A Stromal Solution

The tumor-stroma ratio (TSR) could yield more accurate cancer prognoses and improve personalized treatment. The international multicenter UNITED study began in January 2018 to investigate the promise of TSR – but all pathologists are welcome, so why not join the study?

By Marloes Smit and Wilma Mesker

Increasingly, when a patient presents with cancer, our first response is to turn to personalized approaches. Not every such approach takes the same format – many are genetics-based, whereas others rely on histological features or the tumor's site of origin. What they all have in common, though, is the intent to design a treatment plan that will work better than any other for the specific patient in question.

It's clear that the medical community in general is on a journey toward personalized medicine, and that process is reflected in the treatment of colon carcinoma as much as anywhere else. Colon cancer treatment is currently based on the histological examination of the tumor and lymph nodes – the "TNM," or tumor-node-metastasis, classification. But the TNM system isn't all it's cracked up to be; in TNM stage II, for instance, 25 percent of patients experience disease recurrence. This patient group could certainly benefit from chemotherapy, but their tumor classification does not currently result in selection for more intensive treatment. In contrast, some TNM stage III patients receive unnecessary chemotherapy for disease that is not, in fact, highly aggressive. To more accurately predict which patients are at greatest risk for disease recurrence, we need better prognostic tools – especially in patients with stage II or III disease, where survival rates are currently low, but have a good chance of improvement with appropriate stratification.

The solution may lie in a simple biomarker – one that all pathologists will recognize from their daily practice – that seems to provide more information than we had previously fathomed. The relative amount of stroma present in the primary tumors of epithelial cancer types can be easily determined as part of the routine

At a Glance

- *Colon carcinoma treatment is currently based on the TNM staging system, but there's a need for better prediction of recurrence risk*
- *A simple addition to routine diagnostics – tumor-stroma ratio scoring on H&E slides – can significantly increase accuracy*
- *Tumors are separated into "stroma-low" and "stroma-high" categories, the latter of which carry significantly worse survival rates*
- *If the current multicenter study supports TSR's promise, it can easily be rolled out to other types of cancer as well*

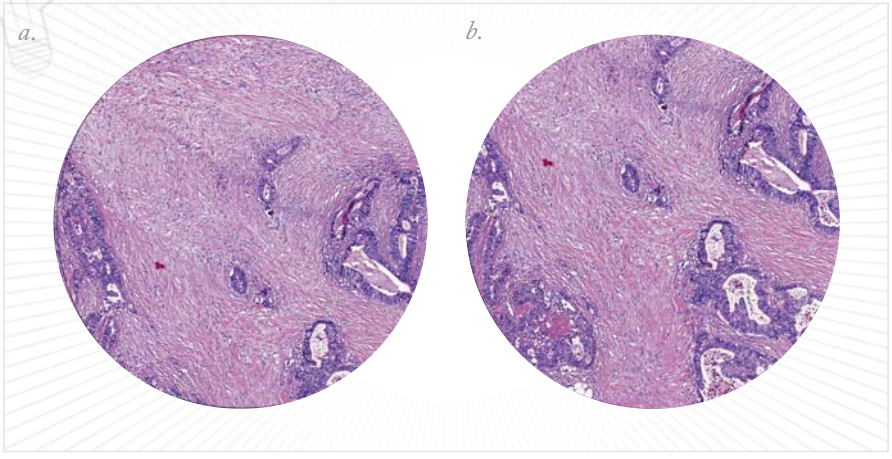

Figure 1. Examples of TSR scoring done incorrectly (A) and correctly (B). Slide A is incorrect because there are tumor cells on only three sides of the view.

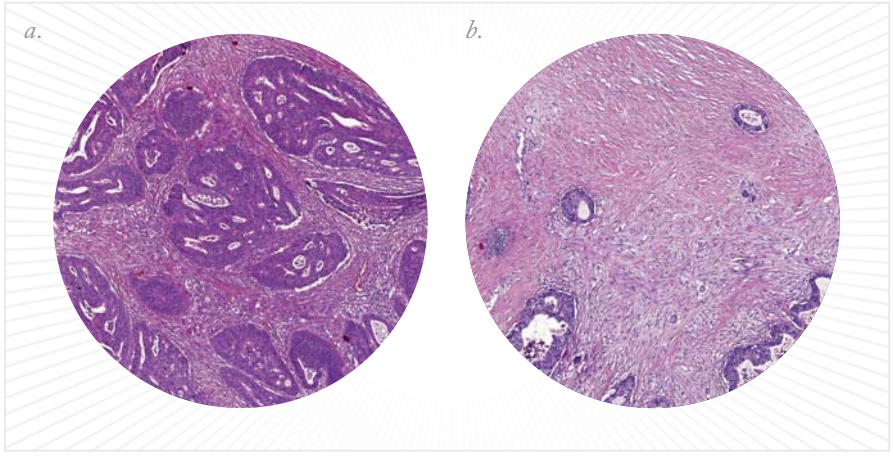

Figure 2. Slides showing a TSR-high/stroma-low (A) and a TSR-low/stroma-high (B) tumor.

diagnostic process. By spending a minute or two examining existing hematoxylin and eosin (H&E)-stained slides, we can establish a tumor-stroma ratio (TSR) at no additional cost, and with the investment of little additional time or effort.

Determining TSR

TSR scoring is easy for pathologists to include in their daily diagnostic routines because it is performed on standard H&E-stained sections. How is it done? First, you select the section that includes the most invasive part of the tumor. Then, use 2.5x or 5x magnification to search for the area of the section that incorporates the most stromal tissue. Zoom in on that area using 10X magnification and, again, select the area with the most stroma. Tumor cells should be present on all sides of the view (see Figure 1). Finally, visually estimate the amount of stroma, reporting in increments of 10 percent.

Several studies have shown the TSR's promise in predicting disease-free and overall survival in patients with stage II or III colon carcinoma (1–6). But what makes the TSR such a strong candidate for inclusion in routine pathology is that the ratio is prognostic in multiple epithelial malignancies, including colon, breast, pancreatic, esophageal, cervical, gastric, lung, and prostate cancer (7). The scoring procedure is exactly the same for every type of carcinoma – so if the TSR is validated in colon cancer, it will be only a small step further to introduce it as a new biomarker in other cancer types. Combined with current routine histological data, it might offer a way to improve personalized treatment and outcomes for a significant proportion of cancer patients.

"TSR scoring is easy for pathologists to include in their daily diagnostic routines."

Exploring the tumor microenvironment

Research studies in the 21st century are focusing more and more on the tumor microenvironment, because it is known to play an important role in a cancer's aggressiveness and overall behavior. Within the scope of the tumor microenvironment, biomarkers – such as tumor budding, CD3+, CD8+, cancer-associated fibroblasts (CAFs) and the amount of tumor stroma – are studied. Unfortunately, many biomarkers and genotype tests are time-consuming or expensive, so only a few can be applied in daily practice.

The TSR is based on the amount of stroma, or fibrosis, within the primary tumor. It separates tumors with a high percentage of stroma from those with a low percentage. Stroma-low tumors ("TSR-high") are those with a stromal percentage of 50 percent or less. Tumors

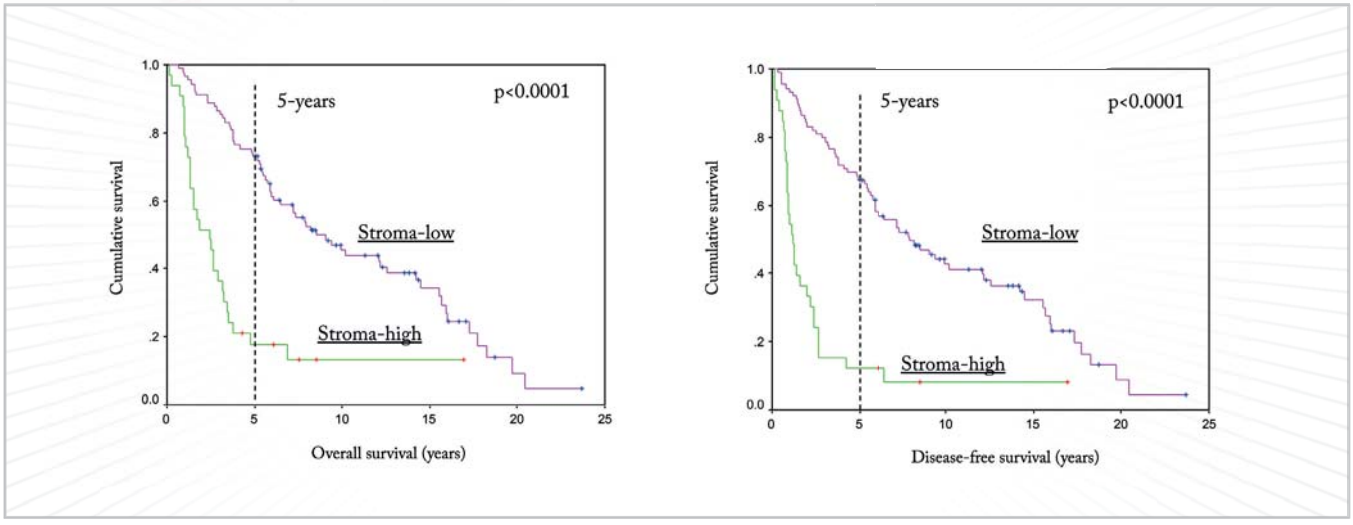

Figure 3. Kaplan-Meier survival curves showing overall (A) and disease-free (B) survival after colon carcinoma diagnosis. Adapted from (1).

with over 50 percent stroma are categorized as stroma-high ("TSR-low," see Figure 2). Patients with these latter tumors tend to have worse disease-free and overall and survival (see Figure 3). The TSR has been validated in various international studies (1–6), resulting in consistent *p*-values and hazard ratios, as well as excellent inter-observer agreement (K > 0.80).

UNITED for better cancer care

Data obtained in earlier research (1–7) support the introduction of the TSR as an extra indicator in the decision-making tree for adjuvant cancer therapy. The College of American Pathologists and the Union for International Cancer Control have discussed the ratio, and both organizations support its introduction into daily practice. However, before it can be used in conjunction with the TNM classification, the TSR must be validated in a prospective multicenter study that also provides a consensus agreement and a quality assessment program. The UNITED (Uniform Noting for International application of the Tumor-stroma ratio as Easy Diagnostic) study is just such an approach: an international multicenter study that will include over 1,500 patients. With a focus on the implementation of the TSR in the clinic for colon carcinoma, the UNITED study is scheduled to begin in January of 2018.

To evaluate the reproducibility of the scoring procedure, as well as to train international pathologists, we developed educational programming that includes an instructional video, web-based training, and an online test of scoring skill (*watchstroma.com*). When a pathologist passes the training and test set, they are included in the prospective trial – but that's not the end of the procedure. To ensure that TSR scoring quality and accuracy are maintained, a quality assessment will be performed every year. At the moment, we have pathologists from 14 countries enrolled in the UNITED study, but we hope to involve many more. All pathologists are welcome, so please consider joining in!

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