

## The Challenge of Mediastinal Staging

Loris Ceron,<sup>1</sup> Lucio Michieletto,<sup>2</sup> Andrea Zamperlin<sup>2</sup> and Laura Mancino<sup>3</sup>

1. Director, Pulmonology Unit, Ospedale dell'Angelo Venice-Mestre; 2. Senior Registrar, Pulmonology Unit, Ospedale dell'Angelo Venice-Mestre;  
3. Senior Registrar, Pulmonology Unit, Ospedale S Bortolo Vicenza

### Abstract

Lung cancer staging is a crucial step in both correct prognosis and therapy. Mediastinal staging in particular is usually accomplished using imaging techniques such as computed tomography and 18F–glucose positron-emission tomography, minimally invasive techniques, i.e. transbronchial needle aspiration with or without ultrasound guidance (endobronchial ultrasound) and transoesophageal ultrasound-guided fine needle aspiration and surgical procedures, i.e. mediastinoscopy, thoracoscopy. Each of these techniques has its own sensitivities, specificities and predictive values that must be thoroughly considered within the staging route, with the aim of achieving the best result with the least resource consumption and the least discomfort to the patient; the correct evaluation of a negative result on the basis of its predictive value is essential as well. In this article we suggest a mathematical model that can predict the probability of nodal metastasis after a certain number of diagnostic procedures has been performed, providing an objective way of evaluating whether a patient is fit for surgery or, conversely, whether further investigations are required.

### Keywords

Transbronchial needle aspiration, transoesophageal fine-needle aspiration, mediastinoscopy, positron-emission tomography, computed tomography, Bayes' theorem

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**Correspondence:** Loris Ceron, Pulmonology Unit, Ospedale dell'Angelo, Via Paccagnella 11, 30174 Mestre-Venice, Italy. E: loris.ceron@ulss12.ve.it

Mediastinal staging in non-small-cell lung cancer (NSCLC) is crucial for correct prognosis and therapeutic choices. When no distal metastases are present, mediastinal involvement is the most important prognostic factor;<sup>1</sup> therefore, mediastinal exploration represents an important resource-consuming step in patient evaluation. Ruling out mediastinal nodal involvement allows the patient to be considered for surgery; otherwise, complementary options such as chemotherapy or radiotherapy must be evaluated, subsequent surgery being suggested only when downstaging is achieved. The term clinical staging or pre-operative staging is commonly used in comparison with pathological staging, achieved during surgical intervention, which represents the gold standard in lung cancer staging.

Nowadays, several techniques are available for pre-operative mediastinal staging. The techniques can be separated into: imaging techniques, such as contrast-enhanced computed tomography (CT) and positron-emission tomography (PET); minimally invasive techniques, such as transbronchial needle aspiration (TBNA), endobronchial ultrasound (EBUS)-guided TBNA and endoscopic ultrasound (EUS)-guided fine-needle aspiration (FNA); and surgical techniques, such as mediastinoscopy, mediastinotomy and thoracoscopy.

Some of these techniques – PET, mediastinoscopy and EUS-FNA – provide very sensitive and specific results. TBNA alone, on the other hand, although highly specific, has not proved to be sufficiently sensitive and may provide false-negative results; its performance improves when supported by EBUS.

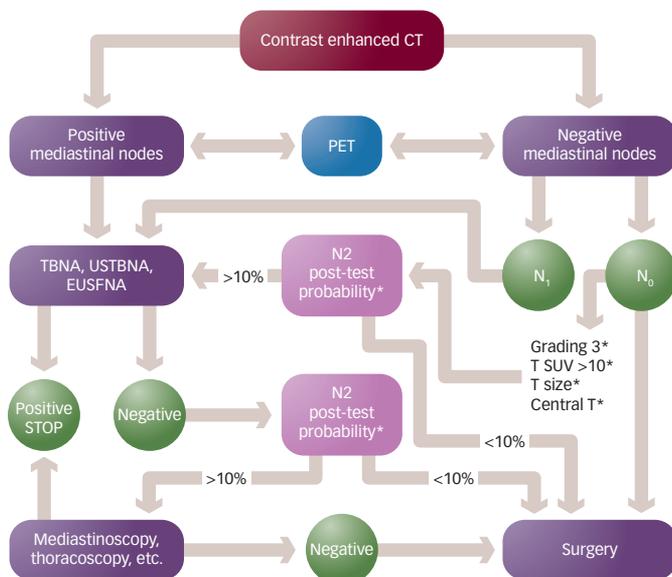
### Available Techniques Computed Tomography

Alongside standard chest X-ray, CT is currently considered the fundamental preliminary examination when evaluating lung cancer. Contrast-enhanced chest CT is highly accurate in detecting lymph node enlargement, although a high interobserver variability rate may exist.<sup>2</sup> The literature reports good specificity of CT (about 80%) and moderate sensitivity (not above 60%).<sup>3</sup> This may imply that an enlarged mediastinal lymph node (short axis  $\geq 1$ cm) in a patient affected by lung cancer may in fact be healthy in four cases out of 10, whereas metastasis may be found in up to 20% of patients with normal size lymph nodes (short axis  $< 1$ cm). Therefore, secondary neoplastic localisation cannot be diagnosed uniquely on the basis of the dimensions of the lymph nodes,<sup>4</sup> and CT thus plays a central role in guiding the choice of the most appropriate procedure for node biopsy. Accordingly, the recent American College of Chest Physicians (ACCP) guidelines on mediastinal staging report that CT may be considered sufficient only in cases of massive mediastinal invasion; in any other cases, further diagnostic techniques should be implemented.<sup>5</sup>

### Positron-emission Tomography

PET is probably the most revolutionary diagnostic technique of the last 20 years in the investigation of NSCLC.<sup>6–9</sup> Its sensitivity and specificity are 75–91% and 78–93%, respectively, depending on lymph node size.<sup>10</sup> Its overall sensitivity and negative predictive value are comparable to those of mediastinoscopy, such that mediastinal negativity on PET paves the way to the use of surgery with no need for further

**Figure 1: Flowchart for a Mediastinal Study**



\*Bayes' theorem.

CT = computed tomography; EUSFNA = endoscopic ultrasound-guided fine-needle aspiration; PET = positron emission tomography; SUV = standardised uptake value; T = tumour; TBNA = transbronchial needle biopsy; USTBNA = ultrasound-directed transbronchial needle aspiration.

examinations.<sup>10-14</sup> However, despite a small amount of reported false-negatives (5–8%), a recent meta-analysis showed that in patients with normal-sized lymph nodes the false-negative rate may reach 25%.<sup>15</sup> This happens above all for central<sup>5,16,17</sup> or large tumours<sup>1,18</sup> or for tumours with an elevated standardised uptake value (SUV).<sup>18,19</sup> Nevertheless, owing to its high performance, PET is considered the reference test for all potentially operable patients.<sup>20</sup>

## Needle Aspiration Techniques

The use of TBNA in lung cancer staging has recently been steadily increasing. The sensitivity and specificity of this technique are around 76 and 98%, respectively.<sup>21</sup> When rapid on-site examination (ROSE) is coupled with TBNA,<sup>22</sup> the performance of TBNA increases owing to the shorter duration and lesser risks of the procedure according to some authors,<sup>23</sup> or because of better accuracy according to others.<sup>24,25</sup>

When supported by other complementary techniques, such as EBUS, TBNA yield may improve, and its sensitivity may rise >90% when a convex probe is used, which allows direct observation of the needle piercing the lymph node.<sup>26-29</sup> However, in clinical practice the worthwhile application of ultrasound appears limited to lymph nodes at American Thoracic Society (ATS) stations one and two (in such cases endoscopists have no definite safe landmarks for the puncture), to small lymph nodes (≤5mm) and when ROSE is not performed.<sup>30,31</sup> Similar to TBNA, EUS-FNA provides high sensitivity and specificity; its major limitations are lymph nodes anterior to the trachea and to the main bronchi.<sup>32-34</sup>

As for other needle aspiration techniques, a positive result can be considered definitive for staging, while surgical confirmation is generally required in the event of a negative result.<sup>5,35</sup> This assumption does not consider any qualitative evaluation of a non-diagnostic sample; in fact, to date no reliable criteria for distinguishing whether a sample comes from a lymph node or not have been identified. Martinez-Olondris et al. in a series of 194 patients demonstrated that the sensitivity of TBNA was 88% when the study included only

adequate samples, namely samples with neoplastic cells or lymphoid cellularity.<sup>36</sup> Others have proposed a score based on the number of lymphocytes on the slide; using EBUS-TBNA and accounting only for the samples with more than 40 lymphocytes per field (magnification x40), the authors produced only one false-negative.<sup>37</sup> Therefore, we can suppose that using semi-quantitative criteria for evaluating adequacy can improve TBNA performance on healthy lymph nodes, modifying the value of a negative result in mediastinal staging.

## Surgical Techniques

Surgical techniques are considered as a source of reference for the evaluation of suspicious lymph nodes following a negative or inadequate cytological result. Of the surgical techniques, mediastinoscopy is the gold standard in the pre-operative staging of lung cancer. Its sensitivity is high (75–90%) and complications are rare, although potentially severe.<sup>5,38-41</sup> However, it can only reach the paratracheal stations (levels one, two and four) and the subcarinal station (level seven, anterior).<sup>5</sup> In general, this technique is not popular among surgeons;<sup>42</sup> in addition, the increasing availability and accuracy of ultrasound-guided minimally invasive techniques have been challenging the reference role of mediastinoscopy in recent years.<sup>43</sup>

Video-assisted thoracic surgery (VATS) can reach several mediastinal levels, in particular nodal stations five and six, but its sensitivity varies widely among series. The aorto-pulmonary window station five can be approached by Chamberlain's anterior mediastinotomy when other techniques are not available or have failed.<sup>5</sup>

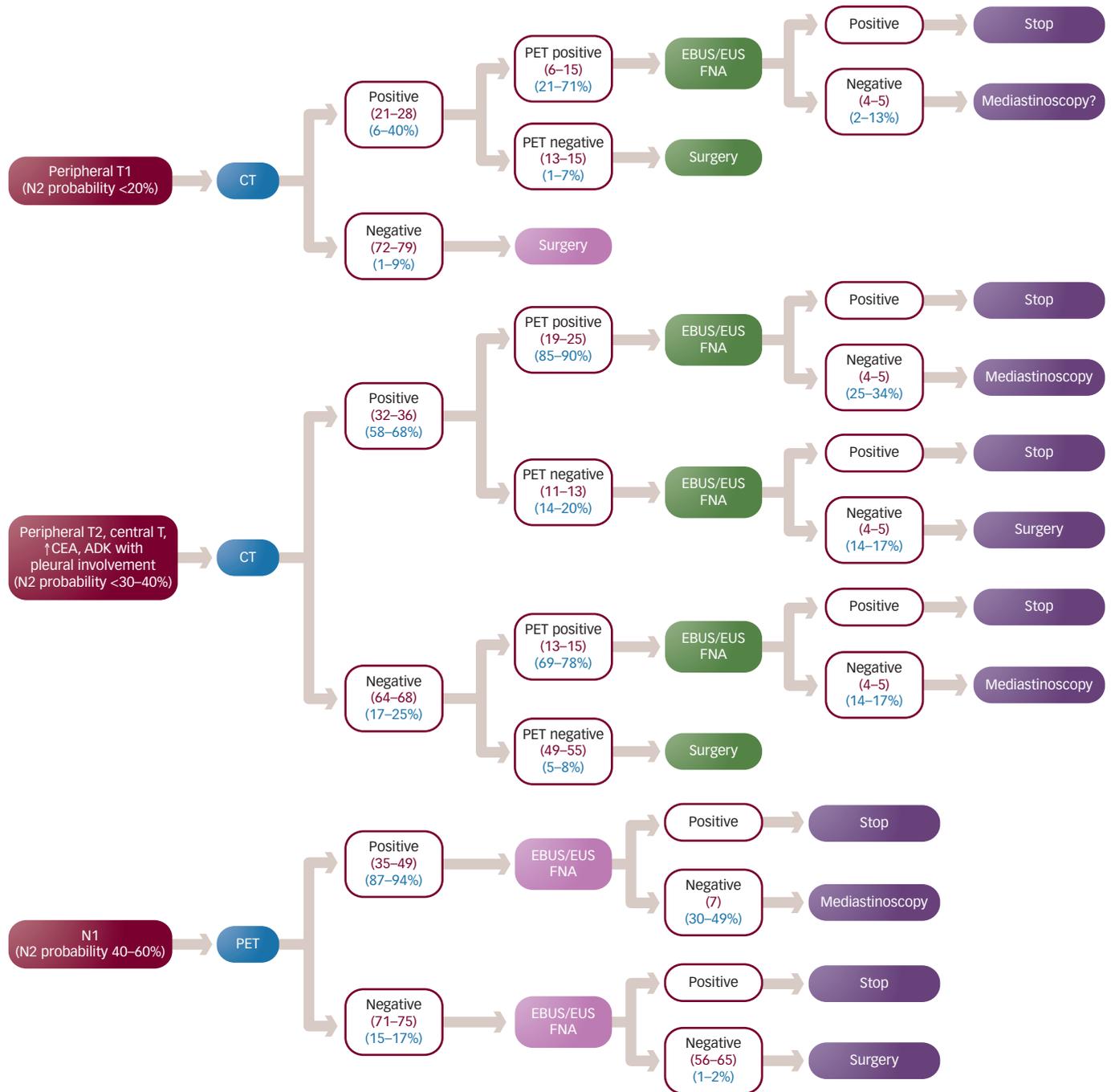
## Staging Protocols for Mediastinum

It is well known that in clinical stage N0, histology–cytology finds nodal metastases in up to 20–25% of cases.<sup>18,44,45</sup> Unexpected mediastinal involvement (even without CT or PET abnormalities in the mediastinum) is more common if pathological hilar (N1) lymph nodes are present.<sup>18,46</sup>

Many risk factors for unforeseen mediastinal metastasis have been described,<sup>8,18,47-58</sup> including tumour size, adenocarcinoma cell type, elevated levels of carcinoembryonic antigen (CEA), central or right upper lobe location, tumour-related symptoms, patient age <65 years, tumour SUV >9–10 and pleural involvement. When risk factors are lacking, some authors suggest avoiding systematic lymph node dissection during surgical resection.<sup>59,60</sup>

The European Society of Thoracic Surgery (ESTS) recommends direct resort to surgery in cT1N0 tumours only for squamous cell carcinoma, and to mediastinoscopy for other cell types; in the other clinical stages, minimally invasive techniques (EBUS-TBNA, EUS-FNA) and, if negative, mediastinoscopy are suggested. When PET is available, surgery is advised in clinical stage 1, except in central tumours, adenopathies >1.6cm and tumours with a low SUV.<sup>1</sup> However, observations that the probability of mediastinal metastasis rises in line with the tumour SUV value<sup>18,19</sup> conflict with the ESTS position. The ACCP<sup>5</sup> guidelines agree on avoiding further examinations in peripheral stage 1 tumours, but do not differentiate among cell types, and suggest cytological sampling irrespective of PET result when CT shows enlarged nodes and surgical confirmation of every negative needle aspirate. This argument is sometimes used due to the moderate negative predictive value of mediastinoscopy, which is not vastly different from that of EBUS-TBNA.<sup>61</sup> As only patients with microscopic node involvement seem to benefit from surgery,<sup>62-69</sup> many surgeons

Figure 2: Simplified Algorithm for Mediastinal Study



Endobronchial ultrasound/endoscopic ultrasound-guided (EBUS/EUS) if tumour (T) standardised uptake value (SUV) >10; patient's age <65 years; right upper lobe of lung (RUL). Red value range = percentage of positive or negative results depending on the pre-test probability considered. Blue value range = post-test probability of mediastinal involvement by the examinations performed.

ADK = adenocarcinoma; CEA = carcinoembryonic antigen; CT = computed tomography; FNA = fine-needle aspiration; PET = positron emission tomography.

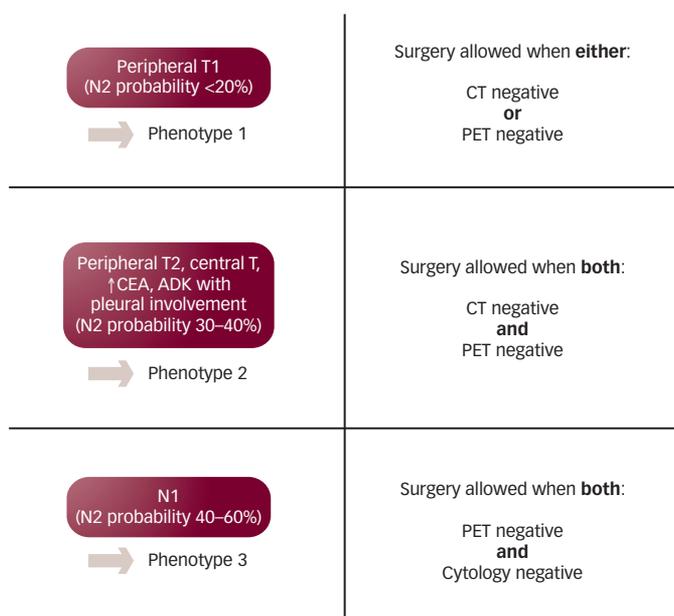
believe that CT and PET negativity on the mediastinum allows biopsy and surgery to be avoided, except in cases of T3 or adenocarcinoma, where mediastinal metastasis gives a poor prognosis. In addition, one must keep in mind that PET alone cannot easily distinguish between the central tumour and mediastinal metastasis.<sup>70-72</sup>

### New Developments

Many of the mediastinal approaches discussed above take into account to some degree of the *a priori* probability that a given tumour will produce mediastinal metastasis, thus identifying different situations in which the same test can be conclusive for a surgical

decision or, conversely, where the probability of occult mediastinal metastasis remains high even in the case of a negative result. Moreover, there is general agreement that a negative cytological result must always be confirmed surgically. However, only a few works have looked for objective criteria to distinguish a negative from an inadequate sample and have suggested different evaluation methods in the two cases.<sup>36,37</sup> No work, to our knowledge, has ever tried to integrate the performance of all diagnostic tests and negative prognostic factors to build up one synthetic model in which the evaluation of negative results (including negative cytological results) is not absolute, but is related to pre-test data and therefore to the

**Figure 3: The Three Clinical–Radiological Phenotypes of Non-small-cell Lung Cancer**



ADK = adenocarcinoma; CEA = carcinoembryonic antigen; CT = computed tomography; PET = positron emission tomography; T = tumour.

predictive value of the test. Recently,<sup>73</sup> we suggested a mathematical model using Bayes' theorem that enables the probability of nodal metastasis to be predicted after a certain number of diagnostic procedures has been performed, providing a simple way of evaluating when a patient can undergo surgery or, conversely, whether further investigations are required.

Figure 1 shows a flowchart focusing on a reasoned study of mediastinum using probability calculations. Figure 2 provides a simplified algorithm in which the pre-test probability of metastasis and the predictive value of each examination (in the case of a positive or negative result) are taken into account for each indicated choice. Surgery is considered a possible choice whenever the probability of mediastinal metastasis falls below 10%.

For example (see Figure 2), in peripheral T1, a CT-negative mediastinum indicates a <10% probability of metastasis; in this case, immediate resort to surgery may be considered reasonable. Positive CT indicates a probability of metastasis of up to about 40%; in this case, negative PET would authorise surgery (1–7% probability of mediastinal metastasis). Conversely, in clinical stage 2 (pre-test probability of mediastinal

metastasis 40–60%), negative PET would not exclude with a sufficient safety margin the presence of mediastinal metastasis (probability 12–17%). Cytological study of the mediastinum must therefore be performed regardless of the PET result. Furthermore, if PET is positive, a negative cytology would not be sufficient and mediastinoscopy will be mandatory. As in any mathematical product, no matter which test (PET or TBNA) is performed first, the result will be the same.

We can therefore identify three main clinical–radiological phenotypes in NSCLC (see Figure 3):

- **Phenotype a:** The probability of mediastinal metastasis is <20%. In this case, negativity on either CT or PET authorises surgery.
- **Phenotype b:** The probability of mediastinal metastasis is about 30–40%. In this case, surgery may be suggested when both CT and PET are negative.
- **Phenotype c:** The probability of mediastinal metastasis is >40%. In this case, surgery is indicated only when both PET and cytology are negative. In any other case, surgical confirmation is necessary.

## Conclusions

Mediastinal staging is crucial to ensure the best therapeutic option is chosen for each patient. A diagnosed stage N0 after CT and PET requires surgery, except in cases of unfavourable grading, large or central tumours or a very high SUV of the primary tumour, given the major probability of metastasis in the mediastinal lymph node even in the case of negative CT and PET. For the same reason, clinical stage N1 suggests the need for minimally invasive and/or surgical biopsy techniques. A negative result of a needle aspiration technique is not considered final since micro-metastasis remains a risk and plagued lymph nodes may be situated next to unaffected ones; therefore, a negative cytological sample generally requires surgical confirmation. However, diagnostic surgery could be avoided in the case of a low post-test probability of neoplastic localisation. To obtain this assessment we have developed a staging proposal on the basis of data provided by the literature and plain statistical concepts using Bayes' theorem; the resulting algorithm may provide a rational opportunity to tackle the challenge of mediastinal staging in lung cancer. The application of this protocol would lead to a better use of available resources (in terms of costs/benefits) by enabling a more precise step-by-step analysis of the staging sequence. Although it may be accepted that irrational use of limited resources is unbearable, we may nonetheless consider that application of multiple (unnecessary) examinations may lead to ambiguity. Nevertheless, the suggested protocol represents a simulation based on statistical projections. We have started a clinical trial to validate our theoretical construct. ■

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