Article published online: 2020-12-31

Tissue is the real issue

Carcinoma of the lung continues to be a major oncological problem with increasing incidence, high stage presentation, and minimal improvement in overall clinical outcome despite various therapeutic options available. Thus, it becomes imperative that modalities for diagnosis and clinical staging be well-established, to make rational management decisions. Imaging techniques such as computerized tomography (CT) scan and positron emission tomography-computed tomography (PET-CT) scan have vastly improved accurate staging of the disease. It is, though, an uncontested fact that tissue (histologic) diagnosis is highly desirable to confirm and subtype the disease and, in the modern era, to carry out molecular studies, which predict response to targeted therapy.

Two papers in this issue of the journal report the author's experience with fine-needle aspiration cytology (FNAC) of intra-thoracic tumors, especially lung masses. While Nasit *et al*.[1], have shared their experience of evaluating 50 anterior mediastinal masses by FNAC and core needle biopsy (CNB), Mondal *et al*.[2], have mainly evaluated lung masses by CT guided FNAC.

The statistical analysis of anterior mediastinal masses (Nasit *et al*.) shows a significantly higher sensitivity rate for CNB (97.95%) than for FNAC (71.42%) ($P < 0.05$). They also point out that CNB has a higher diagnostic rate than FNAC in the non-carcinoma group (100% v/s 62.96%) ($P < 0.05$) while there was no significant difference in carcinoma group ($P > 0.05$). Diagnostic accuracy of FNAC for carcinoma lesions was 81.81%, while for non-carcinoma lesions, it was 62.96%. Mondal *et al*., mainly had carcinomas in their study and showed a diagnostic accuracy for CT guided FNAC of 95% for diagnosing carcinomas, which were subsequently confirmed on bronchoscopic / tru-cut biopsy or resection, as applicable.

Both studies conclude that FNAC, by experienced hands, is a simple, safe, and accurate method of arriving at a diagnosis of carcinoma with low procedure related complication rates. However, the diagnosis of non–carcinomatous lesions (Nasit *et al*.[1]) showed poor accuracy *vis-a-vis* CNB. The findings in both studies are in line with previous reports on the accuracy of FNAC *vis-a-vis* CNB.[3]

What both studies failed to address are the consequences of (i) an inaccurate diagnosis of the subtype of non-small-cell carcinoma on FNAC (ii) molecular testing of lung cancer for targeted therapy, and (iii) revisiting the diagnosis in the future if it becomes necessary (archival tissue).

Although cytology continues to be an integral part of our diagnostic armamentarium, there is an increasing recent trend towards the use of tissue core biopsies, for not only do they afford a chance for accurate histologic sub-classification, they also offer a second chance for confirmation by immunostaining, and, more importantly, provide the residual tissue for molecular testing. While in some instances cytology samples can be processed into cell block preparations, it is often exhausted in the diagnostic process.

Most errors in cytology can be attributed to poor spread of the material, blood admixed spread, drying artifacts, scanty cellularity, and poorly differentiated tumors. Having dedicated technical staff could obviate majority of these factors; but the fact remains that cytologic diagnosis of malignancy relies purely on the appearance of cells, with no architectural clues available as in a biopsy. Arguably, core biopsy offers superior assessment of tissue architecture and a definitive diagnosis, particularly of benign lesions. The recent recommendations[4] for reporting lung cancer mandate that lung carcinoma be classified into adenocarcinoma and squamous carcinoma, and not just small-cell v/s non-small-cell carcinoma. While one admits that distinction between small-cell carcinoma and non-small cell carcinoma is easily done on cytologic preparations, the same is not true for adenocarcinoma v/s squamous carcinoma. Adenocarcinomas nowadays undergo mandatory testing for epidermal growth factor receptor (EGFR) mutation to evaluate response to Tyrosine Kinase Inhibitors (TKIs), and squamous histology being a known predictor of life-threatening hemorrhage with Bevacizumab therapy, it becomes absolutely critical to distinguish these histologic subtypes. With the stakes so high, it is optional, but perhaps preferable to confirm the histologic sub-classification by TTF-1 / P 63 / CK-5/6 immunocytochemistry. While it is eminently possible to carry out immunocytochemistry as well as molecular studies on cytology material, one has to remember that sample size (or the lack of it) and tumor heterogeneity may have an effect on the diagnosis and downstream molecular test results. Looking at the larger picture, CNB provides a repository of archival tissue for future biomarker evaluation, which is not possible with cytology material.

Cytologic techniques still have relevance in appropriate settings. Endoscopic ultrasound-guided fine-needle aspiration (FNA) from esophagus and endobronchial ultrasound-guided transbronchial FNA are shaping up as sensitive techniques to sample the hitherto non-surgically accessible hilar / mediastinal lymph nodes for staging the disease. Cytology in the form of FNA can be useful to confirm metastasis, where the primary histologic diagnosis is already known and one is only looking at presence /

Access this article online	
Quick Response Code:	Website: www.sajc.org
	DOI: 10.4103/2278-330X.105864

absence of tumor cells. The same applies for effusion cytology. In principle, if the aim is to obtain a primary diagnosis rather than staging the disease, tissue biopsy for histology is preferable.

The utility of core biopsy in diagnosis of mediastinal masses, other than carcinoma, cannot be overemphasized. Confident diagnosis of non-Hodgkin's lymphoma or thymoma is a gratifying experience. Disastrous consequences await if each one is called the other, because the treatment for one is non-surgical while the other is surgical. The reason for the huge discordance between cytology and CNB in diagnosis of non-carcinoma lesions (Nasit *et al*.[1]) is clear, because most non-carcinomatous lesions (non-Hodgkin's lymphoma, thymoma, neuroendocrine carcinoma) would require immunocytochemistry in some or the other form, which is not reliably possible on cytology.

While one would prefer that biopsy cores are available for majority of lesions, there are complications of the procedure such as pneumothorax and intra-lesional hemorrhage. An ideal minimally invasive procedure should be able to achieve high diagnostic sensitivity rates with minimal complications and affordable cost. In experienced hands, image-guided CNB procedure comes very close to fulfilling the above criteria.

To sum it up, CNB is vastly superior to cytology in diagnosing non-carcinomatous lesions for the aforementioned reasons. In diagnosis of carcinomas, cytology is equally sensitive, but may potentially be a stumbling block for accurate histologic sub-typing and molecular analysis. It may, thus, be an important tool for confirming the presence of tumor cells in tissue, but less useful than CNB in answering more related questions, which may help formulate management strategies.

The advent of endoscopic ultrasound FNA from esophagus and endobronchial ultrasound-guided transbronchial FNA procedures will revolutionize the staging of mediastinal lymph nodes / non surgically accessible paratracheal / paraesophageal lymph nodes. Similarly, cytology will continue to play an important part in confirming recurrence / metastasis, where accurate histologic sub-typing is not a priority.

We need to formulate a strategy favoring CNB for diagnosis of mediastinal / lung masses with certainty, coupled with cytology for staging the disease / confirming a relapse or metastasis.

Jay Mehta
SRL Diagnostics' Centre of Excellence: Histopathology, Mumbai, India
Correspondence to: Dr. Jay Mehta,
E-mail: drjaymehta@gmail.com

References

1. Nasit JG, Patel M, Parikh B, Shah M, Davara K. Anterior mediastinal masses: A study of 50 cases by fine needle aspiration cytology and core needle biopsy as a diagnostic procedure. South Asian J Cancer 2013; 2 : 7-13.
2. Mondal SK, Nag D, Das R, Mandal PK, Biwas PK, Osta M. CT guided FNAC of lung mass with histological correlation- a study in Eastern India. South Asian J Cancer 2013; 2:14-8.
3. Gong Y, Sneige N, Guo M, Hicks ME, Moran CA. Transthoracic fine-needle aspiration vs concurrent core needle biopsy in diagnosis of intrathoracic lesions: A retrospective comparison of diagnostic accuracy. Am J Clin Pathol 2006;125:438-44.
4. Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger K, Yatabe Y, *et al*. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society International Multidisciplinary Classification of Lung Adenocarcinoma. J Thorac Oncol 2011;6:244-85.

How to cite this article: Mehta J. Tissue is the real issue. South Asian J Cancer 2013;2:5-6.
Source of Support: Nil. **Conflict of Interest:** None declared.