Toward Automatic Tumor-Stroma Ratio Assessment for Survival Analysis in Colorectal Cancer

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Editors: Under Review for MIDL 2022

Abstract

In this paper, we present a fully automated system for tumor-stroma ratio (TSR) scoring in line with current recommendations for pathologists, based on tumor and tumor-adjacent stroma tissue detection. In order to evaluate the scoring system, we perform survival analysis on 221 whole slide image from colorectal cancer patients. We find that the whole slide image-level and region of interest-level TSR are statistically significant predictors of overall survival.

Keywords: Computational pathology, tumor-stroma ratio, colorectal cancer

1. Introduction

Tumor-stroma ratio (TSR) has been shown to be an independent prognostic factor in colorectal cancer (CRC), as well as other cancer types. Tumors with high stromal content, and thus low TSR, are associated with a poor prognosis (van Pelt et al., 2018).

Since TSR is currently not reported in routine diagnostics, there are no binding guidelines. However, there exists a scoring recommendation (van Pelt et al., 2018). On slides from the most invasive tumor part, the area with the highest amount of stroma and where tumor cells are present in all four "directions" of the image field, is selected using a $\times 10$ lens. Then, the amount of tumor and stroma in the region of interest (ROI) are estimated. Patients are divided into a TSR-low and TSR-high group, based on a 50% cutoff.

The most recent work on TSR focuses on a semi-automated approach (Nearchou et al., 2021), where the most invasive area is pre-selected by an expert pathologist.

In this paper, we show how our recently published self-supervised domain adaptation approach Self-Rule to Multi-Adapt (SRMA) (Abbet et al., 2021) framework can provide a fully automated TSR score on a whole slide image (WSI) level as well as select and score the ROI according to the pathologists' recommendations.

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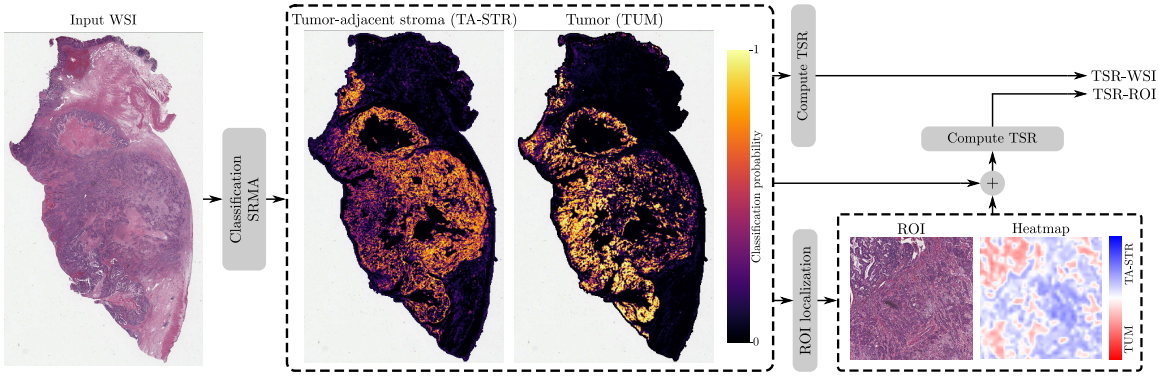

Figure 1: Pipeline of our proposed tumor-stroma ratio (TSR) assessment system.

2. Proposed Tumor-stroma Ratio Scoring System

Figure 1 shows the workflow to automatically score TSR and locate the ROI. Based on the input image, the classification model generates a tumor and tumor-adjacent stroma tissue map, which is then used to compute TSR. We later evaluate the quality of the scoring produced for the WSI as well as the automatically selected ROI.

Tissue Classification. We use our SRMA (Abbet et al., 2021) framework to detect tumor, tumor-adjacent stroma, and other tissue types across WSIs. The model uses self-supervision and unsupervised domain adaptation to align the features of a weakly-labeled tissue dataset (source) to the patient WSIs (target). The framework can directly benefit from publicly available labels, thus alleviating the need for annotations by expert pathologists, which are time-consuming to create.

Region of Interest Detection. We use a sliding window of size 1.25mm to first identify potential candidate locations with tumor cells in all four "directions". Then, based on the prior detections, we select the area with the highest stromal content as our ROI.

Tumor-stroma Ratio. According to the recommendations, TSR is defined as the ratio between tumor (TUM) and tumor-adjacent stroma (TA-STR). The classifier predicts both tissues' distribution to estimate the metrics given by $\text{TSR} = \frac{\text{TUM}}{\text{TA-STR+TUM}}$.

3. Experimental Setup and Results

We select 221 adenocarcinoma patients without preoperative treatment from the CRC TCGA (Tomczak et al., 2015) cohort, for which overall survival data and WSIs used for diagnosis are available. For each patient, we compute the TSR at the slide (TSR-WSI) and region of interest (TSR-ROI) level. Based on the TSR, they are then scored as either TSR-high or TSR-low. The list of used slides and computed TSR values are made available online[1] for future comparison.

We use a Cox proportional hazards model to investigate the association between overall survival and TSR, invasion depth (T), spread to regional lymph nodes (N), as well as TNM stage. Table 1 shows the results. We find that both TSR-WSI and TSR-ROI are statistically relevant in the univariate and multivariate survival analysis.

1. https://zenodo.org/record/6457559

Table 1: Univariate and multivariate survival analysis on TCGA

		Univariate		Multivariate			
Feature		HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
T-stage	T1-2	1					
	T3-4	1.18 (0.87 - 1.62)	0.287				
N-stage	N0	1		1		1	
	N1-2	1.66 (1.27 - 2.17)	< 0.001	1.99 (1.32 - 3.00)	< 0.001	1.77 (1.19 - 2.62)	0.005
TNM	I-II	1		1		1	
	III-IV	1.63 (1.25 - 2.13)	< 0.001	0.81 (0.56 - 1.19)	0.296	0.87 (0.61 - 1.25)	0.461
TSR-WSI	Low	1		1			
	High	0.71 (0.56 - 0.90)	0.006	0.66 (0.52 - 0.85)	0.001		
TSR-ROI	Low	1				1	
	High	0.67 (0.53 - 0.85)	0.001			0.68 (0.53 - 0.87)	0.002

Abbreviations: HR (hazard ratio), CI (confidence interval)

4. Conclusion

We present a fully automated framework for TSR assessment on H&E stained images. Additionally, we also provide a method to automatically locate the ROI for TSR scoring following the same guidelines as pathologists. The automatic TSR shows statistically relevant results on survival analysis for both the WSI and ROI score. Currently, TSR is not included in clinical reports, even though it has been shown to be of prognostic value. Using the proposed framework would allow to automatically include it in reports without generating more work for pathologists. In future work, we plan to investigate the consistency and aggregation capability of TSR across multiple slides from a patient, examine the connection between TSR and other clinical parameters, as well as verify these results in additional CRC cohorts.

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