Section: Pathology

Original Research Article

A 5 YEAR RETROSPECTIVE STUDIES OF CNS TUMOURS AND CORRELATION OF SQUASH CYTOLOGY AND HISTOPATHOLOGY

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Abstract

Background: Despite advancements in the diagnosis of Central nervous system (CNS) tumors, the squash cytology (SC) remains as the sensitive and specific intra-operative screening technique for these tumors and the histopathology examination (HPE) retains its gold standard status. Here we reassess the diagnostic accuracy and utility of SC in correlation with HPE of CNS tumors in 5-year consecutive samples of tertiary care hospital. **Materials and Methods:** Five year (Jan 2018 to Jan 2023) retrospective samples diagnosed as CNS tumors both by SC and HPE were retrieved from the Department of Pathology, Gandhi Medical College & Hospital, Secunderabad, Telangana. The clinical and radiological data of these cases were also reviewed. Two independent pathologists reviewed the samples and came to diagnostic consensus. The diagnostic accuracy and utility were analysed using appropriate statistical method. **Result:** A total of 279 SC and HPE samples were evaluated. CNS tumors diagnosed by SC exhibited 99.1% correlation with HPE diagnosis. **Conclusion:** SC is a rapid, sensitive and specific diagnostic technique and exhibits 99.1% correlation with HPE diagnosis proving its diagnostic accuracy even in the current era.

INTRODUCTION

In India CNS tumors account for 5–10 per 1,00,000 population of which two percent of them are malignant.[1] Rapid and accurate diagnosis is mandatory in the management of these tumors. Though histopathological examination (HPE) is considered as gold standard for the diagnosis of these lesions, it is time consuming. A rapid & equally accurate intraoperative diagnostic modality like squash cytology (SC) aids in overcoming the time constraint,[2] and helps the neurosurgeon to plan and modify the extent of surgery.[3] Another intraoperative technique, Frozen section is available for knowing extent of the disease especially clearance of surgical margins. However, when compared to SC, frozen section exhibits morphological artefacts limiting the ability to diagnose accurately. Most of the CNS lesions are soft and provides excellent cytological details on squash smear preparation.[4,5] This technique of intraoperative SC was introduced in 1930 by Eisenhardt and Cushing.[6] A representative small tissue fragment is placed on a labelled glass slide which is then gently crushed and rotated with a second slide held at right angle to get an even spread of the sample tissue. These slides are transferred to 95% ethanol for fixation before staining with H& E. In this study we evaluated the utility & the accuracy of squash cytology in comparison with the gold standard HPE.

MATERIALS AND METHODS

The present study is a retrospective observational study conducted in the department of pathology for a period of 5 years (January 2018 to January 2023). This study is approved by the Institutional Ethics Committee (Rc.no.IEC/GMC/2022/08/07 of Gandhi Medical College, Secunderabad, Telangana, India). Total of 279 CNS tumors with adequate preoperative radiological, intraoperative cytopathological and postoperative histopathological evaluation were included in the present study.

The slides (Squash Cytology and Histopathology) pertaining to the CNS tumors were retrieved from the archives of Department of Pathology, Gandhi Medical College, Secunderabad, Telangana, India. These slides were independently evaluated by three

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pathologists (Dr. Saritha, Dr. Sreelakshmi, Dr. Devojee) and cases for which IHC was available were also reviewed for diagnostic confirmation. The results obtained from the evaluation of these pathologists were compared. In case of any discrepancy in the diagnosis between the pathologists were resolved by simultaneous re-reviewing of these slides by all the pathologists and coming to a diagnostic consensus. Finally, the utility and diagnostic accuracy of squash smear cytology in comparison with gold standard histopathology was analysed.

RESULTS

A total of 279 cases [Table: 1] were included in our study to analyse the diagnostic accuracy and correlation of intraoperative squash smear cytology with histopathology of central nervous system tumors. In the Present study age distribution ranged from 8 to 82 years. Majority of patients were males 49% and 51% were females [Table 2]. Headache (72.5%), nausea & vomiting (52.5%), Motor weakness (32.5%) and seizures (31%) were the most common presenting signs and symptoms followed by altered consciousness (40%), speech defect (10%) and neurological deficit (9.5%) respectively. Of all CNS tumors 93% brain tissue and 7% spinal cord tissue biopsies and tumors were received. For brain space occupying lesions (SOL), Frontal SOL (16.8%), Cerebropontine angle (11.8%), Parietal (10.4%), Temporal (7.9%), Cerebellum (8.2%) were the most common sites. Astrocytoma (34.40%) and Meningioma (24.37%) were the most common tumors followed by Schwannoma (12.54%), Metastasis (5.73%), Pituitary adenoma (4.30%) and Medulloblastoma (3.58%) were the major tumors. Among less common tumors were Ependymoma (2.95%), oligodendroglioma (2.50%), craniopharyngioma (2.15%), Hemangioblastoma (1.79%), lymphoma(1.79%), choroid plexus tumors (1.43%), Neurofibroma(0.71%), Dysembryoplastic NeuroEpithelial Tumor (DNET)(0.71%), oligoastrocytoma (0.35% each), Teratoma (0.35% each) and Diffuse melanocytosis of leptomeninges (0.35% each).

Radiological findings of either MRI or CT of CNS tumours were analysed. On evaluation of 279 cases, majority of cases showed radiological findings of meningioma (32%) [Figure 3A], schwannoma (17%) [Figure2A], high grade glioma (15%), low grade glioma (12%) [Figure1A] and other less findings were of sellar tumours (11%), metastasis (3%) [Figure7A] respectively.

On Squash cytology Astrocytoma (35.12%)-[Figure1B] and Meningioma (23.29%)-[Figure3B] were the most common tumors followed by Schwannoma(12%) –[Figure2B], Metastasis(8%), Pituitary adenoma(4%)-[Figure4B] and Medulloblastoma(4%)-[Figue5B] were the major tumors. Among less common tumors were craniopharyngioma (2.51%), Ependymoma (2.15%), oligodendroglioma (1.80%), choroid plexus tumors (1.80%)-[Figue6B], Hemangioblastoma (1.43%), lymphoma(1.43%), Neurofibroma(0.71%), DNET(0.71%), oligoastrocytoma (0.35%), Teratoma(0.35%) and Diffuse melanocytosis of leptomeninges (0.35%) respectively. The frozen section evaluation is not the scope of our study.

The frequent findings on SC includes fibrillary background in Astrocytomas, dyscohesive uniform cells with round nucleus and fine granular chromatin and increased capillary network in oligodendroglioma, cohesive syncytial clusters of cells with moderate amount of eosinophilic cytoplasm with oval nucleus and fine chromatin in meningioma, dyscohesive small dark cells in medulloblastoma, round nucleus with salt and pepper chromatin in pituitary adenoma, interwined fascicles and cohesive sheets of spindle shaped cells with spindled wavy nuclei in schwannoma.

On Histopathology Astrocytoma (34.40%) [Figure1C] and Meningioma (24.38%) [Figure3C] were the most common tumors followed by Schwannoma (12.9%) [Figure2C], Metastasis (5.78%)-[Figure7C], Pituitary adenoma (4.30%) [Figure4C] and Medulloblastoma (3.58%) [Figure5C] were the major tumors. Among less common tumors were Ependymoma (2.86%), oligodendroglioma (2.50%), craniopharyngioma (2.15%), Hemangioblastoma (1.80%), lymphoma (1.80%), choroid plexus tumors(1.43%) [Figure6C] Neurofibroma(0.71%),DNET(0.71%), oligoastrocytoma (0.35%), Teratoma(0.35%) and Diffuse melanocytosis of leptomeninges (0.35%) respectively.

Immunohistochemistry is used to investigate cellular differentiation in CNS tumors and as an independent prognostic tool. Most commonly used markers are GFAP (Glial Fibrillary Acidic Protein), S-100 [Figure 2D], Epithelial Membrane Antigen, Ki-67 [Figure 1D]. Ki67/ MIB1 detect proliferating cells there by helping in grading astrocytomas.

On correlating squash cytology and histopathology in the present study given in [Table: 3] showed 100% accuracy in diagnosing Medulloblastoma, DNET, Oligoastrocytoma, Teratoma. In 99.60% of accuracy were seen in tumors of Pituitary adenoma, lymphoma, Hemangioblastoma, oligodendroglioma. 1 case of lymphoma and 1 case of Hemangioblastoma were reported as metastatic deposits in Squash smear cytology. 2 cases of oligodendroglioma were reported as low-grade astrocytoma on squash cytology.

Comparative efficacy of SC to HPE diagnosis were given in [Table: 4] Accuracy of squash cytology in ranged from 94% (Astrocytoma) to 100 % (Medulloblastoma). The maximum 100%Sensitivity was seen in medulloblastoma, choroid plexus tumors, craniopharyngioma and minimum for ependymoma (62.5%) and oligodendroglioma (71.4%). The Specificity was maximum (100%) for Meningioma, schwannoma, neurofibroma, medulloblastoma,

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pituitary adenoma and minimum for Astrocytoma (95%) and Metastasis (97.3%).

The maximum 100% Positive predictive value was seen in medulloblastoma, schwannoma, neurofibroma, Meningioma and minimum was seen in Metastasis (68.1%). The maximum 100% Negative predictive value was seen in medulloblastoma, neurofibroma, craniopharyngioma and minimum was seen in astrocytoma (96%).

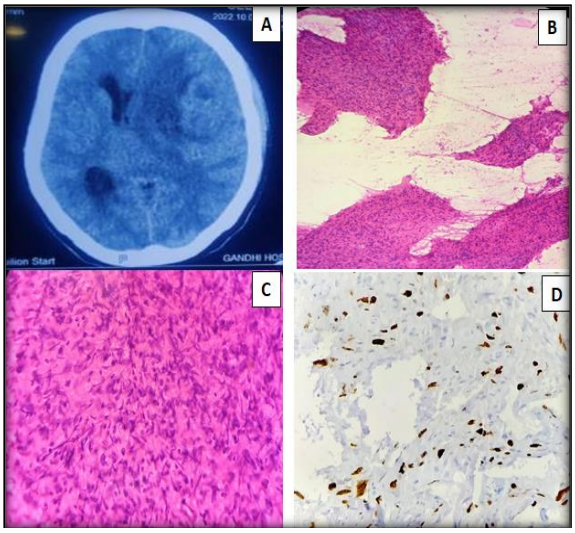

Figure 1 ASTROCYTOMA: A-Non Contrast CT Findings are well defined intraaxial isodense lesion with few hypodense areas with surrounding vasogenic edema. B-Squash cytology shows hypercellular smear with neoplastic astrocytes, marked nuclear atypia, necrosis (H & E, 10 x); C-Section shows diffusely arranged markedly pleomorphiuc tumor cells, increased N:C ratio with endothelial proliferstion (H &E, 40 x); D-Ki-67% -Positivity (IHC-40X)

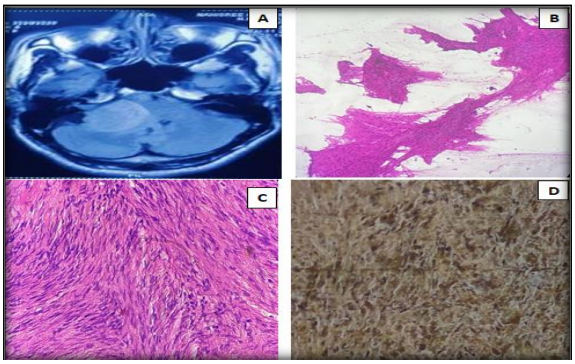

Figure 2 SCHWANOMMA: A-MRI Findings are well defined homogenously hyperintense extra axial lesion noted in expanded right cp angle cistern with mild widening of right internal auditory canal. B-Squash cytology shows cohesive sheets of spindle cells with spindled wavy nuclei (H & E, 40 x); C-Section shows compact cellular Antoni A and less cellular loosely textured Antoni B areas(H &E, 40 x); D-S-100 Positivity (IHC-40X)

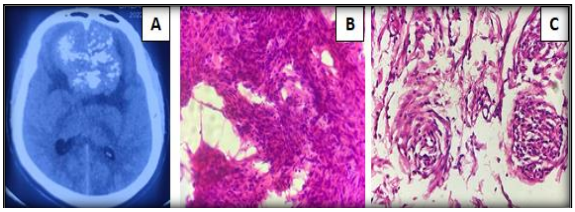

Figure 3 MENINGIOMA: A-Non contrast CT Findings are well defined extraaxial isodense lesion along falx on either side of anterior interhemispheric fissure with multiple calcific foci within. B-Squash cytology shows cohesive syncytial clusters of cells with moderate amount of eosinophilic cytoplasm with oval nuclei and fine chromatin (H & E, 40 x); C-Section shows interlacing fascicles, whorls of meningothelial and fibrous patterns of neoplastic cells (H &E, 40 x)

Table 1: Distribution of CNS Neoplasms

S. No	Tumour	Number of Cases	Percentage %
1	Astrocytoma	96	34.40%
2	Oligodendroglioma	7	2.50%
3	Oligoastrocytoma	1	0.35%
4	Ependymoma	8	2.95%
5	Choroid plexus tumors	4	1.43%
6	DNET	2	0.71%
7	Medulloblastoma	10	3.58%
8	Schwannoma	35	12.54%
9	Neurofibroma	2	0.71%
10	Meningioma	68	24.37%
11	Haemangioblastoma	5	1.79%
12	Diffuse melanocytosis of leptomeninges	1	0.35%
13	Lymphoma	5	1.79%
14	Craniopharyngioma	6	2.15%
15	Pituitary adenoma	12	4.30%
16	Teratoma	1	0.35%
17	Metastasis	16	5.73%
	Total	279	100%

Table 2: Age and Sex wise incidence of CNS Tumours

S. No	Age Group	Males	Females	Total
1	0-10	11	8	19
2	11-20	9	10	19
3	21-30	12	15	27
4	31-40	25	19	44

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5	41-50	30	41	71
6	51-60	30	25	55
7	61-70	18	23	41
8	71-80	1	-	1
9	>80	1	1	2
	Total	137	142	279

Table 3: Correlation between Histopathological and Squash Cytology diagnosis

S. No	Histopathological diagnosis	No of cases	Squash cytology diagnosis	Diagnostic accuracy (%)
1	Astrocytoma	96	Astrocytoma - 89, metastatic deposits - 4, Ependymoma - 1, Tuberculous granuloma with cystic change - 2	94.20%
2	Oligodendroglioma	7	Oligodendroglioma - 5, Low grade Astrocytoma - 2	99.20%
3	Oligoastrocytoma	1	Oligoastrocytoma – 1	100%
4	Ependymoma	8	Ependymoma - 5, Low grade astrocytoma - 2, Atypical choroid plexus papilloma - 1	98.50%
5	Choroid plexus tumors	4	Choroid plexus papilloma - 4	99.60%
6	DNET	2	DNET – 2	100%
7	Medulloblastoma	10	Medulloblastoma - 10	100%
8	Schwannoma	35	Schwannoma - 33, Low grade astrocytoma - 2	99.20%
9	Neurofibroma	2	Neurofibroma – 2	100%
10	Meningioma	68	Meningioma - 65, Low grade glioma - 2, metastatic deposits – 1	98.90%
11	Haemangioblastoma	5	Hemangioblastoma - 4, metastatic deposits - 1	99.60%
12	Diffuse melanocytosis of leptomeninges	1	Diffuse melanocytosis of leptomeninges - 1	100%
13	Lymphoma	5	Lymphoma - 4, metastatic deposits - 1	99.60%
14	Craniopharyngioma	6	craniopharyngioma - 6	99.60%
15	Pituitary adenoma	12	Pituitary adenoma - 11, Craniopharyngioma - 1	99.60%
16	Teratoma	1	Teratoma – 1	100%
17	Metastasis	16	Metastatic deposits - 15, Low grade astrocytoma - 1	97.10%
overall correct diagnosis by squash cytology - 99.1%				

Table 4: Comparative Efficacy of Squash Cytology as Compared to Histopathological Diagnosis

S. No	CNS lesions	Total	Squash diagnosis	HPE diagnosis	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
1	Astrocytoma	96	98	96	92.7	95	90.8	96.1	94.2
2	Oligodendroglioma	7	5	7	71.4	100	100	99.2	99.2
3	Oligoastrocytoma	1	1	1	100	100	100	100	100
4	Ependymoma	8	6	8	62.5	99.6	83.3	98.9	98.5
5	Choroid plexus tumors	4	5	4	100	99.6	80	100	99.6
6	DNET	2	2	2	100	100	100	100	100
7	Medulloblastoma	10	10	10	100	100	100	100	100
8	Schwannoma	35	33	35	94.2	100	100	99.1	99.1
9	Neurofibroma	2	2	2	100	100	100	100	100
10	Meningioma	68	65	68	95.5	100	100	98.6	98.9
11	Haemangioblastoma	5	4	5	80	100	100	99.6	99.6
12	Diffuse melanocytosis of leptomeninges	1	1	1	100	100	100	100	100
13	Lymphoma	5	4	5	80	100	100	99.6	99.6
14	Craniopharyngioma	6	7	6	100	99.6	85.7	100	99.6
15	Pituitary adenoma	12	11	12	91.6	100	100	99.6	99.6
16	Teratoma	1	1	1	100	100	100	100	100
17	Metastasis	16	22	16	93.7	97.3	68.1	99.6	97.1

Table 5: Diagnostic Accuracy of Squash smear cytology in others study

S. No	Name of the Study	Diagnostic Accuracy
1	Present Study	99.1%
2	Govindaraman PK et al	90.67%
3	Agarwal M et al	95%
4	Duvuru P	95.36%
5	Khuroo MS et al	90.5%
6	Kalpana Study	91.1%
7	Sumit et al	88.5%
8	Imtiaz et al	84.0%

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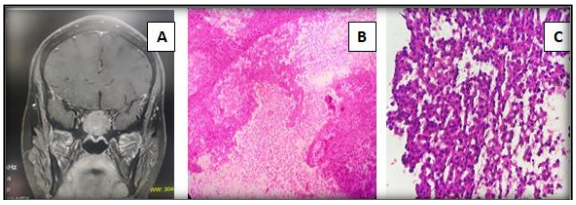

Figure 4 PITUITARY ADENOMA: A-MRI Findings are T1 well defined homogenously enhancing lesion noted in sella with suprasellar extension indenting optic chaisma. B-Squash cytology shows discohesive pattern of small to medium sized cells with eccentric round to oval nuclei, speckled chromatin,granulated cytoplasm. (H & E, 40 x); C-Section shows neoplastic cells with moderate amount of eosiphilic cytoplasm, uniform nuclei with stippled chromatin and inconspicuous nucleoli. (H &E, 40 x)

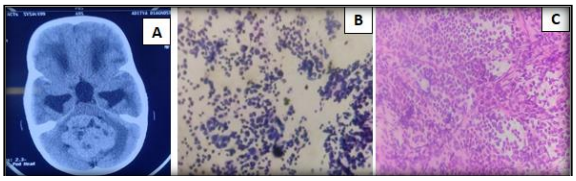

Figure 5 MEDULLOBLASTOMA: A-CT Findings are heterogeneously enhancing lesion with few non enhancing areas within noted in vermis in midline compressing 4th ventricle and causing dilatation of bilateral 3rd ventricle. B-Squash cytology shows discohesive small dark cells in a diffuse pattern (H & E, 40 x); C-Section shows syncytial arrangement of undifferentiated small round blue cells (embryonal cells) with brisk mitosis (H &E, 40 x)

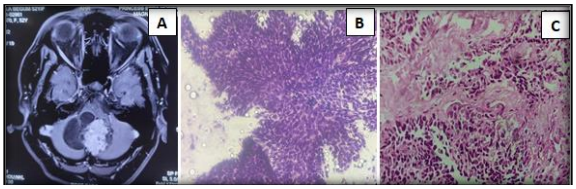

Figure 6 CHOROID PLEXUS PAPILLOMA: A-MRI Findings are T1 well defined homogenously enhancing lesion noted in 4th ventricle with surrounding peritumoral cystic lesions noted along anterolateral aspect of lesion on right side. B-Squash cytology shows papillaroid structures lined by columnar cells with no pleomorphism (H&E, 40 x); C-Section shows increased cellularity, nuclear pleomorphism.(H &E, 40 x)

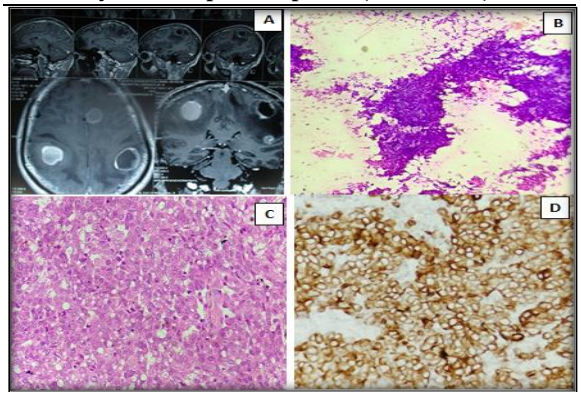

Figure 7: METASTASIS: A-CT Findings are multiple well defined intraaxial lesions with surrounding vasogenic edema with few of them showing peripheral ring enhancement noted in left frontal,bilateral parietal lobes.B-Squash cytology shows cohesive clusters of polygonal cells with moderate amount of eosinophilic cytoplasm, high N:C ratio,hyperchromatic nuclei with no fibrillary background (H & E, 40 x); C-Section shows sheets of polygonal cells with abundant moderate eosinophilic cytoplasm, vesicular nucleus, prominent nucleoli (H &E, 40 x); D-CK-7 Positivity (IHC-40X)

DISCUSSION

Intraoperative diagnosis of CNS tumors is of prime importance in aiding neurosurgeon to make rapid and critical decisions while on the operating table. For these tumors planned for surgery Preoperative radio imaging delineates the location and extent of the tumor. Intraoperative SC diagnosis is a simple, safe, fairly accurate, rapid and reliable tool that requires minimum equipment and technical skill for the diagnosis of CNS tumors.[7] SC helps the neurosurgeon to plan and modify the extent of surgery intra operatively.[3] However, Histopathology is considered the Gold Standard investigation for the definitive diagnosis of CNS tumors.[8] The present study reconfirms the correlation of intraoperative SC diagnosis with radio imaging studies and HPE.

The SC smears can be prepared from very tiny specimens ample allowing tissue to be preserved for further HPE.[9] The turnaround time for the SC is within 15-20 min as it can be done even when the sample is scanty.[10] In the present study, out of 279 CNS tumors, 93% were from brain tumors and 7% from spinal cord. The incidence of CNS tumors was frequently observed in fourth decade by Dogar et al,[11] Govindaraman et al,[12] Deshpande et al,[13] Goyani et al,[14] whereas other studies reported as sixth decade by Acharya et al,[10] Kaki et al.[15] In contrast current study exhibited peak incidence of CNS tumors in the fifth decade. Our study demonstrated female predominance similar to studies by Kaki et al,[15] Govindaraman et al,[12] and Patil et al,[16] whereas studies by Goyani et al,[14] Dogar et al,[11] Deshpande et al,[13] Jindal et al,[17] demonstrated male predominance. In our study frontal region was common site of these tumors while parietal region was the most common site of involvement in the studies done by Goyani et al,[14] Kaki et al,[15] and Dogar et al.[11] Additionally, other study exhibited fronto-temporal region as predominant site of involvement by Nanarng et al.[18]

Correlation between SC and HPE diagnosis was observed in 99.1% of cases. The diagnostic accuracy of SC for CNS tumor ranged from 94% (Astrocytoma) to 100% (Medulloblastoma). On SC Astrocytoma and Meningioma were the most common tumors followed by Schwannoma, Metastasis, Pituitary adenoma and Medulloblastoma. Among less common tumors 100% of accuracy was seen with Neurofibroma, DNET, Oligoastrocytoma, Teratoma and Diffuse melanocytosis of leptomeninges. Whereas 99.6% of accuracy was seen with Craniopharyngioma. Choroid plexus tumors, Hemangioblastoma, Lymphoma and

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Oligodendroglioma exhibited 99.2% and Ependymoma 98.50% accuracy respectively.

Out of 35 cases diagnosed as Schwannoma on HPE, two cases were missed by SC which was reported as low-grade astrocytoma contributing to 99.2% diagnostic accuracy. Similarly, SC missed 3 cases of meningioma which was reported as low-grade glioma and Metastatic deposit one each producing accuracy rate of 98.9%. Out of 96 Astrocytomas diagnosed on HPE, only 89 were picked up by SC (accuracy rate of 94.2 %.). Four, two, and one of these cases were misdiagnosed by SC as Metastatic deposits, tuberculous granuloma with cystic change and ependymoma respectively. Misdiagnosis on cytology were characterised by, poor cellularity, morphological similarity of cells, non-representativeness of the sample, reactive cells, and increased vascularity. Patil et al,[16] Govindaraman et al,[12] Nanarng et al,[18] de Souza Balsimelli et al,[19] and Mitra et al,[2] had also misdiagnosed various CNS lesions and analysed pitfalls in their study. The documentation of Deshpande et al,[13] showed lack of architecture on cytology, biopsies from cyst wall, reactive changes, inflammation, necrosis obscuring morphology, increased fibrous component as the common causes for inconclusive cases in their study. Diagnostic accuracy of SC in the present study [Table 5] was 99.1% whereas other studies exhibited variable accuracies ranging from 84% to 95.4% (Govindaraman PK et al,[12] 90.67%, Kalpana deshpandee et al [13] 91.1%, Agrawal M et al,[20] 95%, Duvuru P et al,[21] 95.4%, Khuroo et al,[22] study 90.56%,Sumit et al,[2] study 88.5%, Imtiaz et al,[23] study 84.0%, Iqbal M et al,[24] study 94%, Shukla K et al,[25] Rapid intraoperative diagnosis is of greatest value to select treatment options and we recommend Squash smear to use regularly for diagnosis of CNS tumors.

CONCLUSION

Intraoperative diagnosis of CNS tumors by SC technique is a rapid, accurate and inexpensive technique and its diagnosis should always be confirmed with histopathological examination which is the gold standard in spite of its SCs diagnostic accuracy owing to occurrence of minimal pitfalls.

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