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Improving Standards in Flexible Bronchoscopy for Lung Cancer

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Abstract

Question

Can the detection rate of flexible bronchoscopy for lung cancer be increased by a series of simple quality improvement measures?

Methods

Bronchoscopy-associated clinical parameters were prospectively recorded between from 2001-2007 in patients with suspected lung malignancy. The detection rate of bronchoscopy, diagnostic yield of each biopsy modality, and the possible impact of different service improvement measures were assessed.

Results

746 bronchoscopies were performed in 704 patients. The detection rate of bronchoscopy for malignancy was 83.6%, and increased over time (detection rate in 2001 67.3% (95% CI = 52.9 to 79.7), detection rate in 2007 89.7% (% CI = 81.3 to 95.2), $p<0.001$). Detection rate increased for both bronchoscopically visible (75.0% in 2001 to 94.5% in 2007) and non-visible tumour (41.7% in 2001 to 81.2% in 2007), $p<0.001$ for both analyses. Prior CT availability was associated with a higher diagnostic yield that did not reach statistical significance. Logistic regression analysis identified tumour visibility, year of study, use of transbronchial needle aspiration and pathologist identity as independent predictors of a positive diagnosis.

Answer

A significant increase in bronchoscopic detection rate for malignancy occurred in association with a number of simple improvement measures.

Abbreviation list

CT Computed tomography, and taken to refer to contrast-enhanced computed tomography scan of the chest and upper abdomen

CXR Chest radiograph

EBUS Endobronchial ultrasound

FB Flexible bronchoscopy

TBNA Transbronchial needle aspiration

Keywords

Bronchoscopy; Carcinoma, Non-small-cell lung; Small Cell Lung Carcinoma; Lung Neoplasms; Quality Assurance, Health Care

Introduction

Lung cancer is the leading cause of death from malignant disease in the developed world, causing 22% of cancer deaths in the UK in 2007[1]. Rapid, accurate pathological diagnosis and staging are vital for good patient care. Flexible bronchoscopy (FB) is perhaps the most important single technique in lung cancer diagnosis, and therefore maximizing the detection rate of FB should be a key objective.

The detection rate (or diagnostic sensitivity) of FB for malignancy varies widely in published series[2]. It is higher when endobronchial tumour is visible than when peripheral nodules not visible endobronchially are sampled. Prior computed tomography (CT) scanning increases the detection rate of FB for malignancy[3] and is recommended in national guidelines[4]. (Note: where CT scans are referred to in this paper, they are taken to be contrast-enhanced scans of the chest and upper abdomen). Transbronchial needle aspiration (TBNA)[5, 6], and more sophisticated techniques like endobronchial ultrasound (EBUS)[7, 8]and electromagnetic navigation bronchoscopy[9, 10] can further increase the detection rate. The great majority of lung cancer bronchoscopy in the UK, however, is performed by practitioners who lack access to, or training in, these modalities.

From 2001, a series of measures aimed at quality improvement in bronchoscopy were introduced and a continuous, prospective audit of detection rate was begun.

Methods

Consecutive patients undergoing bronchoscopy for suspected lung malignancy from July 2001 to December 2007 were entered prospectively into the audit. The chair of the Oxford ethics committee (the equivalent of an IRB) confirmed that an application for approval was not required for this study, which assesses the quality of routine patient care.

Inclusion Criteria

1. Patient undergoing bronchoscopy from July 2001 to December 2007
2. Suspected lung malignancy from chest radiograph (CXR) or CT

Exclusion Criteria

1. Normal CXR prior to procedure
2. Lung malignancy not suspected prior to bronchoscopy

Data Collected

Along with demographic data, data recorded were:

- Whether CT was present for the procedure
- Visual classification of tumour (see below)
- Diagnostic modalities employed (i.e. bronchial biopsy, brushing or washing, or TBNA)
- Identity of bronchoscopist and reporting pathologist
- Results of each diagnostic sample
- Whether FB was diagnostic of malignancy
- Final diagnosis

Visual classification of endobronchial appearance was divided into one of three categories: definite endobronchial tumour (e.g., exophytic mass within the bronchus), possible tumour (oedema, erythema constriction or compression) or no visible abnormality. The operator entered data prospectively at the time of bronchoscopy. The histocytopathological result of each sample was classified thus: definite malignancy was considered positive, and all other results, including “highly

suspicious of malignancy" and similar descriptions were considered negative. In patients with negative FB, a final diagnosis was confirmed: by alternative histocytological sampling, by establishment of a benign disease, or by follow up until death.

Bronchoscopy

All bronchoscopy procedures were performed or supervised by Consultant Respiratory Physicians. A video bronchoscopy system was used (EB1830T3 bronchoscopes, EPM1000 processor, Pentax Medical UK). The selection and sequence of sampling techniques were left to the operator. For visible endobronchial tumour forceps biopsy, brushing and washing samples were obtained prior to January 2003. After this date bronchial washings were no longer routinely performed in the presence of probable or definite tumour[11] following an audit demonstrating no significant additive diagnostic yield. TBNA was used to sample accessible lymph nodes, submucosal abnormalities or necrotic endobronchial lesions. Fluoroscopy and rapid on-site cytological examination were not used.

During the period 2001-2007 a number of changes were introduced to the bronchoscopy service. These included:

- The appointment of a lead clinician and lead nurse for bronchoscopy in 2001.
- Increasing emphasis on obtaining a CT prior to FB, permitting increased clinicoradiological collaboration prior to FB.
- Increasing use of distal bronchial brushings to sample tumours not visible endobronchially, using the method described by Lee and others[12].
- Bronchial brush diameter was changed from 2mm (Olympus BC202D – 2010) to 5 mm diameter (Olympus BC202D - 5010) in March 2002.
- Routine use of TBNA by the lead clinician for bronchoscopy from August 2002.

These changes were intended as quality improvement measures. In addition, a change occurred in the reporting pathologists. Pathologist A was reporting until retirement in March 2002. Pathologist B and C were reporting from July 2001 until the end of the audit period.

Outcome Measures

The primary outcome measure was the change over time in the detection rate of bronchoscopy in the diagnosis of lung malignancy. A diagnosis of lung malignancy was considered secure when histologically confirmed by any method, or when clinical follow up was consistent with lung malignancy in the absence of a histocytological diagnosis.

Secondary outcome measures were the impact of CT availability, TBNA, and the type of bronchial brushes used upon the detection rate of bronchoscopy for lung malignancy. The detection rate of individual biopsy techniques, and of FB overall, were studied using summary statistics and statistical modelling (logistic regression) to examine predictive factors for a positive diagnosis including time.

Tests for trend in proportion was conducted using the Cochran-Armitage trend test (STATA version 9) and measures of association (chi squared analysis) and logistic regression models were used (SPSS version 14).

Details of protocols for CT scanning and pathology specimen preparation are available in an online supplement.

Results

Summary data

Between July 2001 and December 2007, 746 bronchoscopies were performed on 704 patients. Age ranged from 29 to 94 years, mean (SD) 69.1 (10.6) years. The majority of patients (n= 446, 63.4%) were male. A final malignant diagnosis was made in 631/704 (89.6%) patients referred with suspected intrathoracic malignancy. In 553/631 (87.6% true positive rate, 95% CI = 85.1% to 90.2%) this diagnosis was confirmed bronchoscopically. In 11 patients there was radiological progression consistent with lung malignancy without histological confirmation. Of the 73 patients with a benign diagnosis this was based on histological grounds in 4 (organising pneumonia, hamartoma, tuberculosis and sarcoidosis) and on sequential radiological examination showing stability or resolution in the remaining 69. Detailed breakdown of final diagnoses is shown in Table 1.

Overall numbers of diagnostic FB for lung malignancy decreased over the study period (114 in the first 12 month period versus 95 in the last 12 month period). The total number of FB conducted and their indication is shown in Table 2.

Change in detection rate

There was a statistically significant improvement in overall detection rate of FB for lung malignancy from 67.3% (95% CI = 52.9 to 79.7) in 2001 to 89.7% (95% CI 81.3 to 95.2) in 2007 (Cochran-Armitage test for trend p=0.003) (Table 3). The detection rate when tumour was visible endobronchially rose from 75.0% (95% CI 58.8 to 87.3) in 2001 to 94.5% (95% CI 84.9 to 98.9) in 2007 (p=0.006), and when tumour was not visible from 41.7% (95% CI 15.2 to 72.3) in 2001 to 81.2% (95% CI 63.6 to 92.8) in 2007 (p=0.005). Overall sensitivities over time (by 30 procedure periods) are demonstrated in figure 1 for cases overall (Panel A) and for visible versus non-visible tumours (Panel B). All biopsy modalities increased in detection rate over time (Table 3 and Figure 2) with the exception of brush biopsies in visible tumours.

Impact of CT

The availability of CT increased over the study period (Table 3). For both bronchoscopically visible and non-visible tumour, CT prior to the procedure was associated with an increased detection rate,

but this did not reach statistical significance (Visible tumour: no CT performed, detection rate = 177/203 (83.2%), CT performed, detection rate 243/264 (92.0%), chi^2 1df = 2.99, p=0.08. Non-visible tumour; no CT performed, detection rate = 33/58 (56.9%), CT performed, detection rate 97/138 (70.3%), chi^2 1df = 3.28, p=0.07).

Impact of service provision changes on detection rate

A logistic regression model was used to assess the overall impact of measured factors on the likelihood of a positive bronchoscopic diagnosis of lung malignancy. Year of study was initially assessed to account for measured and unmeasured variable change over time. Subsequent variables were assessed individually with year of study, and if significant were included in the final model. Two separate models were constructed to assess the predictive factors for a positive bronchoscopic diagnosis with all procedures and then with non-visible tumour cases only.

For the all-cases combined model, the identity of the operator and prior CT scan were not significantly associated with a positive bronchoscopic diagnosis. Identity of the reporting pathologist (2df, p=0.006), visibility of the tumour (1df, p<0.001) and use of TBNA (1df, p=0.035) were independent predictors of a positive bronchoscopic diagnosis, with year of study (1df, p=0.09) showing a trend towards prediction.

For the non-visible tumour model, identity of pathologist or operator, CT prior to bronchoscopy and use of TBNA were not statistically significantly associated with a positive bronchoscopic diagnosis. Year of study (1df, p=0.011) was the only independent predictor of a positive bronchoscopic diagnosis.

As year of study and availability of CT were highly associated (Table 3), an interaction term for year of study*CT availability was used, which showed no significant interaction.

Impact of bronchial brush diameter

Bronchial brush diameter was changed in April 2002 (after 89 procedures in the audit) from 2mm to 5mm. When visible tumours were sampled, 2mm brushes were associated with a significantly lower

diagnostic yield than 5mm brushes (2mm diagnostic yield = 39/58 (67.2%), 5mm diagnostic yield = 298/372 (80.1%), c^2 1df = 4.9, p=0.027). Comparing non-visible tumour in which a diagnostic brush was attempted, 2mm brushes were again associated with a significantly lower diagnostic yield (2mm diagnostic yield = 5/14 (35.7%), 5mm diagnostic yield = 61/118 (51.7%), chi^2 1df = 5.43, p=0.02).

Discussion

There was a significant and continuing improvement in detection rate of FB for thoracic malignancy over the audit period, from 67.3% to 89.7%. This occurred in association with improvement measures that are either universally adoptable (e.g., pursuit of CT scanning prior to FB, change in bronchial brush size), or require only modest resources to implement (e.g., TBNA). These results, therefore, have relevance more widely than in specialist centres in resource-rich countries alone. The proportional improvement was greatest for non-visible tumour, where the detection rate improved from 41.7% to 81.2% over the duration of the study.

Our audit of 746 FB in 704 patients is one of the larger reported series. There are three comparable published series[13-15]. We believe ours is the first to assess prospectively the change in detection rate over time, with all FB procedures recorded in exact sequential order. FB detection rate for both central (visible) and peripheral bronchogenic carcinoma has recently been systematically reviewed on behalf of the American College of Chest Physicians (ACCP)[2]. For visible tumour, the overall detection rate from 35 studies reporting on a total of 4,507 patients was 88%, while for peripheral tumour, in 34 studies reporting on 5,742 patients, it was 78%. Current British Thoracic Society (BTS) guidelines[16] suggest a target detection rate for FB of 80% for visible endobronchial tumour. We believe the evidence of our own study and the ACCP review[2] suggests that this target is set unacceptably low.

We believe that our study is the first to demonstrate the impact over time of the introduction of TBNA within a lung cancer service. A learning curve is evident, with the percentage of diagnostic specimens rising from 50% in 2003 to 78% in 2007 (Figure 2). This effect is expected and has been described before[17, 18], although a recent study reported high initial diagnostic yield by a team of experienced bronchoscopists[19]. TBNA requires no capital investment, was first described via FB more than 25 years ago, is cost-effective and very safe[5, 20]. It is, however, under-utilized in both UK and US hospitals[21, 22] with only 27% of UK bronchoscopists reporting having used the technique in the preceding 12 months[22]. We believe that in each hospital where FB is performed for diagnosing lung cancer, there should be at least one operator who develops skill in TBNA. Shah

and colleagues reported the impact of TBNA use in lung cancer diagnosis and staging in two London teaching hospitals[6]. They found that TBNA was the sole diagnostic modality in 30 patients, out of 433 FB-LC performed (7%). TBNA has an established role in the sampling of mediastinal and hilar lymph nodes[23, 24], and submucosal lesions[25], and has been proposed for sampling peripheral pulmonary nodules[26] and endobronchial tumour[27]. In our centre it has been used exclusively for sampling mediastinal and hilar lymph nodes, and submucosal tumour. EBUS-TBNA has shown increased detection rate for staging mediastinal and hilar lymph nodes in lung cancer compared with conventional TBNA and it is likely that this technique will grow in importance. It does however require significant training and capital investment.

Previous studies have found that a pre-procedure CT increases FB diagnostic yield. In a randomised two-group study[3], all patients with suspected lung cancer underwent CT scanning. In group A, the results of the CT were reviewed before FB, allowing a change of biopsy procedure if indicated. In group B, all patients proceeded to FB with the bronchoscopist blinded to the CT result. Detection rate of FB was 89% in group A but in 71% in group B ($p=0.012$). CT scanning can be expected to increase the diagnostic yield of bronchoscopy for peripheral lung malignancy, by providing an accurate segmental location for the primary tumour, or an extrabronchial target for TBNA. The presence on CT scan of a bronchus leading to the lesion is known to increase the detection rate[28]. The failure to demonstrate an independent effect of prior CT scanning on the detection rate for non-visible tumour is particularly surprising in our study, given the difficulty the bronchoscopist encounters in selecting a target for sampling when no CT is available and no abnormality is visible endobronchially. The absence of a demonstrated effect may be due to generally increased CT scanning prior to bronchoscopy that occurred over the course of the study, in association with a number of measured and non-measured variables resulting in increased diagnostic yields in later years, masking the added value of CT scanning. Lest it be thought that the need for CT prior to lung cancer bronchoscopy is so well established that it no longer requires emphasis, it is perhaps worth pointing out that in the most recent UK national audit of lung cancer practice, covering 2008, only 76% of patients in England and Wales had a CT prior to FB[29].

In most UK centres bronchoscopy is performed by the majority of chest physicians, with many regarding it as an essential part of their activities[22]. This study supports the establishment of a specialist, multidisciplinary bronchoscopy team, and of cancer multidisciplinary teamworking in general. The concentration of cases suitable for TBNA on the bronchoscopy list of the lead clinician for lung cancer and bronchoscopy permitted the development of expertise in TBNA without diluting the experience across several operators. Collaboration between chest physician and pathologist, and the appointment of a specialised bronchoscopy nurse, facilitates optimal preparation of cytological specimens, but these measures are not easily amenable to quantification. The influence of the pathologist on the likelihood of a positive bronchoscopic diagnosis is important. It is easier for a pathologist to give a confident positive malignant diagnosis if he or she has access to full clinical and radiological data via a chest MDT meeting, particularly for cytological samples with scant cellular material or where a bronchial biopsy is negative but the cytology appears malignant. The highly significant influence of year of study in multiple regression analysis of our data is a surrogate for the measured and unmeasured variables that changed over the course of our study. As such we believe it may represent the impact of developing a specialist, collaborative team devoted to optimum lung cancer care.

During our study the numbers of FB performed for lung malignancy fell. This may have been due to increasing use of less invasive techniques such as ultrasound-guided fine needle aspiration of supraclavicular lymph nodes[30], and better case selection. It is a weakness of our study that we did not collect data on the proportion of all lung cancer patients diagnosed bronchoscopically, nor on the average number of diagnostic procedures per patient per year. It would be expected, within a high-quality lung cancer service, that the latter number would be minimized. These would be appropriate subjects for further study.

Summary

This study suggests that simple, inexpensive and readily implemented service developments may significantly improve the detection rate of FB for lung malignancy. In particular, it is recommended

that all lung cancer diagnostic bronchoscopy should be performed by teams who have access to and develop expertise in TBNA. Bronchial brushes having a larger diameter appear to offer a higher diagnostic yield. Future British Thoracic Society guidelines on bronchoscopy should set higher targets for detection rate for lung cancer.

Acknowledgements

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Figure legends

Figure 1. FB detection rate over time (by periods of 30 procedures each), Panel A = Overall detection rate, Panel B = detection rate for visible versus non-visible tumour.

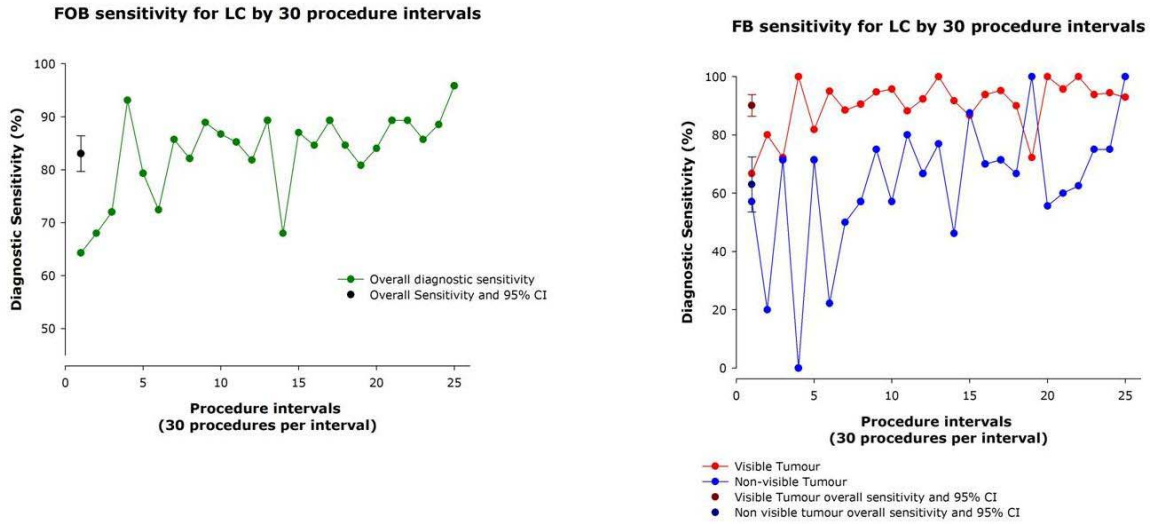
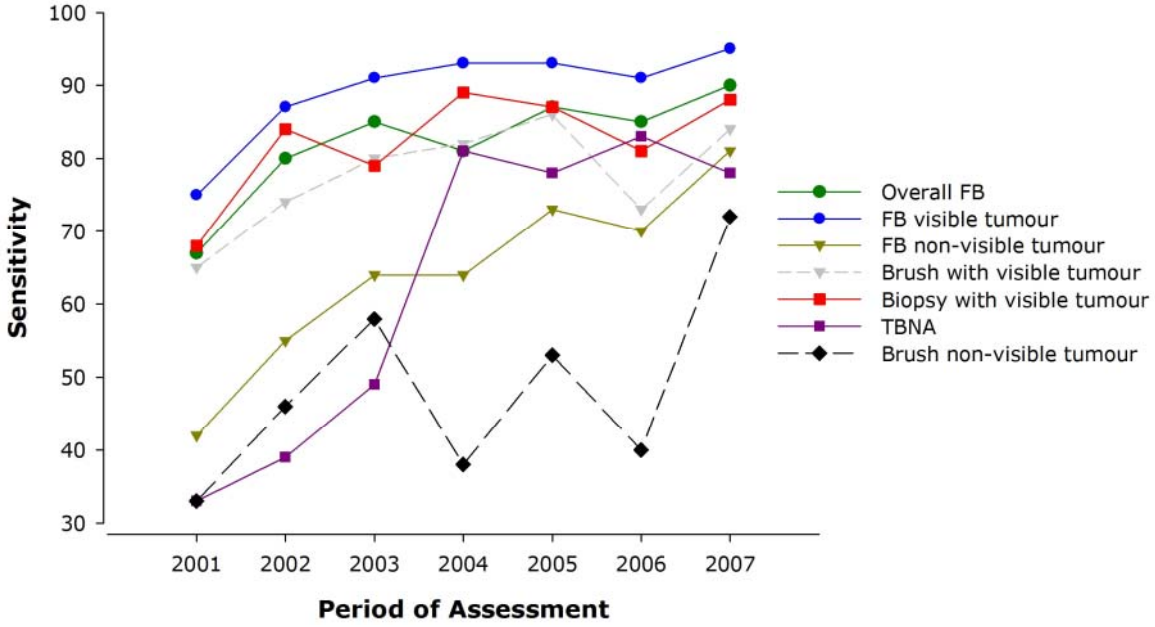


Figure 2. Diagnostic yield of all modalities over time.

Sensitivity of bronchoscopic diagnostic techniques over time



Tables

Diagnosis		Total group (M:F ratio)	Bronchoscopic diagnosis of malignancy
NSCLC	**Total**	491 (317:174)	440
	Squamous Cell	228 (157:71)	223
	Adenocarcinoma	120 (67:53)	106
	Unclassified	143 (93:50)	111
Small Cell Lung Cancer		83 (49:34)	78
Mesothelioma		1	1
Carcinoid		12	12
Intrathoracic metastases	**Breast**	5	3
	Colorectal	5	4
	Renal Cell	5	4
	Oesophageal	4	2
	Endometrial	2	2
	Melanoma	3	3
	Choriocarcinoma	1	*
	Haemangioblastoma	1	*
Lymphoma		5	2
Carcinosarcoma		2	2
Presumed Lung Cancer		11	*
Benign disease		73	*
Totals		704	553

Table 1. Final diagnoses in all patients undergoing FB for suspected lung malignancy.

	Year of study							Total
	2001*	2002	2003	2004	2005	2006	2007	
Total Number of FB	59	113	148	125	97	109	95	746
Number of FB in patients with final diagnosis of malignancy[$]	52	106	138	104	86	96	87	669
Number of FB positive for malignancy**	35	85	117	83	75	82	78	555
Number of FB in patients with Final Benign Diagnosis	7	7	10	21	11	13	8	77
% bronchoscopy where final diagnosis malignant	88.1	93.8	93.2	83.2	88.7	88.1	91.6	n/a

Table 2. Number of FB performed per year. [$] The total number of FB in patients with malignancy exceeds the total number of patients diagnosed with malignancy because repeat FB were performed following prior false-negative FB or because of tumour relapse. ** The total number of FB positive for malignancy (555) exceeds the total number of patients diagnosed with malignancy bronchoscopically (553) because 2 patients had a repeat bronchoscopy to diagnose tumour relapse. *2001 ran from July to December only

Method Assessed	Year of Study							Total	Statiscal significance and trend**
	2001	2002	2003	2004	2005	2006	2007		
All FB TP/(TP+FN) (%)	35/52 (67)	85/106 (80)	117/138 (85)	83/104 (80)	75/86 (87)	82/96 (85)	78/87 (90)	559/669 (84)	c^2 6df = 14.7, p=0.02 Trend p=0.003
FB where Tumour Visible**	30/40 (75)	73/84 (87)	96/105 (91)	54/58 (93)	56/60 (93)	63/69 (91)	52/55 (95)	424/471 (90)	c^2 7df = 13.9, p=0.03 Trend p=0.006
FB Non-visible Tumour**	5/12 (42)	12/22 (55)	21/33 (64)	29/45 (64)	19/26 (73)	19/27 (70)	26/32 (81)	131/197 (67)	c^2 7df = 8.8, p=0.19 Trend p=0.005
Brush Visible Tumour#	24/37 (65)	62/84 (74)	81/101 (80)	47/57 (82)	48/56 (86)	48/66 (73)	46/55 (84)	356/456 (78)	c^2 7df = 9.6, p=0.14 Trend p=0.11
Brush Non-visible Tumour	4/12 (33)	6/13 (46)	15/26 (58)	12/32 (38)	10/19 (53)	8/20 (40)	7/18 (72)	73/146 (50)	c^2 7df = 9.2, p=0.16 Trend p=0.14
Biopsy Visible Tumour#	27/40 (68)	59/70 (84)	77/97 (79)	48/54 (89)	47/54 (87)	52/64 (81)	45/51 (88)	355/430 (83)	c^2 7df = 10.6, =0.10 Trend p=0.056
TBNA+	1/3 (33)	11/28 (39)	24/49 (49)	21/26 (81)	21/27 (78)	29/35 (83)	31/40 (78)	138/208 (66)	c^2 7df = 27.8, p<0.001 Trend p<0.001
CT Availability*	12/51 (24)	47/106 (44)	71/137 (52)	56/101 (55)	52/86 (61)	78/96 (81)	87/87 (100)	403/663 (61)	c^2 7df = 120.4, p<0.001 Trend p<0.001

Table 3. Detection rate of bronchoscopy for lung malignancy. The table shows summary results from patients with a final diagnosis of malignancy. (* = CT availability prior to bronchoscopy in patients with a final diagnosis of lung malignancy only, ** = Cochran-Armitage trend test), #no of positive brushings (biopsies)/total number of brushings (biopsies) in patients with a final diagnosis of malignancy. + number of TBNA samples positive for malignancy/total

number of TBNA samples obtained from patients with a final diagnosis of malignancy. False positive rate of bronchoscopy for lung cancer was 0%. ** In 5 FB tumour visibility was not recorded.