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Comment on 'Tumour-infiltrating inflammation and prognosis in colorectal cancer: systematic review and meta-analysis'

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Sir,

We read with interest the recent meta-analysis by Mei *et al* (2014). In this study, Mei *et al* examined the prognostic value of the local inflammatory infiltrate in colorectal cancer as measured by both the generalised inflammatory infiltrate and by immunohistochemical analysis of T-lymphocytic subsets. The authors concluded that, in comparison with assessment of T-cell subset density, semiquantitative assessment of the generalised inflammatory infiltrate at the invasive margin, utilising the Jass score or Klintrup–Mäkinen grade (Jass *et al*, 1987; Klintrup *et al*, 2005), was a more robust prognostic marker of cancer-specific, overall and disease-recurrence-free survival. Indeed, in patients undergoing resection for Stage I–III disease, a high-density generalised inflammatory infiltrate was associated with an almost 60% increase in overall survival.

The present study mirrors recent results from both our group and others (Vayrynen *et al*, 2013; Richards *et al*, 2014). In 365 patients undergoing potentially curative resection for Stage I–III colorectal cancer, Klintrup–Mäkinen grade strongly correlated with T-cell subtype density in the invasive margin, tumour stroma and cancer cell nests (Richards *et al*, 2014). Furthermore, on univariate analysis, a strong Klintrup–Mäkinen grade was associated with improved cancer-specific survival (hazard ratio 0.54, 95% confidence interval 0.43–0.68); indeed this was comparable if not superior to the prognostic utility of measuring T-cell subtype density or the use of a composite score, such as the Galon Immune Score. Similarly, in a cohort of 117 patients with Stage I–IV colorectal cancer undergoing resection, Vayrynen *et al* (2013) found that Klintrup–Mäkinen grade closely correlated with not only T-cell density, but also macrophage, neutrophil and dendritic cell density at both the invasive margin and within the intratumoural compartment. In addition, Klintrup–Mäkinen score was associated with recurrence-free survival.

Therefore, taken together, these results are consistent with the concept that increased density of an inflammatory cell infiltrate in the tumour microenvironment represents a coordinated effective immune response and that individual inflammatory cell types offer little additional prognostic value. If this proves to be the case, then it may be that the conspicuous inflammatory cell infiltrate, long recognised by investigators to be associated with good outcome, is the normal immune response to a colorectal cancer and that the abnormal response is a scarce or absent inflammatory cell infiltrate, representing an uncoordinated immune response. The implications of such a hypothesis are several and profound. First, the immune context in which an inflammatory cell is found in the tumour microenvironment would become of paramount importance. Second, it would move the focus of investigations from the nature of the inflammatory cell infiltrate in those with a conspicuous inflammatory cell infiltrate to those with a scarce or absent inflammatory cell infiltrate (eg, see Mohammed *et al*, 2012; Richards *et al*, 2012). Third, it would become a pre-requisite of all investigations that the density of the tumour inflammatory cell infiltrate in the tumour microenvironment is defined.

With this in mind we have recently validated an automated, computer-based scoring method with similar prognostic value to the Klintrup–Mäkinen grade (Forrest *et al*, 2014). It is hoped that introduction of such a tool will facilitate the incorporation of such an assessment of the generalised inflammatory cell infiltrate into routine clinical practice and provide a solid platform for the further investigation of the importance of inflammatory cell infiltrate (absent–scarce/conspicuous) in determining outcome in patients with colorectal cancer.

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Response to comment on 'Tumour-infiltrating inflammation and prognosis in colorectal cancer: systematic review and meta-analysis'

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Sir,

We are most grateful to Professor Park, McMillan and Roxburgh (2014) for their interest and valuable comments on our manuscript titled 'Tumour-infiltrating inflammation and prognosis in colorectal cancer: systematic review and meta-analysis' (Mei *et al*, 2014). They cited several recently published studies with consistent results, pointing out some other important relationships among inflammatory cell infiltrate, the tumour microenvironment and immune response in colorectal cancer (CRC), which were not discussed in detail in our original publication because of the length of the publication. Therefore, some major concerns, such as the following, must be addressed.

First, the analytical methods used in our publication for the generalised tumour inflammatory infiltrate were relatively standardised ones and included the Jass classification, the Klintrup—Makinen (K–M) criteria and Crohn's-like reaction criteria. The pooled hazard ratios and 95% CIs for overall survival, cancer-specific survival and disease/recurrence-free survival in a subset of highly generalised tumour inflammatory infiltrate were <1, indicating a robust survival marker for CRC. However, conflicting results (with HRs and 95% CI across 1) were noted among individual studies as heterogeneity originated from local inflammatory reaction grading systems, patient characteristics, follow-up schemes and some other factors, which was especially evident among individual T-cell subtypes. More detailed