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# Current management of glioma in Pakistan

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## Abstract

To date, information on the management of specific neurosurgical tumors, such as glioma, in Pakistan remains scattered and scarce. Our review synthesizes the predicaments of glioma management routinely presented to the neurosurgery, medical oncology, radiation oncology, and radiology departments in Pakistan. Expert opinions were integrated from each of the relevant fields in the form of personal citations. The data presented in our review were collected from various PubMed and non-PubMed indexed articles, coupled with various health reports from the Government of Pakistan along with the World Health Organization. Through these data, it was postulated that the utilization of innovative and instrumental technologies is a constant struggle for neurosurgeons in Pakistan, considering the cost-effectiveness. Hence, this results in significant limitations for surgeons to provide the best outcome for their patients. As most Pakistanis (74%) pay out of pocket, measuring cost-effectiveness is extremely crucial. It was found that significant differences in intra-operative and postoperative care existed among various centers. Public sector institutions fared much worse. The role of diagnostics in glioma surgery is severely limited across centers in Pakistan and as such, research and training need to be addressed promptly. In order to achieve success in glioma management, the data in our article demonstrate various facets of health care that need to be addressed simultaneously and swiftly. Surgical access needs to be improved; only then, optimal management of glioma can be accomplished in Pakistan.

**Keywords:** Glioma, management, Pakistan, surgery, treatment

## INTRODUCTION

Management of glioma based on the National Comprehensive Cancer Network guidelines,<sup>[1]</sup> which consist of maximum safe resection followed by concurrent chemotherapy and radiation therapy, is a worldwide accepted standard. Whether this standard is followed or not depends on the capacity of health-care delivery in different parts of the world. Besides, the expenditure by the government in health-care delivery, demographics of the country, and socioeconomic condition of the population based on per capita income also determine the quality of health-care delivery.

Apart from the standard treatment (surgery, radiation, and chemotherapy), there are many other factors that improve the management of glioma. These additional factors in the form of methods, technologies, and techniques may or may not be supported by robust scientific evidence. These may include but are not limited to the state-of-the-art technology, such as magnetic resonance imaging (MRI) with diffusion tensor

imaging capabilities, neuronavigation, intraoperative MRI, quality operative microscopes, and quality operating room proficiencies. Technologies such as fluorescence microscopy for resection of brain tumor using 5-aminolevulinic acid are not used in all the operating rooms of developed countries.<sup>[2]</sup> Similarly, the intraoperative MRI facility is not present in all the major hospitals of North America, Europe, or other developed countries.<sup>[2]</sup> Standard radiosurgery is offered in most of the major cities in the developed world, but highly specialized radiotherapy with proton beam radiotherapy is present only in a very few centers across the world. Temozolomide, which is the first line of chemotherapy available in most of the glioma management centers, is available almost all over the world, but specialized chemotherapeutic agents are not so readily available in developing countries.<sup>[3]</sup> When considering clinical

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trials with experimental drug therapy, immunotherapy, or gene therapy, a significant disparity exists globally. These protocols based on clinical trials are poorly present or nonexistent in developing countries.

Glioma surgery in Pakistan is a complex, multifaceted dilemma. The outcome of glioma management is complicated by delayed diagnosis, lack of care in hospitals, delayed waiting time, and out-of-pocket payments in Pakistan.<sup>[4]</sup> This review investigates the current strategies and modalities of the treatment of different types of gliomas in Pakistan along with the consistent challenges posed to the patients and providers. Given the high workload, lack of advanced imaging and equipment, lack of adequate oncological services, and lack of quality control, glioma surgery may not be performed at the finest level in all the institutions despite the presence of trained neurosurgeons. Herein, we present a comprehensive review of costs and unique predicaments specific to a developing country with regard to glioma treatment. A thorough comparison between private and public sectors providing glioma treatment is presented in this article. In future, success in glioma surgery can be achieved with refined research and training, equitable access to advanced surgical care, provision of health-care delivery systems, and enhanced financing.

## DATABASE SEARCH STRATEGY

The articles included in this review were retrieved from several databases such as PubMed and Google Scholar. They were found over a large span, that is, 20 years, as information was scarce. Research has barely been attempted in Pakistani demographics for brain tumors. This is the first analysis of glioma pertaining to Pakistani population. In this manner, our study is unique in the South Asian region. The MeSH terms included glioma, brain tumors, Pakistan, treatment, surgery, management, chemotherapy, and radiotherapy.

## EPIDEMIOLOGY

Pakistan has an ever-increasing population rate, with the current estimate at 207.7 million.<sup>[5]</sup> Primary studies on glioma incidence have not been previously conducted in Pakistan. The overall incidence rate of central nervous system tumors is 6.7/100,000, of which 51% comprises gliomas.<sup>[6]</sup> Therefore, extrapolating the worldwide incidence to the Pakistani population means the current burden of glioma in Pakistan is 7097 cases.

## ROLE OF DIAGNOSTICS

Diagnostics play a substantial role in glioma surgery. To optimize treatment, glioma patients need to be followed up closely with postoperative MRI.<sup>[7]</sup> Most centers across Pakistan have a fully operable 1.5 Tesla machine. A 3 Tesla machine is only available at Aga Khan University Hospital (AKUH) and Armed Forces Institute of Radiology and Imaging, Pakistan. Moreover, only AKUH has diffusion tensor imaging and functional MRI facilities. While neuronavigation is available

at many other facilities, it is not fully utilized for maximum safe resection, as tractography is not performed at other centers.

The cost of an MRI varies widely among private (Rupee [Rs.] 23,680; United States dollar [USD] 167) versus public facilities (Rs. 5000; USD 35). An additional Rs. 13,510 (USD 95) is charged for contrast. The cost of functional MRI is an overwhelming Rs. 69,700 (USD 493).<sup>[8]</sup> While patients get initial imaging done readily, the cost immediately piles up with repetitive images needed throughout the course of the treatment regimen. Only a few centers have formally trained neuroradiologists in Pakistan.

## SURGERY

There are significant differences in quality care between private and public sectors, entailing both intra-operative and postoperative care. In public sector institutions, there is a high burden of patients due to much lower costs, and administrative issues result in further turbulence in the provision of quality patient care. Some public sector hospitals such as Lahore General Hospital and Dow University Hospital, Karachi, Pakistan, have functioned exceptionally well at performing the arduous task of maintaining minimal costs with a difficult combination of providing substantial treatment.

Certain differences generally exist between private and public sector institutions. While private sector institutions have more accountability, better quality and standards, and a multidisciplinary approach to patients, they remain beyond reach for the larger public. Public sectors, on the other hand, remain less costly, but there is a serious lack of enough beds, lengthy waiting time, and minimal checks and balances. Table 1 compares the finances between private and public sector hospitals.

The waiting time is an important parameter to consider in glioma surgery.<sup>[9]</sup> In private sector institutions, such as in AKUH, the average waiting time for surgical resection for high-grade glioma is <2 weeks, unless emergent care is required for significant mass effect or impending herniation. For low-grade glioma, the waiting time for surgical resection is longer. For public sector hospitals, although clinics generally walk in without waiting time, it may take more than 6 weeks for surgical resection.<sup>[10]</sup>

Awake craniotomy is a standard method for glioma surgery, particularly focusing on eloquent areas, which has been established only in one center (AKUH) in Pakistan. While

**Table 1: Comparison of costs among private and public institutions in USD**

	Private	Public
Surgical resection	4025.82	353.36
Intensive care unit stay	618.38	141.34
3-Dimensional radiotherapy per session	72.79	7.07

Dollar rate: 1.00 USD equals 141.50 Pakistani rupee. USD: United States dollar

several hurdles may exist owing to the limitation of resources, lack of neuro-anesthesia training, and low overall literacy in Pakistan, the outcomes remain promising owing to patient’s and surgeon’s satisfaction.<sup>[7,11]</sup>

### Follow-up of patients

Another prevalent reason for poor outcomes is the issue of loss of follow-up. Despite the detailed peri-operative discussion, a prevalent notion among uneducated patients is that surgical resection is the terminal cure for brain tumors. Consequently, patients often fail to visit the oncology department after discharge from the hospital.<sup>[10]</sup> In such circumstances, the postoperative MRI may not get performed at regular intervals, and it becomes difficult to identify recurrence in time. The topmost reasons for loss to follow-up according to our institutional review include communication gap, financial burden, inconvenience, and inaccessibility from far-flung areas.

### Postoperative care

The average length of stay in AKUH is 5 days.<sup>[10]</sup> The average length of stay varies between public and private sectors. In public sectors, patients sometimes must be admitted several days in advance to get on the list for surgery. Similarly, the discharge stay may be more than needed, but that is highly variable across the country. Postoperative nursing care is still not up to international standards at many other private centers, as only three private hospitals (AKUH, Shaukat Khanum Memorial Hospital [SKMH], and Shifa International Hospital) and none of the public sector hospitals are Joint Commission International Accredited. Surgical morbidity increases with an inadequate level of postoperative care in public and private sectors.

### Availability of high-end technology

Most centers currently have the availability of operative neurosurgical microscopes. Neuronavigation and ultrasonic aspirator are available in less than a tenth of all the centers that perform glioma resection, while operative exoscope is available only at AKUH. The problem with most of these equipment is that the added costs of disposables required for their use act as a deterrent.<sup>[10]</sup>

Fluorescent microscopy facility is available only at AKUH along with 5-aminolevulinic acid which is a technique in

differentiating normal brain tissue from the tumor.<sup>[12,13]</sup> Because 5-aminolevulinic acid is costly (approximately USD 1200) and can increase the cost of surgery by as much as 25%, fluorescein is used as an inexpensive alternative. The problem with fluorescein is that it can appear in normal tissue with a high nonspecificity of fluorescence.<sup>[14]</sup>

The selection of innovative and instrumental technologies while weighing the cost-effectiveness is a constant struggle for neurosurgeons in Pakistan. It results in significant limitations for surgeons in providing the best outcome for their patients. Table 2 compares the cost of craniotomy along with innovative technologies.

## HISTOPATHOLOGY

Several tertiary care centers across the country have an adjoining histopathology laboratory. If a histopathology laboratory is not associated with the center, the specimen is sent elsewhere in the city for analysis. A few laboratory centers including AKUH and SKMH have the state-of-the-art technology with the latest molecular tests, such as isocitrate dehydrogenase, O-6-methylguanine-DNA methyltransferase, and 1p19q co-deletion. Frozen section is available at most major centers such as AKUH, SKMH, and Dow University Hospital.<sup>[15]</sup> Due to volume overload, it may take 2 weeks for a final histopathological report.

## TUMOR BOARDS

Tumor boards serve as multidisciplinary conduits of communication, teaching, coordination among specialists, and future research directions.<sup>[16]</sup> There are nonspecialized tumor boards available across the country, but, unfortunately, very few centers in Pakistan are currently conducting specialized tumor boards dedicated to brain tumors, with a few exceptions such as AKUH, SKH, and Lahore General Hospital. Nevertheless, informal discussions on difficult cases may exist at all cancer centers, as teamwork and a holistic approach are vital for patient outcomes.

## RADIOTHERAPY

Because Pakistan is a developing country, only a few key centers play a major role in providing radiotherapy. The rest

**Table 2: Cost comparison of craniotomy to added technological advancements**

Technology	Cost in rupees	Cost in USD	Proportion (%)
Craniotomy	569,654	4025	60
Ultrasonic aspirator	60,000	424	7
Functional magnetic resonance imaging	83,210	588	9
Neuronavigation	60,000	424	6
Exoscope	20,000	141	2
Fluorescent microscopy with 5-aminolevulinic acid	169,800	1200	15
Fluorescent microscopy with fluorescein	12,000	84	1
Total	946,364	6688	100

Dollar rate: 1.00 USD equals 141.50 Pakistani rupee. USD: United States dollar

of the centers have an unmet need for facilities, technological staff, nurses, and trained personnel. Eighteen centers belong to Pakistan Atomic Energy Commission, a government body.<sup>[17]</sup> Nine other private centers are functioning throughout the four provinces. Unfortunately, some centers do not follow internationally accepted treatment guidelines, despite the availability of high-quality radiotherapy machines. Two centers in Pakistan are offering stereotactic radiosurgery (gamma knife and cyberknife in Karachi), and only four centers in Pakistan are offering intensity-modulated radiation therapy.

Considering logistic issues, every center has its own treatment guideline regarding low-grade glioma, keeping the prompt provision of radiotherapy following surgical resection in consideration. At AKUH, radiotherapy for all gliomas is typically commenced 4–6 weeks after surgical resection. For high-grade gliomas, the radiation oncologists aim to start treatment within 4 weeks of surgical resection, and as soon as the wound is healed. While public sector hospitals are appealing due to cost, gaps within treatment routinely occur due to out-of-order machines. The patients hence wait for months for the resumption of treatment. It may take 4–6 months for radiotherapy to start at public sector hospitals after surgical resection. Because not all centers have a coexisting radiotherapy department, the patients must search for radiotherapy elsewhere, thereby not fulfilling the treatment guidelines. At AKUH, three-dimensional (3D) radiotherapy costs Rs. 10,300 (USD 73), whereas intensity-modulated radiation therapy costs Rs. 17,000 (USD 120) per session. The total cost of radiotherapy alone climbs up to Rs. 400,000 (USD 2827) to Rs. 600,000 (USD 4240) depending on the case in most private sectors. SKMH is an exception as a private center that offers radiotherapy free of charge. At some public centers, such as Karachi Institute of Radiotherapy and Nuclear Medicine, the cost is minimal at Rs. 1000 (USD 7) per session for 3D technology. The total average cost of radiotherapy for a public sector hospital is hence Rs. 30,000 (USD 212).<sup>[18]</sup>

## CHEMOTHERAPY

More than fifty hospitals have the capacity to deliver chemotherapy across Pakistan. Yet, very few hospitals have an adequate health-care system with trained personnel. Another

21 centers are solely dedicated to cancer care.<sup>[4]</sup> Furthermore, in developing countries, temozolomide is primarily imported from other countries and with the growing economic constraints, cost of chemotherapeutic drugs rapidly rises.<sup>[2]</sup>

Availability of drugs is uncertain in some centers across Pakistan although it is mostly available at others, including AKUH. Cost of temozolomide adds to the patient's expenses as the monthly expense come close to Rs. 150,000 (USD 1060). Depending on the manufacturing country of the drug, the cost declines (Rs. 31,000; USD 219). The availability and utilization of bevacizumab (Avastin) vary at different centers, as the cost is hefty for the patient population at Rs. 102,192 (USD 722) for 400 mg of bevacizumab.<sup>[15]</sup>

## FINANCES

The burden of glioma patients in Pakistan is further complicated by reduced spending on health. The gross national income per capita for Pakistanis is USD 5840, which, although on a rising trend, is drastically lower compared to that of other countries.<sup>[9]</sup> According to World Health Organization statistics of 2014, the total expenditure on health per capita is USD 129, whereas the total expenditure on health as a percentage of gross domestic product is 2.6%.<sup>[19]</sup> Altogether, the total health expenditure as of 2015–2016 was Rs. 907,504 million (USD 6413 million) as drafted by the National Health Accounts. Government spending from various sources is a mere 32% of the total health expenditure, whereas out-of-pocket payments form an immense 58%, as of 2015 government data.<sup>[20]</sup> There is an urgent need to address health-care spending specifically toward cancer. Table 3 depicts health-care expenditure from all sources from 2015 to 2016.

As Pakistan is a low middle-income country, surgical access remains a hindrance to adequate care. Currently, 24.3% of Pakistan's population lives below the poverty line.<sup>[21]</sup> Considering all these statistics, in addition to the fact that most of the population live in rural areas, surgical access for glioma surgery remains cumbersome for patients. A study conducted by Samad *et al.*<sup>[22]</sup> portrayed barriers behind accessing surgical care. Gender is the topmost reason as women are twice more likely to delay access compared to men. Various other reasons include insufficient knowledge of treatment options and disease

**Table 3: Total health expenditures (2015–2016) by financing agents in millions of rupees and United States dollar millions<sup>[20]</sup>**

Financing agents	Millions of rupees	USD equivalent millions (USD)	Proportion (%)
Federal government	67,062	473.94	7.38
Provincial government	187,096	1322.23	20.62
District/tehsil government	39,405	278.48	4.34
Social security funds	9538	67.41	1.05
Autonomous bodies/corporations	14,287	100.97	1.57
Private household out-of-pocket payment	522,571	3693.08	57.58
Local nongovernmental organizations	44,271	312.87	4.87
Official donor agencies	15,210	107.49	1.68
Total health expenditure	907,504	6413.46	100

Dollar rate: 1.00 USD equals 141.50 Pakistani Rupee. USD: United States dollar

implications, financial constraints, and environmental-related aspects (such as geographical location and city disturbances).<sup>[22]</sup>

Finances between private and public sectors also differ. While private hospitals such as SKMH, Shifa International Hospital, and AKUH have a functional health-care system with adequate administration, hefty hospital charges may turn many patients away. Nevertheless, a lot of these expensive centers notably provide welfare to deserving patients. Figure 1 provides comparisons of all the current treatment modalities for glioma surgery.

### CAPACITY BUILDING

According to estimates, Pakistan’s population-to-surgeon ratio is one of the worst in the world (second only to a few sub-Saharan African countries), and there is a deficit of 17 million surgeries every year.<sup>[23]</sup> Data published in 2011 revealed an estimated 42 dedicated neurosurgery centers across the country, with only about 1500 dedicated neurosurgery beds, a number extremely low for Pakistan’s population.<sup>[24]</sup> While all these centers can deal with neurotrauma, spine, and even basic neurosurgical oncology, due to limited resources, only a few centers in Pakistan are fully exercising their potential to treat gliomas. According to the regulatory body for neurosurgery residency, College of Physicians and Surgeons, Pakistan, at present, there are 330 practicing neurosurgeons.<sup>[25]</sup>

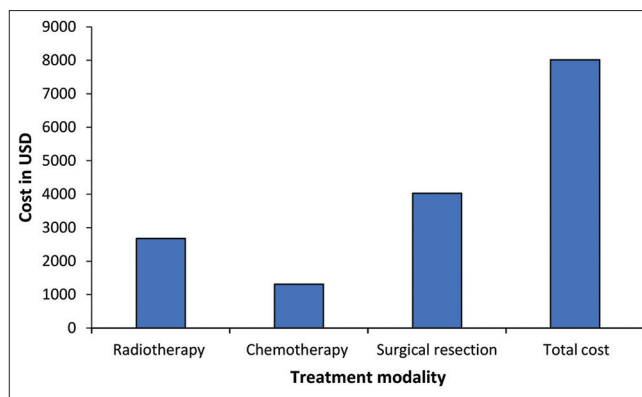
While the worldwide ratio is one neurosurgeon per 230,000 people (and approximately one neurosurgeon for 61,000 persons in the USA),<sup>[26]</sup> the ratio in Pakistan is one neurosurgeon per 629,620 people. Hence, the ratio of US neurosurgeons is 10.3 times more, and worldwide, neurosurgeons are 2.7 times more compared to Pakistan.<sup>[24]</sup>

### QUALITY OF TRAINING IN PAKISTAN

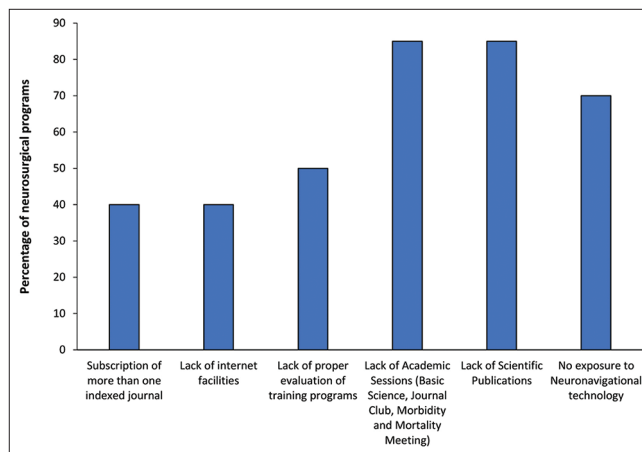
As it currently stands, few neurosurgical residency programs are providing exceptional training, whereas most are struggling to maintain quality. Comprehensive teaching – including basic neuroscience lectures, hands-on surgical workshops, and research – is a significant cornerstone of any neurosurgical residency. Very few fellowship-trained oncological neurosurgeons are available, with AKUH being the only center that has recently started providing an academic fellowship in neurosurgical oncology. Moreover, there is no organized society dedicated to neurosurgical oncology. Presently, there are 177 trainees in 31 teaching institutes across the country, with approximately 50 supervisors.<sup>[25]</sup>

### QUALITY OF RESEARCH IN PAKISTAN

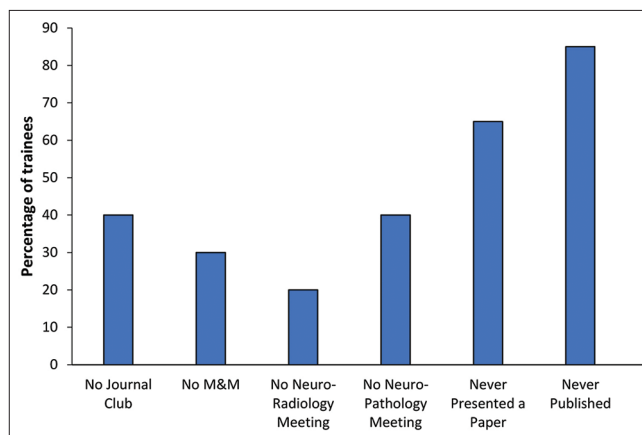
Another arena not well developed across Pakistan is basic science research focusing on neuro-oncology. Our laboratory is focusing on the diagnostic and therapeutic potential of microRNA in glioma, and glioma-initiating cells. Most centers



**Figure 1:** Comparison of costs of the modalities of treatment in United States dollar (USD) in a private hospital. Dollar rate: 1.00 USD equals 141.50 Pakistani rupee. Chemotherapy costs of temozolomide averaged for six cycles. Radiotherapy (three dimensional) averaged for thirty fractions



**Figure 2:** Quality of research and training in neurosurgical residency programs in Pakistan<sup>[24]</sup>



**Figure 3:** Academic shortcomings of neurosurgical trainees in Pakistan.<sup>[24]</sup> M&M: Morbidity and mortality meeting

perform either very little research or mainly retrospective studies, with little progress over the last half decade.<sup>[27]</sup> Centers have not focused on randomized controlled trials or clinical

trials either. Figures 2 and 3 represent the quality of research and training in Pakistan, along with the academic shortcomings of neurosurgical trainees.

From all the literatures published within Pakistan in the last 10 years, a large proportion is composed of case studies and case series. These are often seen from large tertiary care centers within the region, whereas primary and secondary health-care centers have a very low representation in literature. This is often due to a lack of neurosurgical expertise within these centers. Most clinical research is published. AKUH remains the largest research publishing center within the country, with a high number of prospective and retrospective, cohort and cross-sectional studies.<sup>[3]</sup>

From a city comparison, hospitals in Lahore such as SKMH and the Lahore General Hospital have a rapidly growing number of publications, followed closely by Karachi. This is reflective of Lahore having a much larger catchment area. However, most of these studies are published in non-PubMed indexed, and local journals, which allows for a wide deviation of quality of paper, and greatly limits the readership of the paper.

## CONCLUSION

Issues surrounding glioma surgery in Pakistan can only be tackled with a holistic approach toward multiple and multilayered constraints. There is an urgent need to deal with various obstacles to achieve seamless outcomes for glioma surgery. Improved health-care delivery systems to provide systematic care and to achieve greater follow-ups, enhanced funding to achieve newer advancements in care, and improvement of education and research at an increasing number of centers are all required on an immediate basis. Without these quick and dire approaches, outcomes may remain dismal for years. Problem-solving of a specific neurosurgical issue such as glioma surgery can only be attempted when other various facets of health care are addressed simultaneously. One also needs to reflect on the cost paid by the family to treat glioblastoma comprehensively, when the overall life expectancy of the disease is increased on an average by only 9 months.

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## Conflicts of interest

There are no conflicts of interest.

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