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We appreciate the response from members of the NICE 151 clarifying the rationale for their decision making. Much reliance was placed on the analysis of a single retrospective study in which 48 patients had a lung metastasectomy for colorectal cancer.(1) PulMiCC, the only randomised controlled trial (RCT) was dismissed because of its size.(2) This trial included 46 patients in the metastasectomy arm so unless NICE has a prespecified threshold of 47, two fewer patients is not a credible reason for discounting data from the only RCT.

The reviewers did state that the retrospective study was of low quality and high risk of bias which is most definitely correct. The 48 patients selected for surgery had relatively low rates of the well-established bad prognostic characteristics:- >3 metastases(4%), bilateral(19%) multi-lobe(10%) multi-organ(12.5%) and 33% were <12 months since primary resection. These adverse prognostic features were all much higher in the 57 patients selected not to undergo metastasectomy: 67%, 65%, 77%, 37% and 49% respectively. There may have been further differences, that were unknown or not recordable, that influenced the decision for or against metastasectomy. The absence of a randomised control group, as is the case in the many other similar studies, means that it is not a good test of the effectiveness of lung metastasectomy, but confirms that patients with a mix of bad prognostic features are likely to die sooner than those with favourable features.

The PulMiCC RCT (dismissed by the GDG) had a well matched control group of 47 patients with a 5 year survival of 30%. Similar survival rates were found in the control arms of the other two trials of local treatment with radiofrequency ablation and stereotactic ablative radiotherapy. The special feature of controlled trials is the control group. That is where we look to see if the treatment made a difference. Why then would you reject an RCT in favour of a non-controlled study which was not much larger? The committee knew that the PulMiCC trial data had been analysed and was out for publication, but no enquiry was made to us about the results.

PulMiCC did have recruitment difficulties and then, only 18% of the 512 patients who gave informed consent to enter the trial were randomised. The DMEC requested an analysis of reasons for them not proceeding to randomisation.(3) In a sample of 155

patients from the 3 largest recruiting sites we found that among 41 patients who preferred to make their own decision, 19(46%) almost half, chose surveillance not metastasectomy, but of 78, in whom the clinical team overrode randomisation, 77(99%) had surgery. The potentially eligible patients who consented to join the study after receiving comprehensive even-handed information reflected an equipoise that was not eventually shared by their doctors.

The authors describe metastasectomy as a 'widespread national practice'. Surely it is the role of NICE to question an established practice based on flawed observational evidence and for which the only randomised trial, although small, was large enough to have to have shown the amount of benefit so widely believed.(4)

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4. Fallowfield L, Macbeth F, Treasure T. Colorectal cancer: summary of NICE guidance. *BMJ Rapid Responses*,. 2020(<https://www.bmj.com/content/368/bmj.m461/rr-2>).