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# Prediction of the recurrence risk in stage IB-IIC cutaneous melanoma through artificial intelligence (AI) techniques on hematoxylin-eosin stain (H&E) images

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## Introduction

Malignant melanoma is one of the most aggressive skin cancers [1]. Characteristics of the primary tumor, such as location, stage, ulceration, mitotic index as well as loco-regional lymph node involvement play a key role in the prediction of the risk of recurrence in melanoma patients [2].

Since the early 1990s, a crucial advance in the management of melanoma patients has involved the sentinel lymph node (SLN) biopsy technique. The frequency of SLN metastasis is growing with the increase in thickness of primary lesion and other clinic-pathologic prognostic factors, such as ulceration and number of mitoses. Although the new AJCC classification has improved the assessment of recurrence risk stratification, both stage IB-IIC (with negative SLN) and stage III (with positive SLN) melanoma patients represent a heterogeneous population in terms of recurrence risk. Despite the absence of lymph node involvement, stage IB-IIC patients have a very high risk of melanoma recurrence and death. Stages IIB and IIC are even associated with a higher risk than stage IIIA, and a similar risk if compared to stage IIIB [3]. Within this emerging scenario, digital pathology image-based prediction models can be designed. Due to ongoing developments in technology, e.g., cloud storage systems and computer processing powers, digital slides have become the predominant imaging modality in pathology departments across the world (digital pathology). Risk stratification and treatment benefit prediction models are urgent to improve patient selection as well as to avoid costly and toxic treatments to patients at low risk of recurrence. Application of artificial intelligence (AI) based-models has gaining increasing interest in the filed of digital pathology to identify non-invasive prognostic factors.

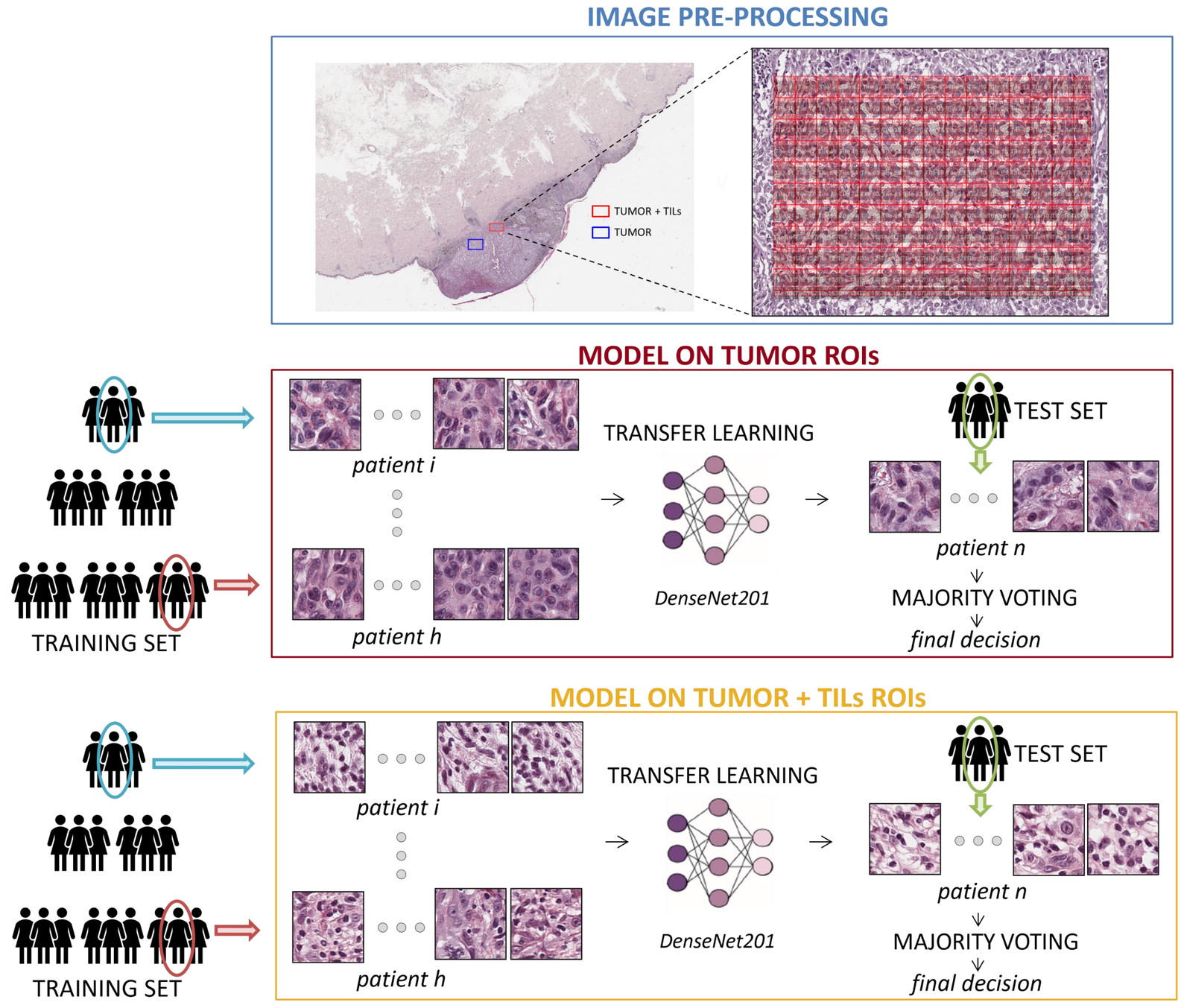


*Fig. 1. Workflow of the proposed approach.*

## Materials and Methods

In this study, we wanted to contribute to this topic by proposing an AI model, which exploited digital slides referred to primary lesion to predict 2-year recurrence-free (RF) status in stage IB-IIC melanoma patients. To the aim, Regions of Interest (ROIs) containing tumor cells alone (TUMOR ROIs) or with tumor-infiltrating lymphocytes (TUMOR+TILs ROIs) have been selected by expert pathologists on H&E digitalized slides. Each ROI was automatically divided into sub-regions, i.e., tiles with 200×200 pixels at 40×magnification, and then analyzed separately by an AI model (Fig. 1). A cohort of 71 melanoma patients, who are cared for at our Institute, was enrolled. The following criteria were required for inclusion: (i) melanoma patients from stage IB-IIC with completely resected primary tumor (T) and negative sentinel lymph node; (ii) availability of primary tumor specimen; (iii) availability of information of 2-year RF status (a follow-up of at least 24 months for disease-free patients, or who presented disease relapse during follow-up). The dataset of patients at disposal was divided in turn into training and test sets, in agreement with a five-fold cross validation procedure.

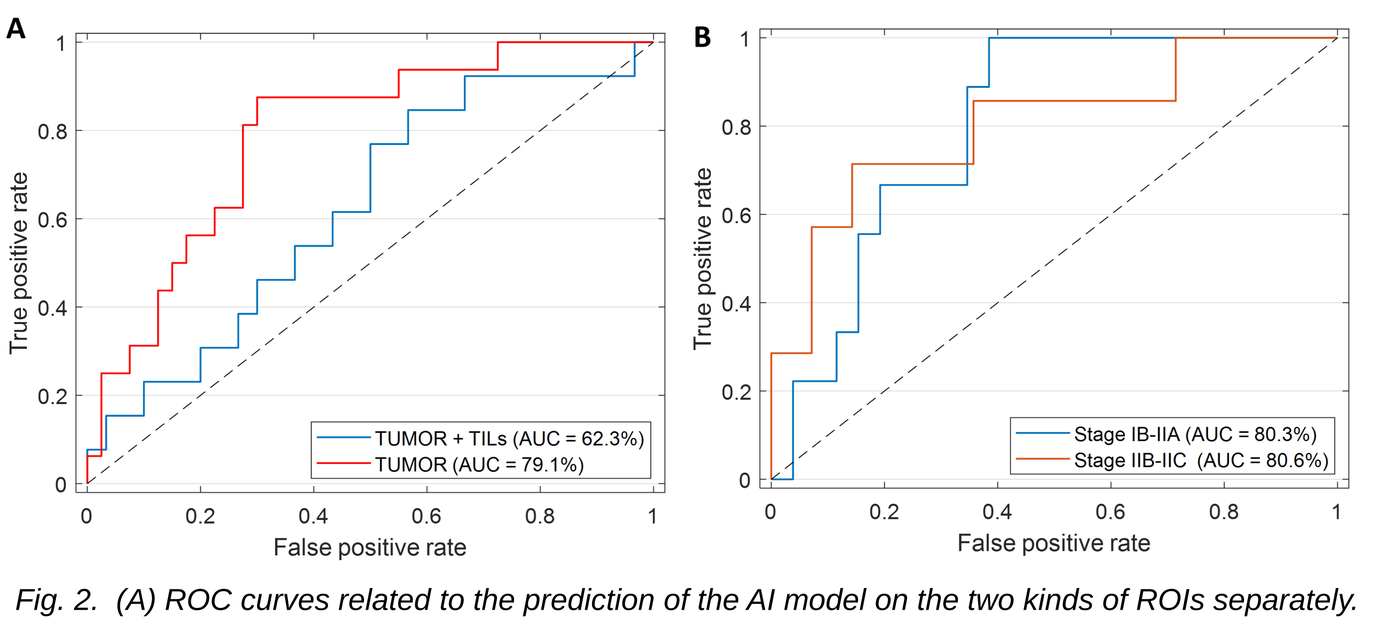


*Fig. 2. (A) ROC curves related to the prediction of the AI model on the two kinds of ROIs separately. (B) ROC curves related to the prediction of the AI model on TUMOR ROIs related to sub-populations divided by stage.*

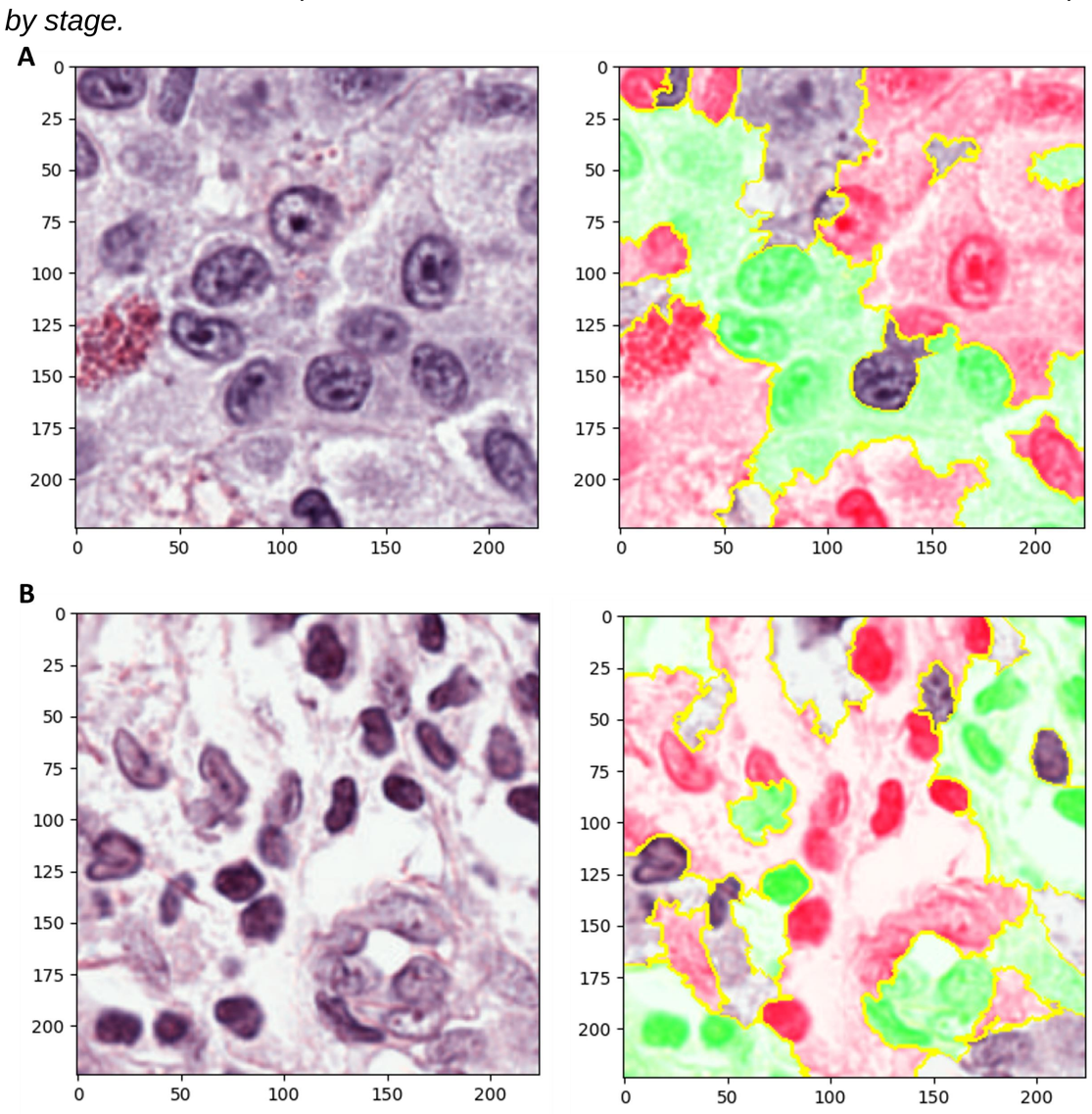


*Fig. 3. (A) A TUMOR ROI and a TUMOR+INFIL ROI (B) related to a correctly classified non-RF patient (left panels ) alongside to the same ROIs overlaid by the areas which mostly contribute to the decision of the AI model (right panels). The red color highlights the negatively contributing areas to the assignment to non-RF class, whereas the green represents the positively contributing areas to the assignment to non-RF class.*

## Results and Discussion

Overall, 20 patients had a recurrence (non-RF cases) and 51 did not (RF cases) with a median RFS of 15 months and a median follow-up of 31 months, respectively. TUMOR ROIs (AUC = 79.1%, sensitivity = 81.2%, specificity = 70.0%, accuracy = 73.2%) have revealed more informative than TUMOR + TILs ROIs (AUC = 62.3%, sensitivity = 76.9%, specificity = 43.3%, accuracy = 53.4%). For the best model (i.e., that exploiting TUMOR ROIs), the performances were also computed on sub-cohorts divided by stage: stage IB-IIA (AUC = 80.3%, sensitivity = 55.6%, specificity = 84.6%, accuracy = 77.1%), stage IIB-IIC (AUC = 80.6%, sensitivity = 57.1%, specificity = 85.7%, accuracy = 76.2%). Fig. 2 shows the ROC curves related to the two kinds of ROIs (Fig. 2A), and the two sub-populations (Fig. 2B), respectively.

In the vein of explainable AI, Fig.s 3A-B depict a TUMOR ROI and a TUMOR+INFIL ROI (B) related to a correctly classified non-RF patient (left panels) alongside to the same ROIs overlaid by the areas which mostly contribute to the decision of the AI model (right panels). The red color highlights the negatively contributing areas to recurrence, whereas the green represents a positive contribution with respect the occurrence of recurrence.

Afterwards, these images were visually analyzed by expert pathologists. On TUMOR + TILs ROIs, a visual morphological meaning was found. The red areas greatly corresponded to TILs which are well-known to have a protective effect on the spread of the disease; the green areas overlaid tumor cells which contribute to recurrence. Conversely, the pathologists did not notice perceivable-to-humans morphological differences among more and less aggressive tumor cells involved on TUMOR ROIs alone.

This interesting result as well as the difference of information content contained into the two kinds of ROIs will be deeper investigated by means of immunohistochemical panels.

## Conclusions

In conclusion, a fundamental peculiarity of the proposed model consits the automatic identification of quantitative imaging information from the raw digitalized slides directly. In other words, we used a computerized system to automatically extract information that are usually evaluated manually and visually by pathologists. The promising results achieved in this preliminary work suggest how our proposal, after further validations of wider cohorts of patients as well as technical refinement, has the potential to fulfil the predictive task with great improvement in the management of a cohort of melanoma patients, which is heterogeneous in terms of recurrence risk.

## References

[1] https://doi.org/10.1016/j.ejcsup.2013.07.012
[2] https://doi.org/10.1200/JCO.1999.17.3.976
[3] https://doi.org/10.1200/EDBK_239283