Bronchoscopy of lesions suspicious of malignancy: Predictors of a higher diagnostic yield, the optimal combination of sampling techniques, and evaluation of endobronchial ultrasound with a rotating miniprobe

A retrospective cohort study and a prospective open randomised real-life study among physicians with various levels of experience

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Scientific environment

The study was performed in the Department of Thoracic Medicine, Haukeland University Hospital and the Department of Internal Medicine, Helse Sunnmøre, Ålesund Hospital, Norway.

The Bergen respiratory research group is part of the Institute of Internal Medicine, Haukeland University Hospital. Currently, more than 10 PhD students are associated with the group. Within the last 20 years, more than 25 doctoral theses have been produced from the group. The group was awarded best research group at the Medical Faculty, University in Bergen in 2007, and it was evaluated as “very good” in the latest evaluation from the Norwegian Research Council in 2004.

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Abstract

Aims

(1) To evaluate various predictors for a higher diagnostic yield in bronchoscopy

(2) To evaluate different combinations of sampling techniques in bronchoscopy of endobronchial visible lesions and peripheral lesions not visible by bronchoscopy

(3) To evaluate endobronchial ultrasound (EBUS) with a rotating miniprobe for localisation of peripheral lesions in a real-life situation among pulmonologists at various levels of expertise

Methods

I: A retrospective cohort study evaluated the results in the study centre before the introduction of EBUS. The study searched for predictors of a higher diagnostic yield and evaluated different combinations of sampling techniques. All 1438 bronchoscopies performed in 2003 and 2004 at Haukeland University Hospital, Bergen, Norway, were retrospectively reviewed and 363 patients with proven malignant lung disease were included in the study. Sex, age, endobronchial visibility, location (lobe), distance from the carina and tumour size were evaluated as possible predictors for a higher detection rate for cancer. Sampling techniques performed were biopsy, transbronchial needle aspiration (TBNA), brushing, small volume lavage (SVL), and aspiration of fluid from the entire procedure. The predictors of a higher detection rate were analysed in bivariate analyses and in multivariate logistic regression. McNemars test compared different combinations of sampling techniques. A cost-minimisation analysis evaluated different combinations of sampling techniques for visible lesions.

II: A prospective open randomised trial evaluated EBUS for peripheral lesions and searched for the optimal combination of sampling techniques in peripheral lesions. The study period was from 2005 to 2008 at Haukeland University Hospital and

Aalesund Hospital, Norway. The included 264 patients had peripheral lesions on the CT scan and no obvious endobronchial visible tumour on bronchoscopy. A simple randomisation without stratification assigned the patients to either EBUS or conventional bronchoscopy without EBUS. EBUS was performed with a 1.7 mm rotating probe with guide sheath. The study protocol recommended fluoroscopy for both study arms. An intention-to-treat analysis evaluated EBUS and a multivariate analysis was performed to avoid confounding. A cost-effectiveness analysis evaluated different combinations of biopsy, brushing, TBNA and washing.

Results

The detection rate for cancer in the retrospective study was 17 % in patients with no endobronchial visible lesions, 34 % in patients with endobronchial constriction or compression and 77 % in patients with endobronchial visible lesions. The multivariate logistic regression analysis retained endobronchial visibility and size as significantly predictors of a higher detection rate for cancer. Biopsy and brushing combined with endobronchial needle aspiration (EBNA) was the most economical combination of sampling techniques for endobronchial lesions in a cost-minimisation analysis.

The detection rate for cancer in the prospective study was 36 % in the EBUS group and 44 % in the non-EBUS group (ns). The prospective study included only patients without endobronchial visible lesions. There was a significant interaction between size and randomisation to EBUS. Patients with lesions below 3 cm had a significantly higher detection rate in the non-EBUS group. Lesions visualised by EBUS had a higher detection rate for cancer than lesions not visualised by EBUS (62 % vs. 19 %, $p<0.01$). The cost of one additional positive sample was 1211 euro when brushing was added to biopsy. Based on a willingness to pay of 2800 euro for an additional positive sample, biopsy and brushing was the most cost-effective combination of sampling techniques for lesions not visible by bronchoscopy. The addition of TBNA or washing had cost-effectiveness ratios above 2800 euro.

Conclusions

1) Endobronchial visibility and lesion size were significant predictors of a higher detection rate for cancer in bronchoscopy.

2) For visible lesions, biopsy and brushing combined with EBNA was the most economical combination of sampling techniques. For lesions not visible by bronchoscopy, biopsy together with brushing was the most cost-effective combination of sampling techniques.

3) Overall, EBUS did not increase the detection rate for cancer in peripheral lesions when pulmonologists at various levels of expertise performed the bronchoscopies. However, visualisation by EBUS predicted a high detection rate for cancer.

List of publications

Paper I: Roth, K., Hardie, J. A., Andreassen, A. H., Leh, F., and Eagan, T. M. L. "Predictors of Diagnostic Yield in Bronchoscopy: a Retrospective Cohort Study Comparing Different Combinations of Sampling Techniques", BMC Pulmonary medicine 2010;8(2).

Paper II: Roth, K., Hardie, J. A., Andreassen, A. H., Leh, F., and Eagan, T. M. L. "Cost Minimization Analysis for Combinations of Sampling Techniques in Bronchoscopy of Endobronchial Lesions", Respiratory Medicine 2009;103(6):888-94.

Paper III: Roth, K., Eagan, T. M. L., Andreassen, A. H., Leh, F., and. Hardie, J. A. "A Randomised trial of Endobronchial Ultrasound guided sampling in Peripheral Lung Lesions". Lung Cancer 2011; 74(2):219-25.

Post publication correspondence:

Letter to the editor concerning our paper:

Leiro-Fernández, V., Botana-Rial, M., Represas, C., Fernández-Villar, A. Significance of endobronchial lesion appearance in the diagnostic value of different endoscopic techniques. Respiratory Medicine, 2010, 104(9):1386

Our response:

Roth, K., Eagan, T., Hardie, J. Response to Leiro-Fernández et al. Respiratory Medicine, 2010, 104(9):1387

Contents

1. TERMS AND ABBREVIATIONS

1.1 Terms

α	When the sample size is calculated, α is the predefined accepted probability for a type I mistake (a false positive result). α is set as 0.05.
β	In sample size calculations β is the predefined accepted probability for a type II mistake (a false-negative result due to insufficient study size). β is usually set as 0.1 or 0.2.
Cohort study	A study that follows a group of people for a period of time.
Confidence interval	An estimate of the variability in the data. The estimate measures the range of values with α above a specified level. A 95 % confidence interval is the range of values with α above 0.05.
Cost-effectiveness analysis	An analysis of alternative strategies that compares the increase in cost to the increase in effectiveness for the alternatives in contrast to a reference strategy.
Cost-minimisation analysis	An analysis that reveals the least costly strategy.

Decision tree	A figure in a decision analysis that displays the actual strategies with all possible outcomes.
Detection rate	The percentage of pathological cases correctly detected by an investigation. The detection rate for cancer is analogue to sensitivity for cancer.
Diagnostic yield	The ability to detect distinct diagnoses compared to a gold standard. The diagnostic yield can include benign and malignant disease.
Incremental cost-effectiveness ratio	The increase in the cost divided by the increase in the effectiveness. If the diagnostic yield defines the effectiveness, the incremental cost-effectiveness ratio will be the price for one additional positive sample.
Likelihood ratio	The likelihood ratio is sensitivity divided by (1-spesifisity).
Logistic regression	Logistic regression describes the probability (p) for an outcome based on the value of a variable (x). The current study used logistic regression to find significant predictors of the diagnostic yield in bronchoscopy. Logistic regression is based on the log odds (log odds is $\log_e(p/(1-p))$). The logistic function $e^{\alpha+\beta x}/(1+ e^{\alpha+\beta x})$ describes the probability for outcome=1 in a group. Logit = $\log_e(p/(1-p)) = \alpha+\beta x$
Logistic model	The logistic model defines the logistic function: $e^{\alpha+\beta x}/(1+ e^{\alpha+\beta x})$. α is a constant and β is the coefficient for x. X is a significant predictor for

	the outcome when the confidence interval for β not includes 0 and the confidence interval for e^{β} does not include 1.
Multiple regression	Multiple regression is a logistic regression analysis that analyses the effect of multiple variables on the outcome. For each variable, the analysis reveals a β that is the effect of that variable. Each variable has a significant effect on the outcome when the 95 % confidence interval for β of the variable does not include zero (and the confidence interval for e^{β} does not include 1).
Odds	The proportion with outcome=1 (p) divided by the proportion with outcome=0 (1-p) in a group. (p/(1-p))
Odds Ratio	The odds in one group divided by the odds in another group.
Open randomised trial	A trial where the allocation to different interventions is random, but the patient and the investigator are aware of the allocation.
p-value	The p value represents the probability for a type 1 mistake in the study.
Power	The power is the study's ability to detect a difference and thus to reject the null hypothesis and to avoid a type 2 mistake. Power=1- β. A usual desired power of a study is at least 80 % or 90 %.

Predictive value	The proportion of patients with disease when a test is positive is the positive predictive value of a test. The negative predictive value of the test is the proportion with no disease when the test is negative.
Prospective study	A study that starts at a specific date and that includes and follows patients forward in time until the end of inclusion and the end of follow up. The prospective study can study cause and effect.
Randomised trial	The selection of interventions is random.
Retrospective study	A study that selects patients and register variables from a defined period prior to the start up date. Retrospective studies can describe the effect of different variables on each other, but are not able to settle cause and effect.
Sensitivity	The sensitivity is the number with positive test and proven disease divided by all with proven disease.
Specificity	Specificity is the number with negative test and no proven disease divided by all with no proven disease. Together with sensitivity, specificity displays the validity of the test
Solitary pulmonary nodule	A nodule surrounded on all sides by healthy pulmonary parenchyma.
Standard deviation	The standard deviation describes the variation from the average value. It is calculated as the

	square root of the variance. (The variance is the sum of squared deviations from the mean). 95 % of the values in the dataset will be within 1.96 standard deviations below the mean and 1.96 standard deviations above the mean in a perfect Gauss curve.
Type I mistake	The 0 hypothesis is rejected although it is true. (False positive.)
Type II mistake	The 0 hypothesis is not rejected although it is false. (False negative.)
Willingness to pay	In cost-effectiveness analyses, the willingness to pay is the amount of money reasonable to pay for an increase in the outcome with one unit. For example, the price can be for one additional quality adjusted life year (QALY). When the diagnostic yield is the outcome, the willingness to pay is the accepted price for one additional positive sample.

1.2 Abbreviations

ATS	American thoracic society
BAL	Bronchoalveolar lavage
CONSORT	Consolidated standards of reporting trials
CT	Computed tomography
DRG	Diagnosis related group
EBNA	Endobronchial needle aspiration
EBUS	Endobronchial ultrasound
EGFR	Epidermal growth factor receptor
ERS	European respiratory society
ICER	Incremental cost-effectiveness ratio
MHz	Megahertz
NOK	Norwegian kroner
NS	Not significant
PET	Positron emission tomography
PhD	Philosophiae doctor
QALY	Quality adjusted life years
SE	Standard error
SNOMED	Systemised nomenclature of medicine

SPECT	Single photon emission computed tomography
STARD	Standards for reporting of diagnostic accuracy
SVL	Small volume lavage
TBNA	Transbronchial fine-needle aspiration
VAS	Visual analogue scale

2. INTRODUCTION

2.1 The subject of the current thesis

A pulmonary lesion suspicious of malignancy is a common indication for bronchoscopy. The lesions can be visible through the bronchoscope or beyond the visual field. Different sampling techniques like biopsy, brushing, needle aspiration, and washing are available for the physician. For lesions located beyond the visual field, different guidance systems are available to assist in finding the right bronchial branches. Virtual navigation from reformatted computed tomography (CT) scans can guide a magnetic probe to the lesion. Endobronchial ultrasound (EBUS) with a rotating miniprobe can visualise the lesion, when there is contact between the probe and the lesion. Use of a guide sheath can lead the sampling devices back to the lesion detected by virtual navigation or EBUS.

Regardless of the use of guidance system, diagnostic yield from a bronchoscopic procedure will seldom be one hundred percent, neither in visible lesions nor in lesions beyond the visual field. Several factors are likely to influence on the diagnostic yield. Combinations of sampling techniques, the size and histology of the lesion, the physicians' level of experience, the selection of the patients, and the follow-up have been significant predictors in previous studies (summarised in Table 2). A sufficiently long and thorough follow up will be able to detect the false negative cases. The diagnostic yield could also depend on the interpretation of the pathological results. Cells suspicious of malignancy are likely cancerous, but may lead to a repeat of the procedure to attain a definite diagnosis. Previous studies have shown a large variation in diagnostic yields. The above-mentioned variables are potentially some of the reasons for this variation. The large variation in the results from previous studies (Figure 3) illustrates the importance to determine the diagnostic yield and to analyse

the predictors in our own centre. This will hopefully lead to improvement of our own diagnostic yield and thus improved care, over time.

The three papers in the current study evaluated different predictors of a higher diagnostic yield in bronchoscopy and compared combinations of sampling techniques. A retrospective cohort study evaluated the diagnostic yield of bronchoscopy in the study centre and detected the main predictors of a higher diagnostic yield. The inclusion criteria were wide. The study evaluated the predictors for a higher diagnostic yield in bivariate analyses and in multivariate analyses to avoid confounding. Due to the retrospective nature of the first study, the choice of sampling techniques was exclusively up to the physician performing the procedure. In a prospective study, physicians at various levels of experience performed EBUS during bronchoscopy on patients with peripheral lesions.

When the physician is choosing between different combinations of sampling techniques, he/she must know something about the increase in the diagnostic yield. He/she also needs knowledge about the cost of the different strategies. A cost-minimisation model was used to analyse the costs of diagnosing visible lesions with different sampling techniques. The model included calculated costs in the bronchoscopy unit and in the pathological department. The cost of a missed diagnosis, the average cost for each sampling technique, and the diagnostic yield of each combination of sampling techniques defined the model. The cost-minimisation analysis recommended the combination of sampling techniques that had the least costly average price that led to diagnosis.

EBUS with a miniprobe is a possible tool to increase the diagnostic yield in peripheral lesions. A prospective open randomised trial evaluated the use of EBUS in our centre. All our physicians were trained to control the fluoroscope and to use EBUS with a guide sheath. An on-site cytotechnician evaluated the transbronchial fine-needle aspiration (TBNA) smears. The study protocol recommended the use of all sampling techniques (biopsy, brushing, TBNA, and washing). We assumed a diagnostic yield of 40 % with fluoroscopy guidance and with all sampling techniques in the non-EBUS

group. The diagnostic yield in the EBUS group was predicted to 60 % based on previous studies. Standard sample size calculation estimated that 240 patients had to be included in the study (α=0.05, power=90 %).

An intention-to-treat analysis evaluated the use of EBUS. A multivariate analysis was used to control for potential confounding. A cost-effectiveness analysis evaluated different combinations of sampling techniques. The average diagnostic yield for benign and malignant disease was the measure of effectiveness. The cost-effectiveness analysis calculated the incremental cost-effectiveness ratio (ICER) based on the increase in cost divided by the increase in effectiveness. ICER represented the cost of one additional positive sample. The willingness to pay for one additional positive sample was the average calculated cost of a repeated procedure. When the ICER for a combination with an additional sampling technique was lower than the willingness to pay, the sampling technique was cost-effective.

The results of the studies presented in this philosophiae doctor (PhD) thesis revealed predictors for a higher diagnostic yield. These predictors can guide adjusted or stratified analyses in future studies. Further, the current PhD thesis presents the most economical combination of sampling techniques in visible and non-visible lesions and evaluated EBUS in a real-life setting.

2.2 Historical background

2.2.1 Bronchoscopy

Gustav Killian introduced bronchoscopy in Europe when he removed a foreign body from the trachea with an oesophagoscope in 1897(1). Killian was known to encourage his students to analyse their results(2) and research on this method was thus started. The father of bronchoscopy in the United States was Chevalier Jackson. Jackson

introduced a bronchoscope with integrated suction in 1904. Still, for both it was a challenge to get good illumination of the bronchial tree. Killian used a light bulb integrated in the handle of the bronchoscope, with a prism to reflect the light. Jackson used distal illumination with a mignon bulb at the tip of the bronchoscope. A major leap forward came when Shigeto Ikeda constructed fibreglass illumination for the rigid bronchoscope in 1962. The fiberglass illumination contained approximately 15000 glass fibers with a size less than 15 mm(2). The fibers transported light to the distal end of the bronchoscope, and images to the proximal part. Ikeda designed the flexible fiberbronchoscope in 1964, and it was commercially available in 1970 from Olympus. His paper from 1971 described flexible bronchoscopy with brushing and curette biopsy(3). Ikeda further developed the bronchoscope with video technique in 1983-1987(2). Anderson replaced the surgical biopsy with transbronchial biopsy in 1963(4). Sackner described bronchoalveolar lavage in 1972(5). TBNA was described by Schieppati in 1949(6), but got little attention before Wang reported his results in 1978(7).

2.2.2 Ultrasound

The brothers Jaques and Pierre Curie described the ultrasound waves in 1880. They found that certain crystals exposed to alternating mechanical stress were excited and produced piezoelectricity(8). Piezoelectricity was omitted from the excited crystals as waves. After World War II, the knowledge of ultrasound from the Sound Navigation and Ranging (SONAR) was explored for medical purposes. The A-mode ultrasonic instrument presented blips on an oscilloscope screen. These blips marked the distance from the transducer to the lesion. Shigeru Nakajima and Rokuro Uchida built Japan's first A-mode instrument in 1949, simultaneously with John Wild in the United States(9). Some of the first reports about the diagnostic value of ultrasound came from George Ludwig, United States(10), John Wild, United States(11) and Karl Dussik, Austria(12). The compound 2,5 megahertz (MHz) two dimensional B-mode

was constructed by Ian Donald in 1957(13). John Wild and John Reid developed a small sonographic probe for the rectum in 1957(14). A similar device was used by Hürter et al. in the first report about endobronchial ultrasound with a rotating miniprobe in the lungs(15). The miniprobe was commercially available in 1999. Kurimoto et al. described in 2004 the use of a guide sheath which was guided into the correct position with a curette(16). The curette is a bendable device; it can be rotated 360 degrees, but must be removed before the miniprobe is inserted for identification of the lesion.

2.2.3 Lung cancer

Morgagni reported the first case of lung cancer in 1761(17). The disease was rare until the beginning of the nineteenth century. When Adeler published his report in 1912, he found only 374 published cases with verified lung cancer worldwide(18). Lung cancer increased like an epidemic during the 19th century. Doll's famous report about smoking and lung cancer was published in 1950(19), but Lickint from Germany assumed the association between lung cancer and smoking already in 1929(20). The early German reports have often been ignored, probably because they were associated with the Nazi regime(21).

The age adjusted incidence of lung cancer in Norway was 10.1/100 000 for men and 2.6/100 000 for women in 1954 The incidence increased to 34.2/100 000 for men and 24.8/100 000 for women in 2008(22). Lung cancer in Norway increased from average 285 cases each year in 1954-1958 (220 men and 65 women) to 2529 cases in 2008 (1422 men and 1107 women). Currently lung cancer has the second highest incidence of all cancers for men and the third highest incidence for women in Norway. In Norway, 4.4 % of all men and 3.1 % of all women will develop lung cancer by the age of 75 years(22).

Detection of lung cancer

The radiological evaluation of lesions suspicious of malignancy was initiated by Röntgens discovery in 1895(23) making it possible to visualise hyperdense areas of the lung parenchyma. The single photon emission computed tomography (SPECT) device was invented by David Kuhl in 1964(24). SPECT visualised functional information with a gamma camera that detected injected radioactive isotopes. Godfrey Hounsfield invented the computed tomography (CT) imaging in 1972(25). CT was able to give information about small lesions and provided information about the spatial extension of the lesions. Gordon Brownell and Charles Burnham contributed to the development of the positron emission tomography (PET) scanner in the 1950's and 1960's(26). The radiopharmaceutical 2-fluorodeoxy-D-glucose (2FDG) was first administrated to humans by Abass Alavi in 1976(27). Ron Nutt and David Townsend invented the PET/CT in 2000(28). The PET/CT combines the functional information from PET with the detailed anatomical CT picture. It is a sensitive device to detect metastases.

Lung cancer management

Surgery in the lung was first performed by Milton Anthony in 1821(18). The first lobectomy for lung cancer was performed by H. Morriston Davies in 1912, but Evarts Graham became known as father of lung surgery with his pneumonectomy of lung cancer with a surviving patient in 1933(29;30).

Wilhelm Conrad Röntgen discovered the X-rays in 1895 for which he received the Nobel Prize in physics in 1901(23). Emil Grubbe tried to treat breast cancer with irradiation the same year(31;32). Tudor Edwards reported a paper in 1946 that described insertion of radon seeds through the bronchoscope into the bronchus. The radon seeds were left in situ for several days similar to brachytherapy(33). Johnson summarised the first randomised studies of irradiation therapy from the 1960's(34). Stereotactic irradiation with high irradiation dose in the tumour and low dose in

protected vital organs was available for brain tumours in the early 1980's(35). Stereotactic body radiation therapy for lung cancer was introduced in 1994-1995(36;37).

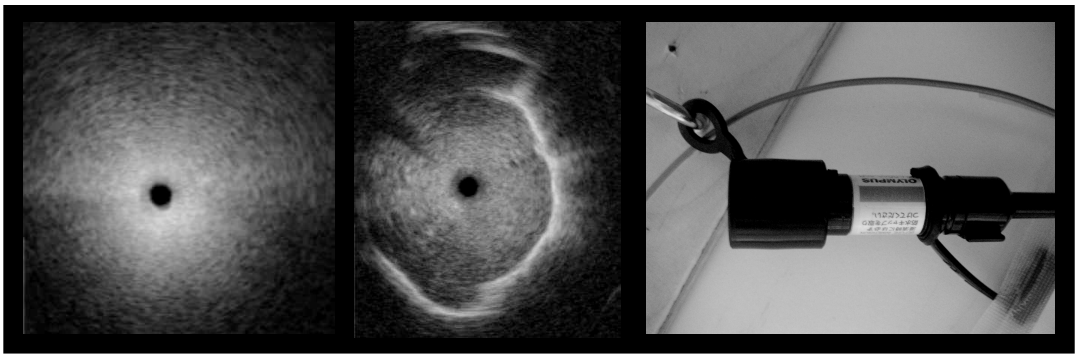
Lois Goodman and Alfred Gilman tried to develop antidotes for the nerve gas organophosphates in the early 1940's when they discovered that nitrogen mustards destroyed lymphatic tissue(38-40). Randomised trials of chemotherapy alone or in combination with surgery and radiotherapy were initiated in the 1960's for lung cancer(41). Combinations with Cisplatin were introduced in the late 1970's and are still standard therapy. New insight in the mechanisms of cell growth led to targeting therapy against tyrosine kinase activity of the epidermal growth factor receptor (EGFR) in 2002(42).

2.3 Technical description of the endobronchial ultrasound miniprobe

Ultrasound miniprobes are commercially available from Fujinon and Olympus. The Fujinon miniprobes are available in different frequencies (12,15,20,25 MHz) and with outer diameter of 1.9-2.6 mm(43). The miniprobes from Olympus are available with outer diameter between 1.7 and 2.5 mm (frequencies 12, 20 or 30 MHz)(44). Olympus also provides a guide sheath that covers the miniprobe when it is inserted into the lesion(45). The guide sheath remains in the lesion when the miniprobe is removed, and it can thus guide the insertion of the brush, biopsy equipment or TBNA needle(16). Miniprobes from Fujinon and from Olympus have a separate driving unit that rotates the whole probe. There is a single transmitter and a single detector in the miniprobe. When the transmitter and the detector are rotating, the visual ultrasound picture is 360 degrees around the miniprobe. The visual output depends on the frequency and the contact with the lesion. It is not possible for ultrasound waves to

move through air because of air reflection. When the ultrasound transducer is adjacent to solid material, it reveals a picture of the lesion. A low frequency will improve the depth of penetration with low resolution. A high frequency probe will have a narrow penetration with high resolution. The usual miniprobe has 20MHz frequency with a visual output of approximately 4 cm(46).

Figure 1 (A-C): Ultrasound pictures of air and a malignant lesion



1A:Ultrasound picture of air *1B:Ultrasound picture of a malignant lesion (within the white borders)* *1C:The miniprobe*

2.4 The diagnostic approach to visible and peripheral lesions

Table 1 presents a query in PubMed for papers concerning diagnostic bronchoscopy published after 1970. There were about 80 publications yearly until 2005, after which the publication rate increased to 160 publications yearly. Hürter et al. wrote the first publication on endobronchial ultrasound in 1992(15). Most publications analysed EBUS-TBNA for lymph nodes, while only approximately 20 % of the 280 EBUS publications evaluated the miniprobe for peripheral lesions.

Table 1: PubMed search for articles on bronchoscopy and endobronchial ultrasound in the diagnosis of lung cancer.

Year	Bronchoscopy in the diagnosis of lung cancer*	Endobronchial ultrasound in the diagnosis of lung cancer**	Endobronchial ultrasound in the diagnosis of peripheral lung cancer***
Before 1970	315		
1970-74	335		
1975-79	297		
1980-84	313		
1985-89	377		
1990-94	385	1	1
1995-99	482	8	2
2000-04	631	36	9
2005-09	797	151	33
2010	172	84	9
Sum	4104	280	54

*PubMed search term: (Diagnosis/Broad[filter]) AND (bronchoscopy) AND (lung cancer)
** PubMed search term: (Diagnosis/Broad[filter]) AND (endobronchial ultrasound) AND (lung cancer)
*** (Diagnosis/Broad[filter]) AND (endobronchial ultrasound) AND (lung cancer) AND (peripheral)

2.4.1 Papers published on bronchoscopy without endobronchial ultrasound

Papers with detection rates for cancer without EBUS are summarised in Table 2. The confidence intervals presented in Figure 2 and Figure 3 were calculated based on the binominal distribution[a]. Figure 2 and Figure 3 visualise the spread of reported

[a] The standard error (SE) of the detection rate (p) was: Square root (p*(1-p)/n). n: number of cases in the study. The 95 % confidence interval was calculated to be from p-1.96*SE(p) to p+1.96*SE(p)(47).

detection rates in papers about bronchoscopy for visible and peripheral lesions respectively. The papers were identified from Schreiber et al.'s summary of published evidence(48), Rivera et al.'s evidence-based clinical practical guideline(49), and a PubMed search. Schreiber et al. searched MEDLINE and Cochrane from 1966 to 2001 for studies that had at least 50 patients with suspected lung cancer. Rivera et al. updated the search and included studies up to 2004. The PubMed search included studies from 2000 to 2010. (Search term: (Diagnosis/Broad[filter]) AND (bronchoscopy) AND (lung cancer) AND (biopsy) AND "2000/01/01"[Publication Date] : "2010/12/31"[Publication Date]).

Table 2: Published papers with detection rates for cancer in central visible lesions and in peripheral lesions

Year	Authors (ref#)	Inclusion criteria	n	Centre	Performing physicians' level of experience	Predictors evaluated	Study design	Statistical analysis of predictors	Significant predictors of a higher diagnostic yield	Cost analysis	Sampling techniques performed, guidance	Recommended combination of sampling techniques	Detection rate for cancer in visible lesions	Detection rate for cancer in peripheral lesions	
														<3cm	>3cm
1971	Hattori et al.(50)	Peripheral lung lesions	436	Not described	Not described	Size	Not described	Bivariate	No tests applied	Not performed	Brushing with fluoroscopy	None recommended	No visible lesions	42/63 (66.7 %)	127/142 (89.4 %)
1971	Oswald et al.(51)	Primary lung cancer at discharge	1518	St. Bartholomew's Hospital and Brompton Hospital	Not described	Size	Retrospective	Not performed	No tests applied	Not performed	Biopsy, use of fluoroscopy was not described	Biopsy and sputum, but sputum is time consuming	Central: 264/434 (60.8 %)	Peripheral: 123/435 (28.3 %)	
1974	Solomon et al.(52)	Lesions suspicious of malignancy or haemoptysis	103	Not described properly	Not described	None	Prospective	Not performed	None evaluated	Not performed	Biopsy, brushing, washing, fluoroscopy, endotracheal tube without cuff.	Brushing	10/11 (90.9 %)	31/36 (86.1 %)	
1975	Zavala et al.(53)	Lesions suspicious of malignancy or haemoptysis	600	University of Iowa Hospitals	Not described	None	Prospective	Not performed	None evaluated	Not performed	Biopsy, brushing, and curette, fluoroscopy	Biopsy and brushing, add curette for peripheral lesions	182/193 (94.3 %)	97/137 (70.8 %)	
1976	Kvale et al.(54)	Lesion suspicious of malignancy, haemoptysis, diffuse pulmonary disease	228	Not described	Not described	Endo-bronchial visibility	Retrospective	Not performed	No tests applied	Cost of washing was discussed	Biopsy, brushing, and washing, fluoroscopy for 10/15 (66.6 %)	Biopsy and brushing	60/69 (87.0 %)	7/15 (46.7 %)	
1977	Chopra et al.(55)	Visible lesions with a definite tissue diagnosis	70	Not described	Not described	None	Retrospective	Not performed	None evaluated	Not performed	Biopsy, brushing, and washing, fluoroscopy	Biopsy, brushing, and sputum	38/64 (59.4 %)	No peripheral lesions included	
1977	Stringfield et al.(56)	Patients with proven lung cancer	107	Ann Arbor Veterans Administration Hospital	Various levels of experience	Size, location	Retrospective	Bivariate	Size, location	Not performed	Biopsy, brushing, and washing, fluoroscopy	Biopsy, brushing, and washing	66/78 (84.6 %)	14/29 (48.3 %)	
1978	Chaudhary et al.(57)	Proven malignant disease in the lung	114	Veterans Administration Hospital, Lexington, Kentucky	Two experienced physicians	None	Retrospective	Not performed	None evaluated	Not performed	Biopsy, brushing, and washing, use of fluoroscopy not described	Biopsy, washing, brushing, and post-bronchoscopy sputum	The overall result for bronchoscopy was not reported, biopsy and washing: 95.8 %		
1979	Cortese et al.(58)	Peripheral lesions, proven primary lung cancer	48	Not described	Not described	Size, distance from hilum, location	Retrospective	Not performed	No tests applied	Not performed	Biopsy, brushing, and washing, fluoroscopy	Biopsy and brushing	No visible lesions	29/48 (60.4 %). Lesions <2 cm: 0 %	
1979	Radke et al.(59)	Localised peripheral infiltrate visible by fluoroscopy	95	Henry Ford Hospital	Not described	Size, location, histology	Prospective	Bivariate	Histology, size	Not performed	Biopsy and brushing, fluoroscopy	Brushing and biopsy	No visible lesions	45/71 (63.4 %)	

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														<3cm	>3cm
1981	Buirski et al.(60)	Endobronchial visible lesions	60	Not described	Not described	None	Prospective	Not performed	Location	Not performed	Brushing, biopsy, EBNA	Biopsy, needle aspiration, and brushing	92 %	No peripheral lesions included	
1981	Ono et al.(61)	Lesion below 2 cm, no metastases, proven lung cancer	52	National Cancer Center Hospital	Not described	None	Retro-spective	Not performed	No tests applied	Not performed	Curette, bronchography, fluoroscopy, endotracheal tube, local sedation	Curette	No visible lesions	<2cm: 40/46 (87.0 %)	
1982	Gellert et al.(62)	Endobronchial visible lesion and biopsy taken	271	London Chest Hospital	Not described	None	Retro-spective	Not performed	No tests applied	Not performed	Biopsy	At least five biopsies for visible lesions	169/215 (78.6 %)	No peripheral lesions included	
1982	Pilotti et al.(63)	Histological proven lung cancer	370	Studio e la Cura dei Tumori, Milan	Not described	Endo-bronchial visibility	Retro-spective	Not performed	No tests applied	Not performed	Brushing, not fluoroscopy	None recommended	224/286 (78.3 %)	24/84 (28.6 %)	
1982	Popovich et al.(64)	Proven lung carcinoma	46	Henry Ford Hospital	Not described	Endo-bronchial visibility	Retro-spective	Not performed	No tests applied	Not performed	Brushing and biopsy, use of fluoroscopy not described	Cytology and one biopsy for visible lesions, up to 10 biopsies for peripheral lesions	25/26 (96.2 %)	15/20 (75.0 %)	
1982	Wallace et al.(65)	Peripheral lung lesion less then or equal to 4cm surrounded by lung tissue	133	University of California, and The Veterans Administration Hospital	Not described	Size, location	Retro-spective	Bivariate	Size, location	Not performed	Biopsy, brushing, and washing, use of fluoroscopy not described	Washing, brushing, biopsy, and sputum	The results were a mix of visible and non-visible lesions. None of the benign lesions were diagnosed by bronchoscopy.		
1983	Lam et al.(66)	Performed bronchoscopy, final malignant diagnosis	484	Queen Mary Hospital, Hong Kong	Not described	None	Retro-spective	Not performed	None evaluated	Not performed	Biopsy, brushing, BAL, use of fluoroscopy not described	Washing, brushing, and biopsy	309/329 (93.9 %)	133/155 (85.6 %)	
1983	Lundgren et al.(67)	Final primary lung carcinoma, all sampling techniques applied	59	University hospital, Umeå	One experienced pulmonologist	None	Retro-spective	No predictors evaluated	None evaluated	Not performed	Biopsy, brushing, washing, EBNA/TBNA, fluoroscopy	Biopsy and washing	34/34 (100 %)	9/13 (69.2 %)	
1983	Shure et al.(68)	Endobronchial visible lesion	18	San Diego Administration Medical Center	Various levels of experience	Number of biopsies taken	Prospective	Bivariate, Cochrane Q test	Number of biopsies taken	Not performed	Biopsy	2-3 biopsies for endobronchial lesions	18/18 (100 %)	No peripheral lesions included	

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1983	Zisholz et al.(69)	Proven lung cancer	51	Metro-politan Hospital, New York	Not described	Histology	Retro-spective	Bivariate	Histology	Not performed	Biopsy, brushing, and washing, use of fluoroscopy not described	Biopsy, brushing, and washing	Combined for visible and non-visible lesions: 37/51 (72.5 %)		
1984	Cox et al.(70)	Visible on chest radiograph, proven bronchial carcinoma	100	London hospital	Not described	Size, distance from central bronchi	Retro-spective	Bivariate	Distance from central bronchi	Not performed	Biopsy, brushing, and washing, not fluoroscopy	Fluoroscopy should be used for peripheral lesions	45/53 (84.9 %)	28/47 (59.6 %)	
1984	Horseley et al.(71)	Submucosal needle aspirations performed	171	University of Alberta	Not described	None	Retro-spective	Not performed	None evaluated	Not performed	EBNA, brushing, washing, and biopsy	EBNA should be added	Needle aspiration 66/102 (64.7 %)	No peripheral lesions included	
1987	Schenk et al.(72)	Lesion suspicious of malignancy and later proven lung cancer	91	Not described	Various levels of experience	Location, histology	Prospective	Not performed	No tests applied	Not performed	Biopsy, brushing, washing, EBNA/TBNA, fluoroscopy	TBNA for extra-tracheal and extra-bronchial lesions	The overall diagnostic yield with biopsy, brushing, washing and TBNA was 58/91 (64 %)		
1988	Naidich et al.(73)	Solitary pulmonary nodule	65	Not described	Not described	Size, location, CT bronchus sign	Retro-spective	Bivariate	CT bronchus sign.	Not performed	Biopsy and washing, use of fluoroscopy not described	None recommended	No visible lesions	30/61 (49.2 %)	
1988	Shiner et al.(74)	Peripheral lesion above 2 cm, not visible by bronchoscopy	71	Not described	One experienced pulmonologist	Location	Retro-spective	Not performed	No tests applied	Not performed	Biopsy, brushing, fluoroscopy	Biopsy and brushing	No visible lesions	38/51 (74.5 %)	
1989	Gay et al.(75)	A lesion suspicious of malignancy, TBNA performed	84	Mayo Clinic, Rochester	Not described	None	Retrospective	Not performed	None evaluated	Not performed	EBNA/TBNA	TBNA for lesions suspicious of small cell cancer or metastasis	TBNA: 25/68 (36.8 %) for the study population with visible and peripheral lesions		
1989	Mori et al.(76)	Peripheral lung cancer with tumours 2 cm or less	108	Japanese National Cancer Center Hospital	Not described	Size, location	Retrospective	Not performed	No tests applied	Not performed	Curette, washing, fluoroscopy, selective bronchography	Add curettage	No visible lesions	< 2cm: Curettage: 70/85 (82.4 %)	
1989	Wagner et al.(77)	Transbronchial needle aspiration performed for visible lesions, constriction or compression,	104	The Methodist Hospital, Houston	Not described	None	Retrospective	Not performed	No tests applied	Not performed	Biopsy, brushing, washing, and EBNA/TBNA	EBNA was the only diagnostic method in few cases	48/72 (66.7 %)		

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1990	Mak et al.(78)	Malignant diagnosis obtained by bronchoscopy. Washing, brushing and biopsy performed.	188	Whittington Hospital	Four experienced pulmonologists	None	Retro-spective	Not performed	None evaluated	Not performed	Biopsy, brushing, and washing, not fluoroscopy	Biopsy, brushing, and washing	109/125 (87.2 %)	35/63 (55.6 %)	
1990	Saita et al.(79)	Endoscopic visible lesion, one operator and one pathologist	142	University of Catania	Experienced pulmonologists	None	Retro-spective	Not performed	None evaluated	Not performed	Biopsy and brushing	Biopsy and brushing for visible lesions	94.1 %	No peripheral lesions included	
1991	Popp et al.(80)	Lesion suspicious of malignancy, later proven malignancy	186	Not described	Not described	Location, endo-bronchial visibility	Retro-spective	Bivariate	Location, endo-bronchial visibility	Not performed	Biopsy, brushing, and imprint cytology from the biopsy, fluoroscopy	Biopsy, brushing, imprint cytology, and histology	Brushing: 119/145 (82.1 %) Biopsy: 134/145 (92.4 %)	Brushing: 31/41 (75.6 %) Biopsy: 28/41 (68.3 %)	
1991	Buccheri et al.(81)	Lesion suspicious of malignancy, proven malignant disease	1045	A. Carle Hospital	Three experienced physicians	Visibility, location	Retro-spective	Bivariate	Location, endo-bronchial visibility	Not performed	Biopsy, brushing, and washing, use of fluoroscopy not described	Biopsy and brushing, washing uncertain.	Biopsy: 85 %, Brushing: 40 %, Washing: 37 %	Biopsy: 71 %, Brushing:17 %, Washing: 37 %	
1992	Pirozynzki et al.(82)	Peripheral lung lesions, no endoscopic findings, BAL performed	145	Not described	Not described	None	Retro-spective	Not performed	None evaluated	Not performed	Biopsy, brushing, TBNA, and BAL, fluoroscopy	BAL should be added	No visible lesions	BAL: 94/145 (64.8 %)	
1993	de Gracia et al.(83)	Lesion suspicious of malignancy, no endobronchial findings	67	Not described	Not described	Radio-graphic pattern	Prospective	Bivariate	Radio-graphic pattern	Not performed	Washing, BAL, post BAL bronchoscopic aspirate, not fluoroscopy	BAL and washing when fluoroscopy is not available	No visible lesions	31/55 (56.4)	
1993	Torrington et al.(84)	Surgery for lesions suspicious of malignancy	91	Walter Reed Army Medical Center	Not described	None	Retro-spective	Not performed	None evaluated	Not performed	Biopsy, brushing, and washing, fluoroscopy in 15 patients	None recommended	No visible lesions	16/79 (20.3 %)	
1994	Debeljak et al.(85)	BAL in lesion suspicious of malignancy	117	Not described	Not described	Size	Prospective	Bivariate	Size	Not performed	Biopsy, brushing, and BAL, fluoroscopy	TBB and brushing	No visible lesions	BAL: 17/61 (27.9 %) TBB: 43/61 (70.5 %) Brushing: 26/61 (42.6 %)	

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1994	Milman et al.(86)	Transbronchial biopsy performed. No endobronchial visible lesions.	405	Gentofte Hospital, University of Copenhagen, Denmark	Not described	Size	Retro-spective	Bivariate	Size	Not performed	Biopsy, fluoroscopy	Bronchoscopy with ≥4 biopsies for central lesions, transthoracic percutaneous needle biopsy for peripheral lesions	No visible lesions	61/125 (48.8 %)	
1995	Castella et al.(87)	TBNA for central and peripheral lesions performed in malignant disease	194	Not described	Not described	Endobronchial visibility	Retro-spective	Bivariate	Endobronchial visibility	Not performed	Biopsy, brushing, washing, and TBNA, fluoroscopy	Add TBNA. (No additional increase in the diagnostic yield of biopsy, brushing and washing)	TBNA: 34/39 (87.2 %)	TBNA: 31/45 (68.9 %)	
1995	Gasparini et al.(88)	Peripheral lesion suspicious of malignancy	1027	Regional hospital of Anacona, Italy	Highly experienced staff	None	Prospective	Not performed	None evaluated	Not performed	Biopsy, TBNA, fluoroscopy, ROSE	Biopsy and TBNA, percutaneous needle if negative	No visible lesions	Biopsy: 218/404 (54.0 %), TBNA: 242/349 (69.3 %), Biopsy and TBNA: 75.4 %	
1995	Piaton et al.(89)	Bronchial aspiration in bronchoscopy	1128	11 different units in France	Not described	None	Retro-spective	Not performed	None evaluated	Not performed	Biopsy and washing, use of fluoroscopy not described	Biopsy and washing	The study does not distinguish between visible and non-visible lesions. Overall detection rate for cancer: Washing: 519/574 (90.4 %)		
1996	Chechani et al.(90)	Solitary pulmonary nodule or mass, no endobronchial visible lesions	49	Harry Truman Hospital, Colombia and Eastern New Mexico medical center Roswell	Not described	Size, sharp border	Prospective	Bivariate	Fuzzy border, size	Not performed	Biopsy, brushing, washing, and TBNA, fluoroscopy	Biopsy, brushing, and TBNA, washing not recommended	No visible lesions	32/40 (80.0 %)	
1996	Govert et al.(91)	Visible lesions, brushing and washing performed	201	Duke University Medical Center	Not described	None	Retro-spective	Not performed	None evaluated	Cost-effectiveness analysis	Biopsy, brushing, and washing	Biopsy and brushing or washing	151/177 (85.3 %)	No peripheral lesions included	
1997	Sing et al.(92)	Lung carcinoma, sputum or brushing performed	415	Robert-Koch-Klinik, University of Freiburg	Not described	Histology, T stage, visibility	Retro-spective	Not performed	No statistical tests applied	Not performed	Brushing, use of fluoroscopy not described	Sputum for peripheral lesions, brushing for central visible lesions	Brushing: 91/142 (64.1 %)	Brushing: 14/64 (21.9 %)	
1998	Aristizabal et al.(93)	Pulmonary nodule or mass without CT sign of endobronchial disease. Final malignant disease.	64	University of Alabama Hospital	Not described	Location, CT bronchus sign	Retro-spective	Not performed	CT bronchus sign	Not performed	Biopsy and washing, fluoroscopy	None recommended	No visible lesions	15/64 (23.4 %)	

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														<3cm	>3cm
1998	Bilaceroglu et al.(94)	Solitary pulmonary nodule, no endobronchial masses	92	Not described	Experienced pulmonologists	CT bronchus sign	Prospective	Bivariate	Ct bronchus sign	Not performed	Biopsy, brushing, TBNA, and washing, fluoroscopy	Biopsy, brushing, and TBNA, washing not recommended	No visible lesions	57/84 (67.9 %)	
1998	Mclean et al.(95)	Lesion suspicious of malignancy	1802	Scottish multi-centre	Various levels of experience	Visibility	Prospective	Bivariate	Visibility	Not performed	Biopsy, brushing, and washing, use of fluoroscopy not described	Biopsy and washing, or biopsy and brushing, perhaps all three	80,00 %	9,00 %	
1998	Wong-surakiat et al.(96)	Non visible peripheral lesions suspicious of malignancy	55	Not described	Not described	Size, histology	Prospective	Not performed	No tests applied	Not performed	Biopsy and BAL, probably not fluoroscopy, but not properly described	BAL should be added for peripheral lesions	No visible lesions	BAL: 14/35 (40.0 %)	
1999	Dasgupta et al.(97)	Endobronchial visible lesions	55	Not described	Not described	None	Prospective	Not performed	None evaluated	Not performed	Biopsy, brushing, washing, and EBNA	TBNA for peribronchial disease, TBNA, biopsy and brushing for exophytic lesions	53/55 (96.4 %)	No peripheral lesions included	
1999	Govert et al.(98)	Endobronchial visible lesions	65	Duke University Medical Center	Not described	None	Prospective	Not performed	None evaluated	Not performed	Biopsy, washing, and EBNA, ROSE	EBNA with immediate cytological interpretation, biopsy, washing and brushing if negative	54/57 (94.7 %)	No peripheral lesions included	
1999	Reichen-berger et al.(99)	Peripheral pulmonary lesion	172	University Hospital of Basel	Not described	Size	Retrospective	Bivariate	Size	Not performed	Biopsy, brushing, washing, TBNA, fluoroscopy	Add TBNA to biopsy, brushing, and washing	No visible lesions	TBNA: 14/50 (28.0 %)	TBNA: 31/46 (67.4 %)
2000	Baaklini et al.(100)	No visible lesions. Biopsy, brushing and washing taken. Final diagnosis available	177	Houston Veterans Affairs Medical Center	Various levels of experience	Size, location	Retrospective	Bivariate	Size, central vs peripheral location	Not performed	Biopsy, brushing, and washing, fluoroscopy	Biopsy, brushing and washing	No visible lesions	97/151 (64.2 %)	
2000	Bungay et al.(101)	Lesion suspicious of malignancy, not pulmonary collapse, proven malignancy	62	Not properly described	Various levels of experience	CT distance, edge, visibility, CT bronchus sign	Retrospective	Bivariate	CT distance, edge, visibility, CT bronchus sign	Not performed	Biopsy, use of fluoroscopy was not described	No recommendation	The study does not divide between visible and non-visible lesions. The overall diagnostic yield for malignant lesions were 38/62 (61.3 %)		

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														<3cm	>3cm
2000	Diette et al.(102)	Lung mass or hilar adenopathy	204	Johns Hopkins Medical Institutions	Various levels of experience	ROCE, fluoroscopy, procedure time, age, Fentanyl dose	Prospective	Multivariate	Age, ROCE, Fentanyl dose	Not performed	Biopsy, brushing, and EBNA/TBNA, the use of fluoroscopy not described, ROSE	On site assessment of the smear is recommended	The study does not divide between visible and non-visible lesions. The overall diagnostic yield for benign and malignant lesions were 61.2 %		
2000	Hsiao et al.(103)	Lesion suspicious of malignancy, proven lung cancer	358	Chang Gung Memorial Hospital	Not described	None	Retro-spective	Not performed	None evaluated	Not performed	Biopsy, brushing, and washing, not fluoroscopy	Biopsy	Biopsy: 201/251 (80.1 %)	Biopsy alone: 58/107 (54.2 %)	
2000	Lam et al.(66)	Lesion suspicious of malignancy, bronchoscopy by one study physician, proven malignant disease	100	Not described	One experienced pulmo-nologist	Location, histology, TNM stage, age, gender	Prospective	Bivariate	None were significant	Not performed	Biopsy, brushing, and BAL, use of fluoroscopy not described	Biopsy and BAL	85/100 (85.0 %) (64 visible lesions, 23 endobronchial abnormalities and 13 peripheral lesions)		
2000	Tang et al.(104)	Peripheral lesion not visible by bronchoscopy, BAL performed	72	Chang Gung Memorial Hospital	Not described	None	Retro-spective	Not performed	None evaluated	Not performed	BAL and biopsy without fluoroscopy	Biopsy and BAL	No visible lesions	27/37 (73.0 %)	
2001	Gunen et al.(105)	Lesion suspicious of malignancy, candidate for surgery, primary lung cancer	75	SSK Süreyya-pasa Center for Chest Diseases	Not described	None	Prospective	Not performed	None evaluated	Not performed	Not described	Blind biopsy from the main carina and upper lobe in addition to biopsies from the lesions	38/38 (100 %)	9/14 (64.3 %)	
2001	Jones et al.(106)	Endobronchial visible lesion, biopsy, brushing and washing performed	514	Hope Hospital	Not described	None	Retro-spective	Not performed	None evaluated	Not performed	Biopsy, brushing, and washing	Biopsy and brushing, screen washing if both are negative	459/514 (89.3 %)	No peripheral lesions included	
2001	Karahalli et al.(107)	Endobronchial visible malignant lesions	98	Not described	Two experienced physicians	None	Retro-spective	Not performed	None evaluated	Not performed	Biopsy, brushing, washing, and EBNA	Biopsy and brushing. TBNA may increase the diagnostic yield.	88/98 (89.8 %)	No peripheral lesions included	
2002	Baba et al.(108)	Endobronchial non visible lesion, resected, below 15 mm, primary lung cancer	91	Not described	Not described	Size, histological differentiation	Retro-spective	Bivariate	Histological differentiation	Not performed	Biopsy, brushing, TBNA, use of fluoroscopy not described	No recommendation, add CT guided needle biopsy	No visible lesions	Below 1,5 cm: 64/81 (79.0 %)	No lesions above 3 cm

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2002	Gaber et al.(109)	Lesion suspicious of malignancy, visible lesion	50	Torbay Hospital	Three experienced physicians	None	Prospective	Not performed	None evaluated	Not performed	Biopsy, brushing, BAL, whole brush	Biopsy, brushing, BAL, not the whole brush	35/39 (89.7 %)	Benign and malignant: 2/11 (18.2 %)	
2003	Bandoh et al.(110)	Solitary pulmonary nodule, curettage and washing performed.	100	Kagawa Medical University Hospital	Various levels of experience	Size, location	Prospective	Bivariate	No significant predictor in the study group	Not performed	Biopsy, washing, and curette, fluoroscopy, reconstruction of CT images	Multiplanar reconstruction of CT images, curettage with ultrafast Papanicolau stain	No visible lesions	82/88 (93.2 %)	
2003	Diaz et al.(111)	Proven pulmonary metastases	113	Not described	Not described	Histology	Retro-spective	Not performed	No tests applied	Not performed	Biopsy, brushing, washing, fluoroscopy	Biopsy and brushing	Bronchial metastases: 48/57 (84.2 %)	Bronchial metastases: 34/56 (60.7 %)	
2003	Kawaraya et al.(112)	Peripheral non visible lesion, proven lung cancer	1372	Not described	Not described	None	Retro-spective	Not performed	No tests applied	Not performed	Biopsy, brushing, washing, curette, TBNA, fluoroscopy	Biopsy, brushing, TBNA, and curettage with imprint cytology and cytology of the rinse fluid	No visible lesions	1212/1372 (88.3 %)	
2003	Skaansar et al.(113)	All bronchoscopies performed	132	Hamar hospital	Various levels of experience	None	Retro-spective	Not performed	None evaluated	Not performed	Biopsy, brushing, and washing, use of fluoroscopy not described	No recommendation	35/41 (85.4 %)	18/37 (48.6 %)	
2003	Trkanjec et al.(114)	Solitary pulmonary nodule, no visible endobronchial lesions, negative sputum	50	Not described	Not described	Size, number of specimens	Prospective	Bivariate	Size, number of specimens	Not performed	Biopsy, biopsy imprint, brushing, washing, BAL, use of fluoroscopy not described	Biopsy and BAL	No visible lesions	25/31 (80.6 %)	
2004	Estarriol et al.(115)	Lung lesion surrounded by healthy lung tissue, visible by fluoroscopy	164	Not described	One experienced pulmonologist	Size, location, CT bronchus sign	Prospective	Bivariate	Size, CT bronchus sign, location	Not performed	Biopsy, fluoroscopy	Only biopsy applied	No visible lesions	29/54 (53.7 %)	84/110 (76.4 %)
2005	Kaçar et al.(116)	Endobronchial visible lesions, biopsy, TBNA brushing and washing performed	95	Not described	Not described	None	Prospective	Not performed	None evaluated	Not performed	Biopsy, brushing, washing, EBNA	Biopsy, TBNA, and brushing	91/95 (95.8 %)	No peripheral lesions included	

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														<3cm	>3cm
2005	van der Drift et al.(117)	Lesions suspicious of malignancy and final malignant diagnosis	221	Not described	Various levels of experience	None	Prospective	Not performed	None evaluated	Cost minimisation analysis	Biopsy, brushing, washing, fluoroscopy	Biopsy and brushing or washing for visible lesions, biopsy and washing for non visible lesions	129/137 (94.2 %)	47/84 (56.0 %)	
2006	Gildea et al.(118)	Peripheral lung lesion or mediastinal lymph node	60	Not described	Two experienced physicians	Size	Prospective	Bivariate	No significant predictors in the study group	Not performed	Biopsy, brushing, TBNA, washing and BAL, fluoroscopy, navigation	Navigation is promising, especially for small lesions	No visible lesions	32/43 (74.4 %)	
2006	Heyer et al.(119)	Solitary pulmonary lesion, above 2 cm, >2 cm from pleura, previous bronchoscopy negative	33	Not described	Two experienced physicians	None	Prospective	Not performed	None evaluated	Not performed	Biopsy, CT guidance	Ct guided bronchoscopic biopsy when bronchoscopy is negative	No visible lesions	>2cm, previous bronchoscopy negative: 11/24 (45.8 %)	
2006	Joos et al.(120)	All bronchoscopies performed	616	Not described	Not described	None	Retrospective	Not performed	None evaluated	Not performed	Biopsy, washing, EBNA/TBNA, fluoroscopy	Add TBNA to biopsy and washing	92 %	Not reported	
2006	Schwartz et al.(121)	Peripheral lesion not visible by bronchoscopy	15	Not described	Not described	None	Prospective	Not performed	None evaluated	Not performed	Biopsy, brushing, fluoroscopy, navigation	Navigation is effective and safe	No visible lesions	6/10 (60.0 %)	
2006	Uchida et al.(122)	Peripheral lesions, fluoroscopy guided, ROCE performed	657	Not described	Not described	ROSE	Retrospective	Bivariate	ROSE	Not performed	Curette, brushing, biopsy, TBNA, fluoroscopy, ROSE, and ultrathin bronchoscopy	ROSE and fluoroscopy guided bronchoscopy	No visible lesions	393/528 (74.4 %) without ROSE, 477/528 (90.3 %) with ROSE	
2007	Eberhardt et al.(123)	Peripheral lesion suspicious of malignancy	89	University of Heidelberg and Harvard University Medical School, Boston	Highly experienced staff (not described)	Size, location	Prospective	Bivariate	No significant predictor in the study group	Not performed	Biopsy, brushing, washing, TBNA, navigation, not fluoroscopy	Add navigation	No visible lesions	42/70 (60.0 %) (Most lesions below 3 cm)	
2007	Lee et al.(124)	Endoscopic visible lesion	230	Three hospitals affiliated with Seoul National University, South Korea	Various levels of experience	Age, gender, smoking, morphology location, histology	Prospective	Bivariate	No significant predictors	Not performed	Biopsy, prebiopsy washing or postbiopsy washing	Biopsy and washing. Pre or post biopsy timing does not matter	200/207 (96.6 %)	No peripheral lesions included	

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														<3cm	>3cm
2007	Liam et al.(125)	Bronchoscopy performed, proven lung cancer	503	Not described	Three experienced physicians	Location, size, endo-bronchial visibility	Retro-spective	Bivariate	Visibility, location of visible lesions	Not performed	Biopsy, brushing, washing, BAL, not fluoroscopy	No recommendation	283/340 (83.2 %)	71/163 (43.6 %)	
2007	Makris et al.(126)	Peripheral lesion, negative bronchoscopy, negative transthoracic needle aspiration	40	Not described	Two experienced physicians	Stage, size, volume, location, depth from pleura	Prospective	Bivariate	No significant predictor in the study	Not performed	Biopsy, navigation, not fluoroscopy, general anaesthesia	Navigation and biopsy	No visible lesions	20/33 (60.6 %)	
2007	Shinagawa et al.(127)	Small peripheral nodules	95	Hokkaido University Hospital	Not described	None	Prospective	Not performed	None evaluated	Not performed	Biopsy, ultrathin bronchoscope, CT-guided, navigation	Ct guided bronchoscopy with navigation	No visible lesions	40/44 (90.9 %)	No lesions above 3 cm
2007	Tachihara et al.(128)	Peripheral lesion surrounded by pulmonary parenchyma, not visible by bronchoscopy	94	Not described	Not described	Size, location	Prospective	Bivariate	Size	Not performed	Biopsy, brushing, fluoroscopy, navigation, standard or ultrathin bronchoscope	Biopsy, brushing, navigation	No visible lesions	Malignant and benign lesions: 60/96 (62.5 %)	No lesions above 3 cm
2007	Tremblay et al.(129)	Visible lesions, no bleeding disorder or cardiac pacemaker	39	Not described	Not described	None	Prospective	Not performed	None evaluated	Not performed	Biopsy, hot biopsy	Hot biopsy is not recommended	35/40 (87,5 %)	No peripheral lesions included	
2008	Danila et al.(130)	Patients where lung biopsy was performed	304	Vilnius University Hospital	Two experienced physicians	None	Retro-spective	Not performed	None evaluated	Not performed	Biopsy, fluoroscopy	Biopsy	No visible lesions described	Benign and malignant disease: 257/304 (84.5 %)	
2008	Kanemoto et al.(131)	Lesion below 2 cm, no visible lesions, brushing, washing and biopsy performed, final diagnosis available	108	Tsukuba Hospital and Tsukuba Medical Center	Various levels of experience	Size	Retro-spective	Bivariate	Size	Not performed	Biopsy, brushing, washing, fluoroscopy	No recommendation	No visible lesions	Below 2 cm: 35/82 (42.7 %)	No lesions above 3 cm
2008	Oki et al.(132)	Localised peripheral lesions, no visible lesions	98	Not described	Various levels of experience	Size, location	Prospective	Bivariate	No significant predictor in the study group	Not performed	Biopsy and washing, fluoroscopy, ultrathin bronchoscope	Ultrathin bronchoscope	No visible lesions	50/68 (73.5 %), (<2cm:77 %,≥2cm:73 %)	

Year	Authors (ref#)	Inclusion criteria	n	Centre	Performing physicians' level of experience	Predictors evaluated	Study design	Statistical analysis of predictors	Significant predictors of a higher diagnostic yield	Cost analysis	Sampling techniques performed, guidance	Recommended combination of sampling techniques	Detection rate for cancer in visible lesions	Detection rate for cancer in peripheral lesions	
														<3cm	>3cm
2008	Ost et al.(133)	Peripheral nodules or masses, mediastinal lymphadenopathy, above 40 years, above 10 pack years, FEV , above 800 ml	50	Not described	One physician	Size	Prospective	Bivariate	Size	Not performed	Biopsy, TBNA, brushing, BAL, fluoroscopy, CT guided bronchoscopy	Ct guided bronchoscopy was not better than conventional bronchoscopy	No visible lesions	33 %	88 %
2008	Roth et al.(134)	Lesion suspicious of malignancy, later proven malignant disease histologically or by follow up	367	Haukeland University Hospital, Bergen, Norway	Various levels of experience	Endo-bronchial visibility, size, distance to carina, location	Retro-spective	Multivariate	Endobronchial visibility, size	Presented in a separate paper(135)	Biopsy, brushing, TBNA, washing, aspiration from the whole procedure, fluoroscopy in 48 of 131 cases	Cost minimisation analysis::Biopsy and TBNA for peripheral lesions, biopsy, EBNA and brushing for visible lesions	108/141 (76.6 %)	5/58 (8.6 %)	17/74 (23.0 %)
2009	Dobler et al.(136)	Visible lesion, final pulmonary malignant disease	155	Liverpool Hospital, Sydney	One physician carried out or supervised	None	Retro-spective	Not performed	None evaluated	Not performed	Biopsy, brushing, and washing	Biopsy, brushing, and washing	136/155 (87.7 %)	No peripheral lesions included	
2009	Franke et al.(137)	Pulmonary nodule or mass, biopsy and transbronchial catheter aspiration performed	51	Not described	One selected	Size, location	Prospective	Not performed	No statistical tests applied	Not performed	Biopsy, transbronchial catheter aspiration, fluoroscopy	Transbronchial catheter aspiration and biopsy	No visible lesions	10/14 (71.4 %)	26/34 (76.5 %)
2009	Iwano et al.(138)	Peripheral lung cancer located distal to the sub-segmental bronchus, virtual bronchoscopy with biopsy performed	122	Not described	Fifteen pulmonologists with 9-23 years of experience	Size, opacity, CT bronchus sign, order of bronchus, location	Retro-spective	Bivariate	Opacity; solid had higher diagnostic yield than non-solid	Not performed	Biopsy, virtual bronchoscopy, fluoroscopy, ultrathin bronchoscopy	Ultrathin bronchoscopy, virtual navigation and biopsy	No visible lesions	54/76 (71.1 %)	42/46 (91.3)
2009	Lamprecht et al.(139)	Peripheral lung lesion traditionally not reachable with bronchoscopy	13	Not described	One selected	Size	Retro-spective	Bivariate	No significant predictors	Not performed	Biopsy, virtual bronchoscopy, ROSE, not fluoroscopy, PET	Biopsy, navigation, ROSE, PET-CT	No visible lesions	4/6 (66.7 %)	2/3 (66.7 %)

Year	Authors (ref#)	Inclusion criteria	n	Centre	Performing physicians' level of experience	Predictors evaluated	Study design	Statistical analysis of predictors	Significant predictors of a higher diagnostic yield	Cost analysis	Sampling techniques performed, guidance	Recommended combination of sampling techniques	Detection rate for cancer in visible lesions	Detection rate for cancer in peripheral lesions	
														<3cm	>3cm
2010	Aktas et al.(140)	Visible exophytic lesions, age above 20 years	41	Not described	Not described	None	Prospective	Not performed	None evaluated	Not performed	Biopsy, cryobiopsy	Cryobiopsy better than conventional biopsy	38/41 (92.7 %)	No peripheral lesions included	
2010	Boon-sarngsuk et al.(141)	Pulmonary nodule or mass with no sign of atelectasis	330	Not described	Various levels of experience	Age, gender, smoking, cough, haemoptysis, size, location, visibility	Retro-spective	Multivariate	Size, visibility	Not performed	Biopsy, brushing, washing, not fluoroscopy	No recommendations, biopsy and washing most important	Benign and malignant: 112/139 (80.6 %)	Benign and malignant: 72/191 (37.7 %)	
2010	Botana-Rial et al.(142)	Peripheral lung lesions, no endobronchial visible lesion	273	Not described	Not described	Size, localisation, bronchus sign	Retro-spective	Multivariate	Size and bronchus sign. Malignant lesions had higher diagnostic yield.	Not performed	Biopsy, fluoroscopy	No recommendations	No visible lesions	Biopsy alone: 114/213 (53.5 %)	
2010	Hautmann et al.(143)	Peripheral lesion not visible by bronchoscopy, non diagnostic bronchoscopy	15	Not described	Not described	None	Prospective	Not performed	None evaluated	Not performed	Biopsy, CT guidance	Ct guided transbronchial biopsy when bronchoscopy fail to reach the lesion	No visible lesions	11/14 (78.6 %)	
2010	Schumann et al.(144)	Visible lesion, oxygen saturation above 90 % with oxygen, age above 18 years	296	University Clinic of Ulm	Not described	None	Prospective	Not performed	None evaluated	Not performed, commented by Medford in a separate paper	Biopsy and cryoprobe biopsy	Add cryoprobe biopsy for visible lesions	Benign and malignant: Cryoprobe: 265/296 (89.5 %)	No peripheral lesions included	
2010	Seijo et al.(145)	Pulmonary nodule or mass	51	Not described	Not described	Bronchus sign, size, distance to pleura, location, PET-CT uptake, distance to nodule	Prospective	Multivariate	CT bronchus sign	Not performed	Biopsy, TBNA, navigation, not fluoroscopy	Navigation is not recommended when CT bronchus sign is absent	No visible lesions	24/32 (75.0 %)	

Figure 2: Detection rates for cancer in endobronchial visible lesions

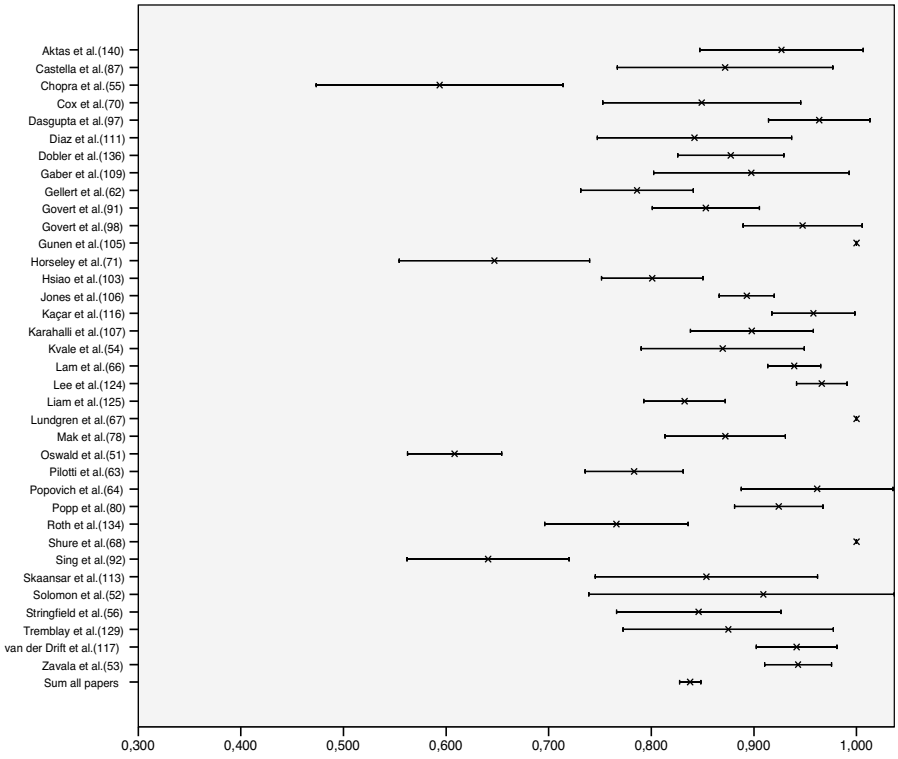
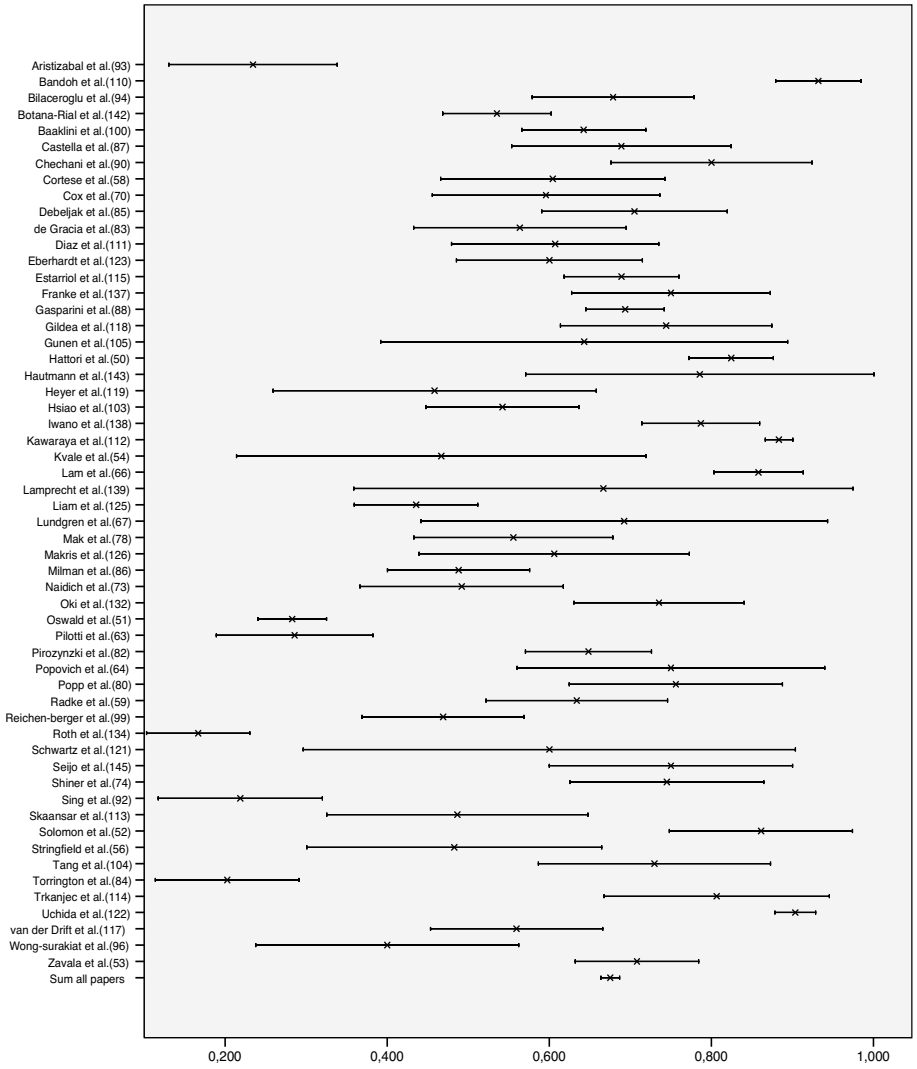


Figure 3: Detection rates for cancer in peripheral lesions



We initiated the work presented in the current PhD thesis in 2005. By then 67 studies had reported detection rates for cancer (Table 2). The first studies were descriptions of diagnostic yields in endobronchial visible lesions and in peripheral lesions(50;51;53). The discussion about the optimal combination of sampling

techniques was introduced by Solomon in 1974(52). Previous papers recommended different combinations of sampling techniques: brushing alone(50;52), biopsy alone(62;68;86;115), biopsy and sputum(51), biopsy and brushing(54;58;59;79;81;85;106), or biopsy, brushing and washing(57;65;69;78;100;146). Some studies used a curette with good results (53;61;76;110), others recommended to add endobronchial needle aspiration (EBNA) for visible lesions or TBNA for peripheral lesions(71;72;75;87;88;90;94;97-99;107;112). Bronchoalveolar lavage (BAL) was recommended in some papers(66;82;96;104;109;114;147). The papers based the recommendations on the diagnostic yields. Many studies were without statistical analyses, some used McNemars test for matched pairs. There were no randomised trials.

When the physician decides the optimal combination of sampling techniques, the increase in the diagnostic yield and the increase in cost must be considered. The discussion of costs was introduced by Kvale et al. in 1976(54). Kvale et al. recommended biopsy and brushing, but not washing. Govert et al. performed a cost-effectiveness analysis in 1996 (91), but the choice of end-point (quality adjusted days) made the analysis hard to interpret. The British Thoracic Society Guidelines on Diagnostic Flexible Bronchoscopy recommended biopsy, brushing, and washing in 2001(148). Rivera et al. recommended addition of TBNA(149). By the initiation of the current study there was a need of a analysis for the optimal combination of sampling techniques that included costs and effectiveness.

As previously mentioned, the choice of sampling techniques is only one of the factors determining diagnostic yield. Previous studies identified different predictors of a higher diagnostic yield. The first studies identified size and endobronchial visibility as possible predictors, but no statistical tests were used to confirm the results(50;51;54). Stringfield et al. identified size and distance from the main carina as significant predictors of a higher diagnostic yield in 1977(56). The predictors of higher diagnostic yield identified before the initiation of the current study were: size(56;59;60;65;85;86;90;99;100;115), location(56;60;65;80;81;115), endobronchial

visibility(80;81;87;95), CT bronchus sign(73;93;94;101;115), and radiographic pattern(90;101;147). With so many different bivariate associations, confounding is a problem unless a multivariate analysis is performed. The only multivariate analysis published before the initiation of the current study was in Diette et al.'s report from 2000. The report analysed only rapid on-site evaluation (ROSE) of the cyto-pathological material(102) and was not adjusted for size or endobronchial visibility.

Figure 2 and Figure 3 displays the diagnostic yields in previous studies for endobronchial visible lesions and for peripheral lesions. Some previous studies were from selected patients or from highly specialised centres where only a few physicians performed the bronchoscopies. There was a need for more studies where all lesions suspicious of malignancy were included and investigated by physicians with various levels of experience.

2.4.2 Studies of bronchoscopy with EBUS miniprobe

Table 3 describes the studies of endobronchial ultrasound with a miniprobe for peripheral lesions. The studies were identified by a search in PubMed and Embase (Search term: (Diagnosis/Broad[filter]) AND (endobronchial ultrasound) AND (lung cancer) AND (peripheral)). Steinfort's metaanalysis(150) and Anantham's review(151) were searched for additional papers. Figure 4 and Figure 5 display the visualisation rates and the detection rates for cancer with confidence intervals, stratified by the physicians' level of experience.

Table 3: Visualisation rates and detection rates for peripheral lesions in studies with an EBUS miniprobe

Year	Authors (ref#)	Inclusion criteria	n	Centre	Performing physicians	Equipment	Study design	Repot of non inclusion	Sample size calculation	Cost analysis	Lesions localised with EBUS		Detection rate for cancer with EBUS		Conclusion
											<3cm	>3cm	<3cm	>3cm	
1992	Hurter et al.(15)	Lesion suspicious of malignancy	100	Not described	Not described	20 MHz rotating probe, balloon for central lesions, guide sheath for peripheral	Prospective cohort	No	No	No	19/26 (73.1 %)		Not reported		EBUS might be an alternative to fluoroscopy for localising peripheral tumours
2002	Herth et al.(152)	Peripheral lesion suspicious of malignancy	50	Not described	Highly specialised staff (not described)	20 MHz rotating probe without guide sheath, only biopsy	Prospective randomised crossover study	No	No	No	46/50 (92 %)		Combined for benign and malignant: 17/21 (80 %)	Combined for benign and malignant: 23/29 (79 %)	EBUS might guide the sampling from peripheral lesions without fluoroscopy, learning curve: 40-50 procedures, tendency to be better than fluoroscopy for lesions below 3cm
2004	Kikuchi et al.(153)	Peripheral lesion surrounded by pulmonary parenchyma and not visible	24	Hokkaido Medical Hospital, Iwamizaw General Hospital	Not described	20 MHz probe with guide sheath and curette, fluoroscopy, biopsy, and brushing	Prospective cohort	No	No	No	19/24 (79.2 %)	No lesions above 3 cm	12/18 (66.7 %)	No lesions above 3 cm	EBUS with guide sheath, brushing and biopsy is safe and effective, a cost effectiveness study is planned
2004	Kurimoto et al.(16)	Solitary pulmonary lesion	150	National Hiroshima Hospital and Hiroshima City Hospital	Not described	20 MHz rotating probe, guide sheath, fluoroscopy, brushing, and biopsy	Prospective cohort	No	No	No	140/150 (93.3 %), 121 in the lesion, 19 adjacent to the lesion		Combined for benign and malignant: 92/124 (74 %)	Combined for benign and malignant: 24/26 (92 %)	EBUS with guide sheath collected samples from peripheral lesions precisely, protected against bleeding and delineated the inner structure of the lesions
2004	Shirakawa et al.(154)	Peripheral lung lesion, no endo-bronchial visible lesions	92	Not properly described	Two experienced physicians	20MHz rotating probe, fluoroscopy, curette, guide sheath at the end of the study, biopsy and brushing	EBUS compared to historical controls. Not intention to treat analysis.	No, only that those EBUS not could be performed in were excluded	No	No	38/50 (78 %) when EBUS was performed, 33 in the lesion, 5 adjacent to the lesion		17/24 (70.8 %)		EBUS had the same overall success rate as non-EBUS, but higher success rate when the probe was localised inside the lesion
2004	Yang et al.(155)	Lesions not visible by broncho-scopy, biopsy attempted, malignant disease	218	Chang Gung Memorial Hospital	Not described	20MHz rotating probe without guide sheath	Retrospective comparison of EBUS and non EBUS	Yes	No	No	114/122 (93.4 %), (366/408 (89.7 %) in the unselected group)		80/122 (65.6 %), <2cm: 6/16 (54.5 %), >2cm: 68/103 (66.0 %)		EBUS can precisely localise peripheral lung cancer and achieve a higher diagnostic yield than non-EBUS

Year	Authors (ref#)	Inclusion criteria	n	Centre	Performing physicians	Equipment	Study design	Report of non inclusion	Sample size calculation	Cost analysis	Lesions localised with EBUS		Detection rate for cancer with EBUS		Conclusion
											<3cm	>3cm	<3cm	>3cm	
2005	Asahina et al.(156)	Peripheral lesion not visible by bronchoscopy	29	Hokkaido University Hospital	Seven experienced physicians	20MHz probe with guide sheath and curette, fluoroscopy, virtual navigation, biopsy, and brushing	Prospective	No	No	No	24/30 (80 %)	No lesions above 3 cm	17/23 (73.9 %)	No lesions above 3 cm	Virtual navigation guided EBUS with guide sheath was safe and effective
2005	Becker et al.(157)	Lesion beyond the visual field of bronchoscopy	30	Not properly described	Highly specialised staff (not described)	Navigation (Superdimension), EBUS miniprobe, biopsy, use of fluoroscopy not described	Prospective	No	No	No	25/30 (86 %)		Benign and malignant: 20/29 (69 %)		Navigation will be a valuable tool for peripheral lesions
2005	Paone et al.(158)	Peripheral lesion, not outpatients, accepting the randomization protocol	206	Not properly described	Two experienced physicians	20 MHz rotating probe, biopsy	Prospective randomised EBUS/non EBUS	Yes	Yes, but not a decision	No	Not reported		24/32 (75,0 %)	24/29 (82.8 %)	EBUS has higher diagnostic yield than non EBUS for lesions below 3 cm
2006	Herth et al.(159)	Peripheral lesion not visible by bronchoscopy and not visible by fluoroscopy	54	Not described	Highly specialised staff (not described)	20 MHz rotating probe, guide sheath, biopsy	Prospective cohort	Yes	No	No	48/54 (89 %) (most lesions below 3 cm)		28/39 (71.8 %) (The lesions were not visible by fluoroscopy)		EBUS were able to guide the samplings from lesions not visible by fluoroscopy
2007	Chung et al.(160)	Peripheral lesion not visible by bronchoscopy, but visualised by EBUS	113	Chang Gung Memorial Hospital	Not described	20 MHz rotating probe, distance measurement in one group, biopsy	Randomised EBUS with/without distance measurement	Yes	No	No	113/158 (71,5 %) were visualised prior to study inclusion		62/82 (75.6 %) in lesions visualised by EBUS		EBUS located within the lesion and distance measurement predicted increased diagnostic yield in a multivariate analysis
2007	Dooms et al.(161)	Pulmonary nodule or solid mass surrounded by pulmonary parenchyma not entirely within 10 mm from pleura	50	Not described	One experienced physician	20 MHz rotating probe, without guide sheath or fluoroscopy	Prospective cohort	No	No	No	37/50 (74.0 %), (<2cm:2/11(18 %), >2cm: 35/39 (90 %))		Benign and malignant disease: 34/50 (68 %), (<2cm:18 %, >2cm: 82 %)		EBUS is effective for detecting and diagnosing peripheral pulmonary masses above 20 mm, but the yield is unsatisfactory for lesions below 20mm
2007	Eberhardt et al.(162)	Peripheral lesion surrounded by parenchyma, no CT evidence for endobronchial disease	118	Thorax Klinik and BIDMC	Highly specialised staff (not described)	General anaesthesia or moderate sedation, 20MHz rotating probe with guide sheath. Superdimension navigation, biopsy	Randomised EBUS/navigation / EBUS and navigation	No	No	No	Not reported		51/63 (81.0 %)		The combination of EBUS and navigation is better than each procedure alone

Year	Authors (ref#)	Inclusion criteria	n	Centre	Performing physicians	Equipment	Study design	Report of non inclusion	Sample size calculation	Cost analysis	Lesions localised with EBUS		Detection rate for cancer with EBUS		Conclusion
											<3cm	>3cm	<3cm	>3cm	
2007	Yamada et al.(163)	Lesion below 3 cm, EBUS performed	155	Hokkaido University Hospital	Eight experienced physicians	20 MHz rotating probe, guide sheath, biopsy, and brushing	Retro-spective	No	No	No	132/155 (85.1 %)		90/128 (70.0 %)	No lesions above 3 cm	The probe within the lesion predicted a higher diagnostic yield, the optimal number of biopsies was five
2007	Yoshikawa et al.(164)	Peripheral lesion surrounded by lung parenchyma, not visible by bronchoscopy	121	Hokkaido Cancer Center	Not described	20 MHz rotating probe, guide sheath, and fluoroscopy. Curette if the lesion was not reached, biopsy, brushing and curetting	Prospective cohort	No	No	No	Not reported		94/107 (87.9 %)		EBUS can be performed without fluoroscopy for lesions above 2 cm, with a bronchial branch to the lesion and when the lesion is solid
2008	Asano et al.(165)	Peripheral pulmonary lesion surrounded by pulmonary parenchyma and not visible by bronchoscopy	31	Gifu Prefectural General Medical Center	Not described	Navigation, thin bronchoscope (4.0mm), 20 MHz rotating probe, guide sheath, biopsy, brushing	Prospective cohort	No	No	No	22/24 lesions (91.7 %)	8/8 lesions (100 %)	16/20 (80.0 %)	7/7 (100 %)	The combination of navigation, thin bronchoscope and EBUS is promising
2008	Fielding et al.(166)	Solitary pulmonary nodule or small sub-segmental infiltrate without endobronchial disease	138	Not described	Not described	2 mm ultrasound probe with guide sheath, biopsy and brushing	Prospective cohort	No	No	No	Not reported		46/73 (63.0 %)		EBUS with guide sheath had fewer cases of pneumothorax than CT FNA when the lesions not touched the visceral pleura
2008	Koh et al.(167)	Peripheral lesion surrounded by lung parenchyma and not visible by bronchoscopy or patients with lymph nodes close to the bronchial tree	38	Royal Melbourne Hospital	Not described	20 MHz rotating probe, guide sheath, fluoroscopy, biopsy and brushing	Prospective cohort	Yes (4 patients with visible lesions)	No	No	Not reported		Benign and malignant lesions: 18/29 (62 %), <3cm:9/18 (50.0 %), >3cm:8/11 (72.7 %)		EBUS makes it possible to take biopsies from small peripheral lesions, but requires a learning curve
2009	Eberhardt et al.(168)	Solitary pulmonary nodule below 20 mm, not visible on fluoroscopy, with malignant characteristics	100	Not described	Highly specialised staff (not described)	20 MHz rotating probe with guide sheath	Prospective cohort	Yes	No	No	<2cm: 67/100 (67.0 %)	No lesions above 3 cm	<2cm: 41/87 (47.1 %)	No lesions above 3 cm	EBUS is safe and effective for lesions below 20 mm
2009	Chao et al.(169)	Peripheral pulmonary lesions detected by EBUS	182	Chang Gung Memorial Hospital	Not described	20MHz rotating probe, not guide sheath, distance measurement with tape, not fluoroscopy, biopsy, TBNA, BAL	Prospective randomised	Yes	No	No	281/362 (77.6 %)		Only results for lesions visualised by EBUS: Benign and malignant disease: without TBNA: 57/94 (60.6 %), with TBNA: 69/88 (78.4 %)		EBUS and TBNA is promising for peripheral lesions. TBNA important when the probe is adjacent to the lesion
2009	Huang et al.(170)	Peripheral lesions surrounded by pulmonary parenchyma without any visible lesions	83	Taiwan University Hospital	Not described	20MHz rotating probe, distance measurement, biopsy, brushing or washing	Prospective cohort	No	No	No	60/83 (72.3 %), <2cm: 17/35 (48.6 %), >2cm: 43/48 (89.6 %)		39/52 (75 %)		Lesion size predicted visualization by EBUS. Location and the position of the EBUS probe predicted the yield

Year	Authors (ref#)	Inclusion criteria	n	Centre	Performing physicians	Equipment	Study design	Report of non inclusion	Sample size calculation	Cost analysis	Lesions localised with EBUS		Detection rate for cancer with EBUS		Conclusion
											<3cm	>3cm	<3cm	>3cm	
2009	Oki et al.(171)	Solitary pulmonary nodule or mass without bronchoscopic visible lesions	71	Nagoya Medical Center	Various levels of experience	20MHz rotating probe 1.4mm, thin bronchoscope (3.4mm), fluoroscopy, biopsy, washing	Prospective cohort	Yes	No	No	65/71 (91.5 %)		35/44(79.5 %), <2cm:;4/6 (66.7 %), >2cm: 31/38 (81.6 %)		EBUS in the combination with a thin bronchoscope was feasible and accurate for the diagnosis of peripheral lesions
2010	Disayabutr et al.(172)	Peripheral lesion without any bronchoscopic visible signs of disease	152	Siriraj Hospital	Not described	Rotating ultrasound probe, distance measurement, fluoroscopy in 52 %	Prospective cohort	No	No	No	150/152 (98.7 %)		58/99 (58.6 %)		EBUS is regarded as safe and accurate
2010	Eberhardt et al.(173)	Small peripheral nodule suspicious of cancer	54	Not described	Highly specialised staff (not described)	General anaesthesia, navigation system with extended working channel, EBUS probe, suction catheter and biopsy	Prospective cohort	All included	No	No	30/55 (54.5 %)	No lesions above 3 cm	Navigation and EBUS: 34/47 (72.3 %)	No lesions above 3 cm	Navigation and EBUS combined is useful with high diagnostic yields, suction catheter performs very well for small lesions
2010	Mizugaki et al.(174)	Small nodule that underwent EBUS TBB with guide sheath and PET. No visible lesions, nodule surrounded by pulmonary parenchyma	107	Hokkaido University Hospital	Eight experienced physicians	20 MHZ rotating probe, guide sheath, curette, fluoroscopy, biopsy and brushing	Retro-spective	No	No	No	79/92 (85.9 %)	No lesions above 3 cm	66/91 (72.5 %)	No lesions above 3 cm	The combination of FDG-PET and EBUS gave a high diagnostic yield
2011	Roth et al.(175)	Lesion suspicious of malignancy, not endobronchial visible lesions	264	Haukeland University Hospital and Aalesund Hospital	Various levels of experience	20 MHz rotating probe, guide sheath, fluoroscopy, curette for guidance, biopsy, brushing, TBNA, washing	Prospective randomised study EBUS/non-EBUS	Yes	Yes	Cost-effectiveness analysis	13/46 (28.3 %)	38/71 (53.5 %)	4/35 (11.4 %)	27/51 (52.9 %)	EBUS did not increase the detection rate for cancer when the procedures were performed by physicians with various levels of experience

Figure 4: Visualisation rates with EBUS

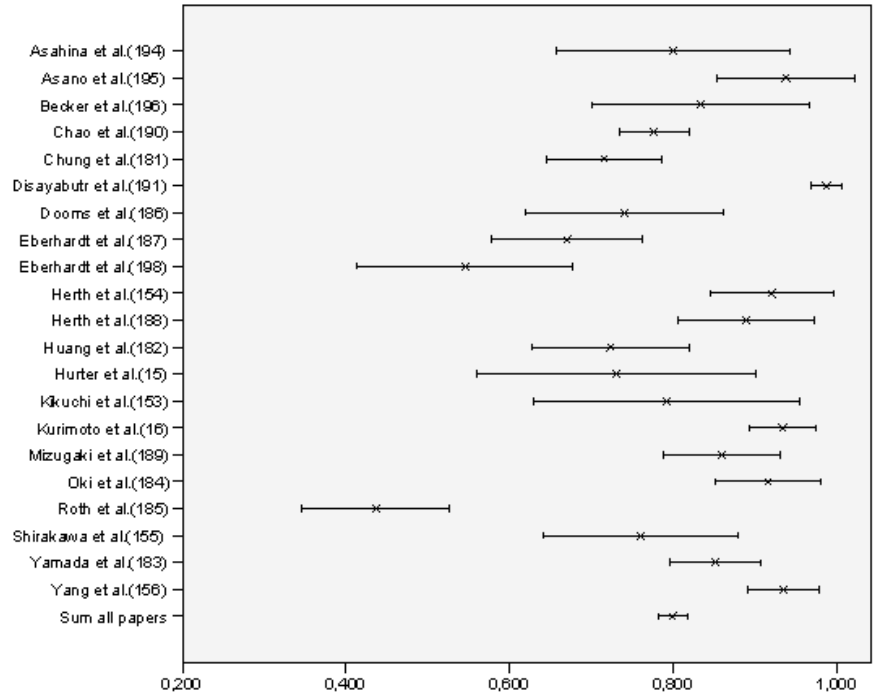
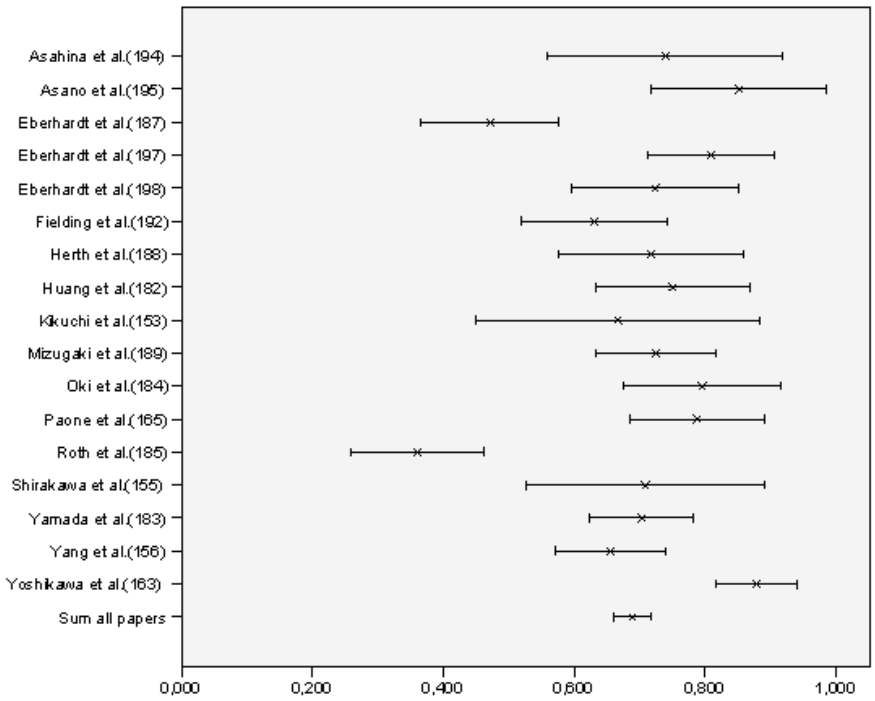


Figure 5: Detection rates for cancer with EBUS in peripheral lesions



Few studies of EBUS with miniprobe were published before the current study was initiated in 2005. In the European Respiratory Society/American Thoracic Society (ERS/ATS) statement on interventional bronchoscopy from 2002, Bollinger et al. concluded that EBUS was promising, but the diagnostic outcome had to be compared in prospective studies(176).

The main challenges with EBUS in the diagnostic approach of peripheral lesions are to visualise the lesion and subsequently to obtain a proper sample from the lesion.

1) Visualisation of the lesions

Hurter et al. visualised 73 % of the lesions in his first report(15). Kikuchi et al. reported a high visualisation rate for lesions below 3 cm (79 %)(153). Kurimoto et al. visualised 80 % inside the lesion and 13 % adjacent to the lesion(16). Overall the visualisation rates in the studies published before 2005 was between 73 % and 93 %(15;16;152-155).

2) Detection rates for cancer

Only studies that reported the detection rate for cancer were included in Figure 5. The detection rates for cancer in studies before 2005 were 55 % for lesions below 2 cm(155), 66.7 % for lesions below 3 cm(153) and overall between 66 % and 71 %(153-155).

There were few comparative studies between EBUS and conventional sampling techniques before 2005. Herth et al. published a randomised crossover study that included 50 patients. They performed most of the procedures in general anaesthesia with highly trained staff. The procedures were performed with EBUS and without EBUS in each patient. The patients were randomised to EBUS first or non-EBUS first. The knowledge of the correct position with EBUS could bias the results from the non-EBUS group. The diagnostic yield for benign and malignant disease was 76 % without EBUS, compared to 80 % with EBUS, but there was a trend for EBUS to be superior for lesions smaller than 3 cm(152). Shirakwa et al. compared the results of EBUS performed by two physicians to a historical group with patients investigated by the same physicians(154). The detection rate for cancer was 71 % with EBUS compared to 70 % in the historical control group without EBUS. Yang et al. retrospectively compared EBUS to non-EBUS(155). The detection rate for cancer was 66 % in the EBUS group compared to 43 % in the non-EBUS group ($p<0.01$).

When the current study was initiated, the usefulness of EBUS was unknown in a setting where pulmonologists at various levels of experience performed the bronchoscopies.

2.5 Evaluation of costs and effectiveness in diagnostic approaches

2.5.1 Cost analyses of strategies

Several analyses are available to evaluate the costs and the effectiveness of diagnostic strategies. The most common analyses are the cost-benefit analysis, the cost-utility analysis, the cost-minimisation analysis and the cost-effectiveness analysis(177). The cost-benefit analysis measures the cost and the outcome (benefit) in monetary values. One type of cost-benefit analysis compares the cost of the strategy to the average willingness to pay for the outcome(178). The cost-utility analysis presents the number of utility measurement units a strategy can achieve. The most common utility-based measurement is the quality adjusted life year (QALY). The cost-utility analysis calculates the number of QALY gained by each strategy. Alternative strategies can be compared by calculations of cost per QALY(179). The cost-minimisation analysis compares the costs of different strategies to a similar outcome(180). All costs of the different strategies are calculated and the costs are compared to find the least costly strategy. The cost-effectiveness analysis compares the increase in cost with the increase in effectiveness. The incremental cost-effectiveness ratio (ICER) gives the costs per life year gained, per symptom free day or for an additional positive sample. These costs can be compared for different strategies and sensitivity analyses can reveal the threshold values for costs and effectiveness measurements(181;182). The threshold values are the highest cost or the lowest effectiveness for the strategy to be

cost-effective. The willingness to pay decides whether a strategy with higher costs and higher effectiveness is cost-effective or not.

2.5.2 Costs

There are different types of costs: the health service costs, the costs held by the patients, and external costs for the society. The health provider's perspective includes only costs for the hospital; the patient's perspective includes only costs for the patient. The recommended perspective is the societal perspective which include all costs for the health provider, the patient, and the society(182). The value of the investment and the reward will be valued differently at different times. An investment in the future is less valued and the value of a future reward is less valued than a present reward. Economical analyses discount the monetary value of the costs and the rewards, but the discussion about the discount rate is not settled. A range between 3 % and 6 % yearly might be appropriate(180;182).

2.5.3 Effectiveness

In the comparison of different combinations of sampling techniques, the increase in the diagnostic yield is easy to interpret. The diagnostic yield can be the effectiveness measurement. The incremental cost divided by the incremental effectiveness (ICER) will represent the cost of an additional positive sample. Another option is to evaluate the average cost to diagnosis for different strategies in a cost-minimisation analysis. Two previous studies analysed costs of different combinations of sampling techniques. Govert et al. introduced quality reduced days as an effectiveness measurement(91). The willingness to pay was calculated to 500$ for avoiding a reduced quality of life day in the diagnostic approach. Biopsy and brushing, or biopsy

and washing was recommended for endobronchial visible lesions. Sensitivity analyses revealed that brushing or washing had to increase the diagnostic yield of bronchoscopy with more than 3 % to be cost-effective. Van der Drift et al. analysed the addition of brushing and washing to biopsy with simulation of costs. The average costs of transthoracic sampling, mediastinoscopy, and thoracotomy were added when a diagnostic sampling technique was removed(117). A cost-minimisation analysis recommended biopsy with brushing or washing for visible lesions. For non-visible lesions, the paper recommended biopsy and washing. Van der Drift et al. stated that there was a need for additional studies that compared costs and effectiveness in combinations of sampling techniques for visible lesions and peripheral lesions.

Paper 2 in the current study presented a cost-minimisation analysis for visible lesions. The analysis assumed that all lesions were diagnosed within three bronchoscopies. The cost-effectiveness analysis in Paper 3 used the diagnostic yield as the effectiveness measurement.

3. AIMS

The main aim of the study was to identify weak points in the diagnostic process of lung cancer, to improve the diagnostic yield, and to avoid the use of unnecessary sampling devices. An effective diagnostic approach will reduce the waiting time for the patient and will be cost-effective for the institution. The current study limited the evaluation of the diagnostic approach to three aims:

(1) To evaluate various predictors for a higher diagnostic yield in bronchoscopy.

(2) To evaluate different combinations of sampling techniques in bronchoscopy of endobronchial visible lesions and peripheral lesions not visible by bronchoscopy.

(3) To evaluate endobronchial ultrasound (EBUS) with a rotating miniprobe for peripheral lesions in a real-life situation among pulmonologists at various levels of expertise.

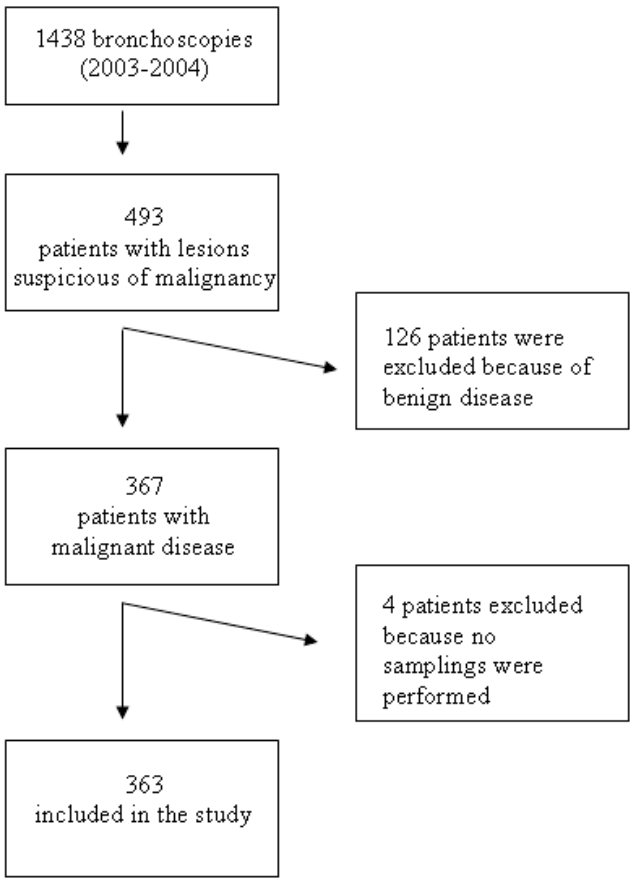
4. MATERIAL AND METHODS

The retrospective cohort study evaluated different predictors of the diagnostic yield in bronchoscopy, and compared different combinations of sampling techniques for visible lesions. The prospective open randomised trial evaluated the effectiveness of endobronchial ultrasound for peripheral lung lesions, and compared different combinations of sampling techniques for peripheral lesions in a cost-effectiveness analysis.

4.1 Study design for the retrospective study

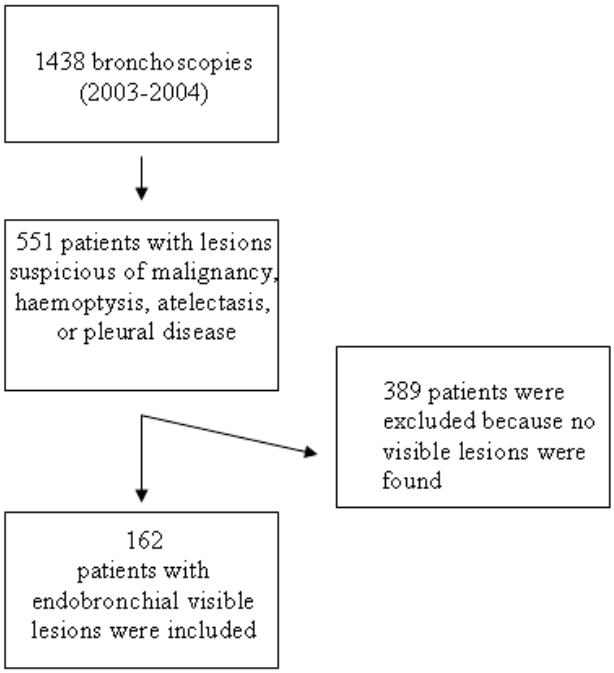
Kjetil Roth (KR) and Tomas Mikal Eagan (TME) read the bronchoscopy reports and registered the indications and the findings in all 1438 bronchoscopies performed in 2003 and 2004 at Haukeland University Hospital. The follow-up included 493 patients with lesions suspicious of malignancy and lasted to November 2005. Of the 493 patients, 367 had malignant disease. We excluded four patients without any samplings. Thus, 363 patients remained in the final analysis presented in Paper 1.

Figure 6: Flow chart for Paper 1:



Paper 1 was restricted to those with a lesion suspicious of malignancy as an indication for bronchoscopy. Patients examined with indications haemoptysis, atelectasis or pleural disease were not included in Paper 1. Paper 2 included all patients among the 1438 bronchoscopies from 2003 to 2004 that had visible lesions. The malignant and the benign lesions were included in the cost-minimisation analysis in Paper 2.

Figure 7: Flow chart for Paper 2:



4.2 Methods for the retrospective study

The bronchoscopies were performed with Olympus BF 1T 160 bronchoscopes, using Boston "Radial Jaw 3" for biopsies, Boston 21 gauche "stifcor" or "eXcelon" needles for EBNA/TBNA, and Boston "Cellebrity" for brushings. Patients were semi-sedated with pethidine hydrochloride 25-75 mg or midazolam 2.5-5 mg. The physicians used fluoroscopy guidance in some of the samplings (48/131or 36.6 %). Twenty-three medical doctors performed the procedures without the help of an on-site cytotechnician. The washing was an aspiration of a sample from the fluid obtained during the whole procedure.

4.3 Data collection in the retrospective study

An electronic search for procedure codes and a manual search in the planning registry for all bronchoscopies performed, detected all bronchoscopies done from 2003 to 2004. The indication for bronchoscopy, the endobronchial findings and the complications was obtained from the bronchoscopy reports. Friedemann Leh (FL) provided the results from the pathological department electronically in systemised nomenclature of medicine (SNOMED) codes. KR and TME retrospectively reviewed the CT scans and the chest radiographs of the patients included in the study; and registered the size and the location of the lesions. To assure that all patients with malignant disease were included in the study, KR reviewed SNOMED codes from the pathological department, the electronically obtained mortality data and all future medical record diagnoses until November 2005. Patients discharged with a lesion suspicious of malignancy were followed manually by repeated searches in the patient medical records until November 2005.

4.4 Processing the data file in the retrospective study

4.4.1 Inconsistencies

KR compared the codes from the patient medical records to the SNOMED codes, any inconsistencies were looked up manually in medical records. The size of the lesions was within the possible range. If the nurse registered that a procedure like biopsy, brushing or TBNA was performed, but no SNOMED code was available, the procedure was regarded as not performed.

Merging errors could occur when the data from the SNOMED registry was merged with the data set. All SNOMED codes obtained were controlled by the diagnosis registry and in patient medical records to avoid merging error.

4.4.2 Missing values

The physicians registered the localisations of the lesions based on the appearance in the CT scan. It was not possible to determine the location in 12 cases. Also, three additional cases had lesions on both sides and thus 15 cases had indeterminate location data. The distance from the lesion to the carina was the distance between the carina and the proximal border of the lesion on the chest radiograph. For the patients without chest radiographs before the procedure, the physicians measured the distance on the scout from the CT scan. It was not possible to measure the distance to carina in 40 patients. In four patients with chest radiographs, it was impossible to see the lesion or to determine the edge of the lesion. In 36 patients without chest radiographs it was impossible to get a CT scout or to use the scout to determine the distance from carina. Both the variables distance to carina and location were included in the multivariate analysis with indeterminate as separate entities.

All sampling techniques (biopsy, brushing, TBNA, and washings) were performed in only 38 cases with visible lesions, 21 cases with compression of a visible bronchus or impression of the lesion into the bronchus, and 4 cases with non-visible lesions. The evaluation of combinations of sampling techniques was restricted to pairs of sampling techniques. For visible lesions, biopsy and EBNA (n=86), biopsy and brushing (n=46), and EBNA and brushing (n=47) were evaluated. For non-visible lesions biopsy and TBNA (n=48), biopsy and brushing (n=42), and TBNA and brushing (n=51) were evaluated. 162 patients were included in the cost-minimisation analysis in Paper 2. 127 were biopsied, 50 underwent biopsy and brushing, and 41 biopsy, brushing, EBNA, and washing.

4.4.3 Variables

Paper 1

The main outcome variable was the detection rate of cancer in the first bronchoscopy. Some patients had multiple bronchoscopies, but only the first bronchoscopy was included in the analysis. The dichotomous outcome variable was positive for a final diagnosis obtained by the first bronchoscopy, and negative for negative or uncertain results from the pathological department. The evaluated predictors for a higher diagnostic yield were distance from carina, localisation, size, and endobronchial visibility. The multivariate analysis included age and gender. Age was categorised in four quartiles. Distance from carina, age, and size were categorised to make the interpretation easier. The size of the lesions was divided into categories resembling Chechani's report from 1996(90). The categories were reduced to only four: I: <2cm, II: 2-3cm, III: 3-4cm, and IV: >4cm. The distance from the carina of 5 cm approximately divided the data set in two. Location was divided into categories by side and by lobe. Mediastinum was treated as a separate entity apart from the lobes. The cases with indeterminate data were treated as separate entities.

Paper 2

The costs of the different sampling techniques were estimated in Norwegian kroner (NOK) 2007-value and adjusted to 2004-value with the consumer price index for Norway. The costs were then recalculated to euro, to be comparable to other countries. The time consumption of the workers in the bronchoscopy lab and in the department of pathology were estimated based on 24 bronchoscopies registered in detail, 25 registries from the pathologist, and 11 registries from the cytotechnicians. Staff in the department of pathology provided expert opinions for some of the time estimations. (Appendix A1 describes the calculation of costs.)

The diagnostic yield for each combination of sampling techniques was the combined diagnostic yield for malignant and benign lesions (average detection rate for cancer and the average ability to give a definite result for benign lesions in the initial bronchoscopy). The cost-minimisation analysis assumed that the diagnostic yields for visible lesions were similar in the first, the second, and the third bronchoscopy. The cost-minimisation model assumed that bronchoscopy secured a diagnosis for visible lesions within three bronchoscopies. A model with different strategies to a final diagnosis was built based upon the diagnostic yield of the different combinations of sampling techniques. The least costly strategy was preferred.

4.4.4 Statistical analyses

Paper 1

Chi-square tests were used to analyse the bivariate relations between the different predictors and the detection rates for cancer. A p-value below 0.05 was considered significant. The Chi-square test is valid for independent samples; it compares the actual distributions to expected distributions. All $(\text{observed-expected})^2/\text{expected}$ are summarised and compared to a Chi-square distribution for the actual degrees of freedom. The p-value represents the probability for the actual distribution to happen by chance.

A multivariate logistic regression analysis was performed to detect confounding. In the logistic regression model the probability for a positive diagnosis (y=1) is defined by a constant (α) and the effect of a variable (βx). $p(y=1)=(e^{\alpha+\beta x}/(1+ e^{\alpha+\beta x})$. Multiple variables can be evaluated: $p(y=1)=(e^{\alpha+ \beta 1x1+\beta 2x2+\beta 3x3\ldots} /(1+ e^{\alpha+ \beta 1x1+\beta 2x2+\beta 3x3\ldots})$ where $\beta_1 x_1$ represents the first variable $\beta_2 x_2$ the second etc. The predictors are significant when the confidence interval for e^{β} does not include 1.

McNemars test was used to compare different combinations of sampling techniques. McNemars test of A and B compares the number of cases with A+B- to the number of cases with A-B+. All statistical analyses in Paper 1 were performed in SPSS(183).

Paper 2

The cost-minimisation analysis was performed in TreeAgePro Healthcare(184). We constructed a decision model based on the diagnostic yield of different combinations of sampling techniques and on the estimated cost for each sampling technique. Only visible lesions were included. We assumed that bronchoscopy secured a diagnosis for all visible lesions within three bronchoscopies. A comparison of costs and diagnostic yields calculated the least costly way to a final diagnosis. Sensitivity analyses were used to compare the costs and the diagnostic yields in the different strategies. The costs and the diagnostic yields were increased and decreased to reveal the threshold values for the least costly strategy.

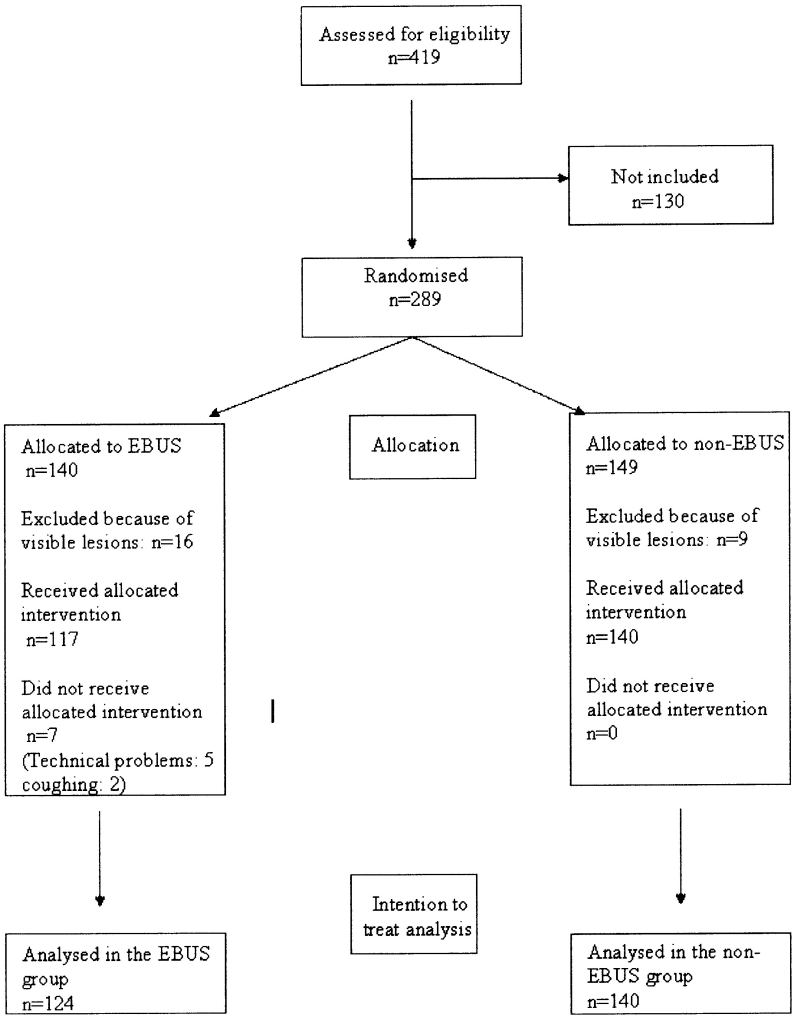
4.5 Approvals for the retrospective study

The Regional Norwegian Ethical Committee (008.05) and the Norwegian Social Science Data Service (12244) approved the retrospective study.

4.6 Study design for the prospective study: study sample

The prospective study was an open randomised trial. The sample size was calculated to 120 patients in both study arms based on a predicted rise in the diagnostic yield from 40 % in the non-EBUS group to 60 % in the EBUS group (standard sample size calculation, α=0.05, power: 90 %). The predicted diagnostic yields were based on preliminary results of bronchoscopy with fluoroscopy in the retrospective study(134) for the non-EBUS group, and on previous studies for the EBUS group(16;152;154;155;164). The inclusion started in June 2005 at the Department of Thoracic Medicine, Haukeland University Hospital, Bergen. In October 2006 Ålesund hospital was included as the second centre. There were 289 patients when the inclusion closed in January 2009. The bronchoscopies revealed 25 patients with unsuspected visible endobronchial lesions, thus 264 patients remained in the study population. Based on a quality registry for all bronchoscopies in the study period, it was possible to identify 130 additional patients that could have been included in the study. These patients had lesions suspicious of malignancy on the CT scan and the bronchoscopy registry reported no visible lesions. The main reasons for non-inclusion were periods with equipment failure, patients not willing to participate, and an incorrect assumption that there was an endobronchial visible lesion based on the CT scan.

Figure 8: Consort flow diagram for the prospective study:

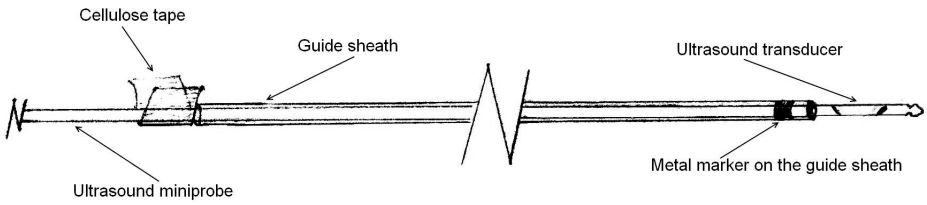


4.7 Methods for the prospective study

Twenty-nine physicians performed the procedures transorally with Olympus BF 1T 160 bronchoscopes. The patients were semi-sedated with pethidine hydrochloride 25-75 mg or midazolam 2.5-5 mg. After reviewing the study information with the potential subject and obtaining informed consent, the physicians opened an envelope revealing randomisation to EBUS or non-EBUS before the bronchoscopy. Prior to the procedure, the physicians identified the optimal segment for sampling by CT scans in both the EBUS group and in the non-EBUS group. After initial inspection of the central airways, the physicians excluded patients with endobronchial visible lesions. Fluoroscopy guided the TBNA, biopsy, and brushing towards the lesion in the non-EBUS group and guided the EBUS probe towards the lesion in the EBUS group.

The EBUS miniprobe was an Olympus 20 MHz 1.7 mm rotating probe with guide sheath. It was marked with cellulose tape proximally to the guide sheath before the bronchoscopy. The cellulose tape marked the position when the ultrasound transducer was just outside the guide sheath orifice. (Figure 9)(16).

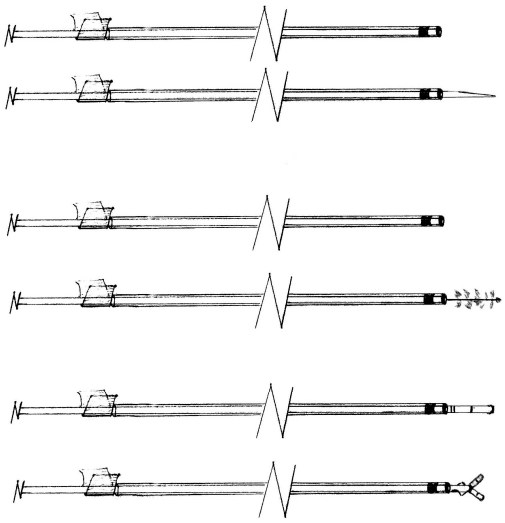
Figure 9: The EBUS miniprobe in the guide sheath



The TBNA needle, the brush and the biopsy forceps were also marked with cellulose tape before the bronchoscopy. The TBNA and the brush were marked with the tip of

the needle sheath or the brush sheath adjacent to the guide sheath orifice. The cellulose tape marked the position where it was possible to open the biopsy forceps just outside the guide sheath (Figure 10).

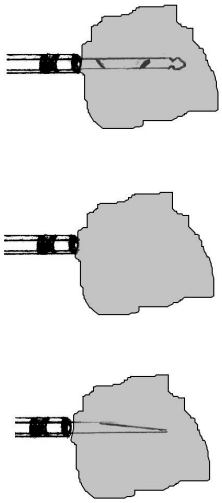
Figure 10: The optimal position for the cellulose plaster on TBNA, brushing, and biopsy



The upper picture displays the retracted position of the device, the lower picture the pulled out or opened position of TBNA, brushing and biopsy.

The miniprobe with a guide sheath was directed towards the lesion guided by fluoroscopy. Only air reflection was seen until contact between the ultrasound miniprobe and the lesion. If the EBUS signal indicated that the probe was inside the lesion, the miniprobe was removed and the samples were taken through the guide sheath as described by Kurimoto(16). A small metal marker on the guide sheath was visible by fluoroscopy to verify the stable correct position of the guide sheath (Figure 9). The guide sheath remained in position just in front of the lesion (Figure 11).

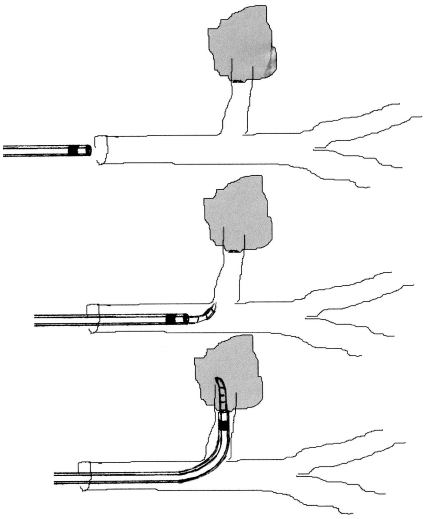
Figure 11: The optimal position of the guide sheath adjacent to the lesion



The ultrasound miniprobe is retracted from the lesion. The guide sheath is left just in front of the lesion. The sampling device is guided into the lesion by the guide sheath.

In difficult cases the miniprobe was removed from the guide sheath and a curette was inserted in order to guide the sheath into the lesion (Figure 12)(153).

Figure 12: A curette can lead the guide sheath into the optimal bronchial branch



Rapid on-site evaluation (ROCE) was available for both groups. The sampling was initiated with two TBNA punctures of the lesions. While the cytotechnicians evaluated the TBNA smears directly in the bronchoscopy lab, the physicians took four biopsies. If the smears were representative, the physicians concluded the investigation with brushing and small volume lavage. He/she repeated the TBNA if the cytotechnicians found the smears to be non-representative. Biopsies and small volume lavage (SVL: 10-20 ml saline was flushed into the actual bronchial branch) were fixed in formalin. TBNA and brushings were fixed in alcohol on a glass slide. In addition, a sample of 10–20 ml aspirated from the suctioned rinsing during the entire bronchoscopy procedure was fixated in formalin. Two hours after the bronchoscopy the patients filled out a form with a visual analogue scale (VAS) where zero was no discomfort and 10 extremely high grade of discomfort during the procedure.

4.8 Data collection in the prospective study

KR performed a simple randomisation without stratification in the computer programme Microsoft Excel. A physician informed the patient about the procedure and asked if the patient would participate in the study. The patient filled in an informed consent form. The physician opened a sealed envelope before the bronchoscopy, with randomisation to EBUS or non-EBUS and excluded patients with visible endobronchial lesion. The physician registered electronically the findings during bronchoscopy for the included patients. He/she measured the sizes and registered the locations based on the CT scans. Whether the lesion was visualised by EBUS or reached by fluoroscopy were registered. KR followed all patients with a non-malignant bronchoscopy conclusion until September 2009 unless operation or autopsy confirmed a malignant diagnosis prior to this. The patients were followed by searches in the patient medical records and by chest radiograph and CT scan descriptions. The final diagnosis was obtained electronically from the SNOMED registry. The diagnosis from the SNOMED code was controlled by diagnoses from the patients medical records and diagnoses in the death registry. A quality registry detected the non-included patients.

4.9 Processing the data file in the prospective study

4.9.1 Inconsistencies

Some reports had inconsistencies between randomisation and EBUS performance. KR controlled these by a manual search in the patient medical records and in the randomisation sheet. Cases with registered EBUS and randomisation to non-EBUS were typing errors. If EBUS not was performed in the EBUS group, KR controlled that the information was true. The codes from the medical records controlled the

SNOMED codes. KR controlled all the final SNOMED codes for each patient with manual searches in the patients' medical records. The size of the lesions was within the possible range.

4.9.2 Typing errors

Typing errors could occur in the data obtained from the physician who performed the bronchoscopy. Typing errors of size and location were possible, but the lesions were within a reasonable range. KR categorised the difficulty to reach the target based on the CT scans. This categorisation was not controlled.

Merging errors could occur when the nurse registry was combined with the data filled in by the physicians and when the SNOMED codes were merged into the data set. KR controlled that the SNOMED codes for each sampling technique were from the same date and the same location. The results were confirmed in the diagnosis registry and by manual follow up in the patient medical records.

4.9.3 Missing values

Though EBUS was not performed in 7 of 124 patients in the EBUS group, these seven cases were included in the intention-to-treat analysis. KR registered the size and the location retrospectively when there was missing data. There were no missing values for baseline characteristics, final diagnoses, or for the predictors of a higher detection rate for cancer. It was not possible to perform biopsy, brushing, TBNA, and washing in all cases. The cost-effectiveness analysis included 178 patients with all sampling techniques performed. The physicians used fluoroscopy in 121 of 124 procedures (98 %) in the EBUS group, 137/140 (98 %) in the non-EBUS group. The procedure time was registered in all cases, but because the SPSS data entry

station(185) made a new file when the programme abruptly was ended, some data were lost and the procedure time was available for only 221 of 264 cases. 175 of 264 patients completed discomfort forms.

4.9.4 Variables

The main outcome variable was the diagnostic yield in peripheral lesions stratified by EBUS. The main analyses of sensitivity, specificity, positive predictive value and negative predictive value included both the malignant and the benign cases. The subgroup analyses and the multivariate analysis included only the cases with malignant disease. Size, endobronchial difficulty, endobronchial visibility, and location were possible predictors for a higher diagnostic yield. Gender and age were not included in the multivariate analysis because there were no significant associations with the outcome. Based on previous randomised studies of endobronchial ultrasound, size was divided into lesions above 3cm and lesions below 3 cm(152;158). KR reviewed all CT scans and classified the endobronchial difficulty grade. Endobronchial difficulty was divided into four categories based on previous reports of the CT bronchus sign(93;94) and comparable to Yoshikawa's three categories(164). The four categories were: I) A bronchial branch straight to the lesion. II) No direct path to the lesion, but one or two divisions to pass beyond the visible divisions. III) No direct path to the lesion, but three or more divisions to pass beyond the visible divisions. IV) No bronchial branch leading to the lesion. The physicians excluded patients with endobronchial lesions, but they did not exclude patients with endobronchial constriction or compression. Endobronchial visibility adjusted the analysis to avoid confounding from constriction and compression. Location was analysed by lobe.

The costs of the sampling techniques were from the values presented in Paper 2, adjusted to euro 2007 value. The willingness to pay for one additional positive sample

was 2800 euro based on the cost of one additional bronchoscopy and the cost of five days in a day ward. The day ward cost was the diagnosis related group (DRG) cost. The willingness to pay for one additional positive sample represented the average cost of a repeated investigation.

4.9.5 Statistical analyses

The bivariate analyses were performed with Chi-square tests when the expected counts in all cells were above 5. The Fisher's exact test was performed when the expected count was below 5. A multivariate logistic regression evaluated the results to avoid confounding and to display interactions. The statistical analyses were performed in SPSS(183) and the interaction was analysed in STATA(186).

The cost-effectiveness analysis was performed in TreeAgePro Healthcare(184). The main outcome was defined as the combined diagnostic yield for malignant and benign lesions in the initial bronchoscopy. All equipment costs and the personnel costs in the bronchoscopy unit and the pathological department were included and ICER was calculated. ICER is the increase in cost divided by the increase in effectiveness. It represents the cost of one additional positive sample. The willingness to pay for one additional positive sample was the average cost for an additional diagnostic procedure. The cost-effectiveness analysis compared different strategies with addition of other sampling techniques to biopsy. Each addition was cost-effective when the ICER was below the willingness to pay. Sensitivity analyses for costs and detection rates for cancer revealed the threshold values for each strategy to be cost-effective.

4.10 Approvals for the prospective study

The Regional Norwegian Ethical Committee (008.05) and the Norwegian Social Science Data Service (12244) approved the retrospective study.

The Regional Norwegian Ethical Committee (69.05) and the Norwegian Social Science Data Service (12562) approved the prospective study. The prospective study had ClinicalTrials.gov number NCT00398970.

5. SYNOPSIS OF PAPERS

The results of these studies are presented in three papers, each published in international peer-review journals:

5.1 Paper 1

Roth, K., Hardie, J. A., Andreassen, A. H., Leh, F., and Eagan, T. M. L. Predictors of Diagnostic Yield in Bronchoscopy: a Retrospective Cohort Study Comparing Different Combinations of Sampling Techniques. BMC Pulmonary medicine 26-1-2010;8(2).

Bronchoscopy is the main diagnostic method in the diagnostic approach for lesions suspicious of malignancy in the lung. The predictors of a higher diagnostic yield can demonstrate the main challenges in the diagnostic process and guide the choice of sampling techniques. It is important to be aware of these predictors in the evaluation of studies of bronchoscopy.

The objective of the first paper was to identify the main predictors for a higher diagnostic yield in bronchoscopy and to compare the diagnostic yield in different combinations of sampling techniques.

The detection rate for cancer was 17 % in lesions not visible by bronchoscopy, 34 % when bronchoscopy revealed constriction or compression from the lesion, and 77 % in procedures with endobronchial visible lesions. Gender, age, size of the lesion, distance from carina, endobronchial visibility, and location (lobe) were analysed as possible predictors for a higher diagnostic yield. Endobronchial visibility, size, and distance from carina were significant in bivariate analyses, but only size and

endobronchial visibility remained significant in the multivariate analysis. Biopsy and TBNA had the highest diagnostic yield among pairs of sampling techniques in visible and non-visible lesions. The combined diagnostic yield for biopsy and TBNA was significantly higher than the diagnostic yield for each sampling technique alone.

5.2 Paper 2

Roth, K., Hardie, J. A., Andreassen, A. H., Leh, F., and Eagan, T. M. L. Cost Minimization Analysis for Combinations of Sampling Techniques in Bronchoscopy of Endobronchial Lesions. Respiratory Medicine 2009;103(6):888-94.

A comparison of different sampling techniques should simultaneously evaluate both costs and the diagnostic yields. The objective of the second paper was to find the least costly strategy for obtaining the final diagnosis of endobronchial visible lesions.

The cost of each sampling technique included the costs in the bronchoscopy unit and the costs in the department of pathology. The equipment costs and the average time consumptions for the different groups of employees were calculated. The model assumed that the diagnostic yield in the second and the third bronchoscopy was similar to the diagnostic yield in the first bronchoscopy and that bronchoscopy secured a diagnosis for all cases within three bronchoscopies. The diagnostic yield for benign and malignant disease increased from 76 % for biopsy alone to 79 % for biopsy and brushing. Biopsy, brushing, and EBNA had a diagnostic yield of 86 %, washing did not increase the diagnostic yield. The cost-minimisation analysis revealed biopsy, brushing and EBNA as the least costly strategy for attaining the final diagnosis. Biopsy and brushing was less costly than biopsy alone when brushing increased the diagnostic yield with 2 % and the cost of brushing was below 83 euro. The combination of biopsy, brushing, and EBNA was less costly than biopsy and

brushing when EBNA increased the diagnostic yield with 5 % and the cost of EBNA was below 205 euro.

5.3 Paper 3

Roth, K., Eagan, T. M. L., Andreassen, A. H., Leh, F., and. Hardie, J. A. A Randomised trial of Endobronchial Ultrasound guided sampling in Peripheral Lung Lesions. Lung Cancer 2011 (In Press);doi:10.1016/j.lungcan.2011.02.013

Endobronchial ultrasound with a guide sheath is a possible tool to increase the diagnostic yield in bronchoscopy of peripheral lung lesions. When the ultrasound transducer is inside the lesion, the ultrasound picture verifies the position. The guide sheath can direct the various sampling techniques into the lesion.

The objective of the third paper was to evaluate endobronchial ultrasound for localising and sampling peripheral lung lesions in a setting with multiple physicians at various levels of experience. A cost-effectiveness analysis evaluated different combinations of sampling techniques in peripheral lesions.

The sensitivity for cancer was 36 % in the EBUS group and 44 % in the non-EBUS group (not significant (NS)). Size and endobronchial difficulty were significant predictors for a higher diagnostic yield. In the multivariate analysis there was an interaction between the use of EBUS and lesion size; lesions smaller than 3 cm had a significantly lower diagnostic yield in the EBUS group compared to the non-EBUS group.

The detection rate for cancer increased from 37 % for biopsy alone to 44 % for biopsy and brushing. The cost increased from 50 euro for biopsy alone to 112 euro for biopsy and brushing. ICER for biopsy and brushing was 1211 euro compared to biopsy

alone. This was below the willingness to pay for one additional positive sample (2800 euro). Additional washing or TBNA had ICER of 4761 euro for biopsy, brushing, and washing and 8262 euro for biopsy, brushing, washing, and TBNA. Both were above the willingness to pay. Biopsy and brushing was the most cost-effective combination of sampling techniques for peripheral lesions when brushing increased the diagnostic yield with minimum 3 % and the cost of brushing was below 142 euro.

6. DISCUSSION

6.1 Discussion of the methods

6.1.1 Study design

A retrospective cohort study analysed different predictors of the diagnostic yield and evaluated different combinations of sampling techniques for endobronchial visible lesions. A prospective randomised trial evaluated endobronchial ultrasound with a miniprobe and different combinations of sampling techniques for peripheral lesions. Generally, a retrospective study is least costly, allows inclusion of all patients, can detect associations between variables, but cannot prove causal relationships between exposure and outcome. Only predictors available before the choice of sampling technique were included in the analysis. Sex, age, size, and location based on the CT results were available before the bronchoscopy. The physician was aware of the endobronchial visibility before the sampling started, thus the analysis included endobronchial visibility as a potential predictor. The histological result was not available before the bronchoscopy.

The main weakness of the retrospective design is the lack of standardisation. The physicians performed the procedures without a protocol. The appearance of the lesions on CT thorax probably influenced the choice of sampling techniques and the use of fluoroscopy. The physicians applied all sampling techniques in only few cases. There was a possibility for a selection bias in the evaluation of sampling techniques.

A randomised controlled trial evaluates the effect of the different randomised modalities on an outcome. The confounding factors will have a similar distribution in the exposed and non-exposed cases, thus there should be no net effect of the various confounding factors. A double blind controlled randomised trial also has the

possibility to eliminate confounding effects of the physician's or the patient's awareness of the modality choice. In an open prospective trial, the choice of modality is random, but physicians and patients will be aware of the assigned groups. A weakness of the prospective trial is the effect of non-inclusion. If the non-inclusion is random, the results are valid. If selection is limited to a restricted group, the result will be valid only for groups with similar limitations. The two main weaknesses of the current prospective trial were the effect of the learning curve and the effect of non-inclusion. The introduction of new modalities will have a learning curve where the diagnostic yield gradually increases. The aim of the study was to evaluate endobronchial ultrasound in a setting where several physicians at various levels of experience performed the bronchoscopies. The high number of physicians who participated resulted in only a few included cases for each physician. The results might have been different with a higher level of experience. The non-inclusion might have introduced selection bias. The results might have been different with another selection.

6.1.2 Validity

Validity of a test is the test results compared to a gold standard. Büttner defined validity as the ability of a diagnostic measure to answer a medical question correctly(187). Sensitivity and specificity compare the test results to a gold standard. Sensitivity is the tests ability to detect positive cases; specificity is the tests ability to score negative cases as negative. The test results will depend on the definition of the gold standard. If only cases with a final pathological malignant diagnosis are included in the gold standard, all cases with clinically defined malignant disease will be excluded. Cases with clinically proven cancer will always have a negative bronchoscopy and the diagnostic yield will be higher if these cases were excluded. If clinically defined malignant disease and malignant disease without reconfirmation are included in the gold standard, these cases will be more prone to false positivity than

the cases with malignant disease confirmed by CT-biopsy, operation or autopsy. The current study tried to reflect a real-life situation. All cases without a confirmed malignant diagnosis were followed clinically. Clinically proven lung cancer was included in the gold standard.

Reliability is the stability of the test. The stability is measured by test-retest reliability, internal consistency or interrater reliability(188). Test-retest reliability measures the ability to give the same result in a repeated test in the same patient. Internal consistency is the ability to get the same result in equivalent patients. Interrater reliability measures the tests ability to get the same result with different observers. It was not considered ethically acceptable to perform repeated bronchoscopies on the patients to measure the reliability of the bronchoscopy results.

6.1.3 Internal validity

The internal validity describes the influence of bias and confounding on the results in the study population. Selection into the study or the information given by the patient are possible systematic errors or biases. Systematic errors and confounding can interfere with the results of the study.

Selection bias

Selection bias appears when the selection process disturbs the study results. In the retrospective study, the physician who performed the bronchoscopy decided on the use of sampling techniques. In very difficult cases, the physician might have chosen washing alone. The comparison of different sampling techniques was probably valid for cases with those sampling techniques performed, but there was a possibility that cases without the actual sampling techniques were different. Even in the prospective study, it was not possible to perform all sampling techniques in every case (all sampling techniques were performed in 178 of 264 cases). The results of the comparison between the techniques might be prone to selection bias. Brushing

increased the diagnostic yield with 9 % (from 64 % to 73 %) in cases with a bronchial branch going directly towards the lesion. The increase was 7 % (from 33 % to 40 %) in cases with one or two bronchial divisions to pass before reaching the lesion, and 5 % (from 23 to 28 %) in cases with three or more bronchial branches to pass before the target lesion. The cases with no bronchial branch to the lesion had no increase in the diagnostic yield with brushing. This exemplifies that a selection of patients based on endobronchial difficulty might influence the choice of sampling techniques.

The predictors for a higher diagnostic yield (size and endobronchial visibility) in the retrospective study were unlikely affected by selection bias. There might have been some missing cases due to wrong identification from the patient medical records, but a systematically selection bias was unlikely.

Non-inclusion in the prospective study was a possibility for selection bias as we later identified 130 additional patients that should have been included in the study. Table 4 compares the non-included patients to the patients in the study. There was a significant higher rate of men in the study population and a trend for more lesions in the upper lobe for the non-included cases. Reluctance of women to participate in randomised studies might be an explanation for the difference in gender. Location and gender were not significant predictors of the diagnostic yield in the study. A difference in size between the groups was expected if the physicians were reluctant to include the difficult cases. There were no differences in size between the included and the non-included cases.

Table 4: Comparison of the included and the non-included cases

	Included in the study	Not included in the study	p
Sex			<0.01
Male	64 %	51 %	
Female	36 %	49 %	
Lobe			0.06
Upper lobe	53 %	63 %	
Middle lobe/Lingula	14 %	6 %	
Lower lobe	34 %	32 %	
Size			0.12
<2cm	27 %	20 %	
2-3cm	18 %	28 %	
3-4cm	18 %	19 %	
>4cm	37 %	33 %	

It seems unlikely that the difference in gender influenced the results, but selection bias from other unknown factors cannot be ruled out. The similar distribution of size among the included and the non-included cases suggests that the effect of selection bias was probably small.

Information bias

Information bias can occur when there is a systematic error in the information given by patients or the health providers. The most common information bias is recall bias. Sick patients remember more than healthy patients do. In an open randomised study, the investigator can register different information from a procedure with intervention, than from a procedure without an intervention because he or she is prejudiced about the intervention.

The information in the retrospective study was from the physicians' registrations in the patients medical records. The investigator who registered the medical records was blinded for the final diagnosis of the patient at the time when he registered the findings. In the prospective randomised trial, the physicians performing the

bronchoscopies registered the findings. The randomisation was open, but the physician was not aware of the final diagnosis when he/she registered the information. Only the registration of the size of the lesions was prone to information bias due to the open randomisation. The pathologists were not aware of the randomisation when the diagnoses were reported. KR classified endobronchial difficulty blinded for the randomisation.

Confounding

Confounding is when other factors, known or unknown, influence on the measured association between an exposure of interest and a given outcome. The confounding factors are extraneous to the suggested pathway(189). Confounding can disturb the results of a cohort study. Randomisation effectively excludes confounding if the distribution of the confounding factors is even among different groups. Thus, the evaluation of EBUS was probably not confounded, but the analysis of different predictors for a higher diagnostic yield might have been confounded in the retrospective or in the prospective study. The current studies did not include histology as a possible predictor of the diagnostic yield, though some previous studies have(59;66;69;92;96;108;111;124). The physician is not aware of the tumour histology when he/she chooses the guidance methods or the sampling techniques for the bronchoscopy procedure. The difference in endobronchial visibility of different cancer types might have confounded the results of histology being a predictor in previous studies. Sing et al found a central location for small cell lung cancer in 17/23 (74 %) and for adenocarcinoma in 25/64 (39 %)(92).

To minimise confounding, the current study presented bivariate analyses and multivariate analyses. The bivariate analyses revealed whether the association between the predictor and the outcome was significant or not. To consider the confounding effect and to adjust the known predictors properly, multivariate analyses were performed. Even though the known predictors of a higher diagnostic yield were included in the retrospective and the prospective multivariate analyses, residual confounding could still exist.

Interactions

Interactions appear when the effect of the association between the variable of interest and the outcome is inconsistent in different categories of the variable. To avoid confounding by interactions the data can be stratified and the effect visualised in different strata of the actual variable(190). There was one interaction between size of the lesion and use of endobronchial ultrasound in the prospective study. The stratified data revealed that endobronchial ultrasound had a lower diagnostic yield than conventional bronchoscopy for small lesions. The physicians performing the procedures in our study were just starting to learn how to use EBUS. Small lesions can be difficult to identify with EBUS and small movements on the guide sheath can displace the sampling position. Thus, the skills of the operator might be more important for small lesions than for large lesions.

6.1.4 External validity

The external validity evaluates whether the effects found in the study can be extrapolated to the target population under consideration or not(191). The inclusion and exclusion criteria and the description of the study population are important factors for external validity. To consider if studies of bronchoscopy are generally relevant, the characteristics of the included patient group, the physicians' level of experience, and the cost level in the country being studied, should be analysed.

Inclusion criteria, exclusion criteria and patient characteristics

Retrospective study

A wide inclusion secured that all patients were evaluated. Only four cases where no sampling techniques were attempted were excluded. All patients with suspected malignant disease were included, not only those with a confirmed malignant diagnosis. The retrospective nature of the study made it possible to include cases at all levels of difficulty. We believe that the main results of bronchoscopy and the detection of predictors for a higher diagnostic yield in the current study population can be generalised to other centres where pulmonologists at various levels of experience perform the bronchoscopies. Only cases with the actual sampling techniques performed were included in the analysis of the optimal combination of techniques. Thus, the results might not be valid for all kinds of lesions.

Prospective study

All cases where physicians found peripheral lesions on CT scans were to be included. Lesions that were deemed likely to be visible by bronchoscopy were to be excluded. The patient characteristics revealed that small lesions and hard-to-reach lesions were included. The non-included cases were not significantly different regarding size. The results can be generalised for patient populations where all kind of peripheral lesions are included. Previous studies indicated that endobronchial ultrasound should be reserved for small lesions(158) and patients with no CT bronchus sign should be excluded(164). The subgroup analyses from the current study did not support this selection.

The performing physicians' level of experience

The physicians that performed the bronchoscopies in the retrospective study and the prospective study were unselected and with various levels of experience. Most of the physicians were specialists in pulmonology, but trainees participated as well. The results of the study can be used in a setting where physicians at various levels of experience perform the bronchosopies. The results of the study may not be applicable to a practice where only selected sub-specialists in bronchoscopy or endoscopic ultrasound perform the procedures.

The level of costs

The cost-minimisation analysis in Paper 2 was dependent on the level of costs in the health care system being studied. The equipment costs may be similar in different countries, but the wages for the staff and the cost of the waiting time for the patient will probably be valued differently. The sensitivity analysis in Paper 2 demonstrated that the results can be generalised if the cost of one day in a day ward was valued above 311 euro, the total cost of brushing was below 83 euro and the total cost of EBNA was below 205 euro.

The cost-effectiveness analysis in Paper 3 compared increase in cost to increase in the diagnostic yield. The willingness to pay for one additional positive sample will depend on how each health care system values the waiting time and the cost of an additional diagnostic procedure. The sensitivity analysis in Paper 3 revealed that the result can be generalised if the cost of brushing was below 142 euro. Acceptability analyses (not published) revealed that the result can be generalised if the willingness to pay for one additional positive sample was above 1350 euro and below 4350 euro.

6.1.5 The STARD initiative and the CONSORT statement

The Cochrane Diagnostic and Screening Test Methods Working Group initiated a working group for improved quality of reporting diagnostic studies in 1999. The

Standards for Reporting of Diagnostic Accuracy (STARD) was published in 2003(192). STARD is a 25-item checklist that guides publications and help readers to judge the potential bias in studies. The checklist clarifies the selection of participants, recommends a description of methods and results. Paper 1 presented a retrospective cohort study that reported diagnostic accuracy; the STARD checklist guided the publication. Paper 1 did not describe test reproducibility (point 13) due to the consideration that it was unethical to repeat the bronchoscopy in the patients. The time from test to final diagnosis (point 17), was available, but not described in Paper 1.

The Consolidated Standards of Reporting Trials (CONSORT) statement was published in 1996(193) and revised in 2001(194). The CONSORT statement intended to improve the reports from randomised controlled trials. It recommends that design, conduct, analysis, and interpretation should be available for the reader with complete transparency from the authors. The checklist describes a recommendation for the report of inclusion, a clarification of the outcome, a presentation of the sample size settled, and the randomisation process. The presentation of the results is summarised in the report. CONSORT recommends complete transparency from the authors for the type of analysis (intention-to-treat analysis or not) and for the number of subgroup analyses performed. A flow diagram visualise the recruitment of cases into the study. It describes the non-included cases, the excluded cases and the cases lost to follow up. Paper 3 was a randomised controlled trial, it presented the CONSORT flow diagram and the checklist guided the publication.

6.2 The main methological strengths and weaknesses in the current study

6.2.1 The retrospective study

Strengths

Design: The retrospective cohort study included all plausible patients, thus sample-selection bias was unlikely.

Validity: A clinical gold standard controlled the results concerning the final diagnosis.

Bias and confounding: The electronically obtained information avoided information bias. Multivariate analyses allowed for control of confounding factors based on the results of bivariate analyses.

Statistical analysis: A cost-minimisation analysis compared the increase in cost to the increase in diagnostic yield. Sensitivity analyses found threshold values for costs and increases in diagnostic yields.

External validity: It is possible to generalise the results to a practice where physicians at different levels of experience do the bronchoscopies.

Weaknesses

Design: A prospective cohort study allows for better planning of the bronchoscopy procedure, registers the possible predictors and standardise the choice of sampling techniques. The choice of sampling techniques, and whether to use fluoroscopy, was left to the physician to decide in the retrospective study.

Validity: The gold standard was a confirmed pathological diagnosis for some patients, but only clinical follow up for other patients. A presumed effect of cytostatic drugs might hide a false positive bronchoscopy result in the clinical follow-up.

Bias and confounding: The non-standardised selection of sampling techniques made the result for each sampling technique prone for method-selection bias. Even though known predictors of a higher diagnostic yield adjusted the multivariate analysis, unknown factors could confound the results.

Statistical analysis: The cost-minimisation analysis visualise all costs to a common end-point, but the result of a cost-effectiveness analysis is easier to compare to other studies. The cost-minimisation analysis does not reveal the price for one additional positive sample.

External validity: The results cannot be generalised to a practise where only highly trained staff perform the procedures. The choice of sampling techniques and guidance was not standardised due to the retrospective nature of the study.

6.2.2 The prospective study

Strengths

Design: The sample size calculation gave the inclusion number. The prospective design made it possible to plan the investigations and to do the bronchoscopies standardised. The prospective randomised study is the best study design to evaluate a diagnostic tool. The intention-to-treat analysis resembles a clinical situation where the equipment might fail during the procedure.

Validity: A gold standard based on reconfirmation of the pathological results and clinical follow-up controlled the results. The reconfirmation made it possible to describe false positive cases. The clinical follow-up avoided exclusion of false negative cases.

Bias and confounding: There was no difference in tumour size between the non-included cases and the included cases. A randomised design and a multivariate analysis protected the analysis against confounding.

Statistical analysis: Paper 3 presented all subgroup analyses performed. A multivariate analysis controlled the bivariate analyses. The comparison of different combinations of sampling techniques compared the increase in cost to the increase in diagnostic yield. Sensitivity analyses revealed threshold values.

External validity: The results are comparable to other centres for bronchoscopy of peripheral lesions when pulmonologists at various levels of experience perform the investigations.

Weaknesses

Design: The non-inclusion represented a threat for selection bias. The study did not evaluate the learning curve of the physicians.

Validity: The gold standard was a confirmed diagnosis of malignancy in some cases and clinical follow-up in other cases. The clinical follow-up could have hidden false positive cases if the patient got treatment and the lesion disappeared. If the tumour was growing very slowly, false negative cases could theoretically be undetected.

Bias and confounding: The cases not included represented a threat for selection bias. The selective evaluation of the cases with all sampling techniques performed was prone to selection bias.

Statistical analysis: Introduction of diagnostic yield as an endpoint in the cost-effectiveness analysis made it difficult to compare the results to other studies. The publication of subgroup analyses might be a risk for detecting p values below 5 % by chance (type I mistake). Paper 3 did not present a Bonferroni correction (division of the significance level by the number of subgroup analyses).

External validity: The results might not be valid in a centre where highly trained staff performs the bronchoscopies.

6.3 Discussion of the main results

6.3.1 The main recommendations for bronchoscopy in published reviews

When the British Thoracic Society published their guidelines for bronchoscopy in 2001, they distinguished between visible lesions and peripheral lesions(148). The guidelines recommended a diagnostic yield above 80 % for visible lesions. They recommended fluoroscopy for localised peripheral lesions and the combination of biopsy, brushing and washing based on the papers from McLean et al.,(95) Gellert et al.,(62) and Mak et al.(78) The guidelines did not recommend TBNA or curettage.

Schreiber et al. described the diagnostic yield of different sampling techniques for endobronchial visible lesions and for peripheral lesions in 2003(48). The size of the peripheral lesions was a predictor for the diagnostic yield. Few of the studies in Schreiber's report included all patients with suspected lung cancer(48).

Rivera et al. recommended bronchoscopy for central lesions and transthoracic needle aspiration for peripheral lesions in 2003. The paper recommended re-evaluation of benign results from central lesions to avoid false negative cases. The updated 2007 paper recommended an EBUS radial probe as the diagnostic approach for lesions below 2 cm when performed by expert hands(49).

Ernst et al. published the recommendations for radial EBUS probe in 2003(46). EBUS was an extraordinarily safe procedure to visualise lesions, to describe tumour invasion and for differentiation between vascular and non-vascular structures. The paper recommended that trainees performed at least 50 procedures with EBUS with balloon to establish competency of the anatomic structures of mediastinum, but did not recommend a number for competence in peripheral lesions.

Chhajed et al. recommended conventional bronchoscopy with fluoroscopy first for peripheral lesions. If the result was negative, EBUS, navigation or CT-guided sampling was recommended(195).

When Herth et al. described the future of bronchoscopy in 2006 he described endobronchial ultrasound, electromagnetic navigation, and autofluorescence endoscopy as the recent developments in bronchoscopy(196). The paper recommended that the newest tools should be available and that specialists should have sufficient knowledge of the tools to improve the diagnostic yield and the exact staging of cancer.

EBUS-TBNA and transoesophageal ultrasound-guided fine-needle aspiration are new complementary techniques that can reduce the need for mediastinoscopy(197).

The current study published the diagnostic yield in endobronchial visible lesions and in peripheral lesions for physicians with various levels of experience. It evaluated predictors of a higher diagnostic yield and controlled the already recommended combination of sampling techniques. Among the different new development in bronchoscopy, this study evaluated endobronchial ultrasound with a miniprobe.

6.3.2 Benign lesions

The main challenge in bronchoscopy is to get a representative sample from malignant disease in the lung. Rivera et al. and Schreiber et al. included only detection rates for cancer in the summaries of published evidence(48;49). It is possible to get a final diagnosis by bronchoscopy for some benign lung tumours. An answer from the pathological department with hamartoma or tuberculosis is probably a definite diagnosis, but inflammation can be malignant disease. 136 cases in the retrospective study had at least one sample with inflammation, 127 (93%) of these cases had a final malignant diagnosis. None of the benign cases in the retrospective or the prospective

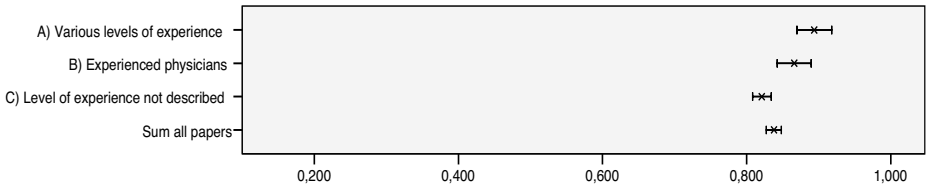
study got a final diagnosis by the first bronchoscopy. The benign cases were included in the cost analyses because the recommended combination of sampling techniques will be used in benign and malignant lesions.

6.3.3 Diagnostic yield in bronchoscopy

Endobronchial visible lesions

The recommended diagnostic yield of 80 %(148) in visible lesions is probably possible to achieve. The average detection rate for cancer in the studies presented in Table 2 was 4022/4782 (84 %). Figure 13 visualises the detection rate for cancer in papers with experienced physicians and from studies with physicians with various levels of experience. The level of experience did not predict the detection rate for cancer in visible lesions.

Figure 13: Detection rates for cancer in endobronchial visible lesions



The papers included in Figure 13: A(56;68;113;117;124;134), B(67;78;107;109;125;136), and C(51-55;62-64;70;71;80;87;91;92;97;98;103;105;106;111;116;129;140;146)

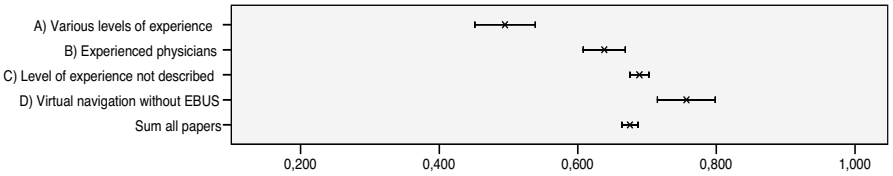
The papers published after 2004 had detection rates for cancer above 80 % for visible lesions(106;116;117;124;125;129;136;140). Even though Paper 1 presented a detection rate for cancer of 77 %, slightly below the recommended, selected cases in

Paper 2 had a detection rate for cancer of 90 % when biopsy, brushing, and EBNA was performed by physicians with various levels of experience.

Peripheral lesions not visible by bronchoscopy

There is no recommended minimum diagnostic yield for peripheral lesions. The average detection rate for cancer was 69 % in a summary published in 2003 by Schreiber et al.(48) and 78 % in a the summary from Rivera et al.(49). Figure 14 visualises that the results from the peripheral lesions depend on the physicians' experience. Visible lesions are easy to detect and to sample, the path to peripheral lesions can be hard to identify.

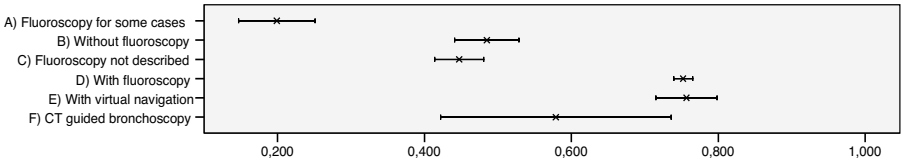
Figure 14: Detection rates for cancer in peripheral lesions



The papers included in Figure 14: A(56;100;113;117;132;134), B(67;74;78;88;94;115;119;125;137), C(50-54;58;59;63;64;70;73;80;82-85;87;90;92;93;96;99;103-105;111;112;114;122;142;143;146), and D(110;118;121;123;126;138;139;145)

The average detection rate for cancer in papers presented in Table 2 was 4179/6190 (68 %) for peripheral lesions. Paper 1 presented a detection rate for cancer of 17 %. The main reasons for the difference between the results from our study and in the previously published studies were probably the use of fluoroscopy, the physicians' levels of experience, and the difference in selection of patients. Figure 15 displays the difference in results from studies with fluoroscopy and studies without fluoroscopy.

Figure 15: The effect of guidance on the detection rate for cancer in peripheral lesions



The papers included in Figure 15: A(54;84;134), B(63;70;78;103;104;125), C(51;64;73;92;96;105;113;114;146), D(50;52;53;56;58;59;67;74;82;83;85-88;90;93;94;99;100;111;112;115;117;122;132;137;142), E(110;118;121;123;126;138;139;145), and F(119;143)

Paper 1 was from a retrospective study where the physicians individually decided on the sampling techniques and the use of fluoroscopy. The physicians used fluoroscopy in only 48/131 (37 %) of the cases. The detection rate for cancer was 17/48 (35 %) with fluoroscopy and 4/83 (5 %) without fluoroscopy. This result was comparable to the results presented in the Scottish multicentre study with a detection rate for cancer of 9 %(95). Paper 3 controlled the results from Paper 1 performed with fluoroscopy. Physicians in the non-EBUS group had a detection rate for cancer of 44 % when fluoroscopy guided the biopsies and brushings. This is comparable to the average results from studies where physicians with various levels of experience performed the bronchoscopies (Table 2: 246/501 (49 %)).

A weakness of many previous reports was the lack of description of the physicians' level of experience. Another weakness was the selective inclusion of patients. Some reports included only patients with a histological proven malignant diagnosis(51;56-58;61;63;64;66;67;69;70;72;81;92;93;101;105;108;111;112;125;131;146), others only those with some specified sampling techniques applied(82;85-87;104;130;131;137). Lesions had to be visible by fluoroscopy in one report(115), other reports included only small lesions below 3 cm(61;76;108;127;128;131). These selections might have influenced the diagnostic yields. The diagnostic approach to small peripheral lesions is different from study centre to study centre. Some try to take biopsies from these difficult-to-reach lesions; others only do washings or refer the patients directly to CT-guided biopsy or operation. The current study included all small peripheral lesions. Other studies might have excluded these lesions without reporting the exclusion.

The studies presented in Table 2 have shown that a detection rate for cancer in peripheral lesions of 70 % is possible to achieve when experienced physicians perform the bronchoscopies in selected patients. Paper 1 and Paper 2 suggest that a detection rate for cancer of 40 % is a more realistic estimate for a situation where physicians at various levels of experience perform the bronchoscopies in an unselected patient sample.

6.3.4 Predictors of a higher diagnostic yield in bronchoscopy

Studies published before initiation of the current study evaluated predictors of a higher diagnostic yield in bivariate analyses. The main weakness of those analyses was the possibility for other factors to confound the results. Diette et al. presented a multivariate analysis, but the analysis was not adjusted for size or endobronchial visibility(102). Size and endobronchial visibility were significant predictors of a higher diagnostic yield in the multivariate analysis presented in Paper 1. After this publication, Boonsarngsuk et al. presented a multivariate analysis with a similar result(141). Botana-Rial et al. and Sejo et al. excluded the visible lesions and presented multivariate analyses for predictors of the diagnostic yields in peripheral lesions(142;145). CT bronchus sign and size were significant predictors in Bontana-Rial et al.'s study without navigation(142) while Sejo et al. found CT bronchus sign to be the only significant predictor in bronchoscopy with navigation(145).CT bronchus sign is the presence of an endobronchial pathway to the lesion. When a physician uses the CT scan to plan the bronchoscopy, a lesion with a bronchial branch straight from the main bronchus is regarded as easy-to-reach. Yoshikawa et al. presented endobronchial difficulty in three categories (clear, possible, and impossible). The current study tried to design a less subjective classification based on how many bronchial divisions the sampling device had to pass beyond the visual field. Paper 3 divided endobronchial difficulty into four categories. (I: a bronchial branch straight to the lesion, II: no direct path to the lesion, but one or two divisions to pass beyond the visible divisions, III: no direct path to the lesion, but three or more divisions to pass beyond the visible divisions, and IV: no bronchial branch leading to the lesion). Endobronchial difficulty was significant in bivariate and multivariate analyses. In the analysis of the non-EBUS group in Paper 3, size in four categories (<2cm, 2-3cm, 3-4cm, and >4cm) was significant in a bivariate analysis, but not significant in a multivariate analysis (data not presented in Paper 3). Based on results from Paper 1, Paper 3 and the multivariate analyses from other publications, data should be analysed separately for endobronchial visible lesions and for peripheral

lesions. In peripheral lesions, endobronchial difficulty or CT bronchus sign is the most important predictor of the diagnostic yield, the effect of size is uncertain.

6.3.5 The optimal combination of sampling techniques in bronchoscopy

Paper 2 recommended biopsy, TBNA, and brushing for endobronchial visible lesions based on a cost-minimisation analysis. Paper 3 recommended biopsy and brushing for peripheral lesions based on a cost-effectiveness analysis. Studies published after the initiation of the current study recommended different combinations of sampling techniques for peripheral lesions. The recommendations have been biopsy, TBNA, and brushing(116), biopsy and washing(124), biopsy and brushing or washing(117), biopsy, brushing, and washing(136), biopsy, brushing, and TBNA(116), biopsy, washing, and TBNA(120), or transbronchial catheter aspiration and biopsy(137). Cryoprobe biopsy has been recommended for visible lesions(140;144), while hot biopsy did not give additional value(129). Most papers compare the diagnostic yields without any analyses of the costs. Govert et al. presented a cost-effectiveness analysis before the initiation of the current study. The end-point was reduced quality days(91). The analysis recommended a combination of biopsy and brushing or washing for endobronchial visible lesions. Biopsy, brushing, and washing were analysed. Reduced quality days is not a widely accepted end-point. The willingness to pay for a reduced quality day is hard to estimate. A sensitivity analysis revealed that brushing or washing had to increase the diagnostic yield with 3 % to be cost-effective.

Van der Drift et al. presented a cost-minimisation analysis in 2005. The title indicated a cost-effectiveness analysis, but the study was actually a cost-minimisation analysis of the addition of washing or brushing to biopsy(117). The study recommended a combination of biopsy and brushing or washing for visible lesions. For peripheral lesions, the combination of biopsy and washing was most economical. The paper did

not present sensitivity analyses of the results. A cost-minimisation analysis reveals the least costly strategy to a common end-point, a cost-effectiveness analysis might be better(198). When a centre wants to interpret the results from the economical analyses, the sensitivity analyses might be more valuable than the main results. Paper 2 recommended biopsy, EBNA, and brushing for endobronchial visible lesions. The cost of brushing had to be below 83 euro and brushing had to increase the diagnostic yield with 2 % to be economical. The cost of brushing was estimated to 43 euro in Paper 2. Previous studies estimated the cost of brushing to 177$(91) and 103$(117) (approximately 70-120 euro). The increase in the diagnostic yield of brushing compared to biopsy alone was 3 % in Paper 2. An increase in the diagnostic yield above 2 % with brushing have been demonstrated in many studies(54;91;95;97;106;107;116). The cost of EBNA had to be below 205 euro and EBNA had to increase the diagnostic yield with 5 %. The cost of EBNA was estimated to 159 euro in Paper 2. One previous study estimated the cost of EBNA to 174$(117) (approximately 120 euro). The increase in the diagnostic yield of EBNA was 7 % in Paper 2. Other studies reported an increase above 5 % of EBNA(60;97;116;117). The cost of a repeated procedure had to be at least 1786 euro for the conclusion to be true.

The current study and the other published studies recommend the use of biopsy. Biopsy is inexpensive and has a high diagnostic yield. Even though the current study has analysed costs and diagnostic yields of different additional sampling techniques, there is still uncertainty regarding some parts of the conclusion. Increasing the number of biopsies was not compared to the addition of other sampling techniques. The study protocol recommended four biopsies, but Gellert et al. recommended five(62), Popovich et al. recommended one for visible lesions and up to ten for peripheral lesions(64). The studies did not compare a higher number of biopsies to an additional sampling technique.

After the implementation of EBUS-TBNA for lymph nodes, there might be a possibility that it is better to sample the lymph nodes than to use time on the

peripheral lesions. Lymph node sampling will give the diagnosis and staging information in one procedure.

The studies that included biopsy in the evaluation of sampling techniques recommended its use for central and peripheral lesions. The current study indicated that TBNA and brushing gave additional value for central lesions and recommended biopsy and brushing for peripheral lesions.

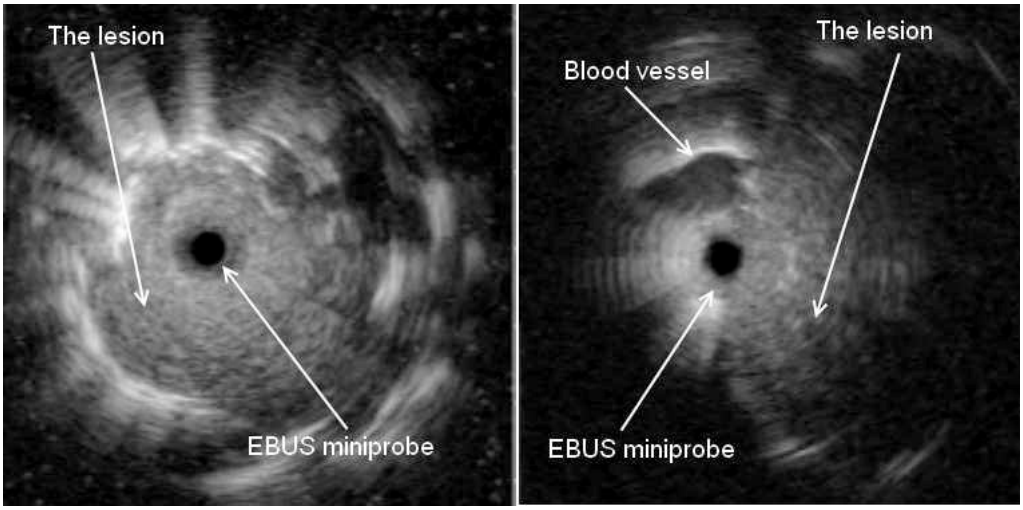
6.3.6 Endobronchial ultrasound

The current study evaluated visualisation of the lesions by EBUS and the physicians' ability to get a proper diagnostic sample from the lesion with EBUS.

Visualisation of the lesions

The optimal position for the EBUS probe is inside the lesion. When the EBUS probe is inside the lesion, the ultrasound picture shows the lesion surrounding the probe (Figure 16). EBUS can visualise the lesion from a bronchial branch adjacent to the lesion (Figure 16), but the position is not optimal for sampling(160;163;170).

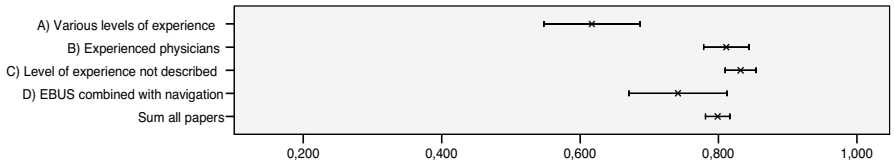
Figure 16: Visualisation by EBUS from inside a lesion and adjacent to a lesion



Inside the lesion Adjacent to the lesion

EBUS visualised the lesions from inside in 37 of 80 (46 %) of the malignant cases. The EBUS probe was adjacent to the lesion in additional eight cases. None of the cases with the ultrasound probe adjacent to the lesions got the diagnosis by the first bronchoscopy. The overall visualisation rate was 1568/1963 (80 %) in published studies (Figure 17).

Figure 17: Visualisation rates by EBUS in published papers



The papers included in Figure 17: A(171;175), B(152;154;158;159;161;163;168;174), C(15;16;153;155;160;164;166;167;169;170;172) and D(156;157;162;165;173)

Huang et al. analysed the predictors of a higher visualisation rate(170). Lesion size and malignant disease were significant in a multivariate analysis. Endobronchial difficulty or CT bronchus sign was not analysed. The size of the lesion was an important predictor for the visualisation rate in the current study. The visualisation rate was 38/71 (54 %) for lesions above 3 cm, compared to 13/46 (28 %) for lesions below 3 cm ($p<0.01$). The endobronchial difficulty also predicted the visualisation rate in a bivariate analysis. The visualisation rate was 62 % in cases with a bronchial branch going straight to the lesion, 50 % if there were 1-2 divisions to pass, 42 % if there were more than 3 divisions to pass and 22 % in those with no bronchial branch going towards the lesion ($p=0.05$).

The physicians' ability to manipulate the miniprobe into the correct bronchial branch will probably depend on experience. Most of the previous studies have been with experienced physicians(152;154;158;159;161;163;168;174).
Some studies did not report the physicians' level of experience(15;16;153;155;160;164;166;167;169;170;172). In addition to the current study, Oki et al. reported results from physicians with various levels of experience(171). Oki et al combined EBUS with an ultrathin bronchoscope and had a very high visualisation rate (92 %). The paper does not describe whether all attending

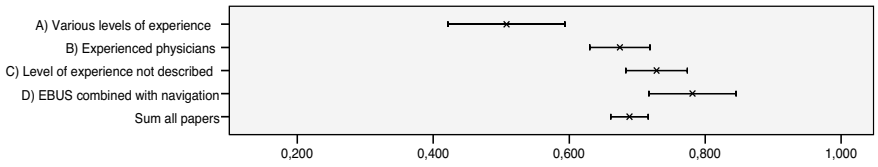
pulmonologists performed the investigations or if only selected physicians did. The attending physicians in the paper from Oki et al. were pulmonologists or supervised pulmonary residents.

The inclusion into the different studies will probably affect the visualisation rate. No studies included only large lesions, but there is a possibility that some studies excluded lesions without any bronchial branches into the lesions. Some institutions do not consider such lesions for diagnostic bronchoscopy. The main reason for the low visualisation rate in the current study was probably the design where all physicians who attended the bronchoscopy lab performed the investigations. Another explanation might be the wide inclusion of all kinds of lesions including those with no bronchial branch towards the lesions.

Detection rate for cancer

Detection rate for cancer depends on the physicians' ability to localise the lesion with EBUS and the ability to remove the miniprobe and to get the sampling device back into the correct position. The detection rate for cancer was 36 % with EBUS in the current study, 62 % in the lesions visualised by EBUS and 17 % in the cases not visualised by EBUS. The aim of the study was to achieve an average diagnostic yield of 60 % in the EBUS group. The average diagnostic yield in the publications from Table 3 was 752/1092 (69 %). Only Oki et al. published a paper from physicians with various level of experience. The detection rate for cancer was 80 % with an ultrathin bronchoscope in the paper from Oki et al.(171). Figure 18 displays the results from the studies in Table 3.

Figure 18: Detection rates for cancer with EBUS in peripheral lesions



The papers included in Figure 18: A(171;175), B(154;158;159;163;168;174), C(153;155;164;166;170), and D(156;162;165;173)

The low detection rate for cancer was due to a low visualisation rate. A design with fewer physicians might have given a higher visualisation rate and a higher .

Some of the other studies had advantages like an ultrathin bronchoscope(171) or navigation(157;162;165;173). Use of fluoroscopy did not affect the results of the studies. The average detection rate for cancer was 752/1092 (69 %) in all studies with EBUS compared to 178/286 (62 %) in the studies where fluoroscopy guided the EBUS miniprobe(16;153;154;156;167;171;174;175). Studies with a guide sheath had an average detection rate for caner of 253/429 (59 %)(15;16;153;154;156;165-168;174;175).

When the lesions were visualised, the physicians removed the miniprobe and left the guide sheath in front of the lesion. If the patient was coughing, the guide sheath could easily move away from the lesion. Thus, studies performed with general anaesthesia would have the advantage of the patient not moving at all(162;173). Use of the guide sheath was a possible explanation for the slightly lower detection rate for cancer in the EBUS group compared to the non-EBUS group. The guide sheath was useful when EBUS visualised the lesions. The sheath guided the sampling devices towards the lesion with a detection rate for cancer of 62 % in visualised lesions. However, per protocol, our physicians also used the guide sheath for sampling from lesions not visualised by EBUS. Sampling without a guide sheath with a wider sampling area

might give better results for these lesions. Eberhardt et al. have published a paper with suction from a catheter close to the lesion(173). This sampling technique also samples from a wider area and is promising.

In the present EBUS study, the physicians were in the beginning of the learning curve with EBUS. They were only able to achieve visualisation from inside the tumour in 46 % of the lesions. When a malignant lesion was visualised, the detection rate for cancer was only 62 %.

Comparison of EBUS and non-EBUS for peripheral lesions

The main aim of Paper 3 was to compare the diagnostic yield of bronchoscopy with EBUS to the diagnostic yield of bronchoscopy without EBUS in a real-life setting. The predicted diagnostic yield in the non-EBUS group was 40 %, the detection rate for cancer in the study was 43 %. The detection rate for cancer in the EBUS group was 36 %, far from the predicted 60 %. Thus, there was no increase in the diagnostic yield with EBUS in a situation where physicians with various levels of experience performed the bronchoscopies. Subgroup analyses in Paper 3 showed that the physicians were able to get a very high detection rate for cancer with EBUS in easy-to-reach lesions (89 %), but the detection rate for cancer was high also for easy-to-reach lesions in the non-EBUS group (72 %, NS). We expected EBUS to be a good tool for hard-to-reach lesions, but in the current study, non-EBUS had higher detection rates for cancer if there were no bronchial branches going straight to the lesions. As discussed previously, the navigation towards the lesion can be complicated and learning might improve the results. For inexperienced physicians sampling without a guide sheath from a wider area was better than localised sampling with EBUS. A guide sheath in a difficult position might easily slip away during breathing or coughing. The multivariate analysis in Paper 3 found an interaction between size and use of EBUS. For lesions below 3 cm the detection rate for cancer in the EBUS group was lower than the detection rate for cancer in the non-EBUS group. This result is contrary to the results from experienced physicians where the

EBUS group had a higher diagnostic yield than the non-EBUS group in small lesions(152;158).

Few studies have compared the diagnostic yield with EBUS to the diagnostic yield without EBUS in peripheral lesions. The first study by Herth et al. was from the Heidelberg group(152). Although not described in the paper, very experienced physicians performed the bronchoscopies with the patients in general anaesthesia. The paper did not report the non-inclusion or whether hard-to-reach lesions with no bronchial branches to the lesions were included or not. The study had a crossover design where the physician performed a bronchoscopy with EBUS and without EBUS in the same patient. Having first determined the position by EBUS might have biased the results in the non-EBUS group. The study achieved a high diagnostic yield in the EBUS group (80 %), but there was no significant increase compared to the non-EBUS group (76 %). There was a tendency for EBUS to be better for small lesions. The Heidelberg group has shown high detection rates for EBUS in lesions invisible by fluoroscopy (159;168) and when EBUS was combined with navigation(157;162). Eberhardt et al. found a significant higher detection rate for the combination of navigation and EBUS compared to each method alone.

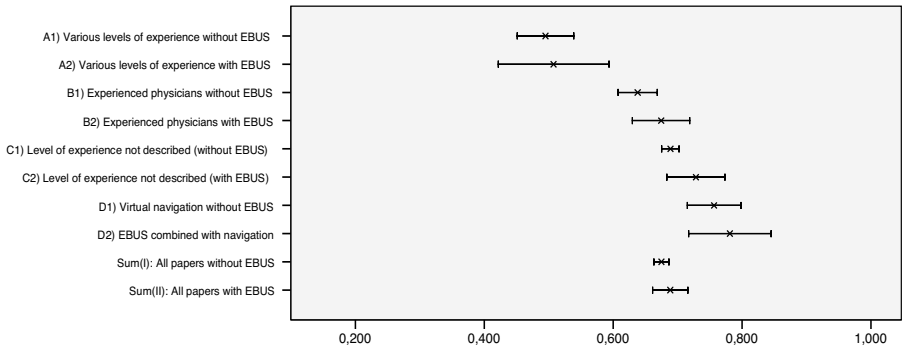
Yang et al. published a paper in 2004 with a comparison between EBUS and non-EBUS. This was a retrospective study of the patients investigated before the introduction of EBUS compared to those investigated with EBUS. There was a significant increase in detection rate for cancer. The detection rate was 43 % without EBUS and increased to 66 % with EBUS. The study had a wide inclusion, but did not describe the level of experience of the performing physicians.

Shirakawa et al. compared EBUS performed by two experienced physicians to a historical control group where the two physicians performed the bronchoscopies(154). Their conclusion was that EBUS improves the diagnostic accuracy, but the detection rate for cancer was 71 % in the EBUS group and 70 % in the non-EBUS group.

Paone et al. performed a randomised trial with sample size calculation, but without a conclusion for the mnumber needed in the study(158). Two experienced physicians performed all procedures. They investigated all patients with bronchoscopy before the inclusion. 386 of 799 patients were excluded because of low compliance. Compliance was defined as the supposed ability to accomplish a follow up algorithm. The study found a significant increase in the detection rate for cancer. The detection rate for cancer increased from 55 % in the non-EBUS group to 79 % in the EBUS group. Subgroup analyses revealed there was no increase in the diagnostic yield with EBUS for lesions above 3 cm. This study has shown that EBUS can increase the detection rate for cancer in small lesions when performed by experienced physicians in selected patients.

Figure 19 is a comparison of the average detection rate for cancer in studies without EBUS (Figure 14) and the detection rate for cancer in studies with EBUS (Figure 18).

Figure 19 Comparisons of studies with EBUS and studies without EBUS



The papers included in Figure 19: A1(56;100;113;117;132;134), A2(171;175), B1(67;74;78;88;94;115;119;125;137), B2(154;158;159;163;168;174), C1(50-54;58;59;63;64;70;73;80;82-85;87;90;92;93;96;99;103-105;111;112;114;122;142;143;146), C2(153;155;164;166;170), D1(110;118;121;123;126;138;139;145), and D2(156;162;165;173)

The average detection rate for cancer was 4179/6190 (68 %) in studies without EBUS and 752/1092 (69 %) in studies with EBUS. There were no large differences in results of the studies with EBUS and the non-EBUS studies for the subgroups displayed in Figure 19. The comparison did not adjust the results of the studies for size or endobronchial difficulty. All studies that reported detection rates for cancer in peripheral lesions were included regardless of inclusion criteria. There might be a possibility for bias because some studies of EBUS only included small lesions(162;163). If only small lesions or hard-to-reach lesions were included, a lower diagnostic yield might be expected. The average detection rate for cancer for lesions below 3 cm were similar in studies with EBUS (304/481 (63 %)) and in studies without EBUS (407/659 (62 %)). (Values from Table 2 and Table 3)

One randomised trial found an increase in diagnostic yield with EBUS for small peripheral lesions when experienced physicians performed EBUS in selected patients(158). However, a comparison of all published studies did not reveal any

significant benefit of EBUS. There was no increase in the diagnostic yield with EBUS performed by physicians at various levels of experience in the current study.

6.4 Conclusions

Endobronchial visibility and lesion size were predictors for a higher diagnostic yield in the current study of bronchoscopy. A novel classification of endobronchial difficulty, presented in Paper 3, was a significant predictor in a separate analysis of peripheral lesions. The optimal combination of sampling techniques was biopsy, brushing and EBNA for visible lesions. For peripheral lesions, biopsy and brushing was the optimal combination. There was no increase in the diagnostic yield by use of EBUS performed by physicians at various levels of experience.

7. Suggestions for future research

7.1.1 Navigation

Previous studies found an advantage of the Superdimension navigation system combined with EBUS(162). There is a need of cost-effectiveness studies for these devices. The navigation probes are expensive and disposable with design for one-time use only. The EBUS probe is vulnerable. LungPoint has developed a new navigation system(199) that reads the bronchoscopy picture. The system is expensive to buy, but does not have single use expenses. The usefulness of the LungPoint system and virtual bronchoscopy systems integrated in the regular CT working stations, are possible platforms for future research on bronchoscopy for visualization and sampling from peripheral lesions.

7.1.2 Bronchography

Catheter bronchography is an inexpensive and simple method to display the bronchial branches. The physician infuses diluted contrast medium (like Iohexol) through a catheter into the actual bronchial segments. Two previous studies had very high diagnostic yields with bronchography for small lesions below 2 cm(61;76). Catheter bronchography is a possible intervention that can be tested in future studies.

7.1.3 BAL

The current study did not evaluate BAL in the diagnostic approach. BAL is the installation of 50 ml saline into the actual bronchial branch. Some studies have shown good results of BAL for peripheral lesions(66;104;114). The possibility to use BAL alone for difficult-to-reach lesions is a suggestion for future research.

7.1.4 Curettage

The current study used the curette to manipulate the guide sheath into the correct position. Some studies had good results of the curette as a sampling technique(53;61;76;110;112). The curette as a sampling technique is a possible device that needs further evaluations in future studies.

7.1.5 Catheter aspiration

Eberhardt et al. has shown promising results for catheter aspiration from the area of the lesions(162). The technique is promising, but future studies must evaluate its potential.

7.1.6 EBUS

The current study did not recommend EBUS for inexperienced physicians when the lesions were small or hard-to-reach. Easy-to-reach lesions above 3 cm have a good diagnostic yield with fluoroscopy, biopsy, and brushing regardless of the use of EBUS. The usefulness of EBUS for small lesions with experienced physicians is still not settled even though one randomised study has shown promising results(158).

7.1.7 The diagnostic approach to visible and peripheral lesions

Based on the current knowledge all pulmonologists can sample visible lesions with good results. The current study recommended biopsy, brushing, and EBNA for visible lesions, but future studies can evaluate whether a higher number of biopsies can replace brushing or EBNA. Physicians with various levels of experience can sample

easy-to-reach lesions above 3 cm with fluoroscopy, biopsy, and brushing. Hard-to-reach lesions and lesions below 3 cm are possibly to be reserved for experienced physicians. We need future studies to settle if catheter bronchography, navigation, EBUS, curette, BAL or catheter aspiration are cost-effective devices for the experienced physician. Future studies can settle whether bronchoscopy or CT-guided biopsy is preferable for lesions without any bronchial branches directly to the lesions. The introduction of EBUS-TBNA for lymph nodes might change the need for sampling from peripheral lesions.

8. Source of data

1. Marsh, B. R. Historic Development of Bronchoesophagology. Otolaryngology-Head and Neck Surgery 1996;114(6):689-716.

2. Becker, H. D. Bronchoscopy: The Past, the Present, and the Future. Clinics in Chest Medicine 2010;31(1):1-18.

3. Ikeda, Tsuboi, T, Ono, R, and Ishikawa, S. Flexible Bronchofiberscope. Jap J Clin Oncol 1971;1(1):55-65.

4. Thirumala RD and Mosenifar Z. Transbronchial Biopsy. http://emedicine.medscape.com/article/1894323-overview 2011.

5. Sackner, M. A., Wanner, A., and Landa, J. Applications of Bronchofiberoscopy. Chest 1972;62(5):S70-&.

6. Wang K.P., Mehta, A., and Turner, J. F. Transbronchial Needle Aspiration for Cytology and Histology Specimens. Flexible bronchoscopy 2004;Blackwell Science.

7. Wang, K. P., Terry, P., and Marsh, B. Bronchoscopic Needle Aspiration Biopsy of Paratracheal Tumors. American Review of Respiratory Disease 1978;118(1):17-21.

8. Frentzel-Beyme, B. The History of Diagnostic Ultrasound. Radiologe 2005;45(4):363-70.

9. Woo, J. A Short History of the Development of Ultrasound in Obstetrics and Gynecology. http://www.ob-ultrasound.net/history1.html 2002.

10. Ludwig, G. D., Bolt, R. H., Heuter, T. F., and Ballantine, H. T. Factors Influencing the Use of Ultrasound As A Diagnostic Aid. Transactions of the American Neurological Association 1950;225-8.

11. Wild, J. J. The Use of Ultrasonic Pulses for the Measurement of Biological Tissues and the Detection of Tissue Density Changes. Surgery 1950;27:183-8.

12. Http://Www.Ob-Ultrasound.Net/Dussikbio.Html. Web page 2011.

13. Donald, I. Use of Ultrasonics in Diagnosis of Abdominal Swellings. British Medical Journal 1963;(536):1154-5.

14. Wild, J. J. and Reid, J. M. Current Developments in Ultrasonic Equipments of Medical Diagnosis. IRE Trans.Ultrason.Engng 1957;5:44-56.

15. Hurter, T. and Hanrath, P. Endobronchial Sonography - Feasibility and Preliminary-Results. Thorax 1992;47(7):565-7.

16. Kurimoto, N., Miyazawa, T., Okimasa, S., Maeda, A., Oiwa, H., Miyazu, Y., and Murayama, M. Endobronchial Ultrasonography Using a Guide Sheath Increases the Ability to Diagnose Peripheral Pulmonary Lesions Endoscopically. Chest 2004;126(3):959-65.

17. Morgagni, G. B. De Sedibus Et Causis Morborum Per Anatomen Indagatis. (Serial) 1761.

18. Spiro, S. G. and Silvestri, G. A. One Hundred Years of Lung Cancer. American Journal of Respiratory and Critical Care Medicine 1-9-2005;172(5):523-9.

19. Doll, R. and Hill, A. B. Smoking and Carcinoma of the Lung - Preliminary Report. British Medical Journal 1950;2(4682):739-48.

20. Doll, R. Uncovering the Effects of Smoking: Historical Perspective. Stat Methods Med Res 1998;7(2):87-117.

21. Smith, G. D. and Egger, M. The First Reports on Smoking and Lung Cancer - Why Are They Consistently Ignored? Bulletin of the World Health Organization 2005;83(10):799-800.

22. Www.Kreftregisteret.No. Web page 2010.

23. "Wilhelm Conrad Röntgen - Biography". Nobelprize.Org. http://nobelprize.org/nobel_prizes/physics/laureates/1901/rontgen-bio.html 2010.

24. Kuhl, D. E., Hale, J., and Eaton, W. L. Transmission Scanning - A Useful Adjunct to Conventional Emission Scanning for Accurately Keying Isotope Deposition to Radiographic Anatomy. Radiology 1966;87(2):278-&.

25. Hounsfield, G. N. Emi Scanner. Proceedings of the Royal Society of London Series B-Biological Sciences 1977;195(1119):281-9.

26. Brownell, G. The History of Positron Imaging. http://www.mit.edu/~glb/alb.html 1999.

27. Alavi, A. and Reivich, M. The Conception of FDG-PET Imaging. Seminars in Nuclear Medicine 2002;32(1):2-5.

28. Townsend, D. W. and Beyer, T. A Combined PET/CT Scanner: the Path to True Image Fusion. British Journal of Radiology 2002;75:S24-S30.

29. Graham, E. A. Pneumectomy With Cautery. A Safer Substitute for the Ordinary Lobectomy in Cases of Chronic Suppuration of the Lung. J Am Med Assoc 1923;81(12):1010-2.

30. Horn, L. and Johnson, D. H. Evarts A. Graham and the First Pneumonectomy for Lung Cancer. Journal of Clinical Oncology 1-7-2008;26(19):3268-75.

31. Http://Radonc.Ucsd.Edu/Patientinformation/History.Asp. Web page 2010.

32. Heron, J. F. Some Historical Data on Radiotherapy. http://www.oncoprof.net/Generale2000/g08_Radiotherapie/Index/g08-gb_idx02.html 2010.

33. Edwards, A. T. Carcinoma of the Bronchus. Thorax 1946;1(1):1-25.

34. Johnson, R. J., Walton, R. J., Lim, M. L., Zylak, C. J., and Painchaud, L. A. A Randomized Study on Survival of Bronchogenic Carcinoma Treated With Conventional or Short Fractionation Radiation. Clinical Radiology 1973;24(4):494-7.

35. Leksell, L. Stereotactic Radiosurgery. Journal of Neurology Neurosurgery and Psychiatry 1983;46(9):797-803.

36. Blomgren, H., Lax, I., Naslund, I., and Svanstrom, R. Stereotaxic High-Dose Fraction Radiation-Therapy of Extracranial Tumors Using An Accelerator - Clinical-Experience of the First 31 Patients. Acta Oncologica 1995;34(6):861-70.

37. Hiraoka, M., Matsuo, Y., and Takayama, K. Stereotactic Body Radiation Therapy for Lung Cancer: Achievements and Perspectives. Japanese Journal of Clinical Oncology 2010;40(9):846-54.

38. Gilman, A. The Initial Clinical Trial of Nitrogen Mustard. American Journal of Surgery 1963;105(5):574-8.

39. Goodman, L. S., Wintrobe, M. M., Dameshek, W., Goodman, M. J., and Gilman, A. Nitrogen Mustard Therapy - Use of Methyl-Bis(Beta-Chloroethyl)Amine Hydrochloride and Tris(Beta-Chloroethyl)Amine Hydrochloride for Hodgkins Disease, Lymphosarcoma, Leukemia and Certain Allied and Miscellaneous Disorders. Jama-Journal of the American Medical Association 1946;132(3):126-32.

40. Ritchie, M. Alfred Gilman 1908-184. http://www.nap.edu/html/biomems/agilman.pdf 1996.

41. Stewart, L. A. Chemotherapy in Non-Small Celi Lung Cancer: a Meta-Analysis Using Updated Data on Individual Patients From 52 Randomised Clinical Trials. BMJ 1995;311:899-909.

42. Mitsudomi, T. Advances in Target Therapy for Lung Cancer. Japanese Journal of Clinical Oncology 2010;40(2):101-6.

43. Http://Www.Fujinon.De/En/Medical-Products/Products/Miniprobe-Ultrasound-System/. Web page 2010.

44. Http://Www.Olympusamerica.Com/Msg_Section/Msg_Eus.Asp. Web page 2010.

45. Http://Www.Olympusamerica.Com/Msg_Section/ET/Procedures /Peripheral_Bronchoscopy.Asp. Web page 2010.

46. Ernst, A., Feller-Kopman, D., and Herth, F. J. F. Endobronchial Ultrasound in the Diagnosis and Staging of Lung Cancer and Other Thoracic Tumors. Semin Thorac Cardiovasc Surg 2007;19:201-5.

47. Altman, D. G. Practical Statistics for Medical Research. Chapman & Hall, London 1991.

48. Schreiber, G. and McCrory, D. C. Performance Characteristics of Different Modalities for Diagnosis of Suspected Lung Cancer - Summary of Published Evidence. Chest 2003;123(1):115S-28S.

49. Rivera, M. P and Mehta, A. C. Initial Diagnosis of Lung Cancer: ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition). Chest 2007;132(3 Suppl):131S-48S.

50. Hattori, S., Matsuda, M., NISHIHAR.H, and Horai, T. Early Diagnosis of Small Peripheral Lung Cancer - Cytologic Diagnosis of Very Fresh Cancer Cells Obtained by Tv-Brushing Technique. Acta Cytologica 1971;15(5):460-&.

51. Oswald, N. C., Hinson, K. F. W., Canti, G., and Miller, A. B. Diagnosis of Primary Lung Cancer With Special Reference to Sputum Cytology. Thorax 1971;26(6):623-&.

52. Solomon, D. A., Solliday, N. H., and Gracey, D. R. Cytology in Fiberoptic Bronchoscopy - Comparison of Bronchial Brushing, Washing and Post-Bronchoscopy Sputum. Chest 1974;65(6):616-9.

53. Zavala, D. C. Diagnostic Fiberoptic Bronchoscopy - Techniques and Results of Biopsy in 600 Patients. Chest 1975;68(1):12-9.

54. Kvale, P. A., Bode, F. R., and Kini, S. Diagnostic Accuracy in Lung-Cancer - Comparison of Techniques Used in Association With Flexible Fiberoptic Bronchoscopy. Chest 1976;69(6):752-7.

55. Chopra, S. K., Genovesi, M. G., Simmons, D. H., and Gothe, B. Fiberoptic Bronchoscopy in Diagnosis of Lung-Cancer - Comparison Pre-Bronchoscopy and Post-Bronchoscopy Sputa, Washings, Brushings and Biopsies. Acta Cytologica 1977;21(4):524-7.

56. Stringfield, J. T., Markowitz, D. J., Bentz, R. R., Welch, M. H., and Weg, J. G. Effect of Tumor Size and Location on Diagnosis by Fiberoptic Bronchoscopy. Chest 1977;72(4):474-6.

57. Chaudhary, B. A., Yoneda, K., and Burki, N. K. Fiberoptic Bronchoscopy - Comparison of Procedures Used in Diagnosis of Lung-Cancer. Journal of Thoracic and Cardiovascular Surgery 1978;76(1):33-7.

58. Cortese, D. A. and Mcdougall, J. C. Biopsy and Brushing of Peripheral Lung-Cancer With Fluoroscopic Guidance. Chest 1979;75(2):141-5.

59. Radke, J. R., Conway, W. A., Eyler, W. R., and Kvale, P. A. Diagnostic-Accuracy in Peripheral Lung Lesions - Factors Predicting Success With Flexible Fiberoptic Bronchoscopy. Chest 1979;76(2):176-9.

60. Buirski, G., Calverley, P. M. A., Douglas, N. J., Lamb, D., Mcintyre, M., Sudlow, M. F., and White, H. Bronchial Needle Aspiration in the Diagnosis of Bronchial-Carcinoma. Thorax 1981;36(7):508-11.

61. Ono, R., Loke, J., and Ikeda, S. Bronchofiberscopy With Curette Biopsy and Bronchography in the Evaluation of Peripheral Lung Lesions. Chest 1981;79(2):162-6.

62. Gellert, A. R., Rudd, R. M., Sinha, G., and Geddes, D. M. Fiberoptic Bronchoscopy - Effect of Multiple Bronchial Biopsies on Diagnostic Yield in Bronchial-Carcinoma. Thorax 1982;37(9):684-7.

63. Pilotti, S., Rilke, F., Gribaudi, G., and Spinelli, P. Cytologic Diagnosis of Pulmonary-Carcinoma on Bronchoscopic Brushing Material. Acta Cytologica 1982;26(5):655-60.

64. Popovich, J., Kvale, P. A., Eichenhorn, M. S., Radke, J. R., Ohorodnik, J. M., and Fine, G. Diagnostic-Accuracy of Multiple Biopsies From Flexible Fiberoptic Bronchoscopy - A Comparison of Central Versus Peripheral Carcinoma. American Review of Respiratory Disease 1982;125(5):521-3.

65. Wallace, J. M. and Deutsch, A. L. Flexible Fiberoptic Bronchoscopy and Percutaneous Needle Lung Aspiration for Evaluating the Solitary Pulmonary Nodule. Chest 1982;81(6):665-71.

66. Lam B., Wong M.P., Ooi C., Lam W.K., Chan K.N., Ho J.C., and Tsang K.W. Diagnostic Yield of Bronchoscopic Sampling Methods in Bronchial Carcinoma. Respirology 2000;5(3):265-70.

67. Lundgren, R., Bergman, F., and Angstrom, T. Comparison of Trans-Bronchial Fine Needle Aspiration Biopsy, Aspiration of Bronchial Secretion, Bronchial Washing, Brush Biopsy and Forceps Biopsy in the Diagnosis of Lung-Cancer. European Journal of Respiratory Diseases 1983;64(5):378-85.

68. Shure, D. and Fedullo, P. F. The Role of Transcarinal Needle Aspiration in the Staging of Bronchogenic-Carcinoma. Chest 1984;86(5):693-6.

69. Zisholtz, B. M. and Eisenberg, H. Lung-Cancer Cell Type As A Determinant of Bronchoscopy Yield. Chest 1983;84(4):428-30.

70. Cox, I. D., Bagg, L. R., Russell, N. J., and Turner, M. J. Relationship of Radiologic Position to the Diagnostic Yield of Fiberoptic Bronchoscopy in Bronchial-Carcinoma. Chest 1984;85(4):519-22.

71. Horsley, J. R., Miller, R. E., Amy, R. W. M., and King, E. G. Bronchial Submucosal Needle Aspiration Performed Through the Fiberoptic Bronchoscope. Acta Cytologica 1984;28(3):211-7.

72. Schenk, D. A., Bryan, C. L., Bower, J. H., and Myers, D. L. Trans-Bronchial Needle Aspiration in the Diagnosis of Bronchogenic-Carcinoma. Chest 1987;92(1):83-5.

73. Naidich, D. P., Sussman, R., Kutcher, W. L., Aranda, C. P., Garay, S. M., and Ettenger, N. A. Solitary Pulmonary Nodules - Ct-Bronchoscopic Correlation. Chest 1988;93(3):595-8.

74. Shiner, R. J., Rosenman, J., Katz, I., Reichart, N., Hershko, E., and Yellin, A. Bronchoscopic Evaluation of Peripheral Lung-Tumors. Thorax 1988;43(11):887-9.

75. Gay, P. C. and Brutinel, W. M. Trans-Bronchial Needle Aspiration in the Practice of Bronchoscopy. Mayo Clinic Proceedings 1989;64(2):158-62.

76. Mori, K., Yanase, N., Kaneko, M., Ono, R., and Ikeda, S. Diagnosis of Peripheral Lung-Cancer in Cases of Tumors 2 Cm Or Less in Size. Chest 1989;95(2):304-8.

77. Wagner, E. D., Ramzy, I., Greenberg, S. D., and Gonzalez, J. M. Trans-Bronchial Fine-Needle Aspiration - Reliability and Limitations. American Journal of Clinical Pathology 1989;92(1):36-41.

78. Mak, V. H. F., Johnston, I. D. A., Hetzel, M. R., and Grubb, C. Value of Washings and Brushings at Fiberoptic Bronchoscopy in the Diagnosis of Lung-Cancer. Thorax 1990;45(5):373-6.

79. Saita, S., Tanzillo, A., Riscica, C., Maresca, A., Potenza, E., and Darrigo, M. Bronchial Brushing and Biopsy - A Comparative-Evaluation in Diagnosing Visible Bronchial Lesions. European Journal of Cardio-Thoracic Surgery 1990;4(5):270-2.

80. Popp, W., Rauscher, H., Ritschka, L., Redtenbacher, S., Zwick, H., and Dutz, W. Diagnostic Sensitivity of Different Techniques in the Diagnosis of Lung-Tumors With the Flexible Fiberoptic Bronchoscope - Comparison of Brush Biopsy, Imprint Cytology of Forceps Biopsy, and Histology of Forceps Biopsy. Cancer 1-1-1991;67(1):72-5.

81. Buccheri, G., Barberis, P., and Delfino, M. S. Diagnostic, Morphological, and Histopathologic Correlates in Bronchogenic-Carcinoma - A Review of 1,045 Bronchoscopic Examinations. Chest 1991;99(4):809-14.

82. Pirozynski, M. Bronchoalveolar Lavage in the Diagnosis of Peripheral, Primary Lung-Cancer. Chest 1992;102(2):372-4.

83. de Gracia, J., Bravo, C., Miravitlles, M., Tallada, N., Orriols, R., Bellmunt, J., Vendrell, M., and Morell, F. Diagnostic-Value of Bronchoalveolar Lavage in Peripheral Lung-Cancer. American Review of Respiratory Disease 1993;147(3):649-52.

84. Torrington, K. G. and Kern, J. D. The Utility of Fiberoptic Bronchoscopy in the Evaluation of the Solitary Pulmonary Nodule. Chest 1993;104(4):1021-4.

85. Debeljak, A., Mermolja, M., Sorli, J., Zupancic, M., Zorman, M., and Remskar, J. Bronchoalveolar Lavage in the Diagnosis of Peripheral Primary and Secondary Malignant Lung-Tumors. Respiration 1994;61(4):226-30.

86. Milman, N., Faurschou, P., Munch, E. P., and Grode, G. Transbronchial Lung-Biopsy Through the Fiber Optic Bronchoscope - Results and Complications in 452 Examinations. Respiratory Medicine 1994;88(10):749-53.

87. Castella, J., Buj, J., Puzo, C., Anton, P. A., and Burgues, C. Diagnosis and Staging of Bronchogenic Carcinoma by Transtracheal and Transbronchial Needle Aspiration. Annals of Oncology 1995;6:21-4.

88. Gasparini, S., Ferretti, M., Secchi, E. B., Baldelli, S., Zuccatosta, L., and Gusella, P. Integration of Transbronchial and Percutaneous Approach in the Diagnosis of Peripheral Pulmonary Nodules Or Masses - Experience With 1,027 Consecutive Cases. Chest 1995;108(1):131-7.

89. Piaton, E., Grilletravigneaux, M. H., Saugier, B., and Pellet, H. Prospective-Study of Combined Use of Bronchial Aspirates and Biopsy Specimens in Diagnosis and Typing of Centrally Located Lung-Tumors. British Medical Journal 11-3-1995;310(6980):624-7.

90. Chechani, V. Bronchoscopic Diagnosis of Solitary Pulmonary Nodules and Lung Masses in the Absence of Endobronchial Abnormality. Chest 1996;109(3):620-5.

91. Govert, J. A., Kopita, J. M., Matchar, D., Kussin, P. S., and Samuelson, W. M. Cost-Effectiveness of Collecting Routine Cytologic Specimens During Fiberoptic Bronchoscopy for Endoscopically Visible Lung Tumor. Chest 1996;109(2):451-6.

92. Sing, A., Freudenberg, N., Kortsik, C., Wertzel, H., Klosa, B., and Hasse, J. Comparison of the Sensitivity of Sputum and Brush Cytology in the Diagnosis of Lung Carcinomas. Acta Cytologica 1997;41(2):399-408.

93. Aristizabal, J. F., Young, K. R., and Nath, H. Can Chest CT Decrease the Use of Preoperative Bronchoscopy in the Evaluation of Suspected Bronchogenic Carcinoma? Chest 1998;113(5):1244-9.

94. Bilaceroglu, S., Kumcuoglu, Z., Alper, H., Osma, E., Cagirici, U., Gunel, O., Bayol, U., Celikten, E., Perim, K., and Kose, T. CT Bronchus Sign-Guided Bronchoscopic Multiple Diagnostic: Procedures in Carcinomatous Solitary Pulmonary Nodules and Masses. Respiration 1998;65(1):49-55.

95. Mclean, A. N., Semple, P. D., Franklin, D. H., Petrie, G., Millar, E. A., and Douglas, J. G. The Scottish Multi-Centre Prospective Study of Bronchoscopy for Bronchial Carcinoma and Suggested Audit Standards. Respiratory Medicine 1998;92(9):1110-5.

96. Wongsurakiat P., Wongbunnate S., Dejsomritrutai W., Charoenratanakul S., Tscheikuna J., Youngchaiyud P., Pushpakom R., Maranetra N., Nana A., Chierakul N., Sakiyalak U., and Ruengjam C. Diagnostic Value of Bronchoalveolar Lavage and Postbronchoscopic Sputum Cytology in Peripheral Lung Cancer. Respirology 1998;3(2):131-7.

97. Dasgupta, A., Jain, P., Minai, O. A., Sandur, S., Meli, Y., Arroliga, A. C., and Mehta, A. C. Utility of Transbronchial Needle Aspiration in the Diagnosis of Endobronchial Lesions. Chest 1999;115(5):1237-41.

98. Govert, J. A., Dodd, L. G., Kussin, P. S., and Samuelson, W. M. A Prospective Comparison of Fiberoptic Transbronchial Needle Aspiration and Bronchial Biopsy for Bronchoscopically Visible Lung Carcinoma. Cancer Cytopathology 25-6-1999;87(3):129-34.

99. Reichenberger, F., Weber, J., Tamm, M., Bolliger, C. T., Dalquen, P., Perruchoud, A. P., and Soler, M. The Value of Transbronchial Needle Aspiration in the Diagnosis of Peripheral Pulmonary Lesions. Chest 1999;116(3):704-8.

100. Baaklini, W. A., Reinoso, M. A., Gorin, A. B., Sharafkanch, A., and Manian, P. Diagnostic Yield of Fiberoptic Bronchoscopy in Evaluating Solitary Pulmonary Nodules. Chest 2000;117(4):1049-54.

101. Bungay, H. K., Pal, C. R., Davies, C. W. H., Davies, R. J. O., and Gleeson, F. V. An Evaluation of Computed Tomography As an Aid to Diagnosis in Patients Undergoing Bronchoscopy for Suspected Bronchial Carcinoma. Clinical Radiology 2000;55(7):554-60.

102. Diette, G. B., White, P., Terry, P., Jenckes, M., Rosenthal, D., and Rubin, H. R. Utility of on-Site Cytopathology Assessment for Bronchoscopic Evaluation of Lung Masses and Adenopathy. Chest 2000;117(4):1186-90.

103. Hsiao CJ., Tang C.C., Hui-Chen, Wang C.H., Yu C.T., Kuo H.P., and Lin H.C. The Value of Transbronchial Lung Biopsy in the Diagnosis of Peripheral Lung Tumors According to Cell Type. Chang Gung Med J 2000;23(10):584-9.

104. Tang C.C., Hsiao CJ., Chen, H., Wang C.H., Lin H.C., Yu C.T., and Kuo H.P. Value of Bronchoalveolar Lavage Combined With Transbronchial Lung Biopsy in the Diagnosis of Peripheral Lung Cancer. Chang Gung Med J 2000;23(11):695-700.

105. Gunen, H., Kizkin, O., Tahaoglu, C., and Aktas, O. Utility of Blind Forceps Biopsy of the Main Carina and Upper-Lobe Carina in Patients With Non-Small Cell Lung Cancer. Chest 2001;119(2):632-7.

106. Jones, A. M., Hanson, I. M., Armstrong, G. R., and O'Driscoll, B. R. Value and Accuracy of Cytology in Addition to Histology in the Diagnosis of Lung Cancer at Flexible Bronchoscopy. Respiratory Medicine 2001;95(5):374-8.

107. Karahalli, E., Yilmaz, A., Turker, H., and Ozvaran, K. Usefulness of Various Diagnostic Techniques During Fiberoptic Bronchoscopy for Endoscopically Visible Lung Cancer: Should Cytologic Examinations Be Performed Routinely? Respiration 2001;68(6):611-4.

108. Baba, M., Iyoda, A., Yasufuku, K., Haga, Y., Hoshino, H., Sekine, Y., Shibuya, K., Iizasa, T., Saitoh, Y., Hiroshima, K., and Fujisawa, T. Preoperative Cytodiagnosis of Very Small-Sized Peripheral-Type Primary Lung Cancer. Lung Cancer 2002;37(3):277-80.

109. Gaber, K. A., Goldman, J. M., and Farrell, D. J. Cytological Examination of the Whole Endobronchial Brush in Bronchoscopic Diagnosis of Lung Cancer. Respiratory Medicine 2002;96(4):259-61.

110. Bandoh, S., Fujita, J., Tojo, Y., Yokomise, H., Satoh, K., Kobayashi, S., and Ishida, T. Diagnostic Accuracy and Safety of Flexible Bronchoscopy With Multiplanar Reconstruction Images and Ultrafast Papanicolaou Stain - Evaluating Solitary Pulmonary Nodules. Chest 2003;124(5):1985-92.

111. Diaz, G., Jimenez, D., Dominguez-Reboiras, S., Carrillo, F., and Perez-Rodriguez, E. Yield of Bronchoscopy in the Diagnosis of Neoplasm Metastatic to Lung. Respiratory Medicine 2003;97(1):27-9.

112. Kawaraya, M., Gemba, K., Ueoka, H., Nishii, K., Kiura, K., Kodani, T., Tabata, M., Shibayama, T., Kitajima, T., and Tanimoto, M. Evaluation of Various Cytological Examinations by Bronchoscopy in the Diagnosis of Peripheral Lung Cancer. British Journal of Cancer 17-11-2003;89(10):1885-8.

113. Skaansar K. Fleksibel Bronkoskopi. Tidsskr Nor Lægeforen 2003;123(11):1529-30.

114. Trkanjec, J. T., Peros-Golubicic, T., Grozdek, D., Ivicevic, A., and Alilovic, M. The Role of Transbronchial Lung Biopsy in the Diagnosis of Solitary Pulmonary Nodule. Collegium Antropologicum 2003;27(2):669-75.

115. Estarriol, M. H., Goday, M. R., Sanchez, M. V., Padro, X. B., Sot, M. T. C., and Quetglas, F. S. Bronchoscopic Lung Biopsy With Fluoroscopy to Study 164 Localized Pulmonary Lesions. Archivos de Bronconeumologia 2004;40(11):483-8.

116. Kaçar, N., Tuksavul, F., Edipoglu, O., Ermete, S., and Guclu, S. Z. Effectiveness of Transbronchial Needle Aspiration in the Diagnosis of Exophytic Endobronchial Lesions and Submucosal/Peribronchial Diseases of the Lung. Lung Cancer 2005;50(2):221-6.

117. van der Drift, M. A., van der Wilt, G. J., Thunnissen, F. B. J. M., and Janssen, J. P. A Prospective Study of the Timing and Cost-Effectiveness of Bronchial Washing During Bronchoscopy for Pulmonary Malignant Tumors. Chest 2005;128(1):394-400.

118. Gildea, T. R., Mazzone, P. J., Karnak, D., Meziane, M., and Mehta, A. C. Electromagnetic Navigation Diagnostic Bronchoscopy - A Prospective Study. American Journal of Respiratory and Critical Care Medicine 1-11-2006;174(9):982-9.

119. Heyer, C. M., Kagel, T., Lemburg, S. P., Walter, J. W., de Zeeuw, J., Junker, K., Mueller, K. M., Nicolas, V., and Bauer, T. T. Transbronchial Biopsy Guided by Low-Dose MDCT: A New Approach for Assessment of Solitar Pulmonary Nodules. American Journal of Roentgenology 2006;187(4):933-9.

120. Joos, L., Patuto, N., Chhajed, P. N., and Tamm, M. Diagnostic Yield of Flexible Bronchoscopy in Current Clinical Practice. Swiss Medical Weekly 4-3-2006;136(9-10):155-9.

121. Schwarz, Y., Greif, J., Becker, H. D., Ernst, A., and Mehta, A. Real-Time Electromagnetic Navigation Bronchoscopy to Peripheral Lung Lesions Using Overlaid CT Images - The First Human Study. Chest 2006;129(4):988-94.

122. Uchida, J., Imamura, F., Takenaka, A., Yoshimura, M., Ueno, K., Oda, K., Nakayama, T., Tsukamoto, Y., Higashiyama, M., and Kusunoki, Y. Improved Diagnostic Efficacy by Rapid Cytology Test in Fluoroscopy-Guided Bronchoscopy. Journal of Thoracic Oncology 2006;1(4):314-8.

123. Eberhardt, R., Anantham, D., Herth, F., Feller-Kopman, D., and Ernst, A. Electromagnetic Navigation Diagnostic Bronchoscopy in Peripheral Lung Lesions. Chest 2007;131(6):1800-5.

124. Lee, H. S., Kwon, S. Y., Kim, D. K., Il Yoon, H., Lee, S. M., Lee, J. H., Lee, C. T., Chung, H. S., Han, S. K., Shim, Y. S., and Yim, J. J. Bronchial Washing Yield Before and After Forceps Biopsy in Patients With Endoscopically Visible Lung Cancers. Respirology 2007;12(2):277-82.

125. Liam C.K., Pang Y.K., and Poosparajah S. Diagnostic Yield of Flexible Bronchoscopic Procedures in Lung Cancer Patients According to Tumour Location. Singapore Med J 2007;48(7):625-31.

126. Makris, D., Scherpereel, A., Leroy, S., Bouchindhomme, B., Faivre, J. B., Remy, J., Ramon, P., and Marquette, C. H. Electromagnetic Navigation Diagnostic Bronchoscopy for Small Peripheral Lung Lesions. European Respiratory Journal 2007;29(6):1187-92.

127. Shinagawa, N., Yamazaki, K., Onodera, Y., Asano, F., Ishida, T., Moriye, H., and Nishimura, M. Virtual Bronchoscopic Navigation System Shortens the Examination Time - Feasibility Study of Virtual Bronchoscopic Navigation System. Lung Cancer 2007;56(2):201-6.

128. Tachihara, M., Ishida, T., Kanazawa, K., Sugawara, A., Watanabe, K., Uekita, K., Moriya, H., Yamazaki, K., Asano, F., and Munakata, M. A Virtual Bronchoscopic Navigation System Under X-Ray Fluoroscopy for Transbronchial Diagnosis of Small Peripheral Pulmonary Lesions. Lung Cancer 2007;57(3):322-7.

129. Tremblay, A., Michaud, G., and Urbanski, S. J. Hot Biopsy Forceps in the Diagnosis of Endobronchial Lesions. European Respiratory Journal 2007;29(1):108-11.

130. Danila, E., Zurauskas, E., Loskutoviene, G., Zablockis, R., Nargela, R., Birzietyte, V., and Valentinaviciene, G. Significance of Bronchoscopic Lung Biopsy in Clinical Practice. Advances in Medical Sciences 2008;53(1):11-6.

131. Kanemoto, K., Satoh, H., Ishikawa, H., Kagohashi, K., Kurishima, K., and Sekizawa, K. Diagnostic Procedures for Small Pulmonary Nodules Detected by Mass-Screening. Anticancer Research 2008;28(5B):3153-5.

132. Oki, M., Saka, H., Kitagawa, C., Tanaka, S., Shimokata, T., Mori, K., and Kajikawa, S. Novel Thin Bronchoscope With a 1.7-Mm Working Channel for Peripheral Pulmonary Lesions. European Respiratory Journal 2008;32(2):465-71.

133. Ost, D., Shah, R., Anasco, E., Lusardi, L., Doyle, J., Austin, C., and Fein, A. A Randomized Trial of CT Fluoroscopic-Guided Bronchoscopy Vs Conventional Bronchoscopy in Patients With Suspected Lung Cancer. Chest 2008;134(3):507-13.

134. Roth, K., Hardie, J. A., Andreassen, A. H., Leh, F., and Eagan, T. M. L. Predictors of Diagnostic Yield in Bronchoscopy: a Retrospective Cohort Study Comparing Different Combinations of Sampling Techniques. BMC Pulmonary medicine 2008;8(2).

135. Roth, K., Hardie, J. A., Andreassen, A. H., Leh, F., and Eagan, T. M. L. Cost Minimization Analysis for Combinations of Sampling Techniques in Bronchoscopy of Endobronchial Lesions. Respiratory Medicine 2009;103(6):888-94.

136. Dobler, C. C. and Crawford, A. B. H. Bronchoscopic Diagnosis of Endoscopically Visible Lung Malignancies: Should Cytological Examinations Be Carried Out Routinely? Internal Medicine Journal 2009;39(12):806-11.

137. Franke, K. J., Nilius, G., and Ruhle, K. H. Transbronchial Catheter Aspiration Compared to Forceps Biopsy in the Diagnosis of Peripheral Lung Cancer. European Journal of Medical Research 28-1-2009;14(1):13-7.

138. Iwano S., Imaizumi K., Okada T., Hasegawa Y., and Naganawa S. Virtual Bronchoscopy-Guided Transbronchial Biopsy for Aiding the Diagnosis of Peripheral Lung Cancer. Eur J Radiol 2009;(Article in press, available online).

139. Lamprecht, B., Porsch, P., Pirich, C., and Studnicka, M. Electromagnetic Navigation Bronchoscopy in Combination With PET-CT and Rapid On-Site

Cytopathologic Examination for Diagnosis of Peripheral Lung Lesions. Lung 2009;187(1):55-9.

140. Aktas, Z., Gunay, E., Hoca, N. T., Yilmaz, A., Demirag, F., Gunay, S., Sipit, T., and Kurt, E. B. Endobronchial Cryobiopsy or Forceps Biopsy for Lung Cancer Diagnosis. Annals of Thoracic Medicine 2010;5(4):242-6.

141. Boonsarngsuk, V., Raweelert, P., Sukprapruet, A., Chaiprasithikul, R., and Kiatboonsri, S. Factors Affecting the Diagnostic Yield of Flexible Bronchoscopy Without Guidance in Pulmonary Nodules or Masses. Singapore Medical Journal 2010;51(8):660-5.

142. Rial, M. B., Delgado, M. N., Sanmartin, A. P., Leiro-Fernandez, V., Duran, M. T., Represas, C. R., and Fernandez-Villar, A. Multivariate Study of Predictive Factors for Clearly Defined Lung Lesions Without Visible Endobronchial Lesions in Transbronchial Biopsy. Surgical Endoscopy and Other Interventional Techniques 2010;24(12):3031-6.

143. Hautmann, H., Henke, M. O., and Bitterling, H. High Diagnostic Yield From Transbronchial Biopsy of Solitary Pulmonary Nodules Using Low-Dose CT-Guidance. Respirology 2010;15(4):677-82.

144. Schumann, C., Hetzel, J., Babiak, A. J., Merk, T., Wibmer, T., Moller, P., Lepper, P. M., and Hetzel, M. Cryoprobe Biopsy Increases the Diagnostic Yield in Endobronchial Tumor Lesions. Journal of Thoracic and Cardiovascular Surgery 2010;140(2):417-21.

145. Seijo L.M., de Torres J.P., Lozano M.D., Bastarrika G., Alcaide A.B., Lacunza M.M., and Zulueta J.J. Diagnostic Yield of Electromagnetic Navigation Bronchoscopy Is Highly Dependent on the Presence of a Bronchus Sign on CT Imaging: Results From a Prospective Study. Chest 2010;138(6):1316-21.

146. Lam, W. K., So, S. Y., Hsu, C., and Yu, D. Y. C. Fiberoptic Bronchoscopy in the Diagnosis of Bronchial-Cancer - Comparison of Washings, Brushings and Biopsies in Central and Peripheral Tumors. Clinical Oncology 1983;9(1):35-42.

147. Degracia, J., Bravo, C., Miravitlles, M., Tallada, N., Orriols, R., Bellmunt, J., Vendrell, M., and Morell, F. Diagnostic-Value of Bronchoalveolar Lavage in Peripheral Lung-Cancer. American Review of Respiratory Disease 1993;147(3):649-52.

148. Honeybourne, D., Babb, J., Bowie, P., Brewin, A., Fraise, A., Garrard, C., Harvey, J., Lewis, R., Neumann, C., Wathen, C. G., and Williams, T. British Thoracic Society Guidelines on Diagnostic Flexible Bronchoscopy. Thorax 2001;56:I1-I21.

149. Rivera, M. P., Detterbeck, F., and Mehta, A. C. Diagnosis of Lung Cancer - The Guidelines. Chest 2003;123(1):129S-36S.

150. Steinfort, D. P., Khor, Y. H., Manser, R. L., and Irving, L. B. Radial Probe Endobronchial Ultrasound for the Diagnosis of Peripheral Lung Cancer: Systematic Review and Meta-Analysis. Eur Respir J 2010;[Epub ahead of print].

151. Anantham, D., Koh, M. S., and Ernst, A. Endobronchial Ultrasound. Respiratory Medicine 2009;103(10):1406-14.

152. Herth, F. J. F., Ernst, A., and Becker, H. D. Endobronchial Ultrasound-Guided Transbronchial Lung Biopsy in Solitary Pulmonary Nodules and Peripheral Lesions. European Respiratory Journal 2002;20(4):972-4.

153. Kikuchi, E., Yamazaki, K., Sukoh, N., Kikuchi, J., Asahina, H., Imura, M., Onodera, Y., Kurimoto, N., Kinoshita, I., and Nishimura, M. Endobronchial Ultrasonography With Guide-Sheath for Peripheral Pulmonary Lesions. European Respiratory Journal 2004;24(4):533-7.

154. Shirakawa, T., Imamura, F., Hamamoto, J., Honda, I., Fukushima, K., Sugimoto, M., and Shirkakusa, T. Usefulness of Endobronchial Ultrasonography for Transbronchial Lung Biopsies of Peripheral Lung Lesions. Respiration 2004;71(3):260-8.

155. Yang, M. C., Liu, W. T., Wang, C. H., Lin, H. C., Chen, H. C., Chou, C. L., Hsueh, S., and Kuo, H. P. Diagnostic Value of Endobronchial Ultrasound-Guided Transbronchial Lung Biopsy Peripheral Lung Cancers. Journal of the Formosan Medical Association 2004;103(2):124-9.

156. Asahina, H., Yamazaki, K., Onodera, Y., Kikuchi, E., Shinagawa, N., Asano, F., and Nishimura, M. Transbronchial Biopsy Using Endobronchial Ultrasonography With a Guide Sheath and Virtual Bronchoscopic Navigation. Chest 2005;128(3):1761-5.

157. Becker, H. D., Herth, F., Ernst, A., and Schwarz, Y. Bronchoscopic Biopsy of Peripheral Lung Lesions Under Electromagnetic Guidance. Journal of bronchology 2005;12(1):9-13.

158. Paone, G., Nicastri, E., Lucantoni, G., Iacono, R. D., Battistoni, P., D'Angeli, A. L., and Galluccio, G. Endobronchial Ultrasound-Driven Biopsy in the Diagnosis of Peripheral Lung Lesions. Chest 2005;128(5):3551-7.

159. Herth, F. J. F., Eberhardt, R., Becker, H. D., and Ernst, A. Endobronchial Ultrasound-Guided Transbronchial Lung Biopsy in Fluoroscopically Invisible Solitary Pulmonary Nodules - A Prospective Trial. Chest 2006;129(1):147-50.

160. Chung, Y. H., Lie, C. H., Chao, T. Y., Wang, Y. H., Lin, A. S., Wang, J. L., and Lin, M. C. Endobronchial Ultrasonography With Distance for Peripheral Pulmonary Lesions. Respiratory Medicine 2007;101(4):738-45.

161. Dooms, C. A., Verbeken, E. K., Becker, H. D., Demedts, M. G., and Vansteenkiste, J. F. Endobronchial Ultrasonography in Bronchoscopic Occult Pulmonary Lesions. Journal of Thoracic Oncology 2007;2(2):121-4.

162. Eberhardt, R., Anantham, D., Ernst, A., Feller-Kopman, D., and Herth, F. Multimodality Bronchoscopic Diagnosis of Peripheral Lung Lesions - A Randomized Controlled Trial. American Journal of Respiratory and Critical Care Medicine 1-7-2007;176(1):36-41.

163. Yamada, N., Yamazaki, K., Kurimoto, N., Asahina, H., Kikuchi, E., Shinagawa, N., Oizumi, S., and Nishimura, M. Factors Related to Diagnostic Yield of Transbronchial Biopsy Using Endobronchial Ultrasonography With a Guide Sheath in Small Peripheral Pulmonary Lesions. Chest 2007;132(2):603-8.

164. Yoshikawa, M., Sukoh, N., Yamazaki, K., Kanazawa, K., Fukumoto, S. I., Harada, M., Kikuchi, E., Munakata, M., Nishimura, M., and Isobe, H. Diagnostic Value of Endobronchial Ultrasonography With a Guide Sheath for Peripheral Pulmonary Lesions Without X-Ray Fluoroscopy. Chest 2007;131(6):1788-93.

165. Asano, F., Matsuno, Y., Tsuzuku, A., Anzai, M., Shinagawa, N., Yamazaki, K., Ishida, T., and Moriya, H. Diagnosis of Peripheral Pulmonary Lesions Using a Bronchoscope Insertion Guidance System Combined With Endobronchial Ultrasonography With a Guide Sheath. Lung Cancer 2008;60(3):366-73.

166. Fielding, D. I. K., Robinson, P. J., and Kurimoto, N. Biopsy Site Selection for Endobronchial Ultrasound Guide-Sheath Transbronchial Biopsy of Peripheral Lung Lesions. Internal Medicine Journal 2008;38(2):77-84.

167. Koh, M. S., Tee, A., Wong, P., Antippa, P., and Irving, L. B. Advances in Lung Cancer Diagnosis and Staging: Endobronchial Ultrasound. Internal Medicine Journal 2008;38(2):85-9.

168. Eberhardt, R., Ernst, A., and Herth, F. J. F. Ultrasound-Guided Transbronchial Biopsy of Solitary Pulmonary Nodules Less Than 20 Mm. European Respiratory Journal 2009;34(6):1284-7.

169. Chao, T. Y., Chien, M. T., Lie, C. H., Chung, Y. H., Wang, J. L., and Lin, M. C. Endobronchial Ultrasonography-Guided Transbronchial Needle Aspiration Increases the Diagnostic Yield of Peripheral Pulmonary Lesions A Randomized Trial. Chest 2009;136(1):229-36.

170. Huang, C. T., Ho, C. C., Tsai, Y. J., Yu, C. J., and Yang, P. C. Factors Influencing Visibility and Diagnostic Yield of Transbronchial Biopsy Using Endobronchial Ultrasound in Peripheral Pulmonary Lesions. Respirology 2009;14(6):859-64.

171. Oki, M., Saka, H., Kitagawa, C., Kogure, Y., Mori, K., and Kajikawa, S. Endobronchial Ultrasound-Guided Transbronchial Biopsy Using Novel Thin Bronchoscope for Diagnosis of Peripheral Pulmonary Lesions. Journal of Thoracic Oncology 2009;4(10):1274-7.

172. Disayabutr, S., Tscheikuna, J., and Nana, A. The Endobronchial Ultrasound-Guided Transbronchial Lung Biopsy in Peripheral Pulmonary Lesions. J Med Assoc Thai. 2010;93(Suppl 1):S94-S101.

173. Eberhardt, R., Morgan, R. K., Ernst, A., Beyer, T., and Herth, F. J. F. Comparison of Suction Catheter Versus Forceps Biopsy for Sampling of Solitary Pulmonary Nodules Guided by Electromagnetic Navigational Bronchoscopy. Respiration 2010;79(1):54-60.

174. Mizugaki, H., Shinagawa, N., Kanegae, K., Yamada, N., Asahina, H., Kikuchi, E., Oizumi, S., Tamaki, N., and Nishimura, M. Combining Transbronchial Biopsy Using Endobronchial Ultrasonography With a Guide Sheath and Positron Emission Tomography for the Diagnosis of Small Peripheral Pulmonary Lesions. Lung Cancer 2010;68(2):211-5.

175. Roth, K, Eagan, T. M, Andreassen, A. H, Leh, F, and Hardie, J. A. A Randomised Trial of Endobronchial Ultrasound Guided Sampling in Peripheral Lung Lesions. Lung Cancer 2011;74(2):219-25.

176. Bolliger, C. T. and Mathur, P. N. ERS/ATS Statement on Interventional Pulmonology. European Respiratory Journal 2002;19(2):356-73.

177. Robinson, R. Economic-Evaluation and Health-Care. What Does It Mean. British Medical Journal 11-9-1993;307(6905):670-3.

178. Robinson, R. Economic-Evaluation and Health-Care - Cost-Benefit-Analysis. British Medical Journal 9-10-1993;307(6909):924-6.

179. Robinson, R. Economic-Evaluation and Health-Care. Cost-Utility Analysis. British Medical Journal 2-10-1993;307(6908):859-62.

180. Robinson, R. Economic-Evaluation and Health-Care. Costs and Cost-Minimization Analysis. British Medical Journal 18-9-1993;307(6906):726-8.

181. Robinson, R. Economic-Evaluation and Health-Care - Cost-Effectiveness Analysis. British Medical Journal 25-9-1993;307(6907):793-5.

182. Gold, M, Siegel, J, Russel, L, and Weinstein, M. Cost-Effectiveness in Health and Medicine. Oxford university press 1996.

183. SPSS for Windows. Rel. 15.0.1.1 Chicago. SPSS Inc 2007.

184. TreeAgePro Healthcare 1.4.1. Williamstown. TreeAge Software Inc 2008.

185. SPSS Data Entry Station. Rel. 4.0.0 Chicago. SPSS Inc 1996.

186. Stata Statistical Software: Release 11. StataCorp. College Station, TX: StataCorp LP. 2009.

187. Buttner, J. Diagnostic Validity As a Theoretical Concept and As a Measurable Quantity. Clinica Chimica Acta 25-4-1997;260(2):131-43.

188. Kimberlin, C. L. and Winterstein, A. G. Validity and Reliability of Measurement Instruments Used in Research. American Journal of Health-System Pharmacy 1-12-2008;65(23):2276-84.

189. Klein-Geltink, J. E., Rochon, P. A., Dyer, S., Laxer, M., and Anderson, G. M. Readers Should Systematically Assess Methods Used to Identify, Measure and Analyze Confounding in Observational Cohort Studies. Journal of Clinical Epidemiology 2007;60(8):766-72.

190. Normand, S. L. T., Sykora, K., Li, P., Mamdani, M., Rochon, P. A., and Anderson, G. M. Readers Guide to Critical Appraisal of Cohort Studies: 3. Analytical Strategies to Reduce Confounding. British Medical Journal 30-4-2005;330(7498):1021-3.

191. Slack, M. K. and Draugalis, J. R. Establishing the Internal and External Validity of Experimental Studies. American Journal of Health-System Pharmacy 15-11-2001;58(22):2173-81.

192. Bossuyt, P. M., Reitsma, J. B., Bruns, D. E., Gatsonis, C. A., Glasziou, P. P., Irwig, L. M., Lijmer, J. G., Moher, D., Rennie, D., and De Vet, H. C. W. Towards Complete and Accurate Reporting of Studies of Diagnostic Accuracy: The STARD Initiative. Clinical Chemistry 2003;49(1):1-6.

193. Begg, C., Cho, M., Eastwood, S., Horton, R., Moher, D., Olkin, I., Pitkin, R., Rennie, D., Schulz, K. F., Simel, D., and Stroup, D. F. Improving the Quality of Reporting of Randomized Controlled Trials - The CONSORT Statement. Jama-Journal of the American Medical Association 28-8-1996;276(8):637-9.

194. Moher, D., Schulz, K. F., and Altman, D. G. The CONSORT Statement: Revised Recommendations for Improving the Quality of Reports of Parallel-Group Randomised Trials. Lancet 14-4-2001;357(9263):1191-4.

195. Chhajed, P. N. and Tamm, M. Bronchoscopy for Small Pulmonary Nodules and Mediastinal Staging of Lung Cancer - Just Do It! American Journal of Respiratory and Critical Care Medicine 1-11-2006;174(9):961-2.

196. Herth, F. J. F., Eberhardt, R., and Ernst, A. The Future of Bronchoscopy in Diagnosing, Staging and Treatment of Lung Cancer. Respiration 2006;73(4):399-409.

197. Annema, J. T. and Rabe, K. F. State of the Art Lecture: EUS and EBUS in Pulmonary Medicine. Endoscopy 2006;38:S118-S122.

198. Briggs, A. H. and O'Brien, B. J. The Death of Cost-Minimization Analysis? Health Economics 2001;10(2):179-84.

199. Eberhardt, R., Kahn, N., Gompelmann, D., Schumann, M., Heussel, CP., and Herth, F. J. F. LungPoint--a New Approach to Peripheral Lesions. Journal of Thoracic Oncology 2010;5(10):1559-63.