Automatic segmentation of tumor infiltrating lymphocytes, neoplastic tissue and stroma in whole slide breast histopathology using residual neural networks.

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Introduction

Tumor infiltrating lymphocytes consist of all lymphocytic populations that have invaded the tumor tissue (both lymphocytes and plasma cells). They have been described in a number of solid tumors, including the breast cancer, and are emerging as an important biomarker in predicting the efficacy and outcome of treatment. In the CLEOPATRA study of advanced HER2-positive breast cancer TIL values were significantly associated with overall survival [1]. There is also evidence that TNBC patients with residual disease, who have higher number of TILs, have more favorable outcomes of therapy.

TILs have been shown to provide prognostic and potentially predictive value, particularly in triple-negative and HER 2-overexpressing BC. International TILs Working Group 2014 has proposed recommendations for integrating this parameter in standard histopathological practice. [2]

Digital image analysis has been proposed as a means to increase the precision of TILs quantification [3].

Aims

Our aim was to streamline TILs segmentation and quantification in breast cancer histopathology slides by using an automatic classification model.

Methods

We worked with breast histopathology slides provided by the Pathomorphology Unit University Hospital. Image acquisition was done using an Olympus BX53 microscope. Slides were subsequently divided into smaller images. 281 representative samples were chosen and segmented into three categories: TILs, neoplastic cells and stroma according to the criteria defined by the International Working Group for TILs in Breast Cancer (2014), with the use of Labelbox segmentation tools. The masks and images were used to train a neural network based on ResNet34 architecture using Python Fastai. Additionally, the data was augmented using built in transformations (DeterministicDihedral, Zoom, Warp, Contrast and RandomErasing) to compensate for small number of images and better generalize patterns. Following training and optimalization the model was tested on 21 new images. TILs percentage area, derived from pixel counts, was compared between human and machine segmented images.

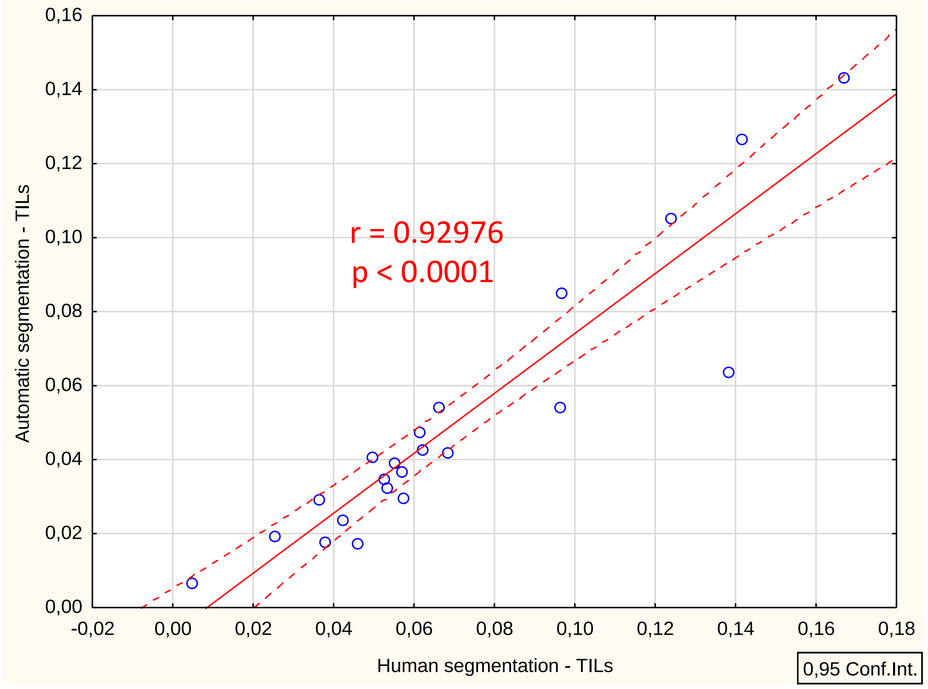

Fig.1 – Correlation of TIL area based on human segmentation to area from automatic segmentation.

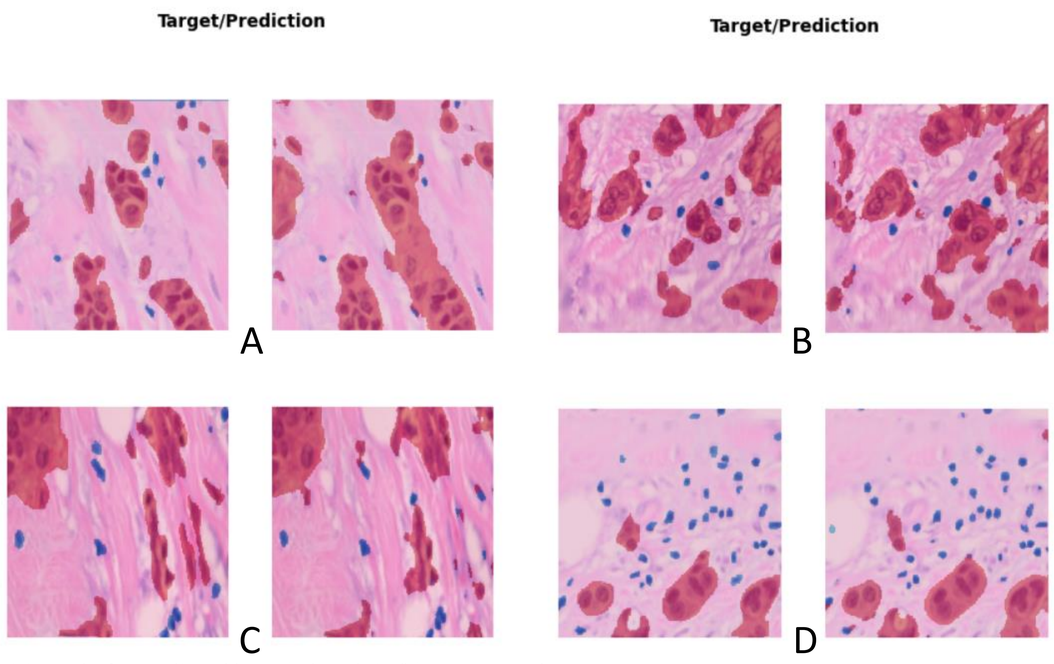

Fig.2 – Examples of segmented images (Blue – TIL / Red – neoplastic cells/ Transparent - stroma).

Results

The pretrained ResNet34 model has undergone 20 epochs of fine tuning, resulting in final training and validations loss of 0.301and 0.290 respectively (Fig. 3). We have obtained a strong correlation between human and machine segmented TIL area (r = 0.93, p < 0.0001, Fig. 1).

Fig. 3 – Training and validation loss during training, final train_loss = 0.301, val_loss = 0.290.

Conclusions

We were able to obtain TILs area predictions highly correlating with manual segmented images, in spite of high loss values, which were probably connected with insufficient data quantity. We have also tried using more robust ResNet architectures (ResNet50 and ResNet101), however with worse results, again due to small amount od images and computational limitations.

All in all, we think that the use of this model could improve the diagnostic process, allowing faster and more frequent assessment of the TILs area which is important in terms of dynamically developing cancer immunotherapy.

As a next step we would like to test this approach in relation to the clinical status of the patients. Finally, our goal would be to develop a fully automated workflow for classifying TILs and use it as a prognostic biomarker.

References

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