Development of TLS Detect, a deep learning tool to predict the presence of tertiary lymphoid structures (TLS) on pan-tumor routine whole slide images

Abstract #4

OWKIN TLS Detect

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Background

Tertiary Lymphoid Structures (TLS) are organised immune cell aggregates comprising B cells, T cells and dendritic cells. In solid tumours, their presence in the tumour microenvironment has been linked to improved survival and mature TLS have been related to increased responses to immunotherapy.

The assessment of TLS by pathologists is time-consuming and often requires additional sections using immunohistochemistry (IHC) or immunofluorescence stainings.

To address this challenge, we developed TLS Detect based on a deep-learning model, to automatically predict the presence or absence of TLS in routine haematoxylin-eosin (H&E) ± saffron (HES)-stained digital pathology slides.

Objectives

Train a model on a pancancer dataset with robust patient level labels.

Evaluate the transferability of model performances to a new pancreatic indication.

Method

Data and annotations

Training on BIP: Bergo Immuno Pancancer cohort, annotated using HES and CD20 IHC paired slides following Bergonié standard[1].

Validation TCGA-PDAC: Subset of TCGA-PAAD cohort filtering with only the ductal adenocarcinoma samples annotated by a pathologist using the H&E slide and validated by another pathologist.

	Lung (NSCLC)	HNSCC	Sarcoma	Bladder	Colon	ORL	other
BIP	376	51	46	31	26	12	133

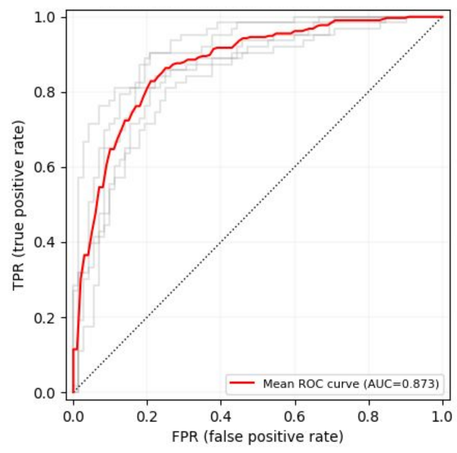
	Cohort name	Number of cases	Number of slides	TLS+ slides n (%)
Training cohorts	BIP	675	675	(47.58%)
Validation cohorts	TCGA-PDAC	157	182	(70.3%)

Model

It combines self supervised learning to extract features from each image, and a multiple instance learning model, Chowder[2], to predict TLS status from these features.

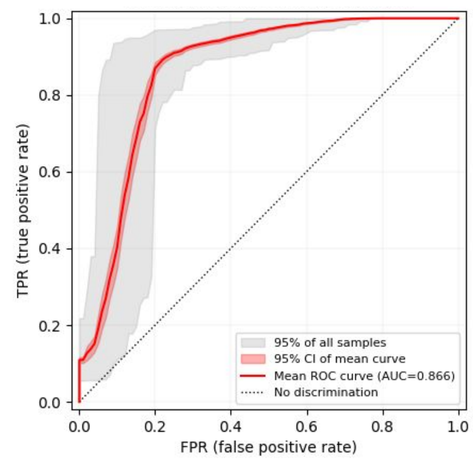
Results

Training on BIP cohort: evaluating
AUC of 0.87



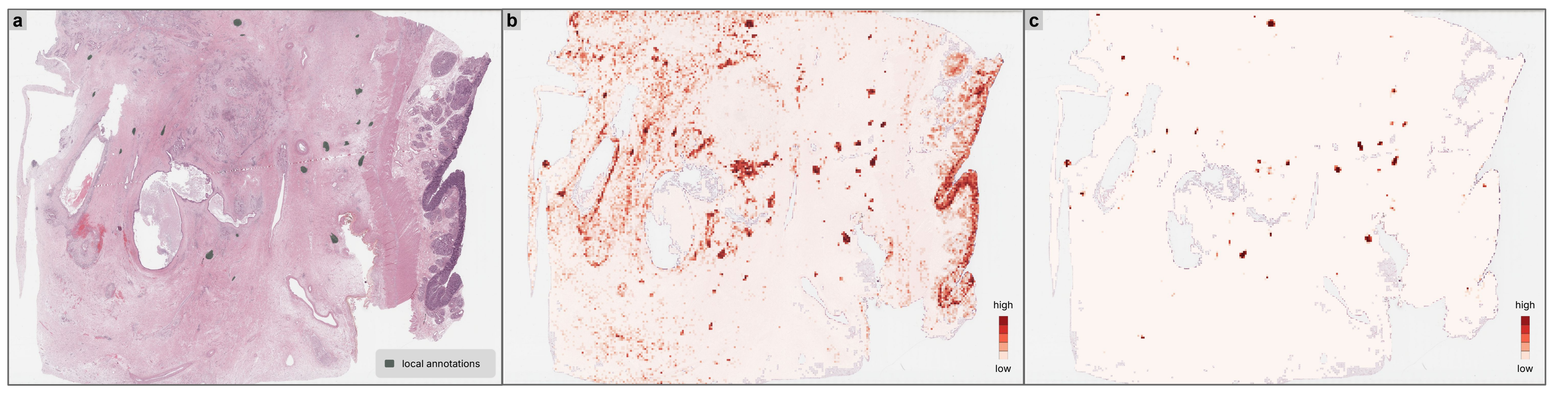
	Sensitivity @0.5	Specificity @0.5	PPV @0.5	NPV @0.5
TLS Detect	**0.82** ±0.04	**0.81** ±0.06	**0.79** ±0.05	**0.84** ±0.03

Validating on TCGA PDAC: patient classification
AUC of 0.87



	Sensitivity @0.5	Specificity @0.5	PPV @0.5	NPV @0.5
TLS Detect	**0.98** [0.96-1.00]	**0.43** [0.29-0.56]	**0. 80** [0.74-0.86]	**0.92** [0.81-1.00]

Interpretability: the model well correlates the local position of TLS using slide level annotations



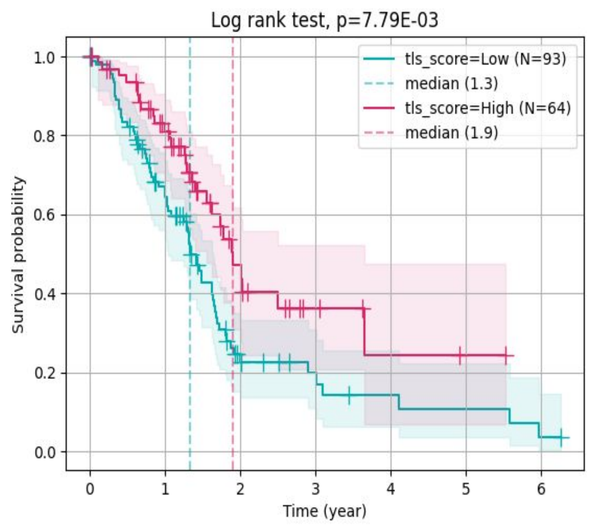
a: Input slide with local annotation for visual check. These annotations were not used during training.

b: Heatmap interpretability: Initialisation of the model with pretrained weights to classify presence/absence of lymphocytes.

c: Heatmap interpretability: Finetuned model after semi-supervised training that correctly correlates the tiles containing TLS with the global label

Results

Validating on TCGA PDAC: prognostic value of the model



To validate the prognosis value of our model on a PDAC cohort, we performed a survival analysis on the overall survival of patients.

We obtained a HR of 0.62 (ci: [0.44, 0.86] , p=0.018).

Discussion

- → Cross-validation of the model demonstrated robust performance, indicating consistent reliability across multiple trainings.
- → The model achieved an AUC of 0.86 in external validation, translating in a high sensitivity, highlighting the model's ability to generalise beyond training data.
- → Limitations of the model include the false detection of confounding structures such as mucosa-associated lymphoid tissue (MALT) and lymph nodes.
- → As a research tool, TLS Detect offers a standardized approach to screen for the presence of tertiary lymphoid structures based on H&E whole slide image analysis, with robust performance across different cohorts.

References & acknowledgements

1. Vanhersecke L, et al. Standardized pathology screening of mature tertiary lymphoid structures in cancers. Laboratory Investigation 103.5, 100063 (2023).
2. Courtiol, Pierre, et al. "Classification and disease localization in histopathology using only global labels: A weakly-supervised approach." arXiv preprint arXiv:1802.02212 (2018).

Conclusions

Our deep learning model is able to accurately predict the presence of TLS on H&E/HES stained histology slides

TLS Detect provides a simple and standardized approach to screen for presence of TLS from routine WSIs and will support the adoption of this biomarker

Future work should focus on refining the local detection of TLS, enhancing the precision of this innovative approach in the field of oncology