Review

Mediastinal Staging in Lung Cancer
The quest for a cost-effective strategy

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Key words
- lung cancer
- mediastinum
- staging
- cost-effectiveness
- probability analysis

Abbreviations
ACCP: American College of Chest Physicians
AJCC: American Joint Committee on Cancer
APW: aortopulmonary window
CT: computed tomography
DW-MRI: diffusion-weighted MRI
EBUS-TBNA: endobronchial ultrasound TBNA
EUS-NA: endoscopic ultrasound needle aspiration
IASLC: International Association for the Study of Lung Cancer
MLN: mediastinal lymph node
MRI: magnetic resonance imaging
n-PTP: negative post-test probability
p-PTP: positive post-test probability
PET: positron-emission tomography
QALY: quality-adjusted life years
STIR-SE-MRI: short-inversion time, inversion recovery, turbo spin-echo MRI
SUV_{max}: maximum standard uptake value
SVC: superior vena cava
TBNA: transbronchial needle aspiration
VAM: video-assisted mediastinoscopy
VATS: video-assisted thoracoscopy

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SUMMARY. **Lung cancer is the most lethal cancer worldwide. The most favourable prognosis is achieved with complete resection of the malignant tumour, which is only feasible in the absence of both distant metastases and mediastinal involvement. The suitability for surgery in patients without metastases is therefore determined by accurate mediastinal staging. The methods available for this purpose include imaging and invasive techniques, but as no single method is sufficiently accurate at ruling in and ruling out mediastinal involvement in lung cancer a strategy based on the sequential use of staging methods is required. The cost-effectiveness of such a strategy depends on the sequence of the methods chosen and the requirement for further confirmation of the results of each method. The management of positive results derived from the various staging methods is well documented, but not the management of negative results, for which the current literature is not conclusive. The estimation by probability analysis of negative post-test probabilities following the use of the various methods can assist in the management of negative results and also provides guidance for future research related to the design of the most cost-effective strategy for staging mediastinal involvement in lung cancer.** ***Pneumon 2014, 27(1):52-67*****.**

INTRODUCTION

Lung cancer is the most lethal cancer worldwide, with an overall 5-year survival of 15-17%.[1] When malignancy is anatomically restricted to the diseased lung a favourable prognosis is achieved with complete resection of the malignant tumour[2]; otherwise, complete resection is usually not feasible and patients derive greater benefit from treatment with chemotherapy and radiation.[2] Systemic spread of lung cancer occurs by dissemination of malignant cells via the lymphatics into the intrathoracic lymph nodes, or via the blood stream to reach distant sites.[3] The determination of the anatomical extent of malignant disease is called "staging".[2,4,5]

The mediastinum is the intrathoracic compartment lying between

Χρηματοδότηση: Η παρούσα εργασία δεν υποστηρίχθηκε οικονομικά από υποτροφία ή άλλη πηγή

the lungs, to which it is connected by blood and lymph vessels that serve the functions of lung perfusion and drainage.[6] Determination of the presence or absence of malignancy in the mediastinal lymph nodes (MLNs), called "mediastinal staging", is of vital importance in the management of lung cancer in patients without distant metastases, since the suitability for surgery in these patients is almost exclusively dependent on the absence of disease in the mediastinum.[2,7,8]

This is a review of the currently accepted principles of mediastinal staging in lung cancer and the available methods. The groundwork is set for the determination of a cost-effective mediastinal staging strategy based on estimated post-test probabilities of mediastinal involvement using the various methods.

PRINCIPLES OF MEDIASTINAL STAGING

Lung cancer staging is based on the tumour-nodes-metastases (TNM) system, which aims to assess the local extent of the pulmonary tumour (the T-descriptor) and to detect or exclude the presence of malignant cells in regional lymph nodes (the N-descriptor) and at distant sites (the M-descriptor).[2,5,9] The 7th Edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual TNM-version is shown in Tables 1 and 2.[10-12]

The International Association for the Study of Lung Cancer (IASLC) has developed a new anatomical map of regional lymph nodes using the major thoracic vessels as landmarks. This map permits the radiographic classification of regional lymph nodes, eliminating the need for surgery that characterized the older maps (Mountain-Dressler and Naruke)which were originally described to assist communication between thoracic surgeons during surgical lymphadenectomy and used surgical landmarks for this purpose.[5,10,12,13] In the IASLC map, depicted in Figure 1, the regional lymph nodes are classified into 14 stations and 7 zones.[5,10,12] Lymph nodes in the peripheral zones (stations 12-14) and the hilar/interlobar zones (stations 10-11) comprise nodal category N1 in the TNM-system, the malignant involvement of which is considered as intrapulmonary spread of the tumour and allows for curative resection. In contrast, nodes in the upper (stations 2-4), aortopulmonary (stations 5-6), subcarinal (stations 7) and lower (stations 8-9) zones represent the group of MLNs the malignant involvement of which implies spread of the tumour outside the lung and precludes curative-intent surgical resection in the majority of patients. According

TABLE 1. Descriptors in the 7th Edition of TNM-Classification for Lung Tumors[10,11].

Tumor	
T_x	Tumor cannot be assessed; positive sputum or bronchial washing cytology without visual evidence of tumor by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤3cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus • T1a: ≤2cm • T1b: >2-3cm
T2	Tumor 3-7cm in greatest dimension or tumor with any of the following features: i) involves main bronchus ≥2cm from carina, ii) invades visceral pleura, iii) associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung • T2a: >3-5cm • T2b: >5-7cm
T3	Tumor >7cm in greatest dimension; or tumor that invades any of the following: chest wall, diaphragm, mediastinal pleura, pericardium; or tumor in the main bronchus <2cm from carina; or associated atelectasis or obstructive pneumonitis of the entire lung; or separate tumor nodule(s) in the same lobe as the primary
T4	Tumor of any size that invades any of the following: carina, trachea, mediastinum, heart, oesophagus, great vessels, recurrent laryngeal nerve, vertebra; or separate tumor nodule(s) in a different ipsilateral lobe to that of the primary
Regional Lymph Nodes	
N_x	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes, including involvement by direct invasion
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph nodes
Distant Metastasis	
M0	No distant metastasis
M1	Distant metastasis • M1a: Separate tumor nodule(s) in a contralateral lobe; or tumor with pleural nodules or malignant pleural or pericardial effusion • M1b: Distant metastasis

TABLE 2. Stages in the 7th Edition of TNM-Classification for Lung Tumors[10,11]

	Descriptor		
Stage	**Tumor**	**Nodes**	**Metastasis**
Occult carcinoma	T_x	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1a,b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T1a,b	N1	M0
	T2a	N1	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T3	N1	M0
	T4	N0/N1	M0
	T1a,b/T2a,b/T3	N2	M0
Stage IIIB	T4	N2	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1a,b

to the TNM-system, infiltrated MLNs comprise nodal category N2 if ipsilateral or N3 if contralateral to the tumour. Involvement of the subcarinal and supraclavicular zones is considered N2 and N3 disease respectively, regardless of the side of tumour location. Finally, the division between right and left upper zones has been transferred from the midline, where it was in the older node-maps, to the left lateral border of the trachea, so that a lymph node just anterior to the trachea is now considered right paratracheal.[14]

APPROACH TO STAGING THE MEDIASTINUM

The approaches for the investigation of the presence or absence of malignancy in MLNs include the histopathological examination of tissue obtained from the mediastinum using invasive techniques (invasive mediastinal staging) and the evaluation of MLN characteristics with imaging methods (non-invasive mediastinal staging). The burden of intranodal tumour (i.e., size of >2mm, 0.2-2mm called

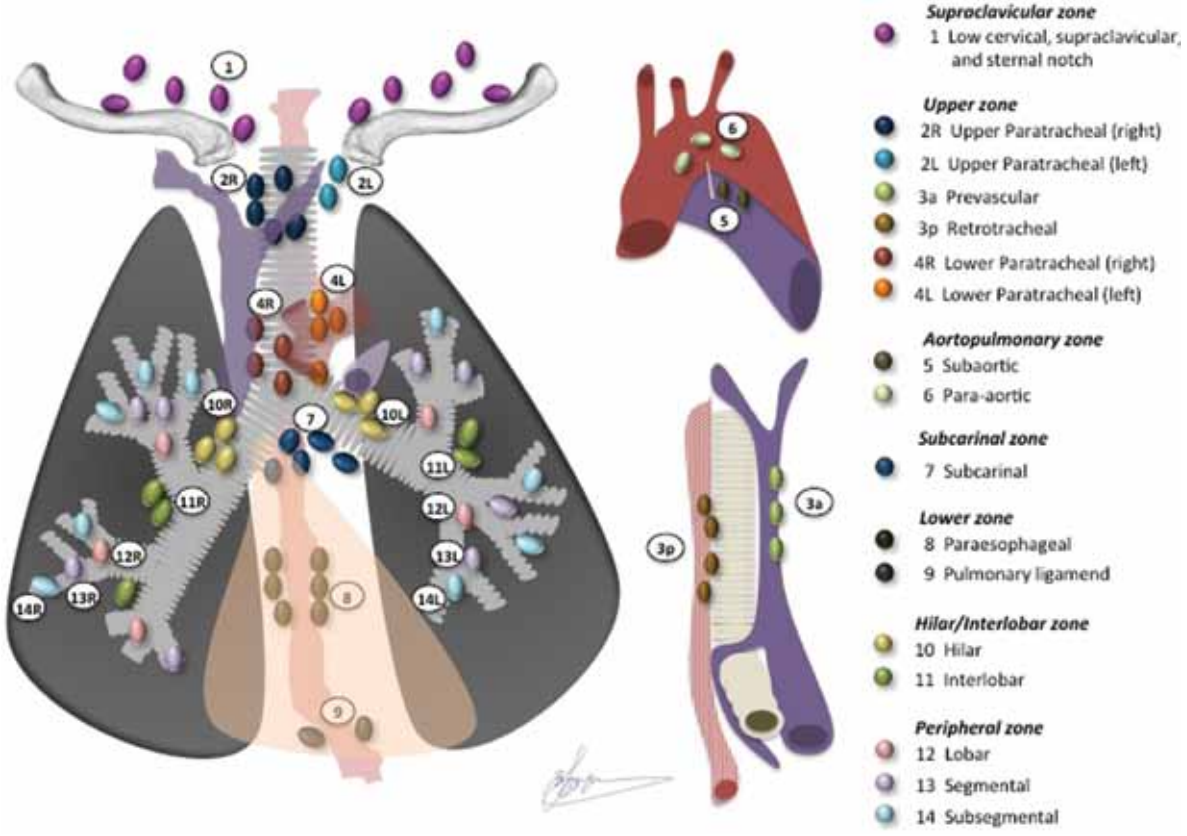

FIGURE 1. The International Association for the Study of Lung Cancer (IASLC) map of regional lymph nodes for determination of the N-descriptor in the tumour-nodes-metastases (TNM) staging of lung cancer. Regional lymph nodes are classified into 7 zones (in bold letters) and 14 stations.[5,10,12]

"micrometastasis" or <0.2mm/isolated malignant cell), the employed staging method and the thoroughness with which it is performed all effect the ability to detect malignancy in MLNs when it is present.[15,16] For any method to achieve its peak performance for this purpose, specific technical prerequisites need to be fulfilled (Table 3).[15]

Non-invasive mediastinal staging

Non-imaging methods

Non-imaging methods [e.g., clinical findings such as hoarseness and the superior vena cava (SVC) syndrome, blood biomarkers, and clinical predictive rules] while

TABLE 3. Classification of the thoroughness of mediastinal staging[15]

Approach	Thoroughness	Definition
Radiologic		
Chest CT	A. Complete assessment	• IV contrast - ≤5mm slice – size of the largest node for each mediastinal and hilar N1 lymph node station is provided
	B. Systematic assessment	• Clear statement for each mediastinal and N1 node station whether nodes are enlarged* - ≤8mm slice - ±contrast
	C. Selective assessment	• Mediastinal nodes ≥1cm stated in report but not by node station - ±contrast
	D. Poor	• Unclear statement of abnormal nodes and/or location of nodes
Metabolic		
PET	A. Complete assessment	• Integrated PET/CT scanner - glucose <200mg/dl – clear statement for each mediastinal and N1 node station whether nodes have greater uptake than the mediastinal background or not
	B. Systematic assessment	• Dedicated PET - clear statement for each mediastinal and N1 node station whether nodes have greater uptake than the mediastinal background or not
	C. Selective assessment	• Vague description of level of FDG-uptake or location of suspicious nodes OR PET read without CT correlation
	D. Poor	• No FDG-uptake in primary tumor or no dedicated PET-scanner
Minimally invasive (needle-based)		
TBNA, EBUS-TBNA, EUS-NA, TTNA	A. Complete sampling	• Sampling of each visible node in each node station (1, 2R, 2L, 3, 4R, 4L, 7, 8; and 5, 6 if LUL tumor) - ≥3 passes per node or ROSE
	B. Systematic sampling	• Nodes in each station sampled (2R, 2L, 4R, 4L; and 5, 6 if LUL tumor) - ≥3 passes per node or ROSE
	C. Selective sampling	• Biopsy of ≥1 node station, which must include a node suspicious by imaging (or ≥1cm in U/S if present) OR <3 passes and no ROSE
	D. Poor	• Visual assessment only (no node biopsied or no lymphatic tissue in aspirates)
Surgical		
Mediastinoscopy, Chamberlain, VATS	A. Complete removal	• Complete lymphadenectomy by extended- or video-mediastinoscopy (1, 2R, 2L, 3, 4R, 4L, 7, 8; and 5, 6 if LUL tumor)
	B. Systematic sampling	• Mediastinoscopy with sampling of 2R, 2L, 4R, 4L, 7; and 5, 6 if LUL tumor
	C. Selective sampling	• Mediastinoscopy with biopsy of ≥1 station, and must include any node suspicious by imaging
	D. Poor	• Mediastinoscopy with visual assessment only (no node biopsy or no nodal tissue in samples)

*: ≥1cm in short-axis dimension on transverse slice

CT: computed tomography, PET: positron-emission tomography, FDG: ^{18}F-fluoro-2-deoxy-D-glucose, ROSE: rapid on-site cytopathological examination, TBNA: transbronchial needle aspiration, EBUS-TBNA: endobronchial ultrasound TBNA, EUS-NA: endoscopic ultrasound needle aspiration, TTNA: transthoracic needle aspiration, VAM: video-assisted mediastinoscopy, VATS: video-assisted thoracoscopy, prevalence= (true positives + false negatives) / total number of patients, sensitivity= true positives / (true positives + false negatives) specificity= true negatives / (true negatives + false positives)

being helpful are inaccurate and cannot be used to confirm mediastinal metastasis.[2] Although hoarseness and SVC syndrome are highly suggestive for the presence of enlarged MLNs causing compression of the recurrent laryngeal nerve or the SVC, respectively, they are rarely (i.e., in 2-18% and 4% of cases respectively) present during staging.[17,18] Several blood biomarkers, including carcinoembryonic antigen (CEA), cytokeratin 19 (CK-19) and the platelet count, have been found significantly lower in stage I than in stage II-IV patients, but they cannot discriminate between N1 and N2-3 disease.[19-21] Finally, a clinical predictive rule using variables that are usually available prior to mediastinal staging (i.e., histology, mediastinal infiltration, central tumour, symptoms, tumour diameter, and age) was found to be only moderately accurate (AUC: 0.70, range 0.66-0.75, 95% CI).[22]

Imaging methods

The cornerstone of non-invasive mediastinal staging is imaging, which provides the opportunity to evaluate certain characteristics of MLNs.[2,8]

Chest radiograph

The use of chest X-ray to detect mediastinal involvement should be discouraged as multiple studies have shown that this form of imaging is neither sensitive nor specific in detecting or ruling out mediastinal involvement with tumour.[2,8,13]

Computed Tomography (CT)

Chest CT provides an anatomical roadmap of the mediastinum.[2,8,23] A short-axis lymph node diameter of ≥1 cm is considered to be enlargement.[2] The separation of MLNs into benign and malignant using the 1 cm cutoff , however, presents a significant rate of misclassification[2,8]; ~40% of nodes ≥1 cm in diameter are benign while ~20% of nodes <1 cm are malignant.[2] The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of CT for mediastinal adenopathy are 55%, 81%, 58% and 87%, respectively.[2]

The American College of Chest Physicians (ACCP) guidelines classify mediastinal involvement in lung cancer patients into four CT radiographic groups based on the prevalence of malignancy (Figure 2).[2] Group A is characterized by the presence of amorphous tissue in the mediastinum that encircles the vessels and airways in such a way that discrete lymph nodes cannot be discriminated. This finding is defined as "mediastinal infiltration" and although rare is highly specific (~100%) for mediastinal involvement.[2] Group B includes patients with discretely enlarged (≥1cm) MLNs. The prevalence of malignancy in these nodes is ~60%.[2] Radiographic groups C and D comprise patients with normal-sized (<1cm) MLNs, which also have a probability of malignant infiltration of 20-25% if accompanied by a central (the proximal one third of the hemithorax) tumour or N1-disease (Group C) and 10% (13% if ≥3 cm and 9% if <3 cm) in the case of peripheral (the outer two thirds of the hemithorax) tumours (Group D).[2]

Positron-emission tomography (PET)

This modality exploits the affinity of malignant cells for glucose.[2] The radiolabeled glucose analogue ^{18}F-fluoro-2-deoxy-D-glucose (FDG) follows the same cellular uptake pattern and metabolic pathway as glucose. After the first step of glycolysis, however, FDG metabolism is arrested due to the inability of the enzyme systems to further metabolize ^{18}F-FDG-6-phosphate.[24] Malignant cells can be detected by tracing the accumulated radio-analogue with a PET-camera.[2,24]

The information that PET provides is related, not to the morphological characteristics of the various anatomical structures, but to the metabolic behaviour of cells in various tissues. As a consequence, and given that the spatial resolution of PET-scanners does not allow for accurate depiction of anatomical structures, the exact anatomical localization of malignant lesions with PET is usually difficult.[25] In addition, inflammation due to infection or other inflammatory processes (e.g., granulomatous diseases) is also characterized by increased FDG uptake, giving rise to false-positive results. False-negative results may be due to the inability of current PET-scanners to detect lesions <7-10mm or to the fact that some well-differentiated low-grade malignancies, such as typical carcinoid tumours and certain types of adenocarcinoma, exhibit minimal FDG uptake.[2,26]

Despite these limitations, PET is invaluable in detecting extrathoracic sites of metastatic disease (with 10% higher sensitivity than the standard approach). It is amenable to sampling and more accurate than CT in mediastinal staging, changing CT-based N-staging in 35% of cases and decreasing the need for invasive staging by ~17% when added to CT.[2,26] In a systematic review of 4,105 patients, the overall sensitivity, specificity, PPV and NPV of PET were 80%, 88%, 75% and 91%, respectively.[2]

FDG uptake is sometimes treated not as a qualitative variable (i.e., uptake versus no uptake) but as a quantita-

tive variable (uptake quantification), using a certain cutoff in maximum standard uptake value (SUV_{max}) to detect malignancy.[27,28] However, it is documented that visual interpretation of PET-scans, especially by experienced observers, is more accurate than SUV_{max} quantification.[29] If SUV_{max} quantification is to be used, the cutoff of ≥2.5 for the detection of malignancy has the minimum sum of false-positive and false-negative rates.[29] Lymph node to primary tumour SUV_{max} ratio ≥0.56 and lymph node to liver SUV_{max} ratio ≥1.5 in MLNs with SUV_{max} ≥2.5 have been reported to increase the specificity of PET to 94% and 93%, respectively.[30,31] Further studies are required to confirm these findings.

PET-CT

Combining PET with CT allows for simultaneous evaluation of the morphological and metabolic MLN characteristics and also permits more accurate localization of "suspicious" nodes for subsequent sampling. Technically, this can be achieved either by visual correlation of CT and PET images read side by side or by incorporating the detection of FDG into chest CT images using integrated PET-CT scanners.[2]

Despite being more accurate than CT alone or PET alone in single centre studies, two meta-analyses and a systematic review showed that although the specificity

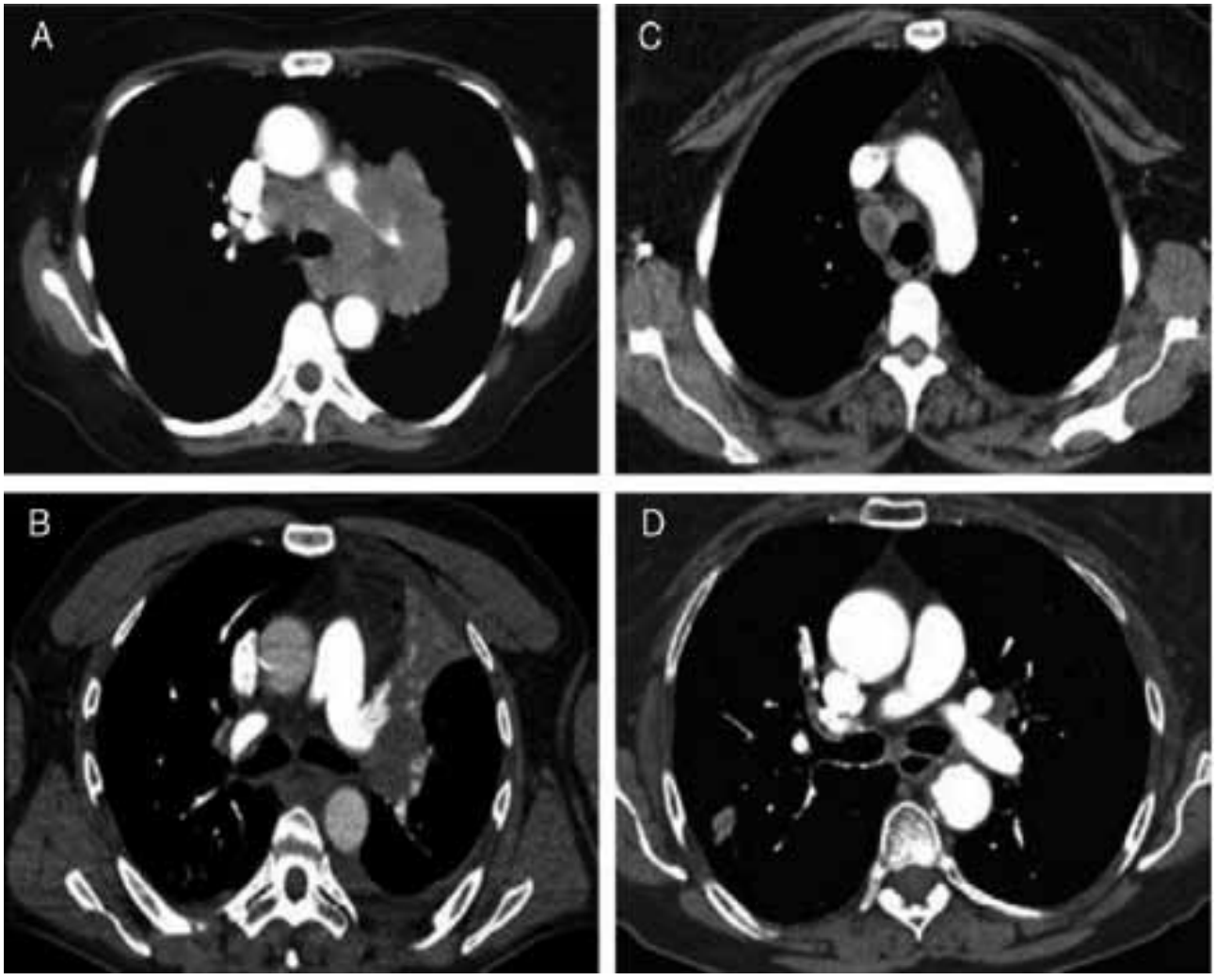

FIGURE 2. American College of Chest Physicians radiographic classification, based on computed tomography (CT) scan, of mediastinal involvement in lung cancer (with permission from ACCP). Group A: mediastinal infiltration by tumour, Group B: enlarged discrete mediastinal lymph nodes, Group C: central tumour or tumour with enlarged N1 nodes but a normal mediastinum, Group D: peripheral tumour with normal-sized intrathoracic lymph nodes.

(90-92%) of integrated PET-CT is slightly higher than that of PET, its sensitivity (62-73%) is significantly lower.[2,32,33] Silvestri and colleagues found the overall PPV and NPV of PET-CT to be 63% and 90%, respectively.[2]

Since PET has been found more sensitive (100%) but less specific (78%) with enlarged and less sensitive (82%) but more specific (93%) with normal-sized nodes, the classification of patients according to PET-CT findings into groups with different probabilities of mediastinal involvement was proposed to increase its accuracy in certain patient groups.[8,34] With the use of both CT and PET criteria MLNs can be classified into normal (PET-negative nodes <1cm) and abnormal (PET-negative nodes >1cm or PET-positive nodes <1cm or PET-positive nodes >1cm).[35] Malignancy is present in up to 80% of PET-CT abnormal MLNs, while the probability of mediastinal involvement with PET-CT normal MLNs depends on the characteristics of the primary tumour (size, location, histology) and the presence of N1-disease.[2,8,36-40] Specifically, peripheral tumours <3cm are accompanied by occult N2-disease in only 4-6% of cases in contrast with ~15% for central or larger (3-5cm) tumours.[2,41,42] In patients with N1-disease, the probability of occult mediastinal involvement is 30%.[2,36] Those with peripheral non-adenocarcinoma tumours <3cm have a low likelihood of metastases in MLNs.[42]

Magnetic Resonance Imaging (MRI)

MRI provides information about the mediastinum without the use of ionizing radiation.[43] Through its sharp spatial resolution and ability to create high soft tissue contrast, it provides high-quality depiction of the transition from one tissue to another, which is the reason for its use in the evaluation of Pancoast tumours.[2,43,44] Until recently, the MRI criteria for identifying malignant MLNs were identical to those used with CT, based solely on node size, and thus exhibiting similar performance characteristics and limitations.[44] Novel MRI techniques that allow for evaluation of MLN composition, such as short-inversion time, inversion recovery, turbo spin-echo (STIR-SE) and diffusion-weighted (DW) MRI, are superior to CT and may rival even PET in their accuracy in mediastinal staging.[44-46] Further studies are required to confirm the superiority of these new methods, however.

PET-MRI

Infiltrated PET-positive MLNs present eccentric cortical thickening or obliterated fatty hilum while non-infiltrated MLNs show low signal intensity on T2-weighted MRI.[47] Accordingly, a two-step approach, PET-scan followed by MRI in PET-positive nodes to more accurate discrimination between infiltrated and non-infiltrated MLNs might be reasonable, but this needs further research.[8]

In summary, imaging can suggest mediastinal involvement, but because of the unacceptably high rates of false-positive and false-negative scans tissue confirmation is required to ensure that patients with potentially curative cancer are not precluded from surgery.

Invasive mediastinal staging

The techniques currently available for obtaining tissue from the mediastinum can be classified into minimally invasive and surgical methods. The specificity of all invasive techniques, dependent on cytological or histological examination, is considered to be 100%, although most studies do not confirm the positive results of the techniques with a more specific method.[2]

Minimally invasive techniques

Minimally invasive techniques aim to sample MLNs by needle aspiration, usually with the patients either conscious or under deep sedation in the outpatient setting.

Transbronchial needle aspiration (TBNA)

The concept of MLN sampling through the bronchial wall was first described by Schieppati in 1949 and optimized by Wang during early 1980s, and the technique has been providing mediastinal staging in lung cancer for over two decades.[48,49] TBNA is a safe procedure with no associated mortality and rare major complications (pneumothorax, pneumomediastinum, haemomediastinum, bacteraemia and pericarditis).[50-53] Over the past decade, however, the use of TBNA has been reduced considerably because of its poor performance characteristics and the evolution of better technology, namely endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA), which provides more accurate mediastinal staging.[2]

TBNA does not allow for more than selective mediastinal staging since only subcarinal and paratracheal lymph nodes can be reliably approached, and this is the main reason for its rather low sensitivity (mean 39%, range 17-61% 95%CI) reported in a meta-analysis by Holty and colleagues.[2,54] This meta-analysis also showed that TBNA sensitivity depends on the prevalence of mediastinal involvement in the studied population.[54] In a population with high prevalence (81%) of N2-3 disease, Silvestri and colleagues reported a sensitivity of 78% with an average

false-negative rate of 23%.[2] The highest sensitivity is achieved when the lymph nodes sampled are enlarged and/or PET-positive and in location subcarinal or right paratracheal, when larger (19-gauge versus 22-gauge) needles are employed and when both cytological and histological samples are obtained or at least four aspirations in a single node-station are performed.[55-61] The use of rapid on-site cytopathological examination (ROSE) of aspirates does not increase the sensitivity of TBNA, but it does improve cost-effectiveness.[62]

Endobronchial ultrasound-TBNA (EBUS-TBNA)

Through simultaneous use of ultrasound (US) during bronchoscopy to locate and visualize the nodes of interest and to access more nodal stations, EBUS-TBNA has improved the ability to stage the mediastinum accurately.[63] EBUS-TBNA can safely reach upper and lower paratracheal, subcarinal, and hilar lymph nodes.[2,51] The only major complication of the procedure is pneumothorax, with an incidence of 0.07-0.2%.[64-67]

EBUS-TBNA is superior to CT and PET in mediastinal staging of lung cancer.[68] A systematic review of EBUS-TBNA involving 2,756 patients, reported sensitivity, specificity, PPV and NPV of 89%, 100%, 100% and 91% respectively, for this purpose.[2] Its use for enlarged and/or PET-positive MLNs increases the sensitivity of the method, which rises to 94% (range 93-96%, 95%CI) compared with 76% (range 65-85%, 95%CI) for unselected nodes.[64] To achieve the best results in the absence of ROSE at least three aspirations per node are required, while the use of ROSE can further reduce the number of aspirations without reducing the accuracy of the method.[69-71] In contrast to traditional TBNA, the needle size (22-gauge, 21-gauge or 19-gauge) does not affect the sensitivity of EBUS-TBNA.[70,72]

Endoscopic ultrasound needle aspiration (EUS-NA)

With US-guided needle aspiration through the oesophageal wall, the paraoesophageal, pulmonary ligament, subcarinal and occasionally subaortic nodes can safely be sampled.[2,73] No major complications have been reported while even minor complications, such as transient fever, sore throat, cough, nausea and vomiting, are rare (0.8%).[74] Two meta-analyses have reported sensitivity of 83% and 89%, respectively.[2,74] The sensitivity of the method is higher when enlarged MLNs are compared to normal-sized MLNs (87-92% versus 50-66%), while the overall false-negative rate is 14%.[2,74]

EBUS/EUS-NA

The combined use of EBUS and EUS provides the opportunity to reach nearly all MLNs other than the para-aortic and pre-vascular nodes.[2,8] The procedure may be performed either with the sequential use of two dedicated echo-endoscopes or with an EBUS-scope placed first in the airways and then in the oesophagus.[8] In a meta-analysis, EBUS/EUS-NA showed a sensitivity of 86% and was more sensitive than either technique separately (EBUS-TBNA: 75%, EUS-NA: 69%).[75] Wallace and colleagues reported that EBUS/EUS-NA can reduce the requirement for further surgical procedures by ~30%.[76] In a systematic review involving 811 patients, however, EBUS/EUS-NA presented sensitivity and NPV of 91% and 96%, respectively, and its performance was only slightly higher than that of each technique alone.[2]

Navigational bronchoscopy

Navigational bronchoscopy offers guidance through the tracheobronchial tree during bronchoscopy and although it is mainly used to guide sampling of pulmonary nodules, its usefulness in mediastinal staging is also under investigation.[77-80]

Transthoracic needle aspiration (TTNA)

Sampling of MLNs with TTNA is performed by the insertion of a needle through the thoracic wall under fluoroscopic or CT guidance.[2] Although the sensitivity of the technique is high (94%) when sampling bulky MLNs, its performance in smaller nodes is expected to be significantly lower. The high (~10%) incidence of pneumothorax requiring chest tube placement and the practical inability of the technique to sample more than1 nodal station restrict its use to highly selected patients.[2]

Surgical techniques

Surgical techniques of sampling MLNs are performed under general anaesthesia and in most cases require hospitalization, which often does not exceed one day, especially in specialized centres. They offer the opportunity for complete excision of MLNs and subsequent full histopathological examination.

Mediastinoscopy

Mediastinoscopy is the least invasive surgical procedure and the only technique offering simultaneous access to both sides of the mediastinum. The associated

morbidity and mortality are 2% and 0.08%, respectively.[2] The procedure is accomplished through an incision just above the suprasternal notch, followed by insertion of a mediastinoscope alongside the trachea to biopsy the upper and lower paratracheal, the pretracheal, and the anterior subcarinal lymph nodes.[2,78] The nodes of the lower and aortopulmonary zones and as the posterior subcarinal nodes are inaccessible with conventional mediastinoscopy[2], although the latter can be reached with video-assisted mediastinoscopy (VAM). In a systematic review of 9,267 patients, the sensitivity and false-negative rate were 78%, 89% and 9%, 8% for conventional mediastinoscopy and VAM, respectively.[2] Even in patients with a low prevalence of mediastinal involvement, mediastinoscopy retains its low false-negative rate.[2] About one half (42-57%) of the false-negative results are due to difficulties in accessing certain lymph node stations, while the remainder are attributed to lack of diligence in systematic lymph node dissection and sampling.[2,15]

Extended cervical mediastinoscopy

Extended cervical mediastinoscopy is a variant of classical mediastinoscopy providing access to the aortopulmonary window (APW) lymph nodes by directing the mediastinoscope lateral to the aortic arch.[81] In patients with left upper lobe tumours, the combination of classical with extended mediastinoscopy had sensitivity and NPV of 71% and 91%, respectively.[2] This technique has been reported to be associated with a mortality rate of 0.9-1.2% and complications (aortic injury, circulatory and/or respiratory insufficiency, arrhythmia, pneumothorax, stroke, recurrent laryngeal nerve palsy) at a rate of 6.8-13.2%.[2,8,78] In addition, 15.2-21.6% of patients without mediastinal involvement are finally denied curative surgical treatment for their cancer because of substantial clinical deterioration following the procedure.[81] Accordingly, extended mediastinoscopy is not considered as a routine staging method and its use outside specialized centres is not recommended.[2,78,82]

Video-assisted thoracoscopy (VATS)

Theoretically, VATS provides access to most MLNs, but in practice its usefulness is limited by the fact that only one side of the mediastinum can be assessed at each procedure. It is mainly used, therefore, for targeted sampling of lymph nodes (e.g., APW nodes) that cannot be easily accessed with other techniques. It is a safe procedure with no associated mortality and a complication rate of 2% (range: 0-9%).[2] In a systematic review, the sensitivity and false-negative rates of VATS in mediastinal staging were estimated to be 99% and 4%, respectively.[2]

Left anterior mediastinotomy (Chamberlain procedure)

Left anterior mediastinotomy is used for selective sampling of the APW lymph nodes through an incision in the second or third intercostal space just to the left of the sternum.[2] The overall sensitivity and false-negative rates of this technique in mediastinal staging are 71% and 9%, respectively.[2] The associated morbidity and mortality are low, with only rare reports of haemorrhage requiring thoracotomy.[2,78]

MEDIASTINAL STAGING STRATEGY

For a method to be sufficiently accurate to rule in and rule out mediastinal involvement reliably, the probability of mediastinal involvement after a positive (positive post-test probability, p-PTP) or negative (negative post-test probability, n-PTP) result with this method should be respectively***.[83] The post-test probability of mediastinal involvement depends on the pre-test probability and the performance characteristics of the chosen staging method(the Bayes theorem).[83] The overall prevalence (pre-test probability) of mediastinal involvement in patients with potentially resectable lung cancer is 40-50%.[1,84] At this level of pre-test probability, no single method is able to rule in and rule out mediastinal involvement definitively (Figure 3). As a consequence, the combined use of multiple methods is required for this purpose, with the order in which these methods will be used representing a mediastinal staging strategy. Farhaj and colleagues have demonstrated the superiority of using a strategy over a single technique for staging the mediastinum of lung cancer by documenting a lower mortality in those undergoing bi- (HR: 0.58) or tri-modality (HR: 0.49) compared with single modality mediastinal staging.[85]

Cost-effectiveness assessment

The effectiveness of a mediastinal staging strategy is evaluated by its ability to prevent futile surgery while allowing for curative thoracotomies. This ability can be measured either directly, by the accuracy with which the staging detects and excludes mediastinal involvement, or indirectly, by the improvement in specific health measures, such as life-years or quality-adjusted life years (QALY).[84,86,87] The QALY-index is commonly used for this

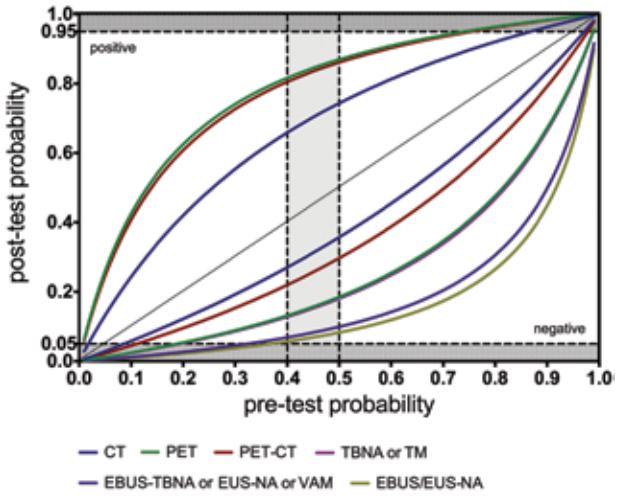

FIGURE 3. Curves of positive and negative post-test probability for mediastinal involvement using various mediastinal staging methods as a function of the pre-test probability of N2-3 disease. Construction of the curves was based on the estimation of post-test probabilities for all (0-100%) values of pre-test probability using the likelihood ratios derived from overall sensitivities and specificities of the methods (see Table 4) according to Bayes theorem.[83] Positive post-test probabilities of invasive techniques are not depicted since they are equal to 100% at all levels of pre-test probability. The shaded area between the vertical dotted lines represents the overall prevalence (40-50%) of mediastinal involvement in patients with potentially resectable lung cancer. CT: computed tomography, PET: positron emission tomography, TBNA: transbronchial needle aspiration, TM: transcervical mediastinoscopy, EBUS-TBNA: endobronchial ultrasound TBNA, EUS-NA: endoscopic ultrasound needle aspiration, VAM: video-assisted mediastinoscopy.

purpose, and represents the years lived after the application of the strategy as a function of the quality of health, expressed in utility values and measured by instruments such as the European Quality-5D questionnaire, over the life of the patient.[88,89]

The cost of such a strategy includes the financial cost of the use of facilities and equipment (direct) and that from the management of complications (indirect).[78,90-92] The overall cost increases incrementally from imaging to minimally invasive to surgical techniques.[2,78,90,91] The cost of a strategy thus depends largely on the percentage of patients requiring confirmation of ambivalent results from initial staging methods by the use of more invasive techniques for more accurate staging. The strategy with maximal effectiveness that uses invasive methods in the fewest number of patients provides the most favourable cost-effectiveness ratio.

Sequence of methods in a cost-effective strategy

Although imaging techniques (i.e., CT followed by PET, or PET-CT) have proved to be cost-effective as the initial methods in a mediastinal staging strategy, there is lack of agreement with regard to the selection of the subsequent invasive techniques, the order of their application and the point at which the investigation for mediastinal malignancy should be considered sufficiently accurate.[90,93-95]

Most authors agree that the US-guided endoscopic techniques (EBUS-TBNA, EUS-NA or EBUS/EUS-NA), rather than a surgical approach directly after imaging, present the most favourable cost-effectiveness profile.[96-98] In a multicentre randomized controlled trial (the ASTER trial), Annema and colleagues compared mediastinoscopy with EBUS/EUS-NA followed by mediastinoscopy only when negative, and showed that the latter strategy was associated with a more than 50% reduction in futile surgery (18% versus 7%).[84] From the results of the same trial, Sharples and colleagues concluded that EBUS/EUS-NA followed by mediastinoscopy only when negative was both more accurate and less costly than mediastinoscopy alone[95]. Harewood and colleagues, using a cost-minimizing model to compare seven strategies involving the separate use or combinations of invasive techniques, found the endoscopic techniques more cost-effective than imaging or surgical approaches.[92] Traditional TBNA had significantly lower sensitivity and NPV for this purpose, resulting in both lower effectiveness and higher cost.[92]

Recently, Sogaard and colleagues compared six different strategies based on a probabilistic analysis by which the hypothetical expected cost (€) and outcome (gained life-years) of each strategy were assessed.[90] The strategy with the most favourable cost-effectiveness ratio (18,067€±2,319€/1.282±0.605 life-years gained, per patient) was CT, followed by PET-CT, followed by confirmation of only PET-CT positive results with EBUS-TBNA, and referral for curative thoracotomy of patients with a PET-CT-negative mediastinum. The same strategy, but with additional confirmation of all PET-CT negative results, was more costly (18,616€±2,254€/1.284±0.606 life years gained, per patient) but also significantly more accurate (98% versus 88%), suggesting the presence of heterogeneity in the prevalence of mediastinal involvement among patients with a negative PET-CT mediastinum.

The decision for further confirmation of negative results

Although the recommended order (imaging followed by endoscopic sampling followed by surgical techniques)

TABLE 4. Post-test probabilities of mediastinal involvement with various methods according to the prevalence of disease (based on data from ACCP Guidelines, 3rd ed.)[2]

Method	Prevalence (%)	Sensitivity (%)	Specificity (%)	LR(+)	LR(-)	p-PTP % (median)	n-PTP % (median)
CT	31-99	67	74	2.58	0.45	54-100 (83)	17-98 (45)
	21-30	63	87	4.85	0.43	56-66 (62)	11-15 (13)
	1-20	41	83	2.41	0.71	2-38 (22)	1-15 (8)
	overall: 30	55	81	2.89	0.56	55	19
PET	31-99	85	87	6.54	0.17	75-100 (92)	7-94 (24)
	21-30	77	83	4.53	0.28	55-66 (61)	7-11 (9)
	1-20	71	92	8.88	0.32	8-69 (51)	0-7 (4)
	overall: 28	80	88	6.67	0.23	74	8
PET-CT	overall: 22	62	90	6.20	0.42	64	11
TBNA	overall: 81	78	100	-	0.22	[100]	48
EBUS-TBNA	80-99	96	100	-	0.04	[100]	14-80 (25)
	60-79	91	100	-	0.09	[100]	12-25 (17)
	40-59	87	100	-	0.13	[100]	8-16 (11)
	20-39	87	100	-	0.13	[100]	3-8 (5)
	1-20	78	100	-	0.22	[100]	0-5 (3)
	overall: 58	89	100	-	0.11	[100]	13
EUS-NA	80-99	96	100	-	0.04	[100]	14-80 (25)
	60-79	92	100	-	0.08	[100]	11-23 (15)
	40-59	88	100	-	0.12	[100]	7-15 (11)
	20-39	61	100	-	0.39	[100]	9-20 (14)
	overall: 58	89	100	-	0.11	[100]	13
EBUS/EUS-NA	40-65	96	100	-	0.04	[100]	3-7 (4)
	20-39	82	100	-	0.18	[100]	4-10 (7)
	overall: 33	91	100	-	0.09	[100]	4
Mediastino-scopy	40 (cN0-3)	83	100	-	0.17	[100]	10
	16 (cN0)	47	100	-	0.53	[100]	9
	overall: 33	78	100	-	0.22	[100]	10
VAM	overall: 31	89	100	-	0.11	[100]	5
VATS	overall: 63	99	100	-	0.01	[100]	2

LR: likelihood ratio, p-PTP: positive post-test probability, n-PTP: negative post-test probability, CT: computed tomography, PET: positron-emission tomography, TBNA: transbronchial needle aspiration, EBUS-TBNA: endobronchial ultrasound TBNA, EUS-NA: endoscopic ultrasound needle aspiration, VAM: video-assisted mediastinoscopy, VATS: video-assisted thoracoscopy, prevalence= (true positives + false negatives) / total number of patients, sensitivity= true positives / (true positives + false negatives) specificity= true negatives / (true negatives + false positives)

in which various methods should be used in a cost-effective mediastinal staging strategy, and the management of lung cancer patients with positive results on imaging (requirement for tissue confirmation) or invasive (establishment of mediastinal involvement) tests are well documented, the current literature does not adequately answer how patients with negative results on PET-CT and/or invasive methods should be managed. A clinical model recently proposed for the detection of occult N2-disease in patients with PET negative mediastinum was

only moderately accurate (AUC: 0.65) for this purpose.[99]

To answer this question, the step needs to be determined at which the effectiveness target of n-PTP <5% for patients with different pre-test probabilities of mediastinal involvement is reached. By using the prevalence (pre-test probability) of N2-3 disease in various CT-radiographic groups and the performance characteristics of various methods (see Table 4), a Bayesian approach can be applied to estimate the post-test probabilities of mediastinal involvement for any patient with each method.[2] Such a probability analysis is shown in Figure 4 and its key points are: a) with peripheral tumours <3cm, PET-CT normal mediastinum rules out N2-3 disease in 97% of cases, b) with peripheral tumours >3cm or central tumours or N1-disease, PET-CT normal mediastinum cannot rule out mediastinal involvement, and EBUS-TBNA is necessary for this purpose, c) with enlarged or PET-positive MLNs, a negative EBUS-TBNA should be followed by mediastinoscopy to rule out mediastinal involvement, d) in patients with both enlarged and PET-positive MLNs, negative EBUS-TBNA and mediastinoscopy results cannot rule out N2-3 disease.

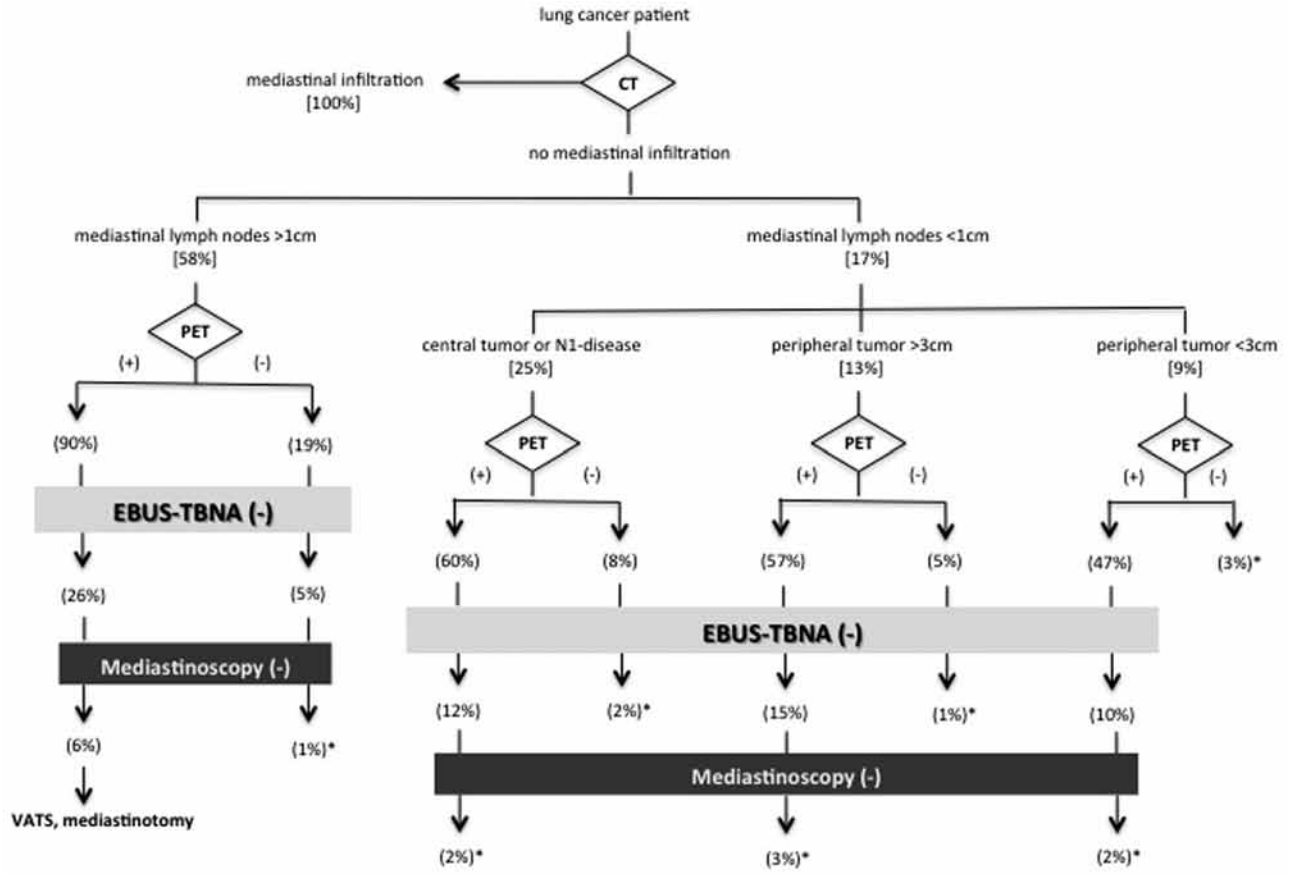

FIGURE 4. Estimated post-test probabilities of mediastinal involvement with the sequential use of staging methods of gradually increasing invasiveness (non-invasive, followed by minimally-invasive, followed by surgical) in patients with various prevalences (pre-test probability) of N2-3 disease. EBUS-TBNA was the endoscopic method selected in this analysis because it is the most readily available technique among pulmonologists and presents performance comparable with that of EUS-NA and EBUS/EUS-NA.[2] Positive post-test probabilities of invasive sampling techniques (EBUS-TBNA and mediastinoscopy) are not shown since they all equal 100% and can definitively rule in mediastinal involvement. Numbers in brackets are probabilities reported in ACCP guidelines.[4] Numbers in parentheses are post-test probabilities calculated according to the Bayes theorem with the use of the following equations[83]: a) post-test probability = post-test odds / (post-test odds + 1), b) post-test odds = pre-test odds x likelihood ratio (LR), c) pre-test odds = pre-test probability / (1-pre-test probability), d) LR(+) = sensitivity / (1-specificity), e) LR(-) = (1-sensitivity) / specificity.
*: negative post-test probability sufficient to rule out mediastinal involvement. CT: computed tomography, PET: positron emission tomography, EBUS-TBNA: endobronchial ultrasound-transbronchial needle aspiration, VATS: video-assisted thoracoscopy.

CONCLUSION

Mediastinal staging is critical in the management of lung cancer since it determines the suitability for surgery in those patients without distant metastases. A sequential mediastinal staging strategy based on the complementary use of various methods (imaging, minimally-invasive, and surgical) is associated with higher accuracy and lower mortality than the use of any one method alone. The employment of endoscopic sampling methods (EBUS-TBNA, EUS-NA or EBUS/EUS-NA) directly after imaging (CT followed by PET or PET-CT) and before the use of surgical sampling techniques provides the most favourable cost-effectiveness ratio in such a strategy. The requirement for further confirmation of results in this strategy is also a critical factor in determining cost-effectiveness. The currently recommended management of positive results includes tissue confirmation in patients with CT or/and PET positive mediastinum, and no further investigation in those with positive pathology from invasive MLN sampling. The optimal management of negative results is yet to be determined. Pending the results of appropriately designed and conducted clinical studies addressing this question, the management of negative results should be based on the post-test probabilities of mediastinal involvement using the various staging methods, which can be estimated by probability analysis.

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