TECHNOLOGY ASSESSMENT REPORT

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MINISTRY OF HEALTH MALAYSIA

ENDOBRONCHIAL ULTRASOUND (EBUS)

Health Technology Assessment Unit

Medical Development Division

Ministry of Health Malaysia

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MINISTRY OF HEALTH MALAYSIA

Health Technology Assessment Report

ENDOBRONCHIAL ULTRASOUND (EBUS)

interpretation and synthesis of scientific research and/or technology

document may not fully reflect all scientific research available. Additionally, other relevant scientific findings may have been reported since completion

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EXECUTIVE SUMMARY

the biopsy channels of regular fiberoptic bronchoscopes. The probes are constructed with balloons at the tip. By filling the balloon with water, close contact to the bronchial

up to 4 cm can be achieved with a 20-MHz probe. This is sufficient to examine all the structures necessary for local staging. BF-UC160F-OL8 & BF-UC260F-OL8 Ultrasonic Bronchofibervideoscope which is specifically designed for ultrasound-guided TBNA

needle under ultrasound imaging, confirming the position of the needle tip during TBNA procedures. Furthermore, the Power Doppler facility allows the blood flow conditions

EBUS guided transbronchial aspiration (EBUS-TBNA) improved the results of N-staging of lung cancer, especially in difficult lymph node levels without any clear endoscopic landmarks. The possibility of identifying N2 and N3 stages by means of a nonsurgical

than did bronchoscopy or HR-CT

iii. EBUS-guided TBNA added little time but increased the diagnostic yield significantly compared to conventional TBNA in stations other than subcarinal nodes

staging in lung cancer is higher with EBUS-TBNA than it is with other modalities. It

≥ 20 mm and for localizing and diagnosis of solitary pulmonary nodules that cannot be visualized by fluoroscopy

vi. Diagnosis obtained by EBUS-guided TBNA / EBUS-guided TBB averted the need

Regional Respiratory Centres in Malaysia. However, centres utilizing this technology

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HEALTH TECHNOLOGY ASSESSMENT ENDOBRONCHIAL ULTRASOUND (EBUS)

1. INTRODUCTION

1.1 Lung cancer

males (13.8% of cancer in males) and the 8 commonest among the females (3.8%). The Age-standardized incidence rate (ASR) was 20.3 for males and 6.5 for females.

(7.8%).

(SCLC) or non-small cell type lung cancer (NSCLC), and the presence of mediastinal involvement or distant spread of the tumour. The treatment of SCLC is mainly chemotherapy whereas NSCLC treatment is fully stage dependent ranging from

experimental chemotherapy / radiotherapy. Non-small cell lung cancer (NSCLC) usually metastasizes first to hilar and mediastinal lymph nodes. Subsequently,

For staging of the NSCLC, the TNM classification has been developed in which T stands for local tumour extension, N for lymph node metastasis and M for distant

for the description of the N factor of the TNM classification. The TNM classification is subdivided in cTNM and a pTNM where the cTNM
while the pTNM is based on the pathological results of the operation.
lymph node enlargement occurs in up to 38% of NSCLC at diagnosis. Mediastinal lymph node staging can be divided into imaging and sampling. Computed Tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET)

lesions can be performed by mediastinoscopy, thoracoscopy, transthoracic fine-

with fine needle aspiration.

1.2 Endobronchial ultrasound (EBUS)

Transbronchial needle aspiration (TBNA) of mediastinal lesions, has been reported since 1940's and can be performed during routine bronchoscopy. Currently, "blind" TBNA is only performed by 27% of chest physician because of the lack of real time monitoring of the needle. The yield of TBNA can be increased, especially for those nodes outside the subcarinal region, by using endobronchial ultrasound (EBUS) to locate the node prior to TBNA.
under local anaesthesia. Limitation of this radial EBUS "localisation method" is that

real-time ultrasound control from the trachea bronchial tree. With EBUS-TBNA the para-tracheal (stations 2 and 4), subcarinal (station 7) hilar and intrapulmonary nodes (stations 10 and 11) can be reached.

EBUS guided transbronchial aspiration (EBUS-TBNA) improved the results of N-staging of lung cancer, especially in difficult lymph node levels without any clear endoscopic landmarks. The possibility of identifying N2 and N3 stages by means of a

approach under fluoroscopic or CT guidance is the standard procedure. However,

instead of fluoroscopic guidance and also plays an important role in the strategy for

1.3 Competing diagnostic technologies

Neither CT scan nor MRI are able to distinguish malignant from hyper plastic, granulomatous or fibrotic lesions. With reported sensitivities and specificities of 69% and 71% for CT scan and 45% and 65% for MRI, both techniques prove too

fluoro-2-deoxyflucose (FDG) and CT scan showed that PET was significantly more accurate than CT scan in demonstrating nodal metastasis.

stations (level 2R, 2L, 4R and 4L) and the anterior subcarinal lymph node station (level 7), access to the posterior and inferior mediastinum is limited and requires either

Endoscopic ultrasound with fine needle aspiration (EUS-FNA) offers a minimally

limitation of EUS-FNA is its inability to visualise stations anterior and superior to the

made by the Consultant Respiratory, who is also the Director of the Respiratory Medical Institute (IPR). It is intended for the use of health planners and policy makers.

2. TECHNICAL FEATURES - EBUS

Traditional methods for observing the presence and progress of lung disease such as CT

channels of regular fiberoptic bronchoscopes. At the tip of these probes is a small

sonic waves are transmitted to the tissues and reflected according to the impedance (resistance) to sound waves of different tissue structures. In between the generation

surrounding air reflects most of the sound waves. Therefore, the probes are constructed with balloons at the tip. By filling the balloon with water, close contact to the bronchial wall is established and filling the balloon with water can transmit the sound waves at

can be achieved with a 20-MHz probe. This is sufficient to examine all the structures

BF-UC160F-OL8 Ultrasonic Bronchofibervideoscope

Olympus Co. has created endobronchial ultrasonic devices with different specifications. Among the models include the BF-UC160F-OL8 & BF-UC260F-OL8 Ultrasonic Bronchofibervideoscope which is specifically designed for ultrasound-guided TBNA

optical system design that exploits both video and fiberoptic technologies. These scopes

ultrasound imaging, confirming the position of the needle tip during TBNA procedures. Furthermore, the Power Doppler facility allows the blood flow conditions to be checked

devices. For each scope, there is a specifically designed single use aspiration needle

biopsy channel, the position of the needle tip can be confirmed in real-time during the

3. POLICY QUESTION

Should EBUS be made available in Regional Respiratory Centres in Malaysia?

4. OBJECTIVE

and other lung diseases, specifically in the diagnostic and therapeutic properties

Centres

5. METHODOLOGY

5.1 Literature search strategy

searches included PUBMED, OVID, Proquest, Cochrane databases, Food and Drug Administration (FDA) and HTA databases and related links. Google was used to search

5.2 Selection criteria and method

iii. Populationgroup:Patientswithenlargedmediastinalnodes/hilarlymphadenopathy, patients referred for EBUS TBNA, patients with central lung tumour / established

iv. Interventions: Endobronchial ultrasound (EBUS) TBNA

v. Comparators : Blind (Conventional) TBNA, Transesophageal ultrasound guided aspiration (EUS-FNA), Computed Tomgraphy (CT), Bronchoscopy and Computed Tomography (CT), Transbronchial lung biopsy under fluoroscopy guidance only, Possitron Emission Tomograpgy (PET) and mediastinoscopy.

- Safety, adverse events or complications
- Diagnostic yield of EBUS – detection rate, positive rate, sensitivity, specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV), definitive diagnosis and staging. Correlation between EBUS classification and postoperative classification for tumour involvement, correlation between EBUS image and

- Cost analysis

5.3 Data extraction

All the relevant articles were retrieved and appraised by two reviewers using Critical Appraisal Skills Programme (CASP) depending on the type of study design.

5) and was discussed with the expert committee before deciding on the eligibility

commentaries were excluded. All articles were classified according to the levels of evidence for assessing diagnosis using Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001). (Appendix 1)

6. RESULTS AND DISCUSSION

to be presented in the evidence tables for accuracy/effectiveness/ safety of EBUS in

6.1 Diagnostic accuracy / effectiveness

The accuracy / effectiveness of EBUS in diagnosis and therapeutic strategies of central tumour, in diagnosis of mediastinal / hilar lymph nodes and staging of lung

6.1.1 EBUS in the Diagnostic and Therapeutic Strategies of Central Cancer

A total of five articles related to centrally located lung cancer and tumour invasion of the bronchial wall were identified. Determination of the depth of invasion of

most important finding for determining the appropriate mode of therapy, whether

Kurimoto et al. described the correspondence between the microscopic findings of

wall in extrapulmonary and intrapulmonary bronchi was described as a five-

invasion between EBUS findings and histological findings in 23 out of 24 (95.8%)

(EBUS) images and histologic findings in normal and tumour-invaded bronchial

The layers were confirmed by microscopic findings. EBUS images of the

bronchi. However, there was an additional findings: a membranous portion lacking

1.90 mm) and the actual histological measurement 1.03 mm (range, 0.62-1.75)

Comparison of the echo intensity of the ultrasonogram of the bronchus produced

(NIH Image) was described by Nakamura et al.
echo intensity curves showed five peaks and troughs, indicating that the normal bronchial wall is a laminar structure consisting of five ultrasonically different

and fourth layer were significantly greater with the 30-MHz probe than the 20-

of the normal five layers and the tumour has invaded beyond the bronchial wall.

et al. studied the ability of EBUS to differentiate between airway infiltration

within the chest who underwent surgery following chest CT and bronchoscopic

present in 49 patients (47%) and tumour impression in 56 patients (53%). The pathologic examination after surgery showed tumour invasion in 55 patients (52%) and tumour impression in 50 patients (48%). Examination of the tracheobronchial tree with EBUS for possible infiltration by a central tumour yielded an accuracy

of 94%, a sensitivity of 89%, and a specificity of 100% which is higher than chest CT. Chest CT scanning yielded an accuracy of 51%, a sensitivity of 75%, and a specificity of 28%. The correlation between EBUS classification and the postoperative classification of airway involvement was highly significant (correlation 0.89, $p<0.01$).

therapy (PDT) among patients with centrally located lung cancer.

and HR-CT. According to evaluation by EBUS, 9 of these 18 lesions including three CIS were diagnosed as intracartilaginous, because the cartilage was not

as determined by bronchoscopy, five lesions protruded beyond the cartilage when image by EBUS and was later confirmed histopathologically.
depth of the tumour invasion estimated by HR-CT indicated that 11 lesions

were invisible on HR-CT, invaded beyond the cartilage as shown by EBUS. EBUS

than did bronchoscopy or HR-CT.

the histopathologic findings were identical in the six patients. None of these patients has developed a recurrence. Median follow–up: 22.3±13.8 months.

bronchoscopy and HR-CT to improve the efficacy of PDT in patients with centrally

6.1.2 EBUS of mediastinal / hilar lymph nodes in the Diagnosis and Staging of Lung Cancer

One of the primary goals of EBUS was the detection and the TBNA of mediastinal

of 16 articles were identified. There were three Randomized Control Trials, 11

Herth et al. published his earlier experience using EBUS-TBNA in 242 patients

patients (86%) the lymph nodes were successfully accessed by TBNA (specific diagnosis or lymphocytes on specimen) and was able to establish diagnosis or a definitive staging in 172 patients out of 242 patients (71%).

EBUS and EBUS plus CT were more accurate than CT alone in imaging of the

EBUS for hilar lymph nodes was twice of CT scan (54% and 27% respectively). However, positive rate of EBUS and CT scan was the same 27%.The detection rates for mediastinal lymph nodes by EBUS and Chest CT scan were 86% and

ability of EBUS was superior to that of CT scan in identifying lymph nodes < 10 mm in diameter. Detection accuracy of lymph node metastasis by Chest CT scan and EBUS in 16 surgical cases showed that the sensitivity and specificity of EBUS alone was 67% and 92% respectively. The sensitivity and specificity of chest CT was 75% and 83% respectively. Combination of EBUS plus chest CT yielded a sensitivity of100% and a specificity of 77%. Overall accuracy of EBUS

Herth et al. and Munavvar et al. investigated the results of EBUS guided TBNA as compared to conventional TBNA.
enlarged lymph nodes referred for TBNA were randomized into two groups: 100 patients underwent EBUS guided TBNA and 100 patients underwent conventional TBNA.

subcarinal lymph nodes were randomized and analyzed separately (group A)

were randomized into group B by computer. The yield of TBNA in group A for conventional TBNA was 74% compared to 86% in the EBUS-guided group. The difference was statistically non significant (p=0.3). In the group B, the overall yield of conventional TBNA was 58% compared to 84% in the EBUS-guided TBNA. The difference was statistically significant (p<0.001). The combined yield for groups A and B was 71% for conventional TBNA versus 80% for EBUS guidance (p < 0.05).
in diagnostic yield from 46.2% with conventional TBNA to 88.9% with EBUS guided TBNA.

Diagnostic rate of EBUS guided TBNA was shown to be significantly higher

bronchoscope as shown by Kanoh et al. Fifty-five patients with mediastinal and / or hilar lymphadenopathy were randomized into EBUS-D and EBUS-S group. Diagnostic rate of EBUS-D was significantly higher than EBUS-S (97% versus 76%, p=0.025).

needle aspiration of mediastinal and hilar lymph nodes using convex probe (CP) EBUS were demonstrated by Herth et al., Yasufuku et al. and Krasnik et al.
Herth et al. in a study involving 502 patients referred for TBNA for diagnosis of

diagnostic yield of 535 out of 572 nodes (93.5%) was reported. Analysing the diagnostic yield for 502 patients, a definitive diagnosis was established in 470 patients (93%). The sensitivity was 94%, specificity 100%, accuracy 94%, PPV 100% and NPV 11%. Procedure was not influenced by lymph node location and Yasufuku et al. yielded an overall sensitivity, specificity and diagnostic accuracy rate of direct CP-EBUS guided TBNA in distinguishing benign and

lesions, the aspirated materials obtained was diagnostic in all cases. EBUS-FNA identified malignant cells in 13 lesions and benign cells in two.

Plat et al. demonstrated that EBUS-TBNA allowed diagnosis to be reached in 27 out of 33 (82%) of patients with Positron Emission Tomography with 18-fluorodeoxyglucose (FDG-PET) positive mediastinal lesions referred for staging and / or diagnosis. Seventy eight percent (21/27) were diagnosed after previous EBUS localization. Previous localization with EBUS was associated with a TBNA

sampling of mediastinal lymph nodes) was avoided by the positive results of TBNA in 25 cases (76%) of patients. Nakajima et el. described the ability of EBUS-TBNA in diagnosing pre tracheal lymph node metastases from renal

Comparison of Endobronchial ultrasound guided transbronchial biopsy (EBUS-TBNA) and Transesophageal fine needle aspiration (EUS-FNA) was evaluated by

lymph nodes (1cm) as assessed by contrast-enhanced computed tomography

in positions 5,6, or 11 (which are accessible only by bronchoscopy) and stations 8 and 9 (which are accessible only by esophagoscopy).Patients were

on their image findings. Patients underwent ultrasound–guided transbronchial (EBUS-TBNA) and transesophageal needle biopsies (EUS-FNA) in a cross over design. Transbronchial approach was successful in 142 patients (88%), and was

diagnostic in 76%. For each station, the number of positive samples (successful) for the transbronchial / transesophageal approaches was: 2R; 19/13; 2L: 16/19; 3: 17/15; 4R: 19/12; 4L: 17/20; 7:19/20; 10R: 18/9; and 10L: 17/18. Combining the

nodes was achieved in 97% of patients and resulted in a specific diagnosis in

were neither clinically nor statistically significant. Combining both approaches is

EBUS-TBNA has been used to stage 256 patients in published papers. Correct prediction of lung cancer staging was assessed by Yasufuku

suspected of malignancy detected on CT were included in the study. In 105 patients, EBUS-TBNA was successfully performed to obtain samples from 163

(2.8%).The diagnostic value of EBUS-TBNA in correct prediction of lymph node

specificity of 100%, positive predictive value (PPV) of 100%, negative predictive value (NPV) of 89.5%, and diagnostic accuracy rate of 96.3%. As a result, 29 mediastinoscopies, 8 thoracotomies, 4 thoracoscopies, and 9 CT-guided PCNB were avoided by EBUS-TBNA.

EBUS-TBNA has a high sensitivity as well as specificity compared to CT or PET Yasufuku et al. in a

suspected lung cancer, demonstrated that the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of EBUS-TBNA in the correct prediction of mediastinal lymph nodes staging were 92.3%, 100%, 100%, 97.4%, and 98.0% respectively. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of CT in the prediction of mediastinal lymph node staging were 76.9%, 55.3%, 37.0%, 87.5% and 60.8% respectively. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of PET in

91.5% and 72.5% respectively. There is a significant difference in the accuracy of the three different modalities ($p<0.00001$). Similarly, EBUS-TBNA had 100% sensitivity, specificity and PPV compared to PET/CT which had sensitivity of 67%, specificity of 68%, PPV of 40% and NPV of 87% as shown by Krasnik

endobronchial ultrasound real-time fine needle aspiration for staging of

20 patients with known or suspected lung cancer, EBUS-TBNA was performed together with additional EUS examination in whom the staging CT scan had

inferiorly placed lymph nodes in station 7). EBUS-TBNA was undertaken in 18 out of 20 patients and additional EUS-FNA in six out of seven patients. From 18 patients undergoing EBUS-TBNA ±EUS-FNA, 11 patients resulted in

false negative. For the 18 patients who underwent EBUS-TBNA the sensitivity, specificity and accuracy were 85% (95% CI- 54.6-98.1), 100% (95% CI-47.8-

100) and 89% (95% CI -65.3-98.6) respectively. Additional findings attributable to the EUS-FNA were noted in every case. EBUS-TBNA can be used to identify

to the posterior –inferior lymph node stations 5, 7, 8 and 9.

6.1.3 EBUS in Peripheral Pulmonary Lesions

Twelve studies, including three Randomized Control Trials were identified and

by Kurimoto et al. and Chao et al.
were identified by EBUS based on the internal structure of the lesion.

patent vessels and patent bronchioles; type 1b, without vessels and bronchioles); type 11, hyperechoic dots and linear arcs pattern type(11a, without vessels; type 11b, with patent vessels); and type 111, heterogenous pattern (type 111a, with hyperechoic dots and short lines; type 111b, without hyperechoic dots and short lines). Twenty-three of 25 type 1 lesions (92.0%) were benign, while 98 of 99 type 11 and 111 lesions (99.0%) were malignant. Twenty- one of 24 type 11 lesions (87.5%) were well-differentiated adenocarcinomas, and all type 111b lesions were malignant, including 18 poorly differentiated adenocarcinomas (81.8%).

In another study, Chao et al. described four image patterns: (1) continuous hyperechoic margin outside the lesion, (2) homogenous or heterogenous internal echoes, (3) hyperechoic dots in the lesion, and (4) concentric circles along the echo probe. Comparisons of EBUS image patterns to clinical diagnosis in 93

0.030) respectively. Images with homogenous internal echoes were more likely to be non neoplasm lesions by univariate analysis ($p<0.001$) but the significance of internal echoes was lost after multivariate analysis (0.674). Approximately

Usually the procedure is performed as a transbronchial biopsy with fluoroscopy

patients referred for transbronchial biopsy (TBBX) for peripheral lesions underwent fluoroscopy-guided and EBUS-guided TBBX in random order. In EBUS-guided TBBX diagnosis was established in 40 patients (80%). Under fluoroscopic guidance, diagnosis was established in 38 patients (76%). There is a non significant trend for EBUS to be better than fluoroscopy for lesions < 3 cm in diameter (80% versus 57%). In nine patients (18%), the diagnosis obtained by bronchoscopy saved a surgical procedure (sarcoidosis (2), tuberculosis (2), infection (1), metastatic disease (1), and small cell lung cancer (3).

assigned to EBUS-TBB or TBB only. A definitive diagnosis was obtained by EBUS-TBB in 66 of 87 patients (75.8%) and by conventional TBB in 62 of 119 patients (52.1%). Analysis of patients with malignant disease in the EBUS-

significantly higher than TBB (p=0.004 and p=0.007, respectively). Sensitivity

of patients with > 3 cm showed no significant difference in diagnostic ability

in lesions < 2cm, [23% (TBB) versus 71% (EBUS-TBB)] p=0.001.

Chung et al. in his randomized control trial involving 158 patients showed that measuring and applying the distance between the orifice of the bronchus and

biopsies (TBBs) for peripheral lesion.
two groups – EBUS-D group (EBUS TBBs with measured distance prior to biopsy) and EBUS group (without measured distance).The diagnostic yield of TBBs in group EBUS-D patients was 78.9% (45/57) which was significantly higher than in group EBUS patients 57.1% (32/56) (p=0.013). Gender, age, size of lesions,

the two groups. Factors that influenced the diagnostic yield of EBUS-guided TBB include probe location within the lesion on EBUS image (p=0.001) and measured distance before biopsy (p=0.002), were statistically significant.

The ability of EBUS together with fluoroscopy to guide transbronchial lung biopsy as compared to fluoroscopy alone to guide transbronchial lung biopsy

combined EBUS and fluoroscopy guidance (Cases) and 42 patients underwent transbronchial lung biopsy under fluoroscopy guidance only (Controls). In 38 cases out of 50 cases (76%) EBUS could describe the peripheral lesion (33 from inside and 5 from adjacent bronchus). Lung cancer was diagnosed in 24 patients

cancer diagnosis and specificity for cancer exclusion were 100%, respectively (15/15, 18/18). Compared to the controls, in whom the biopsy site was determined by fluoroscopy only, the sensitivity tended to be superior by EBUS, although it did not reach statistical significance (p=0.06). However, specificity and accuracy were statistically significant (both p=0.02). In 25/30 cases (83.3%) with successful

The ability of endobronchial ultrasound (EBUS) using guide sheath (EBUS-GS)

lesions defined as a mass (>30 mm; 24 of 26 lesions, 92%) was significantly higher than that for lesions defined as nodules ≤ 30mm; 92 of 124 lesions, 74%) p=0.04. When the lesion was ≤ 30mm, size does not affect the yield by EBUS-GS. The yield for lesions ≤ 10 mm did not decrease (76%). EBUS–GS is particularly useful for lesions ≤ 20 mm that are undetectable by fluoroscopy.

that diagnostic sensitivities were 44.4% (8 of 18) for lesions < 20 mm in mean diameter and 91.7% (11 of 12) for lesions 20 to 30 mm in diameter.

EBUS-guided TBBX has been shown to be effective in localising and diagnosing fluoroscopically invisible pulmonary nodules as shown by a study conducted

pulmonary nodules which could not be visualized by fluoroscopy who were

with EBUS-guided TBBX (89%). The lesion could not be visualized in six patients,

left upper lobe. A diagnosis was established in 38 of these patients (70%). The diagnosis obtained by EBUS-guided TBBX averted the need for more surgery in

6).

Similarly, the diagnostic efficacy of EBUS-guided transbronchial biopsy, in the absence of fluoroscopic guidance, was evaluated in a series of consecutive

of 50 patients (74%) and histologic diagnosis could be established in 31 of these 37 (84%), cytology diagnosis in one and no diagnosis in 5 patients. For EBUS invisible lesion (n=13), no diagnosis was obtained in 11 and cytology diagnosis was obtained in 2. In 34 patients (68%), a pathologic (histology+cytology) diagnosis

decreased to 18% whereas for lesions ≥ 20 mm diagnostic pathologic yield was 32/39 (82%).

Yoshikawa et al. evaluated the diagnostic value of EBUS with a guide sheath for peripheral pulmonary lesions without X-Ray fluoroscopy.

fluoroscopy and 86.2% for all bronchoscopic procedures. The diagnostic yield for PPLs > 20 mm in diameter (75.6%) was significantly higher than that for lesions ≤ 20 mm (29.7%) p<0.01. When the bronchus leading to the PPL was identified on the CT scan, the yield was 79.2%. Solid lesions had a higher diagnostic yield (67.0%) compared to non solid lesions (35%; p < 0.05). Multivariate analysis

predictors of diagnostic sensitivity by EBUS-GS guided bronchoscopy (p<0.05).

6.1.4 EBUS in Interventional Bronchoscopy

used before mechanical tumour destruction (346 cases, 29%), in airway stent placement (235 cases, 20%), before and during Neodynium: yttrium aluminium garnet (Nd:YAG) laser resection (148 cases, 13%), Argon- plasma coagulation APC (262 cases, 23%), brachytherapy (134, 11%), foreign body removal (22, 2%) and abscess drainage (27, 2%). In 43% of the cases where EBUS was used, it resulted in change of therapy or better guidance of the intervention. Changes of treatment

or APC was stopped when EBUS demonstrated close relationships with vessels. Severe bleed of fistula formation did not develop in any of the cases where EBUS

patients. Lymph node metastasis was confirmed by EBUS guided transbronchial

6.1.5 EBUS in management of other lung diseases

tumour. Galluccio G and Lucantoni G described the use of EBUS-FNA in

resection by video-assisted thoracoscopy (VATS). The excision was incomplete

EBUS (after 7 days) confirmed the complete

monthly CT follow-up showed no cyst's regrowth was found after 18 months.

ill-defined and absent in places; this is continued along the trachea into both

fibrous changes and inflammatory cell infiltration. Relapsing polychondritis

this continued along the central airway. The hyperechoic third and fifth layers of

swollen, indicating cartilage degeneration. Biopsy of tracheal cartilage confirmed chronic chondritis with plasma cell and lymphocytic infiltration. Two months after

bronchoscopy showed a pulsatile identification of the right lateral wall by the

in asthmatic airway was demonstrated by Yamasaki et al.

tracheobronchial wall as five bands. After 2 weeks of montelukast 10 mg daily,

thickness to the total wall thickness (% submucosal thickness), was reduced

6.2 Safety

2007 depending on the models and specifications. is classified under Class 11 Regulatory Class. The device has been installed in Europe, USA, Japan and

safety of EBUS when used in mediastinal / hilar lymph nodes diagnosis and staging

associated with EBUS-TBNA procedures.

2 cases. One patient developed pneumothorax (2%) which was treated with tube Chung et al. in his study involving 158 patients noted that there was a brisk haemorrhage in five patients as a result of forceps biopsy (3 in group EBUS-D and 2 in group EBUS). Self-limited pneumothorax secondary to

Kurimoto et al. noted moderate bleeding in two patients (1%). None

or other clinically significant morbidity.
developed pneumothorax (4.2%) which was treated by tube thoracostomy. No major

observed in three patients. One patient (2%) had a pneumothorax that was treated

bronchoscopic haemostasis was noted in one patient. No significant adverse effects
Yoshikawa et al. noted that
(0.8%), who did not need to be treated.

tachycardia, in 52 patients (5.5%) out of 1,174 patients. This was associated with

caused haemodynamic compromise. No other complications associated with EBUS

6.3 Cost effectiveness

Becker DH and Herth F estimated the fixed costs and long term investment are approximately $80,000 to $ 100,000 (US).
by the supplier for Olympus Compact Endoscopic Ultrasound Centre and Ultrasonic Bronchofibervideoscope is RM 262,000.00. The price for Olympus Compact Endoscopic Ultrasound Centre, Ultrasonic Bronchofibervideoscope and Endoscopic Video Imaging System is RM 410,000.00

6.4 Training

The technology implies a switch from a surgeon (mediastinoscopy) to pulmonologist / endoscopist. The mean examination time for EBUS procedures ranges from three minutes to fifteen minutes.

proven benefit in many bronchoscopic procedures.

7. CONCLUSION

7.1 Diagnostic accuracy / Effectiveness

7.1.1 EBUS in the Diagnostic and Therapeutic Strategies of Central Cancer

invasion than did bronchoscopy or HR-CT.

7.1.2 EBUS of mediastinal / hilar lymph nodes in the Diagnosis and Staging of Lung Cancer

i. EBUS-TBNA added little time but increased the diagnostic yield significantly compared to conventional TBNA in stations other than subcarinal nodes

node staging in lung cancer is higher with EBUS-TBNA than it is with other

iii. EBUS-TBNA should be considered for staging mediastinal lymph nodes as

iv. The combine approach of EUS-FNA and EBUS-TBNA may replace more

7.1.3 EBUS in Peripheral Pulmonary Lesions

bronchoscopic occult pulmonary masses ≥ 20 mm

of solitary pulmonary nodules that cannot be visualized by fluoroscopy

v. Endobronchial ultrasonography with guide sheath–guided transbronchial biopsy (EBUS-GS guided TBB) without the use of radiographic fluoroscopy

7.1.4 EBUS in Interventional Bronchoscopy

7.1.5 EBUS in management of other lung diseases

7.2 Safety

7.3 Cost effectiveness

7.4 Training

8. RECOMMENDATION

Regional Respiratory Centres in Malaysia. However, centres utilizing this technology

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Appendix 1

Levels of Evidence Scale - Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001)

Level	Therapy/ Prevention, Aetiology/Harm	Prognosis	Diagnosis	Differential diagnosis/symptom prevalence study	Economic and decision analyses
1a	) of RCTs	) of studies; CDR†	SR (with homogeneity*) studies; CDR† with 1b	homogeneity*) of	SR (with homogeneity*)
1b	Individual RCT (with Confidence)	80% follow-up; CDR†	Validating** cohort study with good††† reference standards; or CDR†		costs or alternatives; systematic review(s) of the evidence; and
1c			SnNouts††		analyses ††††
2a	) of	) of groups in RCTs	SR (with homogeneity*)	homogeneity*) of 2b	SR (with homogeneity*)
2b	quality RCT; e.g., <80% follow-up)	patients in an RCT; CDR†	good†††reference standards; CDR† after		costs or alternatives; limited review(s) of the studies; and including
2c	"Outcomes" Research; Ecological	"Outcomes" Research			
3a	) of		SR (with homogeneity*)	homogeneity*) of 3b	SR (with homogeneity*)
3b	Individual Case-Control Study		Non-consecutive study;	Non-consecutive	
4	Case-series (and)	Case-series (and)	Case-control study, poor	Case-series	
5	"first principles"	research or "first principles"	bench research or "first principles"	research or "first principles"	"first principles"

Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998.

Notes

Users can add a minus-sign "-" to denote the level of that fails to provide a conclusive answer because of:

- EITHER a single result with a wide Confidence Interval (such that, for example, an ARR in an RCT is not statistically significant but whose confidence intervals fail to exclude clinically important benefit or harm)
- OR a Systematic Review with troublesome (and statistically significant) heterogeneity.
- Such evidence is inconclusive, and therefore can only generate Grade D recommendations.

	By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a "-" at the
†	Clinical Decision Rule. (These are algorithms or scoring systems which lead to a prognostic estimation or a diagnostic category.)
	See note #2 for advice on how to understand, rate and use trials or other studies with wide confidence
	patients died before the Rx became available, but some now survive on it; or when some
	study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and non-exposed individuals and/or failed to identify or appropriately control known confounders and/ or failed to carry out a sufficiently long and complete follow-up of patients. By poor quality study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls and/or failed to identify
	Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into "derivation" and "validation" samples.
††	An "Absolute SpPin" is a diagnostic finding whose pecificity is so high that a diagnosis. An "Absolute SnNout" is a diagnostic finding whose N
	benefits.
†††	the 'reference') implies a level 4 study.
††††	
	Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (e.g. using a regression analysis) to find which factors are 'significant'.
	emerge (eg 1-6 months acute, 1 - 5 years chronic)

Grades of Recommendation

A	
B	***or***
C	***or***
D	***or***

"Extrapolations" are where data is used in a situation which has potentially clinically important differences than the original study situation.

Appendix 2

HEALTH TECHNOLOGY ASSESSMENT (HTA) - PROTOCOL ENDOBRONCHIAL ULTRASOUND (EBUS)

1. BACKGROUND INFORMATION

commonest cancer in males (13.8% of cancer in males) and the 8
females (3.8%). The Age-standardized incidence (ASR) was 20.3 for males and 6.5 for females.

of all cancers in males. Similarly, the incidence is lower among females (7.8%).

Conventional radiologic imaging is suboptimal in the detailed delineation of these structures.

needle aspiration (TBNA) – EBUS scope.

For applications inside the central airways, flexible catheters and probe have been developed

can be visualized. The probes can be applied with regular flexible endoscopes that have a biopsy

XBF-UC40P) has been developed that makes needle punctures under real-time endoscopic

needle inserted through the biopsy channel during scanning. Current indications according to the

structures. Medical indications are early detection and tumour staging, inflammatory destruction

2. POLICY QUESTION

Should EBUS be made available in Regional Respiratory Centres in Malaysia?

3. OBJECTIVE

lung diseases, specifically in the diagnostic and therapeutic properties

Centres

4. SCOPE

The scope of this report is regarding the use of Endobronchial Ultrasound (EBUS), irrespective

4.1 INCLUSION CRITERIA

4.1.5 Competing technologies for similar application

4.2 EXCLUSION CRITERIA

5. ASPECT TO BE CONSIDERED

5.1 EFFECTIVENESS

The effectiveness of using EBUS in the management of lung diseases, specifically in the

5.2 SAFETY

5.3 COST EEFFECTIVENESS

5.4 ORGANIZATIONAL ASPECTS

-

- To find out the resources available and needed if this technology is to be introduced particularly the financial resources and man-power.
- Training needed in implementation

6. STRATEGY

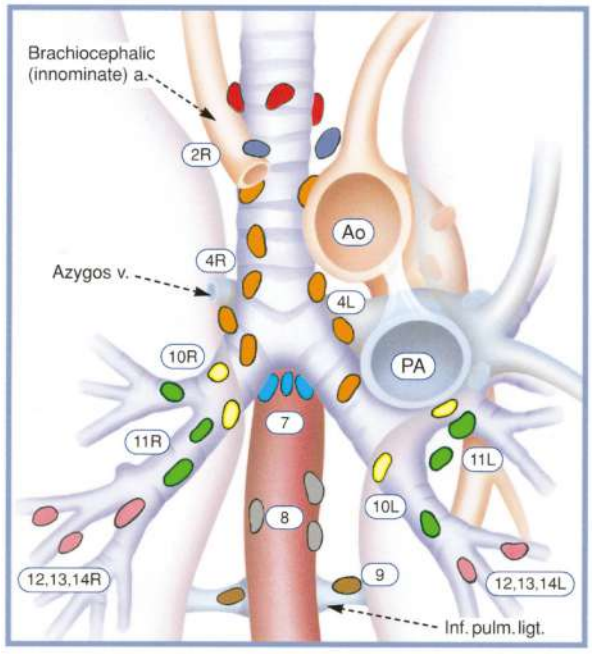
- Adopt or adapt other HTA
- New HTA

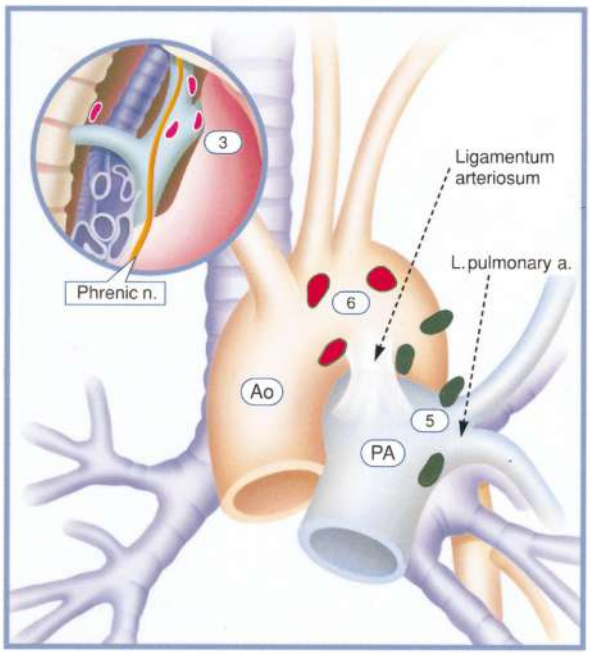
7. METHODOLOGY

- Review existing HTA
- Retrieval of evidence
- Analysis of evidence
- HTA writing
- Feedback on draft report and preparation for final report
- Presentation of report to HTA TAC
- Presentation of report to HTA & CPG Council
- Implementation of HTA report

Appendix 3

Regional Lymph Node Stations For Lung Cancer Staging (Mountain & Dresler, 1997)





Superior Mediastinal Nodes

- 1 Highest Mediastinal
- 2 Upper Paratracheal
- 3 Pre-vascular and Retrotrachea
- 4 Lower Paratracheal (including Azygos Nodes)

N_2 = single digit, ipsilateral
N_3 = single digit, contralateral or supraclavicular

Aortic Nodes

- 5 Subaortic (A-P window)
- 6 Para-aortic (ascending aorta or phrenic)

Inferior Mediastinal Nodes

- 7 Subcarinal
- 8 Paraesophageal (below carina)
- 9 Pulmonary Ligament

N_1 Nodes

- 10 Hilar
- 11 Interlobar
- 12 Lobar
- 13 Segmental
- 14 Subsegmental

Regional lymph node stations for lung cancer staging. Adapted from Naruke et al and the ATS/ North American LCSG2

Appendix 4

Table 1 : Lymph Node Map Definitions (Mountain & Dresler, 1997)

Nodal Station	
N2 nodes—All N2 nodes lie within the mediastinal pleural envelope	
	Nodes lying above a horizontal line at the upper rim of the bracheocephalic (left innominate)
	Nodes lying above a horizontal line drawn tangential to the upper margin of the aortic arch and below the inferior boundary of No. 1 nodes
	Prevascular and retrotracheal nodes may be designated 3A and 3P; midline nodes are
	and contained within the mediastinal pleural envelope; the lower paratracheal nodes on the Researchers may wish to designate the lower paratracheal nodes as No. 4s (superior) and No. 4i (inferior) subsets for study purposes; the No. 4s nodes may be defined by a the azygos vein; the No. 4i nodes may be defined by the lower boundary of No. 4s and the lower boundary of No. 4, as described above
5. Subaortic (aorto-pulmonary window)	artery and proximal to the first branch of the left pulmonary artery and lie within the
6. Para-aortic nodes (ascending aorta or phrenic)	Nodes lying anterior and lateral to the ascending aorta and the aortic arch or the innominate
	Nodes lying caudal to the carina of the trachea, but not associated with the lower lobe
8. Paraesophageal nodes (below carina)	Nodes lying adjacent to the wall of the esophagus and to the right or left of the midline,
	Nodes lying within the pulmonary ligament, including those in the posterior wall and lower
N1 nodes - All N1 nodes lie distal to the mediastinal pleural reflection and within the visceral pleura	
	The proximal lobar nodes, distal to the mediastinal pleural reflection and the nodes adjacent to the bronchus intermedius on the right; radiographically, the hilar shadow may be created
	Nodes lying between the lobar bronchi
	Nodes adjacent to the distal lobar bronchi
	Nodes adjacent to the segmental bronchi
	Nodes around the subsegmental bronchi

ppendix 5

Evidence table Question EFFECTIVENESS OF EBUS IN LUNG TUMOUR
Is EBUS effective when used in the analysis/ diagnosis of Central Cancer?

NO. 1

Bibliographic Citation	Kurimoto N, Muragawa M, Yoshioka S, Nishisaka T, Inai K, Dohi K. (1999). Assessment of usefulness of endobronchial *CHEST*
Study Type / Methodology	Cross sectional study between August 1994 and April 1998. Needle-puncture experiment was performed on the normal tissue of 45 specimens from human tracheas and histopathologic findings were compared.
LE (Level of Evidence)	
Number of patients & patient characteristics	
Intervention	Endobronchial ultrasonography (EBUS) images
Comparison	Histopathological findings
Length of follow up (if applicable)	Nil
Outcome measures/ Effect size	The cartilaginous portions of extrapulmonary bronchi and the intrapulmonary bronchi exhibited five-layer Starting on the luminal side, the first layer (hyperechoic) was a marginal echo, the second layer (hypoechoic) was the submucosal tissue, the third layer (hyperechoic) was the marginal echo on the inner side of the bronchial cartilage, the forth layer (hypoechoic) was bronchial cartilage and the fifth layer (hyperechoic) was the marginal echo on the outer side of the cartilage. In the membranous portions, the first layer (hyperechoic) was a echoic Comparisons between the ultrasonograms and the histologic findings in 24 lung cancer cases revealed that depth diagnosis was the same in 23 lesions (95.8%) and was different in lesion (4.2%).
General Comments	

NO. 2

Bibliographic Citation	Baba M, Sekine Y, Suzuki M, Yoshida S, Shibuya K, Iizasa T, Saitoh Y, Onuma E K, Ohwada H, Fujisawa T (2002). Correlation between endobronchial ultrasonography (EBUS) images and histologic findings in normal and tumour- *Lung Cancer*
Study Type / Methodology	Cross sectional study from January 1996 to October 1999 UM-BS20-26R, 20 MHz radial scanner and a BF-XT30 bronchoscope. (20MHZ radial scanner).
LE (Level of Evidence)	
Number of patients & patient characteristics	61 patients, including 59 with lung cancer, one with unilateral end stage fibrotic lung, who underwent lobectomy, 46 males and 15 females, with a mean age of 65.0 years (range, 34-85).
Intervention	EBUS images, histologic findings.
Comparison	Nill
Length of follow up (if applicable)	Nil
Outcome measures/ Effect size	Correlation of image of the trachaeobronchial wall structure, measurement of depth of tumour invasion and histologic findings. **EBUS findings of normal intrapulmonary bronchi :** imaged the wall structure of normal intrapulmonary bronchi. The layers were confirmed by microscopic findings. **EBUS findings of normal extrapulmonary bronchi** finding: a membranous portion lacking the cartilage was seen. **EBUS findings of the bronchial walls associated with malignant tumours :** radiation of the 20 MHz transducer reached 1.5 – 2 cm in depth, EBUS could visualize adjacent structures including findings consisted of five thickened, nine nodular, and seven polypoid, were judged as having no invasion to the cartilage layer by EBUS. All of these sites were confirmed histologically to have involvement of the cartilage layer. **The EBUS- determined of the bronchial cartilage, and its correlation with the actual histologic measurement** (range, 0.62 -1.75 mm). The mean thickness of the ultrasonographic measurements of the same cartilage was 1.01 mm (range, 0.63-1.90 mm). A good correlation was observed between the EBUS – determined thickness of the bronchial cartilage and the actual histological measurement (correlation ratio of 0.7773, $P < 0.0001$).
General Comments	

NO. 3

Bibliographic Citation	Nakamura Y, Endo C, Sato M, Sakurada A, Watanabe S, Sakata R, Kondo T (2004). A new technique for endobronchial ultrasonography and comparison of two ultrasonic probes*. Analysis with a plot profile of the image analysis software NIH image. *CHEST*
Study Type / Methodology	Cross sectional study from February to March 2002. EBUS system used had the following specifications : an EU-M30 processor; a UM-BS20-26R ultrasonic probe (20-MHz radial scanner); a XUM-BS30-26R ultrasound probe (30 –MHz radial scanner) and a MAJ-643R (latex balloon sheath of the ultrasonic probe). The same bronchial lesion in each specimen was observed using two different types of probes ; 20MHz and 30 MHz. The captured ultrasound was analyzed using freeware image analysis software (NIH Image, Version 1.62; national Institutes of Health, Bethesda).
LE (Level of Evidence)	
Number of patients & patient characteristics	
Intervention	Freeware image analysis software (NIH image)
Comparison	Nill
Length of follow up (if applicable)	Nil
Outcome measures/ Effect size	*t* Echo intensity curves showed five peaks and troughs, indicating that the normal bronchial wall is a laminar structure consisting of five ultrasonically different structures. echo intensity between the third and fourth layer as well as the second and fourth layer were significantly greater carcinoma is not W in shape, indicating that the bronchial wall is not composed of the normal five layers and the
General Comments	

NO. 4

Bibliographic Citation	Herth F, Ernst A, Schulz M, Becker H (2003). Endobronchial ultrasound reliably differentiates between airway infiltration and compression by tumour*. *CHEST,*
Study Type / Methodology	Cross sectional study from May 1999 to July 2000. All patients underwent CT of the chest, followed by bronchoscopy with EBUS. All findings were correlated with final The CT imaging was performed on a Siemens Somatom Plus (Siemens ;Munich).The mass neighboring the wall was classified as infiltrating the airway wall versus just compressing it. Bronchoscopy was performed in the usual manner with one type of bronchoscope (P20, T40; Olympus: Tokyo EBUS was then performed to visualize the bronchial wall and its layers. Tumour infiltration was determined to be Final pathologic findings were compared to findings by the chest CT and EBUS. The pathologist was blinded to the results of CT and EBUS examination.
LE (Level of Evidence)	
Number of patients & patient characteristics	Average age 60.1 years (range- 32 to 82 years).
Intervention	
Comparison	CT scan
Length of follow up (if applicable)	Nil
Outcome measures/ Effect size	Comparison of final histologic findings to findings by chest CT scan and EBUS examination. 105 patients (78 male and 27 female: average age 59.2 years: range, 32 to 82 years) underwent surgery following the chest CT and bronchoscopic examination and could thus be analyzed. Tumour involvement of at least the outermost layer of the airway was considered infiltration by the pathologist. The CT scan was read in 81 patients (77%) as being consistent with tumour invasion of the airway and with tumour impression in 24 patients (23%). The pathologic examination after surgery showed tumour invasion in 55 patients (52%) and tumour impression in 50 patients (48%). EBUS examination showed tumour invasion was present in 49 patients (47%) and tumour impression in 56 patients (53%). The pathologic examination after surgery showed tumour invasion in 55 patients (52%) and tumour impression in 50 patients (48%). Examination of the tracheobronchial tree with EBUS for possible infiltration by a central tumour yielded an accuracy of 94%, a sensitivity of 89%, and a specificity of 100%. Chest CT scanning yielded an accuracy of 51%, a sensitivity of 75%, and a specificity of 28%. The correlation between EBUS classification and the postoperative classification of airway involvement was highly significant (correlation 0.89, $p<0.01$). There was a statistically non significant correlation between chest CT and postoperative classification (correlation 0.06, $p=0.4$) The EBUS examinations added an average 3.5 min (range 2.4 to 5.9 min) to the time needed for a standard
General Comments	

NO. 5

Bibliographic Citation	Miyazu Y, Miyazawa T, Kurimoto N, Iwamoto Y, Kanoh K, Kohno N (2002). Endobronchial ultrasonography in *Respir Crit Care Med*
Study Type / Methodology	Cross sectional study from September 1997 and August 2001 at Hiroshima City Hospital. All patients had a HR-CT scan and the images were evaluated by two experienced radiologists and the depth of EBUS was performed under local anaesthesia using endobronchial ultrasonography (EU-M 20; Olympus), a 2.5 Frequency radial mechanical transducer type ultrasonic probe (UM-BS20-26R; Olympus) and a flexible balloon flexible bronchoscope (BF-IT20; Olympus). If the tumour was intracartilaginous, indicating that the tumour was contained within the mucosa and / or
LE (Level of Evidence)	
Number of patients & patient characteristics	Patients with 18 biopsy-proven squamous cell carcinomas, which satisfied the criteria of a centrally located early stage lung cancer. (The criteria were a negative chest roentgenogram, no nodal enlargement on CT (clinical stage, Tis or T1, N0M0), an intraluminal tumour size ≤ 2 cm, and a visible proximal and distal margin).
Intervention	(HR-CT) to select appropriate candidates for photodynamic therapy (PDT) with curative intent ion of patients with
Comparison	Bronchoscpy and HR-CT scan
Length of follow up (if applicable)	
Outcome measures/ Effect size	Response to Photodynamic Therapy (PDT) All 18 lesions were considered to be candidates for PDT according to bronchoscopy and HR-CT. According to evaluation by EBUS, 9 of these 18 lesions including three CIS were diagnosed as intracartilaginous, because EBUS and the histopathologic findings were identical in the six patients. None of these patients has developed a recurrence. Median follow –up : 22.3±13.8 months. Although 14 lesions were < 1cm in diameter as determined by bronchoscopy, five lesions protruded beyond the cartilage when image by EBUS and was later confirmed histopathologically. The depth of the tumour invasion estimated by HR-CT indicated that 11 lesions were invisible, three lesions were although they were invisible on HR-CT, invaded beyond the cartilage as shown by EBUS. HR-CT. Conclusion: EBUS is a safe and useful technique that might be considered in addition to conventional bronchoscopy and HR-CT to improve the efficacy of PDT in patients with centrally located early-stage lung cancer.
General Comments	

Evidence table EFFECTIVENESS OF EBUS IN LUNG TUMOUR
Question Is EBUS effective when used in the analysis/diagnosis of mediastinal/hilar/intrathoracic lymph nodes?
NO. 1

Bibliographic Citation	Herth F, Becker H D, Ernst A (2004). Conventional vs endobronchial ultrasound-guided transbronchial needle *CHEST*
Study Type / Methodology	RCT between June 2001 and March 2002. Through a bronchoscope with 2.8 mm working channel , a flexible ultrasound probe with a 20-MHz transducer (UM-2R/3R with driving unit MH-240 and a processor EU-M 20 and 30, Olympus was introduced. The probe was removed from the working channel and TBNA was performed. TBNA. Cytology specimens were obtained with a 22-gauge needles (MW 522, Bard: Billeriea, MA) All patients of both groups without a specific diagnosis, irrespective of the presence or absence of lymphocytes in The pathologist was unaware of the method used to obtain the specimen.(blinded)
LE (Level of Evidence)	
Number of patients & patient characteristics	All patients with enlarged mediastinal lymph nodes referred for TBNA (75 women and 125 men). Mean age 51.9 years ± 22.6 years (SD) All patients were randomized in an EBUS-guided and a conventional TBNA arm. Patients with subcarinal lymph nodes were randomized and analyzed separately (group A) and patients with lymph
Intervention	EBUS guided TBNA
Comparison	Conventional TBNA
Length of follow up (if applicable)	Nil
Outcome measures/ Effect size	Diagnostic yield of EBUS guided TBNA and conventional TBNA A positive result was either a specific diagnosis (eg. malignant cells) or a lymphocyte-positive specimen, indicating The mean lymph node size was 1.76±0.47 cm (range , 0.8 to 4.3 cm) in group A and 1.53±0.43 cm (range, 0.7 to 2.3 cm) in group B. In group A (subcarinal lymph node), the yield of conventional TBNA was 74% compared to 86% in the EBUS-guided group. The difference was statistically non significant (p=0.3). the overall yield of conventional TBNA was 58% compared to 84% in the EBUS-guided TBNA. The difference was statistically significant ($p<0.001$). The combined yield for groups A and B was 71% for conventional TBNA versus 80% for EBUS guidance ($p < 0.05$). The mean time required for EBUS plus TBNA was 6.3 min and the mean time for conventional TBNA was 3.8 min ($p< 0.05$).
General Comments	

NO. 2

Bibliographic Citation	Kanoh K, Miyazawa T, Kurimoto N, Iwamoto Y, Miyazu Y, Kohno N (2005). Endobronchial ultrasonography guidance *Chest*
Study Type / Methodology	RCT between January 2000 to August 2003 Patients were randomized to undergo EBUS-D (n-29) or EBUS-S (n=25). One patient from EBUS-D was excluded because liquid was aspirated from the lesion (pericardial cyst). EBUS guided TBNA using double-channel bronchoscope, EBUS-D through which both a TBNA catheter and an Ultrasonic probe (UM-BS20-26R, Olympus), double-channel flexible bronchoscope (XBF-2T40Y2, Olympus Ultrasonic probe (UM-BS20-26R, Olympus), single-channel flexible bronchoscope (BF-1T-30, Olympus)
LE (Level of Evidence)	
Number of patients & patient characteristics	Patients with mediastinal and / or hilar lymphadenopathy.
Intervention	EBUS guided TBNA using double-channel bronchoscope (EBUS-D)
Comparison	EBUS guided TBNA using single-channel bronchoscope, EBUS-S
Length of follow up (if applicable)	Nil
Outcome measures/ Effect size	Diagnostic yield of TBNA, diagnostic rate in first and second passes Diagnostic rate of EBUS-D was significantly higher than EBUS-S (97% versus 76%, p=0.025). No statistically significant differences in the diagnostic rate of first passes (75.9% versus. 64.0%), the diagnostic respectively p=0.036).
General Comments	

NO. 3

Bibliographic Citation	Herth FJF, Lunn W, Eberhardt R, Becker H D, Ernst A (2005). Transbronchial versus transesophageal ultrasound- *Am J Respir Crit Care Med,*
Study Type / Methodology	Cross sectional study (cross over design) from January 2002 to January 2004 include hilar lymph nodes in positions 5,6, or 11 (which are accessible only by bronchoscopy) and stations 8 and 9 (which are accessible only by esophagoscopy) . findings. Patients underwent ultrasound –guided transbronchial and transesophageal needle biopsies in a cross over design. Different operators performed endoesophageal ultrasound-guided and endronchial ultrasound –guided **The Endobronchial procedure :** A flexible ultrasound probe with 20-MHz transducer (UM-2R/3R with a driving unit MH-240 and processor EU-M 20 and 30 was introduced through a bronchoscope (Olympus p 20 and Olympus p 40D). 22-gauge needles (MW 522; **The endoesophageal procedure :** UC 30P; Olympus Optical) was introduced up to the level of the celiac axis and gradually withdrawn upward for Fine needle aspiration was performed with a 22-gauge Vilmann-Hancke needle (GIP Medizin Technik, Grassau, Germany) on suspicious lesions. Cytologist blinded to the details of the patients. No rapid onsite cytology was performed. definitive diagnosis.
LE (Level of Evidence)	
Number of patients & patient characteristics	Patients with enlarged mediastinal lymph nodes (1 cm) as assessed by contrast-enhanced computed tomography Mean age 53.2 years, SD (11.8 years), range of 33 to 76 years.
Intervention	
Comparison	
Length of follow up (if applicable)	Nil
Outcome measures/ Effect size	Percentage of successful puncture as defined as either obtaining a specific diagnosis or by detecting lymphocytes Percentage of patients diagnosed and biopsy time (measured from when the lymph node station was identified with ultrasound until the aspiration needle was removed with the sample). Transbronchial approach was successful in 142 patients (88%), and was diagnostic in 85%. Endoesophageal For each station, the number of positive samples (successful) for the transbronchial / transesophageal approaches was: 2R; 19/13; 2L: 16/19; 3: 17/15; 4R: 19/12; 4L:17/20; 7:19/20; 10R: 18/9; and 10L: 17/18. Combining the result of both approaches, a successful puncture of the included enlarged lymph nodes was achieved in 97% of patients and resulted in a specific diagnosis in 94%. 9 patients without a specific diagnosis underwent surgical procedure, but a more specific diagnosis could not be obtained in five of the nine. Mean examination time was 3.2 minutes for endobronchial technique (SD±2, median, 3.2 minutes; range, 2-10 minutes; interquartile range, 25-75; percentile, 2-3.9) and 4.1 minutes for the transesophageal technique (SD±2.35; median, 3.5 minutes; range, 2-11 minutes; interquartile range, 25-75; percentile 2.9-5). The difference was significant ($p<0.001$). **Conclusion :** the difference between approaches were neither clinically nor statistically significant. Combining both approaches is
General Comments	

NO. 4

Bibliographic Citation	Herth FJF, Eberhardt R, Vilmann P, Krasnik M, Ernst A (2006). Real-time endobronchial ultrasound guided *Thorax,* 61 (9): 795-798.
Study Type / Methodology	Cross sectional study from June 2002 to September 2004. Chest x-ray and CT scan of the chest were routinely performed. Conventional flexible bronchoscopy (BF-7160, Olympus) followed by EBUS-TBNA using a new ultrasound biopsy bronchoscope model XBF-UC260F-OL8, Olympus and 22-gauge needle (XNA-202C, Olympus Cytopathologist was blinded to the details of the patients. Diagnosis based on samples obtained through EBUS-TBNA were confirmed by open thoracotomy, thoracoscopy, Surgical biopsy (mediastinoscopy) was performed in all patients in whom a specific diagnosis was not determined by biopsy specimens obtained by EBUS-TBNA
LE (Level of Evidence)	
Number of patients & patient characteristics	Patients with mediastinal and / or hilar lymphadenopathy.
Intervention	Real time EBUS-TBNA
Comparison	EBUS guided TBNA using single-channel bronchoscope, EBUS-S
Length of follow up (if applicable)	Nil
Outcome measures/ Effect size	of confirmed diagnosis made possible with EBUS-TBNA). 572 lymph nodes were identified by CT scanning to be enlarged more than 1 cm. (Mean 1.14 / per patient, range 1-3). Mean (SD) of lymph node size was 1.6 (0.26) cm (range 0.8-3.2). Overall diagnostic yield 535 out of 572 nodes (93.5%). 94.8%, PPV 100%, NPV 11%, sensitivity 95%, specificity 100%. accuracy was 93.6%, PPV 100%, NPV 14%, sensitivity 93.5%, specificity 100%. Analysing the diagnostic yield for 502 patients, was able to establish a definitive diagnosis in 470 patients (93%). The sensitivity was 94%, specificity 100%, accuracy 94%, PPV 100% and NPV 11%. Not influenced by lymph node location and size. Mean procedure time was 12.5 minutes (8-21). No difference in time required between types of anesthesia. Conclusion:
General Comments	

NO. 5

Bibliographic Citation	Yasufuku K, Chiyo M, Sekine Y, Chhajed PN, Shibuya K, Iizasa T, Fujisawa T (2004). Real-time Endobronchial *Chest,*
Study Type / Methodology	Cross sectional study between March 2002 and September 2003. Chest X-ray and CT scan chest were performed on all patients. Conventional flexible bronchoscopic examination of bronchial tree followed by CP -EBUS-guided TBNA (transbronchial needle aspiration) Convex probe (CP) EBUS were used (model XBF-UC260F-OL8, Olympus) Cytologist blinded to the details of the cases. Real-time CP-EBUS-guided TBNA diagnosis was confirmed by open thoracotomy, thoracoscopy or clinical
LE (Level of Evidence)	
Number of patients & patient characteristics	Mean age, 64.3 years, SD (10.4 years), range, (37-86 years) Patients having mediastinal and/ hilar lymphadenopathy of >1 cm and with known or suspected malignancy.
Intervention	Real- time EBUS-TBNA.
Comparison	Nil
Length of follow up (if applicable)	Not mentioned
Outcome measures/ Effect size	Diagnostic yield (cytology results of EBUS-TBNA sample) All lymph nodes detected on CT scan could be visualized by CP-EBUS. Overall sensitivity, specificity and diagnostic accuracy rate of direct CP-EBUS guided TBNA in distinguishing benign
General Comments	

NO. 6

Bibliographic Citation	Herth F J, Becker H D, Ernst A (2003). Ultrasound -guided transbronchial needle aspiration. An experience in 242 *Chest,*
Study Type / Methodology	Cross sectional study between January 1999 and January 2000. EBUS using bronchoscope (Olympus p 20 and Olympus p 40 D model), ultrasound probe with a transducer (UM-2R/3R) and processer EU-m 20 and 30: Olympus) TBNA was performed using 22-gauge for cytology specimens and 19-gauge needles for histology specimens. All patients without a specific diagnosis underwent a surgical biopsy procedure.
LE (Level of Evidence)	
Number of patients & patient characteristics	(160 men and 82 women). Mean age, 60.0 years, SD (11.8 years), range, (33-76 years) All patients referred for diagnostic TBNA of mediastinal lymph nodes.
Intervention	Endobronchial ultrasound (EBUS) for TBNA guidance during bronchoscopy
Comparison	Nil
Length of follow up (if applicable)	Not mentioned
Outcome measures/ Effect size	Diagnostic yield (cytology and histology results of EBUS-TBNA) In 207 out of 242 patients (86%) the lymph nodes were successfully accessed by TBNA (specific diagnosis or lymphocytes on specimen). Able to established diagnosis or a definitive staging in 172 patients out of 242 patients (71%). Negative biopsy result need to be followed with surgery since 27 out of 35 proved to be malignant. The mean time required for EBUS plus TBNA was 5.7 min.
General Comments	

NO. 7

Bibliographic Citation	Okamoto H, Watanabe K, Nagatomo A, Kunikane H, Aono H, Yamagata T, Kase M (2002). Endobronchial *CHEST*
Study Type / Methodology	Cross sectional study from July 1996 to April 2000. EBUS performed using the Olympus UM3R or XUM-B20R -26 radial scanning probe (Olympus) of 20 MHz through a bronchofiberscope to evaluate mediastinal and hilar lymph nodes metastases. The distal end of the EBUS probe was connected to an ultrasound unit (EU-M30 Endoscopic Ultrasound Center; Olympus) CT scan of chest was performed (model TCT900S: Toshiba). Other staging procedures include Chest radiography, CT scan of the brain, CT or ultrasonography of abdomen and isotope bone scanning. Lung cancer was histologically or cytologically confirmed by bronchofiberscopy.
LE (Level of Evidence)	
Number of patients & patient characteristics	(32 males and 5 females). Median age 68 years, range (35-79) years.
Intervention	EBUS-TBNA
Comparison	CT scan
Length of follow up (if applicable)	Nil
Outcome measures/ Effect size	Detection rate, positive rate of EBUS. Sensitivity, specificity, overall accuracy of the diagnosis of lymph node metastases by Chest CT, EBUS or both. **Definition :** Detection rate=number of patients in whom a lymph node was detected / number of patients in whom a lymph node Positive rate= number of patients with lymph node swelling ≥ 10 mm in diameter/ number of patients in whom a Detection rate of EBUS was twice of CT scan (54% and 27% respectively). Positive rate of EBUS and CT scan was In all 20 patients in whom hilar lymph nodes were observed, all were clearly identified regardless of whether there The detection rates for lymph node by EBUS and Chest CT scan were 86% and 49% respectively. The diagnostic ability of EBUS was superior to that of CT scan in identifying lymph nodes < 10 mm in diameter. Detection accuracy of lymph node metastasis by Chest CT scan and EBUS in 16 surgical cases. EBUS alone –sensitivity 67%, specificity 92%. Chest CT scan - sensitivity 75%, specificity 83% . EBUS plus chest CT scan - sensitivity 100%, specificity 77%. Time = additional 10 minutes to the duration of bronchoscopic procedures.
General Comments	

NO. 8

Bibliographic Citation	Plat G, Pierard P, Haller A, Hutsebaut J, Faber J, Dusart M, Eisendrath P, Sculier J-P, Ninane V (2006). Endobronchial *Eur Respir J*
Study Type / Methodology	Cross sectional study from January 2003 to June 2004 at Institut Bordet, Saint-Pierre Hospital, Brussels, Belgium. In all patients with abnormal FDG-PET scan, TBNA sampling of lymph nodes was performed after EBUS. Procedure performed under local anesthesia and out- patient basis. In patients four to six punctures were performed. No rapid on-site cytological examination was used. TBNA was considered as contributive whenever a clear definite In case of negative results, further surgical staging / diagnostic procedure or adequate clinical follow- up.
LE (Level of Evidence)	
Number of patients & patient characteristics	All consecutive patients referred for staging and / or diagnosis of mediastinal Positron emission tomography with 18-fluorodeoxyglucose (FDG-PET) positive lesions were included.
Intervention	EBUS-TBNA
Comparison	Nil
Length of follow up (if applicable)	
Outcome measures/ Effect size	Diagnostic /staging yield and the number of avoided surgical procedures. A total number of 139 samples (mean number of TBNA samples per patient was 4.2±1.5) were obtained in 39 lymph TBNA allowed diagnosis to be reached in 27/33 (82%) of patients, of whom 78% (21/27) were diagnosed after previous EBUS localization. Previous localization with EBUS was associated with a TBNA diagnostic yield of 88%. Surgical sampling (mediastinoscopy or other surgical sampling of mediastinal lymph nodes) was avoided by the positive results of TBNA in 25 cases (76%) of patients. Conclusion: The present study shows that TBNA combined with EBUS is a very safe and effective method to assess patients May replace majority of surgical mediastinal staging /diagnostic procedures.
General Comments	

NO. 9

Bibliographic Citation	Krasnik M, Vilmann P, Larsen SS, Jacobsen GK (2006). Preliminary experience with a new method of endoscopic *Thorax,*
Study Type / Methodology	Cross sectional study The flexible Ultrasonic bronchoscope used was a prototype developed by Olympus (XBF-UC40P). The outer 7.5 MHz with a penetration depth of 5 cm. The endoscope was connected to an Olympus ultrasound (US) processor (EU-C60). Power Doppler facilities was available. A balloon sheath which can be filled with water can be mounted around the transducer for better ultrasonic coupling with the bronchial wall. 22 gauge needle Olympus (XNA-200C)
LE (Level of Evidence)	
Number of patients & patient characteristics	Selection based on CT scanning (10 pt) and PET (1 pt). Mean age 58 years (43-75 years). of recurrent cancer with metastatic spread to the mediastinum (lung, breast, kidney and laryngeal cancer), 3 patients had mediastinal or hilar lesion of unknown origin (inconclusive bronchoscopy result) , 1 patient suspicion of breast cancer with mediastinal spread not shown by CT.
Intervention	EBUS- FNA (fine needle aspiration) done under GA.
Comparison	Nil
Length of follow up (if applicable)	Nil
Outcome measures/ Effect size	Diagnostic yield (obtaining biopsy specimens) from mediastinal and hilar lesions. FNA identified malignant cells in 13 lesions and benign cells in two. Based on the diagnosis obtained by EBUS-FNA, patients were given the appropriate treatment.
General Comments	

NO. 10

Bibliographic Citation	Nakajima T, Yasufuku K, Wong M, Iyoda A, Suzuki M, Sekine Y, Shibuya K, Hiroshima K, IIzasa T, Fujisawa T (2007). *Respiratory,*
Study Type / Methodology	Case report Chest CT showed a small peripheral nodule in the right upper lobe, 5x5 mm in diameter, and a pretracheal lymph The convex probe endobromchial ultrasonography equipped with a 7.5 MHz linear probe on its tip (XBF-U260F-OL8; Olympus) was used to perform EBUS-TBNA to evaluate the pretracheal lymph node. EBUS-TBNA was performed to obtain smears for cytological evaluation and histological cores for pathological
LE (Level of Evidence)	
Number of patients & patient characteristics	53 year old man referred to department of Thoracic Surgery, Chiba University, Japan for treatment of a small peripheral lung nodule in May 2005. Patient had undergone an operation for Right Renal Cell Carcinoma, pathological stage
Intervention	EBUS-TBNA
Comparison	Nil
Length of follow up (if applicable)	Nil
Outcome measures/ Effect size	Diagnostic yield (cytology and histology) result. Histological findings and immunohistochemistry by CD10 antibody revealed mediastinal lymph node metastases from RCC. However, cytological smears only showed a few atypical cells that were not diagnostic.
General Comments	

NO. 11

Bibliographic Citation	Munavvar M, Gupta V, Patel V, Edwards J, Mills J (2006). Utility of endobronchial ultrasound (EBUS): a comparative study between conventional transbronchial nodal aspiration (TBNA) and EBUS guided TBNA. *Thorax,* 62 (2): ii102
Study Type / Methodology	Cross sectional study from May 2006 to July 2006 at Lancashire Teaching Hospitals. 12 patients and nodes used blind TBNA Cases selected based on CT appearances.
LE (Level of Evidence)	
Number of patients & patient characteristics	EBUS guided TBNA -8 patients, 5 males and 3 females). Age range – 45-81 (mean 66.4) Conventional TBNA. 12 patients , (6 males and 6 females). Age range 56-83 (mean 70.5).
Intervention	EBUS guided TBNA
Comparison	Conventional TBNA (Blind TBNA)
Length of follow up (if applicable)	Nil
Outcome measures/ Effect size	Diagnostic yield (cytology results) Diagnostic yield improved from 46.2% with blind TBNA to 88.9% with EBUS Conclusion: EBUS guided TBNA is a novel way to diagnose and stage lung cancers allowing a more rapid and accurate diagnosis Difficult lesions < 1cm in size can be targeted, which is not usually accessible by conventional TBNA.
General Comments	

Evidence table EFFECTIVENESS OF EBUS IN LUNG TUMOUR
Question Is EBUS effective when used in the staging of lung cancer?
No. 1

Bibliographic Citation	Yasufuku K, Nakajima T, Motoori K, sekine Y (2006).Comparison of endobronchial ultrasound, positron emission tomography, and CT for lymph node staging of lung cancer*. *CHEST*
Study Type / Methodology	Cross sectional study from December 2003 and March 2005. (Chiba University Hospital, Japan) Patients underwent CT, PET and EBUS-TBNA for mediastinal staging prior to surgery. Chest and upper abdomen CT were performed with contrast single injection and multicolour –row CT. Radiologist Whole-body FDG-PET (GE, PET Advance Nxi, GE Medical Systems) was performed. FDG-PET was considered positive for an N1,N2, or N3 lymph node if the PET report stated that there was hypermetabolic activity consistent with malignant disease defined as standardized uptake value >2.5 EBUS-TBNA was performed with flexible ultrasound puncture bronchoscope with a linear scanning transducer with a frequency of 7.5 MHz on the tip (CP-EBUS;XBF-UC260F OL8 Olympus). It is connected to a dedicated ultrasound scanner (EU-C2000 Olympus) with Doppler-flow imaging for detection of blood vessels. All procedures sampled with a dedicated 22-gauge TBNA needle under direct EBUS guidance. Surgical histology was used as a gold standard to confirm lymph node metastasis unless patients were found inoperable for N3 or extensive N2 disease proven by EBUS-TBNA.
LE (Level of Evidence)	
Number of patients & patient characteristics	Potentially operable patients with proven (n=96) or radiologically suspected (n=6) lung cancer. Median age=67.8 (44-85)
Intervention	EBUS-TBNA
Comparison	Thoracic CT and PET
Length of follow up (if applicable)	Not mentioned
Outcome measures/ Effect size	Diagnostic yield (sensitivities, specificity, PPV, NPV, accuracy) of EBUS-TBNA, CT and PET in mediastinum and EBUS-TBNA was successfully performed in 147 mediastinal and 53 hilar lymph nodes. Thirty-seven lymph nodes were malignant and 163 were benign based on EBUS –TBNA. EBUS-TBNA resulted in 24 true positive, 76 true negative, no false positive and only two false negative. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of EBUS-TBNA in the correct prediction CT detected mediastinal and / or hilar lymph nodes in all of the patients enrolled in the study. CT resulted in 20 true positive, 42 true negative, 34 false positive and 6 false negative. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of CT in the prediction of mediastinal lymph node staging were 76.9%,55.3%, PET identified 89 hot spots in 43 patients. Of the 43 PET positive cases, 23 patients had false positive findings based The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of PET in the prediction There is a significant difference in the accuracy of the three different modalities (p<0.00001). The mean examination time of EBUS-TBNA was 14.9 minutes, SD 7.3 min, range 4-29 minutes. Conclusion : EBUS-TBNA has a high sensitivity as well as specificity compared to CT or PET for mediastinal staging in patients
General Comments	

NO. 2

Bibliographic Citation	Rintoul R C, Skwarski K M, Murchison J T, Wallace W A, Penman I D (2005). Endobronchial and endoscopic ultrasound-guided real-time fine needle aspiration for mediastinal staging. *Eur Respir J*
Study Type / Methodology	Cross sectional study. (Royal Infirmary, Edinburgh, UK) EBUS was performed using a novel prototype linear array ultrasound bronchoscope (XBF-UC260F-OL8; Olympus). Image processing is performed by an Olympus ultrasound processor (EU-C2000; Olympus). TBNA was performed using a dedicated prototype 22 gauge needle (XNA-200C-5, Olympus). Additional EUS examination in whom the staging CT scan had demonstrated enlarged lymph nodes in the posterior lymph nodes in station 7). EUS-FNA was performed using a curved linear-array endoscope Olympus GF-UC240P- FNAs were performed through the wall of the esophagus under real-time guidance using Wilson-Cook 22 gauge FNA needles (EUSN-3). For both EBUS-TBNA and EUS-FNA, successive passes were made until endoscopist judged an adequate specimen had been obtained, i.e. when macroscopically visible material had been obtained from 2-3 needle passes. No cytopathologist was present during the procedure. Samples were collected into cytological fixative for cytological
LE (Level of Evidence)	
Number of patients & patient characteristics	Median age 65 years (45-86). 20 patients with known or suspected lung cancer (CT findings showing mediastinal lymph node enlargement or the presence of paratracheal or parabronchial masses).
Intervention	EBUS-TBNA was undertaken in 18 out of 20 cases and EUS-guided fine needle aspiration in six out of seven cases.
Comparison	Nil
Length of follow up (if applicable)	
Outcome measures/ Effect size	Diagnostic yield (positive cytology, sensitivity, specificity, accuracy) of EBUS-TBNA for mediastinal staging. TBNA was undertaken in 18 out of 20 patients and additional EUS-FNA in six out of seven patients. From 18 patients undergoing EBUS-TBNA ±EUS-FNA, 11 patients resulted in aspirate positive for malignancy, and For the 18 patients who underwent EBUS-TBNA the sensitivity, specificity and accuracy were 85% (95% CI- 54.6-98.1), 100% (95% CI-47.8-100) and 89% (95% CI -65.3-98.6) respectively. It has been demonstrated that real-time EBUS-guided TBNA access to the posterior –inferior lymph node stations 5, 7, 8 and 9. Conclusion:
General Comments	

NO. 3

Bibliographic Citation	Yasufuku K, Chiyo M, Koh Eitetsu K, Moriya Y, Iyoda A, Sekine Y, Shibuya K, Iizasa T, Fujisawa T (2005). Endobronchial *Lung cancer*
Study Type / Methodology	Cross sectional study from June 2002 to April 2004, Chiba University Hospital . Conventional flexible bronchoscope was first performed followed by examination of the mediastinum using CP-EBUS (XBF-UC260F-OL8, Olympus). The CP-EBUS is integrated with a convex transducer (7.5 MHz). The ultrasound image is processed in a dedicated ultrasound scanner EU-C2000, Olympus) and is visualized along the conventional A dedicated 22-gauge needle was developed to perform transbronchial aspiration (NA-201SX-4022, Olympus). stained by Diff-Quik staining for immediate interpretation by an on site cytopathologist to confirm adequate cell material. Specimens were categorized as positive (tumour cells), negative (lymphoid but no tumour cells), or inconclusive (poor cellularity or unable to perform adequate punctures). If adequate tissue was not identified by on site cytology after five passes, the procedure was terminated. Cytopathologist blinded to the details of the cases. EBUS-TBNA diagnosis was confirmed either by open thoracostomy, thoracoscopy or clinical follow-up.
LE (Level of Evidence)	
Number of patients & patient characteristics	larger than 1 cm or mediastinal lesion suspected of malignancy detected on CT were included in the study. Proven lung cancer (n=88), or suspected NSCLS (n=20), fulfilled the criteria were included in the study. 86 males and 22 females. Median age 65.3 years, range (37-85 years)
Intervention	EBUS-TBNA was performed on an outpatient basis under conscious sedation.
Comparison	Nil
Length of follow up (if applicable)	
Outcome measures/ Effect size	Correct prediction of lymph node staging. In 105 patients, EBUS-TBNA was successfully performed to obtain samples from 163 lymph nodes. Specimens from three patients were recorded as inconclusive (2.8%). Out of these patients, EBUS- TBNA demonstrated N2 disease in 56 patients and N3 disease in 8 patients. All of the Forty four patients with suspected malignant lymphadenopathy had benign disease by EBUS-TBNA. Out of these confirmed benign lymphadenopathy in all but four patients. Each of the four patients had micro-metastasis in a lymph node not assessed by CP-EBUS. radiation therapy (n=3), heavy ion therapy (n=2), or photodynamic therapy (n=2) demonstrating a lack of clinical or The diagnostic value of EBUS-TBNA in correct prediction of lymph node status including areas not assessable by EBUS had a sensitivity of 94.6%, specificity of 100%, positive predictive value of 100%, negative predictive value of As a result, 29 mediastinoscopies, 8 thoracotomies, 4 thoracoscopies, and 9 CT-guided PCNB were avoided by EBUS-TBNA. Conclusion: EBUS-TBNA is a minimal invasive procedure with a high diagnostic rate and many patients will benefit from the procedure. EBUS-TBNA should be considered for staging of mediastinal lymph nodes as well as diagnosis of lung
General Comments	

NO. 4

Bibliographic Citation	Krasnik M, Hearth F, Vilmann P, Larsen S S (2005). A comparison of endobronchial ultrasound guided biopsy and *CHEST*, 128 (4) :
Study Type / Methodology	Cross sectional study. Mediastinal involvement of lung cancer was defined as tumour-stage ≥111A (N2) corresponding to N2-N3. The PET/CT and EBUS-TBNA diagnosis were confirmed either by open thoracotomy / scopy, mediastinoscopy or
LE (Level of Evidence)	
Number of patients & patient characteristics	Patients considered to be potential candidates for resection of verified or suspected NSCLC.
Intervention	EBUS-TBNA.
Comparison	PET / CT
Length of follow up (if applicable)	Not mentioned
Outcome measures/ Effect size	Diagnostic values of PET/CT and EBUS-TBNA, with regard to the diagnosis of mediastinal involvement of lung 10 patients had a positive PET/CT for mediastinal involvement, while mediastinal involvement were found in 5 patients with EBUS-TBNA. The sensitivity of PET/CT and EBUS-TBNA were 67% and 100% respectively. PET/CT had a specificity of 68%, positive predictive value (PPV) of 40% and negative predictive value (NPV) of EBUS-TBNA had a specificity of 100%, PPV of 100% and NPV of 100% for mediastinal involvement. Conclusion: EBUS-TBNA had a sensitivity, NPV and PPV for diagnosing advanced lung cancer, superior to PET/CT.
General Comments	

NO. 5

Bibliographic Citation	Rintoul R C, Skwarski K M, Murchison J T, Hill A, Walker S W, Penman I D (2004). Endoscopic and endobronchial ultrasound real-time fine-needle aspiration for staging of mediastinum in lung cancer. *Chest,*
Study Type / Methodology	Case reports (Western General Hospital, Edinburgh, UK) EBUS-FNA was performed to examine pretracheal, peritracheal, subcarinal, and hilar lymph nodes stations (stations 1,2,3,4,7 and 10) under conscious sedation. EUS-FNA was performed to examine the posterior and inferior mediastinal lymph nodes staions (stations 5,7,8 and 9) also under conscious sedation
LE (Level of Evidence)	
Number of patients & patient characteristics	2 (1 in each report) Case report 1. 68- year- old ex-smoker. CT scan revealed right paratracheal (station 4R) and subcarinal lymphadenopathy (station 7). No primary mass lesion was apparent. Case report 2. 45 years old man presented with hemoptysis. CT revealed 4x3 cm mass in left upper lobe with mediastinal
Intervention	EBUS-FNA and EUS-FNA
Comparison	Case report 1. Nil
Length of follow up (if applicable)	Nil
Outcome measures/ Effect size	Histology results from EBUS-FNA and EUS-FNA Case report 1. Combined ultrasound examinations staged the patient as T3N2 and histology from EBUS-FNA and EUS core biopsy specimens stage 111A NSCLC. Case report 2. The findings of EBUS-FNA of the pretracheal lymph nodes were negative for malignancy. The findings of EUS were Final pathologic staging was pT2N1, with enlarged pretracheal and subcarinal nodes clusters showing reactive inflammatory changes only.
General Comments	

Evidence table : EFFECTIVENESS OF EBUS IN LUNG TUMOUR
Question : Is EBUS effective when used in the analysis/diagnosis of peripheral pulmonary lesions/solitary pulmonary nodules?

NO. 1

Bibliographic Citation	Chung Y H, Lie C H, Chao T Y, Wang Y H, Lin A S, Wang J L, Lin M C (2006). Endobronchial ultrasonography with *Respiratory Medicine,* doi: 10.1016/j.med.2006.08.014
Study Type / Methodology	Randomized Control Trial. fOctober 2004 to July 2005 at Chang Gung Memorial Hospital, Taiwan. Patients were randomly divided into two groups for transbronchial biopsy (TBBs) using different methods, the group Chest roentgenogram and computerized tomography (CT) were used to determine the size and location of peripheral A flexible video bronchoscopy unit (P260F, Olympus, Tokyo, Japan) was used for all procedures in this study. A lesion was defined as peripheral when it was beyond the segmental bronchus and not visible by bronchoscopy. Procedure performed by five well trained bronchoscopists who had more than 10 years experience. EBUS was performed using an endoscopic ultrasound system (EU-M30S, Olympus, Tokyo, Japan), equipped with a 20MHz mechanical radial type miniature probe (UM-S20-20R, Olympus, Tokyo Japan) with the outer diameter of 1.7 mm. In group EBUS-D (57 patients), once the location of the lesion was identified by EBUS, the distance from the bronchial orifice to pulmonary lesion was measured, then the biopsy forceps (FB-19C-1 or FB-15-C-1, Olympus) In group EBUS (56 patients) the biopsy were performed regardless of distance. In patients in whom TBBs were not diagnostic underwent percutaneous CT-guided needle aspiration cytology or biopsy, or operation to obtain a final diagnosis
LE (Level of Evidence)	
Number of patients & patient characteristics	Patients with solitary peripheral pulmonary lesions (PPL) which were visualized on EBUS image were included in the Mean age 59.4 ± 12.8 yr (SD).
Intervention	
Comparison	
Length of follow up (if applicable)	Not mentioned
Outcome measures/ Effect size	Diagnostic yields of TBBs (positive histology). 71.5%. Mean diameter of PPLs was 24.5± 8.2 mm (10-44 mm). Final diagnosis was established from TBBs in 77 of 113 patients (68.1%). In the remaining 36 patients, final diagnosis were made by operation in 19 patients, 12 patients underwent percutaneous CT-guided aspiration cytology or biopsy. One patient's pulmonary lesion disappeared after **Comparison between EBUS-D and EBUS groups** The diagnostic yield of TBBs in group EBUS-D patients was 78.9% (45/57) which was significantly higher than in Group EBUS patients 57.1% (32/56) (p=0.013). Gender, age, size of lesions, locations of lesions, time of EBUS, **Diagnostic yield of EBUS-guided TBB (77/113)** The diagnostic yield of TBBs was 87.5%, 85.0% and 66.7% in lesions > 3 cm, lesions > 2 cm but l≤ 3 cm and lesions ≤ 2 cm in diameter, respectively. **Factors that influenced the diagnostic yield of EBUS-guided TBB (77/113).** Probe location within the lesion on EBUS image (P=0.001) and measured distance before biopsy (p=0.002), were statistically significant. 29.7 s (65-273s).
General Comments	

NO. 2

Bibliographic Citation	Paone G, Nicastri E, Lucantoni G, Iacono R D, Battistoni P, D'Angeli A L, Galluccio G (2005). Endobronchial *CHEST,*
Study Type / Methodology	293 eligible patients were randomly assigned to EBUS-TBB (144 patients) or TBB (149 patients). However, only 221 patients undergone bronchoscopy (97 EBUS –TBB) and 144 (TBB) because 28 undergone lung surgery before bronchoscopy and 23 did not accept randomization protocol, in 12 patients primary lesion was identified in another The patients were further stratified into 3 subsets: patients with lesions >3cm in diameter, < 3cm in diameter and < Chest CT was performed with 5 mm slices and made available to the two bronchoscopists during the endoscopic EBUS-TBB ultrasound analysis was performed using an endoscopic ultrasound system (EU-M 30; Olympus) equipped with a 20-MHz flexible probe, following careful examination of the upper airways and bronchial tree. After localization of target lesion the probe was removed and five biopsy samples were taken in the same place indicated by the probe using flexible transbronchial biopsy forceps. The material sampled was analyzed by two study -blinded pathologists for definitive histologic assessment Control Bronchoscopy was performed by two independent bronchoscopists using a flexible bronchoscope (Olympus BF B3 or BF T20; Olympus under local anesthesia. Equal number of biopsies was performed using identical forceps that segmental bronchus previously localized with the CT scan. The material sampled was analyzed by two study -blinded pathologists for definitive histologic assessment Patients with no definitive diagnosis at bronchoscopy, underwent other procedures eg. percutaneous needle aspiration, thoracotomy or clinical /radiologic follow up to confirm non neoplastic diseases.
LE (Level of Evidence)	
Number of patients & patient characteristics	221 patients (recruited), 206 patients analyzed. Mean age and SD for EBUS-TBB group = 65±12 years and for TBB group = 68±10 years.
Intervention	Endobronchial ultrasound –driven transbronchial biosy (EBUS-TBB)
Comparison	Coventional TBB (transbronchial biopsy).
Length of follow up (if applicable)	Not mentioned
Outcome measures/ Effect size	Diagnostic yield (histology positive biopsies), sensitivity, specificity, PPV, NPV and accuracy. these, 87 patients undergone EBUS -TBB and 119 undergone conventional TBB. No significant difference in the A definitive diagnosis was obtained by EBUS-TBB in 66 of 87 patients (75.8%) and by conventional TBB in 62 of 119 patients (52.1%). In the study group (EBUS-TBB), the diagnostic yields were 69.2% (18 of 26 benign lesions) and 78.7% (48 of 61 malignant lesions). In the control group (TBB) the diagnostic yields were 44.4% (16 of 36 benign lesions) and 55.4% (46 of 83 malignant lesions). accuracy of EBUS-TBB is significantly higher than TBB (p=0.004 and p=0.007, respectively). Sensitivity, specificity, NPV, PPV and accuracy of EBUS-TBB group were 78.7%, 100%, 66.7%, 100%, 85% Sensitivity, specificity, NPV, PPV and accuracy of TBB group were 55.4%, 100%, 49.3%, 100%, 69% respectively. Analysis of subsets of patients with > 3 cm showed no significant difference in diagnostic ability between the two while EBUS-TBB maintained its diagnostic yield . The sensitivity and the accuracy is significantly higher (75 versus 30.7%) and (83% versus 53%) respectively. In patients with lesions < 2cm, the sensitivity of EBUS-TBB is significantly higher (71% versus 23%) p=0.001. The overall mean time for (including instrument set-up and interpretation of findings required to perform the biopsies) was 9.8 min (range, 7 to 14 min) for EBUS-TBB and 8.1 min (range, 6 to 12 min) for TBB.
General Comments	

NO. 3

Bibliographic Citation	Shirakawa T, Imamura F, Hamamoto J, Honda I, Fukushima K, Sugimoto M, Shirkakusa T (2004). Usefulness of
Study Type / Methodology	Between January to Dec. 2001, two bronchoscopists skilled in EBUS performed EBUS (EBUS group= cases). A radial type 20-MHz miniature probe (UM-3R, UM-4R, US-20-20R, Olympus, Tokyo) was used. After bronchoscopic Olympus). Under fluoroscopic control when the probe was considered to have reach the lesion the US was started. A cytology brush and /or biopsy forceps were introduced to obtain specimens under fluoroscopic guidance. A Control group lesions using fluoroscopy only, before the introduction of EBUS.
LE (Level of Evidence)	
Number of patients & patient characteristics	92 cases (January and December 2001.) Cases -50 patients comprising 27 males and 23 females, aged 41-88 years (average 68.4 years). Chest X-ray showed 30 nodules < 20 mm (including shadows and cavitation), 3 infiltrates < 20 mm, 4 infiltratates > (April 1999 to February 2000) Control - 42 patients (22 males and 20 females) with an average age of 65.3 years. 23 nodules < 20 mm, 3 infiltrates < 20 mm, 11 nodules > 20 mm , 5 infiltrates > 20 mm
Intervention	Ttransbronchial lung biopsy under combined EBUS and fluoroscopy guidance.
Comparison	Transbronchial lung biopsy under fluoroscopy guidance only.
Length of follow up (if applicable)	Nil
Outcome measures/ Effect size	Diagnostic yield, sensitivity , specificity and accuracy for the two methods. In 38 cases (76%) EBUS could describe the peripheral lesion (33 from inside and 5 from adjacent bronchus). The overall ratio of correct diagnosis of lung cancer by EBUS-guided transbronchial lung biopsy (sensitivity) was 17/24 cases (70.8%) and the specificity was 17/24 (75.8%). When the EBUS probe could be introduced inside the lesion, the sensitivity for cancer diagnosis was 100% (15/15) and the specificity for cancer exclusion was 100% (18/18). The overall accuracy of EBUS guided bronchoscopy to distinguish between lung cancer and benign diseases was 84% (42/50 cases) and in patients in whom internal insertion was successful 100% (33/33). placed probes compared to fluoroscopy guidance, although it did not reach statistic significant (p=0.06). Comparing successful EBUS-guided with fluoroscopy guided biopsies, the specificity excluding lung cancer by bronchoscopy was superior with EBUS guidance and achieved statistical significance (p=0.002). In 25/30 cases (83.3%) with successful placement, a position change was not necessary during the whole procedure. In 3/5 cases approached from adjacent bronchus, the patient position had to be changed at least twice and in 9/10 patients in whom the lesion could not be localized by EBUS, repeated change of position was necessary for fluoroscopic observation.
General Comments	

NO. 4

Bibliographic Citation	Hearth FJ F, Ernst A, Becker HD (2002). Endobronchial ultrasound-guided transbronchial lung biopsy in solitary *Eur Respir J*
Study Type / Methodology	Cross sectional study from November 2000 to February 2001. Flouroscopy was provided using a monoplanar C-arm (Suprer 50 CP, Philips). Biopsies were performed with regular disposable forceps (FB-20C Olympus Fibreoptic bronchoscopes (model BF IT-30, BF IT 40 and BF XT 20; Olympus) were used. EBUS was performed with a flexible probe and processor unit (UM-3R, UM-4R, US20-20R, Olympus). Biopsies were performed with regular disposable forceps. Forceps were changed between EBUS and fluoroscopic examinations to avoid cellular cross All patients in whom a definite diagnosis could not be established underwent surgical procedure.
LE (Level of Evidence)	
Number of patients & patient characteristics	37 males and 13 females with an average age of 62.5 ±10.5 years (range 25-81 years).
Intervention	Endobronchial ultrasound (EBUS) guided transbronchial biopsy.
Comparison	
Length of follow up (if applicable)	Not mentioned
Outcome measures/ Effect size	The mean diameter of the lesion was 3.31±0.92 cm (range 2-6 cm). Mean number of specimens obtained was 4.34 ±0.55 (EBUS) and 4.56 ± 0.61 under fluoroscopy (not significant). In EBUS-guided TBBX diagnosis was established in 40 patients (80%). Under fluoroscopic guidance, diagnosis was established in 38 patients (76%). Non significant trend for EBUS to be better than fluoroscopy for lesions < 3 cm in diameter (80% versus 57%). In nine patients (18%), the diagnosis obtained by bronchoscopy saved a surgical procedure (sarcoidosis (2), tuberculosis (2), infection (1), metastatic disease (1), and small cell lung cancer (3). EBUS guided TBBX is simple to perform (6 min). At least equivalent to fluoroscopy without the accompanying
General Comments	

NO. 5

Bibliographic Citation	Kurimoto N, Miyazawa T, Okimasa S, Maeda A, Oiwa H, Miyazu Y, Murayama M (2004). Endobronchial ultrasonography *Chest*
Study Type / Methodology	Cross sectional study between May 2001 and November 2002 at National Hiroshima Hospital and Hiroshima City A flexible fiberoptic bronchoscope (BF IT-30,40, or 240R; Olympus Optical). Miniature ultrasound probe (20 MHz, mechanical- radial type) [UM-S20-20R; Olympus Optical; Tokyo, Japan]. Endoscopic ultrasound system (EU-M30; Olympus Optical). A guide sheath (Olympus Optical) was manufactured especially for this purpose. A bronchial brush (BC-202D-5010; Olympus Optical) or biopsy forceps (BF-19C-1; Olympus Optical) for TBB is introduced into the specially made guide Once the location of the lesion was identified precisely by the EBUS, the probe was withdrawn, leaving the guide The amount of bleeding that occurs with the guide sheath removal was estimated. Bleeding ≥ 60 ml was considered severe, and ≥ 30 ml was considered moderate when there is no danger to the airway. In patients with non diagnostic EBUS-GS, diagnosis established by CT guided transthoracic needle aspiration,
LE (Level of Evidence)	
Number of patients & patient characteristics	Consecutive patients with a solitary pulmonary lesion detected by chest radiograph and CT. Patient underwent bronchoscopy between May 2001 and November 2002.
Intervention	
Comparison	Nil
Length of follow up (if applicable)	Not mentioned
Outcome measures/ Effect size	Diagnostic yield (positive brushing cytology and biopsy specimen) Overall yield of EBUS-GS was 77% (116 of 150 lesions). Diagnostic yield of EBUS-GS in malignant and benign lesions was 81% (82 of 101 lesions), and 69% (34 of 49 lesions), respectively. The diagnostic yield from brushing cytology was 60% (90 of 150 lesions), while the yield from TBB was 81% (89 of 110 lesions). The yield of TBB was significantly higher both for malignant and benign lesions p=0.01 and p=0.02 diagnostic yield (105 of 121 lesions, 87%) than when the probe was adjacent to the lesion on the EBUS image (8 of 19 lesions, 42%) p<0.0001. The diagnostic yield from EBUS-GS for lesions defined as a mass (>30 mm; 24 of 26 lesions, 92%) was significantly defined as nodules ≤ 30mm; 92 of 124 lesions, 74%) p=0.04. When the lesion was ≤ 30mm, size does not affect the yield by EBUS-GS. The yield for lesions ≤ 10 mm did not decrease (76%). EBUS –GS is particularly useful for lesions ≤ 20 mm that are undetectable by fluoroscopy. The yield from the left upper apical posterior segment (6 of 15 lesions, 40%) was significantly lower than that from other locations (p=0.003). The overall time of EBUS-GS was 8.83±0.77 min, mean scanning time was 61.5 ± 23 s, and mean fluoroscopy time was 59.0 ± 45.2 s (± SD).
General Comments	

NO. 6

Bibliographic Citation	Kikuchi E, Yamazaki K, Sukoh N, Kikuchi J, Asahina H, Imura M, Onodera Y, Kurimoto N, Kinoshita I, Nishimura M (2004). Endobronchial ultrasonography with guide-sheath for peripheral pulmonary lesions. *Eur Respir J*
Study Type / Methodology	Cross sectional study between December 1, 2002, and July 31, 2003 at Hokkaido University Medical Hospital and EBUS was performed EU-M30S; Olympus Tokyo, equipped with 20 MHz mechanical radial type probe (XUM-S20-17R; Olympus, having an external diameter of 1.4 mm. FBs with the working channel 2.0 mm in diameter were used. The probe with the GS was confirmed to reach the lesion by EBUS imaging and X-ray fluoroscopy. After localizing the When the lesion was not identified on the EBUS image, the probe was removed and a double hinged- curette
LE (Level of Evidence)	
Number of patients & patient characteristics	Pulmonary lesions (PPLs) ≤ 30 mm in mean diameter referred for diagnostic bronchoscopy were included in the 10 males and 14 females with an average age of 67.5 ± 14.8 yrs (range 24-83 yrs).
Intervention	
Comparison	Nil
Length of follow up (if applicable)	Nil
Outcome measures/ Effect size	Diagnostic yield (able to get a definitive diagnosis) Nineteen peripheral lesions (79.2%) were visualized by EBUS. The mean diameter of the PPLs was 18.4 ± 6.3 mm (8.0-27.5 mm). The mean number of specimens obtained using Diagnosis was made in 14 cases (58.3%). A total of five lesions that were visible by EBUS and for which diagnosis could not be obtained had insufficient biopsy and brush samples taken. Conclusion: Endobronchial ultrasonography with guide sheath – guided transbronchial biopsy was feasible and effective for
General Comments	

NO. 7

Bibliographic Citation	Yoshikawa M, Sukoh N, Yamazaki K, Kanazawa K, Fukumoto S-I, Harada M, Isobe H (2007). Diagnostic value of endobronchial ultrasonography with a guide sheath for peripheral pulmonary lesions without x-ray fluoroscopy*. *Chest*
Study Type / Methodology	Cross sectional study from June 2004 to July 2005, Hokkaido Cancer Centre. CT scanning was performed using a multi detect or CT scanner. EBUS was performed using (EU-M30S; Olympus Tokyo, Japan), equipped with a 20-MHz mechanical radial- type probe (XUM-S20-17R; Olympus) and a GS (XBOI-836-12; Olympus). The probe and GS were confirmed to reach the lesion by EBUS images. Once a typical EBUS without fluoroscopy. When the EBUS image could not be obtained they made the shift to examination under fluoroscopy. They attempted curette was removed and the GS was left in place. The probe was inserted again through the GS to confirm the EBUS image. Once the location of the lesion was identified, TBB/and or bronchial brushing was performed. Biopsy The diagnosis in the biopsy finding-negative patients were established by video-assisted thoracoscopic surgery,
LE (Level of Evidence)	
Number of patients & patient characteristics	121 consecutive patients (72 male and 49 female) with 123 PPLs. Mean age was 66.2 years (range, 38 to 82 years).
Intervention	EBUS-GS without fluoroscopy
Comparison	Nil
Length of follow up (if applicable)	Not mentioned
Outcome measures/ Effect size	Feasibility, efficacy and safety. Mean diameter of PPLs was 31.0±15.9 mm (range, 11.0 to 98.0 mm). The diagnostic yield was 61.8% by EBUS-GS guided TBB and bronchial brushing without fluoroscopy and 86.2% The diagnostic yield for PPLs > 20 mm in diameter (75.6%) was significantly higher than that for lesions ≤ 20 mm (29.7%) $p<0.01$. The yields of the lesions in the right middle lobe (90%) and the left lingular segment (80%) were higher than those in other locations ($p<0.05$). When the bronchus leading to the PPL was identified on the CT scan, the yield was 79.2%. Solid lesions had a higher diagnostic yield (67.0%) compared to nonsolid lesions (35%; $p < 0.05$). sensitivity by EBUS-GS guided bronchoscopy ($p<0.05$). Conclusioms: EBUS-GS bronchoscopy without the use of radiographic fluoroscopy is effective for diagnosing
General Comments	

NO. 8

Bibliographic Citation	Herth F J F, Eberchardt R, Becker H D, Ernst A (2006). Endobronchial ultrasound-guided transbronchial lung biopsy in fluoroscopically invisible solitary pulmonary nodules: a prospective trial. CHEST, 129:147-150
Study Type / Methodology	All patients with solitary pulmonary nodule (SPN) referred for diagnostic broncoscopy were enrolled. All chest CT were reviewed and the size of lesions were recorded by their longest diameter. After which patients fluoroscopy was performed using mono-planar C-arm (Suprer 50 CP; Philips Company). If the lesion is visible fluoroscopically, the procedure was continued with TBBX in the standard manner and the patient was excluded from the trial. If the lesion could not be visualized by fluoroscopy, the patient was included in the trial and TBBX was EBUS performed with a flexible probe and processor unit (UM-3R, UM-4R, US2020R; Olympus). The EBUS probe
LE (Level of Evidence)	
Number of patients & patient characteristics	Mean age 46.3 years, range (35 to 78 years). Patients with solitary pulmonary nodules which could not be visualized by fluoroscopy who were referred for
Intervention	Endobronchial ultrasound-guided transbronchial lung biopsy in fluoroscopically invisible pulmonary nodules.
Comparison	Nil
Length of follow up (if applicable)	Nil
Outcome measures/ Effect size	Diagnostic yield (Histology positive) A bronchoscopic diagnosis of fibrosis or inflammation was considered nondiagnostic..The mean ± SD diameter of the lesion was 2.2 ±0.7 cm (range, 1.4 to 3.3 cm). The lesion was localized in 48 patients with EBUS-guided TBBX (89%). The lesion could not be visualized in six patients, four of those lesions were located in the right upper lobe and two were in the left upper lobe. A diagnosis was established in 38 of these patients (70%). In 10 patients the lesions was localized, but the pathologist was unable to establish a definitive diagnosis. In 16 patients referred for surgical biopsy, surgical findings showed malignant lesion in 10 patients and benign lesion In 15 patients (28%), histologic findings showed benign lesions, in 39 patients (72%) the ecimens were malignant. The diagnosis obtained by EBUS-guided TBBX averted the need for more surgery in 17% of patients. The mean examination time (including biopsies) was 12.3 min (range, 6 to 18 min). Conclusion: EBUS-guided TBBX is safe and very effective method for solitary pulmonary nodules (SPNs) that cannot be visualized by fluoroscopy. The procedure may increase the yield of endoscopic biopsy in patients with these nodules and avert
General Comments	

NO. 9

Bibliographic Citation	Dooms C A, Verbeken E K, Becker H D, Demedts M G, Vansteenkiste J F (2007). Endobronchial ultrasonography in
Study Type / Methodology	Cross sectional descriptive study from 1st January 2005 to 31st May 2005. Spiral chest CT was reviewed before the procedure and the diameter of the lesion was measured on the soft-tissue Bronchoscopy using local anesthesia was performed with a flexible bronchoscope (BF-ITI60; Olympus). The EBUS system (processor EU-M20 and driving unit MH-240; Olympus) equipped with a 20-MHz mechanical radial mini probe (UM-BS20-26R; Olympus) with a balloon sheath (MAJ-643R; Olympus). The distance of the lesion Biopsy was performed using biopsy forceps (FB-20C-1; Olympus). No biopsy specimen were taken in whom EBUS
LE (Level of Evidence)	
Number of patients & patient characteristics	Average age = 69 years. Patients with a pulmonary nodule or solid mass having normal endoluminal findings on routine diagnostic (A pulmonary nodule or solid mass was defined as a lesion surrounded by pulmonary parenchyma on computed tomography)
Intervention	EBUS-guided transbronchial biopsy (TBBs).
Comparison	Nil
Length of follow up (if applicable)	Nil
Outcome measures/ Effect size	Diagnostic yield (histologic and cytology positive) in bronchoscopic occult pulmonary lesion. The mean diameter of the lesions on CT was 36.6±19.7mm (range, 8-90 mm). The bronchoscopic occult lesion could be visualized with EBUS in 37 of 50 patients (74%) and histologic diagnosis could be established in 31 of these 37 (84%), cytology diagnosis in one and no diagnosis in 5 patients. For EBUS invisible lesion (n=13), no diagnosis was obtained in 11 and cytology diagnosis was obtained in 2. In 34 patients (68%), a pathologic (histology +cytology) diagnosis could be established: 28 primary lung cancer and For lesion <20 mm in the greatest diameter, the pathologic diagnostic yield decreased to 18% whereas for lesions ≥ 20 mm diagnostic pathologic yield was 32/39 (82%). Conclusion: EBUS-guided TBB is effective for localizing and diagnosing bronchoscopic occult pulmonary masses ≥ 20 mm, but
General Comments	

NO. 10

Bibliographic Citation	Asahina H, Yamazaki K, Onodera Y, Kikuchi E, Shinagawa N, Asano F, Nishimura M (2005). Transbronchial biopsy using endobronchial ultrasonography with a guide sheath and virtual bronchoscopic navigation. CHEST, 128:1761-
Study Type / Methodology	Cross sectional study from 1st January 2004 and 31st August 2004, Hokkaido University Hospital, Japan. VB All patients underwent CT in order to generate VB images to guide TBB. CT was performed using a multidetector CT scanner. Images were reconstructed from helical CT data and transferred to a work site. All VB images were EBUS-GS-guided TBB and Bronchial brushings using endoscopic ultrasound system (EU-M30S; Olympus) equipped mm external diameter; Olympus). EBUS imaging and radiograph fluoroscopy were used to confirm that the probe In lesions where EBUS-GS-guided TBB with VB navigation was non diagnostic, diagnosis was established on
LE (Level of Evidence)	
Number of patients & patient characteristics	(≤ 30 mm in mean diameter) who were referred to Hokkaido University Hospital for bronchoscopy. Average age was 62.2±11.6 (± SD) years, range, 43 to 84 years. Mean diameter of peripheral pulmonary lesions was 18.9±6.5 mm (range, 10.0 to 30.0 mm). Distribution of lesions: right upper lobe n=11 (36.7%), right middle lobe, n=1 (3.3%), right lower lobe, n=7 (23.3%), left upper lobe, n=7 (23.3%), and left lower lobe, n=4 (13.3%).
Intervention	Virtual Bronchoscopy (VB) images were constructed from helical CT data. TBB was then performed using EBUS-GS with VB navigation.
Comparison	Nil
Length of follow up (if applicable)	Nil
Outcome measures/ Effect size	Safety and diagnostic yield (sensitivity, specificity, PPV, NPV, accuracy) histology and cytology) for small peripheral Bronchi seen on VB imaging were highly consistent with the actual structures confirmed by fiberoptic EBUS detected 24 of the 30 peripheral pulmonary lesions (80.0%). Mean number of specimens obtained using EBUS-GS-guided TBB with VB navigation was 2.8 ± 2.4. Diagnosis was possible in 19 lesions (63.3%). Pathologic diagnosis was made for 14 lesions (46.7%) and a cytologic diagnosis was made for 16 lesions (53.3%). Of the 30 lesions in which final diagnosis was made, sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were 63.3% (19/30), 100% (7/7), 100% (17/17), 53.9% (7/13) and 76.7% (23/30) Diagnostic sensitivities of EBUS-GS-guided TBB with VB navigation in malignant and benign lesions were 73.9% (17/23) and 28.6% (2/7) respectively. Significant differences were found in diagnostic sensitivity of this procedure with regard to lesion size (P=0.006) number of samples taken (p=0.003) and total examination time (p=0.0280). Diagnostic sensitivities were 44.4% (8 of 18) for lesions < 20 mm in mean diameter and 91.7% (11 of 12) for lesions Average durations of the initial EBUS examination of lesions, first biopsy and the total procedure were 9.56 min,
General Comments	

NO. 11

Bibliographic Citation	Chao T Y, Lie C H, Lie C H, Chung Y H, Wang J L, Wang Y H, Lin M C (2006). Differentiating peripheral pulmonary *CHEST,*
Study Type / Methodology	Cross sectional study from June 2004 and June 2005 . (Taiwan) EBUS was conducted using an endoscopic ultrasound system (EU-M30; Olympus) equipped with a 20-MHz miniature radial probe (UM-S20-20R; Olympus). Once the images of the peripheral lesions were obtained and their location were identified, TBB, TBNA or BAL were who had a definite diagnosis, and compared with previous published document, 6 well-trained bronchoscopists
LE (Level of Evidence)	
Number of patients & patient characteristics	Patients with peripheral lesions that could not be detected with flexible video bronchoscopy.
Intervention	
Comparison	Nil
Length of follow up (if applicable)	Nil
Outcome measures/ Effect size	Correlation of EBUS image characteristics and histopathologic results to differentiate neoplasm and non neoplasm. Based on the initial 20 patients, who had a definite diagnosis, four image patterns were issued: (1) continuous hyperechoic margin outside the lesion, (2) homogenous or heterogenous internal echoes, (3) hyperechoic dots in the lesion, and (4) concentric circles along the echo probe. In the following 131 patients, excluding excluding five cases due to inconsistent typing, 93 patients (73.8%) established a diagnosis. Comparisons of EBUS image patterns to clinical diagnosis in 93 patients showed that images with concentric rings were more likely to be non neoplasm lesions by univariate and multivariate analysis ($p < 0.001$ and $p< 0.030$) analysis ($p<0.001$)but the significance of internal echoes was lost after multivariate analysis (0.674). EBUS duration = 3.94±2.31 minutes-.
General Comments	

NO. 12

Bibliographic Citation	Kurimoto N, Murayama M, Yoshioka S, Nishisaka T (2002). Analysis of internal structure of peripheral pulmonary *Chest,*
Study Type / Methodology	Descriptive study. (VALIDATION) Dec. 2000 and whose surgical specimens could be sectioned were reviewed. The histopathologic findings were (85.1%). Of these patients, a definitive histopathologic diagnosis was made in 124 (73.8%). The internal structure of these lesion were analyzed and the lesions were typed based on these findings. **Correlation between the preoperative EBUS Images and the histopathological findings** Bronchoscopy was performed with a flexible bronchoscope under local anesthesia without sedation. Surgery specimens were fixed in formalin and EBUS findings were correlated with the histopathology or hematoxylin-eosin **Typing of 124 lesions based on the internal structure by EBUS.** Peripheral pulmonary lesions were classified based on their internal structure, focusing on internal echoes and the also obtained by high resolution CT (HRCT) scanning EBUS was performed using an endoscopic ultrasound system (EU-M30: Olympus: Tokyo, Japan) equipped with a 20 MHz mechanical radial probe with an external diameter of 2.5 mm (Um-3R: or 2,0 mm (UM-4R: Olympus).
LE (Level of Evidence)	
Number of patients & patient characteristics	
Intervention	
Comparison	Nil
Length of follow up (if applicable)	Nil
Outcome measures/ Effect size	Correlation between EBUS Images and the histology of surgical specimen to develop a classification system for Correlation Between EBUS Images and the Histopathology was described. **Tumour typing based on the internal structure visualized by EBUS.** Three classes and six subclasses of lesions were identified by EBUS based on the internal structure of the lesion. Type 1, homogenous pattern (type 1a, with patent vessels and patent bronchioles; type 1b, without vessels and bronchioles); type 11, hyperechoic dots and linear arcs pattern type(11a, without vessels; type 11b, with patent vessels); and type 111, heterogenous pattern (type 111a, with hyperechoic dots and short lines; type 111b, without hyperechoic dots and short lines). Twenty-three of 25 type 1 lesions (92.0%) were benign, while 98 of 99 type 11 and 111 lesions (99.0%) were Twenty- one of 24 type 11 lesions (87.5%) were well-differentiated adenocarcinomas, and all type 111b lesions were malignant, including 18 poorly differentiated adenocarcinomas (81.8%) Conclusion:
General Comments	

Evidence table : EFFECTIVENESS OF EBUS INTERVENTIONAL BRONCHOSCOPY
Question : Is EBUS effective when used in therapeutic intervention?

NO. 1

Bibliographic Citation	Herth F, Becker H D, LoCicero 111 Jr J, Ernst A (2002). Endobronchial ultrasound in therapeutic bronchoscopy. *Eur Respir J*
Study Type / Methodology	Cross sectional study from January 1998 to January 2001. combined with flexible instruments) under general anesthesia and jet ventilation or with a flexible instrument under Endobronchial ultrasound was performed with a flexible 20 MHz probe (UM-2R/3R with driving unit MH-240 and processor EU-M 20 and 30; Olympus) through the working channel of a flexible bronchoscope (models BF P20D, BF IT 10, and BF IT 30; Olympus). Indications for therapeutic intervention, for EBUS and the results especially if the findings resulted in change of
LE (Level of Evidence)	
Number of patients & patient characteristics	Mean age 58.8 years (range 24-83 years)
Intervention	
Comparison	Nil
Length of follow up (if applicable)	Nil
Outcome measures/ Effect size	EBUS was used before mechanical tumour destruction (346 cases, 29%), in airway stent placement (235 cases, 20%), before and during Neodynium: yttrium aluminium garnet (Nd:YAG) laser resection (148 cases, 13%), Argon-plasma coagulation APC (262 cases, 23%) , brachytherapy (134, 11%), foreign body removal (22, 2%) and abscess drainage (27, 2%). Changes of treatment were for example the use of longer stents for endoscopically unappreciated submucosal or Tumour debridement with laser or APC was stopped when EBUS demonstrated close relationships with vessels. Severe bleed of fistula formation did not develop in any of the cases where EBUS was used to guide tumour Lymph node metastasis was confirmed by EBUS guided transbronchial needle aspiration in all these cases. The mean total procedure time (including bronchoscopy and EBUS) was 23.2 min (range 5.7-43.5). The mean time for EBUS examinations was 5.3 min (range 3.1-14.4).
General Comments	

Evidence table : EFFECTIVENESS OF EBUS IN OTHER LUNG DISEASES
Question : Is EBUS effective when used in management of other lung disease?

NO. 1

Bibliographic Citation	Galluccio G, Lucantoni G (2006). Mediastinal bronchogenic cyst's recurrence treated with EBUS-FNA with long-term *European Journal of Cardio-thoracic Surgery*, 29;627-629
Study Type / Methodology	Case report (Center of Thoracic Endoscopy, Forlanini, Rome, Italy) Fiberoptic bronchoscopy performed using a flexible bronchoscope (Olympus BF 3) equipped with a 20 MHz flexible probe connected to an endoscopic ultrasound system EU-M30 (Olympus, Tokyo). After localization of the cyst, FNA was performed, in the same place indicated by EBUS, using a 22-gauge full length Patient was subjected to a 6-month CT follow-up.
LE (Level of Evidence)	
Number of patients & patient characteristics	thoracoscopy (VATS). The excision was incomplete because of pericystic adhesions to the bronchial wall.
Intervention	EBUS-guided FNA for a complete aspiration of the cyst.
Comparison	Nil
Length of follow up (if applicable)	
Outcome measures/ Effect size	EBUS (after 7 days) confirmed the complete aspiration previously performed and the total collapse of the inner (2006). 6 monthly CT follow-up showed no cyst's regrowth was found after 18 months
General Comments	

NO. 2

Bibliographic Citation	Yamasaki A, Tomita K, Sano H, Watanabe M, Makino H, Kurai J, Hitsuda Y, Shimizu E (2003). Measuring subepithelial *Lung*
Study Type / Methodology	Case report (Tottori University, Japan) Peak expiratory flow (PEF) were monitored twice daily before and 15 minutes after inhaling 40 µg of protacerol and Airway measurement with conventional computed tomography (CT). Assessed airway wall thickness based on wall Endobronchial ultrasonograph usingy EU-M 20 (Olympus, Tokyo Japan), UM-BS20-26R; Olympus, MAJ-643R; Olympus, BF-1T20; Olympus).
LE (Level of Evidence)	
Number of patients & patient characteristics	A 42 years old man with mild persistent asthma, had his symptoms control with □
Intervention	and montelukast 10 mg / day for 2 weeks.
Comparison	Nil
Length of follow up (if applicable)	Nil
Outcome measures/ Effect size	five bands. After 2 weeks of montelukast 10 mg daily, the submucosal thickness which was measured as a ratio of the second layer thickness to the total wall thickness (% submucosal thickness), was reduced by 46.7% . Airway measurement with conventional computed tomography (CT). Peak expiratory flow increased 21% with procaterol. After montelukast administration, baseline PEF showed 7%
General Comments	

NO. 3

Bibliographic Citation	Miyaza Y, Miyazawa T, Kurimoto N, Iwamoto Y, Hitsuda Y, Ishida A, Kanoh K, Kohno N (2003). Endobronchial *Ches*
Study Type / Methodology	Case reports (Hiroshima Hospital, Japan) No evidence of auricular or nasal abnormalities. Flexible bronchoscopy demonstrated malacia of the tracheobronchial tree, collapse of the airway on expiration. CT images demonstrated diffuse thickening of the tracheobronchial wall affected tracheobronchial tree was measured using EBUs before stenting. Through a flexible bronchoscope , four uncovered Ultraflex stents were implanted. Four uncovered Ultraflex stents were implanted to maintain the airway.
LE (Level of Evidence)	
Number of patients & patient characteristics	Case 1 Case 2
Intervention	Case 1 : EBUS for diagnosis and EBUS as a guide for implantation of uncovered Ultraflex stents. Case 2 : EBUS for diagnosis and EBUS as a guide for implantation of uncovered Ultraflex stents.
Comparison	Nil
Length of follow up (if applicable)	Case 1 : Not mentioned Case 2 : 2 months
General Comments	

NO. 4

Bibliographic Citation	Lee P, Low S-Y, Liew H-L, tan D, Eng P (2007). Endobronchial ultrasound for detection of tracheomalacia from *Respirology*
Study Type / Methodology	Case report (Singapore General Hospital) performed. EBUS of the bronchial wall was performed with a 20-MHZ, radial ultrasonic probe (model UM-3R; Olympus, Tokyo, Japan).
LE (Level of Evidence)	
Number of patients & patient characteristics	67 years old Chinese female. She was previously evaluated for asymptomatic right paratracheal mass on CXR. Smoker-smoked 25 pack-years, and had a subtotal thyroidectomy for multinodular goiter. CT showed a Double Arch Aorta (DAA) encircling oesophagus with tracheal compression.
Intervention	
Comparison	Nil
Length of follow up (if applicable)	Nil
Outcome measures/ Effect size	Flexible bronchoscopy showed a pulsatile identification of the right lateral wall by the vascular ring, which cause
General Comments	

Evidence table : SAFETY
Question : Is EBUS safe when used in the analysis / diagnosis of mediastinal / hilar / intrathoracic lymph nodes and staging of lung cancer?

NO. 1

Bibliographic Citation	Herth F, Becker H D, Ernst A (2004). Conventional vs endobronchial ultrasound-guided transbronchial needle *CHEST*
Study Type / Methodology	RCT between June 2001 and March 2002. Through a bronchoscope with 2.8 mm working channel , a flexible ultrasound probe with a 20-MHz transducer (UM-2R/3R with driving unit MH-240 and a processor EU-M 20 and 30, Olympus was introduced. The probe was removed from the working channel and TBNA was performed. TBNA. Cytology specimens were obtained with a 22-gauge needles (MW 522, Bard: Billeriea, MA) All patients of both groups without a specific diagnosis, irrespective of the presence or absence of lymphocytes in The pathologist was unaware of the method used to obtain the specimen.(blinded)
LE (Level of Evidence)	
Number of patients & patient characteristics	All patients with enlarged mediastinal lymph nodes referred for TBNA (75 women and 125 men). Mean age 51.9 years ± 22.6 years (SD) All patients were randomized in an EBUS-guided and a conventional TBNA arm. Patients with subcarinal lymph nodes were randomized and analyzed separately (group A) and patients with lymph
Intervention	EBUS guided TBNA
Comparison	Conventional TBNA
Length of follow up (if applicable)	Nil
Outcome measures/ Effect size	No complications, either related to the procedure or to bronchoscopic damage were observed with the use of EBUS and / or TBNA.
General Comments	

NO. 2

Bibliographic Citation	Kanoh K, Miyazawa T, Kurimoto N, Iwamoto Y, Miyazu Y, Kohno N (2005). Endobronchial ultrasonography guidance *Chest*
Study Type / Methodology	RCT between January 2000 to August 2003 Patients were randomized to undergo EBUS-D (n-29) or EBUS-S (n=25). One patient from EBUS-D was excluded because liquid was aspirated from the lesion (pericardial cyst). EBUS guided TBNA using double-channel bronchoscope, EBUS-D through which both a TBNA catheter and an Ultrasonic probe (UM-BS20-26R, Olympus), double-channel flexible bronchoscope (XBF-2T40Y2, Olympus Ultrasonic probe (UM-BS20-26R, Olympus), single-channel flexible bronchoscope (BF-1T-30, Olympus)
LE (Level of Evidence)	
Number of patients & patient characteristics	Patients with mediastinal and / or hilar lymphadenopathy.
Intervention	EBUS guided TBNA using double-channel bronchoscope (EBUS-D)
Comparison	EBUS guided TBNA using single-channel bronchoscope, EBUS-S
Length of follow up (if applicable)	Nil
Outcome measures/ Effect size	No complications were observed in the EBUS-D group, but self limiting hemorrhage < 30 ml occurred in one patient
General Comments	

NO. 3

Bibliographic Citation	Herth FJF, Lunn W, Eberhardt R, Becker H D, Ernst A (2005). Transbronchial versus transesophageal ultrasound- *Am J Respir Crit Care Med,*
Study Type / Methodology	Cross sectional study (cross over design) from January 2002 to January 2004 include hilar lymph nodes in positions 5,6, or 11 (which are accessible only by bronchoscopy) and stations 8 and 9 (which are accessible only by esophagoscopy) . findings.
LE (Level of Evidence)	
Number of patients & patient characteristics	Patients with enlarged mediastinal lymph nodes (1 cm) as assessed by contrast-enhanced computed tomography Mean age 53.2 years, SD (11.8 years), range of 33 to 76 years.
Intervention	
Comparison	
Length of follow up (if applicable)	Nil
Outcome measures/ Effect size	
General Comments	

NO. 4

Bibliographic Citation	Herth F J, Becker H D, Ernst A (2003). Ultrasound -guided transbronchial needle aspiration. An experience in 242 *Chest,*
Study Type / Methodology	Cross sectional study between January 1999 and January 2000. EBUS using bronchoscope (Olympus p 20 and Olympus p 40 D model), ultrasound probe with a transducer (UM-2R/3R) and processer EU-m 20 and 30: Olympus) TBNA was performed using 22-gauge for cytology specimens and 19-gauge needles for histology specimens. All patients without a specific diagnosis underwent a surgical biopsy procedure.
LE (Level of Evidence)	
Number of patients & patient characteristics	(160 men and 82 women). Mean age, 60.0 years, SD (11.8 years), range, (33-76 years) All patients referred for diagnostic TBNA of mediastinal lymph nodes.
Intervention	Endobronchial ultrasound (EBUS) for TBNA guidance during bronchoscopy
Comparison	Nil
Length of follow up (if applicable)	Not mentioned
Outcome measures/ Effect size	No complication associated with the use of EBUS and TBNA.
General Comments	

NO. 5

Bibliographic Citation	Yasufuku K, Nakajima T, Motoori K, sekine Y (2006).Comparison of endobronchial ultrasound, positron emission tomography, and CT for lymph node staging of lung cancer*. *CHEST*
Study Type / Methodology	Cross sectional study from December 2003 and March 2005. (Chiba University Hospital, Japan) Patients underwent CT, PET and EBUS-TBNA for mediastinal staging prior to surgery.
LE (Level of Evidence)	
Number of patients & patient characteristics	Potentially operable patients with proven (n=96) or radiologically suspected (n=6) lung cancer. Median age=67.8 (44-85)
Intervention	EBUS-TBNA
Comparison	Thoracic CT and PET
Length of follow up (if applicable)	Not mentioned
Outcome measures/ Effect size	EBUS-TBNA procedure was uneventful, and there were no complications. All patients tolerated the procedure very
General Comments	

NO. 6

Bibliographic Citation	Yasufuku K, Chiyo M, Koh Eitetsu K, Moriya Y, Iyoda A, Sekine Y, Shibuya K, Iizasa T, Fujisawa T (2005). Endobronchial *Lung cancer*
Study Type / Methodology	Cross sectional study from June 2002 to April 2004, Chiba University Hospital . Conventional flexible bronchoscope was first performed followed by examination of the mediastinum using CP-EBUS (XBF-UC260F-OL8, Olympus). The CP-EBUS is integrated with a convex transducer (7.5 MHz). The ultrasound image is processed in a dedicated ultrasound scanner EU-C2000, Olympus) and is visualized along the conventional A dedicated 22-gauge needle was developed to perform transbronchial aspiration (NA-201SX-4022, Olympus). stained by Diff-Quik staining for immediate interpretation by an on site cytopathologist to confirm adequate cell material. Specimens Were categorized as positive (tumour cells), negative (lymphoid but no tumour cells), or inconclusive (poor cellularity or unable to perform adequate punctures). If adequate tissue was not identified by on site cytology after five passes, the procedure was terminated. Cytopathologist blinded to the details of the cases. EBUS-TBNA diagnosis was confirmed either by open thoracostomy, thoracoscopy or clinical follow-up.
LE (Level of Evidence)	
Number of patients & patient characteristics	larger than 1 cm or mediastinal lesion suspected of malignancy detected on CT were included in the study. Proven lung cancer (n=88), or suspected NSCLS (n=20), fulfilled the criteria were included in the study. 86 males and 22 females. Median age 65.3 years, range (37-85 years)
Intervention	EBUS-TBNA was performed on an outpatient basis under conscious sedation.
Comparison	Nil
Length of follow up (if applicable)	
Outcome measures/ Effect size	The EBUS-TBNA procedure was uneventful and there were no complications.
General Comments	

NO. 7

Bibliographic Citation	Rintoul R C, Skwarski K M, Murchison J T, Hill A, Walker S W, Penman I D (2004). Endoscopic and endobronchial ultrasound real-time fine-needle aspiration for staging of mediastinum in lung cancer. *Chest,*
Study Type / Methodology	Case reports (Western General Hospital, Edinburgh, UK) EBUS-FNA was performed to examine pretracheal, peritracheal, subcarinal, and hilar lymph nodes stations (stations 1,2,3,4,7 and 10) under conscious sedation. EUS-FNA was performed to examine the posterior and inferior mediastinal lymph nodes staions (stations 5,7,8 and 9) also under conscious sedation
LE (Level of Evidence)	
Number of patients & patient characteristics	2 (1 in each report) Case report 1. 68- year- old ex-smoker. CT scan revealed right paratracheal (station 4R) and subcarinal lymphadenopathy (station 7). No primary mass lesion was apparent. Case report 2. 45 years old man presented with hemoptysis. CT revealed 4x3 cm mass in left upper lobe with mediastinal
Intervention	EBUS-FNA and EUS-FNA .
Comparison	Case report 1. Nil Case report 2. Compared with surgical frozen section.
Length of follow up (if applicable)	Nil
Outcome measures/ Effect size	No complication and discharged on the same day and treated accordingly.
General Comments	

Evidence table : SAFETY
Question : Is EBUS safe when used in the analysis/diagnosis of peripheral pulmonary lesions/solitary pulmonarymodules?
NO. 1

Bibliographic Citation	Chung Y H, Lie C H, Chao T Y, Wang Y H, Lin A S, Wang J L, Lin M C (2006). Endobronchial ultrasonography with *Respiratory Medicine,* doi: 10.1016/j.med.2006.08.014
Study Type / Methodology	Randomized Control Trial, October 2004 to July 2005 at Chang Gung Memorial Hospital, Taiwan. Patients were randomly divided into two groups for transbronchial biopsy (TBBs) using different methods, the group
LE (Level of Evidence)	
Number of patients & patient characteristics	Patients with solitary peripheral pulmonary lesions (PPL) which were visualized on EBUS image were included in the Mean age 59.4 ± 12.8 yr (SD).
Intervention	
Comparison	
Length of follow up (if applicable)	Not mentioned
Outcome measures/ Effect size	There was a brisk hemorrhage in five patients as a result of forceps biopsy (3 in group EBUS-D and 2 in group EBUS). Self-limited pneumothorax secondary to TBBs occurred in one group EBUS patient, but did not necessitate
General Comments	

NO. 2

Bibliographic Citation	Paone G, Nicastri E, Lucantoni G, Iacono R D, Battistoni P, D'Angeli A L, Galluccio G (2005). Endobronchial *CHEST,*
Study Type / Methodology	293 eligible patients were randomly assigned to EBUS-TBB (144 patients) or TBB (149 patients). However, only 221 patients undergone bronchoscopy (97 EBUS –TBB) and 144 (TBB) because 28 undergone lung surgery before bronchoscopy and 23 did not accept randomization protocol, in 12 patients primary lesion was identified in another The patients were further stratified into 3 subsets: patients with lesions >3cm in diameter, < 3cm in diameter and <
LE (Level of Evidence)	
Number of patients & patient characteristics	221 patients (recruited), 206 patients analyzed. Mean age and SD for EBUS-TBB group = 65±12 years and for TBB group = 68±10 years.
Intervention	Endobronchial ultrasound –driven transbronchial biosy (EBUS-TBB)
Comparison	Coventional TBB (transbronchial biopsy).
Length of follow up (if applicable)	Not mentioned
Outcome measures/ Effect size	Important side effects were observed only in patients who underwent TBB (bleeding n=7, and pneumothorax n=3). No complication found in EBUS-TBB group.
General Comments	

NO. 3

Bibliographic Citation	Hearth FJ F, Ernst A, Becker HD (2002). Endobronchial ultrasound-guided transbronchial lung biopsy in solitary *Eur Respir J*
Study Type / Methodology	Cross sectional study from November 2000 to February 2001. Flouroscopy was provided using a monoplanar C-arm (Suprer 50 CP, Philips). Biopsies were performed with regular disposable forceps (FB-20C Olympus Fibreoptic bronchoscopes (model BF IT-30, BF IT 40 and BF XT 20; Olympus) were used. EBUS was performed with a flexible probe and processor unit (UM-3R, UM-4R, US20-20R, Olympus). Biopsies were performed with regular disposable forceps. Forceps were changed between EBUS and fluoroscopic examinations to avoid cellular cross All patients in whom a definite diagnosis could not be established underwent surgical procedure.
LE (Level of Evidence)	
Number of patients & patient characteristics	37 males and 13 females with an average age of 62.5 ±10.5 years (range 25-81 years).
Intervention	Endobronchial ultrasound (EBUS) guided transbronchial biopsy.
Comparison	
Length of follow up (if applicable)	Not mentioned
Outcome measures/ Effect size	Self limited bleeding in 2 cases. One patient developed pnuemothorax (2%) which was treated with tube
General Comments	

NO. 4

Bibliographic Citation	Kurimoto N, Miyazawa T, Okimasa S, Maeda A, Oiwa H, Miyazu Y, Murayama M (2004). Endobronchial ultrasonography *Chest*
Study Type / Methodology	Cross sectional study between May 2001 and November 2002 at National Hiroshima Hospital and Hiroshima City
LE (Level of Evidence)	
Number of patients & patient characteristics	Consecutive patients with a solitary pulmonary lesion detected by chest radiograph and CT. Patient underwent bronchoscopy between May 2001 and November 2002.
Intervention	
Comparison	Nil
Length of follow up (if applicable)	Not mentioned
Outcome measures/ Effect size	Moderate bleeding was noted in two patients (1%). None of the patients required bronchial intubation. There was no death, pneumothorax, or other clinically significant morbidity
General Comments	

NO. 5

Bibliographic Citation	Kikuchi E, Yamazaki K, Sukoh N, Kikuchi J, Asahina H, Imura M, Onodera Y, Kurimoto N, Kinoshita I, Nishimura M (2004). Endobronchial ultrasonography with guide-sheath for peripheral pulmonary lesions. *Eur Respir J*
Study Type / Methodology	Cross sectional study between December 1, 2002, and July 31, 2003 at Hokkaido University Medical Hospital and EBUS was performed EU-M30S; Olympus Tokyo, equipped with 20 MHz mechanical radial type probe (XUM-S20-17R; Olympus, having an external diameter of 1.4 mm. FBs with the working channel 2.0 mm in diameter were used. The probe with the GS was confirmed to reach the lesion by EBUS imaging and X-ray fluoroscopy. After localizing the When the lesion was not identified on the EBUS image, the probe was removed and a double hinged- curette
LE (Level of Evidence)	
Number of patients & patient characteristics	Pulmonary lesions (PPLs) ≤ 30 mm in mean diameter referred for diagnostic bronchoscopy were included in the 10 males and 14 females with an average age of 67.5 ± 14.8 yrs (range 24-83 yrs).
Intervention	
Comparison	Nil
Length of follow up (if applicable)	Nil
Outcome measures/ Effect size	One patient developed pneumothorax (4.2%) which was treated by tube thoracostomy. No major bleeding occurred
General Comments	

NO. 6

Bibliographic Citation	Yoshikawa M, Sukoh N, Yamazaki K, Kanazawa K, Fukumoto S-I, Harada M, Isobe H (2007). Diagnostic value of endobronchial ultrasonography with a guide sheath for peripheral pulmonary lesions without x-ray fluoroscopy*. *Chest*
Study Type / Methodology	Cross sectional study from June 2004 to July 2005, Hokkaido Cancer Centre. CT scanning was performed using a multidetector CT scanner. EBUS was performed using (EU-M30S; Olympus Tokyo, Japan), equipped with a 20-MHz mechanical radial- type probe (XUM-S20-17R; Olympus) and a GS (XBOI-836-12; Olympus). The probe and GS were confirmed to reach the lesion by EBUS images. Once a typical EBUS without fluoroscopy. When the EBUS image could not be obtained they made the shift to examination under fluoroscopy. They attempted curette was removed and the GS was left in place. The probe was inserted again through the GS to confirm the EBUS image. Once the location of the lesion was identified, TBB/and or bronchial brushing was performed. Biopsy repeated until adequate specimens were collected. The diagnosis in the biopsy finding-negative patients were
LE (Level of Evidence)	
Number of patients & patient characteristics	121 consecutive patients (72 male and 49 female) with 123 PPLs. Mean age was 66.2 years (range, 38 to 82 years).
Intervention	EBUS-GS without fluoroscopy
Comparison	Nil
Length of follow up (if applicable)	Not mentioned
Outcome measures/ Effect size	**Pneumothorax occurred** in one patient (0.8%), who did not need to be treated.
General Comments	

NO. 7

Bibliographic Citation	Dooms C A, Verbeken E K, Becker H D, Demedts M G, Vansteenkiste J F (2007). Endobronchial ultrasonography in *J Thorac Oncol*
Study Type / Methodology	Cross sectional descriptive study from 1 Spiral chest CT was reviewed before the procedure and the diameter of the lesion was measured on the soft-tissue Bronchoscopy using local anesthesia was performed with a flexible bronchoscope (BF-ITI60; Olympus). The EBUS system (processor EU-M20 and driving unit MH-240; Olympus) equipped with a 20-MHz mechanical radial mini probe (UM-BS20-26R; Olympus) with a balloon sheath (MAJ-643R; Olympus). The distance of the lesion Biopsy was performed using biopsy forceps (FB-20C-1; Olympus). No biopsy specimen were taken in whom EBUS
LE (Level of Evidence)	
Number of patients & patient characteristics	Average age= 69 years. **a** pulmonary nodule or solid mass having normal endoluminal findings on routine diagnostic (A pulmonary nodule or solid mass was defined as a lesion surrounded by pulmonary parenchyma on computed tomography)
Intervention	EBUS-guided transbronchial biopsy (TBBs).
Comparison	Nil
Length of follow up (if applicable)	Nil
Outcome measures/ Effect size	Moderate bleeding requiring only bronchoscopic hemostasis was noted in one patient. No significant adverse
General Comments	

NO. 8

Bibliographic Citation	Asahina H, Yamazaki K, Onodera Y, Kikuchi E, Shinagawa N, Asano F, Nishimura M (2005). Transbronchial biopsy *CHEST,*
Study Type / Methodology	Cross sectional study from 1
LE (Level of Evidence)	
Number of patients & patient characteristics	(≤ 30 mm in mean diameter) who were referred to Hokkaido University Hospital for bronchoscopy. Average age was 62.2±11.6 (± SD) years, range, 43 to 84 years. Mean diameter of peripheral pulmonary lesions was 18.9±6.5 mm (range, 10.0 to 30.0 mm). Distribution of lesions: right upper lobe n=11 (36.7%), right middle lobe, n=1 (3.3%), right lower lobe, n=7 (23.3%), left upper lobe, n=7 (23.3%), and left lower lobe, n=4 (13.3%).
Intervention	Virtual Bronchoscopy (VB) images were constructed from helical CT data. TBB was then performed using EBUS-GS with VB navigation.
Comparison	Nil
Length of follow up (if applicable)	Nil
Outcome measures/ Effect size	For all 29 patients (30 peripheral pulmonary lesions) EBUS-GS-guided TBB was performed safely with no
General Comments	

NO. 9

Bibliographic Citation	Herth F J F, Eberchardt R, Becker H D, Ernst A (2006). Endobronchial ultrasound-guided transbronchial lung biopsy in fluoroscopically invisible solitary pulmonary nodules: a prospective trial. *CHEST,*
Study Type / Methodology	All patients with solitary pulmonary nodule (SPN) referred for diagnostic broncoscopy were enrolled. All chest CT were reviewed and the size of lesions were recorded by their longest diameter. After which patients fluoroscopy was performed using mono-planar C-arm (Suprer 50 CP; Philips Company). If the lesion is visible fluoroscopically, the procedure was continued with TBBX in the standard manner and the patient was excluded from the trial. If the lesion could not be visualized by fluoroscopy, the patient was included in the trial and TBBX was performed under EBUS guidance.EBUS performed with a flexible probe and processor unit (UM-3R, UM-4R, US2020R; Olympus).
LE (Level of Evidence)	
Number of patients & patient characteristics	Mean age 46.3 years, range (35 to 78 years). Patients with solitary pulmonary nodules which could not be visualized by fluoroscopy who were referred for
Intervention	Endobronchial ultrasound-guided transbronchial lung biopsy in fluoroscopically invisible pulmonary nodules.
Comparison	Nil
Length of follow up (if applicable)	Nil
Outcome measures/ Effect size	Self limited bleeding was observed in three patients.One patient (2%) had a pneumothorax that was treated by tube
General Comments	

Evidence table : SAFETY
Question : Is EBUS safe when used in therapeutic intervention?

NO. 1

Bibliographic Citation	Herth F, Becker H D, LoCicero 111 Jr J, Ernst A (2002). Endobronchial ultrasound in therapeutic bronchoscopy. *Eur Respir J*
Study Type / Methodology	Cross sectional study from January 1998 to January 2001. combined with flexible instruments) under general anesthesia and jet ventilation or with a flexible instrument under Endobronchial ultrasound was performed with a flexible 20 MHz probe (UM-2R/3R with driving unit MH-240 and processor EU-M 20 and 30; Olympus) through the working channel of a flexible bronchoscope (models BF P20D, BF IT 10, and BF IT 30; Olympus). Indications for therapeutic intervention, for EBUS and the results especially if the findings resulted in change of
LE (Level of Evidence)	
Number of patients & patient characteristics	Mean age 58.8 years (range 24-83 years)
Intervention	
Comparison	Nil
Length of follow up (if applicable)	Nil
Outcome measures/ Effect size	Self limited cardiac arrhythmias such as transient atrial tachycardia, were observed in 52 patients (5.5%). This was
General Comments	