



Tumor aggressiveness in lung cancers of people who never smoked versus those who smoked: expanded IELCART experience

Rowena Yip¹, Wenchao Ma¹, Natela Paksashvili¹, Min Liang¹, Akmaral Ainakulova¹, Qin Peng¹, Alexandra Panina¹, David F. Yankelevitz¹, Claudia I. Henschke¹
¹*Department of Diagnostic, Molecular, and Interventional Radiology, Icahn School of Medicine of Mount Sinai, New York, NY, USA*
Correspondence: rowena.yip@mountsinai.org



INTRODUCTION

Nearly 1 in 5 people who die of lung cancer worldwide have never smoked, and screening programs are increasingly considering whether eligibility should extend beyond conventional smoking-based criteria. Whether lung cancers in people who have never smoked are radiographically more indolent and therefore might warrant different management remains unresolved.

In a pilot cohort of 158 patients, tumors in never-smokers had lower PET SUVmax and longer volume doubling time (VDT) than in smokers on unadjusted analysis, but these differences were no longer significant after adjusting for age, sex, and histology. We tested whether this conclusion holds in a substantially expanded, contemporary IELCART cohort.

METHODS

The Initiative for Early Lung Cancer Research on Treatment (IELCART) is a prospectively enrolled cohort of patients undergoing treatment for lung cancer across the Mount Sinai Health System (MSHS), with continuous enrollment since 2016. All patients enrolled in IELCART at MSHS from 2016 through July 2026 were included in this analysis if they had a first primary NSCLC measuring 30 mm or less in maximum diameter, no clinical evidence of metastasis, and a tumor manifesting as a solid nodule. Never smoking was defined per CDC criteria as having smoked fewer than 100 cigarettes in one's lifetime.

Patients with both a pre-treatment PET scan and at least two CT scans obtained 90 days or more apart were eligible for assessment of PET SUVmax and CT volume doubling time (VDT), the two radiologic measures of tumor aggressiveness used in this study; VDT was estimated from radiologist-reported nodule diameter on LDCT. Both measures were Box–Cox transformed prior to modeling given their skewed distributions. Comparisons by smoking status were performed using unadjusted analyses and multivariable linear regression, adjusting sequentially for age and sex, and then additionally for tumor histology.

DISCUSSION AND CONCLUSION

In this expanded cohort, the earlier finding remained consistent: apparent differences in radiographic measures of tumor aggressiveness by smoking status were largely explained by differences in age, sex, and especially histology. Once nodule evaluation is warranted, smoking status alone should not determine different CT follow-up intervals for assessing growth; if screening is offered to selected people who never smoked, their nodules should be managed in the same way as those of people who smoke.

Actionable Take Away Message

- Smoking status should not determine differential CT surveillance intervals; the same volumetric protocol should apply to all patients regardless of smoking history.
- Tumor histology, not smoking status, is the principal driver of radiographic aggressiveness; nodules in screening-eligible never-smokers should be managed identically to those in smokers.

Future Direction for Research

- External validation is warranted to confirm whether this histology-mediated pattern generalizes across populations with differing never-smoker case mixes.
- Combining automated volumetry with molecular correlation (EGFR, KRAS, ALK) in future screening cohorts could clarify whether any residual smoking-independent aggressiveness exists once histology is accounted for.

REFERENCES & ACKNOWLEDGEMENTS

References

- Adler S, Yip R, Chan H, Cai Q, Zhu Y, Triphuridet N, Kaufman A, Taioli E, Flores R, Henschke CI, Yankelevitz DF; IELCART Investigators. Comparison of lung cancer aggressiveness in patients who never smoked compared to those who smoked. Lung Cancer. 2022 Sep;171:90-96.
- Flores R, Taioli E, Yankelevitz DF, Becker BJ, Jirapatnakul A, Reeves A, Schwartz R, Yip R, Fevrier E, Tam K, Steiger B, Henschke CI; Initiative for Early Lung Cancer Research on Treatment Investigators. Initiative for Early Lung Cancer Research on Treatment: Development of Study Design and Pilot Implementation. J Thorac Oncol. 2018 Jul;13(7):946-957.
- Siddique M, Yip R, Henschke CI, Yankelevitz DF. PET standardized uptake values of primary lung cancer for comparison with tumor volume doubling times. Clin Imaging. 2021 May;73:146-150. doi: 10.1016/j.clinimag.2020.11.048.

Acknowledgements

This work was supported by the Simons Foundation International, Ltd.



Artificial Intelligence (AI) Use Disclosure

No AI Tools were used in the development or preparation of this poster presentation.

RESULTS

The expanded cohort included 1,155 eligible patients with ≤3cm NSCLC, of whom 272 (23.5%) had never smoked and 883 (76.5%) had smoked. Among them, 442 patients had both pre-treatment PET and at least two CT scans 90 days or more apart, allowing assessment of PET SUVmax and VDT. Among these 442 patients, never-smokers were more often female (70% vs. 50%), younger, and had fewer smoking-related comorbidities; histology also differed sharply, with typical carcinoid far more common (25% vs. 3.8%) and squamous cell carcinoma virtually never seen (0% vs. 21%) among never-smokers. Tumor location (p=0.20) and distance from the pleura (p=0.50) did not differ by smoking status.

Unadjusted, never-smokers had lower median PET SUVmax (2.8 vs. 4.2, p<0.001) and longer median VDT (536 vs. 213 days, p<0.001). These differences persisted after adjusting for age and sex alone (SUVmax p=0.004; VDT p=0.001), but were no longer significant once histology was added to the model (SUVmax p=0.08; VDT p=0.22).

Characteristic	Overall N = 442	Never Smoked N = 101	Smoked N = 341	p-value
Sex				<0.001
Female	242 (55%)	71 (70%)	171 (50%)	
Male	200 (45%)	30 (30%)	170 (50%)	
Age (y) *	70 (65 - 77)	69 (63 - 75)	70 (65 - 77)	0.04
Smoking Pack-years*	21 (3, 45)	0 (0, 0)	32 (16, 50)	<0.001
Cardiac disease	68 (15%)	8 (7.9%)	60 (18%)	0.03
Vascular disease	281 (64%)	55 (54%)	226 (66%)	0.04
COPD	142 (32%)	4 (4.0%)	138 (40%)	<0.001
Diabetes	94 (21%)	22 (22%)	72 (21%)	>0.9
Other Cancers	152 (34%)	37 (37%)	115 (34%)	0.7
Other diseases	253 (57%)	57 (56%)	196 (57%)	>0.9
Treatment				0.002
Radiation	74 (17%)	6 (5.9%)	68 (20%)	
Surgery	368 (83%)	95 (94%)	273 (80%)	
Histology				<0.001
Adenocarcinoma	292 (66%)	67 (66%)	225 (66%)	
Atypical Carcinoid	4 (0.9%)	2 (2.0%)	2 (0.6%)	
Squamous Cell	72 (16%)	0 (0%)	72 (21%)	
Typical Carcinoid	38 (8.6%)	25 (25%)	13 (3.8%)	
Other	36 (8.1%)	7 (6.9%)	29 (8.5%)	
Nodule Size (mm) *	15.0 (11.0, 20.5)	15.5 (10.8, 21.9)	14.8 (11.0, 20.3)	0.80
PET SUV*	3.7 (2.0 - 8.1)	2.8 (1.4 - 5.5)	4.2 (2.1 - 9.1)	<0.001
Volume Doubling Time (days)	247 (123 - 613)	536 (220 - 813)	213 (115 - 479)	<0.001

*Median (IQR)

