Initial Diagnosis of Lung Cancer*

ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition)

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Background: **Lung cancer is usually suspected in individuals who have an abnormal chest radiograph finding or have symptoms caused by either local or systemic effects of the tumor. The method of diagnosis of suspected lung cancer depends on the type of lung cancer (*ie*, small cell lung cancer [SCLC] or non-SCLC [NSCLC]), the size and location of the primary tumor, the presence of metastasis, and the overall clinical status of the patient.**

Objectives: **To determine the test performance characteristics of various modalities for the diagnosis of suspected lung cancer.**

Methods: **To update previous recommendations on the initial diagnosis of lung cancer, a systematic search of MEDLINE, Healthstar, and Cochrane Library databases to July 2004, and print bibliographies was performed to identify studies comparing the results of sputum cytology, bronchoscopy, transthoracic needle aspiration (TTNA), or biopsy with histologic reference standard diagnoses among at least 50 patients with suspected lung cancer. Recommendations were developed by the writing committee, graded by a standardized method, and reviewed by all members of the lung cancer panel prior to approval by the Thoracic Oncology Network, Health and Science Policy Committee, and the Board of Regents of the American College of Chest Physician.**

Results: **Sputum cytology is an acceptable method of establishing the diagnosis of lung cancer with a pooled sensitivity rate of 0.66 and specificity rate of 0.99. However, the sensitivity of sputum cytology varies by location of the lung cancer. For central, endobronchial lesions, the overall sensitivity of flexible bronchoscopy (FB) for diagnosing lung cancer is 0.88. The diagnostic yield of bronchoscopy decreases for peripheral lesions. Peripheral lesions smaller or larger than 2 cm in diameter showed a sensitivity of 0.34 and 0.63, respectively. In recent years, endobronchial ultrasound (EBUS) has shown potential in increasing the diagnostic yield of FB while dealing with peripheral lesions without adding to the risk of the procedure. In appropriate situations, its use can be considered before moving on to more invasive tests. The pooled sensitivity for TTNA for the diagnosis of lung cancer is 0.90. A trend toward lower sensitivity was noted for lesions < 2 cm in diameter. The accuracy in differentiating between SCLC and NSCLC cytology for the various diagnostic modalities was 0.98, with individual studies ranging from 0.94 to 1.0. The average false-positive rate and FN rate were 0.09 and 0.02, respectively.**

Conclusions: **The sensitivity of bronchoscopy is high for the detection of endobronchial disease and poor for peripheral lesions < 2 cm in diameter. Detection of the latter can be aided with the use of EBUS in the appropriate clinical setting. The sensitivity of TTNA is excellent for malignant disease. The distinction between SCLC and NSCLC by cytology appears to be accurate.**

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Key words: bronchoscopy; endobronchial ultrasound; esophageal ultrasound; lung neoplasm; needle aspiration; sensitivity and specificity; sputum cytology; transthoracic needle aspiration

Abbreviations: CI = confidence interval; EBUS = endobronchial ultrasound; EUS = esophageal ultrasound; FB = flexible bronchoscopy; FDG = fluoro-18–2-deoxyglucose; FN = false negative; FNA = fine-needle aspiration; FP = false positive; NA = needle aspiration; NSCLC = non-small cell lung cancer; PET = positron emission tomography; SCLC = small cell lung cancer; TBNA = transbronchial needle aspiration; TTNA = transthoracic needle aspiration; US = ultrasound

The findings of CT scans of the chest and clinical presentation usually allow a presumptive differentiation between small cell lung cancer (SCLC) and non-SCLC (NSCLC). Massive lymphadenopathy and direct mediastinal invasion are well-recognized phenomena in patients with small cell carcinoma.[1,2] A mass in or adjacent to the hilum is a particular characteristic of small cell cancer and is seen in about 78% of cases.[1,2] Not infrequently, SCLC presents with paraneoplastic syndromes.[3] These include the syndrome of inappropriate antidiuretic hormone, ectopic adrenocorticotropic hormone production, and the Lambert-Eaton syndrome. If SCLC is suspected, the diagnosis should be achieved by whatever means is easiest (*ie*, sputum cytology, thoracentesis if an accessible pleural effusion is present, fine-needle aspiration [FNA] of a supraclavicular node or metastatic site, and bronchoscopy with or without transbronchial needle aspiration [TBNA] of mediastinal nodes or submucosal process). If the diagnosis of SCLC is established in a biopsy specimen of the primary lesion, the distinction between limited or extensive disease is then made radiographically. Routine staging of SCLC includes a CT scan of the chest and abdomen or a CT scan of the chest with cuts going through the entire liver and adrenal glands, a CT scan or MRI scan of the brain, and a bone scan. The reader is referred to the "Management of Small Cell Lung Cancer" chapter for a more detailed discussion of the staging and management of SCLC.

In patients suspected of having NSCLC, the method of achieving a diagnosis is usually dictated by the presumed stage of the disease. Patients with suspected lung cancer who present with a pleural effusion should undergo thoracentesis first in order to differentiate between a malignant effusion (due to malignant involvement of the pleura) and a paramalignant effusion (due to other factors such as lymphatic blockade, atelectasis, or hypoproteinemia). Distinction between the two is important because the finding of malignant cells in the pleural fluid alters the stage and treatment of the particular patient. Pleural metastases are more common in the visceral pleura[4] and tend to be focal when there is involvement of the parietal pleura. Because of this, pleural fluid cytology is a more sensitive diagnostic test than percutaneous pleural biopsy, with the latter being a blind sampling procedure.[5–7] When three separate pleural fluid specimens from a patient with malignant pleural disease are submitted to an experienced cytologist, one should expect a positive diagnosis in about 80% of patients.[7,8] Percutaneous, closed pleural biopsy is reported to be diagnostic for malignancy in about 50% of cases.[6] Thoracoscopic biopsy of the pleura is safe and can provide a definitive diagnosis with a high degree of accuracy and minimal risk to the patient.[9,10] The reported sensitivity rate ranges between 0.80 and 0.99, the specificity rate ranges between 0.93 and 1, and the negative predictive value ranges between 0.93 and 0.96.[9,11–13] False-negative (FN) results are more common with mesothelioma than primary lung carcinoma.[11]

Patients with metastatic NSCLC (stage IV disease) usually present with constitutional symptoms (*eg*, fatigue and weight loss), organ-specific symptoms (*eg*, bone pain and neurologic symptoms), and/or abnormal laboratory findings (*eg*, anemia, elevated alkaline phosphatase levels, and/or elevated liver enzyme levels). In many of these patients, FNA or a needle biopsy of a site of metastasis represents the most efficient way to both make a diagnosis and to confirm the stage of disease. In some cases, however, the metastatic site may be technically difficult to biopsy. If metastatic disease can be predicted with a high degree of accuracy on the basis of radiographic findings (*ie*, multiple brain, liver, or bone lesions), it may be more efficient to achieve a diagnosis of the primary lung lesion by whatever method is easiest for the patient (*eg*, sputum cytology, bronchoscopy, or transthoracic needle aspiration [TTNA]). This decision must be made by weighing the technical considerations involved in each approach as well as the reliability of diagnosing an extrathoracic lesion as a site of metastasis based on radiographic appearances alone (see "Noninvasive Staging of Non-small Cell Lung Cancer" chapter). A joint decision among a radiologist, pulmonologist, and medical or radiation oncologist is the desirable approach.

NSCLC can present with extensive infiltration of the mediastinum, which is defined as a mass that infiltrates and encases the mediastinal structures where no discrete mediastinal lymph nodes are visible. In such patients, the diagnosis should be achieved by the method that has the most favorable risk/benefit ratio. Bronchoscopy with TBNA for cytologic or histologic examination of mediastinal

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lymph nodes has been shown to be a safe procedure.[14–17] Technical aspects that are frequently emphasized to be important in achieving a high success rate include accurate preparation of the specimen, rapid on-site evaluation by a cytopathologist, and using the larger 19-gauge needles, which provide better tissue samples for histologic evaluation.[18,19] The overall sensitivity of TBNA is 0.76, and the specificity is 0.96.[14–22] (See the "Invasive Clinical Staging of Non-small Cell Lung Cancer" chapter for a more detailed review of the performance characteristics of TBNA for staging the mediastinum.) The negative predictive value of TBNA is not high enough (0.71) to obviate the need for further confirmation of negative results. Mediastinoscopy is warranted in patients with nondiagnostic results.

TTNA (CT scan-guided) of mediastinal masses can be performed safely.[23] The role of TTNA in patients with extensive mediastinal disease (defined as such extensive mediastinal tumor growth that discrete lymph nodes can no longer be discerned) is usually to confirm the presence of SCLC or NSCLC who are not surgical candidates because of the extent of mediastinal disease.

In the case of a small (< 3 cm), solitary, peripheral lung lesion that is suspicious for lung cancer in a patient who appears to have early-stage disease and is a surgical candidate, the diagnostic dilemma generally centers around whether or not to obtain a biopsy specimen to confirm the diagnosis of cancer before surgical resection is carried out. When the lesion is moderately to highly suspicious for lung cancer, an excisional biopsy performed via thoracoscopy has a much higher sensitivity than TTNA and is the most definitive method of establishing a definitive diagnosis. (See the "Solitary Pulmonary Nodule" chapter for a more detailed review of the diagnostic approach to the solitary pulmonary nodule.)

Recommendations

1. In patients suspected of having SCLC based on the radiographic and clinical findings, it is recommended that the diagnosis be confirmed by the easiest method (*eg*, sputum cytology, thoracentesis, FNA, bronchoscopy including TBNA, endobronchial ultrasound [EBUS]-needle aspiration [NA], and esophageal ultrasound [EUS]-NA), as dictated by the patient's presentation. Grade of recommendation, 1C

2. In patients suspected of having lung cancer who have an accessible pleural effusion, thoracentesis is recommended to diagnose the cause of the pleural effusion. Grade of recommendation, 1C

3. In patients suspected of having lung cancer who have an accessible pleural effusion, if the pleural fluid cytology finding is negative (after at least two thoracenteses), thoracoscopy is recommended as the next step if establishing the cause of the pleural effusion is thought to be clinically important. Grade of recommendation, 1C

4. In patients suspected of having lung cancer who have a solitary extrathoracic site that is suspicious of a metastasis, it is recommended that tissue confirmation of the metastatic site be obtained if an FNA or biopsy of the site is feasible. Grade of recommendation, 1C

5. In patients suspected of having lung cancer, who have lesions in multiple distant sites that are suspected of metastases, but in whom biopsy of a metastatic site would be technically difficult, it is recommended that the diagnosis of the primary lung lesion be obtained by the easiest method (*eg*, sputum cytology, bronchoscopy, or TTNA). Grade of recommendation, 1C

6. In patients suspected of having lung cancer, who have extensive infiltration of the mediastinum based on radiographic studies, it is recommended that the diagnosis of lung cancer be established by the easiest and safest method (*eg*, bronchoscopy with TBNA, EBUS-NA, EUS-NA, TTNA, or mediastinoscopy). Grade of recommendation, 1C

Diagnosis of Primary Tumor

A variety of techniques (*eg*, sputum cytology, flexible bronchoscopy [FB], and TTNA) are available as methods of achieving a definitive diagnosis. Positron emission tomography (PET) scanning has emerged as a helpful adjunct in both the diagnosis and staging of lung cancer.

The main goals in selecting a specific diagnostic modality are to (1) maximize the yield of the selected procedure for both diagnosis and staging and (2) to avoid unnecessary invasive tests for the patient, with special attention to the projected treatment plan. Four key questions to determine the test performance characteristics of various modalities for the diagnosis of lung cancer were formulated. A systematic search of the MEDLINE, Healthstar, and Cochrane Library databases to July 2001 and print bibliographies was performed by the Duke University Center for Clinical Health Policy Research. Studies of at least 50 patients with suspected lung cancer or radiographic follow-up of at least 1 year were selected. The following diagnostic tests were considered: sputum cytologic examination (expecto-

rated or aspirated, spontaneous or induced); FB (including any of biopsy, brushing, washing, TBNA, or BAL); and TTNA. Studies were required to report sufficient data to permit the completion of a 2-×-2 table comparing test results with a reference standard diagnosis. If too few studies met this criterion, then studies that described the diagnostic yield (sensitivity) among patients with lung cancer were considered. When possible, diagnostic performance was estimated separately for patients with central (endobronchial) lesions, peripheral lesions > 2 cm in diameter, and peripheral lesions < 2 cm in diameter. The systematic search was published in the Lung Cancer Guidelines published by the American College of Chest Physicians in 2003.[24]

An updated literature review from July 2001 to July 2004 that compared the results of sputum cytology, FB, and TTNA with histologic reference standard diagnoses among at least 50 patients with suspected lung cancer was performed. The previously published reviews and the current systematic reviews were analyzed and the data were compiled to generate updated tables. Recommendations based on a critical review of the published evidence are provided.

Sputum Cytology

Key Question 1: What are the performance characteristics of sputum cytology for the diagnosis of lung cancer with special consideration for the location of the tumor?

Sputum cytology is the least invasive means of obtaining a diagnosis in a patient who is suspected of having lung cancer. The diagnostic accuracy of sputum cytology, however, is dependent on rigorous specimen sampling (at least three specimens) and preservation techniques, as well as on the location (central vs peripheral) and size of the tumor. Unfortunately, many institutions do not have an established program for sputum collection and processing, and therefore present data with a much lower sensitivity than the data presented here (which come from institutions with well-established sputum analysis programs). Patient characteristics associated with positive cytologic diagnosis on sputum include the following: bloody sputum; low FEV_1 values; large lung tumors (> 2.4 cm); centrally located tumors; and squamous cell cancers.[25]

Sputum cytology is particularly useful in patients who present with centrally located tumors (*ie*, SCLC or squamous call carcinoma) and in those who present with hemoptysis. The sampling of sputum specimens should certainly be considered in a patient who presents with a central lesion with or without radiographic evidence of metastatic disease, in whom a semi-invasive procedure such as bronchoscopy or TTNA might pose a higher risk. The previously published[24] and the more recently performed systematic literature reviews found 17 studies[26–42] providing data on the performance characteristics of sputum cytology for the diagnosis of suspected lung cancer (Table 1). Sensitivity ranged from 0.42 to 0.97; specificity ranged from 0.68 to 1.0. The pooled sensitivity was 0.66, and the pooled specificity was 0.99. The single study conducted in patients evaluated for suspected lung cancer[27] had a sensitivity of 0.87 and a specificity of 0.90. Pooling all studies, regardless of the indication for sputum testing, the false-positive (FP) rate was 0.09 and the FN rate was 0.06.

Böcking et al[26] have shown that the sensitivity of sputum cytology for detecting lung cancer is highly dependent on the number of sputum specimens collected per patient, ranging from approximately 0.68 for a single specimen, to 0.78 for two specimens, to 0.85–0.86 for three or more specimens. Studies of the accuracy of sputum cytology for the diagnosis of lung cancer are difficult to summarize because of a variety of methodological problems.[24] The studies show highly variable estimates of sensitivity and no clear reasons for the variation. There is evidence to suggest that the number of sputum samples and the specimen adequacy are strongly related to the sensitivity of the technique. There is insufficient detail about these features to determine whether these factors explain the heterogeneity of the test accuracy results.

Recommendation

7. In patients suspected of having lung cancer, who present with a central lesion with or without radiographic evidence of metastatic disease, in whom a semi-invasive procedure such as bronchoscopy or TTNA might pose a higher risk, sputum cytology is recommended as an acceptable method of establishing the diagnosis. However, the sensitivity of sputum cytology varies by the location of the lung cancer. It is recommended that further testing be performed with a nondiagnostic sputum cytology test if the suspicion of lung cancer remains. Grade of recommendation, 1C

FB

Key Question 2: What are the performance characteristics of FB and its ancillary procedures for the diagnosis of central (endobronchial) as opposed to peripheral tumors and to peripheral tumors < 2 cm and > 2 cm in size?

Table 1—*Sensitivity and Specificity of Sputum Cytology for Diagnosis of Bronchogenic Carcinoma*

Study/Year	Patients, No.	Indication	Sensitivity	Specificity	FP Rate	FN Rate	Prevalence
Erkilic et al[42]/2003	697	Lung mass	0.69	0.99	0.04	0.04	0.12
Böcking et al[26]/1992	1,888	Mixed	0.86	1.00	0.04	0.02	0.12
Kern[28]/1988	1,289	Mixed	0.97	0.68	0.20	0.06	0.57
Risse et al[29]/1985	1,830	Mixed	0.60	0.98	0.11	0.08	0.17
Johnston and Bossen[30]/1981	9,892	Mixed	0.44	1.00	0.03	0.03	0.05
Jay et al[27]/1980	224	Lung mass	0.87	0.90	0.21	0.06	0.31
Yoneyama and Canlas[31]/1978	547	Mixed	0.83	1.00	0.04	0.02	0.12
Gagneten et al[32]/1976	506	Mixed	0.57	0.99	0.01	0.30	0.50
Rosa et al[33]/1973	1,003	Mixed	0.71	1.00	0.01	0.15	0.38
Dahlgren and Lind[34]/1972	121	Mixed	0.42	0.95	0.02	0.76	0.83
Koss et al[35]/1964	1,307	Mixed	0.71	0.98	0.12	0.06	0.17
Hinson and Kuper[36]/1963	528	Mixed	0.60	0.97	0.06	0.24	0.43
Russell et al[37]/1963	3,440	Mixed	0.51	1.00	0.02	0.07	0.13
Allen and Whittlesey[38]/1960	254	Mixed	0.90	1.00	0.00	0.06	0.41
Koss[39]/1958	607	Mixed	0.60	0.98	0.07	0.11	0.24
Spujt et al[40]/1955	4,933	Mixed	0.53	1.00	0.00	0.04	0.09
Liebow et al[41]/1948	108	Mixed	0.43	0.95	0.12	0.33	0.45
Total	29,245		0.66	0.99	0.09	0.06	0.15

FB with its attendant procedures is a valuable diagnostic procedure in the workup of a patient suspected of having lung cancer. A comprehensive literature search on studies published from 1970 to 2001 was performed[24] to determine the sensitivity of FB for the diagnosis of bronchogenic carcinoma. Studies with < 50 patients and those that reported exclusively on interoperator performance variabilities or focused on technical aspects (*eg*, needle size or cytology preparation) were excluded. Forty-four studies[14,43–85] met the inclusion criteria. An additional nine studies[86–94] using the same inclusion criteria were found during the updated literature review. Most of the studies identified were limited to patients with pathologically confirmed bronchogenic carcinoma and provided data only on the diagnostic yield (test sensitivity). The data were further analyzed with respect to the diagnosis of central disease with an endobronchial component and peripheral disease beyond the segmental level.

The decision about whether to pursue a diagnostic bronchoscopy for a lesion that is suspicious for lung cancer largely depends on the location of the lesion (central vs peripheral). Central lesions can present as an exophytic endobronchial mass, submucosal spread, or a peribronchial tumor causing extrinsic compression. Thirty-five studies[14,44–48,50–72,86–90] of patients with central disease were identified (Table 2). Among a total of 4,507 patients, the overall sensitivity of FB was 0.88. Direct forceps biopsy of visible central lesions is the technique used most frequently, and the sensitivity of this test by itself was 0.74. At least three forceps biopsies of the visible lesion are recommended. The sensitivity from washings and brushings is somewhat lower (0.48 and 0.59, respectively), but these tests are often combined with forceps biopsies. The addition of TBNA to obtain cytology or histology samples when there is submucosal tumor spread or peribronchial tumor causing extrinsic compression increases the sensitivity of bronchoscopy.[95,96]

Peripheral lesions are defined in most studies as lesions that are not visible beyond the visual segmental bronchi; thus, it is not surprising that the sensitivity of FB for diagnosing peripheral lung cancers is lower than for central lesions. Thirty-four studies[43,46,49,50,51,58,59–62,64,65,68–85,91–94] reported on the sensitivity of FB for peripheral lesions (Table 3). Transbronchial biopsies provided the highest sensitivity (0.57; 21 studies), followed by brush biopsy (0.54; 18 studies) and BAL/washings (0.43; 14 studies). Although TBNA showed a high sensitivity (0.65; seven studies), the data deserve cautious interpretation because of the limited number of studies and the large differences in sample size.[24] The overall sensitivity for all modalities in the diagnosis of peripheral disease was 0.78 (16 studies).

A few points must be made in order to interpret the results of bronchoscopy in the diagnosis of peripheral lung cancers. First, most of the studies used fluoroscopy routinely for peripheral lesions, which increases the reported sensitivity of bronchoscopy.[97] Second, the number of transbronchial biopsy samples taken is important, with a sensitivity of 0.45 for one sample and 0.70 for six samples being reported in one study.[98] And last, the sensitivity of bronchoscopy is reported to be higher if the CT scan

Table 2—*Sensitivity of FB Diagnostic Procedures for Central Bronchogenic Carcinoma

Study/Year	Patients,† No.	Sensitivity				
		All Methods	Endobronchial Biopsy	Brush	Wash	EBNA/TBNA
Hsu et al[86]/2004	24					0.71
Win et al[87]/2003	78	0.85	0.61	0.27	0.45	0.42
Gaber et al[88]/2002	39	0.90	0.79	0.74	0.54	
Karahalli et al[89]/2001	98	0.90	0.83	0.68	0.32	0.69
Jones et al[90]/2001	514	0.89	0.72	0.72	0.48	
Baaklini et al[51]/2000	22	0.82				
Bungay et al[52]/2000	24	0.92				
Dasgupta et al[53]/1999	32	0.97				0.78
Govert et al[54]/1999	57	0.95	0.74		0.63	0.82
McLean et al[55]/1998	71		0.82			
Bilaceroglu et al[56]/1997	68	0.96		0.66		0.90
Sing et al[43]/1997	53			0.64		
Govert et al[57]/1996	177	0.85	0.81	0.48	0.43	
Castella et al[58]/1995	39					0.87
Utz et al[14]/1993	88					0.36
Buccheri et al[59]/1991	708		0.80	0.35	0.31	
Popp et al[60]/1991	99		0.93	0.79		
Mak et al[61]/1990	125	0.87	0.76	0.52	0.50	
Gay and Brutinel[62]/1989	53					0.23
Saita et al[63]/1989	105		0.48	0.30		
Wagner et al[44]/1989	72	0.67	0.58	0.39	0.35	0.36
Schenk et al[45]/1987	91	0.71	0.56	0.40	0.29	0.45
Cox et al[64]/1984	33	0.94	0.84	0.83	0.76	
Lam et al[65]/1983	329	0.94	0.82	0.74	0.76	
Zisholtz and Eisenberg[66]/1983	51	0.73	0.67	0.65	0.44	
Gellert et al[67]/1982	218		0.78			
Pilotti et al[46]/1982	286			0.78		
McDougall and Cortese[68]/1981	16		0.50	0.23		
Radke et al[69]/1979	15	0.87				
Chaudhary et al[47]/1978	95		0.76	0.53	0.78	
Chopra et al[48]/1977	51		0.66	0.72	0.51	
Stringfield et al[70]/1977	78		0.85			
Kvale et al[71]/1976	71		0.71	0.77	0.63	
Zavala[72]/1975	193	0.94	0.97	0.93		
Oswald et al[50]/1971	434		0.61			
Summary	4,507	0.88	0.74	0.61	0.47	0.56

*EBNA = endobronchial needle aspiration.

†Represents the maximum number of patients included in sensitivity calculations for any one method.

shows a bronchus extending to the peripheral lesion (0.60 vs 0.25, respectively).[99,100]

The sensitivity of bronchoscopy for diagnosing peripheral lesions is most affected by the size of the lesion. Ten studies[49,51,68–70,84–86,92,93] were identified that reported on the sensitivity of bronchoscopy (brush and/or biopsy) for peripheral lesions with a size < 2 cm or > 2 cm in diameter (Table 4).The sensitivity for peripheral lesions of < 2 cm in diameter was 0.34. Peripheral tumors with a diameter of > 2 cm resulted in a sensitivity of 0.63. Six studies[47,48,75,77,79,83] reported on the sensitivity of postbronchoscopy sputa as an adjunct to the abovementioned bronchoscopic techniques, which was 0.35 (Table 5).

Following in the footsteps of the gastroenterologists, pulmonologists have started using ultrasound (US) technology in the diagnosis and staging of bronchogenic carcinoma. Of the two kinds of ultrasonic probes (*ie*, convex and radial), the radial probe is used to locate the peripheral lesion, which was previously thought to be inaccessible by conventional bronchoscopy.[101,102] A flexible double-hinged curette or an electromagnetic device is used, if necessary, to maneuver an extended working channel to the area of interest, under fluoroscopic guidance. The latter is used to facilitate the probe as well as the sampling tools. Due to the steep learning curve associated with the device, its use is limited to tertiary care centers.

Kurimoto et al[103] carried out an open-label, prospective, nonrandomized trial using a radial probe in

Table 3—*Sensitivity of FB Diagnostic Procedures for Peripheral Bronchogenic Carcinoma*

Study/Year	Patients,* No.	Sensitivity				
		All Methods	Transbronchial Biopsy	Brush	BAL	TBNA
Kawaraya et al[91]/2003	1,372	0.88	0.77	0.57		0.35
Trkanjec et al[92]/2003	50	0.86	0.62	0.16	0.29	
Bandoh et al[93]/2003	97	0.60				
Baba et al[94]/2002	87	0.75	0.53	0.44		0.67
Baaklini et al[51]/2000	129	0.61				
Gasparini et al[73]/1999	480	0.76	0.50			0.70
Reichenberger et al[74]/1999	103		0.39	0.36	0.28	0.47
Aristiazabal et al[75]/1998	64		0.34			
Bilaceroglu et al[76]/1998	92	0.64				
Wongsurakiat et al[77]/1998	30	0.50	0.17		0.47	
Sing et al[43]/1997	22			0.22		
Castella et al[58]/1995	45					0.69
Debeljak et al[78]/1994	39		0.77	0.59	0.36	
de Gracia et al[79]/1993	55				0.33	
Torrington and Kern[80]/1993	91		0.20			
Utz et al[14]/1993						
Pirozynski[81]/1992	145		0.33	0.30	0.65	0.58
Buccheri et al[59]/1991	337		0.75	0.44	0.33	
Popp et al[60]/1991	87		0.80	0.83		
Mak et al[61]/1990	63	0.56	0.37	0.29	0.38	
Rennard et al[82]/1990	730				0.47	
Gay and Brutinel[62]/1989	20					0.65
Wagner et al[44]/1989						
Mori et al[83]/1989	85	0.84		0.84	0.42	
Naidich et al[84]/1988	65	0.48				
Cox et al[64]/1984	22	0.36	0.29	0.22	0.36	
Lam et al[65]/1983	155	0.86	0.61	0.52	0.52	
Pilotti et al[46]/1982	84			0.29		
Wallace and Deutsch[85]/1982	143		0.19			
McDougall and Cortese[68]/1981	130	0.62	0.48	0.36	0.36	
Radke et al[69]/1979	82	0.51				
Stringfield et al[70]/1977	29		0.48			
Kvale et al[71]/1976	29		0.27	0.21	0.12	
Zavala[72]/1975	137	0.71	0.69	0.70		
Hattori et al[49]/1971	208			0.83		
Oswald et al[50]/1971	435		0.28			
Summary	5,742	0.78	0.57	0.54	0.43	0.65

*Represents the maximum number included in sensitivity calculations for any one method.

150 patients with peripheral lung lesions. A final diagnosis was established in all patients with a variety of means. US-guided sampling established the diagnosis in 77% of cases; 69% of lesions were benign, and 82% of lesions were malignant. There was no difference in the diagnostic yield (range, 69 to 77%) based on the size of the lesion (< 10 mm, 10 to 14 mm, 15 to 20 mm, and 20 and 29 mm), except when the lesion was > 3 cm in size (yield, 92%). There were no complications. The authors concluded that sampling guided by the radial US probe significantly increases the diagnostic yield of FB while dealing with peripheral lung lesions < 20 mm in size. In another study,[104] information from a multiplaner volume reformation of the CT scan images were used to guide the endobronchial accessories to sample peripheral lesions. The study[104] demonstrated that the diagnostic yield of FB could be increased up to at least 82%, irrespective of the size and location of the lesion.

A convex US probe is mainly used for the sampling of the mediastinal lymph nodes to aid in disease staging and is discussed in more detail in the "Invasive Staging of Lung Cancer" chapter. A number of newer modalities such as ultrathin bronchoscopy, CT fluoroscopy, multiplanar volume reformation, and electromagnetic navigation are being studied for their impact on the diagnostic yield of FB for lung cancer, yet no recommendation can be made based on the preliminary results

The FN rate for bronchoscopy has not yet been defined. Most clinicians would pursue the diagnosis

Table 4—*Sensitivity of FB Diagnosis of Bronchogenic Carcinoma by Size of Lesion

Study/Year	Lesion < 2 cm				Lesion > 2 cm			
	Patients, No.	Pos	Neg	Sens	Patients, No.	Pos	Neg	Sens
Trkanjec et al[92]/2003	17	9	8	0.53	33	27	6	0.82
Bandoh et al[93]/2003	25	8	17	0.32	72	50	22	0.69
Baaklini et al[51]/2000	16	4	12	0.25	135	93	42	0.69
Gasparini et al[73]/1999	195	82	113	0.42	300	169	131	0.56
Naidich et al[84]/1988	15	4	11	0.27	46	26	20	0.57
Wallace and Deutsch[85]/1982	65	3	62	0.05	78	24	54	0.31
McDougall and Cortese[68]/1981	9	1	8	0.11	36	21	15	0.58
Radke et al[69]/1979	21	6	15	0.29	76	49	27	0.64
Stringfield et al[70]/1977	3	1	2	0.33	26	13	13	0.50
Hattori et al[49]/1971	17	13	4	0.76	182	150	32	0.82
Summary	383	131	252	0.34	984	622	362	0.63

*Neg = negatives; Pos = positives; Sens = sensitivity.

further in the case of a nondiagnostic bronchoscopy of a visible endobronchial abnormality. The FN rate can be estimated to be fairly high in the case of peripheral lesions, especially smaller ones, because of the relatively low sensitivity in this setting. Bronchoscopy has an important role in the diagnosis of benign conditions, but the chance of finding a benign condition in a patient who is clinically suspected of having lung cancer is only 1%.[105]

Recommendations

8. In patients suspected of having lung cancer who have a central lesion, bronchoscopy is recommended to confirm the diagnosis. However, it is recommended that further testing be performed if bronchoscopy results are nondiagnostic and suspicion of lung cancer remains. Grade of recommendation, 1C

9. In expert hands, a radial probe US device can increase the diagnostic yield of FB while dealing with peripheral lesions of < 20 mm in size. Its use can be considered prior to referring the patient for TTNA. Grade of recommendation, 2B

TTNA

Key Question 3: What are the performance characteristics for TTNA as a diagnostic modality with particular emphasis on the size and location of the suspected cancer?

In the previously published lung cancer guidelines, Schreiber and McCrory[24] analyzed data from a metaanalysis[106] of 46 studies and an additional 19 studies[107–125] that focused on the performance characteristics of TBNA or biopsy for the diagnosis of localized pulmonary lesions. The metaanalysis by Lacasse et al[106] encompassed a comprehensive search (up to 1995) of reports published in the English language on the use of NA or biopsy for the evaluation of solitary or multiple pulmonary lesions. At least 90% of the study populations had parenchymal pulmonary lesions as opposed to mediastinal, hilar, or pleural lesions. All diagnoses were verified by surgical biopsy, biopsy of an adjacent site with tumor involvement, culture results, or clinical follow-up for at least 1 year. Cytology findings alone, even when confirmed by findings from another site, was not accepted as a reference standard. At least 90% of patients in each study had a histologic reference standard diagnosis. Forty-two[86,125–166] of the 46 studies in the metaanalysis were used for the final analysis. Five studies with < 50 patients included in the metaanalysis were excluded.[24] In the reanalysis of the data, Schreiber and McCrory[24] considered only the following cut point: definite malignancy or suspicion of malignancy as test-positive, and all other test results, including nondiagnostic, benign, nonspecific, and specific benign diagnoses, as test-negative (this corresponded to cut point "b" in the published metaanalysis).

Five studies,[166–170] published from 2001 to 2004 were identified and incorporated into the reanalysis for this current chapter (Table 6). The pooled sensitivity of TTNA for the diagnosis of peripheral bronchogenic carcinoma was 0.90 (95% confidence interval [CI], 0.88 to 0.91). Individual study estimates ranged from 0.62 to 0.99. There was little difference in specificity for any group of studies analyzed. Overall, only a few studies described the test performance data (*ie*, sensitivity and specificity) according to location of lesion; thus, there were limited data with which to address the question of differences in test performance based on lesion location.[24]

TTNA of a peripheral lung lesion can be per-

formed under either fluoroscopic or CT scan guidance. Lacasse et al[106] did not find any differences in test-operating characteristics between CT scan and fluoroscopic guidance of TTNA in their original metaanalysis. However, with substantially more data from CT scan-guided TTNA studies, the analysis by Schreiber and McCrory[24] found that studies using CT scan guidance showed higher sensitivity than those using fluoroscopy guidance. Using a random-effects model, the pooled sensitivities were 0.92 (95% CI, 0.90 to 0.94) and 0.88 (95% CI, 0.85 to 0.90), respectively, for studies of CT scan-guided and fluoroscopy-guided TTNA. Two studies[108,125] reported direct comparisons between aspiration cytology and cutting needle biopsy histologic diagnosis. Both studies found that transthoracic needle core biopsy when compared with FNA showed similar sensitivity for malignancy (Bilaceroglu et al,[76] 86% vs 92%, respectively; Bandoh et al,[93] 98% vs 98.4%, respectively) and better ability to determine a specific diagnosis for nonmalignant lesions (Bilaceroglu et al,[76] 100% vs 44%, respectively; Bandoh et al,[93] 100% vs 50%, respectively).

In summary, for peripheral lung lesions the sensitivity of TTNA is higher than that of bronchoscopy. In patients who have lung cancer, TTNA has approximately a 90% chance of providing confirmation of the diagnosis. Furthermore, given the FP rate of 0.01 to 0.02, a positive TTNA finding for cancer is reliable. On the other hand, the FN rate of TTNA is high (range, 0.20 to 0.30)[171]; thus, TTNA is generally not useful in ruling out cancer. In patients with lesions that are even moderately suspicious for lung cancer, and who appear to have early-stage disease and are candidates for surgical resection, the high FN rate of TTNA makes reliance on a negative result untenable; therefore, further testing to establish a definitive diagnosis is necessary.

Establishing a specific benign diagnosis such as tuberculosis, fungal infection, or hamartoma on TTNA results is quite valuable, particularly in patients in whom the clinical and radiologic findings strongly suggest a benign diagnosis. In such cases, a specific benign diagnosis based on TTNA findings further decreases the risk of missing a cancer.

PET scanning using fluoro-18–2-deoxyglucose (FDG) has proven to be an excellent modality for evaluating solitary pulmonary nodules. In a meta-analysis[172] of the available data on FDG-PET scanning, the average sensitivity and specificity of FDG-PET scanning for detecting a malignancy was reported to be 0.97 and 0.78, respectively. Like any test, PET scanning has some limitations. The current generation of PET scanners can miss lesions that are < 1 cm in size,[172–174] and FN results can occur when dealing with carcinoid tumors or bronchoalveolar carcinomas.[172,174,175] FP results may be seen with certain inflammatory or infectious lesions such as tuberculomas, histoplasmomas, and rheumatoid nodules.[180,182] (The reader is referred to the chapter on "Solitary Pulmonary Nodules" for a more detailed discussion of FDG-PET scanning in the evaluation of the solitary pulmonary nodule.)

Recommendation

10. In patients suspected of having lung cancer who have a small (< 2 cm) peripheral lesion, and who require tissue diagnosis before further management can be planned, TTNA is recommended. However, it is recommended that further testing be performed if TTNA results are nondiagnostic and suspicion of lung cancer remains. Grade of recommendation, 1B

Cell Type Accuracy

Key Question 4: What is the diagnostic error when differentiating between NSCLC and SCLC generated by various diagnostic techniques (*eg*, bronchoscopy, TTNA, and sputum cytology)?

In a patient with lung cancer, distinguishing between SCLC and NSCLC is of paramount importance as each of these cancers is treated in a radically different manner. The distinction between SCLC

Table 5—*Sensitivity of Postbronchoscopy Sputum for Diagnosis of Bronchogenic Carcinoma*

Study/Year	Patients, No.	Postbronchoscopy Sputum		
		Positive	Negative	Sensitivity
Wongsurakiat et al[77]/1998	26	2	24	0.08
de Gracia et al[79]/1993	43	13	30	0.30
Mori et al[83]/1989	81	17	64	0.21
Chaudhary et al[47]/1978	114	58	56	0.51
Chopra et al[48]/1977	51	24	27	0.47
Kvale et al[71]/1976	22	3	19	0.14
Summary	337	117	220	0.35

Table 6—*Sensitivity and Specificity of TTNA and/or Transthoracic Needle Biopsy for Diagnosis of Peripheral Bronchogenic Carcinoma

Study/Year	Patients, No.	Type of Needle	Radiologic Assistance	Sensitivity	Specificity	FP Rate*	FN Rate*	Prevalence
Geraghty et al[166]/2003	846	C	CT scan	0.91	0.99	0	0.19	0.74
Yamagami et al[167]/2003	110	C	CT scan	0.95	1	0	0.15	0.78
Arslan et al[168]/2002	121	A	CT scan	0.89	1	0	0.27	0.78
Tan et al[169]/2002	100	A	Fluo, CT scan	0.93	0.96	0.01	0.18	0.76
Wallace et al[170]/2002	57	A, C	CT scan	0.82	1	0	0.28	0.68
Lopez Hanninen et al[114]/2001	79	C	CT scan	0.96	1.00	0	0.06	0.63
Laurent et al[115]/2000	202	C	CT scan	0.94	1.00	0	0.18	0.80
Hirose et al[116]/2000	50	C	CT scan	0.83	1.00	0	0.19	0.58
Charig and Phillips[117]/2000	185	C	CT scan	0.93	1.00	0	0.48	0.93
Swischuk et al[118]/1998	612	C	Fluo, CT scan	0.96	0.99	0	0.13	0.76
Lucidarme et al[119]/1998	89	C	CT scan	0.93	1.00	0	0.26	0.84
Larscheid et al[120]/1998	130	A, C	CT scan	0.91	1.00	0	0.26	0.80
Yankelevitz et al[121]/1997	114	A	CT scan	0.94	1.00	0	0.16	0.76
Westcott et al[122]/1997	62	A, C	Fluo, CT scan	0.93	1.00	0	0.12	0.67
Santambrogio et al[123]/1997	220	A	CT scan	0.93	0.99	0.01	0.11	0.64
Cattelani et al[124]/1997	119	A	CT scan	0.93	1.00	0	0.13	0.67
Li et al[107]/1996	97	A	CT scan	0.89	1.00	0	0.43	0.88
Klein et al[108]/1996	129	A, C	CT scan	0.95	1.00	0	0.08	0.64
Milman et al[109]/1995	103	A	Fluo	0.69	1.00	0	0.49	0.76
Böcking et al[125]/1995	371	A, C	CT scan	0.99	0.94	0.02	0.04	0.79
Zakowski et al[110]/1992	176	A	Fluo, CT scan	0.84	1.00	0	0.47	0.84
Yang et al[111]/1992	120	A	US	0.62	1.00	0.00	0.63	0.82
Cristallini et al[112]/1992	390	A, B	Fluo, CT scan	0.94	0.99	0.00	0.16	0.77
Calhoun et al[113]/1986	197	A	Fluo	0.87	1.00	0.00	0.35	0.81
Knudsen et al[127]/1996	128	A	US	0.95	0.95	0.02	0.09	0.68
Gasparini et al[73]/1999	589	A, C	Fluo, CT scan	0.93	0.99	0.00	0.15	0.72
Garcia Rio et al[128]/1994	84	A	CT scan	0.84	1.00	0.00	0.39	0.80
Burbank et al[129]/1994	60	C	CT scan	0.95	1.00	0.00	0.11	0.72
Targhetta et al[130]/1993	64	B	US	0.91	1.00	0.00	0.31	0.83
Grode et al[131]/1993	219	A, B, C	Fluo	0.89	1.00	0.00	0.31	0.80
Collins et al[132]/1992	129	B, C	Fluo, CT scan	0.94	1.00	0.00	0.39	0.91
Veale et al[133]/1988	100	A	Fluo	0.84	1.00	0.00	0.52	0.87
Simpson et al[134]/1988	227	B	Fluo	0.82	1.00	0.00	0.73	0.93
Lovett et al[135]/1988	92	A	Fluo	0.90	1.00	0.00	0.38	0.86
Levine et al[136]/1988	58	NR	Fluo	0.71	1.00	0.00	0.30	0.60
Balslov et al[137]/1988	284	C	Fluo	0.78	1.00	0.00	0.37	0.73
Weisbrod et al[138]/1987	133	C	Fluo	0.78	1.00	0.00	0.36	0.71
Stanley et al[139]/1987	440	A	Fluo, CT scan	0.97	0.97	0.01	0.09	0.73
Winning et al[140]/1986	165	A	Fluo	0.77	1.00	0.00	0.43	0.76
Nahman et al[141]/1985	120	B	Fluo	0.98	0.94	0.01	0.11	0.86
Lees et al[142]/1985	86	A, B	Fluo, CT scan, US	0.85	1.00	0.00	0.42	0.83
Greene et al[143]/1985	150	B	Fluo	0.97	1.00	0.00	0.13	0.81
Crosby et al[144]/1985	180	A	Fluo, CT scan, US	0.82	1.00	0.00	0.69	0.93
Stevens and Jackman[145]/1984	348	A, B, C	Fluo	0.92	0.99	0.00	0.13	0.64
Harrison et al[146]/1984	89	C	Fluo	0.96	1.00	0.00	0.14	0.78
McEvoy et al[147]/1983	81	C	Fluo	0.87	1.00	0.00	0.45	0.86
Johnson et al[148]/1983	200	A, B	Fluo, CT scan	0.95	0.98	0.01	0.09	0.68
Vine et al[149]/1982	91	C	Fluo	0.87	1.00	0.00	0.22	0.69
Samuelsson et al[126]/1982	367	A	Fluo	0.97	0.96	0.02	0.06	0.67
Pilotti et al[150]/1982	130	A	Fluo	0.92	0.93	0.01	0.39	0.88
Jamieson et al[151]/1981	82	A, B	Fluo	0.94	1.00	0.00	0.19	0.80
Allison and Hemingway[152]/1981	147	B	Fluo	0.89	1.00	0.00	0.15	0.62
Westcott[153]/1980	400	B	Fluo	0.98	0.94	0.02	0.05	0.73
Taft et al[154]/1980	100	B	Fluo	0.83	0.95	0.01	0.42	0.80
Poe and Tobin[155]/1980	95	B	Fluo	0.90	0.94	0.01	0.32	0.81
Pak et al[156]/1981	52	A, B	Fluo	0.98	0.00	0.18	1.00	0.83
Flower and Verney[157]/1979	282	B	Fluo	0.87	0.96	0.02	0.25	0.72
Sagel et al[158]/1978	1,153	B	Fluo	0.96	0.99	0.00	0.13	0.78

(*Continued*)

Table 6—*Continued*

Study/Year	Patients, No.	Type of Needle	Radiologic Assistance	Sensitivity	Specificity	FP Rate*	FN Rate*	Prevalence
Lalli et al[159]/1978	1,204	B	Fluo	0.85	0.99	0.00	0.36	0.78
House and Thomson[160]/1977	88	B	Fluo	0.96	0.97	0.02	0.06	0.65
Francis[161]/1977	244	B	Fluo	0.82	0.95	0.03	0.29	0.68
Pavy et al[162]/1974	59	B	Fluo	0.86	1.00	0.00	0.54	0.89
Stevens et al[163]/1968	100	B	Fluo	0.90	0.95	0.03	0.14	0.62
Nasiell[164]/1967	144	B	Fluo	0.72	1.00	0.00	0.29	0.60
King and Russell[165]/1967	59	A	Fluo	0.88	1.00	0.00	0.35	0.81
Summary				0.90 (0.88 0.91)	0.97 (0.96 0.98)			

*A = aspiration needle; B = aspiration biopsy needle; C = cutting biopsy needle; Fluo = fluoroscopy; NR = not reported.
†The FP rate is 1 − the positive predictive value of the test; the FN rate is defined here as 1 − the negative predictive value of the test. Both are highly dependent on the prevalence of disease.

and NSCLC on sputum cytology, TTNA cytology, and bronchoscopic washings, brushings, and BAL cytology is quite reliable. Table 7 summarizes 21 studies, some of which address several diagnostic modalities (TTNA, 14 studies; expectorated sputa, 5 studies; bronchoscopy brush sample, 2 studies; TBNA, 4 studies).[29,44,46,50,116,122,127,131,136,139,148,154,157,162,175–185] The studies selected for reviews of the diagnostic accuracy of TTNA and bronchoscopy were systematically reviewed to find data on differences in diagnosis between SCLC and NSCLC based on the cytologic vs histologic diagnoses.[24] These studies show that the overall accuracy of SCLC vs NSCLC is 0.98, with individual study results ranging from 0.94 to 1.0. Indeed, the chance that a preoperative diagnosis of NSCLC is in error (the tumor is actually SCLC) is 0.02 (range, 0.01 to 0.07). On the other hand, the error rate of a diagnosis of SCLC (the tumor is actually NSCLC) is on average 0.09, with individual studies ranging from 0 to 0.33. As such, if the diagnosis of SCLC is made from a cytologic specimen but the radiographic and clinical findings do not support the diagnosis of SCLC, a biopsy specimen should be obtained if possible in order to perform a histologic evaluation.

Recommendations

11. In patients suspected of having lung cancer, the diagnosis of NSCLC made on cytology results (*eg*, sputum, TTNA, or bronchoscopic specimens) is highly reliable and can be accepted with a high degree of certainty. Grade of recommendation, 1B

12. The possibility of an erroneous diagnosis of SCLC on a cytology specimen must be kept in mind if the clinical presentation or clinical course is not consistent with that of SCLC. In such a case, it is recommended that further testing (biopsy for histologic evaluation) be performed to establish a definitive cell type. Grade of recommendation, 1B

Conclusion

A variety of techniques is available to assist the clinician in achieving a definitive diagnosis of lung cancer. Selection of the most appropriate test is best done in a multidisciplinary fashion with input from a pulmonologist, chest radiologist, and thoracic surgeon. Furthermore, the most appropriate test is usually determined by the type of lung cancer (SCLC or NSCLC), the size and location of the tumor, and the presumed stage of the cancer.

A diagnosis should be obtained by whatever method is easiest in patients who are presumed to have SCLC or who have very clear evidence of advanced NSCLC (*eg*, a large pleural effusion or metastatic disease). Sputum cytology is a reasonable first step in patients with central lesions with or without evidence of metastatic disease in whom a semi-invasive procedure might pose a higher risk; however, diagnostic accuracy depends on the rigorous acquisition, handling, and interpretation of samples. FB is the most useful test for central lesions, whereas in the case of peripheral lesions, the sensitivity of TTNA is higher than that of bronchoscopy.

Summary of Recommendations

1. In patients suspected of having SCLC based on the radiographic and clinical findings, it is recommended that the diagnosis be confirmed by the easiest method (*eg*, sputum cytology, thoracentesis, FNA, and bronchoscopy including TBNA, EBUS-NA,

and EUS-NA), as dictated by the patient's presentation. Grade of recommendation, 1C

2. In patients suspected of having lung cancer who have an accessible pleural effusion, thoracentesis is recommended to diagnose the cause of the pleural effusion. Grade of recommendation, 1C

3. In patients suspected of having lung cancer who have an accessible pleural effusion, if the pleural fluid cytology finding is negative (after at least two thoracenteses), thoracoscopy is recommended as the next step if establishing the cause of the pleural effusion is thought to be clinically important. Grade of recommendation, 1C

4. In patients suspected of having lung cancer who have a solitary extrathoracic site that is suspicious of a metastasis, it is recommended that tissue confirmation of the metastatic site be obtained if an FNA or biopsy of the site is feasible. Grade of recommendation, 1C

5. In patients suspected of having lung cancer, who have lesions in multiple distant sites that are suspected of metastases but in whom the biopsy of a metastatic site would be technically difficult, it is recommended that diagnosis of the primary lung lesion be obtained by the easiest method (eg, sputum cytology, bronchoscopy with TBNA or EBUS-NA, EUS-NA, or TTNA). Grade of recommendation, 1C

6. In patients suspected of having lung cancer, who have extensive infiltration of the mediastinum based on radiographic studies, it is recommended that the diagnosis of lung cancer be established by the easiest and safest method (*eg*, bronchoscopy with TBNA, EBUS-NA, EUS-NA, TTNA, or mediastinoscopy). Grade of recommendation, 1C

7. In patients suspected of having lung cancer, who present with a central lesion with or without radiographic evidence of metastatic disease, in whom a semi-invasive procedure such as bronchoscopy or TTNA might pose a higher risk, sputum cytology is recommended as an acceptable method of establishing the diagnosis. However, the sensitivity of sputum cytology varies by the location of the lung cancer. It is recommended that further testing be performed

Table 7—*Accuracy of Cytology for Distinguishing Between SCLC and NSCLC (Histology "Gold Standard")*

Study /Year	Patients, No.	Technique	Accuracy	FP Rate	FN Rate	Prevalence
Pilotti et al[46]/1982	252	Brush	0.96	0.00	0.04	0.15
Matsuda et al[176]/1986	443	Brush	0.94	0.11	0.04	0.24
Oswald et al[50]/1971	476	Sputum	0.97	0.21	0.01	0.08
Payne et al[177]/1981	656	Sputum	0.99	0.08	0.01	0.07
Clee et al[178]/1982	140	Sputum	0.98	0.00	0.02	0.15
Pilotti et al[179]/1982	400	Sputum	0.97	0.12	0.02	0.12
Risse et al[29]/1985	143	Sputum	0.97	0.03	0.03	0.24
Payne et al[177]/1981	126	TBNA	0.98	0.00	0.03	0.08
Wagner et al[44]/1989	18	TBNA	0.94	0.00	0.10	0.50
Clee et al[178]/1982	33	TBNA/brush	1.00	0.00	0.00	0.12
Clee et al[178]/1982	50	TBNA/brush	0.98	0.00	0.02	0.18
Pavy et al[162]/1974	17	TTNA	0.94	0.00	0.07	0.24
Flower and Verney[157]/1979	77	TTNA	0.97	0.50	0.00	0.03
Taft et al[154]/1980	33	TTNA	1.00	0.00	0.00	0.06
Payne et al[177]/1981	65	TTNA	0.98	0.33	0.00	0.03
Johnson et al[148]/1983	200	TTNA	0.98	0.00	0.03	0.15
Johnston[180]/1984	1,015	TTNA	0.98	0.12	0.01	0.09
Zaman et al[181]/1986	1,209	TTNA	0.98	0.09	0.01	0.10
Young et al[182]/1987	72	TTNA	0.99	0.00	0.01	0.03
Stanley et al[139]/1987	323	TTNA	0.99	0.04	0.00	0.10
Lovett et al[135]/1988	61	TTNA	1.00	0.00	0.00	0.07
Grode et al[131]/1993	224	TTNA	1.00	0.00	0.00	0.10
Knudsen et al[127]/1996	80	TTNA	0.99	0.25	0.00	0.04
Westcott et al[122]/1997	62	TTNA	1.00	0.00	0.00	0.06
Larscheid et al[120]/1998	130	TTNA	1.00	0.00	0.00	0.25
Mean			0.97			0.18
Total	6,305		0.98	0.09	0.02	0.12

dology finding if suspicion of lung cancer remains. Grade of recommendation, 1C

8. In patients suspected of having lung cancer who have a central lesion, bronchoscopy is recommended to confirm the diagnosis. However, it is recommended that further testing be performed if bronchoscopy results are nondiagnostic and suspicion of lung cancer remains. Grade of recommendation, 1C

9. In expert hands, use of radial probe US device can increase the diagnostic yield of FB while dealing with peripheral lesions of < 20 mm in size. Its use can be considered prior to referring the patient for TTNA. Grade of recommendation, 2B

10. In patients suspected of having lung cancer who have a small (< 2 cm) peripheral lesion, and who require tissue diagnosis before further management can be planned, TTNA is recommended. However, it is recommended that further testing be performed if TTNA results are nondiagnostic and suspicion of lung cancer remains. Grade of recommendation, 1B

11. In a patient suspected of having lung cancer, the diagnosis of NSCLC made on cytology findings (*eg*, sputum, TTNA, or bronchoscopic specimens) is highly reliable and can be accepted with a high degree of certainty. Grade of recommendation, 1B

12. The possibility of an erroneous diagnosis of SCLC in a cytology specimen must be kept in mind if the clinical presentation or clinical course is not consistent with that of SCLC. In such a case, it is recommended that further testing (*ie*, biopsy for histologic evaluation) be performed to establish a definitive cell type. Grade of recommendation, 1B

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