World Journal of Respirology

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DOI: 10.5320/wjr.v5.i2.166

World J Respirol 2015 July 28; 5(2): 166-175
ISSN 2218-6255 (online)

Current methods of staging and restaging of the mediastinal nodes in non-small-cell lung cancer

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Author contributions: Zielinski M designed, performed research, analyzed data and wroted the paper.

Conflict-of-interest statement: The author declares no conflicts of interest.

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Received: November 24, 2014
Peer-review started: November 26, 2014
First decision: January 20, 2015
Revised: April 13, 2015
Accepted: July 7, 2015
Article in press: July 8, 2015
Published online: July 28, 2015

Abstract

To analyze the current methods of primary staging and repeated staging (restaging) of the mediastinal nodes in non-small-cell lung cancer (NSCLC), all methods currently used for staging of NSCLC are analyzed. These methods include imaging techniques [computer tomography (CT), positron emission tomography (PET) combined with CT (PET/CT)], endoscopic/ultrasound techniques (endobronchial ultrasound/transbronchial needle aspiration) and endoscopic ultrasound/fine needle aspiration and surgical techniques [standard cervical mediastinoscopy, video-assisted mediastinoscopy, extended mediastinoscopy, video-assisted mediastinoscopic lymphadenectomy, transcervical extended mediastinal lymphadenectomy, anterior mediastinotomy (Chamberlain procedure) and video-assisted thoracic surgery]. The diagnostic yield of Chest CT is regarded insufficient for both, primary staging and restaging. The PET/CT became a standard imaging technique preceding curative surgery of radical chemo-radiotherapy. The issue of intraoperative staging is also described. Finally, the author's proposed algorithm of staging, both for primary staging and restaging after neoadjuvant therapy is presented. Detailed staging of NSCLC enables selection of patients with early stage disease for curative surgical/multimodality treatment and helps to avoid unnecessary surgery in advanced disease.

Key words: Lung cancer; Staging; Endoscopy; Surgery; Mediastinum

Core tip: All methods currently used for staging of non-small-cell lung cancer are analyzed. These methods include imaging techniques [computer tomography (CT), positron emission tomography (PET) combined with CT (PET/CT)], endoscopic/ultrasound techniques endobronchial ultrasound/transbronchial needle aspiration and endoscopic ultrasound/fine needle aspiration and surgical techniques standard cervical mediastinoscopy, video-assisted mediastinoscopy, extended mediastinoscopy, video-assisted mediastinoscopic lymphadenectomy, transcervical extended mediastinal lymphadenectomy, anterior mediastinotomy (chamberlain procedure) and video-assisted thoracic surgery. The issue of intraoperative staging is also described. Finally, the author's proposed algorithm of staging, both for primary staging and restaging after neoadjuvant therapy is presented.

Zielinski M. Current methods of staging and restaging of the mediastinal nodes in non-small-cell lung cancer. *World J Respirol* 2015; 5(2): 166-175 Available from: URL: http://www.wjgnet.com/2218-6255/full/v5/i2/166.htm DOI: http://dx.doi.org/10.5320/wjr.v5.i2.166

INTRODUCTION

The prognosis of lung cancer is still very bad with only 16.3% of all patients with of treatment for individual patients in aim to provide the best chance of cure in the lung cancer surviving 5 years[1]. One of the main important issues is a proper choice early stage of the disease and to avoid unnecessary invasive surgical or multimodality treatment in cases with the advanced disease. Estimation of the TNM factors is the key of the process of staging. Because non-small-cell lung cancer (NSCLC) is often found in a disseminating phase this is most important to rule-out distant metastases (M1). Even in stage Ⅳ, however NSCLC is a treatable, although not curable disease due to the survival advantage and improvement in quality of life over best supportive care (BSC) after platinum-based chemotherapy[2]. In patients with M1 there is no role for any curative approach like surgery or radical chemo-radiotherapy and chemotherapy or best supportive care are the only reasonable options. The only exception from this rule are the isolated brain metastases without any other symptoms of loco-regional or distal dissemination in patients who are otherwise amenable to treatment with surgery or irradiation. In the part of these patients subsequent surgical treatment is undertaken with reported 5-year survival 13% (7%-21%)[3].

For patients with ⅢB NSCLC with good performance status radical chemoradiotherapy is the preferred treatment option[4].

The limits of effectiveness of surgery are also clearly understood with more benefit than harm in stage Ⅰ amenable to resection alone because radical surgery still offers the best chance of cure despite recent reports on effectiveness of stereotactic body radiotherapy (SBRT), also described as Stereotactic ablative radiotherapy (SABR) emerging as an alternative to surgery[5-8]. SABR was shown to be superior to conventional radiotherapy in regard to local control and overall survival[9]. In patients with stage Ⅱ NSCLC surgery with adjuvant chemotherapy is regarded the standard of care with neoadjuvant chemotherapy followed by surgery as an alternative in patients with N1 nodes discovered preoperatively[10]. The most controversial group are patients with stage ⅢA, N2 metastatic mediastinal nodes for whom multimodality treatment with or without subsequent surgery should be considered[3,11].

Therefore, the critical issue in planning of the treatment in patients with NSCLC is a proper staging allowing for choice of the best therapy for individual patients. Staging of the mediastinal nodes is critical to differentiate between patients in stage Ⅰ and Ⅱ who could benefit from curative surgery or radiotherapy, stage ⅢA who should undergo multimodality treatment and stages ⅢB-Ⅳ managed without operation. Repated staging (restaging) regards patients who underwent neoadjuvant treatment and are considered candidates for subsequent radical surgery.

In the clinical practice, mediastinal nodal staging include imaging, endoscopic and surgical techniques. Recently, there has been an increasing interest in genetic and proteomic which are still experimental, however. The results of current studies are promising and it is possible that in the future circulating subtypes of micro RNA, DNA and the other biomarkers might be very useful in staging of NSCLC[12-14]. However, currently, these techniques does not allow for accurate staging of the mediastinal nodes, however. Therefore the issue of biomarkers will not be addressed in this article.

The aim of this study is to summarize current experience on staging and restaging of NSCLC.

LITERATURE RESERCH

This article is based on the search made in PubMed for English language publications on staging of NSCLC from the period 2009-2014. Keywords: lung cancer, nsclc staging, nsclc invasive staging, ebus, eus, mediastinoscopy, vats were used. Some other important earlier publications were considered, as well. Only the publications in a peer-reviewed journals, the publications including large numbers of patients, with clearly presented methodology and results were used in this study. The results of the prospective randomized trials, practice guidelines, systematic reviews, and meta-analyses were regarded especially important were included preferentially. This is not a systematic review because the choice of the articles citated in this paper was dependent on the subjective opinion of the author. Therefore, the methodology of a Systematic Review was not obeyed, like the one presented by the PRISMA methodology[15]. All methods currently used for staging of NSCLC are analyzed. These methods include imaging techniques [computer tomography (CT), positron emission tomography (PET) combined with CT (PET/CT)], endoscopic/ultrasound techniques [endobronchial ultrasound/transbronchial needle aspiration (EBUS/TBNA) and endoscopic ultrasound/fine needle aspiration (EUS/FNA)] and surgical techniques [standard cervical mediastinoscopy (CM), video-assisted mediastinoscopy (VAM), extended mediastinoscopy, video-assisted mediastinoscopic lymphadenectomy (VAMLA), transcervical extended mediastinal lymphadenectomy (TEMLA), anterior mediastinotomy (Chamberlain procedure) and video-assisted thoracic surgery (VATS)].

RESULTS

Primary staging

Imaging studies: Chest CT is generally the preliminary step of diagnosis of NSCLC providing important information on staging of the disease. A staging process is continued in patients with clinical stages Ⅰ-Ⅲb who are candidates for surgery or multimodality treatment. Chest CT is most often performed with the use of the contrast-enhanced (CE) technique allowing for differentiation of the mediastinal nodes from the mediastinal and hilar structures. The most common criterion of abnormality of the mediastinal nodes is the short-axis diameter of (> 1.0 cm) on a transverse scan. The reported pooled sensitivity, specificity and Negative Predictive Value (NPV) of chest CT were 55% (20%-91%), 81% (50%-97%) and 83% (54%-97%)[16]. There is a general agreement that Computer Tomography is insufficient in reliable staging of the mediastinal nodes.

PET: Introduction of PET has been a major progress in diagnosis and management of NSCLC. There are several advantages of use of PET including improvement of the primary staging and restaging after neoadjuvant chemotherapy or chemoradiotherapy. PET was useful in discovery of the clinically silent distant metastases which was dependent on the clinical stage of the disease: such metastases were found in 19% of patients, including 7.5% of those with stage Ⅰ disease, 18% of those with stage Ⅱ disease and 24% of those with stage Ⅲ disease by CT[17]. Pooled sensitivity and specificity and NPV of PET/CT for staging of the mediastinal nodes were approximately 77% (33%-100%), 86% (43%-100%) and 91% (79%-100%), respectively[16]. Generally, PET was found to be more sensitive than CT for identifying the mediastinal lymph node involvement in patients with known or suspected NSCLC, although this advantage was denied by the Danish authors[18]. The limitation of PET was a small diameter of the malignant lesion (< 4 mm)[19,20]. Due to this limitation PET is less sensitive in normal size mediastinal nodes. In one study, the sensitivity was 32.4% for the small nodes (< 1 cm) and 85.3% for the nodes > 1 cm[21]. The reported sensitivity and specificity of PET in discovery of the mediastinal nodes metastases were 80% and 88%, respectively[16]. Mediastinal nodes which are positive on PET should be confirmed by biopsy due to the possible false positive results, especially in case of inflammatory process in the lungs. The use of PET is indicated especially in patients with large, centrally-located adenocarcinomas, as well as in patients with hilar nodal enlargement[4,20].

The therapeutic impact of PET/CT has been studied in regard to the number of futile thoracotomies, defined as surgery for a benign lesion, intraoperative detection of N2, N3 or other stage ⅢB disease, exploratory thoracotomy for some other reason, or tumor recurrence or death within 1 year[21,22].

It was reported that the risk of death was twice as high when the Standardized Uptake Value (SUV) was above the median value and the greater FDG uptake was independently associated with a worse prognosis among patients with malignant nodules that were surgically resected, even after adjusting for age, tumor size, histology and type of resection[23-28].

Restaging of NSCLC after neoadjuvant treatment is another application of PET/CT.

In one review, sensitivity and specificity of PET for identifying residual N2 disease were only 64% and 85%, respectively which suggested that the diagnostic yield of PET/CT was inferior in restaging in comparison to the primary staging[29].

Another issue is reduction of SUV after neoadjuvant treatment. According to the results of one study, reductions in FDG uptake of at least 75% in the primary tumor and at least 50% in the involved lymph nodes were strongly associated with a complete response[30]. In the recent ACCP guidelines and ESTS guidelines PET/CT was recommended for staging of NSCLC before curative-intent treatment. In case positive results of PET tissue confirmation by biopsy is necessary[11,16,17].

Endoscopy/ultrasound: EBUS/TBNA and EUS/FNA are now considered the next phase of the mediastinal staging after CT and PET/CT. EBUS and EUS are complementary techniques allowing for visualization and biopsy of most of the mediastinal nodes. EBUS is better for examination of the right paratracheal nodes (stations 2R and 4R), for the upper paratracheal nodes (station 2L) and for the bilateral hilar nodes (N1). EUS is preferable for the lower paratracheal nodes (station 4L), and for the periesophageal and pulmonary ligament nodes (stations 8 and 9). Staging of the aorta-pulmonary window nodes (station 5) and paraaortic nodes (station 6) with EUS is a controversial issue. For the subcarinal nodes (station 7) both techniques are possibly equally good. In several studies combination of EBUS and EUS, so called combined ultrasound (CUS) were shown to be the best diagnostic yield[31,32]. With current EBUS endoscopes it is possible to perform both studies with one EBUS instrument introduced sequentially to the trachea and bronchi and then to the esophagus during one procedure performed in mild sedation. During the EBUS, EUS and CUS studies 1-4 nodal stations are usually needle-biopsied. Some authors recommend on site cytological examination to confirm that the proper cytological material has been taken during biopsy, the other authors questioned such policy, however[33-36]. Serious complications of EBUS and EUS were found in 0.3% and 0.05%, respectively in the review reported by von Bartheld *et al*[37]. The reported diagnostic yield for EBUS and EUS were dependent on the prevalence of the mediastinal metastases and was the lowest in the normal mediastinal nodes on CT and PET/CT. The reported sensitivity, specificity and NPV for EBUS were 89% (46%-97%) 100% (96%-100%) and 91% (60%-99%), and for EUS were

89% (45%-100%), 100% (90%-100%) and 86% (68%-100%), respectively[16].

Surgical staging

Current ACCP and ESTS guidelines recommend to omit surgical staging in patients with small tumors (< 3 cm) localized in the peripheral (outer third of the lung) without positive mediastinal and hilar (N1) nodes on PET/CT. In these patients the risk of false negative mediastinal nodes is low and the patients can be referred directly to pulmonary resection. Surgical staging is necessary in patients with larger tumors (> 3 cm), centrally located, with positive N1 nodes and with the positive mediastinal nodes on CT or PET/CT (even if negative on EBUS/EUS). In such patients the risk of mediastinal nodes metastases is at least 20%-25% so it is necessary to confirm the absence on such metastases with surgical staging.

Cervical mediastinonoscopy formerly described as a gold standard of the mediastinal staging is still widely used[38-40]. Currently, VAM is a recommended version of mediastinoscopy, due to the improved technology, allowing for better view, simultaneous observation of the procedure on the screen with trainees and possible recording of the procedure. Both CM and VAM require general anaesthesia and can be performed as outpatient procedures. CM and VAM enable visualization and biopsy of the paratracheal nodes, bilaterally (station 2R,4R,2L,4L) and the subcarinal nodes (station 7). The other nodal stations are out the reach of CM and VAM. Reported sensitivity and NPV are 78% (32%-92%) and 91% (80%-97%) for CM and 89% (78%-97%) and 92% (83-96%) for VAM, respectively[16]. The advantage of VAM *vs* CM regards mainly better training and comfort of thr surgeon, diagnostic superiority of VAM over CM is less clear[41].

The diagnostic yield of EBUS/EUS and mediastinoscopy was compared in the prospective randomized multi-institutional ASTER study[42]. It was found that EBUS/EUS followed by mediastinoscopy had greater sensitivity for mediastinal nodal metastases in comparison to mediastinoscopy alone 94% (62/66; 95%CI: 85%-98%) *vs* 79% (41/52; 95%CI: 66%-88%) (P = 0.02) and resulted in fewer unnecessary thoracotomies 18%; (95%CI: 12%-26%) in the mediastinoscopy group *vs* 7%; (95%CI: 4%-13%) in the endosonography/mediastinoscopy group (P = 0.02)[39]. Contrary results were reported in the retrospective study comparing EBUS and EUS with TEMLA (see below)[43]. Primary staging was performed in 623 patients: EBUS in 351, EUS in 72 and CUS in 200 patients. TEMLA was performed for primary staging in 276 patients. There was no mortality and morbidity after EBUS/EUS. One patient died after TEMLA and morbidity rate after TEMLA was 7.2%. There was a significant difference between EBUS/EUS and TEMLA for sensitivity (87.8% and 96.2%; P < 0.01) and negative predictive value (NPV) (82.5% and 99.6%; P < 0.01) in favor of TEMLA. The undisputed benefit of EBUS is possibility to differentiate between N0 and N1 for NSCLC[44].

There are several techniques allowing for biopsy of the paraaortic nodes (station 6) and the aortopulmonary window nodes (station 5) including extended mediastinoscopy, anterior mediastinotomy, VATS and TEMLA.

Extended mediastinoscopy is technique added to the standard mediastinoscopy to reach and biopsy the station 5 and 6 nodes. The key of this procedure is to perform a finger dissection to create a tunnel in the mediastinum in front of the ascending aorta and to introduce a mediastinoscope through this tunnel to visualize and biopsy the stations 5 and 6 nodes. The pooled reported sensitivity and specificity of the Extended Mediastinoscopy were 71% and 91%, respectively[16,45,46].

The anterior mediastinotomy (chamberlain procedure) is performed in general anaesthesia to reach station 5 and 6 on the left side or the station 3A,4R and 10R on the right side. The mediastinum is entered from the front after resection of the second of third costal cartillage or intercostally, without resection of ribs. This technique does not allow to reach the other mediastinal nodal stations. The reported pooled sensitivity and specificity of the Chamberlain procedure were 71% (44%-81%) and 91% (89%-95%), respectively[16].

VATS is a technique allowing to reach virtually all mediastinal nodal stations but only unilaterally, although an access to the left paratracheal nodes is very challenging and limited. The disadvantages of VATS include greater invasiveness in comparison to mediastinoscopy, the use of general anaesthesia, selective lung ventillation and several VATS ports and the use of postoperative chest drainage. These reasons limit the use of VATS for preoperative staging. The additional advantage of VATS is the possibility to evaluate T stage and to rule-out pleural dissemination. The reported sensitivity and specificity and NPV of VATS for mediastinal staging were 99% (58%-100%), 100% and 96% (88%-100%), respectively[16,47].

VAMLA and TEMLA are new techniques intended for performance of the mediastinal lymphadenectomy (complete removal of the whole mediastinal nodes with the surrounding adipose tissue) to improve the accuracy of staging instead of obtaining the pieces of the nodes obtained with the CM[48-50].

Due to this advantage, the diagnostic yields of VAMLA and TEMLA were much higher in comparison to the standard mediastinoscopy (as was proved for TEMLA)[51]. VAMLA and TEMLA are performed through the neck incision (like mediastinoscopy). Both techniques became feasible after introduction of the two-blade Linder-Dahan mediastinoscope which enabled much wider access to the mediastinum, however, contrary to the VAMLA most part of the TEMLA procedure is performed in the open technique,

Table 1 Diagnostic yield of staging procedures in non-small-cell lung cancer (%)

Diagnostic technique	Sensitivity Mean (range)	Specificity Mean (range)	Negative predictive value Mean (range)
Chest CT	55 (20-91)	81 (50-97)	83 (54-97)
PET/CT	77 (33-100)	86 (43-100)	91 (79-100)
EBUS/TBNA	89 (46-97)	100 (96-100)	91 (60-99)
EUS/FNA	89 (45-100)	100 (90-100)	86 (68-100)
Mediastinoscopy	78 (32-92)	100	91 (80-97)
Video-mediastinoscopy	89 (78-97)	100	92 (83-96)
VATS	99 (58-100)	100	96 (88-100)
VAMLA	93.8	100	96
TEMLA	96.2	100	98.9

CT: Computer tomography; PET: Positron emission tomography; EBUS/TBNA: Endobronchial ultrasound/transbronchial needle aspiration; EUS/FNA: Endoscopic ultrasound/fine needle aspiration; VAMLA: Video-assisted mediastinoscopic lymphadenectomy; TEMLA: Transcervical extended mediastinal lymphadenectomy; VATS: Video-assisted thoracic surgery.

without the use of a mediastinoscope. The nodal stations 1,3A, 3P, 5 and 6 are not removed with VAMLA but can be removed by TEMLA. In case of VAMLA, however stations 5 and 6 can be reached with use of additional Extended Mediastinoscopy. The other differences between VAMLA and TEMLA include more nodal stations and the mean number of nodes removed with TEMLA in comparison to VAMLA (11 *vs* 5 nodal stations and 20.8 *vs* 37.9 nodes, respectively) but also shorter mean operative time (54 min for VAMLA *vs* 128 min for TEMLA) and lesser invasiveness of VAMLA. There was no mortality and lower morbidity after VAMLA and 0.3% mortality and 6.6% morbidity for TEMLA, it was not clear however, if the results of VAMLA represented 30-d mortality and morbidity as was reported for TEMLA (the mortality of TEMLA was all due to no-surgical reasons). The diagnostic yield was slightly better for TEMLA than for VAMLA with reported sensitivity, specificity and NPV 96.2%, 100%, 98.9% and 93.8%, 100% and 96%, respectively[52,53]. It was not clear, however if the results for VAMLA were calculated for all nodal stations or only for those accessible for VAMLA. The other difference between VAMLA and TEMLA was the elevation of the sternum with a special retractor connected with the Rochard frame which widened the approach to the mediastinum and facilitated performance of TEMLA.

Restaging of NSCLC after neoadjuvant treatment

Restaging of the mediastinal nodes is an extremely important part of multimodality treatment of stage ⅢA NSCLC. In several studies it was found that the results of survival in patients with residual metastatic nodes much inferior in comparison to the patients in whom the nodes are N0-1 after neoadjuvant therapy. This is especially pronounced in patients with residual multi-level metastatic nodes[54-56]. Therefore, a decision if to offer surgery to the patients after neoadjuvant therapy should be based on the reliable restaging. There are several methods of restaging of the mediastinal nodes after neoadjuvant treatment Imaging studies include CT which has relatively low diagnostic yield (sensitivity 41%-59%, specificity 62%-75% and accuracy 58%-60%) and PET combined with CT (PET/CT) with sensitivity 61%-77%, specificity 85%-90% and accuracy 78%-83%[16,29,30]. PET/CT was found to be superior to CT (accuracy 89% *vs* 36% for stage Ⅰ)[16].

Restaging with endoscopic techniques include EBUS, EUS and combined EBUS/EUS. EBUS was used in the multi-institutional report (Copenhagen, Boston, Heidelberg, Chiba) on 124 patients restaged after induction therapy with sensitivity 76%, specificity 100%, PPV 100%, NPV 20%, accuracy 77%[57]. The results of the other study with use of EBUS were similar[19]. In the other study sensitivity and NPV of restaging with EBUS were 66.7% and 77.5%, respectively[58]. The reported sensitivity and NPV for restaging with EUS were 44% and 58%, respectively[59-61].

Surgical techniques of restaging include repeated mediastinoscopy (remediastinoscopy), VATS and TEMLA. Generally, remediastinoscopy seems to be a technique of moderate diagnostic yield with sensitivity of 61%-83% (with exception of sensitivity 29% in the study published by De Leyn *et al*[62]).

Restaging with VATS was described in the recent multi-institutional study reporting sensitivity of VATS of 67% (95%CI: 47-83), and negative predictive value (NPV) of 73% (95%CI: 56-86)[47].

The results of TEMLA in restaging of the mediastinal nodes reported sensitivity of 95.7% and NPV of 97.6%. In the retrospective study comparing the diagnostic yield of EBUS and EUS with TEMLA for restaging of NSCLC the endoscopic/ultrasound staging was performed in 88 patients and TEMLA in 78 patients. There was a significant difference between EBUS/EUS and TEMLA for sensitivity (64.3% and 100%, $P < 0.01$) and NPV (82.1% and 100%; $P < 0.01$) in favor of TEMLA[43,63].

Diagnostic yield of staging and restaging techniques for NSCLC are shown in Tables 1 and 2.

Intraoperative staging

Intraoperative biopsy or removal of the mediastinal nodes described as lymphadenectomy is a final step of staging. According to the ESTS guidelines there are several methods of intraoperative staging including selective biopsy of the piece of the nodes or nodes, sampling (removal of the whole node), systematic sampling (removal of the whole nodes from the nodal stations predetermined before an operation), systematic nodal dissection (systematic lymphadenectomy), lobe-specific nodal dissection and extended lymphadenectomy. Systematic nodal

Table 2 Diagnostic yield of restaging procedures in non-small-cell lung cancer after neoadjuvant therapy (%)

Diagnostic technique	Sensitivity Mean (range)	Specificity Mean (range)	Negative predictive value Mean (range)
Chest CT	55 (20-91)	81 (50-97)	83 (54-97)
PET/CT	77 (33-100)	86 (43-100)	91 (79-100)
EBUS/TBNA	89 (46-97)	100 (96-100)	91 (60-99)
EUS/FNA	89 (45-100)	100 (90-100)	86 (68-100)
Mediastinoscopy	78 (32-92)	100	91 (80-97)
Video-mediastinoscopy	89 (78-97)	100	92 (83-96)
VATS	99 (58-100)	100	96 (88-100)
VAMLA	93.8	100	96
TEMLA	96.2	100	98.9

CT: Computer tomography; PET: Positron emission tomography; EBUS/TBNA: Endobronchial ultrasound/transbronchial needle aspiration; EUS/FNA: Endoscopic ultrasound/fine needle aspiration; VAMLA: Video-assisted mediastinoscopic lymphadenectomy; TEMLA: Transcervical extended mediastinal lymphadenectomy; VATS: Video-assisted thoracic surgery.

dissection is recommended in all cases to ensure complete resection[64]. This technique includes removal of at least three mediastinal nodal stations with the surrounding fatty tissue are removed (the subcarinal nodes must be removed in every case). Additionally, hilar and intrapulmonary nodes should removed, as well. There is an a general agreement that systematic lymphadenectomy enables the most detailed study of the mediastinum due to the largest number of the removed nodes, the therapeutic benefit of systematic lymphadenectomy has not been proved unequivocally, however. Is the studies of Wu *et al*[65] and Keller *et al*[66] the authors found that systematic nodal dissection (SND) was superior to mediastinal lymph nodal sampling (MLS) in surgical treatment of non-small cell lung cancer (NSCLC).

The survival benefit was not confirmed by the results of the prospective randomized American College of Surgery Oncology Group Z0030 Trial reported by Darling *et al*[67] who concluded that in the clinical stage Ⅰ NSCLC if systematic and thorough presection sampling of the mediastinal and hilar lymph nodes was negative, mediastinal lymph node dissection did not improve survival in patients with early stage non-small cell lung cancer, but these results were not generalizable to patients staged radiographically or those with higher stage tumors.

Lobe-specific systematic nodal dissection is a technique in which specific nodal stations according to the location of the tumor are removed. This procedure is acceptable for peripheral squamous T1 tumors, if hilar and interlobar nodes are negative on frozen section studies; it implies removal of, at least, three hilar and interlobar nodes and three mediastinal nodes from three stations in which the subcarinal is always included[68]. Ma *et al*[69] found no difference between Systematic Lymphadenectomy (SL) and Lobe-Specific Lymphadenectomy (LL) in regard to migration of N staging, Overall Survival and Disease-Free Survival for cT1aN0M0 tumors with high rate of Ground-Glass Opacity (GG0). Shapiro *et al*[70] found that lobe-specific N2 nodal evaluation resulted in a recurrence rate similar to that of complete mediastinal evaluation. The authors concluded that lobe-specific mediastinal nodal evaluation appeared acceptable in patients with early-stage NSCLC.

Contrary results were reported by Maniwa *et al*[71] who found that the recurrence of mediastinal node cancer in patients undergoing Systematic Lymphadenectomy was significantly greater than that in those undergoing Lobe-Specific Lymphadenectomy. Selected lymph node biopsies and sampling are justified only to prove nodal involvement when resection is not possible, not for radical surgery[64].

DISCUSSION

Staging of NSCLC is currently an increasingly complex process with staging of the mediastinal nodes being a central part of this process. There is a general agreement that chest CT is insufficiently accurate to predict metastatic involvement in patients with a discrete enlargement of the nodes or normally looking mediastinum. PET/CT emerged as a standard of staging in the patients considered candidates for surgical treatment. The main value of PET/CT is discovery of possible clinically silent metastasis[32]. PET/CT will probably never replace CT completely, because anatomical details of the chest are visualized much more precisely on good quality CT than on PET/CT. In the clinical stage IA peripheral tumors negative PET/CT is possibly sufficient to refer patients directly to surgery. In all other patients with possibly curable tumors, invasive staging is necessary, however. During the last decade the role of EBUS and EUS rose substantially. These studies are currently recognized as the second step of staging after CT and PET/CT due to minimal invasiveness. It seems reasonable to combine endoscopic/ultrasound and surgical staging, this approach has been recently supported by results of our group[31]. The results reported by the leading experts on EBUS/EUS are impressive and lead them to claim that due to the advantages and possible superiority of EBUS and EUS in comparison to mediastinoscopy the latter one is no longer necessary. Herth *et al*[32] concluded that the combination of EBUS and EUS "may be able to replace more invasive methods as a primary staging method for patients with lung cancer". Tournoy *et al*[72] concluded that "EUS-FNA reduces the need for surgical staging procedures in patients with (suspected) lung cancer in whom a mediastinal exploration is needed". According to Vilmann *et al*[73] "It seems therefore logical to assume that the combination of EUS-FNA and EBUS-TBNA will replace more invasive methods such as mediastinoscopy for diagnosis and staging of lung cancers in the near

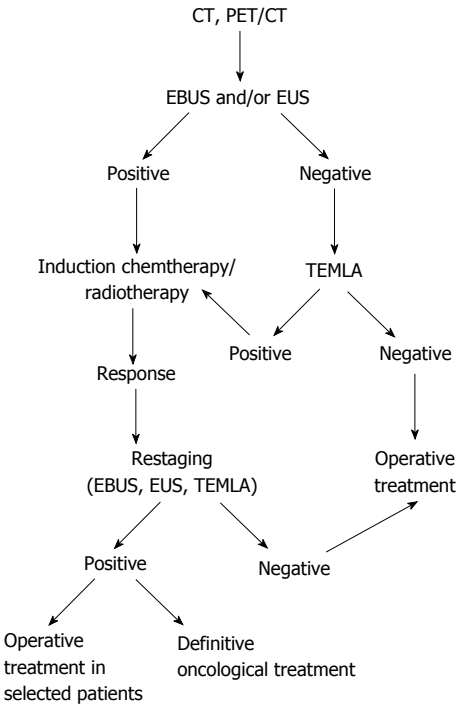

Figure 1 Institutional staging and restaging algorithm for non-small-cell lung cancer. CT: Computer tomography; PET: Positron emission tomography; EBUS: Endobronchial ultrasound; EUS: Endoscopic ultrasound; TEMLA: Transcervical extended mediastinal lymphadenectomy.

future"[73]. The same authors called the combination of EBUS and EUS "the complete medical mediastinoscopy" and claimed that "A recent publication from our group has documented a sensitivity and specificity of 100% when EUS-FNA and EBUS-TBNA is used in combination for staging of the mediastinum". However, surgical staging is not the past history. Even in some recent publication cervical mediastinoscopy was still regarded the gold standard of the mediastinal staging (Shrager)[40]. It is not clear if the results reported by the most experienced endoscopists could be achieved also by the average performers of EBUS and EUS. The reported results of mediastinoscopy pooled in the ACCP publication included broader number of publication, not only the best experts but also some poorer results that were compared to EBUS/EUS in aim to show superiority of endoscopy/ultrasound over surgical staging[16]. Therefore, the better results of EBUS/EUS might not be the proof that this modality was really better than mediastinoscopy. The final step of mediastinal nodal staging is a systematic lymphadenectomy performed during pulmonary resection of preoperatively, by means of VAMLA or TEMLA.

The importance of lymphadenectomy is limited not only to staging but this procedure may has also a therapeutic role, although the reported results are equivocal. The results of American College of Surgery Oncology Group Z0030 Trial did not confirm any beneficial influence of lymphadenectomy in comparison to sampling in clinical stage Ⅰ NSCLC but it is still possible that there might be such influence in stage Ⅱ and Ⅲ as was reported by Wu *et al*[65] and Keller *et al*[66] who found that lymphadenectomy improved the results of survival in comparison to sampling.

Due to the extremely large number of publication regarding mediastinal staging it is an imperative for every practitioner involved in diagnosis and treatment of NSCLC to form his/her own opinion how to choose the best possible way of staging. What was presented in this paper is a subjective view differing from the data presented in the most comprehensive systematic reviews[16]. For example, in my opinion, the value of relatively new techniques as PET/CT, EBUS or EUS is exaggerated, currently. In the past, the same happened to the chest CT. In the early 1980, it has been reported that sensitivity of chest CT in staging of lung cancer exceeded 80% to fall down to about 55%, according to the recent publications[74,75]. The time will solve if sensitivity of EBUS will still be around 90% as is being currently reported by the best experts. The real value of this technique will be shown in hands of an average endoscopist, who do not publish their results. In this article I made an attempt to present the staging and restaging algorithm which I recommended (Figure 1).

CONCLUSION

Current staging for NSCLC which is a complex process including several imaging, endoscopy/ultrasound and surgical techniques enables optimal selection of patients with early stage disease for curative treatment and helps to avoid unnecessary surgical or multimodality treatment in the advanced disease.

ACKNOWLEDGMENTS

The author thanks Mr Michael Clarc for language correction of the manuscript.

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