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Original Article

Diagnostic Accuracy of Touch Cytology of Central Nervous System Lesions

Tania Khattak[1], KhalidJavaid[2], Anwar Ul Haque[1], Farooq Azam[3] and Tariq Khan[4]

[1.]Department of Pathology, Northwest School of Medicine, Hayatabad, Peshawar, [2.] Department of Pathology, Khyber Girls Medical College, Hayatabad, Peshawar, [3.] Department of Neurosurgery, Lady Reeding Hospital, Peshawar, [4.] Department of Neurosurgery, Northwest School of Medicine, Hayatabad, Peshawar

ABSTRACT

Introduction: Quick intraoperative diagnosis is especially important in CNS tumors where second surgery may be avoided thus saving patients from many complications. Touch imprint cytology is simple, quick and cost-effective method for the rapid diagnosisand is quite applicable to central nervous system tumors. Other methods for per operative consultation of lesions include squash smear cytology and Frozen section. The drawback of squash smear technique is that the entire tissue is squashed into the slide and no representative tissue is left for routine histopathology. Exerting too much pressure on cells badly affect their morphology. Frozen section requires special and expensive equipment. The rapid freezing causes several artifacts Touch cytology is equally effective without their associated complications.

Objective: To correlate per operative Touch imprint cytology on brain tumors with conventional histopathology.

Methodology: This was Experimental diagnostic accuracy study with cross sectional time perspective Conducted in Department of Pathology, Northwest General Hospital and Research Center Peshawar. Fresh brain and spinal cord tumors including 2 non neoplastic specimens were obtained. Before putting them in the formalin for routine surgical pathology examination, touch imprint cytology smear was prepared by gently touching the freshly removed lesion on glass slide at several places. Half of the slides were air dried and half of them were fixed in 100% alcohol. Air dried slides were stained with Diff Quick stain and alcohol fixed slides were stained with hematoxylin and eosin. These slides were immediately stained under microscope and diagnosis was given.

Results: All the smears were quite cellular; the nuclear details were excellent. The samples were of divergent nature. Breakdown of the 28 samples was as follows: meningioma (8), astrocytoma (3), primitive neuro-ductal tumors (2), pituitary adenoma (2), Schwannoma (2), arachnoid cyst (1), colloid cyst (1), dermoid cyst (1), medulloblastoma (1), glioblastoma multiforme (1), metastatic clear cell carcinoma (1), teratoma (1), benign vascular lesion (1),Leukemia/ Lymphoma (1), and Inflammatory lesion, spine(1). The finding of all these cases on touch cytology smear were same except in one case where Schwannoma, a benign peripheral nerve sheath tumor was diagnosed as other related benign peripheral nerve sheath tumor i.e. neurofibroma. There was 100 percent accuracy in terms of benign versus malignant and 96 percent accuracy in terms of precise diagnosis.

Conclusion: The touch cytology smear cells were "fresh from oven" abundant and were free from artifacts. Their morphological details were absolutely preserved. Touch cytology is simple useful technique to get almost immediate diagnosis on CNS neoplastic and non-neoplastictumors; which may be used alone or complimentary to frozen section where quick diagnosis is needed.

Keywords: Brain tumors, CNS tumors, Spinal cord tumors, Space occupying lesion (SOL), Touch cytology

Introduction

The CNS neoplasms and other mass lesions are biopsied to determine the diagnosis. Routine histopathology may take 2 to 3 days. At time quick diagnosis is needed to determine the course and extent of the operating procedure and to initiate specific treatment. For quick diagnosis, frozen section is needed which requires cryostat facility.

Frozen section undoubtedlyprovides rapid and reliable diagnosis;however, frozen section may induce some artifacts due to rapid ice crystals formation which may hinder satisfactory microscopic examination.

CORRESPONDENCE AUTHOR
Dr. Tania Khattak
Department of Pathology
Northwest School of Medicine, Hayatabad, Peshawar

An alternative and rather complementary technique is Touch Cytology.Imprint Cytology is a touch preparation in which tissue is touched on a slide and it leaves behind its imprint in the form of cells on the glass slide. Usually enough cells and small tissue fragments get attached to the slide which can be rapidly stained and examined under microscope. These cells are fresh and free from artifacts. Various comparative studies have shown that Touch Cytology is comparable to frozen section in terms of sensitivity, specificity and accuracy. Therefore, present study measures the correlation of cytological diagnosis by imprint with histological diagnosis and evaluated the accuracy and usefulness of this. It can be used for the diagnosis of benign and malignant lesions in a shorter period. It can also be used for intraoperative consultation for diagnosis.

Majority of the diagnostic tests or procedures require long time to report and expensive as well. The delays in the diagnosis of lesion in CNS or neurological disorders are typically distressing to the affected patients and their families which deprive them from the quality of life. Even routine histopathology may take2-3 days for the diagnosis [13]. The treatment of the patient could be started quickly if the test is able to provide quick and accurate results. The case reports have shown the ability of the touch imprint cytology for quick and less expensive option for diagnosing the central nervous system tumors.

Central Nervous system tumors constitute 1.3% of all cancers in adults and are considered the 10th most common tumors. In the developed countries it is the seventh common cause of mortality in adults.[1]In children younger than 15 years, brain tumors are second onlyamong cancers, to acute Lymphoblastic Leukemia which is the most common.[2]Many techniques are used for the intra operative diagnosis of CNS lesions. These include frozen sectioning technique, squash smear and touch cytology. Brain tissues usually show ice crystal artifact in the frozen section because high lipid and water content which may lead to difficulty in diagnosis.

The accurate and timely diagnosis of the lesions and tumors is important for timely appropriate treatment. Misdiagnosed and lately diagnosed patients do not receive right or timely treatment and end up with problems such as second operation, surgical complications and may result in poor prognosis. Therefore, prompt diagnostic methods are used to verify the tumors and correlate with clinical findings. Wide ranges of tests are used for this purpose including chemical tests, hematological tests, radiological tests and most importantly histopathological tests.

This study was conducted to correlate per operative Touch imprint cytology on brain tumors with conventional histopathology as gold standard in terms of sensitivity, specificity and diagnostic accuracy.

Methodology

This was an experimental study with a cross sectional time perspective. The experimental design was adopted to incorporate the preparation and study of specimens for touch cytology and the cross-sectional design was selected to describe and compare the findings of both touch cytology and histopathology. The study setting of this study was Northwest General Hospital and Research Centre from October 2019 to March 2020.The sample size is calculated as follows on 1.3% prevalence rate from previous study, which was 28.[1] The sampling technique used was Consecutive Sampling Technique.All the patients, both genders, all age groups presenting to and being operated for CNS (SOL) lesions in Northwest General Hospital and Research Center were included in study. Those patients who were operated upon for lesions other than suspected neoplasm and other masses were excluded.Data for the research was collected after taking permission from Ethical committee. The data was collected from samples obtained from CNS lesions of patients operated in the operation theatre of Northwest General Hospital and Research Centre Peshawar. Written informed consent was obtained from all the participants prior to data collection.

The tissues were submitted fresh, held lightly by forceps and gently touched at several places in the slides. Theblood-stained specimen, the tissue was gently touched with gauze piece. Several slides were prepared, and half were air dried and subsequently stained with Diff-Quick.Other half slideswere put in Alcohol and then stained with hematoxylin and eosin. These slides were examined under microscope for pathological findings and compared to findings on permanent section.The data was analyzed using SPSS 24. The demographic characteristics such as age, and gender were tabulated in form of frequency and percentages.

Results

Among the 28 study cases males constituted 61%.There was wide range of the ages with a mean age of41.91 year with standard deviation of 17.94. There was one participant whose age was one year

and one of the participants whose age was 80 years. The types of the lesions and their frequencies are given in table 1.

Table 1: Demographic variables of cases n=28

Gender	**N(%)**
Male	17(61)
Female	11(39)
Age	**Years**
Mean	38.96
Minimum	1.00
Maximum	80.00
Confidence Level (95.0%)	6.94

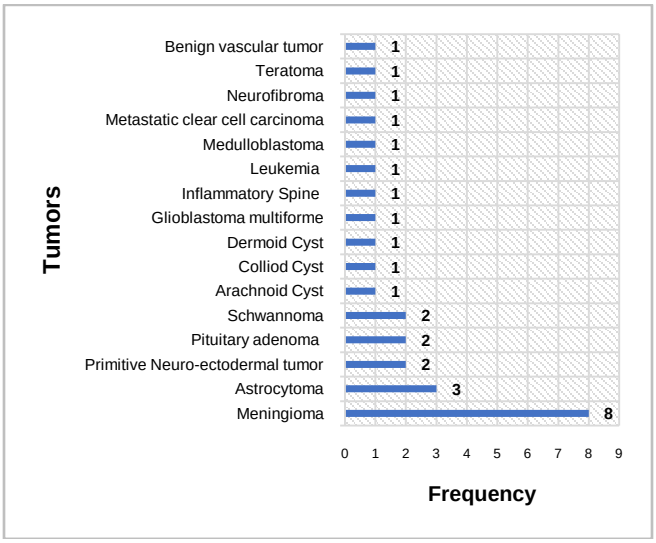

Figure 1: Types of tumors identified from histopathology n=28

In almost all cases there was concurrence between touch cytology and histopathology; however minor differences were noted in a few cases; which were as follows. In one case the touch cytology diagnosis was astrocytoma/ependymomawhile histopathology report insular Astrocytoma in one of the cases. In another case the touch cytology reported Pituitary cells with eosinophilic cytoplasm consistent with eosinophilic pituitary adenoma while and histopathology reported Pituitary adenoma. In another case also represented meningothelial cells with no atypia in touch cytology test while histopathology reported Arachnoid cyst. A contrasting report was found in a case histopathology reporting Schwannoma while touch cytology reported neurofibroma. Table – 2

Table 2: Comparison of touch cytology and histopathology findings

Case	Touch Cytology Finding	Histopathology Finding
1	Pituitary cells with eosinophilic cytoplasm	Eosinophilic type Pituitary Adenoma
2	Clusters of cells, round nuclei and moderate cytoplasm	Pituitary Adenoma
3	Meningioma	Meningioma
4	Colloid cyst	Colloid cyst
5	Scattered groups of benign meningothelial cells	Meningioma
6	Meningothelial cells with no atypia	Arachnoid cyst
7	Meningioma	Meningioma
8	Meningioma	Meningioma
9	Glioblastoma multiforme	Glioblastoma multiforme
10	Astrocytoma	Astrocytoma
11	Benign vascular lesion	Benign vascular lesion
12	Leukemia/ lymphoma	Acute myelomonocytic leukemia
13	Astrocytoma	Astrocytoma
14	Metastatic clear cell carcinoma	Metastatic clear cell carcinoma
15	Meningioma	Meningioma
16	Astrocytoma vs Ependymoma	Insular Astrocytoma
17	Meningioma	Meningioma
18	Primitive Neuro ectodermal tumor	Primitive Neuro ectodermal tumor
19	Compatible with osteomyelitis	Compatible with inflammatory condition
20	Meningioma	Meningioma
21	Schwannoma	Schwannoma
22	Medulloblastoma	Medulloblastoma
23	Neurofibroma	Neurofibroma
24	Neurofibroma	Schwannoma
25	Epidermoid/ dermoid cyst	Epidermoid cyst
26	Primitive neuroectodermal tumor.	Primitive neuroectodermal tumor.
27	Teratoma	Teratoma
28	Smear shows numerous meningothelial cells	Meningioma

The samples were compared with touch cytology findings. The outcome variables i.e. touch cytology did not find significant difference of findings when compared with the standard test.The calculated accuracy of the test was 95% and confidence interval showed range of 75.13% to 99.87%.

Here we present a few representative examples of our cases. Figure 1 shows classical psammoma body on touch cytology. Figure 2 shows corresponding histopathology appearance of the tumor with psammoma bodies.

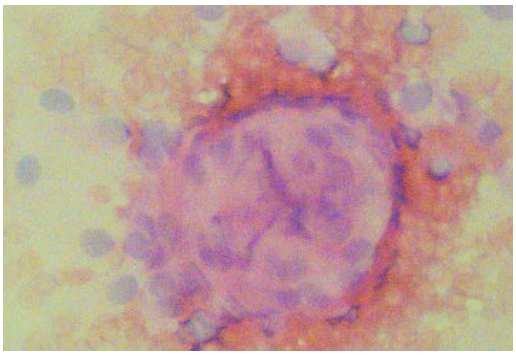

Figure-1. Psammoma body on touch cytology (H&E X400)

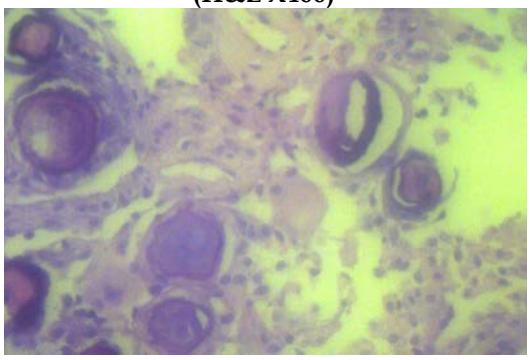

Figure-2. Psammoma bodies in meningioma (H&E X100)

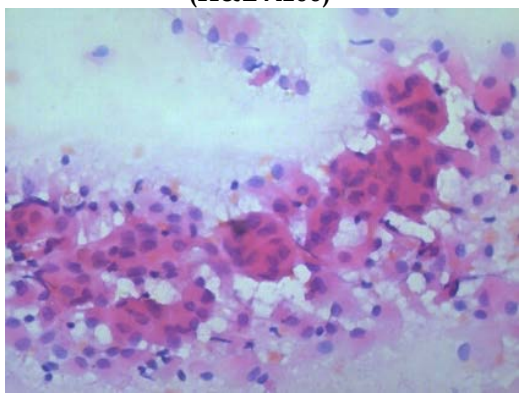

Figure-3. Meningothelial cells of meningioma on Touch Cytology (H&E X100)

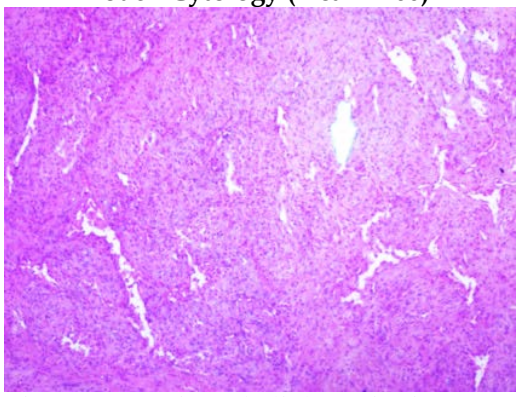

Figure-4. Meningothelial meningioma on histopathology (H&E X100)

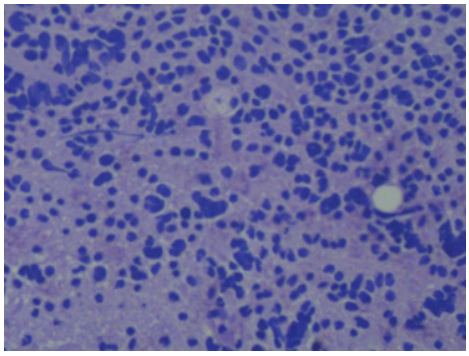

Figure-5. Highly pleomorphic and necrotic cells of glioblastoma multiforme (H&E X 400)

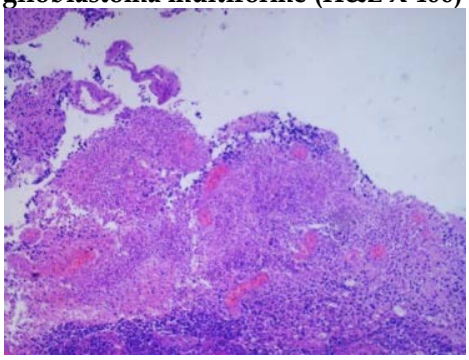

Figure-6. Glioblastoma histopathology. Necrotic cells and fibrin thrombi (H&E X 100)

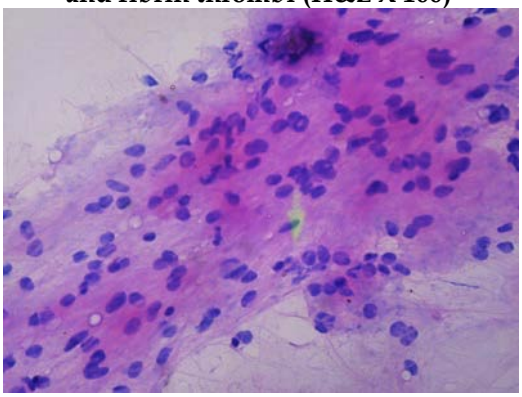

Figure-7. Astrocytoma Grade 2 Touch Cytology (H&E x 400)

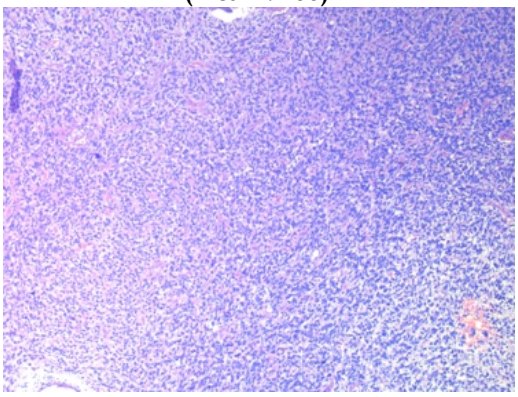

Figure-8. Astrocytoma Grade 2 Histopathology (H&E X 100)

Discussion

Histopathology and cytology studies make definite diagnosis while all other tests are supportive. Routine histopathology or Surgical pathology may take several days which of course Neurosurgeon will not desire as second craniotomy on the patient would be highly unwanted due to effects of first surgery. If a quick diagnosis could be obtained right on the table that would be wonderful. For immediate diagnosis choice is between touch cytology and Frozen section. As a matter of fact, both could be done simultaneously and would be complimentary to each other. Frozen sections however require special equipment and induce some freezing artifacts making interpretation at times difficult. Apart from histopathology and cytopathology diagnoses, various molecular, immunohistochemistry, genetic and the chemical tests study the molecular basis of the brain cell tumors. These tests include immunohistochemistry, Fluorescence in Situ Hybridization (FISH), Multiplex ligation analysis (MLPA), Pyrosequencing, Direct sequencing, Next Generation Sequencing (NGS)and DNA methylation-based classification.[3] Immunohistochemistry may help in determining precisely the cells of origin of tumor. This of course does not detect mutations. If treatment is mutation specific, then this test is not much helpful. The FISH test possesses the ability to preserve the cellular structure and cytological features of the tumor. The result from FISH test can be produced within one to two days. FISH test have the limitation to detect the hotspot mutations therefore minute detail could still remain undetected.[4] The MLPA is a PCR-based technique and could detect wide variety of tumors with confidence. The test requires the expertise. This is time consuming and accurate analysis could be challenging.[5] The pyrosequencing technique to diagnose the central nervous system cell tumors is based on the synthesis principle. This test could detect only single mutation and does not possess the ability to detect the translocation and copy number changes in the cell. Therefore, many physicians do not prefer it when immediate diagnosis is needed for an urgent intervention.[6]Among the sequencing techniques, the direct sequencing is considered the gold standard. However, direct sequencing has shown low sensitivity and cannot detect the translocations. This is time consuming as well to produce the result up to three days. The next generation sequencing (NGS) diagnostic test has shown the ability to detect the multiple mutations in the single analysis. However, generally the test is expensive and time consuming to produce the result in five to six days.[7] Therefore, implication in urgent interventional scenario does not seem effective. The DNA methylation-based classification is valued for its higher level of standardization. This diagnostic test has shown to be effective in developing diagnosis in the most challenging cases. The molecular subtyping of tumors could also be performed in such tumors as medulloblastoma, ependymoma, atypical teratoid rhabdoid tumor (AT/RT) and meningioma. The test cannot be offered to every patient with central nervous system tumor due to its cost and also test result is generally reported after five days[8]. As a result, the tumors specific treatment could start only after the established diagnosis. The sensitive and specific chemical tests to diagnose the central nervous system cell tumors are generally expensive and time consuming. The imaging diagnostic tests play a decisive role in the management of patients with brain tumors. These tests include magnetic resonance imaging (MRI) and computed tomography (CT) and positron emission tomography (PET)scans.[9] However all imaging tests still require histopathological confirmation.

Touch cytology is used for rapid and reliable tentative diagnosis of a pathological lesion. In the past, work has been done on the touch imprint cytology of different organs for many years, and pathologists are using cytology to differentiate and diagnose the types of tumors. This provides useful information to the clinicians and surgeons for suitable and timely treatment.[9-11]One study conducted on diagnostic accuracy of touch imprint cytology in Ovarian neoplasm at PIMS Pakistan, where 60 ovarian tumors were studied. As compared to the permanent section, the results showed that 55 out of 60 cases were correctly diagnosed on touch cytology alone. The study had sensitivity and specificity of 93% and 83.3% respectively.[10]Filter paper assisted cell transfer (FACT) technique for interoperation diagnosis of CNS tumors showed overall diagnostic concordance rates between frozen section and FACT smears 90% and 87.5% respectively.[12]A study related to touch imprint cytology (TIC) performed in Turkey and the values of touch imprint cytology of Core Needle Biopsy (CNB) in the diagnosis of spinal were assessed. The results revealed that TIC and CNBs were non diagnostic in 62% and 45% of all cases respectively. Malignancy could be identified and typed in 23% of imprint presentations and 35% of CNBs. After comparison, the

diagnostic categories were just the same in 70% of the cases.[12]

In this study, the age of the cases ranged from one year to eighty years. The variability among the cases suffering from central nervous system tumor make it challenging for the pathologists to establish accurate diagnosis due to morphological variations. However, mean age of this study was 41.91with 17.94 standard deviation. A study conducted in India showed the kind of similar result with slightly higher mean in age of patient's i.e. 59.9 with range of 12-95 years.[14]

Our study report revealed that middle age people develop CNS tumor most commonly than in any of other age group. For that reason, As the patient present in OPD with the complaint of CNS tumor, timely diagnosis plays vital role in survival of patients. In our study males constituted 60% of the patients.

Out of 28 cases; in 8 cases meningioma was found. The imprint touch cytology of soft tissue tumor reported to diagnose 51.2% benign tumor and 48.8% samples estimated malignant tumor.[15]There were 3 cases of astrocytoma and 2 cases of Pituitary adenoma two cases, primitive neuro-ductal tumors two cases and Schwannoma two cases.In addition, the sample revealed arachnoid cyst, metastatic clear cell carcinoma, benign vascular lesion, inflammatory spine, colloid cyst, lymphoma, glioblastoma multiforme each among the 28 cases.Tumors of the nervous system are the second most common childhood tumor after leukemia which constitute 35% of all childhood malignancies and accounts for the leading cause of death in children.[16] Central nervous system tumors of children different remarkably from adult tumors due to site of origin, clinical presentation and tendency to disseminate. Therefore early detection prevent any kind of morbidity on an individual especially to a young age patients.[17]Similar kind of result is noted in a study done in USA that meningiomas are the most common brain tumors, representing approximately 35 % of all brain tumors diagnosed and about third of all tumors of the central nervous system.[18]The central nervous tumors have significant effects on the life of the affected but also on the family members.The quick diagnosis and early management of brain lesions improve the quality of life patient and decrease the burden of stress and economic viability.[19]As early detection facilitate surgeon for timely management of the disease with good prognosis. It also reduces the cost of all expense of patients due to investigations, treatment, hospitalization and other tangible financial burden. Through the imprint touch cytology which is proven as rapid, cheaper, needs less equipment and resources than the other types of diagnostic procedures. Healthcare sector being low priority for budget allocation is not an old concern in the developing countries. Therefore, accessible and affordable healthcare is essential to combat the brain lesions. The touch imprint cytology being quicker and less expensive may be a light in the dark of health care economic burden.

The outcome variables i.e. touch cytology did not find significant difference of findings when compared with the standard test.But the duration of time and other sophisticated requirements to do the gold standard in histopathology would delay result and other necessary interventions and prevent from recovery. A similar kind of report was seen in a study in Pakistani context and reveals same kind of result that the accuracy of each method alone of IC and frozen section was 96.6%.[20]Whereas Iranian study supported the fact that histopathological findings were not necessary when immediate intervention for needed.[21]Moreover, when most of the specimens underwent histopathological examination confirmed the findings of touch imprint cytology. The similar pattern was identified in the current study- the findings of the 26 out of 28 cases were similar among the touch cytology and histopathology. Noteworthy, more confidence in the histopathology reporting was observed. The neuroscience education accentuates higher level of competence to establish the diagnosis with more confidence and accurately.[22]Therefore, expertise to prepare, examine and identifying specimen is imperative competence.

Ability of TIC to identify malignancy with specific subtype is 95%. report relevancy to be 96.6%.The range for overall accuracy rate in literature varied from 66% to 100%. Our result is varied from 75.1%-99.9% comparable with those of another study where the accuracy ranged from 92 to 98.3%.[23]Therefore, touch imprint cytology represents acceptable statistics to establish diagnosis when immediate intervention requires to manage the central nervous system tumors. The strengths of this study unfold as an interventional and comparative study to compare the findings of touch cytology and gold standard histopathology findings. A robust and careful process of specimen preparation, examination and reporting was adopted. All the ethical consideration was considered for data collection and reporting of the results. The study has established much needed evidence to adopt touch cytology where histopathology findings deem unnecessary.

The study has number of limitations to have small number of cases due to time pressures. Therefore, correlation analysis was not undertaken. There was missing demographic data among the cases and study was carried out at single institute. However, some samples were taken from surgeries performed at Pak international hospital whose biopsies were sent to Northwest general hospital Histopathology laboratory.

Touch imprint cytology should be taken up as a quick and less expensive diagnostic tool to diagnose central nervous system tumors. The robust training to prepare, examine and reports the diagnose should be designed for confident and accurate reporting. The resource limited institution should be encouraged to adopt touch cytology to offer accessible and affordable solution for establishing the diagnosis. Moreover, a multicenter study having larger sample size with robust experimental design is recommended to generate higher level of evidence.

Conclusion

Overall, the usefulness of Touch cytology is not limited to simple benign and non-benign tumor differentiation as this study sample could distinguish other differential diagnosis as well. The various literatures have shown the comparison of efficacy of touch cytology with frozen section method and very few researchers had focus on comparison between histopathology and touch cytology. The overall result of this study revealed that the touch cytology can give quicker positive prediction diagnosis than the histopathology techniques. Although no one can deny the fact that the accuracy of histopathology for the diagnosis is better than the touch cytology but due to growing number of patients with CNS lesions and with dire need for the quick and timely diagnosis demands the use of touch cytology. Moreover, this study shows excellent accuracy range from 70-100% which has supported by many studies and it proves to be dependable intra operative diagnostic modalities. Touch cytology alone would provide a correct, quick and timely diagnosis in many cases with minimal finance and limited resources, equipment could be quite suitable

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CONTRIBUTION OF AUTHORS:

- Dr. Tania Khattak conceived the idea, organized the project and carried out the research
- Dr. Khalid Javaid supervised the research, guided and helped wherever necessary
- Dr. Anwar Ul Haque examined the slides and helped in microscopic interpretation and conclusion
- Dr. Farooq Azam and Tariq Khanperformed the surgeries, submitted the cases and helped with histories and clinical information