

# Endoscopic Ultrasound, Positron Emission Tomography, and Computerized Tomography for Lung Cancer

Annette Fritscher-Ravens, Bruce L. Davidson, Hans-Peter Hauber, Karl H. Bohuslavizki, Christoph Bobrowski, Christian Lund, Wolfram Trudo Knöfel, Nib Soehendra, Lars Brandt, Margaret S. Pepe, and Almuth Pforte

Departments of Interdisciplinary Endoscopy, Internal Medicine (Pulmonology), Nuclear Medicine, Radiology, and General Surgery, University Hospital, Hamburg, Germany; Pulmonary-Critical Care Division, University of Washington School of Medicine and Swedish Medical Center; and Department of Biostatistics, University of Washington School of Public Health, Seattle, Washington

Staging of patients with lung cancer to determine operability is intended to efficiently limit futile thoracotomies without denying possibly curative surgery. Currently available staging tests are imperfect alone and in combination. Imaged suspected metastases often require tissue confirmation before surgery can be denied. Endoscopic ultrasound (EUS) may help identify inoperable patients by providing tissue proof of inoperability in a single staging test, with similar sensitivity for identifying inoperable patients as other staging tests. Therefore, we compared computed tomography, positron emission tomography (PET), and EUS with fine-needle aspiration under conscious sedation, each test interpreted blinded with respect to the other tests, for identifying inoperable patients in a consecutive cohort of 79 potentially operable patients with suspected or proven lung cancer. An economic analysis was also performed. Thirty-nine patients were found inoperable (a 40th patient's inoperability was missed by all preoperative staging tests). The sensitivity of computerized tomography was 43%. PET and EUS each had similar sensitivities (68 and 63%, respectively) and similar negative predictive values (64 and 68%, respectively), but EUS's superior specificity (100 vs. 72% for PET) and considerably lower expense means it may be preferred to PET early in staging to identify inoperable patients.

**Keywords:** staging; mediastinum; metastasis; cost-effectiveness

An estimated 169,500 new lung cancers will be diagnosed each year in North America. Eighty percent will be non-small cell cancer, hence possibly curable with current diagnostic and surgical approaches (1). Newer investigational screening tests attempting to diagnose early asymptomatic lung cancer, such as fluorescent bronchoscopy (2) and low-dose, noncontrast spiral computerized tomography (CT) (3) are increasingly employed in some communities (4). Thus, an increasing number of patients (some without tissue evidence of cancer) suspected of having curable lung cancer can be expected to require staging evaluation.

CT of the chest is standard in the evaluation of these patients. Although it helps identify some conditions precluding curative surgery (e.g., invasion of the main pulmonary artery or left ventricle), it is neither very sensitive nor specific for detection of small mediastinal metastases, which make a patient inoperable by current criteria (4).

Positron emission tomography (PET) is reported to be more accurate than CT and sensitive for detecting lung cancers other

than bronchioloalveolar cell, making it an attractive candidate for proving the presence or absence of cancer and also identifying metastatic sites (5, 6). However, PET has limited diagnostic specificity for identifying primary lesions as well as mediastinal and distant metastases. Investigators who have studied PET's accuracy in staging lung cancer conclude by recommending (5) that physicians require tissue proof that mediastinal and distant PET-positive lesions are truly tumorous before denying attempted surgical cure because false positives are common (25% mediastinal, 31% distant metastases, respectively). Consequently, a PET-negative result may conclude a workup, but a PET-positive result requires further invasive diagnosis to obtain tissue. Moreover, the \$2,200 "cost" of PET scanning (the amount Medicare pays as reimbursement in the United States) would add considerably to the expense of lung cancer workup were PET routinely employed.

An alternative staging workup strategy might be to evaluate potentially operable patients with suspected or proven lung cancer by a single highly specific test to identify those with contralateral mediastinal tumor spread. The latter would be ineligible (by currently accepted criteria) for curative resection in other than an approved research protocol. Such a test is endoscopic ultrasound (EUS) with fine-needle aspiration (EUS-FNA) of lymph nodes, performed by esophagoscopy under conscious sedation. EUS-FNA is not only a screening tool for inoperable metastases, but, because it takes a tissue sample, can provide the first proof of cancer (vs. tuberculosis, for example) in patients with diseased mediastinal lymph nodes and suspicious coin lesions (7, 8). A small cohort study suggests that EUS may have comparable accuracy with PET (9). However, how well EUS compares with PET for identifying inoperability in a large cohort of consecutive patients is unknown. We designed a prospective study in which consecutive unselected potentially operable patients with suspected or proven lung cancer would undergo chest CT and PET scanning, as well as EUS. Patients found operable after this workup were sent for surgery. The objectives were to compare the accuracy of the different staging tests for excluding inoperable patients and use the results for an economic analysis of different modeled strategies. Some of these results were previously published in the form of an abstract (10). Six of the 79 patients in this report were inadvertently included in the aforementioned small cohort study (9).

## METHODS

Additional details regarding staging test methods are available in the online supplement.

From April 1998 to May 2000, consecutive patients with suspected or proven lung cancer who were referred by specialty or general practitioners in the Hamburg, Germany metropolitan area to Eppendorf Hospital were included in the study. At the time of referral, all were believed to be candidates for curative thoracic surgery, having had prior radiographs and bronchoscopy demonstrating apparent eligibility for resection (four patients had undergone transbronchial needle aspiration, used to help obtain a primary diagnosis). Patients underwent PET,

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Correspondence and requests for reprints should be addressed to Bruce L. Davidson, M.D., M.P.H., 801 Broadway, Suite 915, Seattle, WA 98122. E-mail: brucedavidson@pobox.com

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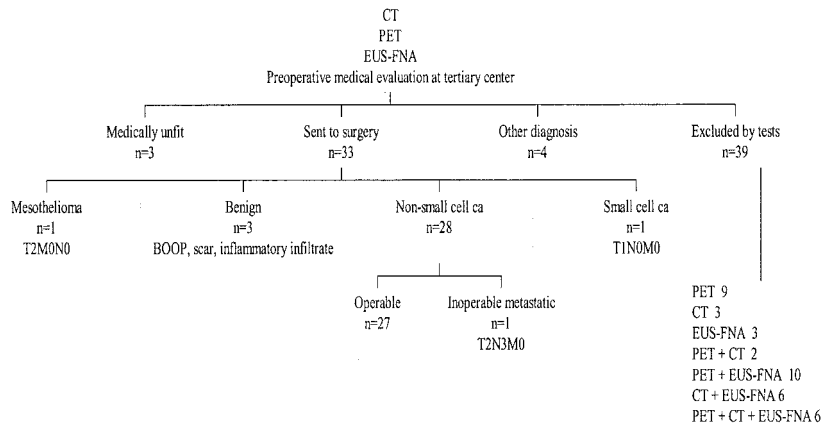


Figure 1. Patient flow of 79 patients referred for evaluation for surgery for non-small cell lung cancer.

EUS, EUS-FNA if nodes were seen at EUS, and CT of the chest and upper abdomen if there was no high-quality CT study already available. Each examination was interpreted by experienced specialty physicians blinded to the results of the other examinations. Patients gave written informed consent for the procedures and the use of their clinical data, and the Human Studies Committee approved the research.

**Staging**

Chest and upper abdominal CT were performed with contrast injection, slice thickness of 5 mm, and pitch of 1.6. Except for tumor invasion of vital structures proving a T4 inoperable tumor, positive CT findings of inoperable metastasis required confirmation by tissue sampling.

PET scanning followed 6 hours of fasting and a plasma glucose proven less than 200 mg/dl. Attenuation-corrected data were converted to standardized uptake values and set with a maximum of 5. Scan reading was qualitative, performed by two independent, experienced nuclear medicine physicians blinded to the results of the other tests. All positive PET findings required tissue confirmation.

EUS was done by one experienced endoscopist (A.F.-R.) using a linear echoendoscope with conscious sedation. Mediastinal lymph nodes seen were classified as abnormal because normally nodes are not visible on EUS. FNA of the most suspicious nodes was undertaken unless not technically accessible. Suspicious features included a round shape with sharp demarcation of the borders, hypochoic features, and inhomogeneous internal texture. Contralateral nodes were always chosen for biopsy if accessible. If only one node was seen, it was always punctured for biopsy. Generally, one to two punctures were required to obtain adequate specimens, which were air-dried on slides and underwent Giemsa staining and evaluation by an experienced cytopathologist (8).

**Inoperability**

Tissue was obtained by needle biopsy from possible metastatic lesions (identified by CT, PET, or EUS) that would confer inoperability, to confirm or refute if they were true positive for cancer. Patients without apparent inoperable lesions and those whose biopsies failed to confirm inoperability remained operative candidates. Patients were staged pre- and postoperatively by widely accepted criteria (11). Operated patients had proven or suspected lung cancer, were judged sufficiently medically fit, had not been found prethoracotomy to have benign disease, and were Stage I, II, or had clinical minimal IIIa disease with no documented extrathoracic spread and no intrathoracic contraindication to possibly curative surgery.

**Outcomes**

Detection of inoperable cancer was the outcome measure. Each patient was finally determined to have been operable (Stage I, II, or minimal IIIa disease) or inoperable (Stage IIIa [bulky disease], IIIb, or IV), based on preoperative imaging and biopsy results, surgical findings (if the patient went to surgery), and at least 6 months of follow-up (4, 10). The follow-up allowed reimaging of locations that had been CT- or

PET-positive but biopsy-negative (apparent false positives), to determine if they were now positive for tumor (i.e., true positives missed by biopsy due to sampling error). Patients with preoperative needle biopsies showing inoperability did not undergo additional open biopsy because it was considered unethical in light of the very low false-positive rate of cytology (12).

**Data Analysis**

An “intent-to-diagnose” approach (13), which included all patients medically fit for surgery who were not found preoperatively to have benign disease, was used. The denominator for sensitivity for detection of inoperable cancer was the number of patients found to have inoperable lung cancer (because of extra- or intrathoracic incurable tumor involvement) after pre- or postoperative staging and clinical follow-up. The denominator for specificity was the number of patients in the cohort sent for surgery who, after surgery, had not been found to have inoperable lung cancer (some might be found to have benign disease, but not inoperable cancer). McNemar’s test was used to compare paired binary sensitivities and specificities, and the procedure of Leisenring and coworkers was used for predictive values (14).

TABLE 1. CHARACTERISTICS OF PATIENTS CONSIDERED FOR SURGERY FOR PROVEN OR SUSPECTED LUNG CANCER (n = 79)

	Not Operated (n = 46)	Operated (n = 33)
Mean age, yr	65	60
Range, yr	44–81	43–76
Men/women	34/12	23/10
Mean PO <sub>2</sub> , mm Hg, on room air	72	75
Mean VC, % predicted	63	65
Mean FEV <sub>1</sub> , % predicted	63	65
Tumor type		
Small cell	1	1
Non-small cell	32	28
Mesothelioma	0	1
Benign diagnoses	4	3
Mediastinal lymphadenopathy		
Nodes by CT, n	37	12
Size range, mm	10–31	10–26
Median size, mm	19	18
Nodes by EUS, n	40	29
Size range, mm	7–44	4–35
Median size, mm	24	14

Definition of abbreviations: CT = computerized tomography; EUS = endoscopic ultrasound.

**Economic Analysis**

We estimated and compared costs for taking 100 potentially operable patients through four simplified modeled strategies for clinical staging: CT alone, CT and PET, CT and EUS-FNA, and CT and mediastinoscopy. The proportions of patients found inoperable before surgery, incurable at surgical staging, and operated on unnecessarily were taken from our cohort for the CT alone, CT-PET and CT-EUS-FNA strategies, and estimated from the literature (15) for the CT-mediastinoscopy strategy (a 10% false-negative and 0% false-positive rate). Costs were estimated from USA Medicare reimbursement rates for participants for 2001 from eastern Pennsylvania (16), the 2000 DRG Handbook (17), and Medicare hospital reimbursement for outpatient procedures from analyses for 2002.

**RESULTS**

**Study Cohort**

Patient flow in the study cohort is summarized in Figure 1. Demographic characteristics of the 79 patients are displayed in Table 1.

Reasons for removing the 46 patients ineligible for surgery from the original cohort are outlined in Figure 1, and subgroups of the whole are presented with more detail in Table 2. Benign diagnoses (one lung abscess, one pulmonary tuberculosis, two pneumonias) and medical contraindications (one with severe mitral regurgitation and left ventricular impairment, two with very limited pulmonary reserve by physiologic testing) removed seven patients. A total of 39 patients removed from consideration for surgery were found to have small cell cancer, Stage IIIa (bulky disease), IIIb, or IV cancer in their preoperative staging workup. At surgery, a 40th patient was identified with an N3 mediastinal node not identified preoperatively by any staging test (see below). Among the 13 inoperable patients missed by PET (one of whom was missed by all staging tests), 6 were excluded from surgery by both EUS-FNA and CT.

**Diagnostic Accuracy of Staging Tests**

Table 3 presents diagnostic values for the individual staging tests. The sensitivities of EUS-FNA and PET were similar (63 and 68%, 95% confidence interval for the difference, -19 to 29%,

**TABLE 2. PATIENTS ULTIMATELY DETERMINED TO BE INOPERABLE (n = 40)**

CT	EUS	PET	n
+*	+	+	6
+	+	-	6
+	-	+	2
+	-	-	3
-	+	+	10
-	+	-	3
-	-	+	9
-	-	-	1†

Definition of abbreviations: CT = computerized tomography; EUS = endoscopic ultrasound; PET = positron emission tomography.

\* '++' Indicates identified as inoperable by the test and '--' indicates not so identified.

† Identified as inoperable (T2N3M0) at attempted curative surgery.

p = 0.82). The specificities were 100 and 72%, (p = 0.004), positive predictive values 100 and 75% (p = 0.008, Fisher's exact test), and negative predictive values 68 and 64% (95% confidence interval for the difference, -19 to 11%, p = 0.58), respectively. EUS-FNA identified 25 inoperable patients, but it missed 15 inoperable patients (Tables 3 and 4). These 15 were patients with negative EUS evaluation or negative FNA biopsies of lymph nodes who had either T4 tumors by CT scan, suspicious adrenal or liver nodules imaged by CT and/or PET that proved positive on needle biopsy, bone lesions on PET confirmed by biopsy or radionuclide scanning, a contralateral lung nodule positive on transthoracic needle biopsy, and one patient missed by all tests but found to have N3 disease at surgery in a node cluster (the node sampled by EUS-FNA was negative). There were no complications from EUS.

PET identified 36 but 9 were false positives based on tissue sampling and clinical follow-up (see below). CT identified 20 inoperable patients, 3 of whom were considered false positives from tissue sampling and follow-up.

Altogether, PET and CT were false positive in 10 patients (2 patients were false positive by both tests). Of these, two pa-

**TABLE 3. DIAGNOSTIC ACCURACY OF ENDOSCOPIC ULTRASOUND-FINE-NEEDLE ASPIRATION, AND POSITRON EMISSION TOMOGRAPHY FOR FINDING INOPERABLE LUNG CANCER IN 72 PATIENTS WHO WOULD OTHERWISE BE CANDIDATES FOR SURGERY (% AND 95% CONFIDENCE INTERVALS)**

		Inoperable Cancer, Final Diagnosis*	
		+	-
		(n = 40)	t(n = 32)
EUS	+	25	0
	-	15	32
	+	27	9
PET	-	13	23
	CT	EUS-FNA	PET
	Sensitivity	17/40 (43%; 27-59)	25/40 (63%; 46-77)
Specificity	29/32 (91%; 75-98)	32/32 (100%; 89-100)	23/32 (72%; 53-86)
Positive predictive value	17/20 (85%; 62-97)	25/25 (100%; 86-100)	27/36 (75%; 58-88)
Negative predictive value	29/52 (56%; 41-70)	32/47 (68%; 53-81)	23/36 (64%; 46-79)
No. of potentially operable patients needed to be staged by the test to exclude one inoperable patient	5	3	3

Definition of abbreviations: CT = computerized tomography; EUS = endoscopic ultrasound; FNA = fine-needle aspiration; PET = positron emission tomography.

\* Does not include patients determined preoperatively to be medically unfit (n = 3) or having benign diagnoses (n = 4).

**TABLE 4. STAGING OF OPERATED PATIENTS (n = 33)**

Postoperative Stage	Number of Patients
T1N0M0	3
T1N1M0	2
T1N2M0	2
T2N0M0	6*
T2N1M0	3
T2N2M0	5
T2N3M0	1†
T3N0M0	3
T3N1M0	1
T3N2M0	3
Small cell carcinoma: T1N0M0	1‡
Benign lesions	3
Total	33

*Definition of abbreviations:* CT = computerized tomography; EUS = endoscopic ultrasound; FNA = fine-needle aspiration; PET = positron emission tomography.

\* One was mesothelioma.

† PET showed N2, CT showed false-negative mediastinal nodes, and EUS-FNA showed false-negative N3 biopsy.

‡ CT: N2; PET: N1; EUS-FNA: N0.

tients died (one from pulmonary embolism 6 months after surgery with autopsy negative for tumor, and one at 7 months from progressive primary tumor but after negative imaging for growth of the contralateral false-positive lesion). Eight patients were alive, 14 to 41 months after surgery, with imaging tests showing no tumor growth in the suspicious areas imaged by CT or PET.

Of 33 operated patients, 5 had no certain preoperative diagnosis of cancer. Postoperative findings of the operated patients are presented in Table 4. At surgery, one patient proved to have mesothelioma and another patient had small cell lung cancer. Three other patients proved to have benign diagnoses. Of these three patients, two patients had chronic nonspecific inflammatory changes and the third patient had bronchiolitis obliterans with organizing pneumonia.

One of the operated patients had a nonoperable T2N3M0 tumor. Preoperative staging by CT showed false negative (< 1 cm) contralateral mediastinal nodes, PET showed only ipsilateral mediastinal adenopathy (N2), and EUS-FNA showed benign histology of an abnormal contralateral mediastinal (N3) node.

#### Economic Analysis

Table 5 presents estimated costs in US dollars for each of the staging tests. Details of calculations are presented in the online supplement. For mediastinoscopy, not employed in our cohort,

a false-negative rate of 10% was used from the literature to arrive at estimates for unnecessary thoracotomies. We found PET to be more expensive than all other tests. Adding EUS-FNA after CT scanning (which all patients will have had) does not increase the number of patients falsely deemed inoperable by CT alone and reduces by over 50% the proportion of remaining surgical candidates with inoperable disease.

#### DISCUSSION

This is the first large study to compare EUS with PET for staging potentially operable patients. We have shown that EUS has comparable sensitivity and negative predictive value with PET but has the advantage of not requiring confirmation of a positive result. Our findings are important because as a single procedure, EUS has the potential to provide superior diagnostic utility to PET at considerably less cost to society. Although PET can identify extrathoracic sites of metastasis and EUS cannot, EUS seems well suited to the biology of lung cancer, which, in inoperable patients, appears to involve N3 nodes detectable by EUS as often as PET-positive confirmed metastases.

Our empiric results for the diagnostic accuracy of PET are fully consistent with those of previous reports. In the only other published study of PET for identifying inoperability (13), evaluation of 89 compliant patients randomized to undergo PET and conventional workup resulted in 60 attempted curative thoracotomies. Among those patients, PET's positive and negative predictive values were 81 and 71%, respectively, similar to the 75 and 64% we found. These investigators found PET added to conventional workup to be 79% sensitive for identifying futile thoracotomies (13), whereas we found it 94% sensitive (Table 5), employing a more limited outcome definition. We confirmed that PET is more sensitive than CT for identifying metastases disqualifying patients from surgery (68% for PET vs. 43% for CT in our cohort,  $p = 0.04$ ), and not only for identifying positive mediastinal lesions (5, 6). We also confirmed the important findings (5, 18) calling attention to PET's limited specificity. For example, in the subset of patients with chest CT scans negative for inoperable adenopathy, van Tinteren and coworkers (13) reported PET found six true positives and three false positives; in our cohort, the results in that subset were three and two, respectively. Pieterman and coworkers (5) reported the positive predictive value of PET to be 74% for identifying patients with metastasis to mediastinal lymph nodes and 69% for identifying distant metastases. Our results support the guidance from these authors, editorialists (18), van Tinteren and coworkers (13), and a recent review (4), which emphasize that the high frequency of false-positive

**TABLE 5. COST AND CONSEQUENCES OF DIFFERENT STAGING STRATEGIES IN 100 CONSECUTIVE PATIENTS**

Staging	Cost (U.S. dollars)	False Negatives*	False Positives†
CT	\$549	32	4
CT + PET	\$2,799 (PET \$2,250)	6	31
CT + EUS-FNA	\$1,695 (EUS-FNA \$1,146)	14	4
CT + mediastinoscopy	\$2,642 (outpatient mediastinoscopy \$2,093)	10	4

*Definition of abbreviations:* CT = computerized tomography; EUS = endoscopic ultrasound; FNA = fine-needle aspiration; PET = positron emission tomography.

Assumptions: (1) Biopsy costs incurred to exclude false positives not included in the table. (2) All EUS has FNA and associated cytopathology costs (in fact, if EUS is negative for lymphadenopathy, FNA is not done). (3) Thoracotomy (DRG 75) cost is for lobectomy. Chest wall resection would add \$350, pneumonectomy would add \$450, etc. (4) Unnecessary thoracotomies assume no further workup before surgery. (5) The 10% false-negative rate for CT + mediastinoscopy is taken from the literature (see text).

\* Unnecessary thoracotomies at the rate of \$22,536 each; see details in the online supplement.

† Possibly surgically curable patients denied surgery unless tissue confirmation sought; see details in the online supplement.

PET scans in the mediastinum (and distal sites) necessitates tissue confirmation before patients are denied surgery.

Several factors suggest caution before widely generalizing our findings. We have shown potential benefit of the early inclusion of EUS in identifying inoperable patients, but not necessarily in prolonged survival of those operated. Our sample size cannot allow us to firmly exclude the possibility that PET might be proved significantly more sensitive than EUS if many more patients were studied. For example, if the true sensitivity of PET is 68% and that of EUS is truly 10% less, 58%, this could be demonstrated with a comparable study of 500 patients. Moreover, we did not evaluate conventional mediastinal node sampling, bronchoscopic ultrasound, or a variety of different possible algorithms involving bone and brain imaging because our goal was to compare the accuracy of the modalities we studied (using tissue and thoracotomy as gold standards) rather than to compare a variety of possible staging workups. The applicability of our economic analysis is subject to varying and ever-changing reimbursement decisions by health insurers. EUS requires an experienced operator for best results and still has suboptimal sensitivity because sampling is limited by accessibility to the esophagus and inherent sampling error. Finally, it is possible that in the future, advances in lung cancer treatment will cause patients with contralateral nodal metastases to be considered operable.

We conclude that EUS has an important place early in the staging of apparent surgical candidates with suspected or proven lung cancer. Although its sensitivity and negative predictive value appear comparable with those of PET scanning, the superior specificity and positive predictive value of EUS allow many patients to be definitively classified as inoperable with a single procedure that is considerably less expensive than PET. Given EUS's lower cost and the reduced need for subsequent invasive testing, practitioners may prefer EUS, where available, early in staging workups. Confirmation of these findings in a management study of a larger group of patients would be desirable.

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## References

- Jemal A, Thomas A, Murray T, Thun M. Cancer statistics, 2002. *CA Cancer J Clin* 2002;52:23–47.
- Lam S, MacAulay C, leRiche JC, Palcic B. Detection and localization of early lung cancer by fluorescence bronchoscopy. *Cancer* 2000; 89:2469–2473.
- Jett JR. Spiral computed tomography screening for lung cancer is ready for prime time. *Am J Respir Crit Care Med* 2001;217:251–256.
- Spiro SG, Porter JC. Lung cancer: where are we today? Current advances in staging and nonsurgical treatment. *Am J Respir Crit Care Med* 2002;166:1166–1196.
- Pieterman RM, van Putten JW, Meuzelaar JJ, Mooyaart EL, Vaalburg W, Koeter GH, Fidler V, Pruim J, Groen HJM. Preoperative staging of non-small cell lung cancer with positron emission tomography. *N Engl J Med* 2000;343:254–261.
- Dwamena BA, Sonnad SS, Angobaldo JO, Wahl RL. Metastases from non-small cell lung cancer: mediastinal staging in the 1990s: meta-analytic comparison of PET and CT. *Radiology* 1999;213:530–536.
- Gress FG, Savides TJ, Sandler A, Kesler K, Conces D, Cummings O, Mathur P, Ikenberry S, Bilderback S, Hawes R. Endoscopic ultrasonography, fine-needle aspiration biopsy guided by endoscopic ultrasonography, and computed tomography in the preoperative staging of non-small cell lung cancer: a comparison study. *Ann Intern Med* 1997;127:604–612.
- Fritscher-Ravens A, Soehendra N, Schirrow L, Sriram PV, Meyer A, Hauber HP, Pforte A. Role of transesophageal endosonography-guided fine needle aspiration in the diagnosis of lung cancer. *Chest* 2000;117:339–345.
- Fritscher-Ravens A, Bohuslavizki KH, Brand L, Bobrowski C, Lund C, Knofel T, Pforte A. Mediastinal lymph node involvement in potentially resectable lung cancer: comparison of CT, positron emission tomography, and endoscopic ultrasonography with and without fine-needle aspiration. *Chest* 2003;123:442–451.
- Fritscher-Ravens A, Hauber HP, Bohuslavizki K, Bobrowski C, Davidson BL, Lund C, Knofel WT, Soehendra N, Pforte A. Role of endoscopic ultrasound with fine needle aspiration versus positron emission tomography for deciding operability of lung cancer patients [abstract]. *Am J Respir Crit Care Med* 2001;163:A69.
- Mountain CF. Revisions in the international system for staging lung cancer. *Chest* 1997;111:1710–1717.
- Atay Z. The reliability of cytodiagnosis in determining malignancy and histogenetic tumor type. In: Nakhosteen JA, Maassen W, editors. *Bronchology: research, diagnostic, and therapeutic aspects*. Boston: Martinus Nihjoff Publishers; 1981. p. 37–42.
- Van Tinteren H, Hoekstra OS, Smit EF, van den Bergh JHAM, Schreurs AJM, Stallaert RALM, van Velthoven PCM, Comans EFI, Diepenhorst FW, Verboom P, 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;359:1388–1392.
- Leisenring W, Alonzo T, Pepe MS. Comparisons of predictive values of binary medical diagnostic tests for paired designs. *Biometrics* 2000; 56:345–351.
- Kaiser LR, Friedberg JS. Role of surgery in the multimodality management of non-small cell lung cancer. *Semin Thorac Cardiovasc Surg* 1997;9:60–79.
- Anonymous. Medicare special bulletin: 2001 Medicare fee schedule and updates. Camp Hill, PA: Xact Medicare services; 2000.
- Anonymous. The DRG handbook. Philadelphia, PA: Dorland Healthcare Information; 2000.
- Berlangieri SU, Scott AM. Metabolic staging of lung cancer. *N Engl J Med* 2000;343:290–291.