eAppendix1: Literature search strategies

Umbrella search for previous (2nd) version of lung cancer guidelines

1. Coin Lesion, Pulmonary/ra, ri, di [Radiography, Radionuclide Imaging, Diagnosis]
2. coin lesion, pulmonary/
3. solitary lung nodul$.mp.
4. solitary pulmonary nodul$.mp.
5. or/2-4
6. "Sensitivity and Specificity"/
7. 5 and 6
8. limit 7 to (humans and english language)
9. limit 8 to abstracts
10. limit 9 to yr="1995 - 2005"
11. limit 10 to yr="2000 - 2005"
12. prevalence/ or incidence/
13. ep.fs.
14. (or/12-13) and 5
15. limit 14 to (humans and english language)
16. limit 15 to abstracts
17. from 16 keep 1-73
18. from 11 keep 1-114
19. "Predictive Value of Tests"/
20. logistic models/ or risk assessment/ or risk factors/
21. (or/19-20) and 5
22. limit 21 to (humans and english language)
23. limit 22 to abstracts
24. limit 23 to yr="1995 - 2005"

Updated searches

CXR and lung nodules, October 10, 2011

1. exp Solitary Pulmonary Nodule/ n=1601
2. exp Radiographic Image Enhancement/ n=174388
3. exp Radiography, Dual-Energy Scanned Projection/ n=153
4. exp Subtraction Technique/ n=10048
5. exp Image Processing, Computer-Assisted/ n=109716
6. exp Radiographic Image Interpretation, Computer-Assisted/ n=6314
7. 2 or 3 or 4 or 5 or 6 n=261740
8. exp Radiography, Thoracic/ n=11604
9. 1 and 7 n=1066
10. 9 and 8 n=175
11. limit 10 to (abstracts and english language and humans and yr="2005 -Current") n=93

CT morphology and likelihood of cancer

MEDLINE Search History

#1 Search (computed tomography characteristics) AND lung nodules
23:05:14 227

#2 Search chest computed tomography characteristics and solitary pulmonary nodules
16:54:39 59
#3 Search CT characteristics of solitary pulmonary nodules
23:04:29 121

#4 Search (radiography, thoracic[MeSH Terms]) AND solitary pulmonary nodules
17:01:15 372

#9 Search (coin lesion, pulmonary) AND radiography, thoracic [MeSH Terms] 22:59:00
358

#10 Search (coin lesion, pulmonary) AND computed tomography characteristics
23:08:23 136

#11 Search ((coin lesion, pulmonary) AND radiography, thoracic [MeSH Terms]) AND characteristics
23:03:17 34

EMBASE Session Results

#1 'lung coin lesion'/exp AND [humans]/lim
n= 756

#2 'computer assisted tomography'/exp
n= 463,598

#3: #1 AND #2
n=244

Cochrane Library

MeSH descriptor: Solitary Pulmonary Nodule [explode all trees], n=52

Methods to detect growth, including volumetric analysis

MEDLINE Search History

#1 Search (coin lesion, pulmonary) AND volume
15:03:50 138

#2 Search (coin lesion, pulmonary) AND growth
15:02:14 157

#3 Search (coin lesion, pulmonary) and growth detection
15:05:47 22

EMBASE Session Results

#1 'lung coin lesion'/exp
790

#2 volume
561,122

#3 #1 AND #2
17

#4 'growth'/exp OR growth
2,964,266

#5 #1 AND #4
55

Cochrane Library

MeSH descriptor: Solitary Pulmonary Nodule [explode all trees], n=52

Pulmonary nodules and prediction models, October 10, 2011

1	Exp Solitary Pulmonary Nodule	1594
2	Nodul$ AND (pulmonary OR lung).mp	8353
3	Exp Risk Factors	362338
4	Exp Logistic Models	60147
5	Exp Likelihood Functions	12194
6	Exp Predictive Value of Tests	94759
7	Exp Probability	589348
8	Exp Models, Biological	362531
9	3 OR 4 OR 5 OR 6 OR 7 OR 8	999634
10	(1 OR 2) AND 9	690
11	Limit 10 to (English language and humans and year= 2005 to current)	321
12	Limit 11 to review articles	44
13	11 NOT 12	277

Pulmonary nodules and PET, October 10, 2011

1	Exp Solitary Pulmonary Nodule	1594
2	Nodul$ AND (pulmonary OR lung).mp	8353
3	Exp Positron-Emission Tomography	20089
4	1 OR 2	8353
5	3 AND 4	392
6	Limit 5 to (English language and humans and year= 2005 to current)	297
7	Limit 6 to review articles	46
8	6 NOT 8	251

PET Inclusion Criteria

a. Controlled or uncontrolled study of PET imaging (including PET or PET/CT) in patients with lung nodules (at least 50% of participants with one or more lung nodules measuring no more than 30 mm in diameter)

b. Study reported 1 or more measures of diagnostic accuracy (sensitivity/specificity or likelihood ratios or ROC curves) or compared outcomes between groups assigned to PET or no PET (e.g. survival, costs, correct diagnoses)

c. At least 10 patients with and 10 patients without malignant nodule (in studies of accuracy); at least 20 patients per group in studies of outcomes

TTNA and lung nodules, October 10, 2011

1. exp Solitary Pulmonary Nodule/ n=1601
2. (nodul$ and (pulmonary or lung)).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] n=8392
3. 1 or 2 n=8392
4. exp Biopsy, Fine-Needle/ or exp Biopsy, Needle/ n=30832
5. 3 and 4 n=483
6. limit 5 to (abstracts and english language and humans and yr="2005 -Current") n=181
7. limit 6 to "review articles" n=26
8. 6 not 7 n=155

TTNA inclusion criteria:

1. Study examined one or more methods of TTNA
2. Study reported accuracy for identifying malignancy or risk of complications among patients with lung nodules
3. For heterogeneous samples, at least 75% of patients with lung nodules or results reported separately for patients with lung nodules
4. Study enrolled at least 40 patients with lung nodules, including at least 20 with malignancy and 20 without malignancy

eAppendix 2: Studies of morphological characteristics on CT and risk of cancer

Diederich, 2005[1]

Risk of Bias

Prospective:	No
Consecutive Enrollment?:	No
Blinded Interpretation?:	No

Patient Characteristics

Inclusion Criteria:	Subjects in whom pulmonary nodules had been detected that decreased in size or resolved completely at follow-up.
Subjects, N:	56
Age:	55 (mean); 40-76 (range)
% Men:	63

Technical Methods

Section Thickness:	collimation of 5 mm using single slice CT scanner; if non-calcified nodules detected, thin-section unenhanced low-dose CT with collimation of 1-3mm
Low Dose?	Yes

Nodule Characteristics

Nodules, N	133 resolving nodules
% sub-solid	solid 85; part-solid 10; non-solid 5
Overall prevalence of malignancy (%)	Overall number (%) of resolving nodules; completely 107 (80); incompletely 26 (20)
Reference standard	

CT Characteristics

Size/(%) with characteristic	**Number (%) resolved**
</=5 mm; 52 (39)	completely 43 (40); incompletely 9 (34)
>10 mm; 10 (8)	completely 8 (8); incompletely 2 (8)
Solid; 113 (85)	completely 91 (85); incompletely 21 (81)
part-solid; 14 (10)	completely 11 (10); incompletely 3 (11)
non-solid; 6 (5)	completely 5 (5); incompletely 2 (8)
well-defined; 103 (77)	completely 80 (75); incompletely 24 (92)
ill-defined; 30 (23)	completely 27 (25); incompletely 2 (8)
non-lobulated; 97 (73)	completely 78 (73); incompletely 7 (27)
Lobulated; 36 (27)	completely 29 (27); incompletely 19 (73)
Cavitation; 1 (.75)	
Speculation; 0	

eAppendix 2: Studies of morphological characteristics on CT and risk of cancer

Felix et al, 2011[2]

Risk of Bias

Prospective:	Yes
Consecutive Enrollment?:	Yes
Blinded Interpretation?:	No

Patient Characteristics

Inclusion Criteria:	Patients considered high-risk for lung cancer. Participants had no serious illness and considered fit for thoracic surgery. Patients were divided into 4 groups: patients with history of lung cancer (operated and in remission); patients with history of head and neck cancer (treated and in remission); current or former cigarette smokers with respiratory symptoms (cough or dyspnoea); asymptomatic patients with history of cigarette smoking of at least 15 cigarettes per day during at least 20 years, current or former (quit less than 15 years ago).
Subjects, N:	280
Age:	58.6 (mean); 33.9-80 (range)
% Men:	79

Technical Methods

Section Thickness:	"0.75-mm slice collimation; data were reconstructed into 1-mm-thick sections with 0.8-mmintervals using a high-resolution reconstruction kernel and displayed at standard window setting (width, 1600 HU; level,−400 HU)"
Low Dose?	"exposure time of 0.5 s, table feed of 18mm per rotation, 120 kVp, and 60–80 mAs"

Nodule Characteristics

Nodules, N	362 at baseline--41 localized GGOs; 34 GGOs appeared on annual repeat screenings
% sub-solid	Solid: 89.8, nodular GGO 10.2
Overall prevalence of malignancy (%)	Resolving Localized GGOs n=32 (18%); Non-resolving Localized GGOs n=41 (21%)
Reference standard	No comparison group reported

CT Characteristics

Size/(%) with characteristic	
<5 mm; 14 (18.7)	
5-10 mm; 34 (45.3)	
10-20 mm; 18 (24)	
20-30 mm; 9 (12)	
Type	**Prevalence of malignancy, by characteristic (%)**
Nodular GGOs; 63 (84)	Disappearance Yes=25, No=37
Lobular GGOs; 6 (8)	Disappearance Yes=6, No=0
Flat GGOs; 6 (8)	Disappearance Yes=1, No=5
Shape in axial plane	
Round; 43 (57.3 (1 flat GGO)	Disappearance 13; No Disappearance 29

Oval; 5 (6.7)	Disappearance 3; No Disappearance 2
Complex; 19 (25.3) (3 flat GGOs)	Disappearance 9; No Disappearance 9
Polygonal; 8 (10.7) (2 flat GGOs)	Disappearance 7; No Disappearance 1
Shape in other planes	
Round; 42 (56%)	Disappearance 13; No Disappearance 28
Oval; 5 (6.7)	Disappearance 3; No Disappearance 2
Complex; 16 (21.3)	Disappearance 9; No Disappearance 7
Polygonal; 6 (8) (6 lobular GGOs)	Disappearance 6; No Disappearance 0
Flat; 6 (8) (6 flat GGOs)	Disappearance 1; No Disappearance 4
Newly appeared; 32	Disappearance 23; no disappearance 9
Margins type 1	
Smooth	43 (57.3)
Slightly irregular	27 (36)
Spiculated	5 (6.7)
Margins type 2	
Convex	61 (31.3)
Concave	14 (18.7)

eAppendix 2: Studies of morphological characteristics on CT and risk of cancer

Harders, 2011[3]

Risk of Bias

Prospective:	Yes
Consecutive Enrollment?:	Yes
Blinded Interpretation?:	Yes

Patient Characteristics

Inclusion Criteria:	All adult patients with no previous malignancies referred from their general practitioner to Dept of Pulmonology for evaluation of suspected lung cancer. Consecutive patients with SPNs 5-30 mm that fulfilled general SPN criteria were eligible.
Subjects, N:	213
Age:	65 (mean); 32-87 (range)
% Men:	46.5

Technical Methods

Section Thickness:	1 mm
Low Dose?	high resolution spiral CT

Nodule Characteristics

Nodules, N	213
% sub-solid	solid nodules 92%, partly sold nodules 7%, non-solid nodules 1%
Overall prevalence of malignancy (%)	Prevalence 58% (51-65%); Sensitivity 98% (94-100%); Specificity 23% (14-33%); PPV 64% (57-71%; NPV 91% (71-99%); Diagnostic Accuracy 87% (83-92%)
Reference standard	Histopathology (transthoracic fine or coarse needle aspiration biopsy or surgical resection) and CT follow-up (based on international standard-3,6,12,24 months or longer)

CT Characteristics

Margin Risk Categories (MRC)	Number of subjects with nodule characteristic	Prevalence of malignancy, by characteristic (%) /	Likelihood Ratio of Positive Test
3= High (spiculated, ragged)	67/196 (34)	59/196 (30)	5.5 (2.8 to 11)
2= Intermediate (lobulated)	73/196 (37)	43/196 (22)	2.0 (1.6 to 2.6)
1= Low (smooth, polygonal)	56/196 (29)	10/196 (5)	1.0
Calcification Patterns			
4= Malignant (dystrophic, amorphous)	3/196 (1.5)	3/196 (1.5)	N/A
3= Indeterminate (eccentric)	3/196 (1.5)	3/196 (1.5)	N/A
2= Benign (central, lamellar, chondroid)	5/196 (2.6)	0	N/A
1= None	185/196 (94.4)	106/196 (54)	N/A

eAppendix 2: Studies of morphological characteristics on CT and risk of cancer

Malignancy Potential Rating (MPR) (based on weighting of nodule attenuation, margin risk category, calcifications and other characteristics)			
5= Definitely malignant	88/213 (41.3)	81/213 (38)	8.3 (4 to 17)
4= Probably malignant	39/213 (18.3)	21/213 (9.9)	2.9 (2.1 to 4.1)
3= Indeterminate	64/213 (30)	20/213 (9.4)	1.3 (1.1 to 1.4)
2= Probably benign	14/213 (6.6)	2/213 (0.9)	1.1 (1.0 to 1.2)
1= Definitely benign	8/213 (3.8)	0	1.0

eAppendix 2: Studies of morphological characteristics on CT and risk of cancer

Kamiya, 2011[4]

Risk of Bias

Prospective:	No
Consecutive Enrollment?:	No
Blinded Interpretation?:	No

Patient Characteristics

Inclusion Criteria:	Subjects included patients with peripheral solid pulmonary nodules measuring from 5 to 30 mm in diameter as imaged by thin-section multidetector-row CT (MDCT) from January 2000 to September 2009. Nodules showing pure ground glass opacit without change in size were excluded because they might have included obth natures such as BAC, atypicla ademonatous hyperplasia, and benign focal fibrosis.
Subjects, N:	58
Age:	Not reported
% Men:	Not reported

Technical Methods

Section Thickness:	Not reported
Low Dose?	Not reported

Nodule Characteristics

Nodules, N	58
% sub-solid	Not reported
Overall prevalence of malignancy (%)	25/58 (43%)
Reference standard	histology

CT Characteristics

CT characteristic, e.g. GGO, size<5 mm	Number (%) of nodules with characteristic	Prevalence of malignancy, by characteristic (%)
lobulated	16	12 (75)
ragged	6	6 (100)
round	19	4 (21)
polygonal	16	3 (19)
spiculated	1	0 (0)

Accuracy

No significant difference of nodule perimeter to approximate oval circumference according to nodule size between malignant and benign nodules (26.5 + 23.3 vs. 16.6 + 16.9 mm), but malignant nodules were longer than benign nodules (P=.07)

When nodule size was set to less than 20 mm in diameter, malignant and benign nodules consisted of 18 and 30; statistical value between malignant and benign nodules about difference of maximum nodule perimeter to approximate oval changed to 0.94

eAppendix 2: Studies of morphological characteristics on CT and risk of cancer

Mori, 2005[5]

Risk of Bias

Prospective:	No
Consecutive Enrollment?:	Yes
Blinded Interpretation?:	No

Patient Characteristics

Inclusion Criteria:	Patients who had undergone chest CT for the detailed examination of SPNs in the department from February 1998 to April 2000. The patients had only 1 target nodule by CT.
Subjects, N:	62
Age:	60 (mean); 5-84 (range)
% Men:	42

Technical Methods

Section Thickness:	2 mm
Low Dose?	Not reported

Nodule Characteristics

Nodules, N	62

CT Characteristics

Prevalence of malignancy, by characteristic (%)	**Mean linear discriminant function scores for benign (BN) and malignant (MN) nodules** before enhancement:BNs -2.06 + 2.70, MNs 2.09 + 1.50; 2 and 4 minutes after enhancement: MNs 9.59 + 5.04 and 15.1 + 6.50; BNs -9.43 + 5.94 and -16.1 + 9.94; scores for MNs were significantly higher than those for BNs at all 3 points: before enhancement ($P < 0.001$), 2 minutes after enhancement ($P < 0.001$), and 4 minutes after enhancement ($P < 0.001$)
Sensitivity	before enhancement: 94%; 2 minutes after enhancement: 100%; 4 minutes after enhancement: 100%
Specificity	before enhancement: 74%; 2 minutes after enhancement: 89%; 4 minutes after enhancement: 100%
PPV	before enhancement: 83%; 2 minutes after enhancement: 92%; 4 minutes after

	enhancement: 100 %
NPV	before enhancement: 91%; 2 minutes after enhancement: 100%; 4 minutes after enhancement: 100%
Accuracy	**<u>Areas under ROC curve</u>** **Attenuation** before contrast enhancement: 0.58 + 0.07, 2 minutes after: 0.69 + 0.07, 4 minutes after: 0.57 + 0.08; **Curvedness Value** before contrast enhancement: 0.78 + 0.06, after 2 minutes: 0.83 + 0.05, after 4 minutes: 0.76 + 0.06; **Shape Index** before contrast enhancement: 0.90 + 0.04, after 2 minutes: 0.89 + 0.05, after 4 minutes: 0.90 + 0.04

eAppendix 2: Studies of morphological characteristics on CT and risk of cancer

Xu, 2008[6] (Limited value of shape margin and CT density)

Risk of Bias

Prospective:	Yes
Consecutive Enrollment?:	Not reported
Blinded Interpretation?:	No

Patient Characteristics

Inclusion Criteria:	Participants were between 50 and 75 years of age and were recruited via population registries through the mail. They had to be current or former smokers with a smoking history of >15 cigarettes/day for >25 years or >10 cigarettes/day for >30 years. People with a history of other cancers were only eligible if curatively treated at least 5 years ago without signs of recurrence at the time of inclusion.
Subjects, N:	405
Age:	62 ± 5 years (mean); 50-75 (range)
% Men:	93

Technical Methods

Section Thickness:	0.75 mm section thickness; data were reconstructed at 1.0 mm slice thickness, with 0.7 mm reconstruction increment.
Low Dose?	Yes

Nodule Characteristics

Nodules, N	469 solid purely intra-parenchymal nodules: 387 indeterminate solid pulmonary nodules and 82 screen-positive soliid pulmonary nodules
% sub-solid	0
Overall prevalence of malignancy (%)	13
Reference standard	baseline low-dose multi-detector CT scan

CT Characteristics

CT characteristic, e.g. GGO, size<5 mm	Number (%) of nodules with characteristic	Prevalence of malignancy, by characteristic (%) /	Likelihood Ratio of Positive Test
Category			**Likelihood of lung cancer**
Category III: Indeterminate nodules (nodules with volumes between 50 and 500 mm3)	387 (82)	27	**>500 mm3 vs. 50-500 mm3**
Category IV: Screen-positive nodules (nodules larger than 500 mm3)	82 (18)	73	26, 95% CI (13-50), p=0.000
Margin			**Lobulated vs. smooth**
Smooth	262 (56)	2	univariate: 37, 95% CI (5-283), p=0.001; multivariate: 11, 95% CI (1-92), p=0.03
Lobulated	106 (23)	22	**Spiculated vs. smooth**
Spiculated	101 (21)	76	univariate: 210, 95% CI (28-1554), p=0.000; multivariate: 7, 95% CI (1-101), p=ns

Xu, 2008 (Limited value of shape margin and CT density) (cont'd)

Shape			**Irregular vs. round and polygonal**
Round	324 (69)	17	univariate: 29, 95% CI (14-61), p=0.000; 6, 95% CI (1-37), p=0.04
Polygonal	37 (8)	0	
Irregular	108 (23)	83	
CT density (HU)			**Ln-volume**
<0	165 (35)	39	univariate: 5, 95% (3-6), p=0.000; multivariate: 3, 95% CI (2-4), p=0.000
0-100	275 (59)	61	**Ln-density**
>100	29 (6)	0	0.6, 95% CI (0.3-1.1), p=ns

Accuracy	**Mean CT density (HU)** AUC 0.37, 95% CI 0.32-0.43)
Correlations	no correlation between nodule volume and mean nodule density, neither in lung cancer positive nor in lung cancer negative cases (Pearson's correlation test, r=-0.05 and 0.06, respectively, p=ns)

eAppendix 2: Studies of morphological characteristics on CT and risk of cancer

Xu, 2009[7] (Smooth or attached indeterminate nodules)

Risk of Bias

Prospective:	No
Consecutive Enrollment?:	Not reported
Blinded Interpretation?:	No

Patient Characteristics

Inclusion Criteria:	Participants with 1 to 5 solid indeterminate noncalcified lung nodules between 50 and 500 mm3, corresponding to a diameter of 4.6-9.8 mm at baseline screening, were selected between April 2004 and May 2006.
Subjects, N:	658
Age:	62 (mean); 52-78 (range)
% Men:	96

Technical Methods

Section Thickness:	0.75 mm section thickness; data were reconstructed at 1.0 mm section thickness, with 0.7 mm reconstruction increment
Low Dose?	Yes

Nodule Characteristics

Nodules, N	891 solid indeterminate noncalcified nodules
% sub-solid	0
Overall prevalence of malignancy (%)	13
Overall prevalence of malignancy (%)	16/891=1.8%; after 3-month follow-up 10/68 (15%); after 1-year follow-up 5/10 (50%)
Reference standard	baseline low-dose multi-detector CT scan; noncalcified nodules were classified as malignant only on the basis of histologic examination findings of tissue specimens

CT Characteristics

CT characteristic, e.g. GGO, size<5 mm	**Number (%) of nodules with characteristic**	**Prevalence of malignancy, by characteristic (%) /**	**Likelihood Ratio of Positive Test**
Morphology	**Volume doubling time (VDT) at 3-month follow-up n=875; 1-year follow-up n=878**	**Univariate logistic regression between variables and presence of lung cancer during 1-year follow-up in 891 nodules**	**Multivariate logistic regression between variables and presence of lung cancer during 1-year follow-up in 148 nodules**
Spherical	387 (82)	27	7/67=10.4%
Nonspherical	82 (18)	73	9/81=11.1%; OR not significant for the 3 models
Margin			**Lobulated vs. smooth**
Smooth	262 (56)	2	
Lobulated	106 (23)	22	6/90=6.7%
Spiculated	68 (8); 64 (7)	10/69=14.5%; OR=4.7 (1.6, 13.5)	10/58=17.2%; OR not significant for the 3 models

eAppendix 2: Studies of morphological characteristics on CT and risk of cancer

Xu, 2009 (Smooth or attached indeterminate nodules) (cont'd)			
Location			
Intraparenchymal	407 (47); 400 (46)	16/412=3.9%; OR N/A	
Attached	468 (53); 478 (54)	0/503=0; OR N/A	
Juxtavascular	123 (26); 131 (27)		
Fissure attached	190 (41); 191 (40)		
Pleural based	155 (33); 156 (33)		
Median baseline volume (mm3)	875 (100); 878 (100)	**Baseline volume** <130: 3/668=0.4%; OR=1 >130: 13/223=5.8%; OR=13.7 (3.9, 48.6)	<130: 3/81=3.7%; OR=1 for the 3 models >130: 13/67=19.4%; OR=6.3 (1.7,23.0) for model 1, OR=4.9 (1.2,20.1) for model 2, not significant for model 3
		VDT at 3 months (d) >400: 6/807=0.7%; OR=1 <400: 10/68=14.7%; OR=23.0 (8.1, 65.5)	>400 at 3 months: 6/125=4.8%; OR=1 for models 2 and 3 <400 at 3 months: 10/21=47.6%; not included in model 1, OR=15.6 (4.5,53.5) for model 2, not included in model 3
		VDT at 1 year (d) >400: 1/868=0.1%: OR=1 <400: 5/10=50.0%; OR=867.0 (85.2, 8822.4)	>400 at 1 year: 1/131=0.8% <400 at 1 year: 5/8=62.5%; not included in models 1 and 2, OR=213.3 (18.7, 2430.9)

eAppendix 2: Studies of morphological characteristics on CT and risk of cancer

1 Diederich S, Hansen J, Wormanns D. Resolving small pulmonary nodules: CT features. European radiology 2005; 15:2064-2069

2 Felix L, SerraTosio G, Lantuejoul S, et al. CT characteristics of resolving ground-glass opacities in a lung cancer screening programme. Eur J Radiol 2011; 77:410-416

3 Harders SW, Madsen HH, Rasmussen TR, et al. High resolution spiral CT for determining the malignant potential of solitary pulmonary nodules: refining and testing the test. Acta Radiologica 2011; 52:401-409

4 Kamiya H, Murayama S, Kakinohana Y, et al. Pulmonary nodules: a quantitative method of diagnosis by evaluating nodule perimeter difference to approximate oval using three-dimensional CT images. Clin Imaging 2011; 35:123-126

5 Mori K, Niki N, Kondo T, et al. Development of a novel computer-aided diagnosis system for automatic discrimination of malignant from benign solitary pulmonary nodules on thin-section dynamic computed tomography. Journal of Computer Assisted Tomography 2005; 29:215-222

6 Xu DM, van Klaveren RJ, de Bock GH, et al. Limited value of shape, margin and CT density in the discrimination between benign and malignant screen detected solid pulmonary nodules of the NELSON trial. Eur J Radiol 2008; 68:347-352

7 Xu DM, van der Zaag-Loonen HJ, Oudkerk M, et al. Smooth or attached solid indeterminate nodules detected at baseline CT screening in the NELSON study: cancer risk during 1 year of follow-up. Radiology 2009; 250:264-272

eAppendix 3: Studies of CT with dynamic contrast enhancement

Bai, 2009[1]

Risk of Bias

Prospective:	No
Consecutive Enrollment?:	No
Blinded Interpretation?:	No

Patient Characteristics

Inclusion Criteria:	Patients with SPNs who underwent chest x-ray and conventional CT scans from November 202 to June 2007 were selected.
Subjects, N:	68
Age:	52.8 (mean); 28-79 (range)
% Men:	56

Technical Methods

Section Thickness:	2-4 mm
Low Dose?	Slides were examined at low-power magnification

Nodule Characteristics

Nodules, N	68
% sub-solid	Not reported
Overall prevalence of malignancy (%)	36/68=53%
Reference standard	Based on Swenson group result, cut-off value, which resulted from subtracting the pre-contrast value from average CT value after enhancement-plain.

CT Characteristics

CT characteristic, e.g. GGO, size<5 mm	**Number (%) of nodules with characteristic**
Peak height of SPN (PH_{SPN}) (mean ± SD)	Malignant 96.15±11.55
	Benign 47.24±9.15
	Inflammatory 101.15±8.41
SPN-to-aorta peak height ratio (PH_{SPN}/PH_{AA}) (mean ± SD)	Malignant 30.56±4.24
	Benign 14.30±4.01
	Inflammatory 42.56±4.68
Perfusion values of SPN (P_{SPN}) (mean ± SD)	Malignant 0.16±0.02
	Benign 0.05±0.01
	Inflammatory 0.16±0.01
Average CT value before enhancement	Malignant 47.57±1.50
	Benign 42.88±9.69
	Inflammatory 36.11±2.75
Microvessels in x200 field (MVD)	Malignant 36.88±6.76
	Benign 4.51±0.60
	Inflammatory 26.11±5.43

Sensitivity	94% (34 of 36 malignant nodules)
Specificity	50% (16 of 32 benign nodules)
PPV	68% (34 of 50 malignant readings)
NPV	89% (16 of 18 benign readings)

eAppendix 3: Studies of CT with dynamic contrast enhancement

Accuracy	74% (50 of 68 nodules)
Correlations	P_{SPN}, PH_{SPN}, PH_{SPN}/PH_{AA} and MVD showed positive corrleation between the malignant and benign SPN (r value was 0.541, 0.647, 0.474, and 0.378, 0.526, 0.590 respectively, $P<0.05$)

eAppendix 3: Studies of CT with dynamic contrast enhancement

Ikeda, 2007[2]

Risk of Bias

Prospective:	Yes
Consecutive Enrollment?:	No
Blinded Interpretation?:	No

Patient Characteristics

Inclusion Criteria:	Patients with GGO nodules
Subjects, N:	33
Age:	68 (mean); 55-79 (range)
% Men:	48

Technical Methods

Section Thickness:	1.25 mm
Low Dose?	No, high resolution CT

Nodule Characteristics

Nodules, N	43 GGO nodules
% sub-solid	Not reported
Overall prevalence of malignancy (%)	Not reported
Reference standard	Not reported

CT Characteristics

Histogram pattern	**Number (%) of nodules with characteristic**	**Mean values of 75th percentile of AAH, BAC, and adnocarcinoma**
1 peak	adenomatous hyperplasia (AAH) 10; bronchioloalveolar carcinoma (BAC) 13; adenocarcinoma 7	" AAH 609+/=45, BAC 450+/=147, and adenocarcinoma 319+/= 97 HU, respectively, which shows a significant difference between AAH and BAC and between BAC and adenocarcinoma (p 0.05)"
2 peaks	adenomatous hyperplasia (AAH) 0; bronchioloalveolar carcinoma (BAC) 8; adenocarcinoma 5	**Mean values of mean CT** AAH -660+/= 35, BAC -556 +/= 95, and -442+/=99 HU, with significant difference between AAH and BAC and between BAC and adnocarcinoma (p<0.01)

Sensitivity	Sensitivity for differentiation between AAH and	0.9	Sensitivity for differentiation between adenocarcinoma and BAC with cutoff	0.75

	BAC with cutoff value of -584 HY at 75th percentile		value of -584 HY at 75th percentile	
Specificity	Specificty for differentiation between AAH and BAC with cutoff value of -584 HY at 75th percentile	0.76	Specificty for differentiation between adenocarcinoma and BAC with cutoff value of -584 HY at 75th percentile	0.81
Accuracy	Accuracy for differentiation between AAH and BAC with cutoff value of -584 HY at 75th percentile	0.81	Accuracy for differentiation between adenocarcinoma and BAC with cutoff value of -584 HY at 75th percentile	0.79

eAppendix 3: Studies of CT with dynamic contrast enhancement

Li, 2010[3]

Risk of Bias

Prospective:	No
Consecutive Enrollment?:	Not reported
Blinded Interpretation?:	Yes, each perfusion measurement was analyzed with the observer uanware of the patients' clinical data.

Patient Characteristics

Inclusion Criteria:	Patients with a newly detected SPN at cross-sectional imaging or conventional radiography were recruited according to the following criteria: presence of SPN 30 mm or less in diameter, without evidence of calcification or fat attenuation, absence of contraindication to the administration of contrast medium and probable ability to co-operate with the procedure.
Subjects, N:	77
Age:	56 (mean); 24-79 (range)
% Men:	68

Technical Methods

Section Thickness:	Images were reconstructed with 3 mm slice thickness and 3 mm slice increment using a standard reconstruction algorithm.
Low Dose?	Not reported

Nodule Characteristics

Nodules, N	77 non-calcified
% sub-solid	Not reported
Overall prevalence of malignancy (%)	60
Reference standard	Intra-observer reliability of the measurements was tested by using the Bland and Altman methods.

CT Characteristics

CT characteristic, e.g. GGO, size<5 mm	Number (%) of nodules with characteristic	Likelihood Ratio of Positive Test
Perfusion, Peak Enhancement Intensity (PEI), Time to Peak (tTP) and Blood Volume (BV) Measurements for SPNs	**Median (25th-75th percentile of IQR)**	
Perfusion	Malignant 61.5 (38.0-86.2); Benign 13.1 (7.2-22.9); Active infections 76.3 (42.0-166.5)	Perfusion: malignant vs. benign (P=0.000); malignant vs active infections (P=0.375); benign vs active infections (P=0.000)
Peak enhancement intensity (PEI) (HU)	Malignant 60.2 (36.5-72.1); Benign 11.3 (6.0-23.5); Active infections 61.8 (39.2-156.3)	PEI: malignant vs. benign (P=0.000); malignant vs active infections (P=0.617); benign vs active infections (P=0.000)
Time to peak (TTP)	Malignant 32.5 (26.8-37.6); Benign 28.0 (20.0-38.5); Active infections 26.5 (19.0-36.5)	TTP: malignant vs. benign (P=0.087); malignant vs active infections (P=0.163); benign vs active infections (P=0.585)

Blood volume (BV)	Malignant 33.1 (20.4-49.5); Benign 3.4 (0.0-8.7); Active infections 22.5 (17.5-36.8)	BV: malignant vs. benign (P=0.000); malignant vs active infections (P=0.317); benign vs active infections (P=0.000)
Accuracy	**Repeatability: Differences between measurements mean (SD), 95% CI** Perfusion: 1.26 (3.63), 0.43 to 2.09 PEI: 0.68 (3.73), -0.16 to 1.53 TTP: -0.04 (0.19), -0.08 to 0.00 BV: 0.91 (3.73), 0.06 to 1.76	
Correlations	**Repeatability: Intraclass correlation coefficient (ICC) (95% CI)** Perfusion: 0.9981 (0.9969 to 0.9988) PEI: 0.9979 (0.9967 to 0.9987) TTP: 0.9998 (0.9998 to 0.9999) BV: 0.9939 (0.9905 to 0.9962)	

eAppendix 3: Studies of CT with dynamic contrast enhancement

Orlacchio, 2007[4]

Risk of Bias

Prospective:	baseline CT scans were retrospectively reviewed; PET/MDCT was carried out 1-3 months after baseline CT scan; the results from each were compared retrospectively
Consecutive Enrollment?:	Not reported
Blinded Interpretation?:	No

Patient Characteristics

Inclusion Criteria:	All patients had already undergone CT scans for different indications, and each was found to have a solitary nodule in the lung parenchyma. Inclusion criteria were: single solid mass smaller than 3 cm, round or oval shape, no unequivocal signs of benign or malignant disease, normally ventilated peripheral parenchyma, absence of hilar or mediastinal node enlargement at baseline CT, no extrathoracic findings suggestive of distant metastasis at baseline CT, N0M0 nodule in previously resected pulmonary neoplasm, and M0MX nodule in previously resected extrathoracic neoplasm
Subjects, N:	56
Age:	63 (mean)
% Men:	64

Technical Methods

Section Thickness:	CT slice thickness 3.75 mm (reconstructed at 1.25 mm) to approximate width of PET section)
Low Dose?	Not reported

Nodule Characteristics

Nodules, N	56
% sub-solid	no cases of non-solid or sub-solid nodules
Overall prevalence of malignancy (%)	46
Reference standard	baseline CT scan

CT Characteristics

CT characteristic, e.g. GGO, size<5 mm	Number (%) of nodules with characteristic	Prevalence of malignancy, by characteristic (%) /	Likelihood Ratio of Positive Test
Density change postcontrast	probable benignancy: <15 HU	probable malignancy: >15 HU	No significant differences were found between the mean dimensions of benign and malignant lesions.
Doubling time	probable benignancy: >465 days	probable malignancy: <400 days	Malignant lesions had a significantly shorter DT and significantly greater enhancement (p<0.001) compared with benign nodules.
Standardized uptake value	probable benignancy: <2.5	probable malignancy: >2.5	

eAppendix 3: Studies of CT with dynamic contrast enhancement

mean diameter of malignant lesions was 1.8+1.2 cm	
CT characteristic, e.g. GGO, size<5 mm	
mean diameter of benign lesions was 2+1 cm	
mean volume of malignant lesions was 222 days	
mean SUV of malignant lesions was 4.7 vs. 1.08 of benign lesions	
malignant lesions had mean enhancement after contrast administration of 44.8 HU as opposed ot 4.8 HU in benign lesions	
Sensitivity	Doubling time (DT) < 400 days: 76.9; contrast enhancement (HU) > 15: 92.3; standarized uptake value (SUV) > 2.5: 76.9
Specificity	DT<400 days: 93.3; HU>15: 100; SUV>2.5: 100
PPV	DT<400: 90.9; HU>15: 100; SUV>2.5: 100

eAppendix 3: Studies of CT with dynamic contrast enhancement

NPV	DT<400: 82.3; HU>15: 93.7; SUV>2.5: 83.3
Accuracy	DT<400: 85.7; HU>15: 96.4; SUV>2.5: 89.2
Correlations	In malignant nodules, a significant correlation was found between SUV and DT (r=-0.89, p=0.0001) and SUV and enhancement (r=0.32; p=0.001); no significant correlations were identified for benign lesions.

eAppendix 3: Studies of CT with dynamic contrast enhancement

1 Bai RJ, Cheng XG, Qu H, et al. Solitary pulmonary nodules: comparison of multi-slice computed tomography perfusion study with vascular endothelial growth factor and microvessel density. Chin Med J (Engl) 2009; 122:541-547

2 Ikeda K, Awai K, Mori T, et al. Differential diagnosis of ground-glass opacity nodules: CT number analysis by three-dimensional computerized quantification. Chest 2007; 132:984-990

3 Li Y, Yang ZG, Chen TW, et al. First-pass perfusion imaging of solitary pulmonary nodules with 64-detector row CT: comparison of perfusion parameters of malignant and benign lesions. Br J Radiol 2010; 83:785-790

4 Orlacchio A, Schillaci O, Antonelli L, et al. Solitary pulmonary nodules: morphological and metabolic characterisation by FDG-PET-MDCT. Radiol Med 2007; 112:157-173

eAppendix 4: Studies of CT methods to detect nodule growth

Revel, 2006[1]

Risk of Bias

Prospective:	no, retrospective
Consecutive Enrollment?:	Not reported
Blinded Interpretation?:	Not reported

Patient Characteristics

Inclusion Criteria:	
Subjects, N:	
Age:	
% Men:	

Technical Methods

Section Thickness:	1.25mm slices
Low Dose?	

Nodule Characteristics

Nodules, N	63
% sub-solid	0%, all solid
Overall prevalence of malignancy (%)	17
Reference standard	
Definition for positive test (growth)	doubling time and volume variation

Accuracy for identifying malignancy

Sensitivity	91% (CI 0.59 - 1.0)
Specificity	90% (CI 0.79 - 0.97)
AUC or other metric	negative and positive predictive values for diagnosing malignancy respectively were 98% (CI 0.89 - 1.00) and 67% (CI 0.38 - 0.88)

Measurement of Growth

Measurement Variability	"Seven of the 11 malignant nodules corresponded to primary lung carcinomas and four to metastases. The interscan interval ranged from 0.8 to 6 months (median, 1.9 months). The relative volume variation of the malignant lesions ranged from 22% to 462% (mean, 102%; median, 55%). The diameter variation, measured with electronic calipers on a PACS screen, was more than 2 mm for six of the 11 nodules and less than 1 mm (not significant [NS]) for the other five nodules (Figs. 1 and 2). These five nodules were rescanned within 8 weeks after the baseline CT examination, at the time of core biopsy or surgical resection. On this basis, the sensitivity of the software-calculated doubling time for malignancy was 91% (95% CI, 0.59–1.00), whereas the sensitivity of manual diameter-change measurement was 54% (95% CI, 0.23–0.83).

The software-calculated doubling times of the malignant nodules were always less than 500 days (range, 37–297 days; mean, 116 days; median, 91 days), except for one adenocarcinoma (646 days) (Fig. 3). On this basis, the sensitivity of the software-calculated doubling time for malignancy was 91%(95%CI, 0.59–1.00). The mean and median doubling times for all 11 malignant lesions were 164 and 117 days, respectively."

eAppendix 4: Studies of CT methods to detect nodule growth

Jennings, 2006[2]

Risk of Bias

Prospective:	No, retrospective identification of subjects from a tumor registry
Consecutive Enrollment?:	not reported
Blinded Interpretation?:	one reviewer used, not blinded

Patient Characteristics

Inclusion Criteria:	diagnosis of stage I lung cancer between Feb 1996 and June 2004, without previous diagnosis. All chest CT examinations performed before the initiation of treatment and documented in departmental archives. Only the exams performed by using single-breath hold spiral CT were included. Patients who had undergone at least two pretreatment exams performed 25 days apart with the same scanner
Subjects, N:	149
Age:	72 (median), 43-87 (range)
% Men:	99

Technical Methods

Section Thickness:	median section was 5.5mm
Low Dose?	settings were 120 kVp, 200mAs, and pitch of 1.5

Nodule Characteristics

Nodules, N	149 tumors
% sub-solid	Not reported
Overall prevalence of malignancy (%)	Not reported
Reference standard	one board certified radiologist with 20 years of specialized experience in chest imaging and 1 year of experience in using the image viewing and manipulation software
Definition for positive test (growth)	doubling time was calculated by using the volume and intersecting interval

Accuracy for identifying malignancy

Sensitivity	
Specificity	
AUC or other metric	

Measurement of Growth

Measurement Variability	

eAppendix 4: Studies of CT methods to detect nodule growth

Marchiano, 2009[3]

Risk of Bias

Prospective:	Yes, all solid pulmonary nodules were prospectively recorded in a database, with a maximum limit of four nodules for each subject
Consecutive Enrollment?:	Yes, all participants in the study were consecutive
Blinded Interpretation?:	Not blinded, each CT study was examined by two of seven alternating radiologists. Discrepencies were resolved by consensus

Patient Characteristics

Inclusion Criteria:	subjects aged 50-75years who are current or former (having quit <10 years previously) smokers of 20 pack years or more with no recent history of cancer within the previous 5 years, and recalled for a repeat CT examination in 3 months
Subjects, N:	101
Age:	58 (mean); 49-73 (range)
% Men:	70

Technical Methods

Section Thickness:	1 mm-thick sections at 1-mm increments and 5-mm-thick sections at 5-mm increments
Low Dose?	Not reported

Nodule Characteristics

Nodules, N	233 nodules
% sub-solid	
Overall prevalence of malignancy (%)	None of the nodules showed malignant characteristics at the first annual repeat exam
Reference standard	
Definition for positive test (growth)	

Accuracy for identifying malignancy

Sensitivity	Not reported
Specificity	Not reported
AUC or other metric	Not reported

Measurement of Growth

Measurement Variability	The mean volume of the 233 nodules at baseline was 99.1 mm3 | 127.5 (standard deviation), and the median volume was 67 mm3 (range, 5– 839 mm3). The mean volume at 3 months was 97.6 mm3 | 129.3, and the median volume was 64 mm3 (range, 5–869 mm3). The mean volume at 12 months was 98.2 mm3 | 127.6, and the median volume was 63 mm3 (range, 5–866 mm3).

eAppendix 4: Studies of CT methods to detect nodule growth

van Klaveren, 2009[4]

Risk of Bias

Prospective:	Yes, RCT
Consecutive Enrollment?:	Not reported
Blinded Interpretation?:	Not reported

Patient Characteristics

Inclusion Criteria:	not reported, participants from the NELSON study
Subjects, N:	7557
Age:	Not reported
% Men:	Not reported

Technical Methods

Section Thickness:	thickness of 1 mm that were reconstructed at overlapping 0.7mm intervals
Low Dose?	Not reported

Nodule Characteristics

Nodules, N	8623
% sub-solid	0.1
Overall prevalence of malignancy (%)	
Reference standard	
Definition for positive test (growth)	Growth was defined as an increase in volume of at least 25% between the two scans. The first-round screening test was considered to be negative if the volume of a nodule was less than 50 mm3, if it was 50 to 500 mm3 but had not grown by the time of the 3-month follow-up CT, or if, in the case of those that had grown, the volume-doubling time was 400 days or more.

Accuracy for identifying malignancy

Sensitivity	In round one, the sensitivity of the screen was 94.6% (95% confidence interval [CI], 86.5 to 98.0) and the negative predictive value 99.9% (95% CI, 99.9 to 100.0).
Specificity	
AUC or other metric	Volume Doubling Time

Measurement of Growth

Measurement Variability	

eAppendix 4: Studies of CT methods to detect nodule growth

de Hoop, 2010[5]

Risk of Bias

Prospective:	No, all measurements were performed retrospectively
Consecutive Enrollment?:	Yes
Blinded Interpretation?:	2 reviwers used; authors did not state whether they were blinded

Patient Characteristics

Inclusion Criteria:	All participants were recruited from the randomized Dutch-Belgian lung cancer screening trial. All participants were current or former heavy smokers. All CT examinations performed between April 2004 and April 2009 at one of the study sites were included.
Subjects, N:	45
Age:	62 (mean); 53-73 (range)
% Men:	93

Technical Methods

Section Thickness:	axial images of 1 mm thickness, with reconstruction thickness of 0.7 mm
Low Dose?	Exposure settings were 30 mAs at 120 kVp for patient weighing less than 80 kg and 30 mAs at 140 kVp for those weighing more than 80 kg

Nodule Characteristics

Nodules, N	52 GGNs
% sub-solid	Not reported
Overall prevalence of malignancy (%)	13/52 malignant GGNs 25%
Overall sensitivity (%)	Not reported
Reference standard	Not reported
Definition for positive test (growth)	Not reported

Accuracy for identifying malignancy

Sensitivity	Not reported
Specificity	Not reported
AUC or other metric	Not reported

Measurement of Growth

Measurement Variability	Diameter measurements: mean 0.05 95% CI for limits of agreement for intraobserver variability was -2.5, 2.7 mm and mean 0.06 -2.8, 3.3 mm for interobserver variability; Volume measurements: mean 0.15, 95% CI was -0.14, 0.16 for intraobserver variability and mean 0.18, -0.25, 0.15 for interobserver variability; Mass measurements: mean 0.07, 95% CI was -0.11, 0.12 for intraobserver variability and mean 0.09, -0.18, 0.12 for interobserver variability; the intra-and interobserver CVs for mass were significantly lower than those for volume; the diameter variabilities were significantly higher than those for volume and mass ($P < .001$)

de Hoop, 2010 (cont'd)

Growth-to-Variability Ratio	Mean time between first and last CT examination of 13 malignant lesions was 33 months. Diameter of malignant GGNs increased by a mean of 53% (range 9-194%); volume increased by mean of 202% (range 23-714%); mass increased by mean of 254% (range, 36-699%--significantly greater than increases in volume and diameter ($P < .01$); mean growth-to-variability ratios: 11 for diameter, 28 for volume, 35 for mass ($P = .03$)
Time to Detection of Growth	For the 13 malignant GGNs, mean time required for growth to exceed the upper limit of agreement was significantly longer ($P = .02$) for diameter (715 days) and volume (673 days) than for mass (425 days). None of the cases showed a shorter time to growth detection for volume or diameter than for mass.

eAppendix 4: Studies of CT methods to detect nodule growth

1 Revel MP, Merlin A, Peyrard S, et al. Software volumetric evaluation of doubling times for differentiating benign versus malignant pulmonary nodules. AJR Am J Roentgenol 2006; 187:135-142

2 Jennings SG, Winer-Muram HT, Tann M, et al. Distribution of stage I lung cancer growth rates determined with serial volumetric CT measurements. Radiology 2006; 241:554-563

3 Marchiano A, Calabro E, Civelli E, et al. Pulmonary nodules: volume repeatability at multidetector CT lung cancer screening. Radiology 2009; 251:919-925

4 van Klaveren RJ, Oudkerk M, Prokop M, et al. Management of lung nodules detected by volume CT scanning. N Engl J Med 2009; 361:2221-2229

5 de Hoop B, Gietema H, van de Vorst S, et al. Pulmonary ground-glass nodules: increase in mass as an early indicator of growth. Radiology 2010; 255:199-206

Executive Summary

Evidence to support Diagnosis Chapter
PICO Question 1

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Evidence to support Diagnosis Chapter PICO Question 1

The question

How does the test performance of radial endobronchial ultrasound (EBUS) guided sampling of peripheral lung nodules for establishing a diagnosis of malignancy compare to other methods of sampling (conventional bronchoscopy, electromagnetic navigation bronchoscopy, transthoracic needle aspiration biopsy)?

PICO

PICO Category	Question Specific
Population	patient suspected of having lung cancer who presents with a peripheral lung nodule on imaging
Intervention	radial probe endobronchial ultrasound
Comparison	conventional bronchoscopy, electromagnetic navigation bronchoscopy, transthoracic needle aspiration biopsy
Outcome	diagnosis of malignancy

Summary of Methods

Methods of the ACCP were strictly adhered to for the conduct of the search, selection, evaluation and reporting of evidence. These methods include the following steps:

Key Question Development
Systematic Literature Search and Study selection
Study quality assessment
Data extraction
Meta-analysis or Qualitative Summary

Note: PICO questions were developed and assigned by the ACCP with some refinement through consultation of evidence provider with chapter editor.

Systematic Literature Search

Inclusion and exclusion criteria were established prior to the search. Multiple iterations of searching involving various combinations of search terms were applied to several databases to maximize retrieval. Databases searched include Medline, Embase, and Cochrane. Handsearching of references and PubMed searches of related content were also utilized.

Exclusion and Inclusion Criteria applied to abstracts

Articles were excluded from further review if any of the exclusion criteria were met.

Exclusion Criteria	Inclusion Criteria
No original data or not systematic review or meta-analysis	Original study or systematic review or meta-analysis
Does not include human data	Human study
Not in English	English language
Meeting abstract (no full article available for review)	Applies to PICO question
Case report or case series	
Letter	
Does not apply to the PICO question	

Searches

Database	Search Terms	Retrieval	After Exclusion/Inclusion to Abstract
Medline	Search of Steinfort	1,385	58
Medline	(Diagnosis/Broad[filter]) AND (endobronchial[All Fields] AND ("ultrasonography"[Subheading] OR "ultrasonography"[All Fields] OR "ultrasound"[All Fields] OR "ultrasonography"[MeSH Terms] OR "ultrasound"[All Fields] OR "ultrasonics"[MeSH Terms] OR "ultrasonics"[All Fields]) AND (solitary [All Fields] OR nodule [All Fields] OR peripheral [All Fields])	82	20
Embase	endobronchial AND ('ultrasound'/exp OR ultrasound)AND (solitary OR nodule OR peripheral)	206	24
Cochrane	Endobronchial Ultrasound	2	0

Study retrieval

One systematic review was located, with systematic literature search completed through end of 2009. No additional studies were identified that were missed by those authors up to that date, excepting the two studies they excluded for small sample size (less than 30 subjects total). Search for additional studies meeting all exclusion/inclusion criteria published since 2009 was conducted, however most new studies combined EBUS with other modalities or new technologies (virtual bronchoscopy, PET, or novel thin bronchoscope), evaluated use for other than peripheral pulmonary nodules, or were case reports. Two studies did meet all inclusion and exclusion and were evaluated to supplement the systematic review.

Steinfort et al. Radial Probe endobronchial ultrasound for the diagnosis of peripheral lung cancer: systematic review and meta-analysis. Eur Respir J 2011; 37:902-910.

Studies published post Steinfort:
Roth et al. In press A randomised trial of endobronchial ultrasound guided sampling in peripheral lung lesions. Lung Cancer 2011.
Disayabutr et al. The endobronchial ultrasound-guided transbronchial lung biopsy in peripheral pulmonary lesions J Med Assoc Thai 2010;93(suppl 1) S94-101.

Steinfort et al. In press. Comparative effectiveness of radial probe endobronchial ultrasound versus CT-guided needle biopsy for evaluation of peripheral pulmonary lesions. A randomized pragmatic trial. Respiratory Medicine (2011).

Study quality assessment

Steinfort Systematic Review - GOOD quality systematic review
The ACCP quality assessment tool for systematic review was applied. The authors adhered to nearly all standards for systematic review and the overall quality grade was good. However, the underlying studies as reviewed by Steinfort rated very low using the QUADAS scale. Most were single arm studies, either prospective case series or retrospective audits. Three were reported as RCTs, however in one the randomization was for sampling since all had EBUS guidance. The other two RCTs were relevant to the PICO question, one comparing EBUS to flexible bronchoscopy (Paone) and the other comparing EBUS to EMN. These two studies were therefore examined separately.

Summary of RCTs in Steinfort
Paone et al. Endobronchial ultrasound driven biopsy in the diagnosis of peripheral lung lesions. Chest 2005;128:3551-3557.
This study was in a single academic hospital in Rome and had what seem to be excessive challenges in patient commitment to study. They screened 799 patients with PPL and excluded 386 of them because of previous low compliance/follow-up issues. Even after that, the study suffered from differential follow-up in the test groups, with the EBUS losing 10% (10 of 97) and flexible bronchoscopy group losing 4% of subjects (5 of 124). Other exclusions resulted in total study population of 206. The study did measure sensitivity and specificity for both groups, for EBUS = 0.79 (95% CI=0.68-0.89) and for flexible bronchoscopy = 0.55 (95% CI = 0.45-0.66). They provided an analysis by lesion size and for lesions less than 2 cm, performance of EBUS stayed high while performance of flexible bronchoscopy dropped; 0.71 (95% CI=0.47-0.95) for EBUS and 0.23 (95%CI=0.03-0.43) for FBB. Specificity was 1.0 in all groups. Patients in the EBUS group suffered no complications of pneumothorax or bleeding; while 2.5% and 6% of the flexible bronchoscopy group suffered those complications.

Eberhardt et al Multimodality bronchoscopic diagnosis of peripheral lung lesions: a randomized controlled trial. Am J Respir Crit Care Med 2007;176:36-41.
Randomization method was not described, numbers of patients in each group were similar, but fewer patients in the ENB group had nodules <20mm (10% vs 23% and 25% in the other 2 arms). Sensitivity was presented separately for malignant (M) and benign disease (B); in the EBUS group these were 0.72 M and 0.57 B and in the ENB group 0.55 M and 0.70 B. Difference in the yield for malignant disease was significant, but the benign sample was much too small. Complications were similar in both groups, 5% experiencing pneumothorax in each and no cases of bleeding that required intervention were reported.

Summary of 3 new studies

Disayabutr et al. The endobronchial ultrasound-guided transbronchial lung biopsy in peripheral pulmonary lesions J Med Assoc Thai 2010;93(suppl 1) S94-101.
This study was a prospective case series of EBUS performed at a single academic hospital in Thailand and included all patients presenting with pulmonary lesions beyond segmental bronchus by radiograph or CT (n=152). The study only reported results as diagnostic yield, overall 0.66 and 0.81 for benign lesions and 0.59 for malignant. They did not provide diagnostic yield data by lesion size, and said that size of lesion did not affect diagnostic yield. Less than a third of the lesions were nodules (<3 cm).

Roth et al. In press A randomised trial of endobronchial ultrasound guided sampling in peripheral lung lesions. Lung Cancer 2011.
This study used simple randomization to assign patients presenting to single academic hospital in Norway to EBUS or non EBUS bronchoscopy to evaluate lesions suspicious of malignancy in the lungs. The authors report overall sensitivity of 0.36 for EBUS and 0.44 for non-EBUS. For lesions less than 3 cm, they report sensitivity of 0.11 for EBUS and 0.31 for non-EBUS. The authors acknowledge as a weakness

of their study that a "significant" number of their bronchoscopists performed only a few procedures with EBUS. In addition, bronchoscopists in this study had a wide range of experience with bronchoscopy (from 30 years to less than a year) with a total of 29 different bronchoscopists evaluating 264 subjects.

Steinfort et al. In press. Comparative effectiveness of radial probe endobronchial ultrasound versus CT-guided needle biopsy for evaluation of peripheral pulmonary lesions. A randomized pragmatic trial. Respiratory Medicine (2011).
This RCT compared performance of EBUS to CT-PNB. It was well-designed but suffered some challenges in execution that may bias the results. Similar to the Paone study, 358 potential subjects were referred but 273 were exclude for various reasons. Because the authors allowed clinical input to determine if patients were eligible for the randomization or would be better suited to one or the other methods, there were 28 known exclusions on this basis and another 20 suspected. The authors believe this would reduce the observed discrepancy in complication rates. However, an additional bias could also be responsible for the observed difference in complication rates (pneumothorax) since radiology fellows performed some of the CT-TNB, but a single physician (the lead author) performed all EBUS procedures. Overall complication rates in the procedures performed by fellows were reported at 50%. The study was very small (32 EBUS and 16 CT) and the authors finding of non-inferiority in diagnostic accuracy could be a result of insufficient power to detect a clinically important difference.

Summary of Findings From Steinfort et al Systematic Review

Outcomes	EBUS	# of EBUS Participants (studies)	Comparison	# of comparison participants (studies)	GRADE
Overall sensitivity*	0.73 (0.70-0.76)	1090 (13)	0.79 (0.75-0.84)	452 (7)	
Overall specificity	1.00 (0.99-1.00)	1090 (13)			
Pooled sensitivity for lesions <25 mm	0.71 (0.66-0.75)	580 (7)			
Diagnostic Yield for lesions ≤ 20 mm	56.3% (51-61)	364 (10)			
Diagnostic Yield for lesions > 20 mm	77.7% (73-82)	367 (10)			
Pooled rate of pneumothorax	1%	1090 (14) (sic)			
Bleeding requiring intervention	none reported				

** Heterogeneity in sensitivity was noted. Sub group analysis suggests underlying prevalence of malignancy in the study cohort is a source of heterogeneity.*

Major limitations of Steinfort include:
Poor quality of underlying studies
Unclear selection criteria for subjects
No data on bronchoscopist experience

Grading the Evidence

Using the methods of GRADE, since the underlying studies in the systematic review were principally of designs other than RCTs and were of low quality, there is risk of bias in the estimation. The grade of the body of evidence would have to start at a low level and could only be upgraded if there was a large, consistent effect noted, a dose-response, or residual confounding would likely reduce any observed efect (GRADE working group). Thus the evidence summarized by the systematic review would have to be considered weak.

The addition of the 3 small studies since the systematic review does not provide much additional evidence to assist in the interpretation. The small RCT by Steinfort (32 EBUS and 16 CT TNB) suffered from enough bias to question the observed saftey profile and did not find a difference in diagnostic accuracy (though EBUS was less). The study by Roth found low detection rate for cancer in both groups, with EBUS being lower, likely because of the overall inexperience of the bronchoscopists in the study since the goal was to evaluate actual practice with varied level of expertise.

There remains a need for well designed and well executed studies of sufficient size in order to quantify the diagnostic accuracy of EBUS in clinical practice and to characterize the patients likely to benefit from its use.

Executive Summary

Evidence to support Diagnosis Chapter
PICO Question 2

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Evidence to support Diagnosis Chapter PICO Question 2

The question

How does the test performance of flexible bronchoscopy using electromagnetic navigation to sample pulmonary nodules <2 cm in diameter and located in the peripheral one third of the lung compare to conventional bronchoscopy for establishing a diagnosis?

PICO

PICO Category	Question Specific
Population	patient suspected of having lung cancer who presents with a peripheral lung nodule < 2 cm on imaging
Intervention	Flexible bronchoscopy using electromagnetic navigation
Comparison	conventional flexible bronchoscopy
Outcome	diagnosis of malignancy

Summary of Methods

Methods of the ACCP were strictly adhered to for the conduct of the search, selection, evaluation and reporting of evidence. These methods include the following steps:

Key Question Development
Systematic Literature Search and Study selection
Study quality assessment
Data extraction
Meta-analysis or Qualitative Summary

Note: PICO questions were developed and assigned by the ACCP with some refinement through consultation of evidence provider with chapter editor.

Systematic Literature Search

Inclusion and exclusion criteria were established prior to the search. Multiple iterations of searching involving various combinations of search terms were applied to several databases to maximize retrieval. Databases searched include Medline, Embase, and Cochrane. Handsearching of references and PubMed searches of related content were also utilized.

Exclusion and Inclusion Criteria applied to abstracts

Articles were excluded from further review if any of the exclusion criteria were met.

Exclusion Criteria	Inclusion Criteria
No original data or not systematic review or meta-analysis	Original study or systematic review or meta-analysis

Exclusion Criteria	Inclusion Criteria
Does not include human data	Human study
Not in English	English language
Meeting abstract (no full article available for review)	Applies to PICO question
Case report or case series	
Letter	
Does not apply to the PICO question	

Searches

Database	Search Terms	Retrieval	After Exclusion/Inclusion to Abstract
Medline	navigational[All Fields] AND ("bronchoscopy"[MeSH Terms] OR "bronchoscopy"[All Fields])	8	2
Medline	(Diagnosis/Broad[filter]) AND (electromagnetic navigation) AND (peripheral OR solitary OR nodule)	17	8
Medline	(("electromagnetic phenomena"[MeSH Terms] OR ("electromagnetic"[All Fields] AND "phenomena"[All Fields]) OR "electromagnetic phenomena"[All Fields] OR "electromagnetic"[All Fields]) AND navigation[All Fields]) AND (solitary[All Fields] OR nodule[All Fields] OR peripheral[All Fields]) AND ("humans"[MeSH Terms] AND English[lang])	22	8
Embase	electromagnetic AND navigation AND ('bronchoscopy'/exp OR bronchoscopy)	46	10
Cochrane	electromagnetic navigation	2 clinical trials no systematic reviews and 3 HTAs	0

Study retrieval

Studies:
Becher, H. D., F. Herth, et al. (2005). "Bronchoscopic biopsy of peripheral lung lesions under electromagnetic guidance: A pilot study." Journal of Bronchology 12(1): 9-13.
Eberhardt, R., R. K. Morgan, et al. (2010). "Comparison of suction catheter versus forceps biopsy for sampling of solitary pulmonary nodules guided by electromagnetic navigational bronchoscopy." Respiration 79(1): 54-60.

Eberhardt, R., D. Anantham, et al. (2007). "Multimodality bronchoscopic diagnosis of peripheral lung lesions: a randomized controlled trial." Am J Respir Crit Care Med 176(1): 36-41.
Eberhardt, R., D. Anantham, et al. (2007). "Electromagnetic navigation diagnostic bronchoscopy in peripheral lung lesions." Chest 131(6): 1800-1805.
Gildea, T. R., P. J. Mazzone, et al. (2006). "Electromagnetic navigation diagnostic bronchoscopy: A prospective study." American Journal of Respiratory and Critical Care Medicine 174(9): 982-989.
Hautmann, H., A. Schneider, et al. (2005). "Electromagnetic catheter navigation during bronchoscopy: Validation of a novel method by conventional fluoroscopy." Chest 128(1): 382-387.
Makris, D., A. Scherpereel, et al. (2007). "Electromagnetic navigation diagnostic bronchoscopy for small peripheral lung lesions." European Respiratory Journal 29(6): 1187-1192.
Schwarz, Y., J. Greif, et al. (2006). "Real-time electromagnetic navigation bronchoscopy to peripheral lung lesion using overlaid CT images: The first human study." Chest 129(4): 988-994.
Seijo, L. M., J. P. De Torres, et al. (2010). "Diagnostic yield of electromagnetic navigation bronchoscopy is highly dependent on the presence of a bronchus sign on CT imaging: Results from a prospective study." Chest 138(6): 1316-1321.
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.

Study quality assessment

All case series were of poor quality according to the QUADAS instrument
The RCT was fair

Summary of Findings

Outcomes	EMN	# of EMN Participants (studies)	Comparison EBUS	# of comparison participants (studies)	GRADE
Diagnostic Yield for lesions ≤ 20 mm	43-75% *	86 (4)	78%	9 (1)	Weak evidence

**The RCT was 75%*

Major limitations include:
Very limited data - few studies overall and only 4 provided or allowed analysis by nodule size of 2 cm or less
Poor quality of contributing studies - all but one were very small case series
Many of the small case series were supported by the manufacturer
Selection criteria for subjects predominantly described subjects unsuitable for other methods of sampling and could not be extrapolated broadly
No data on bronchoscopist experience

Using the methods of GRADE, since the underlying studies were of designs other than RCTs and were of low quality, there is risk of bias in the estimation and the body of evidence would remain at a low level of evidence.