Transection of the arterial ligament for extended mediastinal lymph node dissection by video-assisted thoracoscopic surgery: invaluable technique for the right patient

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Lung cancer remains the leading cause of cancer-related deaths worldwide, with non-small cell lung cancer (NSCLC) accounting for 85% of cases (1). Five-year survival is heavily dependent upon cancer stage and follows the tumor, node, and metastasis staging model (TNM), with lymph node (LN) metastasis being an important determinant of prognosis (2). Stage I NSCLC includes tumors less than 4 cm in diameter without metastasis to LNs. Published practice guidelines recommend preoperative staging with positron emission tomography (PET) or PET-computed tomography (CT), with subsequent preoperative pathologic tissue diagnosis for mediastinal staging in centrally located tumors, tumors >3 cm, and for enlarged or PET-positive LNs (2,3). Endobronchial ultrasonography (EBUS) with fine needle aspirate is the recommended first choice where available; if unavailable or if aspirate is negative in the setting of high suspicion for involved LNs, recommendations are to proceed with cervical mediastinoscopy.

Recommended treatment for early stage NSCLC includes surgical resection and systematic mediastinal LN dissection (MLND) or mediastinal LN sampling (MLNS) of at least 3 N2 nodal stations (3). Either is currently recommended by the National Comprehensive Cancer Network guidelines (3), and there is ongoing debate regarding the benefit of a systematic MLND versus MLNS with several studies demonstrating a survival benefit (4-6), while others have not (7-10). The American College of Surgery Oncology Group (ACOSOG) Z0030 trial showed no difference in overall or disease-free survival at 5 years between MLND and MLNS, as well as no difference in local, regional, or distant recurrence (11). However, 4% of patients in ACOSOG Z0030 had occult pN2 disease, and Bille *et al*. demonstrated a 9% rate of occult pN2 disease, of which 34% of these pN2 patients demonstrated skip metastasis with no associated pN1 disease (12). The benefits of MLND for this subset of patients are prognostic, guiding appropriate adjuvant therapies, and potentially enabling R0 resection. For left-sided lung resections, intrathoracic access to the mediastinal 2L and 4L stations during resection is technically challenging due to their anatomic relationship to the aorta, left pulmonary artery, and the arterial ligament that joins them. Both the ACOSOG Z0030 trial and the study by Bille *et al*. omitted 2L and 4L LN stations at the time of surgical resection (11,12), and yet 16% of patients with pN2 disease had LN metastasis that occurred beyond the lobe-specific lymphatic drainage (12). The present study performed by Shibano *et al*. entitled "Left mediastinal node dissection after arterial ligament transection via video-assisted thoracoscopic surgery for potentially advanced stage I non-small cell lung cancer" aims to describe a video-assisted thoracoscopic surgery (VATS) technique that allows access to the 2L and 4L LN stations to perform an extended MLND and provides the results of this innovative technique (13).

Shibano *et al*. is a single arm, single institution, retrospective review of 75 patients from 2008 to 2015 (13). Patients were diagnosed with clinical stage I NSCLC by chest CT as

categorized by the 7th edition of the International Association for the Study of Lung Cancer (14) and underwent preoperative PET-CT to assist with selecting potentially node-positive stage I NSCLC. The selection criteria included: (I) a standardized uptake value (SUV) of the primary tumor greater than 3 on PET (n=63); (II) SUV of ipsilateral LNs was higher than contralateral LNs (n=12); (III) preoperative carcinoembryonic antigen (CEA) was greater than upper end of normal (n=22), and (IV) hilar or mediastinal metastasis was suggested by intraoperative pathological analysis (n=28). Patients underwent left VATS anatomical lung resection, systematic MLND of stations 3a, 5, and 6, and then the arterial ligament was exposed and divided with an ultrasonic energy device to allow *en bloc* resection of stations 2L, 4L, and 7. During this dissection, the phrenic, vagus, and recurrent laryngeal nerves were skeletonized. The mean operative time was 238±58 minutes, and a video of the dissection was provided to guide the readership in the conduct of this technique (15). Fifty-seven left upper lobectomies, 15 left lower lobectomies, and 3 segmentectomies were performed. There were no intraoperative complications and no in-hospital mortalities. Postoperative complications included recurrent laryngeal nerve paralysis (n=11, of which 8 recovered and 3 were permanent), arrhythmia (n=7), pneumonia (n=2), superior mesenteric artery embolism (n=1), chylothorax (n=1), and prolonged air leak >7 days (n=1). An important aspect of postoperative care included routine bronchoscopy on postoperative day 7 for concern of ischemic bronchitis, though no patients developed this complication. This planned bronchoscopy heavily factored into the unusually long median hospital length of stay of 12 days (range, 7–132 days).

An average of 32.7±12.9 hilar and mediastinal LNs were dissected, with nodal metastasis identified in 34 patients (6 pN1, 27 pN2 and 1 pN3). These findings equated to a 45.3% upstaging rate. Of tested variables thought to be associated with nodal upstaging, only tumor location within the left lower lobe was statistically significant (12 of 16 patients upstaged, P<0.01). With a median follow-up of 52 months, there was recurrence or metastasis in 29 patients, with 2 patients developing carinal locoregional LN recurrence. The study reports an overall survival at 3 and 5 years of 91.3% and 81.5%, respectively. When stratified by pathologic stage, 3- and 5-year survival were 92.2% and 88.4% for p-stage I, 100% and 60% for p-stage II, and 87.7% and 81.0% for p-stage III, respectively. The authors conclude that their improved survival outcomes compared to published literature suggest that an extended MLND may be beneficial among radiographically negative, but potentially node-positive NSCLC patients (13).

Shibano *et al.* aptly present a technique for transection of the arterial ligament to facilitate access to the 2L and 4L LNs. Clearly, this approach provides for improved exposure of these nodal stations and allowed for an *en bloc* resection. In the hands of an experienced VATS thoracic surgeon, this technique would expand one's armamentarium for clearance of these technically challenging mediastinal nodal basins. The authors deserve praise for their development and implementation of this novel approach. However, this should be tempered by the fact that the study has several limitations which must be considered prior to wide application of this technique. The study was single-armed, retrospective, and performed at a single institution. As mentioned in the manuscript, without an appropriate control arm, there are no meaningful comparisons that can be made regarding the complication rates and survival data. Likewise, the reported operative time, length of hospital stay, dissected LN numbers, and upstaging rate have no baseline standard from which to draw conclusions. Comparisons to previously published literature are similarly fraught with bias and type I error without accounting for patient and surgical variables.

The fundamental premise of the manuscript is preselection of potentially node positive NSCLC patients according to the previously described criteria, which included 28 patients with the suggestion of hilar or mediastinal metastasis by intraoperative pathological analysis. Of the 34 patients with nodal upstaging, 89.2% were selected for inclusion based on the suspected nodal metastasis during surgery. The inclusion of patients into the clinical stage I NSCLC study group based upon intraoperative pathological analysis imparts selection bias and, ultimately, confounds the described nodal upstaging rate of 45.3%, which is higher than previously reported rates of 4–28% (11,12,16,17). Although the manuscript acknowledges this study limitation, there were unfortunately no attempts described to account for this confounder. Additionally, in patients with central tumors or suspicious PET-avid LNs, invasive pathologic staging is indicated using EBUS or cervical mediastinoscopy (2,3). This well-accepted algorithm was not utilized on the study population, even when PET-CT suggested LN involvement, limiting applicability to a clinical setting in which standard protocols are followed. Moreover, this practice of omitting pathological staging in recommended situations further confounds the upstaging rate, as there likely would have been patients upstaged preoperatively. In

S1224

White and Antonoff. Role for VATS arterial ligament transection

other words, a group of the included patients were upstaged with this technique because they had incorrect preoperative staging related to incomplete staging evaluation.

Regarding the surgical technique and post-operative complications and care, there is no discussion of the additional operative time required, or of the learning curve required to perform the technique. Based on time stamps, the included video demonstrates an additional 111 minutes to complete the station 2L, 4L, and 7 dissection. The manuscript reports a mean operative time of 238±58 minutes, which indicates that the additional dissection and *en bloc* LN resection adds considerably to overall operative time. Another major technical consideration is the skeletonization of the phrenic, vagus, and recurrent laryngeal nerves. Although no phrenic nerve injuries were reported, there was a 14.6% rate of recurrent laryngeal nerve paralysis, of which 27.3% were permanent (3 of 11 injuries). The median hospital length of stay was 12 days (range, 7–132 days) and can partially be attributed to routine bronchoscopy on postoperative day 7 for all patients. This length of stay is 2–3 times as long previously published results after VATS lobectomy (18,19).

Unfortunately, the limitations of the study detract from the usefulness of the clinical outcomes. Without a control for comparisons, meaningful conclusions for the reported survival for the treatment group cannot be drawn regarding the effect of systematic VATS MLNDs via transection of the arterial ligament. It does appear that the addition of the 2L and 4L dissection adds considerably to the operative time, has a substantial rate of recurrent laryngeal nerve paralysis, and contributed to a 2–3 folds longer length of hospital stay postoperative than what has been published previously (18,19). The recent manuscript by Amer *et al.* details a single center experience with VATS mediastinal nodal dissection for patients from 2007 to 2017. Although not limited to stage I NSCLC or left-sided cancer, of the 600 patients in the cohort, 240 patients underwent major left-sided pulmonary resections for NSCLC with systematic nodal dissection, which included routine exploration of 3a, 3p, 2L, and 4L nodal stations. The manuscript provides detailed descriptions, videos, and explanations of the surgical technique using a bipolar articulating diathermy device. The arterial ligament required transection in only 4 patients to provide improved exposure to the 4L node station, and a 1.3% recurrent laryngeal nerve palsy is reported (20).

Despite the limitations in the study by Shibano *et al.*, the ability to access and resect the 2L and 4L nodal stations via VATS is an important surgical technique, and the authors should be commended for their innovation in this regard. For patients with stage I NSCLC, the debate for routine systematic MLND that includes stations 2L and 4L continues. Perhaps, as the role of targeted therapies and immunotherapies in stage IIIA (N2) NSCLC becomes clarified, the VATS technique for arterial ligament transection may be necessary to access stations 2L, 4L, and 7 during complete MLND in consolidative surgical resection as part of a multimodal treatment strategy. The strategy described by Shibano *et al.* is an important addition to the VATS surgeon's toolbox, and without a doubt, this approach may be particularly useful if applied appropriately, thoughtfully, and with a clear understanding of the potential risks and drawbacks. Like all decisions in our field, patient selection will be of utmost importance.

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None

Footnote

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