Lung Cancer Diagnosis by Fine Needle Aspiration Is Associated With Reduction in Resection of Nonmalignant Lung Nodules

Julie A. Barta, MD, Claudia I. Henschke, PhD, MD, Raja M. Flores, MD, Rowena Yip, MPH, David F. Yankelevitz, MD, and Charles A. Powell, MD

Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Radiology, and Department of Thoracic Surgery, Icahn School of Medicine at Mount Sinai, New York, New York

Background. **The rates of resection of nonmalignant lung nodules suspected preoperatively to be lung cancer vary widely and are reported to be as high as 40%. We determined the impact of the frequent use of computed tomography (CT)-guided fine needle aspiration (FNA) on the resection rate of nonmalignant nodules and frequency of resections of benign disease among patients undergoing evaluation for lung cancer resection operation in an academic medical center.**

Methods. **Eligible patients underwent CT-guided FNA, surgical resection, or both during the 12-month period between July 2013 and July 2014 for known or suspected first primary resectable stage I–III lung cancer. Patient data were extracted from the electronic medical records.**

Results. **One hundred ninety-seven patients underwent surgical resection; among them the overall resection rate of nonmalignant lesions was 13.1% (26/197). For those with preoperative FNA, the rate was 7.9% (11/139), and for those with no biopsy, the rate was 25.9% (15/58) (p = 0.001). The sensitivity and specificity of FNA biopsy were 96% and 98%, respectively. The false-negative rate was 3.9% (5/128).**

Conclusions. **The resection rate of nonmalignant nodules was significantly lower for patients with preoperative CT-guided FNA biopsy than in those without. The diagnostic accuracy of FNA in these patients at moderate to high risk for lung cancer is higher than that of positron emission tomography, with a low rate of adverse events. These findings suggest that the frequent use of preoperative diagnostic confirmation by FNA results in a low rate of nonmalignant resection.**

(Ann Thorac Surg 2017;103:1795–801)

Surgical resection is the preferred approach for early-stage non-small cell lung cancer, which remains the leading cause of cancer death in the United States and the world [1]. The widespread implementation of low-dose computed tomography (CT) screening for lung cancer in the United States promises to reduce lung cancer mortality, but it is essential that standardized protocols for nodule evaluation be developed to help maximize the benefits and minimize the risks of population-based screening [2]. Among the risks of lung cancer screening programs is surgical resection performed for intent to cure malignant disease in patients without lung cancer [2].

The currently reported rates of surgical resection of non-malignant nodules range from 9% to 40%, and there is no consensus for an accepted rate of benign disease in patients undergoing resection for suspected lung neoplasms [3–5]. Within CT-screening cohorts with stringent nodule management protocols, the resection rates of nonmalignant lesions vary from 21% for operations not resulting in a diagnosis of lung cancer in the National Lung Screening Trial data [4, 6] to 34% in the Pittsburgh Lung Screening Study [7] to 11% in the International Early Lung Cancer Action Program [4]. In the latter study, had the screening protocol for growth assessment been followed as recommended, the frequency would have decreased from 11% to less than 2% [4]. On the basis of these and other trials to date, the International Association for the Study of Lung Cancer has recommended that the rate of resections for benign disease be below 15% [8].

Preoperative diagnostic nonsurgical biopsy with the use of CT-guided fine needle aspiration (FNA) has high utility and accuracy in establishing the diagnosis of lung cancer, in immunohistochemical subtyping, and in

The Supplemental Materials can be viewed in the online version of this article [http://dx.doi.org/10.1016/j.athoracsur.2016.11.055] on http://www.annalsthoracicsurgery.org.

Drs Henschke and Yankelevitz disclose a financial relationship with Cornell Research Foundation and General Electric; Dr Powell with Genentech.

Accepted for publication Nov 7, 2016.

Address correspondence to Dr Powell, Division of Pulmonary, Critical Care, and Sleep Medicine, One Gustave L. Levy Place, Box 1232, New York, NY 10029; email: charles.powell@mssm.edu.

Published by Elsevier Inc.

0003-4975/$36.00
http://dx.doi.org/10.1016/j.athoracsur.2016.11.055

providing specimens for molecular analysis and future testing as required [9]. CT-guided FNA has a sensitivity of 92% and a specificity of 97% for the diagnosis of lung cancer [10], with higher accuracy in larger solid and subsolid nodules [11]. Potential adverse events include pneumothorax, with 6.6% of all biopsies resulting in pneumothorax requiring a chest tube, and in hemorrhage [12].

To minimize the risk of resecting nonmalignant lesions, our academic medical center frequently performs CT-guided FNA biopsy in patients with lung nodules before surgical resection, with rates of use among surgeons varying from 11% to 93%. The objectives of this retrospective study was to determine the resection rate of nonmalignant lesions in a high-volume academic medical center lung cancer program and to characterize the role of preoperative FNA.

Patients and Methods

Study Population

The study population for retrospective review was identified by use of the Mount Sinai Thoracic Surgery and Radiology databases, which record thoracic operations and CT-guided lung biopsies, respectively (Fig 1). Eligible patients included all those with surgical resection, CT-guided FNA, or both performed during the 12-month period between July 30, 2013, and July 30, 2014, for known or suspected first primary lung cancer presenting with a lung nodule or mass. Cases were included if patients were at least 18 years of age with no history of cancer (except nonmelanomatous skin cancer) treated within the past 5 years. Of the patients with diagnoses of a malignant lung nodule during the study period, those with resectable early-stage lung cancer (stages IA, IB, IIA, IIB, and IIIA) were included; those who underwent neoadjuvant chemotherapy were excluded. Patient demographics, smoking and medical histories, nodule characteristics, procedure-related data, and clinical outcomes were abstracted from the electronic medical record. The study protocol (GCO# 12-0836) was approved by the Mount Sinai Hospital Institutional Review Board.

Lung nodules on the CT scan just before FNA or operation were reviewed by a radiologist at the time of biopsy. Images were reviewed again during data abstraction to determine nodule type (nonsolid, part-solid, solid) for reports that did not include these data. Patients with multiple nodules who underwent diagnostic studies for separate lesions were assessed on the basis of the dominant nodule. Details regarding 18-fluorodeoxyglucose positron emission tomography (FDG-PET) positivity and cytologic diagnosis, and the definitions of true-positive, true-negative, false-positive, and false-negative results, are discussed in the Supplemental Methods.

Statistical Analysis

A resection rate of nonmalignant nodules was calculated for the entire cohort of patients, for patients who had an FNA before surgical resection, for patients who did not have an FNA before resection, and separately for each operating surgeon in the Department of Thoracic Surgery. Sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) were calculated for all lung nodules for FNA and PET scan. Patients who underwent surgical resection and received diagnoses of lung cancer were compared with those who underwent resection for their benign lung nodules, with adjustment for relevant clinical covariates. A χ^2 analysis was performed for categoric variables, and a two-sided Student's *t* test was performed for continuous variables (age, years smoking, PET standard uptake value, and nodule size). The sensitivity and specificity of FNA and PET to detect lung cancer were calculated. The diagnostic accuracy of FNA and PET was assessed by use of the area under the receiver operating characteristic curve (ROC). The prevalence of lung cancer was addressed as a joint function of potential risk indicators by use of univariate and multivariate logistic regression analysis. All statistical analyses were performed with SAS (Statistical Analysis System, version 9.2, Cary, NC).

Results

Patient Characteristics

Of 656 potentially eligible patients identified through two databases, 264 patients who underwent FNA, lung resection, or both for known or suspected first primary lung cancer were included in this analysis (Fig 1). The patient demographics and nodule characteristics can be found in Table 1 and Supplemental Table 1. The nodule sizes and frequency of preoperative PET were significantly different between the groups with preoperative FNA and no preoperative FNA (20.5 mm vs 26.4 mm, $p = 0.01$; and 86% vs 60%, $p < 0.0001$, respectively).

Diagnosis and Clinical Outcomes

Among the 264 patients included in this study, 197 had surgical resection. Of 188 lung cancer cases identified among the 264 total patients, 140 were diagnosed by FNA and 48 by histologic diagnosis after operation. Of the 197 patients who had a surgical resection, the resection rate of nonmalignant lesions (NMRR) was 13% (26/197) (Table 2). The subgroup of patients who underwent preoperative FNA followed by resection had an NMRR of 7.9% (11 of 139 resections). By contrast, the cohort of patients who proceeded directly to operation without a preceding diagnostic procedure was found to have an NMRR of 25.9% (15 of 58 resections). Those patients who did not have an FNA before operation had a significantly higher resection rate of nonmalignant lesions ($p = 0.001$). Among the four thoracic surgeons with the highest volume of cases (166 cases, or 84.3% of the total), the NMRR ranged from 7.2% to 38.9%, with a median value of 13% (Fig 2). The two surgeons with the lowest NMRR were found to have operated on patients with the highest frequency of preoperative FNA (89.2% and 94.4%), whereas the patients of the surgeon with the highest NMRR had the lowest frequency of preoperative FNA (5.6%).

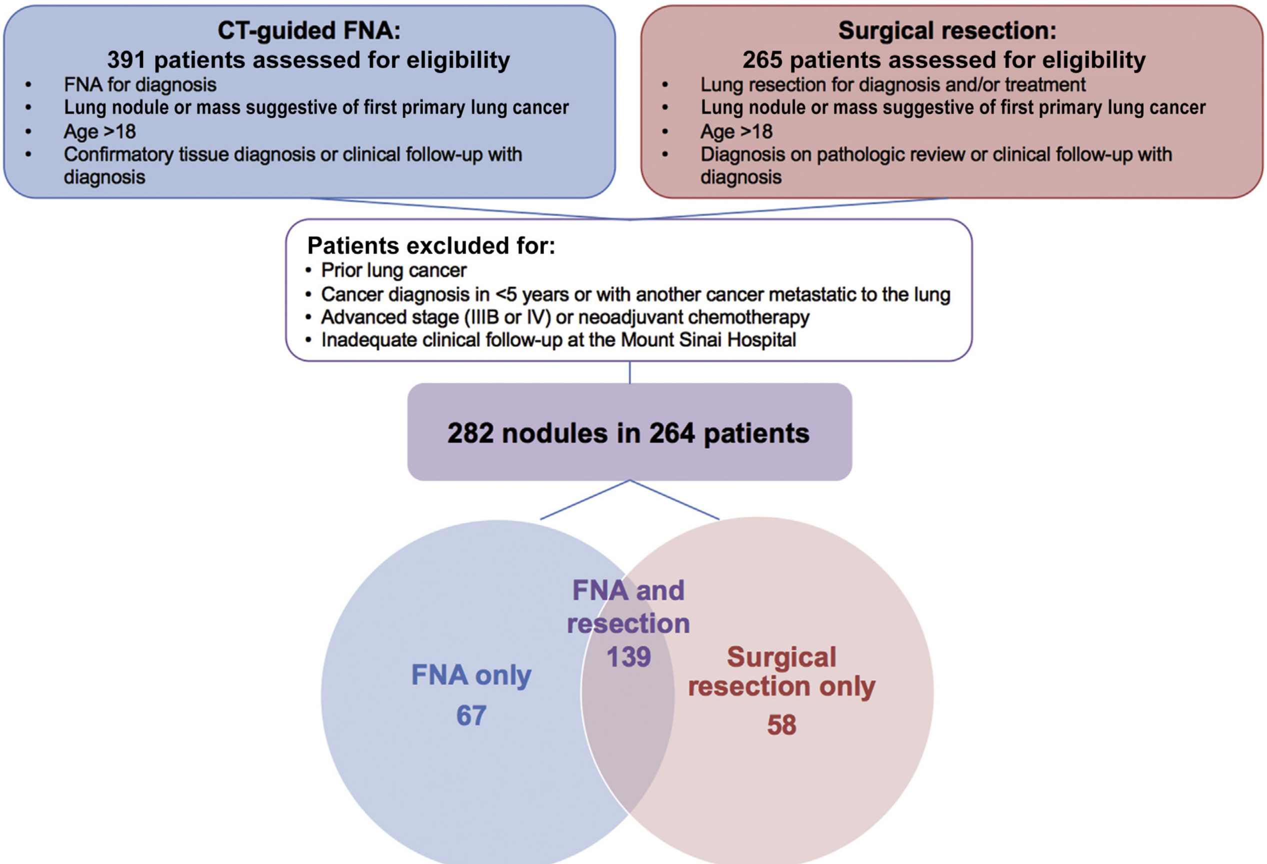

Fig 1. Inclusion of patients from fine-needle aspiration (FNA) and resection databases. The study population was identified by the use of databases from the Departments of Radiology and Thoracic Surgery. The separate cohorts were merged into a single cohort for analysis. (CT = computed tomography.)

Diagnostic Accuracy of FNA

The FNA results and patient outcomes are shown in Table 1 and Figure 3. Two hundred six patients underwent percutaneous lung biopsy for diagnosis. Of those, 141 nodules (68%), including one with a false-positive test result, had a malignant or suspicious cytology result, and 43 (21%) had a benign result. The remaining nodules were atypical (12 nodules, or 6%) or nondiagnostic (10 nodules, or 5%). A malignant diagnosis was confirmed in 189 patients (72%) by either surgical resection (171 patients, or 65%), growth on surveillance CT (1 patient, or <1%), or clinical confirmation with subsequent response to chemotherapy or radiation (17 patients, or 6%). The remaining 75 patients (28%) had a confirmatory diagnosis of benign disease by either surgical resection (26 nodules, or 10%), stability or resolution on CT surveillance (40 nodules, or 15%), or clinical diagnosis (9 nodules, or 3%).

Of the entire cohort, 206 patients (78%) had an FNA. As noted in Table 3 and Supplemental Table 3, the PPV was 99% (140/141) and the NPV was 91% (59/65) when a positive FNA result was defined by a cytologic diagnosis of malignant or suspicious and all others as a negative FNA result. The sensitivity was 96% (140/146), the specificity was 98% (59/60), and the diagnostic accuracy was 97% (199/206). When only those with a malignant result were considered to be positive, the PPV was 100% (127/127), the NPV was 76% (60/79), the sensitivity was 87% (127/146), the specificity was 100% (60/60), and the diagnostic accuracy was 91% (187/206). An ROC curve was created for FNA result (Fig 4A) with the area under the curve (AUC) = 0.99 (95% CI, 0.97 to 1.00, p <0.0001). Post-FNA pneumothorax was the most common adverse event, with a rate of 29.1% (53 of 182 FNAs performed at the Mount Sinai Hospital); 4.9% of patients (9 of 182 FNAs) required drainage by tube thoracostomy.

Predictive Factors for Malignant Disease

A PET scan was performed in 212 patients (80%). The sensitivity was 68% (114/168), the specificity was 55% (24/44), and the diagnostic accuracy was 65% (138/212). The PPV for PET was 85% (114/134), and the NPV was 31% (24/78). An ROC curve was created for FDG avidity on PET (Fig 4B), with AUC = 0.63 (95% CI, 0.53 to 0.73, $p = 0.03$). We performed a multivariate logistic regression analysis to determine which patient-related and nodule-related characteristics were significantly associated with lung cancer diagnosis. Logistic regression identified two variables that were associated with a positive diagnosis of

Table 1. Patient Demographics and Nodule Characteristics

Factor	All Patients n = 264		FNA Cohort n = 206		No FNA Cohort n = 58		*p* Value
Patient demographics							
Age, mean ± SD, y	66.6 ± 11.6		67.0 ± 11.1		65.2 ± 13.3		0.32
Women, n (%)	153	(58%)	123	(60%)	30	(52%)	0.28
Smoking history, n (%)[a]							
Never smoker	70	(27%)	53	(26%)	17	(29%)	0.88
Current smoker	42	(16%)	33	(16%)	9	(16%)	
Former smoker	150	(57%)	118	(57%)	32	(55%)	
Nodule characteristics							
Nodule size, mean ± SD, mm[b]	21.7 ± 12.3		20.5 ± 11.3		26.4 ± 14.9		0.01
Nodule size, median (range), mm[b]	19	5–75	17.5	5–75	22	5–60	
Nodule type, n (%)[c]							
Nonsolid	13	(5%)	9	(4%)	4	(9%)	0.06
Part-solid	36	(14%)	34	(17%)	2	(4%)	
Solid	202	(80%)	161	(79%)	41	(87%)	
PET scan performed, n (%)	212	(80%)	177	(86%)	35	(60%)	<.0001
PET SUVmax, mean ± SD	5.4 ± 5.4		5.3 ± 5.6		6.1 ± 4.4		0.49
Positive PET result[d] (SUVmax >2), n (%)	134	(63%)	110	(62%)	24	(69%)	0.47
FNA performed, n (%)	206	(78%)	206	(100%)	0	(0%)	
FNA categorization, n (%)							
Malignant	127	(62%)	127	(62%)			
Suspicious	14	(7%)	14	(7%)			
Atypical	12	(6%)	12	(6%)			
Nondiagnostic	10	(5%)	10	(5%)			
Benign	43	(21%)	43	(21%)			
Outcomes							
Malignant diagnosis, n (%)							
Surgical resection, malignant disease	171	(65%)	128	(62%)	43	(74%)	<.0001
CT surveillance, growth	1	(0%)	1	(0%)	0	(0%)	
Other treatment for lung cancer	17	(6%)	17	(8%)	0	(0%)	
Nonmalignant diagnosis, n (%)							
Surgical resection, benign disease	26	(10%)	11	(5%)	15	(26%)	
CT surveillance, no growth	40	(15%)	40	(19%)	0	(0%)	
Clinical diagnosis, benign disease	9	(3%)	9	(4%)	0	(0%)	

[a] For smoking history, only 262 (FNA, 204; no FNA, 58) available. [b] For nodule size, only 257 (FNA, 204; no FNA, 53) available. [c] For nodule type, only 251 (FNA, 204; no FNA, 47) available. [d] For PET SUVmax, only 178 (FNA, 151; no FNA, 27) available.

CT = computed tomography; FNA = fine-needle aspiration; PET = positive emission tomography; SUVmax = maximum standard uptake value.

lung cancer: number of years smoking ($p = 0.0124$) and nodule size ($p = 0.0124$).

Characteristics of the Nonmalignant Disease at Resection Cohort

Twenty-six (9.8%) of the overall group of 264 patients had nonmalignant disease at surgical resection (Supplemental Table 2). This group was composed of younger patients (age 61.9 ± 13.5 years vs 66.4 ± 10.5 years, $p = 0.05$) and, as expected, a higher frequency of never smokers (46%, or 12 of 26, vs 23%, or 39 of 171 patients, $p = 0.04$). A higher percentage of patients underwent sublobar resection in the nonmalignant group (92%, or 24 of 26, vs 45%, or 77 of 171, $p < 0.0001$) The most common final diagnosis was granulomatous disease (13 of 26, or 50%). The remaining cases included benign tumors, chronic inflammation, interstitial fibrosis, organizing pneumonia, and an intraparenchymal lymph node, among others.

Nine patients who had neither surgical resection nor follow-up imaging included patients with final diagnoses such as sarcoidosis, bacterial pneumonia, hamartoma, cyst, and granuloma. All had initial imaging and clinical characteristics typical for these diagnoses. The FNAs for all but two nodules in this group were noted to be benign, and the false-positive rate was 0% (0/9 nodules).

Comment

This retrospective, observational cohort study examines the impact of FNA on surgical resection for nonmalignant

Table 2. Surgical Diagnosis for Patients With and Without Preoperative FNA

	Resection of Malignant Disease, n (%)	Resection of Nonmalignant Disease, n (%)[a]
FNA group (n = 139)	128 (92.1)	11 (7.9)
No FNA group (n = 58)	43 (74.1)	15 (25.9)

[a] Relative risk = 1.24 (95% CI, 1.06 to 1.46; $p = 0.001$).

CI = confidence interval; FNA = fine-needle aspiration.

Table 3. Sensitivity, Specificity, PPV, NPV, and Diagnostic Accuracy for All FNA Patients (n = 206)

FNA Result	Sensitivity	Specificity	PPV	NPV	Diagnostic Accuracy
Malignant	87%	100%	100%	76%	91%
Malignant and suspicious	96%	98%	99%	91%	97%

FNA = Fine needle aspiration; NPV = negative predictive value; PPV = positive predictive value.

diagnosis in a large academic medical center. The resection rate for nonmalignant disease was significantly lower in patients who underwent preoperative FNA than in those who did not (11/139, or 7.9%, vs 15/58, or 25.9%, $p = 0.001$). Additionally, we showed an inverse relationship between resection for nonmalignant disease and use of preoperative FNA. The diagnostic accuracy for FNA of 97% was higher than that of PET (65%), with an acceptably low rate of adverse events.

Our cohort, composed of patients referred to our tertiary care center for management of lung nodules and suspected of having a first primary lung cancer, is of particular interest because of the lack of existing evidence for optimal preoperative diagnostic management in a high-risk group such as ours, which was composed of 73% current and former smokers, 39% with chronic obstructive pulmonary disease, and mean nodule size 22 mm [13]. We show that patients who underwent preoperative FNA had a significantly lower risk of resection for nonmalignant disease. Significant differences in mean nodule size and PET scan performance between the FNA and no-FNA cohorts, however, may reflect inherent differences between the groups in pretest probability of lung cancer (Table 1). Finally, we found variability in the NMRR among thoracic surgeons within our institution, with the lowest rates in patients of surgeons with the highest rates of preoperative FNA biopsy (Fig 2).

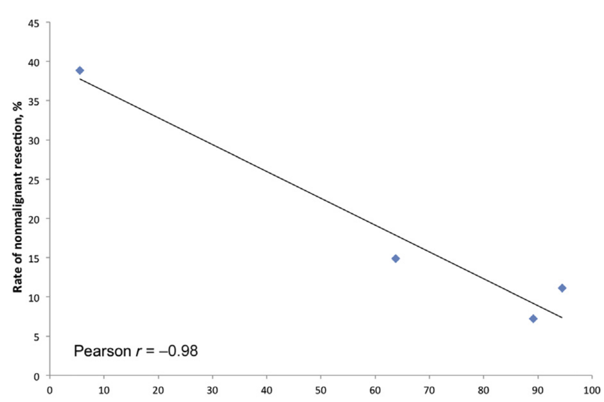

Fig 2. Rates of fine-needle aspiration (FNA) use and resection of nonmalignant disease among thoracic surgeons. The resection rate of nonmalignant lesions (NMRR) is graphed for the four surgeons with the highest volume of cases with corresponding rates of preoperative FNA use for 166 surgical resections. The remaining six surgeons at the institution, who performed fewer than ten resections each, were not included in this analysis because of their low operative volume. When combined into a single group, these surgeons' NMRR and FNA use followed the best-fit line depicted in this figure.

The accuracy of FNA is dependent on many factors, including cytologic interpretation of the obtained aspirate. Currently, there is no standard categorization for reporting lung cytopathology. Minot and colleagues [14] described in their retrospective review of false-negative results from CT-guided FNAs and core biopsies that cases "suspicious for malignancy" had a high likelihood of being malignant on follow-up.. Here, we showed high sensitivity (96%) and specificity (98%) when defining a positive FNA result as one that was either malignant or suspicious, and these findings are widely supported in the literature in studies from both our institution and others [10, 15–17]. Including suspicious results as positive may account for variability in cytologic diagnosis. In a recent large cohort of CT-guided FNAs in Japan, Takeshita and colleagues [16] reported similar results, with sensitivity of 91% and specificity of 99%, using a dichotomous benign versus malignant cytologic diagnostic approach.

Notably, five patients in our study had FNAs yielding a "benign" result—including atypical, nondiagnostic, and benign categories—with subsequent surgical resection revealing neoplasms (2 of 12 atypical FNA results, 1 of ten nondiagnostic FNA results, and two of 43 benign FNA results). Thus, our NPV of 91% reflects not only "truly negative" FNA results but also those with cytologic uncertainty, and it ultimately reinforces the need for concomitant risk prediction based on clinical risk factors. The characteristics associated with such false-negative results (3.9% false-negative rate, or five false-negative FNAs out of 128 resection-proven lung cancers) was evaluated by Gelbman and colleagues [15], who reported 18 false-negative results among 170 FNA biopsies yielding a benign result and found that increased lesion size, fewer needle adjustments, lack of positive microbial cultures, and occurrence of pneumothorax were associated with false-negative results. Although we did not demonstrate 2-year stability of the remaining lung nodules yielding a benign result of FNA because of the timing of our study (data abstraction began 18 months after the first diagnostic studies included in our cohort), the median timeframe for follow-up CT among patients with a

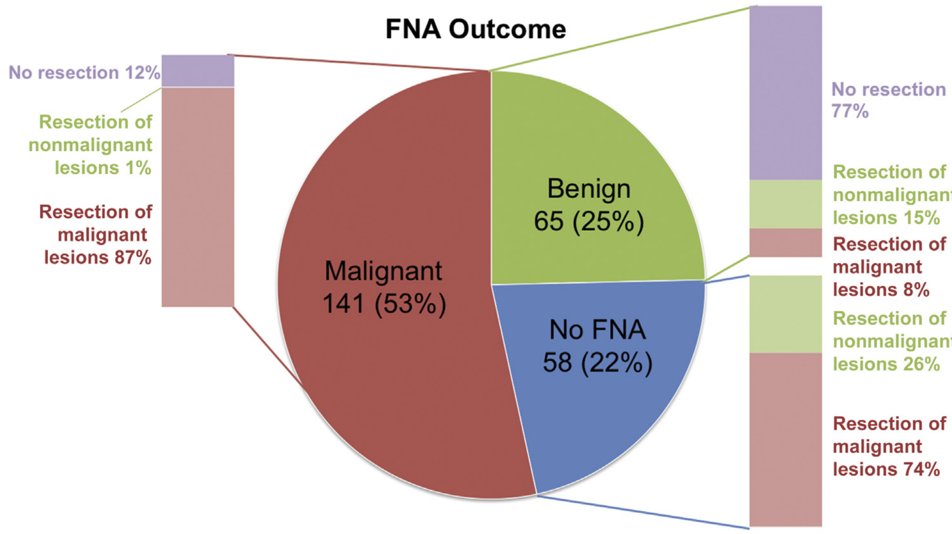

Fig 3. Fine-needle aspiration (FNA) results and resection outcomes. Diagnosis by FNA is shown, along with surgical resection outcomes for each FNA subgroup. Malignant designation includes FNAs with malignant and suspicious categorizations. Benign designation includes FNAs with atypical, nondiagnostic, and benign categorizations. Patients with a malignant diagnosis on FNA who did not undergo subsequent surgical resection include those who received primary treatment with chemotherapy or radiation.

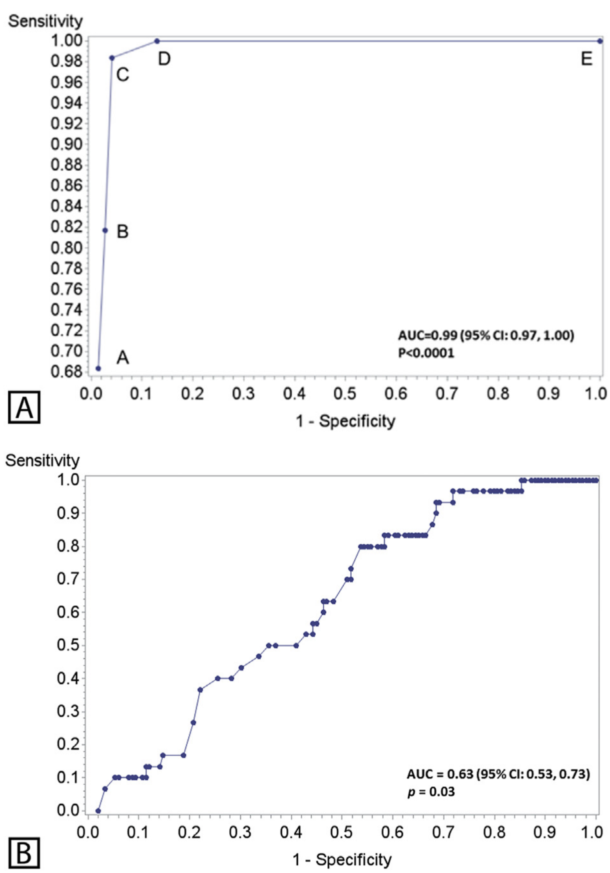

Fig 4. Receiver operating characteristic (ROC) curves for (A) fine-needle aspiration (FNA) and (B) positron emission tomography (PET). Above, ROC curves for all patients who underwent preoperative FNA (206 patients) or PET (212 patients) with confirmed diagnosis based on pathologic examination of resected specimens, surveillance computed tomography, or clinical diagnosis. (A) Points A to E represent benign, nondiagnostic, atypical, suspicious, and malignant cytology results, respectively. (AUC = area under the curve; CI = confidence interval.)

benign FNA result was 12 to 18 months, with benignity confirmed by either resection of nonmalignant disease or radiographic resolution/stability.

Although it was not the primary focus of this study, we also performed an analysis of preoperative PET for detection of lung cancer. We found that the sensitivity and specificity of PET were lower than those commonly shown by other investigators. Veronesi and colleagues [18] recently showed, in a lung cancer screening cohort, that PET has a low sensitivity and diagnostic accuracy in nodules smaller than 15 mm and in subsolid nodules. Our cohort had 81 patients (31%) with nodules smaller than 15 mm, 65 of whom had a PET, and 49 patients (19%) with subsolid nodules, 43 of whom had a PET. This may explain the low sensitivity and high false-negative rates noted in our cohort. As in the study by Veronesi and colleagues, our standard uptake value cutoff was 2.0, although other literature suggests that a higher cutoff of 2.5 to 3 is a better predictor and leads to fewer futile thoracotomies [19].

The main limitation of this study is its single-center design. The expertise of our FNA operators, and our access to high-quality components of comprehensive lung cancer care, may not be generalizable to other centers. For instance, rapid on-site cytologic evaluation, which has been shown to significantly increase accuracy with percutaneous FNA [20], may contribute to the high sensitivity of FNA that we report here but may not be available at all centers. Additionally, the focus of this study was on transthoracic biopsy as a diagnostic modality, which is reflective of the high use of this procedure at our institution. This may not be generalizable to other institutions that use bronchoscopy more frequently. Furthermore, we focused on patients with a suspected first primary lung cancer; thus the study does not include low-risk patients who underwent neither FNA nor resection, or certain high-risk patients such as those with a previous lung cancer at any time. Finally, our study population was composed only of patients fit enough to undergo an FNA procedure or surgical resection, excluding those with severely diminished lung function and other nonsurgical candidates. Within the selected group, however, a range of nodule sizes and types and smoking statuses are represented, and the observed malignancy rate of 71% among patients referred for surgical evaluation is similar to that of other surgical cohorts [4]. Therefore, although our results may not be applicable to other groups such as those undergoing lung cancer screening, we would expect cancer centers with a high volume of surgical referrals and FNA procedures to find a similar benefit from this practice.

The NMRR depends not only on institutional experience and practice but also on the frequency of benign disease and the accuracy of preoperative risk assessment [3–5]. Existing lung cancer prediction models, developed and validated in general populations or specifically in high-risk individuals, have been evaluated in surgical cohorts and have shown limited utility in reducing nontherapeutic resections [21, 22]. By contrast, it has been noted that needle biopsy of suspicious moderate-risk to high-risk lung nodules in surgical candidates may lead to decreased costs and a lower probability of resecting nonmalignant lesions [23, 24]. It is essential to exercise clinical judgment in identifying patients who may benefit from preoperative FNA, inasmuch as the procedure is not without cost and risk, particularly in a population that often has underlying pulmonary disease.

The frequent use of preoperative FNA biopsy for diagnostic confirmation in patients with high-risk nodules has a high diagnostic accuracy and a low rate of adverse events, and it reduces the rate of resection of nonmalignant disease. Furthermore, its clinical utility lies in its high specificity, which may help diminish potential harms from lung cancer screening such as the high rate of false-positive results. Therefore, we propose that for lung nodules suspected to be early-stage, first primary lung cancers, FNA should be considered for frequent use, since preoperative biopsy may decrease the rate of resection of nonmalignant disease with little added morbidity.

Charles Powell is supported by NIH RO1CA163772.

References

1. Spira A, Halmos B, Powell CA. Update in lung cancer 2014. Am J Respir Crit Care Med 2015;192:283–94.
2. Mazzone P, Powell CA, Arenberg D, et al. Components necessary for high-quality lung cancer screening: American College of Chest Physicians and American Thoracic Society Policy Statement. Chest 2014;147:295–303.
3. Smith MA, Battafarano RJ, Meyers BF, Zoole JB, Cooper JD, Patterson GA. Prevalence of benign disease in patients undergoing resection for suspected lung cancer. Ann Thorac Surg 2006;81:1824–9.
4. Flores R, Bauer T, Aye R, et al. Balancing curability and unnecessary surgery in the context of computed tomography screening for lung cancer. J Thorac Cardiovasc Surg 2014;147:1619–26.
5. Grogan EL, Weinstein JJ, Deppen SA, et al. Thoracic operations for pulmonary nodules are frequently not futile in patients with benign disease. J Thorac Oncol 2011;6:1720–5.
6. Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395–409.
7. Wilson DO, Weissfeld JL, Fuhrman CR, et al. The Pittsburgh Lung Screening Study (PLUSS): outcomes within 3 years of a first computed tomography scan. Am J Respir Crit Care Med 2008;178:956–61.
8. Field JK, Smith RA, Aberle DR, et al. International Association for the Study of Lung Cancer Computed Tomography Screening Workshop 2011 Report. J Thorac Oncol 2012;7:10–9.
9. Travis WD, Brambilla E, Noguchi M, et al. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society: international multidisciplinary classification of lung adenocarcinoma: executive summary. Proc Am Thorac Soc 2011;8:381–5.
10. Schreiber G, McCrory DC. Performance characteristics of different modalities for diagnosis of suspected lung cancer: summary of published evidence. Chest 2003;123:115S–28S.
11. Yamauchi Y, Izumi Y, Nakatsuka S, et al. Diagnostic performance of percutaneous core-needle lung biopsy under ct scan fluoroscopic guidance for pulmonary lesions measuring ≤10 mm. Chest 2011;140:1669–70.
12. Wiener RS, Schwartz LM, Woloshin S, Welch HG. Population-based risk for complications after transthoracic needle lung biopsy of a pulmonary nodule: an analysis of discharge records. Ann Intern Med 2011;155:137–44.
13. Gould MK, Donington J, Lynch WR, et al. Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e93S–120.
14. Minot DM, Gilman EA, Aubry M-C, et al. An investigation into false-negative transthoracic fine needle aspiration and core biopsy specimens. Diagn Cytopathol 2014;42:1063–8.
15. Gelbman BD, Cham MD, Kim W, et al. Radiographic and clinical characterization of false negative results from CT-guided needle biopsies of lung nodules. J Thorac Oncol 2012;7:815–20.
16. Takeshita J, Masago K, Kato R, et al. CT-guided fine-needle aspiration and core needle biopsies of pulmonary lesions: a single-center experience with 750 biopsies in Japan. Am J Roentgenol 2014;204:29–34.
17. Gulati CM, Schreiner AM, Libby DM, Port JL, Altorki NK, Gelbman BD. Outcomes of unresected ground-glass nodules with cytology suspicious for adenocarcinoma. J Thorac Oncol 2014;9:685–91.
18. Veronesi G, Travaini LL, Maisonneuve P, et al. Positron emission tomography in the diagnostic work-up of screening-detected lung nodules. Eur Respir J 2015;45:501–10.
19. Uehara H, Tsutani Y, Okumura, et al. Prognostic role of positron emission tomography and high-resolution computed tomography in clinical stage Ia lung adenocarcinoma. Ann Thorac Surg 2013;96:1958–65.
20. Austin JH, Cohen MB. Value of having a cytopathologist present during percutaneous fine-needle aspiration biopsy of lung: report of 55 cancer patients and metaanalysis of the literature. Am J Roentgenol 1993;160:175–7.
21. Isbell JM, Deppen S, Putnam JB Jr, et al. Existing general population models inaccurately predict lung cancer risk in patients referred for surgical evaluation. Ann Thorac Surg 2011;91:227–33; discussion 233.
22. Deppen SA, Blume JD, Aldrich MC, et al. Predicting lung cancer prior to surgical resection in patients with lung nodules. J Thorac Oncol 2014;9:1477–84.
23. Deppen SA, Davis WT, Green EA, et al. Cost-effectiveness of initial diagnostic strategies for pulmonary nodules presenting to thoracic surgeons. Ann Thorac Surg 2014;98:1214–22.
24. Gilbert S, Zhang H, Villeneuve PJ, et al. Optimizing health care resource utilization in the surgical management of patients with suspected lung cancer. Ann Thorac Surg 2012;94:1667–72.