Implementation of endoscopic ultrasound for lung cancer staging

Jouke T. Annema, MD, PhD, Roman Bohoslavsky, MSc, Sjaak Burgers, MD, PhD, Marianne Smits, MD, Babs Taal, MD, Ben Venmans, MD, PhD, Hans Nabers, MD, PhD, Ben van de Borne, MD, PhD, Roland van Balkom, MD, PhD, Tjeerd Haitjema, MD, PhD, Alle Welling, MD, Gerald Staaks, MD, Olaf M. Dekkers, MD, PhD, Harm van Tinteren, MD, PhD, Klaus F. Rabe, MD, PhD

Leiden, The Netherlands

Background: EUS-guided FNA is currently advocated in lung cancer staging guidelines as an alternative for surgical staging to prove mediastinal metastases. To date, training requirements for chest physicians to obtain competency in EUS for lung cancer staging are unknown.

Objective: To test a training and implementation strategy for EUS for the diagnosis and staging of lung cancer.

Design: Prospective national multicenter implementation trial. Nine (chest) physicians from 5 hospitals participated in a dedicated EUS educational program (investigation of 50 patients) for the diagnosis and staging of lung cancer. EUS outcomes of trainees were compared with those of the training center.

Setting: Four general hospitals, the national cancer center (implementation centers), and a tertiary referral center (expert center).

Patients: This study involved 551 consecutive patients with (suspected) lung cancer, all candidates for surgical staging, who underwent EUS in 1 of the 5 implementation centers (n = 346) or the single expert center (n = 205). Surgical-pathological staging was the reference standard in case no mediastinal metastases were found.

Results: EUS had a sensitivity of 83% versus 82% and accuracy of 89% versus 88% for mediastinal nodal staging (implementation center vs expert center). Surgery was spared because of EUS findings in 51% versus 54% of patients. A single complication occurred in each group.

Limitation: Surgical-pathological verification of mediastinal nodes was not available in all patients staged negative at EUS.

Conclusion: Chest physicians who participate in a dedicated training and implementation program for EUS in lung cancer staging can obtain results similar to those of experts for mediastinal nodal staging. (Gastrointest Endosc 2010;71:64-70.)

Abbreviations: EBUS, endobronchial ultrasound; EUS-FNA, EUS-guided FNA; N2, metastasis in ipsilateral mediastinal/subcarinal lymph nodes; N3, metastasis in contralateral mediastinal lymph nodes; PET, positron emission tomography; T4, mediastinal tumor invasion.

DISCLOSURE: *Supported by a grant from The Netherlands Organisation for Health Research and Development (Zon-Mw), provided to Dr Annema and Dr Rabe. The current study was supported within an initiative of implementation programs aiming to investigate how methods with proven accuracy and cost-effectiveness could be implemented into clinical practice. Zon-Mw had no role in the design of the study, data collection, analysis, or reporting. All authors had full access to the data. All authors disclosed no financial relationships relevant to this publication.*

0016-5107/$36.00
doi:10.1016/j.gie.2009.07.027

Lung cancer is diagnosed annually in an estimated 1.35 million people throughout the world, leading to 1.18 million deaths—more than any other cancer—and therefore causes a huge public health problem.[1] In patients with suspected lung cancer, assessing a tissue diagnosis and the extent of the disease is crucial for both prognosis and treatment planning. Patients with proven non-small cell lung cancer without evidence of regional and distant metastases (stages I and II) are preferentially treated with surgical resection of the tumor-containing lobe.[2] In the presence of mediastinal nodal metastases (stage III), multiple-modality treatment is indicated.[3] In the initial work-up of patients with suspected lung cancer, imaging with CT and, increasingly, 18-fluorodeoxyglucose positron emission tomography (PET) is performed. Because of

limitations in the sensitivity and specificity of both CT (51% and 85%, respectively)[4] and PET (74% and 85%, respectively)[4,5] tissue staging is mandatory in patients with either enlarged (>1 cm short axis) or PET-positive nodes.[6]

Mediastinoscopy, still regarded as the reference standard for mediastinal tissue staging, has a pooled sensitivity of 78% for nodal staging.[7] Limitations of mediastinoscopy are its diagnostic reach, the invasiveness of the procedure, and the requirement for operative facilities and its associated high costs. The use of mediastinoscopy for lung cancer staging is currently under discussion because of the increasing clinical availability of minimally invasive echoendoscopic needle sampling methods.[8,9]

Transesophageal EUS-guided FNA (EUS-FNA) is a novel method for mediastinal tissue staging in patients with lung cancer,[10,11] with a pooled sensitivity of 84%.[7,12] EUS-FNA has been shown to reduce the necessity for surgical staging by 49% to 70% because of the detection of nodal metastases (N2/N3) or mediastinal tumor invasion (T4).[13-15] Additionally, EUS is an ambulatory, minimally invasive procedure, preferred by patients above surgical staging,[16] and it is cost-effective in comparison to surgical alternatives.[17] In recent guidelines, EUS-FNA is suggested as an alternative for surgical staging to provide tissue proof of nodal metastases.[7,18]

EUS-FNA is generally perceived as a complex diagnostic method that requires a long learning curve.[19] Regarding mediastinal staging of lung cancer, EUS training and implementation requirements for chest physicians are unknown.

To investigate this, we developed an implementation strategy for EUS for the diagnosis and staging of lung cancer and hypothesized that chest physicians would obtain outcomes similar to those of experts. We aimed to compare sensitivity and accuracy of nodal staging as well as spared surgical interventions due to EUS findings between implementation and referral centers.

Capsule Summary

What is already known on this topic

- Endoscopic ultrasound (EUS-FNA), a novel method for mediastinal tissue staging in patients with lung cancer, is perceived as a complex diagnostic method with a long learning curve.

What this study adds to our knowledge

- Chest physicians participating in an EUS implementation program-including investigation of fifty patients-obtained sensitivity and accuracy in mediastinal staging of lung cancer similar to those of experts with longstanding experience.

DESIGN, PATIENTS, AND METHODS

Implementation strategy

Initially, several lectures regarding EUS were given at various lung cancer meetings in The Netherlands, with the aim being to disseminate information to chest physicians and lung surgeons on the indications for EUS-FNA in lung cancer staging. Subsequently, 9 physicians from 5 different hospitals were trained to perform EUS. Seven were chest physicians who had neither used US (either transthoracic or endobronchial US [EBUS]) before in clinical practice nor had been exposed to gastroscopy prior to the training. Two gastroenterologists had been trained in radial EUS and linear EUS (75 procedures each) for GI indications. They had no experience in EUS for lung cancer staging nor specific knowledge on this topic. Chest physicians learned how to introduce a gastroscope into the esophagus in at least 25 patients from a gastroenterologist in their own hospitals. After following a dedicated EUS course for a full day, the practical EUS training consisted of 16 half-day sessions in which, on a weekly basis, 3 patients, on average, were investigated by 1 or 2 experts (J.T.A., K.F.R.) in the presence of 2 trainees. During these sessions, the trainees initially only watched the procedures, and in the second half of the training they learned to find the various nodal stations themselves. Special attention was paid to EUS anatomy, interpretation and reporting of EUS findings, and how to advise referring physicians. After 12 training sessions, in which 36 patients were investigated, trainees started to perform EUS in their own hospitals. From this time, patients were included in the study. Nine to 12 months after the initial training, trainees returned for 4 additional sessions. In total, trainees participated in the investigation of 50 patients. Hospitals in which EUS was implemented (referred to as implementation centers) were medium to large, nonuniversity teaching hospitals (Medical Center Leeuwarden, Medical Center Alkmaar, Catherina Hospital Eindhoven, Meander Medical Center Amersfoort) and the National Cancer Institute. Trainees were instructed in the Leiden University Medical Center—a university hospital and tertiary referral center for EUS/EBUS—where EUS-FNA has been performed for the diagnosis and staging of lung cancer since 1999. Both trainers (J.T.A., K.F.R.) had each performed over 1000 EUS-FNA procedures in lung cancer patients.

Patients

Patients with suspected non-small cell lung cancer who were candidates for surgical resection of the lung tumor and in whom mediastinal tissue staging was indicated (because of enlarged mediastinal or PET-positive nodes or a centrally located tumor) were eligible for the study. Between January 1, 2005 and January 1, 2007, 644 consecutive patients (425 from the implementation centers and 219

from the expert center) who underwent EUS for mediastinal assessment, as an alternative to surgical staging, were included in this trial. Not considered for analysis were the 93 patients (79 from the implementation centers and 14 from the expert center) who underwent EUS for indications other than diagnosis or staging of lung cancer (sarcoidosis, n = 17; tuberculosis, n = 3; lymphoma, n = 12; mesothelioma, n = 22; restaging of lung cancer after neoadjuvant chemotherapy, n = 25; staging of extrathoracic tumors, n = 14). Therefore, a total of 551 patients were included for the present analysis.

Procedures

EUS-FNA was performed in a standardized way as previously described[16] at all 6 study sites. Systematically, all mediastinal regions that can be detected from the esophagus were visualized. Nodes that were suspicious for malignancy on EUS images, because of their size (short axis >1 cm), echo texture (hypoechoic), shape (round), or US borders (sharp), were aspirated. In most cases in both study cohorts, EUS samples were judged on site for adequacy by either the EUS investigators or cytotechnicians. Surgical staging, mostly mediastinoscopy, was performed in patients in whom no mediastinal metastases were found by EUS-FNA. Minimally, biopsy specimens were taken from stations 4L, 7, and 4R. In patients who underwent thoracotomy, mediastinal exploration involved systematic lymph node sampling or dissection. Study findings were entered in a Web-based database designed for this trial.

Outcomes

Primary outcomes of the implementation study were (1) sensitivity and accuracy of EUS-FNA for the detection of mediastinal metastases and (2) spared surgical procedures because of EUS findings. Outcomes of implementation centers were compared with outcomes of the expert center. Surgical-pathological staging of the mediastinum was regarded as the reference standard for the assessment of nodal metastases. EUS-FNA aspirates demonstrating lymph node metastases were regarded as true positives. Surgical confirmation of these tumor-positive nodes was regarded as unethical. Major outcomes of implementation centers of the first and the second year after introduction were compared to test for a period effect. Secondary outcomes were complications and proportion of aspirates that demonstrated adequate material.

We hypothesized that EUS implementation would be successful if the sensitivity of EUS-FNA in the implementation group differed less than 15% from those of the control group. We estimated that the prevalence of mediastinal metastases would be 50%. Further, the ratio of the number of patients diagnosed by the implementation centers with respect to the expert center was estimated to be 1.5. With a total sample size of 428 evaluable patients, a test of proportions with a 1-sided 0.05 significance level would have 85% power to reject the null hypothesis that the test and the reference accuracy are not equivalent. To compensate for patients who were not able to be evaluated, we planned to enroll 550 patients.

Statistics

Sensitivity, negative predictive value, and accuracy were calculated for both the implementation and control groups (for definitions, see Appendix, available online at www.giejournal.org). In addition, we performed a stratified comparison of sensitivity, negative predictive value, and accuracy to adjust for differences in lymph node size (<1 cm vs >1 cm) and PET scan use (PET vs no PET) to exclude the possibility that differences between the implementation and control groups were missed because of imbalance in these characteristics. Baseline characteristics were compared with a chi-square test for categorized data and a *t* test for continuous variables. Differences in proportions were expressed as difference ± 90% confidence intervals.

Ethics

The ethical committee of the Leiden University Medical Center as well as those of the 5 implementation hospitals approved this study. Oral and written informed consent for study participants was obtained before study inclusion.

RESULTS

Patient characteristics

Patient characteristics of the 551 patients with suspected lung cancer are summarized in Table 1. The study population in the implementation and expert centers were comparable with respect to age, sex, and location of the lung tumor. In the implementation centers, compared to the expert center, more patients presented with enlarged (short axis >1 cm on CT) (77% vs 60%, respectively) or PET-positive N2/N3 nodes (42% vs 27%, respectively). At inclusion, patients were intended to undergo mediastinoscopy (87% vs 89%), thoracotomy (12% vs 9%), or other operations (1%, both) in case no nodal metastases were to be found at EUS (implementation vs expert centers). The final diagnoses of the 551 patients were non-small cell carcinoma (n = 487, 88%), small cell lung cancer (n = 30, 6%), infections (n = 17, 3%), sarcoidosis (n = 11, 2%), and other diseases (n = 6, 1%).

Diagnostic procedures

Mediastinal metastases were found by EUS in 143 (41%) patients in the implementation centers and in 81 (40%) patients in the expert center (Table 2). In 48 of the 189 patients who underwent subsequent surgical staging or thoracotomy, nodal metastases were found

TABLE 1. EUS-FNA for the diagnosis and staging of lung cancer

Characteristic	Implementation centers (N = 346)	Expert center (N = 205)	All centers (N = 551)
Age, years (mean, SD)	64.4 (10.3)	64.8 (9.7)	64.5 (10.1)
Men (%)	71	65	69
Location lung tumor			
Intrapulmonary mass	336 (97%)	196 (96%)	532 (97%)
Mediastinal mass	10 (3%)	9 (4%)	19 (3%)
CT scan			
Nodes >1 cm	266 (77%)	122 (60%)	388 (70%)
Nodes <1 cm	80 (23%)	83 (40%)	163 (30%)
Positron emission tomography scan			
Performed	232 (67%)	73 (36%)	305 (55%)
Suspect N2/N3	145 (42%)	55 (27%)	200 (36%)

SD, Standard deviation.

TABLE 2. EUS findings for the diagnosis and staging of lung cancer

Characteristic	Implementation centers (N = 346)	Expert center (N = 205)	All centers (N = 551)
Nodes tumor positive			
Metastases, tissue proven	143 (41%)	81 (40%)	224 (41%)
Metastases, suspected on EUS	3 (<1%)	11 (5%)	14 (3%)
Nodes tumor negative			
Reactive	135 (39%)	45 (22%)	180 (33%)
Granulomas	6 (2%)	3 (1%)	9 (2%)
Not representative	27 (8%)	14 (6%)	41 (7%)
No FNA performed	32 (9%)	51 (25%)	83 (15%)

(Fig. 1). Metastases that were missed by EUS-FNA were located within reach of EUS in 42 patients (90%) and were most frequently located in the subcarinal region. The reference standard, surgical exploration of the mediastinum, was not performed in 83 patients (24%) in the implementation centers and 55 patients (27%) in the expert center because of presumed stage T4 (n = 43), distant metastasis (n = 19), infections (n = 17), small cell lung cancer (n = 16), nonsurgical treatment (radiotherapy/chemotherapy) (n = 14), clinical deterioration (n = 12), alternative diagnoses (n = 10), or other reasons (n = 7).

One major complication occurred in each group. In 1 patient with a large goiter and swallowing problems, a rupture of the sinus piriformis occurred. After administration of intravenous antibiotics, the patient recovered uneventfully. In another patient, a rupture of the esophageal wall occurred, probably because of improper use of the sheet of the needle. After the lesion was clipped, the patient's clinical course was uneventful.

Sensitivity and accuracy of the EUS-FNA procedure

Sensitivity and accuracy of EUS-FNA for detecting mediastinal metastases was based on 413 patients—263 from the implementation centers and 150 from the expert center—who either underwent thoracotomy with mediastinal exploration or in whom nodal metastases were found at surgical staging or EUS-FNA. The prevalence of mediastinal disease was similar: 65% versus 66% (implementation centers vs expert center). There were no differences in sensitivity, accuracy, and negative predictive value regarding mediastinal nodal staging between the implementation centers and the expert center (Table 3). Stratified analysis to adjust for imbalance in nodal size or PET use did not materially influence these findings. For the total of 413 patients, sensitivity, negative predictive value, and accuracy of EUS for mediastinal metastases were 83% (95% CI, 78-87), 75% (95% CI, 69-82), and 89% (95% CI, 85–92), respectively. Results of the 7 chest physicians were similar to those of the 2 gastroenterologists.

Spared surgical procedures

Based on EUS findings, a surgical procedure was spared in 51% of patients in the implementation centers and 54% of patients in the expert center. Surgery was prevented based on tissue-proven N2/N3 metastases in 40%, M1 disease (left adrenal metastases) in 2%, and sonographic evidence for mediastinal tumor invasion (T4) in 14% of patients (Table 4). An alternative diagnosis (small cell lung cancer, sarcoidosis, or lymphoma) was established in 3% of patients.

DISCUSSION

This implementation trial for EUS-FNA demonstrates that chest physicians, after participating in a rather limited

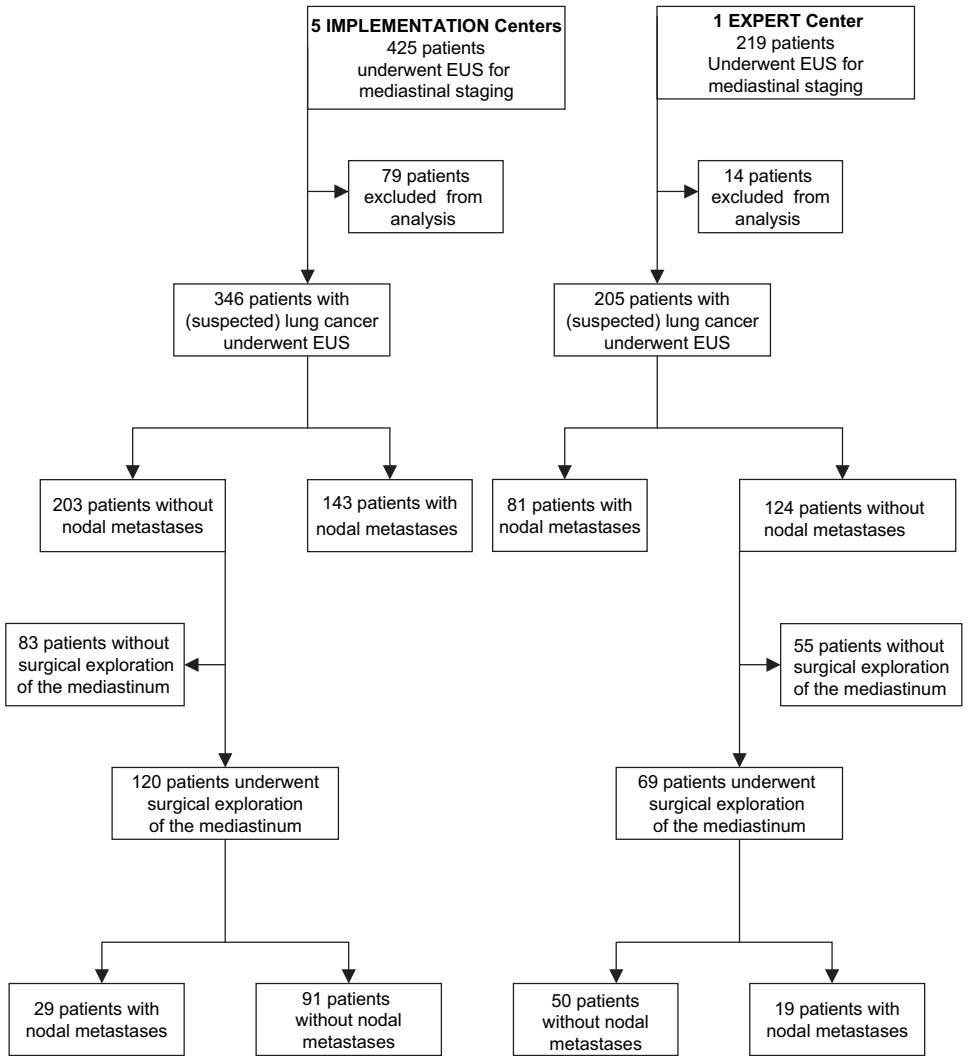

Figure 1. Flow chart of patients undergoing EUS-FNA for mediastinal assessment.

but dedicated EUS implementation program, can obtain results similar to those of experts regarding mediastinal staging of lung cancer. For the assessment of mediastinal metastases, sensitivity (83% vs 82%) and accuracy (89% vs 88%) did not differ between implementation centers and the expert center. Both the implementation centers and expert referral center achieved the high expected number of spared surgical procedures based on EUS findings (51% vs 54%), which is in agreement with the current literature. Published data from expert centers have shown that EUS can prevent surgical staging in 49% to 70% of cases.[13-15]

Our present data indicate that active participation in EUS investigations in 50 patients results in accurate mediastinal nodal assessment. In the field of gastroenterology, physicians are advised to perform 150 to 200 EUS procedures in order to gain competency in all aspects of radial and linear EUS, including pancreatic and rectal indications.[19,20] The sensitivity of 83% and accuracy of 89% for the combined groups (Table 3) are similar to those reported in 2 meta-analyses.[7,12] The reference standard procedure was not performed in 83 patients in whom no mediastinal metastases were found at EUS. This was based on either distant metastases (M1) or tumor invasion (T4) assessed by EUS or based on clinical information in the course of the diagnostic work-up. These patients were excluded from analysis. The exclusion equally affected both the implementation centers and the expert reference center.

Based on the data of this trial and the increasing knowledge on the sensitivity and accuracy of endoscopic methods for lung cancer staging, the question is not whether, but how, EUS-FNA should be implemented for the care of patients with lung cancer because the advantages are so obvious. We hypothesize that chest physicians are most suited for the task, as they have a central position in the care of patients with lung cancer, are primarily responsible for assessing the indication for an EUS

TABLE 3. Diagnostic values of EUS-FNA for the evaluation of mediastinal nodes in patients with suspected lung cancer (N = 413)

Hospital	No.	Sensitivity (%)	Negative predictive value (%)	Accuracy (%)
Implementation centers				
A	56	89	67	91
B	47	85	72	89
C	74	81	75	88
D	14	100	100	100
E	72	73	77	86
A-E	263	83	76	89
Expert center				
F	150	82	74	88
Difference (90% CI)		1.3 (-7.4 to 10.0)	1.9 (-10.3 to 13.4)	1.0 (-5.0 to 6.9)
All centers				
A-F	413	83	75	89

No., Number of patients used for the calculation of EUS outcomes; *A-E,* various hospitals in which EUS was implemented (implementation centers); *F,* the expert center.
For a comparison of sensitivity, negative predictive value, and accuracy between implementation and expert centers, we calculated the % difference with a 90% confidence interval (CI).

TABLE 4. Impact of EUS-FNA on surgical staging

Surgery prevented	Implementation centers (N = 346)	Expert center (N = 205)	All centers (N = 551)
Yes, based on:	176 (51%)	111 (54%)*	287 (52%)
N2/N3	125 (36%)	61 (30%)	186 (33%)
T4	24 (7%)	18 (9%)	42 (8%)
T4 N2/N3	16 (5%)	15 (7%)	31 (6%)
(N2) M1	4 (1%)	6 (3%)	10 (2%)
Small cell lung cancer	3 (1%)	8 (4%)	11 (2%)
Alternative diagnoses	4 (1%)	3 (%)	7 (1%)

*Comparison of prevented surgical interventions: implementation centers versus expert center = -3.3% difference, 90% confidence interval (-10.9 to 4.3).

investigation, and are responsible for further patient management.[21] In the future, EUS will have to be positioned against EBUS, the other echoendoscopic technique by which mediastinal nodes can be sampled. These methods are complementary, as they target different areas of the mediastinum.[22] A recent study suggests that ''near complete'' echoendoscopic mediastinal staging can be achieved in an ambulatory setting by combining EUS and EBUS.[23] To answer this question, a randomized, controlled, clinical trail is required in which complete echoendoscopic staging (EUS-FNA and EBUS-guided transbronchial needle aspiration combined) is compared with optimal surgical staging.[24]

In conclusion, for mediastinal staging of lung cancer, chest physicians participating in an EUS implementation program obtained sensitivity and accuracy similar to that of experts with longstanding experience with the method in a tertiary referral center. The impact on spared surgical staging was equal in both groups, indicating that this implementation strategy might qualify as a model to facilitate large-scale dissemination of complex endoscopic procedures such as EUS-FNA.

REFERENCES

1. Youlden DR, Cramb SM, Baade PD. The international epidemiology of lung cancer: geographical distribution and secular trends. J Thorac Oncol 2008;3:819-31.
2. Scott WJ, Howington J, Feigenberg S, et al. Treatment of non-small cell lung cancer stage I and stage II: ACCP evidence-based clinical practice guidelines (2nd ed). Chest 2007;132(suppl 3):234S-42S.
3. Robinson LA, Ruckdeschel JC, Wagner H Jr, et al. Treatment of non-small cell lung cancer-stage IIIA: ACCP evidence-based clinical practice guidelines(2nd ed). Chest 2007;132(suppl 3):243S-65S.
4. Silvestri GA, Gould MK, Margolis ML, et al. Noninvasive staging of non-small cell lung cancer: ACCP evidenced-based clinical practice guidelines (2nd ed). Chest 2007;132(suppl 3):178S-201S.
5. Ung YC, Maziak DE, Vanderveen JA, et al. 18Fluorodeoxyglucose positron emission tomography in the diagnosis and staging of lung cancer: a systematic review. J Natl Cancer Inst 2007;99:1753-67.
6. Dooms C, Vansteenkiste J. Positron emission tomography in nonsmall cell lung cancer. Curr Opin Pulm Med 2007;13:256-60.
7. Detterbeck FC, Jantz MA, Wallace M, et al. Invasive mediastinal staging of lung cancer: ACCP evidence-based clinical practice guidelines (2nd ed). Chest 2007;132(suppl 3):202S-20S.
8. Rusch VW. Mediastinoscopy: an endangered species? J Clin Oncol 2005;23:8283-5.
9. Janes SM, Spiro SG. Esophageal endoscopic ultrasound/endobronchial ultrasound-guided fine needle aspiration: a new dawn for the respiratory physician? Am J Respir Crit Care Med 2007;175:297-9.
10. Fritscher-Ravens A, Petrasch S, Reinacher-Schick A, et al. Diagnostic value of endoscopic ultrasonography-guided fine-needle aspiration cytology of mediastinal masses in patients with intrapulmonary lesions and nondiagnostic bronchoscopy. Respiration 1999;66:150-5.
11. Silvestri GA, Hoffman BJ, Bhutani MS, et al. Endoscopic ultrasound with fine-needle aspiration in the diagnosis and staging of lung cancer. Ann Thorac Surg 1996;61:1441-5.
12. Micames CG, McCrory DC, Pavey DA, et al. Endoscopic ultrasound-guided fine-needle aspiration for non-small cell lung cancer staging: a systematic review and metaanalysis. Chest 2007;131:539-48.
13. Annema JT, Versteegh MI, Veselic M, et al. Endoscopic ultrasound-guided fine-needle aspiration in the diagnosis and staging of lung cancer and its impact on surgical staging. J Clin Oncol 2005;23:8357-61.

14. Larsen SS, Krasnik M, Vilmann P, et al. Endoscopic ultrasound guided biopsy of mediastinal lesions has a major impact on patient management. Thorax 2002;57:98-103.
15. Tournoy KG, De Ryck F, Vanwalleghem LR, et al. Endoscopic ultrasound reduces surgical mediastinal staging in lung cancer: a randomized trial. Am J Respir Crit Care Med 2008;177:531-5.
16. Annema JT, Versteegh MI, Veselic M, et al. Endoscopic ultrasound added to mediastinoscopy for preoperative staging of patients with lung cancer. JAMA 2005;294:931-6.
17. Kramer H, van Putten JW, Post WJ, et al. Oesophageal endoscopic ultrasound with fine needle aspiration improves and simplifies the staging of lung cancer. Thorax 2004;59:596-601.
18. De Leyn P, Lardinois D, Van Schil PE, et al. ESTS guidelines for preoperative lymph node staging for non-small cell lung cancer. Eur J Cardiothorac Surg 2007;32:1-8.
19. Rösch T. State of the art lecture: endoscopic ultrasonography: training and competence. Endoscopy 2006;38(suppl 1):S69-72.
20. Eisen GM, Dominitz JA, Faigel DO, et al. Guidelines for credentialing and granting privileges for endoscopic ultrasound. Gastrointest Endosc 2001;54:811-4.
21. Annema JT, Rabe KF. Why respiratory physicians should learn and implement EUS-FNA. Am J Respir Crit Care Med 2007;176:99.
22. Herth FJ, Lunn W, Eberhardt R, et al. Transbronchial vs. transesophageal ultrasound-guided aspiration of enlarged mediastinal lymph nodes. Am J Respir Crit Care Med 2005;171:1164-7.
23. Wallace MB, Pascual JM, Raimondo M, et al. Minimally invasive endoscopic staging of suspected lung cancer. JAMA 2008;299: 540-6.
24. Annema JT, Tournoy KG, Rabe KF. Lung cancer staging with minimally invasive endoscopic techniques. JAMA 2008;299:2510-1.

Received March 11, 2009. Accepted July 15, 2009.

Current affiliations: Divisions of Pulmonary Medicine (J.T.A., K.F.R.) and Clinical Epidemiology (O.M.D.), Leiden University Medical Center, Leiden, Biometrics Department (R.B., H.v.T.), Pulmonary Medicine (S.B.), Gastroenterology (M.S., B.T.), Netherlands Cancer Institute Amsterdam, Pulmonary Medicine Medical Center, Leeuwarden (B.V., H.N.), Pulmonary Medicine, St. Catherine's Hospital Eindhoven (B.v.d.B., R.v.B.), Pulmonary Medicine, Medical Center Alkmaar (T.H., A.W.), Pulmonary Medicine, Meander Medical Center Amersfoort (G.S.), The Netherlands.

Presented in part at Digestive Disease Week, May 22, 2007, Chicago Illinois, European Respiratory Society, September 16, 2007, Stockholm, Sweden, American Thoracic Society, May 20, 2008, Toronto, Ontario, Canada, and American Society of Clinical Oncology, May 20, 2008, Chicago, Illinois.

Reprint requests: Jouke T. Annema, MD, PhD, Department of Pulmonology C3 P, Albinusdreef 2, PO box 9600, 2300 RC, Leiden University Medical Center, Leiden, The Netherlands.

If you would like to chat with an author of this article, you may contact Dr. Annema at j.t.annema@lumc.nl.

APPENDIX

Definition of diagnostic values

Sensitivity was defined as the total number of patients with tissue-proven N2-N3 metastases by EUS, divided by the total number of patients with proven N2-N3 metastases.

Negative predictive value was defined as the total number of patients in whom EUS correctly assessed no N2-N3 metastases, divided by the total number of patients in whom EUS assessed no N2/-N3 metastases.

Accuracy was defined as the total number of patients in whom EUS correctly assessed no N2-N3 metastases plus the total number of patients in whom EUS correctly assessed N2-N3 metastases, divided by the total number of evaluated patients.

Participating hospitals

MCL = Medical Center Leeuwarden
MCA = Medical Center Alkmaar
CZE = Catherin Hospital Eindhoven
MMC = Meander Medical Center Amersfoort
NCI = National Cancer Institute
LUMC = Leiden University Medical Center