

Patterns of care in recurrent glioblastoma in Switzerland: a multicentre national approach based on diagnostic nodes

T. Hundsberger¹ · A. F. Hottinger² · U. Roelcke³ · P. Roth⁴ · D. Migliorini⁵ · P. Y. Dietrich⁵ · K. Conen⁶ · G. Pesce⁷ · E. Hermann⁸ · A. Pica⁸ · M. W. Gross⁹ · D. Brügger¹⁰ · L. Plasswilm¹⁰ · M. Weller⁴ · P. M. Putora¹⁰

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Abstract Despite moderate improvements in outcome of glioblastoma after first-line treatment with chemoradiation recent clinical trials failed to improve the prognosis of recurrent glioblastoma. In the absence of a standard of care we aimed to investigate institutional treatment strategies to identify similarities and differences in the pattern of care for recurrent glioblastoma. We investigated re-treatment criteria and therapeutic pathways for recurrent glioblastoma of eight neuro-oncology centres in Switzerland having an established multidisciplinary tumour-board conference. Decision algorithms, differences and consensus were analysed using the objective consensus methodology. A total of 16 different treatment recommendations were identified based on combinations of eight different decision criteria. The set of criteria implemented as well as the set of treatments offered was different in each centre. For specific situations, up to 6 different treatment recommendations were provided by the eight centres. The only

wide-range consensus identified was to offer best supportive care to unfit patients. A majority recommendation was identified for non-operable large early recurrence with unmethylated MGMT promoter status in the fit patients: here bevacizumab was offered. In fit patients with late recurrent non-operable MGMT promoter methylated glioblastoma temozolomide was recommended by most. No other majority recommendations were present. In the absence of strong evidence we identified few consensus recommendations in the treatment of recurrent glioblastoma. This contrasts the limited availability of single drugs and treatment modalities. Clinical situations of greatest heterogeneity may be suitable to be addressed in clinical trials and second opinion referrals are likely to yield diverging recommendations.

Keywords Recurrent glioblastoma · Diagnostic nodes · Objective consensus · Decision making · Re-treatment criteria

On behalf of the Swiss Group for Clinical Cancer Research (SAKK) Central Nervous System working group.

✉ T. Hundsberger
thomas.hundsberger@kssg.ch

¹ Department of Neurology and Department of Haematology/Oncology, Cantonal Hospital St. Gallen, Rorschacherstr. 95, 9007 St. Gallen, Switzerland

² Department of Clinical Neurosciences & Oncology, University Hospital, Lausanne, Switzerland

³ Department of Neurology and Brain Tumour Centre, Cantonal Hospital Aarau, Aarau, Switzerland

⁴ Department of Neurology, and Brain Tumor Centre, University Hospital, Zurich, Switzerland

⁵ Department of Oncology, University Hospital Geneva, Geneva, Switzerland

⁶ Department of Oncology, University Hospital Basel, Basel, Switzerland

⁷ Department of Radiation Oncology, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland

⁸ Department of Radiation Oncology, University Hospital Bern, Bern, Switzerland

⁹ Department of Radiation Oncology, University Hospital Basel, Basel, Switzerland

¹⁰ Department of Radiation Oncology, Cantonal Hospital St. Gallen, St. Gallen, Switzerland

Introduction

Glioblastoma is the most common and devastating primary brain tumour with an annual incidence of about three per 100,000 [1] persons. It is associated with great morbidity and early mortality. Even after multimodal treatment with temozolomide chemoradiation (RT/TMZ → TMZ) progression-free survival (PFS) and overall survival (OS) remain poor with 6.9 and 14.2 months, respectively [2]. Recently, four large phase III trials failed to improve outcome after first-line therapy in terms of OS [3–6]. Hence, effective salvage treatment of recurrent glioblastoma remains a demanding problem in neuro-oncology.

The oral alkylating agent TMZ is widely used for the treatment of recurrent glioblastoma (TMZ re-challenge) [7–11]. However, the optimal dosing schedule and the minimal time interval from first line TMZ are unknown. This topic was investigated in a single prospective phase II trial using a metronomic TMZ schedule [9]. Patients with a tumour recurrence at least 3 months after RT/TMZ or 2 months after completion of RT/TMZ and six maintenance cycles of TMZ reached modest PFS rates after 6 months (PFS-6) of 27.3 and 35.7 %, respectively. Recently, two dose-intensified TMZ schedules have been prospectively investigated at first relapse after at least two cycles of maintenance TMZ after RT/TMZ to avoid interference with pseudoprogression [11]. None of the regimes were superior with a median time to treatment failure of 1.8 months [Arm A: one week on (120 mg/m² per day)/one week off] and 2.0 months [Arm B: three weeks on (80 mg/m² per day)/one week off], respectively. However, methylation of the MGMT promoter was a strong positive prognostic factor of PFS-6 (methylated 39.7 % vs. unmethylated 6.9 %) [11]. Small targeted drugs like enzastaurin or cediranib failed to show benefit in recent phase III trials when compared to lomustine in recurrent glioblastoma [12, 13]. Therefore, lomustine has advanced to a widely used alkylating drug either alone or in combination whenever TMZ is not considered to be appropriate for the treatment of recurrent glioblastoma [14, 15]. In contrast to the European Union, bevacizumab, an anti-angiogenic agent targeting VEGF-A, has been approved in selected countries (i.e. North America, Switzerland) for the treatment of recurrent glioblastoma based on uncontrolled phase II studies [16, 17].

Due to the limited efficacy of second-line systemic treatment, focal strategies with re-operation and re-irradiation have also been introduced as salvage treatments. However, little evidence for these therapies is available as most studies investigated only small or retrospective patient cohorts [18–25]. Furthermore, availability of stereotactic radiotherapy or radiosurgery and financial

resources of health care systems account for significant differences in use between countries and even national regions.

As effective treatment options are scarce and controlled trials are rare for recurrent glioblastoma, therapeutic decisions are mostly based on low level evidence [26]. Beyond evidence, experience (eminence-based medicine) may provide additional guidance. Possibly, further information can be extracted from the community, for example as patterns of care studies [27]. Patterns of care studies often rely on specific scenarios which are presented to participants, these are then analysed; the limitation being that the answers are restricted to only these specific scenarios. When the collected information is appropriately formatted [28], e.g. decision trees are collected, patterns of practice can be analysed for multiple combinations of parameters [29]. In the setting of low evidence for salvage treatment we aimed to collect treatment algorithms from Swiss neuro-oncological centres which derive their treatment recommendations from multidisciplinary tumour boards. The collected information was used to perform a comprehensive patterns care and patterns of algorithms analysis for the treatment of recurrent glioblastoma.

Materials and methods

Based on specific parameters (characteristics of the patient and the disease) recommendations can be defined. The concept of diagnostic nodes (Dodes) has been developed [28, 29] to allow for a cross-comparison of recommendations in decision-tree format and has been applied in a clinical setting [30, 31]. Dodes are organized into decision trees using pre-defined categories. Standardized nomenclature of parameters and recommendations is a prerequisite for automated comparisons and an unbiased evaluation. Based on Dodes and the objective consensus methodology [29], consensus and heterogeneity were analysed (Fig. 1).

Hospitals with an interdisciplinary neuro-oncology unit including at least full-time service of neuro-surgery, radiotherapy and medical neuro-oncology with a dedicated neuro-oncology tumour board being represented in the Swiss Group for clinical cancer research (SAKK) were asked to participate in the study. Treatment recommendations for recurrent glioblastoma were collected without specifications in formatting. Free-text, Microsoft PowerPoint slides and hand-drawn diagrams were converted without changing content into treatment algorithms and after several bilateral exchanges defined as final by 1st of January 2015. These were again discussed among the participating centres. Two centres took patient preference explicitly into account; these were related to the decision

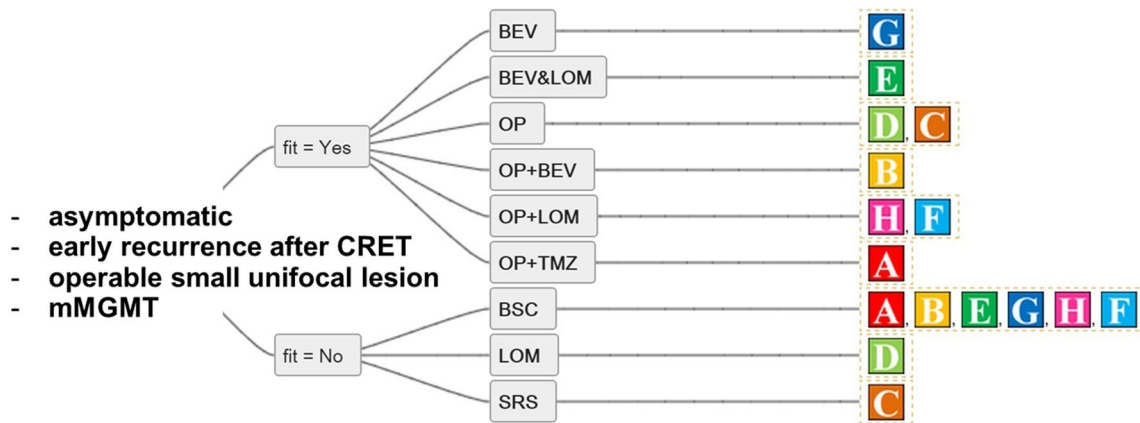


Fig. 1 Analysis by the objective consensus method. Example of an early recurrent, small and resectable glioblastoma harbouring a methylated MGMT (mMGMT) promoter. For fit patients heterogeneous treatment options were recommended among the centres (A–H), whereas in unfit patients 6 out of 8 centres (A, B, E, G, H,

F) suggested BSC and only two centres (C, D) recommended alternative treatments. *Bev* bevacizumab; *Lom* lomustine; *OP* operation; *TMZ* temozolomide; *BSC* best supportive care; *SRS* stereotactic radiosurgery; & combined treatment; + sequential treatment

for active treatment versus best supportive care (BSC). Despite these criteria being important for daily practice, they were eliminated for the analysis as they do not rely on a tumour board decision and of course should apply to every clinical decision. Similar criteria were fused into new comprehensive categories to simplify their usage and enable cross-comparability (i.e. the criteria fitness based upon performance status, co-morbidities and age). The resulting data were presented to the participants and minor corrections were applied. The interpretation by all participants resulted in the final discussion.

Results

In total, 8 Swiss centres (Aarau, Basel, Bellinzona, Bern, Geneva, Lausanne, St. Gallen, Zurich) participated and provided written or schematic information of their interdisciplinary local treatment strategy for recurrent glioblastoma. The original treatment algorithms included a total of 23 re-treatment criteria and a list of 16 treatment options (Table 1; Fig. 2).

Processing and simplification

As the considerable variability of the re-treatment criteria lead to an exponential rise in possible combinations, we simplified and integrated similar criteria with minor differences (Table 1). For example, the various thresholds of Karnofsky performance scale (KPS), age, Eastern cooperative oncology group performance status (ECOG) and the presence of co-morbidities were summarized as “fit” or “unfit”. Additionally, tumours were summarized as “resectable” or “non-resectable” according to their

occurrence in eloquent areas and non-diffuse/localized distribution. Need for steroid use and symptomatic recurrent glioblastoma were merged to only one category. After simplification the trees were analysed with the so defined 8 essential criteria. All centres used resectability, fitness and time of recurrence as re-treatment criteria. Five centres (A, C-E, H) used the MGMT promoter status. However, we gathered no information which method and threshold for MGMT promoter methylation status was used in clinical practise. Four centres used tumour size (B, C, G, H) and unifocality (C, E, F, H). Only three and two centres, respectively, took symptoms (F, G, H) and complete resection of enhancing tumour (CRET) (A, B) into account.

Re-treatment criteria

All centres dichotomised their decision to actively treat recurrent glioblastoma with anti-tumour strategies by using the performance status (PS). Generally, “unfit” patients with a low PS were referred to BSC without offering active oncological treatment. The KPS and the ECOG were both reported. However, the lowest threshold for active anti-tumour re-treatment varied considerably (KPS from 50 to 90; ECOG 0–1) (Table 1). The same was true for age (between 50 and 75 years). However, age was only reported as a re-treatment criterion in 2 out of 8 centres.

Re-treatment options

Five treatments were offered against recurrent glioblastoma in at least 4 centres (Fig. 2). These were the combination of re-operation with either TMZ or bevacizumab, monotherapy with either TMZ or bevacizumab and BSC. Interestingly, the time required to consider TMZ re-

Table 1 Overview of original re-treatment criteria, assessment procedures and the derived standardized criteria used for comparison

Re-treatment criteria	Assessment	Simplified criteria
Performance status	KPS </> 50; 60; 70; 90 ECOG </= 1 Good/bad	Fit versus unfit
Age	</> 50 years; </> 75 years	
Tumour volume	>/> 65 ml; </> 1.5 cm	Operable versus not operable
rGBM characteristics	New/distant lesion Diffuse/local lesion Resectable (yes/no) Single/multiple lesions Growth kinetics (slow/rapid)	
Time from last TMZ treatment	</> 2;4;6 months	Early versus late
Time from last radiotherapy	</> 6 months	
Re-resection	Total; subtotal	CRET versus non-CRET
Symptomatic rGBM	Yes/no	Symptomatic versus asymptomatic
Steroid use	Yes/no	
Methylated MGMT promoter	Yes/no	Unchanged

Among 8 neuro-oncology centres 23 re-treatment criteria were disclosed. Based on unification and simplification similar criteria were partially re-named and merged

KPS Karnofsky performance status; ECOG Eastern Cooperative Oncology Group performance status; rGBM recurrent glioblastoma; CRET complete resection of contrast enhancing tumour; TMZ temozolomide

	treatments							
	centre: A	B	C	D	E	F	G	H
OP			+	+			+	
SRS			+				+	
BEV	+	+	+	+			+	+
TMZ	+	+	+		+	+	+	+
RT	+	+		+				
LOM				+		+		+
BEV&LOM					+			
OP+TMZ	+	+			+	+		+
OP+BEV&LOM					+			
BSC	+	+			+	+	+	+
OP+LOM	+					+		+
OP+BEV	+	+				+		+
OP+RT&TMZ	+							
OP+RT	+	+						
RT&TMZ	+							
RT&BEV						+		

Fig. 2 Implemented treatment strategies among the centres A–H (cross, reported; white, not reported); OP operation; SRS stereotactic radiotherapy; Bev bevacizumab; TMZ temozolomide; RT radiotherapy; LOM lomustine; BSC best supportive care

challenge ranged from 2 to 6 months. Four centres additionally relied on the MGMT promoter methylation status to indicate an alkylator-based systemic treatment (TMZ or

lomustine). Various re-treatment modalities and schemes were reported among the centres (Fig. 2). These included re-operation, re-irradiation, chemotherapy or immunotherapy, either as a monotherapy or as a multimodal treatment. For example, therapy varied by the combination of anti-neoplastic agents (bevacizumab, lomustine, temozolomide, bevacizumab/lomustine given in standard dosing), the schedule of re-irradiation (40 Gy in 1.66 fractions, 42 Gy in 2.66 fractions, 35 Gy in 3.5 fractions, 20 Gy in 2.0 fractions), re-irradiation with and without TMZ or bevacizumab and the method of re-irradiation (stereotactic radiotherapy (SRT), 3D-conformal or intensity modulated radiotherapy). Furthermore, criteria like the localisation and distribution of the tumour (local/distant recurrence; single/multiple/diffuse recurrence; operable/not-operable) were also taken into account (Table 1).

Consensus treatment strategies

Figure 3 displays a comprehensive and condensed view of the re-treatment recommendations for recurrent glioblastoma where a majority recommendation was present (5 out of 8 centres; 63 %). Seven out of 8 re-treatment criteria are implemented (time of recurrence, operability, size of the tumour, symptoms, fitness, MGMT promoter methylation and unifocality). The CRET criterion, which was only used in 2 centres (A, B), was not relevant to reach a majority treatment recommendation. Strong consensus was generally achieved in unfit patients. In all but one scenario 6 out

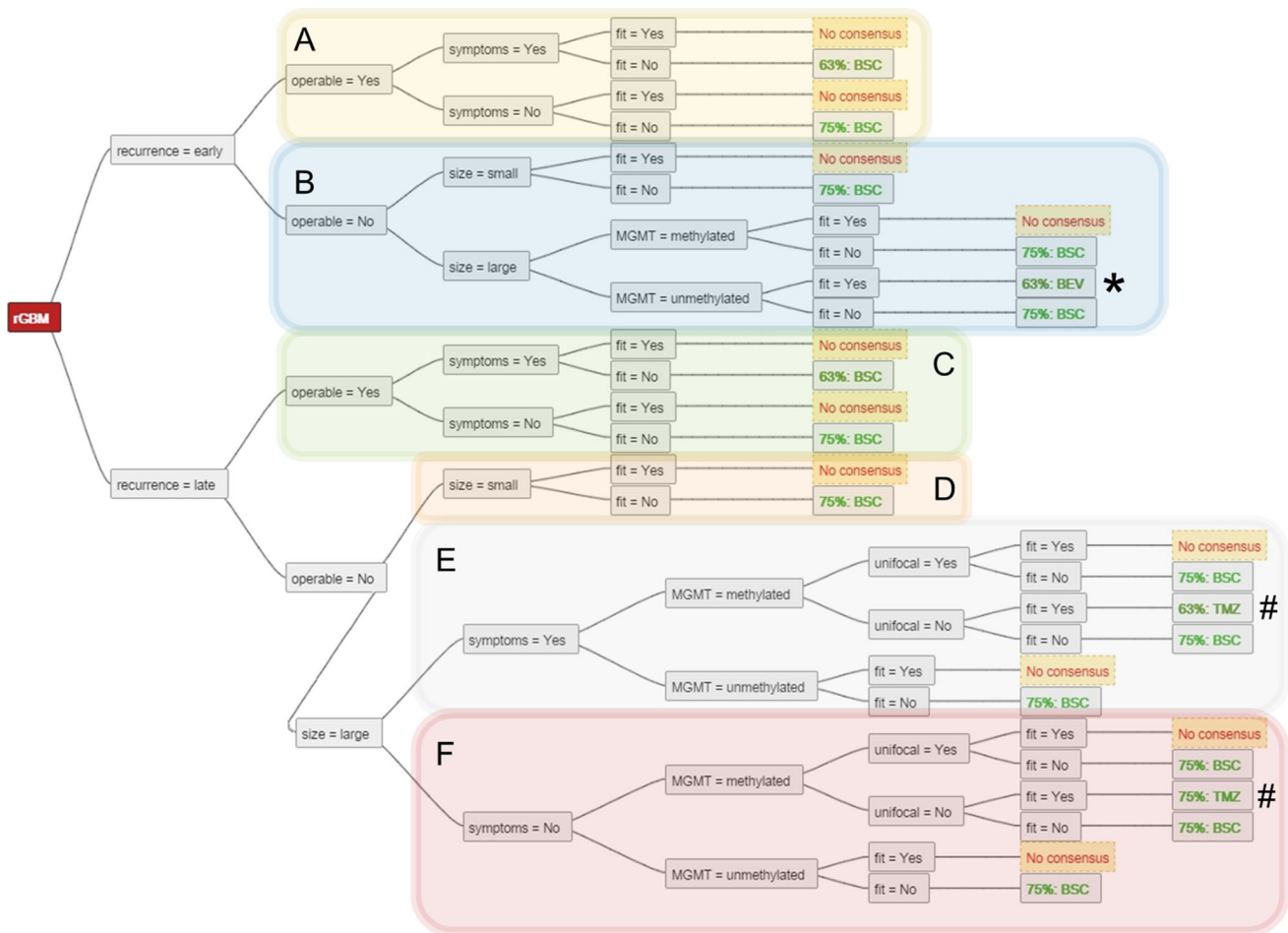


Fig. 3 The most common recommendations tree reveals areas of consensus (at least 5 out of 8 centres, >63 %) for patients who are unfit (A–F). The most common recommendation is best supportive care (BSC). Only on 3 clinical scenarios either bevacizumab (BEV,

asterisk) or temozolomide (TMZ, hash) (B,E,F) is recommended by the majority of centres depending on the presence of symptoms. Only 7 out of 8 re-treatment criteria (all but the CRET criterion, see Fig. 3) were relevant for achieving a majority recommendation

of 8 centres recommended BSC instead of an anti-tumour treatment (fit = no). In contrast, in fit patients majority consensus was rare (fit = yes). Five out of 8 centres would treat fit patients with bevacizumab when a large non-operable early recurrent glioblastoma with an unmethylated MGMT promoter is present (asterisk in Fig. 3). Additionally, TMZ would be the preferred recommendation (hash in Fig. 3) in fit patients with a late recurrent, non-unifocal, non-operable and large glioblastoma with a methylated MGMT promoter with (5 out of 8 centres, 63 %) or without clinical symptoms (6 out of 8 centres, 75 %).

Discussion

In the absence of a standard of care for recurrent glioblastoma the aim of the present study was to investigate applied treatment strategies in 8 neuro-oncology centres in Switzerland. As we anticipated great heterogeneity we

further aimed to identify clinical criteria which lead to individualized treatment decisions and to check if these criteria overlap between different centres. Our expectations in this regard were met as we identified various treatment modalities and multiple schedules as well as a plethora of various criteria for the treatment of recurrent glioblastoma. Based on these results, it is very unlikely that patients with recurrent glioblastoma obtain the same treatment recommendation twice if they seek a second opinion in Switzerland. On the one hand this is due to individualized treatments for a given patient and takes patient- and centre-specific factors into account (i.e. availability of certain treatment options). On the other hand different recommendation can cause a decision dilemma for the patient.

Original parameters could be processed and reformatted with the help of a standardized procedure (Dodes). This method enables the identification of the most common treatment recommendations for any specific parameter combination [29]. The process was feasible and produced

the most commonly agreed upon treatment recommendation derived from heterogeneous references. The data presented here might therefore serve as one basis to develop a nationwide treatment guideline. Moreover, areas of controversy or low overlap can be used to address clinically important questions for future clinical trials.

All centres used the PS to decide about the indication of a tumour specific therapy. PS was measured with the KPS and ECOG which are well known instruments of daily oncological practice [14]. Additionally, age was a relevant criterion to guide treatment in some centres. PS and age are established prognostic factors for first-line as well as for second-line treatments [14, 32–36]. Recent studies set a threshold of KPS 60 % (corresponding to ECOG 2) as a prerequisite for tumour specific treatment interventions [4, 5, 37, 38] as inferior PS is associated with increased side effects from any intervention and lowers the chance of clinical benefit [14, 36, 39]. The greatest consensus in our analysis was identified in unfit patients corresponding to a low PS. These patients would be mostly referred to BSC as the strategy of choice independent of operability, MGMT promoter methylation or time of recurrence, among other criteria (Fig. 3). Accordingly, this approach represents a robust consensus recommendation. This result is not trivial, as three out of eight centres did not actively claimed BSC as a primary re-treatment modality even after several feedback rounds (Fig. 2). However, we are confident that a low PS would lead to the implementation of BSC without additional tumour specific treatment in daily practise in all centres. This issue might reflect a limitation of the study that not all applied treatment strategies are specifically enumerated by the participants.

Despite the negative prognostic impact of mental and cognitive decline [39] none of the centres reported mental status or a formal cognitive testing (i.e. MiniMental Status Exam) as an aid to decide about treatment for recurrent glioblastoma. It is tempting to speculate that the physicians felt they integrate all dimensions of neurological function in clinical decision making and do not need these scales for whatever reason (i.e. time consuming procedure). Comorbidities and their formal investigation were also rarely taken into account (i.e. Charlson co-morbidity score) and none of the centres reported usage of a structured geriatric assessment [40–43]. Hence, the issue of fitness for re-treatment in recurrent glioblastoma mostly relies on a subjective perspective of the physician.

Various strategies of re-operation, re-irradiation, systemic therapy and multimodal treatments were reported [14]. Major level of consensus was reached for TMZ re-challenge in lesions with a methylated MGMT promoter even in the absence of a controlled trial at the time of investigation. Only recently, the DIRECTOR and the BELOB trial demonstrated the prognostic value of the

MGMT-promoter methylation for PFS-6 and PFS-9, respectively, with significantly better outcome in recurrent glioblastoma with a methylated MGMT promoter [11, 15]. However, the optimal time span between first-line and second-line TMZ at recurrence still remains elusive.

The anti-angiogenic agent bevacizumab is approved for the treatment of recurrent glioblastoma in selected countries including Switzerland. Somewhat surprisingly, only in fit, non-operable patients with a large lesion and an unmethylated MGMT promoter a majority of centres (63 %) would offer bevacizumab. No consensus was obvious in all other occasions, despite approval and its steroid-sparing properties. The reason for this low overlap might be related to the absence of a controlled clinical trial for the use of bevacizumab in recurrent glioblastoma or the recently reported failure in the first-line treatment setting [4, 38]. Moreover, conflicting results about a negative impact on neuro-cognition may also hamper widespread use of this compound [44, 45].

Re-irradiation alone or in combination with systemic treatment did not reach any consensus. In addition to the paucity of controlled clinical trials this might reflect heterogeneity of radiation dose and technique. Despite the low efficacy of re-irradiation as a monotherapy observed in a controlled phase II trial with PFS-6 rates of 3.8 % [24] a second radiation either alone or in combination with systemic therapy still remained a salvage treatment in five out of eight centres. However, this applies only in a selected patient population with good prognostic criteria. Of note, the same is true for re-operation which is mostly recommended in combination with other treatments in 7 out of 8 centres. Additionally, a controlled clinical trial demonstrating efficacy of this approach is also lacking. However, positive prognostic criteria (KPS > 80, tumour size \leq 50 ml, non-eloquent region) for the estimation of prolonged postoperative survival after re-operation have been reported [46]. In this regard it has to be mentioned that local treatment strategies are driven by the experience of the local physicians, the availability to diverse radiation techniques and the attitude of neuro-surgeons to offer glioblastoma resection at recurrence.

Conclusion

The neuro-oncologist may be equally soothed or unsettled by these results. For certain clinical scenarios, 8 centres provided 6 different treatment recommendations. This sheds an interesting light on the value and risk of obtaining a second opinion in this context. Despite experience and access to published literature, the interpretation and clinical implementation of this was very different among Swiss neuro-oncology centres.

The application of a decision tree analysis (objective consensus) was able to identify decision criteria relevant in clinical practice across centres. Future trials and guidelines should take these criteria into account to ease the transition of trial results and recommendations into clinical neuro-oncology.

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Compliance with ethical standards

Conflict of interest AFH, UR, DM, PYD, KC, EH, AP, MWG, DB disclosed no conflict of interest.

Ethical standards No specific patient data was used in this project.

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