



Vein-first vs. artery-first: “does the order of vessel ligation during pulmonary lobectomy for NSCLC affect circulating tumor cells and patient survival?”

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In the May 2019 issue of *JAMA Surgery*, Wei and colleagues report the results of a fascinating two part study: the first consists of a multicenter, randomized clinical trial evaluating whether ligating effluent veins first during thoroscopic lobectomy can reduce the dissemination of tumor cells in patients with non-small cell lung cancer (clinical stage I–II) (1); the second comprises a propensity-matched retrospective analysis of overall survival (OS) and disease-free survival (DFS) in patients undergoing vein-first versus artery-first lobectomies.

In the first part of the study, Wei and colleagues randomized 86 patients to receive vein-first *vs.* artery-first ligation during lobectomy and measured incremental change of folate receptor-positive circulating tumor cells (FR⁺CTCs) in peripheral blood. The vein-first group had significantly decreased levels of FR⁺CTCs in peripheral blood compared to the artery-first group. In the second part of the study, Wei and colleagues conducted a retrospective evaluation of data collected in the Western China Lung Cancer Database. Using propensity score matching, the investigators identified 210 pairs of patients undergoing lobectomy and concluded that the vein-first procedure has significantly increased rates of 5-year OS (73.6% *vs.* 57.6%, $P=0.002$) and 5-year DFS (64.6% *vs.* 48.4%, $P=0.001$). Subgroup analysis showed that this survival advantage applied to patient undergoing lobectomy for stage I and II disease, but not stage III disease.

Their work gives credence to the hypothesis that

manipulation of the lung during resection for malignancy can cause release of tumor cells into the blood, which may eventually cause metastasis and adversely affect the prognosis (1). The sequence of vessel ligation during lobectomy for non-small cell lung cancer (NSCLC) as an independent prognostic variable has never been examined in a randomized, prospective setting. Even though multiple studies in the last 20 years have demonstrated increased circulating tumor cells in peripheral blood in patients undergoing lobectomy, retrospective analysis by Refaely *et al.* did not show that sequence of vessel interruption during lobectomy affects tumor recurrence (2,3). If peripheral circulating tumor cells are increased after surgical manipulation, especially when the lobar artery is ligated first, the benefits of the vein-first lobectomy may eventually be demonstrated to justify its adoption as standard of care.

Propensity score matching, however, is an imperfect science, and is not as authoritative as a well-designed randomized trial. Patients were not matched for operating surgeon; therefore, it is possible that either selection bias not corrected by propensity matching, or other differences in surgical technique between surgeons performing V-first versus A-first lobectomy, could account for some of the survival difference. For instance, the investigators do not provide information about the number of lymph nodes or lymph node stations assessed in V-first versus A-first lobectomy. Could A-first lobectomy patients be understaged? A-first lobectomy took longer, and involved

more blood loss, although these numbers do not at first glance appear clinically significant. When looking at this retrospective data, are we really testing different techniques, or simply different surgeons? How much does the surgeon factor affect outcomes?

Nonetheless, the findings of Wei and colleagues remain compelling; it is rare that a fine point of surgical technique such as whether or not to ligate the artery or vein first is demonstrated to be associated with a significant difference in outcome. In comparing video-assisted thoracic surgery (VATS) *vs.* open lobectomy, Yamashita and colleagues found that VATS lobectomy was associated with a higher risk of seeding tumor cells into the circulation during the operation (2). This phenomenon was suggested to be related to a more frequent and forceful retraction and manipulation of the diseased lobe to attain better fields of vision during VATS lobectomy (2). It is possible that ligating the vein early and first during VATS lobectomy could negate this risk. In the Discussion section, the investigators debunk the commonly held belief that division of the artery first reduces blood loss and engorgement of the lung to be resected during lobectomy. Therefore, should we as a field shift towards a vein-first technique when performing minimally invasive lobectomy?

At the minimum, the findings by Wei and colleagues should alert surgeons to the potential danger of tumor dissemination during VATS lobectomy for NSCLC and suggest that an artery-first technique for lobectomy has the potential to adversely influence long-term survival of patients with NSCLC. The long-term follow up of their prospective cohort will supply data on the clinical significance of the vein-first ligation approach and help answer the important question of whether sequence of vessel interruption during lobectomy for NSCLC affects disease recurrence and patient survival.

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