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Commentary

The role of artificial intelligence to quantify the tumour-stroma ratio for survival in colorectal cancer

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In this article of *EBioMedicine*, Ke Zhao and colleagues [1] show that it is possible to quantify the tumour-stroma percentage by artificial intelligence, using a convolutional neural network on whole-slide images (WSI). Moreover, the prognostic effect of the tumour-stroma ratio (TSR) for overall survival was confirmed, showing the robustness of the TSR method. It was suggested that this algorithm could possibly accelerate the clinical implementation of the TSR. To better understand the value of this contribution, it is important to know the background of the pathology workflow and the TSR.

In the last couple of years pathology has moved towards a more digitalised workflow. More and more pathology laboratories are going digital. Sections are no longer examined using conventional microscopy by the pathologist, but are scanned for digital viewing on a computer. In this shift towards a digital workflow, automation of tissue parameters is of interest. Research is exploring possibilities of developing new algorithms to support the pathologists in daily practice and to reduce their workload. Most of the algorithms are still only used in research setting, but look quite promising, as is the algorithm developed by Zhao et al. [1].

Colorectal cancer is a disease with high mortality burden. Decision making for adjuvant treatment is based on clinical and pathological criteria, as the tumour node metastasis (TNM) staging system and some already determined high-risk factors [2]. Within each stage diverse prognosis is observed. There is a clear clinical need to better select patients at risk for recurrence or cancer related death, therefore new high-risk factors are being investigated. A promising bio-

marker is the TSR, which is based on the tumour-microenvironment, more precisely, the amount of tumour-stroma within the primary tumour [3]. For each different tumour stage, TSR divides patients in two groups; patients with high-risk of recurrence or death (stroma-high tumours with >50% stroma) and patients with low-risk (stroma-low tumours ≤50% stroma). The clinical impact can be found in improved adjuvant treatment decision-making. Patients with a stroma-low tumour (low-risk of recurrence), but normally adjuvantly treated (stage III) [2], can be discussed to be spared from chemotherapy. On the other hand, a patient with stage II CRC with a stroma-high tumour, normally not adjuvantly treated [2], could be considered for chemotherapy.

The method for scoring the TSR is developed for conventional microscopy, with one field of view with the highest amount of stroma decisive for stroma-high [4]. Geessink et al. scored the TSR with deep learning algorithms in a manual selected spot chosen by one of the researchers [5]. They investigated the prognostic effect of the TSR in rectal cancer and could confirm this. The method used was similar to the visual microscopic method described by van Pelt et al. [4]. When using digital slides, the whole tumour area can be taken into account. Zhao et al. indicate the stroma percentage per slide calculated by the algorithm as the area of stroma divided by the total area of stroma and tumour taken together. This may result in an average percentage of stroma that is lower than scored in only one hotspot (according to the visual TSR protocol), which makes it difficult to compare the obtained results with current TSR literature. It would be of interest to see whether the well-known scoring of the TSR in one hotspot is comparable with scoring the stroma-percentage on the whole tumour area.

Scoring TSR digitally with artificial intelligence, or deep learning algorithms, offers additional challenges. It is important to be aware that the algorithm is sensitive to variation in colours. Stain normalisation before running the algorithm should be a step to consider [6]. This applies to inter laboratory staining differences as well as intra laboratory differences.

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The basis of the TSR algorithm for WSI analysis is set and has shown to be a prognostic factor for overall survival. Scoring TSR with the automated method used by Zhao et al. [1] should preferentially be validated in a larger, prospective study. For the TSR in colon cancer a prospective European validation study, the UNITED study, is currently underway [7]. This study consists of an E-learning module with quality control, and will compare visual with automated TSR scoring, with the scope to be implemented in daily routine pathology practise. The article of Zhao et al. [1] is anticipating to the need for automation of the routine pathology process, deep-learning algorithms for TSR on WSI is a good first step.

Contributors

MS wrote the first draft of the commentary, WM reviewed and corrected the manuscript. Both authors read and agreed to the final version of the manuscript.

Declaration of Interests

The authors declare no conflicts of interest.

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