RESEARCH PAPER

A Comparative Study of Diagnostic Accuracy of Frozen Section With Routinely Performed Permanent Histopathological Sections in CNS Lesions

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ABSTRACT

Objective: To analyze the diagnosis made on frozen section with the diagnosis made on H&E histopathology slides of various brain and spinal cord tumors.

Materials and Methods: Tissue specimens were obtained from a patient during operation and kept in normal saline for intraoperative or perioperative consultation. The gross specimens were inspected, dissected and sections were taken, following which the impression of frozen section analysis was compared to final histopathology report of permanent sections. The accuracy rate, sensitivity and specificity of the frozen section reporting were determined in comparison to the routine histopathology reporting. The present study includes the clinical data of patients whose intraoperative tissue samples were sent for frozen section analysis followed by routine preparation of formalin fixed paraffin embedded permanent histopathology tissue sections in the Department of Neurosurgery and Pathology of a tertiary care centre of Southern Rajasthan.

Results: This study was conducted on 67 patients having female predominance, with a sensitivity of 92.86% and specificity of 100.0%.

Conclusion: This research shows a very high degree of correlation between intraoperative frozen section analysis and final diagnosis obtained on permanent paraffin embedded histopathological examination technique. Accuracy of frozen section analysis at our tertiary care centre can be interpreted as comparable with most international and national quality control statistics. The results suggest that specific measures such as methodical gross examination, ideal cryostat temperature, avoiding technical errors in sectioning and staining along with clinico-radiological correlation and good rapport with the surgeon can reduce the number of discrepancies.

Keywords: Frozen Section; Permanent Histopathology; CNS Tumours; Diagnostic Accuracy; Intraoperative Consultation

How to cite this article: Sharma P, Purohit P, Kumari K, Mangal G, A Comparative Study of Diagnostic Accuracy of Frozen Section With Routinely Performed Permanent Histopathological Sections in CNS Lesions. Int J Drug Deliv Technol. 2026;16(72s): 1095-1102. DOI: 10.25258/ijddt.16.72s.120

Source of support: Nil

Conflict of interest: None

INTRODUCTION

Frozen section interpretation of brain tissue along with squash smear cytology provides guidance for precise targeting of the lesion and its surgical resection. Intraoperative squash smear cytology is an easy to perform, inexpensive procedure which permits high diagnostic accuracy when done along with frozen section. The lesions of CNS are a consequence of various infections, inflammation, or a wide spectrum of life-threatening malignancies1,2. Tumors of the central nervous system (CNS) constitute approximately 2% of all malignancies.

Most common CNS tumor includes astrocytoma, ependymoma, glioblastoma, oligodendroglioma and various subtypes/combinations.

Astrocytoma: Occurs throughout the CNS but is preferentially located in the cerebral hemispheres, especially the frontal lobes3. It occurs most often in adults between the ages of 20–40 years. Grossly, it is an ill-

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defined neoplasm with blurring of grey-white junction and expansion of the infiltrated brain areas which typically invades surrounding brain without overt tissue destruction. It shows variable microcystic change imparting a spongy appearance and variable amount of calcification which gives a gritty sensation. On frozen section and squash smears, it is hypercellular showing infiltrating neoplastic cells with oedema. Nuclear pleomorphism, mitotic activity, necrosis or microvascular proliferation along with vascular thrombosis and myxoid background may be present. Smears most commonly show predominantly smaller cells with fine fibrillar processes, elongated nuclei, nuclear atypia and may show mitotic figures.

IHC – GFAP, Olig 2, IDH1, p53 positive and ATRX negative.

Glioblastoma: Most common and most malignant astrocytic glioma in adults4. It accounts for 14.3% of all primary CNS tumours and 49.1% of all malignant CNS tumours in adults, and up to 2.2% of all CNS tumours in children5. Most commonly in supratentorial regions (frontal, temporal, parietal and occipital lobes), with highest incidence in the frontal lobes. Many cases show infiltration into cortex and across the corpus callosum with spread to the contralateral hemisphere. Grossly, it is an ill-defined whitish grey mass with areas of haemorrhage and necrosis. On frozen section, histology is defined by increased cellularity, brisk mitotic activity and microvascular proliferation or necrosis. Necrosis can be either geographic or pseudo-palisading type.

IHC – GFAP, Olig2, S100, ATRX positive and IDH1 negative.

Ependymomas: Most commonly have ventricular involvement and arise in the cerebrum and spinal cord. They are well circumscribed and occur in the supratentorial region, posterior fossa, and spinal cord. Grossly, these are grey-red tumours with or without cystic degeneration, haemorrhage, or necrosis. Ependymomas of the fourth ventricle are typically exophytic. On frozen section, they present as cellular tumours with typically sharply circumscribed borders, which may be infiltrative. Monomorphic round to oval cells with speckled chromatin, perivascular pseudorosettes, true ependymal rosettes, lumina and fibrillar areas are seen.

IHC – S100, GFAP, Vimentin, CD56 positive and Olig 2 negative.

Oligodendroglioma: Can occur anywhere in the neuroaxis; the most common locations are6 frontal lobes (59%), temporal lobes (14%), parietal lobes (10%) and occipital lobes (1%). Rarely observed in midline structures, brainstem, cerebellum, or spinal cord. Grossly, it is a variably well-defined, grey-pink mass. Histologically, cell morphology resembles nonneoplastic oligodendrocytes with round monotonous nuclei and perinuclear halos. On frozen section it is a moderately cellular, diffusely infiltrating neoplasm. Glia show mild to moderate nuclear atypia. Nuclei are round with speckled chromatin. Perinuclear halos cannot be seen on frozen section or squash smear preparations7.

IHC – IDH, Olig2, GFAP, ATRX positive and keratins negative.

Meningioma: Most common primary CNS tumour, arising from arachnoid cap cells associated with dura mater or choroid plexus, accounting for 36% of all CNS tumours8, growing along the external surface of the brain, spinal cord, or rarely within the ventricular system. WHO grade I meningiomas have a low mitotic index (<4/10 high power field), no brain invasion and <3 atypical features (necrosis, small cell change, sheeted architecture, macronuclei and hypercellularity).

- Grade I variants: angiomatous, fibroblastic, lymphoplasmacytic-rich, meningothelial, metaplastic, microcystic, psammomatous, secretory and transitional.
- Grade II variants: atypical, chordoid, clear cell.
- Grade III variants: anaplastic, papillary, rhabdoid.

Grossly, it is a rounded and well circumscribed tumour attached to the dura, which separates readily from the brain. It may grow en plaque (along the dural surface) and cause reactive (hyperostotic) bone changes9. An arachnoid plane exists between the meningioma and CNS parenchyma.

Medulloblastoma: The most common CNS embryonal tumour of childhood and second only to pilocytic astrocytoma among all intracranial neoplasms. It is graded as WHO grade IV with poor prognosis. Grossly, it is an irregular mass involving the cerebellum and fourth ventricle. Microscopically, the classic tumour shows small blue round cell morphology with syncytial arrangement of densely packed undifferentiated (embryonal) cells. Mitosis, apoptotic bodies, and Homer Wright rosettes are also seen. Other histologic variants include desmoplastic/nodular medulloblastoma, medulloblastoma with extensive nodularity, and large cell/anaplastic medulloblastoma.

Craniopharyngiomas: Adamantinomatous craniopharyngioma is a histologically benign, partially cystic epithelial neoplasm of the suprasellar or sellar region. It is always WHO grade I. Grossly, it is a lobular and cystic tumour with calcifications, and cysts containing dark “motor oil” fluid composed of cholesterol and haemorrhage. Microscopically, it shows cords, lobules, nodular whorls, and trabeculae of well differentiated squamous epithelium bordered by palisading columnar epithelium. Peripheral cells surround looser, plumper cells called the stellate reticulum. Nodules of plump, anucleate squamous cells (ghost cells) and wet keratin are also seen.

Brain Metastasis: Brain metastases are a common complication of cancer and the most common type of brain tumour. Primary cancers such as lung, breast, and melanoma are most likely to metastasize to the brain. Small-cell lung cancer has a high propensity to spread to the brain. Other malignancies such as prostate and head and neck cancers rarely result in brain metastases.

Tuberculosis of CNS: Tuberculomas constitute 33% of intracranial space-occupying lesions in patients in developing countries10. On microscopy, granuloma formation and necrosis are seen.

Sacral Ependymoma: Occasionally occurs primarily in the sacrum or para-sacral soft tissues, without an associated intradural mass. Histopathology of sacral ependymoma typically shows features of myxopapillary ependymoma with a more epithelial appearance. Ectopic ependymal tissue in the sacrum and congenital ependymal cell rests are the source of these sacral ependymomas.

Multiple Myeloma and Plasmacytoma: Frequently affect the spine and the epidural space. Histopathology of these tumours shows neoplastic plasma cells exhibiting eccentric nuclei with clock-face chromatin and cytoplasmic basophilia. Binucleation may be present. Diagnosis of solitary plasmacytoma should be rendered only after a thorough negative haematologic evaluation.

MATERIAL AND METHODS

It was a cross-sectional study which included the clinical data of patients operated for brain tumours in the Neurosurgery department whose intraoperative tissue samples were sent for frozen section analysis followed by routine preparation of formalin fixed paraffin embedded permanent histopathology tissue sections in the Department of Pathology, at a tertiary care centre of Southern Rajasthan, during a period of 17 months.

A total of 67 patients were included in the study, constituting 31 males and 36 females, with inclusion and exclusion criteria as follows:

Inclusion criteria

In patients requiring frozen section for primary diagnosis:

a) When pre-operative diagnosis or biopsy is not possible.

b) Unexpected intra-operative findings and to assess the presence of synchronous lesions.

c) To assess the margin status.

d) To assess the extent of disease.

Exclusion criteria

a) When intra-operative pathological diagnosis has no immediate surgical implications.

b) Technically difficult specimens such as heavily ossified tissue, distorted cell morphology, or severely necrosed tissue.

Tissue specimens were obtained from the patient intraoperatively and kept in normal saline for intraoperative or perioperative consultation. The gross specimens received were inspected, dissected and sections were taken. Blocks were cut on the cryostat (Leica CM 3050 S) using Optimal Cutting Temperature (OCT) compound as the embedding medium, followed by rapid Haematoxylin-Eosin staining. The frozen section diagnosis was immediately communicated to the operating surgeons. Frozen tissue as well as the remaining non-frozen tissue was fixed in 10% formalin solution, and processing was done for routine paraffin sections followed by Haematoxylin-Eosin staining the next day as per standard protocols, which was followed by reporting.

STATISTICAL ANALYSIS

The data were entered in MS Excel Software version 20 and analysed using SPSS, IBM Corp, Version 23. The descriptive data were expressed in proportions, mean and frequency tables.

Formulas used for calculation of Sensitivity (Sn), Specificity (Sp), Positive Predictive Value (PPV) and Negative Predictive Value (NPV) were:

$Sn = TP / (TP + FN)$ $Sp = TN / (TN + FP)$ $PPV = TP / (TP + FP)$ $NPV = TN / (TN + FN)$

RESULTS

A total of 67 patients were included in the study.

Table 1 shows the age and gender-wise distribution of all cases. Mean age was 39.96 ± 16.53 years. The largest number of cases were seen in the age group of 19–30 years (27 cases; 40.2%), followed by 31–50 years (19 cases; 76.5%) and 51–70 years (9 cases; 13.3%). The lowest number of cases were seen in the age group of <18 years (12 cases; 17.4%). The majority of the cases were females (59.3%).

Table 1: Demographic Variables of Patients (N = 67)

Age (in years)	Value
Mean ± SD	39.96 ± 16.53
Median (IQR)	34 (31)
Range (Max – Min)	51 (67–16)

Age group (years)	No.	%
<18	12	17.4
19–30	27	40.2
31–50	19	76.5
51–70	9	13.3
Total	67	100.00%

Table 2 shows the distribution of cases based on frozen section diagnosis, in which astrocytoma was found to be most common (27 cases), followed by brain metastasis (10 cases), glioblastoma grade IV (15 cases), and oligodendroglioma, plasmocytoma, ependymoma and others as mentioned in Table 2.

Table 2: Distribution of Cases Based on Frozen Section Diagnosis (N = 67)

Frozen Section Diagnosis	No. of cases	Percentage
Astrocytoma	27	40.29
Glioblastoma Grade IV	15	22.3
Ependymoma	3	4.47
Oligodendroglioma	2	2.9
Medulloblastoma	2	2.9
Meningioma	2	2.9
Plasmocytoma	1	1.4
Brain Metastasis	10	14.9
Fibrous tissue – No pathology seen	1	3.7
Hemangioblastoma	1	3.7
Normal Cerebellar Tissue	1	3.7
Schwannoma	2	2.9
Total	67	100.0

Table 3 shows the comparison of concordance of frozen section analysis with histopathological evaluation, based on the nature of the lesion (malignant vs. benign).

Table 3: Comparison of Concordance of Frozen Section Analysis with Histopathological Evaluation Based on the Nature of Lesion (N = 67)

	Malignant	Benign	Total
Concordant	33 (TP)	33 (TN)	66
Discordant	00 (FP)	1 (FN)	1

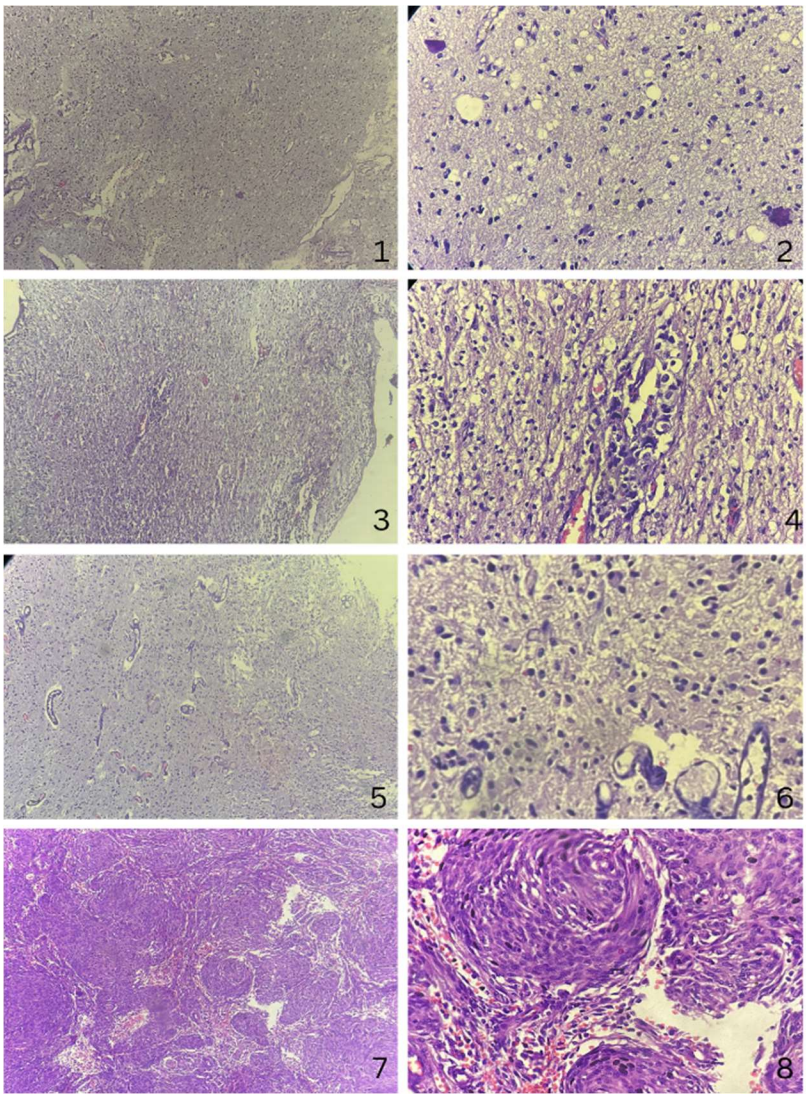
Total	33	34	67

Table 4 shows the sensitivity and specificity of the study. This study has a sensitivity of 92.86% and specificity of 100.0%.

Table 4: Percentage of Sensitivity, Specificity, PPV, NPV and Accuracy Based on the Nature of Lesion

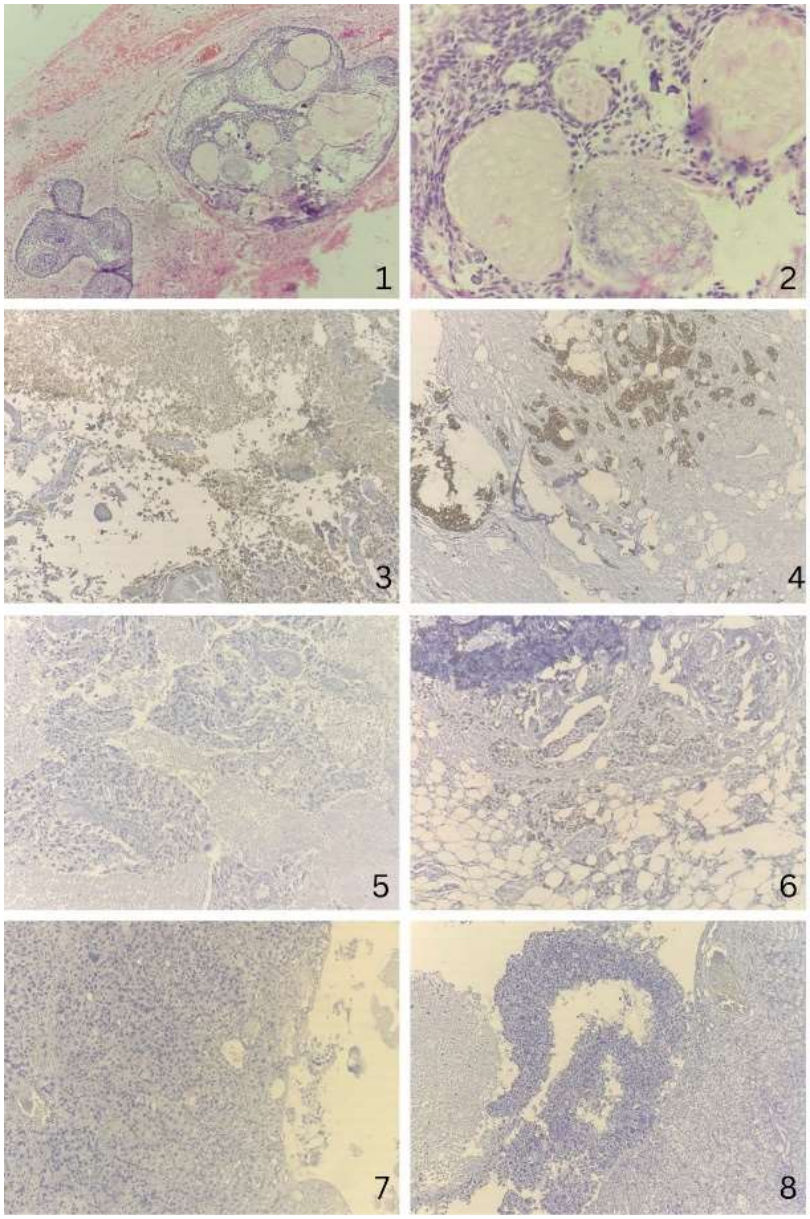
Parameter	Value
Sensitivity	92.86%
Specificity	100.00%
PPV	100.00%
NPV	92.86%
Accuracy	96.3%

Figure 1



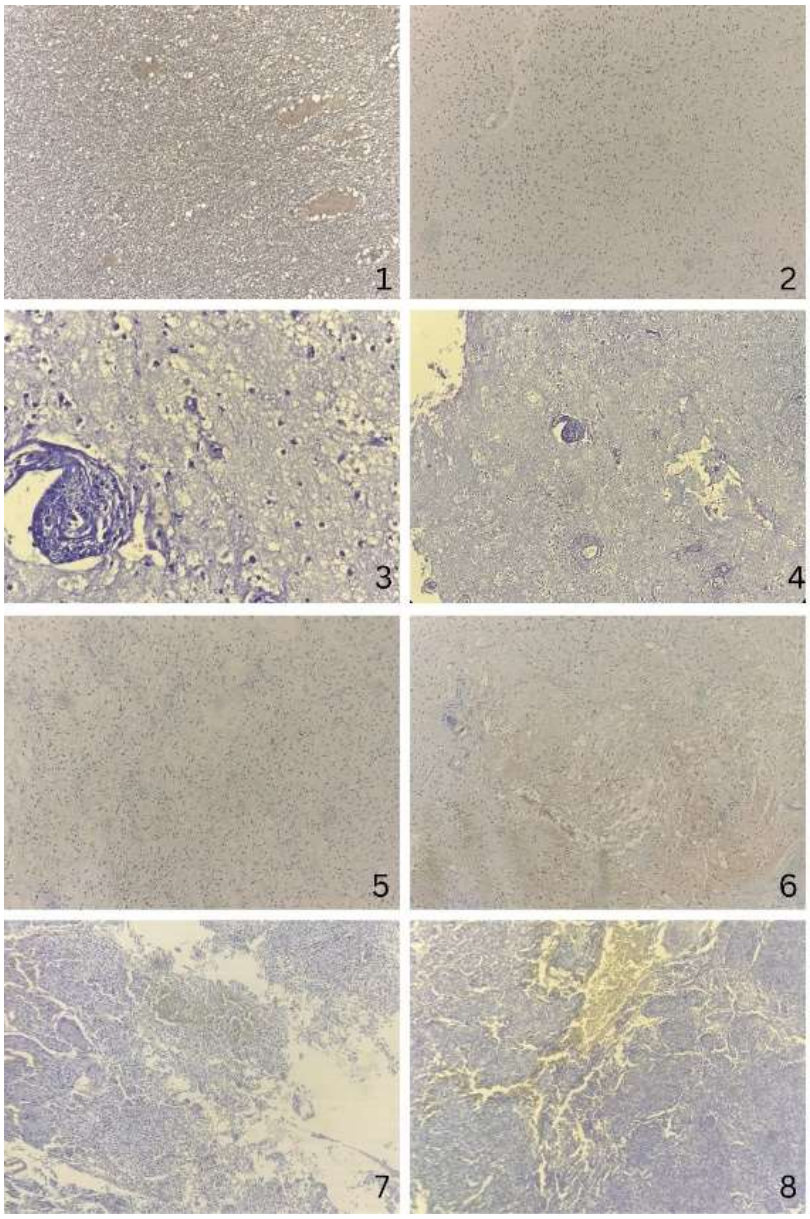
(a) 1,2. H&E shows Plasmacytoma (10x, 40x); 3,4. Breast IDC metastasis in brain (10x, 40x); 5,6. Astrocytoma (10x, 40x), H&E; 7,8. Transitional Meningioma (10x, 40x), H&E.

Figure 2



(b) 1,2. Craniopharyngioma (10x and 40x); 3. CK7 positive for IDC breast metastasis in brain (10x); 4. CK7 positive control squamous epithelium (10x); 5. Her2neu positive; 6. ER control positive for IDC metastasis in brain (10x); 7. Her2neu negative; 8. PR positive IDC in metastasis to brain (10x).

Figure 3



(c) 1. Olig2 positive control; 2. Olig2 positive oligodendroglioma; 3,4. H&E Oligodendroglioma (40x, 10x); 5. ATRX positive IHC (10x); 6. GFAP positive in astrocytoma (10x); 7. PR diffuse positive IHC (10x); 8. GFAP negative in oligodendroglioma (10x).

DISCUSSION

The diagnosis and management of CNS tumours have been more difficult compared to other visceral tumours due to the inaccessibility of these lesions for simple tissue diagnostic procedures such as fine-needle aspiration cytology or incision biopsy. With advances in neuroimaging, the management of such tumours has been revolutionised, and the advent of stereotactic biopsy or endoscopic approach has made it possible to approach these inaccessible lesions to obtain tissue for diagnosis11,12.

Several studies conducted to compare the results of squash cytology with frozen section have concluded that the accuracy of cytology was as good as frozen section13–15, and that cytology alone can guide the neurosurgeon in the intraoperative period in a resource-limited setting where

frozen section is not performed routinely for logistic and technical reasons16.

In the present study, the intraoperative diagnosis was sought on open craniotomy specimens.

Comparison of concordance of frozen section analysis with histopathological evaluation based on the nature of the lesion was done, and out of a total of 67 cases, 66 were concordant and 1 was discordant — a case in which a cyst wall without squamous lining was seen on frozen section, but which was diagnosed later as craniopharyngioma grade 1 on histopathology. Thus, this study has a sensitivity of 92.86% and specificity of 100.0%.

In conclusion, intraoperative frozen section shows high diagnostic accuracy. It can provide a preliminary diagnosis in CNS lesions, enabling the surgeon to plan further management on the operating table.

CONCLUSION

To conclude, this research shows a remarkably high degree of correlation between intraoperative frozen section analysis and final diagnosis obtained on permanent paraffin embedded histopathological examination technique. The accuracy of frozen section diagnosis at our tertiary care centre can be interpreted as comparable with most international and national quality control statistics for the frozen section method. The results suggest that specific measures such as methodical gross examination, ideal cryostat temperature, avoiding technical errors in sectioning and staining, along with clinico-radiological correlation and good rapport with the surgeon, can reduce the number of discrepancies.

ACKNOWLEDGEMENT

The authors thank the Department of Pathology and Department of Neurosurgery, Ananta Institute of Medical Sciences and Research Centre, Rajsamand, and Geetanjali Medical College and Hospital, Udaipur, for their support in carrying out this study.

FINANCIAL SUPPORT AND SPONSORSHIP

Nil.

CONFLICTS OF INTEREST

There are no conflicts of interest.

ETHICAL APPROVAL

This study was approved by the Institutional Ethics Committee prior to commencement. Written informed consent was obtained from all patients / legal guardians prior to inclusion in the study.

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