9-8-2023

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SNI: General Neurosurgery

**Editor**
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*Review Article*

# Unveiling the potential application of intraoperative brain smear for brain tumor diagnosis in low-middle-income countries: A comprehensive systematic review

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Received: 09 June 2023
Accepted: 15 August 2023
Published: 08 September 2023

**DOI**
10.25259/SNI_491_2023

**Quick Response Code:**

## ABSTRACT

**Background:** Immediate intraoperative histopathological examination of tumor tissue is indispensable for a neurosurgeon to track surgical resection. A brain smear is a simple, rapid, and cost-effective technique, particularly important in the diagnosis of brain tumors. The study aims to determine the effectiveness of intraoperative brain smear in the diagnosis of brain tumors in low- and middle-income countries (LMICs), while also evaluating its sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy.

**Methods:** A comprehensive search of the literature was conducted using PubMed, Scopus, and Google Scholar. The retrieved articles were independently screened by two reviewers. The data was extracted, processed, and organized using Microsoft Excel.

**Results:** A total of 59 out of 553 articles screened were included in the final analysis. The sensitivity and specificity of the intraoperative smear of brain tumors were found to be over 90% in most studies. The PPV was consistently above 90% in 11 studies, reaching 100% in one study and the NPV varied, ranging from 63% to 100%, and the accuracy was found to be >80% in most studies. One recurrent theme in the majority of the included studies was that an intraoperative brain smear is a cost-effective, quick, accessible, and accurate method of diagnosing brain tumors, requiring minimal training and infrastructure.

**Conclusion:** Intraoperative brain smear is a simple, rapid, cost-effective, and highly sensitive diagnostic modality for brain tumors. It can be a viable and accessible alternative to more traditional methods such as frozen sections and can be incorporated into neurosurgical practice in LMICs as a reliable and efficient diagnostic tool.

**Keywords:** Brain tumors, Intraoperative brain smear, Low- and middle-income countries

## INTRODUCTION

Brain tumors are a group of malignancies that can originate from cells within the brain (primary tumors) or from systemic tumors that have spread to the brain (secondary tumors).[38] A global

age-standardized incidence of primary malignant brain tumors is 2.6 per 100,000 for females and 3.7 per 100,000 for males annually.[7] Between 1990 and 2016, the rate of central nervous system (CNS) cancer increased by 9.3% in countries with a low sociodemographic index, 7.0% in countries with a low-middle sociodemographic index, 26.1% in countries with a middle sociodemographic index, and 22.0% in countries with a high sociodemographic index.[51]

For a neurosurgeon, an instant intraoperative histopathological examination of tumor tissue is a critical tool to monitor surgical resection by differentiating normal brain histology from a tumor.[69] An early diagnosis can potentially help the neurosurgeon determine the scope of the operation.[52] The current modalities available for intraoperative brain tumor examination include stimulated Raman histology, frozen sections (hematoxylin and eosin-stain), and cytological methods.

The process of obtaining a frozen section, the gold standard for intraoperative histopathological examination, is time-consuming and can delay surgical treatment. It involves delivering tissue to a laboratory, processing the specimen, preparing slides by technicians, and interpreting the slides by a pathologist.[52] Frozen section results can take 20–23 min,[3,48] compared to histopathology, which takes 2–3 days.[30] The propensity of brain tissue to form ice-crystal artifacts makes frozen slices difficult to analyze,[63] and the interpretation of frozen sections can have a high error rate due to factors such as tumor heterogeneity, surgeon error, pathologist interpretation error, and technical artifacts.[53] In addition, the process is labor-intensive, expensive, and requires specialized personnel, making it less financially feasible for patients in resource-limited countries.[22] However, an intraoperative brain smear is another diagnostic option and can be performed within 10–20 min.[25]

Since 1930, when Eisenhardt and Cushing proposed the use of a touch imprint for rapid tumor identification, cytological methods have been utilized to diagnose brain tumors.[15] The available brain smear techniques are touch or imprint smear and squash or crush smear. Brain smear is a simple and quick process. The nature of CNS tumors is particularly soft and gel-like; squash smears are particularly advantageous, as it uses this property to cause cytological features to be clearly observed in smears. The precise location, radiological results, and clinical presentation of the patient aid the pathologist in determining the cytological diagnosis.[27]

The main goals of intraoperative neuropathologic consultation for neurosurgeons are to guarantee that the diagnostic specimen was collected with the least amount of trauma and to ensure an immediate and appropriate treatment.[62] The smear preparation technique has been proven to be helpful as a supplement to imprint cytology for better diagnostic accuracy. Brain smears consider both cytological and architectural aspects of CNS tumors, in addition to background matrix and necrosis.[10,40]

Brain smear techniques are relatively cheap compared to other modalities available and can be conducted within the operating room without any specialized equipment or specialized technicians being involved, which holds advantages for low- and middle-income countries (LMICs).[52]

The objective of this study is to determine the usefulness of intraoperative brain smears in the diagnosis of brain tumors in LMICs through a systematic review of the existing literature. The review aims to evaluate the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of intraoperative brain smears as a diagnostic tool in LMICs.

## MATERIALS AND METHODS

This systematic review was conducted following our research protocol, which was based on the research question using population, intervention, control, and outcome. The preferred reporting items for systematic reviews and meta-analyses reporting standards were followed.[41,43]

### Eligibility criteria

This review analyzes the use of intraoperative brain smears during surgical procedures of brain tumors, both primary and metastatic. Studies eligible for inclusion were observational studies, including cohort studies, and randomized and nonrandomized controlled trials. The literature searched included articles that presented epidemiological, clinical, and laboratory aspects of the use of brain smears during tumor procedures. All age groups were included in this review. Studies were excluded from the study: editorials, case reports, case series ($n < 10$), studies published as abstracts only, letters to the editor, book chapters, and theses, as well as articles on spine tumors or other brain pathologies.

Final histopathology served as the gold standard test for evaluating diagnostic accuracy. This provided a definitive diagnosis based on tissue examination and has been widely recognized for its reliability and validity. Only studies utilizing the final histopathology report as the reference standard were included in our analysis.

### Search strategy

A comprehensive search was conducted across multiple electronic databases, including PubMed, Scopus, and Google Scholar, with no language restrictions. The search encompassed articles from inception to December 25, 2022, and all searches were performed on the same date. We searched for relevant phrases in the Medical Subject

Headings database and selected the following free-text terms as keywords: "brain neoplasms" OR "brain tumor*" AND "brain smear" OR "intraoperative cytology" OR "intraoperative squash cytology" OR "imprint cytology" OR "touch cytology" to yield a comprehensive and inclusive dataset. The included studies were searched for forward citations to ensure that all the relevant literature are included in the study. The detailed search strategy for each database is available in the supplementary document.

### Study selection

All retrieved studies' titles and abstracts were initially screened by two reviewers (SAA and HH) for duplication and relevancy according to our research question. The final study selection was made after an independent review by two reviewers (SAA and HH) of the full texts of all possibly pertinent studies. A consensus was reached by a third author (MS) to settle conflicts.

### Data extraction

Study characteristics (study title, authors, date of publication, publication type, study location, and sample size), population characteristics, study objective, advantages of the mentioned brain smear techniques, test characteristics (accuracy, sensitivity, specificity, PPV, and NPV), and study outcomes were extracted from eligible articles. Two authors independently extracted the data (SAA, HH). A third author (MS) corrected errors in data extraction and double-checked the information collected. Two authors (SAA and AA) independently evaluated each study's quality using the Newcastle–Ottawa scale quality assessment.[68]

The review underwent rigorous data validation, involving cross-referencing data from multiple sources, applying validation criteria, and resolving discrepancies through reviewer consensus. Data cleaning removed errors and inconsistencies while missing data were managed using the method of exclusion.

### Data analysis

The data were processed and analyzed using Microsoft Excel. For ease of reporting and comprehension, the extracted data were cleaned and organized into tables.

## RESULTS

Our initial search for relevant studies identified a total of 553 articles. After removing duplicates and reviewing the titles and abstracts, 88 studies were reviewed in full text. A total of 59 articles were included in the final analysis.[2,4-6,10-21,23-29,31-33,35-37,39,42,44-47,49,50,52,54-67,70-75] The majority of studies included in this review were conducted in LMICs, with single-center retrospective or prospective designs. Many of these studies were conducted in India. Out of the 59 studies, 52 were conducted in LMIC settings, of which 39 were conducted in India, as shown in Table 1. The most common brain tumors evaluated using this technique were gliomas, meningiomas, pituitary adenomas, and schwannomas. The majority of the articles compared the squash smear diagnostic technique with final histopathology or frozen sections, while in a few studies, imprint cytology was also considered.

The process of screening and selecting these studies, including the removal of duplicates and review of titles and abstracts, is shown in Figure 1. The kappa score, a measure of inter-rater reliability, between the two reviewers (HH and SAA) was high at both the title and abstract screening stage (Cohen's k = 0.81) and the full-text review stage (Cohen's k = 0.83).[9] The majority of the studies demonstrated high quality, with only six studies classified as having moderate quality. The detailed quality assessment is shown in Table 2.

The results of the analysis indicate that the sensitivity of intraoperative smear in detecting brain tumors was found to be more than 90% in the majority of cases (12 studies) and 100% in two studies. However, it should be noted that one study reported a sensitivity of 56%. In terms of specificity, the findings showed greater variability, with six studies reporting a specificity of >90%, while one study reported a specificity of 100%. The lowest reported specificity was observed in the range of 75–76%.

The PPV was reported above 90% in the majority of the studies (11 studies) and in one study, it was 100%. However, the lowest value reported was 75%. The NPV demonstrated a wide range, with the lowest value reported being 63% and the highest being 100%, as documented in three studies. However, the majority of studies (seven in total) that reported NPV fell within the range of 80–100%.

Overall, the accuracy of intraoperative smears for detecting brain tumors was reported >80% in the majority of studies (47 studies). It is important to note that the accuracy of any diagnostic test can be influenced by various factors, including the specific technique used and the characteristics of the population being tested. The detailed results of the studies on sensitivity, specificity, PPV, NPV, and accuracy are shown in Table 3 and Figure 2.

Articles in this review also discussed numerous advantages of intraoperative smear including cost-effectiveness, minimal infrastructure requirements, rapid (10–15 min), accessibility, and accuracy in diagnosis. Intraoperative smear was reported to be relatively inexpensive compared to more complex tests, and it can be performed using basic equipment and facilities.

## DISCUSSION

This is the first comprehensive review that evaluates the sensitivity, specificity, positive and NPVs, and accuracy of an

**Table 1:** Baseline characteristics of included studies.

| S. No. | Study name | Country | Study design | Sample size | Pediatric and/or adult | Squash and/or imprint smear cytology |
|---|---|---|---|---|---|---|
| 1. | Tele 2006[70] | India | Prospective | 100 | Adult | Squash |
| 2. | Chand *et al.* 2016[11] | India | Prospective | 80 | Adult | Squash |
| 3. | Balsimelli *et al.* 2019[5] | Brazil | Retrospective | 133 | Adult | Squash |
| 4. | Fujita *et al.* 2022[16] | Japan | Retrospective | 71 | Adult | Squash |
| 5. | Hiryur *et al.* 2019[20] | India | Cross-sectional | 65 | Adult | Squash |
| 6. | Jain K *et al.* 2022[23] | India | Prospective | 55 | Paediatric | Squash |
| 7. | Krishnani *et al.* 2012[34] | India | Retrospective | 334 | Both | Squash |
| 8. | Kumarguru *et al.* 2021[36] | India | Retrospective | 50 | Adult | Squash |
| 9. | Maity *et al.* 2019[39] | India | Prospective | 42 | Pediatric | Squash |
| 10. | Ud Din *et al.* 2011[73] | Pakistan | Prospective | 171 | Both | Squash |
| 11. | Nasreen *et al.* 2015[46] | Bangladesh | Cross-sectional | 64 | Both | Squash |
| 12. | Patil *et al.* 2016[52] | India | Retrospective | 50 | Both | Squash |
| 13. | Savargaonkar *et al.* 2001[63] | USA | Retrospective | 103 | Both | Squash |
| 14. | Acharya *et al.* 2016[1] | India | Prospective Longitudinal | 222 | Both | Squash |
| 15. | Samal *et al.* 2017[61] | India | Prospective | 63 | Adult | Squash |
| 16. | Jain S *et al.* 2022[24] | India | Prospective | 53 | Both | Squash |
| 17. | Govindaraman *et al.* 2017[18] | India | Prospective | 75 | Adult | Squash |
| 18. | Kishore *et al.* 2018[33] | India | Prospective | 127 | Both | Squash |
| 19. | Zulkarnain *et al.* 2020[75] | Malaysia | Cross-sectional | 22 | Both | Squash |
| 20. | Sarkar *et al.* 2017[62] | India | Prospective | 107 | Both | Squash |
| 21. | Salami *et al.* 2015[60] | Nigeria | Retrospective | 69 | Both | Both |
| 22. | Sharma *et al.* 2011[65] | India | Cross-sectional | 149 | Adult | Both |
| 23. | Hamasaki *et al.* 2017[19] | Canada | Retrospective | 400 | Both | Both |
| 24. | Agrawal *et al.* 2014[2] | India | Retrospective | 41 | Adult | Squash |
| 25. | Anita *et al.* 2019[4] | India | Prospective | 16 | Adult | Squash |
| 26. | Goel *et al.* 2007[17] | India | Retrospective | 3057 | Adult | Squash |
| 27. | Jaiswal *et al.* 2012[25] | India | Retrospective | 326 | Adult | Squash |
| 28. | Jindal *et al.* 2017[27] | India | Retrospective | 150 | Pediatric | Squash |
| 29. | Jindal *et al.* 2017[28] | India | Prospective | 150 | Both | Squash |
| 30. | Lone *et al.* 2018[37] | Indian-occupied Kashmir | Retrospective | 550 | Both | Squash |
| 31. | Nalinimohan *et al.* 2018[44] | India | Prospective | 131 | Adult | Squash |
| 32. | Olasode *et al.* 2004[49] | Nigeria | Pilot Study | 18 | Adult | Squash |
| 33. | Pala *et al.* 2022[50] | Turkey | Prospective | 55 | Adult | Squash |
| 34. | Qiao *et al.* 2019[54] | USA/China | Retrospective | 403 | Adult | Squash |
| 35. | Raju *et al.* 2018[55] | India | Prospective | 50 | Both | Squash |
| 36. | Rani *et al.* 2014[57] | India | Comparative | 110 | Both | Squash |
| 37. | Roessler *et al.* 2002[59] | Austria | Retrospective | 4172 | Adult | Squash |
| 38. | Shah *et al.* 1998[64] | India | Cross-sectional | 180 | Adult | Squash |
| 39. | Shukla *et al.* 2006[67] | India | Comparative | 278 | Both | Squash |
| 40. | Tena-Suck *et al.* 2012[71] | Mexico | Retrospective | 30 | Both | Squash |
| 41. | Kumar *et al.* 2013[35] | India | Retrospective | 63 | Both | Squash |
| 42. | Yadav *et al.* 2022[74] | India | Retrospective | 273 | Both | Squash |
| 43. | Bhagyalakshmi *et al.* 2012[6] | India | Prospective | 81 | NR (Mean Age - 35) | Squash |
| 44. | Nigam *et al.* 2012[47] | India | Prospective | 75 | Both | Squash |
| 45. | Shrestha *et al.* 2014[66] | Nepal | Prospective | 60 | NR | Squash |
| 46. | Mitra *et al.* 2010[42] | India | Prospective | 114 | NR | Squash |
| 47. | Rao *et al.* 2009[58] | India | Retrospective | 120 | NR | Squash |
| 48. | Kini *et al.* 2009.[32] | India | Prospective | 100 | NR | Squash |

*(Contd...)*

**Table 1:** *(Continued)*.

| S. No. | Study name | Country | Study design | Sample size | Pediatric and/or adult | Squash and/or imprint smear cytology |
|---|---|---|---|---|---|---|
| 49. | Jha *et al*. 2013[26] | India | Prospective | 35 | Both | Squash |
| 50. | Tena-Suck *et al*. 2015[72] | Mexico | Retrospective | 22 | Adult | Squash |
| 51. | Chaturvedi *et al*. 2013[12] | India | Retrospective | 333 | Adult | Squash |
| 52. | Cheunsuchon *et al*. 2014[13] | Thailand | Retrospective | 698 | Both | Squash |
| 53. | Deshpande *et al*. 2010[14] | India | Prospective | 250 | Both | Squash |
| 54. | Ramana *et al*. 2018[56] | India | Prospective | 111 | Both | Squash |
| 55. | Brommeland *et al*. 2003[10] | Norway | Comparative | 153 | Adult | Imprint |
| 56. | Nanarng *et al*. 2015[45] | India | Prospective | 75 | Both | Both |
| 57. | Khamechian *et al*. 2012[31] | Iran | Prospective | 139 | Adult | Imprint |
| 58. | Hitchcock *et al*. 1986[21] | England | Cross-sectional | 100 | Adult | Both |
| 59. | Kang *et al*. 2019[29] | Korea | Retrospective | 454 | NR | Both |

NR: Not reported

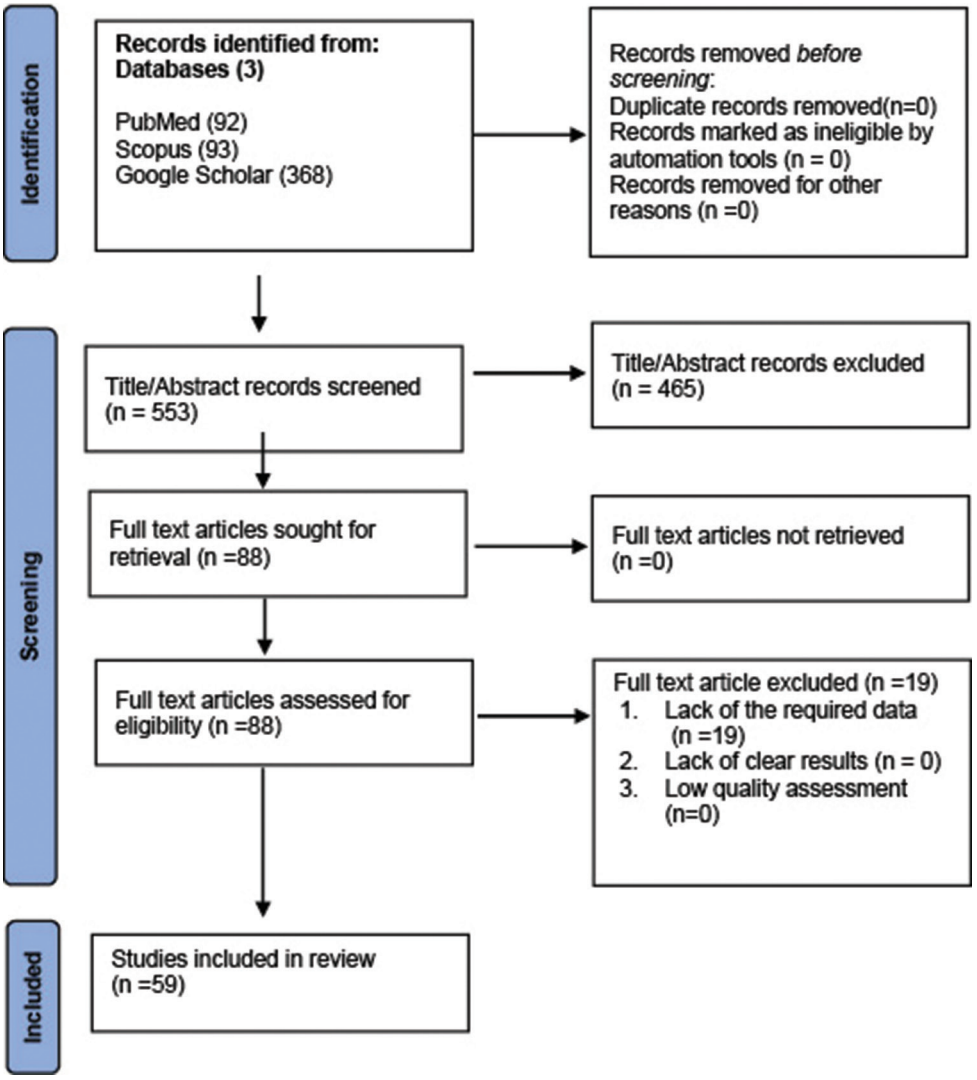


**Figure 1:** Preferred reporting items for systematic reviews and meta-analyses flow diagram. Number (*n*).

**Table 2:** Quality assessment of the included studies.

| S. No. | Study name | Selection (4) | Comparability (2) | Exposure/outcome (3) | Overall star rating (9) |
|---|---|---|---|---|---|
| 1. | Tele *et al.* 2006[70] | ☆☆☆ | ☆☆ | ☆☆ | 7 |
| 2. | Chand *et al.* 2016[11] | ☆☆☆ | ☆☆ | ☆☆☆ | 8 |
| 3. | Balsimelli *et al.* 2019[5] | ☆☆☆☆ | ☆☆ | ☆☆ | 8 |
| 4. | Fujita *et al.* 2022[16] | ☆☆☆ | ☆☆ | ☆☆ | 7 |
| 5. | Hiryur *et al.* 2019[20] | ☆☆☆ | ☆ | ☆☆ | 6 |
| 6. | Jain K *et al.* 2022[23] | ☆☆☆ | ☆ | ☆☆ | 6 |
| 7. | Krishnani *et al.* 2012[34] | ☆☆☆☆ | ☆☆ | ☆☆☆ | 8 |
| 8. | Kumarguru *et al.* 2021[36] | ☆☆☆ | ☆☆ | ☆☆ | 7 |
| 9. | Maity *et al.* 2019[39] | ☆☆☆ | ☆☆ | ☆☆ | 7 |
| 10. | Ud Din *et al.* 2011[73] | ☆☆☆☆ | ☆☆ | ☆☆ | 8 |
| 11. | Nasreen *et al.* 2015[46] | ☆☆☆ | ☆☆ | ☆☆☆ | 8 |
| 12. | Patil *et al.* 2016[52] | ☆☆☆ | ☆☆ | ☆☆☆ | 8 |
| 13. | Savargaonkar *et al.* 2001[63] | ☆☆☆☆ | ☆☆ | ☆☆☆ | 8 |
| 14. | Acharya *et al.* 2016[1] | ☆☆ | ☆☆ | ☆☆ | 6 |
| 15. | Samal *et al.* 2017[61] | ☆☆☆ | ☆☆ | ☆☆☆ | 8 |
| 16. | Jain S *et al.* 2021[24] | ☆☆☆ | ☆☆ | ☆☆ | 7 |
| 17. | Govindaraman *et al.* 2017[18] | ☆☆☆ | ☆☆ | ☆☆ | 7 |
| 18. | Kishore *et al.* 2018[33] | ☆☆☆☆ | ☆☆ | ☆☆☆ | 9 |
| 19. | Zulkarnain *et al.* 2020[75] | ☆☆☆☆ | ☆☆ | ☆☆☆ | 9 |
| 20. | Sarkar *et al.* 2017[62] | ☆☆☆ | ☆ | ☆☆ | 6 |
| 21. | Salami *et al.* 2015[60] | ☆☆☆ | ☆☆ | ☆☆☆ | 8 |
| 22. | Sharma *et al.* 2011[65] | ☆☆☆☆ | ☆☆ | ☆☆☆ | 9 |
| 23. | Hamasaki *et al.* 2017[19] | ☆☆☆☆ | ☆☆ | ☆☆☆ | 9 |
| 24. | Agrawal *et al.* 2014[2] | ☆☆☆ | ☆☆ | ☆☆☆ | 8 |
| 25. | Anita *et al.* 2019[4] | ☆☆☆ | ☆ | ☆☆ | 6 |
| 26. | Goel *et al.* 2007[17] | ☆☆☆☆ | ☆☆ | ☆☆ | 8 |
| 27. | Jaiswal *et al.* 2012[25] | ☆☆☆☆ | ☆☆ | ☆☆ | 8 |
| 28. | Jindal *et al.* 2017[27] | ☆☆☆☆ | ☆☆ | ☆☆☆ | 9 |
| 29. | Jindal *et al.* 2017[28] | ☆☆☆☆ | ☆☆ | ☆☆☆ | 9 |
| 30. | Lone *et al.* 2018[37] | ☆☆☆☆ | ☆☆ | ☆☆ | 8 |
| 31. | Nalinimohan *et al.* 2018[44] | ☆☆☆☆ | ☆☆ | ☆☆☆ | 9 |
| 32. | Olasode *et al.* 2004[49] | ☆☆☆ | ☆☆ | ☆☆☆ | 8 |
| 33. | Pala *et al.* 2022[50] | ☆☆☆ | ☆☆ | ☆☆☆ | 8 |
| 34. | Qiao *et al.* 2019[54] | ☆☆☆☆ | ☆☆ | ☆☆ | 8 |
| 35. | Raju *et al.* 2018[55] | ☆☆☆ | ☆☆ | ☆☆ | 7 |
| 36. | Rani *et al.* 2014[57] | ☆☆☆☆ | ☆☆ | ☆☆☆ | 9 |
| 37. | Roessler *et al.* 2002[59] | ☆☆☆☆ | ☆☆ | ☆☆☆ | 9 |
| 38. | Shah *et al.* 1998[64] | ☆☆☆☆ | ☆☆ | ☆☆ | 8 |
| 39. | Shukla *et al.* 2006[67] | ☆☆☆☆ | ☆☆ | ☆☆ | 8 |
| 40. | Tena-Suck *et al.* 2012[71] | ☆☆☆ | ☆☆ | ☆☆ | 7 |
| 41. | Kumar *et al.* 2013[35] | ☆☆☆ | ☆☆ | ☆☆☆ | 8 |
| 42. | Yadav *et al.* 2022[74] | ☆☆☆☆ | ☆☆ | ☆☆☆ | 9 |
| 43. | Bhagyalakshmi *et al.* 2012[6] | ☆☆☆ | ☆☆ | ☆☆☆ | 8 |
| 44. | Nigam *et al.* 2012[47] | ☆☆☆ | ☆☆ | ☆☆☆ | 8 |
| 45. | Shrestha *et al.* 2014[66] | ☆☆☆ | ☆☆ | ☆☆☆ | 8 |
| 46. | Mitra *et al.* 2010[42] | ☆☆☆☆ | ☆☆ | ☆☆☆ | 9 |
| 47. | Rao *et al.* 2009[58] | ☆☆☆☆ | ☆☆ | ☆☆☆ | 9 |
| 48. | Kini *et al.* 2009.[32] | ☆☆☆☆ | ☆☆ | ☆☆ | 8 |
| 49. | Jha *et al.* 2013[26] | ☆☆☆ | ☆☆ | ☆☆☆ | 8 |
| 50. | Tena-Suck *et al.* 2015[72] | ☆☆☆ | ☆ | ☆☆ | 6 |
| 51. | Chaturvedi *et al.* 2013[12] | ☆☆☆☆ | ☆☆ | ☆☆ | 8 |
| 52. | Cheunsuchon *et al.* 2014[13] | ☆☆☆☆ | ☆☆ | ☆☆☆ | 9 |
| 53. | Deshpande *et al.* 2010[14] | ☆☆☆☆ | ☆☆ | ☆☆ | 8 |
| 54. | Ramana *et al.* 2018[56] | ☆☆☆☆ | ☆☆ | ☆☆☆ | 9 |

*(Contd...)*

**Table 2:** *(Continued).*

| S. No. | Study name | Selection (4) | Comparability (2) | Exposure/outcome (3) | Overall star rating (9) |
|---|---|---|---|---|---|
| 55. | Brommeland *et al.* 2003[10] | ☆☆☆☆ | ☆☆ | ☆☆☆ | 9 |
| 56. | Nanarng *et al.* 2015[45] | ☆☆☆ | ☆☆ | ☆☆☆ | 8 |
| 57. | Khamechian *et al.* 2012[31] | ☆☆☆☆ | ☆☆ | ☆☆ | 8 |
| 58. | Hitchcock *et al.* 1986[21] | ☆☆☆☆ | ☆☆ | ☆☆ | 8 |
| 59. | Kang *et al.* 2019[29] | ☆☆☆☆ | ☆☆ | ☆☆☆ | 9 |

The table displays the individual scores (☆) obtained by each study, indicating the score achieved out of the maximum possible score (shown in parentheses) for each category. In addition, it presents the combined overall score (Overall star rating). It is important to note that each (☆) represents one point

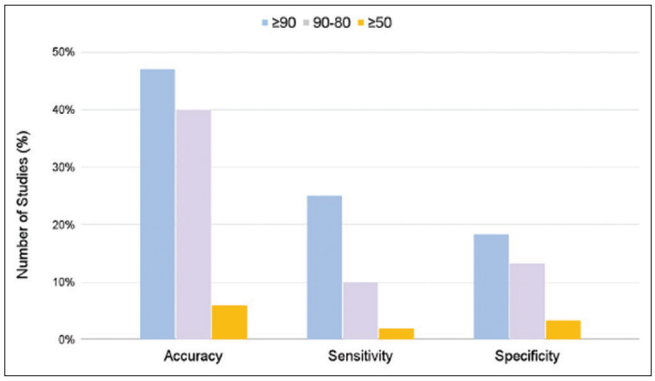


**Figure 2:** The Y-axis of the graph represents the frequency (%) of studies reporting the values of accuracy, sensitivity, and specificity of brain smear, while the X-axis represents the actual values of accuracy, sensitivity, and specificity. The values on the X-axis are categorized as ≥ 90, 90–80, and ≥ 50, which correspond to different levels of sensitivity, specificity, and accuracy.

intraoperative brain smear. It also highlights its advantages for resource-limited settings where there is a shortage of trained histopathologists and histopathology facilities.

This review reported the diagnostic accuracy of the intraoperative brain smear as >80%, as reported in the majority of studies. Sensitivity and specificity values were similarly high, with more than 90% reported in most studies. In addition, most studies reported positive and NPVs >90%. The main advantages reported include it being a rapid, simple, reliable, and cost-effective tool for diagnosis. Other advantages include high accuracy,[20] ease of smear given the friable quality of brain tumors,[23] and use of minimal brain tissue.[2] Thus, the use of intraoperative brain smear techniques has proven to be an effective tool in the diagnosis of brain tumors in patients undergoing surgery. This approach can efficiently reduce and potentially eliminate the need for additional surgeries to achieve negative margins in such patient populations.

A frequently cited benefit of intraoperative brain smears, as noted in many of the studies, is the considerably shorter time required for diagnosis compared to conventional techniques. As per the study by Jaiswal *et al.*,[25] the time required for reporting the results of intraoperative brain smears is approximately 10–20 min from the point of receipt. This stands in stark contrast to the duration of at least 2–3 working days required for final histopathology,[30] making intraoperative brain smear a much swifter alternative. In comparison to histopathology, frozen section – another frequently utilized technique for intraoperative diagnosis of brain tumors – also represents a time-saving method, with the diagnosis being made within 20–23 min.[3,48] However, this method requires the availability of a cryostat machine and various laboratory equipment – which is often not available in LMIC settings. While the advantages of intraoperative brain smears are numerous, it also does not compromise on accuracy, sensitivity, and specificity of the diagnosis. Histopathological diagnosis is typically considered the gold standard of diagnosis, and squash smear diagnosis has proven to have comparable high accuracy rates, ranging from 85% and above in our review. One study found the sensitivity and specificity of frozen sections to be slightly higher than squash smear (86.67% vs. 91.67%); however, this study did not find any significant difference in their accuracy levels, indicating the techniques are complementary procedures.[24]

False positives and false negatives were reported in a few of the studies, as a small minority of the total sample size. One reason for this misdiagnosis through a squash smear was due to specific tumors such as ependymomas and meningiomas not being able to smear due to their firm nature.[52] Other reasons include distortion of histological detail on the smear and sampling errors.[44] Lymphomas, in particular, were misdiagnosed due to lymphogranuloma bodies being appreciated better on histopathological diagnosis than smears.[7] Trouble was also faced by multiple authors during the grading of astrocytomas, mainly due to their heterogeneity.[44,57]

Intraoperative brain smears are highly accurate (95.3%) and reliable as a primary diagnostic tool for planning treatment.[46] The accuracy of this tool for detecting brain tumors is reported to be 80% or above in the majority of our studies. However, few studies in this review assessed the diagnostic accuracy of intraoperative squash smears using only specific kinds of tumors. For example, Qiao *et al.* studied the accuracy of squash smear on pituitary microadenomas.[54] They reported an accuracy rate of 80.9% and commented

**Table 3:** Characteristics of Intra-operative brain smear.

| S. No. | Study name | Sample size | Country | Study design | Pediatric and/or adult | Squash and/or imprint smear cytology | Test characteristic | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Sensitivity % | Specificity % | PPV % | NPV % | Accuracy % |
| 1. | Bhagyalakshmi *et al.* 2012[6] | 81 | India | Prospective | NR (Mean Age – 35) | Squash | 90 | 100 | NR | NR | 96.20 |
| 2. | Tele *et al.* 2006[69] | 100 | India | Prospective | Adult | Squash | 86 | 98 | 97 | 90 | 92 |
| 3. | Chand *et al.* 2016[11] | 80 | India | Prospective | Adult | Squash | 96 | 100 | NR | NR | 91 |
| 4. | Balsimelli *et al.* 2019[5] | 133 | Brazil | Retrospective | Adult | Squash | 98 | 94 | 99 | 84 | 85 |
| 5. | Fujita *et al.* 2022[16] | 71 | Japan | Retrospective | Adult | Squash | 56 | 87 | NR | NR | 80 |
| 6. | Hiryur *et al.* 2019[20] | 65 | India | Cross-sectional | Adult | Squash | 90 | NR | NR | NR | NR |
| 7. | Jain K *et al.* 2022[23] | 55 | India | Prospective | Pediatric | Squash | 88 | 90 | 96 | 69 | 63 |
| 8. | Krishnani *et al.* 2012[34] | 334 | India | Retrospective | Both | Squash | 98 | 87 | 98 | 87 | 94 |
| 9. | Kumarguru *et al.* 2021[36] | 50 | India | Retrospective | Adult | Squash | 100 | 88 | 97 | 100 | 72 |
| 10. | Maity *et al.* 2019[39] | 42 | India | Prospective | Pediatric | Squash | 92 | 87 | 96 | 77 | 73 |
| 11. | Ud Din *et al.* 2011[73] | 171 | Pakistan | Prospective | Both | Squash | 94 | 87 | 98 | 63 | 94 |
| 12. | Nasreen *et al.* 2015[46] | 64 | Bangladesh | Cross-sectional | Both | Squash | 87 | 100 | 100 | 93 | 95 |
| 13. | Patil *et al.* 2016[52] | 50 | | | | | 100 | 100 | 100 | 100 | 92 |
| 14. | Savargaonkar *et al.* 2001[63] | 103 | USA | Retrospective | Both | Squash | 94 | NR | NR | NR | 94 |
| 15. | Acharya *et al.* 2016[1] | 222 | India | Prospective Longitudinal | Both | Squash | 84 | NR | NR | NR | 83 |
| 16. | Samal *et al.* 2017[61] | 63 | India | Prospective | Adult | Squash | 94 | 85 | 98 | 66 | 93 |
| 17. | Jain K *et al.* 2021[23] | 53 | India | Prospective | Both | Squash | 86 | 87 | 81 | 91 | 84 |
| 18. | Govindaraman *et al.* 2017[18] | 75 | India | Prospective | Adult | Squash | 98 | 93 | 97 | 99 | 90 |
| 19. | Kishore *et al.* 2018[33] | 127 | India | Prospective | Both | Squash | 99 | 75 | 99 | 75 | 95 |
| 20. | Zulkarnain *et al.* 2020[75] | 22 | Malaysia | Cross-sectional | Both | Squash | 100 | 76 | 75 | 100 | 86 |
| 21. | Sarkar *et al.* 2017[62] | 107 | | | | | 94 | 97 | 94 | 97 | 100 |
| 22. | Salami *et al.* 2015[60] | 69 | Nigeria | Retrospective | Both | Both | 75–84* | 91–89* | NR | NR | 84–83* |
| 23. | Sharma *et al.* 2011[65] | 149 | India | Cross-sectional | Adult | Both | 90 - squash<br>92 - imprint | 87.5 - squash<br>90.6 - imprint | NR | NR | 89.3 - squash<br>92.0 - imprint |
| 24. | Hamasaki *et al.* 2017[19] | 400 | Canada | Retrospective | Both | Both | 97 | 100 | NR | NR | 95 |
| 25. | Agrawal *et al.* 2014[2] | 41 | India | Retrospective | Adult | Squash | NR | NR | NR | NR | 95 |
| 26. | Anita *et al.* 2019[4] | 16 | India | Prospective | Adult | Squash | NR | NR | NR | NR | NR |
| 27. | Goel *et al.* 2007[17] | 3057 | India | Retrospective | Adult | Squash | NR | NR | NR | NR | 84 |
| 28. | Jaiswal *et al.* 2012[25] | 326 | India | Retrospective | Adult | Squash | NR | NR | NR | NR | 83 |
| 29. | Jindal *et al.* 2017[27] | 150 | India | Retrospective | Pediatric | Squash | NR | NR | NR | NR | 94 |
| 30. | Jindal *et al.* 2017[28] | 150 | India | Prospective | Both | Squash | NR | NR | NR | NR | 94 |
| 31. | Lone *et al.* 2018[37] | 550 | Indian-occupied Kashmir | Retrospective | Both | Squash | NR | NR | NR | NR | 86 |

*(Contd...)*

**Table 3:** *(Continued).*

| S. No. | Study name | Sample size | Country | Study design | Pediatric and/or adult | Squash and/or imprint smear cytology | Test characteristic | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Sensitivity % | Specificity % | PPV % | NPV % | Accuracy % |
| 32. | Nalinimohan *et al.* 2018[44] | 131 | India | Prospective | Adult | Squash | NR | NR | NR | NR | 95 |
| 33. | Olasode *et al.* 2004[49] | 18 | Nigeria | Pilot study | Adult | Squash | NR | NR | NR | NR | 94 |
| 34. | Pala *et al.* 2022[50] | 55 | Turkey | Prospective | Adult | Squash | NR | NR | NR | NR | 96 |
| 35. | Qiao *et al.* 2019[54] | 403 | USA/China | Retrospective | Adult | Squash | NR | NR | NR | NR | 80 |
| 36. | Raju *et al.* 2018[55] | 50 | India | Prospective | Both | Squash | NR | NR | NR | NR | 82 |
| 37. | Rani *et al.* 2014[57] | 110 | India | Comparative | Both | Squash | NR | NR | NR | NR | 93 |
| 38. | Roessler *et al.* 2002[59] | 4172 | Austria | Retrospective | Adult | Squash | NR | NR | NR | NR | 95 |
| 39. | Shah *et al.* 1998[64] | 180 | India | Cross-sectional | Adult | Squash | NR | NR | NR | NR | 89 |
| 40. | Shukla *et al.* 2006[67] | 278 | India | Comparative | Both | Squash | NR | NR | NR | NR | 87 |
| 41. | Tena-Suck *et al.* 2012[71] | 30 | Mexico | Retrospective | Both | Squash | NR | NR | NR | NR | 83 |
| 42. | Kumar *et al.* 2013[35] | 63 | India | Retrospective | Both | Squash | NR | NR | NR | NR | 88 |
| 43. | Yadav *et al.* 2022[74] | 273 | India | Retrospective | Both | Squash | NR | NR | NR | NR | 95 |
| 44. | Nigam *et al.* 2012[47] | 75 | India | Prospective | Both | Squash | NR | NR | NR | NR | 89 |
| 45. | Shrestha *et al.* 2014[66] | 60 | Nepal | Prospective | NR | Squash | NR | NR | NR | NR | 88 |
| 46. | Mitra *et al.* 2010[42] | 114 | India | Prospective | NR | Squash | NR | NR | NR | NR | 89 |
| 47. | Rao *et al.* 2009[58] | 120 | India | Retrospective | NR | Squash | NR | NR | NR | NR | 95 |
| 48. | Kini *et al.* 2009.[32] | 100 | India | Prospective | NR | Squash | NR | NR | NR | NR | 86 |
| 49. | Jha *et al.* 2013[26] | 35 | India | Prospective | Both | Squash | NR | NR | NR | NR | 82 |
| 50. | Tena-Suck *et al.* 2015[72] | 22 | Mexico | Retrospective | Adult | Squash | NR | NR | NR | NR | 70 |
| 51. | Chaturvedi *et al.* 2013[12] | 333 | India | Retrospective | Adult | Squash | NR | NR | NR | NR | 85 |
| 52. | Cheunsuchon *et al.* 2014[13] | 698 | Thailand | Retrospective | Both | Squash | NR | NR | NR | | 89 |
| 53. | Deshpande *et al.* 2010[14] | 250 | India | Prospective | Both | Squash | NR | NR | NR | NR | NR |
| 54. | Ramana *et al.* 2018[56] | 111 | India | Prospective | Both | Squash | NR | NR | NR | NR | 90 |
| 55. | Brommeland *et al.* 2003[10] | 153 | Norway | Comparative | Adult | Imprint | NR | NR | NR | NR | 91 |
| 56. | Nanarng *et al.* 2015[45] | 75 | India | Prospective | Both | Both | NR | NR | NR | NR | 89 |
| 57. | Khamechian *et al.* 2012[31] | 139 | Iran | Prospective | Adult | Imprint | NR | NR | NR | NR | 84 |
| 58. | Hitchcock *et al.* 1986[21] | 100 | England | Cross-sectional | Adult | Both | NR | NR | NR | NR | NR |
| 59. | Kang *et al.* 2019[29] | 454 | Korea | Retrospective | NR | Both | NR | NR | NR | NR | 98 |

NR: Not reported, *Low-grade-high-grade neoplasm. PPV: Positive predictive value, NPV: Negative predictive value

on how the decreased quantity of tissue available for diagnosis was best used by squash smear diagnosis. The few false-positive cases they encountered were due to misinterpretation of histology. Tena-Suck *et al*. did a study on craniopharyngiomas, reporting an accuracy rate of 83.33%.[71] Another study was conducted, testing the smear technique on just chordomas; the reported accuracy was 70%, which may be due to the small sample size ($n$ = 22) and insufficient sample tissue. The accuracy of brain smears increased in correlation with clinical details and radiological findings.[72]

This review highlighted some of the limitations of squash smears in the diagnosis of certain brain tumors. One is the misrepresentation of tumor tissue due to absent histological artifacts, which leads to inaccurate diagnoses being made.[28] This may be the case due to inadequate tissue being present on the smear slide. Another limitation is that not all brain tumors are soft enough to undergo the squash smear. Tumor types such as meningiomas and ependymomas are firmer in nature and, hence, can be better diagnosed through frozen sections rather than squash smears.[52] To avoid such issues, squash smear techniques could be used exclusively on soft, friable brain tumors, and frozen section diagnosis could be reserved for firmer tumors – where the equipment is available. To tackle the misrepresentation of tumors, using an adequate tissue sample while preparing smear slides is important. This could ensure enough cytological features are represented on the slide to make an accurate diagnosis.

This study is the first systematic review, to the best of our knowledge, conducted on the utility of intraoperative brain smears in brain tumor diagnosis. Overall, the results show that intraoperative brain smear is a rapid, simple, safe, cost-effective, and fairly accurate method of diagnosis of brain tumors which can improve service delivery efficiency and reduce the burden on healthcare systems in LMICs. This method could be especially beneficial in resource-limited settings, where the equipment for frozen sections is not often available and histopathological diagnosis also faces obstacles. There is a lack of trained histopathologists, limited availability of laboratory infrastructure, and limited advanced equipment to support the high demand for histopathological diagnosis. Our study reports the advantages of brain smear specifically for resource-limited settings, where other modalities of diagnosis are often not available.

### Limitation

This systematic review has some limitations, which should be taken into consideration when interpreting the findings. The majority of the articles taken into consideration were observational studies and may not provide strong evidence for the diagnostic accuracy of brain smears. Most of the studies reviews were also conducted in LMICs, namely, India, so the results may not be applicable to other parts of the world.

### Future direction

Further research is necessary to fully explore and understand the feasibility and implementation of intraoperative brain smears as a diagnostic modality for brain tumors in LMICs. Conducting further controlled studies, especially those that gather data from a larger range of countries, will provide better insight into the utility of the brain smear. Further, a comparison of the brain smear technique with other diagnostic modalities available will also provide valuable insight. Finally, guideline development regarding the use of brain smears in brain tumor diagnosis will be necessary for regulating the approach and improving the quality of care given worldwide.

## CONCLUSION

Our systematic review revealed that intraoperative brain smear is a simple, rapid, cost-effective, and highly sensitive diagnostic modality for brain tumors in LMICs. It appears from the included literature that brain smears in settings with limited resources can be a viable and accessible alternative to more traditional methods such as frozen sections. Furthermore, the results of the studies reviewed suggest that brain smears could be incorporated into neurosurgical practice in LMICs as a reliable and efficient diagnostic tool.

### Declaration of patient consent

Patients' consent not required as patients' identities were not disclosed or compromised.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

### Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The author(s) confirms that there was no use of Artificial Intelligence (AI)-Assisted Technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

## REFERENCES

1. Acharya S, Azad S, Kishore S, Kumar R, Arora P. Squash smear cytology, CNS lesions-Strengths and Limitations. Natl J Lab Med 2016;5:1-7.
2. Agrawal M, Chandrakar SK, Lokwani D, Purohit MR. Squash cytology in neurosurgical practice: A useful method in resource-limited setting with lack of frozen section facility. J Clin Diagn Res 2014;8:C09-12.

3. Ahmad Z, Barakzai MA, Idrees R, Bhurgri Y. Correlation of intra-operative frozen section consultation with the final diagnosis at a referral center in Karachi, Pakistan. Indian J Pathol Microbiol 2008;51:469-73.
4. Anita AM, Bhargava N, Patil AG, Andola SK. Clicopathological correlation in metastatic central nervous system tumor. J Med Sci Clin Res 2019;7:692-6.
5. Balsimelli LB, Oliveira JC, Adorno FÁ, Brites CA, Bublitz GS, Tavares LC, *et al*. Accuracy of intraoperative examination in central nervous system lesions: A study of 133 cases. Acta Cytol 2019;63:224-32.
6. Bhagyalakshmi A, Prasad KV, Uma P, Rao PS, Prasad PK, Hygreev RB. Role of squash smears, imaging and histopathology in diagnosing CNS lesions-a prospective study. Natl J Basic Med Sci 2012;2:213-20.
7. Bondy ML, Scheurer ME, Malmer B, Barnholtz-Sloan JS, Davis FG, Il'Yasova D, *et al*. Brain tumor epidemiology: consensus from the Brain Tumor Epidemiology Consortium. Cancer 2008;113:1953-68.
8. Boopathy T, Karthika V. An analysis of CNS tumors in squash preparations with histological correlation. IOSR J Dent Med Sci 2017;16:81-6.
9. Brenner H, Kliebsch U. Dependence of weighted kappa coefficients on the number of categories. Epidemiology 1996;7:199-202.
10. Brommeland T, Lindal S, Straume B, Dahl IL, Hennig R. Does imprint cytology of brain tumours improve intraoperative diagnoses? Acta Neurol Scand 2003;108:153-6.
11. Chand P, Amit S, Gupta R, Agarwal A. Errors, limitations, and pitfalls in the diagnosis of central and peripheral nervous system lesions in intraoperative cytology and frozen sections. J Cytol 2016;33:93-7.
12. Chaturvedi S, Pant I, Dua R, Gupta S. Analyzing agreement patterns of intraoperative central nervous system lesion reporting according to type and grade. J Cytol 2013;30:179-84.
13. Cheunsuchon P. Accuracy of intraoperative consultation of central nervous system lesions in Siriraj hospital. Siriraj Med J 2014;66:113-9.
14. Deshpande K, Surase S, Shedge R, D'costa G, Bharambe B. Accuracy and diagnostic yield of intraoperative squash smear technique in the rapid diagnosis of CNS lesions. Bombay Hosp J 2010;52:153-60.
15. Eisenhardt L, Cushing H. Diagnosis of intracranial tumors by supravital technique. Am J Pathol 1930;6:541-552.7.
16. Fujita H, Tajiri T, Machida T, Nomura N, Toguchi S, Itoh H, *et al*. Scoring system for intraoperative diagnosis of intracranial schwannoma by squash cytology. Cytopathology 2022;33:196-205.
17. Goel D, Sundaram C, Paul TR, Uppin SG, Prayaga AK, Panigrahi MK, *et al*. Intraoperative cytology (squash smear) in neurosurgical practice-pitfalls in diagnosis experience based on 3057 samples from a single institution. Cytopathology 2007;18:300-8.
18. Govindaraman P, Arumugam N, Ramasamy C, Prakasam G. Role of squash smear in intraoperative consultation of central nervous system tumors. J Sci Soc 2017;44:7.
19. Hamasaki M, Chang KH, Nabeshima K, Tauchi-Nishi PS. Intraoperative squash and touch preparation cytology of brain lesions stained with H+E and Diff-Quik™: A 20-year retrospective analysis and comparative literature review. Acta Cytol 2018;62:44-53.
20. Hiryur SP, Patel U, Sivaranjini N. Comparative study of frozen section and squash preparation for intraoperative diagnosis of CNS lesions and their correlation with paraffin sections in a tertiary care hospital, Vadodara. Int J Clin Diagn Pathol 2019;2:263-7.
21. Hitchcock E, Morris CS, Sotelo MG, Salmon M. Comparison of Smear and imprint techniques for rapid diagnosis in neuro-oncology. Surg Neurol 1986;26:176-82.
22. Jaafar H. Intra-operative frozen section consultation: Concepts, applications and limitations. Malays J Med Sci 2006;13:4-12.
23. Jain K, Sengupta M, Maity P, Chatterjee U, Chaudhuri S, Rajyalakshmi E, *et al*. Comparison of frozen section and squash cytology as intra-operative diagnostic tool in pediatric CNS tumors. Neurol India 2022;70:714-20.
24. Jain S, Kaushal M, Choudhary A, Bhardwaj M. Comparative evaluation of squash smear and frozen section in the intraoperative diagnosis of central nervous system tumours. Cytopathology 2022;33:107-13.
25. Jaiswal S, Vij M, Jaiswal AK, Behari S. Intraoperative squash cytology of central nervous system lesions: A single center study of 326 cases. Diagn Cytopathol 2012;40:104-12.
26. Jha B, Patel V, Patel K, Agarwal A. Squash smear technique in intraoperative diagnosis of CNS tumors 889. Int J Med Sci Public Health 2013;4:889-92.
27. Jindal A, Diwan H, Kaur K, Sinha VD. Intraoperative squash smear in central nervous system tumors and its correlation with histopathology: 1 year study at a tertiary care centre. J Neurosci Rural Pract 2017;8:221-4.
28. Jindal A, Kaur K, Mathur K, Kumari V, Diwan H. Intraoperative squash smear cytology in CNS lesions: A study of 150 pediatric cases. J Cytol 2017;34:217-20.
29. Kang M, Chung DH, Kim NR, Cho HY, Ha SY, Lee S, *et al*. Intraoperative frozen cytology of central nervous system neoplasms: An ancillary tool for frozen diagnosis. J Pathol Transl Med 2019;53:104-11.
30. Karnam S, Girish HC, Murgod S, Nayak VN, Varsha VK, Yanduri S. Rapid tissue processing technique: A novel method using methyl salicylate. J Oral Maxillofac Pathol 2018;22:443.
31. Khamechian T, Alizargar J, Mazoochi T. The value of touch preparation for rapid diagnosis of brain tumors as an intraoperative consultation. Iran J Med Sci 2012;37:105-11.
32. Kini JR, Jeyraj V, Jayaprakash CS, Indira S, Naik CN. Intraoperative consultation and smear cytology in the diagnosis of brain tumours. Kathmandu Univ Med J (KUMJ) 2008;6:453-7.
33. Kishore S, Thakur B, Bhardwaj A, Kusum A. Diagnostic accuracy of squash cytology and role of GFAP immuno expression in glial tumors. Indian J Pathol Oncol 2020;5:12-7.
34. Krishnani N, Kumari N, Behari S, Rana C, Gupta P. Intraoperative squash cytology: Accuracy and impact on immediate surgical management of central nervous system tumours. Cytopathology 2012;23:308-14.
35. Kumar Verma S, Kumar R, Srivani J, Jonathan J. Diagnostic accuracy of squash preparations in central nervous system tumors. Iran J Pathol 2013;8:227-34.
36. Kumarguru BN, Santhipriya G, Kumar SK, Kumar RR, Ramaswamy

AS, Janakiraman P. A comparative study of squash smear cytology diagnosis and radiological diagnosis with histopathology in central nervous system lesions. J Cytol 2022;39:1-8.
37. Lone MI, Jeelani T, Rashid G, Bashir N, Angmo D. Intraoperative squash cytology and histopathological correlation of primary temporal lobe lesions: A 6 year study at tertiary care centre of Kashmir, India. Int J Res Med Sci 2018;6:2148-52.
38. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, *et al*. The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol 2007;114:97-109.
39. Maity P, Sengupta M, Jain K, Chaudhuri S, Chatterjee U, Datta C, *et al*. Utility of intraoperative squash cytology in diagnosis of paediatric central nervous system lesions. Diagn Cytopathol 2019;47:428-33.
40. Marshall LF, Adams H, Doyle D, Graham DI. The histological accuracy of the smear technique for neurosurgical biopsies. J Neurosurg 1973;39:82-8.
41. McInnes MD, Moher D, Thombs BD, McGrath TA, Bossuyt PM, and the PRISMA-DTA Group, *et al*. Preferred reporting items for a systematic review and meta-analysis of diagnostic test accuracy studies: The PRISMA-DTA statement. JAMA 2018;319:388-96.
42. Mitra S, Kumar M, Sharma V, Mukhopadhyay D. Squash preparation: A reliable diagnostic tool in the intraoperative diagnosis of central nervous system tumors. J Cytol 2010;27:81-5.
43. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. BMJ 2009;339:332-6.
44. Nalinimohan C, Padmaja K, Shailaja P, Deshpande AK. Intraoperative squash cytology of central nervous system lesions: review of an eight-year experience. Indian J Pathol Res Pract 2018;7:1095-8.
45. Nanarng V, Jacob S, Mahapatra D, Mathew JE. Intraoperative diagnosis of central nervous system lesions: Comparison of squash smear, touch imprint, and frozen section. J Cytol 2015;32:153-8.
46. Nasreen S, Shahab M, Ahamad U, Rahman N. Intraoperative diagnosis of Cns tumor by crush cytologic technique and its histopathological correlation. J Chittagong Med Coll Teach Assoc 2015;26:40-3.
47. Nigam SK, Nigam N, Mishra A. Diagnostic accuracy of squash Smear technique in brain tumors. J Evol Med Dent Sci 2012;1:538-45.
48. Novis DA, Zarbo RJ. Interinstitutional comparison of frozen section turnaround time. A College of American Pathologists Q-Probes study of 32868 frozen sections in 700 hospitals. Arch Pathol Lab Med 1997;121:559-67.
49. Olasode BJ, Ironside JW. The brain smear, a rapid affordable intraoperative diagnostic technique for brain tumours appropriate for Africa. Trop Doct 2004;34:223-5.
50. Pala EE, Doğan E, Ekmekçi S, Özamrak BG, Çamlar M. Pala, *et al*. Diagnostic value of smears and frozen sections in neuropathology practice diagnostic value of smears and frozen sections in neuropathology practice: Institutional Experience. J Tepecik Educ Res Hosp 2022;32:51-8.
51. Patel AP, Fisher JL, Nichols E, Abd-Allah F, Abdela J, Abdelalim A, *et al*. Global, regional, and national burden of brain and other CNS cancer, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2019;18:376-93.
52. Patil SS, Kudrimoti JK, Agarwal RD, Jadhav MV, Chuge A. Utility of squash smear cytology in intraoperative diagnosis of central nervous system tumors. J Cytol 2016;33:205-9.
53. Plesec TP, Prayson RA. Frozen section discrepancy in the evaluation of nonneoplastic central nervous system samples. Ann Diagn Pathol 2009;13:359-66.
54. Qiao N, Swearingen B, Hedley-Whyte ET, Tritos NA. The utility of intraoperative cytological smear and frozen section in the surgical management of patients with Cushing's disease due to pituitary microadenomas. Endocr Pathol 2019;30:180-8.
55. Raju VS, Srirangaramasamy J, Balasubramanian D, Balamurugan M, Rajesh H, Murugan N. Diagnostic accuracy of squash cytology for rapid intraoperative diagnosis in tumors of nervous system. IOSR J Dent Med Sci 2018;17:27-32.
56. Ramana PV, Shyamala S. Diagnostic accuracy of central nervous system tumors by squash cytology. Int Arch Integr Med 2018;5:29-35.
57. Rani H, Kulkarni P, Dinesh US, Rao RV, Melkundi S. Comparison of squash smears and frozen sections versus paraffin sections in the intra-operative diagnosis of central nervous system lesions. El Med J 2014;2:101.
58. Rao S, Rajkumar A, Ehtesham MD, Duvuru P. Challenges in neurosurgical intraoperative consultation. Neurol India 2009;57:464-8.
59. Roessler K, Dietrich W, Kitz K. High diagnostic accuracy of cytologic smears of central nervous system tumors. A 15-year experience based on 4,172 patients. Acta Cytol 2002;46:667-74.
60. Salami A, Azeez A, Malomo A, Oluwasola A, Adeleye A, Ogun G, *et al*. Correlation of intraoperative cytological and final histological diagnoses: A retrospective 10-year study of neurosurgical cases from Ibadan, Nigeria. Diagn Cytopathol 2015;43:195-201.
61. Samal S, Kalra R, Sharma J, Singh I, Panda D, Ralli M. Comparison between crush/squash cytology and frozen section preparation in intraoperative diagnosis of central nervous system lesions. Oncol J India 2017;1:25.
62. Sarkar S, Sengupta M, Datta C, Chatterjee U, Ghosh SN. Evaluation of intraoperative cytological smears for diagnosis of brain tumors with special reference to immunohistochemistry. Indian J Med Paediatr Oncol 2017;38:296-301.
63. Savargaonkar P, Farmer PM. Utility of intra-operative consultations for the diagnosis of central nervous system lesions. Ann Clin Lab Sci 2001;31:133-9.
64. Shah AB, Muzumdar GA, Chitale AR, Bhagwati SN. Squash preparation and frozen section in intraoperative diagnosis of central nervous system tumors. Acta Cytol 1998;42:1149-54.
65. Sharma N, Misra V, Singh PA, Gupta SK, Debnath S, Nautiya A. Comparative efficacy of imprint and squash cytology in diagnosing lesions of the central nervous system. Asian Pac J Cancer Prev 2011;12:1693-6.
66. Shrestha S, Thapa BK, Bhattarai B. Smear technique for intraoperative diagnosis of central nervous system neoplasms. J Pathol Nepal 2014;4:544-7.
67. Shukla K, Parikh B, Shukla J, Trivedi P, Shah B. Accuracy of cytologic diagnosis of central nervous system tumours in crush preparation. Indian J Pathol Microbiol 2006;49:483-6.
68. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in

meta-analyses. Eur J Epidemiol 2010;25:603-5.
69. Sullivan R, Alatise OI, Anderson BO, Audisio R, Autier P, Aggarwal A, *et al*. Global cancer surgery: Delivering safe, affordable, and timely cancer surgery. Lancet Oncol 2015;16:1193-224.
70. Tele F. An Analysis of CNS Tumors in Squash Preparations with Histological Correlation; 2006.
71. Tena-Suck M, Salinas-Lara C, Vega-Orozco R, Rembao-Bojorquez D, Gelista N. Crush intraoperatory analysis in craniopharyngioma. Diagn Cytopathol 2012;40:865-70.
72. Tena-Suck ML, Estrada-Natoli L, Corona-Cobian LE, Torral-Rizo VH. Chordomas; crush intraoperative analysis. J Cytol Histol 2015;6:3.
73. Ud Din N, Memon A, Idress R, Ahmad Z, Hasan S. Central nervous system lesions: Correlation of intraoperative and final diagnoses, six year experience at a referral centre in a developing country, Pakistan. Asian Pac J Cancer Prev 2011;12:1435-7.
74. Yadav M, Sharma P, Singh V, Tewari R, Mishra PS, Roy K. An audit of diagnostic disparity between intraoperative frozen section diagnosis and final histopathological diagnosis of central nervous system lesions at a tertiary care center. J Lab Physicians 2022;14:384-93.
75. Zulkarnain S, Yunus N, Kandasamy R, Zun AB, Mat Zin AA. Evaluation study of intraoperative cytology smear and frozen section of glioma. Asian Pac J Cancer Prev 2020;21:3085-91.

**How to cite this article:** Shakir M, Altaf A, Hussain H, Abidi SA, Petitt Z, Tariq M, *et al*. Unveiling the potential application of intraoperative brain smear for brain tumor diagnosis in low-middle-income countries: A comprehensive systematic review. Surg Neurol Int 2023;14:325.



## SEARCH STRATEGY

**Concept#1: (Intraoperative)**

"Intraoperative Period"[Mesh] OR "Intraoperative Care"[Mesh]

**Concept#2: (Brain Smear)**

("Brain Smear" OR "Intraoperative cytology" OR "Intraoperative squash cytology" OR "Intraoperative squash smear" OR "Squash Smear" OR "Imprint cytology" OR "touch cytology")

**Concept#3 (Brain Tumor)**

"Brain Neoplasms"[Mesh] OR "Central Nervous System Neoplasms"[Mesh] OR "Brain tumor*" OR "brain cancer*" OR "CNS tumor*" OR "Nervous system tumor*" OR "Neuro-Oncology" OR "Intracranial neoplasm*" OR "Primary brain tumor*"

**PubMed**

(("Brain Neoplasms"[Mesh] OR "Central Nervous System Neoplasms"[Mesh] OR "Brain tumor*" OR "brain cancer*" OR "CNS tumor*" OR "Nervous system tumor*" OR "Neuro-Oncology" OR "Intracranial neoplasm*" OR "Primary brain tumor*") AND ("Brain Smear" OR "Intraoperative cytology" OR "Intraoperative squash cytology" OR "Intraoperative squash smear" OR "Squash Smear" OR "Imprint cytology" OR "touch cytology"))

**Scopus**

(("Brain Neoplasms" OR "Central Nervous System Neoplasms" OR "Brain tumor*" OR "brain cancer*" OR "CNS tumor*" OR "Nervous system tumor*" OR "Neuro-Oncology" OR "Intracranial neoplasm*" OR "Primary brain tumor*") AND ("Brain Smear" OR "Intraoperative cytology" OR "Intraoperative squash cytology" OR "Intraoperative squash smear" OR "Squash Smear" OR "Imprint cytology" OR "touch cytology"))

**Google Scholar: (Using Publish or Perish)**

"Brain Neoplasms" | "Central Nervous System Neoplasms" | "Brain tumor" | "Primary brain tumor" "Brain Smear" | "Intraoperative cytology" | "Intraoperative squash cytology" | "Intraoperative squash smear" | "Squash Smear" | "Imprint cytology" | "touch cytology"