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REPLY: THE MOLECULAR BASIS OF TUMOR BIOLOGY—AN EVOLVING FIELD WITH FAR-REACHING

IMPLICATIONS IN THE DIAGNOSIS, PROGNOSTICATION, AND TREATMENT OF OUR

Reply to the Editor:

Williams and colleagues¹ have provided a highly thoughtful and interesting letter to the editor regarding Corsini and colleagues' recent article² on the prognostic impact of site of colorectal primary in patients undergoing pulmonary metastasectomy. This well-designed, albeit single-center retrospective review adds to a growing knowledge base on factors affecting survival in the setting of colorectal pulmonary metastases. This study provides new information to consider when counseling patients regarding prognosis and surgical decision-making, and it highlights a new variable that should be factored into the design of future trials looking at outcomes following pulmonary metastasectomy for colorectal metastases.

An interesting perspective was raised in the letter to the editor regarding the possibility that tumor biology has a larger impact on patient outcomes than the intervention of pulmonary metastasectomy itself. As Williams and colleagues mention in their letter, the recent results from the randomized control trial PulMiCC (Pulmonary Metastasectomy vs Continued Active Monitoring in Colorectal Cancer)³ have challenged the belief that 5-year survival is minimal without pulmonary metastasectomy in this patient population. Although not the primary focus of the CLOCC (Chemotherapy and local ablation vs chemotherapy)⁴ and SABR-COMET (Stereotactic ablative radiotherapy vs standard of care palliative treatment in patients with oligometastatic cancers)⁵ trials, both these studies also demonstrate control group 5-year survival rates similar to the 29% seen in the control group in the PulMiCC trial. This provides opposing data to the previously held notion that 5-year survival is close to zero without local intervention and raises the question of whether the survival advantage of pulmonary metastasectomy is less than previously thought.

This interesting and timely topic raised by Williams and colleagues¹ is relevant, as the interventions to which we subject patients, whether they be ablation, radiation, or

surgical resection, are not without their own complications. We agree with the authors that larger trials specifically looking at the benefit of treating pulmonary metastases in this patient population are needed to provide appropriate, evidence-based counseling to patients before they embark on these interventions.

Our understanding of tumor biology and underlying tumor genotypes continues to expand. For example, mutations in *BRAF* and *KRAS* are known to be associated with a worse prognosis in metastatic colon cancer. Specific mutations in these oncogenes, among others, have been associated with site-specific patterns of spread, as well as recurrence patterns after local treatment.⁶ This increasingly available information on the underlying molecular biology of our patients' tumor profiles allows tailored prognostication, targeted treatment interventions, and informed surveillance strategies. With studies such as Corsini and colleagues', our knowledge base continues to grow, adding site of colorectal primary to the list of factors affecting outcome following pulmonary metastasectomy. With ongoing characterization of the genotypic profile of right versus left versus rectal primary colorectal tumors, the molecular basis for the observed survival differences following metastasectomy can be further elucidated.

Surgeons need to continue to collaborate to advance our knowledge on the molecular basis of tumor biology, as this will guide the ongoing evolution of tailored diagnosis, prognostication, and treatment of our patients.

Emily M. Mackay, MD, MSc^a
Anna L. McGuire, MD, MSc^{b,c}

Divisions of^aGeneral Surgery
^bThoracic Surgery

Department of Surgery

Vancouver General Hospital

University of British Columbia

Vancouver, British Columbia, Canada

^cVancouver Coastal Health Research Institute

Vancouver General Hospital

Vancouver, British Columbia, Canada

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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.

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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.

Robert B. Cameron, MD

Division of Thoracic Surgery

Department of Surgery

David Geffen School of Medicine at UCLA

Division of Thoracic Surgery

Department of Surgery and Perioperative Care