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Purpose/Objective(s): Improved stratification is needed in HPV-negative HNSCC patients with intermediate and select high-risk disease. Significant molecular and immune response features have not been well-integrated with clinicopathologic factors to predict outcomes in this population. We sought to develop and validate an integrated molecular and clinicopathologic machine learning-based predictor for OS and PFS in this population to inform a future trial design. We hypothesize that our predictor will stratify patients better than a predictor derived from standard techniques.

Materials/Methods: We included 253 patients from TCGA with pathologic stage III-IVB (excluded T4b; included N3a) HPV-negative HNSCC with microscopic ENE and intermediate-risk disease (close margins/LVSI/PNI), treated with surgery and RT +/- chemotherapy. We split the data into training (70%) and testing (30%) sets. We identified 29 relevant molecular features (genomic: mutation vs. no mutation, transcriptomic: ≥ vs. < upper third quartile of log2 transformed mRNA expression) associated with significant HNSCC pathways, including cellular proliferation, cellular differentiation, cell cycle control, adhesion and invasion, antitumor immune response, and apoptosis. We also identified 19 demographic, behavioral, and clinicopathologic factors. We performed random survival forest modeling on OS and PFS and validated the machine learning-based predictor on the testing set, using ROC/AUC. Variables of importance were identified using the "Janitza" method. We also built a predictor using standard "best" Cox proportional hazards modeling and compared AUC values for OS and PFS versus our machine learning-based values.

Results: The median OS and PFS times were 4.4 years and 3 years, respectively. After accounting for pairwise correlations, we kept 38 variables for model building. Using the training set, significant variables of most importance for OS included age, female sex, PNI, LVSI, ≥ four pathologically involved lymph nodes, microscopic ENE, TP53 missense and nonsense mutations, and expression of PD1, LAG3, TIM3, L1CAM, CASP8, PIK3CA, E2F2, E2F4, FAT1, and NOTCH1 (all P-values < .05). Significant variables of importance for PFS included age, female sex, ≥ four pathologically involved lymph nodes, microscopic ENE, anatomic subsite, TP53 nonsense mutations, and expression of PD1, L1CAM, PIK3CA, and FAT1 (all P-values < .05). Using the testing set, we validated the 38-variable predictor on OS and PFS with AUC values of 0.82 and 0.75, respectively. In contrast, the "best" Cox models resulted in low AUC values for OS and PFS (0.65 and 0.66, respectively).

Conclusion: We developed and validated a machine learning-based predictor for OS and PFS that outperforms standard Cox predictors in HPV-negative HNSCC. This study provides a rationale to use the predictor as a stratifier in a prospective clinical trial of surgery, radiotherapy, and PD1 blockade in patients with microscopic ENE and intermediate-risk disease.

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Association of a Deep Learning Estimation of Chest Imaging Age With Survival in Patients With Non-Small Cell Lung Cancers Undergoing Radiation

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Purpose/Objective(s): Recent work has challenged emphasis of chronologic age in cancer treatment decision-making. For patients with non-small cell lung cancer (NSCLC), cardiopulmonary risk histories widely vary, possibly impacting "biologic age." We aimed to apply an externally-derived deep learning model to estimate chest imaging age (ChIA) from digitally reconstructed radiographs (DRRs) created from simulation computed tomography (CT) scans of patients with locally advanced NSCLC (LA-NSCLC). We hypothesized ChIA could serve as a prognostic imaging biomarker in this population.

Materials/Methods: We previously pretrained a Resnet34 convolutional neural network (CNN) to predict chronologic age using normal chest radiographs (CXRs) from public cohorts (CheXpert, NIH, and PadCHEST, n = 24,934). We fine-tuned the CNN to predict ChIA based on time to death using CXRs from 13,657 (25%) patients of the Prostate, Lung, Colorectal and Ovarian Cancer Trial, testing in the remaining 75% (n = 40,967) and the National Lung Screening Trial (n = 5,414). We applied the model to simulation CT DRRs in an institutional cohort of patients with LA-NSCLC receiving lung radiation (Lung-RT, n = 847). Recursive partitioning analysis (RPA) identified a cut point associated with overall survival (OS) in Lung-RT, above which patients were classified ChIA-high. We evaluated association between ChIA and OS using Kaplan-Meier calculations and Cox regression analyses and then validated in the multi-institutional RTOG 0617 trial (n = 460).

Results: In Lung-RT, median age was 67 (Range 21-90) years and median ChIA was 67 (Range 57-80) years. In RTOG 0617, median age was 64 (37-83) years, and median ChIA was 66 (52-77) years. Age/ChIA correlation coefficients were 0.29 (95% CI 0.23-0.35, $P < 0.001$) and 0.32 (95% CI 0.23-0.40, $P < 0.001$), respectively. Table 1 shows OS after median follow-up in Lung-RT of 56 (95% CI 53-58) months, and in RTOG 0617 of 36 (95% CI 32-37) months. In Lung-RT, adjusting for age, race, and sex, ChIA-high patients had HR 1.22 (95% CI 1.00-1.49, $P = 0.049$) for OS. In RTOG 0617, adjusting for trial arm, age, gender, race, ethnicity, performance status, histology, and stage, ChIA-high patients had HR 1.41 (95% CI 1.02-1.91, $P = 0.037$) for OS.

Conclusion: Our work validates use of a deep learning CXR-based model to predict ChIA using DRRs created from routine simulation CTs of patients with LA-NSCLC. In an institutional and multi-institutional trial cohort, ChIA-high patients had worse survival than ChIA-low patients, suggesting potential use of ChIA as a prognostic imaging biomarker enabling de-emphasis of chronologic age in treatment decision-making.

Abstract 1038 – Table 1: ChIA and OS in lung-RT and RTOG 0617

	Lung-RT			RTOG 0617		
	ChIA-high	ChIA-low	*P* value	ChIA-high	ChIA-low	*P* value
Median OS in months (95% CI)	27 (21-32)	36 (32-46)	0.002	18 (14-22)	27 (23-30)	0.009
3-year OS	40%	50%	0.003	28%	40%	0.006

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