Identifying Spatial Predictors of Survival in Lung and Ovarian Cancer Patients Using Penalized Cox and AFT Models

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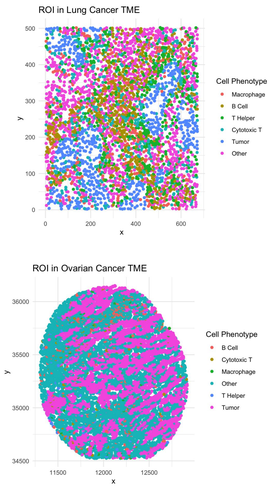
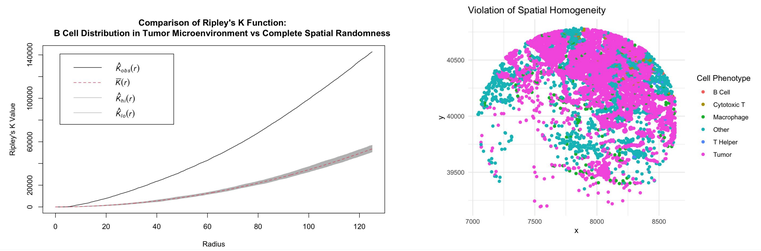
Introduction

- **Ovarian and lung cancers** present significant treatment challenges, which necessitates research into factors that influence patient survival. Analyzing the **spatial distributions of cells** within the tumor microenvironment (TME) can help identify predictors of survival.
- **Multiplex Imaging** allows for direct observation of cell phenotypes within a tissue sample at single-cell resolution while preserving the spatial context.
- The lung cancer dataset includes 761 images for **153 patients**. The ovarian cancer dataset includes 128 images for **128 patients**. The datasets include information about the spatial location and type of each cell as well as other demographic variables.
- **Ripley's K-function** assesses spatial clustering of a particular cell type or between two cell types.



- The **permuted K-function** addresses spatial inhomogeneity in multiplex images by randomly reassigning cell types in each image while keeping all positions fixed. This represents the K-function under spatial randomness.



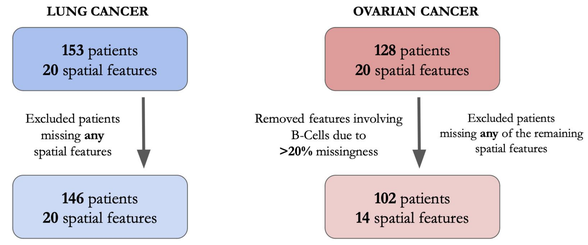
Research Questions

- How do the **Cox proportional hazards model** and the **Accelerated Failure Time (AFT) model** compare in predicting survival in lung and ovarian cancer patients?
- Which **spatial features** are significant predictors of survival in lung and ovarian cancer patients?

Data

- **Cancer Types:** Used both the lung and ovarian cancer datasets
- **Cell Types:** Included tumor, B cell, macrophage, cytotoxic T, and T helper cells
- **Spatial Features:** Calculated cell proportions and Ripley's K and K-cross functions
- **Demographic Variables:** Age, gender, and stage at diagnosis was included in the lung cancer data, while only age was included for the ovarian cancer data.
- **Image Selection:** The image with the greatest number of cells was selected for each lung cancer patient.

Data Preprocessing



Methods

Cox Proportional Hazards Model

$$\lambda_i(t) = \lambda_0(t)e^{\beta^T Z_i}$$

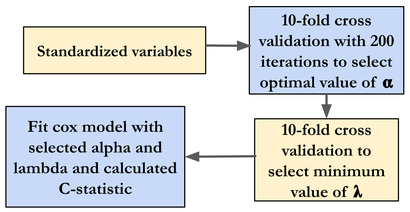
- The Cox model is semi-parametric and models patient risk, or hazard, at a time point, indirectly implying survival time.

Accelerated Failure Time Model (AFT)

$$\log T_i = \beta^T Z_i + e_i$$

- We chose a semi-parametric AFT model, which does not assume an underlying error distribution for the model. The AFT model directly models the logarithm of survival time.

Elastic Net Penalization for Variable Selection



	Cox	AFT
Lung	0.05	0.05
Ovarian	0.95	0.95

Figure 1. α values selected by cross validation

Harrell's C-Statistic for Model Comparison

- The proportion of subject pairs whose observed and predicted outcomes agree/are concordant with each other.

$$c = \frac{\sum_{i \neq j} 1\{\eta_i < \eta_j\}1\{T_i > T_j\}d_j}{\sum_{i \neq j} 1\{T_i > T_j\}d_j}$$

Results

C-Statistic for Cox and AFT Models for Each Dataset

Lung		Ovarian	
Cox	AFT	Cox	AFT
0.66	0.33	0.64	0.38

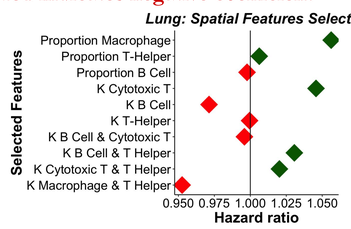
- The Cox model had better predictive performance for both datasets.

Cox Model Results

*Green indicates positive coefficient, red indicates negative coefficient

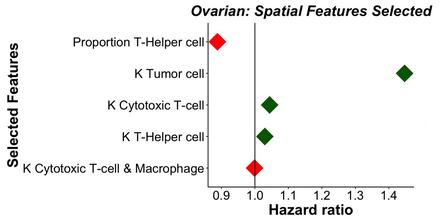
Lung Cancer

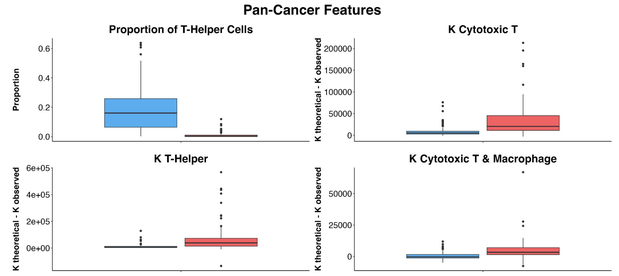
1. Age
2. Gender
3. Stage 3+
4. Proportion Macrophage
5. Proportion T-Helper
6. Proportion B Cell
7. K Cytotoxic T
8. K B Cell
9. K T-Helper
10. K B Cell & Cytotoxic T
11. K B Cell & T Helper
12. K Cytotoxic T & T-Helper
13. K Macrophage & T-Helper



Ovarian Cancer

1. Age
2. Proportion T-Helper
3. K Tumor
4. K Cytotoxic T
5. K T-Helper
6. K Cytotoxic T & Macrophage





Conclusions

Lung

- Tertiary lymphoid structures (TLS) with accumulations of **B and Cytotoxic T cells** in the TME are associated with improved survival and anti-tumor immunity in cancer patients.
- A **high density and frequency of B Cells** is associated with increased survival and delayed tumor progression.

Ovarian

- Previous research is consistent with **tumor cell clustering** being associated with lower survival.
- Previous research has also found that ovarian cancer patients with **high abundance and low spatial clustering of T-cell subsets** had highest survival.

Limitations & Future Research

Limitations

- Doesn't include other lifestyle and demographic variables that can affect survival
- The missingness in the ovarian data set led us to exclude B-cells from the analysis
- Limited sample size and only used **one image** per patient.

Future Research

- Using other feature selection approaches
- Accounting for multiple images per patient: mixed effects survival models, combining images
- Use other spatial statistics beyond K functions

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