See Article page 1623.

Commentary: Catch me if you can: Does reducing circulating tumor cells with early pulmonary vein ligation improve survival after lobectomy?

Jules Lin, MD

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CENTRAL MESSAGE

The authors conclude that early pulmonary vein ligation can reduce circulating tumor cells, but further studies are needed to determine the effect on disease-free and overall survival.

In this issue of the *Journal*, Duan and colleagues[1] evaluated early versus late pulmonary vein ligation and concluded that early ligation can prevent circulating tumor cells from entering the circulation. The potential benefit of decreasing circulating tumor cells on survival is appealing, since 90% of cancer-related deaths are due to metastatic disease,[2] and the rate of recurrence for surgically resected lung cancers is 30% to 77%.[3]

A randomized study of 86 patients by Wei and colleagues[4] also reported that early pulmonary vein ligation significantly decreased circulating tumor cells. While Duan and colleagues[1] obtained samples directly from the pulmonary vein, in the study by Wei and colleagues,[4] circulating tumor cells were determined in peripheral blood samples. Although pulmonary vein samples may better reflect changes in pulmonary vein circulating tumor cells due to surgical manipulation, whether these shed cells translate into viable peripheral circulating tumor cells and potential metastases remains unclear. The authors have not shown a difference in peripheral circulating tumor cells resulting from late pulmonary vein ligation, which would significantly strengthen the results of this study. On the contrary, the authors state that in their preliminary studies, there was no correlation in peripheral circulating tumor cells with early or late pulmonary vein ligation.

While the authors have shown an increase in pulmonary vein circulating tumor cells captured in the pulmonary vein stump with early ligation, the clinical significance of these findings is unclear. As shown in the preligation pulmonary vein blood samples, there is a steady state of circulating tumor cells that are shed by the tumor at baseline even with early-stage lung cancers and subsolid nodules. Are the cells that are captured in the pulmonary vein stump with early ligation viable and able to form metastases? Most circulating tumor cells released from the primary tumor will likely be destroyed in the circulation, and only a subset of cells will be able to develop into metastases.[5] The authors have not demonstrated that the difference in pulmonary vein circulating tumor cells captured with early ligation affects peripheral blood circulating tumor cells as mentioned previously. Even more importantly, they have not demonstrated that this difference affects disease-free or overall survival.

Kuroda and colleagues[6] reported a positive correlation between the number of pulmonary vein circulating tumor cells and tumor spread through air spaces as well as worse overall survival. In addition, Wei and colleagues[4] performed a retrospective analysis of the Western China Lung Cancer Database and found significantly worse overall and lung-cancer specific survival in patients who had the pulmonary artery branches ligated first. Although Duan and colleagues[1] did not include the data in the current study,

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they found no significant difference in survival with early or late pulmonary vein ligation.

The possibility of improving long-term survival by changing our surgical techniques is intriguing, but larger, randomized validation studies with clear documentation of the surgical approach, measurement of peripheral circulating tumor cells, and sufficient follow-up are needed to determine whether catching escaping circulating tumor cells will increase disease-free and overall survival.

References

1. Duan X, Yang Z, Hao X, Shou S, Liu Z, Zhang K, et al. Early ligation of the pulmonary vein can reduce the dissemination of shed tumor cells during thoracoscopic lobectomy. *J Thorac Cardiovasc Surg*. 2022;164:1623-35.e2.
2. Woo D, Yu M. Circulating tumor cells as "liquid biopsies" to understand cancer metastasis. *Transl Res*. 2018;201:128-35.
3. Subotic D, Van Schil P, Grigoriu B. Optimizing treatment for postoperative lung cancer recurrence. *Eur Respir J*. 2016;47:374-8.
4. Wei S, Guo C, He J, Tan Q, Mei J, Yang Z, et al. Effect of vein-first vs artery-first surgical technique on circulating tumor cells and survival in patients with non–small cell lung cancer: a randomized clinical trial and registry-based propensity score matching analysis. *JAMA Surg*. 2019;154:e190972.
5. Ruzycka M, Cimpan MR, Rios-Mondragon I, Grudzinski IP. Microfluidics for studying metastatic patterns of lung cancer. *J Nanobiotechnol*. 2019;17:1-30.
6. Kuroda H, Masago K, Takahashi Y, Fujita S, Sasaki E, Nakada T, et al. Positive correlation between the number of circulating tumor cells in the pulmonary vein and tumor spread through air spaces in resected non–small cell lung cancer. *Anticancer Res*. 2021;41:5499-505.

See Article page 1623.

Commentary: A surgical shotgun?

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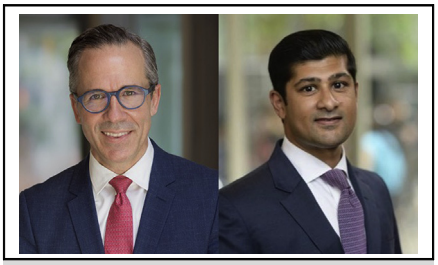

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CENTRAL MESSAGE

Early ligation of the pulmonary vein may present a simple means toward reducing the shed of circulating tumor cells during lobectomy.

It has been hypothesized in patients and shown in preclinical studies that local treatment of cancer, whether surgery or radiation therapy, can lead to mechanical disruption of the tumor, shedding of tumor cells, suppression of antitumor immunity, and enhancement of the metastatic process.[1,2] Specific to lung cancer, previous studies have shown increases in pulmonary venous and peripheral blood circulating tumor cells (CTCs) following surgery, raising the question of whether ligating the pulmonary vein and cessation of effluent flow early during lobectomy might reduce shedding of CTCs. One notable study even suggested that late division of the pulmonary vein was associated with decreased overall and progression-free survival.[3] While an intriguing combination of randomized trial along with retrospective propensity-matched data, the methodology of that study has been questioned regarding measurement of CTCs and study design.[4]

In the current issue of the *Journal*, Duan and colleagues[5] provide more prospective evidence of the potential for surgical "shotgunning" of tumor cells into the blood, showing that CTCs in the postoperative pulmonary vein stump were 9-fold greater than at the beginning of the case. The number of CTCs was significantly greater in the stumps of patients

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