The Importance of Accurate Lymph Node Staging in Early and Locally Advanced Non-small Cell Lung Cancer: An Update on Available Techniques

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Abstract

Medical oncologists are faced with multiple factors to consider when staging a patient with suspected or confirmed non-small cell lung cancer (NSCLC). Identifying pathological nodal (N2) disease is, however, of great importance because its presence significantly affects outcomes and potential treatment strategies. Recent data supporting the use of adjuvant or neoadjuvant therapies in these patients suggests that every reasonable effort should be made to assess the lymph node status accurately in patients with clinical early stage disease as well as in those with clinically staged N2 disease who have undergone preoperative treatments. Newer procedures such as integrated positron emission tomography computed tomography and esophageal or endobronchial endoscopic ultrasound with fine needle aspiration are minimally invasive techniques that may enhance the accuracy of mediastinal staging, traditionally devoted to mediastinoscopy. As their availability widens, they are likely to become an important part of staging and treatment paradigms. Intraoperatively, a growing body of evidence suggests that lymph node dissection can be performed safely, and should replace sampling as a more effective means of identifying unsuspected N2 disease. This paper will review the current literature on staging NSCLC with regard to the detection of nodal disease through preoperative staging of the mediastinum, the use of intraoperative lymph node sampling or dissection at the time of resection, and procedures for use in restaging patients with clinical stage IIIA N2 disease who have undergone preoperative chemotherapy (with or without radiotherapy).

Keywords: Non-small cell lung cancer, Staging, Lymph node, Preoperative, Intraoperative, Techniques.

INTRODUCTION

The accurate determination of disease stage in non-small cell lung cancer (NSCLC) is important because of the associated therapeutic and prognostic implications. A careful initial diagnostic evaluation to define the location and to determine the extent of primary and metastatic tumor involvement is critical for the appropriate care of patients. Most critically, staging determines the candidacy for potentially curative resection. The rate of futile thoracotomies resulting from inaccurate preoperative staging has been reported to be approximately 40%.[1,2]

Initial clinical staging is based on a combination of both clinical factors (such as physical examination, radiological tests, and laboratory studies) and pathological evaluation obtained before resection (tumor and lymph node biopsies obtained through various means). True pathological staging can, however, only be performed at the time of resection. A distinction between the clinical stage and the true pathological stage should be considered when evaluating reports of survival outcome, as prognosis varies between these two types of staging (Table l).[3]

This article will focus on lymph node staging, the procedures for which can be divided into non-invasive and invasive strategies. Invasive techniques are further subdivided into surgical and non-surgical procedures. These strategies, along with the abbreviations that will be used in this article are listed in Table 2. Several clinical practice guidelines are available that offer advice to the practising oncologist on how to navigate these choices.[4-7] Although these guidelines agree that an initial clinical work-up should include computed tomography (CT), subsequent staging, particularly of the mediastinum, is not as clearly defined. In addition, newer staging procedures, including esophageal-endoscopic ultrasound with fine needle aspiration (EUS-FNA), endobronchial ultrasound with transbronchial needle aspiration (EBUS-TBNA), video-assisted mediastinoscopic lymphadenectomy or transcervical extended mediastinal lymphadenectomy (TEMLA), for example, are becoming available, but are not universally applied. A wide spectrum of factors must be considered when

determining the appropriate tests to assess the lymph nodes in NSCLC, which includes not only the sensitivity and specificity of the test, but the ability to perform the procedure on an individual patient (inpatient versus outpatient and whether it is scheduled together with the primary tumor resection), the morbidity of the procedure, the surgical expertise required, the accessibility of the presumptive tumor locations and suspicious nodes, the requirement for general anesthesia, and in the case of mediastinoscopy, whether the procedure can be repeated.

TABLE 1: *Five-year Survival from Time of Surgery in Non-small Cell Lung Cancer.*

	Stage	Clinical, %	Pathological, %
Early Stage	IA (Tl N0 M0)	61	67
	IB (T2 N0 M0)	38	57
	IIA (Tl N1 M0)	34	55
	IIB (T2 Nl M0, T3 N0M)	22-24	38-39
Stage III	IIIA (T3 N0-2 M0, Tl-3 N2 M0)	9-13	23-25
	IIIB (T4 N0-2 M0, Tl-3 N3 M0)	3-7	NA

Stage III disease is particularly challenging because it encompasses a heterogeneous group of tumors for which management strategies are still controversial. Many patients with stage III tumors are borderline resectable, and thus the roles of preoperative chemotherapy or combined modality treatment are yet to be defined (Figure 1). It is, however, clear that because the presence of N2 disease may preclude operability, or because preoperative treatment may be required before resection, accurate preoperative staging of the mediastinum is imperative to providing appropriate care to these patients. Whereas non-invasive procedures are preferable, CT alone is not optimal to detect N2 disease. In the Z0050 trial of the American College of Surgeons Oncology Group (ACOSOG), only 32% of patients with pathologically confirmed N2/N3 disease were correctly staged by non-invasive means (CT).[8]

Many studies have now documented the survival advantages of either postoperative adjuvant chemotherapy or neoadjuvant chemotherapy (with or without radiotherapy) for patients with stage III N2 disease. In the large prospective Adjuvant Navelbine International Trialist Association (ANITA) trial of adjuvant chemotherapy,[9] 5-year survival for patients with stage III N2 disease who received radiation was 47% after adjuvant cisplatin-vinorelbine chemotherapy compared with 21% after observation alone following surgery. In a smaller study,[10,11] an impressive median survival of 28 months was found in a phase II trial of neoadjuvant cisplatin-docetaxel. Sixty percent of patients in that study were downstaged with chemotherapy to pN0/N1, a significant factor associated with long-term survival. This neoadjuvant combination with radiation is currently being evaluated in phase III trials.[12,13] These clinical data establish the fact that determining the presence of N2 disease, whether it be preoperatively, intraoperatively, or after neoadjuvant therapy is imperative to providing optimal care to patients with pathological stage IIIA disease. This paper will review current literature on staging NSCLC with regard to the detection of N2 disease through preoperative staging of the mediastinum, the use of intraoperative lymph node sampling or dissection at the time of resection, and procedures to use in restaging patients with clinical stage III N2 disease who have undergone preoperative chemotherapy (with or without radiotherapy).

STAGING THE MEDIASTINUM

From a safety standpoint, non-invasive techniques are preferred to invasive techniques in staging the mediastinum. It is also well established that accuracy suffers when using non-invasive measures alone. When to use an invasive technique has not been well defined. For example, would mediastinoscopy be performed routinely in a patient with a peripheral stage I, Tl tumor? Should it be performed routinely in any stage patient or used only to confirm suspicious nodes on imaging? The use of integrated positron emission tomography (PET)-CT is improving the ability to define suspicious nodes non-invasively. Newer minimally invasive techniques such as EUS-FNA or EBUS-TBNA are also changing the paradigm for invasive staging.

Non-Invasive Methods

PET imaging is superior to chest CT for detecting mediastinal lymph node metastases. Results from a meta-analysis by Toloza et al.[14] demonstrated that when compared with CT, PET has greater sensitivity (84 versus 57%), specificity (89 versus 82%), positive predictive value (79 versus 56%), and negative predictive value (93 versus 83%), based on pooled results from the analysed trials. Further evidence comes from the Z0050 trial of the ACOSOG.[8] In that trial, PET was performed in 303 eligible patients considered to be surgical candidates

(stages I-IIIA) after standard imaging procedures (which included CT of the chest and upper abdomen, bone scintigraphy, and contrast-enhanced CT or magnetic resonance imaging [MRI] of the brain). Looking specifically at nodal status, the correct classification of N1 or N2/N3 disease was statistically significantly more frequent with PET compared with CT. For N1 disease, correct classification with PET and CT, respectively, occurred in 42 and 13% of cases ($p = 0.02$). For N2/N3 disease, corresponding values were 58% with PET and 32% with CT ($p = 0.004$). In that study, the sensitivity of PET to detect N2/N3 disease was 61% compared with 37% with CT. As a result of the collective data, PET is now considered the gold standard for initial non-invasive mediastinal staging.

TABLE 2: *Lymph Node Staging Procedures.*

Non-invasive	Invasive
Computed tomography (CT) Magnetic resonance imaging (MRI) ^{18}F-fluoro-deoxy-D-glucose positron emission tomography scan (PET) Integrated positron emission-computed tomography (PET-CT)	**Non-Surgical** Esophageal endoscopic ultrasound with fine needle aspiration (EUS-FNA) Endobronchial ultrasound with transbronchial needle aspiration (EBUS-TBNA) Transbronchial needle aspiration (TBNA) Pleuroscopy **Surgical** Mediastinoscopy Video-assisted mediastinoscopic lymphadenectomy (VAMLA) Transcervical extended mediastinal lymphadenectomy (TEMLA) Anterior mediastinotomy (Chamberlain procedure) Video-assisted thoracic surgery (VATS)

FIGURE 1: *A treatment decision tree for patients with N2 disease.*
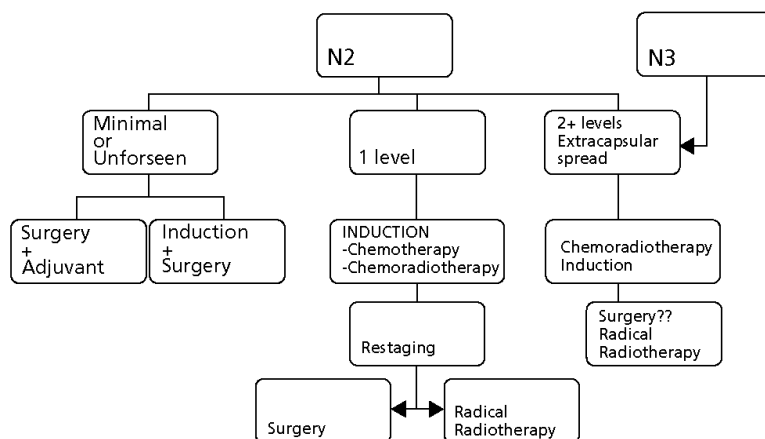
Nonetheless, whether the very early stage patient requires PET is still not well defined. A retrospective study evaluated whether PET standardized uptake value (SUV) of the primary lesion, independent of size, correlates with the presence of nodal or distant metastases at the time of presentation.[15] This theory is based on the fact that various studies have suggested that the magnitude of SUV with PET inversely correlates with survival.[16-18] In multivariate analysis, SUV was a significant predictor of advanced disease at presentation ($p = 0.04$).[15] The model in that study suggests that an SUV of 7 corresponds to a 50% or greater chance of having nodal or distant disease. If these findings can be validated through prospective evaluation, then perhaps targeted evaluation may make sense. For example, utilizing additional means to identify metastatic disease (e.g. MRI, mediastinoscopy) in a subgroup of patients with elevated SUV in the primary tumor might be a feasible option.

More recently, evaluations of integrated PET-CT have suggested that this technology is superior to PET alone. Evaluating either the tumor stage ($n = 40$) or the nodal stage ($n = 37$), Lardinois and colleagues[19] demonstrated that PET-CT is particularly effective at improving tumor staging compared with PET alone. Integrated PET-CT correctly identified the tumor stage in 88% of patients compared with 40% with PET alone. Although the correct stage was identified with PET in an additional 40% of patients (as well as 10% with PET-CT), staging in these

patients was deemed equivocal. With respect to nodal staging, PET-CT correctly identified the stage in 81% of patients compared with 49% with PET alone; an additional 38% were correct but equivocal with PET and 3% with PET-CT. Overall, integrated PET-CT was statistically significantly more accurate at identifying both tumor and nodal staging than PET alone ($p \leq 0.013$). It should also be noted that integrated PET-CT was more accurate than the visual correlation of PET and CT for tumor staging ($p = 0.013$), although not for nodal staging. In a study that evaluated the efficacy of clinical staging with integrated PET-CT, as well as complementary methods, Cerfolio and colleagues[20] determined the efficacy parameters for integrated PET-CT at the individual nodal stations in 383 patients presenting to the University of Alabama (Table 3). A comparison of the efficacy of integrated PET-CT versus PET at specific nodal stations was performed at the same center in 129 patients. Integrated PET-CT was statistically superior for all N2 stations as a group in sensitivity, specificity, positive predictive value, and accuracy, and for all N1 stations as a group in sensitivity, specificity, positive predictive value, negative predictive value, and accuracy. The specific nodal stations for which statistical superiority was observed with integrated PET-CT compared with PET in sensitivity and positive predictive value are detailed in Table 4. Importantly, PET-CT had greater sensitivity and positive predictive value at nodal stations 5 and 7. Nonetheless, integrated PET-CT is not failsafe, and its usefulness lies in its greater ability to identify areas for further testing with biopsy.

TABLE 3: *Efficacy of Integrated Positron Emission-Computed Tomography for Each N2 Nodal Station in 383 Patients Undergoing Preoperative Staging.[20]*

Nodal Stations	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Accuracy (%)
2R, 2L	86	99	94	98	98
4L, 4R	96	91	62	99	93
6	62	94	31	98	92
5	78	97	36	97	94
7	75	91	61	95	89
8, 9	50	99	40	99	97

FN, False negatives; FP, false positives; TN, true negatives; TP, true positives. Accuracy TP+ TN/(TN + FN + TP + FP); negative predictive value TN/ (TN + FN); positive predictive value TP/(TP + FP); sensitivity TP/(TP + FN); specificity TN/(TN + FP).

TABLE 4: *Individual Nodal Stations at which Sensitivity and Positive Predictive Value Differed Significantly ($p \leq 0.05$) between Integrated Positron Emission Tomography-Computed Tomography and Dedicated Positron Emission Tomography in Preoperative Staging of 129 Patients.[21]*

Nodal Station	Sensitivity (%)		Positive Predictive Value (%)	
	PET-CT	PET	PET-CT	PET
2R			75	50
4R	100	86	70	55
4L			40	18
5	100	25	50	25
7	50	20	40	20
10L	100	40	39	14
11	100	40	71	29

CT, Computed tomography; PET, positron emission tomography; PET-CT, integrated PET and CT.

Invasive Methods

Mediastinoscopy remains the standard confirmatory procedure for suspicious nodes identified with CT or PET. A number of mediastinal nodal stations are, however, not accessible with this modality (Figure 2). This drawback leaves the potential for undetected N2 disease. Although performing mediastinoscopy with video-assisted mediastinoscopic lymphadenectomy improves the yield of lymph nodes removed at most accessible stations, the specific stations explored remains the same as in conventional mediastinoscopy.[22-24]

Other procedures (e.g. anterior mediastinotomy, pleuroscopy) may be used in concert with mediastinoscopy, thus expanding the number of stations explored. Using the newer TEMLA procedure, additional stations (1, 3A, 5, 6, and 8) can also be accessed.[25,26] In a study of 41 patients, the sensitivity and negative predictive value were improved with TEMLA compared with standard (cervical) mediastinoscopy (sensitivity 100 versus 37.5%; negative predictive value 100 versus 66.7%, respectively).[26] Although postoperative complications were not significantly different between the two methods, pain intensity was statistically significantly greater with TEMLA. Nevertheless, all mediastinoscopic procedures require surgical intervention.

Less invasive procedures have been studied that may improve the detection of N2 disease beyond that of standard mediastinoscopy. EUS-FNA is, among others, a minimally invasive procedure that recent evidence suggests may be useful. Whether adding EUS-FNA to mediastinoscopy would improve staging was assessed in 100 patients with confirmed NSCLC deemed resectable.[27] Mediastinal tumor invasion (T4) or lymph node metastases (N2/N3) were identified in a greater percentage of patients undergoing both procedures compared with either procedure alone (36% EUS-FNA plus mediastinoscopy versus 20% mediastinoscopy alone and 28% EUS-FNA alone). Sixteen per cent of thoracotomies could thus have been avoided by using EUS-FNA in addition to mediastinoscopy. Disease detected by adding EUS-FNA was N2 metastasis in 9%, T4 tumor invasion in 4%, and both (N2 and T4) in 3% of patients. Two per cent of EUS-FNA results were, however, false positives. In two patients, lymph nodes located immediately adjacent to the primary tumor were mistakenly judged to be malignant, when in fact the sample had been taken from the tumor instead. As such, the authors recommend mediastinoscopy rather than EUS-FNA for evaluating lymph nodes adjacent to the primary tumor.

FIGURE 2: *Shaded areas indicate the nodal stations within the reach of mediastinoscopy.*
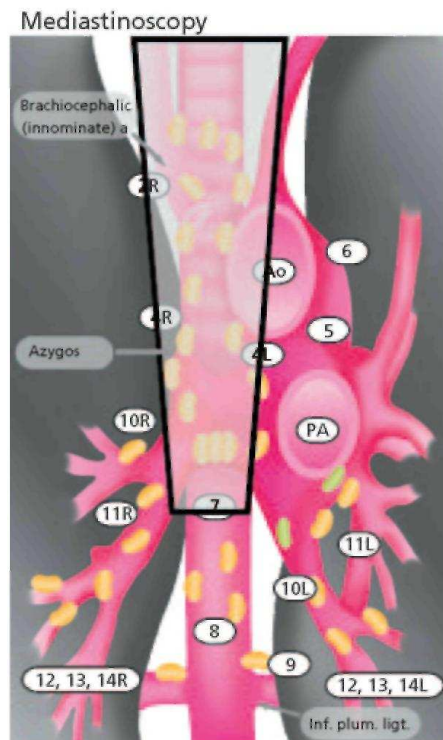
A randomized trial in Denmark[28] found that futile thoracotomies could be prevented by using EUS-FNA up front in all patients rather then reserving it for those with enlarged nodes in the EUS-FNA-accessible regions on CT. Patients with suspected or newly diagnosed NSCLC who were candidates for invasive staging before resection were randomly assigned to either conventional work-up (EUS-FNA in selected patients; $n = 51$) or routine EUS-FNA ($n = 53$). All patients underwent mediastinoscopy unless contraindicated. The percentage of futile thoracotomies with routine EUS-FNA was 9% versus 25% with conventional work-up ($p = 0.03$).

The addition of EUS-FNA appears to be particularly useful for nodal stations 5, 8, and 9, as these are stations that are inaccessible by mediastinoscopy, along with station 7, in which the sensitivity and positive predictive value of integrated PET-CT were found lacking in the study at the University of Alabama (Table 3).[20] In that study of 383 patients who underwent both integrated PET-CT and CT, the incidence of unsuspected N2 disease was evaluated. After PET-CT and CT, patients with suspicious nodes at the 2R/2L and 4R/4L levels were assessed by mediastinoscopy. Those with suspicious nodes at stations 5, 7, 8, and 9 were assessed by EUS-FNA.

A total of 28 patients (14%) had unsuspected N2 disease based on initial PET-CT and CT. The highest percentage of unsuspected disease occurred in the 50 clinical stage II patients (28% compared with 8.6% of clinical stage I patients, and < 1% of clinical stage III or IV patients). The most common location for unsuspected disease was in the posterior mediastinal nodes (those accessible by EUS-FNA). In clinical stage II patients, 86% of those with unsuspected N2 disease had metastasis in the posterior mediastinal nodes. The same investigators also evaluated the positive predictive value and accuracy of EUS-FNA compared with standard PET or CT in 104 patients who specifically presented with suspicious nodes at stations 5, 7, 8, or 9 by these imaging methods.[29] The positive predictive value (95% confidence interval; CI) was 40.3% (29.1-55.1) with PET, 39.2% (26.7-49.4) with CT, and 100% (90.5-100) with EUS-FNA ($p < 0.001$ for EUS-FNA compared with either PET or CT). Accuracy was also significantly better with EUS-FNA ($p < 0.001$). Importantly, the investigators determined that, conservatively, 57% of the patients avoided surgery to determine their lymph node status. Also of note is the fact that, of 37 patients in whom EUS-FNA identified malignant disease, 31% had previously undergone mediastinoscopy that determined benign disease in the anterior mediastinum.

A more recent minimally invasive technique is EBUS-TBNA. Exploring almost the same nodal stations as mediastinoscopy, EBUS-TBNA will surely become more common in staging the mediastinum. As the development of real-time ultrasound-guided transbronchial needle aspiration has become available, more teams use this technique for the initial sampling of nodal stations 1-5, 7, 10, and 11. Recent publications have shown a sensitivity of 85-96%, a specificity of 100%, and an accuracy of 89-97%.[30-32] The most recent data by Herth et al.[33] demonstrated a negative predictive value of 96% (in normal-sized lymph nodes, based on chest CT). Using such a minimally invasive technique leaves a clean field, providing the option, in the event of a negative result, to perform mediastinoscopy before making a surgical decision. Whether it would be of interest to add EUS-FNA to this endobronchial ultrasound staging is probably parallel to the discussion on cervical mediastinoscopy. EBUS-TBNA and EUS-FNA have been studied in combination in 33 patients, with a promising accuracy of 100% for diagnosing mediastinal cancer.[34] Alternatively, if only nodal station 7 is to be sampled, transbronchial needle aspiration alone has demonstrated similar sensitivity to the endobronchial ultrasound-guided technique.[35]

At present, these data suggest that adding EUS-FNA or EBUS-TBNA may be particularly useful in preventing unnecessary thoracotomies by identifying patients who are truly stage III rather than I or II. Only the presence of N2 or M1 disease currently alters preoperative decision making. In the future, however, if neoadjuvant therapy for stages IB and II become the standard of care, the differences between clinical and pathological staging and the efficacy of preoperative staging will become even more important.

INTRAOPERATIVE NODAL STAGING: DISSECTION VERSUS SAMPLING

No clear consensus exists regarding whether to perform lymph node sampling or full nodal dissection in resectable patients. The true value of dissection compared with its purported risks has not been adequately studied in prospective studies. Evidence suggests that dissection does indeed identify N2 disease otherwise missed by conventional staging and sampling. In 208 patients without bulky disease who were consecutively resected at three centers, sampling was performed first followed by full dissection in each patient.[36] A total of 60 patients were identified as having N2 disease; 31 of these (52%) were identified with sampling alone. Of those with multilevel N2 disease, sampling only identified 40%. Of the 60 patients with N2 disease, 24 had skip metastases to the mediastinal nodes with normal N1 nodes. Although this report did not specify the clinical compared with pathological stage in these patients, a switch from stage I to IIIA might, based on recent evidence with adjuvant chemotherapy, alter the postoperative treatment plan and affect long-term survival.

Although evidence of a survival benefit from adjuvant chemotherapy has been difficult to assess, currently available data demonstrate a potential dichotomy between stages I and II/III disease. The 1995 meta-analysis that demonstrated a survival benefit for adjuvant cisplatin-based chemotherapy in NSCLC[37] has been supported by subsequent randomized trials (Table 5).[9,38-41] Nonetheless, another large trial (Adjuvant Lung Project Italy; ALPI) failed to demonstrate a survival advantage.[42] A metaanalysis of the five largest recent adjuvant trials of cisplatin-based adjuvant therapy (Lung Adjuvant Cisplatin Evaluation; LACE) has helped to clarify the issue and these results were recently presented.[43] Included in this analysis were individual patient data from the following trials: ALPI, Adjuvant Navelbine International Trialist Association (ANITA), Big Lung Trial (BLT), International Adjuvant Lung Cancer Trial (IALT), and JBR.10. Results demonstrated an overall hazard ratio (HR) of death of 0.89 (95% CI 0.82-0.96; $p<0.005$) with chemotherapy. The absolute benefit in 5-year survival was 4.2%. The benefit, however, varied by stage, with the greatest benefit shown in stages II (HR 0.83; 95% CI 0.73-0.95) and III (HR 0.83; 95% CI 0.73-0.95), and possibly no benefit at all in stage IA (HR 1.41; 95% CI 0.96-2.09). The HR in stage IB was 0.93 (95% CI 0.78-1.10). This meta-analysis suggests a clear difference between stages II/III and stage I NSCLC in survival benefit from adjuvant chemotherapy. This difference

highlights the need for accurate pathological staging to identify appropriate candidates for adjuvant chemotherapy. The use of lymph node dissection rather than sampling can improve the accuracy of pathological staging and ultimately have an important effect on treatment outcomes for early-stage NSCLC.

Despite the enhanced ability of mediastinal lymph node dissection to detect N2 disease, and thus appropriately identify chemotherapy candidates, sampling is frequently performed instead of dissection because of concerns about increased postoperative morbidity and mortality with full dissection. To address these concerns specifically, the ACOSOG conducted a large randomized prospective trial (Z0030) that compared the two procedures.[44] The primary objective was to determine whether overall long-term survival is affected by the choice of procedure. Immediate postoperative complications and mortality were evaluated as a secondary objective, and a preliminary report of these findings was recently published. Patients with clinically resectable T1-2, NO or non-hilar N1, M0 NSCLC with no evidence of mediastinal involvement based on either CT or mediastinoscopy, if performed, were eligible. All patients underwent lymph node sampling at the time of resection. Those with no evidence of cancer upon sampling were randomly assigned to either sampling only (i.e. no further dissection) or full lymph node dissection. Lymph node dissection was performed in 525 patients, whereas sampling alone was performed in 498 patients. Although dissection led to slightly increased blood loss ($p = 0.033$), a median operative time of 15 min longer ($p < 0.0001$), and greater chest tube drainage ($p = 0.056$), the duration of hospitalization was no different between the groups (median 6 days; $p = 0.4$). Furthermore, no difference occurred in the rate of any specific postoperative complication between the groups.

Postoperative mortality was also not statistically different between groups (2.0% with sampling versus 0.76% with dissection; $p = 0.157$). These data show that avoiding dissection because of potential increases in morbidity and mortality is not necessary. A previous study suggested that survival may be improved with dissection.[45] With short-term follow-up, the impact of dissection on long-term survival in that study is not yet known. Mediastinal lymph node disease (N2) was, however, discovered in 20 patients who otherwise had negative sampling (3.8%). These results corroborate the increased accuracy of dissection and furthermore prove that the procedure is a safe alternative to sampling.

TABLE 5: *Adjuvant Chemotherapy in Early-Stage NSCLC: Summary of Selected Phase III Trials.*

Study	Regimen	Stage	N	Survival Median, months	Survival 5-Year, %
Kato (2004)[39]	UFT	IA-IB	491	NR	88*
	Observation		488	NR	85
IALT (2004)[38]	CDDP-based	IA-IIIA	932	50.8	45*
	Observation		935	44.4	40
JBR.10 (2004)[41]	Cisplatin/Vinorelbine	IB-II	243	94*	69*
	Observation		238	73	54
CALGB 9633 (2004)[40]	Paclitaxel/Carboplatin	IB	173	95	59
	Observation		171	78	57
Douillard† (2006)[9]	Vinorelbine/Cisplatin	IB-III A	407	65.7*	51
	Observation		433	43.7	43

NR, Not reported; NRe, not reached.
Statistically significant;
†7-year: 45 versus 37%.

RESTAGING AFTER NEOADJUVANT THERAPY IN STAGE IIIA N2

How to re-stage patients after neoadjuvant therapy has its own challenges, particularly in patients who have already undergone mediastinoscopy. Repeating mediastinoscopy can be difficult because of adhesions and fibrosis resulting from the initial procedure. In one of the largest studies of remediastinoscopy after neoadjuvant therapy, the procedure was not possible in five out of 165 patients (3%) because of adhesions.[46] Although EUS-FNA would be useful, its availability is still limited. Video-assisted thoracoscopic surgery (VATS) may be a feasible alternative to remediastinoscopy as suggested by a phase II study by the Cancer and Leukemia Group B (CALGB)[47] Of 70 attempted procedures, 53 (76%) were successful. The remaining 17 (24%) failed with the majority as a result of adhesions/ fibrosis. CT, PET, or integrated PET-CT are currently the primary options in this setting.

Recent evidence suggests that integrated PET-CT is perhaps the most valuable non-invasive tool. The Leuven Lung Cancer Group compared integrated PET-CT with remediastinoscopy in 30 patients who underwent preoperative chemotherapy for stage IIIA N2 disease, and were consecutively resected at a single institution.[48] N2 disease was pathologically confirmed in 17 patients. PET-CT correctly identified N2 disease in 13 (76%); remediastino-scopy correctly identified N2 disease in five (29%). Nevertheless, all teams do not report the same difficulties with remediastinoscopy as reported by the Leuven Group. Other groups have reported sensitivity of 70-74%, specificity of 100%, and accuracy of 80-92.5% with remediastinoscopy.[46,49-51] Positive and negative predictive values for remediastinoscopy have been reported as 100 and 75-86%.[46,50] In practice, however, many surgeons hesitate to perform a second aggressive look at the mediastinum. Once again, this difficulty could be avoided if the initial invasive staging was performed using ultrasound techniques.

Comparing PET-CT with either PET or CT alone, PET-CT showed greater sensitivity, specificity, accuracy, positive predictive value, and negative predictive value than either of the other two alone in the Leuven Group study.[48] Cerfolio and colleagues[52] also found integrated PET-CT superior to CT alone for restaging in a prospective trial of 93 patients with biopsy-confirmed stage IIIA N2 disease. Of interest in that study was an analysis of the magnitude of change of maximal SUV in mediastinal nodes on repeat PET-CT. A reduction in the maximum SUV of a previously involved N2 node by more than 50% led to a high likelihood that the node was now benign (positive likelihood ratio 7.9). The investigators noted, however, that a positive result still necessitates biopsy as residual cancer may not in fact be present despite an elevated SUV.

In conclusion, medical oncologists are still faced with multiple factors to consider when staging each patient and a lack of the availability of newer procedures remains a challenge. Identifying pathological N2 disease is, however, of great importance because its presence significantly affects outcomes and potential treatment strategies. Recent data supporting the use of adjuvant or neoadjuvant therapies in these patients suggest that every reasonable effort should be made to assess N2 disease accurately in patients with clinical stage I-II disease, as well as in those with clinical stage IIIA N2 disease who have undergone preoperative treatments. Newer procedures such as integrated PET-CT, EUS-FNA and EBUS-TBNA are non or minimally invasive techniques that may enhance the accuracy of preoperative or post-therapy mediastinal staging. As their availability widens, they are likely to become part of the standard treatment paradigms. Intra-operatively, a growing body of evidence suggests that lymph node dissection can be performed safely and should replace sampling as a more effective means of identifying unsuspected N2 disease.

REFERENCES

1. Herder GJM, Verboom P, Smit EF, et al. Practice, efficacy and cost of staging suspected non-small cell lung cancer: a retrospective study in two Dutch hospitals. *Thorax* 2002;57: 11-14.

2. Van Tinteren H, Hoekstra OS, Smit EF, et al. Effectiveness of positron emission tomography in the preoperative assessment of patients with suspected non-small-cell lung cancer: the PLUS multicentre randomised trial. *Lancet* 2002;359:1388-1393.

3. Mountain CF. Revisions in the international system for staging lung cancer. *Chest* 1997;111:1710-1717.

4. Detterbeck FC, DeCamp MM, Kohman LJ, et al. Invasive staging: the guidelines. *Chest* 2003;123:167-175.

5. Felip E, Stahel RA, Pavlidis N, et al. ESMO minimum clinical recommendations for diagnosis, treatment and follow-up of non-small-cell lung cancer (NSCLC). *Ann Oncol* 2005; 16 (Suppl. 1):i28-i29.

6. National Comprehensive Cancer Network. Clinical practice guidelines in oncology. Non-small cell lung cancer. Available at: http://www.nccn.org/professionals/physician_gls/PDF/ nscl.pdf. v.2.2006. Accessed: 25 August 2006.

7. Silvestri GA, Tanoue LT, Margolis ML, et al. The noninvasive staging of non-small cell lung cancer: the guidelines. *Chest* 2003;123:147-156.

8. Reed CE, Harpole DH, Posther KE, et al. Results of the American College of Surgeons Oncology Group Z0050 Trial: the utility of positron emission tomography in staging potentially operable non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2003;126:1943-1951.

9. Douillard J, Rosell R, Delena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. *Lancet Oncol* 2006;7: 719-727.

10. Betticher DC, Hsu Schmitz SF, Totsch M, et al. Mediastinal lymph node clearance after docetaxel-cisplatin neoadjuvant chemotherapy is prognostic of survival in patients with stage IIIA pN2 non-small-cell lung cancer: a multicenter phase II trial. *J Clin Oncol* 2003;21:1752-1759.

11. Betticher DC, Hsu Schmitz SF, Totsch M, et al. Prognostic factors affecting long-term outcomes in patients with resected stage IIIA pN2 non-small-cell lung cancer: 5-year follow-up of a phase II study. *Br J Cancer* 2006;94:1099-1106.

12. Radiation Therapy Oncology Group. Cisplatin and docetaxel with or without radiation therapy in treating patients who are undergoing surgery for newly diagnosed stage III non-small cell lung cancer. 2006. Available at: http://www.clinicaltrials. gov/ct/show/NCT00113386?order=l. Accessed: March 2007.

13. Swiss Institute for Applied Cancer Research. Chemotherapy with or without radiation therapy before surgery in treating patients with stage IIIA non-small cell lung cancer. 2006. Available at: http://www.clinicaltrials.gov/ct/show/ NCT00030771?order=l. Accessed: March 2007.

14. Toloza EM, Harpole L, McCrory DC. Noninvasive staging of non-small cell lung cancer: a review of the current evidence. *Chest* 2003;123 (1 Suppl.):137S-146S.

15. Sachs S, Bilfinger TV, Komaroff E, Franceschi D. Increased standardized uptake value in the primary lesion predicts nodal or distant metastases at presentation in lung cancer. *Clin Lung Cancer* 2005;6:310-313.

16. Dhital K, Saunders CA, Seed PT, et al. [(18)F]Fluorodeoxy-glucose positron emission tomography and its prognostic value in lung cancer. *Eur J Cardiothorac Surg* 2000;18: 425-428.

17. Jeong HJ, Min JJ, Park JM, et al. Determination of the prognostic value of [(18)F]fluorodeoxyglucose uptake by using positron emission tomography in patients with non-small cell lung cancer. *Nucl Med Commun* 2002;23:865-870.

18. Vansteenkiste JF, Stroobants SG, Dupont PJ, et al. Prognostic importance of the standardized uptake value on (18)F-fluoro-2-deoxy-glucose-positron emission tomography scan in non-small-cell lung cancer: an analysis of 125 cases. Leuven Lung Cancer Group. *J Clin Oncol* 1999;17:3201-3206.

19. Lardinois D, Weder W, Hany TF, et al. Staging of non-small-cell lung cancer with integrated positron-emission tomography and computed tomography. *N Engl J Med* 2003;348:2500-2507.

20. Cerfolio RJ, Bryant AS, Ojha B, Eloubeidi M. Improving the inaccuracies of clinical staging of patients with NSCLC: a prospective trial. *Ann Thorac Surg* 2005;80:1207-1214.

21. Cerfolio RJ, Ojha B, Bryant AS, et al. The accuracy of integrated PET-CT compared with dedicated PET alone for the staging of patients with nonsmall cell lung cancer. *Ann Thorac Surg* 2004;78:1017-1023.

22. Hiirtgen M, Friedel G, Toomes H, Fritz P. Radical video-assisted mediastinoscopic lymphadenectomy (VAMLA) - technique and first results. *Eur J Cardiothorac Surg* 2002;21:348-351.

23. Leschber G, Holinka G, Linder A. Video-assisted mediastinoscopic lymphadenectomy (VAMLA) - a method for systematic mediastinal lymphnode dissection. *Eur J Cardiothorac Surg* 2003;24:192-195.

24. Witte B, Wolf M, Huertgen M, et al. Video-assisted mediastinoscopic surgery: clinical fesibility and accuracy of mediastinal lymph node staging. *Ann Thorac Surg* 2006;82: 1821-1827.

25. Kuzdzal J, Zielinski M, Papla B, et al. Transcervical extended mediastinal lymphadenectomy-the new operative technique and early results in lung cancer staging. *Eur J Cardiothorac Surg* 2005;27:384-390.

26. Kuzdzal J, Zielinski M, Papla B, et al. The transcervical extended mediastinal lymphadenectomy versus cervical mediastinoscopy in non-small cell lung cancer staging. *Eur J Cardiothorac Surg* 2007;31:88-94.

27. Annema JT, Versteegh MI, Veselic M, et al. Endoscopic ultrasound added to mediastinoscopy for preoperative staging of patients with lung cancer. *JAMA* 2005;294:931-936.

28. Larsen SS, Vilmann P, Krasnik M, et al. Endoscopic ultrasound guided biopsy performed routinely in lung cancer staging spares futile thoracotomies: preliminary results from a randomised clinical trial. *Lung Cancer* 2005;49:377-385.

29. Eloubeidi MA, Cerfolio RJ, Chen VK, et al. Endoscopic ultrasound-guided fine needle aspiration of mediastinal lymph node in patients with suspected lung cancer after positron emission tomography and computed tomography scans. *Ann Thorac Surg* 2005;79:263-268.

30. Yasufuku K, Chiyo M, Sekine Y, et al. Real-time endobronchial ultrasound-guided transbronchial needle aspiration of mediastinal and hilar lymph nodes. *Chest* 2004;126:122-128.

31. Rintoul RC, Skwarski KM, Murchison JT, et al. Endobronchial and endoscopic ultrasound-guided real-time fine-needle aspiration for mediastinal staging. *Eur Respir J* 2005;25: 416-421.

32.   Yasufuku K, Chiyo M, Koh E, et al. Endobronchial ultrasound guided transbronchial needle aspiration for staging of lung cancer. *Lung Cancer* 2005;50:347-354.

33.   Herth FJ, Ernst A, Eberhardt R, et al. Endobronchial ultrasound-guided transbronchial needle aspiration of lymph nodes in the radiologically normal mediastinum. *Eur Respir J* 2006;28:910-914.

34.   Vilmann P, Rrasnik M, Larsen SS, et al. Transesophageal endoscopic   ultrasound-guided   fine-needle   aspiration (EUS-FNA) and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) biopsy: a combined approach in the evaluation of mediastinal lesions. *Endoscopy* 2005;37:833-839.

35.   Patelli M, Agli LL, Poletti V, et al. Role of fiberscopic transbronchial needle aspiration in the staging of N2 disease due to non-small cell lung cancer. *Ann Thorac Surg* 2002;73: 407-411.

36.   Massard G, Ducrocq X, Kochetkova EA, et al. Sampling or node dissection for intraoperative staging of lung cancer: a multicentric cross-sectional study. *Eur J Cardiothorac Surg* 2006;30:164-167.

37.   Non-small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. *BMJ* 1995; 311:899-909.

38.   Arriagada R, Bergman B, Dunant A, et al. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *N Engl J Med* 2004;350:351-360.

39.   Kato H, Ichinose Y, Ohta M, et al. A randomized trial of adjuvant chemotherapy with uracil-tegafur for adenocarcinoma of the lung. *N Engl J Med* 2004;350:1713-1721.

40.   Strauss GM, Herndon JE, Maddaus MA, et al. Adjuvant chemotherapy in stage IB non-small cell lung cancer (NSCLC): update of Cancer and Leukemia Group B (CALGB) protocol 9633. ASCO Annual Meeting Proceedings Part I. Vol 24 (June 20 Supplement). *J Clin Oncol* 2006; 7007.

41.   Winton TL, Livingston R, Johnson D, et al. A prospective randomised trial of adjuvant vinorelbine (VIN) and cisplatin (CIS) in completely resected stage IB and II non small cell lung cancer (NSCLC) Intergroup JBR.10 [Abstract 7018]. *Proc Am Soc Clin Oncol* 2004; 22:621s.

42.   Scagliotti GV, Fossati R, Torri V, et al. Randomized study of adjuvant chemotherapy for completely resected stage I, II, or IIIA non-small-cell lung cancer. *J Natl Cancer Inst* 2003;95: 1453-1461.

43.   Pignon JP, Tribodet H, Scagliotti GV, et al. Lung Adjuvant Cisplatin Evaluation (LACE): a pooled analysis of five randomized clinical trials including 4,584 patients. ASCO Annual Meeting Proceedings Part I. Vol 24 (June 20 Supplement). *J Clin Oncol* 2006; 7008.

44.   Allen MS, Darling GE, Pechet TTV, et al. Morbidity and mortality of major pulmonary resections in patients with early-stage lung cancer: initial results of the randomized, prospective ACOSOG Z0030 trial. *Ann Thorac Surg* 2006; 81:1013-1020.

45.   Wu Y, Huang ZF, Wang SY, et al. A randomized trial of systematic nodal dissection in resectable non-small cell lung cancer. *Lung Cancer* 2002;36:1-6.

46.   Stamatis G, Fechner S, Hillejan L, et al. Repeat mediastinoscopy as a restaging procedure. *Pneumologie* 2005;59:862-866.

47.   Jaklitsch MT, Gu L, Harpole DH, et al. Prospective phase II trial of pre-resection thoracoscopic (VATS) restaging following neoadjuvant therapy for IIIA(N2) non-small cell lung cancer (NSCLC): results of CALGB 39803. ASCO Annual Meeting Proceedings. Vol 23 (June 1 Supplement). *J Clin Oncol* 2005; 7065.

48.   De Leyn P, Stroobants S, De Wever W, et al. Prospective comparative study of integrated positron emission tomography-computed tomography scan compared with remediastinoscopy in the assessment of residual mediastinal lymph node disease after induction chemotherapy   for mediastinoscopy-proven stage IIIA-N2 non-small-cell lung cancer: a Leuven Lung Cancer Group study. *J Clin Oncol* 2006;24:3333-3339.

49.   Mateu-Navarro M, Rami-Porta R, Bastus-Piulats R, et al. Remediastinoscopy after induction chemotherapy in non-small cell lung cancer. *Ann Thome Surg* 2000;70:391-395.

50.   Van Schil P, van der Schoot J, Poniewierski J, et al. Remediastinoscopy after neoadjuvant therapy for non-small cell lung cancer. *Lung Cancer* 2002;37:281-285.

51.   De Waele M, Hendriks J, Lauwers P, et al. Nodal status at repeat mediastinoscopy determines survival in non-small cell lung cancer with mediastinal nodal involvement, treated by induction therapy. *Eur J Cardiothorac Surg* 2006;29: 240-243.

52.   Cerfolio RJ, Bryant AS, Ojha B. Restaging patients with N2 (stage IIIa) non-small cell lung cancer after neoadjuvant chemoradiotherapy: a prospective study. *J Thorac Cardiovasc Surg* 2006;131:1229-1235.