




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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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

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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 <i>et al.</i> 2016 ^[11]	India	Prospective	80	Adult	Squash
3.	Balsimelli <i>et al.</i> 2019 ^[5]	Brazil	Retrospective	133	Adult	Squash
4.	Fujita <i>et al.</i> 2022 ^[16]	Japan	Retrospective	71	Adult	Squash
5.	Hiryur <i>et al.</i> 2019 ^[20]	India	Cross-sectional	65	Adult	Squash
6.	Jain K <i>et al.</i> 2022 ^[23]	India	Prospective	55	Paediatric	Squash
7.	Krishnani <i>et al.</i> 2012 ^[34]	India	Retrospective	334	Both	Squash
8.	Kumarguru <i>et al.</i> 2021 ^[36]	India	Retrospective	50	Adult	Squash
9.	Maity <i>et al.</i> 2019 ^[39]	India	Prospective	42	Pediatric	Squash
10.	Ud Din <i>et al.</i> 2011 ^[73]	Pakistan	Prospective	171	Both	Squash
11.	Nasreen <i>et al.</i> 2015 ^[46]	Bangladesh	Cross-sectional	64	Both	Squash
12.	Patil <i>et al.</i> 2016 ^[52]	India	Retrospective	50	Both	Squash
13.	Savargaonkar <i>et al.</i> 2001 ^[63]	USA	Retrospective	103	Both	Squash
14.	Acharya <i>et al.</i> 2016 ^[1]	India	Prospective Longitudinal	222	Both	Squash
15.	Samal <i>et al.</i> 2017 ^[61]	India	Prospective	63	Adult	Squash
16.	Jain S <i>et al.</i> 2022 ^[24]	India	Prospective	53	Both	Squash
17.	Govindaraman <i>et al.</i> 2017 ^[18]	India	Prospective	75	Adult	Squash
18.	Kishore <i>et al.</i> 2018 ^[33]	India	Prospective	127	Both	Squash
19.	Zulkarnain <i>et al.</i> 2020 ^[75]	Malaysia	Cross-sectional	22	Both	Squash
20.	Sarkar <i>et al.</i> 2017 ^[62]	India	Prospective	107	Both	Squash
21.	Salami <i>et al.</i> 2015 ^[60]	Nigeria	Retrospective	69	Both	Both
22.	Sharma <i>et al.</i> 2011 ^[65]	India	Cross-sectional	149	Adult	Both
23.	Hamasaki <i>et al.</i> 2017 ^[19]	Canada	Retrospective	400	Both	Both
24.	Agrawal <i>et al.</i> 2014 ^[2]	India	Retrospective	41	Adult	Squash
25.	Anita <i>et al.</i> 2019 ^[4]	India	Prospective	16	Adult	Squash
26.	Goel <i>et al.</i> 2007 ^[17]	India	Retrospective	3057	Adult	Squash
27.	Jaiswal <i>et al.</i> 2012 ^[25]	India	Retrospective	326	Adult	Squash
28.	Jindal <i>et al.</i> 2017 ^[27]	India	Retrospective	150	Pediatric	Squash
29.	Jindal <i>et al.</i> 2017 ^[28]	India	Prospective	150	Both	Squash
30.	Lone <i>et al.</i> 2018 ^[37]	Indian-occupied Kashmir	Retrospective	550	Both	Squash
31.	Nalinimohan <i>et al.</i> 2018 ^[44]	India	Prospective	131	Adult	Squash
32.	Olasode <i>et al.</i> 2004 ^[49]	Nigeria	Pilot Study	18	Adult	Squash
33.	Pala <i>et al.</i> 2022 ^[50]	Turkey	Prospective	55	Adult	Squash
34.	Qiao <i>et al.</i> 2019 ^[54]	USA/China	Retrospective	403	Adult	Squash
35.	Raju <i>et al.</i> 2018 ^[55]	India	Prospective	50	Both	Squash
36.	Rani <i>et al.</i> 2014 ^[57]	India	Comparative	110	Both	Squash
37.	Roessler <i>et al.</i> 2002 ^[59]	Austria	Retrospective	4172	Adult	Squash
38.	Shah <i>et al.</i> 1998 ^[64]	India	Cross-sectional	180	Adult	Squash
39.	Shukla <i>et al.</i> 2006 ^[67]	India	Comparative	278	Both	Squash
40.	Tena-Suck <i>et al.</i> 2012 ^[71]	Mexico	Retrospective	30	Both	Squash
41.	Kumar <i>et al.</i> 2013 ^[35]	India	Retrospective	63	Both	Squash
42.	Yadav <i>et al.</i> 2022 ^[74]	India	Retrospective	273	Both	Squash
43.	Bhagyalakshmi <i>et al.</i> 2012 ^[6]	India	Prospective	81	NR (Mean Age - 35)	Squash
44.	Nigam <i>et al.</i> 2012 ^[47]	India	Prospective	75	Both	Squash
45.	Shrestha <i>et al.</i> 2014 ^[66]	Nepal	Prospective	60	NR	Squash
46.	Mitra <i>et al.</i> 2010 ^[42]	India	Prospective	114	NR	Squash
47.	Rao <i>et al.</i> 2009 ^[58]	India	Retrospective	120	NR	Squash
48.	Kini <i>et al.</i> 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.	Cheunschon 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

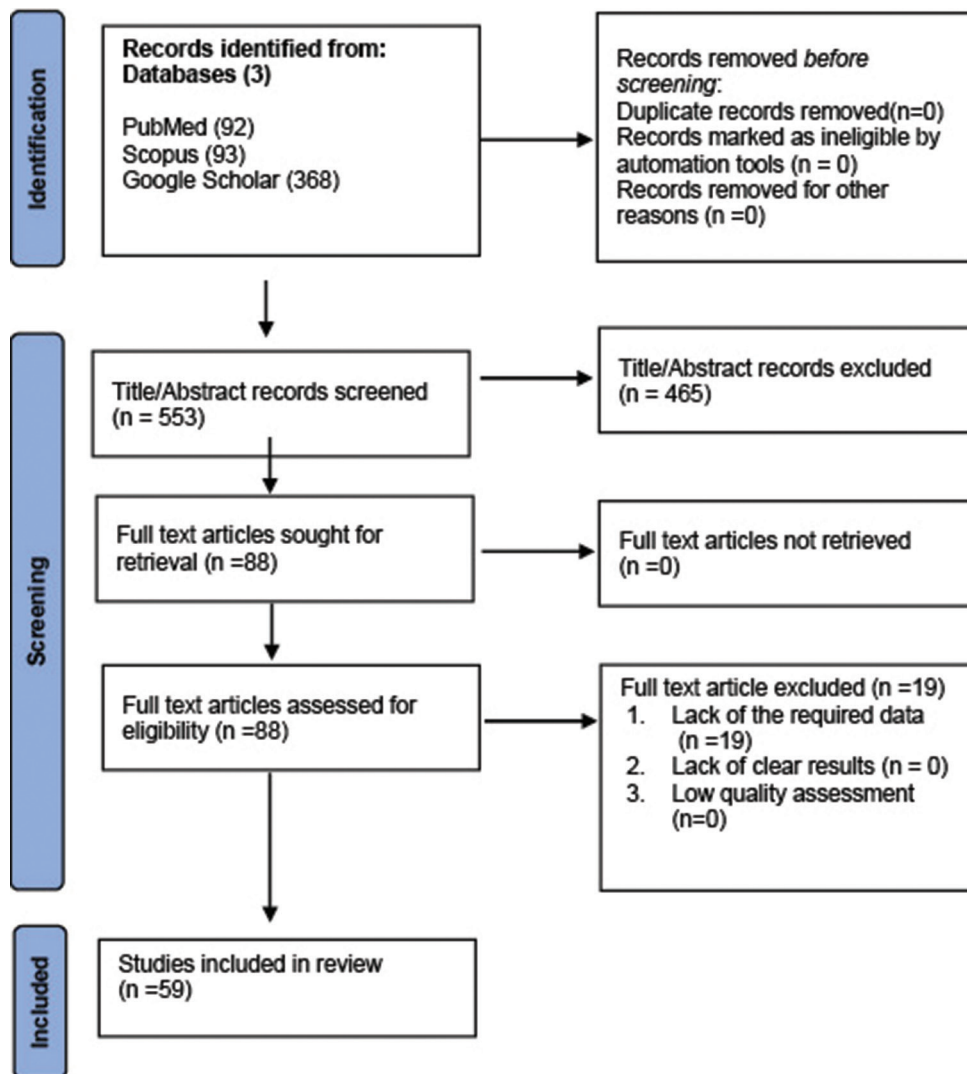


Figure 1: Preferred reporting items for systematic reviews and meta-analyses flow diagram. Number (n).

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 <i>et al.</i> 2006 ^[70]	☆☆☆	☆☆	☆☆	7
2.	Chand <i>et al.</i> 2016 ^[11]	☆☆☆	☆☆	☆☆☆	8
3.	Balsimelli <i>et al.</i> 2019 ^[5]	☆☆☆☆	☆☆	☆☆	8
4.	Fujita <i>et al.</i> 2022 ^[16]	☆☆☆	☆☆	☆☆	7
5.	Hiryur <i>et al.</i> 2019 ^[20]	☆☆☆	☆	☆☆	6
6.	Jain K <i>et al.</i> 2022 ^[23]	☆☆☆	☆	☆☆	6
7.	Krishnani <i>et al.</i> 2012 ^[34]	☆☆☆☆	☆☆	☆☆☆	8
8.	Kumarguru <i>et al.</i> 2021 ^[36]	☆☆☆	☆☆	☆☆	7
9.	Maity <i>et al.</i> 2019 ^[39]	☆☆☆	☆☆	☆☆	7
10.	Ud Din <i>et al.</i> 2011 ^[73]	☆☆☆☆	☆☆	☆☆	8
11.	Nasreen <i>et al.</i> 2015 ^[46]	☆☆☆	☆☆	☆☆☆	8
12.	Patil <i>et al.</i> 2016 ^[52]	☆☆☆	☆☆	☆☆☆	8
13.	Savargaonkar <i>et al.</i> 2001 ^[63]	☆☆☆☆	☆☆	☆☆☆	8
14.	Acharya <i>et al.</i> 2016 ^[1]	☆☆	☆☆	☆☆	6
15.	Samal <i>et al.</i> 2017 ^[61]	☆☆☆	☆☆	☆☆☆	8
16.	Jain S <i>et al.</i> 2021 ^[24]	☆☆☆	☆☆	☆☆	7
17.	Govindaraman <i>et al.</i> 2017 ^[18]	☆☆☆	☆☆	☆☆	7
18.	Kishore <i>et al.</i> 2018 ^[33]	☆☆☆☆	☆☆	☆☆☆	9
19.	Zulkarnain <i>et al.</i> 2020 ^[75]	☆☆☆☆	☆☆	☆☆☆	9
20.	Sarkar <i>et al.</i> 2017 ^[62]	☆☆☆	☆	☆☆	6
21.	Salami <i>et al.</i> 2015 ^[60]	☆☆☆	☆☆	☆☆☆	8
22.	Sharma <i>et al.</i> 2011 ^[65]	☆☆☆☆	☆☆	☆☆☆	9
23.	Hamasaki <i>et al.</i> 2017 ^[19]	☆☆☆☆	☆☆	☆☆☆	9
24.	Agrawal <i>et al.</i> 2014 ^[2]	☆☆☆	☆☆	☆☆☆	8
25.	Anita <i>et al.</i> 2019 ^[4]	☆☆☆	☆	☆☆	6
26.	Goel <i>et al.</i> 2007 ^[17]	☆☆☆☆	☆☆	☆☆	8
27.	Jaiswal <i>et al.</i> 2012 ^[25]	☆☆☆☆	☆☆	☆☆	8
28.	Jindal <i>et al.</i> 2017 ^[27]	☆☆☆☆	☆☆	☆☆☆	9
29.	Jindal <i>et al.</i> 2017 ^[28]	☆☆☆☆	☆☆	☆☆☆	9
30.	Lone <i>et al.</i> 2018 ^[37]	☆☆☆☆	☆☆	☆☆	8
31.	Nalinimohan <i>et al.</i> 2018 ^[44]	☆☆☆☆	☆☆	☆☆☆	9
32.	Olasode <i>et al.</i> 2004 ^[49]	☆☆☆	☆☆	☆☆☆	8
33.	Pala <i>et al.</i> 2022 ^[50]	☆☆☆	☆☆	☆☆☆	8
34.	Qiao <i>et al.</i> 2019 ^[54]	☆☆☆☆	☆☆	☆☆	8
35.	Raju <i>et al.</i> 2018 ^[55]	☆☆☆	☆☆	☆☆	7
36.	Rani <i>et al.</i> 2014 ^[57]	☆☆☆☆	☆☆	☆☆☆	9
37.	Roessler <i>et al.</i> 2002 ^[59]	☆☆☆☆	☆☆	☆☆☆	9
38.	Shah <i>et al.</i> 1998 ^[64]	☆☆☆☆	☆☆	☆☆	8
39.	Shukla <i>et al.</i> 2006 ^[67]	☆☆☆☆	☆☆	☆☆	8
40.	Tena-Suck <i>et al.</i> 2012 ^[71]	☆☆☆	☆☆	☆☆	7
41.	Kumar <i>et al.</i> 2013 ^[35]	☆☆☆	☆☆	☆☆☆	8
42.	Yadav <i>et al.</i> 2022 ^[74]	☆☆☆☆	☆☆	☆☆☆	9
43.	Bhagyalakshmi <i>et al.</i> 2012 ^[6]	☆☆☆	☆☆	☆☆☆	8
44.	Nigam <i>et al.</i> 2012 ^[47]	☆☆☆	☆☆	☆☆☆	8
45.	Shrestha <i>et al.</i> 2014 ^[66]	☆☆☆	☆☆	☆☆☆	8
46.	Mitra <i>et al.</i> 2010 ^[42]	☆☆☆☆	☆☆	☆☆☆	9
47.	Rao <i>et al.</i> 2009 ^[58]	☆☆☆☆	☆☆	☆☆☆	9
48.	Kini <i>et al.</i> 2009 ^[32]	☆☆☆☆	☆☆	☆☆	8
49.	Jha <i>et al.</i> 2013 ^[26]	☆☆☆	☆☆	☆☆☆	8
50.	Tena-Suck <i>et al.</i> 2015 ^[72]	☆☆☆	☆	☆☆	6
51.	Chaturvedi <i>et al.</i> 2013 ^[12]	☆☆☆☆	☆☆	☆☆	8
52.	Cheunsuchon <i>et al.</i> 2014 ^[13]	☆☆☆☆	☆☆	☆☆☆	9
53.	Deshpande <i>et al.</i> 2010 ^[14]	☆☆☆☆	☆☆	☆☆	8
54.	Ramana <i>et al.</i> 2018 ^[56]	☆☆☆☆	☆☆	☆☆☆	9

(Contd...)

Table 2: (Continued).

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

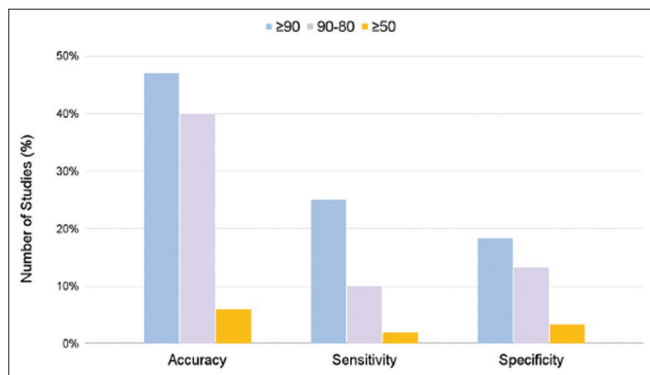


Figure 2: The Y-axis of the graph represents the frequency (%) of studies reporting the values of accuracy, sensitivity, and specificity of brain smear, while the X-axis represents the actual values of accuracy, sensitivity, and specificity. The values on the X-axis are categorized as ≥ 90 , 90–80, and ≥ 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	NR	96.20
2.	Tele et al. 2006 ^[69]	100	India	Prospective	Adult	Squash	86	98	97	90	90	92
3.	Chand et al. 2016 ^[11]	80	India	Prospective	Adult	Squash	96	100	NR	NR	NR	91
4.	Balsimelli et al. 2019 ^[5]	133	Brazil	Retrospective	Adult	Squash	98	94	99	84	84	85
5.	Fujita et al. 2022 ^[16]	71	Japan	Retrospective	Adult	Squash	56	87	NR	NR	NR	80
6.	Hiriyur et al. 2019 ^[20]	65	India	Cross-sectional	Adult	Squash	90	NR	NR	NR	NR	NR
7.	Jain K et al. 2022 ^[23]	55	India	Prospective	Pediatric	Squash	88	90	96	69	69	63
8.	Krishnani et al. 2012 ^[34]	334	India	Retrospective	Both	Squash	98	87	98	87	87	94
9.	Kumarguru et al. 2021 ^[36]	50	India	Retrospective	Adult	Squash	100	88	97	100	100	72
10.	Maity et al. 2019 ^[39]	42	India	Prospective	Pediatric	Squash	92	87	96	77	77	73
11.	Ud Din et al. 2011 ^[73]	171	Pakistan	Prospective	Both	Squash	94	87	98	63	63	94
12.	Nasreen et al. 2015 ^[46]	64	Bangladesh	Cross-sectional	Both	Squash	87	100	100	93	93	95
13.	Patil et al. 2016 ^[52]	50	USA	Retrospective	Both	Squash	100	100	100	100	100	92
14.	Savargaonkar et al. 2001 ^[68]	103	USA	Retrospective	Both	Squash	94	NR	NR	NR	NR	94
15.	Acharya et al. 2016 ^[11]	222	India	Prospective Longitudinal	Both	Squash	84	NR	NR	NR	NR	83
16.	Samal et al. 2017 ^[61]	63	India	Prospective	Adult	Squash	94	85	98	66	66	93
17.	Jain K et al. 2021 ^[23]	53	India	Prospective	Both	Squash	86	87	81	91	91	84
18.	Govindaraman et al. 2017 ^[18]	75	India	Prospective	Adult	Squash	98	93	97	99	99	90
19.	Kishore et al. 2018 ^[33]	127	India	Prospective	Both	Squash	99	75	99	75	75	95
20.	Zulkarnain et al. 2020 ^[75]	22	Malaysia	Cross-sectional	Both	Squash	100	76	75	100	100	86
21.	Sarkar et al. 2017 ^[62]	107	India	Retrospective	Both	Both	94	97	94	97	97	100
22.	Salami et al. 2015 ^[60]	69	Nigeria	Retrospective	Both	Both	75-84*	91-89*	NR	NR	NR	84-83*
23.	Sharma et al. 2011 ^[65]	149	India	Cross-sectional	Adult	Both	90 - squash 92 - imprint	87.5 - squash 90.6 - imprint	NR	NR	NR	89.3 - squash 92.0 - imprint
24.	Hamasaki et al. 2017 ^[19]	400	Canada	Retrospective	Both	Both	97	100	NR	NR	NR	95
25.	Agrawal et al. 2014 ^[2]	41	India	Retrospective	Adult	Squash	NR	NR	NR	NR	NR	95
26.	Anita et al. 2019 ^[4]	16	India	Prospective	Adult	Squash	NR	NR	NR	NR	NR	NR
27.	Goel et al. 2007 ^[17]	3057	India	Retrospective	Adult	Squash	NR	NR	NR	NR	NR	84
28.	Jaiswal et al. 2012 ^[25]	326	India	Retrospective	Adult	Squash	NR	NR	NR	NR	NR	83
29.	Jindal et al. 2017 ^[27]	150	India	Retrospective	Pediatric	Squash	NR	NR	NR	NR	NR	94
30.	Jindal et al. 2017 ^[28]	150	India	Prospective	Both	Squash	NR	NR	NR	NR	NR	94
31.	Lone et al. 2018 ^[37]	550	Indian-occupied Kashmir	Retrospective	Both	Squash	NR	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.	Nalimohan et al. 2018 ^[44]	131	India	Prospective	Adult	Squash	NR	NR	NR	NR	NR	NR	95
33.	Olasode et al. 2004 ^[49]	18	Nigeria	Pilot study	Adult	Squash	NR	NR	NR	NR	NR	NR	94
34.	Pala et al. 2022 ^[50]	55	Turkey	Prospective	Adult	Squash	NR	NR	NR	NR	NR	NR	96
35.	Qiao et al. 2019 ^[54]	403	USA/China	Retrospective	Adult	Squash	NR	NR	NR	NR	NR	NR	80
36.	Raju et al. 2018 ^[55]	50	India	Prospective	Both	Squash	NR	NR	NR	NR	NR	NR	82
37.	Rani et al. 2014 ^[57]	110	India	Comparative	Both	Squash	NR	NR	NR	NR	NR	NR	93
38.	Roessler et al. 2002 ^[59]	4172	Austria	Retrospective	Adult	Squash	NR	NR	NR	NR	NR	NR	95
39.	Shah et al. 1998 ^[64]	180	India	Cross-sectional	Adult	Squash	NR	NR	NR	NR	NR	NR	89
40.	Shukla et al. 2006 ^[67]	278	India	Comparative	Both	Squash	NR	NR	NR	NR	NR	NR	87
41.	Tena-Suck et al. 2012 ^[71]	30	Mexico	Retrospective	Both	Squash	NR	NR	NR	NR	NR	NR	83
42.	Kumar et al. 2013 ^[35]	63	India	Retrospective	Both	Squash	NR	NR	NR	NR	NR	NR	88
43.	Yadav et al. 2022 ^[74]	273	India	Retrospective	Both	Squash	NR	NR	NR	NR	NR	NR	95
44.	Nigam et al. 2012 ^[47]	75	India	Prospective	Both	Squash	NR	NR	NR	NR	NR	NR	89
45.	Shrestha et al. 2014 ^[66]	60	Nepal	Prospective	NR	Squash	NR	NR	NR	NR	NR	NR	88
46.	Mitra et al. 2010 ^[42]	114	India	Prospective	NR	Squash	NR	NR	NR	NR	NR	NR	89
47.	Rao et al. 2009 ^[58]	120	India	Retrospective	NR	Squash	NR	NR	NR	NR	NR	NR	95
48.	Kini et al. 2009 ^[32]	100	India	Prospective	NR	Squash	NR	NR	NR	NR	NR	NR	86
49.	Jha et al. 2013 ^[26]	35	India	Prospective	Both	Squash	NR	NR	NR	NR	NR	NR	82
50.	Tena-Suck et al. 2015 ^[72]	22	Mexico	Retrospective	Adult	Squash	NR	NR	NR	NR	NR	NR	70
51.	Chaturvedi et al. 2013 ^[12]	333	India	Retrospective	Adult	Squash	NR	NR	NR	NR	NR	NR	85
52.	Cheunsuchon et al. 2014 ^[13]	698	Thailand	Retrospective	Both	Squash	NR	NR	NR	NR	NR	NR	89
53.	Deshpande et al. 2010 ^[14]	250	India	Prospective	Both	Squash	NR	NR	NR	NR	NR	NR	NR
54.	Ramana et al. 2018 ^[56]	111	India	Prospective	Both	Squash	NR	NR	NR	NR	NR	NR	90
55.	Brommeland et al. 2003 ^[10]	153	Norway	Comparative	Adult	Imprint	NR	NR	NR	NR	NR	NR	91
56.	Nanarng et al. 2015 ^[45]	75	India	Prospective	Both	Both	NR	NR	NR	NR	NR	NR	89
57.	Khamechian et al. 2012 ^[31]	139	Iran	Prospective	Adult	Imprint	NR	NR	NR	NR	NR	NR	84
58.	Hitchcock et al. 1986 ^[21]	100	England	Cross-sectional	Adult	Both	NR	NR	NR	NR	NR	NR	NR
59.	Kang et al. 2019 ^[29]	454	Korea	Retrospective	NR	Both	NR	NR	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

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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.

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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”