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REPLY: DISCUSSIONS REGARDING PULMONARY METASTASECTOMY ARE SIMILAR TO AMERICAN POLITICS: BOTH ARE EXTREMELY POLARIZING,

UNSATISFYING, INCONCLUSIVE, AND UNDERTAKEN AT YOUR OWN PERIL

Reply to the Editor:

Providing commentary to a spirited discussion on pulmonary metastasectomy is similar to mediating a debate between Democratic and Republican presidential candidates in American politics—the views are amazingly polarized and strongly held but truly satisfying answers are nearly impossible to discern. In responding to Corsini and colleagues' recent report (with my accompanying commentary) on the prognostic significance of right- versus left-sided colorectal tumors in pulmonary metastasectomy,^{1,2} Williams and colleagues³ emphasize that outcomes in colorectal cancer, as in all cancers, are dominated by tumor biology; a point that no one will (or should) debate. They also stress the importance of randomized clinical trials (whenever possible) in determining clinically effective cancer therapies, again a universally accepted oncologic tenet. However, subsequent statements become less factual and involve more partisanship interpretation. For instance, median overall survival (OS) data from the Pulmonary Metastasectomy versus continued active monitoring In Colorectal Cancer (PulMiCC) multicenter randomized trial are cited as evidence that pulmonary metastasectomy

provides no real benefit (3.5 years following metastasectomy vs 3.8 years in the observation arm).⁴ This comparison, albeit intriguing, fails to support scientifically sound conclusions regarding metastasectomy, however, for several reasons. First, the study design required a sample size of 300 to 450 randomized patients.⁴ Williams and colleagues noted poor accrual, with 93 randomized patients but 28 from one center ultimately excluded, leaving only 65 analyzed patients. In addition, 2 had benign nodules, also calling into question the control group's true pathologic accuracy, similar to issues raised in stereotactic body radiation therapy trials. Thus, with a mere 14% to 21% (63-65/300-450) of necessary accrual, statistical principles preclude making any conclusive trial comparisons. Second, the assertion that there is a "consensus belief that without metastasectomy five-year survival would be zero," and that the important new finding of the PulMiCC trial was that the control group 5-year estimated OS was greater than expected (29%), comparable with reported metastasectomy OS, again is partisan politics. The 5-year OS of large numbers of unselected patients with stage IV colorectal cancer has been >8% even before potential improvements from recent advances in systemic therapies.⁵ Patients with more limited disease considered for metastasectomy, resected or not, certainly would have significantly better expected survival than that, perhaps even 29%. Finally, the timing of the survival analysis may be suboptimal. Evaluating median OS and a minimally important clinical difference after only 3 years overemphasizes the early survival curves when OS with and without metastasectomy may be similar due to earlier dropout of patients with more aggressive tumor biology. Patients exhibiting more indolent and limited metastatic cancer biology, which has been demonstrated in animal models,⁶ may require longer time periods, even 5 to 10 years, to clearly demonstrate significant surgical benefit. In fact, the separation/flattening of the PulMiCC estimated survival curves between the fourth and fifth years (38% for metastasectomy and 29% for control by 5 years) suggests this.

Randomized clinical trials clearly are warranted. NCT03599752⁷ is one such trial, randomizing high-risk patients to chemotherapy with or without metastasectomy, although low- and not high-risk disease may be where benefit exists. Finally, enhanced local consolidative therapies, adding stereotactic body radiation therapy and thermal ablation to surgery, could improve any existing potential benefit even more.

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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.