Invited Editorial

Outcome in colorectal cancer – tumour, stroma and so much more

J. H. Park*, D. C. McMillan

Academic Unit of Surgery
School of Medicine, Dentistry & Nursing,
University of Glasgow,
Glasgow,
United Kingdom

*Corresponding author
(james.park@glasgow.ac.uk)

Keywords: colorectal cancer, prognosis, inflammation, tumour microenvironment

Our increasing understanding of cancer progression and dissemination has directed us from a tumour cell-centric model to one where the tumour microenvironment (local and systemic) is also recognised to play a pivotal role [1, 2]. This has been reflected in the numerous attempts to molecularly classify the intrinsic characteristics of the tumour cell over the past two decades resulting in subtypes for most common cancers. For example, in 2015, a consortium proposed four consensus subtypes for colorectal cancer (MSI immune, canonical, metabolic, and mesenchymal) based on six classifications systems reported to have prognostic value [3]. Such studies have identified a stromal element as being associated with high risk of recurrent disease and poorer survival [4, 5]. However, despite compelling evidence supporting their use, such systems have largely failed to translate into routine pathological assessment, and their clinical utility remains to be fully determined and realised.

The present study by Danielsen and colleagues in this issue adopts a pragmatic approach to incorporating characteristics of both the cancer cell and tumour microenvironment [6]. In a combined large retrospective cohort of 2624 patients with stage I-III colorectal cancer (from two previously described observational studies and the QUASAR 2 trial population) they developed and validated a prognostic score based on tumour cell ploidy status and the extent of tumour stromal infiltration. Utilising this score in the context of stage II disease, and controlling for a number of clinicopathological characteristics, it was possible to stratify patients into three clinically distinct groups with five-year cancer-specific survival of 90% (diploid tumour, low stroma), 83% (either non-diploid or high stroma) and 73% (non-diploid and high stroma) respectively ($P<0.001$). The authors concluded that adoption of the ploidy/stroma score may be useful in selecting patients with stage II disease for adjuvant chemotherapy, where clinical benefit of additional therapy is often unclear. For example, those patients deemed to have a good prognosis (approximately one third of the cohort) may avoid chemotherapy, the intermediate group

(approximately half) could be considered for single-agent therapy, and the poor prognosis group offered oxaliplatin-based combination chemotherapy. Indeed, such an approach may be more readily applicable to clinical practice than more comprehensive molecular and transcriptomic characterisation, and may ultimately aid in decision-making regarding prognosis and benefit of adjuvant therapy, particularly in patients with stage II disease.

However, a number of technical and theoretical issues are worthy of discussion. The authors employed digital pathology-based assessment to assess extent of tumour stromal infiltration and it remains to be determined whether the increased objectivity of such a system offers additional benefit over simple, manual semi-quantitative assessment as initially described by Mesker, and validated across a number of solid tumour types including colorectal cancer [4, 5, 7, 8]. Of those tumour characteristics assessed in routine pathology only those patients recruited to QUASAR 2 (n=1092) had venous and lymphatic invasion assessed and only those patients from the Gloucester Colorectal Cancer Study cohort (n=954) had peritoneal involvement assessed, and it remains to be determined whether the ploidy/stroma score has prognostic value independent of optimal histopathological assessment.

From a theoretical standpoint the omission of an assessment of the tumour inflammatory cell infiltrate may be problematical. There is extensive evidence that the extent of inflammatory cell infiltrate has prognostic value in node negative colorectal cancer. Indeed, reported studies date back almost 100 hundred years [9] and forms the basis of the Immunoscore [10, 11] and scores based on the assessment of the extent of tumour inflammatory cell infiltrate and tumour stroma [12, 13]. Therefore, it remains to be determined whether ploidy offers additional prognostic value to these inflammation-based scores. Given the increasing role of immunotherapy in patients with colorectal cancer [14], it would be anticipated that at least

some measure of the local immune response be incorporated into novel, tumour microenvironment-based scoring systems and would also inform the nature of the tumour host interaction and outcome in patients with node negative colorectal cancer [15].

Irrespective, the present report of Danielsen and colleagues will stimulate further studies into the routine assessment of the tumour-host interaction and outcome in patients with colorectal cancer.

References

1. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011; 144: 646-674.
2. McAllister SS, Weinberg RA. The tumour-induced systemic environment as a critical regulator of cancer progression and metastasis. Nature Cell Biology 2014; 16: 717-727.
3. Guinney J, Dienstmann R, Wang X et al. The consensus molecular subtypes of colorectal cancer. Nat Med 2015; 21: 1350-1356.
4. Huijbers A, Tollenaar RA, v Pelt GW et al. The proportion of tumor-stroma as a strong prognosticator for stage II and III colon cancer patients: validation in the VICTOR trial. Annals of Oncology 2013; 24: 179-185.
5. Park JH, Richards CH, McMillan DC et al. The relationship between tumour stroma percentage, the tumour microenvironment and survival in patients with primary operable colorectal cancer. Annals of Oncology 2014; 25: 644-651.
6. Danielsen HE, Hveem TS, Domingo E et al. Prognostic markers for colorectal cancer; estimating ploidy and stroma. Annals of Oncology (In Press).
7. Dekker TJ, van de Velde CJ, van Pelt GW et al. Prognostic significance of the tumor-stroma ratio: validation study in node-negative premenopausal breast cancer patients from the EORTC perioperative chemotherapy (POP) trial (10854). Breast Cancer Research and Treatment 2013; 139: 371-379.
8. Courrech Staal EF, Wouters MW, van Sandick JW et al. The stromal part of adenocarcinomas of the oesophagus: does it conceal targets for therapy? Eur J Cancer 2010; 46: 720-728.
9. Roxburgh CSD, McMillan DC. The role of the in situ local inflammatory response in predicting recurrence and survival in patients with primary operable colorectal cancer. Cancer Treatment Reviews 2012; 38: 451-466.
10. Galon J, Mlecnik B, Marliot F et al. Validation of the Immunoscore (IM) as a prognostic marker in stage I/II/III colon cancer: Results of a worldwide consortium-based analysis of 1,336 patients. Journal of Clinical Oncology 2016; 34.
11. Mlecnik B, Van den Eynde M, Bindea G et al. Comprehensive Intrametastatic Immune Quantification and Major Impact of Immunoscore on Survival. J Natl Cancer Inst 2018; 110.
12. Park JH, McMillan DC, Powell AG et al. Evaluation of a tumor microenvironment-based prognostic score in primary operable colorectal cancer. Clinical Cancer Research 2015; 21: 882-888.
13. Hynes SO, Coleman HG, Kelly PJ 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.
14. Le DT, Uram JN, Wang H et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med 2015; 372: 2509-2520.
15. Roseweir AK, McMillan DC, Horgan PG, Edwards J. Colorectal cancer subtypes: Translation to routine clinical pathology. Cancer Treat Rev 2017; 57: 1-7.