Technology Assessment Program
Office of Patient Care Services

Bibliography*: Electromagnetic Navigation Bronchoscopy

*Selected, quality filtered, not subject to external review

Policy issue: The VA Chief Patient Care Services Officer (CPCSO) and the Acting Chief Consultant, Medical-Surgical Services, requested an evidence review of electromagnetic navigation bronchoscopy (ENB), in particular the superDimension® inReach™ system (superDimension® Ltd, Plymouth, MN; www.superDimension.com).

The CPCSO asked that the VA Technology Assessment Advisory Group (TAAG) within the Office of Patient Care Services handle this request, which was created to deliver evidence-based recommendations for use of new technologies in VA in a timely manner. As part of this process, the VA Technology Assessment Program (VATAP) is charged with providing the best available evidence on a topic to the TAAG within a two-week time period. The evidence would help support guidance for acquisition and use of ENB in VA.

Specifically, VATAP was asked to review the clinical evidence for each potential application of the superDimension® inReach™ system and other available ENB systems, and identify competing technologies.

Background: Lung cancer remains a leading cause of cancer mortality. In 2007 an estimated 213,380 persons were diagnosed with, and 160,390 persons died of, cancer of the lung and bronchus.[1] According to NCI SEER Cancer Statistics Review, stage of disease at diagnosis is an important determinant of outcome for persons with lung cancer.[2] Lung cancer is associated with overall low survival rates and treatment failure, the main reason being late diagnosis of metastatic disease at initial clinical presentation:

Stage	Distribution of Stage at Diagnosis	5-year Survival Rates
Localized	16%	49.1%
Regional	35%	15.2%
Distant metastasis	41%	3.0%
Unknown	8%	8.1%

Diagnosis and Staging of Lung Cancer

(Source for this section: American College of Chest Physicians (ACCP) Evidence-based Clinical Practice Guidelines (2007)[3])

Diagnosis

The choice of techniques used to achieve a definitive diagnosis of lung cancer will depend on the diagnostic performance of each technique, as well as the probability and type of lung cancer, size and location of the primary tumor, presence of metastasis and the overall clinical status of the patient. The main goals are to maximize the yield for both diagnostic and staging purposes and to minimize risk to the patient.

Lung lesions detected on computerized tomography (CT) and/or positron emission tomography (PET) may be potentially resectable, but histologic confirmation is needed to overcome high false positive rates. Fiberoptic bronchoscopy (FB) is an endoscopic procedure that allows both

[1] http://seer.cancer.gov/csr/1975_2004/results_single/sect_01_table.01.pdf accessed February 28, 2008.
[2] http://seer.cancer.gov/statfacts/html/lungb_print.html accessed February 28, 2008.
[3] ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition). Chest. 2007;132(3 SUPPL).PP. 1S-19S, 94S-107S, 108S-130S, 131S-148S, 202S-222S.

visualization of the airways to the visual segmental bronchi and cytologic sampling. It is an invaluable tool for sampling central airway lesions, mediastinal nodes and parenchymal masses. Peripheral lung lesions (PLL) are generally defined as lesions that are not visible beyond the visual segmental bronchi and present a challenge to diagnose using FB.

The overall sensitivity of FB of PLLs using transbronchial biopsy, brush biopsy, bronchial alveolar lavage, or transbronchial needle aspiration was 0.78 based on a literature review of 16 studies. Sensitivity was higher with the use of fluoroscopy, multiple sampling, presence of a bronchus extending to the peripheral lesion on CT, lesion diameter > 2 cm, and adjunctive use of post-bronchoscopy sputum analysis.

The false negative rate for FB has not been defined but is estimated to be fairly high in the case of PLLs, especially smaller ones < 2 cm in diameter, because of its relatively low sensitivity in this setting. In the case of a peripheral solitary pulmonary nodule, the ACCP advises against biopsy with FB because of the low likelihood of obtaining a diagnostic specimen.

If FB is nondiagnostic or not attempted, other technologies may be employed to achieve a definitive diagnosis. Transthoracic needle aspiration (TTNA) is recommended in patients suspected of having lung cancer who have a small (<2 cm) PLL, and who require tissue diagnosis before further management can be planned. TTNA can be performed under either fluoroscopic or CT guidance. For PLLs, TTNA has a higher pooled sensitivity (.90, 95% confidence interval 0.88 to 0.91) than that of FB. Its sensitivity depends on nodule size, needle size, number of needle passes, and the presence of on-site cytopathology examination. Minor pneumothorax may occur in approximately 25% of TTNA procedures and major pneumothorax requiring chest tube drainage may occur in approximately 5% of procedures. In patients with an already compromised respiratory system, pneumothorax may further exacerbate pulmonary function.

TTNA is most appropriate for when there is discordance among the clinical probability of cancer, imaging test results, patient preferences, or the risk for surgical complications. TTNA can reliably rule in cancer (false positive rate .01-.02), but with a high false negative rate (.20-.30), TTNA is generally not useful in ruling out cancer, and further testing to establish a definitive diagnosis is necessary if suspicion of cancer remains.

Unfortunately, like TTNA, alternatives for obtaining a biopsy specimen such as video-assisted thoracoscopy or thoracotomy also carry a risk of complications such as pneumothorax or bleeding. Endobronchial ultrasound (EBUS) under fluoroscopic guidance may be considered for use by skilled experts prior to referring the patient for TTNA. Advances such as ultrathin bronchoscopy, multiplanar volume reformation imaging, and ***electromagnetic navigation*** as complements to FB have the potential to improve the diagnostic yield of peripheral lung lesions.

Staging

Accurate staging is essential to guiding treatment decisions and determining prognosis. Staging of the mediastinum becomes particularly important in the absence of distant metastases. Noninvasive imaging of the mediastinum with CT and/or PET is typically performed but is also associated with a high number of false positives and may produce false negatives in some patients with normal size lymph nodes, thereby necessitating invasive staging to obtain tissue confirmation. In addition, invasive procedures may be used to confirm the diagnosis of

malignancy, for example, in the case of a patient with massive mediastinal infiltration by a presumed malignancy.

Many invasive tests exist to stage the mediastinum and should be viewed as complementary to one another. Choice of procedure will depend on the extent of mediastinal involvement seen on imaging, location of the primary tumor (central or peripheral), patient tolerance and risk, and physician experience and skill:

- Surgical procedures- mediastinoscopy, anterior mediastinotomy, thoracoscopy.
- Needle procedures- TTNA, transbronchial needle aspiration (TBNA) (a.k.a. Wang procedure), endobronchial ultrasound with needle aspiration (EBUS-NA), and esophageal endoscopic ultrasound with needle aspiration (EUS-NA).

In general, needle techniques are most useful in patients with discreet, enlarged mediastinal nodes. Surgical procedures, and specifically mediastinoscopy, are considered the "gold standard" techniques to which the performance of other procedures is compared. The sensitivity of the various techniques is similar for staging the mediastinum, but the false-negative (FN) rate of needle techniques, particularly in patients with normal node morphology, is generally higher (approx. 20% or more) than that of mediastinoscopy (approx. 10%). Thus, negative results from needle procedures would not sufficiently rule out malignancy, and additional staging procedures would need to be performed. ***Electromagnetic navigational bronchoscopy*** as a complement to FB has been proposed as a means of improving the diagnostic yield of TBNA.

Treatment

Treatment options for lung cancer, primarily for non-small cell lung cancer, include surgery, chemotherapy, and radiation therapy, administered individually or in combination. Patients who are medically unfit for surgery or who decline surgery may be considered for external-beam radiation therapy (EBRT) for treatment of the primary tumor. Stereotactic radiosurgery is emerging as an alternative way of delivering EBRT. Delivery of EBRT depends on accurate targeting of the lung tumors, which can be complicated by respiratory motion. Placement of radiographically visible fiducial markers directly in or near the tumor is essential to mark the tumor's position. Fiducials can be placed into lung tumors in three ways:

- Transthoracically under either fluoroscopic or CT guidance;
- Intravascularly;
- Transbronchially using FB.

The risk profile of the FB approach compares favorably to the others, but the inability of FB to visualize PLLs limits its use in guiding EBRT. ***Electromagnetic navigational bronchoscopy*** as a complement to FB may offer a means of precisely placing fiducials into PLLs endoscopically.

Electromagnetic navigation bronchoscopy (ENB)

ENB is a real-time navigation system that combines three-dimensional CT imaging with real-time fiberoptic bronchoscopy using a low frequency electromagnetic field locator to guide the bronchoscope and bronchial tools to a target in or adjacent to the bronchial tree. ENB is able to extend the reach of the bronchoscope to areas of the lung such as the peripheral regions that cannot be visualized or easily accessed by traditional FB with the goal of obtaining a successful

cytologic specimen and, ultimately, a definitive diagnosis. ENB has been proposed as a means to augment the diagnostic yield of FB to avoid the need for surgical biopsy.

Regulation of ENB

As the predicate device, the superDimension® Bronchus® endobronchial electromagnetic guidance system (superDimension®; Hertzliya, Israel), received FDA 510(k) premarket approval in 2004 as a Class II device "*for use in imaging the upper airways and tracheobronchial tree to aid the physician in guiding endoscopic tools in the pulmonary tract. It does not make a diagnosis and is not a bronchial tool.*"[4] It was recently renamed inReach™ (personal communication: Chet Galek, superDimension representative, February 26, 2008).

FDA approval for fiducial placement of markers used in EBRT is pending review (Personal communication: Chet Galek, superDimension representative, February 27, 2008).

Methods: In March 2008, VATAP conducted preliminary searches in the HTA database (www.inahta.org) and the Cochrane Library databases to identify existing systematic reviews and health technology assessments[5] (HTA) on ENB published in English and publicly available. VATAP also queried members of the International Network of Agencies for HTA via its listserv for available systematic reviews or HTAs.

VATAP then conducted multiple searches of MEDLINE®, EMBASE®, SciSearch®, and BIOSIS® covering the years 1990 to the present, for primary studies using a wide variety of free text phrases and index terms to retrieve ENB such as: electromagn* navigation* or electromagn* bronchscop* or flexible bronchoscop* or biopsy near peripheral* lung* or electromagn* guid* or multilod* bronchoscop* diagnos*, plus searches were done using the device trade names and manufacturer names and their variations.

Inclusion criteria

VATAP included only citations that met the following criteria:

- Primary studies using superDimension® Bronchus®, superDimension® inReach™ or other ENB technology;
- Clear description of methods, study population and technology used;
- The most recent or largest version of a study by the same investigators for the same purpose (to eliminate redundancy).

Meeting abstracts, animal studies, phantom studies and studies already reviewed in published HTAs or evidence reviews were also excluded.

Literature appraisal

Since the point of a systematic review is to examine the ultimate value or benefit derived from a diagnostic test or procedure, a structure for appraising the literature on the efficacy of a diagnostic test can be useful in determining the level of development of the technology and ultimately, its contribution to the patient management process. VATAP has applied a

[4] FDA 510(k) approval K042438, November 8, 2004. http://www.fda.gov/cdrh/pdf4/K042438.pdf
[5] Health Technology Assessment (HTA) is a multidisciplinary field of policy analysis that systematically studies the medical, social, ethical, and economic implications of development, diffusion, and use of health technology.

hierarchical model developed by Fryback and Thornbury[6] to its evaluations of PET scanning, and this framework can be useful for gauging the development and clinical value of ENB.[7]

Briefly, the Fryback and Thornbury framework proceeds from the micro, or local level, at which the concern is the physical imaging process, to the societal efficacy level. It stipulates that for a test or procedure to be efficacious at a higher level, it must first be efficacious at the lower levels, but the reverse is not true:

- Level 1 efficacy studies concern ***technical quality*** of the images and ***feasibility***;
- Level 2 efficacy studies address ***diagnostic performance characteristics*** associated with image interpretation;
- Level 3 efficacy studies address the impact of the testing information on the referring physician's ***diagnostic thinking***, i.e. level of diagnostic certainty;
- Level 4 efficacy studies concern the effect of the test on the ***patient management decisions***;
- Level 5 efficacy studies measure (or compute) effect of the information on ***patient outcomes***, and,
- Level 6 efficacy studies examine ***societal costs and benefits*** of a diagnostic test.

Included studies were appraised by one reviewer (Adams).

Results: Searches and queries of HTA colleagues for existing reviews on superDimension® ENB resulted in two horizon scanning reports:

- CEDIT (2005): The Bronchus® endobronchial electromagnetic guidance system. Ref. 05.10/Re1/06. Comité d'Evaluation et de Diffusion des Innovations Technologiques. Paris. France.

- Avalia-t (2007): Electronagnetic Navigation System in the Diagnosis of Lung Lesions. Technology Briefing, February 2007. Axencia de Avaliacion de Tecnoloxias Sanitarias de Galicia, Avalia-t. Direccion Xeral de Aseguramento e Planificacion Sanitaria. Santiago de Compostela. Espana.

CEDIT (2005) considered only the superDimension® Bronchus system, whereas Avalia-t (2007) included all manufacturers. VATAP used the more recent report from Avalia-t (2007) as the basis for this review and updated their findings with new searches of primary studies. The searches resulted in 64 citations. Based on review of title and abstract information, 22 were retrieved for further evaluation, of which seven met criteria for inclusion in this report. The studies are summarized in Table 1, applying the Fryback and Thornbury framework, and estimates of diagnostic accuracy characteristics from Level 2 studies are presented in Table 2. Details of each study were abstracted in Tables 3 and 4.

[6] Fryback DG and Thornbury JR. The efficacy of diagnostic imaging. Medical Decision Making. 1991;11:88-94.
[7] http://www.va.gov/vatap/pet_topic.htm accessed March 5, 2008.

Table 1. Summary of primary studies of ENB

Note: studies in shaded cells are further summarized in Table 2.

	Fryback and Thornbury Stage of Efficacy Development					
Clinical application	**Level 1 Technical feasibility**	**Level 2 Diagnostic accuracy**	**Level 3**	**Level 4**	**Level 5**	**Level 6**
Diagnosis of peripheral lung lesion/solitary pulmonary lesion	Weiser 2008	Eberhardt 2007a Eberhardt 2007b Makris 2007 Wilson 2007				
Staging of mediastinum		Wilson 2007				
Fudicial marker placement for EBRT	Anantham 2007 Kupelian 2007					

Table 2. Summary of diagnostic accuracy studies of ENB in diagnosing peripheral lung lesions

Diagnostic performance	**Eberhardt 2007a**	**Eberhardt 2007b**			**Makris 2007**	**Wilson 2007**
Sample Size	92 PLL in 89 pts	ENB 39 pts	EBUS 39 pts	EBUS+ENB 40 pts	40 pts	ENB +ROSE 248 pts
DY	67%	59%	69%	88%	68%	70%
Se	.60	.55	.72	.90	.61	.55
Sp	1.00	1.00	1.00	1.00	1.00	.52
PPV	1.00	1.00	1.00	1.00	1.00	1.00
NPV	.44	.44	.44	.75	.35	.48

DY, diagnostic yield
ENB, electromagnetic navigational bronchoscopy
EBUS, endobronchial ultrasound
PLL, peripheral lung lesion
ROSE, rapid on-site cytologic evaluation
Se, sensitivity
Sp, specificity
PPV, positive predictive value
NPV, negative predictive value

Conclusion/discussion: Elelctromagnetic navigational bronchoscopy (ENB) is an emerging technology used to improve the clinical utility of fiberoptic bronchoscopy (FB) in the management of lung cancer. Early studies identified in horizon scanning reports from CEDIT (2005) and Avalia-t (2007) proposed using ENB as a means of avoiding more invasive and higher risk biopsy procedures. Since publication of the Avalia-t (2007) report, new data have emerged that show ENB is a safe technology in the hands of a skilled bronchoscopist without fluoroscopic guidance and without significantly prolonging procedure time.

Two manufacturers market ENB devices for clinical use: superDimension® Ltd, Plymouth, MN and Northern Digital, Inc., Waterloo, Canada. Information on FDA approval could be found only for the superDimension® system. Two studies used the Aurora® system by Northern Digital,

Inc., but neither met criteria for inclusion in this VATAP review: Hautmann (2005)[8] was reviewed previously by Avalia-t (2007) and Deguchi (2006)[9] used a phantom model.

New data using the superDimension® system have emerged on the diagnostic performance in patients with CT-evidence of peripheral lung lesions or solitary pulmonary nodules. These data comprise different patient populations either who were candidates for elective FB (Eberhardt 2007a and 2007b), who had lesions that were inaccessible with FB (Wilson 2007), or who were medically inoperable (Makris 2007). One study conducted a prospective head-to-head comparison of two new emerging technologies ENB vs. EBUS vs. EBUS+ENB (Eberhardt 2007b). Rapid on-site cytologic evaluation (ROSE) was used on all patients in one study (Wilson 2007), which may have enhanced the immediate diagnostic yield, but ROSE is not routinely used in clinical practice.

The growing body of literature suggests that many factors may affect the diagnostic performance of ENB such as: prevalence of malignancy in the population studied, definition of ENB success, % of upper lobe PLL in study (sharper bronchial angle may make navigation even with ENB difficult), diaphragmatic movement, an absent or occluded bronchus leading to the lesion, and procedural differences (number of passes/biopsy specimens, biopsy instrument used, use of fluoroscopy, method of confirmation, use of ROSE or EBUS, and CT-to-body divergence).

The diagnostic yield for ENB ranged from 59% to 68% and was slightly higher when used with EBUS (88%) or ROSE (70%). The sensitivity of ENB ranged from 55%-68%, and both its specificity and positive predictive value were 100%. The negative predictive value across studies ranged from 35%-44%, indicating that ENB can be helpful in ruling in disease but it would not be useful in ruling out malignancy and further workup would be required. Fryback and Thornbury Level 3 and 4 studies would be needed to determine if use of ENB in diagnosing PLLs would reduce the number of surgical biopsy procedures.

New data have emerged for the use of ENB with transbronchial needle aspiration (TBNA) in mediastinal staging and in the placement of fiducial markers used in external beam radiation therapy (EBRT), but this latter application has not yet been FDA-approved. ENB for these indications appears safe and technically feasible, but further data are needed to confirm these findings. Problems with ENB that may lower diagnostic yield include respiratory variations that cause larger than anticipated navigation errors and dislodgement of the extending working channel when biopsy instruments are introduced. For mediastinal staging, TBNA with and without ENB needs further study with attention paid to the reduction in false negative results and to the need for further invasive work up (Fryback and Thornbury Level 3 and 4 studies).

In conclusion, the data are insufficient to determine whether use of ENB will avoid surgical biopsy procedures in surgical candidates because of its low negative predictive value. ACCP (2007) recommends that *"…Until further progress is made in guidance of bronchoscopy, peripheral nodules that do not have a CT-bronchus sign should be pursued with TTNA."* If done by a skilled bronchoscopist, ENB appears to offer promise for:

[8]Hautmann H, Schneider A, Pinkau T, Peltz F, Feussner H. Electromagnetic catheter navigation during bronchoscopy: validation of a novel method by conventional fluoroscopy. Chest 2005;128(1):382-7.
[9]Deguchi D, Maurer JCR, Takabatake H, et al. A method for bronchoscope tracking by combining a position sensor and image registration. Computer Aided Surgery 2006;11(3):109-17.

- patients in whom a diagnostic bronchoscopy has failed and in whom more invasive procedures pose a significant risk, such as those with poor pulmonary function and emphysematous changes, or;
- patients who are medically inoperable or those with nonresectable disease.

Ultimately, head-to-head comparisons of FB with and without ENB are needed to determine the true clinical value of ENB in patients with lung cancer, as indicated not only by diagnostic performance, but also by the impact of the diagnostic information on patient management decisions and outcomes.

Table 3. Diagnostic Accuracy Efficacy Studies of superDimension® Electromagnetic Navigational Bronchoscopy for Peripheral Lung Lesions or Mediastinal Staging

Note: unless otherwise reported, VATAP computed all nondiagnostic results as false negatives in calculations of diagnostic performance.

<table>
<tr><th>Citation/

Navigation system</th><th>Objective(s)/
Study population</th><th>Methods</th><th>Main Results</th><th>Comments</th></tr>
<tr><td>Eberhardt 2007a

superDimension Bronchus®
superDimension Inc.
Plymouth, MN</td><td>Objective: to determine the diagnostic yield of ENB in PLL and solitary pulmonary nodules

N=89
• Adult candidate for elective bronchoscopy
• Informed consent
• Not pregnant
• Peripheral lung lesion or SPN with no evidence of endobronchial pathology
• no implantable pacemakers or defibrillators</td><td>ENB without fluoroscopy v. biopsy by additional procedures eg. CT-FNA, surgery or clinical f/u with imaging
• Primary endpoint=DY
• Secondary endpoints=accuracy of navigation, procedure duration, complications</td><td>Overall results: 92 lesions biopsied in 89 subjects
• Mean lesion size: 24±8 mm (range, 10-58mm)
• Mean number of forceps biopsies performed: 5±1 (range, 0-11)
• DY=67%; DY not affected by lesion location or size
• There was a trend toward a higher ENB yield in diagnosing lesions in the right middle lobe (88%) but not statistically significant.
<table><tr><td></td><td>ENB</td></tr><tr><td>Se</td><td>.60</td></tr><tr><td>Sp</td><td>1.00</td></tr><tr><td>PPV</td><td>1.00</td></tr><tr><td>NPV</td><td>.44</td></tr></table>• Total procedure time ranged from 16.3 to 45.0 min (mean [+/- SD] procedure time, 26.9 +/- 6.5 min).
• Mean navigation error was 9 +/- 6 mm (range, 1 to 31 mm).
• Complications: pneumothorax (2 pts) for which no intervention was required.</td><td>• Note: some study subjects may be represented in Eberhardt 2007b
• No fluoroscopy reduces radiation exposure
• Is the NPV too high to avoid surgery?</td></tr>
<tr><td>Eberhardt 2007b

superDimension Bronchus®
superDimension Inc.
Plymouth, MN

EBUS UM-BS20-26R
Olympus, Tokyo, Japan</td><td>• Objective: to compare the performance and role of EBUS only, ENB only and combined EBUS/ENB in PLL

N=120
• Adult surgical candidates for elective bronchoscopy or surgery who had CT evidence of PLL or SPN
• Pregnant patients and those with implantable pacemakers or defibrillators were excluded</td><td>• Prospective
• Computer generated randomization
• No fluoroscopic guidance
• Forceps biopsy only
• Primary outcome=DY defined as histologic diagnosis consistent with clinical presentation
• Secondary outcome=analysis of DY by lesion size, location, and pathology</td><td>• N=118 (2 declined surgical confirmation and were excluded)
• Mean lesion size: significantly larger in ENB group than other two (p=0.03)
• DY: EBUS (69%) vs. ENB (59%) vs. EBUS+ENB (88%) (p=0.02)
<table><tr><td></td><td>EBUS</td><td>ENB</td><td>EBUS+ENB</td></tr><tr><td>Se</td><td>.72</td><td>.55</td><td>.90 (p=0.009)</td></tr><tr><td>Sp</td><td>1.00</td><td>1.00</td><td>1.00</td></tr><tr><td>PPV</td><td>1.00</td><td>1.00</td><td>1.00</td></tr><tr><td>NPV</td><td>.44</td><td>.44</td><td>.75</td></tr></table>• DY of EBUS and EBUS+ENB were independent of size or lobar location
• DY of ENB significantly lower in lower lobes (29%;p=.01)
• Pneumothorax rate overall=6%, no stat sig difference across groups</td><td>Is the NPV too high to avoid surgery?</td></tr>
<tr><td>Wilson 2007

superDimension Bronchus®
superDimension
Hertzliya, Israel</td><td>• To determine % of patients that had a malignant diagnosis or a plausible nonmalignant diagnosis on the day of the procedure using ENB + ROSE

N=248 patients with 279 PLL and 71 MLL
• Follow up data available for 181
• ENB used routinely in patients with suspicious PLL or MLL that were considered difficult to reach using standard FB
• Community hospital OR setting</td><td>• Retrospective, consecutive case series ENB + ROSE
• Fluoroscopic guidance used in all patients
Outcomes:
• Procedure success ENB+ ROSE
• Diagnostic yield (DY) of ENB+ ROSE on day of procedure = definitive malignant or non malignant dx
• DY of ENB + ROSE on same day + f/u confirmation
• Adverse events</td><td>• Mean size of targeted PLL and lymph nodes was 2.1+/-1.4 (SD) cm and 1.8+/-0.9 (SD) cm, respectively.
• Mean follow-up period was 6+/-5 (SD) months.
• 51% of PLL were in the upper lung lobes.
• ENB + ROSE success=96% of PLL using 3-4 samples per patient with forceps and needle
• ENB + ROSE success= 94.3% of the lymph nodes using 5-6 samples with needle biopsy
• Same day DY of ENB + ROSE=161/248 (65%)
• Same day + f/u DY of ENB + ROSE=12/248 (5%) nondiagnostic confirmed as nonmalignant on f/u
• Same day + f/u DY of ENB + ROSE=8/248 (3%) nondiagnostic confirmed as malignant on f/u
• 67/248 patients (27%) remained inconclusive due to lack of clinical f/u
• Overall DY of ENB + ROSE=173/248 (70%)
<table><tr><td>(calculated by (VATAP)</td><td>ENB + ROSE (for all pts, n=248)</td></tr><tr><td>Se</td><td>.55</td></tr><tr><td>Sp</td><td>.52</td></tr><tr><td>PPV</td><td>1.0</td></tr></table></td><td>• Note: high incidence of granuloma (28%) and inflammation (5%) may be due to high prevalence of histoplasmosis in general population
• High loss to follow up (27%)
• Technique of tissue sampling (forceps, brush, needle) may affect DY
• ROSE not routinely used in all hospital settings
• Confirmation with prospective studies with longer f/u and impact evaluation on patient management and outcomes are needed</td></tr>
</table>

Citation/ Navigation system	Objective(s)/ Study population	Methods	Main Results	Comments
			NPV .48 • DY not influenced by target location (*P*>0.05) • Complications occurred; moderate bleeding (3), pneumothorax (3), hematoma (1), and pneumonia with exacerbation of chronic obstructive pulmonary disease (1). None of the complications were related to use of the ENB system.	
Makris 2007 superDimension Bronchus® superDimension Hertzliya, Israel	• To determine the diagnostic yield and complication rate of ENB in biopsying small PLL N=40 • inoperable • suspicious for cancer based on CT or PET • negative or nondiagnostic TBNA, FB, or TTNA	• Prospective consecutive case series • Successful DY=100 X ENB biopsy diagnosed cases/total no. patients with completed procedures ENB without fluoroscopy • Pneumothorax rate	• Loss to follow up=1; confirmation not feasible=1 • DY=27/40 (68%) Calculated by VATAP / ENB Se 20/33 (61%) Sp 7/7 (100%) PPV 20/20 (100%) NPV 7/20 (35%) • Pneumothorax rate=3/40 (7.5%), 1 required chest drainage	• DY significantly affected by CT-to-body divergence; yield was 77.2% when estimated divergence was <or=4 mm.

CT-FNA, computed tomography fine needle aspiration
DY, diagnostic yield
ENB, electromagnetic navigational bronchoscopy
EBUS, endobronchial ultrasound
PLL, peripheral lung lesion
ROSE, rapid on-site cytologic evaluation
TBNA, transbronchial needle aspiration
TTNA, transthoracic needle aspiration

Se, sensitivity
Sp, specificity
PPV, positive predictive value
NPV, negative predictive value

Table 4. Technical Efficacy Studies of superDimension® Electromagnetic Navigational Bronchoscopy for Placement of Fiducial Markers for External Beam Radiation Therapy

Citation	Objective/Study population	Methods	Results	Comments
Anantham 2007	Objective: to determine feasibility of using ENB to precisely place fiducials into peripheral lung nodules for stereotactic radiosurgery using Cyberknife Inclusion criteria: • Peripheral lung tumors and no CT evidence of endobronchial pathology • No implantable pacemakers or defibrillators	• Success of fiducial placement=presence of at least 3 fiducial markers within 50-60 mm of tumor center for Cyberknife targeting • Failure=need for alternative or additional intrathoracic fiducial placement	N=9 • 39 fiducials markers were successfully deployed in 8/9 patients (89%) • 7/8 (88%) had fiducials placed directly within the tumor • At Cyberknife planning, 7 to 10 days after fiducial placement, 35 of 39 fiducial markers (90%) were still in place and were adequate to allow radiosurgery to proceed. • Complications: No immediate bronchoscopic complications observed; COPD exacerbation (1), transient, self-limiting fever (1)	Equipment funded by company and some authors with financial interest in company
Kupelian 2007	Objective: to describe use of ENB for transbronchial placement of metallic fiducials within PLL treated with EBRT • N=23 • Medically inoperable NSCLC • Pre and post CT to document tumor volume change • 18 Ti lesions; 5 T2 lesions	• 15 placed transcutaneously under CT or fluoroscopic guidance • 8 placed transbronchially • Stability of markers assessed qualitatively and quantitatively	• Complications: 8/15 with transcutaneous marker placement developed pneumothorax; 6/8 required chest tube placement • 8/8 had no pneumothorax with transbronchial placement • Markers stable within tumors throughout the treatment duration regardless of implantation method • Transbronchial placement of fiducial markers is less invasive and safer than transcutaneous	

ANNOTATED BIBLIOGRAPHY (INCLUDED STUDIES)

Anantham, D., D. Feller-Kopman, et al. (2007). "Electromagnetic navigation bronchoscopy-guided fiducial placement for robotic stereotactic radiosurgery of lung tumors: a feasibility study." Chest 132(3): 930-5.

BACKGROUND: Stereotactic radiosurgery (Cyberknife; Accuray Incorporated; Sunnyvale, CA) is a treatment option for patients who are medically unfit to undergo lung tumor resection. For precise tumor ablation, the Cyberknife requires fiducial marker placement in or near the target tumor. Fiducial placement under transthoracic CT guidance is associated with a high risk of iatrogenic pneumothorax. Electromagnetic navigation bronchoscopy (ENB) may offer a less morbid alternative to accurately deploy fiducials to bronchoscopically invisible peripheral lung lesions. OBJECTIVE: Open-label, feasibility study to assess fiducial placement in peripheral lung tumors by ENB. METHOD: Consecutive patients with peripheral lung tumors and who were evaluated to be nonsurgical candidates underwent fiducial placement under ENB. This procedure was considered successful if fiducials were placed in or near the tumors and remained in place without migration for radiosurgery to proceed. The need for alternative or additional intrathoracic fiducial placement was documented as procedure failure. RESULTS: A total of 39 fiducials markers were successfully deployed in eight of nine patients (89%). Of these eight successful cases, seven had fiducials placed directly within the tumor (88%). At Cyberknife planning, 7 to 10 days after fiducial placement, 35 of 39 fiducial markers (90%) were still in place and were adequate to allow radi osurgery to proceed. No immediate bronchoscopic complications were observed. One patient had a COPD exacerbation. Another patient returned within 1 day with transient, self-limiting fever. CONCLUSIONS: ENB can be used to deploy fiducial markers for Cyberknife radiosurgery of lung tumors safely and accurately without the complications associated with transthoracic placement.

Eberhardt, R., D. Anantham, et al. (2007a). "Electromagnetic navigation diagnostic bronchoscopy in peripheral lung lesions." Chest 131(6): 1800-5.

BACKGROUND: Electromagnetic navigation bronchoscopy (ENB) with biopsy under fluoroscopic guidance has enhanced the yield of flexible bronchoscopy in the diagnosis of peripheral lung lesions. However, the accuracy of ENB navigation suggests that the addition of fluoroscopy is redundant. OBJECTIVES: Data were prospectively collected to determine the yield of ENB without fluoroscopy in the diagnosis of peripheral lung lesions. METHOD: ENB was performed via flexible bronchoscopy (superDimension/Bronchus system; superDimension Inc; Plymouth, MN). Biopsy specimens were obtained through the extended working channel after navigation. Fluoroscopy was not utilized, but post-transbronchial biopsy chest radiographs were obtained to exclude pneumothorax. The primary end point was diagnostic yield, and the secondary end points were navigation accuracy, procedure duration, and safety. Analysis by lobar distribution was also performed to assess performance in different lobes of the lung. RESULTS: Ninety-two peripheral lung lesions were biopsied in the 89 subjects. The diagnostic yield of ENB was 67%, which was independent of lesion size. Total procedure time ranged from 16.3 to 45.0 min (mean [+/- SD] procedure time, 26.9 +/- 6.5 min). The mean navigation error was 9 +/- 6 mm (range, 1 to 31 mm). There were two incidences of pneumothorax for which no intervention was required. When analyzed by lobar distribution, there was a trend toward a higher ENB yield in diagnosing lesions in the right middle lobe (88%). CONCLUSIONS: ENB can be used as a stand-alone bronchoscopic technique without compromising diagnostic yield or increasing the risk of pneumothorax. This may result in sizable timesaving and avoids radiation exposure.

Eberhardt, R., D. Anantham, et al. (2007b). "Multimodality bronchoscopic diagnosis of peripheral lung lesions: a randomized controlled trial." American Journal of Respiratory and Critical Care Medicine 176(1): 36-41.

RATIONALE: Endobronchial ultrasound (EBUS) and electromagnetic navigation bronchoscopy (ENB) have increased the diagnostic yield of bronchoscopic diagnosis of peripheral lung lesions. However, the role of combining these modalities to overcome each individual technique's limitations and, consequently, to further increase the diagnostic yield remains untested. Objectives: A prospective randomized controlled trial involving three diagnostic arms: EBUS only, ENB only, and a combined

procedure. METHODS: All procedures were performed via flexible bronchoscopy and transbronchial forceps biopsies were obtained without fluoroscopic guidance. In the combined group, after electromagnetic navigation, the ultrasound probe was passed through an extended working channel to visualize the lesion. Biopsies were taken if ultrasound visualization showed that the extended working channel was within the target. Primary outcome was diagnostic yield. The reference "gold standard" was a surgical biopsy if bronchoscopic biopsy did not reveal a definite histological diagnosis compatible with the clinical presentation. Secondary outcomes were yields by size, lobar distribution, and lesion pathology. Complication rates were also documented. MEASUREMENTS AND MAIN RESULTS: Of the 120 patients recruited, 118 had a definitive histological diagnosis and were included in the final analysis. The diagnostic yield of the combined procedure (88%) was greater than EBUS (69%) or ENB alone (59%; p = 0.02). The combined procedure's yield was independent of lesion size or lobar distribution. The pneumothorax rates ranged from 5 to 8%, with no significant differences between the groups. CONCLUSIONS: Combined EBUS and ENB improves the diagnostic yield of flexible bronchoscopy in peripheral lung lesions without compromising safety.

Kupelian, P. A., A. Forbes, et al. (2007). "Implantation and stability of metallic fiducials within pulmonary lesions." International journal of radiation oncology, biology, physics 69(3): 777-85.

PURPOSE: To report and describe implantation techniques and stability of metallic fiducials in lung lesions to be treated with external beam radiotherapy. METHODS AND MATERIALS: Patients undergoing radiation therapy for small early-stage lung cancer underwent implantation with small metallic markers. Implantation was either transcutaneous under computed tomographic (CT) or fluoroscopic guidance or transbronchial with the superDimension/Bronchus system (radiofrequency signal-based bronchoscopy guidance related to CT images). RESULTS: Implantation was performed transcutaneously in 15 patients and transbronchially in 8 patients. Pneumothorax occurred with eight of the 15 transcutaneous implants, six of which required chest tube placement. None of the patients who underwent transbronchial implantation developed pneumo thorax. Successfully inserted markers were all usable during gated image-guided radiotherapy. Marker stability was determined by observing the variation in gross target volume (GTV) centroid relative to the marker on repeated CT scans. Average three-dimensional variation in the GTV center relative to the marker was 2.6 +/- 1.3 (SD) mm, and the largest variation along any anatomic axis for any patient was <5 mm. Average GTV volume decrease during the observation period was 34% +/- 23%. Gross tumor volumes do not appear to shrink uniformly about the center of the tumor, but rather the tumor shapes deform substantially throughout treatment. CONCLUSIONS: Transbronchial marker placement is less invasive than transcutaneous placement, which is associated with high pneumothorax rates. Although marker geometry can be affected by tumor shrinkage, implanted markers are stable within tumors throughout the treatment duration regardless of implantation method.

Makris, D., A. Scherpereel, et al. (2007). "Electromagnetic navigation diagnostic bronchoscopy for small peripheral lung lesions." Eur Respir J 29(6): 1187-92.

The present study prospectively evaluated the diagnostic yield and safety of electromagnetic navigation-guided bronchoscopy biopsy, for small peripheral lung lesions in patients where standard techniques were nondiagnostic. The study was conducted in a tertiary medical centre on 40 consecutive patients considered unsuitable for straightforward surgery or computed tomography (CT)-guided transthoracic needle aspiration biopsy, due to comorbidities. The lung lesion diameter was mean+/-sem 23.5+/-1.5 mm and the depth from the visceral-costal pleura was 14.9+/-2 mm. Navigation was facilitated by an electromagnetic tracking system which could detect a position sensor incorporated into a flexible catheter advanced through a bronchoscope. Information obtained during bronchoscopy was superimposed on previously acquired CT data. Divergence between CT data and data obtained during bronchoscopy was calculated by the system's software as a measure of navigational accuracy. All but one of the target lesions was reached and the overall diagnostic yield was 62.5% (25-40). Diagnostic yield was significantly affected by CT-to-body divergence; yield was 77.2% when estimated divergence was <or=4 mm. Three pneumothoraces occurred and chest drainage was required in one case. Electromagnetic navigation-guided bronchoscopy has the potential to improve the diagnostic yield of

transbronchial biopsies without additional fluoroscopic guidance, and may be useful in the early diagnosis of lung cancer, particularly in nonoperable patients.

Weiser, T. S., K. Hyman, et al. (2008). "Electromagnetic navigational bronchoscopy: a surgeon's perspective." Annals of thoracic surgery 85(2): S797-801.

Diagnostic yield of flexible bronchoscopy is often limited by the size and location of the lesion of interest. Novel technologies have evolved that can improve the accuracy and expand the applicability of flexible bronchoscopy in rendering a tissue diagnosis for pulmonary nodules. One recent technical advance uses electromagnetic guidance to improve the ability of the bronchoscopist to navigate within the lung parenchyma as well as to localize and biopsy mediastinal pathology. We have gained a preliminary experience with navigational bronchoscopy using electromagnetic guidance to successfully biopsy peripheral lung lesions, place fiducial catheters to aid stereotactic radiotherapy, and to biopsy mediastinal lymph nodes in the staging of lung cancer. Not only will navigational bronchoscopy lead to improvements in the diagnostic yield of standard flexible bronchoscopy, but we envision potential therapeutic modalities that can be used this system.

Wilson, D. S. and R. J. Bartlett (2007). "Improved Diagnostic Yield of Bronchoscopy in a Community Practice: Combination of Electromagnetic Navigation System and Rapid On-site Evaluation." Journal of Bronchology 14(4): 227-232.

Background: Several techniques are currently available to improve the diagnostic yield of routine flexible bronchoscopy. In the present study, we have evaluated the contribution of 2 methods used in our community practice: electromagnetic navigation (EMN, superDimension Ltd, Herzliya, Israel) and rapid on-site cytologic evaluation of obtained tissue samples. The main purpose of the study was to determine the percentage of patients that had a malignant diagnosis or a plausible nonmalignant diagnosis on the day of the procedure. Materials and Methods: Consecutive patients that had EMN-assisted biopsy procedures between June 2005 and July 2006 were studied. Patient records were retrospectively reviewed by the author to determine performance of above-mentioned system, diagnostic yield of flexible bronchoscopy, and adverse events. The majority of patients were followed-up for confirmation of final diagnosis and/or for treatment. Results: A total of 248 patients were included. Mean size of the targeted peripheral lesions and lymph nodes was 2.1+/-1.4 (SD) cm and 1.8+/-0.9 (SD) cm, respectively. Mean follow-up period was 6+/-5 (SD) months. The majority (51%) of the peripheral lesions were in the upper lung lobes. EMN was successful, and tissue samples were obtained from 96% of the peripheral lesions, and 94.3% of the lymph nodes. On the day of the procedure, 161/248 (65%) patients received a definitive malignant or plausible nonmalignant diagnosis. With additional clinical follow-up, 12 patients (5%) with a nonmalignant diagnosis on the day of the procedure were confirmed as having no disease, 8 patients (3%) were confirmed as having malignant disease, and 67 patients (27%) remained inconclusive due to lack of clinical follow-up information, leading to total of 173/248 (70%) of diagnostic cases. Thus, when all inconclusive cases are treated as nondiagnostic, the yield is 70%, and when the estimate of the percent of diagnostic and nondiagnostic cases from the observed data is applied to the inconclusive cases, the estimate of diagnostic yield is 86%. Eight complications occurred; moderate bleeding (3), pneumothorax (3), hematoma (1), and pneumonia with exacerbation of chronic obstructive pulmonary disease (1). None of the complications were related to use of the EMN system. Conclusions: EMN is safe and provides a new noninvasive diagnostic option for smaller peripheral lung lesions and enlarged mediastinal lymph nodes. In a community based practice, EMN in combination with rapid on-site cytologic evaluation can provide for patients with a lung lesion, diagnosis in an expeditious and effective manner.

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