Original Article

Correlation of Imprint and Crush cytology with Bronchoscopic biopsy in the diagnosis of Bronchogenic carcinoma

Pratikchya Karki[1], Samir Neupane[2], Ashesh Dhungana[3], Sumida Tiwari[4]

[1]Pathologist, Province Public Health Laboratory, Province 1,

[2]Department of Pathology , Civil Service Hospital,

[3]Consultant Pulmonologist, Department of Internal Medicine, NAMS, Bir Hospital,

[4]Pathologist, Department of Pathology, NAMS, Bir Hospital

Abstract

Introduction

Lung carcinoma is the most common cancer with 2.1 million (11.6%) newly diagnosed cases in 2018. Over the years, many cytotechniques have been developed but their combination with histology is still an area of controversy. Imprint and crush cytology are considered simple, rapid and cost effective for a low resource setting in the early diagnosis and management of lung cancer. Here, we aimed to assess the diagnostic accuracy of imprint and crush cytology and compare them with histopathology.

Method

A prospective study was conducted from May 2017 to April 2018 at the Pulmonary medicine unit and Department of Pathology at National Academy of Medical Sciences (NAMS), Bir Hospital. A total of 53 patients were enrolled in the study who showed visible mass on bronchoscopy. Three to five bits of tissue were obtained, imprint and crush smear were prepared from them and the tissue were then sent for histopathological examination. The level of significance selected was $p < 0.005$.

Results

The most common age group affected was 60-69 years. 91% cases were smokers, with a male predominance. The most common location of endobronchial growth was left upper lobe. 43 cases were malignant in biopsy. The sensitivity, specificity, accuracy and positive predictive value of imprint cytology was 71.05%, 87.50%, 73.91% and 96.43% respectively while that for crush cytology was 74.36%, 75%, 74.47% and 93.55% respectively. The diagnostic yield of imprint, crush smear and forceps biopsy were 52.8%, 58.4% and 81.1% respectively. Squamous cell carcinoma was the most common carcinoma in this study.

Conclusion

Imprint and crush cytology yield additional information that can be complementary to endobronchial biopsy. They are convenient, do not burden the patients and thus can be carried out wherever possible during bronchoscopy.

Keyword: Crush cytology, Endobronchial biopsy, Imprint cytology, Lung carcinoma.

Introduction

Lung carcinoma is currently the most common cancer in the world. According to the Global Initiative for Cancer registry Development (GLOBOCAN) in 2018, 2.1 million new cases (11.6%) were of lung carcinoma. It is also the most common cancer occurring in men worldwide and most of the cases are seen in emerging economies of the world.[1] About 80% of the cases occur in smokers, either active or passive. Other risk factors are industrial exposure to harmful

Address Correspondence: Dr. Pratikchya Karki, Biratnagar-03

Phone No. 9841969355 E-mail address: pratikchya.karki@gmail.com

chemicals, environmental smoke exposure, air pollution and molecular genetics.[2]

The earliest study on rapid diagnosis and microscopy of tumors can be traced back to Dudgeon and Patrick.[3] Since the advent of fiberoptic bronchoscopy in 1968, cytological diagnosis of lung cancer has advanced from sputum cytology to bronchial aspirate, bronchial wash, bronchial brush and Transbronchial needle aspiration (TBNA). In some settings, other additional procedures like imprint and crush cytology are also used as an adjunct for diagnosis of lung cancers.[4]

Though there are various techniques for rapid diagnosis of lung carcinoma, each of them have their own advantages and limitation. Even the sensitivity of forceps biopsy is dependent on location as well as the morphology of the tumor. Thus it is a standard practice nowadays to combine different cytological procedures during bronchoscopic sampling to achieve a higher yield whenever possible.[5] Crush cytology which has been commonly practiced for CNS tumors[6] can also be applied for endobronchial growth biopsy as a rapid diagnostic method. The pickup rate is considered good and in one study was found to be even better than that for biopsy.[7]

This study aimed to compare the cytological methods (Imprint and crush smear) and endobronchial forceps biopsy in the diagnosis of malignant endobronchial lesions. It also includes their correlation and comparison.

Methods

A prospective study was conducted from May 2017 to April 2018 at the Pulmonary medicine unit, Department of Internal Medicine and Department of Pathology at National Academy of Medical Sciences (NAMS), Bir Hospital. After approval from the Institutional Review Board (IRB), NAMS, the patients who were suspected to have bronchogenic carcinoma on clinico-radiological basis and underwent bronchoscopic biopsy for diagnosis were enrolled in the study. Patients who refuse to take part in the study, age less than 15 years, lesions that were clinico-radiologically inconsistent with diagnosis of malignancy and patients with contraindication to bronchoscopy were excluded.

After history and clinical examination, Complete blood count (CBC), Prothrombin time (PT), X-ray, Computed tomography (CT) scan, sputum smear for AFB and cytology were performed. Relevant history, radiological findings and other investigations were recorded in the proforma developed for the study. Well informed written consent was obtained and the procedure for bronchoscopy was explained to the patient. The procedure was carried out and supervised by chest physician as an elective procedure. Bronchoscopy was done with flexible bronchoscope (Olympus BF 119) of diameter (5.1 mm). After examining the healthy side, the bronchoscope was then passed to the diseased side.

Three to five bits of tissue were obtained and imprint and crush smear were prepared from them and the tissue were then sent for histopathological examination. Imprint smears were prepared from the tissues by rolling the tissue in a glass slide by help of tweezers. Crush smear were prepared from at least one biopsy sample wherein the tissue fragment was taken on a clean glass slide and spread using another glass slide. The biopsies were then collected in a container with 10% formalin. Wet smears were fixed in 100% methanol and were later stained by Papanicolau (Pap) method whereas the air-dried smears were stained with Giemsa stain. Additional procedures like bronchial washings, brush cytology, TBNA, Endobronchial ultrasound (EBUS) and transbronchial biopsy were also performed as per need.

Both histology and cytology was reported by two different pathologist who were blinded to each other's results and the results was subsequently analyzed. The imprint and crush smears were reported as negative, suspicious or positive for malignancy and when positive for malignancy was reported, subtyping was done as much as possible. The histopathology was taken as the diagnostic reference and classification of the tumor was done according to 2015 World Health Organization (WHO) classification of lung tumor. For data analysis, SPSS and Excel program were used. Chi-square test and Fischer exact test was done for comparing the categorical data. P value < 0.005 was considered statistically significant.

Interpretaion of Kappa coefficient:

Kappa <0: less than chance agreement, 0.01-0.20: slight agreement, 0.21-0.40: fair agreement, 0.41-0.60: Moderate agreement, 0.61-0.80: Substantial agreement, 0.81-0.99: Almost perfect agreement.[8]

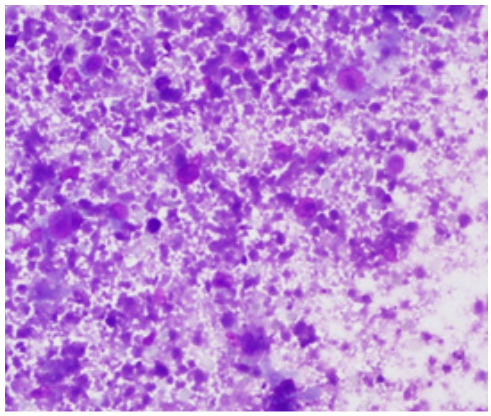
Results

A total of 53 patients were enrolled in the study. The age ranged from 40 to 84 years with a mean age of 62.6 years. Maximum number of lung cancer cases were in the age group of 60-69 years. Most of the cases were males (67.4%) with a male to female ratio of 2:1. 85% of cases were cigarette smokers and among those that were positive for malignancy, 39 cases (91%) were smokers and 4 cases (9%) were non smokers. Involvement of left lung was more compared to right lung, with most common location being left upper lobe (30.2%) followed by right upper lobe (26.4%).

There were 52.8% positive cases and 13.2% suspicious cases in imprint cytology, 58.5% positive and 9.4% suspicious cases in crush cytology and 81.1% positive and 1.9% suspicious cases in forceps biopsy. Biopsy had the maximun number of positive cases (43 out of 53 cases) as compared to other modalities. Squamous cell carcinoma was the most common malignancy followed by adenocarcinoma among imprint and forceps biopsy whereas adenocarcinoma was the most common malignancy detected in crush cytology. Squamous cell carcinoma was the most common tumor among the smokers (48.7%) whereas adenocarcinoma (100%) was the only tumor found in non-smokers (Table 1) (Photomicrograph 1, 2 and 3)

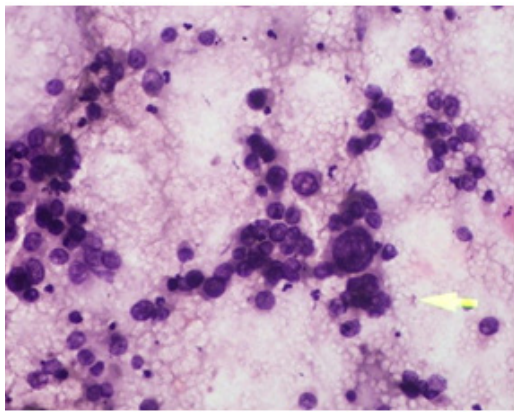
Tables 1: Association of cigarette smoking with type of cancer

Diagnosis	Smoking		Total
	Yes (No/ %)	No (No. / %)	
Squamous cell Ca	19 (48.7%)	0	19
Adenocarcinoma	12(30.7%)	4(100%)	16
Small cell Ca	8(20.5%)	0	8
Total	39 (90.7%)	4 (9.3%)	43(100%)



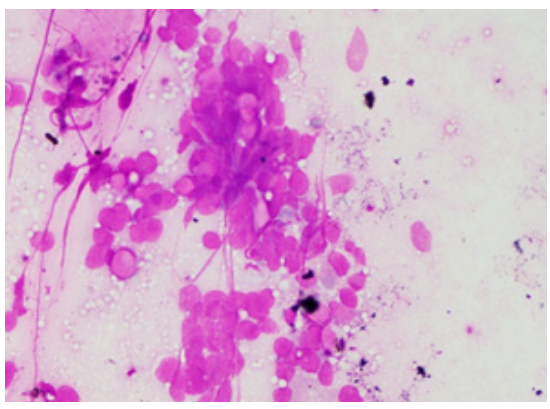
Photomicrograph 1. Crush cytology (x400)

Cytological features of Squamous cell carcinoma displaying scattered atypical squamous cells with irregularly keratinized cytoplasm, hyperchromatic chromatin in a necrotic background. (Giemsa)



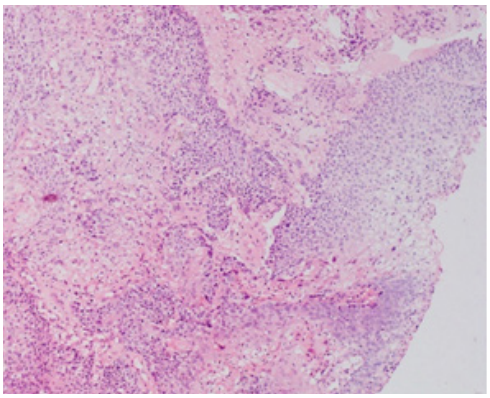
Photomicrograph 2. Imprint cytology (x400)

Cytological features of adenocarcinoma showing loose aggregates of atypical cells with moderate amount of cytoplasm and moderate to marked nuclear pleomorphism. (Pap)



Photomicrograph 3. Imprint cytology. (x400)

Cytological features of small cell carcinoma showing cluster of small cells with scanty cytoplasm, nuclear molding and stippled chromatin. (Giemsa)



Photomicrograph 4. Forceps Biopsy (x100)

Histological features of Squamous cell carcinoma showing stromal invasion by atypical squamoid cells in cords and diffuse pattern. The cells are pleomorphic with hyperchromatic nuclei and abundant eosinophilic cytoplasm. (H & E)

The sensitivity, specificity, accuracy and positive predictive value of imprint cytology was 71.05%, 87.50%, 73.91% and 96.43% respectively (Table 2) while that for crush cytology was 74.36%, 75%, 74.47% and 93.55% respectively (Table 3). The diagnostic yield of imprint, crush smear and forceps biopsy were 52.8%, 58.4% and 81.1% respectively.

Table 2: Statistical analysis of Imprint cytology

Imprint	Diagnosis on biopsy		
	Positive	Negative	Total
Positive	27	1	28
Negative	11	7	18
Total	38	8	46

Table 3: Statistical analysis of Crush cytology

Crush cytology	Diagnosis on biopsy		
	Positive	Negative	Total
Positive	29	2	31
Negative	10	6	16
Total	39	8	47

96.4% and 93.5% cases diagnosed positive by imprint and crush were diagnosed so by biopsy respectively whereas 61.1% and 58.8% cases diagnosed negative by imprint and crush was diagnosed as positive by biopsy respectively. One case diagnosed as positive by imprint was diagnosed as negative in biopsy. The agreement between the imprint and crush smears and biopsy was fair and statistically insignificant (Table 4). For imprint smears, the accuracy of tumor typing was 100% for squamous cell carcinoma, adenocarcinoma and small cell carcinoma and thus the agreement of tumor typing with biopsy was substantial and statistically significant (Table 5). The accuracy of tumor typing was 100% for small cell carcinoma, 92.9% for adenocarcinoma and 91.7% for squamous cell carcinoma in crush smears and the agreement of tumor typing with biopsy was moderate and statistically significant.

Table 4: Statistical analysis of Imprint cytology and bronchial biopsy

Forceps biopsy				
Imprint cytology	Negative	Positive	Suspicious	Total
Negative	7 (38.9%)	11(61.1%)	0	18
Positive	1(3.6%)	27(96.4%)	0	28
Suspicious	1(14.3%)	5(71.4%)	1(14.3%)	7
Total	9	43	1	53

Kappa test, k value: 0.336 and p: 0.103

Table 5: Statistical analysis of Crush cytology and bronchial biopsy

Forceps biopsy				
Crush cytology	Negative	Positive	Suspicious	Total
Negative	6 (35.3%)	10 (58.8%)	1(35.3%)	17
Positive	2(6.5%)	29 (93.5%)	0	31
Suspicious	1	4(80%)	0	5
Total	9	43	1	53

Kappa: 0.276 , p value:0.107

Discussion

Lung carcinoma is one of the leading cause of cancer related death in industrialized countries. Its etiology is not just limited to smoking, but is multifactorial.9 With the advent of specific chemotherapy and several targetable molecular alterations, classifying the tumor as simply Non- small cell lung cancer (NSCLC) is no longer recommended.[10]

Among the 53 patients enrolled, 43 cases were found to be malignant by forceps biopsy alone. Maximum number of lung cancer cases were in the age group of 60-69 years which was similar to a

study done by Koul et al.[11] and Siang et al.[12] Males (67.4%) were predominantly affected, with a male to female ratio of 2:1. This result is similar to the finding mentioned in Spencer's pathology, where the gender distribution for lung cancer is 68% in males and 32% in females.[13] However, this result is in contrast to the findings mentioned in WHO classification of lung tumors which states that the male to female incidence ratio for lung cancer overall decreased from 2.8 to 1.5.[14] The possible explanation can be linked to variation (20-fold) in lung cancer rates by region1 along with historical patterns of cigarette smoking prevalence that has largely affected the distribution of lung cancer.[15]

In our study, 85% of the enrolled patients were smokers, with a male predominance. In a study by Bhat et al., 81.5% cases were smokers[4] and Bodh et al. also found 88.24% males and 50% females were active smokers in their study.[16]

Our study had squamous cell carcinoma as the most common carcinoma in smokers (Photomicrograph 4) whereas adenocarcinoma was the only subtype found in non smokers. In the study by Pradhan et al., squamous cell carcinoma was the most common type (63.64%) followed by adenocarcinoma (29.09%) and small cell carcinoma (7.27%), which is similar to our study.[17] However, in the study by Agrawal et al., adenocarcinoma was the most common type (29.26%).[18]

In our study, involvement of left lung was more compared to right lung, with most common location being left upper lobe (30.2%) followed by right upper lobe (26.4%). This finding was similar to the results from Surveillance, Epidemiology and End Results Program (SEER) study where lung cancer was predominant in upper lobes for all age groups, sex and race. However, they also noted a predominance of right sided lung cancer compared to left, which is in contrast to our study.[19] Siang et al. also found a predominance of primary lung tumors in the upper lobes (47.5%).[12] Though the studies are ongoing, the hypothesis behind upper lobe predilection in smokers has been linked to increased exposure to smoke and that the carcinogens may persist longer due to lesser ventilation, lymphatic clearance and delivery of protective substances when compared to lower lobe. Also, the anatomic, physiologic and functional differences between the upper and lower lobes may be responsible.[20]

In this study, the sensitivity, specificity, accuracy and positive predictive value of imprint cytology was 71.05%, 87.50%, 73.91% and 96.43% respectively with a diagnostic yield of 52.8%. This was the least sensitive procedure among all the three procedure. Though the agreement regarding the diagnosis between imprint and biopsy was fair, there was a substantial agreement regarding tumor typing. In the study by Bhat et al., imprint smears showed better positive yield with sensitivity, specificity, positive predictive value and negative predictive value of 83.6%, 100%, 100% and 79.4% respectively.[4] In the study by Paulose et al., they found a 100% accuracy of tumor typing in imprint smear, which is similar to our study.[21]

The study showed sensitivity, specificity, accuracy and positive predictive value of crush cytology was 74.36%, 75%, 74.47% and 93.55% respectively with a 58.4% diagnostic yield. The agreement for diagnosis between crush cytology and histopathology was fair but regarding the tumor typing, it had moderate agreement and was statistically significant.

In a study by Nayanar et al. squash cytology alone was positive alone in 18 cases among the 100 patients who underwent bronchoscopy. The agreement between squash cytology and histology regarding the subtype was 100% for small cell carcinoma and adenocarcinoma whereas it was 88% for squamous cell carcinoma, which is quite similar to our study.[7] The results of our study is in contrary to the study by Bhat et al., in which the crush cytology had a sensitivity, specificity, positive predictive value and negative predictive value of 81.6%, 100%, 100% and 77.5% respectively.[4]

In our study, bronchial biopsy was taken as the gold standard and had the maximum number of positive cases (43 out of 53). 81.1% cases were diagnosed as positive. 19 cases were typed as squamous cell carcinoma, 16 cases as adeno carcinoma and 8 cases as small cell carcinoma. It is similar to the findings of Ghazarian et al. with a diagnostic yield of 81.1% in bronchial biopsy of macroscopically visible tumors.[22] In contrary,

adenocarcinoma was the most common subtype (51.1%) in endobronchial biopsy, in the study by Pujari et al.[23]

Although according to WHO, adenocarcinoma is said to be on rise and is even considered as more common than squamous cell carcinoma in many of the countries[14], our study revealed squamous cell carcinoma as the most common subtype. The reason for this result in our study can be due to the presence of endobronchial tumors that are more commonly central tumors, the prototype of it being squamous cell carcinoma, as compared to adenocarcinoma which is commonly located at the periphery.[24]

In a study by Wong et al., they demonstrated a variation in diagnostic yield according to the visibility of the lesion with 98.1% for endoscopically visible lesion to 61.5% for endoscopically not visible lesion. The reported diagnostic yield from bronchoscopy varies and the optimal combination of sampling techniques has not been established.[25]

The likely reason of low sensitivity and yield for imprint and crush cytology in our study can be linked to a number of factors like scant tumor cellularity, extensive necrosis and fibrosis of the biopsy specimen, poor smear quality, error in fixation, drying artifact, preparation technique and processing of collected samples. Another reason for reduced yield may be sampling of necrotic tissue and normal bits of tissue, small size of the biopsy specimen which may fail to provide adequate cellularity.[4262728 29]

But it is still recommended to use imprint and crush smear whenever possible as it is cost effective and the speed of this examination and reporting makes it worth performing. Advantage like rapidity of preparation and preservation of cellular details also adds to its usefulness. It does not require any additional effort or equipment and may add to the diagnostic yield. But still histology is needed for assessing grade, invasion and typing. Doing the two procedures together can be termed as complimentary.[29 30] We had a good results regarding the tumor typing, so it can be used in conjunction with histopathology to identify the type of malignancy.

Since biopsy as a standalone procedure may not be able to clinch a diagnosis in each and every case, it can be used in combination with any of the aforementioned cytological procedures, depending on the situation and tumor characteristics. Still, we can consider biopsy to be the gold standard as it is an invaluable procedure since it offers tissue for IHC, which is very much needed in this era of targeted therapy.[31]

Conclusion

We had good agreement regarding the tumor typing between the two cytology procedures with histology. Both the procedures are simple and inexpensive methods and can be prepared rapidly and if processed with precision and can result in good morphological evaluation. Though crush cytology has an additional disadvantage of tissue being used up during the procedure, imprint cytology has the additional benefit of preventing tissue loss and can be performed even if we are faced with less number of biopsies. So with precaution to remove the limiting factors, we can use these procedures whenever possible as they may help in providing additional and faster information regarding the diagnosis.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018 Nov 1;68(6):394–424
2. Kumar V, Abbas AK, Aster JC. Robbins and Cotran Pathologic Basis of Disease. 9th edition. Philadelphia, PA: Elsevier/Saunders; 2015.
3. Dudgeon LS, Patrick CV. A new method for the rapid microscopical diagnosis of tumours: With an account of 200 cases so examined. BJS. 1927 Oct 1;15(58):250–61.
4. Bhat GQ. Correlative Study of Imprint and Crush Cytology with Histopathology in Endobronchial Growths. J Cytol Histol 2013. 4:3. doi: 10.4172/2157-7099.1000177
5. Popp W, Rauscher H, Ritschka L, Redtenbacher S, Zwick H, Dutz W. Diagnostic sensitivity of different techniques in the diagnosis of lung tumors with the flexible fiberoptic bronchoscope. Comparison of brush biopsy, imprint cytology of forceps biopsy, and histology of forceps biopsy. Cancer. 1991 Jan

1;67(1):72–5.

6. Jaiswal S, Vij M, Jaiswal AK, Behari S. Intraoperative squash cytology of central nervous system lesions: a single center study of 326 cases. Diagn Cytopathol. 2012 Feb;40(2):104–12.
7. Nayanar SK, Puthiyaveettil AK, Bhasurangan KC. Utility of squash smear cytology in fiber-optic bronchoscopic biopsies. J Cytol. 2014 Jan;31(1):11–4.
8. Viera AJ, Garrett JM. Understanding interobserver agreement: the kappa statistic. Fam Med. 2005 May;37(5):360–3.
9. Fletcher CD. Diagnostic Histopathology of Tumors. 4th ed. Vol. 1. Elsevier /Saunders; 2013. 207 p.
10. McLean AEB, Barnes DJ, Troy LK. Diagnosing Lung Cancer: The Complexities of Obtaining a Tissue Diagnosis in the Era of Minimally Invasive and Personalised Medicine. J Clin Med. 2018 Jul;7(7):163.
11. Koul PA, Kaul SK, Sheikh MM, Tasleem RA, Shah A. Lung cancer in the Kashmir valley. Lung India. 2010 Jul 1;27(3):131.
12. Siang KC. A Review of Lung Cancer Research in Malaysia. Malaysia. 2016;71:9.
13. Hasleton P, Flieder DB. Spencer's Pathology of the lung. 6th ed. Cambridge Univeristy Press; 2014. 7 p.
14. Travis WD, Brambilla E, Burke AP, Marx A, Nicholson AG. WHO Classification of Lung, Pleura, Thymus and Heart. 4th ed. WHO IARC.2015.
15. Alberg AJ, Brock MV, Ford JG, Samet JM, Spivack SD. Epidemiology of Lung Cancer. Chest. 2013 May;143(5 Suppl):e1S-e29S.
16. Bodh A, Kaushal V, Kashyap S, Gulati A. Cytohistological correlation in diagnosis of lung tumors by using fiberoptic bronchoscopy: Study of 200 cases. Indian J Pathol Microbiol. 2013 Apr 1;56(2):84.
17. Pradhan SB, Shakya S, Shrestha S. Clinico-Pathological Study of Lung Carcinoma. J Pathol Nepal. 2014 Sep 23;4(8):623–5.
18. Agrawal A. Clinical profile of lung cancer in a tertiary care teaching hospital in north india with special reference to acceptance and outcome of treatment. 2018;2(1):5.
19. Byers TE, Vena JE, Rzepka TF. Predilection of lung cancer for the upper lobes: an epidemiologic inquiry. J Natl Cancer Inst. 1984 Jun;72(6):1271–5.
20. Huang Y-H, Hsu K-H, Tseng J-S, Chen K-C, Su K-Y, Chen H-Y, et al. Predilection of contralateral upper lung metastasis in upper lobe lung adenocarcinoma patients. J Thorac Dis. 2016 Jan;8(1):86–92.
21. Paulose RR, Shee CD, Abdelhadi IA, Khan MK. Accuracy of touch imprint cytology in diagnosing lung cancer. Cytopathology. 2004 Apr 1;15(2):109–12.
22. Ghazarian Z, Alziadat M, Sekhon R, Hanna M, Pandya T, Ismail M. Diagnostic Yield of Bronchoscopic Lung Biopsy in Evaluating Lung Cancer. Chest. 2016 Oct 1;150(4):710A.
23. Vv P, Rm L. To study the various bronchoscopic presentations of bronchogenic carcinoma. Int J Sci Res. 2018 Sep;6(8).
24. Ibungo I, Tongbram C, Paley T, Prameshwari N, Ningthoujam D. Diagnostic yield of bronchoscopic biopsy and bronchial washing in endoscopically visible lung malignancies. Int J Med Health Res:4.
25. Wong P, Lee J, Lam F. Bronchoscopy in the diagnosis of lung cancer. Monaldi Arch Chest Dis. 1999;(54):394–8.
26. Zgajnar J, Frkovic-Grazio S, Besic N, Hocevar M, Vidergar-Kralj B, Gerljevic A, et al. Low sensitivity of the touch imprint cytology of the sentinel lymph node in breast cancer patients—results of a large series. J Surg Oncol. 2004 Feb 1;85(2):82–6.
27. Kane SV, Prabhudesai NM, Ojha SS, Shetty NS, Kulkarni AV, Kulkarni SS. The role of squash cytology in rapid on-site adequacy checking and rapid diagnosis in image-guided gun biopsy at a tertiary cancer center. Acta Cytol. 2014;58(1):33–41.
28. Kaur A, Kaur DN, Bhatti A, Hura DKS. The validity of rapid intraoperative and preoperative crush smear cytology in detection of malignancies of the gastro intestinal tract, gall bladder and the breast. Indian J Appl Res. 2018 Sep;7(7).
29. Yadav KK, Bhatti R, Moorchung N, Mutreja D, Carvalho AS. Is crush cytology of central nervous system lesions relevant in surgical practice today? J Neurosci Rural Pract. 2019 Jan 1;10(1):34.
30. Goyal S, Mohan H, Handa U, Saini V. Rinse fluid and imprint smear cytology of bronchial biopsies in diagnosis of lung tumors. Diagn Cytopathol. 2012;40(2):98–103.
31. K VA, B U, Shenoy A, Holla R. Utility of Various Bronchoscopic Modalities in Lung Cancer Diagnosis. Asian Pac J Cancer Prev APJCP. 2017;18(7):1931–6.