Spatial representation of deep-learning markers show additional prognostic value in breast cancer patients

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Aims

This study aims to investigate the spatial distribution of an AI-based prognostic marker (DeepGrade) within tumour areas to identify patterns of spatial heterogeneity

Introduction

Intra-tumour heterogeneity may contribute to an increased risk of recurrence by promoting treatment resistance.

Deep-learning enables systematic extraction of prognostic information from H&E-stained whole-slide histopathology images (WSIs). However, most approaches aggregate local tile-level features without incorporating spatial context.

DeepGrade[1] is an AI-based tool for early breast cancer, trained on NHG1 and NHG3 cases. It stratifies patients into high- and low-risk groups, demonstrating strong prognostic performance.



Figure 1. Area definitions. Example of WSIs with tumor center and tumor front areas indicated as well as cluster area representation.

References:

1. Wang, Y. et al. Improved breast cancer histological grading using deep learning. Ann Oncol. 2022.
2. Chen, R. J. et al. Towards a general-purpose foundation model for computational pathology. Nat. Med. 2024.

Methods

Data preprocessing: Each WSI was preprocessed to generate macenko color normalised tiles of 224 px each

Tumor area definitions: A cancer detection model was developped using Vit-based foundation model (UNI[2]) and tile-level predictions. Tumor front areas were defined as approximately one field of view at 20X representing 0.9mm to 1.3mm.

Model predictions: Initial DeepGrade[1] model was updated using UNI[2] extractor, and tile level predictions. Tiles were defined as high or low risk using NHG1 and NHG3 wearkly supervised labels.

Cluster identification: A cluster was defined if over two-thirds of the surrounding tiles from a given high-risk tile was also high risk.

Patient characterization: Patients from 2 Swedish regions and 5 hospitals with invasive primary breast cancer diagnosed between 2012 and 2020.

Statistical analyses: Difference in proportion of DeepGrade-high tiles within the tumour front area was measured using t-test. Survival analyses were performed in the low-risk group of patients, defined as ER+/HER2-, lymph node negative, NHG1/2. Kaplan Meier curves and univariate cox proportional hazard ratios were measured.

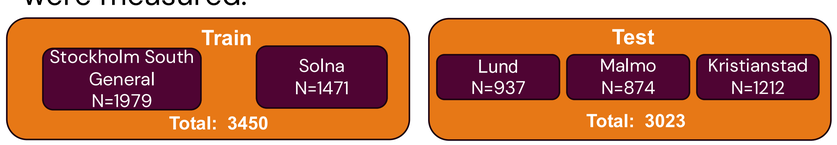


Figure 2. Train and test sets used. Invasive primary breast cancer patients from hospitals in two Swedish regions: Stockholm (train) and Scania (test)

Results

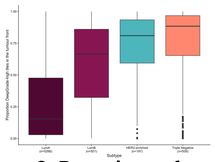


Figure 3. Box plots of DeepGrade high tiles by tumour subtype. There was a significant difference in the proportion of DeepGrade-high tiles in the tumor front between all subtypes except betwee Her2—enriched and triple negative subtypes

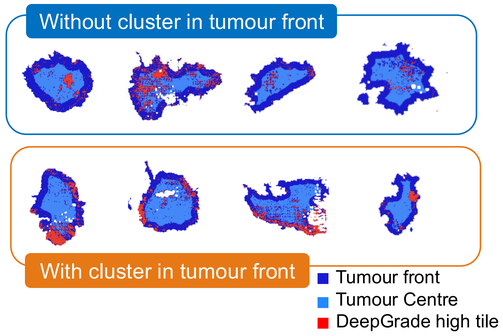
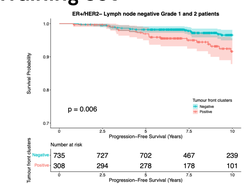


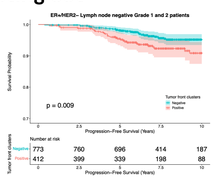
Figure 4. Representative WSIs

Training set



Variable	Level	N	HR (95% CI)	p
Age		1043	0.99 (0.97, 1.02)	0.700
Tumour size	<20mm	778	Reference	
	>=20mm	265	2.49 (1.30, 4.76)	0.006
Tumour_front_cluster	Negative	735	Reference	
	Positive	308	1.96 (1.03, 3.74)	0.040

Testing set



Variable	Level	N	HR (95% CI)	p
Age		1185	0.98 (0.96, 1.00)	0.094
Tumour size	<20mm	918	Reference	
	>=20mm	267	1.67 (0.96, 2.90)	0.068
Tumour_front_cluster	Negative	773	Reference	
	Positive	412	1.88 (1.12, 3.13)	0.016

Figure 5. Survival analyses. The presence of DeepGrade-high tile clusters in the tumour front was prognostic in low-risk group patients.

Conclusions

The presence of DeepGrade-high clusters within the tumour front constitutes an independent prognostic marker. This highlights that the spatial distribution of identified AI-markers within histology slides requires stronger attention

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