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Diagnostic utility of intraoperative squash smear cytology of Intra-cranial lesions in a resource limited setup of central India

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ABSTRACT

Introduction: Intraoperative squash smear cytology is a useful diagnostic tool in case of CNS lesions. In resource poor countries where frozen section is unavailable, cytology is the mainstay method in giving a rapid intra-operative diagnosis which helps Surgeons regarding the extent of excision. The current study aims to assess the feasibility and accuracy of intraoperative squash cytology in evaluation of CNS tumors. Definitive diagnosis is confirmed by histopathological examination.

Materials and methods: This retrospective observational study was carried out at Department of Neuropathology. All patients diagnosed with space occupying lesion (SOL) in CNS were enrolled in the study. Intra-operative cytological diagnosis was compared to histopathological diagnosis. WHO classification of CNS tumors 2021 was used to classify tumors.

Results: Total seventy patients with intracranial SOLs were enrolled in this study who were operated for the same and their specimens were examined. Two samples were found to be inadequate and not included in final analysis. Mean age was 38.8 ± 17.85 (SD). Male–female ratio was 1.5:1 with 41 (60.3%) males and 27 (39.7%) females. 58 had neoplastic and rest 10 had non-neoplastic lesions. Complete concordance was achieved in 61 cases (Diagnostic Accuracy-88.2%). 3 (4.4%) cases showed partial concordance and 4 (5.9%) were discordant. For detection of malignant lesions through squash smear cytology overall Sensitivity was 73.9%, Specificity-97.8%, Positive Predictive Value-94.4% and Negative Predictive Value-88%.

Conclusions: Squash smear cytology is a simple, rapid and cost-effective method relying solely on the expertise of pathologist. High diagnostic accuracy can be achieved with squash cytology by taking clinical and radiological findings into consideration.

1. Inrtroduction

Intraoperative squash smear cytology is a useful diagnostic tool in case of Central Nervous System (CNS) lesions, as these lesions being inherently soft in nature yield excellent quality material on squash smears because of scant connective tissue. While frozen section requires costly setup and leads to freezing artefacts, squash proves to be a rapid and cheaper alternative relying on the competence of pathologist to provide a fair intraoperative diagnosis. It also offers great details of cellular, especially nuclear morphology and tissue distortion is also avoided. Squash smear cytology was first introduced by Eisenhardt and Cushing in 1930.[1]

Intracranial lesions account for 10–17 per 100,000 persons per year which ranges from inflammatory pathologies to malignancies.[2] In resource poor countries where frozen section has limited use in routine diagnostic practice, cytology is the mainstay method in giving a rapid intraoperative diagnosis which can help the surgeon in taking decisions regarding for example; presence of any lesion, differentiating neoplastic from non-neoplastic, the extent of excision.[3] Since the extend of resection of the tumors differ based on the type of tumors, and a limitation being-sometimes it may lead to unnecessary resection of a tumor that can be managed with adjuvant therapy.

The current study aims to study cytomorphological features of various intracranial lesions and to correlate the cytological diagnosis with histopathological diagnosis of various intracranial lesions. We also aim to assess sensitivity, specificity, positive and negative predictive

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value as well the overall diagnostic accuracy of intraoperative squash cytology in diagnosis of intracranial lesions taking histopathology as gold standard.

2. Materials and methods

This retrospective study was carried out at Department of Neuropathology, Netaji Subhash Chandra Bose Govt Medical College, Jabalpur from March 2022 to August 2022.

Inclusion Criteria:

1. Patients clinically and radiologically suspected of having intracranial lesions regardless of age and gender.
2. Cases where both squash cytology and histopathology samples were available.

Exclusion Criteria:

1. Spinal lesions were excluded.
2. Inadequate squash cytology samples were also excluded.

Detailed clinical history including presenting symptoms, location of the lesion, and radiological findings were noted from the hospital records. We received a total of 70 neurosurgical specimens during the study. Sample collection methods varied from stereotactic biopsy to open surgical resection. A prior informed consent was taken from the patient and/or their legal guardian who were planned for excision of the intracranial lesion before the operative procedure, regarding intraoperative squash smear cytology as well further histopathological examination of the excised specimen. We applied squash cytology in all cases irrespective of it being a difficult case or not, as per our institutional protocol, because sometimes benign lesions may be mistaken for malignancy and vice versa. And sometimes neoplasia with tuberculosis and vice versa.

- Specimens were received in normal saline/saline soaked telfa paper/pad. Squash smear was prepared immediately from the freshly collected tissue after gross evaluation.
- Clinical features of the case and gross appearance of the squash sample will be recorded at the time of specimen collection.
- The smears were prepared using 1–2 mm of tissue bits and fixed in 95% ethanol. For staining, commercially available Hematoxylin & Eosin (H & E) stain and Papanicolaou (PAP) stain kits were used. Minimum of 5–6 smears were prepared. The remaining tissue was fixed in formalin and sent for paraffin sections.
- Stained smears were interpreted taking clinical and radiological findings into consideration and Cytomorphology of the stained smears will be evaluated and findings of the squash cytological examination of the sample will be released in 30–40 min, which is a bit longer turnaround time than other institutes-mainly due to travelling of sample. This can be reduced in other setups. The surgeon continues his work in the meantime. The diagnosis was conveyed intraoperatively to the surgeon based on which the extend of resection was decided. The extent of resection will be in the domain of surgeon taking into account with other factors like closeness to the eloquent cortex, age, comorbidities, etc. and therefore not evaluated in the present study.
- After completion of operative procedure, resected biopsy sample was received. After examination of H&E-stained formalin fixed paraffin embedded (FFPE) tissue sections, a final diagnosis was given.
- Intra-operative cytological diagnosis was compared to histopathological diagnosis, which is taken as the gold standard and the results were calculated. WHO classification of CNS tumors 2021 was used to classify the tumors.

2.1. Statistical analysis

Statistical analysis was done by SPSS software version 22. Mean values are presented with standard deviation. Chi-square test was used to test for statistical significance and *P* value less than 0.05 was taken as statistically significant with 95% confidence interval. Overall Sensitivity, Specificity, Positive and Negative Predictive Values (PPV & NPV) along with overall Diagnostic Accuracy was calculated using statistical formulae.

3. Results

A total of seventy patients with intracranial space occupying lesions (SOLs) were enrolled in this study who were operated for the same and their specimens were examined. Clinically, the patients presented with headache, seizures, neurological deficits, vomiting and episodes of loss of consciousness. Patients with pituitary tumors also presented with visual disturbances.

Two samples were found to be inadequate and therefore not included in the final analysis. Mean age of our study group was 38.8 ± 17.85 (SD) and age ranged from 2 months to 78 years. Male to female ratio was found to be 1.5:1 with 41 (60.3%) males and 27 (39.7%) females.

Of these 68 patients, 58 had neoplastic and rest 10 had non-neoplastic lesions. The distribution of tumors according to final histopathological diagnosis and accuracy of squash cytology is tabulated in Table 1. Complete concordance was achieved in 61 cases (88.2%). 3 (4.4%) cases showed partial concordance where the cytological and histopathological diagnosis differed in tumor grade but not in tumor type. 4 (5.9%) cases were discordant (see Table 2). Within the different age groups the diagnostic accuracy in pediatric and young adults (till 19 years) was 72.73% and it was even lower in the age group of below 10

Table 1
Accuracy of squash cytology in diagnosis of different CNS lesions.

S No:	Histopathological diagnosis	Correct cytopathological diagnosis	Total cases	Accuracy (%)
1	Granulomatous inflammatory lesions	6	6	100
2	Chronic inflammatory pathology	2	2	100
3	Benign Cystic lesion	1	1	100
4	Reactive Gliosis	1	2	50
5	Diffuse Astrocytoma Grade 2	4	4	100
6	Diffuse Astrocytoma Grade 3	2	2	100
7	Glioblastoma	5	7	71.4
8	Paediatric type diffuse Low grade glioma	0	1	0
9	Paediatric type diffuse High grade glioma	1	1	100
10	Oligodendroglioma Grade 2	2	2	100
11	Oligodendroglioma Grade 3	1	1	100
12	Pilocytic Astrocytoma	3	3	100
13	Ependymoma	1	1	100
14	Choroid plexus papilloma	1	1	100
15	Medulloblastoma	2	3	66.67
16	Schwannoma	8	8	100
17	Neurofibroma	1	1	100
18	MPNST[a]	1	1	100
19	Meningioma Grade 1	5	5	100
20	Meningioma Grade 2	1	1	100
21	Hemangioblastoma	0	1	0
22	Lymphoma	0	1	0
23	Pituitary Adenoma	3	3	100
24	Craniopharyngioma	3	3	100

[a] Malignant peripheral nerve sheath tumor.

years (50%), that being said $n = 2$. Among adults of age 20–59 years and ≥60 years the diagnostic accuracy was 93.8% and 87.5% respectively.

Non neoplastic lesions included granulomatous and chronic inflammatory pathology, benign cystic lesion and reactive gliosis. One case of neurocysticercosis was also seen which showed mixed inflammatory infiltrate in a degenerative background on squash smears. Histopathology examination confirmed presence of parasitic larva having irregularly shaped multiple membranous folding (Fig. 1).

Of all neoplastic lesions in our study, glial tumors were most common comprising about 30.88% ($n = 21$), among which Glioblastoma was the most common ($n = 7$,10.3%). Fig. 2 shows Glioblastoma with glomeruloid vascular proliferation and extensive areas of palisading necrosis. Two cases of glioblastoma obtained via stereotactic biopsy were mis-reported as low-grade gliomas on cytology. Other glial tumors reported commonly were Diffuse Astrocytoma ($n = 6$,8.8%), Pilocytic Astrocytoma ($n = 3$,4.4%), Oligodendroglioma ($n = 3$,4.4%), and Ependymoma ($n = 1$,1.47%) [Fig. 3].

Nerve sheath tumors were the second most commonly encountered tumors in our study accounting for 14.7% ($n = 10$). Of these Schwannoma was the most common (11.7%, $n = 8$) and all were located at Cerebello-Pontine (CP) angle [Fig. 4] followed by Neurofibroma and MPNST of 1 case each (1.47%). These tumors showed resistance on smearing and produced relatively thick smears than other lesions, making it a helpful diagnostic clue. All these tumors were correctly diagnosed on cytology and showed hundred percent concordance with histology.

There were six cases of Meningioma in our study (8.8%) of which only one case was Grade 2 and the rest were Grade 1. Representative microphotograph in Fig. 4(a) and (b).

In our study we found 7 cases (10.29%) of metastasis from distant primary. In all the cases primary malignancy was unknown and patients directly presented with neurological signs and symptoms. In all these cases cytological diagnosis showed complete concordance with histological diagnosis [Fig. 5(a) and (b)].

Medulloblastoma comprised 4.4% ($n = 3$) of the total cases. All three cases were reported as classic medulloblastoma on histopathology. One case was misdiagnosed as Ependymoma on cytology smears [Fig. 5(c) and (d)].

Overall accuracy with respect to the diagnostic utility of squash cytology was found to be 88.2%. For detection of malignant lesions or differentiating malignant from benign lesions and/or low-grade neoplasms through squash smear cytology the overall Sensitivity was found to be 73.9% and Specificity of 97.8%. Positive Predictive Value was of 94.4% and Negative Predictive Value of 88% was obtained from this study. Type I and Type II errors were 2.2% and 26.1% respectively. *P* value based on Pearson Chi square test for differentiating benign or low-grade lesion from malignant or high-grade lesions, was found to be < 0.001 implying high statistical significance.

4. Discussion

This retrospective observational study was carried out from March 2022 to August 2022 at a tertiary care centre of central India. All patients with clinical diagnosis of space occupying lesion (SOL) in CNS were enrolled in the study. We received a total of 70 neurosurgical specimens during the study. Spinal lesions were excluded from this study. Two samples were found to be inadequate and therefore not included in the final analysis. The youngest patient in our study group was a 2 months old male child and oldest patient was of 78 years. Maximum number of cases were found to be in the age group 50–60 years i.e., in sixth decade ($n = 17$,25%) which was also seen in the study by Acharya et al where maximum number of cases were seen in 41–60 years.[4] Similar result was also noted by Kaki et al.[5] Male preponderance was seen in our study with male to female ratio of 1.5:1 which was also seen in study by Manish Agarwal et al.[6] and Kumarguru BN et al.[7]

Overall diagnostic accuracy of our study in correctly diagnosing brain lesions from intraoperative squash cytology was found to be 88.2% (61 of the total 68 cases) (see Table 2). Similar diagnostic accuracy was also found in other studies as shown in Table 3.

In the study by Jain et al.[15] in 2022 where a comparative evaluation of squash smear and frozen section was done in the intraoperative diagnosis of central nervous system tumors on 53 specimens, and the overall sensitivity & specificity for squash cytology were 86.67% and 87.5%, and for frozen section were 91.67% and 93.10% respectively. Cytological diagnosis showed complete correlation with histopathological diagnosis in 39 cases (73.58%), partial concordance in 8 cases (15.1%) and none in 6 cases (11.32%). Frozen section showed complete concordance in 29 cases (74.35%), partial concordance in 8 cases (20.5%) and no concordance in 2 cases (5.1%) which points to frozen section being a superior method, but sophisticated and costly.

In our study, 10 out of 11 non neoplastic cases were diagnosed correctly on cytology. These included granulomatous lesions favouring tuberculosis, parasitic inflammation, benign cystic lesion and reactive gliosis. One case of reactive gliosis was over diagnosed as low-grade glioma. This could be due to nuclear atypia of reactive astrocytes and presence of fibrillary background which is a common finding in both these cases.

Of all neoplastic lesions in our study, glial tumors were most common comprising about 30.88% ($n = 21$). Similar finding was noted in the study by Philip et al.[16] where gliomas were the commonest CNS

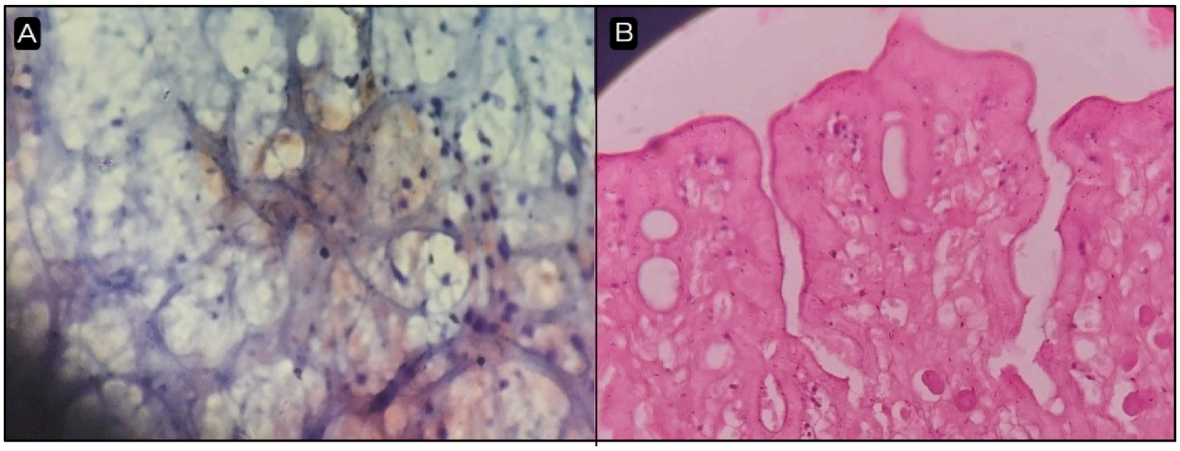

Fig. 1. Neurocysticercosis (a) Squash cytology showing inflammatory infiltrate in a degenerative background. Possibility of parasitic inflammation was suggested (PAP stain, 100×). (b) Paraffin embedded tissue section shows parasite with irregularly shaped multiple membranous folding representing Cysticercus larva (H and E, 400×).

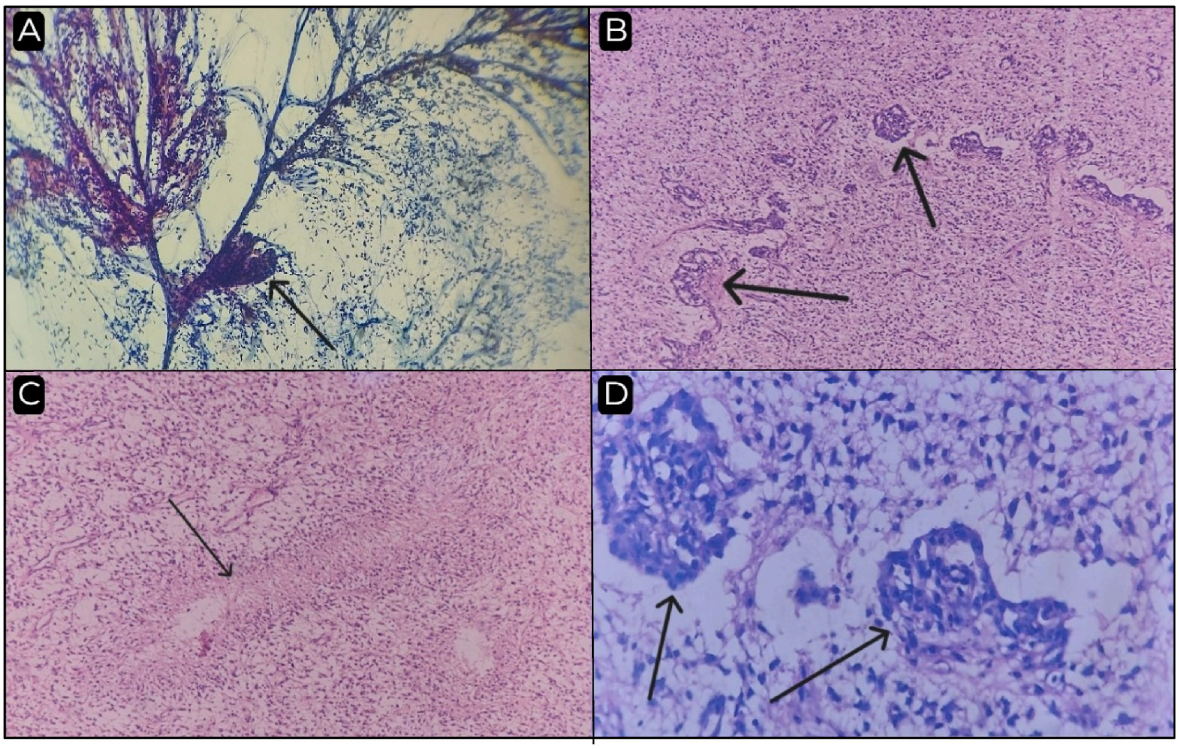

Fig. 2. Glioblastoma (a) Squash cytology showing glomeruloid vascular proliferation (arrow) and hypercellularity in fibrillary background (PAP stain, 100×).(b) Paraffin embedded tissue section reveals increased cellularity and neovascularization (arrow) (H and E stain, 100×). (c)Tissue section showing palisading necrosis (arrow) (H and E stain, 100×) (d) High power image showing cells with increased N:C ratio, atypia and glomeruloid proliferation (arrow) of capillaries in fibrillary background (H and E, 400×).

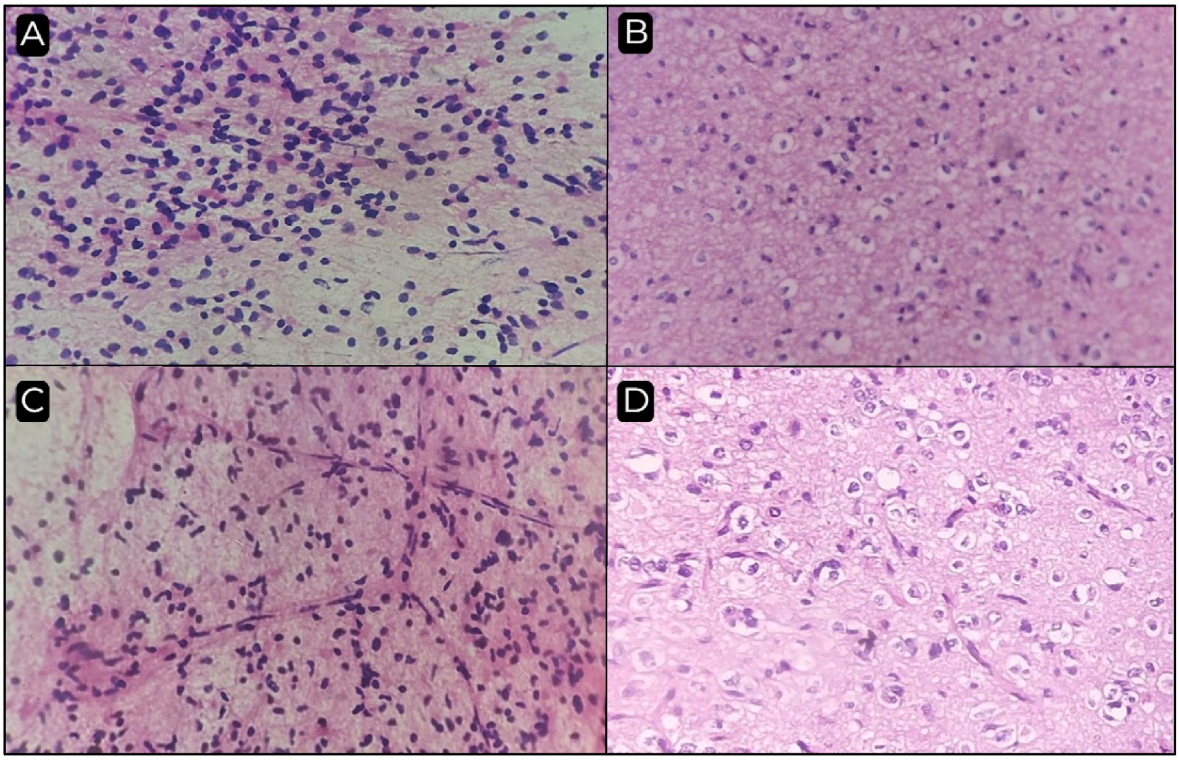

Fig. 3. (a) Squash cytology of diffuse astrocytoma showing astrocytic proliferation with minimal atypia in fibrillary background (H and E, 100×) (b) Paraffin embedded section of diffuse astrocytoma, Grade 2 reveals astrocytes with minimal atypia in microcystic background (H and E, 100×). (c) Squash cytology of low grade oligodendroglioma, showing fine branching network of capillaries resembling chicken-wire architecture. Background is fibrillary with tumor cells showing bland nuclei (H and E stain, 100×).(d) Tissue section of oligodendroglioma grade 2 with cells showing perinuclear cytoplasmic clearing giving it a classic "fried-egg" appearance and proliferating capillaries in the background (H and E, 100×).

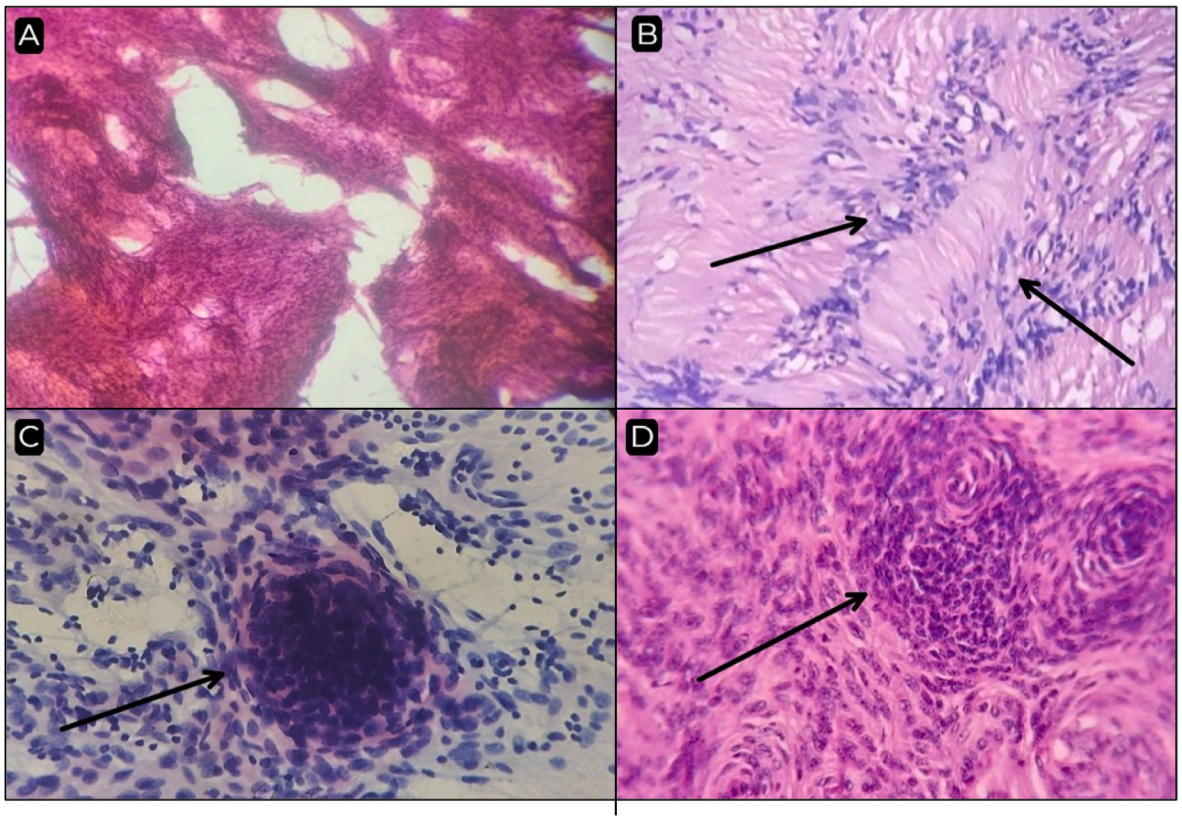

Fig. 4. (a) Schwannoma- Squash cytology smear showing tight aggregates of spindle cells in a clear background (H and E stain, 40×). (b) Schwannoma- Histopathology showing hypercellular Antoni A areas with nuclear palisading (arrow) and tumor cells showing nuclear palisading around fibrillary processes known as Verocay bodies (H and E stain 400×). (c)Meningothelial Meningioma, Grade 2. -Squash smear showing meningothelial whorl (arrow), with epithelioid cells having moderate amount of eosinophilic cytoplasm and round to oval nuclei (H and E stain, 400×). (d) Meningioma Section showed multiple areas of small cell change (arrow) in this case along with hypercellularity and raised mitotic count.

neoplasm accounting for 35.7% of the CNS neoplasms. In our study Glioblastoma was the most common glial neoplasm ($n = 7$,10.3%). 5 out of 7 cases of Glioblastoma showed concordance on histopathology. 2 cases were misdiagnosed as low-grade glioma. These 2 cases were considered under partial concordance in our study. Therefore, diagnostic accuracy for glioblastoma was 71.4%. Study by Jindal et al showed 76.9% accuracy for glioblastoma.[17]

There was error in reporting a case as low grade glioma. It was observed that because of the inflammation the smears looked a little hypercellular compared to normal brain tissue on squash cytology. However, on histopathology, it was seen that there was admixed population of cells giving it a heterogenous appearance unlike in a neoplastic process where we can see only a single type of cell population with pleomorphism. The reactive astrocytes did not show significant nuclear atypia. Hence a final diagnosis of reactive gliosis was given. Khonglah[18] et al reported same error in their study.

Two misdiagnosed cases of glioblastoma were reported as low-grade gliomas on cytology. This could be due to the tiny sample yielded by stereotactic biopsy that failed to show mitosis, necrosis and endothelial proliferation leading to erroneous downgrading of the tumor. It is also found that often features favouring both low- and high-grade type are present in different areas of the same tumor. Hence the biopsy specimen may not be representative of the lesion as a whole thus a limitation inn squash smear cytology. Further studies are required to identify the diagnostic accuracy associated with stereotactic biopsy and any recommendations for its optimal specimen size. The difficulty in correctly diagnosing the grade of gliomas has been reported by previous researchers[4,7] also, making it a pitfall for squash cytology. Contrary to this, a case of paediatric-type diffuse low grade glioma was reported as high-grade glioma on cytology. In this case, few thick-walled arterioles were confused with endothelial proliferation of high-grade gliomas.

A case of medulloblastoma was misdiagnosed as ependymoma. Both these tumors have a tendency to present in paediatric group patients. On cytology, tumor cells showed atypia, high N:C ratio, rosette and pseudo rosette formation, necrosis and lack of fibrillary background. On histology, tumor cells showed small round blue cells arranged in syncytial pattern. Failure to identify tumor architecture is a cytological pitfall, which lead to erroneous diagnosis in this case.

One case of hemangioblastoma was reported in our study. Squash smears were prepared from tiny tissue bits that showed piloid gliosis, reactive astrocytes and few chronic inflammatory cells only. Hence it was reported as glioma. Grossly, tumor was solid with few cystic areas. On tissue sections, a well circumscribed tumor showed two distinct components-vascular component comprising of numerous thin-walled blood vessels and stromal component-showing cells with round to oval nuclei, few cells also showed atypia. Background showed histiocytes. Periphery of the tumor showed piloid gliosis. Diagnostic error on cytology was due to sampling from the non-representative area by the surgeon. Khonglah[18] et al also reported case of hemangioblastoma misdiagnosed as low-grade glioma.

We encountered a single case of primary CNS lymphoma which was erroneously reported as metastatic tumor on cytology. Primary CNS lymphomas are uncommon neoplasms accounting for nearly 3–4% of the CNS tumors.[19] Reporting error was due to our poor expertise with primary CNS lymphomas and extensive necrosis obscuring cytological details on squash sample. On histology, tumor cells were characteristically arranged around blood vessels rimmed by lymphocytes. Singly scattered tumor cells were seen infiltrating brain parenchyma. Extensive areas of necrosis were also seen. Since the surgical resection of these tumors are significantly different, this mis-diagnosis can also affect

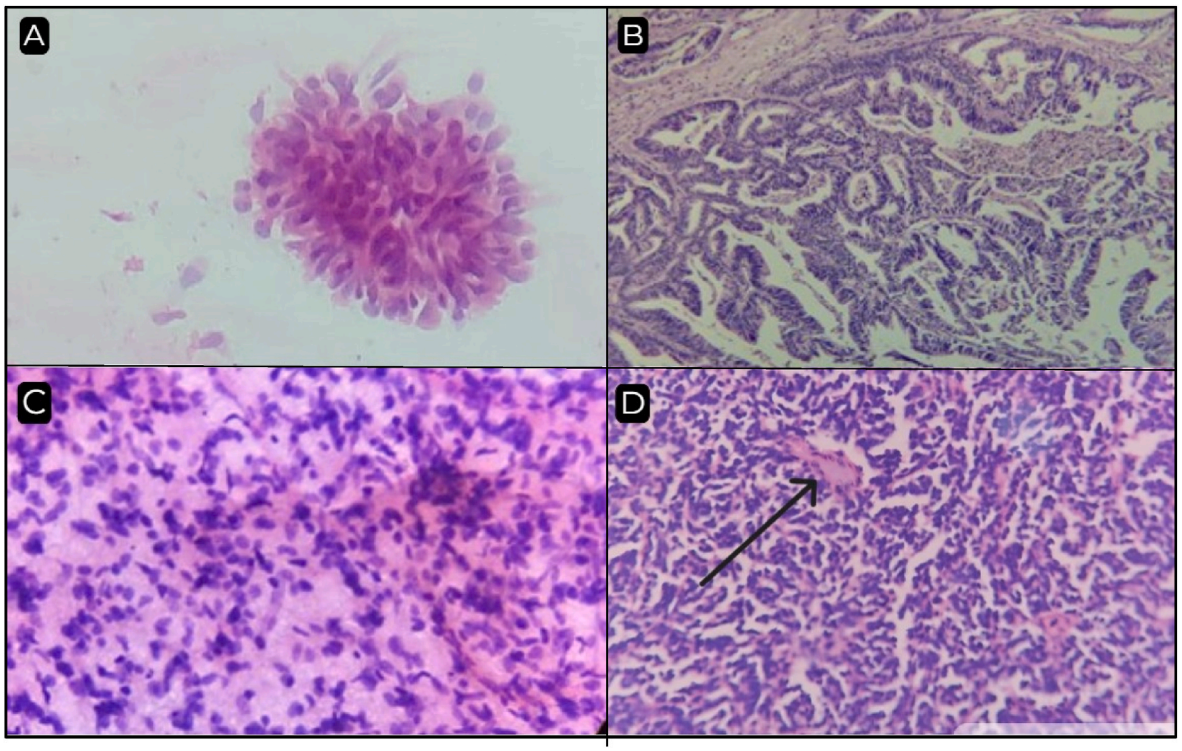

Fig. 5. (a) Metastasis: Squash cytology smear showing metastatic deposit from an unknown primary (H and E, 100×). (b) Metastasis: Tissue section reveals metastatic tumor cells arranged in glandular and papillary architecture (H and E, 100×). (c) Medulloblastoma: Squash cytology smear showing undifferentiated small round blue cells. (d) Classic Medulloblastoma: Tissue section reveals syncytial arrangement of tumor cells with high N:C ratio and presence of Homer Wright rosettes (arrow) (H and E, 100×). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Overall cyto-histological concordance and accuracy.

Total No of cases	**68**
Complete Concordance	61 (88.2%)
Partial Concordance	3 (4.4%)
Discordant	4 (5.9%)
Overall Accuracy	88.2%

Table 3
comparison of diagnostic accuracy of squash cytology of various studies.

Study	Year of study	No Of cases	Diagnostic Accuracy (%)
Goel et al.[8]	2007[a]	3057	85
Pawar et al.[9]	2009	50	88
Mitra et al.[10]	2010	96	88.5
Deshpande et al.[11]	2010	238	91
Shrestha et al.[12]	2014	60	88
Nanarng et al[13]	2015	75	89.2
Govindraman et al.[14]	2017	75	90.67
Our Study	2022	68	88.2

[a] Retrospective study, cases collected from preceding 17 years.

intraoperative decision making where it may lead to unnecessary aggressive resection of a tumor that can otherwise be managed with adjuvant therapy. Details of the partially concordant and discordant cases along with their probable causes are summarised in Table 4.

From a surgeon's perspective the aim in case of benign and malignant lesions varies as, for benign lesions the aim is for complete resection if feasible and in malignant lesions the aim is for a maximum safe cranial decompression along with post-op chemo-radiation.

Table 4
Partial Concordant and Discordant Cases with probable causes of discordancy.

S No:	Histological diagnosis	Cytological diagnosis	No of cases	Possible cause of discordance
1	Reactive Gliosis	Low Grade Glioma	1	Inflammation gives an impression of hypercellularity Minimal atypia in both cases.
2	Glioblastoma	Low Grade Glioma	2	Tiny tissue sample did not reveal necrosis and vascular proliferation on cytology.
3	Paediatric-type Diffuse Low grade Glioma	High Grade Glioma	1	Thick-walled arterioles confused with endothelial proliferation.
4	Medulloblastoma	Ependymoma	1	Clear background, rosette formation, similar age group.
5	Hemangioblastoma	Glial neoplasm with piloid features	1	Squash sample was taken from tumor periphery showing reactive astrocytes with piloid processes.
6	Lymphoma	Metastasis	1	Overlapping features of high-grade CNS tumor.

5. Conclusions

Squash smear cytology provides distinct advantage over frozen section in allowing better demonstration of nuclear morphology in diagnosis of CNS lesions. It is a simple, rapid and cost-effective method relying solely on the expertise of pathologist. High diagnostic accuracy

can be achieved with squash cytology by taking clinical and radiological findings into consideration. This is particularly helpful in resource limited setups where frozen section and IHC could cause a handsome capital investment and not always available especially in third world countries.

6. Limitations of study

This study being retrospective in nature can introduce to some extent selection bias. The squash smear examination by the pathologist being subjective in nature the findings of the study may not be reproducible, which depends on how familiar the pathologist is to this method. Another limitation was that the sample size was less comparing with other studies, hence we believe that a prospective cohort study with a sufficient large sample size will help in this regard. Non-representative tissue samples submitted for squash evaluation can also result in discrepancies.

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Nil.

CRediT authorship contribution statement

Lekha Ramchandani: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Diya Bajaj:** Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Vineeth Kumar RK:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jitin Bajaj:** Validation, Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

CNS	Central Nervous System
H & E	Hematoxylin and Eosin
IHC	Immunohistochemistry
N	C Ratio – Nucleus to Cytoplasmic ratio
SOL	Space occupying lesion
SD	Standard Deviation

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