



# Vein first lobectomy provides survival advantage: too good to be true?

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When a particular treatment for lung cancer promises a double-digit absolute reduction in mortality, people pay attention. In the recent publication by Wei and colleagues (1), the seemingly simple maneuver of dividing the vein before the artery at the time of lobectomy has demonstrated a staggering reduction in mortality. The first thought that comes to mind is that this is revolutionary, and that we may have just discovered the single greatest incremental step in the surgical treatment of lung cancer. However, as the data sinks in, some questions start coming to mind.

Vein-first division is not a novel concept for thoracic surgeons. We had suspected for a long time that tumor spillage may cause poorer outcomes in surgical patients, and this is probably why most thoracoscopic lobectomy procedures evolved to be vein-first type techniques. In this trial, the authors decided to test this hypothesis by a two-step study design. The first step was a small randomized controlled trial to compare levels of circulating tumor cells between patients who received vein-first versus artery-first ligation. In seemingly balanced cohorts of 43 patients each, it was demonstrated that the vein-first group had significantly lower serum levels of circulating tumor cells. Whether this phenomenon had any clinical impact, or any effect on survival, remains unknown, since the sample size was too small to be powered for survival, and the follow-up period too short. However, as the authors state, this is a worthwhile preliminary hypothesis-generating analysis that supports further research in the field.

The second step of this study was a retrospective analysis looking at survival differences between two cohorts

of patients, one which received vein-first lobectomy, and one which received artery-first lobectomy. The two cohorts were propensity matched for many confounders that may have affected survival such as age, tumor stage, nodal stage, and tumor size. The analysis demonstrated that the vein-first cohort had a significantly better overall and cancer specific survival. Supported by the biochemical results of the first phase, the authors concluded that there was a causal relationship between vein-first technique and improved survival when performing lobectomy for lung cancer.

In science, when something seems too good to be true, it likely is. The authors do acknowledge some limitations for their study, and mention that their results should be validated by an independent and larger sample trial. However, a closer look at the data reveals some interesting finds. In the pre-matching cohort, the vast majority of patients underwent vein-first technique, pointing to the fact that the artery-first technique was likely not a random event based on surgeon preference, but likely a marker for a more serious confounder that prevented the surgeon from performing a vein-first lobectomy. Pre-match data in e-table 4 demonstrates that artery-first cases took an average of 30 minutes longer to complete, lost more blood, and had longer chest tube drainage times. Such differences point to more challenging operations, and to potential situations where it was impossible to take the vein first because of tumor location or invasion. Unfortunately, important makers for such a scenario, like tumor location (central versus peripheral) and operative approach (open

versus thoracoscopic), were not measured. It is also noted that in the multivariate regression analysis, artery-first is an independent predictor of shorter survival, along with stage II and stage III disease. One wonders whether the artery-first variable is collinear with advanced stage disease, and what is being observed is the compounded effect of the two together. In other words, were artery-first cases done in patients with larger more central tumors, and in patients with more advanced stages, and in turn, this is why a survival difference is seen?

Clinical trials in thoracic surgery are rare, let alone ones that raise important questions, and the possibility of a giant step towards improving lung cancer survival. For this reason alone, this trial carries great value for the lung cancer community. If it is successfully replicated, then it is nothing short of a revolution.

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## References

1. Wei S, Guo C, He J, 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.

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