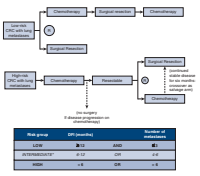
The author reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.



REPLY FROM AUTHOR: WHAT IS THE RIGHT ANSWER FOR PULMONARY METASTATIC DISEASE? MORE CLINICAL TRIALS

Reply to the Editor:

For the last several decades, management strategies for pulmonary metastatic disease have been driven in large part by the results of retrospective reviews. Such analyses clearly set important foundations for subsequent innovation, for future prospective studies, and for ultimate evolution of clinical management paradigms. Nonetheless, we all must recognize that retrospective reviews are inherently limited in their future applicability, with outcomes that may be dependent on variables that are both measured as well as those that are unknown. Efforts to undertake prospective studies in this patient cohort have been limited thus far, with most notable previous efforts undertaken by Treasure and colleagues via the Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) randomized controlled trial.[1,2] We applaud these investigators for their conduct of this trial, their thoughtful analyses of their findings, and their dissemination of their outcomes. Moreover, we greatly appreciate their contemplative and informative reply[3] to our publication[4] in *the Journal*.

With regard to statements in our article that have been called into question, we would argue that these are not implicit assumptions but rather based on the preponderance of retrospective data, which currently serves a key role in this area of research with limited prospective data available. Improvement in prognosis has been clearly demonstrated for appropriately selected surgical patients undergoing pulmonary metastasectomy, and while the definitions of the criteria to identify the best patients may vary, the fact that improved outcomes have been seen for specific subgroups is clearly evident.[5-15] We agree with Treasure and colleagues that these statements are not yet supported by controlled trial evidence, and that further prospective data are in need.

We appreciate the clarification of the outcomes as well as the appropriate interpretation of the PulMiCC trial. We applaud the recruitment of 512 patients to this trial, which, as highlighted by the investigators, did not represent poor accrual. More clearly stated, this trial experienced limitations in the proportion randomized, which is unfortunate, given the strong need for prospective data in this area of investigation.

As further elucidated by the authors, the patients in the PulMiCC trial displayed a mix of risk factors.[3] We find their outcomes in this patient cohort to be highly relevant and critical to keep on the forefront of our discussions as we consider individual patient cases. We also believe that further prospective clinical trials are clearly in need, with the hope that, taken together, a more complete body of prospective data could eventually provide greater guidance for patient management. As a complement to the PulMiCC trial, we believe that it would be helpful to have prospective data in which the use of chemotherapy and ablation are controlled, such that we can better understand the extent to which surgery specifically plays a role.

We are optimistic that our ongoing multicenter randomized trial, NCT03599752,[16] will help further delineate answers to some of these questions regarding the interplay of various modalities of treatment for patients with lung-limited metastatic colorectal cancer. This study, under the umbrella of the American Association for Thoracic Surgery Thoracic Surgery Oncology Group,[17] involves the stratification of patients into 2 groups (Figure 1). For patients with low risk of pulmonary recurrence based on the existing body of retrospective data, patients are randomized to undergo surgery alone versus surgery with perioperative chemotherapy. For patients who are at greater risk of pulmonary recurrence based on retrospective data, the randomization differs. These are the individuals for whom we lack adequate data to convincingly support the practice of surgical resection, yet we know that systemic therapy is highly beneficial. These patients in the trial are randomized to chemotherapy with or without surgery. In this group of individuals, we anticipate that we may ultimately demonstrate findings consistent with those of the PulMiCC trial. Hopefully, as we continue to accumulate a body of prospective data, we will eventually be able to generate recommendations for patient care well supported by greater levels of evidence.

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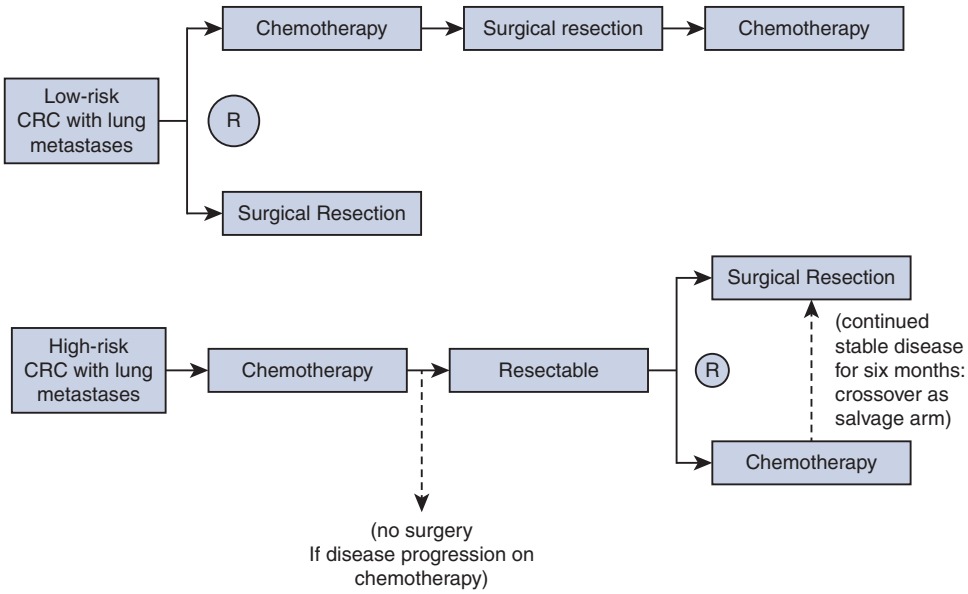

Risk group	DFI (months)		Number of metastases
LOW	**≥ 12**	**AND**	**≤ 3**
*INTERMEDIATE**	*6-12*	*OR*	*4-6*
HIGH	**< 6**	**OR**	**> 6**

FIGURE 1. Schema for TSOG 103. *CRC*, Colorectal cancer; *DFI*, disease-free interval.

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