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29th April 2019

Dear Ruo-Yu Ma,

RE: Submission of revised manuscript number 47534 "Predicting systemic spread in early colorectal cancer – can we do better?"

Thank you for your email dated the 8th of April 2019 enclosing the reviewers' comments on the above manuscript. We have carefully reviewed the comments and revised the manuscript accordingly. Our responses are given in a point-by-point manner below. Changes in the manuscript are shown in yellow.

Response to Reviewer 1:

We thank the reviewer for their positive comments on our manuscript.

Response to Reviewer 2:

We thank the reviewer for their comments and suggestions. The reviewer quotes a low rate of postoperative mortality in their institution and suggests that the risk of lymph node metastasis should be higher than the risk of postoperative mortality before undertaking major surgery. We largely agree with this statement, although it is important to recognise that internationally the risk of postoperative mortality shows marked variation and is largely dependent on comorbidity in the background population. For example, our group has shown that 30 day mortality after major resection in the United Kingdom is 6.7% in the general population and 15% in the elderly (Morris et al 2011). Even in early stage disease (Dukes' A), the postoperative mortality after elective major resection was as high as 4.2%. We have therefore highlighted that international variation in postoperative mortality exists and have suggested

that it is important to accurately estimate the risk of lymph node metastasis and postoperative mortality when deciding whether to use local excision or major resection.

We hope that the revised version is now suitable for publication and look forward to hearing from you in due course.

Yours sincerely,

Dr Scarlet Fiona Brockmoeller and Dr Nick West

Reference:

Morris EJ, Taylor EF, Thomas JD, Quirke P, Finan PJ, Coleman MP, Rachet B, Forman D. Thirty-day postoperative mortality after colorectal cancer surgery in England. *Gut* 2011; 60: 806-13.