Quantitative Digital Pathology Reveals Prognostic Biomarker Performance Varies by Tumor Microenvironment Location and Patient Sex in Lung Squamous Cell Carcinoma

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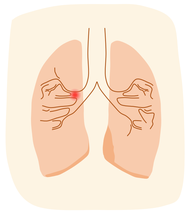
Background and Objectives

Lung squamous cell carcinoma (LUSC)

Type of non-small cell lung carcinoma (NSCLC)

Accounts for 24 % of all lung cancers



Affects larger airways of the lungs

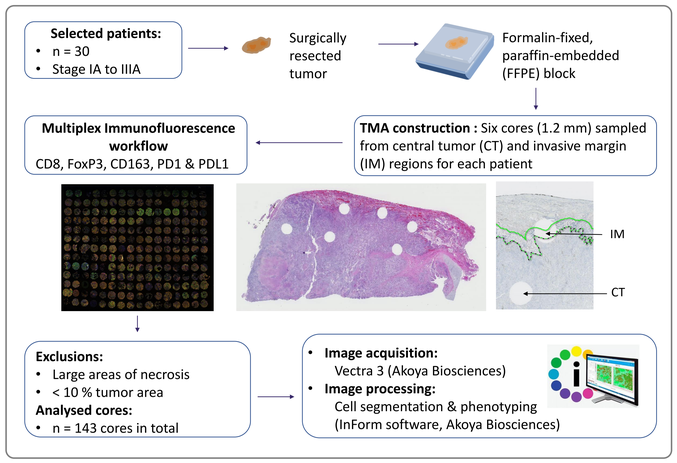
Median 5-yr survival:
50 % for stage IA
20 % for stage IIIA

- Most surgically resected LUSCs relapse and adjuvant chemotherapy improves 5-year survival only by ~5%.
- Ongoing clinical trials are evaluating the efficacy of adjuvant immune checkpoint blockade in resectable LUSC, but the field lacks robust biomarkers to select patients most likely to benefit.
- Inter-sex differences have been demonstrated in response to Immunotherapies and expression of biomarkers in the tumor microenvironment (TME).

Objectives:
- Evaluate TME location in biomarker performance
- Evaluate potential confounders of biomarker interpretation

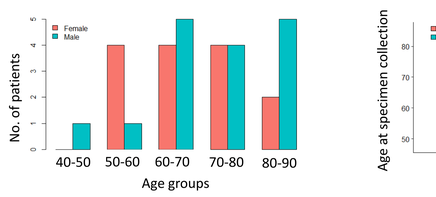
Methodology

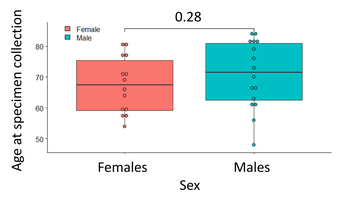
Patient selection:
- Patients with LUSC diagnosis
- No presurgical treatment
- Surgical resection at Johns Hopkins Hospital (2003 – 2006)



Results

No significant difference between median ages of females and males





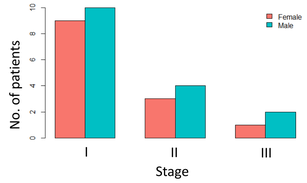
	40-50	50-60	60-70	70-80	80-90	Total
F	0	4	4	4	2	14
M	1	1	5	4	5	16

Total patients: 30

p-value computed by Mann Whitney Wilcoxon Test

Distribution of patients between different stages of disease by sex (A) and age (B)

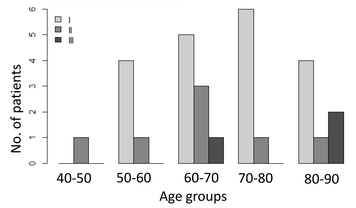
A) Stage ~ Sex



	I	II	III	Total in each sex
F	9 (69 %)	3 (23 %)	1 (7 %)	13
M	10 (62 %)	4 (25 %)	2 (12 %)	16

Total patients: 29

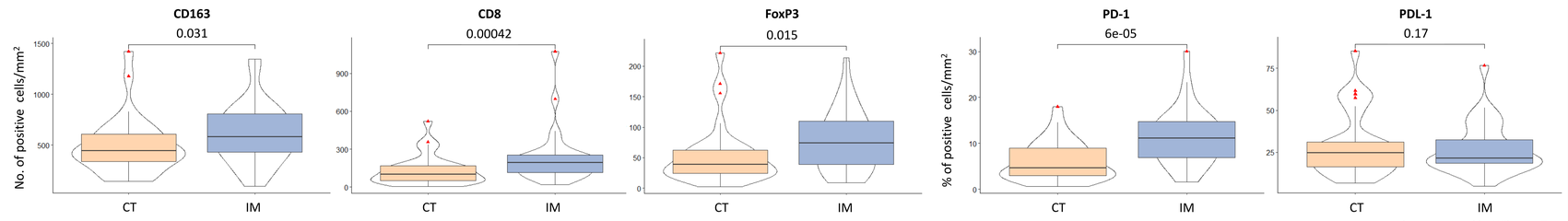
B) Stage ~ Age group



	40-50	50-60	60-70	70-80	80-90	Total in each stage
I	0 (0 %)	4 (21 %)	5 (26 %)	6 (31 %)	4 (21 %)	19
II	1 (14 %)	1 (14 %)	3 (42 %)	1 (14 %)	1 (14 %)	7
III	0 (0 %)	0 (0 %)	1 (33 %)	0 (0 %)	2 (66 %)	3

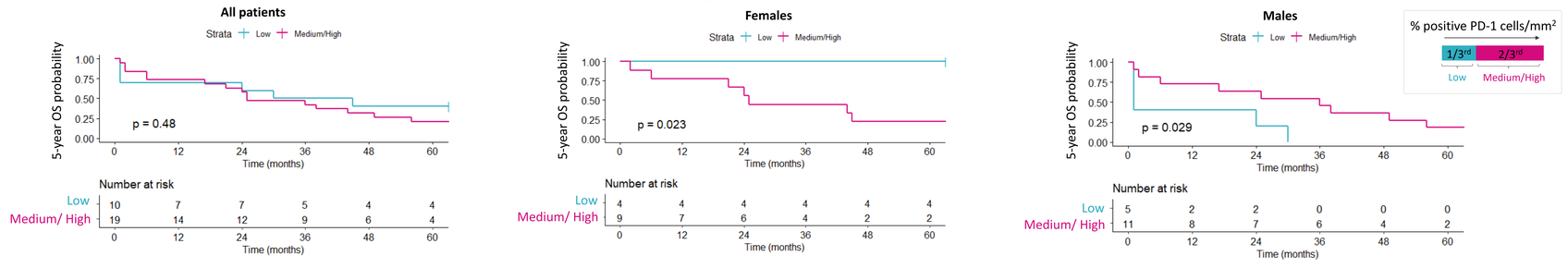
Total patients: 29

Expression of immune cells markers varies with TME location



p-values computed by Wilcoxon Test

PD-1 expression in invasive margin impacts survival differently in females vs males



Survival analysis using Kaplan Meier analysis; p-values computed by Log-Rank Sum Test

Conclusions

- Immune cell densities were significantly higher at the IM than in CT for CD8+ T cells, Foxp3+ regulatory T cells, and CD163+ macrophages. The proportion of cells expressing the targetable immune checkpoint molecule PD-1 was also significantly enriched at the IM
- High proportion of PD-1 cells in the invasive margin were associated with a poor OS in females, but a better OS in males.
- While further validation and mechanistic exploration are needed, this preliminary data demonstrates the power of digital pathology in identifying biomarkers to aid patient management and highlights that spatial heterogeneity in the TME and patient sex may be critical factors in interpretation of tumor microenvironment biomarkers.

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