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REPLY FROM AUTHOR: BIOLOGY IS KING, BUT METASTASECTOMY STILL HAS A ROLE FOR PROPERLY SELECTED PATIENTS

Reply to the Editor:

As our knowledge of and the corresponding body of literature in the area of pulmonary metastatic disease continue to grow, so does our understanding in terms of identifying the best patients to undergo aggressive local therapy. We are honored to read the letter from Williams and colleagues¹ regarding our recent findings demonstrating that location within the colon is yet another factor contributing to patient prognosis.² We absolutely agree with the authors that biology is king, and understanding the relevant prognostic

indicators for pulmonary metastasectomy in colorectal cancer can help us guide patients who may be very heterogeneous in terms of overall risk profiles. In addition to the well-known factors of number of metastases, disease-free interval, extrathoracic metastases, and mediastinal nodal involvement, recent investigations have furthered our understanding as we have been able to incorporate mutational status³ as well as primary tumor laterality² into patient stratification.

Williams and colleagues discuss the Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) trial⁴ and their conclusion that differences attributable to surgery may be less than previously believed.¹ In that trial, the authors used minimization strategies to balance previously known confounders, demonstrating excellent survival in nonsurgical patients. These findings are interesting, relevant, and important to keep in mind during both multidisciplinary tumor board discussions as well as in informed consent discussion with patients. One challenge, however, is that the use of chemotherapy and ablation occurred in a substantial portion both the metastasectomy and nonoperative groups, which may make it challenging to understand the extent to which surgery played a role.

We are optimistic that our ongoing multicenter randomized trial (NCT03599752)⁵ will help further delineate the 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 (AATS) Thoracic Surgery Oncology Group (TSOG),⁶ involves the stratification of patients into 2 groups (Figure 1). In their letter, Williams and colleagues suggest that all patients in TSOG 103 will undergo metastasectomy, and that this is a trial of sequencing rather than a trial to determine the benefit of metastasectomy. For clarity, we have provided the schema of this trial (Figure 1). For patients with low-risk of pulmonary recurrence—and patients for whom there exists a large body of retrospective data demonstrating improved survival with metastasectomy, all patients do undergo metastasectomy, as they are randomized to undergo surgery alone versus surgery with perioperative chemotherapy. However, randomization differs for patients who are at elevated risk of pulmonary recurrence. These are the individuals for whom we lack adequate data to convincingly support the practice of surgical resection, yet for whom systemic therapy will be highly beneficial. For these patients in the trial, they are randomized to chemotherapy with or without surgery.

Ultimately, the questions being asked in TSOG 103 differ from those being asked in PulMiCC, and we expect the results to be helpful in further expanding our knowledge.

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We hope that the findings from both trials may be used in a complementary fashion to further advance our conversations with our multidisciplinary colleagues and with our patients.

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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. Study schema for Thoracic Surgery Oncology Group (TSOG) 103. Patients with lung-limited metastatic colorectal cancer are stratified into groups based on risk of recurrence. All low-risk patients undergo surgical resection, whereas they are randomized to receipt or non-receipt of perioperative chemotherapy. All high-risk patients receive chemotherapy, and they are randomized in terms of the addition of surgical resection. Thus, the study aimed to evaluate (1) the additive benefit of chemotherapy for low-risk patients undergoing surgical resection and (2) the additive benefit of surgery in high-risk patients receiving chemotherapy. Note that patients in the high-risk group who are not randomized to surgery can cross over to the surgical arm if they demonstrate disease stability after 6 months of chemotherapy. CRC, Colorectal cancer; DFI, disease-free interval.

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