Preoperative Nucleosome Liquid Biopsy for Prognostic Stratification in Lung Cancer With Treatment Correlation

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Purpose

Accurate identification of high-risk NSCLC remains challenging, with no approved blood-based assays available and ctDNA approaches limited by suboptimal performance, inefficiency, and cost. To overcome these barriers, this study investigated whether preoperative nucleosome quantification using liquid biopsy could improve clinical risk stratification.

Materials and Methods

We analyzed 558 patients with resectable NSCLC from a previously established cohort (Table 1). Preoperative plasma H3K27me3-nucleosome levels (Nu.Q® H3K27Me3 immunoassay, Belgian Volition;Fig1)stratified patients into high- and low-risk groups using a minimum log-rank p-value cutpoint. Recurrence-free survival was the primary endpoint, and overall survival was secondary. Prespecified subgroup analyses evaluated imaging (Lung-RADS 2/3 vs. 4A–4X; solid component presence) and treatment modifiers, including adjuvant ICI, chemotherapy, and EGFR-TKI. The tumors' pathological features and acoustic signal patterns for further subgroup analyses.
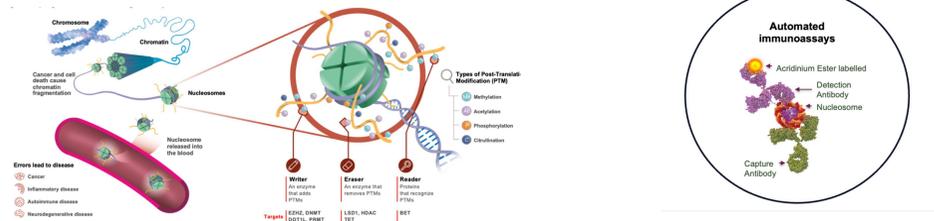

Figure 1 A. Nucleosomes and Epigenetic Modifications   B. Nu.Q® Immunoassays

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%)	

Table 1. Key demographic data

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.

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Results

In 558 operable NSCLC patients, pre-treatment plasma H3K27Me3-nucleosome stratified risk. Low levels had lower recurrence than high (high vs low HR 2.36; 95% CI 1.13–4.92; p=0.02, Fig 2A). At the optimal cut-point (n=496 low; n=62 high), both RFS and OS improved in the low group(Fig. 2); High preoperative H3K27me3-nucleosome levels predicts significantly worse recurrence-free survival in patients without adjuvant therapy, but not in those receiving adjuvant therapy.

Morphology (solid/part-solid) showed nearly significant with HR 2.816 (Fig.4) . High H3K27Me3-nucleosome level relate to older age, larger tumor size, higher stage and higher RADS status. The OS in different RADS showed with HR 3.019 and significant for group difference. (Fig.5)
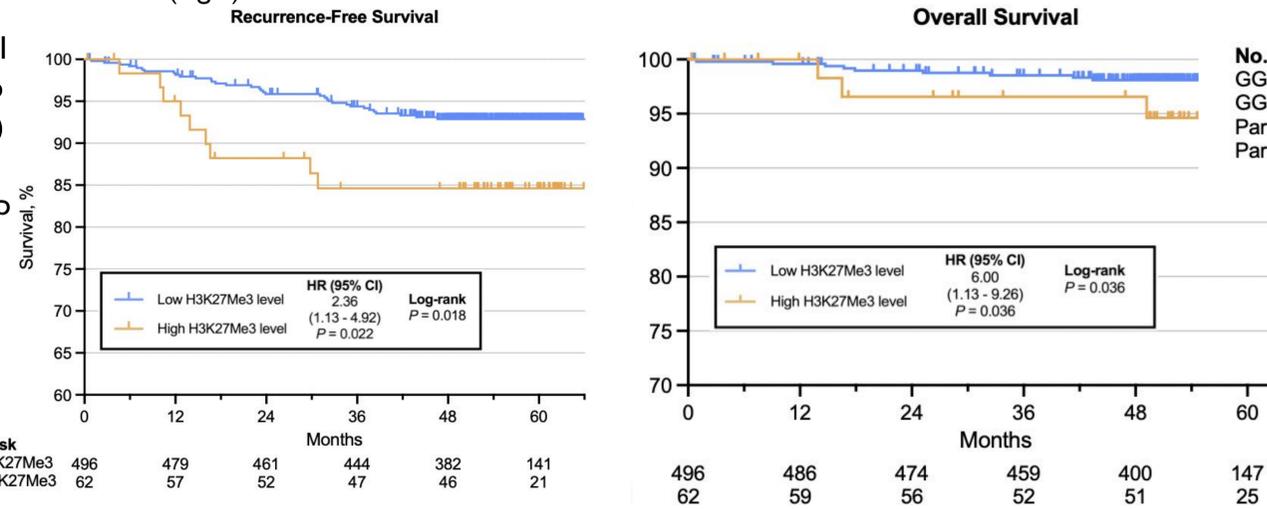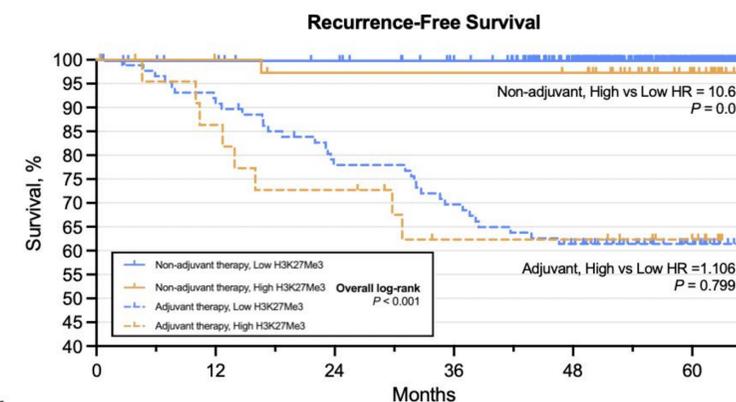

Figure 2. KM plot of recurrence free & Overall survival

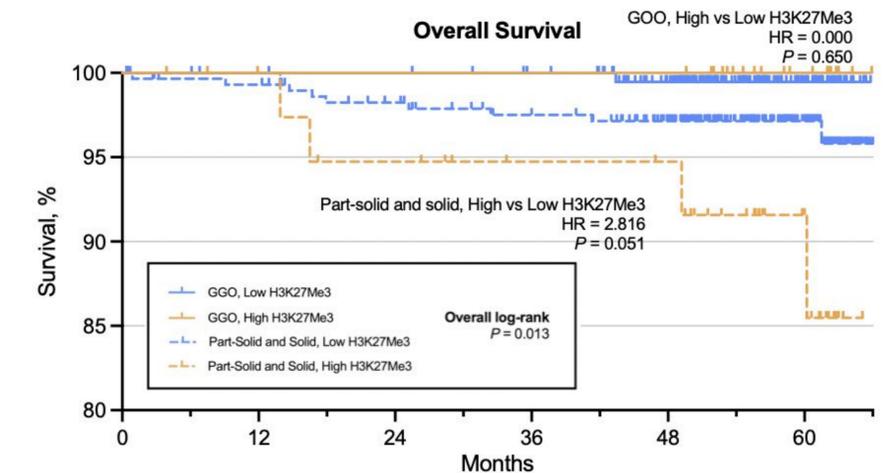Figure 3. KM plot of recurrence free with/without adjuvant treatment
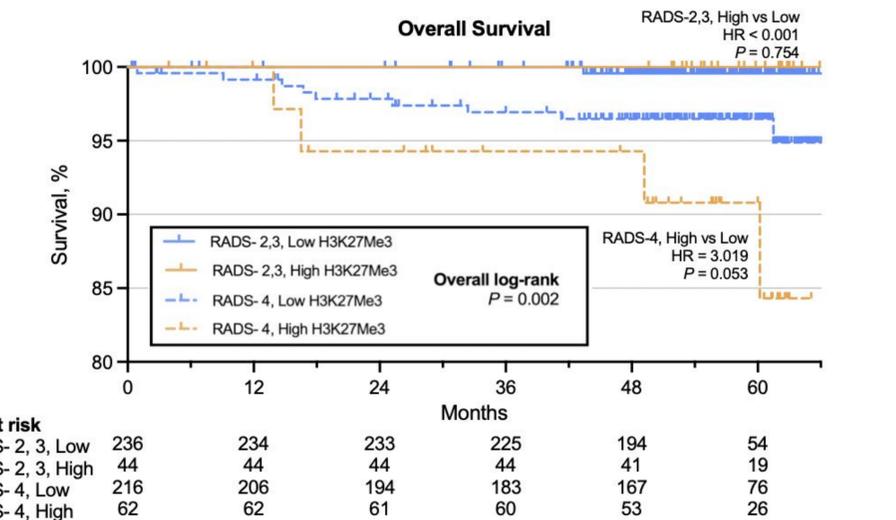

Figure 4. KM plot of OS with different morphology

Figure 5. KM plot of OS for different RADS

Conclusions

Preoperative H3K27me3-nucleosome quantification by liquid biopsy provides strong risk stratification in operable NSCLC, identifying patients who may benefit from closer surveillance or adjuvant therapy. Elevated H3K27me3-nucleosome levels are associated with worse recurrence-free and overall survival, whereas low levels are associated with significantly better outcomes. This biomarker may also help identify occult micrometastatic disease and support systemic treatment decision-making in high-risk patients.