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Reponse to: comment on, 'Tumour-stroma ratio (TSR) in oestrogen-positive breast cancer patients'

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Sir,

We thank Dr Mesker *et al* for their comments on our study, (Downey *et al*, 2014) recognising their significant work promoting the concept of using tumour-stroma ratio (TSR) to determine the outcome in cancer (Mesker *et al*, 2007, 2009; Courrech Stall *et al*, 2010, 2011; de Kruijf *et al*, 2011; Dekker *et al*, 2013; Huijbers *et al*, 2013).

None of our ER-positive cohort (118 female, 62 males; Downey *et al*, 2014) received neoadjuvant therapy of any type. Neoadjuvant treatment induces pathological changes in the tumour, hence would render samples unsuitable for TSR analysis. We were limited in the amount of information that could be supplied in a short communication, however univariate and multivariate outcomes were provided.

We found high stromal content was related to better survival across genders in ER-positive disease (Downey *et al*, 2014), contrasting data in triple-negative breast cancer (de Kruijf *et al*, 2011) and, as highlighted by Mesker *et al*, their own work on ER-positive cases (de Kruijf *et al*, 2011; Dekker *et al*, 2013). As breast cancer is heterogeneous, subtle differences in stromal biology may exist between breast cancer subtypes, potentially impacting on outcome. Notably, tubular carcinoma, a type of invasive breast ductal carcinoma with an abundant stroma (Figure 1), is almost always ER-positive and has a favourable prognosis (Rakha *et al*, 2010).

Methodological heterogeneity exists between sampling methods used to assess TSR. Two key issues stand out: (1) lack of standardisation in TSR measurement, (2) area of tissue selected for analysis. Our in-house computer algorithm method selects a 9 mm^2 area of a digitally scanned H&E image (Downey *et al*, 2014). Recent related work assessed TSR manually in a single section from the most invasive tumour area (Gujam *et al*, 2014). Mesker *et al* favour assessment of the whole slide, even suggesting an evaluation of all available microscope slides. Although rigorous assessment is to be commended, this technique may have practical implications for histopathologists should TSR evaluation ever become routine. Alternative approaches should be considered, compared and validated.

We believe that there is much more to the stroma in dictating outcome, than simply its proportion in relation to tumour. There is a need to examine the cell types that coexist within tumour stroma, for example, fibroblasts and immune cells (Hanahan and Coussens, 2012); a recent issue of this journal showed that patients with a high TSR had significantly reduced inflammatory cell infiltrate within their stroma (Gujam *et al*, 2014). It remains possible that discrepancies observed between studies of TSR in breast cancer may be due in part to components of the stromal microenvironment.

Consistent with all emerging techniques it takes time for the ideal methodology to become accepted in the field. We respectfully suggest the best way to achieve this for TSR is through collaboration, comparing different techniques, using carefully selected sub groups of breast cancer and working towards reaching a consensus, taking account not only of the stroma but the cells within.

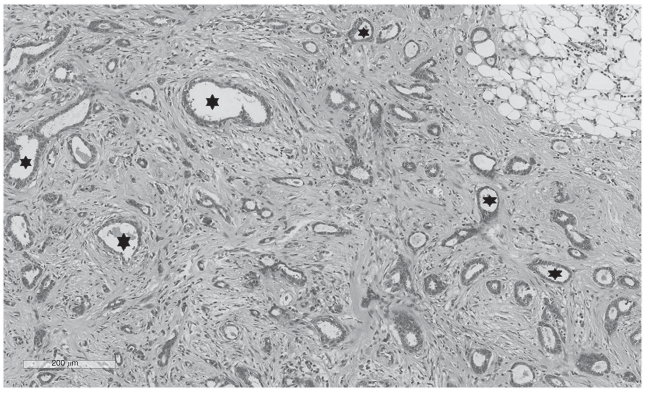

Figure 1. Tubular carcinoma showing arrangement of tumour cells in characteristic tubes (stars) embedded within an abundant multicellular stroma. Scale bar = 200 μm.

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