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In reply to 'Hynes *et al.* Back to the future: routine morphological assessment of the tumour microenvironment is prognostic in stage II/III colon cancer in a large population-based study'

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Sir,

In their recent paper [1], Hynes *et al.* described the use of morphological features of the tumour microenvironment on H&E stained tissue sections for routine assessment of prognosis in stage II/III colon cancer patients. One of these features is the tumour stromal percentage (TSP), which was described by our group in 2007[2]. Although we appreciate the fact that this method is widely used and validated, unfortunately Hynes and colleagues misinterpreted the method described by Mesker *et al.* This had led to the definition of two separate methodologies, i.e. focal and global assessment of the tumour stromal percentage. However, we would like to report that their definition of global scoring as the method used by Mesker *et al*. which they describe as 'an estimation of the tumour stromal percentage at scanning magnification' is misinterpreted. We acknowledge that the method section of the Mesker paper [2] first states that the carcinoma percentage (NB. stromal percentage or TSR in later papers) is estimated on the whole tumour area. However, a detailed protocol is given further on in the paragraph: "H&E sections of the tumor with the most invasive part of the primary tumor were chosen. Using a 2.5x or a 5x objective the invasive area with the desmoplastic stroma was selected. Subsequently, using a 10x objective only the fields were scored where the stroma was infiltrated with small tumor nests within all sides of the image field. The tumor percentage was estimated (per tenfold: 10, 20, 30% etc.) per image field." This means that both focal and global assessment as defined by Hynes *et al.* are in fact the same methods. In addition, both Huijbers *et al.* [3] and Park *et al.* [4] adapted their methods from the methodology of the Mesker paper. Moreover, the paper of Huijbers *et al.* is in fact also from the same research group.

As Park *et al.* already stated in their comment to this paper of Hynes *et al.* [5], it is of interest that the assessment of TSP was not associated with survival in this study population. Hynes and colleagues described a considerable variation between study participants in the selection of 'the most invasive field', and expect this to be a greater problem with more tumour slides to evaluate in daily practice. As stated in the method section of the Mesker paper, the lowest scored tumour percentage (i.e. the highest scored stromal percentage) is decisive for final analyses. Therefore, the number of slides to be evaluated should not influence the final score. However, recognizing the most invasive field of a slide might have influence on the selection of the field of scoring. Not in all slides the structure of the colon is still recognisable due to the infiltration of the tumour into the tissue or the way the tissue is embedded in paraffin, and the most invasive field cannot be determined.

It is now in our opinion, based on experience, that it is not necessary to select the most invasive field within each slide, as the slides used for evaluation are already from the most invasive part of the tumour. This is confirmed by later published results on scoring the stromal percentage in colon cancer, and in other epithelial cancer types as well[6-8].

It would be of interest to analyse if the results published by Hynes and colleagues would change if our suggestions would be taken into consideration.

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2. Mesker WE, Junggeburt JM, Szuhai K, de Heer P, Morreau H, Tanke HJ *et al.* The carcinoma-stromal ratio of colon carcinoma is an independent factor for survival compared to lymph node status and tumor stage. Cell Oncol 2007; 5: 387-398
3. Huijbers A, Tollenaar RA, v Pelt GW, Zeestraten EC, Dutton S, McConkey CC *et al.* The proportion of tumor-stroma as a strong prognosticator for stage II and III colon cancer patients: validation in the VICTOR trial. Ann Oncol 2013; 1: 179-185
4. Park JH, Richards CH, McMillan DC, Horgan PG, Roxburgh CS. The relationship between tumour stroma percentage, the tumour microenvironment and survival in patients with primary operable colorectal cancer. Ann Oncol 2014; 3: 644-651
5. Park JH, Roxburgh CSD, Edwards J, Horgan PG, McMillan DC. In reply to 'Hynes et al. Back to the future: routine morphological assessment of the tumour microenvironment is prognostic in stage II/III colon cancer in a large population-based study'. Histopathology 2017; 2: 326-327
6. Courrech Staal EF, Wouters MW, van Sandick JW, Takkenberg MM, Smit VT, Junggeburt JM *et al.* The stromal part of adenocarcinomas of the oesophagus: does it conceal targets for therapy? Eur J Cancer 2010; 4: 720-728
7. de Kruijf EM, van Nes JG, van de Velde CJ, Putter H, Smit VT, Liefers GJ *et al.* Tumor-stroma ratio in the primary tumor is a prognostic factor in early breast cancer patients, especially in triple-negative carcinoma patients. Breast Cancer Research & Treatment 2011; 3: 687-696
8. van Pelt GW, Hansen TB, E. B, Kjaer-Frifeldt S, van Krieken JHJM, Tollenaar RAEM *et al.* Stroma-High Lymph Node Involvement Predicts Poor Survival More Accurately for Patients with Stage III Colon Cancer. J Med Surg Pathol 2016; 2: