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Value of flexible bronchoscopy in the preoperative work-up of solitary pulmonary nodules

C. Schwarz^, N. Schönfeld*, R. C. Bittner°, T. Mairinger**, H. Rüssmann^^, T. T. Bauer*, D. Kaiser°°, R. Loddenkemper*

^ Charité-Universitätsmedizin Berlin, Christiane Herzog Zentrum
* Klinik für Pneumologie
° Institut für Diagnostische und Interventionelle Radiologie
** Institut für Pathologie
^^ Institut für Mikrobiologie, Immunologie und Laboratoriumsmedizin
°° Klinik für Thoraxchirurgie
Lungenklinik Heckeshorn
HELIOS Klinikum Emil von Behring
Berlin, Germany.

Corresponding Author:
Robert Loddenkemper, M.D.
Lungenklinik Heckeshorn
HELIOS Klinikum Emil von Behring
Walterhöferstr.
10243 Berlin
Germany
Phone: +49/30/8137538
Fax: +49/30/8138170
e-mail: rloddenkemper@dgpberlin.de

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Abstract

The diagnostic value of flexible bronchoscopy (FB) in the preoperative work-up of solitary pulmonary nodules (SPN) is still under debate among pulmonologists, radiologists and thoracic surgeons.

In a prospective observational manner, FB was routinely performed in 225 patients with SPN of unknown origin.

Of the 225 patients 80.5% proved to have lung cancer and 7.6% a metastasis of an extrapulmonary primary, 12% had a benign aetiology. Unsuspected endobronchial involvement was found in 4.4% of all 225 cases (or in 5.5% % of lung cancer cases). In addition, FB clarified the underlying aetiology in 41% of the cases. The bronchoscopic biopsy results from the SPN were positive in 84 of the lung cancer cases (46.5%). Surgery was cancelled due to the results of FB in four cases (one with involvement of the right main bronchus (impaired pulmonary function did not allow pneumonectomy), one with SCLC, two with bacterial pneumonia), and the surgical strategy had to be modified to bilobectomy in one patient.

FB changed the planned surgical approach in five cases substantially. These results suggest that routine FB should be included in the regular preoperative work-up of patients with SPN.

Keywords: flexible bronchoscopy, lung cancer, preoperative evaluation,

solitary pulmonary nodule

The diagnostic value of flexible bronchoscopy (FB) in the preoperative work-up of solitary pulmonary nodules (SPN) is still under debate among pulmonologists, radiologists, and thoracic surgeons. There are significant differences in the management of SPN: Whereas radiologists tend to recommend short-term follow-up or needle aspiration under CT guidance, pulmonologists and thoracic surgeons prefer a more aggressive approach, especially in patients with higher likelihood of malignancy [1].

New pulmonary nodules have a high probability of malignancy. In the American College of Chest Physicians (ACCP) evidenced-based clinical practice guidelines studies are cited in which SPN, detected either by screening or incidentally, were malignant in 33 to 60% with a diameter measuring 11 to 20 mm and in 64 to 82% with a diameter measuring >20 mm [2]. Smaller pulmonary nodules less often have a malignant etiology.

The 2nd Edition of the ACCP evidenced-based clinical practice guidelines recommends a very limited use of bronchoscopy (or transthoracic needle biopsy) in the management of patients who have an indeterminate SPN that measures at least 8-10 mm in diameter and are candidates for curative (surgical) treatment (3). The reasoning against routine preoperative bronchoscopy is that it has been shown rarely to change tumor stage and/or to contraindicate surgery [4, 5].

In most German specialized chest hospitals/departments the endobronchial status is evaluated as a routine preoperatively via FB under local anesthesia in order to exclude additional endobronchial tumor manifestations, to examine vocal cord function, to find anatomic variants, and to obtain tissue specimens, if possible, from the nodule for pathological analysis as well as bronchopulmonary secretions for bacteriological examinations [6]. The aim of this strategy is to determine macroscopic and microscopic findings which might change or obviate the planned surgical approach.

In this prospective study, we wanted to evaluate the potential role of routine preoperative FB in patients with an SPN.

Material and Methods

The study was conducted at Lungenklinik Heckeshorn from June 2004 to March 2007 in a prospective observational manner in adults with SPN. We evaluated patients with SPN according to the radiologic definition as a 3 cm or less single round opacity, which is well marginated and surrounded by lung parenchyma. There were no associated findings like atelectasis, hilar enlargement, or pleural effusion. Only patients presenting with lesions of unknown origin were included. The nodules had been detected on thoracic CT scans (CT) or chest radiographs, confirmed by CT. In order to evaluate the tracheobronchial tree and to take biopsies from the SPN for histological or cytological examination, FB under local anesthesia was routinely performed in all 225 consecutive patients, after written informed consent was obtained. The study is approved by the Ethics Committee of the Charité-Universitätsmedizin Berlin.

FB and transbronchial biopsy were performed in a bronchoscopy suite by a pulmonologist as follows: the patient in the supine position underwent conscious sedation with midazolam, propofol or fentanyl. Local anesthesia with 2% lidocaine spray was instilled in the nares and in the throat to provide additional patient comfort. At the beginning of the procedure, a complete inspection of the larynx and the tracheobronchial tree, including the subsegmental bronchi, was performed in order to look for any abnormalities. As next step the SPN was visualized using a C-arm fluoroscope. Biopsies from the nodules were taken under fluoroscopic guidance in 157 of all 225 (77.7%) cases in whom the lesion was reachable. To reach the SPN, a forceps, brush, and/or catheter were introduced under C-arm fluoroscopic control. In addition, in all cases bronchial secretions were obtained during FB for bacteriologic examination. For safety reasons and to exclude pneumothorax, a chest x-ray was taken on the day following forceps biopsies or sooner if clinical symptoms developed.

In patients with indeterminate tissue results from FB surgery was directly planned, but patients with risk factors for surgery were first transferred to the radiologist for CT-guided transthoracic needle biopsy. Depending on the clinical and functional status of the patient as well as on the histological and anatomic findings, either

lobectomy, wedge resection, segment resection, atypical resection, bilobectomy or pneumonectomy were performed after exclusion of distal metastases (at that time positron emission tomography (PET) was not yet introduced in our hospital).

Statistical analysis

Statistical analyses were performed using commercially available software (SPSS Statistics 19 and Excel). The Student t and Mann–Whitney tests were used to analyze statistical differences in nodule sizes. P values of <0.05 were regarded as significant. Quantitative variables are presented as median and ranges, categorical variables as proportions.

Results

In total, 225 patients were included in the study, 135 men (60%) and 90 women (40%). The median age was 67 and the mean age 66±18 years. Among the 198 patients with malignant aetiology were 118 men (60%) and 80 women (40%), in the 27 patients with benign aetiology 17 (63%) vs. 10 (37%). The median age of the patients with malignancies was 67 and the mean age 67±9 years, in those with benign disease 68 and 63±15 years respectively.

Radiological results

In 71 cases, the SPNs were located in the right upper lobe, in 75 in the left upper lobe, in 43 in the right lower lobe, in 27 in the left lower lobe and in nine in the middle lobe. The size of the SPNs ranged between 0.5 and 3 cm with a median of 2.5 cm and a mean of 2.29±0.6 cm. Mean diameters of malignant and benign nodules were 2.3 cm and 2.2 cm, respectively (Table 1).

Bronchoscopic results:

In all 225 patients, FB was performed, usually via the transnasal route. Macroscopically, in 10 cases (4.4% of all cases or 5.5% of the 181 lung cancer cases) unsuspected malignant involvement of the central bronchial tree was found. Histologically, these proved to be six cases with adenocarcinoma and four with squamous cell cancer. The additional endobronchial tumor manifestations were located in the right upper lobe in three cases (twice segmental bronchus 2 and once in the lobar bronchus adjacent to the main bronchus), in four in the left upper lobe (twice segmental bronchus 1 and twice segmental bronchus 3), in two in the left lower lobe bronchus and in one in the middle lobe bronchus.

The aetiology of all 225 SPNs is shown in table 2. Biopsies from SPNs were taken in 157 patients (77.7%) during FB under fluoroscopic guidance (in the remaining 22.3% it was not possible to reach the SPN). The histological/cytological results of these biopsies from SPNs (table 2) demonstrated malignancy in 88 cases (56%) (histology positive in 42 (48%) and cytology in 46 (52%)), and a benign aetiology in two cases, one chondroma and one granuloma. In addition, two cases of pneumonia were diagnosed bacteriologically. Thus, in total, the underlying morphological (or bacteriological) diagnosis was provided via FB in 92 patients (41%), in the 181 lung cancer cases in 46.5%, including one of two small cell lung cancers.

Anatomic variants of smaller degrees (e.g. accessory segment or two instead of three segments in the right upper lobe) were found in 15 (6.7%) of the 225 patients, but had no impact on the surgical approach.

FB was tolerated well by all patients and there were no serious complications observed except one case with a pneumothorax detected radiologically on the following day, which resolved spontaneously.

Bacteriological results:

Bacteriological findings in bronchial secretions obtained via FB were as follows: oral flora in 205 cases (91.1%), *Haemophilus influenzae* in seven (3.1%), *Streptococcus pneumoniae* in two (0.9%), *Staphylococcus aureus* in seven (3.1%), *Moraxella catarrhalis* in two (0.9%) and *Mycobacterium tuberculosis* in two (0.9%). In two patients each with proof of *Haemophilus influenzae* and *Moraxella catarrhalis* in whom the SPN resolved completely after antibiotic therapy, suggesting pneumonia as cause, surgery was no longer indicated.

Surgical results:

200 (88.8%) of the 225 patients underwent surgical resection. Four patients were excluded due to the results of FB as mentioned above, one patient refused surgery and in the other patients the functional risk was considered to be too high due to advanced COPD, severe cardiac insufficiency, multimorbidity or age, although primarily a surgical approach was envisaged.

In 175 cases (87.5%) a malignant aetiology was demonstrated histologically, 25 cases (12.5%) had a benign aetiology (Table 2). Lung cancer was the most frequent

etiology with 158 cases (79%) with adenocarcinoma as the leading cell type in 129 (81.6%), followed by squamous cell carcinoma with 16 (10.1%), large cell carcinoma with 10 (6.3%), carcinoid with two (1.3%), and one SCLC (Table 2).

The following surgical procedures were used: lobectomy (n=131), segmentectomy (n=30), atypical resection (n=36), bilobectomy (one tumor involved middle and lower lobes) (n=2), and pneumonectomy (n=1). The most frequently applied procedure for lung cancer was lobectomy with systematic mediastinal lymph node dissection (Table 3).

Pathological results:

In all 225 cases either histological and/or cytological (and/or bacteriological) results were obtained, among these 17 negative on FB and not operated on by CT guided needle biopsy (Table 2). NSCLC was the leading diagnosis with 177 cases out of 225 (79%). Metastatic cancer from different primaries (Table 2) was found in 17 cases (7.5%) of which 4 (23.5%) were histologically positive in the bronchoscopic biopsies.

Discussion

Routine flexible brochoscopy (FB) performed prospectively in the preoperative work-up of our 225 patients with a solitary pulmonary nodule (SPN) revealed unsuspected endobronchial involvement in 4.4% of the cases (in the 181 lung cancer patients in 5.5%). Furthermore, 15 cases (6.7%) showed an anatomical variant of the tracheobronchial tree. The underlying morphology could be clarified in a considerable number of cases (41%) by peripheral bronchoscopic biopsies under fluoroscopic guidance (in lung cancer cases in 46.5%). This yield may even be enhanced by additional biopsy techniques as needle aspiration with or without EBUS [7, 8, 9, 10, 11, 12], but were not included in our routine programme in an otherwise operable SPN. In two cases bacterial pneumonia was found as cause of the SPN.

To our knowledge this is the first prospective study evaluating the role of FB in the preoperative work-up of SPN. Torrington and Kern in 1993 published a retrospective study on the utility of FB in the evaluation of SPNs (at that time defined size up to ≤ 6 cm) [4]. In their 91 cases FB revealed one unsuspected vocal cord carcinoma and five cases with additional submucosal or endobronchial tumor manifestations which

were all in the same anatomic locations and did not affect the planned operative procedure. Since their diagnostic yield of biopsies from SPNs was low (nine of 30 transbronchial biopsies and only four of 66 cytologic specimens were positive in the cancer patients) they concluded that routine preoperative FB did not measurably benefit patients with SPNs. These results are apparently the reason not to recommend routine preoperative FB in SPN [3]. However, Torrington and Kern stated 'that before abandoning use of this established practice at our institution, we plan to study its yield prospectively' [4]. Goldberg and coworkers, too, came to the conclusion that no additional useful information was derived from FB, after studying retrospectively the role of FB as preoperative staging procedure in only 33 patients [5].

However, Gasparini and coworkers retrospectively examining 570 patients with SPNs (or mass lesions) detected in 72 (12.6 %) visible lesions in the tracheobronchial tree which led to contraindicating surgery in 12 and to modifying the surgical strategy in 23 patients [7]. Aristizabal et al retrospectively studied the value of FB in addition to chest CT in 64 lung cancer patients with a pulmonary nodule or mass, and detected in 11 cases (17%) a by CT unsuspected endobronchial involvement, of which three were true SPNs [13].

Chhajed and coworkers retrospectively assessed the role of routine FB (combined with PET) in noncalcified pulmonary nodules ≤ 3 cm in size [14]. They observed additional endobronchial tumor manifestations on FB in six of 74 cases (8%), but did not describe if this changed the surgical approach. However, they found PET valuable in 19 of 35 patients with nondiagnostic FB and recommended to perform a PET if FB does not provide the diagnosis. In our hospital PET-CT was introduced only in 2007 and therefore not applied in this study. The role of PET in the preoperative work-up of patients with SPN is still under debate [2, 3, 15]. Wahidi et al found in a review of eight large studies a sensitivity of PET imaging of 80-100% for identifying a malignant SPN, whereas the specificity was much lower (40-100%) and more variable [2]. This was confirmed by a recent review of four studies which showed a sensitivity of 88-97% and a specificity of 83-89% (with an accuracy of 89-93% [16]). In addition to the differentiation between malignant and benign

aetiologies, PET improves the preoperative staging in lung cancer [17, 18] although the prevalence of distant metastatic disease in stage Ia is low (19).

In our study, 225 patients were included prospectively, all fulfilling the inclusion criteria of SPN as described above. Among the 225 cases we found with 88% a high percentage of malignancy of which 181 (91.4%) were lung cancers. This high proportion most likely results from pre-selection of patients who are admitted to our specialized chest hospital. Similar results were found in a study of patients undergoing surgical resection for known or suspected malignancy with a rate of 73% for malignant cancer [20]. In contrast, in a review of lung cancer screening studies, the prevalence of malignant SPN was much lower, varying between 1.1 and 13 % [2]. In a multicenter study by Alzahouri and colleagues in France, out of 11,515 CT scans SPNs were incidentally detected in 152 cases of which 30 (26%) were malignant [21].

Unsuspected additional malignant involvement of the central bronchial tree was detected by FB in 10 of our 181 lung cancer patients (5.5%) which changed the surgical strategy in two: in one patient a bilobectomy became necessary, in the other, with tumor growth in the right main bronchus, the impaired pulmonary function did not allow a pneumonectomy. The finding of a variant of the central tracheobronchial tree in 6.7% had no impact on the surgical strategy in our cases.

In addition, FB provided a diagnosis in 92 of our 225 cases (41%). In 157 cases biopsies could be taken from the SPN under fluoroscopic guidance (77.7%) demonstrating malignancy in 88 of these cases (56.1%), by histology in 47.7% and by cytology in 52.3%, respectively. Thus, these results in most cases obviated the need to obtain an intraoperative histological diagnosis (and convinced some of the patients to agree with the proposed surgical approach). A histological diagnosis was also made in two benign lesions, one chondroma and one granuloma, but both were operated in order to ensure the diagnosis. In two patients with purulent bronchial secretions an unsuspected pneumonia was diagnosed on the basis of the bacteriological results obtained by FB, both responded to antibiotic therapy, thus surgery could be avoided. It is well known that pneumonia may manifest as SPN and may be clinically silent without symptoms [22], as in our two patients.

The pathological results in our 181 lung cancer cases showed adenocarcinoma to be the most frequent cell type (78,5%) followed by squamous cell carcinoma (12.7%), large cell carcinoma (6.5%), small cell carcinoma (1.0%) and carcinoid (1.0%). This distribution of lung cancer cell types is similar to the data compiled by Gould et al from the literature (3). 17 cases (7.5%) were solitary metastases due to extrapulmonary primary tumors which were not known before or which were considered unlikely as cause of the SPN; bronchoscopic biopsies demonstrated their malignant aetiology only in four cases (23.5%).

Among the 27 cases with an SPN of benign aetiology, tumors such as hamartoma (seven cases), fibroma (five cases) and chondroma (one case) were most frequent. Ten cases had an infectious etiology (three tuberculosis, two non-tuberculous mycobacteriosis, two aspergilloma, three pneumonia), three cases had a granuloma of indeterminate origin and one a rounded atelectasis.

Furthermore, during bronchoscopy we found 15 anatomic variants of the bronchial tree. This might be of interest for the surgical strategy but had no impact in our study. In addition, sometimes it might be helpful to the surgeon to know the exact segment of the SPN in order to localize it during surgery, in particular if an atypical resection is planned, and FB combined with fluoroscopic guidance in addition to CT is a suitable technique to assign the nodule to the corresponding segment.

Conclusions

In summary, among the 225 cases with an SPN unsuspected endobronchial involvement was found in 10 lung cancer patients (4.4% of all SPNs or 5.5% of all 181 lung cancers). In one case these findings precluded surgery due to functional limitations for the then necessary extension of the surgical approach and in a second case the extension of surgery from lobectomy to bilobectomy was necessary. In two further cases in which a bacterial pneumonia was diagnosed as cause of SPN surgery was rendered unnecessary. Furthermore, since peripheral bronchoscopic biopsies clarified the underlying morphology in a considerable number of cases, our findings suggest that routine FB, which is a safe technique, should be included in the preoperative work-up of patients with SPN. Thus, in our opinion, preoperative FB

offers several advantages compared to a bronchoscopy performed just at the same time as the planned surgery.

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Table 1: CT size of SPN (in cm)

	All	Malignant	Benign
Mean	2.29	2.3	2.2 (n.s.)
Median	2.5	2.5	2.5 (n.s.)
Range	0.5-3	0.8-3	0.5-3
SD	0.60	0.59	0.63

n.s.=no significant statistical difference

Table 2: The aetiology of 225 cases of SPN undergoing preoperative flexible bronchoscopy [left] with their positive bronchoscopic biopsy results (by histology/cytology [n]) [middle] and the aetiology of those 200 cases finally undergoing surgery [right]

Histological type	**n**	**%**	**(hist/cyt positive[n])**	**n**	**%**
Lung cancer					
Adenocarcinoma	142	63.1	(23/33)	129	64.5
Squamous cell carcinoma	23	10.2	(13/3)	16	8
Large cell carcinoma	12	5.2	(1/10)	10	5.0
Carcinoid	2	0.8	(0/0)	2	1
Small cell lung carcinoma	2	0.9	(1/0)	1	0.5
Total	**181**	**80.5**	**(38/46)**	**158**	**79**
Metastases secondary to					
renal cell carcinoma	5	2.2	(1/0)	5	2.5
breast carcinoma	4	1.8	(2/0)	4	2
rectum cancer	2	0.9	(0/0)	2	1

colon cancer	2	0.9	(1/0)	2	1
melanoma	1	0.4	(0/0)	1	0.5
osteosarcoma	1	0.4	(0/0)	1	0.5
cervix cancer	1	0.4	(0/0)	1	0.5
uterus cancer	1	0.4	(0/0)	1	0.5
Total	**17**	**7.5**	**(4/0)**	**17**	**8.5**
Total (malignant)	**198**	**88.0**	**(42/46)**	**175**	**87.5**
Benign					
Fibroma	5	2.2	(0/0)	5	2.5
Hamartoma	7	3.1	(0/0)	7	3.5
Chondroma	1	0.4	(1/0)	1	0.5
Tuberculosis	3	1.3	(0/0)	3	1.5
Non-tuberculous mycobacteriosis	2	0.9	(0/0)	2	1
Bacterial pneumonia	3	1.3	(2/0)	1	0.5
Aspergilloma	2	0.9	(0/0)	2	1
Granuloma	3	1.3	(1/0)	3	1.5
Rounded atelectasis	1	0.4	(0/0)	1	0.5
Total (benign)	**27**	**12.0**	**(4/0)**	**25**	**12.5**
Total (benign + malignant)	**225**	**100**	**(46/46)**	**200**	**100**

Table3: Surgical procedures

Surgical procedure	**n**	**%**
Lobectomy	131	65.5
Segmentectomy	30	15
Atypical resection	36	18
Bilobectomy	2	1
Pneumonectomy	1	0.5
Total	**200**	**100**