NARRATIVE REVIEW

Global neuro-oncology: what lies ahead for low- and middle-income countries?

Syed Ather Enam[1], Kee B. Park[2], Naureen Mushtaq[3], Muhammad Faraz Raghib[4], Fatima Mustansir[5], Mashal Murad Shah[6], Mohammad Hamza Bajwa[7], Minhal Faisal[8], Michael C. Dewan[9], Tariq Khan[10], Jack P. Rock[11]

Abstract

Over the past few decades, the global healthcare community has achieved remarkable success in controlling many communicable diseases across various regions. However, non-communicable diseases now constitute a significant portion of disease morbidity and mortality, particularly in low- and middle-income countries (LMICs). Among these, cancer, in particular, is witnessing a notable increase in incidence in many LMICs. Among cancers, neurological tumours bear significant impact in terms of long-term disability, escalating costs of comprehensive multidisciplinary care, and often encounter resource-related and systemic delays in care leading to worse outcomes. This opinion paper discusses key concepts in developing global neuro-oncology care, with specific case examples from Pakistan to illustrate methods for improving care in these underserved regions. Additionally, it outlines strategic approaches and potential solutions to address these challenges, aiming to provide a roadmap for enhancing neuro-oncology care in LMICs.

Keywords: Ursidae, Incidence, Noncommunicable Diseases, Communicable Diseases,Health Care, Neoplasms, neurosurgery

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Introduction

Neurosurgery in the context of global surgery has previously taken a backseat to more pressing concerns for general surgical, obstetric, anaesthesia, and orthopaedic capacity; possibly due to a perceived higher cost, complexity, and expertise required for neurosurgical capacity and public health buy-in. Low- and middle-income countries (LMICs) are acutely affected by the shortage in neurosurgeons and access to care; recent data from LMICs shows that general surgeon density (0.13-1.57 per 100,000 population), obstetrician density (0.042-12.5 per 100,000) and anaesthesiologist density (0-4.9 per 100,000) outmatches neurosurgeon density in Pakistan (0.139 per 100,000 people).[1] Dewan et al. estimate an unmet deficit in neurosurgical care of more than 5 million neurosurgical operations globally, requiring an additional 23,000 neurosurgeons in LMICs.[2] Overall, surgery, and in particular neurosurgery, is viewed as expensive, complex, and difficult to maintain quality control in South Asia leading to a large, unmet burden.

It is estimated that by 2030, there will be a cumulative GDP loss of USD 7 trillion incurred by neglecting care for individuals affected by cancer, who could otherwise undergo surgical treatment.[3] Almost half of new cancer cases reported in the world in 2018 were from Asia.[4] While disability adjusted life years (DALYs) decreased in high- and upper-middle income countries (HICs and UMICs), they increased over time in low income regions.[3] Further compounding the situation is extremely low GDP and GNI per capita for LMICs. For Pakistan, the estimated GDP per capita figure for the year 2023 is USD 1,471.[5]

Central nervous system (CNS) (i.e., brain and spinal) tumours are among the top ten conditions that constitute the foundation of essential neurosurgical care.[2] While CNS tumours represent a subset of neurosurgical disease burden in the already niche field of global neurosurgery, we aim to make a case for global neuro-oncology that is, the area for study, research, practice, and advocacy that places priority on improving health outcomes and achieving health equity for all people worldwide who are affected by CNS tumours.

CNS tumours significantly impact global morbidity and mortality. The Global Burden of Disease study estimated 330,000 new cases and 227,000 deaths in 2016, with a 17.3% increase in incidence from 1990 to 2016, notably in South Asia.[6] Stark disparities exist between high-income

[1,7]Department of Neurosurgery, The Aga Khan University, Karachi, Pakistan. [2]Department of Global Health and Social Medicine, Harvard Medical School, Boston, USA. [3]Department of Paediatric Oncology, The Aga Khan University, Karachi, Pakistan. [4]Wayne State University, Michigan, USA.5Department of Surgery, Washington University School of Medicine, Missouri, USA. [6]Department of Surgery, The Aga Khan University, Karachi, Pakistan.[8]The Aga Khan Medical College and University, Karachi, Pakistan. [9]Department of Neurosurgery, Vanderbilt University Medical Centre, Nashville, USA. [10]Department of Neurosurgery Northwest General Hospital and Research Centre, Peshawar, Pakistan.[11]Department of Neurological Surgery, Henry Ford Hospital, Detroit, Michigan, USA.

Correspondence: Syed Ather Enam **Email:** ather.enam@aku.edu

countries (HICs) and low- and middle-income countries (LMICs) in management quality and access. For instance, a UK survey of 136 patients highlighted surgery as the primary treatment, but identified gaps in post-discharge support and research involvement.[7] Contrastingly, in Sudan, only 8 out of 62 paediatric patients underwent complete tumour resection, with a 11% treatment abandonment rate and low 2-year (33%) and 5-year (13%) survival rates, attributed to late-stage diagnosis, lack of multidisciplinary care, and limited neurosurgical access.[8] Similarly, Pakistan demonstrates disparities in surgical access, gender biases, and referral challenges for postoperative adjuvant treatment.[9-12]

Management of CNS tumours

CNS tumour management, though advanced, remains a challenge, especially in LMICs where many technologies are inaccessible. MRI is the primary modality for brain tumour evaluation, with surgical resection being the main treatment, particularly for high-grade gliomas where resection extent influences survival outcomes.[13] Standard care for glioblastoma multiforme (GBM) includes post-resection chemo-radiotherapy with temozolomide.

MRI, craniotomy, chemotherapy, and radiotherapy form the baseline standard in CNS tumour management. Additional tools like magnetic resonance spectroscopy (MRS) help identify high-grade tumours, but are not routinely used. Advanced MRI techniques, intraoperative neuro-navigation, and fluorescence technologies enhance surgical precision, while intraoperative ultrasounds offer a cost-effective imaging alternative. Intraoperative neuromonitoring and neuro-endoscopes, along with newer tools like cavitating ultrasonic aspirators (CUSA), further expand neurosurgical capabilities.[14]

For recurrent GBM, options include nitrosoureas and bevacizumab, with implantable carmustine wafers emerging as a promising alternative.[15] Stereotactic surgery and whole brain radiation therapy are standard for brain metastases management.

The feasibility of advanced neurosurgical tools in LMICs is questionable due to fundamental equipment shortages. For example, neurosurgeons at Alexandria University Hospital in Egypt frequently depend on limited MRI studies and improvise with basic tools under resource constraints.[16] In Pakistan, neuron navigation and ultrasonic aspirators are rare, and although one hospital offers fluorescent microscopy with 5-ALA, its high cost prohibits its use, significantly adding to the total bill. Meanwhile, awake craniotomy is increasingly considered in LMICs for its potential to enhance outcomes affordably.[17-20]

Pakistan brain tumour epidemiological study

Epidemiological studies reveal significant differences in the incidence of brain tumours between HICs and LMICs, variations that can be attributed to disparities in diagnosis, pathology reporting, treatment modalities, and overall healthcare availability. For example, in Pakistan, hospital records often lack postoperative treatment details, and CNS tumours tend to present earlier in life compared to typical adult-onset patterns. Figure 1 shows

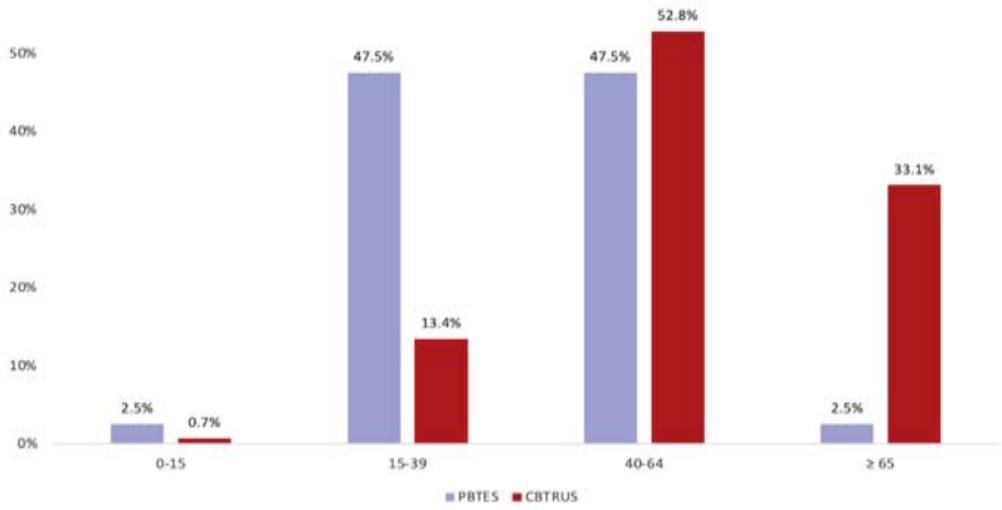

Figure-1: Incidence of brain tumours among different age groups between Pakistan Brain Tumour Epidemiology Study (blue) and Central Brain Tumour Registry of the United States (red).

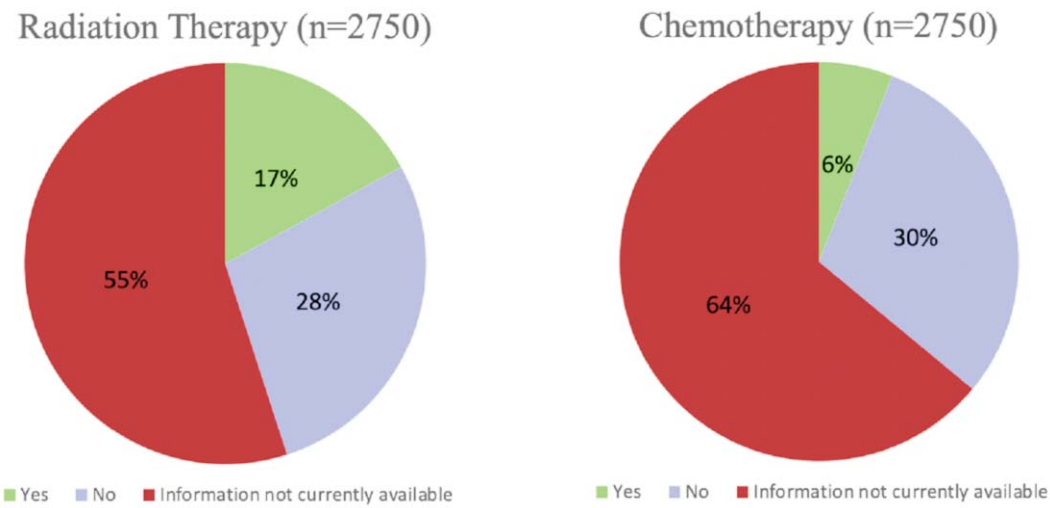

Figure-2: Distribution of postoperative treatment among Central Nervous System tumour patients in a study in Pakistan. Green: treatment received, blue: treatment not received, green: no data available.

the difference in distribution of patients according to age group between Pakistan brain tumour epidemiology study (PBTES) and central brain tumour registry of the United States (CBTRUS).

The accessibility gap for immediate neurosurgery emergency care is exacerbated by the unequal distribution of neurosurgeons and facilities, which are concentrated in urban regions. Additionally, demographic and surgical data on CNS tumours in LMICs remain sparse. Figure 2 illustrates that, in Pakistan, 55–64% of patients lack information on postoperative radiation or chemotherapy. Moreover, the gender gap in brain tumour cases highlights the urgent need to implement targetted awareness initiatives for women, particularly in rural settings.

Financing CNS tumour care

Brain tumour management is notably expensive worldwide. In the United States, it has the highest initial per-patient cost among cancers, averaging nearly $150,000, and leads in last-year-of-life costs, ranging from $135,000 to $210,000 per patient.[21] While precise cost data for Pakistan is lacking and varies between public and private sectors, understanding and prioritizing these costs is crucial.[22] In Pakistan, over 50 hospitals offer chemotherapy, but high import costs for drugs pose financial challenges. Tebha et al. suggest policy reforms for LMICs managing GBM, including cost regulation for chemotherapy and radiation therapy, integrating neuro-oncological care into universal health coverage, and increasing health expenditure.[23]

Barriers in neuro-oncology affordability

Brain tumour treatment in LMICs imposes heavy financial burdens on patients, as they often bear most treatment costs due to insufficient financial risk protection mechanisms. This financial toxicity, characterised by high out-of-pocket expenses, limited household financial capacity, and a lack of insurance or prepayment systems, drives about 100 million people into poverty annually. A 2019 study revealed that 48% of brain tumour patients in Pakistan were from lower socioeconomic backgrounds, with 37% from the middle class.[9] The significant patient costs at both private and public tertiary care hospitals in

Table-1: The table highlights the disparity in costs for surgical resection, Intensive Care Unit stay, 3- Dimensional Radiotherapy (30 cycles), and Temozolomide (for 6 months) between private and public hospitals in Pakistan.

	Private Tertiary Care Hospital Costs (USD 2023)	Public Tertiary Care Hospital Costs (USD 2023)
Surgical Resection	4449	390
ICU Stay	683.32	156
3- Dimensional Radiotherapy (30 cycles)	2413	234
Temozolomide (with radiation and for 6 subsequent months)	4645	

USD 1.00 = PKR 280 (2023)

Pakistan are detailed in Table 1 from Abdullah et al.[24]

Additionally, regular follow-up imaging, essential for monitoring disease progression, further escalates expenses. A study on follow-up attrition found that within one year, 5.67% of patients were lost to follow-up (LTFU) post-diagnosis, 37.5% post-primary surgery, and 31.7% without receiving any adjuvant treatment.[25]

Accessibility

In Pakistan and similar LMICs, barriers to surgical care for brain tumour patients extend beyond cost to include geographical accessibility (Fig.1). Approximately 40% of Pakistan's population lacks access to neurosurgical services within a 2-hour radius. Access diminishes further for advanced micro neurosurgery, with only 28.2% of South Asia's population having access compared to 52.8% for basic services.[26] A 2022 survey reports only 0.14 neurosurgeons per 100,000 people in Pakistan, predominantly in Punjab and Sindh, compelling patients from regions like Khyber Pakhtunkhwa and Baluchistan to travel significant distances for care.[10,27] Moreover, 75% of neurosurgical centres are in urban areas, disadvantaging rural residents. Figure 3 illustrates these travel distances, with only 41% having surgery access within 50 km, and over 15% traveling more than 500 km.

The shortage of specialized professionals like neuro-oncologists and radiation oncologists exacerbates the situation. While private hospitals offer better facilities and expertise, their high costs limit accessibility for most. Conversely, public hospitals, burdened by patient volume, suffer from long waiting times.[28] Only four hospitals in Pakistan are accredited by the Joint Commission International (JCI), reflecting a scarcity of internationally recognized healthcare standards.[29] Additionally, while CT scan availability is high at 97% of centres, MRI and angiography suites are present in only 72% and 49% of centres, respectively.[27] This lack of advanced technology underscores the challenges in CNS tumour care in LMICs.

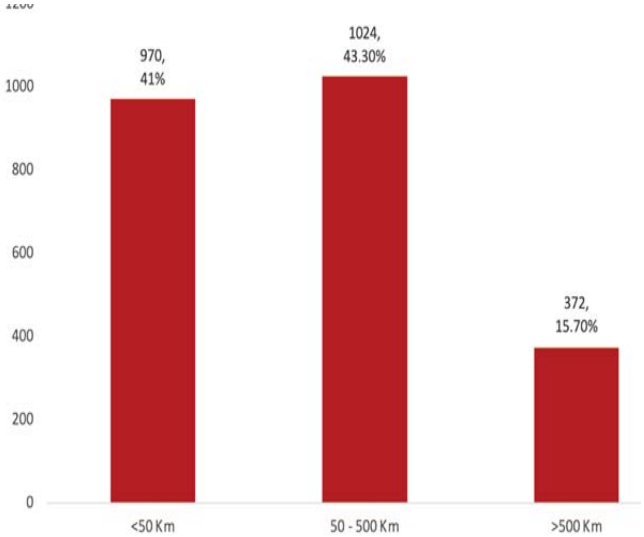

Figure-3: The bars show the number (and percentage) of the patients who had to travel <50 Km, 50-500 Km, and >500 Km respectively.

The way forward

The increasing recognition of equitable surgical care over the past decade has encouraged healthcare professionals (HCPs) to address disparities in specialized fields like neurosurgery. In Pakistan, while comprehensive CNS tumour management is limited to a few hospitals, broader access to neuro-oncological care is achievable through strategic implementations. Insights from the 2019 epidemiological survey have laid the foundation for understanding the national landscape of brain tumour care and disease burden. The next steps include establishing prospective data registries, developing cost-estimation models, and assessing the healthcare economy's infrastructure needs. We advocate for strategies that optimize and redirect existing resources within the country in a manner that aligns with our socioeconomic context, ensuring cost-effectiveness and accessibility.

Tele-medicine

Telemedicine, using information and communication technologies for healthcare service delivery, is vital in settings where distance is a barrier (WHO). While it has been established in developed countries, its adoption in developing nations has been slower.[30] However, the COVID-19 pandemic's disruption of in-person services accelerated its use in LMICs, including Pakistan. In 2020, a tertiary care hospital in Pakistan launched a tele-ICU service to offer free professional advice nationwide for COVID-19 management.[31]

In Turkey, telemedicine proved successful for breast cancer patient consultations at a tertiary care hospital, with physicians finding that one-third of these patients required no further intervention.[32] Neurosurgery outpatient visits via telehealth have also been well-received by patients and providers,[33] and Daggubati et al. have even proposed a model for outpatient neuro-oncological care.[34] Adapting this model could enhance the efficiency of consultations for CNS tumour patients in LMICs. This approach is particularly beneficial for those needing follow-up care post-surgery, potentially reducing the issue of follow-up patient attrition.

Artificial intelligence

Artificial intelligence (AI) and machine learning are poised to significantly impact brain tumour diagnosis and survival prediction. Currently, CNS tumour diagnosis and prognosis typically rely on surgical resection followed by histopathological analysis. However, neuro-oncology radiomics, powered by AI algorithms, offers a promising alternative. This field focusses on detecting complex patterns in advanced MRI scans, facilitating diagnosis, prognosis, and treatment planning. With AI, a 'virtual biopsy' becomes possible by quantitatively analysing a tumour's radiographic characteristics, thus potentially eliminating the need for certain surgical diagnoses. This approach involves aggregating diverse data sets, including radiographic, clinical, pathologic, and physiologic patient data. By reducing reliance on surgical procedures for diagnosis, this method can save both time and costs, nudging neuro-oncology towards precision medicine.

Training of personnel

To address the shortage of HCPs skilled in CNS tumour management, a dual strategy is necessary. First, training neurosurgeons in cost-effective approaches is crucial, emphasizing functional neuroanatomy and minimizing reliance on expensive technologies like neuron navigation and tractography. Instead, we propose focusing on the widespread use of essential tools like microscopes and instruments for basic craniotomy. Additionally, techniques like simple deep white matter stimulation during awake craniotomies can be a cost-effective substitute for tractography and fMRI.

Concurrently, it's vital to promote further specialization among HCPs, including neurosurgeons, neuro-oncologists, neuropathologists, and radiation oncologists. This can be achieved through establishing residency and fellowship programmes across Pakistan. While this ambitious initiative demands more resources than basic neurosurgical training, it is essential for the progress and sustainability of neuro-oncology in the country. Through such programmes, we aim to cultivate HCPs who will become national leaders in neuro-oncology.

Local cancer registries consortium

The incidence of malignant brain tumours is reported as 6.29 per 100,000 person-years in HICs and 4.81 in LMICs.[35] However, these figures likely underestimate the true burden in LMICs due to limited access to diagnostic technology and surgical care. Incomplete case ascertainment in LMICs is a significant issue, as highlighted by International Agency for Cancer Research (IARC) data showing that only 15% of the global population was covered by high-quality cancer registries around 2010, with particularly low coverage in South America (7.5%), Asia (6.5%), and Africa (1%).[4]

Population-based registries are crucial for accurately representing brain tumour epidemiology, informing policy, guiding decision-making, and elucidating causal links between behaviour and diagnosis. For example, Figure 3 compares the age distribution of brain tumour patients in Pakistan and the US. Additionally, establishing brain tumour biorepositories at individual centres is valuable for studying molecular epidemiology in LMICs. Initiatives like the Pakistan Brain tumour Epidemiology Study underscore the increasing burden of brain tumours in LMICs. Continued efforts are needed to ensure cancer registries which are comprehensive and maintain high standards for brain tumour care.

Local brain tumour management guidelines

Customizing brain tumour treatment guidelines to fit local contexts is crucial, particularly in resource-constrained settings like Pakistan, where advanced therapeutic options are limited. For instance, adapting existing guidelines to local conditions has been demonstrated by the Indian Society of Neuro-oncology, which tailored WHO recommendations for adult diffuse gliomas diagnosis to their setting, optimizing the use of molecular tests. [36] Similarly, a group of prostate cancer experts modified the National Comprehensive Cancer Network (NCCN) guidelines for prostate cancer for the Middle East and North Africa region in 2010.[37] Such initiatives show the feasibility of localising pre-existing evidence-based guidelines to better serve the Pakistani population.

Given the shared healthcare infrastructure challenges and resource limitations between neighbouring countries like India and Pakistan, international collaboration in managing CNS cancer can be highly beneficial. The establishment of the Pakistan Society of Neuro-oncology (PASNO) is a step forward in this direction, aiming to unify intellectual and material resources for the development of neuro-oncological care in the region.

The development of local guidelines in LMICs is a critical component in advancing brain tumour care. These guidelines must be tailored to reflect the specific limitations and challenges of each region, such as the scarcity of resources, limited access to state-of-the-art medical technology, and the shortage of specialized healthcare professionals. For example, in Pakistan, guidelines could be designed to suggest alternative, more cost-effective diagnostic tools, propose the use of

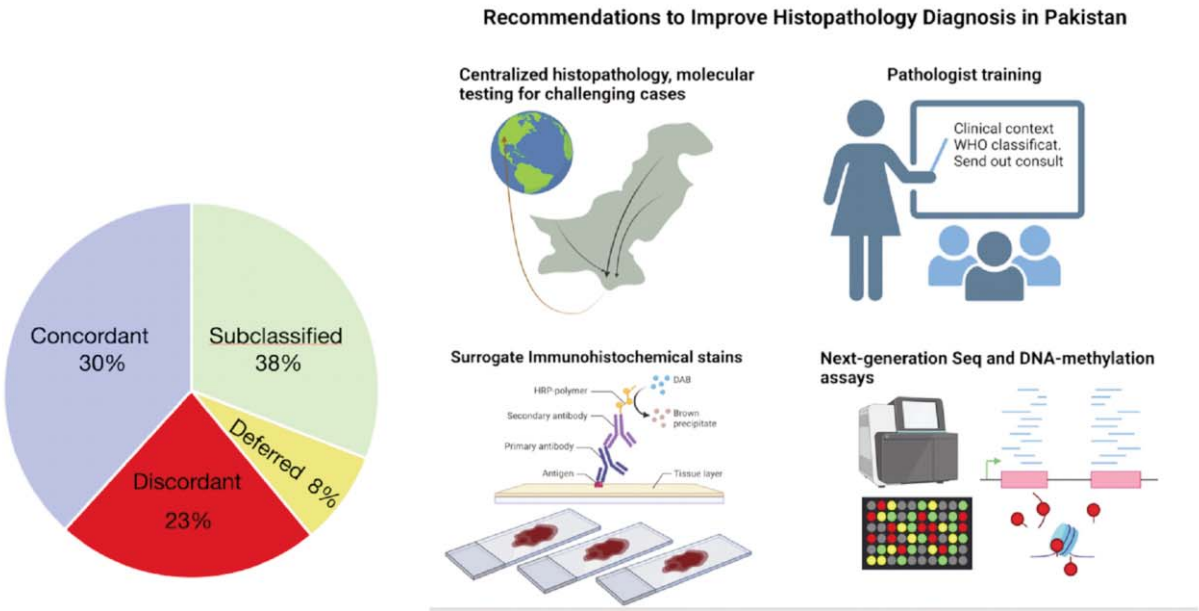

Figure-4: Twinning experience between High Income Countries and Low Middle Income Countries to form an alliance. Different aspects of the twinning process are represented.

telemedicine to extend the reach of neuro-oncology specialists, and emphasize community-based care strategies to alleviate the pressure on centralized healthcare facilities. The formulation of these guidelines requires an inclusive and multidisciplinary approach, engaging neuro-oncologists, healthcare policymakers, patient representatives, and international collaborators. Such a comprehensive strategy ensures that the guidelines are not only practical and resource-sensitive but also adhere to a standard that does not compromise the quality of patient care. The goal is to create a framework that is both adaptable and sustainable, enabling healthcare providers in LMICs like Pakistan to deliver the best possible care to brain tumour patients within the confines of their unique healthcare landscapes.

Figure-5: Image of an Ultra-low Field Magnetic Resonance Imaging being used in a standard size operating room.

Multidisciplinary tumours boards and twinning programmes

Twinning programmes, formal collaborations between medical institutions in HICs and LMICs, significantly enhance cancer care in LMICs. These programmes involve sharing expertise, facilitating fundraising, and providing diagnostic services from HIC institutions to their LMIC counterparts. For example, a paediatric neuro-oncology twinning programme between a tertiary care hospital in Pakistan and a Canadian institute has been successful for over seven years (Fig. 3). This initiative has supported over 400 children with CNS cancers, offering them critical diagnostic and therapeutic services. The programme's expansion to other hospitals aims to create local twinning partnerships between advanced tertiary care centres and rural hospitals. Additionally, it has fostered the development of multidisciplinary tumour boards for CNS cancer patient management.[38]

Role of pathology analysis

Accurate diagnosis is essential for the effective surgical and oncologic treatment of CNS tumours, but histopathology, a key component, is often overlooked in LMICs. Histopathology labs are typically underdeveloped, and pathologists frequently lack specialized training. Our 7-year twinning programme between Sick Kids, Canada,

and AKUH, Pakistan, highlighted these issues. In this programme, 135 challenging paediatric CNS tumour cases were reviewed, revealing a 23% discordance rate in diagnoses. Specifically, 8% of cases were undiagnosed at AKUH and received their diagnoses through expert consultation, while an additional 40% had their diagnoses refined with molecular subclassification, achievable only with specialized molecular or immunohistochemical staining (Figure 4, panel A).

This study underscores the necessity of establishing national or regional referral centres with subspecialty-trained neuropathologists, validating brain tumour-specific immunohistochemical stains, and enabling next-generation sequencing and DNA methylation studies for cases unclassifiable by conventional histopathology (Figure 4, panel B). Figure 4 illustrates the twinning experience and its outcomes: concordant cases had no diagnostic change, discordant cases experienced major or minor diagnostic changes, deferred cases lacked initial diagnoses, and sub-classified cases received refined diagnoses with molecular subtypes after advanced testing.

Ultra-low field mobile MRI

The integration of ultra-low field (ULF) MRI in global neuro-oncology, especially in LMICs, offers a cost-effective and accessible solution for managing CNS tumours. Its affordability and ease of operation make it ideal for use in remote medical centres, significantly reducing the need for expensive setups and specialized personnel. By enabling junior doctors to acquire quality images, ULF MRI addresses the scarcity of resources and reduces patients' travel burdens for routine follow-ups. This advancement not only improves patient compliance but also extends quality neuro-oncological care to underserved areas, marking a crucial step towards equitable healthcare in neuro-oncology.[39]

Conclusion

Tackling neuro-oncology care disparities in LMICs requires a multifaceted approach that integrates innovative technologies, such as telemedicine and artificial intelligence, with traditional healthcare strategies. Strengthening training programmes for healthcare professionals, developing local guidelines tailored to resource constraints, and establishing comprehensive cancer registries are essential steps toward enhancing the management and treatment of CNS tumours in these regions. Collaborative efforts, both within countries and internationally, are crucial in sharing knowledge, resources, and expertise to overcome existing barriers. By adopting sustainable healthcare solutions, LMICs can also advance neuro-oncology care quality, providing hope for CNS tumour patients and contributing to global health equity in neuro-oncology.

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