Review

Current evidence on transcervical mediastinal lymph nodes dissection

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Summary

In the last decade, we witnessed the development of two new, fascinating techniques of mediastinal exploration: the video-assisted mediastinoscopic lymphadenectomy (VAMLA) and the transcervical extended mediastinal lymphadenectomy (TEMLA). During this time, several articles were published, providing a substantial body of evidence regarding different aspects of these techniques. Based on this evidence, we discuss the operative technique, its applications and results as well as questions to be answered and possible future development. The aim of this review is to provide the readers who have no personal experience with these techniques, with the key information regarding the usefulness, advantages and drawbacks of VAMLA and TEMLA.

Keywords: Mediastinum; Lung cancer; Lymphadenectomy; Staging

1. Introduction

Fifty years after Carles's original article on cervical mediastinoscopy, this technique has still been maintaining the position of the gold standard in the pre-treatment surgical staging of lung cancer patients. Simplicity, safety and vast published evidence confirming its value are among its most important advantages. However, with increasing awareness of the importance of accurate mediastinal staging, thoracic surgeons are increasingly concerned with the drawbacks of mediastinoscopy – the most critical of them being that its range is limited to the paratracheal and subcarinal nodes. These drawbacks were the stimulus for developing new methods of surgical staging of the mediastinum, much more extensive, and thus more accurate than mediastinoscopy. Attempts undertaken after the year 2000 in Germany and Poland led to establishing two techniques of mediastinal lymph node dissection using the transcervical approach. In contrast with mediastinoscopy, video-assisted mediastinoscopic lymphadenectomy (VAMLA) and transcervical extended mediastinal lymphadenectomy (TEMLA) include complete removal, rather than biopsy, of mediastinal nodal compartments. During the past years, these techniques matured and some published evidence is available, enabling an appraisal of the usefulness of these two modalities, termed ‘supermediastinoscopies’ by Rami-Porta [1].

2. Published evidence – VAMLA

The history of supermediastinoscopies began with the development by Linder and Dahan of a mediastinoscope equipped with two spreadable blades (Richard Wolf GmbH, Germany), enabling a much better exposure of the mediastinum and bimanual tissue dissection. A refinement of the technique lead to the introduction of a new method of mediastinal dissection, called VAMLA. The original article, reporting the first 46 VAMLA procedures, was published by Huertgen et al. in 2002 [2]. The authors have shown for the first time the feasibility of the complete removal of the whole content of the subcarinal and both paratracheal nodal compartments. The mean number of nodes removed was 20.7. The authors confirmed that VAMLA enables dissection of significantly more subcarinal and right paratracheal nodes than thoracotomy. There was no comparison for the left paratracheal compartment, as it was not routinely dissected at thoracotomy, but, obviously, the advantage of VAMLA is even clearer for this location.

The small number of patients in this initial series did not allow for an analysis of potential complications.

One year later, another series of 25 procedures was published by Leschber and Linder. The authors clearly presented the operative technique, but, perhaps, the most important conclusion was the idea of using VAMLA together...
with video-assisted thoracoscopic surgery (VATS) lobectomy to increase the completeness of mediastinal nodal dissection [3]. Preliminary results of such a combined approach were presented by Witte et al. [4]. The authors compared completeness of lymphadenectomy in two groups of patients who underwent VATS lung resection: in one group, only VATS mediastinal nodal dissection was performed, and, in the second group, it was supplemented by VAMLA dissection. In the VATS + VAMLA group, the mean number of dissected mediastinal lymph node stations was significantly higher than in the VATS group (6.4 vs 3.6). The same was true for the mean weight of the mediastinal specimen (11.2 vs 5.5 g). The authors stressed the particular importance of this combined approach for left-lung tumours.

In 2006, the group from Koblenz published their pooled experience with 144 VAMLA procedures performed over a 5-year period [5]. The mean operative time was 54.1 min (range: 40–175 min). In 19 of the 144 patients (13.2%), the procedure was considered incomplete by the operating surgeon. The reasons for this included calcified lymph nodes, scarring, cervical spine deformities, extreme obesity, extranodal tumour growth or intra-operative complications. The authors stressed that, in some cases, it is more prudent to leave some lymph nodes and avoid risky dissection of vital structures. Complications occurred in eight of 144 patients (5.6%), and included four recurrent nerve palsies, one mediastinitis, two venous lacerations and one arterial injury. However, some of the VAMLA procedures were supplemented by extended mediastinoscopy; hence, it is not quite clear whether all these complications were directly related to VAMLA. The authors noted that, with increasing experience, the rate of complications dropped from 5.3% in the first half of procedures to 2.6% in the second half. As many as 130 of these patients underwent subsequent thoracotomy, enabling evaluation of the completeness of VAMLA nodal dissection. In 25 patients (19.2%), marked scarring of the mediastinum was found at thoracotomy, making dissection difficult. Incomplete VAMLA dissection was confirmed at thoracotomy in 24 of 130 operated patients (18.5%), but only in two of them did they miss nodes harbour metastatic deposits. The sensitivity and negative predictive value (NPV) of the VAMLA were 0.88, and 0.98, respectively.

3. Published evidence — TEMLA

The first article on TEMLA, presenting initial experience and results in 83 patients, was published in 2005 [6]. The article included a detailed description of the operative technique: the dissection was mainly done in an open fashion using a sternal retraction system to elevate the manubrium and increase the diameter of thoracic outlet. The Wolf mediastinoscope was used for dissection of station 7 and 8 only. The range of dissection included stations 1, 2R, 2L, 3a, 4R, 4L, 5, 6, 7 and 8. The mean number of nodes removed was 43 (range: 26–85). The sensitivity and NPV of the TEMLA in detecting mediastinal node metastases were 0.9 and 0.95, respectively. The complication rate was 13.2% (recurrent nerve palsy, respiratory insufficiency, arrhythmia, pneumothorax and mental status deterioration). As with VAMLA, scarring of the mediastinum was noted, making the subsequent dissection at thoracotomy more demanding. Perhaps the most important was the finding that of 56 patients in the whole group, in whom mediastinal nodes were negative at TEMLA, only 44 underwent thoracotomy and lung resection, and the general condition of the remaining 12 deteriorated so severely that they were considered unfit for surgery and referred to oncological therapy.

To compare directly the diagnostic yield of TEMLA and mediastinoscopy, the same Polish group designed a prospective, randomised trial. This trial was terminated after inclusion of 41 patients, due to the highly significant difference in the true negative results between mediastinoscopy and TEMLA (5 vs 0, p = 0.019). The sensitivity and NPV of mediastinoscopy were 0.37 and 0.67, compared with 1.0 and 1.0 in the TEMLA group [7].

Analysing data from the same series, the authors also compared the effect of the bilateral mediastinal dissection on short-term pulmonary function, using the mediastinoscopy group as the control [8]. They did not find a significant difference between the TEMLA group and the mediastinoscopy group regarding the baseline and the first-, third- and fifth-day measurements of spirometric parameters (p > 0.98) and blood-gas analysis (p > 0.31), or of baseline and 3–5-day measurements for diffusion lung capacity for carbon monoxide (DLCO) (p = 0.91) and lung compliance (p = 0.38). The incidence of respiratory insufficiency was not significantly different (p = 0.51), but this small study, including only 21 patients in the TEMLA group and 20 in the mediastinoscopy group, was not designed to detect differences in complication rates.

Interesting results of the pooled analysis of 256 TEMLA procedures were published the same year [9]. This analysis confirmed the high number of mediastinal nodes dissected (mean 38.9, range: 15–85) and the long time of operation (mean 161 min, range: 80–330 min). During subsequent thoracotomy, missed nodes were found in 13 of 138 patients (9.4%), who underwent subsequent thoracotomy, and missed positive nodes in five of 138 patients (3.6%). Sensitivity and NPV of the TEMLA in detecting positive N2-3 nodes were 0.94 and 0.97, respectively. The complication rate (11.3%) was also similar to the original report [6], but, in the pooled analysis, the mortality rate was as high as 1.2%. Further, 38 of the 176 node-negative patients (21.6%) did not undergo surgery, almost the same rate as 21.4% in the first article.

Three years later, an updated series of 587 procedures was published by the same author [10]. The mean operative time and the number of nodes removed did not change. The complication rate was reported to be 6.8%, and the mortality was 0.9%. Sixty-six (15.2%) patients did not undergo thoracotomy despite the negative result of TEMLA, but the reasons for this were not stated.

The last original article on TEMLA concerned its utility in restaging after induction therapy [11]. This retrospective analysis included 63 patients who underwent induction chemo- or chemo-radiotherapy for N2 or N3 non-small-cell lung cancer, and the TEMLA procedure was used as the method of restaging. In 22 patients, TEMLA revealed persisting N2 or N3 disease. The authors operated on 42 patients and found that the sensitivity, accuracy and NPV of
TEMLO in restaging were: 0.95, 0.98 and 0.97, respectively. There were two (4.7%) postoperative bronchopleural fistulas and no other serious complications.

4. Diagnostic utility — staging

The published evidence provides some important information. Both, the German and the Polish groups proved the feasibility of mediastinal lymphadenectomy using the transcervical approach. VAMLA and TEMLO have some similarities, but differ regarding the technique (mediastinoscopic vs mainly open) and extensiveness of nodal dissection. With TEMLO, the extensiveness of dissection was pushed to unprecedented limits, making this technique the most complete one, regarding mediastinal lymph nodes.

However, if the utility of any technique is analysed with regard to the preoperative work-up, one has to keep in mind some basic principles of staging. The ideal staging technique should be: widely available, safe and have a high sensitivity and NPV. Other, also important factors are technical simplicity and cost-effectiveness.

All these variables are relative. Ten years ago, when enthusiastic surgeons were starting to investigate the 'supermediastinoscopies', these new techniques seemed to be safe and much more accurate than the only alternative, that is, standard mediastinoscopy. During this decade, however, important new data became available. After analysis of a larger series of patients, it became clear that risk of the extensive, preoperative dissection of the mediastinum is much bigger than initially expected. It is not a surprise that this is particularly obvious for TEMLO. The mortality rate of 1.2% is much too high as for the diagnostic procedure. Although in the updated series of 587 patients, the mortality dropped to 0.9%, it is still a rate characteristic of many lobectomy series but unacceptable for a staging procedure. Speculations, whether or not all these postoperative deaths were directly attributable to TEMLO, are inappropriate, as the only sound way of reporting postoperative mortality considers all 30-day and all in-hospital deaths as related to the procedure.

Even more important is the rate of postoperative complications. Although the only randomised study comparing TEMLO with standard mediastinoscopy did not show significant differences regarding postoperative complications, the power of this analysis in detecting differences in postoperative adverse events was limited due to the small number of patients in each group (20 and 21 patients, respectively). The study was designed to assess the difference in sensitivity and NPV in mediastinal staging, and not to compare complications. This was clearly stated in the discussion: 'Due to the small number of patients in each group the number of complications was small, making the results of any comparison vague. Any conclusions in this regard may be drawn from analysis of the greater number of patients …' [7]. In the first series published on TEMLO, in the group of 56 patients with negative mediastinal nodes, 12 patients were finally considered unfit for surgery due to the severe respiratory or circulatory deterioration. These 12 patients (21%) initially met the criteria of operability. In the largest series published to date [9], only 138 out of 176 N2-negative patients underwent surgery, resulting in the same rate of those who were denied surgery (21%).

The proportion of 21% of patients, initially fit for pulmonary resection, who lost the chance for curative treatment, is the most important drawback of the staging using the TEMLO technique. Although in the updated series, this rate dropped to 15.2%, it is still unacceptably high.

The least important drawback of the TEMLO is the long operative time. In the same, largest series published to date, it was as high as 161 min [9,10]. Although it may be shortened after several years of gaining experience, it is still comparable to the operative time of pulmonary resections, and may be a serious problem in busy centres with tight operative schedules. Although an analysis of the cost-effectiveness of the 'supermediastinoscopies' was never published, it seems obvious that an operation lasting for 161 min and requiring general anaesthesia has an important impact on the hospital expenses.

As the extent of dissection during VAMLA is more limited, the procedure-related complications are smaller and less frequent. They occurred in 5.6% of patients only, but included recurrent nerve palsies, mediastinitis, venous laceration and arterial injury — all being complications of a serious nature.

It is interesting that all papers regarding VAMLA and TEMLO come from the three centres, where these techniques were developed.

Reverting to the characteristics of the ideal staging technique, we have to conclude that 'supermediastinoscopies', although very sensitive and with high NPV, are neither safe, nor simple, nor widely available nor inexpensive.

Because variables such as safety, simplicity, short time of the procedure and cost-effectiveness are relative, they should be viewed in comparison to other, alternative techniques. Such alternatives were not available 10 years ago. However, increasing availability of positron emission tomography-computed tomography (PET-CT) and the rapid development of endobronchial and endoscopic echosono-graphy have largely changed this situation. The detailed analysis of these techniques is beyond the scope of this review, but they have to be briefly mentioned here. In the recently published study, 120 patients were staged using the combined endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA) and endoscopic ultrasonography-guided fine-needle aspiration (EUS-FNA) approach (combined ultrasound, CUS), and those who were N2-negative underwent TEMLO as a confirmatory test [12]. Only in one patient was more than single-level N2 missed by CUS, confirming the high diagnostic yield of this approach, comparable to that of TEMLO. Further, there were no complications of CUS, the procedure did not require general anaesthesia and operative suite resources and its mean time was only 28 min. Moreover, the technology of advanced endonanesthesia is constantly progressing and the diagnostic yield of these methods will undoubtedly improve further.

5. Therapeutic utility — value of mediastinal lymph node dissection

The question whether extensive mediastinal lymphadenectomy improves survival of patients operated on for non-
small-cell lung cancer remains open. Again, detailed analysis of this issue is beyond the scope of this review. It should be stressed that there are no published data available regarding the influence of VAMLA or TEMLA on the survival of the operated patients.

Theoretically, if the long-term survival analysis showed an improvement big enough to compensate for the 21% loss due to the deterioration of general fitness and the 1.2% post-procedure mortality, it might justify the use of the TEMLA in the pre-treatment staging. However, such a big effect on survival is unlikely to occur.

Another issue is the use of the transcervical lymphadenectomy to increase the completeness of the mediastinal dissection during pulmonary resection. This approach, suggested in 2002 [3], was subsequently used by the Koblenz group [4]. The results regarding long-term survival have not been published yet; however, this approach seems attractive, particularly for left-lower-lobe tumours. Prospective, randomised studies are warranted to draw conclusions regarding its utility in routine surgical practice.

6. Potential effect on the lymphatic system

The effect of the bilateral mediastinal dissection on the physiology of the pulmonary lymphatic system is an important issue. Up to now, our knowledge in this field is very limited. The only study comparing the effect of TEMLA and standard mediastinoscopy on short-term pulmonary function did not show a significant difference in spirometric parameters, blood-gas analysis, DLCO and lung compliance, as mentioned above; however, the value of these results is limited by the small number of patients in this study.

The characteristics of the lymph flow from lungs after mediastinal lymphadenectomy remains unknown. In the 1–2-week period between mediastinal lymphadenectomy (VAMLA or TEMLA) and the removal of the tumour of the lung, lymph is probably produced in the lung parenchyma. As the lymphatics in the mediastinum are disrupted, the lymph flow is certainly changed. Does the lymphatic congestion within the lungs develop, or do alternative lymphatic connections open? It is also possible that the lymph flows to the point where the lymphatic vessels are disrupted and form collections in the mediastinum. The finding of mediastinal widening as seen on chest X-rays after TEMLA might support this view. Theoretically, the mediastinal collection of lymph containing tumour cells might be the source of relapse after operative treatment.

On the other hand, EBUS or EUS needle aspiration does not interfere with the physiological flow through the lymphatics of the mediastinum.

7. Conclusions

VAMLA and TEMLA have shown the feasibility of exploration of the mediastinum using the transcervical approach. These techniques, fasciating from the technical point of view, may have many clinical applications. Future studies will show whether they can contribute to the improvement of survival after curative-intent resection for lung cancer.

Most studies published to date concerned the use of ‘supermediastinoscopies’ in lung cancer staging. Despite initial enthusiasm, the analyses of larger numbers of patients have shown that the rate of adverse effects of these techniques, particularly TEMLA, is much higher than initially expected. The rate of patients who deteriorate after this procedure and the mortality rate do not support its use for staging.

With the trend towards minimally invasive thoracic surgery, the thoracic surgical community has to look for staging modalities being also minimally invasive, but at the same time accurate and safe. Staging technique being more invasive than pulmonary resection itself cannot be accepted.

In a recent editorial, mediastinal staging was compared to the Quest for the Holy Grail [13]. It is true: we need to constantly reassess our practice in the light of new developments because the Holy Grail in medicine is as elusive as the true one was for the medieval knights. What today is considered the gold standard, may be pushed aside tomorrow by new ideas or evolving technologies. Research in surgery, like the Quest for the Holy Grail, is a never-ending story.

References