Is VAMLA/TEMLA the new standard of preresection staging of non–small cell lung cancer?

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Accurate mediastinal staging is the hallmark of a good thoracic oncology program. Mediastinal lymph node staging is important for prognostication and to guide the administration of neoadjuvant and adjuvant therapy. In addition, accurate mediastinal staging is necessary for a fair comparison of different clinical studies. The most important surgical advance in mediastinal lymph node staging in the past few years is transcervical staging, by either sternal elevation or video-assisted mediastinoscopy. The present report summarizes the existing published data evaluating such an approach. (*J Thorac Cardiovasc Surg* 2012;144:S14-7)

Of the 3 elements constituting the TNM staging system, the most difficult element to accurately determine clinically is the nodal component. The reference standard for this component of staging is anatomic surgical resection accompanied by systematic lymph node dissection. Accurate preoperative nodal staging can help avoid futile surgery with its attendant mortality and morbidity. In addition, accurate preresection staging could help select patients for neoadjuvant therapy. Improvements in staging, particularly integrated positron emission tomography/computed tomography (CT) have helped this process significantly.¹ However, the limited specificity associated with imaging necessitates invasive staging for histologic confirmation. Thus, endoscopic ultrasound-guided fine needle aspiration² represents a significant clinical advance. Although endoscopic staging offers a minimally invasive approach, the false-negative rate is high enough to warrant more invasive surgical staging when such testing is negative, especially in clinical situations in which the probability of nodal spread is high. Also, endoscopic staging does not perform well for restaging after neoadjuvant therapy. Thus, even with these advances, surgical preresection staging has a role in the management of lung cancer. The traditional method for surgical preresection staging of lung cancer has been mediastinoscopy. During the past few years, modifications of mediastinoscopy have been evaluated to enable systematic lymph node dissection, instead of sampling, to improve on the accuracy of transcervical surgical mediastinal staging. The 2 principal techniques that have evolved are transcervical extended mediastinal lymphadenectomy (TEMLA) and video-assisted mediastinal

lymphadenectomy (VAMLA). The most important studies evaluating these approaches are summarized in Table 1.

TRANSCERVICAL EXTENDED MEDIASTINAL LYMPHADENECTOMY

TEMLA extends traditional cervical mediastinoscopy using sternal elevation and video mediastinoscopy. All existing published reports of this technique have been from a single center in Zakopane, Poland. Detailed technical reports of this approach have been published both in manuscript form³ and as on-line videos (available from: <http://mmcts.ctsnetjournals.org/cgi/content/full/2006/1009/mmcts.2005.001693> and http://www.ctsnet.org/sections/clinical_resources/thoracic/expert_tech-44.html). The approach starts with a cervical collar incision akin to that for thyroidectomy. Superior and inferior subplatysmal flaps are raised. Bilateral recurrent laryngeal nerves are identified. A sternal lift is performed with a retractor to create space. A plane of dissection is established over the innominate artery, and the right paratracheal space is dissected out by direct visualization. Next, a pretracheal plane of dissection is established to dissect out the subcarinal space. The left paratracheal space is dissected after identification of the left recurrent laryngeal nerve, again by direct visualization. The aortopulmonary lymph node packet is then accessed after mobilization of the brachiocephalic vein. Using this procedure, levels 2L, 4L, 2R, 4R, 7, 8, 5, and 6 can be dissected. An initial large report of this procedure in 256 patients demonstrated excellent staging results with an accuracy of 98% in a patient population with a disease prevalence of stage N2-N3 of 31.3%. The most frequent significant complication was recurrent laryngeal nerve injury, occurring in 2.3% of patients but permanent in only 0.8%.⁴ A head-to-head comparison of TEMLA with mediastinoscopy revealed significantly better sensitivity for TEMLA than for mediastinoscopy.⁵ In that small study, 41 patients were randomized to TEMLA vs mediastinoscopy, with TEMLA revealing metastatic disease in 7 patients and mediastinoscopy revealing metastatic disease in 3 patients. However, the results of mediastinoscopy in that study were much poorer than those reported by others.⁶ The accuracy of TEMLA in restaging disease after neoadjuvant therapy

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Abbreviations and Acronyms

- CT = computed tomography
- EBUS = endobronchial ultrasound
- TEMLA = transcervical extended mediastinal lymphadenectomy
- VAMLA = video-assisted mediastinal lymphadenectomy

again demonstrated stellar results, with a sensitivity of 95.5% and negative predictive value of 97.4%.⁷ In the study by Zielinski and colleagues,⁷ the overall rate of finding unexpected N3 disease was 3 of 63 patients. These results are better than any other method of restaging short of surgical resection. An indirect comparison of endobronchial ultrasound (EBUS)-fine needle aspiration with TEMLA for restaging was published by Szlubowski and colleagues.⁸ In their study, patients underwent restaging with EBUS-fine needle aspiration. Those who were disease negative on EBUS then underwent TEMLA for restaging; 15% of patients with EBUS-negative findings had positive disease found using TEMLA. Despite only a sensitivity of 67%, the investigators concluded that surgical restaging was not mandatory with negative EBUS findings in this setting.⁸

VIDEO-ASSISTED MEDIASTINAL LYMPHADENECTOMY

VAMLA uses a mediastinoscope that can be attached to a camera that displays the image on a video monitor. In addition, the blades of the mediastinoscope used can be spread along the axis of the handle, as well as at the tip, to create a wider space for dissection. The additional room enables bimanual dissection of lymph nodes similar to a video-assisted thoracic surgery approach. The method

was pioneered by Hurtgen and colleagues.⁹ In an initial report of 46 patients, excellent diagnostic accuracy was reported, with 1 recurrent laryngeal nerve injury. A follow-up publication by the same group of 144 patients reported continued excellent staging accuracy. However, 5 recurrent laryngeal nerve injuries were reported. When the lung resection was performed in a staged fashion, marked scarring with difficult re-exploration was noted in 19.2% of these patients. Of these, 9 patients received neoadjuvant therapy. In this subset, the procedure was not possible in 2 patients because of the significant scarring and persistent bulky disease. An independent group also reported their experience with VAMLA in 108 patients with a strategy of concomitant thoracoscopic resection.¹⁰ No additional lymph nodes were identified by video-assisted thoracic surgery after VAMLA. In their series too, the main complication of VAMLA was recurrent laryngeal nerve injury in 5 patients.

INITIAL ROSWELL EXPERIENCE

We adopted TEMLA for patients with a high probability of having nodal disease, including those with large tumors, locally advanced tumors, or resection after neoadjuvant therapy. Unlike previous reports, TEMLA was performed at the same time as definitive resection, provided the frozen section analysis report was negative for N2 disease. Patients with extensive calcific atherosclerotic disease of the innominate artery or patients with previous neck surgery (including previous mediastinoscopy) were not chosen. The outcomes and nodal harvest were measured. In cases in which the nodes from a large dissected nodal packet were not counted, the volume of the sample was measured, and the nodal count was estimated at 1 node/0.5 cm³. TEMLA was attempted on 19 patients and was successfully performed on 18, with 1 technical failure owing to severe adhesions. Of the 18 procedures, 1 was performed for metastatic

TABLE 1. Summary of studies of TEMLA/VAMLA

Investigator	Approach	Patients (n)	Compared with	Performance characteristics	Side effects
Hurtgen et al ⁹	VAMLA	46	Thoracotomy	FNR 0%	1 recurrent laryngeal nerve injury
Leschber et al ¹⁴	VAMLA	23	Thoracotomy (n = 18)	FNR 0%	Blood loss >100 mL in 12%
Witte et al ¹⁵	VAMLA	144	Thoracotomy (n = 130)	FNR 0.9%, sensitivity 100%, specificity 93.8%	Recurrent laryngeal nerve injury 3.4% patients
Witte et al ¹⁶	VAMLA + VATS	18	VATS	More stations and more lymph nodes harvested by VAMLA + VATS	No difference
Yoo et al ¹⁰	VAMLA	108	VATS resection (n = 97)	FNR 0%	Recurrent laryngeal nerve injury in 4.6% patients
Zielinski et al ⁴	TEMLA	256	Thoracotomy (n = 138)	FNR 2.8%	Recurrent laryngeal nerve palsy 2.3%
Kuzdal et al ⁵	TEMLA	21	Mediastinoscopy (n = 20)	NPV of TEMLA 100% vs mediastinoscopy 66.7%	Operative time and pain intensity greater in TEMLA
Zielinski et al ⁷	TEMLA	63	Thoracotomy (n = 42)	NPV of TEMLA 97.4%	

TEMLA, Transcervical extended mediastinal lymphadenectomy; VAMLA, video-assisted mediastinal lymphadenectomy; FNR, false-negative rate; VATS, video-assisted thoracic surgery; NPV, negative predictive value.

thyroid cancer and the rest for lung cancer. Of those 17 patients, 12 (70.6%) had received neoadjuvant chemotherapy. The median intensive care unit and hospital length of stay was 1 and 5 days, respectively. No TEMPLA-related complications occurred, including recurrent laryngeal nerve injury. Of the 17 patients, 15 (88.2%) also underwent concomitant surgical resection. The lymph node harvest data are listed in Table 2. A technical observation made during the conduct of these procedures was that the TEMPLA procedure simplifies the dissection of the main pulmonary artery from the main-stem bronchus, the critical step in thoracoscopic pneumonectomy because a part of the dissection is completed during TEMPLA. In addition, we now use electromyographic monitoring (requires avoidance of muscle relaxation), already routine for many thyroid operations, to help identify and demonstrate preservation of the recurrent nerves at TEMPLA completion. This is especially useful to distinguish TEMPLA-related nerve dysfunction from any transthoracic dissection related injury.

SHOULD VAMLA/TEMLA BE THE NEW STANDARD?

From published data, it is clear that preresection staging is accomplished most accurately using TEMPLA or VAMLA compared to any other preresection investigation. However, this accuracy comes at a price—the most significant of which is recurrent laryngeal nerve injury. The current published data suggest a 1% rate of injury with TEMPLA and a 3% to 5% rate of injury with VAMLA; however, this is in expert hands. It remains to be seen whether this accuracy can be replicated by other centers, because most data presented has been from only a few centers. If the safety and accuracy are replicable, surgeons should integrate this technology with their current practice philosophy. The yield of surgical mediastinal staging in the setting of a small peripheral lung cancer with no suggestion of mediastinal positivity by CT or positron emission tomography–CT scan is too low to justify the risk of TEMPLA or VAMLA.¹¹ Therefore, it is likely that this procedure will be adopted in situations that have a greater yield, just as we have done in our practice. These include larger tumors, central tumors, and tumors with a high uptake on positron emission tomography–CT. The inclusion of larger tumors in this decision rubric is supported by at least a few retrospective studies.^{12,13} However, 1 situation in which the argument for TEMPLA/VAMLA to be the new standard of care is cogent is in restaging after neoadjuvant therapy. In this situation, if one believes that residual mediastinal disease precludes surgical resection, these methods will be superior to all other restaging methods and have a high potential for avoiding futile surgery.

A related, although different, question is the effect that such restaging might have on the overall outcome of patients with NSCLC. It might be a reasonable to consider disease detected by a larger operation such as TEMPLA

TABLE 2. Tumor characteristics and outcomes of patient undergoing TEMPLA at Roswell Park Cancer Institute

Variable	Measure
Total patients (n)	19
Technical success rate (n)	18/19 (94.7)
Pathologic finding (n)	
Metastatic thyroid cancer	1/19
Lung cancer	18/19
Length of stay (d)	
ICU	
Median	1
Range	0–16
Hospital	
Median	1
Range	0–31
Atrial fibrillation	1/18 (8.3)
Patients with concomitant lung resection	15/17 (88.2)
Pneumonia/ARDS	2/18 (16.7)
Confusion	1/18 (8.3)
Tumor characteristics	
Neoadjuvant therapy	12/17 (70.6)
Tumor involving chest wall	1/17 (5.9)
Tumors >6 cm	2/17 (11.8)
Lymph node harvest (n)	
2R	
Median	2
Range	0–6
4R	
Median	4
Range	0–14
2L	
Median	0
Range	0–3
4L	
Median	2
Range	0–19
7	
Median	4.5
Range	1–16

Data in parentheses are percentages. TEMPLA, Transcervical extended mediastinal lymphadenectomy; ICU, intensive care unit; ARDS, acute respiratory distress syndrome.

to be less relevant than that found by mediastinoscopy. This difficult question would take a large randomized clinical trial to answer and is unlikely to occur. In addition, no data are available that prove an improvement in locoregional recurrence rates with these extensive mediastinal staging procedures compared with endoscopic staging or mediastinoscopy.

CONCLUSIONS

TEMLA and VAMLA are improvements in conventional mediastinoscopy with excellent accuracy. The wider adoption of these procedures by the thoracic surgical community will help determine the reproducibility of the safety and accuracy data published thus far. If reproducible, TEMPLA and

VAMLA will constitute a new reference standard for pre-resection staging of non-small cell lung cancer.

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