RESEARCH ARTICLE

Protocol: revolutionizing central nervous system tumour diagnosis in low- and middle-income countries: an innovative observational study on intraoperative smear and deep learning

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Abstract

Objective: : The aim of this study is to assess the feasibility and implementation of a novel approach for intraoperative brain smears within the operating room, which is augmented with deep learning technology.

Materials and methods: This study is designed as an observational to evaluate the feasibility and implementation of using an innovative approach to intraoperative brain smears within the operating room, augmented with deep learning technology. The study will be conducted at Aga Khan University Hospital in Karachi, Pakistan, from May 2024 to July 2026, with an estimated sample size of 258. A neurosurgical trainee, trained by the study neuropathologist, will prepare and examine the smears under a microscope in the operating room. The findings of the trainee will be documented and compared to routine intraoperative consultations (smear and/or frozen section) and final histopathology results obtained from the pathology department. Additionally, the study will incorporate artificial intelligence tools to assist with the interpretation of smear and a telepathology interface to enable consultation from an off-site neuropathologist.

Conclusion: The results of this study will hold significant potential to revolutionise neurosurgery practices in low- and middle-income countries by introducing a cost-effective, efficient, and high-quality intraoperative consultation method to settings that currently lack the necessary infrastructure and expertise. The implementation of this innovative approach has the potential to improve patient outcomes and increase access to intraoperative diagnosis, thereby addressing a significant unmet need in LMICs.

Keywords: Artificial Intelligence, Neuropathology, Neurosurgery, Telepathology, Brain, tumour

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Introduction

Brain tumours are the 10th most common cause of mortality accounting for a quarter of a million deaths in 2019, globally. Although there have been substantial advancements in the biological and molecular understanding of brain tumours, and in their clinical management and neurosurgical techniques, low- and middle-income countries (LMICs) have not benefitted much from these developments. Age-standardized death rates for brain tumours in LMICs are much higher than in developed countries. Multiple factors contribute to the higher mortality rate associated with brain tumours in LMICs, including late and inappropriate diagnosis and lack of access to specialized neuro-oncological facilities. [1,2]

Histopathology is crucial for the diagnosis, prognosis, and therapy of disease. Intraoperative histopathology consultation is an integral component of the management of brain tumours that provides assessment of the adequacy of the material and preliminary diagnosis to help neurosurgeons decide the extent and type of surgical resection.[3–5] Three most commonly used intraoperative diagnostic methods include frozen sections (FS), imprint cytology, and squash cytology. The choice of method depends on personal preference and experience of both the neurosurgeon as well as the pathologist, but overall FS is the most common and widely used technique.[6,7] A frozen section (FS) requires a cryostat, an expensive equipment to maintain freezing temperatures while processing the sample; therefore, limiting widespread use of FS diagnosis in a resource-limited setting. Wide availability of FS in routine neurosurgical practice is further limited due to the absence of skilled histotechnologist and pathologists.[8,9]

Neurosurgical practice in LMICs requires an accurate and rapid, yet simple and cost-effective method for intraoperative diagnosis. A brain smear preparation during surgical procedures offers a rapid, precise, and cost-effective alternative with a diagnostic accuracy of

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94.9%[3], compared to the frozen section which has a diagnostic accuracy of 88.8%.[10] Smear preparations, variants of which are also referred to as "squash" or "wet-film" preparations, are currently performed by pathologists in the histopathology laboratory. Smear preparations typically require less tissue than a frozen section and are safer in case an infectious etiology is encountered in the case.[11]

Here, we propose a modified smear preparation protocol that can be performed and interpreted by neurosurgical team within the operating room with the help of artificial intelligence and an optional tele-pathology consultation with an off-site pathologist. A smear preparation that is conducted in the operating room and read by neurosurgical team can bridge the gap in delayed intraoperative diagnosis, lack of access to trained neuropathologists who are usually available only in specialized neuro-oncological centers.

There are several advantages to training neurosurgical trainees in the preparation and interpretation of brain tumour smear slides, particularly in terms of cost-effectiveness and infrastructure. First, it can reduce the need to send tissue samples to a histopathology laboratory, which can save time and resources, especially in settings where there may be limited access to laboratories or where transportation of tissue samples may be challenging. Second, it can reduce the need for additional surgeries to obtain tissue samples for diagnosis, which not only reduces morbidity but can also lower the overall cost of patient care. Third, it can improve the efficiency of the surgical procedure by allowing the trainees to make a diagnosis or identify any abnormalities in real-time during surgery, which can potentially reduce the length of the surgery and the need for additional interventions. Fourth, it can be more cost-effective to train neurosurgical trainees in histopathology compared to hiring additional histopathologists or sending tissue samples to external laboratories. Fifth, the use of virtual and online training can reduce the need for costly infrastructure, such as physical classrooms or specialized laboratory equipment, and can make the training more accessible to trainees in remote or underserved areas.

Machine learning (ML) and more specifically deep learning (DL) have recently shown huge potential in analysing images for a range of applications. A ground-breaking work reported in ImageNet Large-Scale Visual Recognition Challenge (ILSVRC) 2012 [12], where a Convolutional Neural Network (CNN) almost halved the second-best error rate (from 26.2% to 15.3%), bringing a revolution in imaging domain. For the domain of medical image processing and analysis, applications to which DL have been successfully applied include radiology[13], brain segmentation[14], intraoperative brain tumour diagnosis[15], chest imaging[16] and the segmentation of organs[17]; however, this list is far from extensive. Using deep learning to automate the process of reading brain smear slides has several advantages in low- and middle-income countries (LMICs). First, it has the potential to improve the accuracy of brain tumour diagnosis, which is important in LMICs where access to trained pathologists may be limited and the workload may be high. Second, it can significantly increase the efficiency of the diagnosis process, reducing the workload of trained pathologists and reducing the time that patients have to wait for a diagnosis. DL models are time consuming while training; however, once trained and deployed they can process an image in a fraction of a second to a few seconds. Third, it can lead to cost savings for healthcare systems in LMICs by reducing the need for trained pathologists and the resources required for the diagnosis process. In addition, the recent explainable artificial techniques can help in highlighting the region of interest based on which the image is categorised into certain category that helps in augmenting the decision power of medical professionals. Finally, it can improve access to care for patients in LMICs by increasing the accuracy and efficiency of brain tumour diagnosis, particularly in areas where access to medical professionals and diagnostic facilities may be limited.

The aim of this study is to assess the feasibility and implementation of intra-operative brain smear technique for brain tumour diagnosis by comparing it with frozen section and histopathology report in a LMIC. Additionally, we aim to train neurosurgical trainees and incorporate artificial intelligence in brain smear preparation and interpretation.

Objectives

Primary

•To assess the feasibility of preparing and interpreting intraoperative brain smears within the operating room.

•To determine the sensitivity, specificity, and positive and negative predictive values of intraoperative smear technique in comparison with gold standard final histopathology and conventional frozen section.

•To evaluate the time it takes to interpret the smear technique and its impact on the overall surgical duration and outcome.

•To determine the cost-benefit relative to the frozen section.

Secondary

•To train neurosurgical trainees in the interpretation of common brain tumour smears.

•To incorporate artificial intelligence (AI) based methods in brain smear prep interpretation.

•To design a telepathology interface for consultation with a neuropathologist in challenging cases

Materials and methods

The study has the design of an observational study.
The study will be conducted over a period of two years, from May 2024 to July 2026, during which time the sample collection will take place. The analysis of the collected data is expected to take two weeks. In addition to the sample collection, the study will also include a training component that will span 3 months from July to September 2024 at section of neurosurgery department, Aga Khan University Hospital Karachi, Pakistan (AKUH).

Sampling technique used is non-probability consecutive. The required sample size of this study was calculated using OpenEpi software.[18] The minimum sample size that will be required for the principal study is 258 patients with inflation of 10% for loss to follow-up or missing data. Based on the anticipated sensitivity of 98% and specificity of 100% of intraoperative brain smear3 and a 1.3% prevalence of brain tumours 7 along with a 5% level of significance and precision of 5%.

Inclusion criteria: All patients, both gender and all age groups, who will present to section of neurosurgery and undergo surgery (open craniotomies or stereotactic biopsies) for brain tumours (primary or metastatic) at AKUH will be included. The patients or parents/guardians (in case of paediatrics, ages <18 years) will be provided with written informed consent and confidentiality assurances. The decision to perform the surgery will be based on clinical need and not for the sake of participation in the study.

Exclusion criteria: Since the use of tissue for rapid diagnosis reduces the amount of material available for subsequent permanent section analysis, patients in which limited tumour sample is available (especially midline brain, brainstem and spinal cord cases), traumatic brain injuries (TBI), and CNS aneurysms will be excluded. Those who present or are referred to with a brain tumour confirmed by a biopsy will be excluded. Patients undergoing surgery for masses or lesions other than suspected neoplasms will be excluded.

This study involves a three-armed approach, consisting of (i) obtaining brain smear samples during surgical procedures, (ii) training neurosurgical trainees, and (iii)

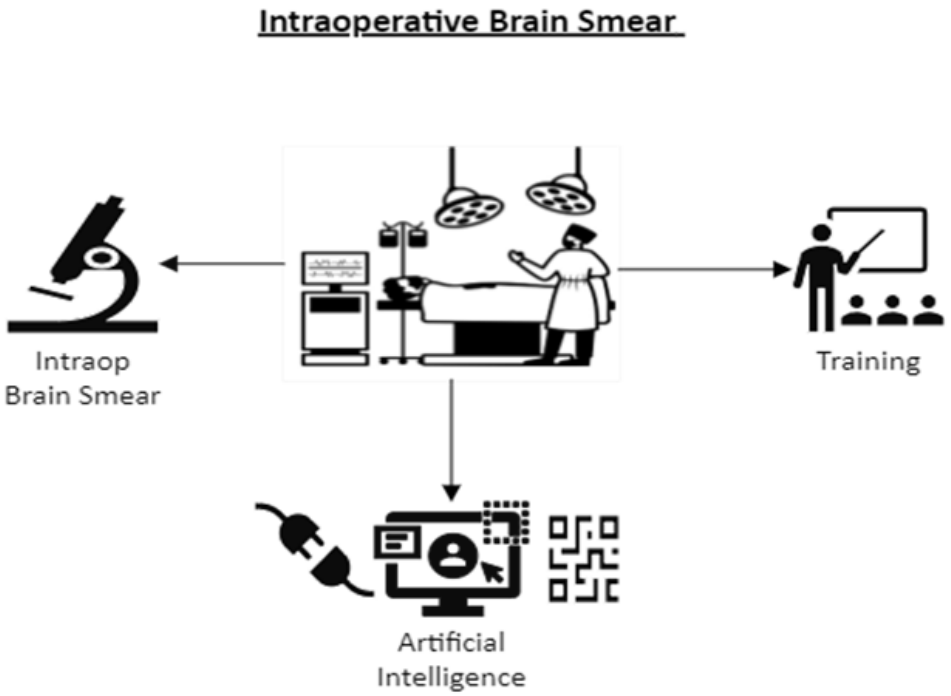

Figure-1: Depicting the three arms of the study.

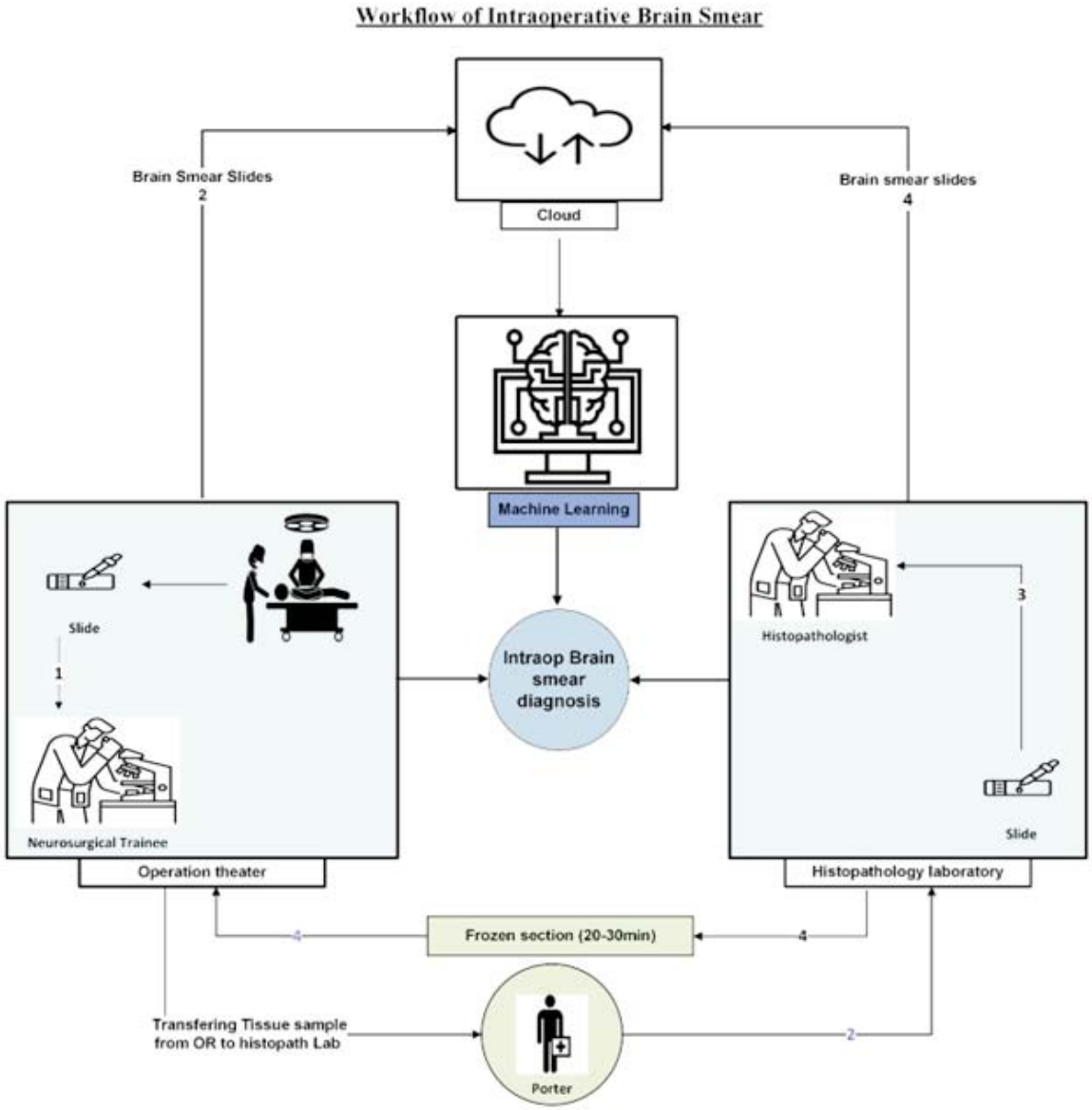

Figure-2: Showing the workflow of intraoperative brain smear and deep learning.

integrating deep learning techniques for interpreting brain smear data, as depicted in (Fig 1). The three arms are interconnected and their workflow is illustrated in (Fig 2).

Intra-operative procedure

Prior to the surgical procedure, a comprehensive explanation of the procedure will be provided to patients who meet the inclusion criteria. In the case of minors under 18 years of age, their parents or legal guardians will also be informed. After the explanation of the procedure, written informed consent will be obtained. The researcher will follow the case during the operative procedure. Surgical team members will allocate the resected tumour sample for routine clinical histopathology and the remaining material will be given to the investigator for the study. According to the size of the specimen and surgical biopsy protocol, the specimen will be dissected into slices after being cut open. The smear will be prepared using two to three tissue bits, each measuring 0.1-0.2 cm, from different sites of the specimen. The slides will be examined independently under a microscope inside the operating room by a neurosurgical trainee previously trained by the study neuropathologist. The neurosurgical trainee involved in the study will be actively participating in the surgery. The smear findings of the neurosurgical trainee will be documented and later compared to the results of routine intraoperative consult (smear and or frozen section) and final histopathology

result obtained from the pathology department. The study histopathologist will not necessarily be involved in reading and signing out the final pathology report.

Touch imprint smear and staining

Two slides will be prepared for the touch imprint smear by lightly touching the brain specimen on a glass slide that has been labeled. Both slides will be fixed in 100% alcohol and subsequently stained with hematoxylin and eosin (H&E). The tissue used for the touch imprint will subsequently be used for smear preparation.

Squash smear and staining

Three squash preparations will be made for each case. A small volume of brain tumour tissue (1-2 mm in largest dimension) will be placed onto a clean, dry, and labelled glass slide. The slide will then be covered with another slide with just enough pressure to spread the tissue into a thin film. Once a thin film of cells has formed, the two slides will be pulled apart. The slides will be immediately immersed in a 95% alcohol solution, and one of the slides will be stained with haematoxylin and eosin (H&E) and the other with Giemsa stain. The third slide will be fixed in alcohol and left unstained to be used if needed.

Microscopic examination

All slides will be stained together and following cover slipping will be examined by neurosurgical team members trained in intraoperative histology analysis. The light microscope for this purpose will be available on a pushcart for easy transport to the operating room. The study pathologist will be consulted by sharing digital images on dedicated telepathology interface developed as part of this study, in case a confident diagnosis is not reached in the operating room. These two results will be compared with the AI based results and a final diagnosis will be reached by the investigators and these results along with the time needed will be documented. After the surgery, the intraoperative diagnosis reached by the investigators (neuropathology trainee) will be compared with the final histologic diagnosis based on routine histology and immunohistochemical techniques.

Artificial intelligence arm of the study

This arm of the study aims to use deep learning to automate the process of reading brain smear slides for the detection of brain tumours. To do this, we will first collect a large dataset of brain tumour smear slides that have been accurately labelled by a pathologist. This dataset will consist of archived pathology cases at AKUH as well as any freely available online datasets. The microscopic images will be preprocessed by resizing or cropping and normalising the pixel values as needed. The dataset will then be split into a training set and a test set.

We will use a convolutional neural network (CNN) as the deep learning model architecture, and will configure the model for training. The model will be trained on the training set and we will monitor its performance on the test set. If needed, we will fine-tune the model to improve its performance on the test set.

Once the model is performing well on the test set, we will use it to classify new brain smear slides and identify any pathologies present on the slides. We will evaluate the model's performance on the new slides using metrics such as accuracy, precision, and recall. Finally, we will document the results of the study, including any limitations or potential sources of error. To evaluate the inter- and intra-observer variability, we will utilize Cohen-kappa (where only two labellers) and Fleiss-kappa coefficient metrics which measures the degree of agreement between/among labellers. This often deals with data that are the result of a judgment, not a measurement. Similarly, its variations will be considered to further validate inter and intra labelling. On the other hand, in the scenario of having less data for training and testing the DL model, we will use k-fold cross-validation. This method involves dividing the data into k equal parts or folds. The model will be trained on k-1 folds and evaluated on the remaining one. This process is repeated k times, with each fold serving as the test set once. The average performance of the model across all k iterations will be calculated and used to predict its performance on new, unseen data.

Training neurosurgical trainees

This arm of the study aims to train neurosurgical trainees in how to prepare and interpret brain tumour smear slides inside the operating room. The training will be conducted through a series of virtual and in-person workshops, and online courses led by the study neuropathologist. The workshops and courses will cover topics such as the indications for preparing brain smear slides, the proper technique for preparing the slides, the interpretation of the slides, and the reporting and communication protocols for the tissue sample.

The virtual workshops will be conducted via videoconferencing software and will allow trainees to participate from any location with an internet connection. The in-person workshops will be held at various locations across the country, and trainees will be responsible for their own travel and accommodation arrangements. The online courses will be self-paced and will be accessible through a learning management system. Lectures/ workshops will be recorded and available on the web as

future reference. To evaluate the level of understanding of brain smear analysis among neurosurgical trainees, a questionnaire consisting of basic neuropathology questions will be administered before and after the training session. The questionnaire will be designed by a trained neuropathologist and the improvement in performance will be determined through a comparison of the pre- and post-session assessments.

Data collection

Data collection for this study will be performed through a pre-formed, password-protected questionnaire for neurosurgical trainees and by a trained neuropathologist. To streamline data collection and reduce the amount of time required, the data will be recorded using a digital questionnaire and later imported to an Excel spreadsheet. This data will include demographics, preoperative diagnosis, location of the tumour, size of the tumour, surgical approach, duration of smear preparation and interpretation, challenges encountered during the preparation and interpretation of the slides, comparison of smear results with final histopathology and frozen section results. Cases will be categorized into three groups: 1) concordant cases when diagnosis of the smear preparation was same as the final histopathological diagnosis; 2) partially concordant when the smear and the final differ in tumour grade or specificity of diagnosis; and, 3) discordant cases - when the final histopathologic diagnosis differed from the smear preparation diagnosis.

Data management/Plan of statistical analysis

The collected data will be cleaned and given value labels in the Excel. The data will be imported and analyzed using SPSS software version 26.0. The qualitative variables will be reported as frequencies and percentages, and the quantitative variables will be reported as mean ± SD. The study will consider a p-value of less than 0.05 to be significant. The feasibility of brain smear will be based on key factors like the time it takes to perform, any challenges encountered during preparation and interpretation, cost, and the perspectives of neurosurgical trainees as rated using a Likert scale. The diagnostic precision of the procedure will be assessed by computing metrics like the area under the curve, sensitivity, specificity, positive predictive value, and negative predictive value. The impact of the procedure's duration on the total duration of the surgery will be analyzed by calculating the mean ± standard deviation (SD) / median (IQR). The cost of each procedure will be calculated by considering factors like the number of smear slides utilized, the cost of the stains, and the expenses associated with the microscope. These factors will be combined to determine the overall cost, which will then be compared to the cost of standard frozen section procedure. To evaluate the inter- and intra-observer variability, kappa statistics will be applied.

Ethical consideration

The participants of the study will be fully informed of the study's objectives, procedures, and their rights as participants. They will have the opportunity to address any concerns arising and they will provide written informed consent. In case of minors under the age of 18 years, their parents or legal guardians will receive a comprehensive explanation of the purpose and procedures of the study and will be asked to provide written informed consent. Participation in the study is voluntary, and participants may withdraw at any time without any negative repercussions or compromise in their treatment plan in anyway. All data will be kept secure in a password-protected (cloud based) database. A unique ID will be assigned to patients to maintain confidentiality. De-identified data will be analysed and presented to the scientific community through publications. The study has received approval (#2024-8527-27676), dated 30th January, 2024, from the Ethical Committee at Aga Khan University Hospital, Karachi.

Risk/benefit assessment

There is neither known health risk nor any specific clinical benefits to the research participant. Additionally, the research participant will not be provided any financial or other incentives. The clinical decision making on study cases will rely exclusively on routine procedures including standard histopathologic diagnosis obtained through routine diagnostic techniques including frozen section and smear preparations performed and read by certified histopathologists as per routine. The results of the intraoperative smear conducted within the operating room will be documented but not communicated to the neurosurgery team, so as not to influence clinical decision making during the procedure.

Costs to the subject

This additional intraoperative research technique will not cost the patient any extra charges.

Expert opinion

Expert opinion was solicited from a panel of experts comprising a neurosurgeon, a neuropathologist, and an artificial intelligence consultant regarding the feasibility and implementation of brain smear in LMIC operating rooms. The panel's insights were informed by their expertise, experience, and working background in LMIC healthcare structures and the constraints of healthcare

care delivery in these settings. The expert opinions of the panelists are presented below.

Neurosurgeon perspective

Brain tumours pose a significant burden on the health outcomes of individuals in (LMICs), where the current state of neurosurgical care is concerning due to a rise in incidence and inadequate resources. The unmet demand for essential neurosurgical interventions in LMICs is estimated to be five million cases, underscoring the issue of unequal healthcare allocation and resource distribution across regions.[19] This inequity is further highlighted by the fact that many LMICs have a ratio of only 0.01-0.[1] neurosurgeons per 100,000 populations[2], despite 80% of approximately 13.8 million neurosurgical cases occurring in these developing regions with limited resources.[20]

Intraoperative diagnosis is one aspect of a multifaceted process of brain tumour management. It plays a pivotal role in achieving safe and maximal resection of brain tumours, and the accuracy of such diagnosis is paramount to favourable patient outcomes. Frozen section is a widely used intraoperative technique for diagnosing brain tumours, and is considered to be one of the most accurate methods. Nevertheless, frozen section has significant limitations in resource-limited settings, particularly in (LMICs).

The financial, logistical, and human resource demands of frozen section limit its feasibility and implementation in LMICs. These limitations include the expense and need for sophisticated equipment, the labour-intensive and time-consuming nature of the technique, the demand for specialized training, and a shortage of skilled personnel, particularly neuropathologists, which is particularly acute in LMICs. In light of these limitations, there is need for innovative, cost-effective, and accurate techniques for intraoperative brain tumour diagnosis.

One such technique is the intraoperative brain smear, which entails the preparation and interpretation of brain smears in the operating room by a trained neurosurgical trainee. Intraoperative brain smear has significant advantages over frozen section, including its simplicity, rapidity, and ease of implementation. Additionally, intraoperative brain smear can expedite intraoperative procedures and reduce the need for specialized personnel, equipment, and infrastructure.

A feasibility study can test the practicality of intraoperative brain smear and its potential for implementation in LMICs. Such a study can evaluate the accuracy, efficiency, and cost-effectiveness of the technique and provide the foundation for broader implementation in other settings. In conclusion, the intraoperative brain smear technique shows promise as a viable and cost-effective alternative to frozen section in LMICs, and its utilization has the potential to improve the standard of care for neuro-oncology patients in these settings.

Neuropathologist perspective

Intraoperative consultation when used judiciously can be a crucial component of surgical management of CNS tumours. While many methodologies have been used for tissue preparation for intraoperative consultation, smear preparations and frozen sections remain the mainstay all over the world. Smear preparations have proven to be highly sensitive and specific and have the inherent benefit of being rapid, low-cost and economical in terms of tissue volume requirement. This study will investigate the feasibility of bringing intraoperative smear preparation interpretation to the operating room by enabling neurosurgery team members to prepare and read the smears without the help of on-site pathologists. Another innovative aspect of this study is the integration of artificial intelligence tools to facilitate the interpretation of smear preparations and the development of a telepathology interface to elicit consultation from an off-site neuropathologist. The results from this study have the potential of transforming neurosurgery practice in the LMIC by bringing quality intraoperative consultation to places that currently lack infrastructure and expertise.

Artificial intelligence consultant perspective

Medical image processing has been essential for detection, classification, and understanding of numerous diseases. According to a report in 2002 from Department of Radiology at the University Hospital of Geneva, between 12,000 and 15,000 images are produced daily. Furthermore, in last decade, many imaging techniques such as X-ray, Magnetoencephalography (MEG), Computed Tomography (CT), Ultrasonography, Single-Photon Emission Computed Tomography (SPECT), Magnetic Resonance Imaging (MRI), etc. have emerged which increased the speed of medical image acquisitions to exhibit the detailed and complete facets of brain tumours but also help doctors to accurately diagnose the tumour and determine the correct treatment mechanism.

Histopathology is considered gold standard for tissue assessment in clinical decision making and in research. However, conventional histological preparation and analysis is known to be time consuming and labour intensive and misclassification can result in major

consequences such as reduce the patient's survivability. However, an efficient computer based diagnostic system can overcome the manual evaluation of medical imaging which is a time-consuming and not perfect as it is prone to human error and dependent on radiologist's skills and knowledge. Recently, DL has demonstrated promising results as a decision support system to assist in the detection of diseases and the establishment of precise medical diagnoses. Such a system can help in not only improving the accuracy of brain tumour diagnosis but also important in LMICs where access to trained pathologists may be limited and the workload may be high. These DL models are fast at runtime i.e.; these can process an image in a fraction of a second to a few seconds for example recently researchers in John Hopkin proposed a model that can classify a brain tumour within 150 seconds.[15] The proposed system with AI/DL in the background and its advance features of explainability in front end within telepathology system having a user-friendly graphical user interface can greatly help LMICs by reducing the need for trained pathologists and the resources required for the diagnosis process. The XAI part will augment the decision power of medical professionals.

Conclusion

In conclusion, considering the above benefits, a feasibility study is required to check the practicality of such an AI based system that will use the histopathological images of intraoperative brain smear, to see the potential for its implementation in LMICs.

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Conflict of Interest: None.

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