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Pre-operative nucleosome liquid biopsy for risk stratification of lung cancer

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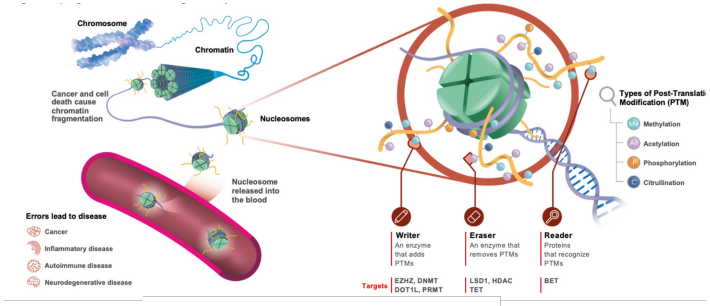
Purpose

Optimal identification of high-risk NSCLC remains unclear, with no approved blood tests and ctDNA approaches limited by performance, inefficiency, and cost. To address these limitations, this study aimed to enhance clinical risk stratification by employing preoperative nucleosome quantification via liquid biopsy.

Materials and Methods

A total of 558 patients with operable NSCLC from a previously enrolled cohort were stratified into high and low preoperative nucleosome H3K27me3-nucleosome groups. To dichotomize the continuous biomarker, we identified the optimal cut-off using a minimum log-rank p-value cutpoint analysis. The primary endpoint was overall survival(OS), with recurrence-free survival(RFS) as a secondary endpoint. Lung-RADS category and CT morphology (solid, part-solid, ground-glass opacity) were recorded and analyzed in prespecified subgroup analyses.



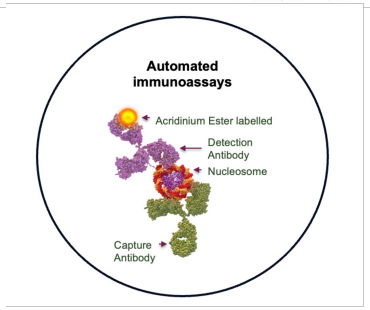


Figure 1 A. Nucleosomes and Epigenetic Modifications B.Nu.Q® Immunoassays

Reference
Chen P-H, Tsai T-M, Lu T-P, Lu H-H, Pamart D, Kotronoulas A, et al.
Accurate Diagnosis of High-Risk Pulmonary Nodules Using a Non-Invasive Epigenetic Biomarker Test. Cancers. 2025;17(6):916. doi: 10.3390/cancers17060916.

Results

In 558 operable NSCLC patients, pre-treatment plasma H3K27Me3-nucleosome stratified risk. Low levels had better recurrence than high (high vs low HR 2.36; 95% CI 1.13–4.92; p=0.02). At the optimal cut-point (n=496 low; n=62 high), both RFS and OS improved in the low group; Morphology (solid/part-solid/GGO) showed no clear group differences. High H3K27Me3-nucleosome level relate to older age, larger tumor size, higher stage and higher RADS status. High H3K27Me3 (cutoff 25.79) also predicted higher recurrence risk (HR 2.36; 95% CI 1.14–4.90; p=0.018) and lower OS (cutoff 20.93).

Variable	All (N=558)	H3K27Me3 high (N=62	H3K27Me3 low (N=496	p (high vs low)
Age, years	59.3 ± 11.6	65.0 ± 10.8	58.6 ± 11.6	<0.001
Tumor size, cm	1.8 ± 1.5	2.7 ± 2.2	1.7 ± 1.3	0.001
Gender				0.303
Female	370 (66.3%)	37 (59.7%)	333 (67.1%)	
Male	188 (33.7%)	25 (40.3%)	163 (32.9%)	
Stage				<0.001
0	74 (13.3%)	7 (11.3%)	67 (13.5%)	
1	425 (76.2%)	38 (61.3%)	387 (78.0%)	
2	32 (5.7%)	10 (16.1%)	22 (4.4%)	
3	27 (4.8%)	7 (11.3%)	20 (4.0%)	
RADS				<0.001
2	232 (41.6%)	20 (32.3%)	212 (42.7%)	
3	48 (8.6%)	3 (4.8%)	45 (9.1%)	
4A	70 (12.5%)	2 (3.2%)	68 (13.7%)	
4B+4X	208 (37.3%)	37 (59.7%)	171 (34.5%)	
Image				0.116
Solid	195 (34.9%)	29 (46.8%)	166 (33.5%)	
Part-Solid	140 (25.1%)	13 (21.0%)	127 (25.6%)	
ground glass opacity	223 (40.0%)	20 (32.3%)	203 (40.9%)	

Table 1. Key demographic data

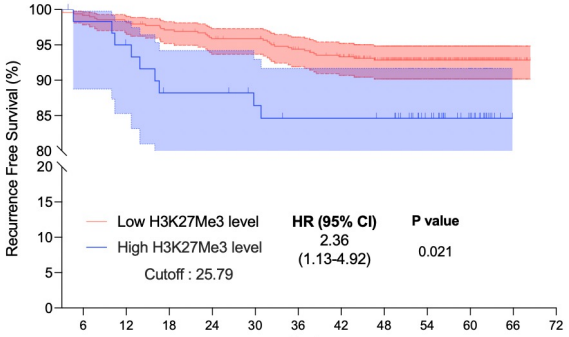


Figure 2. KM plot of recurrence free survival

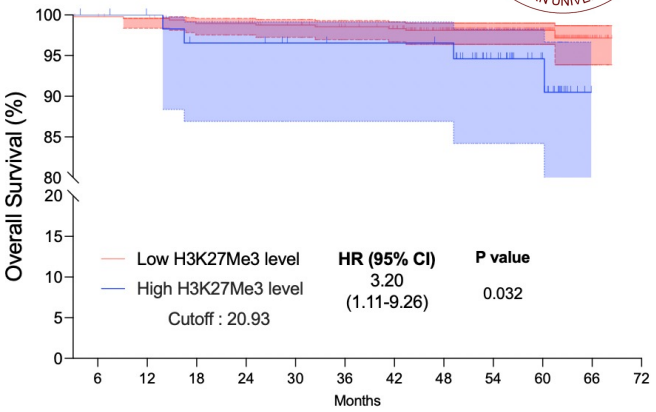


Figure 3. KM plot of overall survival

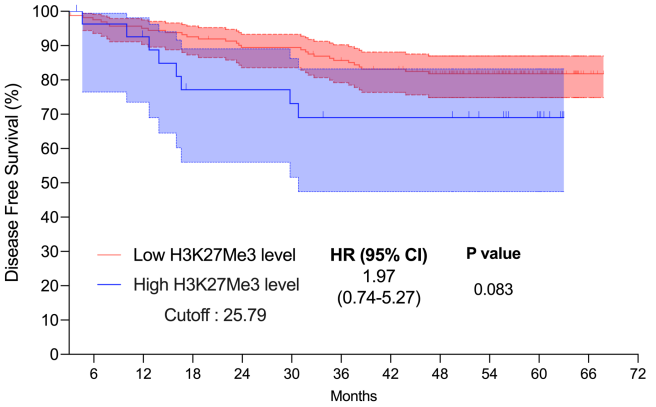


Figure 4. KM plot of recurrence free survival for solid component group

Conclusions

Preoperative H3K27Me3-nucleosome quantification via liquid biopsy strongly risk-stratifies operable NSCLC patients, identifying those most likely to benefit from closer follow-up or adjuvant therapy. High H3K27Me3-nucleosome levels predict poorer recurrence-free and overall survival outcomes, while low H3K27me3 levels indicate significantly better outcomes. This approach may also flag micrometastatic disease, guiding systemic-therapy decisions in high-risk patients.