment characteristics and future specific factors, without any further definition. Multiple answers were possible for these considerations and decisive factors, as well as the option to specify. Baseline characteristics of the respondents included specialty, type of department [general hospital/academic hospital/private practice], age in years [30-39/40-49/50-59/60-70], gender [male/female/would rather not say] and years of experience as a medical specialist (i.e. time since finishing residency) [0-5/6-10/11-20/21-30/>30]. Finally, the respondents were asked for the minimum overall survival (in months) from the date of re-resection for a re-resection to be generally considered proportional.

The survey was distributed via e-mail invitations, primarily to the members of the Dutch Neuro-Oncology Society (Landelijke Werkgroep Neuro-Oncologie, LWNO), a society with approximately two hundred active members. Additional responses were collected by personal invitations to neuro-oncology specialists throughout the Netherlands. Subsequent distribution to members of their local neuro-oncology boards was done by some of them. As a result, response rates could not be reliably assessed. The survey was open for response between July 11th and September 2nd 2022 and we sent multiple reminders to respond. By responding, the participants consented to the anonymous publication of the results. The online survey was made by using the web survey tool SurveyMonkey (Momentive Inc., San Mateo, California, USA, www.surveymonkey.com).

Statistical analysis

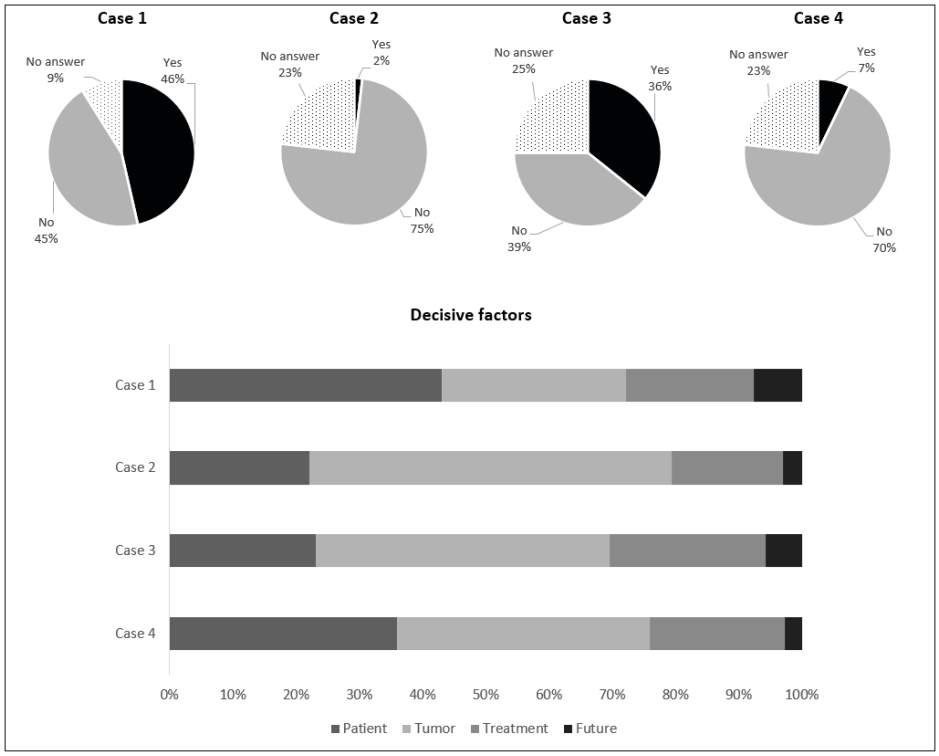
Categorical variables were reported using percentages and counts, taking different subgroup sizes into account. Continuous variables were described using the median and range. Formal statistics were not further applied because of the relatively small numbers, particularly for subgroup analyses, what would lead to unreliability of the conclusions. No separate analyses of the medical oncologists' answers could be done because of the very limited response of these specialists (*n*=2). Statistical analyses were performed using statistical package *IBM SPSS Statistics for Windows* version 28.0.

RESULTS

Respondents' characteristics

The survey was filled out by 56 respondents, of which 43 (77%) completed all four cases. Of all respondents, 27% (15/56) were neurosurgeons, 46% (26/56) neuro-oncologists, 4% (2/56) medical oncologists and 23% (13/56) radiation oncologists. No major numerical differences between medical specialties were observed for age, type of department and years of experience as a medical specialists; we noted some differences in gender distribution, see *Table 1*.

Figure 1. Case-specific answers on the question 'Would you recommend a re-re-section in this case?' together with decisive factors.



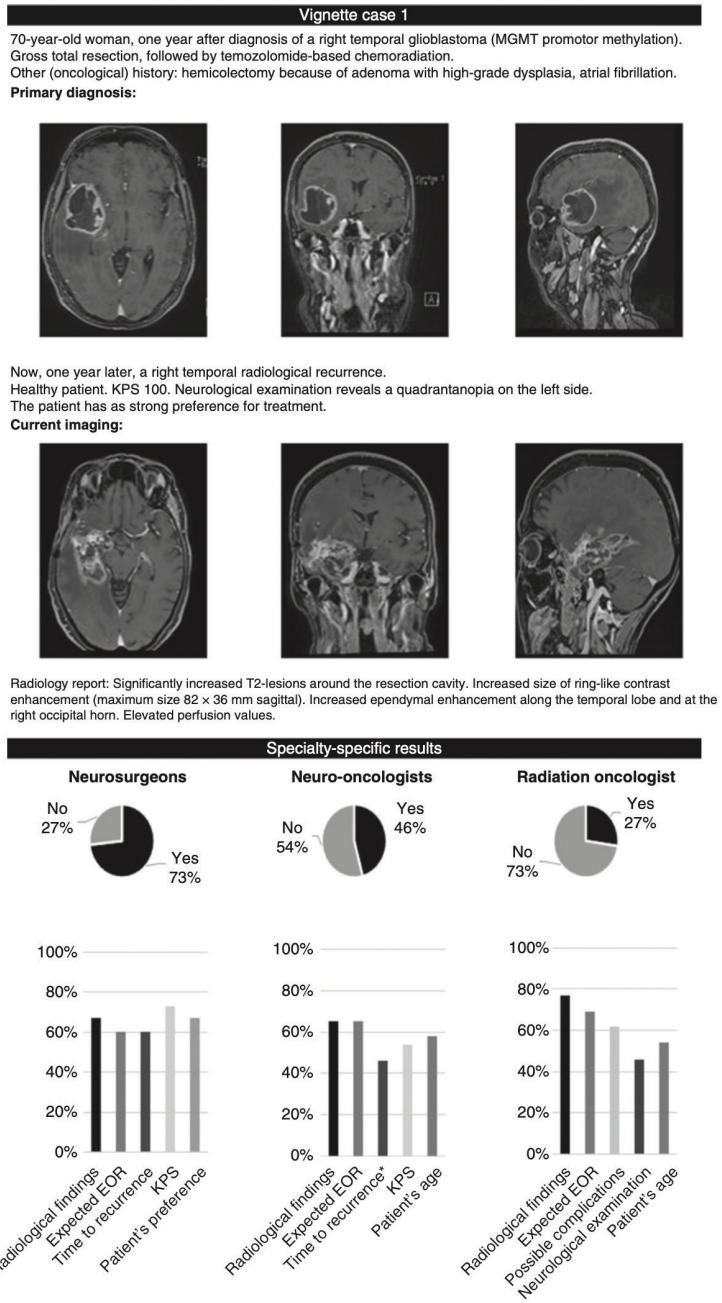
General trends

In two of the four cases, there appeared to be clinical equipoise among the respondents. In case 1, 46% recommended a re-resection whereas 45% did not recommend re-resection, and the remainder did not answer. Likewise, 36% of the respondents was in favour of a re-resection in case 3, compared to 39% who was not in favour. In contrast, case 2 and 4 showed almost unanimity with only 2% and 7% of the respondents recommending a re-resection, respectively (*Figure 1*). Regardless of type of medical speciality, a median of 6 months (range 3-15) of estimated overall survival from the date of re-resection was considered the minimum for a re-resection to be proportional.

Overall, tumor characteristics were most frequently (67%) decisive in the recommendation to perform a re-resection or not. The second most common decisive aspect was patient characteristics (50% of the respondents). Treatment

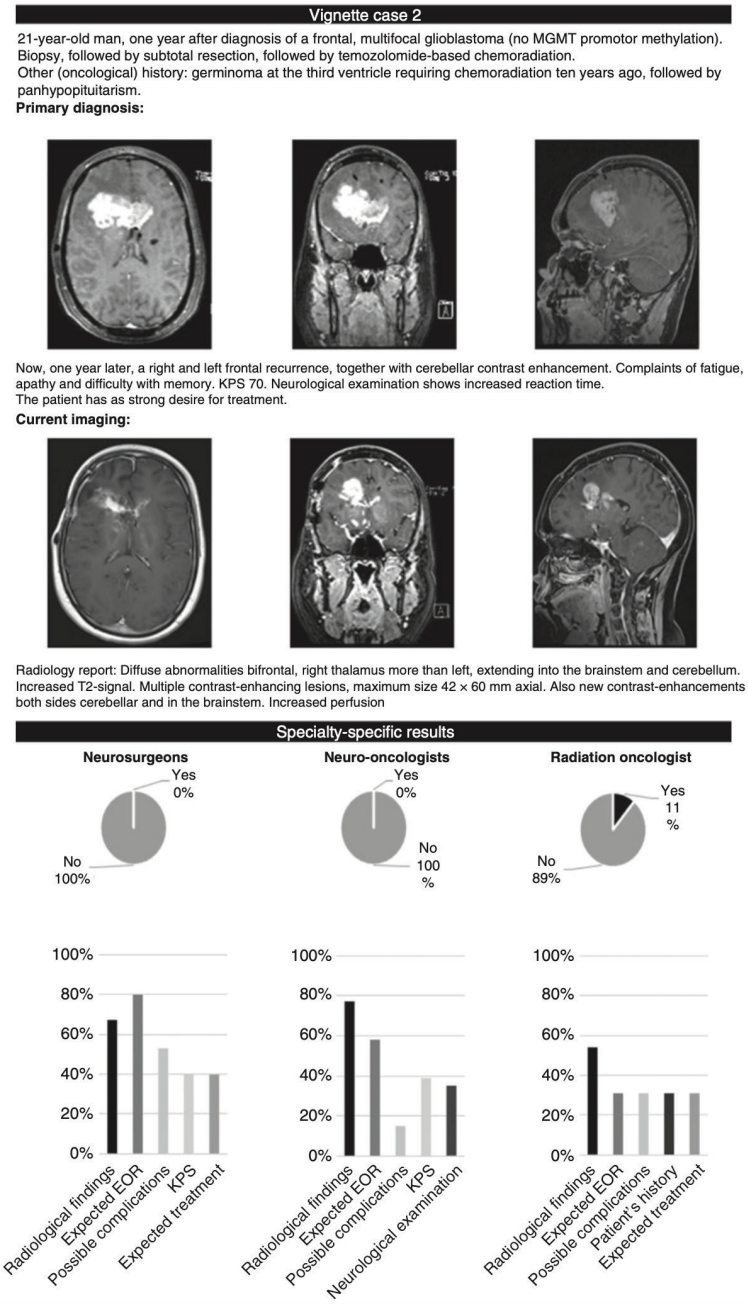
characteristics and future specific factors were less often decisive in the decision: overall 33% and 8%, respectively (see also *Figure 1*). Overall, the radiological findings at the time of recurrence and the expected extent of re-resection were the two most common considerations in all specialties. Interestingly, the patient's preference was a strong case-dependent consideration, ranging from 4% in case 2 to 57% in case 4.

Figure 2. Vignette of case 1 with specialty-specific answers on the question 'Would you recommend a re-resection in this case?' and underlying considerations. MRI images shown are T1-weighted images after contrast administration.



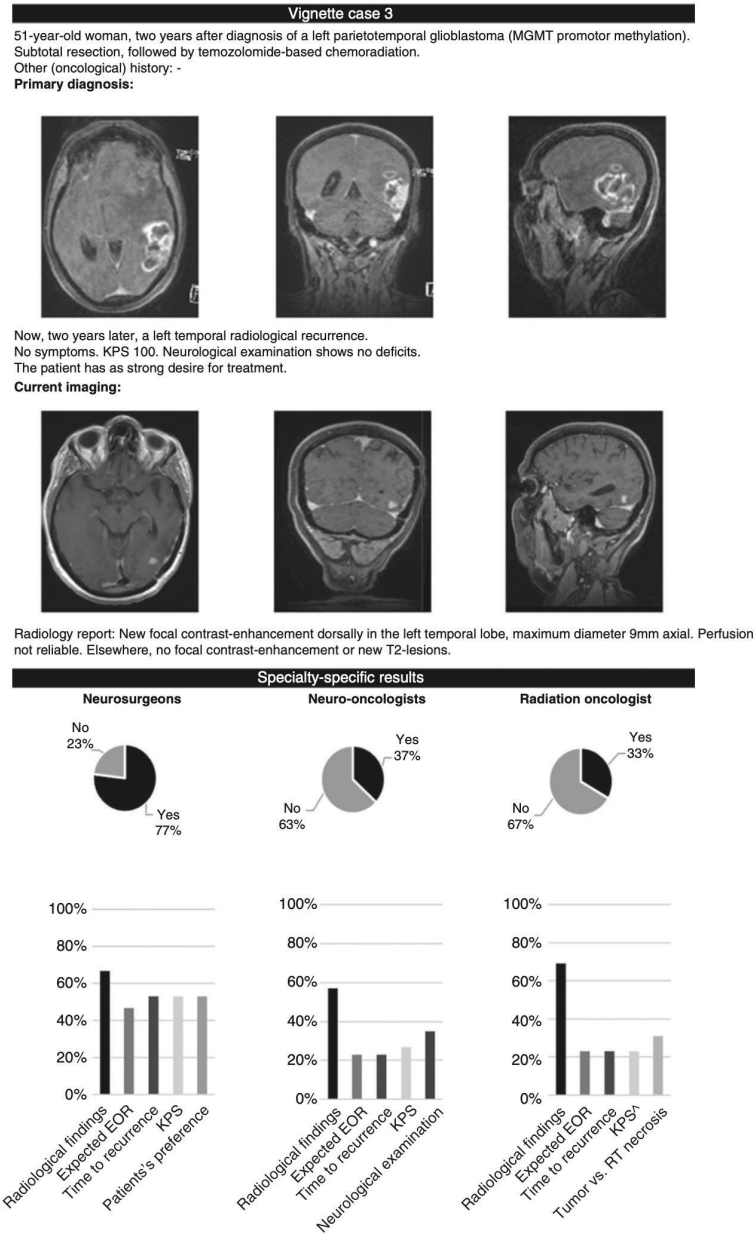
EOR: extent of re-resection, KPS = Karnofsky performance status, MGMT = O^6-methylguanine-DNA methyltransferase, MRI = magnetic resonance imaging, RT necrosis: radiation necrosis. The five most frequently chosen considerations per specialty are depicted. Equal proportions that are not shown: *the findings on the neurological examination.

Figure 3. Vignette of case 2 with specialty-specific answers on the question 'Would you recommend a re-resection in this case?' and underlying considerations. MRI images shown are T1-weighted images after contrast administration.



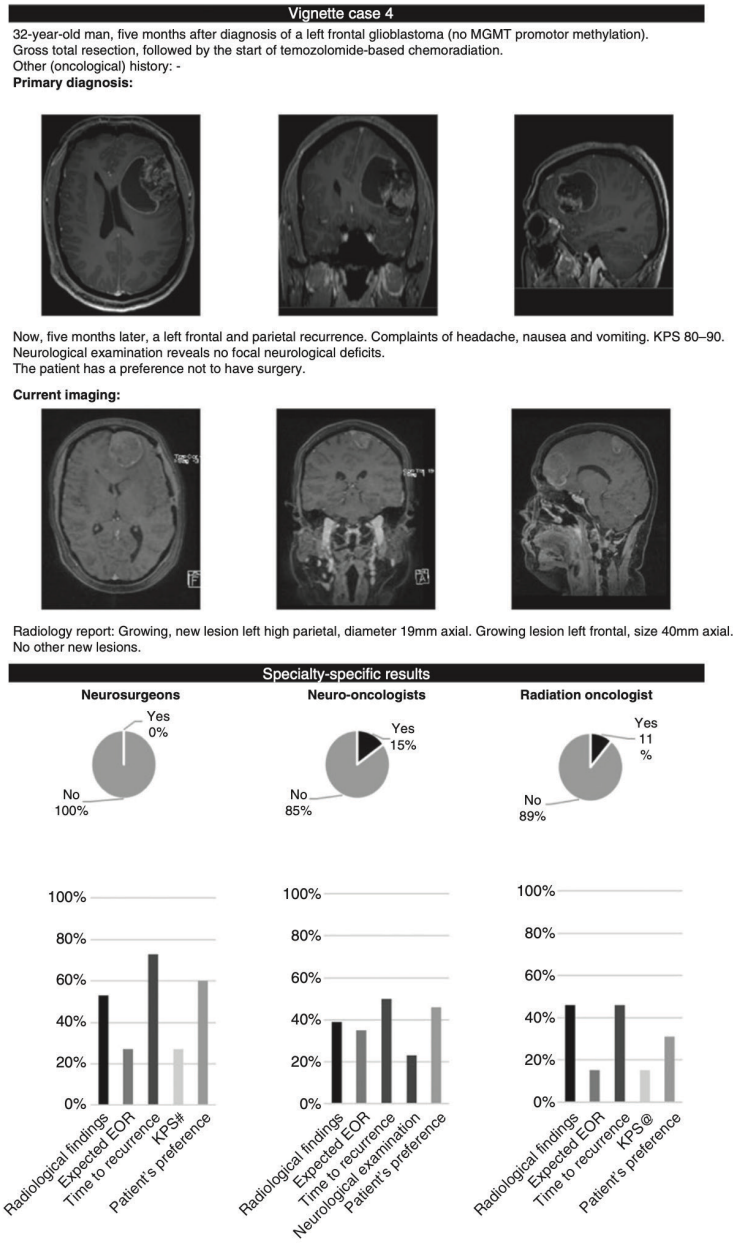
EOR: extent of re-resection, KPS = Karnofsky performance status, MGMT = O^6-methylguanine-DNA methyltransferase, MRI = magnetic resonance imaging, RT necrosis: radiation necrosis.

Figure 4. Vignette of case 3 with specialty-specific answers on the question 'Would you recommend a re-resection in this case?' and underlying considerations. MRI images shown are T1-weighted images after contrast administration.



EOR: extent of re-resection, KPS = Karnofsky performance status, MGMT = O^6-methylguanine-DNA methyltransferase, MRI = magnetic resonance imaging, RT necrosis: radiation necrosis. The five most frequently chosen considerations per specialty are depicted. Equal proportions that are not shown: ^possible complications, expected treatment following re-resection.

Figure 5. Vignette of case 4 with specialty-specific answers on the question 'Would you recommend a re-resection in this case?' and underlying considerations. MRI images shown are T1-weighted images after contrast administration.



EOR: extent of re-resection, KPS = Karnofsky performance status, MGMT = O^6-methylguanine-DNA methyltransferase, MRI = magnetic resonance imaging, RT necrosis: radiation necrosis. The five most frequently chosen considerations per specialty are depicted. Equal proportions that are not shown: #expected treatment follow re-resection, @patient's history, treatment already given.

Practice variation by specialty

Neurosurgeons leaned more often towards performing a re-resection in the patients with a recurrent glioblastoma. In case 1 and 3, cases in which the 'yes/no-ratio' was equal (see *Figure 1*): 73% and 77% of the neurosurgeons recommended a re-resection in these cases, compared to 46% and 37% of the neuro-oncologists and 27% and 33% of the radiation oncologists, respectively. See *Figure 2-5* for specialty- and case-specific trends. Two specialty-specific trends can be observed, the first being a neurosurgeons' tendency to consider KPS more often than the other specialists. A similar trend was noticed for the patient's preference, which was taken into account more often by the neurosurgeons compared to the other specialists. No differences were found for decisive factors between specialists, with tumor-specific factors followed by patient-specific factors as the two most common.

The most eminent examples of practice variation between specialties can be found in case 1 and 3: almost opposite recommendations between neurosurgeons and radiation oncologists, with neuro-oncologists being more equally distributed in their preferences (*Figure 2 and 4*). Of note, practice variation can also be seen within the same specialty when it comes to the same case. For example, some neurosurgeons, with no more than ten years of experience, opted for re-resection because it was a "superficially circumscribed location" and "gross-total resection very well possible" while other neurosurgeons, with more than ten years of experience, looked at the same tumor being "too small" with "limited oncological benefit of re-resection".

Table 1. Respondent's characteristics. Separate results of medical oncologists (n=2) were omitted.

Characteristics	Neurosurgeons *n* = 15	Neuro-oncologists *n* = 26	Radiation oncologists *n* = 13	Total cohort *n* = 56
Gender, no. (%)				
Male	14 (93%)	8 (31%)	6 (46%)	29 (52%)
Female	1 (7%)	17 (65%)	7 (54%)	26 (46%)
Unknown	0 (0%)	1 (4%)	0 (0%)	1 (2%)
Age in years, no. (%)				
30-39	6 (40%)	5 (19%)	4 (31%)	16 (29%)
40-49	4 (27%)	8 (31%)	4 (31%)	16 (29%)
50-59	3 (20%)	8 (31%)	3 (23%)	15 (27%)
60-70	2 (13%)	4 (15%)	2 (15%)	8 (14%)
Unknown	0 (0%)	1 (4%)	0 (0%)	1 (2%)
Department, no. (%)				
General hospital	8 (53%)	14 (54%)	5 (38%)	28 (50%)
Academic hospital	7 (47%)	12 (46%)	6 (46%)	26 (46%)
Private practice	0 (0%)	0 (0%)	1 (8%)	1 (2%)
Unknown	0 (0%)	0 (0%)	1 (8%)	1 (2%)
Years of experience, no. (%)				
0-5	3 (20%)	4 (15%)	4 (31%)	12 (21%)
6-10	6 (40%)	6 (23%)	1 (8%)	13 (23%)
11-20	3 (20%)	9 (35%)	4 (31%)	17 (30%)
21-30	3 (20%)	5 (19%)	3 (23%)	11 (20%)
>30	0 (0%)	2 (8%)	1 (8%)	3 (5%)

No.: number of patients

DISCUSSION

This study surveyed the practice variation in re-resection for recurrent glioblastoma among neuro-oncology specialists throughout the Netherlands. In two of the four cases presented to them, we found equal proportions of specialists in favour and not in favour of a re-resection. Numeric differences suggested that neurosurgeons recommend a re-resection more often than neuro-oncologists and radiation

oncologists. The largest interspecialty variation was seen in case 1 and 3 between neurosurgeons and radiation oncologists, with almost opposite recommendation proportions (see *Figure 2 and 4*). Overall, tumor specific factors were the most frequently (67%) decisive in the decision to perform a re-resection or not.

Practice variation in medicine has been studied before and is a well-known phenomenon [10, 11]. Likewise in neuro-oncology, practice is subject to variation, for instance in mapping procedures in glioma surgery, neuroimaging after glioblastoma surgery or perioperative laboratory testing [12-14]. The need to reduce practice variation in medicine being out of debate, but health professionals are not sure about the feasibility of a reduction [15].

Two main factors can be identified to explain the variability in treatment decisions: the lack of guidelines/large prospective studies and the concept of noise. Both are covered by Kahneman et al, who described noise as the 'unwanted variability of judgements' with the property that the true answer may be even unknowable [16]. This is exactly what happened in our study: one can observe the scattering of the answers while the true answer is unknown or unknowable. Kahneman et al. conclude that medicine is a noisy profession in which the interrater reliability could be powerfully reduced by guidelines [17]. The lack of clear guidelines on recurrent glioblastoma treatment can be explanatory for the findings in the current study. This lack of clear guidelines, in turn, is largely due to the absence of high-quality evidence, e.g. from randomized clinical trials, or from prospective, population-based (registry-based) cohort studies.

More specific explanations for the variation in re-resection as found in our study include the following. First, clinicians have to deal with discrepancies, sometimes subtle, between population-based guidelines and the individual patient in front of them. To decide whether an individual belongs to the 20-30% mentioned in the guidelines [3], is a matter of careful multidisciplinary deliberation, resulting in patient-tailored treatment. The applicability of those guidelines could therefore be fairly questionable, resulting in opposed recommendations on re-resection. Second, more risk-averse specialists, whether or not related to the number of years of experience, may be inclined to not recommend re-resection because of the still ongoing debate about the benefit of re-resection, supported by some studies opposing re-resection [18-20]. What is more, a relationship between specialty and preference can be observed in our results. Neurosurgeons recommended re-resection more often than the other specialists, what might be a reflection of their specific expertise and consulting role in multidisciplinary discussions. Neuro-oncologists most frequently considered the

findings of the neurological examination. Radiation oncologists, in turn, took the radiological findings into account most commonly. The observed case-dependency of considering the patient's preference can be fairly explained by specialists' strong opinion to not perform a re-resection in certain cases (e.g. multifocality). On the other hand, clinical equipoise can be seen especially in those cases in which re-resection is considered one of the realistic options.

This study has some limitations to be mentioned. First, this online survey intended not to be more than a reflection of the actual practice. Given four anonymized cases, it can be challenging for respondents to deliberately give a recommendation without being able to ask for additional details and without knowing the clinical nuances. Second, small numbers hampered subgroup analyses and subsequent quantification of the results. Third, this survey could only have triggered specialists with strong opinions on this topic to respond. This could have led to response bias. Finally, in the Dutch practice, decisions on the treatment of brain tumor patients are made based on multidisciplinary discussion, something that was not accounted for in the current study design. Because of these limitations, the results of this study have to be interpreted with caution.

The focus of this article was to demonstrate that there is practice variation in recommendation of re-resection. Of course, other therapies might be considered (much more) appropriate in specific cases and the presence/absence of adjuvant therapy options could affect the choice to offer the patient surgery as well. Indeed, the clinical benefit of surgery is limited in the absence of adjuvant therapy.[4] Conversely, in patients with good adjuvant treatment options, no consensus exists on whether (cytoreductive) surgery prior to adjuvant treatment improves prognosis. In this setting, our results suggest that different specialists have different views on the added value of surgery. The ongoing randomized controlled RESURGE trial (NCT02394626) aims to further identify the impact of re-resection on the overall survival of glioblastoma patients.

To conclude, our study showed that re-resection of recurrent glioblastoma is subject to practice variation both between and within neuro-oncology specialties. Future research would be of interest to reveal whether this scenario is the same in other countries and how practice variation in this field can be reduced. Due to the different angles these different specialist groups have on patient care, our results underline the crucial function of multidisciplinary tumor board discussion.

AUTHOR CONTRIBUTIONS

MPvO, FYFvV and MLDB contributed to the study conception and design. Material preparation, data collection and analysis were performed by MPvO, FYFdV, RJAN, TJS, RDSNT, WT, JJCV, JJMvdH and MDLB. The first draft of the manuscript was written by MPvO and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

FUNDING

None

ACKNOWLEDGEMENTS

We would like to express our gratitude to all those who helped us gaining insight into the practice variation by filling out our survey. We thank Oncode Institute for making this research financially possible through the Clinical Proof of Concept.

AVAILABILITY OF DATA AND MATERIALS

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST STATEMENT

None of the authors declare a conflict of interest.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Considerations taken into account and decisive factors asked after the question whether the respondent would recommend a re-resection or not.

Considerations	Decisive factors
The patient's current age	Patient specific factors
The patient's medical history	Tumor specific factors
The current KPS	Treatment specific factors
The findings on the neurological examination	Future specific factors
The patient's preference	Please specify
To differentiate between tumor recurrence or radiation necrosis	
The molecular tumor profile	
The current radiological findings	
The time between initial resection and recurrence	
The extent of resection at initial resection	
The treatment already given to the patient	
The expected extent of resection at re-resection	
The possible complications as a result of re-resection	
The possible complications as a result of re-resection	
The expected treatment following re-resection and its possible effect	
The possibility to find new targets for treatment	
The alternatives of a re-resection	
Too little information available	
Other (please specify)	

KPS = Karnofsky performance status.