Details of the research work done in the field of **Thoracic Pathology including Cytopathology and Sinonasal Cancer Pathology** to improve patient care of Lung Cancer and Sinonasal cancer:

Thoracic Pathology

Thoracic pathology is a highly subspecialized and challenging division of diagnostic surgical and cytopathology with significant recent revolutionary advances in the genomics of lung cancer which reshape lung cancer pathology and make it more clinically relevant for improved patient care. The challenges are from the acquisition of adequate sample, channelizing multiple predictive biomarkers' testing to accurate interpretation and diagnosis of the case.

Lung cancer is the most common cancer worldwide and has been the leading cause of cancer related mortality for many years worldwide. Smoking was the main cause of lung cancer however it has been recently noted that it affects young and non-smokers as well. Due to late detection of the disease, overall survival of patients is very less. Detection of predictive biomarkers in non-small cell type of lung cancer gives some hope to patients by providing personalized treatment. However, testing of these biomarkers requires infrastructure, manpower and adequate funding. Availability, accessibility and affordability of these tests are common barriers globally in lung cancer care especially in underserved countries.

The Thoracic Pathology laboratory was set up at the department of pathology, All India Institute of Medical Sciences (AIIMS), New Delhi, in 2012 by me with the single aim of providing better care to patients of lung cancer. Keeping in pace with the rapid global strides in the unravelling of the molecular pathology of lung cancer and the paradigm shift in the management of lung cancer, the laboratory was one of the first in the country in government set-up to implement routine predictive biomarker testing for the targetable epidermal growth factor receptor (*EGFR*) gene mutations in lung cancer patients. I have been working in the field of Thoracic Pathology for last 10 years to improve patient care and streamline predictive biomarker testing in precious small biopsy and cytology specimens. All in-house and outside patients from all over India are consulted, diagnosed, and tested in the Thoracic Pathology Laboratory.

Subdivision of respiratory cytology is increasingly being used in the evaluation of lung lesions especially for diagnosis and complete work-up of clinically suspected lung cancer cases. There are many sampling techniques available to procure specimens for cytologic evaluation of lung tumors. The choice of sampling technique depends upon clinical features of the patient and characteristics of the lesion. Strong emphasis has been given on performing rapid onsite

evaluation (ROSE) and preparing cell blocks for obtaining adequate specimens and doing predictive biomarker testing respectively.

To begin with, characterization of non-small cell carcinoma into squamous and non-squamous morphology was successfully achieved on cytology direct smears by application of immunocytochemistry (***Cytopathology***. 2014 Oct;25(5):330-5) and small biopsy specimens (***Indian J Med Res*.** 2017 Jul;146(1):42-48). Non-squamous morphology is further subject to molecular testing that is why it is essential to separate non-squamous cancers from squamous cell carcinomas.

Additionally, for the similar therapeutic purposes, it is mandatory to accurately recognize adenocarcinoma and its mimics. In that effort, many studies were carried out to help cytopathologists to classify adenocarcinoma into various subtypes by using different cytological parameters with or without doing ancillary studies on different types of cytology preparations. **(*Diagn Cytopathol*.** 2016 Jul;44(7):607-11, ***Acta Cytol***. 2017;61(1):77-83, ***J Cytol*** 2018;35:94-8, ***Cytopathology***. 2018 Apr;29(2):163-171, ***Cancer Cytopathol***. 2019 Aug;127(8):539-548, ***Cytopathology***. 2019 Jan;30(1):82-90, ***Diagn Cytopathol***. 2021 Jan;49(1):77-82). One of which was done in collaboration with 13 cytopathology experts practising worldwide representing International Association for the Study of Lung Cancer (IASLC) Cytology Working Group (***J Thorac Oncol.*** 2022 Jun;17(6):793-805).

Conventional pulmonary adenocarcinomas or nonsquamous carcinomas (also called as non-small cell carcinoma- not otherwise specified) are reflexely tested for recommended panel of 4 ‘must test’ biomarkers that includes *EGFR* gene mutations, *ALK* and *ROS1* gene rearrangements and PDL1 protein immunoexpression. While these tests are done easily on histopathology specimens, performing them on cytology specimens for patient care need an additional layer of standardization and validation. All types of cytology preparations, in my laboratory, are standardized in cost effective manner replicating resource limited settings for predictive biomarker testing of lung cancer specimens. Results of the same are published in reputed peer reviewed cytopathology journals (***Acta Cytol***. 2017;61(6):455-461, ***Cytopathology*.** 2018 Dec;29(6):550-557, ***Cytopathology***. 2021 Mar;32(2):287-289, ***J Am Soc Cytopathol***. 2022 May-Jun;11(3):154-164, ***J Am Soc Cytopathol***. 2022 Sep-Oct;11(5):253-263).

Programmed cell death ligand-1 (PD-L1) testing by validated immunohistochemistry assay and lab developed tests was started as a predictive biomarker for immunotherapy ***(Ann Diagn Pathol*.** 2017 Dec;31:56-61, ***Indian J Med Res***. 2019 Oct;150(4):376-384). Standardization and validation of lab developed tests for *EGFR* and other genetic mutations, *ALK* gene

rearrangements in biopsy specimens are published (***Indian J Cancer***. 2017 Jan-Mar;54(1):209-213, ***Curr Probl Cancer.*** 2019 Oct;43(5):391-401, ***Pathol Oncol Res***. 2020 Oct;26(4):2363-2370). A cost-effective testing algorithm for *ALK* and *ROS1* gene rearrangements has been proposed and described using 1,800 plus non-small cell lung carcinoma cases. This approach is designed for use by both general and specialized pathologists in resource-limited settings (***Arch Pathol Lab Med***. *2023 Dec 6. doi: 10.5858/arpa.2023-0229-OA*).

All these tests have benefitted a huge number of lung cancer patients at AIIMS, New Delhi, who were able to gain timely access to appropriate drugs. Currently, we routinely test blood plasma liquid biopsies for *EGFR* mutation status on cell-free tumor DNA at diagnosis and during tumor progression to ease morbidity of repeat biopsies and expedite targeted treatment (***J Thorac Oncol***. *2022; 17(9): S513,* ***J Cancer Res Clin Oncol.*** *2024;150:371)*. We have also standardised other samples including body fluids for cell-free tumor DNA isolation and mutation testing (***Lab Investigation*** *2023;103:S316,* ***J Am Soc Cytopathol.*** *2024;13:291*). Targeted gene panels for lung cancer diagnosis and monitoring using customized panels on next generation sequencing (NGS) platforms are also validated and are to be implemented shortly for patient care. We have created an archive/bio bank of over 100 fresh frozen resected lung cancer specimens for future research and in process of getting it ISO standardized in collaboration with external experts.

I have been working on molecular subgroups of small cell lung carcinoma and for the first time clearly highlighted and summarized immune landscape of these lethal cancers (***Sci Rep***. 2023 Mar 6;13(1):3739). These findings thus would lead towards future employment of specific immune checkpoint therapy for treatment of these tumors.

With the technological advancements and revolution in molecular profiling of tumors, many uncharacterized tumors are now fitted into specific categories carrying prognostic and therapeutic relevance. NUT carcinoma and SWI/SNF chromatin remodeling complex deficient family of tumors are some of those newly recognized tumors present in thoracic cavity. These are very aggressive tumors and do not respond to conventional chemotherapeutic regime. Multiple clinicopathologic and molecular series of these tumors on cytology and histology specimens from India are published which added an important body of information in the literature (***Acta Cytol***. 2021;65(1):67-74, ***Cancer Cytopathol***. 2021 Jan;129(1):53-61, ***Arch Pathol Lab Med***. 2021 Jan 1;145(1):90-98). As a lead author, I have published multiple white papers/consensus papers, individually as well as with international experts in the field of Pulmonary Cytopathology which

were highly cited [***Cytopathology***. 2014;25(6):356-371 (**Citations 182**), ***Cytopathology*.** 2018 Dec;29(6):505-524 (**Citations 76)**, ***Arch Pathol Lab Med***. 2018 Feb;142(2):253-262 (**Citations 129)**, ***Arch Pathol Lab Med***. 2018 Sep;142(9):1127-1133 **(Citations 71),** ***Cancer Cytopathol***. 2019 May;127(5):325-339 (**Citations 80)]**

Due to significant work and contribution in the field of Thoracic Pathology, I have been invited as Editorial Board Member of World Health Organization (WHO) classification of Thoracic Tumors and WHO reporting system for Lung Cytopathology. I have contributed more than 10 chapters in WHO books as responsible author and more than 20 chapters as coauthors. I Represent India in Pathology Committee of International Association for Study of Lung Cancer (IASLC) as member and co-chair of Cytology working group. I was First Indian to receive prestigious Mary J Matthews Pathology/ Translational Research Award of IASLC. I have many international academic collaborations which help in solving patient problems at national level.

Three illustrations are mentioned below to show work in Thoracic/Pulmonary Cytopathology (**Figure 1**). **Figures 2 and 3** show editorial board of WHO classification of Thoracic Tumors and WHO reporting system for Lung Cytopathology.

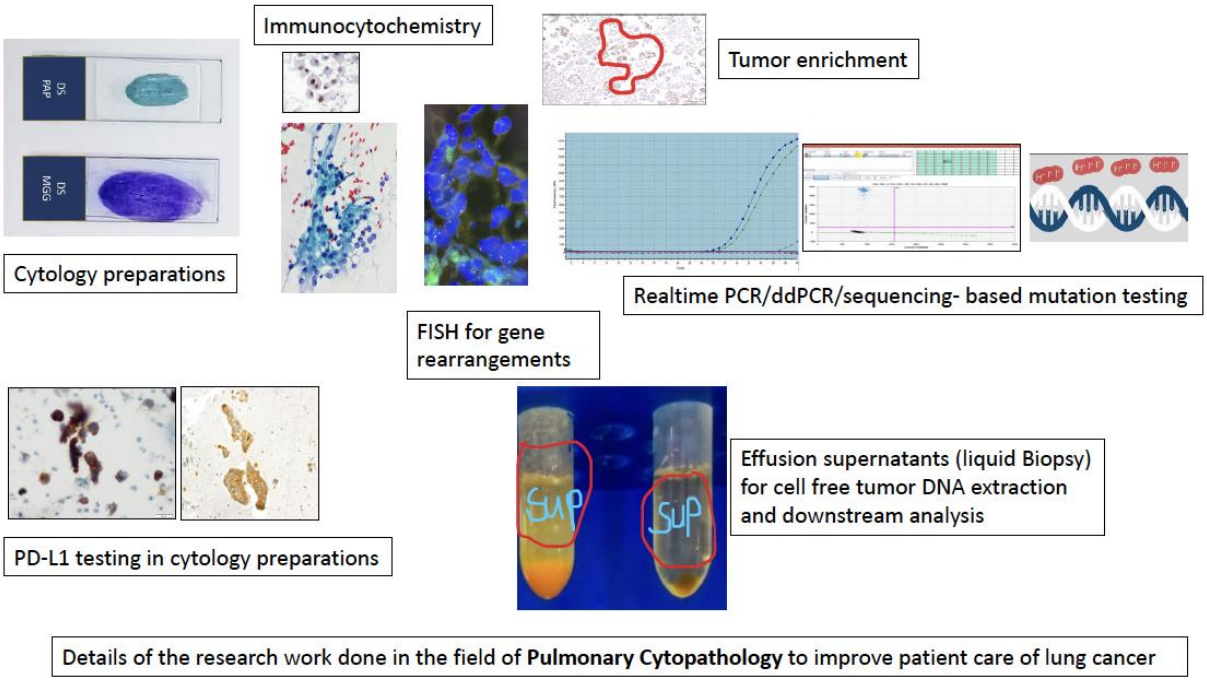
Sinonasal Cancer Pathology

The sinonasal tract pathology has long been neglected due to undifferentiated malignancies occur in this anatomically complex region and most frequent specimens submitted to pathology department are sinus contents which were often regarded as having little or no educational value. Consequently, discoveries in sinonasal tract pathology historically lagged other body sites with classification schemes devised decades earlier persisting with little change. However, Sinonasal tract pathology now can no longer be overlooked. Due to advancements in understanding of genomic profiling of solid tumors, an explosion in the subclassification of sinonasal malignancies has been seen.

I have characterized undifferentiated and poorly differentiated sinonasal carcinomas into well characterized and molecularly defined entities such as NUT carcinoma (***Head Neck Pathol***. 2018 Jun;12(2):230-236, SMARCB1 (INI-1) deficient carcinomas (***Hum Pathol***. 2019 Jan;83:59-67), SMARCA4 (BRG1) deficient carcinomas (***Arch Pathol Lab Med***. 2022 Sep 1;146(9):1122-1130) and DEK::AFF2 fusion sinonasal carcinomas (under publication). Previously unidentified mutations in *IDH* gene in sinonasal undifferentiated carcinomas (SNUC) are reported (***Am J Surg Pathol***. 2022 Sep 1;46(9):1284-1290). Association of high-risk Human Papilloma Virus (HPV)

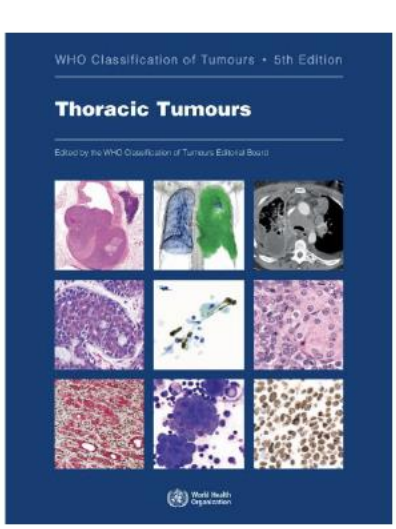
into pathogenesis of sinonasal carcinomas has been explored and reported first time from India (***Virchows Arch***. 2023 Sep;483(3):381-392) where it was noted that p16 expression on immunohistochemistry is a nonspecific surrogate for HPV infection in sinonasal malignancies and it can show positivity in other tumors without any HPV association (***Histopathology***. 2020 Dec;77(6):989-993). Due to prognostic and predictive value associated with all these tumors, it becomes imperative to diagnose them correctly for better patient management and appropriate drug delivery. **Figure 4** shows illustrative representation of work done in the field of Sinonasal Carcinoma pathology

Figure 1



Details of the research work done in the field of **Pulmonary Cytopathology** to improve patient care of lung cancer

Figure 2



Editorial Board

Chair: Dr. Ian A. Cree

Standing members (n=22)

Ming Sound Tsao
John KC Chan
Alex Lazar
Sigurd Lax

Expert members

Borczuk, Alain (New York)
Cooper, Wendy (Sydney)
Dacic, Sanja (Pittsburgh)
Galateau-Salle, Françoise (Lyon)
Jain, Deepali (New Dehli)
Kerr, Keith M. (Aberdeen)
Lantuejoul, Sylvie (Lyon)
Maleszewski, Joseph J (Minneapolis)
Marx, Alexander (Mannheim)
Nicholson, Andrew (London)
Noguchi, Masayuki (Tsukuba)
Scagliotti, Giorgio (Turin)
Travis, William D. (New York)
Yatabe, Yasushi (Tokyo)

~ 177 international authors and 9 IARC Staff

Chapter Author: 14
Responsible Author: 5

Figure 3

The IAC-IARC-WHO Joint Editorial Board

The IAC-IARC-WHO Joint Editorial Board

Expert members: Lung cytopathology

Bubendorf, Lukas
Canberk, Sule
Chandra, Ashish
Engels, Marianne
Hiroshima, Kenzo
Jain, Deepali
Kholova, Ivana
Layfield, Lester J.
Michael, Claire W.
Osamura, Robert Y.
Roy-Chowdhuri, Sinchita
Satoh, Yukitoshi
VanderLaan, Paul A.
Zakowski, Maureen F.

Standing members

Cree, Ian A. (Editorial Board Co-chair)*
Field, Andrew S. (Editorial Board Co-chair)*
Mehrotra, Ravi*
Pitman, Martha Bishop*
Schmitt, Fernando*

Chapter author: 9
Responsible author: 7

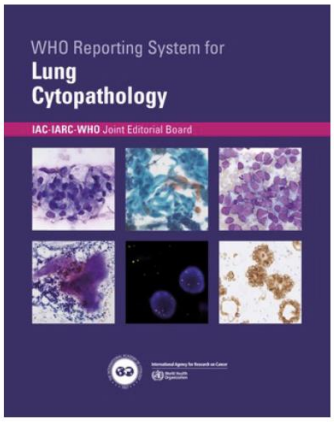
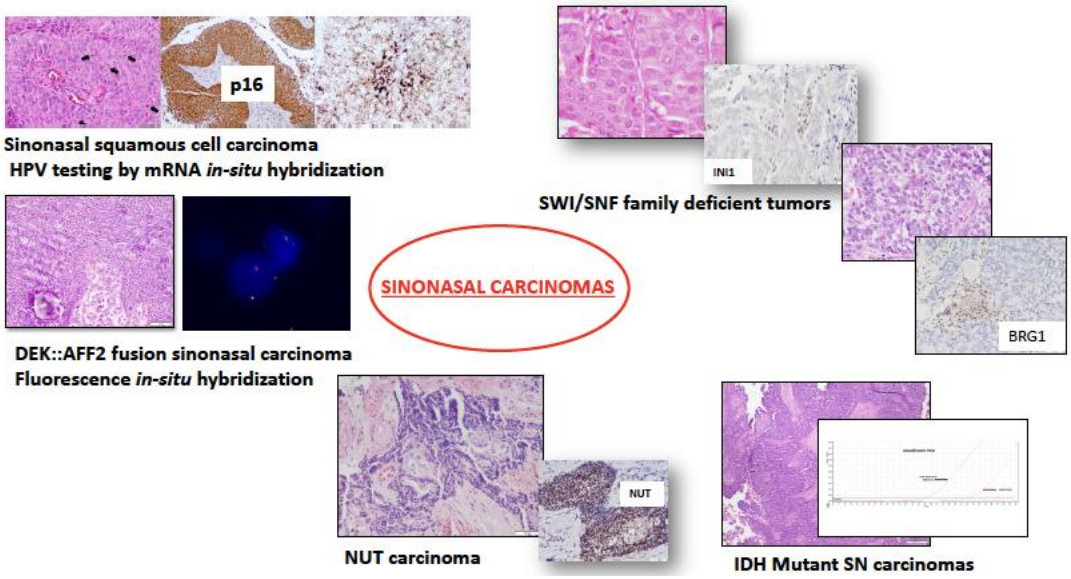


Figure 4



Research work Sinonasal carcinomas

Deepali Jain