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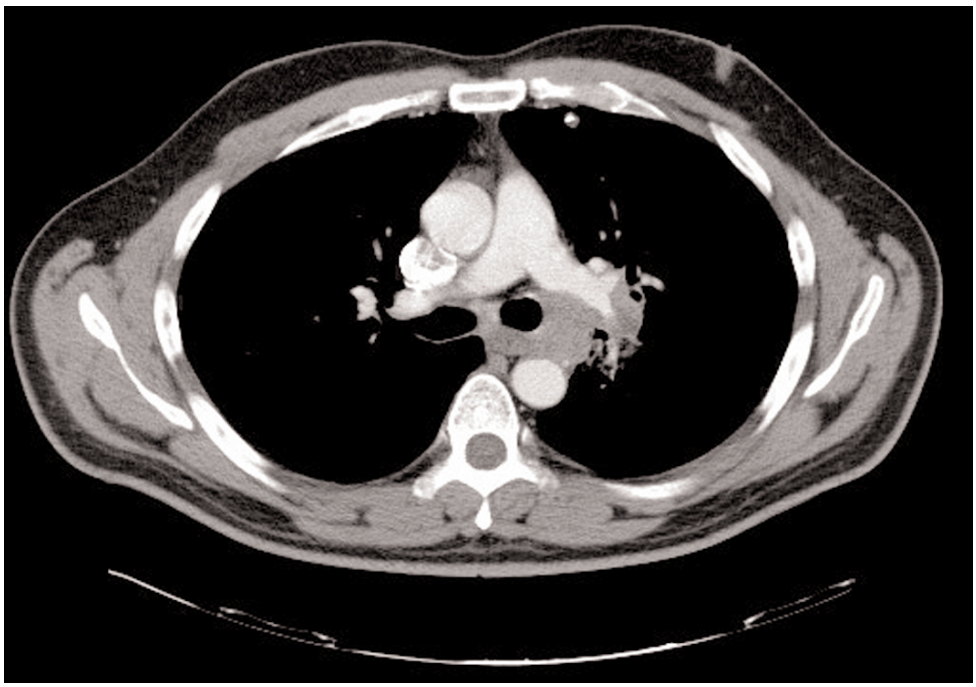
Imaging for staging stage III nonsmall cell lung cancer



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Educational aims

- To explore tumour, node, metastasis staging (anatomical spread of the tumour) with a focus on imaging techniques.
- To explain the principle of guidelines for staging.
- To examine the pros and cons of implementing new techniques in guidelines for staging.

Summary

Accurate locoregional staging is crucial in nonmetastatic nonsmall cell lung cancer (NSCLC).

Staging techniques for stage III NSCLC can be classified as imaging, nonsurgical invasive and surgical invasive procedures. These techniques each have their place in accurate staging, and they are often complimentary.

This review will discuss imaging techniques in particular and examine the interplay between the various staging procedures. The specific topic of optimal restaging after induction in particular patients will also be discussed, with practical suggestions for locoregional staging strategies.

The accurate staging of NSCLC is essential in making judgements about the prognosis and treatment of the disease. Staging evaluates the extent of the primary tumour as well as the degree to which it has spread, both to locoregional lymph nodes (LN) and more distally. The results of staging are expressed using the tumour-node-metastasis (TNM) classification [1].

Early-stage NSCLC (stages I and II) is usually treated by upfront surgical resection, and there is evidence to support the use of post-operative chemotherapy [2]. Advanced NSCLC (stage IV), however, is generally not suitable for radical therapy.

This review will focus on stage III NSCLC. This term covers a wide range of disease with a corresponding variation in prognosis and therapy. Staging is thus vital in guiding the decision between surgical resection and a nonsurgical multimodality approach.

Most patients with stage III NSCLC have mediastinal LN involvement, except those with stage IIIA-T3N1 cancer. Table 1 shows examples of different stage III NSCLC subsets, along with comments on treatment.

The subsets of stage III NSCLC are defined by the T- and N-factors of the TNM classification, and this review will focus on the role of intrathoracic imaging procedures in staging these T- and N-factors.

Noninvasive staging

CT and MRI

Computed tomography (CT) has a more central role than magnetic resonance imaging (MRI) in lung cancer staging. The rapid three-dimensional reformations and virtual bronchoscopy available on modern multi-slice spiral CT scanners have eroded the advantage of MRIs in allowing imaging in different planes.

CT provides excellent anatomical detail and is the best choice with which to assess the T-factor, *e.g.* the relationship of the tumour to fissures (which may determine the type of resection), mediastinal structures or to the pleura and chest wall. The CT criteria for probable resectability in masses contiguous with the mediastinum are a contact of <3 cm with mediastinum, <90° contact with aorta and preserved mediastinal fat layer between the mass and mediastinal structures. The reverse findings (>3 cm contact with mediastinum, >90° contact with aorta and obliteration of the fat plane between the mass and mediastinal structures) are not reliable signs of invasion or irresectability [3–5], meaning that CT often does not rule out surgery. The same is true for chest wall invasion, with the exception of the 100% positive predictive value (PPV) of bony rib destruction with or without soft tissue mass extending into the chest wall [6–8].

With regards to the N-factor, modern contrast-enhanced CT is very accurate in detecting LN enlargement, but the clinical applicability of this for staging the mediastinum is poor: Small nodes may contain metastases, while large nodes may be benign. Consequently, in many instances it is inappropriate to rely on CT alone for N-staging, but the technique is useful in selecting the most appropriate procedure for tissue sampling of suspect LNs.

MRI is an alternative in case of intolerance to *i.v.* ionic contrast media, and can be of additional value in special circumstances, such as assessment of the relationship of the tumour with large blood vessels, soft tissues or vertebral body, especially in sulcus superior tumours. MRI offers no additional information for LN staging when compared with CT [9, 10].

PET

Noninvasive lung cancer staging has been improved substantially by the use of positron emission tomography (PET) with ^{18}F-fluoro-2-deoxy-D-glucose (FDG). However, for the assessment of primary tumour extension, CT, with its better spatial resolution, remains the standard. PET may add information in case of pleural involvement. Small or flat pleural deposits can be missed on PET, probably due to partial volume effects.

On PET, LN stations are considered to be abnormal if their FDG uptake is higher than the background activity of the mediastinum. In many cases, this will indicate malignant involvement, but some granulomatous or other inflammatory diseases also produce increased FDG uptake. A large number of accuracy studies, summarised in several meta-analyses [11–16], have

Table 1 Examples of NSCLC stage III subsets

Stage	Characteristics	Treatment comments
IIIA-T3N1	*No mediastinal LN involvement*	*Can be considered for primary resection*
IIIA-N2	*Metastases to ipsilateral mediastinal LNs*	*Induction chemotherapy combined with surgery and/or radiotherapy*
IIIB-N3	*Contralateral LN metastases*	*Cisplatin-based chemotherapy and high-dose radiotherapy are standard*
IIIB-T4N0-1	*Primary tumour vital structures (e.g. Pancoast type)*	*Surgery may play a role in some patients, usually after induction chemoradiotherapy*

demonstrated convincingly that PET is a superior imaging technique for mediastinal LN staging in potentially operable NSCLC. For the distinction between N0–1 and N2–3 patients, one review yielded an overall sensitivity of 89%, with a specificity and accuracy of 90 and 92%, respectively. For CT, the results were a sensitivity of 65%, a specificity of 80% and an accuracy of 75% [17]. Interpretation of PET images is improved by visual correlation with CT, as localisation of PET abnormalities is improved with the help of the anatomical detail of CT [18, 19].

Restaging after induction therapy

One of the most challenging areas in noninvasive staging is the optimal reassessment of tumour response after induction therapy. This includes the pathological response in the primary tumour, as well as the downstaging of mediastinal LN.

The accuracy of CT in assessing the pathological response of the primary tumour is limited, as small residual masses may contain aggressive tumour remnants, while a small change in tumour volume may conceal a major biological response. PET, on the other hand, usually detects the presence of a residual tumour at the primary site [21–23]. The specificity cannot be reliably assessed in small series, because a pathologically complete response is uncommon in this setting, usually occurring in <10% of patients. PET response in the primary tumour has been seen as highly predictive for a better outcome after combined modality treatment [24, 25].

In the assessment of LN downstaging, CT suffers the same limitations as baseline staging. Currently available evidence suggests that restaging of mediastinal LN after induction by PET may be better than with CT, but is not as accurate as in untreated patients [24, 25].

Invasive staging

TBNA

Standard bronchoscopy is considered obligatory in patients with suspected lung cancer. In addition to pathological confirmation, in many patients it also permits evaluation of the endobronchial extension of the tumour (endobronchial T-stage), which can be decisive in planning the extent of resection or radiotherapy. For the N-stage, a conventional (blind) transbronchial needle aspiration (TBNA) of mediastinal LN can be performed. A high false-negative rate compromises the use of conventional TBNA for routine mediastinal LN staging. TBNA is very useful if it leads to proof of N3 disease. TBNA does not allow direct visual inspection and assessment of extracapsular LN spread.

EUS-FNA

The advent of endoscopic ultrasonography has allowed imaging beyond the mucosa (*e.g.* into the mediastinum) and has improved the diagnostic yield of tissue sampling. Oesophageal ultrasonography (EUS)-fine needle aspiration (FNA) is particularly useful in visualising LNs in the posterior part of levels 4L, 5 and 7, and in the inferior mediastinum at levels 8 and 9, as described on the Mountain-Dressler LN map [26]. Several of these LN levels (5, 8 and 9) are not accessible by bronchoscopy or mediastinoscopy [27]. However, the LN more commonly involved in lung cancer are located in the anterior mediastinum (level 4L anterolateral to the trachea, level 4R or 2) and are hard to reach by EUS-FNA, certainly if they are not enlarged.

EBUS-TBNA

Endobronchial ultrasonography (EBUS) is able to visualise mediastinal LN in the anterior, posterior and inferior mediastinum at levels 2, 3, 4 and 7, as well as hilar LN. It helps to localise puncture sites for either EBUS-guided or EBUS-controlled TBNA.

A prospective randomised study demonstrated that the diagnostic yield of EBUS-guided TBNA is significantly increased when compared

with conventional TBNA in all mediastinal LN levels, except for an equal diagnostic yield in the subcarinal level [28].

The resolution of the 20 MHz EBUS miniprobe allows T4 disease to be excluded in selected cases.

Both EBUS and EUS have also been found to be useful in differentiating between external tumour compression and direct tumour infiltration of large mediastinal vessels or the oesophagus in some patients.

Pleuroscopy

Pleuroscopy (or medical thoracoscopy) is very valuable in cases of pleural effusion, which may be present at diagnosis in up to 15% of all patients with lung cancer. The first diagnostic step is, of course, thoracocentesis. However, in cases of malignant effusion only about one-third of the cytological results of thoracocentesis, and about half of the results of blind pleural punch biopsy, are positive [29]. When the results of effusion cytology are negative or equivocal in a patient with suspect pleural effusion, pleuroscopy under local anaesthesia should be carried out as the next diagnostic step. It allows examination of visceral and parietal pleura, sampling of pleural biopsies and pleural lavage, resulting in a sensitivity of >90% and a specificity of 100% [29].

Mediastinoscopy

Mediastinoscopy has long been the standard tool for staging LN involvement in patients with lung cancer. Cervical mediastinoscopy is the most commonly used procedure [30], giving access to the pre-tracheal, right and left paratracheal and anterior subcarinal LN levels (levels 1, 2R, 4R, 2L, 4L and 7). Ideally, five nodal levels (2R, 4R, 2L, 4L and 7) should be examined, with at least one node sampled from each level, unless none are present after dissection of the region concerned [31].

Cervical mediastinoscopy can be performed as an outpatient procedure and is reported to have very low mortality and morbidity in experienced hands. Contraindications for mediastinoscopy are intolerance of general anaesthesia, extreme kyphosis and cutaneous tracheostomy.

In some patients with central tumours, mediastinoscopy may also improve certainty of the T-stage, as it can prove irresectability owing to invasion of mediastinal central vascular structures.

More recently, the procedure has been performed using a videomediastinoscope [32], which definitely improves visualisation and may lead to a higher accuracy in staging [33, 34]. It also allows recording of the findings, which can be used in teaching.

Anterior mediastinotomy

Anterior mediastinotomy can be of value in patients with left upper lobe tumours. These tumours are known to metastasise predominantly to the aortopulmonary window and paraaortic nodes (levels 5 and 6), which cannot be reached by cervical mediastinoscopy. The technique gives extrapleural access to level 5 and 6 LNs, and also allows assessment of resectability by palpating the tumour. Care must be taken not to damage the left phrenic nerve.

Based on one small retrospective series [35], it has been suggested that this technique has little indication in patients with a negative cervical mediastinoscopy. However, most teams will maintain left anterior mediastinotomy in patients with high suspicion of involvement of LN levels 5 or 6.

Extended mediastinoscopy

Extended mediastinoscopy has been described as a technique to allow exploration of level 5 and 6 nodes *via* the cervical approach [36]. The technique has not become widespread because of its technical challenges and possible complications, such as embolic stroke due to the close contact of the mediastinoscope with the brachiocephalic and left carotid artery [37].

VATS

Video-assisted thoracic surgery (VATS, surgical thoracoscopy) has become an important staging

Box 1 Conditions for omitting invasive staging after PET

- There must be sufficient FDG uptake in the primary tumour.
- There must be no central tumour or important hilar LN disease that could obscure coexisting N2 disease on PET.
- A dedicated PET camera must be used.

tool. With the use of spiral CT, small contralateral nodules can be detected in a substantial number of patients. VATS can be used to biopsy these lesions in the search of unexpected contralateral lung metastasis.

LN beyond the reach of conventional mediastinoscopy can be examined by VATS. The inferior mediastinal LN (levels 7, 8 and 9) can be biopsied. This is indicated if they are suspect (enlarged on CT or FDG-avid on PET). LN stations 5 and 6 can be explored at left thoracoscopy, as an alternative to left anterior mediastinotomy. VATS can also be of help to rule out pleural metastasis, especially when pleural fluid is present.

VATS can be used selectively to evaluate T4 invasion (*e.g.* in the aorta), which may be of help in the decision of straightforward thoracotomy or induction chemoradiotherapy in cases when imaging techniques have not allowed resectable stage T3 disease to be distunguished from irresectable stage T4 disease.

Repeat mediastinoscopy

Repeat mediastinoscopy has been propagated as a tool for restaging of the mediastinum after induction therapy in patients with N2 disease. Downstaging of involved mediastinal LN is an important prognostic factor in these patients, and few patients with persistent N2 disease undergoing resection after induction therapy will survive in the long term. Therefore, thoracic surgeons are frequently faced with the need for re-mediastinoscopy. However, experience suggests fibrosis and dense adhesions make repeat mediastinoscopy technically difficult, if the initial cervical mediastinoscopy was performed thoroughly.

Discussion

As treatment options have widened, the role of staging in NSCLC has expanded. The old CT- and mediastinoscopy-based methods, designed to determine resectability, have been augmented by new tools and new aims.

Imaging

PET has complemented CT greatly in assessing locoregional LN spread. Even the most advanced CT can only show the size of LN, and, as detailed earlier, this is a relative criterion. PET has the potential to characterise primary lesions, evaluate locoregional LN spread and look for distant metastases.

PET has been shown to be significantly more accurate than CT in LN stages, and when CT and PET images are correlated, the negative predictive value (NPV) may be slightly better than that of mediastinoscopy [38]. This high NPV can be used to rule out invasive staging if PET suggests the absence of LN disease. Care must be taken, however, and several conditions must be taken into account (box 1).

As the PPV of PET is not high, tissue confirmation of positive LN findings is needed in order to avoid unnecessary radical surgery.

Used wisely, PET is cost-effective as it reduces the number of futile surgical procedures undertaken [39, 40].

On many occasions where PET produces equivocal results, experienced readers can resolve matters by visual correlation with CT. Combined PET-CT would appear to be the next logical step, but as yet, there is insufficient data to determine whether PET-CT should become standard in NSCLC.

Invasive techniques

Discounting staging during resection, the staging approach against which all others must be judged remains mediastinoscopy (completed by a left anterior approach where necessary). Mediastinoscopy performs well against all criteria (table 2); when sampling bias is taken into account it can appear even better than these data suggest. Consequently, without large randomised trials in unbiased populations, it will not be possible to state whether TBNA/FNA is a valid substitute for mediastinoscopy.

Table 2 Performance of different locoregional staging techniques

	Sensitivity %	Specificity %	NPV %	PPV %	Prevalence# %
CT	*57*	*82*	*83*	*56*	*28*
PET	*84*	*89*	*93*	*79*	*32*
Blind TBNA	*76*	*96*	*71*	*100*	*70*
EUS-FNA	*88*	*91*	*77*	*98*	*69*
Mediastinoscopy	*81*	*100*	*91*	*100*	*37*

#: proportion of patients with metastatic mediastinal nodes in study cohorts. Data from [11, 41].

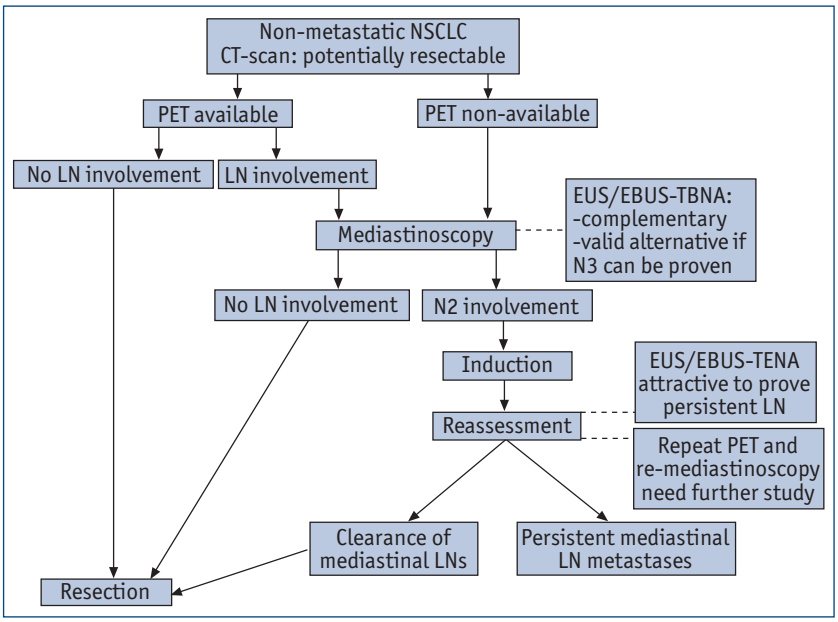

Figure 1

Pragmatic scheme for contemporary locoregional staging of non-metastatic NSCLC. Reproduced from [50], with permission from the publisher.

TBNA/FNA has the advantage that it is less invasive than mediastinoscopy. Combined with a high PPV, this means that in some cases (where N3 disease, and hence nonsurgical stage IIIB NSCLC, can be proven) it is sufficient for locoregional staging. The risk of false-positive findings is considered to be very low and usually to be the result of errors in interpretation [42, 43].

If TBNA/FNA proves only N2 disease, the situation becomes less clear. The likelihood of missing N3 disease in normal-sized contralateral LNs is unknown, as is the certainty of distinguishing between single- and multiple-level N2 disease. Studies on EUS-FNA have claimed that a finding of malignant cytology reduces the number of mediastinoscopies, but these studies have suffered from methodological defects.

EBUS-TNA is the most promising technique, targeting the LN stations (levels 2, 4L arterolateral to the trachea, 4R or 7) most commonly involved in lung cancer. Early results have been very promising [28, 44], suggesting that EBUS-TBNA performs better than blind TBNA and that it has a very high sensitivity.

Restaging

The problem of how to restage NSCLC after induction treatment is an important one, as the information gained will guide the decision about whether to proceed with thoracotomy. Both the pathological response of the primary tumour and the downstaging of mediastinal LNs are known prognostic factors [45–48]. However, they cannot at present be assessed before resection.

The usual procedure is to use CT (a very approximate tool for this purpose) to assess radiological response and assign patients to either surgery or other treatment. This is not satisfactory. PET has been shown to provide more useful data on the prognostic factors of interest, but for reasons that are unclear, PET assessment of LN after induction has a lower sensitivity than at baseline. This reduction notwithstanding, PET response is highly predictive of outcome after combined modality treatment [24, 25].

Despite the important evidence that PET can complement structural imaging in this setting, there is insufficient confirmatory evidence to use PET in therapeutic decisions when restaging patients after induction therapy in stage III NSCLC. The hypothesis that surgery after induction therapy is only beneficial in patients with an objective metabolic response must be challenged in larger prospective outcome studies.

Repeat mediastinoscopy and endoscopic ultrasonography allow assessment of potential downstaging after induction. They do not, however, provide sufficient information about the pathological response of the primary tumour. In addition, repeat mediastinoscopy is technically difficult and, providing the initial

Box 2 Considerations when planning staging protocols

- Staging, like treatment, is a multidisciplinary exercise to be carried out by experts in each discipline.
- Imaging techniques can provide information on LN size and/or metabolism, but invasive tests may be necessary to gather more detailed information.
- Thoracic CT shows the location and extent of the primary tumour, and will serve as an initial, far from accurate, evaluation of locoregional LN spread. It can be used to guide later invasive procedures.
- The high NPV of PET means it can be used to rule out invasive staging in some cases. It can characterise the primary mass and locate distant metastases.
- Positive findings should be confirmed pathologically.
- Mediastinoscopy, with a high NPV and a perfect PPV, is the standard tool for invasive staging in most patients. Visual inspection provides extra information on intra- *versus* extranodal LN disease and sometimes resectability. In left upper lobe tumours with suspicion of LN metastases in levels 5 and 6, left anterior mediastinotomy should complement the cervical approach.
- The high PPV of blind TBNA allows management decisions to be taken in some patients, but the technique has insufficient NPV for clinical decision making.
- Endoscopic ultrasonography has the potential to challenge the primacy of mediastinoscopy. Proof of N3 disease at baseline or persistent LN disease after induction may suffice to guide clinical management. It can also reach nodes inaccessible to mediastinoscopy. The NPV is probably lower than that of mediastinoscopy, which can be a problem in some cases. Endoscopic ultrasonography can exclude T4 disease in some cases.
- PET and remediastinoscopy after induction may be better suited to aiding the decision for or against surgery. However, further evaluation is needed.

mediastinoscopy was carried out thoroughly, often remains incomplete.

However, if persistent mediastinal LN disease can be shown, it may be possible to rule out thoracotomy – such patients have very poor 5-year survival prospects.

A pilot study of LN sampling with EUS-FNA to restage stage IIIA-N2 NSCLC after induction chemotherapy showed a diagnostic sensitivity of 75% [49]. Endoscopy-controlled TBNA/FNA has potential as a complementary or alternative technique: tissue proof of persistent LN disease, without surgery, would be ideal and sufficient for clinical decision-making.

Practical strategies

Local variations in available skills and equipment make it impossible to make a blanket recommendation for locoregional staging in stage III NSCLC. In addition, a balance must be struck between sensitivity and specificity, and this may vary depending on the case.

The various techniques described in this review are more likely to be complementary than competitive, between them providing a comprehensive LN reach with the minimum of invasiveness. The drawback, however, may be cost.

Further compounding the problem of recommendation, the newer ultrasound-controlled procedures have not yet been evaluated thoroughly in comparator trials. Their diagnostic yield is promising enough to launch large randomised trials, with standard procedures as controls. Prospective studies comparing the diagnostic accuracy of EBUS-TBNA and EUS-FNA for routine (re)staging of both enlarged and normal sized LN with both PET and mediastinoscopy are eagerly awaited and may prompt changes in the way lung cancer is staged and restaged.

Figure 1 shows a scheme for locoregional staging of NSCLC, subject to certain considerations (box 2), based on the information currently available.

In conclusion, the staging of stage III NSCLC is a complex multidisciplinary process, and cannot be broken down easily into a set of rules. The constant evolution of the techniques already available, and the arrival of new ones, means clinicians must keep a critical eye on the results of trials, and must adapt their strategies to the needs of their patient population and the abilities and facilities available to them.

Educational questions

1) In the overall staging of the T-factor in NSCLC:
a) MRI is superior to CT, because of its better distinction between malignant and benign tissue.
b) MRI is superior to CT, because it gives more details on endobronchial spread.
c) Both of the above statements are correct.
d) Neither of the above statements is correct.
2) In the overall staging of the N-factor in NSCLC:
a) PET is superior to CT, because of its better spatial resolution.
b) PET is superior to CT, because of its ability to measure metabolism in tissues.
c) Mediastinoscopy is superior to CT, because it reaches every mediastinal lymph node station.
d) Left anterior mediastinoscopy is superior to PET, because para-aortic lymph node stations cannot be assessed on PET.
3) EBUS-TBNA can be a useful adjunct to mediastinoscopy because:
a) It allows sampling of right paratracheal lymph nodes.
b) It allows sampling of left paratracheal lymph nodes.
c) It allows sampling of contralateal hilar lymph nodes.
d) It allows sampling of an adrenal gland mass.

Suggested answers

1. d
2. b
3. c

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