

EP01.11: Molecular Profiling and Clinicopathologic Correlation in Lung Cancers Presenting as Second or Synchronous Primaries

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INTRODUCTION

- Lung cancer may occur as a second primary in patients with a previous malignancy or present synchronously with another primary.
- Distinguishing a new lung primary from pulmonary metastasis is diagnostically challenging but has important implications for staging and treatment.
- Histomorphology alone may be insufficient, particularly in tumors with overlapping morphology.
- Integration of morphology, IHC and molecular profiling can aid in establishing pulmonary origin and identifying actionable molecular alterations.

METHODS

- Retrospective single-institution study conducted at AIIMS, New Delhi, from February 2024–August 2026.
- Included lung adenocarcinomas confirmed as second/synchronous primary in patients with a previous or synchronous non-pulmonary malignancy.
- Other histologies, particularly squamous cell carcinoma, were included only when a distinct histomorphological and immunophenotypic profile supported an independent primary.
- Metastatic lesions were excluded.
- Diagnosis was based on integrated assessment of clinical history, morphology, IHC and molecular findings.
- IHC: TTF-1, Napsin A, p40/p63 and lineage-specific markers as required.
- Molecular testing: *EGFR* by PCR; *ALK/ROS1* by IHC ± FISH; NGS in selected cases.
- Demographic, clinicopathological and molecular data were analyzed descriptively.

DISCUSSION AND CONCLUSION

- Rising second/synchronous lung cancer diagnoses likely reflect intensified imaging surveillance in patients with prior malignancy
- Second/synchronous primary lung cancers showed a heterogeneous clinicopathological and molecular spectrum in our cohort.
- The predominance of antecedent head and neck squamous cell carcinomas may reflect shared tobacco exposure and field cancerization.
- EGFR* alterations were identified in 9/22 (40.9%) evaluable cases, demonstrating that potentially targetable drivers may occur across diverse antecedent malignancies.
- NGS provided additional clinically relevant genomic information in selected diagnostically complex cases.

ACTIONABLE TAKE-AWAY MESSAGE

- A new lung lesion in a patient with previous cancer may represent a new primary — not merely metastasis.**
- Integrated molecular profiling can change both diagnosis and treatment.

FUTURE DIRECTION FOR RESEARCH

- Prospective studies with paired molecular profiling of previous and lung tumors
- Larger cohorts to define the molecular landscape and therapeutic implications in second primary lung cancers.

REFERENCES & ACKNOWLEDGEMENTS

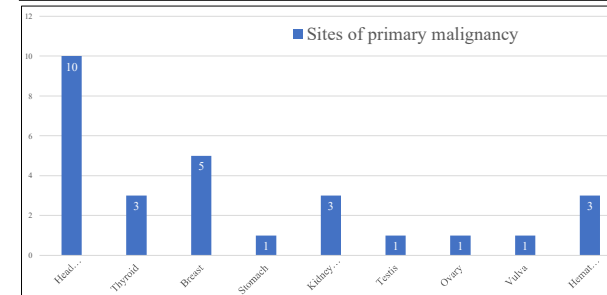
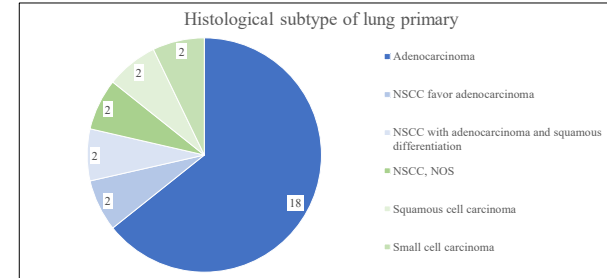
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RESULTS

- Cohort of 28 patients; age range: 46–76 years
- Male predominance: 19/28 (67.9%)
- Smoking status was documented in 16 cases; 8/16 cases were current/former smokers.
- Adenocarcinoma was the predominant lung histology (18/28, 64.3%).
- Head and neck Squamous cell carcinoma was the most common antecedent malignancy (10/28, 35.7%), followed by breast carcinoma (5/28, 17.8%).
- Latency between primary and second malignancies ranged from 0 to 32 years.
- ALK* and *ROS1* rearrangements were negative in all tested cases.
- EGFR* mutations were identified 9/22 (40.9%) evaluable cases: **exon 19 deletion** (n=4), **exon 21 L858R** (n=4) and **exon 18 G719X** (n=1).
- NGS identified additional alterations including *EGFR* exon 18 alterations, *KRAS* G12C, *PIK3CA* H1047R, MSI, *PTEN* and *TP53* in selected cases.

S.N	Age/sex	Smoking history	First/ synchronous primary	<i>EGFR</i> mutation
1	62/F	Non-smoker	Follicular thyroid carcinoma	Exon 19 deletion
2	73/M	Ex smoker	Squamous cell carcinoma, larynx	Exon 19 deletion
3	76/F	Non-smoker	Carcinoma vulva	Exon 21 L858R
4	57/M	Not available	Papillary renal cell carcinoma	Exon 18 G719X
5	54/F	Non-smoker	Papillary thyroid carcinoma, tall cell subtype	Exon 19 deletion
6	55/M	Non-smoker	Squamous cell carcinoma, larynx, Tonsil	Exon 21 L858R
7	53/M	Not available	Mucinous borderline tumor with microinvasion	Exon 21 L858R
8	58/F	Non-smoker	Carcinoma breast	Exon 19 deletion
9	58/F	Non-smoker	Papillary thyroid carcinoma	Exon 21 L858R



NGS FINDINGS

- Case 1: *KRAS* G12C + *PIK3CA* H1047R + MSI; prior high-grade urothelial carcinoma and synchronous colorectal adenomas
- Case 2: Rare *EGFR* exon 18 G719C mutation with therapeutic significance.
- Case 3: *TP53* Y236C + *PTEN* G129R mutations, associated with an aggressive clinical course.

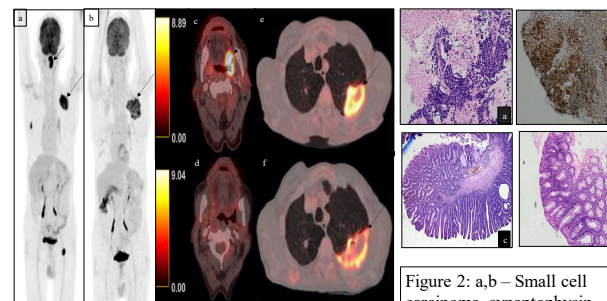


Figure 1: A 69-year-old man with dual primary malignancies (oropharyngeal DLBCL and synchronous extensive-stage SCLC of the left lung) underwent 18F-FDG PET/CT at baseline and after 4 cycles of chemotherapy

Figure 2: a,b – Small cell carcinoma, synaptophysin. c,d: Traditional serrated adenoma and tubular adenoma in a case of adenocarcinoma lung and known case of high-grade urothelial carcinoma