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Deposited on: 04 January 2018
Invited Editorial

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

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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