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Research Article

Practice Patterns for Managing Recurrent Glioblastoma Multiforme

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Abstract

Introduction Glioblastoma multiforme (GBM) is a devastating form of cancer with a poor prognosis despite available treatments. Managing recurrent GBM remains challenging and lacks guidelines. This study aims to provide practice patterns for managing recurrent GBMs in India.

Methods A panel of experts was assembled to develop practice patterns using the Delphi technique. Their responses were analyzed anonymously to ensure impartiality and generate recommendations. The statements were intended to be nonbinding and focused on promoting best practices in the field, without legal or regulatory authority.

Results A total of 23 experts participated in the study, providing their opinions on various aspects of managing recurrent GBM. Consensus was achieved on individualized and multidisciplinary management as the preferred approach. Surgery in combination with other treatments was found to impact survival in patients older than 65 years, with re-surgery and adjuvant radiation and chemotherapy being the preferred options. Gadolinium-enhanced magnetic resonance imaging (MRI) brain with spectroscopy and

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diffusion-weighted imaging was favored. Molecular profiling was considered significant, with O^6-methylguanine DNA methyltransferase methylation being most relevant. Surgery was recommended for recurrent GBMs, primarily based on Karnofsky's performance score (KPS). Surgical adjuncts such as neuronavigation and intraoperative MRI were considered valuable. Radiation therapy, specifically stereotactic radiosurgery, was recommended for selected cases, while opinions on re-chemotherapy were divided. Palliative care was deemed important.

Conclusion This study presents practice patterns for managing recurrent GBM in India, providing standardized recommendations for practice. By implementing these, clinicians can make informed decisions, leading to improved patient outcomes and reduced variability in the management of recurrent GBM.

Introduction

Glioblastoma multiforme (GBM) is one of the most devastating types of cancer in humans, with a survival rate of only 12 to 18 months despite the best surgical and adjuvant treatments available.[1,2] While there have been some exciting advancements in GBM treatment, they are not substantial enough to significantly impact patient outcomes, and the best course of action remains gross total resection followed by chemotherapy and radiotherapy.[3,4] Recurrence is almost inevitable, and managing it is controversial with no agreed-upon guidelines. Despite this, some GBM patients have been reported to live for many years, and the molecular subtyping of GBMs has shed light on some of the factors that might contribute to this favorable outcome.[5,6]

Recurrent GBM is difficult to manage, and its prognosis is poor.[2] While 90% of recurrences occur within 2 to 4 cm of the primary site, midline tumors can recur more extensively.[7,8] The decision to operate on a recurrent GBM is also contentious, with studies suggesting that surgery can add a few months to median survival without significant morbidity or mortality. Factors such as younger age and higher Karnofsky performance score (KPS) are better indicators for selecting patients for re-resection, which can lead to improved quality of life and response to chemotherapy and radiotherapy.[9] A scale has also been developed to predict survival rates after re-resection of GBMs.[10]

There are Canadian recommendations for the treatment of recurrent GBMs[11]; however, they may not hold true in developing and resource-limited settings. Thus, the lack of consensus guidelines or statements for managing recurrent GBM is a significant issue, leading to inconsistencies in clinical decision-making and patient outcomes. The goal of this article was to provide a standardized framework for the clinical management of recurrent GBM in India, which can guide clinicians in making informed decisions about the best treatment options for their patients. By offering practical recommendations based on current knowledge and expert opinions, we aim to improve patient outcomes and reduce variability in clinical practice.

Methodology

An expert group was assembled, comprising individuals who met the following criteria: (1) managing neuro-oncology for more than 5 years specifically involving the treatment of more than 50 recurrent GBM cases and (2) neurosurgeon/radiation oncologist. It was a diverse group having members from both government and private setup and from different regions of India. The questions were made based on the available literature review and from expert opinions, using the Delphi technique. To ensure impartiality and avoid any bias, the responses provided by the expert group were blinded for analysis. This anonymity ensured that the experts provided their honest opinions and recommendations without fear of any potential consequences or judgment.

The statements were aimed to be nonbinding, which meant that they will not have any legal or regulatory authority and cannot be enforced as mandatory requirements for health care professionals to follow. Instead, the statements will serve as recommendations and suggestions for best practices in the relevant field.

The statements were also aimed to be nonmedicolegal, and not to be used as a legal basis for any claims or lawsuits, nor will they be admissible as evidence in any legal proceedings. Instead, they will focus solely on providing guidance for medical professionals and promoting the best possible patient care.

We performed a literature search on PubMed and Google Scholar with the keywords "Recurrent Glioblastoma," "Surgery AND Recurrent Glioblastoma," "Radiotherapy AND Recurrent Glioblastoma," "Chemotherapy AND Recurrent Glioblastoma." The following questions pertaining to establishing diagnosis, selecting the candidates for therapeutic intervention, timing of intervention, available therapeutic options, and palliative care were asked based on the available literature. These are listed in ►**Table 1**. These questions were sent to the experts for both editing and answering.

Analysis

The results were derived in percentages, with high recommendation assigned if the response was greater than

Table 1 Questions asked regarding recurrent glioblastoma multiforme

I. Management options
A. Management of recurrent glioblastoma should be:
a. Individualized and multidisciplinary
b. Generalized and neurosurgeon-only based
c. Individualized and neurosurgeon-only based
d. Generalized and multidisciplinary
B. What impacts survival in recurrent GBM in patients >65 y?
a. Re-surgery
b. Adjuvant radiation and chemotherapy
c. Immunotherapy
d. Carmustine
e. Combination of above
f. None
II. Confirmation of diagnosis
A. What is the standard imaging modality for assessing recurrent GBMs?
a. Gadolinium-enhanced MRI brain
b. Gadolinium-enhanced MRI brain + MR spectroscopy and DWI
c. Dynamic susceptibility contrast (MRI perfusion)
d. PET scan
III. Testing of molecular subtyping
A. Will the molecular profile of the recurrent tumor impact further management decisions?
a. Yes
b. No
c. Maybe
B. The relevant molecular markers influencing decision-making in recurrent GBM
a. O6-methylguanine-DNA methyltransferase (MGMT)
b. BRAF V600E mutation
c. EGFR amplification
d. IDH 1/2 mutation
e. Other .....
IV. Re-surgery
A. Should we offer surgery for recurrent GBM?
a. Yes in all
b. In a few of the selected cases
c. Never
B. If we offer surgery for recurrent GBM, then after how much survival?
a. >6 mo survival after primary surgery plus adjuvant therapy
b. 1-y survival after primary surgery plus adjuvant therapy
c. 1- to 2-y survival after primary surgery plus adjuvant therapy
d. More than 2-y survival after primary surgery plus adjuvant therapy
e. No relation with time

(*Continued*)

Table 1 (*Continued*)

C. If we offer surgery for recurrent GBM, then for what age group?
a. Up to 40 y
b. Up to 60 y
c. No relation with age
D. If offering surgery, what size is appropriate?
a. <2 cm
b. <3 cm
c. <4 cm
d. Any size
e. Not applicable
E. If offering surgery, what Karnofsky's performance score is appropriate?
a. >60
b. >70
c. >80
d. Not applicable
F. For which molecular subtyping will you offer surgery for recurrent GBMs?
a. MGMT methylation
b. Genetic loss on chromosomes 1p/19q (codeletion or loss of heterozygosity [LOH])
c. IDH mutation
d. Any of the above
e. Not applicable
G. Which tumors would you like to operate on if a surgical option is considered for recurrent GBMs?
a. Tumors at poles
b. Midline tumors
c. Both
d. Not applicable
H. What is/are the indications of reoperation in recurrent glioblastoma multiforme?
a. Relieve raised intracranial pressure
b. Obtaining tissue for new histology and molecular profiles
c. Both
I. What surgical adjuncts would you like to use at the second surgery?
a. Neuronavigation
b. Intraoperative ultrasound
c. Intraoperative MRI
d. 5-ALA
e. Fluorescein
f. Combination (please mention)
g. None
J. If surgical option is being considered for recurrent GBMs, which surgery you will like to consider?
a. Gross total resection
b. Gross total resection with Gliadel (carmustine implant)/brachytherapy wafers
c. Maximal safe resection
d. Maximal safe resection with Gliadel (carmustine implant)/brachytherapy wafers
e. Not applicable as no surgical option is required

Table 1 (*Continued*)

V. Re-radiotherapy
A. Should we re-irradiate recurrent GBMs?
a. Yes
b. No
c. In selected cases (please mention the selected cases)
B. Preferred radiation technique for recurrent GBM is:
a. Brachytherapy
b. EBRT
c. Proton therapy
d. Stereotactic radiosurgery
VI. Adjuvant re-chemotherapy
A. Should we give concurrent re-chemotherapy for recurrent GBMs?
a. Yes
b. No
c. In selected cases (please mention the selected cases)
B. Systemic agents preferred for recurrent GBM
a. Bevacizumab
b. Nitrosoureas
c. Temozolomide
d. Combination
VII. Recent advances
A. Among the recent advances, which would revolutionize the treatment of recurrent GBM?
a. Laser interstitial thermal therapy (LITT)
b. Tumor treating fields (TTF)
c. Others (please mention)
d. Not beneficial
VII. Cost-effectiveness
A. Is re-surgery cost-effective?
a. Yes
b. No
B. Is re-irradiation cost-effective?
a. Yes
b. No
C. Is re-chemotherapy cost-effective?
a. Yes
b. No
D. Are newer treatments like bevacizumab, temozolomide, LITT, TTF, etc., cost-effective?
a. Yes
b. No
c. Few are (please mention)
VIII. Palliative care
A. Is palliative care important for recurrent GBM?
a. Yes
b. No

(*Continued*)

Table 1 (*Continued*)

B. If yes, then at which place?
a. Institutional
b. Home based
c. Not applicable

Abbreviations: 5-ALA, 5-aminolevulinic acid; EGFR, epidermal growth factor receptor; DWI, diffusion-weighted imaging; GBM, glioblastoma; IDH, isocitrate dehydrogenase; MGMT, O6-methylguanine-DNA methyltransferase; MRI, magnetic resonance imaging; PET, positron emission tomography.

75%, moderate recommendation for responses between 50 and 75%, weak recommendation for responses between 25 and 50%, and no recommendation for responses less than 25%. This classification system helped provide a clear and transparent representation of the degree of consensus among the experts and the level of confidence in the recommendations.

Results

A total of 23 experts gave their opinions about the questions raised regarding the management of recurrent glioblastoma. There were 22 neurosurgeons including 4 performing radiosurgery. There was also one neurooncologist in the panel. As previously stated, the panel's minimum eligibility requirement was a background encompassing over 5 years of neuro-oncology management experience, specifically involving the treatment of more than 50 recurrent GBM cases. The experience of the panelists ranged from 7 to 35 years in the field. These experts were from different parts of India and were from both central and state institutes. The responses were are discussed in the following sections.

Individualized versus Generalized and Single versus Multidisciplinary Management

A near-complete consensus was reached regarding the individualized and multidisciplinary management of recurrent glioblastoma patients. In all, 91.3% (21/23) responses were in favor of it.

Survival Impact in More than 65 Years of Age

On asking this question, 73.9% of experts (17/23) agreed that re-surgery with a combination of radiotherapy, chemotherapy, and immunotherapy can impact survival, as shown in ►**Fig. 1A**. Of these, re-surgery with temozolomide was the preferred choice.

Standard Imaging Modality for Assessing Recurrent GBMs

There was a divided opinion about standard imaging. For this question, the panelists could select more than one option (combination of investigations). The majority (52.2%; 12/23) agreed with gadolinium-enhanced magnetic resonance imaging (MRI) of the brain + spectroscopy + diffusion-weighted imaging (DWI) to be the preferred modality. The second choice with 34.8% (8/23) was dynamic susceptibility contrast (MRI perfusion) as the modality. The third choice was gadolinium-enhanced MRI with 30.4% (7/23) advocating it. The responses can be better seen in ►**Fig. 1B**.

Molecular Profiling

The majority, 60.9% (14/23), of experts advocated that molecular profiling has a significant role to play in the management of recurrent glioblastoma (►**Fig. 1C**). However, 30.4% (7/23) were not sure. O^6-methylguanine-DNA methyltransferase (MGMT) was the most relevant molecular marker influencing the decision-making for recurrent glioblastoma, which was agreed by 82.6% (19/23) of experts (►**Fig. 1D**). The next was epidermal growth factor receptor (EGFR) amplification agreed upon by 26.1% (6/23) of experts. The majority of clinicians, 43.5% (10/23), opined that they would offer re-surgery if any of the molecular subtyping from MGMT methylation, genetic loss on chromosomes 1p/19q (codeletion or loss of heterozygosity), or isocitrate dehydrogenase (IDH) mutation is present.

Offering Surgery for Recurrent GBMs

In total, 91.3% (21/23) of experts agreed on offering surgery for recurrent GBMs. However, they could not reach a consensus on the appropriate time interval after the primary surgery. An equal percentage of 26.1% (6/23) opined on operating either after 6 months or after 1 year of the first operation. According to 60.9% (14/23) of experts, surgery should not be based on age; it should rather be on the KPS of the patient. About 56.5% (13/23) opined that a cutoff of 70 for the KPS is appropriate and 26.1% (6/23) opined a cutoff greater than 80. Regarding the size of recurrent GBMs, 69.5% (16/23) refuted the size criteria and advocated surgery for any size. In total, 78.3% (18/23) advocated surgery for polar tumors if meeting the previous criteria, while 17.4% (4/23) opined for both polar and midline tumors. Fourteen of 23 experts (60.9%) believed that re-surgery is for both relief of intracranial pressure and obtaining tissue for new histology and molecular profiles.

A combination of surgical adjuncts (neuronavigation, ultrasound, intraoperative MRI, 5-ALA/fluorescein) was deemed necessary for re-surgery by 65.2% (15/23) of experts. Maximal safe resection was the procedure of choice by 56.5% (13/23) of surgeons if they considered the option of re-surgery. The second group (39.1%, 9/23) advocated maximal safe resection with the incorporation of carmustine wafers or brachytherapy.

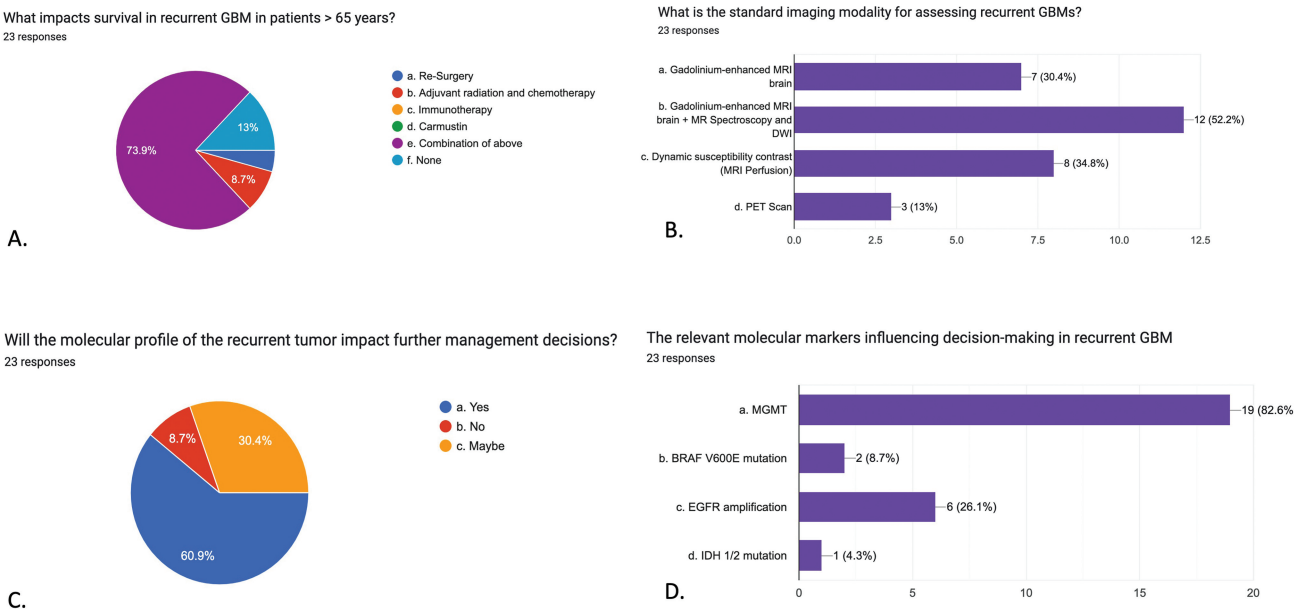

Fig. 1 (**A**) Pie chart mentioning the opinion about the therapy impacting survival in recurrent glioblastoma multiforme (GBM) in patients older than 65 years. (**B**) The standard imaging modality for assessing recurrent GBMs. (**C**) Pie chart about the molecular profiling in recurrent GBMs for management decisions. (**D**) Relevant molecular markers that influence the decision-making in recurrent GBMs.

Radiation Therapy

About 65.2% (15/23) of experts agreed to give radiation therapy to recurrent GBMs in selected cases. These cases include young patients and patients with good KPS scores. The first choice of radiation was stereotactic radiosurgery (47.8%, 11/23) and the second choice was external beam radiation therapy (34.8%, 8/23).

Chemotherapy

The opinion regarding re-chemotherapy was divided with 52.2% (12/23) in favor and 47.8% (11/23) against it. Regarding the agent of choice, 60.9% (14/23) advocated a combination of bevacizumab, nitrosoureas, and temozolomide as the preferred therapy.

Recent Advances

In total, 39.13% experts (9/23) opined that newer modalities from laser interstitial thermal therapy (LITT), tumor treating fields (TTF), etc., do not have revolutionizing potential in managing recurrent glioblastoma patients. However, 34.8% (8/23) and 21.7% (5/23) advocated TTF and LITT as possible revolutionizing agents in the future.

Cost-Effectiveness

Both redo surgery and re-radiation therapy were considered cost-effective by 87% (20/23) and 65.2% (15/23) experts, respectively. The percentage of experts opining cost-effectiveness for re-chemotherapy was low at about 56.5% (13/23). Temozolomide was regarded as cost-effective by 56.5% (13/23) of the newer agents.

Palliative Care

Palliative care was deemed important by 100% (23/23) of experts and 82.6% (19/23) advocated it as a home-based care.

Discussion

The management of recurrent GBM is a challenging and controversial aspect of GBM treatment.[12] Presently, there is a lack of Indian guidelines on the management of recurrent glioblastoma. This article aimed to provide Indian statements for the management of recurrent glioblastoma using the Delphi technique.

The results of the expert opinions indicate some areas of consensus among the experts while highlighting the areas of divergence in clinical practice. The majority of experts agreed on the individualized and multidisciplinary management of recurrent GBM patients, emphasizing the need for personalized treatment approaches and involving multiple specialties.

Regarding the impact on survival in patients older than 65 years, a significant number of experts agreed that a combination of treatments, including re-surgery and adjuvant radiation and chemotherapy, can influence survival outcomes. This highlights the importance of considering age as just one factor and evaluating the overall health and performance status of older patients when making treatment decisions. Similarly, the multimodality treatment was better than any single modality.

Imaging modalities for assessing recurrent GBMs showed some variation in expert opinions. The majority of experts favored gadolinium-enhanced MRI of the brain with additional modalities such as MR spectroscopy and DWI. However, there was also support for using dynamic susceptibility contrast (MRI perfusion) as a valuable imaging tool. These differences in opinion may reflect variations in available resources and expertise in different clinical settings.

Molecular profiling emerged as an important consideration in the management of recurrent GBM, with the majority of experts agreeing that the molecular profile of the recurrent

tumor can impact treatment decisions. The MGMT methylation status was identified as a particularly relevant molecular marker influencing decision-making in view of the response by temozolamide.[13,14] This underscores the importance of molecular subtyping in guiding treatment strategies and personalized medicine approaches.

There was a consensus among the experts on the value of offering surgery for recurrent GBMs, although the appropriate timing and selection criteria for surgery remain areas of divergence. The experts acknowledged the importance of factors such as KPS and tumor location, but there was no consensus on specific age or size for surgery. Recent reviews also highlight the same.[15] This highlights the need for individualized decision-making based on patient characteristics and tumor features. The literature presently has only opinions and case series for re-surgery,[16–18] and a randomized controlled trial is essential.

Radiation therapy and chemotherapy were subjects of debate among the experts. While a significant number of experts supported re-irradiation in selected cases, the preferred radiation technique varied, with stereotactic radiosurgery and external beam radiation therapy being the top choices. This was similar to the level III recommendations given by the Congress of Neurological Surgeons.[19] Similarly, there was divided opinion regarding re-chemotherapy, with a combination of bevacizumab, nitrosoureas, and temozolomide being favored by some experts in view of recent evidence from India.[20,21]

Recent advances in the field of recurrent GBM treatment, such as LITT and TTF, received mixed opinions from the experts. TTF interfere with cytokinesis and chromosome segregation, and has been used as add-on treatment to disrupt mitosis.[22,23] It is also approved by the U.S. Food and Drug Administration for use in recurrent glioblastoma. While some experts expressed optimism about the potential of these therapies to revolutionize treatment, others remained skeptical.

The cost-effectiveness of different treatment options was also a point of discussion. Experts generally considered re-surgery and re-radiation therapy to be cost-effective, but opinions were divided regarding the cost-effectiveness of re-chemotherapy and newer treatments such as bevacizumab and temozolomide.

All experts unanimously agreed on the importance of palliative care for recurrent GBM patients, emphasizing the need for comprehensive supportive care throughout the disease trajectory, with a strong advocation for home-based care.

Recommendations

Based on the results of the expert opinions, the following recommendations can be made for the management of recurrent glioblastoma pertaining to India:

- **Management options:**
  - *Recommendation (high):* Management of recurrent glioblastoma should be individualized and multidisciplinary (91.3% agreement).
  - *Rationale:* Individualized and multidisciplinary management allows for personalized treatment plans tailored to each patient's specific needs and takes advantage of a diverse range of investigation and treatment modalities.
- **Confirmation of diagnosis:**
  - *Recommendation (moderate):* Gadolinium-enhanced MRI of the brain + MR spectroscopy and DWI should be the standard imaging modality for assessing recurrent GBMs (52.2% agreement).
  - *Rationale:* This imaging modality provides a comprehensive evaluation of the tumor, combining anatomical information with functional and metabolic data, which can aid in accurate diagnosis and treatment planning.
- **Testing of molecular subtyping:**
  - *Recommendation (moderate):* The molecular profile of the recurrent tumor should be considered in further management decisions (60.9% agreement). MGMT was the most reliable marker (high recommendation: 82.6%).
  - *Rationale:* Molecular subtyping can provide valuable information about the tumor's characteristics and potential response to specific treatments, enabling more personalized and targeted therapy.
- **Re-surgery:**
  - *Recommendation (high):* Surgery should be offered for recurrent GBM in selected cases (91.3% agreement). It should be for a KPS score of at least 70 and for polar tumors.
  - *Rationale:* Reoperation can provide several benefits, including the relief of raised intracranial pressure and obtaining tissue for new histology and molecular profiles, which can guide subsequent treatment decisions. This, however, should be aimed for patients with good KPS.
- **Radiation therapy:**
  - *Recommendation (moderate):* Re-irradiation should be considered for recurrent GBMs in selected cases, such as young patients and those with a good KPS (65.2% agreement).
  - *Rationale:* Re-irradiation can help control tumor growth and improve patient outcomes in carefully selected cases, taking into account the individual's overall health and treatment response.
- **Chemotherapy:**
  - *Recommendation (moderate):* Re-chemotherapy with a combination of bevacizumab, nitrosoureas, and temozolomide should be considered for recurrent GBMs (60.9% agreement).
  - *Rationale:* Combination chemotherapy regimens have shown promise in the management of recurrent GBMs and can potentially improve patient outcomes by targeting different pathways involved in tumor growth and progression.

- **Palliative care:**
  - *Recommendation (high):* Palliative care should be an important component of the management of recurrent GBMs (100% agreement). It can be home-based (high recommendation—82.6%)
  - *Rationale:* Palliative care focuses on improving the quality of life for patients with advanced cancer, providing symptom management, psychosocial support, and assistance with end-of-life decision-making. Home-based palliative care allows for decreased expenditure and continuation of volitional work by relatives.

Limitations

The study has some limitations. It could have been improved with incorporation of the role of radiation in early recurrences, and evaluation of temozolomide in recurrent lesions where differentiation with necrosis is difficult. Similarly, additional things like new lesions at other sites with primary under control, and wound issues following surgery postradiotherapy could also be evaluated. Literature on these aspects is limited, and these definitely warrant trials. There are financial implications also with the redo surgery, radiotherapy, and chemotherapy, which could influence the decision-making, especially with surgeons in a smaller private setup.

Conclusion

The management of recurrent glioblastoma requires an individualized and multidisciplinary approach. Key recommendations include the use of gadolinium-enhanced MRI of the brain with MR spectroscopy and DWI for accurate diagnosis, consideration of molecular subtyping for treatment decisions, offering re-surgery to obtain tissue for analysis and relieve intracranial pressure in good KPS, and considering re-irradiation and combination chemotherapy in selected cases. Palliative care should also be an integral part of managing recurrent GBMs to improve patients' quality of life. These recommendations provide guidance for health care professionals while considering the consensus reached by experts, but individual patient factors and clinical judgment should also be considered.

Conflict of Interest
None declared.

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