Is bronchoscopy necessary in the preoperative workup of a solitary pulmonary nodule?

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ABSTRACT

Objective: This study evaluated the role of conventional bronchoscopy in the preoperative workup of patients with solitary pulmonary nodules (SPNs).

Methods: Patients with SPNs of unknown origin were enrolled for preoperative bronchoscopy at our institution. Bronchoscopic findings were prospectively collected, and their impact on planned therapy was analyzed.

Results: A total of 1026 patients were included. Bronchoscopy identified unsuspected findings in 80 (7.8%) of them, with a total of 826 (80.5%) malignant nodules. Referent values for bronchoscopic detection of malignant SPNs were: accuracy, 24.3% (95% confidence interval [CI]: 21.7%-27.0%); sensitivity, 5.9% (95% CI: 4.5%-7.4%); specificity, 100%; and negative predictive value, 20.5% (95% CI: 18.0%-22.9%). Malignant bronchoscopic findings were more common in male patients (odds ratio [OR] = 2.1, 95% CI: 1.1-3.9, $P = .021$) and large nodules (OR = 2.3, 95% CI: 1.6-3.3, $P < .001$). Surgery was cancelled in 2 (0.2%) patients and modified in 36 (3.5%) patients because of bronchoscopic findings. In all, for 268 (26.1%) SPNs that presented with ground-glass opacity, the bronchoscopy was unrevealing.

Conclusions: In the preoperative evaluation of SPN, bronchoscopy is most likely to reveal malignancy in larger SPNs and in male patients. Bronchoscopy is not indicated in SPNs that present with ground-glass opacity on computed tomography scan. (J Thorac Cardiovasc Surg 2015;150:36-40)

Yields from bronchoscopy decreased significantly with nodule size.

Central Message

Bronchoscopy identified unsuspected findings in 7.8% of patients with solitary pulmonary nodules, altering therapy in 3.7%. Preoperative bronchoscopy provides greatest benefit with men, and larger nodules.

Perspective

Appropriateness of routine bronchoscopy in preoperative workup of solitary pulmonary nodules (SPNs) is debatable. Our findings show that preoperative bronchoscopy reveals malignancy most often with men, and larger SPNs; its utility is limited with women, and SPNs presenting with ground-glass opacity on computed tomography scan. The data argue against routine bronchoscopy for women with small SPNs, unless central lesions are highly suspected.

See Editorial Commentary page 40.

The appropriateness of routine use of bronchoscopy in the preoperative workup of solitary pulmonary nodule (SPNs) is debatable. Opinions expressed in the literature vary, ranging from the idea that routine preoperative bronchoscopy has no role in conducting tissue diagnosis in small SPNs,¹ to the idea that it is very useful in determining underlying etiology and surgical strategy.² The American College of Chest Physicians guidelines³ recommend bronchoscopy only if an

air bronchogram is present or if the operator has expertise with newer, guided techniques. We hypothesize that bronchoscopy has a limited but useful role in the preoperative assessment of SPNs. The purpose of the current analysis is to define that role by examining, in our patients with SPNs: (1) endobronchial findings; (2) the impact of these findings on therapy; (3) referent values for malignant SPNs; and (4) variables that are associated with bronchoscopic findings.

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Abbreviations and Acronyms

- CI = confidence interval
 CT = computed tomography
 OR = odds ratio
 SPN = solitary pulmonary nodule

METHODS

Patients

This study was conducted in a prospective manner at the Department of Thoracic Surgery, Fudan University Shanghai Cancer Center, from January 2008 to December 2013. We defined an SPN as a single, well-circumscribed radiographic opacity that measures ≤ 3 cm in diameter and is surrounded completely by aerated lung, with an absence of atelectasis, hilar enlargement, or pleural effusion.³ Exclusion criteria for patients were: (1) having a benign SPN, as determined by fine-needle biopsy, and ≥ 1 year of follow up via thoracic computed tomography (CT); (2) refusing or not being suitable for surgery; (3) refusing bronchoscopy or being physically unable to undergo examination to evaluate the whole tracheobronchial tree (Figure 1).

Scan data from chest CT (64-row; slice width: 1.0 mm) were acquired from all patients before bronchoscopy. Individual CT datasets were transferred to a workstation (Advantage Workstation 4.3, GE Healthcare, Barrington, Ill), on which 3-dimensional images of the SPN and adjacent bronchus were created. Bronchoscopic examination and biopsy were performed by the same thoracic surgeon. Transtracheal airway anesthesia was conducted using 2% lidocaine. Additional 2% lidocaine spray was instilled in the nares and throat to provide additional patient comfort.

A flexible bronchoscope was placed in the nose or mouth with the patient in a supine position. Once the bronchoscope was inserted into the upper airway, the vocal cords were inspected. The instrument was advanced to the larynx and further down into the tracheobronchial tree, and each area was inspected as the bronchoscope passed, including the subsegmental bronchi. The bronchoscopist selected the bronchial path to the nodule, based on the CT findings, when it seemed possible to reach the lesion. Biopsies were taken using a brush, needle, forceps, or cytologic washing.

Patients were later scheduled for surgery if the bronchoscopy produced negative results. Depending on the clinical and functional status of the patient, as well as the histologic and anatomic findings, either sublobar resection (wedge/segmental), lobectomy (including sleeve lobectomy), bilobectomy, or pneumonectomy was performed, after exclusion of distal metastases.

After screening, 1026 remaining patients were included in this study; characteristics and radiologic findings are presented in Table 1. Clinicopathologic data on age, gender, smoking history, nodule size measured on CT, type of surgery, and pathology were collected. This study was conducted in accordance with the Helsinki Declaration and approved by the institutional review board of the Fudan University Shanghai Cancer Center, Shanghai, People's Republic of China. All patients provided written informed consent.

Statistical Analysis

Statistical analysis was performed using SPSS (version 19.0, SPSS, Inc, Chicago, Ill). Continuous variables were expressed as the mean $\pm$ SD; categorical variables were expressed as frequency and percentage, for description. Comparison of continuous variables was examined using an independent Student *t* test and the Mann-Whitney *U* test.

Statistical analysis of categorical variables was performed using Pearson χ^2 analysis and the Fisher exact test, as appropriate. Multivariate analysis was conducted using logistic regression to identify independent predictors. The endpoint is the bronchoscopic yield. The variables analyzed included

gender, age, smoking status, and tumor size and location. All statistical analyses were 2-sided.

RESULTS

Bronchoscopic Results

Positive bronchoscopic findings were established in 80 (7.8%) patients, including 38 (3.7%) with incidental endobronchial lesions, 4 with mucosa edema, 1 with variant segment, and 37 (3.6%) in whom the SPN was reachable and biopsies were successfully taken. Histologically, in 37 SPNs successfully biopsied under bronchoscopy, 11 were determined to be malignant, and 26 were benign. For these 26 nodules, 1 was discovered, after surgery, to be adenocarcinoma (false negative).

In 38 cases of endobronchial lesions, bronchoscopic pathology revealed 25 cases of squamous cell cancer, 6 of adenocarcinoma, 3 of carcinoid, 2 of mucoepidermoid carcinoma, and 2 of small cell lung cancer. A total of 826 (80.5%) malignant SPNs were diagnosed according to the pathologic reports of resected specimens, as well as bronchoscopic results. Therefore, referent values for bronchoscopic detection of malignant SPNs were: accuracy, 24.3% (95% confidence interval [CI]: 21.7%-27.0%); sensitivity, 5.9% (95% CI: 4.5%-7.4%); specificity, 100%; positive predictive value, 100%; and negative predictive value, 20.5% (95% CI: 18.0%-22.9%); Table 2.

Treatment

Of the 1024 patients undergoing surgeries, video-assisted thoracoscopic surgery was conducted in 492 (48.0%), and thoracotomy in 532 (52.0%). The surgical approach had to be modified to: a sleeve lobectomy in 10 patients; a bilobectomy in 12 patients; pneumonectomy in 14 patients; and no surgery in 2 cases with small cell lung cancer, owing to the bronchoscopic findings. Therefore, surgeries had to be modified or cancelled in a total of 38 (3.7%) patients (Table 3).

Bronchoscopic Yield, by Parameter

Univariate analysis revealed that bronchoscopic yield is related to gender, smoking status, and nodule size, but may not be associated with patient age and nodule location (Table 4). On multivariate analysis, the rate of positive bronchoscopic findings was significantly higher in men (odds ratio [OR] = 2.277, 95% CI: 1.380-3.757, *P* = .001) and large nodules (OR = 2.425, 95% CI: 1.713-3.433, *P* < .001) (Table 4). Positive bronchoscopic findings were detected in 13.1% (*n* = 49) of nodules of >2 cm and ≤ 3 cm in size. The prevalence decreased to 5.2% (*n* = 24) in the SPNs sized between >1 cm and ≤ 2 cm, and 3.8% (*n* = 7) in the subcentimeter nodules.

The sensitivity of bronchoscopy to detect malignancy declined from 9.1% (*n* = 34), in lesions 2 to 3 cm in size, to 2.8% (*n* = 13) in nodules 1 to 2 cm in size, and to

FIGURE 1. Criteria for selection and exclusion of subjects. SPN, Solitary pulmonary nodule; CT, computed tomography.

1.1% ($n = 2$) in the subcentimeter group. Both of the 2 small cell lung tumors identified by bronchoscopic biopsy were >2 cm in size. Of patients with SPNs between 2 and 3 cm in size, surgeries were cancelled or modified in 27 (7.7%). The types of surgical resection were modified to sleeve lobectomy, bilobectomy, or pneumonectomy in 9 (1.9%) patients who had tumors in the 1 to 2 cm category, and 1 (0.5%) patient in the subcentimeter group (Figure 2). For the 268 (26.1%) SPNs with a ground-glass-opacity component, the results of all the bronchoscopic workups were negative.

DISCUSSION

The incidence of SPNs is increasing, especially with increasing use of chest CT scanning for diagnosis of a multitude of chest diseases. The National Lung Screening Trial documented that screening for lung cancer in current and

TABLE 1. Patient characteristics

Characteristic	Patients ($n = 1026$)
Gender (male/female)	550/476
Age (mean $\pm$ SD, y)	58.4 $\pm$ 10.5
Smoking history	425
Nodules contain GGO component	268
Nodule location	
Left, upper lobe	261
Left, lower lobe	157
Right, upper lobe	343
Right, middle lobe	80
Right, lower lobe	185
Size of nodules on CT (mean $\pm$ SD, cm)	1.88 $\pm$ 0.73
Nodule size (cm)	
≤ 1	186
$>1, \leq 2$	466
$>2, \leq 3$	374

GGO, Ground-glass opacity; CT, computed tomography; SD, standard deviation.

TABLE 2. Sensitivity of bronchoscopy to detect SPN malignancy

Histologic type	Bronchoscopic pathology ($n = 49$)	Final pathology ($n = 826$)	Sensitivity (%)
Lung cancer	48	753	6.4
Adenocarcinoma	9	561	1.6
Squamous cell carcinoma	32	108	29.6
AIS	0	24	0
Small cell carcinoma	2	13	15.3
ASC	0	12	0
AAH	0	11	0
Large cell carcinoma	0	8	0
Carcinoid	3	8	37.5
Mucoepidermoid carcinoma	2	7	28.5
Sarcomatoid carcinoma	0	1	0
Lymphoma	0	2	0
Metastases	1	71	1.4

AIS, Adenocarcinoma in situ; ASC, adenosquamous carcinoma; AAH, atypical adenomatous hyperplasia.

former smokers using a low-dose chest CT scan could reduce lung cancer-specific mortality by 20%, and that surgical resection is a predominant method for the treatment of malignant SPNs and reduction of associated mortality.^{4,5} Controversy remains over the role of conventional bronchoscopy in the evaluation of the SPN. Pulmonologists and thoracic surgeons may have differing opinions on this issue. Pulmonologists are inclined to demand a tissue diagnosis, and to clarify the underlying etiology via bronchoscopy; surgeons need the examination as a means to exclude operative contraindications and make treatment plans.

In this study, bronchoscopy was used as the routine preoperative evaluation of SPNs suspected of being malignant. The yields of bronchoscopy for SPNs have been investigated mainly in terms of positive findings, sensitivity to detect malignancy, and alteration of surgical strategies. Results show that preoperative bronchoscopy is most likely to reveal malignancy in male patients and those with large nodules, but bronchoscopy utility is limited for female patients who have SPNs, or those who have ground-glass opacity on CT scan. This difference may be explained by the fact that central bronchial involvement is more common in men than in women.⁶ The data make a reasonable argument against

TABLE 3. Treatment procedures and those being modified according to the results of bronchoscopy

Treatment	All patients ($n = 1026$)	Patients with treatment being modified ($n = 38$)
Sublobar resection	311	0
Lobectomy	655	0
Sleeve lobectomy	12	10
Bilobectomy	32	12
Pneumonectomy	14	14
Surgery cancelled	2	2

TABLE 4. Predictors of positive bronchoscopic findings

Type of analysis	Positive no. (%)	Odds ratio	95% CI	P value
Univariate				
Gender, male/female	57 (10.4)/23 (4.8)	2.277	1.380-3.757	.001
Age	—	0.998	0.977-1.020	.877
Smoker, never vs ever	38 (6.3)/42 (9.9)	0.615	0.389-0.973	.038
Nodule size	—	2.425	1.713-3.433	.000
Nodule location				
Left, upper lobe	20 (7.7)	—	—	.904
Left, lower lobe	12 (7.6)	0.877	0.441-1.741	.707
Right, upper lobe	24 (7)	0.874	0.400-1.908	.736
Right, middle lobe	8 (10)	0.795	0.411-1.537	.495
Right, lower lobe	16 (8.6)	1.174	0.481-2.865	.725
Multivariate				
Gender, male/female	57 (10.4)/23 (4.8)	2.070	1.114-3.848	.021
Smoker, never vs ever	38 (6.3)/42 (9.9)	1.021	0.578-1.804	.943
Nodule size	—	2.325	1.639-3.300	.000

CI, Confidence interval.

routine bronchoscopy for women who have a small SPN, unless central lesions are highly suspected.

Goldberg and colleagues⁷ retrospectively reviewed the utility of bronchoscopy in 33 SPNs, and revealed no unsuspected endobronchial lesion. Torrington and Kern⁸ found additional submucosal or endobronchial tumor manifestations in 5 of 91 (5.5%) SPNs. However, those findings did not alter surgical strategies. Chhajed and colleagues⁹ combined bronchoscopy and positron emission tomography for the diagnosis of 74 patients with a small pulmonary nodule (≤ 3 cm). Endobronchial lesions were observed in 6 patients (8.1%), but the effect on surgical strategy alteration was not mentioned. In a recent study, Schwarz and colleagues² prospectively performed preoperative flexible bronchoscopy in 225 patients who had SPNs, and they detected unsuspected endobronchial involvement in 4.4%. Surgery was cancelled or modified in 2 cases, owing to those findings.

FIGURE 2. Yields from bronchoscopy decreased significantly with nodule size. D, Diameter.

The value of conventional bronchoscopy to obtain biopsies for pathologic analysis varied according to study population and combination strategy. In a study by van 't Westeinde and colleagues,¹⁰ investigation was made of the role of conventional bronchoscopy in the workup of 308 patients who had suspicious CT scan screen-detected pulmonary nodules; the sensitivity of bronchoscopy to detect malignancy was 13.5%. In the prospective study conducted by Schwarz and colleagues,² the sensitivity of flexible bronchoscopy to detect lung cancer was reported to be 46.5%. One patient with small cell lung cancer who was diagnosed via bronchoscopy was eventually excluded from surgical resection.² When combined with positron emission tomography, bronchoscopy had a diagnostic yield of >50%, as demonstrated by Chhajed and colleagues.⁹ Although the diagnostic value of bronchoscopy was relatively low in the current study, 2 patients with small cell lung cancer diagnosed via bronchoscopy were excluded from surgical resection.

Recommendations and Limitations

Our study has several limitations. First, positron emission tomography and/or CT was applied in only a small proportion of patients, and was therefore not included in this study. The preoperative diagnostic yields of bronchoscopy might be changed with the addition of positron emission tomography scanning. Second, we used conventional bronchoscopy. No fluoroscopy or any other navigational tool was used to guide transbronchial biopsy, and this factor may have made bronchoscopy less effective in obtaining a biopsy.

CONCLUSIONS

We report on 1026 patients who underwent bronchoscopy for preoperative evaluation of an SPN. Results implied that bronchoscopy is most likely to be beneficial in men and those with large nodules, and that bronchoscopy utility is limited for women with SPNs, or those nodules that present with ground-glass opacity on CT scan.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: solitary pulmonary nodule, bronchoscopy, preoperative workup

EDITORIAL COMMENTARY

Conventional bronchoscopy for evaluation of the solitary pulmonary nodule: Beneficial for a select few patients, or are we still “looking for a needle in a haystack”?

Kenneth A. Kesler, MD

See related article on pages 36-40.

Not only can evaluation of the solitary pulmonary nodule (SPN) be vexing, but SPN evaluations are also increasing as a result of the expanding use of computed tomographic (CT) imaging. Clinicians typically take multiple factors into consideration to get a general impression of malignancy risk, including patient age, smoking history, CT characteristics, and positron emission tomographic imaging findings. Calculated risk models have even been established in an attempt to assign chances of SPN malignancy more precisely.¹ Removal through a minimally invasive approach of any nodule larger than 8 mm highly suspected to contain a primary pulmonary malignancy, followed by anatomic pulmonary resection with mediastinal lymph node sampling if non-small cell lung cancer is confirmed

by frozen-section pathologic review, is considered an optimal strategy for most patients with low surgical risk.²

Removal obviously eliminates sampling error inherent in needle biopsy, avoids delay in surgical treatment for patients in whom non-small cell lung cancer is confirmed, and is usually undertaken at low risk levels. For patients with SPNs suspected of malignancy who are reluctant to undergo any surgical intervention before a definitive diagnosis of malignancy, similar patients at higher surgical risk, or patients with SPNs at intermediate risk for malignancy, preoperative biopsy can be useful. Options in these cases include CT-guided needle biopsy or bronchoscopy with brushing, washing, or needle biopsy (unguided or guided) according to SPN location, SPN size, and institutional preference.

In this issue of the *Journal*, Zhang and coworkers³ report on 1026 patients who underwent conventional bronchoscopy for the evaluation of a SPN at their institution. Overall accuracy and negative predictive value in this study were 24.3% and 20.5%, respectively, reinforcing the very well-established need for further investigation of suspect SPN when bronchoscopy results are negative. Higher diagnostic rates were found in male patients and with larger nodules. Conventional bronchoscopy resulted in a 7.8% overall incidence of positive diagnostic findings, including “altering therapy” in 3.7% of their series.

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