

A guideline on guidelines: neuro-oncology guideline standards for low- and middle-income countries

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Abstract

Guidelines for low- and middle-income countries (LMICs) are needed in complex, multidisciplinary areas such as oncology, requiring mobilising considerable resources and specialists for coordinated care. Neuro-oncology guidelines have been primarily established in countries where technological advancements and robust care pathways facilitate broad resource utilisation. In contrast, LMICs require complex and region-specific interventions to provide equitable care. The present opinion paper is a culmination of our own centre's experience collaborating and developing loco-regional guidelines for brain tumour care, keeping in mind LMIC experiences and expertise available. We intend for the process and methodology to apply to a broader audience of other LMIC authors and clinicians collaborating with LMIC institutions to develop guidelines and clinical recommendations.

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Introduction

Standardising oncological care has helped to improve patient care and survival.¹ Guidelines are an essential instrument for ensuring uniform care. The Guidelines International Network database, a global network cataloging clinical guidelines from major institutions and working groups, lists over 3,700 guidelines from 39 countries.² A majority of these are developed at research institutions within HICs.³ Owolabi et al. reported in a systematic review of guidelines on hypertension that only one manuscript was from a low-income country.⁴ When trying to apply clinical standards to neuro-oncology in

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low- and middle-income countries (LMIC) we have observed a lack of local data in major guidelines, absence of collaborations and conformation to best clinical practices amongst local clinicians and researchers, and the lack of consideration of applicability of recommendations.⁵ In neuro-oncology, most guidelines are developed within the global North, with a focus on molecular classification of CNS tumours and updated treatment options, as evidenced by recent updates in the 2021 WHO Classification of Primary Brain Tumours.⁶ Molecular panels can be cost-prohibitive particularly when considering assays and genetic sequencing. To truly reach a cohesive aim for global oncology, we must give more value to the transferability of these recommendations in more resource-limited setting. The 2009 Appraisal of Guidelines for Research & Evaluation (AGREE II) in particular emphasized the value of applicability to guideline development.⁷

The difficulty in implementing guidelines developed in HICs within LMICs has been demonstrated before; stark differences in the availability of resources and specialized skills and a lack of understanding of local contexts and practices can hinder guidelines-based healthcare.⁸ The WHO has highlighted this issue by forming Complex Interventions Working Groups; context-dependent solutions can account for circumstances and variations from region to region.⁹ Reporting standards and templates for systematic reviews and guidelines may be the solution to developing complex, perspectives-based guidelines.¹⁰

Developing this context requires understanding ground-level realities and quantifying system-level deficiencies. Collecting epidemiological data to define the problem and developing locally derived solutions is possible through multi-center collaborations. Local solutions can be a source of frugal innovations to deliver quality care.⁵ Specifically, we need to address the heterogeneity of healthcare systems in LMICs, as they constantly evolve and change with rapid shifts in the availability of resources. Robust infrastructure is not readily available across the country, and supply shortages of medicines

and equipment are too common. Recently, we developed consensus guidelines for management of medulloblastoma, craniopharyngioma, and various other brain tumours in Pakistan (REFERENCES from articles 10-23 of this supplement)¹¹⁻²⁴ In this article, we draw upon our experiences and propose solutions for developing equitable guidelines.

Recommendations development

Evidence suggests higher compliance with guidelines when subject specialists and local clinicians were involved in guideline creation.²⁵ The Delphi technique is an effective way to engage significant numbers of local stakeholders and experts through a series of questionnaires distributed to subject experts in order to achieve consensus. It has been used to develop guidelines on surgical-site infections, prescription of lower-limb prostheses, and rotator cuff pathology, to name a few.²⁶⁻²⁸ Neuro-oncology guideline developers can

take direction from such examples. The involvement of subject experts and the formation of working groups to tackle LMIC-based issues within neuro-oncology effectively is a thoughtful approach –evidence-based discussions generate credibility and acceptance within the local academic community. Priority should be given to experts from varying resource settings that may shed light on healthcare inequalities previously unreported. Whether brain tumour patients are being treated at peripheral rural-care centres or densely-populated urban cities, we intend to develop locally applicable guidelines to provide recommendations that can be followed within the available resources.

Effective guidelines require establishing evidence-based standards of care with resource-stratification and applicability. Recommending technologies that require significant investment and infrastructure may undermine basic surgical and oncological care capacity. Resource

Table-1: Developing guidelines in LMICs.

Assembling a Team

The formation of a multidisciplinary guidelines committee involves:

1. Senior subject-experts with considerable experience in LMICs
2. Junior researchers with expertise in conducting literature review and scientific manuscript writing

It is particularly necessary to include clinicians and researchers from various hospitals, with a spectrum of centres ranging from academic, high volume centres in major cities as well as practitioners in the peripheries. This will promote guidelines ownership and adoption.

Under the guidance of senior members, guidelines working groups can be formed with direction given to junior members in carrying out literature searches for clinical evidence and current recommendations. These can be further refined through the experience and input by subject-experts.

The Process

It is advisable to first hold general meetings with all members of a guidelines committee to reach a consensus on the aims and direction of the proposed guidelines. The committee must define the role of each member in development of guidelines and specific deadlines. It can also be advisable to break into sub-groups with consideration to every associated specialty, with the intention of reconvening.

Particularly for LMIC guidelines, it is imperative to define the following:

1. Contentious points in clinical management that require addressing
2. Gaps in management that are observed in LMICs (e.g. through meetings and research, we have collected anecdotal evidence of a lack of standardised surgical guidelines in operating on prolactinomas)
3. A focus on cost-effectiveness, applicability and ensuring equitable access to standardised care in recommendations

Committees must identify the current standard of care in LMICs and address issues in care with concise and precise recommendations. Further debate and discussion can occur within the committee, resulting in formation of multiple draft papers, reviews by senior members, and ratification by the committee as a whole.

It is essential that points of contention and criticism be met with evidence-guided debate with consideration for all stakeholders.

Post-production

Committees should consider dissemination of their papers locally to increase local access to guidelines and elevate national standards of research. This can be done through national scientific associations and conferences. Endorsements from local hospitals and educational institutions can be vital.

The template for the guidelines paper can be modified and adjusted for use in other, future guidelines publications.

Table-2: Summary of Recommendations**Recommendations**

Developing equitable partnerships with clinicians and researchers in LMICs.
 Considerations for cost-effectiveness and transferability of established solutions in more developed countries.
 Context-based solutions can be more effective and are more acceptable.
 Guideline committees in LMICs should include stakeholders from all disciplines involved in neuro-oncological care.
 Ratification processes, such as the Delphi method or those similar to the NCCN Harmonized Guidelines, can be used for group consensus
 Resource-stratification of recommendations.

stratification of recommendations is a viable solution; 'minimal required' and 'preferred but optional' classifications, similar to the American Society of Clinical Oncology (ASCO) Resource-Stratified Guidelines.²⁹ The aim was to mobilise the resources and expertise available through members of HICs and the international world at large in order to guide cancer prevention and care guidelines across the world. Varying levels of resources in LMICs were addressed through a four-tier resource-stratification system and ensured evidence-based guidelines development through a systematic review and the modified ADAPTE process. Colour-coded frameworks have also been put forward by the NCCN Harmonized Guidelines,³⁰ with recommendations in black denoting generally agreed-upon minimum acceptable standards, grey for optimal but understandably advanced-care recommendations that can be followed but should not be a limiting factor in providing care, and blue for regionally appropriate options of care.

As a result of our own experiences in creating national neuro-oncology guidelines, we propose an approach for developing guidelines in LMICs (Table 1). Guidelines start with a systematic review of the literature and appraisal of current guidelines published within HICs. This undergoes rigorous review and validation of the current recommendations through established instruments, such as the AGREE II tool and ASCO Guideline Endorsement Content Review Form.^{31,32} Guideline committee members should particularly pay attention to the rigor of methodology of previously written guidelines as given in AGREE II; this is a critical factor in determining the quality of evidence produced.

The pooled review and analysis can be modified and updated according to expertise provided by senior guidelines committee members and then be taken to a consensus panel discussion. The committee can undergo various procedures, such as the Delphi technique, process, discuss, and take consensus votes on individual

recommendations and edits. Generally speaking, most ($\geq 75\%$) of the voting members of the panel should strongly agree, or agree, for ratification of each recommendation. These processes can take place through virtual conferences, allowing adequate time and consideration to all members regardless of their location or ability to travel. An excellent example is the development of the NCCN Harmonized Guidelines™ for Sub-Saharan Africa which allowed local community health leaders to vote via device applications on the importance of certain services over others.³⁰ Meetings were conducted twice yearly and allowed guidelines working groups to include multidisciplinary experts for clarification and expertise in discussions. Over three days, these working groups were able to agree on recommendations and harmonise these guidelines.

Once the guidelines have been agreed upon, manuscript preparation will take place. We recommended that a standardised syntax be used throughout the draft paper for clarity, readability, and understanding of what is being said. Resources such as the Guide Lines Into Decision Support (GLIDES) methodology³³ have shown great promise in this regard. After this, dissemination becomes the end goal which can be achieved with the help of international collaborators, for critical appraisal and visibility. Knowledge of ground-level circumstances will play a crucial role in helping global researchers improve research and guidelines while ensuring LMIC perspectives have a central role in the proposal of solutions. HIC international programmes can help early-career LMIC neuro-oncologists investigate and validate these guidelines.

Implementation in neuro-oncology

Based on these infrastructural and financial limitations and unique cultural practices in LMICs, we believe guidelines that are constructed accordingly would be more practical and suitable to our setting. Consider these examples of proposing resource-stratified guidelines in neuro-oncology:

Follow-up compliance

A large part of neuro-oncology care delivery is adequate follow-up and treating recurrent disease. In our clinical settings, we see many patients who fail to follow up and receive adjuvant chemoradiotherapy after tumour resection and will once again present to the emergency department, typically with a more malignant and aggressive tumour. The Pakistan Brain Tumour Consortium (PBTC) conducted a country-wide epidemiological survey of major neurosurgical centers in 2019; we found that most patients who underwent

surgical resection for a brain tumour had no record of receiving adjuvant chemotherapy or radiation therapy³⁴. This is astonishing as gliomas, especially high-grade gliomas, tend to be seen frequently at our centres. The loss of patients to follow-up is a critical reason why morbidity and mortality of brain tumours have become a growing problem in LMICs. Our recommendations are:

- i. Inclusion of minimum follow-up timelines, with extended and shorter dates for follow-ups, when considering patients at higher risk for complications and the need for timely intervention
- ii. Reducing follow-up imaging and testing to a minimum would guide clinical decision-making without becoming a financial barrier for the patient
- iii. Development of low-cost interventions to continue patient follow-ups

A multidisciplinary approach to neuro-oncological patients

A patient with symptoms suggestive of a brain tumour needs a battery of specialists to help accurately diagnose, treat, and further follow up on the later-stage complications and difficulties the patient faces. It is standard within HICs for a patient's case to be discussed at

a multidisciplinary neuro-oncology tumour board.³⁵ Often, the neuro-oncologist or neurosurgeon presents relevant imaging, histopathology, and clinical findings to an audience from various fields. Moreover, this is incredibly fruitful; according to the imaging available, an expert neuro-radiologist can guide the surgical team in opting for a less invasive biopsy approach if maximal safe resection is not indicated. Guidelines on every specialty are considered in treating the disease holistically.³⁶ Tumour boards in LMICs are sparse and scattered discussing Pakistan, for instance, standardised tumour boards with stakeholders from all specialties are present in a few academic institutions, often located in private sector hospitals.³⁷ Figure 1 proposes the steps institutions can take to form multidisciplinary tumour boards and include all concerned specialties.

Diagnostic imaging

Our recommendation for the ideal approach to initial imaging needed to diagnose most brain tumours is MRI imaging with complete protocols, i.e., T1, T2, T1-post contrast, DWI, SWI, and other imaging protocols dependent on the type of tumour diagnosed on scans and preoperative requirements (e.g., Diffusor-tensor imaging). If facilities to attain complete protocols are unavailable, we recommend that patients have an MRI

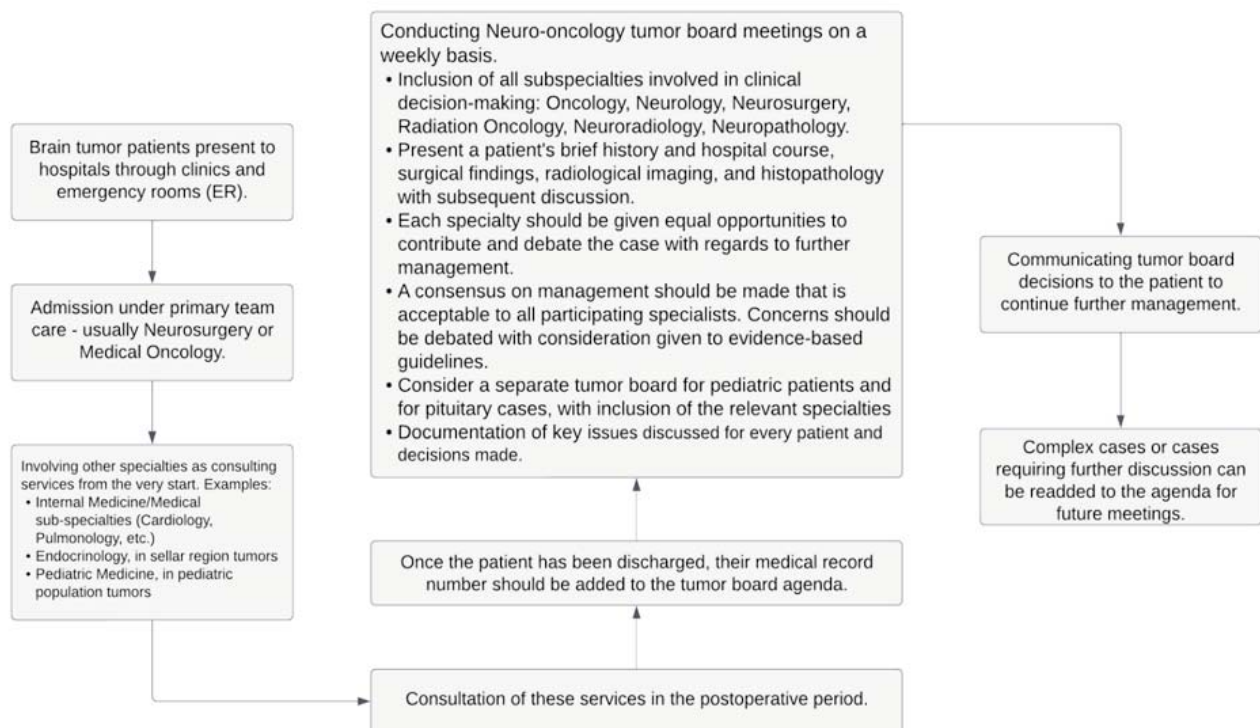


Figure1: Formation of Multidisciplinary Tumour Boards.

scan with a minimum of T1, T2, and T1-post contrast images. CT scans can also be used to supplement findings.

Complex cases in surgical neuro-oncology

Surgery for brain tumours is another infrastructure-dependent factor. Within LMICs, few specialist neurosurgeons have certifications in neuro-oncology or paediatric neurosurgery (in the case of paediatric brain tumour patients). As a result, most cases are handled by general neurosurgeons, some with clinical interests in brain tumour surgery. However, in complex cases especially, management can be variable with a greater propensity for mismanagement or a lack of infrastructure resulting in poor clinical outcomes. The solution would be to develop recommendations that encourage and necessitate the collaboration of low-volume centres with higher-volume academic centres.

Moreover, we can encourage standardised surgical protocols that can be applied in resource-deficient settings. Overburdened urban centres, where long waiting lists, lack of resources, and structural loopholes can result in issues managing brain tumour patients. Our solution would be for guidelines to incorporate minimum required recommendations with standardisation of protocols to ensure patients are treated with standardized surgical practices and followed up timely.

Considering resource constraints, it is more appropriate to consider the available facilities and recommend them accordingly. However, if possible, a more exhaustive battery of radiological investigations can be ordered if a patient can afford these facilities and they are readily available. Nevertheless, in setting up minimum standards for applying these guidelines, we do not alienate hospitals and healthcare centers in most regions. It is crucial to remember that while advanced neurosurgical and oncological protocols may prove to be applicable and better for patients in HICs, it is ultimately a question of transferability. Will the provision of advanced technologies and the pursuit of treatments that are costly and not transferable to the larger region benefit the public health crisis of morbidity secondary to brain tumours? Perhaps LMICs will benefit from targeted and precise practices addressing the most pressing concerns in neuro-oncology.

Conclusion

Preferring quality, evidence, and context-based guidelines over many guidelines that miss the target is our priority within neuro-oncology research in LMICs. By expanding our horizons, we can attempt to identify and meet gaps in neuro-oncological management,

particularly where standardised management and approaches are sorely needed. Standardising, optimizing, and utilising clinical recommendations within these settings may prove fruitful in reducing disease burden and improving patient outcomes (Table 2).

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