



## Evaluation of the comparative efficacy of squash cytology and frozen section in the diagnosis of Central Nervous System tumors: A 3 year experience

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### Abstract

**Background:** A new approach like squash smears and frozen section to diagnose CNS neoplasm intra-operatively can help the neuro-pathologist in an intra-operative setting to diagnose and provide sufficient preliminary information to optimize the surgical management of the patient, especially in stereotactic surgery. Majority of the CNS lesions have better preserved cytological detail in squash smear, however tissue architecture is preserved in frozen section. Hence along with squash smear, frozen section is used to emphasize its advantages for intra-operative diagnosis. Thus a study is undertaken in a tertiary care hospital as to compare the efficacy of squash cytology and frozen section with histopathology diagnosis, considering it as the gold standard.

**Material & Method:** All the neurosurgical specimen with suspected CNS neoplasm received in the Department of pathology of IMS & SUM Hospital for intra-operative consultation was studied prospectively for a period of 3 years (August 2014-July 2017). Intra-operative squash cytology and simultaneous frozen section were done and the diagnosis were compared with the final paraffin-embedded section.

**Result and Observation:** A total of 18.89% of cases were found discordant in squash smears and 21.12% of cases were discordant for frozen section considering the histopathology as gold standard. Technical errors like thick smearing artefact, frozen artefact, limited tissue sample, crushed specimen, cautery induced & crushing artefacts contributed to misdiagnosis.

**Conclusion:** Though the squash smears showed a reasonably higher percentage of diagnostic accuracy over frozen section in intra-operative diagnosis of CNS neoplasm, both the procedures should be used complementarily and not as substitution.

**Study type and design:** Hospital based cross-sectional study & is an observational study.

**Keywords:** central nervous system lesions, comparative efficacy, squash cytology, frozen section, histopathology.

### Introduction

Primary CNS neoplasm are relatively rare, compared to other malignant tumors. The annual

incidence of CNS tumors ranges from 10-17 per 1,00,000 person for intracranial tumors, 1-2 per 1,00,000 person for intra-spinal tumors.<sup>1</sup> At

present neuroscientists are keen in rapid intra-operative diagnosis which can modulate their management and are made easier by -stereotactic or burr-hole biopsy and subjecting it for intra-operative frozen section and cytology. Squash cytology is a simple, rapid, accurate and cost effective method requiring less technical expertise, whereas frozen section requires more technical expertise and expensive equipments.<sup>2,3</sup> Further the non-squashable, and difficult to squash CNS lesion render poor quality to squash cytology. Hence, the need for an alternative method for more conclusive opinion and frozen section can be efficiently used as an aid to squash preparation to overcome such limitation. The present study is designed with an objective to study the cytology of various CNS neoplasm by both squash smear and frozen section, and to assess the accuracy of frozen section and squash cytology as a standalone or complementary techniques comparing it with the gold standard histopathological section.

### Material and Method

The present prospective study was a hospital based cross sectional study conducted in our institution over a period of 3years i.e. Aug 2014- July 2017. All surgical sample of suspected CNS neoplasm operated in the neurosurgery department were received in the Department of pathology. A total of 158 cases were received from neurosurgery department. After exclusion of non-neoplastic cases and deferred cases, 90 cases were included in our study. Squash cytology, followed by frozen section and finally paraffin embedded for permanent histopathology section (after fixing in 10% formalin) is done for each case. IHC stains were done to add to the final histopathological diagnosis.

For squash smearing: slide was prepared by taking 1-2mm of the biopsy material with scalpel blade then at least two squash smears were prepared by crushing the tissue bit between two slides with just enough pressure to prepare a smear, one smear was immediately fixed in 95% ethyl alcohol

for H&E staining & another one was kept dry for MGG/Diff quick (Romanovsky) staining.

For frozen section fresh tissues were processed in Leica CM1860 cryostat at -7 to -10c after fixing in 95% alcohol <3mm thickness (ideal-1-2mm) and stained with H&E stain.

Subsequently for the permanent section, the 10% formalin fixed specimen were processed in graded alcohol and xylene, then paraffin blocking and cutting is done according to standard guideline and stained with routine H&E stain & followed by IHC whenever needed.

Data collected were statistically analyzed and compared between the intra-operative diagnostic procedures [squash cytology and frozen section] to that of final histopathological diagnosis. The results were classified into the following categories true negative [absence of tumor correctly diagnosed]; true positive [presence of tumor correctly diagnosed]; false negative [the cytological or frozen section specimen failed to diagnose as tumor], false positive [cytological or frozen section was incorrectly diagnosed as tumor]. The tumor were classified and graded according to WHO classification of CNS neoplasm 2007. Data analysis was based on Galen and Gambino method which calculated sensitivity, specificity, PPV and NPV.

### Results

Clinically most of our patients presented with features of raised intracranial tension, altered sensorium, seizures and neurological deficit, few with auditory and visual disturbances and some of the pediatric patients presented with hydrocephalus. Most common location of tumor was supratentorial comprising about 72.22% (65cases) followed by infratentorial 16.66% (15cases) and 11.11% (10cases) in the spinal cord region.

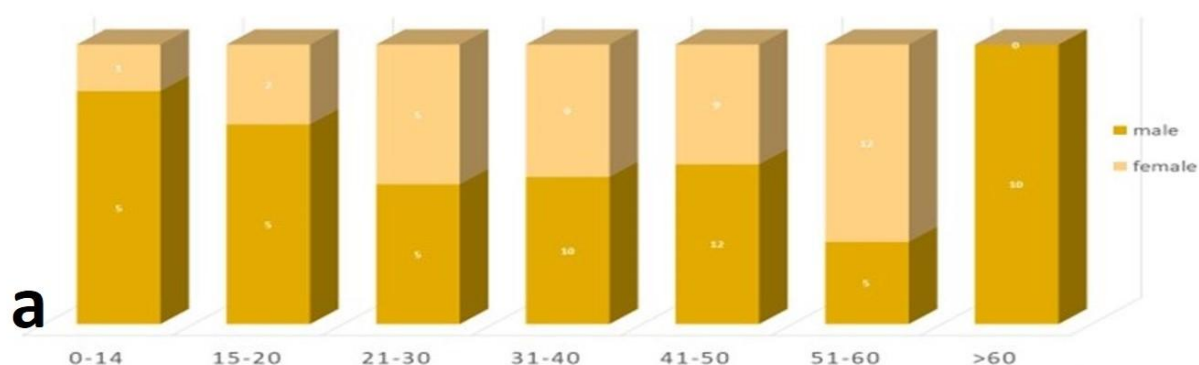
A maximum number of cases was seen in 41-50 years age group 23.33% (21 cases) with a slight male preponderance 57.77% (52 cases), followed by 31-40 years and 51-60 years age group comprising about 19cases(21.11%)and 17cases (18.88%) respectively. Percentage distribution of

CNS lesions according to age and sex are given in [figure-1a].

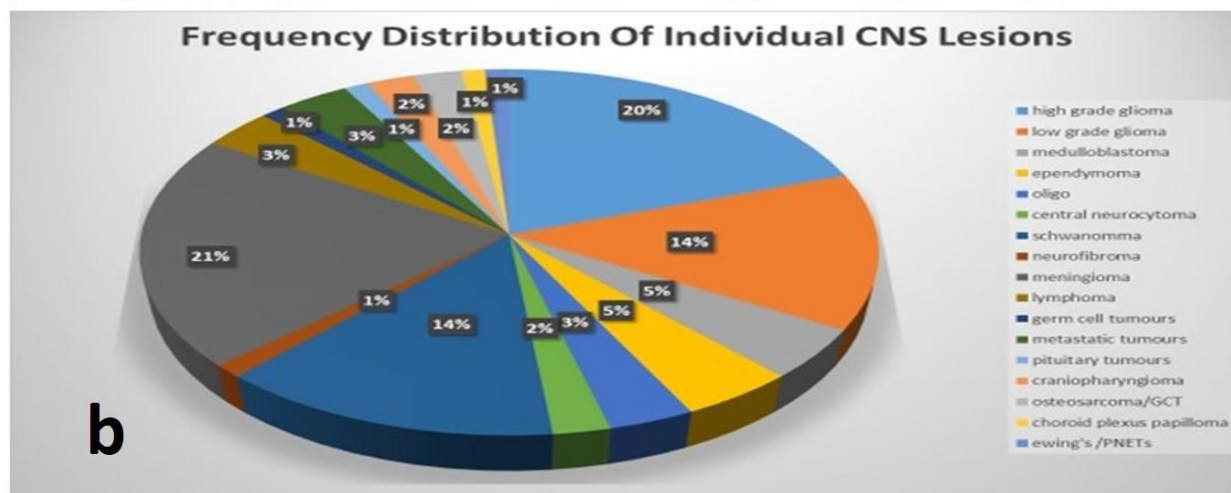
Taking in account of the incidence of individual tumors into consideration in our study astrocytoma showed highest (47.78%) incidence

followed by meningioma (21.11%) and lowest was of choroid plexus papilloma, germ-cell tumor and EWING's/PNET. Frequency distribution of individual CNS tumors are given in [figure-1b]

Percentage Distribution Of CNS Lesions According To Age



Frequency Distribution Of Individual CNS Lesions



**Figure 1:** photograph showing distribution of CNS lesion according to age and sex(a). photograph showing morphologic spectrum of CNS lesions(b).

Regarding the statistical analysis of the cytodagnosis of different CNS tumors in the present study, it was observed that the overall

sensitivity of cytodagnosis of CNS neoplasm showed to be 81.11% and the specificity is 98.89%. [Table1].

**Table 1:** Statistical analysis of cytological diagnosis of CNS tumours

Tumor	Total no.	TP	FN	FP	T N	Sensitivity [%]	Specificity [%]	PPV	NPV
Low grade astrocytoma	17	16	1	3	70	94.12	95.89	84.21	75.00
High grade astrocytoma	12	9	3	2	76	75.00	97.22	81.82	95.89
Oligodendroglioma	3	3	0	1	86	100.00	98.85	75.00	100.00
Central neurocytoma	2	1	1	0	88	50.00	100.00	100.00	98.88
Ependymoma	4	3	1	2	84	75.00	97.67	60.00	98.82
Medulloblastoma	4	3	1	1	85	75.00	98.84	75.00	98.84
Schwanomma	12	10	2	2	76	83.33	97.44	83.33	97.44
Neurofibroma	1	0	1	1	88	0.00	98.88	0.00	98.88
Meningioma	18	15	3	2	70	83.33	97.22	88.24	95.89
Vasoformitive tumours [hemangioblastoma]	2	1	1	1	87	50.00	98.86	50.00	98.86
Germ cell tumours	1	1	0	0	89	100.00	100.00	100.00	100.00
Lymphoma and hematopoietic tumours	3	3	0	1	86	100.00	98.85	75.00	100.00
Metastatic tumours	3	2	1	0	87	66.67	100.00	100.00	98.86
Pituitary adenoma	2	2	0	0	88	100.00	100.00	100.00	100.00
Choroid plexus papilloma	1	1	0	0	89	100.00	100.00	100.00	100.00
Craniopharyngioma	02	2	0	0	88	100.00	100.00	100.00	100.00
Osteosarcoma /GCT	2	0	2	1	87	0.00	98.86	0.00	97.75
Ewing's/PNET	1	1	0	0	89	100.00	100.00	100.00	100.00
<b>TOTAL</b>	<b>90</b>	<b>73</b>	<b>17</b>	<b>17</b>	<b>17</b>	<b>81.11</b>	<b>98.89</b>	<b>81.11</b>	<b>98.89</b>

Regarding the statistical analysis of the cytodiagnosis of different CNS tumors in the present study, it was observed that the overall sensitivity of cytodiagnosis of CNS neoplasm showed to be 81.11% and the specificity is 98.89%.

It was observed that the frozen section showed low sensitivity of 78.89% but a comparable specificity of 98.89% to the squash cytology [Table 2].

**Table 2 :** Statistical analysis of frozen section diagnosis of CNS tumours

Tumour	Total no.	TP	FN	FP	TN	Sensitivity	Specificity	PPV	NPV
Low grade astrocytoma	17	13	4	4	69	76.47	94.52	76.47	94.52
High grade astrocytoma	12	11	1	3	75	91.67	96.15	78.57	98.68
Ependymoma	4	3	1	0	86	75	100	100	98.85
Medulloblastoma	4	2	2	2	84	50	97.67	50	97.67
Oligodendroglioma	3	1	2	1	86	33.33	98.85	50	97.73
Central neurocytoma	2	0	2	0	88	0	100		97.78
Schwanomma	12	11	1	0	78	91.67	100	100	98.73
Neurofibroma	1	1	0	0	89	100	100	100	100
Meningioma	18	17	1	2	70	94.44	97.22	89.47	98.59
Lymphoma	3	1	2	1	86	33.33	98.85	50	97.73
Germ cell tumours	1	0	0	0	90		100		100
Metastasis	3	3	0	0	87	100	100	100	100
Pituitary adenoma	2	1	1	0	89	100	100	100	100
Craniopharyngioma	2	2	0	1	87	100	98.86	66.67	100
Osteosarcoma/GCT	2	1	1	0	88	50	100	100	98.88
Choroid plexus papilloma	1	1	1	0	88	50	100	100	98.88
Ewing's/PNET	1	1	0	1	88	100	98.88	50	100
Hemangioma	2	1	1	1	85	66.67	98.84	66.67	98.84
<b>TOTAL</b>	<b>90</b>	<b>70</b>	<b>20</b>	<b>16</b>	<b>98.95</b>	<b>78.89</b>	<b>98.89</b>	<b>81.61</b>	<b>98.68</b>

It was observed that the frozen section showed low sensitivity of 78.89% but a comparable specificity of 98.89% to the squash cytology

The comparison of sensitivity and specificity of squash cytology and frozen section of CNS tumor, it was found that sensitivity was 81.11%, specificity was 98.89%, PPV was 81.11% and NPV was 98.89%, where a sensitivity of frozen section was 78.89%, specificity was 98.95%, PPV 81.61%, NPV 98.76%.

**Table 3:** Comparison of Cytologic Diagnosis and Frozen Diagnosis with Histological Diagnosis

Tumour type	Cytology	Frozen	Histology	Diagnostic accuracy	
				Cytology (%)	Frozen(%)
Astrocytoma	[low grade]16	13	17	84.21	76.47
	[high grade]9	11	12	75.00	91.66
Ependymoma	3	3	4	75.00	75.00
Oligodendroglioma	3	2	3	100.0	50.00
Medulloblastoma	3	1	4	75	33.33
Central Neurocytoma	1	0	2	50.00	0.00
Neurilemoma	10	11	12	83.33	91.6
Neurofibroma	0	1	1	0.00	100.0
Meningioma	15	17	18	83.33	94.44
Hemangioblastoma, Hemangioma	1	1	2	50.00	50.00
PCSNL	3	1	3	100.00	33.33
Craniopharyngioma	2	2	2	100.00	100.00
Pituitary adenoma	2	2	2	100.00	100.00
Metastatic tumours	2	3	3	66.66	100.00
Germ cell tumours	1	0	1	100.00	0.00
Osteosarcoma/GCT	0	0	2	0.00	0.00
Choroid plexus papilloma	1	0	1	100.00	0.00
Ewing's/PNET	1	1	1	100.00	100.00

**Table – 4A** Major Causes of the Discrepancies in Squash Smear

Tumor Group	Total no. of discrepant cases	Cause of the discrepancy
Low Grade Gliomas	01	Grading error (over grading)
High Grade Gliomas	02	Grading error (under grading)
Meningiomas(fibroblasts)	01	Due to lack of whorls and psammoma bodies.
Embryonal Tumors	01	Lack of rosettes, difficult to spread tissue
Nerve Sheath Tumors	02	Misinterpretation between spindle cell neoplasms
Other tumors including metastatic tumors	02	Lack of architecture in metastatic& high grade glioma
<b>Total</b>	<b>09</b>	

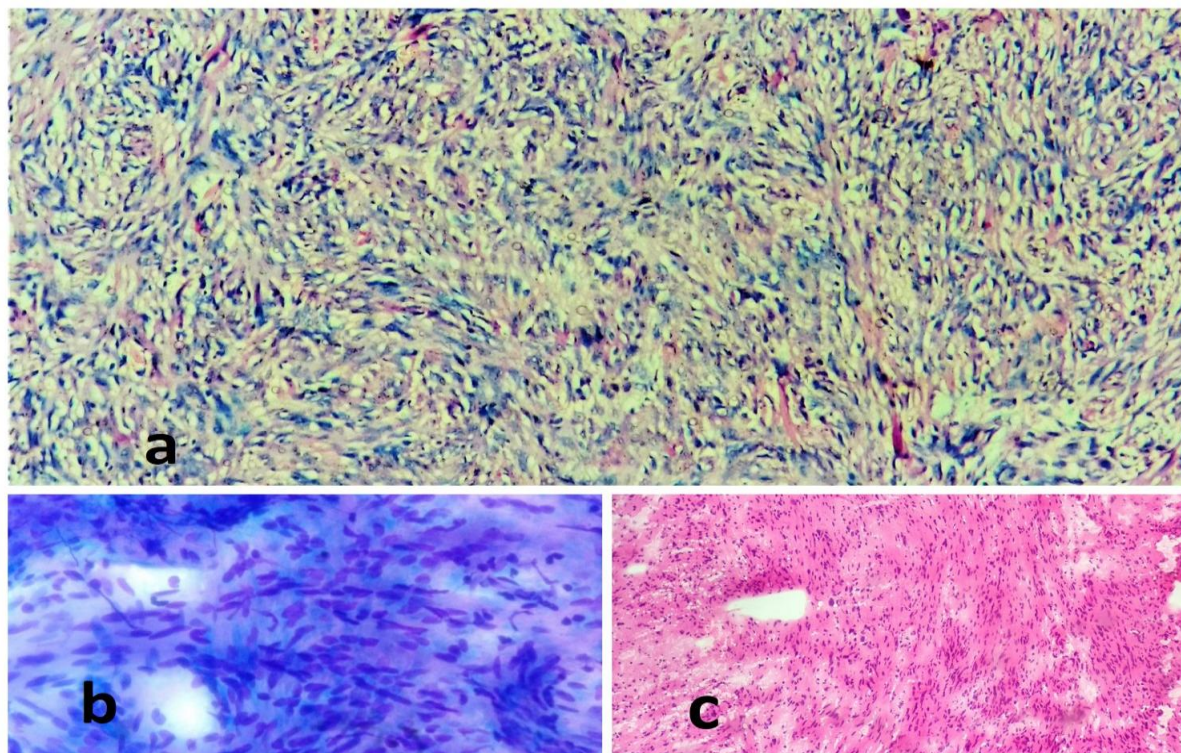
In 81.11% of cases intra-operative squash cytology correlated with the final histopathological diagnosis and 78.88% cases of frozen section well correlated with the HP section [Table-3].

Most common discrepancy are discussed in Table-4[4a, 4b].

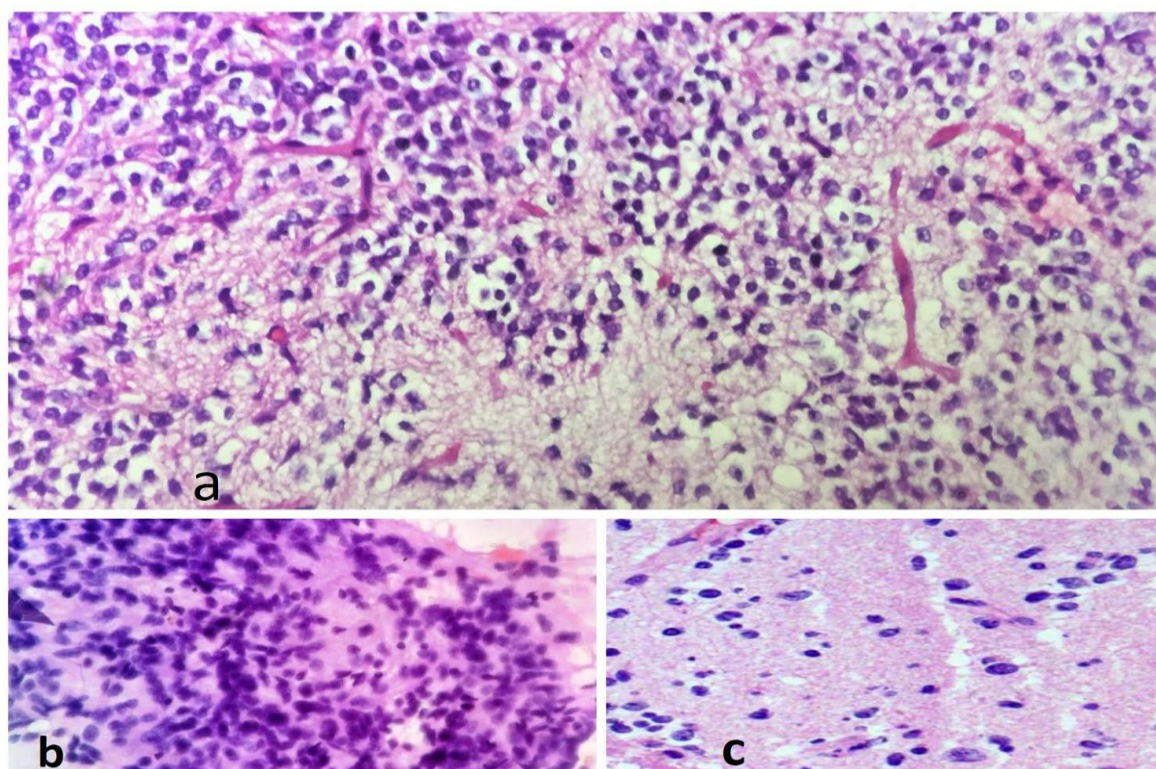
**Table – 4B** Major Causes of the Discrepancies In Frozen Section

Tumor Group	Total no. of discrepant cases	Cause of the discrepancy
Low Grade Gliomas	04	Grading error (over grading)
High Grade Gliomas	01	Grading error (under grading)
Meningiomas	1	The fasciculating pattern of spindle cells
Embryonal Tumors	0	-
Nerve Sheath Tumors	02	Misinterpretation between spindle cell neoplasms
Other tumors including metastatic tumors	02	Misinterpretation between atypical cells of metastatic& high grade glioma & predominant necrotic area.
<b>Total</b>	<b>10</b>	





**Figure-2:** (a) Microphotograph showing spindle shaped meningotheelial cells arranged in fascicles.(HP10x). (b)Microphotograph showing thick squash preparation with spindle cells intertwining misinterpreted as schwannoma (diffquick 40x). (c)microphotograph showing spindle cells some area showing verocay body like area misdiagnosed as schwannoma (FZ, H&E-10x)



**Figure-3:** (a)Microphotograph showing neoplastic round to oval cells with perinuclear halo, chicken wire calcification & retained gliofibrillary background(HP 40x). (b)microphotograph showing cellular smear showing pleomorphic round cells with thin walled blood vessels diagnosed as oligodendroglioma.(diff quick 40x). (c)microphotograph showing round cells some with clear halo , lacking gliofibrillary background misinterpreted as central neurocytoma (FZ)(H&E-40x).



## Discussion

The strength of squash cytology is that it is simple, rapid, robust, provide good cellular details need minimum equipments and technically skill, and also that it requires a very small amount of tissue for analysis, particularly vital in lesions located in functional areas of brain.<sup>4</sup>

Frozen section analysis is also a common intraoperative histopathological diagnostic method particularly in CNS tumors. The reasons for its extensive uses are-rapid analysis and preservation of tissue architecture providing determinative information guiding the surgical management.<sup>5</sup> However expensive equipment, tissue availability, ice crystal formation, freezing artifacts and inferior cytological detail as compared to cytologic preparation are its limitation.<sup>6</sup> As seen in the present study, the architecture and details of tumor cells are maintained in many cases.

In our study, Low grade astrocytoma showed low to moderate cellularity arranged loosely around blood vessels and no endothelial cell proliferation, whereas high grade astrocytoma showed marked cellularity with endothelial cell proliferation and palisading necrosis in frozen section.

Presence of cohesive sheets of cell often with intra-nuclear inclusion with meningothelial whorls and psammoma bodies was diagnostic in squash cytology of meningioma. In our cases Schwannoma showed typical pattern of tightly interweaving fascicles in frozen section and fascicles of spindle cells intertwined with each other giving a twisted rope appearance in squash smear.

Presence of small dark nucleus with nuclear moulding and rosette formation was seen in medulloblastoma. Cellular smear with round cells having a salt and pepper chromatin suggested pituitary adenoma.

Three dimensional papillae with an orderly arrangement of cuboidal cells over a fibrovascular core is diagnostic of choroid plexus papilloma & Lymphoma showed dyscohesive round cells lying discretely in the absence of fibrillary background

with presence of lymphoglandular bodies in the background in squash smears.

In our study the major discrepant cases were categorized in to four groups. These includes: a.Grading error in glioma, b. interpretation in spindle cell lesions, c. interpretation in embryonal tumors, d. other miscellaneous category.

Low grade vs high grade glioma: in the present study among 17[18.88%] cases of low grade astrocytoma diagnosed histologically, 16cases [17.77%] cases corroborated cytologically& only 13 [14.44%] cases corroborated in frozen section. In our study, the cause of 1 discrepant case in cytology was inability to control the thickness of squash preparation which added to the diagnostic problem which gave a pseudo-cellularity which was corroborated with the study samal S.et al who described low grade astrocytoma like pilocytic astrocytoma was over-graded due to increased vascularity and nuclear atypia.<sup>7</sup> In frozen section among the 6 cases of discrepant cases 4 were over-diagnosed as high grade glioma and 2 were under diagnosed as reactive gliosis. Microcystic changes were difficult to access at frozen section because of freezing artifact, obscuring the cytological details and heterogeneous appearance of glioma were the cause of discrepancies.<sup>8</sup>

Two out of three [66.66%] cases of oligodendroglioma was misdiagnosed in frozen section, freezing often produces irregularities in the nuclear contour giving appearance of an astrocytoma thus causing the discrepancy.<sup>7</sup> Thawing of a frozen block followed by processing also introduces additional artefact like nuclear pleomorphism and hyperchromasia which impart an oligodendroglioma features suggestive of astrocytoma.<sup>9</sup> However few authors have reported a higher accuracy of squash cytology in diagnosing oligodendroglioma. sukla k et al(90%) khamechiant et al(100%).<sup>7</sup>

Interpretation in spindle cell lesion: The second group of discrepant cases in our study was interpretation in spindle cell lesions of CNS. Distinguishing fibroblastic meningioma, nerve sheath tumor and schwannoma was challenging at

squash smear. Ten cases out of 12(83.33%) cases of schwannoma could be diagnosed in cytology in our study because neural tumor resist to squash smear imparting a smear artefact. Here frozen section was found to be superior to squash smear. Meningioma are often firm neoplasm and therefore did not yield good smears, the wispy cytoplasm mislead to consider such tumors as astrocytic neoplasm in intra-operative squash cytology.<sup>10</sup> one case of fibroblastic meningioma was misdiagnosed as schwannoma basing on spindle cell morphology which was also diagnosed in frozen section because of absence of characteristic cellular Antony 'A' areas that lacked epithelial whorls characteristic of meningioma. This experience is shared by another author Savita et al.<sup>11</sup> On frozen section a diagnostic syncytial/ whorling pattern and psammomabodies helped to reach the diagnosis thus , rendering frozen section more useful than squash smear in meningioma cases.

Embryonal tumors: 3 out of 4 cases of medulloblastoma were correctly diagnosed, but one case was diagnosed as lymphoma on squash cytology because of presence of highly cellular smear with small round dyscohesive cells and lack of perivascular architecture. Similar discrepancy was also found by another author where the presence of small round dyscohesive cells with high N:C ratio, nuclear hyperchromasia and structure appearing like lymphoglandular bodies gave an erroneous diagnosis of lymphoma.<sup>12</sup> similarly of 50% (2 out of 4 cases) of cases of medulloblastoma could be diagnosed correctly on frozen section of our study. Presence of normal cell of cerebellum resembling lymphocytes admixed with presence of anaplastic dyscohesive cells lead to misdiagnosis of anaplastic medulloblastoma as lymphoma in frozen section.<sup>10</sup>

Ependymoma showed same diagnostic accuracy both in squash smear and frozen section because of presence of typical rosettoid appearance. The characteristic perivascular pseudorosette, vascular proliferation and atypical mitosis was absent in a case of anaplastic ependymoma which lead to

discrepancy in our study. Adesineetal2005 also found the same which probably explain the discrepancy found in our case.<sup>13</sup>

Other discrepant cases: A case of central neurocytoma was misdiagnosed as oligodendroglioma. both these tumors have similar cytomorphological features with presence of monotonous round nuclei having slightly dense but bland chromatin without cytoplasm. Perinuclear halo characteristic of oligodendroglioma on histological preparation is a fixation artifact, is not seen in cytological preparation, n are also missed in frozen section because of freezing artifact. The chicken wire blood vessels were missing in squash cytosmear. Similar experience was shared by Savita et al.<sup>11</sup> The cases of non –Hodgkin's lymphoma 2 was misdiagnosed as high grade gliomas in frozen section because of cellularity, large areas of necrosis and lack of perisinusoidal pattern due to freezing artefacts. However squash preparation spread over anlymphoglandular bodies in squash cytology helped in the correct diagnosis of lymphoma. raoetal also found the same.<sup>14</sup>

A case (one out of three cases) of metastatic adenocarcinoma was misdiagnosed in cytology as GBM because of presence of bizzare type of cell in a necrotic background. However the case was correctly interpreted on frozen section which well delineated the the tissue architecture. A similar interpretation was seen in a study conducted by sumitra et al. Squash was not very helpful in diagnosing metastatic lesion as the neoplastic epithelial cells resist spreading.<sup>15</sup>

In squash cytology lymphoma , choroid plexus papilloma, craniopharyngioma , pituitary adenoma and germcell tumor had characterstic cytological findings in our study. Choroid plexus papilloma ,craniopharyngioma and EWINGS sarcoma are diagnosed well in frozen with all characterstic finding in our study.

Vascular lesions didn't yield good results on intra-operative cytology or frozen section. Both the techniques were non-contributory. These lesions were paucicellular, delicate and hemorrhagic,



rendering an unsatisfactory cytology and frozen section.<sup>10</sup>

For CNS lesions like low grade astrocytoma, oligodendroglioma, medulloblastoma, germ cell tumor, lymphoma, the neurosurgeon should rely more on IOP squash cytology for immediate management of cases. On the contrary for CNS

neoplasm like high grade astrocytoma, ependymoma, schwannoma, neurofibroma, meningioma, metastatic tumors, EWING/PNET, craniopharyngioma, choroid plexus papilloma, a frozen section would serve as a better guide for intra-operative diagnosis and management.

**Table 5:** Comparison of diagnostic accuracy of squash smear and frozen section in various studies

Study	Type of lesions	No. of cases	Squash/imprint cytology[in %] of accuracy	Frozen section [%] of accuracy
Sumitmitra et al, 2010	neoplastic	11	88.5%	90.6%
Nanang et al,2015	Neoplastic/ non neoplastic	75	89.2%	75.3%
Samal et al, 2018	Non neoplastic/neoplastic	63	85.7%	75%
Present study	neoplastic	90	81.88%	78.88%

**Conclusion**

Cytology preparation are much simpler and quicker to generate, have smaller tissue requirements than Frozen section, whereas latter preserves better tissue architecture than squash smear. Though squash smear shows a reasonably high percentage of accuracy in intra-operative diagnosis ,some lesions pose a diagnostic challenge .Hence there is a need to do a frozen section with a view to corroborate the diagnosis of squash cytology. Both the procedures should be used complementarily and not a substitute to each other. Regardless of which approach one decides to use, knowledge of pertinent clinical and radiological information at the time of intra-operative consultation with neurosurgeon is critical in arriving at an accurate diagnosis. Recent advances in neurosurgical techniques viz. stereotactic and burrhole surgeries have aided in sample collection for cytological procedures especially in cases of high grade tumors, tumors at inoperable sites and tumors requiring alternate therapy(CT & RT). Squash cytology and frozen section are immensely important in these cases, guiding intraoperative decisions thus decreasing the morbidity of prolonged surgeries.

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#### Abbreviations

CNS-central nervous system, MGG-may-grunwaldgeimsa, H&E-hematoxylin and eosin, IHC-immuno-histochemistry, PPV-positive predictive value, NPV-negative predictive value.