Reviewer's report

Title: Role of the VEGF ligand to receptor ratio in the progression of mismatch repair-proficient colorectal cancer

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Reviewer: Andrew Vickers

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There are several major problems with the statistics in this manuscript.

First and foremost, the authors conduct huge numbers of statistical tests and then, without any correction for multiple testing, pick out what appear to be a few random associations on the basis of p values that just scrape below the traditional 0.05 cut-point. For example, they claim that one type of ratio is linked to vascular invasion (p=0.038) whereas another was linked to inflammatory response (p=0.045). According to my estimate, the authors conducted over 150 hypothesis tests. Using a simple Bonferroni correction, results in this paper should only be considered significant for p<0.00033. Which is to say that there is nothing significant here at all and the authors should really conclude that measuring the VEGF ligand isn’t a predictor.

Second, the authors introduce an entirely unnecessary ROC analysis. Why dichotomize markers into high and low? This will result in a loss of information. There is really no difficulty in analyzing markers as continuous variables, for example, the authors could compare levels of e.g. VEGFR1 between patients with and without vascular invasion using a Wilcoxon test. The authors make some unusual choices, such as analyzing survival as a binary variable. It is simply not true that calculating an ROC curve for survival data is that complicated (as I recall it is only a couple of lines of code). Might the investigators include a professional statistician?

Third, as far as I can tell, the authors do not follow the REMARK statement. For example, I see no mention of blinding.

Statistical review: Yes, and I have assessed the statistics in my report.