Deep learning tertiary lymphoid structures detection on HES/H&E slides and association with survival outcome in sarcoma

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Background

→**Sarcomas** represent a group of rare and heterogenous cancers presenting significant challenges in diagnosis and treatment.

→**Tertiary lymphoid structures (TLS)** are organized T and B immune aggregates which have been associated with improved **survival**, and mature TLS has emerged as predictive biomarker for **immunotherapy response** in various cancers, including sarcomas.[1,2].

→Current **TLS detection methods** vary across centers, employing different techniques such as hematoxylin and eosin (H&E)/hematoxylin-eosin-saffron (HES), immunohistochemistry (IHC) or immunofluorescence[3].

→Pathological screening is both laborious and time-consuming, and often requires additional paraffin sections, leading to consumption of tumour material.

Objectives

→Develop a **deep-learning model to accurately detect and localize TLS** on H&E/HES-stained whole slide images (WSI) of sarcoma tumors.

→Validate the **prognostic value** of this automatic TLS quantification in sarcomas.

Data

Training cohort:

PERISARC, sarcomas (N=212 patients), HES slides
→Patient-level annotations: 162 TLS+, 50 TLS-
→Local annotations: 2 959 TLS annotations
→TLS annotated using HES and CD20 staining by IHC.

Validation cohorts:

PEMBROSARC, sarcomas (N=234 patients), HES slides
→Patient-level annotations: 46 TLS+, 188 TLS-
→TLS annotated using HES, CD3 and CD20 staining by IHC.

TCGA-SARC, sarcomas (N=254 patients), H&E slides
→Overall survival data.

TCGA-PDAC, adenocarcinomas (N=151 patients, 182 slides), H&E slides
→Slide-level annotations: 128 TLS+, 54 TLS-
→Local annotations: 1140 TLS annotations
→TLS annotated using H&E.

Method

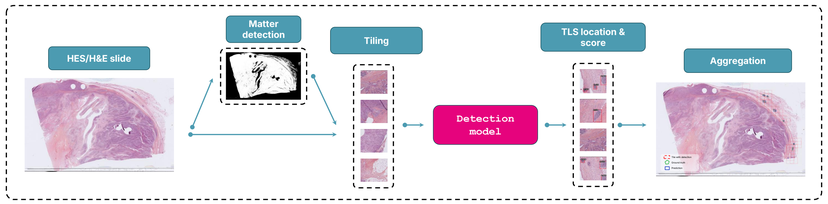
→Input slides are partitioned in smaller tiles of size 1768x1768 px at magnification x10 (~1 µm/pix).

→Our model is an object detection deep learning architecture with Phikon[4] backbone (Owkin's self-supervised feature extractor pretrained on 40M slides).

→For each patient, the model detects TLS by providing a bounding box around each structure as well as a confidence score.

→The model is trained on 16k tiles of a 70% split of the patients on the training cohort. We also used positive sampling and histology-specific augmentation methods[5]. The two last layers of the backbone were unfrozen.

Pipeline TLS detection



Results: Detection performance

→We evaluate the model performance on local detection and on patient global TLS status prediction, depending on the granularity of annotations of each dataset.

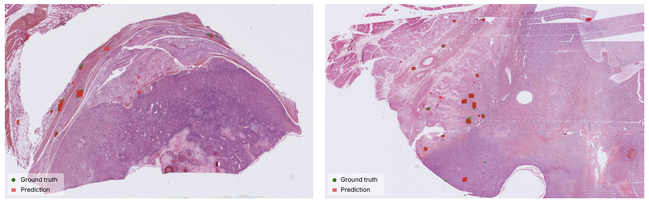
→For local detection performance, we report the average precision (AP) as well as the the recall for a threshold of 0.5 on the confidence scores.

→To aggregate local predictions to a patient level TLS status prediction, we select the maximum value of detections confidence scores for each slide.

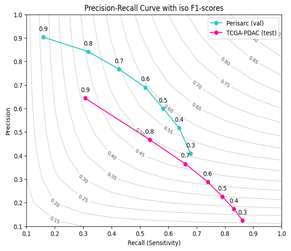
→The performance reported on TCGA-PDAC shows the model's ability to generalize to other indications than the one seen in training.

Cohort	Local Detection		Patient status prediction
	Average Precision (AP)	Recall @ 0.5	ROC-AUC
Perisarc test-set	0.54 [0.484, 0.602]	0.6 [0.571, 0.641]	0.87 [0.832, 0.913]
Pembrosarc	NA	NA	0.84 [0.828, 0.844]
TCGA-PDAC	0.46 [0.406, 0.524]	0.8 [0.764, 0.854]	0.90 [0.891, 0.901]

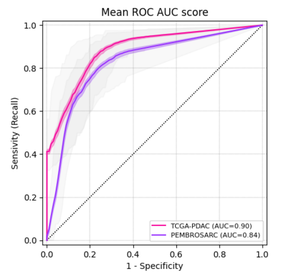
Predictions sample on Perisarc validation set



Precision-Recall Curve for different detection thresholds



Patient-level performance

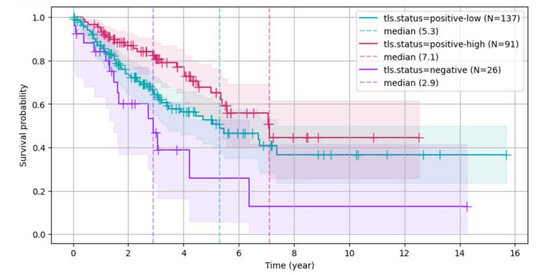


Results: Prognosis value on external cohort

→To validate the prognosis value of our model on a sarcoma cohort, we tested our model on the TCGA-SARC cohort and performed a survival analysis on the overall survival of patients.

→We defined 3 groups based on the median number of predicted TLS per positive slide:
→TLS negative (no predicted TLS)
→TLS positive-low (less than 9 TLS predicted)
→TLS positive-high (more than 9 TLS predicted)

KM Curves for TCGA-SARC (N=254)



→Predicted TLS presence on TCGA-SARC is significantly associated with a **better overall survival** (HR=0.392, 95% CI [0.180, 0.854], p=0.018).

→Among positives, TLS-high slides are significantly associated with a better overall survival than TLS-low slides (HR=0.612, 95% CI [0.402,0.931], p=0.022).

References

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[4] Filiot A, et al. Scaling self-supervised learning for histopathology with masked image modeling. medRxiv 2023-07 (2023).

[5] Shen Y, et al. Randstainna: Learning stain-agnostic features from histology slides by bridging stain augmentation and normalization. International Conference on Medical Image Computing and Computer-Assisted Intervention. Cham: Springer Nature Switzerland (2022).

Conclusions

Our deep learning model is able to **accurately detect TLS on H&E/HES** stained histology slides of sarcoma patients.

Our model provides **robust** TLS assessment, enabling more **uniform clinical studies** and potential integration into **routine diagnostics** while **preserving tumor material**.

Using an external dataset of sarcoma patients, we showed that our model's prediction holds **significant prognostic value** in sarcomas.

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