

BTS Guideline for Pulmonary Nodules

Online Supplementary Appendices

Draft for Public Consultation

October 2026

Contents

Online Supplementary Appendix 1	(Q1 Evidence Review)	2
Online Supplementary Appendix 2	(Q2 Evidence Review)	12
Online Supplementary Appendix 3	(Q3 Evidence Review)	19
Online Supplementary Appendix 4	(Q4 Evidence Review)	51
Online Supplementary Appendix 5	(Q5 Evidence Review)	71
Online Supplementary Appendix 6	(Q6 Evidence Review)	123
Online Supplementary Appendix 7	(Q7 Evidence Review)	147
Online Supplementary Appendix 8	(Q8 Evidence Review)	167
Online Supplementary Appendix 9	(Q9 Evidence Review)	178
Online Supplementary Appendix 10	(Literature search strategy)	189
Online Supplementary Appendix 11	(Research Recommendations)	201

25

Q1

In adults, is there a difference in the likelihood of diagnosing lung cancer in pulmonary nodules detected by low dose computed tomography (CT) screening compared to those detected on CT scans done for other reasons?

26

27

28

Contents

29

Question Evidence Review

3

30

Background

3

31

Outcome

3

32

Evidence Review

3

33

Evidence Statement

6

34

Recommendation

6

35

Research Recommendation

6

36

References

7

37

Question Protocol

10

38

39

40

41

42

Draft For Public Consultation October 2026

43 Question 1 Evidence Review

44 **Q1** In adults, is there a difference in the likelihood of diagnosing lung cancer in pulmonary nodules
45 detected by low dose computed tomography (CT) screening compared to those detected on
46 CT scans done for other reasons?

47 Background

48 Pulmonary nodules can be detected during low dose computed tomography (LDCT) screening for lung cancer,
49 or incidentally on CT scans done for other reasons. People are selected for LDCT screening based their lung
50 cancer risk exceeding specific thresholds, whereas those undergoing CT scans done for other reasons will
51 also include people at a lower risk. This review will aim to determine to what extent the likelihood of lung cancer
52 in a given pulmonary nodule will differ between these two scenarios, and whether the subsequent investigation
53 and management of nodules should differ accordingly.

54 Outcome

55 Lung cancer

56 Evidence Review

57 The initial literature search identified 207 potentially relevant papers, and 53 papers were deemed relevant to
58 the review.¹⁻⁵² Although one paper did directly compare lung cancer incidence in incidentally detected versus
59 screen detected pulmonary nodules, this study was excluded as the data reporting was incomplete.

60 Lung cancer

61 Due to a lack of direct comparison evidence, single arm studies were considered. Thirty-two single arm studies
62 reported on the incidence of lung cancer in subjects with pulmonary nodules detected by LDCT¹⁻³² and 20
63 single arm studies reported on the incidence of lung cancer in subjects with pulmonary nodules detected by
64 incidental detection³³⁻⁵².

65 Actionable pulmonary nodules

66 A pulmonary nodule is defined as “actionable” if it is considered potentially cancerous after an initial
67 examination. The number of subjects with a pulmonary nodule being considered actionable following LDCT
68 screening¹⁻³² was compared with the number of subjects with a pulmonary nodule following incidental
69 detection³³⁻⁵⁰. The data show that the likelihood of an actionable pulmonary nodule following LDCT screening
70 is significantly greater than the likelihood of an actionable pulmonary nodule detected by incidental detection
71 (27.9 ± 15.6 versus 16.7 ± 13.0 % (mean $\pm$ SD) respectively, $p = 0.009$, Mann-Whitney U test). A summary of
72 the data is shown in [Figure Q1a](#) and [Table Q1a](#).

73 Table Q1a: Summary of the likelihood of detecting “actionable” pulmonary nodules by LDCT screening versus
74 incidental detection

% subjects with actionable pulmonary nodules after pulmonary nodule detection						
LDCT detection			Incidental detection			p
Mean $\pm$ SD	Median [IQR]	n	Mean $\pm$ SD	Median [IQR]	n	
27.9 ± 15.6	25.2 [16.4, 37.9]	32 ¹⁻³²	16.7 ± 13.0	11.8 [5.4, 30.9]	18 ³³⁻⁵⁰	0.009*

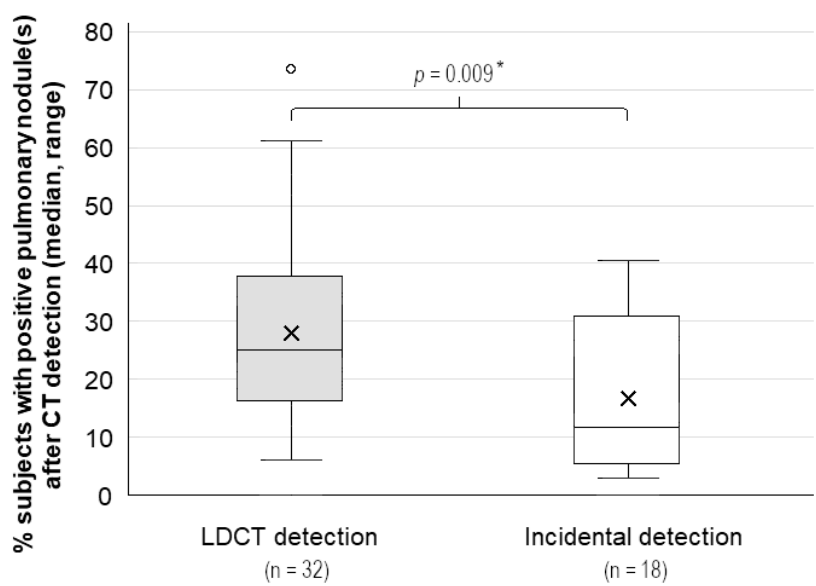
75 * Mann-Whitney U Test

76 IQR – interquartile range; n – number of participants; SD – standard deviation

77

78

79 Figure Q1a: Comparison of the incidence of “actionable” pulmonary nodules detected by LDCT screening
80 versus incidental detection

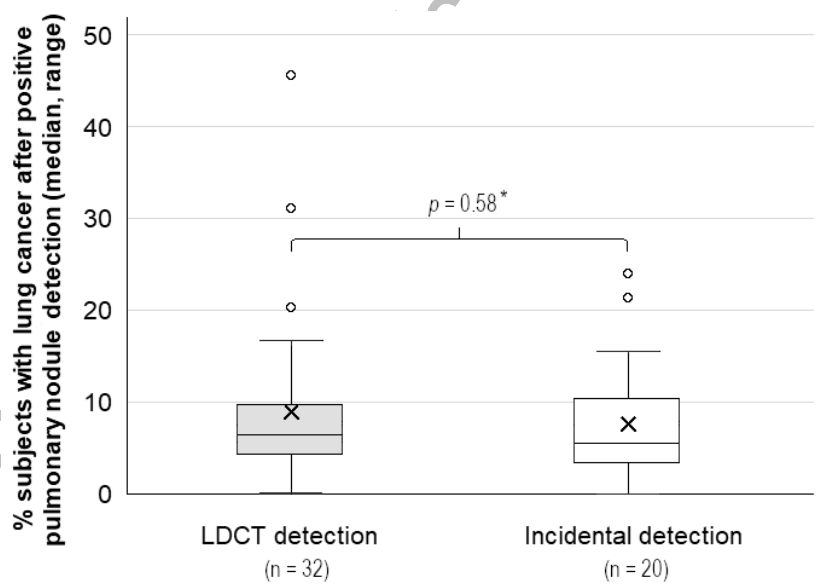


81
82 * Mann-Whitney U Test

83 *Lung cancer per actionable pulmonary nodules*

84 The incidence of lung cancer in subjects with “actionable” pulmonary nodules following LDCT screening¹⁻³²
85 was compared with the incidence of lung cancer in subjects with “actionable” pulmonary nodules following
86 incidental detection³³⁻⁵². The data show no difference in the percentage of subjects with a lung cancer
87 diagnosis following an actionable pulmonary nodule detection by LDCT or incidental detection (8.9 ± 9.1 versus
88 7.7 ± 6.5 % (mean $\pm$ SD) respectively, $p = 0.58$, Mann-Whitney U test). A summary of the data is shown in
89 Figure Q1b and Table Q1b.

90 Figure Q1b: Comparison of the likelihood of diagnosing lung cancer in “actionable” pulmonary nodules
91 detected by LDCT screening versus incidental detection



92
93 * Mann-Whitney U Test

94
95

Table Q1b: Summary of the likelihood of diagnosing lung cancer in “actionable” pulmonary nodules detected by LDCT screening incidental detection

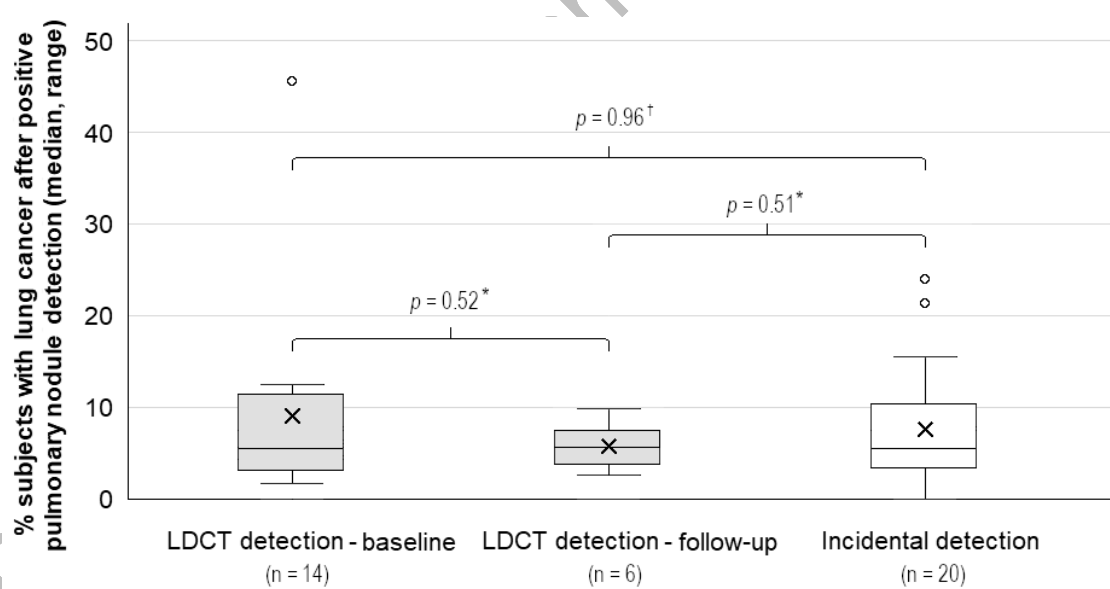
% subjects with lung cancer after actionable pulmonary nodule detection						
LDCT detection			Incidental detection			p
Mean ± SD	Median [IQR]	n	Mean + SD	Median [IQR]	n	
8.9 ± 9.1	6.5 [4.4, 9.7]	32 ¹⁻³²	7.7 ± 6.5	5.6 [3.4, 10.4]	20 ³³⁻⁵²	0.58*

* Mann-Whitney U Test
 IQR – interquartile range; n – number of participants; SD – standard deviation

With / without previous CT imaging

Subgroup comparisons were considered for lung cancers diagnosed after an initial baseline CT scan (T0)¹⁻¹⁴, or after a subsequent follow-up surveillance CT scan (i.e., subjects with or without previous CT imaging)^{9,12-16}. As it was difficult to ascertain if an incidental detection follow-up was a direct follow-up to the initial pulmonary nodule incidental detection (T0), or a surveillance follow-up after T0, the incidental detection data have not been divided into subgroups. Data are shown in Figure Q1c. Comparison of the likelihood of diagnosing lung cancer in pulmonary nodules detected by LDCT screening without previous CT imaging versus with previous CT imaging showed no statistical difference (8.9 ± 11.2 versus 5.8 ± 2.4 (mean ± SD) respectively, p = 0.52, unpaired t-test) (Table Q1c). Similarly comparing of the likelihood of diagnosing lung cancer in pulmonary nodules detected by LDCT screening without previous CT imaging versus incidental detection showed no statistical difference (p = 0.96, Mann-Whitney U Test) (Table Q1d), as did the likelihood of diagnosing lung cancer in pulmonary nodules detected by LDCT screening with previous CT imaging versus incidental detection (p = 0.51, unpaired t-test) (Table Q1e).

Figure Q1c: Comparison of the likelihood of diagnosing lung cancer in pulmonary nodules detected by LDCT screening with previous CT imaging (LDCT detection - follow-up), without previous CT imaging (LDCT detection - baseline) or detected on CT scans done for other reasons (incidental detection)



* Unpaired t-test
 † Mann-Whitney U Test

122 Table Q1c: Summary of the likelihood of diagnosing lung cancer in pulmonary nodules detected by LDCT
 123 screening with versus without previous CT imaging

% subjects with lung cancer after pulmonary nodule detection						
LDCT detection - baseline			LDCT detection - follow-up			p
Mean ± SD	Median [IQR]	n	Mean + SD	Median [IQR]	n	
8.9 ± 11.2	5.4 [3.1, 11.5]	14 ¹⁻¹⁴	5.8 ± 2.4	5.7 [3.8, 7.5]	6 ^{10,13-17}	0.52*

124 * Unpaired t-test

125 IQR – interquartile range; n – number of participants; SD – standard deviation

126 Table Q1d: Summary of the likelihood of diagnosing lung cancer in pulmonary nodules detected by LDCT
 127 screening without previous CT imaging or detected incidentally

% subjects with lung cancer after pulmonary nodule detection						
LDCT detection - baseline			Incidental detection			p
Mean ± SD	Median [IQR]	n	Mean + SD	Median [IQR]	n	
8.9 ± 11.2	5.4 [3.1, 11.5]	14 ¹⁻¹⁴	7.7 ± 6.5	5.6 [3.4, 10.4]	20 ³³⁻⁵²	0.96*

128 * Mann-Whitney U Test

129 IQR – interquartile range; n – number of participants; SD – standard deviation

130 Table Q1e: Summary of the likelihood of diagnosing lung cancer in pulmonary nodules detected by LDCT
 131 screening with previous CT imaging or detected incidentally

% subjects with lung cancer after pulmonary nodule detection						
LDCT detection - follow-up			Incidental detection			p
Mean ± SD	Median [IQR]	n	Mean + SD	Median [IQR]	n	
5.8 ± 2.4	5.7 [3.8, 7.5]	6 ^{10,13-17}	7.7 ± 6.5	5.6 [3.4, 10.4]	20 ³³⁻⁵²	0.51*

132 * Unpaired t-test

133 IQR – interquartile range; n – number of participants; SD – standard deviation

134 Evidence Statement

135 An actionable pulmonary nodule is more likely to be identified on screening low-dose computed tomography
 136 (LDCT) than on a CT scan performed for another reason. (**Ungraded**)

137 The likelihood that a pulmonary nodule is diagnosed as lung cancer is similar whether it is detected through
 138 low-dose computed tomography (LDCT) screening or incidentally on a CT scan performed for another reason.
 139 (**Ungraded**)

140 Recommendation

141 ➤ For adults with pulmonary nodules identified on a CT scan, the investigation and management should not
 142 differ whether detected on low dose computed tomography (LDCT) for lung cancer screening or CT scan
 143 done for other reasons. (**Conditional**)

144 Research Recommendation

145 ▪ Further research is needed to determine the malignancy risk between screening detected pulmonary
 146 nodules and incidentally detected pulmonary nodules.

147

- 149 1. Blanchon T, Brechot JM, Grenier PA, et al. Baseline results of the Depiscan study: A French randomized
150 pilot trial of lung cancer screening comparing low dose CT scan (LDCT) and chest X-ray (CXR). *Lung*
151 *Cancer*. 2007;58(1):50-58.
- 152 2. Diederich S, Thomas M, Semik M, et al. Screening for early lung cancer with low-dose spiral computed
153 tomography: Results of annual follow-up examinations in asymptomatic smokers. *Eur Radiol*.
154 2004;14(4):691-702.
- 155 3. Fabbri AE, Lillie SE, Partin MR, et al. Initial results of a lung cancer screening demonstration project: a
156 local program evaluation. *Am J Manag Care*. 2018;24(6):272-277.
- 157 4. Fan L, Wang Y, Zhou Y, et al. Lung Cancer Screening with Low-Dose CT: Baseline Screening Results in
158 Shanghai. *Acad Radiol*. 2019;26(10):1283-1291.
- 159 5. Henschke CI, McCauley DI, Yankelevitz DF, et al. Early lung cancer action project: a summary of the
160 findings on baseline screening. *Oncologist*. 2001;6(2):147-152.
- 161 6. Jungblut LM, Walter JE, Zellweger C, et al. Swiss pilot low-dose computed tomography lung cancer
162 screening study. *Br J Surg*. 2022;109:2022-2006.
- 163 7. Kang HR, Cho JY, Lee SH, et al. Role of Low-Dose Computerized Tomography in Lung Cancer Screening
164 among Never-Smokers. *J Thorac Oncol*. 2019;14(3):436-444.
- 165 8. Leleu O, Basille D, Auquier M, et al. Lung Cancer Screening by Low-Dose CT Scan: Baseline Results of
166 a French Prospective Study. *Clin Lung Cancer*. 2020;21(2):145-152.
- 167 9. Kerpel-Fronius A, Monostori Z, Kovacs G, et al. Nationwide lung cancer screening with low-dose computed
168 tomography: implementation and first results of the HUNCHEST screening program. *Eur Radiol*.
169 2022;32(7):4457-4467.
- 170 10. Mendoza DP, Petranovic M, Som A, et al. Lung-RADS Category 3 and 4 Nodules on Lung Cancer
171 Screening in Clinical Practice. *AJR Am J Roentgenol*. 2022;219(1):55-65.
- 172 11. Miller DL, Mayfield WR, Luu TD, et al. Community-Based Multidisciplinary Computed Tomography
173 Screening Program Improves Lung Cancer Survival. *Ann Thorac Surg*. 2016;101(5):1864-1869.
- 174 12. Nawa T, Nakagawa T, Kusano S, Kawasaki Y, Sugawara Y, Nakata H. Lung cancer screening using low-
175 dose spiral CT: results of baseline and 1-year follow-up studies. *Chest*. 2002;122(1):15-20.
- 176 13. Henschke CI, Yankelevitz DF, McCauley DI, et al. CT screening for lung cancer: Diagnoses resulting from
177 the New York Early Lung Cancer Action Project. *Radiology*. 2007;243(1):239-249.
- 178 14. Novello S, Fava C, Borasio P, et al. Three-year findings of an early lung cancer detection feasibility study
179 with low-dose spiral computed tomography in heavy smokers. *Ann Oncol*. 2005;16(10):1662-1666.
- 180 15. Aberle DR, DeMello S, Berg CD, et al. Results of the two incidence screenings in the National Lung
181 Screening Trial. *N Engl J Med*. 2013;369(10):920-931.
- 182 16. De Koning HJ, Van Der Aalst CM, De Jong PA, et al. Reduced lung-cancer mortality with volume CT
183 screening in a randomized trial. *N Engl J Med*. 2020;382(6):503-513.
- 184 17. Chong S, Kyung SL, Myung JC, et al. Lung cancer screening with low-dose helical CT in Korea:
185 Experiences at the Samsung Medical Center. *J Korean Med Sci*. 2005;20(3):402-408.
- 186 18. Cilli A, Ozkaynak C, Onur R, et al. Lung cancer detection with low-dose spiral computed tomography in
187 chronic obstructive pulmonary disease patients. *Acta Radiol*. 2007;48(4):405-411.
- 188 19. Kassem K, Shapiro M, Gorenstein L, Patel K, Laird C. Evaluation of high-risk pulmonary nodules and
189 pathologic correlation in patients enrolled in a low-dose computed tomography (LDCT) program. *J*.
190 2019;11(4):1165-1169.
- 191 20. Kerpel-Fronius A, Megyesfalvi Z, Markoczy Z, et al. HUNCHEST-II contributes to a shift to earlier-stage
192 lung cancer detection: final results of a nationwide screening program. *Eur Radiol*. 2024;34(5):3462-3470.
- 193 21. Kim YW, Kang HR, Kwon BS, et al. Low-dose chest computed tomographic screening and invasive
194 diagnosis of pulmonary nodules for lung cancer in never-smokers. *Eur Respir J*. 2020;56(5):11.
- 195 22. Liang D, Shi J, Li D, Wu S, Jin J, He Y. Participation and Yield of a Lung Cancer Screening Program in
196 Hebei, China. *Front*. 2021;11:795528.

23. Liang X, Kong Y, Shang H, et al. Computed tomography findings, associated factors, and management of pulmonary nodules in 54,326 healthy individuals. *J Cancer Res Ther.* 2022;18(7):2041-2048.
24. MacRedmond R, McVey G, Lee M, et al. Screening for lung cancer using low dose CT scanning: results of 2 year follow up. *Thorax.* 2006;61(1):54-56.
25. McWilliams A, Tammemagi MC, Mayo JR, et al. Probability of cancer in pulmonary nodules detected on first screening CT. *N Engl J Med.* 2013;369(10):910-919.
26. Pedersen JH, Ashraf H, Dirksen A, et al. The Danish randomized lung cancer CT screening trial--overall design and results of the prevalence round. *J Thorac Oncol.* 2009;4(5):608-614.
27. Pinsky P, Gierada DS. Long-term cancer risk associated with lung nodules observed on low-dose screening CT scans. *Lung Cancer.* 2020;139:179-184.
28. Roberts HC, Patsios D, Paul NS, et al. Lung cancer screening with low-dose computed tomography: Canadian experience. *Can Assoc Radiol J.* 2007;58(4):225-235.
29. White LJ, Kaur A, Lapel RT, et al. Lung Cancer Screening at a Military Treatment Facility: A Retrospective Review. *Mil Med.* 2020;185(5-6):e864-e869.
30. Wilson DO, Weissfeld JL, Fuhrman CR, et al. The Pittsburgh Lung Screening Study (PLuSS): outcomes within 3 years of a first computed tomography scan. *Am J Respir Crit Care Med.* 2008;178(9):956-961.
31. Xiao H, Shi Z, Zou Y, et al. One-off low-dose CT screening of positive nodules in lung cancer: A prospective community-based cohort study. *Lung Cancer.* 2023;177:1-10.
32. Yang W, Qian F, Teng J, et al. Community-based lung cancer screening with low-dose CT in China: Results of the baseline screening. *Lung Cancer.* 2018;117:20-26.
33. Chilet-Rosell E, Parker LA, Hernandez-Aguado I, et al. The determinants of lung cancer after detecting a solitary pulmonary nodule are different in men and women, for both chest radiograph and CT. *PLoS ONE.* 2019;14(9) (no pagination).
34. Gomez-Saez N, Hernandez-Aguado I, Vilar J, et al. Lung cancer risk and cancer-specific mortality in subjects undergoing routine imaging test when stratified with and without identified lung nodule on imaging study. *Eur Radiol.* 2015;25(12):3518-3527.
35. Gould MK, Tang T, Liu IL, et al. Recent Trends in the Identification of Incidental Pulmonary Nodules. *Am J Respir Crit Care Med.* 2015;192(10):1208-1214.
36. Ha FJ, Tham JLM, Paleri S, et al. Outcomes of incidental findings on multi-detector computed tomography for transcatheter aortic valve implantation assessment: A single-centre study and review of the literature. *Journal of Medical Imaging and Radiation Oncology.* 2019;63(4):446-453.
37. Hammerschlag G, Cao J, Gumm K, Irving L, Steinfert D. Prevalence of incidental pulmonary nodules on computed tomography of the thorax in trauma patients. *Intern Med J.* 2015;45(6):630-633.
38. Harthun NL, Lau CL. The incidence of pulmonary neoplasms discovered by serial computed tomography scanning after endovascular abdominal aortic aneurysm repair. *J Vasc Surg.* 2011;53(3):738-741.
39. Hinton J, Gough S, Ahmed H, et al. Frequency and impact of incidental findings on computed tomography during work-up for transcatheter aortic valve implantation: Single centre experience and review of the literature. *Br J Radiol.* 2019;92(1102) (no pagination).
40. Hussien AF, Jeudy J, Kligerman SJ, White CS. Thoracic Incidental Findings in Preoperative Computed Tomography Evaluation for Transcatheter Aortic Valve Implantation (TAVI). *J Thorac Imaging.* 2016;31(3):183-188.
41. Kan H, van der Zant FM, Wondergem M, Knol RJJ. Incidental extra-cardiac findings on ¹³N-ammonia myocardial perfusion PET/CT. *J Nucl Cardiol.* 2017;24(6):1860-1868.
42. Kasirajan K, Dayama A. Incidental findings in patients evaluated for thoracic aortic pathology using computed tomography angiography. *Ann Vasc Surg.* 2012;26(3):306-311.
43. Kelion A, Sabharwal N, Holdsworth D, et al. Clinical and economic impact of extracardiac lesions on coronary CT angiography. *Heart.* 2022;108(18):1461-1466.
44. Lee JC, Delaney FT. Prevalence and clinical significance of incidental findings on CT attenuation correction for myocardial perfusion imaging. *J Nucl Cardiol.* 2022;29(4):1813-1822.
45. Lehman SJ, Abbata S, Cury RC, et al. Significance of cardiac computed tomography incidental findings in acute chest pain. *Am J Med.* 2009;122(6):543-549.

- 248 46. Venkatesh V, You JJ, Landry DJ, Ellins ML, Sheth T. Extracardiac findings in cardiac computed
249 tomographic angiography in patients at low to intermediate risk for coronary artery disease. *Can Assoc*
250 *Radiol J*. 2010;61(5):286-290.
- 251 47. Vindum HH, Kristensen K, Christensen NL, Madsen HH, Rasmussen TR. Outcome of Incidental
252 Pulmonary Nodules in a Real-World Setting. *Clin Lung Cancer*. 2023;24(8):673-681.
- 253 48. Williams MC, Hunter A, Shah ASV, et al. Impact of noncardiac findings in patients undergoing CT coronary
254 angiography: a substudy of the Scottish computed tomography of the heart (SCOT-HEART) trial. *Eur*
255 *Radiol*. 2018;28(6):2639-2646.
- 256 49. Yorgun H, Kaya EB, Hazirolan T, et al. Prevalence of incidental pulmonary findings and early follow-up
257 results in patients undergoing dual-source 64-slice computed tomography coronary angiography. *J*
258 *Comput Assist Tomogr*. 2010;34(2):296-301.
- 259 50. Zanon M, Pacini GS, de Souza VVS, et al. Early detection of lung cancer using ultra-low-dose computed
260 tomography in coronary CT angiography scans among patients with suspected coronary heart disease.
261 *Lung Cancer*. 2017;114:1-5.
- 262 51. Farjah F, Monsell SE, Smith-Bindman R, et al. Fleischner Society Guideline Recommendations for
263 Incidentally Detected Pulmonary Nodules and the Probability of Lung Cancer. *J*. 2022;19(11):1226-1235.
- 264 52. Farjah F, Monsell SE, Greenlee RT, et al. Patient and Nodule Characteristics Associated With a Lung
265 Cancer Diagnosis Among Individuals With Incidentally Detected Lung Nodules. *Chest*. 2023;163(3):719-
266 730.

Field	Content
Review Question	In adults, is there a difference in the likelihood of diagnosing lung cancer in pulmonary nodules detected by low dose computed tomography (CT) screening compared to those detected on CT scans done for other reasons?
Type of review question	Prognostic review
Objective of the review	Nodules can be detected as part of LDCT screening for lung cancer and also incidentally on CT scans done for other reasons. People are selected for screening based their lung cancer risk exceeding specific thresholds, whereas the population undergoing CT scans for other reasons will also include people at lower risk. This question seeks to determine to what extent the likelihood of lung cancer in a given nodule will differ between these two scenarios, and whether the subsequent investigation and management of nodules should differ accordingly.
Eligibility criteria – population / disease / condition / issue / domain	Adults with pulmonary nodules (18+ years of age)
Eligibility criteria – exposure(s)	Screen-detected pulmonary nodules (via low dose CT)
Eligibility criteria – reference(s)	Non-screen-detected pulmonary nodules (incidentally detected)
Outcomes and prioritisation	Lung cancer
Eligibility criteria – study design	RCTs, comparative studies, case series (>50 cases)
Other inclusion /exclusion criteria	Non-English language excluded unless full English translation Conference abstracts, Cochrane reviews, systematic reviews, reviews Cochrane reviews and systematic reviews can be referenced in the text, but CANNOT be used in a meta-analysis
Proposed sensitivity / subgroup analysis, or meta-regression	Adults with pulmonary nodules - With previous CT imaging - Without previous CT imaging

Selection process – duplicate screening / selection / analysis	Agreement should be reached between Guideline members who are working on the question. If no agreement can be reached, a decision should be made by the Guideline co-chairs. If there is still no decision, the matter should be brought to the Guideline group and a decision will be made by consensus
--	--

Methodology will depend on data type. If sensitivity / specificity data, follow as below, if tabulated data, use a narrative approach and further instruction will be given

Data management (software)	RevMan5 Pairwise meta-analyses (if data in the correct format) Evidence review/considered judgement. Storing Guideline text, tables, figures, etc. Gradeprofiler Quality of evidence assessment
Information sources – databases and dates	MEDLINE, Embase, Central Register of Controlled Trials and Cochrane Database of Systematic Reviews Restricted to articles published from 1990 onwards
Methods for assessing bias at outcome / study level	RevMan5 intervention review template (follow instructions in '<i>BTS Guideline Process Handbook – Prognostic Review (June 2020)</i>')
Methods for quantitative analysis – combining studies and exploring (in)consistency	If 3 or more relevant studies: RevMan5 for meta-analysis, heterogeneity testing and forest plots (if data appropriate) Contact BTS to discuss best method for combining data if not suitable for meta-analysis (follow instructions in '<i>BTS Guideline Process Handbook – Prognostic Review (June 2020)</i>')
Meta-bias assessment – publication bias, selective reporting bias	GRADEprofiler Intervention review quality of evidence assessment for each outcome (follow instructions in '<i>BTS Guideline Process Handbook – Prognostic Review (June 2020)</i>')
Rationale / context – what is known	LDCT screening is restricted to people at higher risk of lung cancer, whereas people having CT scans for other reasons (on which nodules may be detected) will include people at lower risk of lung cancer. The chance of being diagnosed with a malignant nodule is therefore likely to be higher in screening than on scans done for other reasons. There are features on a CT scan which influence the likelihood of a nodule being malignant, but this question seeks to determine the extent to which the reason for the scan itself (screening versus non-screening) influences the likelihood of cancer independent of the nodule/scan findings. This is important in determining whether investigation and management of pulmonary nodules should differ between these two scenarios.

272

273

274

276 **Q2** In adults with pulmonary nodules, is there a difference in the likelihood of diagnosing lung
 277 cancer between patients with or without a previous history of non-lung cancer?

278 **Contents**

279	Question Evidence Review	13
280	Background	13
281	Outcome	13
282	Evidence Review	13
283	Evidence Statement	14
284	Recommendation	14
285	Research Recommendation	14
286	Risk of bias summary	15
287	GRADE analysis	15
288	References	15
289	Question Protocol	17

290

291 **Question 2 Evidence Review**

292 **Q2 In adults with pulmonary nodules, is there a difference in the likelihood of diagnosing lung**
293 **cancer between patients with or without a previous history of non-lung cancer?**

294 **Background**

295 Malignant pulmonary nodules are most commonly primary lung cancer, but on occasions they may be due to
296 metastatic spread or recurrence of a non-lung cancer, especially when a patient has a previous history of non-
297 lung cancer. Currently it is unclear if a different diagnostic approach is needed in these patients. This review
298 aims to determine if a previous history of non-lung cancer influences the likelihood of diagnosing lung cancer
299 in a pulmonary nodule.

300 **Outcome**

301 Lung cancer

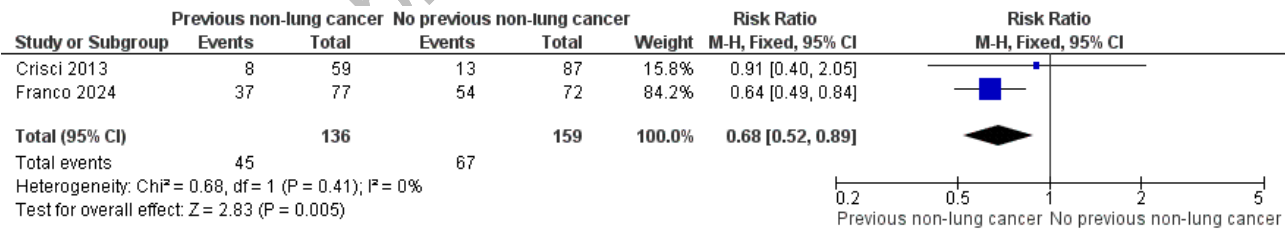
302 **Evidence Review**

303 The initial literature search identified 76 potentially relevant papers, and 25 papers were deemed relevant to
304 the review.¹⁻²⁵ The available evidence was limited and largely derived from small observational studies, with
305 only two comparative studies suitable for meta-analysis. Many studies lacked pathological confirmation of
306 malignancy or combined multiple histological subtypes without clear reporting, limiting interpretation of the
307 data. In several studies it was also difficult to determine whether pulmonary nodules represented primary lung
308 cancer or metastatic disease from a previous malignancy.

309 **Lung cancer**

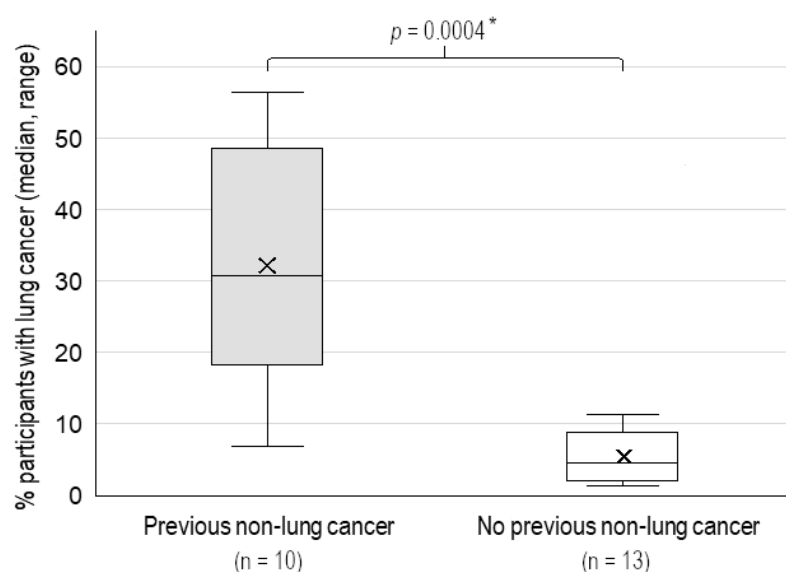
310 Two studies reported on the likelihood of a pulmonary nodule being cancerous following a previous history of
311 non-lung cancer, or no previous history of non-lung cancer.^{1,2} Meta-analysis showed that the likelihood of lung
312 cancer was slightly greater in the pulmonary nodule group with a previous history of non-lung cancer (421 per
313 1000 patients) compared with the no previous history of non-lung cancer group (287 per 1000 patients (219 to
314 375)) (data shown in Figure Q2a).

315 Figure Q2a: Comparison of the likelihood of a pulmonary nodule being cancerous in subjects with and without
316 prior non-lung cancer



317
318 Twenty-five single arm studies also reported on pulmonary nodule malignancy following a previous history of
319 non-lung cancer, or no previous history of non-lung cancer.³⁻²⁵ 10 studies reported on pulmonary nodule
320 malignancy following a previous history of non-lung cancer³⁻¹² and 13 studies reported on pulmonary nodule
321 malignancy following no previous history of non-lung cancer¹³⁻²⁵. Studies which did not declare if participants
322 had a previous history of non-lung cancer were excluded. A summary of the data is shown in Figure Q2b and
323 Table Q2a, and shows a significantly greater likelihood of lung cancer in participant with a previous history of
324 non-lung cancer ($p = 0.0004$, Mann-Whitney U test).

327 Figure Q2b: Comparison of the likelihood of a pulmonary nodule being cancerous in subjects with and without
 328 prior non-lung cancer



329
 330 * Mann-Whitney U Test

331 Table Q2a: Summary of the likelihood of a pulmonary nodule being cancerous in subjects with and without
 332 prior non-lung cancer

% participants with lung cancer						
With previous non-lung cancer			Without previous non-lung cancer			p
Mean ± SD	Median [IQR]	n	Mean ± SD	Median [IQR]	n	
32.2 ± 17.0	30.7 [18.3, 48.5]	10 ³⁻¹²	6.6 ± 4.2	5.4 [2.4, 10.6]	13 ¹³⁻²⁵	0.0004

333 * Mann-Whitney U Test
 334 IQR – interquartile range; n – number of studies; SD – standard deviation

335
 336 **Evidence Statement**

337 A previous history of non-lung cancer appears to increase the likelihood of diagnosing lung cancer in a
 338 pulmonary nodule. (**Very low**)

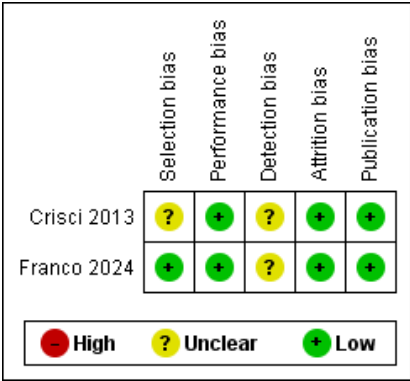
339 **Recommendation**

- 340 ➤ For patients with a pulmonary nodule identified on a CT scan, information about a previous history of non-
 341 lung cancer should be sought. (**Conditional**)

342
 343 **Research Recommendation**

- 344 ▪ Further research is needed to determine if a previous history of non-lung cancer independently increases
 345 the likelihood of pulmonary nodule being a primary lung cancer.

346
 347



349
350
351
352
353

GRADE analysis

In adults with pulmonary nodules, is there a difference in the likelihood of diagnosing lung cancer between patients with or without a previous history of non-lung cancer?					
Population: Adults (18+) with pulmonary nodules					
Exposure: Previous history of non-lung cancer					
Referent: No previous history of non-lung cancer					
Outcome	Number of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects		Quality of the Evidence (GRADE)
			No biopsy	Pre-treatment biopsy	
Lung cancer	295 (2 studies)	RR 0.68 (0.52 to 0.89)	421 per 1000	287 per 1000 (219 to 375)	⊕○○○ VERY LOW ^{a,b,c}
CI: Confidence interval					
Explanations					
a. Some risk of bias across the studies					
b. Some inconsistency across the studies					
c. Some imprecision, CIs cross one MID					

354
355
356
357
358

References

359 1. Crisci R, Divisi D. Clinical management of solitary pulmonary micronodule: a pilot study. *Arch*
360 *Bronconeumol (Engl Ed)*. 2013;49(3):94-98.

361 2. Franco J, Galan G, Bondia E, et al. Indeterminate pulmonary nodules and prior malignancy: survival and
362 recurrence after surgery in newly diagnosed stage I non-small cell lung cancer. *J*. 2024;16(5):2757-2766.

363 3. Caparica R, Mak MP, Rocha CH, et al. Pulmonary nodules in patients with nonpulmonary cancer: not
364 always metastases. *J*. 2016;2(3):138-144.

365 4. Khokhar S, Vickers A, Moore MS, Mironov S, Stover DE, Feinstein MB. Significance of non-calcified
366 pulmonary nodules in patients with extrapulmonary cancers. *Thorax*. 2006;61(4):331-336.

367 5. Lee JE, Jeong WG, Kim YH. Differentiation of primary lung cancer from solitary lung metastasis in patients
368 with colorectal cancer: a retrospective cohort study. *World J Surg Oncol*. 2021;19(1):28.

- 369 6. Nakadate A, Nakadate M, Sato Y, et al. Predictors of primary lung cancer in a solitary pulmonary lesion
370 after a previous malignancy. *Gen Thorac Cardiovasc Surg.* 2017;65(12):698-704.
- 371 7. O JH, Yoo le R, Kim SH, Sohn HS, Chung SK. Clinical significance of small pulmonary nodules with little
372 or no 18F-FDG uptake on PET/CT images of patients with nonthoracic malignancies. *J Nucl Med.*
373 2007;48(1):15-21.
- 374 8. O'Dwyer E, Halpenny DF, Ginsberg MS. Lung cancer screening in patients with previous malignancy: Is
375 this cohort at increased risk for malignancy? *Eur Radiol.* 2021;31(1):458-467.
- 376 9. Rena O, Papalia E, Ruffini E, et al. The role of surgery in the management of solitary pulmonary nodule in
377 breast cancer patients. *Eur J Surg Oncol.* 2007;33(5):546-550.
- 378 10. Rena O, Davoli F, Boldorini R, et al. The solitary pulmonary nodule in patients with previous cancer history:
379 results of surgical treatment. *Eur J Surg Oncol.* 2013;39(11):1248-1253.
- 380 11. Sakamoto M, Murakawa T, Kitano K, Murayama T, Tsuchiya T, Nakajima J. Resection of solitary
381 pulmonary lesion is beneficial to patients with a history of malignancy. *Ann Thorac Surg.* 2010;90(6):1766-
382 1771.
- 383 12. Smyth EC, Hsu M, Panageas KS, Chapman PB. Histology and outcomes of newly detected lung lesions
384 in melanoma patients. *Ann Oncol.* 2012;23(3):577-582.
- 385 13. Blanchon T, Brechot JM, Grenier PA, et al. Baseline results of the Depiscan study: A French randomized
386 pilot trial of lung cancer screening comparing low dose CT scan (LDCT) and chest X-ray (CXR). *Lung*
387 *Cancer.* 2007;58(1):50-58.
- 388 14. Henschke CI, McCauley DI, Yankelevitz DF, et al. Early lung cancer action project: a summary of the
389 findings on baseline screening. *Oncologist.* 2001;6(2):147-152.
- 390 15. Henschke CI, Yankelevitz DF, McCauley DI, et al. CT screening for lung cancer: Diagnoses resulting from
391 the New York Early Lung Cancer Action Project. *Radiology.* 2007;243(1):239-249.
- 392 16. Kim YW, Kang HR, Kwon BS, et al. Low-dose chest computed tomographic screening and invasive
393 diagnosis of pulmonary nodules for lung cancer in never-smokers. *Eur Respir J.* 2020;56(5):11.
- 394 17. MacRedmond R, McVey G, Lee M, et al. Screening for lung cancer using low dose CT scanning: results
395 of 2 year follow up. *Thorax.* 2006;61(1):54-56.
- 396 18. Markowitz SB, Miller A, Miller J, et al. Ability of low-dose helical CT to distinguish between benign and
397 malignant noncalcified lung nodules. *Chest.* 2007;131(4):1028-1034.
- 398 19. Miller DL, Mayfield WR, Luu TD, et al. Community-based multidisciplinary computed tomography
399 screening program improves lung cancer survival. *Ann Thorac Surg.* 2016;101(5):1864-1869.
- 400 20. Nawa T, Nakagawa T, Mizoue T, et al. Long-term prognosis of patients with lung cancer detected on low-
401 dose chest computed tomography screening. *Lung Cancer.* 2012;75(2):197-202.
- 402 21. Novello S, Fava C, Borasio P, et al. Three-year findings of an early lung cancer detection feasibility study
403 with low-dose spiral computed tomography in heavy smokers. *Ann Oncol.* 2005;16(10):1662-1666.
- 404 22. Pinsky P, Gierada DS. Long-term cancer risk associated with lung nodules observed on low-dose
405 screening CT scans. *Lung Cancer.* 2020;139:179-184.
- 406 23. Roberts HC, Patsios D, Paul NS, et al. Lung cancer screening with low-dose computed tomography:
407 Canadian experience. *Can Assoc Radiol J.* 2007;58(4):225-235.
- 408 24. Shan W, Chen Z, Wei D, Li M, Qian L. Lung cancer screening with low-dose computed tomography at a
409 tertiary hospital in Anhui, China and secondary analysis of trial data. *Br J Radiol.* 2021;94(1118) (no
410 pagination).
- 411 25. Xiao H, Shi Z, Zou Y, et al. One-off low-dose CT screening of positive nodules in lung cancer: A prospective
412 community-based cohort study. *Lung Cancer.* 2023;177:1-10.

Field	Content
Review Question	In adults with pulmonary nodules, is there a difference in the likelihood of diagnosing lung cancer between patients with or without a previous history of non-lung cancer?
Type of review question	Prognostic review
Objective of the review	Malignant pulmonary nodules are most commonly primary lung cancer, but on occasions may be due to metastatic spread/recurrence of a non-lung cancer especially when a patient has a previous history of non-lung cancer. This question seeks to determine the extent to which a previous history of non-lung cancer influences the likelihood of diagnosing lung cancer in a nodule, and therefore whether a different diagnostic approach is required in such patients.
Eligibility criteria – population / disease / condition / issue / domain	Adults with pulmonary nodules (18+ years of age)
Eligibility criteria – exposure(s)	A previous history of non-lung cancer
Eligibility criteria – reference(s)	No previous history of non-lung cancer
Outcomes and prioritisation	Lung cancer
Eligibility criteria – study design	RCTs, comparative studies, case series (>50 cases)
Other inclusion /exclusion criteria	Non-English language excluded unless full English translation Conference abstracts, Cochrane reviews, systematic reviews, reviews Cochrane reviews and systematic reviews can be referenced in the text, but CANNOT be used in a meta-analysis
Proposed sensitivity / subgroup analysis, or meta-regression	None

Selection process – duplicate screening / selection / analysis	Agreement should be reached between Guideline members who are working on the question. If no agreement can be reached, a decision should be made by the Guideline co-chairs. If there is still no decision, the matter should be brought to the Guideline development group, and a decision will be made by consensus.
--	--

Methodology will depend on data type. If sensitivity / specificity data, follow as below, if tabulated data, use a narrative approach and further instruction will be given

Data management (software)	RevMan5 Pairwise meta-analyses (if data in the correct format) Evidence review/considered judgement. Storing Guideline text, tables, figures, etc. Gradeprofiler Quality of evidence assessment
Information sources – databases and dates	MEDLINE, Embase, Central Register of Controlled Trials and Cochrane Database of Systematic Reviews Restricted to articles published from 1990 onwards
Methods for assessing bias at outcome / study level	RevMan5 intervention review template (follow instructions in '<i>BTS Guideline Process Handbook – Prognostic Review (June 2020)</i>')
Methods for quantitative analysis – combining studies and exploring (in)consistency	If 3 or more relevant studies: RevMan5 for meta-analysis, heterogeneity testing and forest plots (if data appropriate) Contact BTS to discuss best method for combining data if not suitable for meta-analysis (follow instructions in '<i>BTS Guideline Process Handbook – Prognostic Review (June 2020)</i>')
Meta-bias assessment – publication bias, selective reporting bias	GRADEprofiler Intervention review quality of evidence assessment for each outcome (follow instructions in '<i>BTS Guideline Process Handbook – Prognostic Review (June 2020)</i>')
Rationale / context – what is known	Pulmonary nodules are either benign or malignant; malignant nodules are most commonly primary lung cancer but sometimes will represent metastatic recurrence of a previously diagnosed non-lung cancer. This question seeks to determine the extent to which a previous diagnosis of non-lung cancer will influence the likelihood of a pulmonary nodule being a lung cancer. This may depend on the type of previous non-lung cancer, and the time since diagnosis. The overall aim is to determine whether a different diagnostic approach is needed in these patients.

416

417

418

420 **Q3** **What is the diagnostic accuracy of imaging tests, and the optimal strategy for image utilisation**
 421 **for diagnosing lung cancer in a solid pulmonary nodule?**

422 **Contents**

423	Question Evidence Review	21
424	Background	21
425	Outcomes	21
426	Evidence Review	21
427	Evidence Statements	24
428	Recommendations	24
429	Research Recommendations	25
430	Algorithms	26
431	Solid nodule diagnostic pathway	26
432	Solid nodule follow-up pathway	27
433	New solid nodule follow-up pathway	28
434	Meta-analyses	29
435	Nodule diameter	29
436	Nodule volume	35
437	Upper lobe location	35
438	Spiculation	36
439	FDG-avidity	37
440	Area under the curve (AUC)	38
441	Nodule diameter	39
442	Upper lobe location	40
443	Spiculation	41
444	FDG-avidity	41
445	Risk of bias summaries	42
446	GRADE analyses	43
447	Nodule diameter	43
448	Upper lobe location	43
449	Spiculation	44
450	FDG-avidity	44
451	Recommendation table	45
452	FDG-avidity	45

453 **References** 46

454 **Question Protocol** 48

455
456
457
458
459
460
461
462
463
464
465
466
467
468
469
470
471
472
473
474
475
476
477
478
479
480
481
482
483
484
485
486
487
488
489
490
491
492
493
494
495
496
497
498
499
500
501
502
503
504
505
506
507
508

Draft For Public Consultation October 2026

509 Question 3 Evidence Review

510 Q3 What is the diagnostic accuracy of imaging tests, and the optimal strategy for image utilisation 511 for diagnosing lung cancer in a solid pulmonary nodule?

512 Background

513 Solid pulmonary nodules identified at baseline (prevalence) imaging may represent a range of pathologies,
514 from benign to malignant, and therefore not all solid pulmonary nodules require immediate invasive diagnostic
515 procedures. As the methods for assessing imaging tests can vary (for example, how pulmonary nodules are
516 measured), this review aims determine the optimal strategy for image utilisation for diagnosing lung cancer in
517 a solid pulmonary nodule.

518 Outcomes

519 Nodule diameter; nodule volume; upper lobe location; spiculation; FDG-avidity; Brock risk score; Herder risk
520 score; Mayo risk score; Veterans Affairs (VA) risk score; UK Lung Cancer Screening (UKLS) risk score

521 Evidence Review

522 The initial literature search identified 554 potentially relevant papers, and 28 papers were deemed relevant to
523 the review.¹⁻²⁸

524 There were not enough data to consider all imaging types individually (computed tomography (CT), positron
525 emission tomography computed tomography (PET-CT) and magnetic resonance imaging (MRI)), but all
526 relevant data have been included in the analyses as appropriate.

527 Nodule diameter

528 Five studies reported on the diagnostic accuracy of nodule diameter for diagnosing lung cancer in solid
529 pulmonary nodules.¹⁻⁵ As each study presented different nodule diameter cut-offs, data have been analysed
530 as appropriate.

531 All data

532 Across the studies, 13 datasets were eligible to be included in a meta-analysis to determine the diagnostic
533 accuracy of nodule diameter for diagnosing lung cancer in solid pulmonary nodules.¹⁻⁵ The pooled sensitivity
534 and pooled specificity were 0.35 [0.21, 0.51] and 0.66 [0.50, 0.80] [95% confidence intervals] respectively (data
535 shown in Figure Q3a and Table Q3a).

536 Diameter ≤ 8 mm

537 Four studies reported on nodule diameter ≤ 8 mm.^{1,3-5} Meta-analysis showed a pooled sensitivity of 0.17 [0.08,
538 0.34] and pooled specificity of 0.41 [0.27, 0.56] [95% confidence intervals] (data shown in Figure Q3b and
539 Table Q3b).

540 Diameter > 8 mm and < 20 mm

541 Four studies reported on nodule diameter between > 8 mm and approximately < 20 mm (data cut-offs varied
542 between studies).¹⁻⁴ Meta-analysis showed a pooled sensitivity of 0.69 [0.53, 0.81] and pooled specificity of
543 0.52 [0.35, 0.68] [95% confidence intervals] (data shown in Figure Q3c and Table Q3c). The estimated AUC
544 was 0.643 (Figure Q3d).

545 Diameter > 15 mm

546 Two studies reported on nodule diameter > 15 mm or > 20 mm (data cut-offs varied between studies).^{2,5} Meta-
547 analysis showed a pooled sensitivity of 0.51 [0.35, 0.71] and pooled specificity of 0.81 [0.34, 0.96] [95%
548 confidence intervals] (data shown in Figure Q3e and Table Q3d).

549 Diameter > 10 mm

550 Two studies reported on nodule diameter > 10 mm (data cut-offs were > 10 mm for both datasets).^{2,5} Meta-
551 analysis showed a pooled sensitivity of 0.93 [0.68, 0.97] and pooled specificity of 0.52 [0.14, 0.86] [95%
552 confidence intervals] (data shown in Figure Q3f and Table Q3e).

553 Diameter > 8 mm

554 Five studies reported on nodule diameter > 8 mm or > 10 mm.¹⁻⁵ As data cut-offs varied between the studies,
555 to increase the number of datasets in the analysis, nodule diameter > 8 mm (3 studies)^{1,3,4} and nodule diameter
556 > 10 mm (2 studies)^{2,5} were included. Meta-analysis showed a pooled sensitivity of 0.86 [0.71, 0.94] and pooled
557 specificity of 0.55 [0.31, 0.78] [95% confidence intervals] (data shown in Figure Q3g and Table Q3f). The
558 estimated AUC was 0.793 (Figure Q3h).

559 A summary of all nodule diameter meta-analysis data is shown in Table Q3g.

560 Table Q3g: Comparison of the diagnostic accuracies of differing nodule diameter ranges for diagnosing lung
561 cancer in solid pulmonary nodules

Nodule diameter range	n	Sensitivity [95% CI]	Specificity [95% CI]
> 4 mm (all data)	13 ¹⁻⁵	0.35 [0.21, 0.52]	0.67 [0.50, 0.80]
≤ 8 mm	4 ^{1,3-5}	0.17 [0.08, 0.34]	0.41 [0.27, 0.56]
> 8 mm to < ≈20 mm	4 ¹⁻⁴	0.69 [0.53, 0.81]	0.52 [0.35, 0.68]
> 10 mm	2 ^{2,5}	0.93 [0.68, 0.97]	0.52 [0.14, 0.86]
> 15 mm	2 ^{2,5}	0.51 [0.35, 0.71]	0.81 [0.34, 0.96]
> 8 mm or > 10 mm	5 ¹⁻⁵	0.86 [0.71, 0.94]	0.55 [0.31, 0.78]

562 CI – confidence intervals; n – number of datasets

563 Nodule volume

564 One study reported on the diagnostic accuracy of nodule volume for diagnosing lung cancer in solid pulmonary
565 nodules.³ The data are shown in Table Q3h.

566 Table Q3h: Diagnostic accuracy of nodule volume for diagnosing lung cancer in solid pulmonary nodules

Study	Nodule volume	n	Sensitivity [95 % CI]	Specificity [95 % CI]
He 2022 ³	> 2.17 cm ³	151	0.62 [0.50, 0.72]	0.64 [0.52, 0.75]

567 Due to the lack of diagnostic accuracy data, intervention data were also considered. Two studies reported
568 nodule volume measurements in malignant and benign solid pulmonary nodules, with meta-analysis estimating
569 that malignant solid pulmonary nodules were 0.14 (0.05, 0.24) cm³ (95% confidence intervals) greater than
570 benign solid pulmonary nodules (data shown in Figure Q3i).^{3,6}

572 Upper lobe location

573 Seven studies reported on the diagnostic accuracy of upper lobe location for diagnosing lung cancer in solid
574 pulmonary nodules.^{1,2,4,7-10} Meta-analysis showed a pooled sensitivity of 0.59 [0.50, 0.68] and pooled specificity
575 of 0.55 [0.44, 0.63] [95% confidence intervals] (data shown in Figure Q3j and Table Q3i). The estimated AUC
576 was 0.590 (Figure Q3k).

577 Spiculation

578 Eight studies reported on the diagnostic accuracy of spiculation for diagnosing lung cancer in solid pulmonary
579 nodules.^{1,2,4,8,9,11,12} Meta-analysis showed a pooled sensitivity of 0.56 [0.44, 0.67] and pooled specificity of 0.74
580 [0.57, 0.85] [95% confidence intervals] (data shown in Figure Q3l and Table Q3j). The estimated AUC is 0.702
581 (Figure Q3m).

582 **FDG-avidity**

583 Nine studies reported on the diagnostic accuracy of FDG-avidity for diagnosing lung cancer in solid pulmonary
 584 nodules.¹³⁻²¹ Meta-analysis showed a pooled sensitivity of 0.84 [0.76, 0.89] and pooled specificity of 0.76 [0.66,
 585 0.83] [95% confidence intervals] (data shown in Figure Q3n and Table Q3k). The estimated AUC was 0.869
 586 (Figure Q3o).

587 **Risk calculator models (Brock, Herder, Mayo, VA and UKLS)**

588 Seven studies reported data on the Brock, Mayo, VA and/or UKLS risk calculator models.²²⁻²⁸ Data from two
 589 further studies were excluded as each was comparing an in-house risk calculator model against one, or more
 590 of the risk calculator models listed above. There were no data that could be included in a meta-analysis and
 591 no available data for the UKLS model. Sensitivity and specificity data were not available for the VA and UKLS
 592 model. Available data are shown in Table Q3l.

593 Table Q3l: Comparison of risk calculator models (Brock, Herder, Mayo, VA and UKLS) for identifying lung
 594 cancer in solid pulmonary nodules

Model	Study	Cut-off/Group	AUC	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]
Brock	Hammer 2018 ²²		0.69	-	-
	Susam 2022 ²³	>13.4	0.67	75.2 [69.1, 80.4]	51.8 [41.2, 62.2]
Herder	Perandini 2017 ²⁴		0.76	-	-
	Susam 2022 ²³	>70	0.73	74.3 [68.2, 79.6]	63.9 [53.1, 73.4]
Mayo	Hammer 2018 ²²		0.63	-	-
	Isbell 2011 ²⁵		0.78	-	-
	Perandini 2014 ²⁶		0.77	-	-
	Perandini 2016 ²⁷		0.78	-	-
	Soardi 2017 ²⁸		0.60	-	-
	Susam 2022 ²³	>29.6	0.71	68.9 [62.6, 74.6]	67.5 [56.8, 76.6]
UKLS	-		-	-	-
VA	Hammer 2018 ²²		0.60	-	-

595

596 **Risk calculator model comparison with other diagnostic tests**

597 The risk calculator model AUCs, sensitivities and specificities were compared with the other diagnostic tests
 598 (upper lobe location, spiculation, air bronchogram and bubble-like lucency) in Table Q3m.

599

600

601

602

603

604

605

606

607

608

609

610

611

612 Table Q3m: Area under the curve (AUC), sensitivity and specificity comparisons of risk calculator models
 613 (Brock, Herder, Mayo, VA and UKLS) and other Guideline diagnostic tests for identifying lung cancer in solid
 614 pulmonary nodules

Model / Test	AUC	Sensitivity (%)	Specificity (%)
Brock	0.68 ± 0.02* 22,23	75.2 ²³	51.8 ²³
Herder	0.74 ± 0.02* 23,24	74.3 ²³	63.9 ²³
Mayo	0.71 ± 0.08* 22,23,25-28	68.9 ²³	67.5 ²³
VA	0.60 ²²	-	-
Nodule diameter (> 8 mm to < ≈ 20 mm)	0.63 ¹⁻⁴	68.7 ¹⁻⁴	51.8 ¹⁻⁴
Nodule diameter (> 8 mm or > 10 mm)	0.79 ¹⁻⁵	85.9 ¹⁻⁵	55.4 ¹⁻⁵
Upper lobe location	0.59 ^{1,2,4,7-10}	58.8 ^{1,2,4,7-10}	55.0 ^{1,2,4,7-10}
Spiculation	0.70 ^{1,2,4,8,9,11,12}	55.7 ^{1,2,4,8,9,11,12}	73.6 ^{1,2,4,8,9,11,12}
FDG-avidity	0.87 ¹³⁻²¹	83.6 ¹³⁻²¹	75.7 ¹³⁻²¹

615 * Mean ± SD

616 Evidence Statements

617 Solid pulmonary nodule diameter greater than 8 mm appears to have a high sensitivity and low specificity for
 618 diagnosing lung cancer (**Low**)

619 Solid nodule FDG-avidity appears to have a high sensitivity and moderate specificity for diagnosing lung cancer
 620 (**Low**)

621 Solid nodule upper lobe location appears to have a low sensitivity and low specificity for diagnosing lung cancer
 622 (**Low**)

623 Solid nodule spiculation appears to have a low sensitivity and a moderate specificity for diagnosing lung cancer
 624 (**Very low**)

625 There is insufficient evidence to determine if nodule volume can be used for diagnosing lung cancer in a solid
 626 pulmonary nodule.

627 There is insufficient evidence to determine the diagnostic accuracy of individual risk calculator models (Brock,
 628 Herder, Mayo, VA and UKLS) for diagnosing lung cancer in a solid pulmonary nodule.

629 There is insufficient evidence to determine outcomes in “without recent relevant imaging”, “newly appeared
 630 since recent imaging”, peri-cystic lesions and consolidation solid pulmonary nodule subgroups.

631 There is insufficient evidence to consider CT, PET-CT and MRI imaging techniques separately for diagnosing
 632 lung cancer in a solid pulmonary nodule.

633 Recommendations

634 ➤ The **Solid Nodule Diagnostic Pathway**, incorporating different solid nodule characteristics, should be used
 635 for diagnosing lung cancer in solid pulmonary nodules (**Conditional** – by consensus)

636 ➤ An FDG PET-CT ((fluorodeoxyglucose positron emission tomography computed tomography) scan should
 637 be considered for diagnosing lung cancer risk in solid pulmonary nodules ≥ 8 mm (**Conditional**)

638 Research Recommendations

639 ▪ Further research is needed to confirm the diagnostic accuracy of nodule diameter size for diagnosing lung
 640 cancer in a solid pulmonary nodule

641 ▪ Further research is needed to determine the diagnostic accuracy of nodule volume for diagnosing lung
 642 cancer in a solid pulmonary nodule

- 643 ▪ Further research is needed to determine the optimal strategy for image utilisation when using CT, PET-
644 CT or MRI for diagnosing lung cancer in a solid pulmonary nodule
- 645 ▪ Further research is needed to determine the optimal strategy for image utilisation for “without recent
646 relevant imaging”, “newly appeared since recent imaging”, peri-cystic lesions and consolidation solid
647 nodule subgroups
- 648 ▪ Further research is needed to determine the diagnostic accuracy of risk calculator models (Brock, Mayo,
649 VA and/or UKLS) for diagnosing lung cancer in a solid pulmonary nodule

650

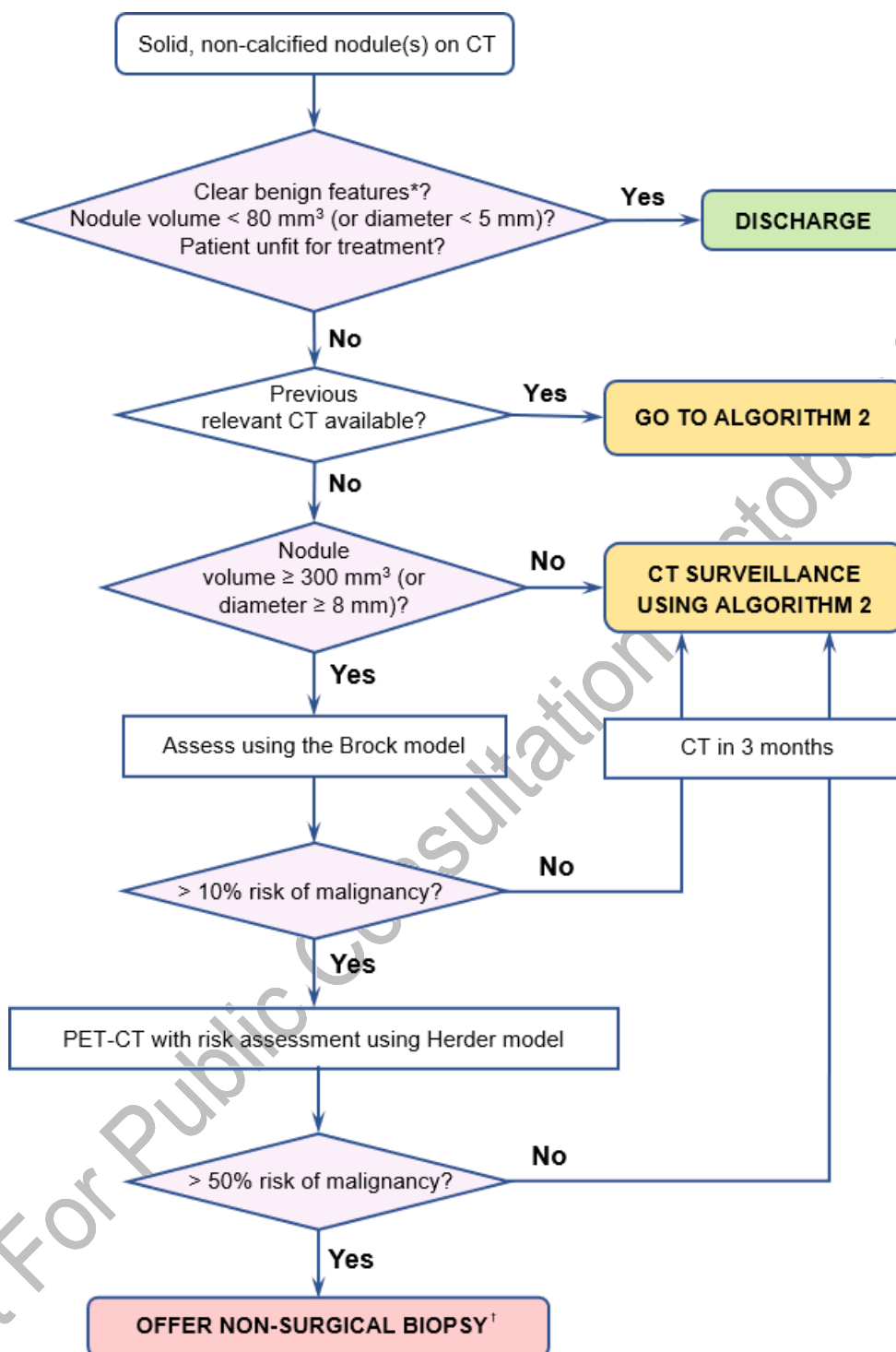
651

652

653

654

Draft For Public Consultation October 2026



656

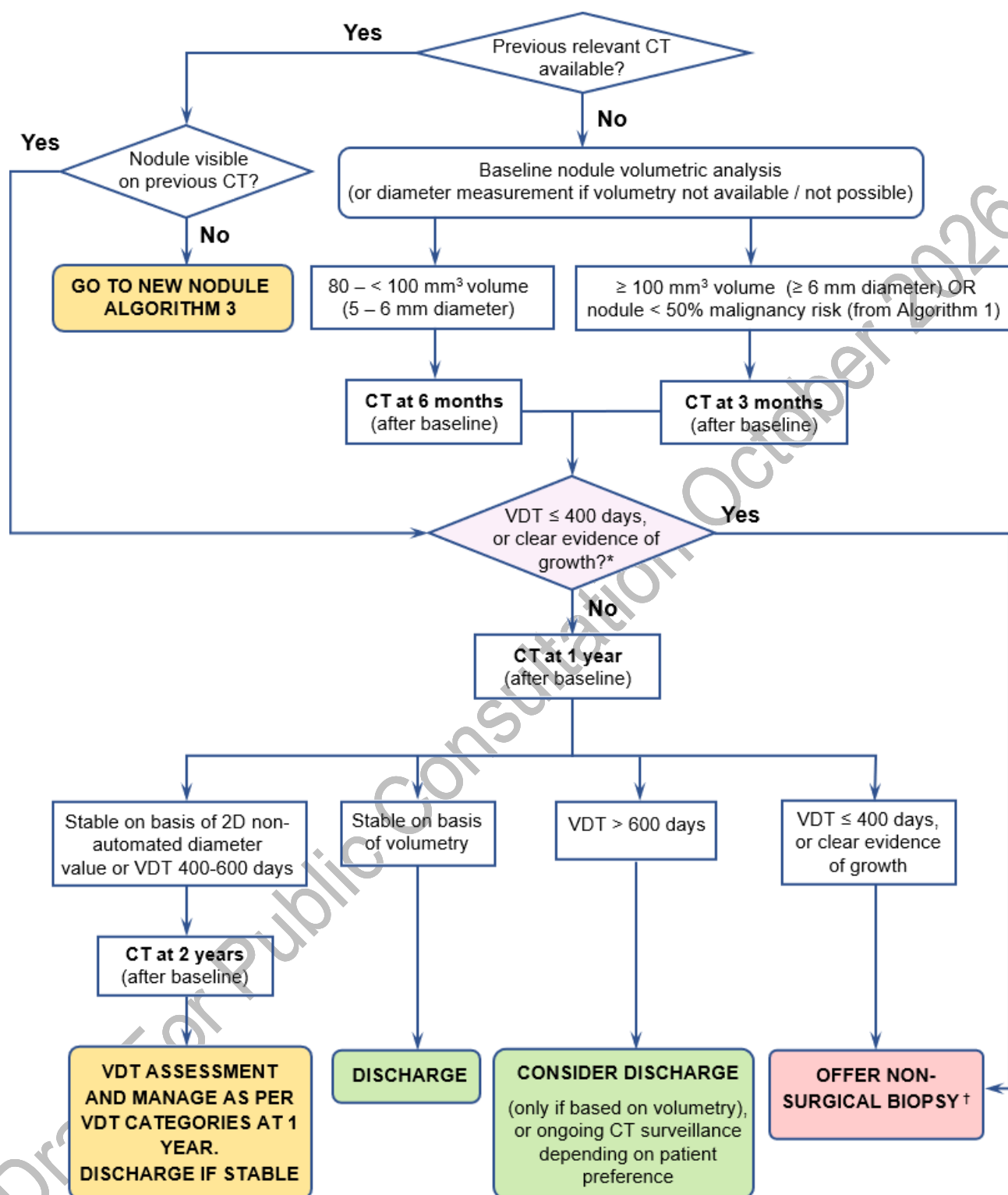
657 * e.g., hamartoma, typical benign intrapulmonary lymph node

658 † Consider definitive management without biopsy if nodule is < 2 cm and risk of malignancy is > 85%

659 CT – computed tomography; FDG-PET-CT – fluorodeoxyglucose positron emission tomography computed tomography;
660 PET-CT – positron emission tomography computed tomography.

661

662



664

665

666 * ≥ 25% increase in volume, or ≥ 2mm in diameter

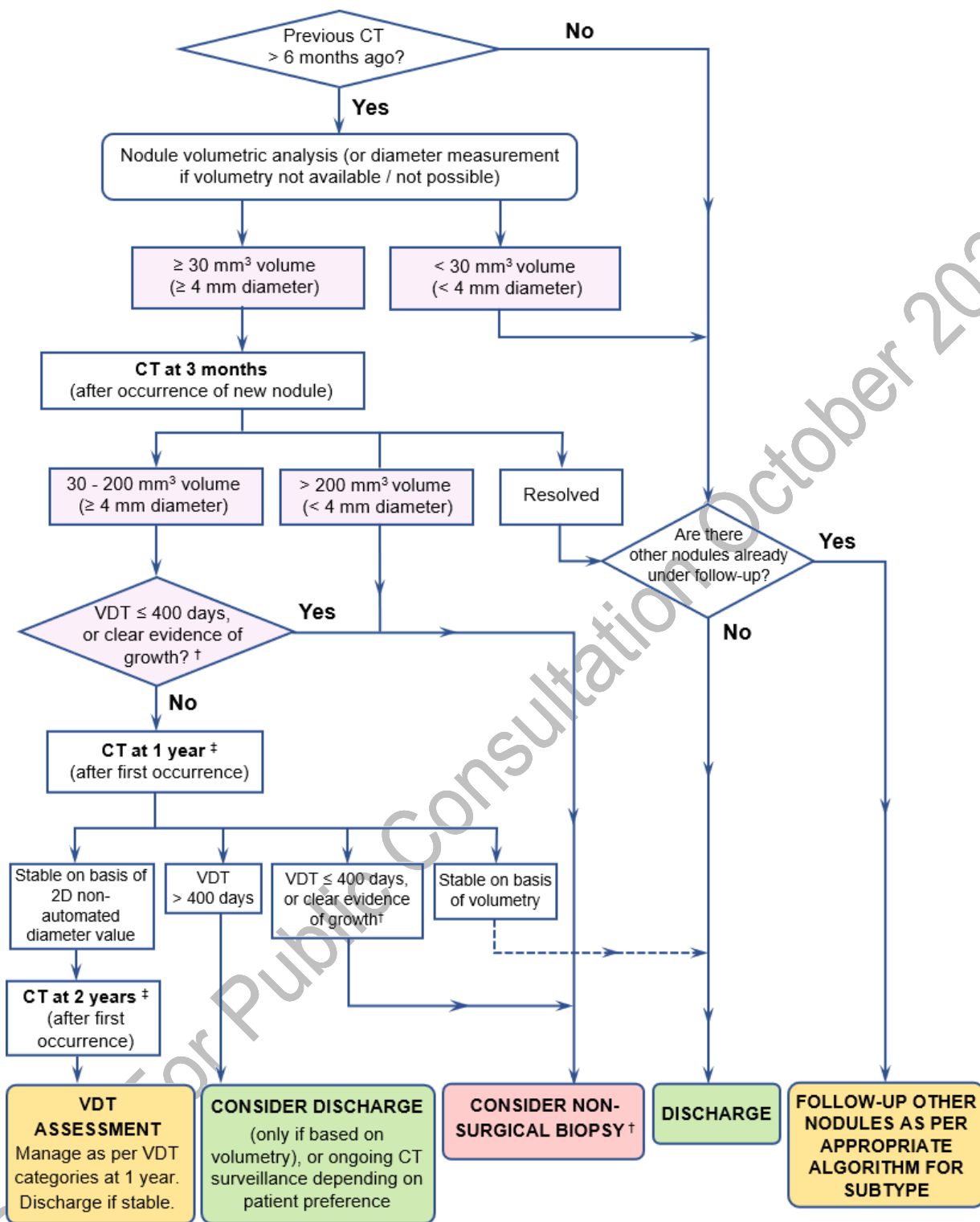
667 † Consider further CT surveillance if nodule is < 200 mm³

668 Brock and Herder models not to be used for nodule discrimination after baseline scan.

669 CT – computed tomography; VDT – volume doubling time

670 (for Algorithm 2 evidence please see 'BTS Guideline for pulmonary nodules – Online Supplementary Appendix 4')

671 **Algorithm 3 New solid nodule follow-up pathway***



672
673
674 * Nodule must be confirmed to be truly new. If nodule is newly detected but visible in retrospect, follow Algorithm 2.

† ≥ 25% increase in volume, or ≥ 2mm in diameter.

‡ If the new nodule was discovered on follow-up CTs performed for other nodules, it is acceptable to modify the surveillance timepoints in this Algorithm and Algorithm 2 to ensure that both the nodule(s) originally under surveillance and the new nodule have sufficient time to permit reliable growth assessment.

675 Brock and Herder models not to be used for nodule discrimination for new nodules.

676 CT – computed tomography; VDT – volume doubling time

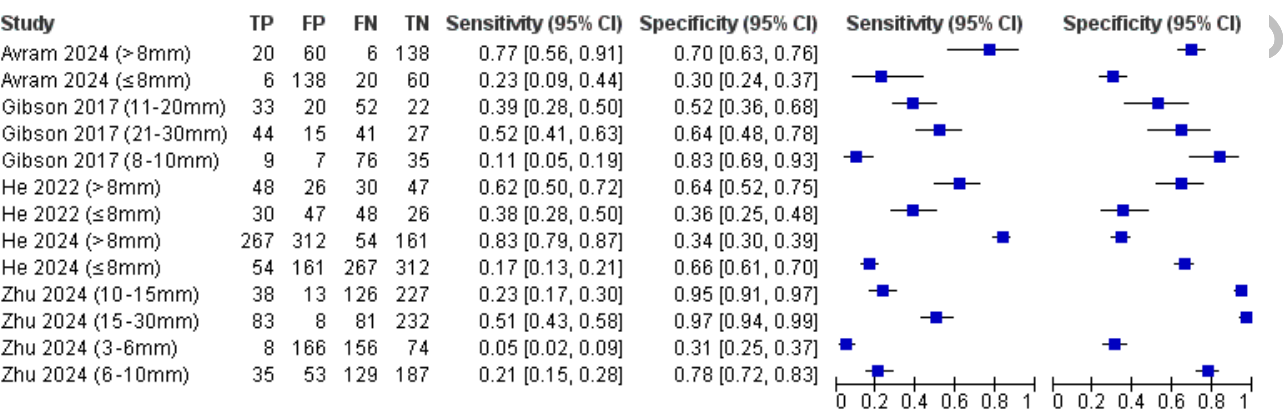
677 **Meta-analyses**

678 **Nodule diameter**

679 *All data*

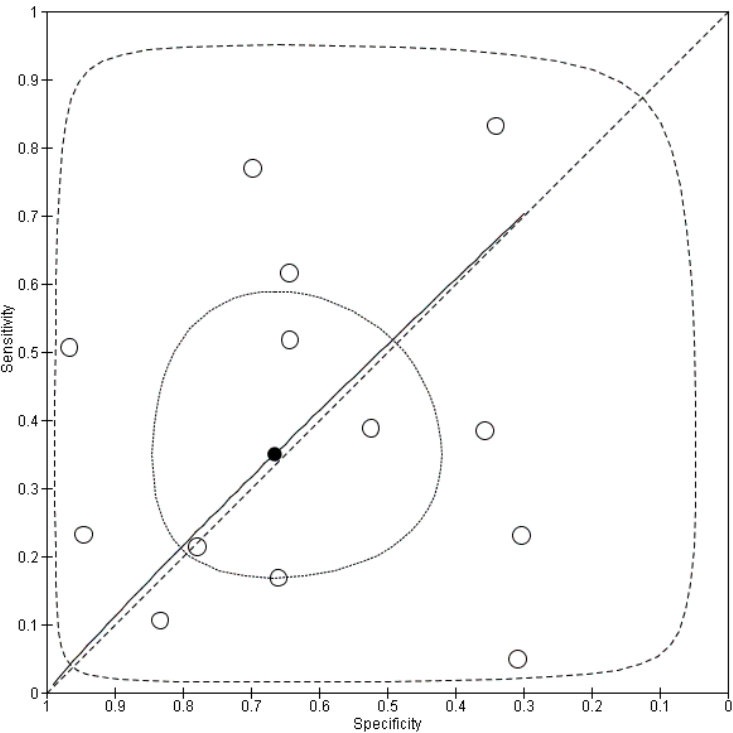
680 Figure Q3a: Forest plot and SROC plot of nodule diameter for diagnosing lung cancer in solid pulmonary
681 nodules

682 i) Forest plot



683

684 ii) SROC plot



685

686

687 Table Q3a: Pooled results of nodule diameter for diagnosing lung cancer in solid pulmonary nodules

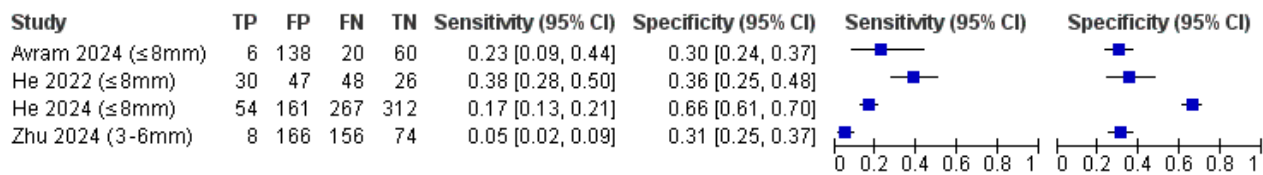
Pooled Sensitivity	0.350	[0.214, 0.515]
Pooled Specificity	0.665	[0.496, 0.800]
LR+	1.045	[0.551, 1.980]
LR-	0.977	[0.701, 1.363]
DOR	1.069	[0.405, 2.825]

688

689 Diameter ≤ 8 mm

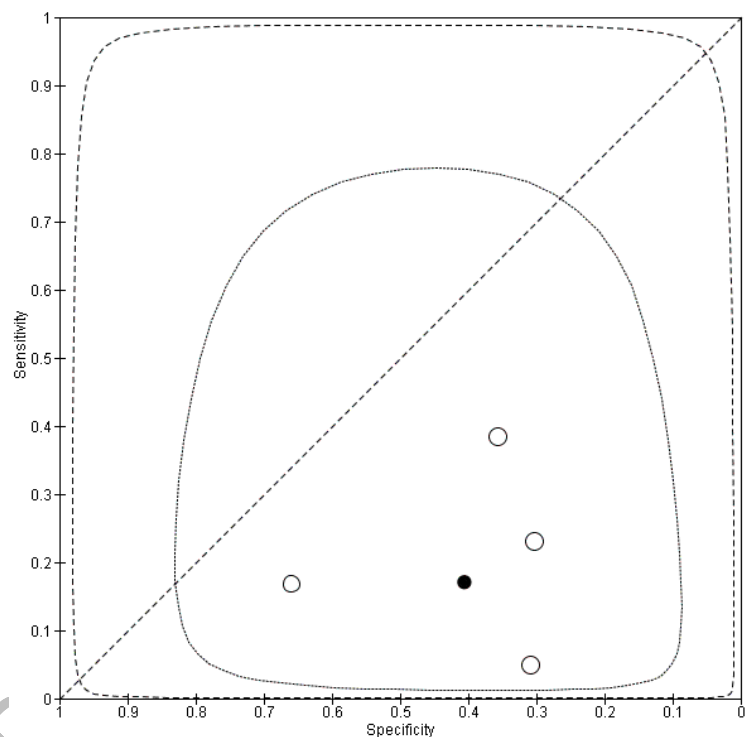
690 Figure Q3b: Forest plot and SROC plot of nodule diameter ≤ 8 mm for diagnosing lung cancer in solid
691 pulmonary nodules

692 i) Forest plot



693

694 ii) SROC plot (not enough data to determine curve)



695

696

697 Table Q3b: Pooled results of nodule diameter ≤ 8 mm for diagnosing lung cancer in solid pulmonary nodules

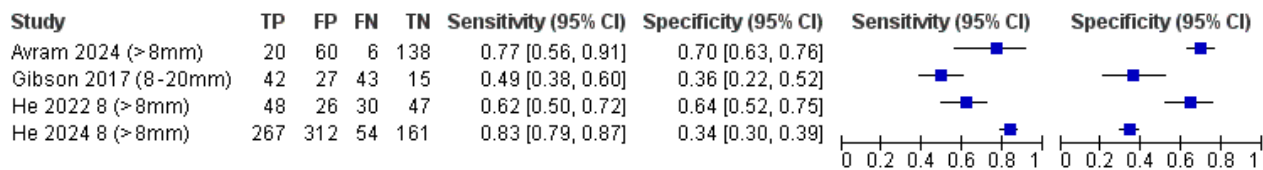
Pooled Sensitivity	0.171	[0.077, 0.337]
Pooled Specificity	0.406	[0.267, 0.561]
LR+	0.288	[0.128, 0.647]
LR-	2.043	[1.349, 3.095]
DOR	0.141	[0.045, 0.441]

698

699 Diameter > 8 mm and < 20 mm

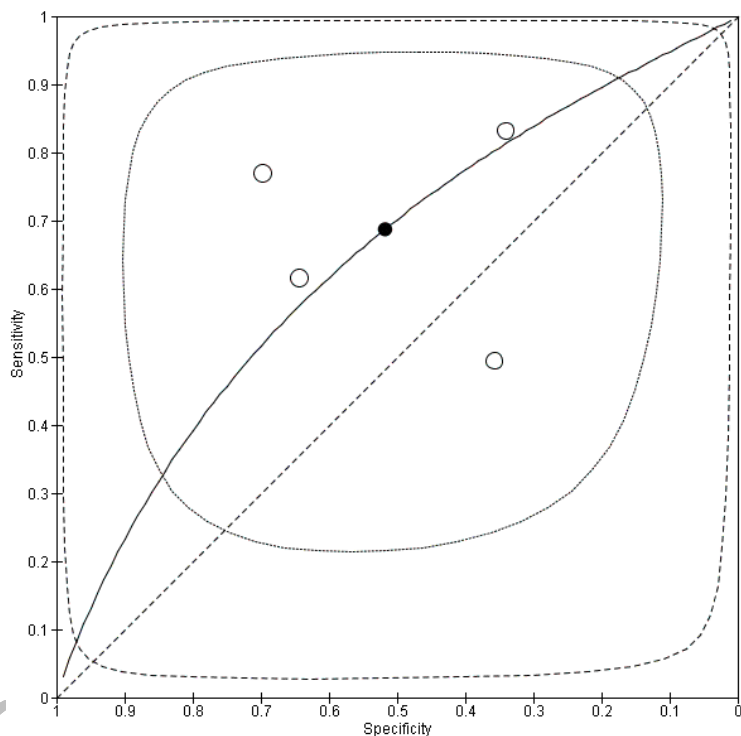
700 Figure Q3c: Forest plot and SROC plot of nodule diameter > 8 mm to approximately < 20 mm for diagnosing
701 lung cancer in solid pulmonary nodules

702 i) Forest plot



703

704 ii) SROC plot



705

706

707 Table Q3c: Pooled results of nodule diameter > 8 mm to approximately < 20 mm for diagnosing lung cancer
708 in solid pulmonary nodules

Pooled Sensitivity	0.687	[0.531, 0.810]
Pooled Specificity	0.518	[0.351, 0.681]
LR+	1.425	[0.961, 2.114]
LR-	0.604	[0.352, 1.035]
DOR	2.359	[0.950, 5.858]

709

710 *Diameter > 15 mm*

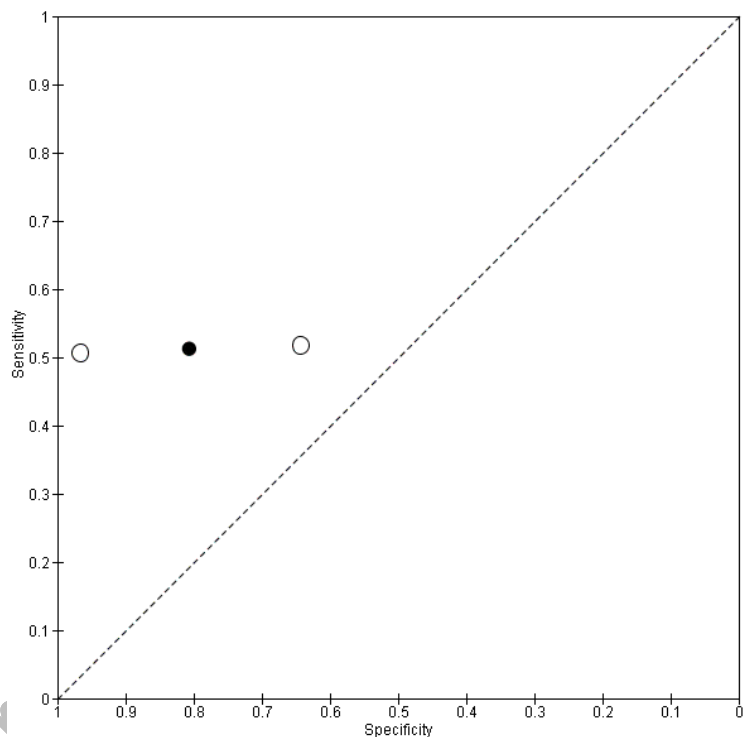
711 Figure Q3e: Forest plot and SROC plot of nodule diameter > 15 mm for diagnosing lung cancer in solid
712 pulmonary nodules

713 i) Forest plot

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Gibson 2017 (21-30mm)	44	15	41	27	0.52 [0.41, 0.63]	0.64 [0.48, 0.78]		
Zhu 2024 (15-30mm)	83	8	81	232	0.51 [0.43, 0.58]	0.97 [0.94, 0.99]		

714

715 ii) SROC plot (not enough data to determine curve, 95% confidence and 95% prediction regions)



716

717

718

719 Table Q3d: Pooled results of nodule diameter > 15 mm for diagnosing lung cancer in solid pulmonary nodules

Pooled Sensitivity	0.513	[0.354, 0.707]
Pooled Specificity	0.807	[0.336, 0.959]
LR+	2.643	[0.755, 13.264]
LR-	0.615	[0.358, 1.522]
DOR	8.179	[0.496, 31.867]

Bayesian meta-analysis, data displayed as posterior median [95% posterior interval]

720

721 Diameter > 10 mm

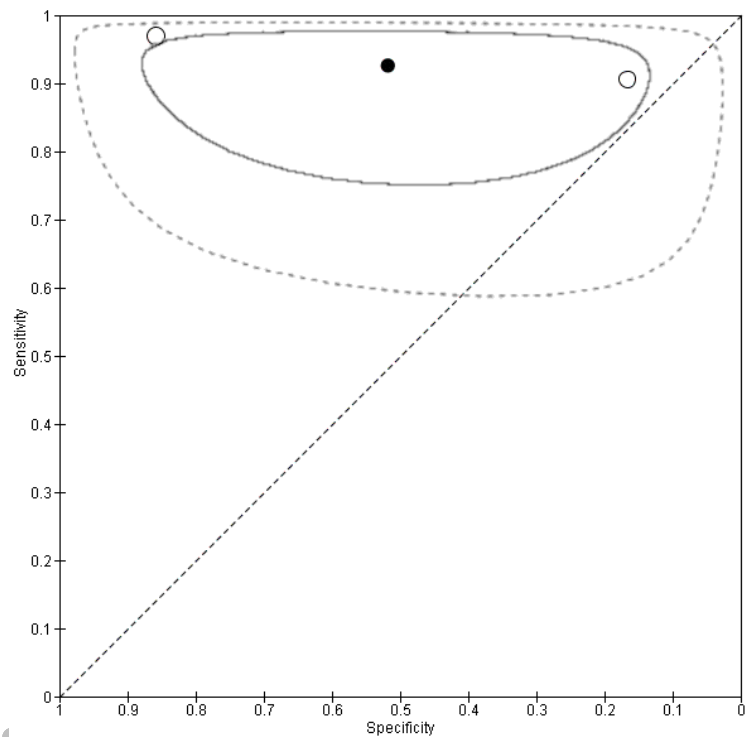
722 Figure Q3f: Forest plot and SROC plot of nodule diameter > 10 mm for diagnosing lung cancer in solid
723 pulmonary nodules

724 i) Forest plot

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Gibson 2017 (>10mm)	77	35	8	7	0.91 [0.82, 0.96]	0.17 [0.07, 0.31]		
Zhu 2024 (>10mm)	159	34	5	206	0.97 [0.93, 0.99]	0.86 [0.81, 0.90]		

725

726 ii) SROC plot (not enough data to determine curve)



727

728

729

730 Table Q3e: Pooled results of nodule diameter > 10 mm for diagnosing lung cancer in solid pulmonary nodules

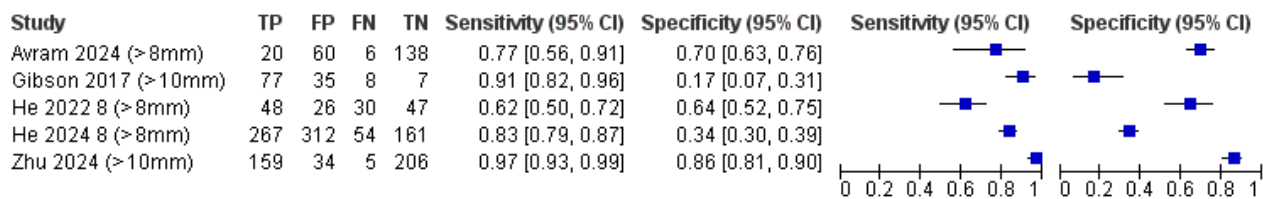
Pooled Sensitivity	0.926	[0.675, 0.970]
Pooled Specificity	0.518	[0.138, 0.859]
LR+	1.877	[0.983, 6.657]
LR-	0.155	[0.046, 1.067]
DOR	12.365	[0.913, 103.457]

Bayesian meta-analysis, data displayed as posterior median [95% posterior interval]

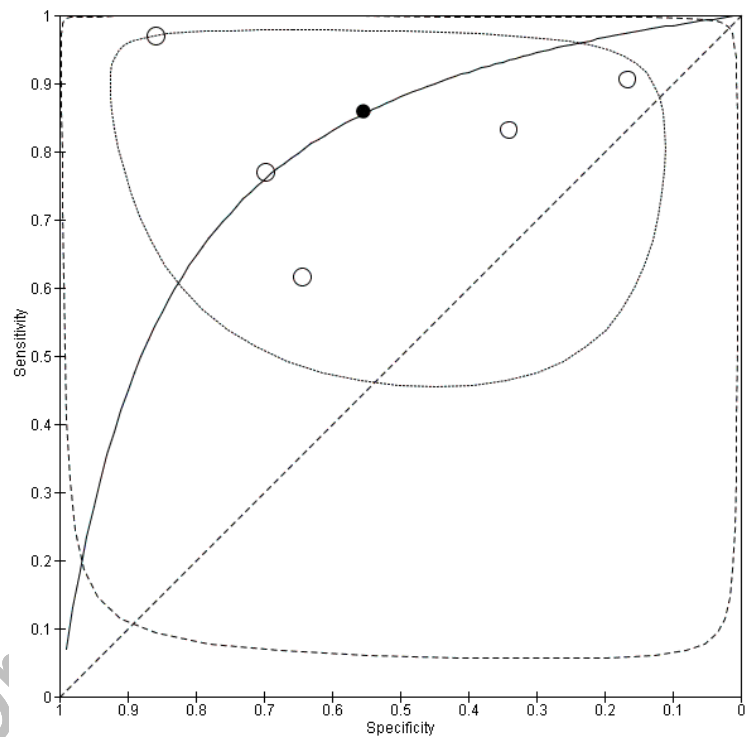
731
732
733 *Diameter > 8mm*

734 Figure Q3g: Forest plot and SROC plot of nodule diameter > 8mm or > 10 mm for diagnosing lung cancer in
735 solid pulmonary nodules

736 i) Forest plot



737
738 ii) SROC plot



741 Table Q3f: Pooled results of nodule diameter > 8mm or > 10 mm for diagnosing lung cancer in solid pulmonary
742 nodules

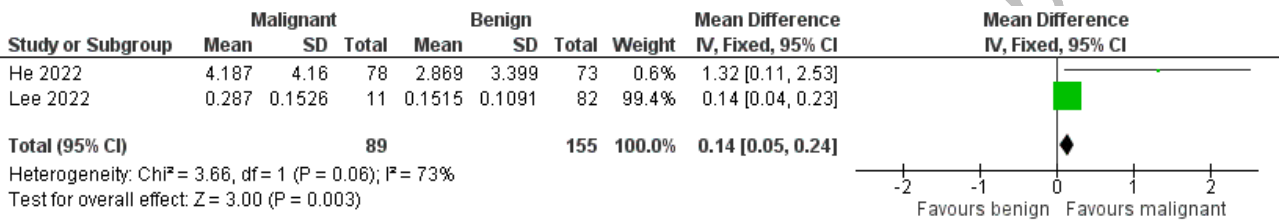
Pooled Sensitivity	0.859	[0.714, 0.937]
Pooled Specificity	0.554	[0.306, 0.777]
LR+	1.926	[1.048, 3.542]
LR-	0.254	[0.097, 0.668]
DOR	7.570	[1.712, 33.473]

743

744

745 **Nodule volume**

746 Figure Q3i: Forest plot of malignant versus benign solid pulmonary nodule volume



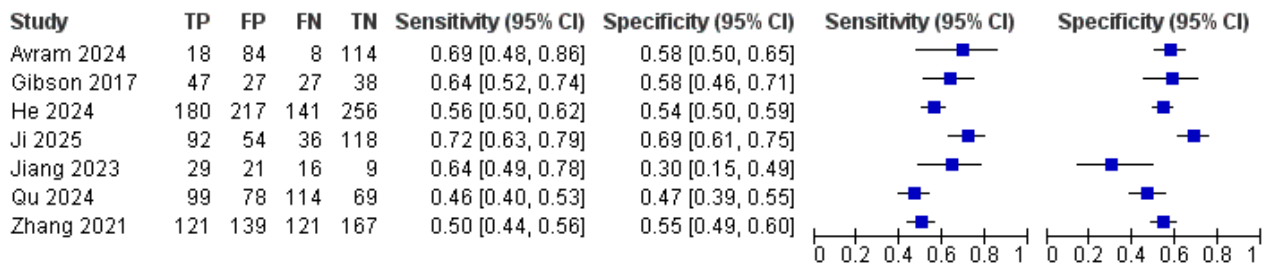
747

748

749 **Upper lobe location**

750 Figure Q3j: Forest plot and SROC plot of upper lobe location for diagnosing lung cancer in solid pulmonary
751 nodules

752 i) Forest plot



753

754

755

756

757

758

759

760

761

762

763

764

765

766

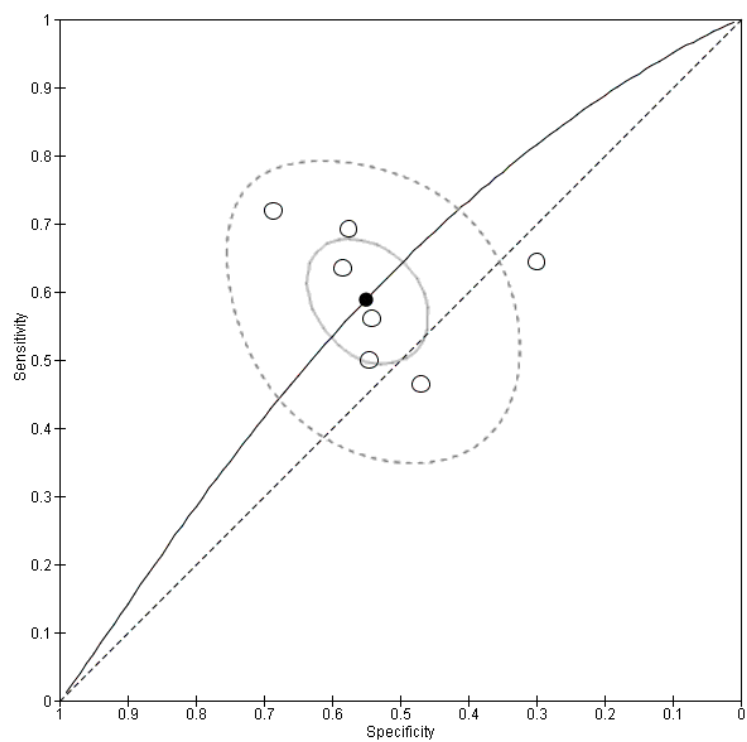
767

768

769

770

771 ii) SROC plot



772

773 Table Q3i: Pooled results of upper lobe location for diagnosing lung cancer in solid pulmonary nodules

Pooled Sensitivity	0.588	[0.502, 0.685]
Pooled Specificity	0.550	[0.445, 0.633]
LR+	1.311	[0.985, 1.711]
LR-	0.747	[0.548, 1.017]
DOR	1.757	[0.969, 3.049]

774

775

776

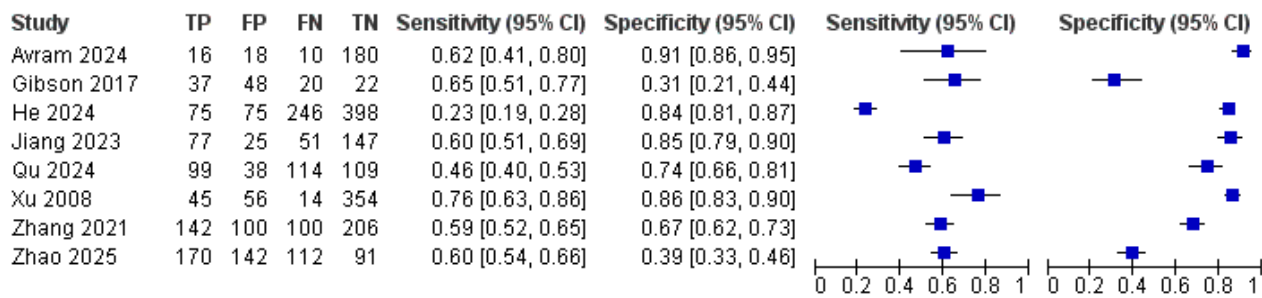
777

778

Spiculation

779 Figure Q3l: Forest plot and SROC plot of spiculation for diagnosing lung cancer in solid pulmonary nodules

780 i) Forest plot



781

782

783

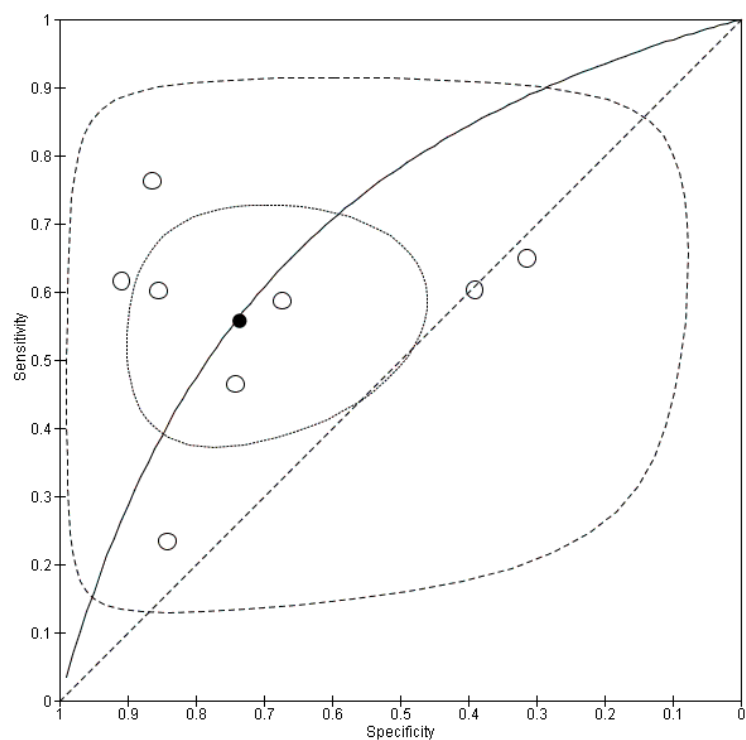
784

785

786

787

788 ii) SROC plot



789

790 Table Q3j: Pooled results of spiculation for diagnosing lung cancer in solid pulmonary nodules

Pooled Sensitivity	0.557	[0.443, 0.666]
Pooled Specificity	0.736	[0.574, 0.852]
LR+	2.108	[1.231, 3.610]
LR-	0.602	[0.449, 0.807]
DOR	3.502	[1.588, 7.723]

791

792

793

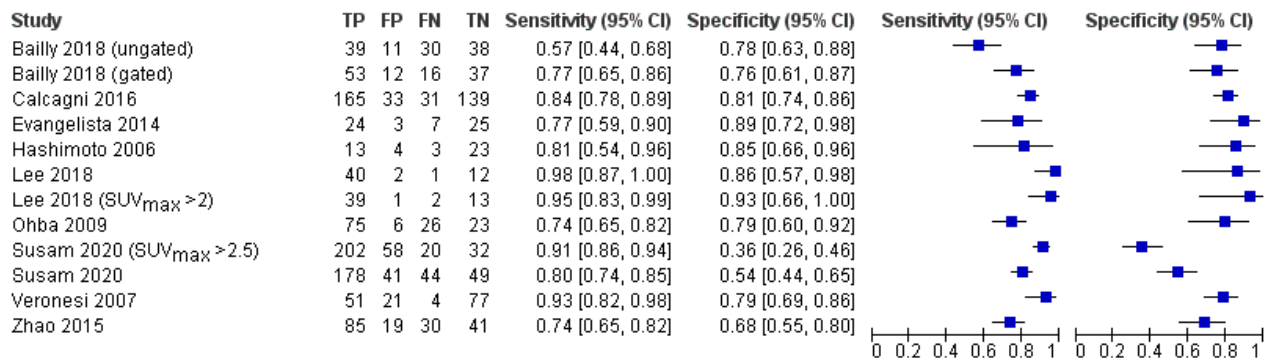
794

795

FDG-avidity

796 Figure Q3n: Forest plot and SROC plot of FDG-avidity for diagnosing lung cancer in solid pulmonary nodules

797 i) Forest plot



798

799

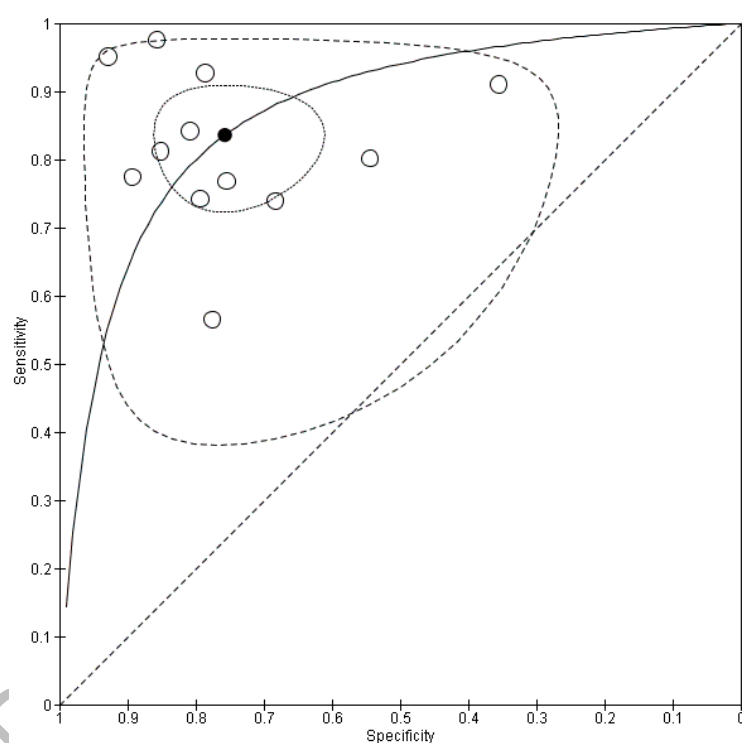
800

(Information on each dataset cut-off is provided in the table overleaf)

Dataset	Cut-offs
Bailly 2018 (ungated) ¹³	SUV _{max} > 2
Bailly 2018 (gated) ¹³	SUV _{max} > 2.5
Calcagni 2016 ¹⁴	FDG uptake > MBP
Evangelista 2014 ¹⁵	SUV _{max} > other regions
Hashimoto 2006 ¹⁶	SUV _{max} > 1.59
Lee 2018 ¹⁷	SUV _{max} > liver
Lee 2018 (SUV _{max} > 2) ¹⁷	SUV _{max} > 2
Ohba 2009 ¹⁸	SUV _{max} > 1.10
Susam 2020 (SUV _{max} > 2.5) ¹⁹	SUV _{max} > 2.5
Susam 2020 ¹⁹	SUV _{max} > 4.5
Veronesi 2007 ²⁰	SUV _{max} > 2
Zhao 2015 ²¹	SUV _{max} > 2

801 FDG – fluorodeoxyglucose; MBP – mediastinal blood pool; other regions – background regions within the scan image;
802 SUV_{max} – maximum standardised uptake value

803 ii) SROC plot



809 Table Q3k: Pooled results of FDG-avidity for diagnosing lung cancer in solid pulmonary nodules

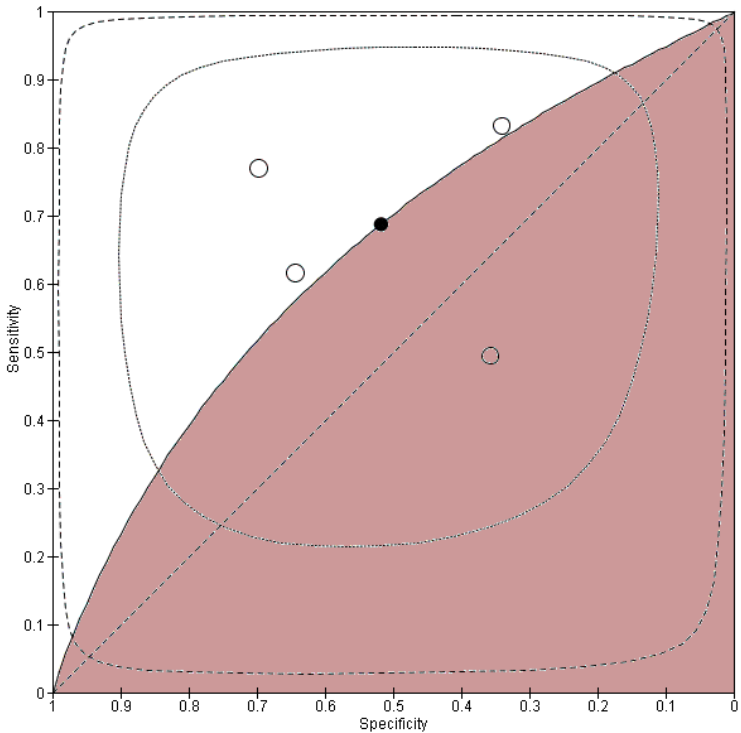
Pooled Sensitivity	0.836	[0.763, 0.890]
Pooled Specificity	0.757	[0.661, 0.833]
LR+	3.444	[2.394, 4.954]
LR-	0.217	[0.145, 0.323]
DOR	15.897	[8.266, 30.576]

814 **Area under the curve (AUC)**

815 **Nodule diameter**

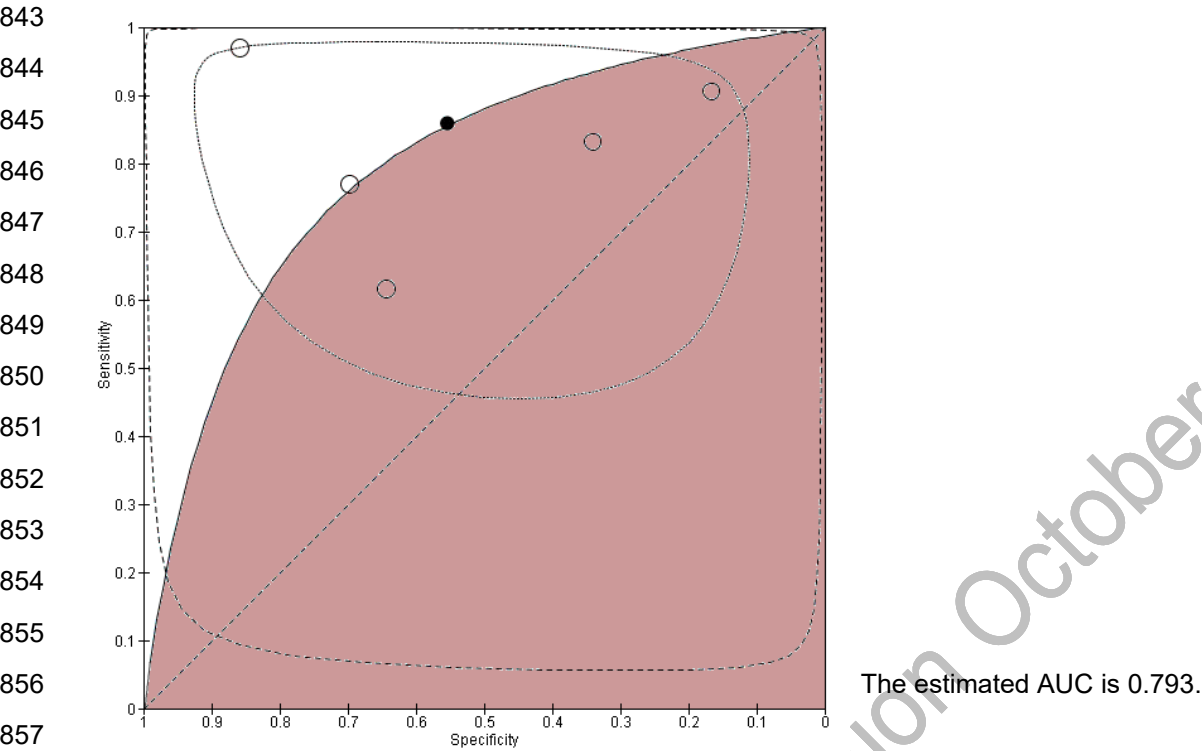
816 *Diameter > 8 mm to approximately < 20 mm*

817 Figure Q3d: AUC of nodule diameter > 8 mm to approximately < 20 mm for diagnosing lung cancer in solid
818 pulmonary nodules



841 Diameter > 8mm or > 10 mm

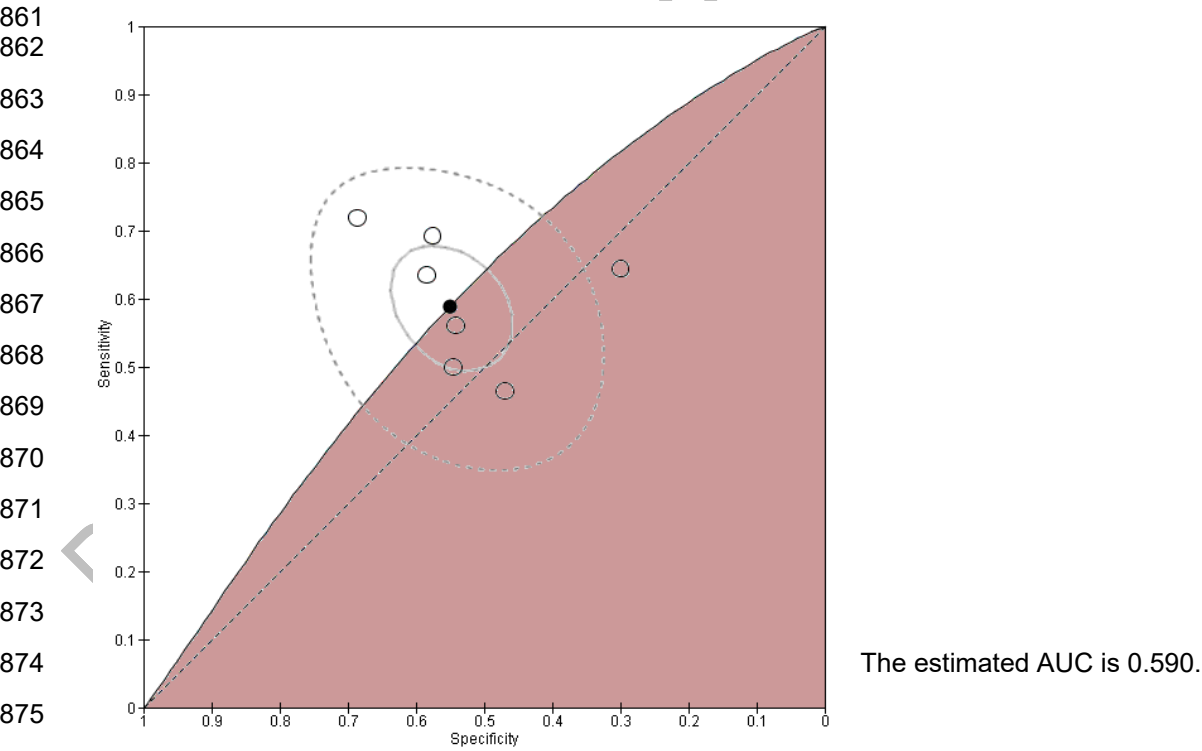
842 Figure Q3h: AUC of nodule diameter> 8mm or > 10 mm for diagnosing lung cancer in solid pulmonary nodules



858

859 **Upper lobe location**

860 Figure Q3k: AUC of upper lobe location for diagnosing lung cancer in solid pulmonary nodules

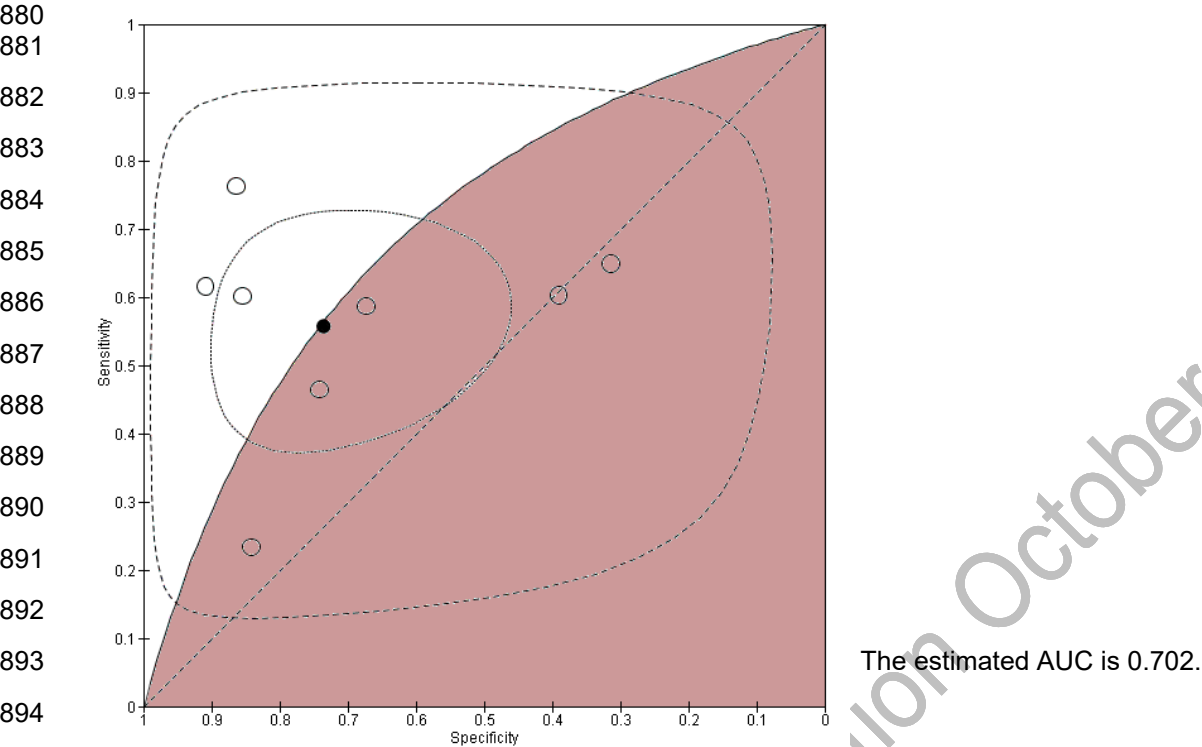


876

877

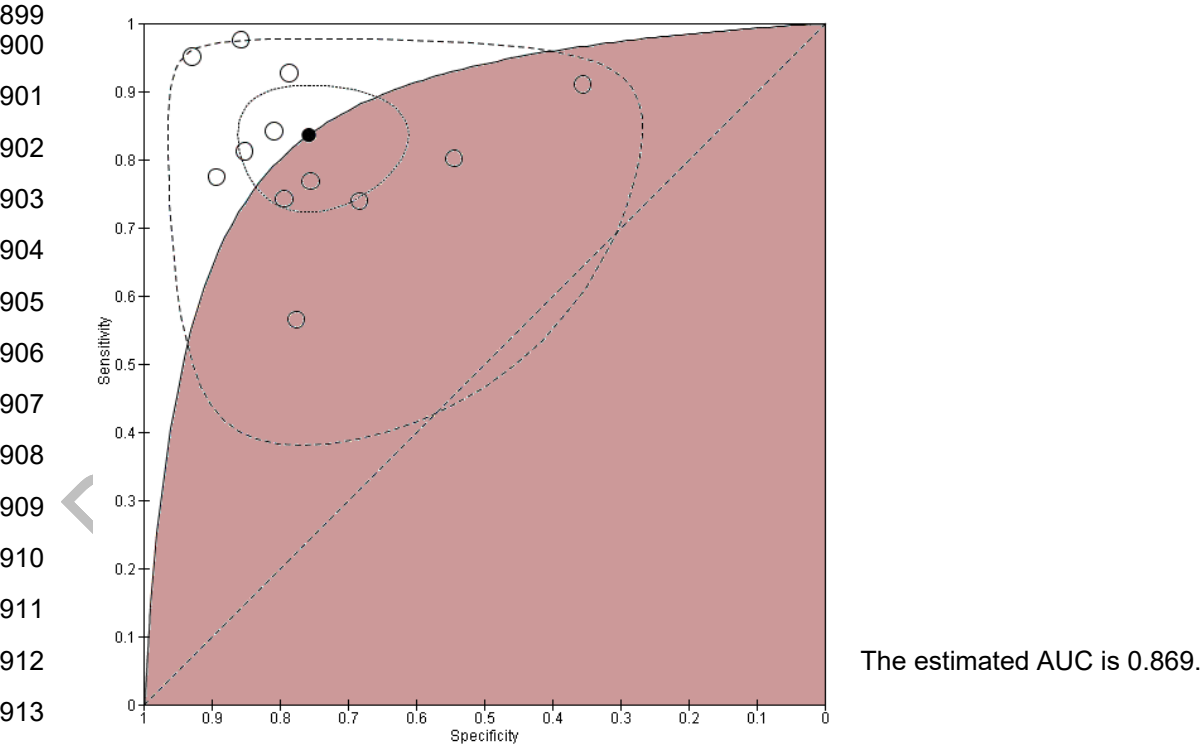
878 **Spiculation**

879 Figure Q3m: AUC of spiculation for diagnosing lung cancer in solid pulmonary nodules



897 **FDG-avidity**

898 Figure Q3o: AUC of FDG-avidity for diagnosing lung cancer in solid pulmonary nodules



Diagnostic accuracy analyses

	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Avram 2024	+	?	?	+	+	+	+
Bailly 2018	+	?	?	+	+	+	+
Calcagni 2016	+	+	+	+	+	+	+
Evangelista 2014	+	+	+	+	+	+	+
Gibson 2017	+	?	?	+	+	+	+
Hashimoto 2006	+	+	+	+	+	+	+
He 2022	+	+	+	+	+	+	+
He 2024	+	+	+	+	+	+	+
Ji 2025	?	?	?	+	+	+	+
Jiang 2023	+	+	+	?	+	+	?
Lee 2018	+	+	+	+	+	+	+
Ohba 2009	?	+	?	?	+	+	+
Qu 2024	+	+	+	+	+	+	+
Susam 2020	+	?	+	+	+	+	+
Veronesi 2007	+	?	?	+	+	+	+
Xu 2008	+	?	?	?	+	+	+
Zhang 2021	+	+	+	+	+	+	+
Zhao 2015	+	+	+	+	+	+	+
Zhao 2025	+	?	?	+	+	+	+
Zhu 2024	+	+	+	+	+	+	?
High ? Unclear + Low							

Intervention analysis

	Selection bias	Performance bias	Detection bias	Attrition bias	Publication bias
He 2022	+	+	?	+	+
Lee 2022	?	+	+	+	+
High ? Unclear + Low					

917 GRADE analyses

918 Nodule diameter > 8 mm

What is the diagnostic accuracy of imaging tests, and the optimal strategy for image utilisation, for diagnosing lung cancer in a solid pulmonary nodule?

Patient or population: Adults aged 18+ with solid pulmonary nodules

New test: Nodule diameter > 8 mm

Pooled sensitivity: 0.86 (95% CI: 0.71 to 0.94) | Pooled specificity: 0.55 (95% CI: 0.31 to 0.78)

Test result	Number of results per 1,000 patients tested (95% CI) Prevalence 5% Typically seen in	Number of participants (datasets)	Certainty of the Evidence (GRADE)
True positives	43 (36 to 47)	674	⊕⊕○○ LOW ^{a,b}
False negatives	7 (3 to 14)	(5)	
True negatives	526 (291 to 738)	1026	⊕⊕○○ LOW ^{a,b}
False positives	424 (212 to 659)	(5)	
CI: Confidence interval			
Explanations			
a. Some risk of bias across the studies			
b. Inconsistency across the specificities			

Upper lobe location

What is the diagnostic accuracy of imaging tests, and the optimal strategy for image utilisation, for diagnosing lung cancer in a solid pulmonary nodule?

Patient or population: Adults aged 18+ with solid pulmonary nodules

New test: Upper lobe location

Pooled sensitivity: 0.59 (95% CI: 0.50 to 0.69) | Pooled specificity: 0.55 (95% CI: 0.45 to 0.63)

Test result	Number of results per 1,000 patients tested (95% CI) Prevalence 5% Typically seen in	Number of participants (datasets)	Certainty of the Evidence (GRADE)
True positives	29 (25 to 34)	1049	⊕⊕○○ LOW ^{a,b}
False negatives	21 (16 to 25)	(7)	
True negatives	523 (423 to 601)	1391	⊕⊕○○ LOW ^{a,b}
False positives	427 (349 to 527)	(7)	
CI: Confidence interval			
Explanations			
a. Some risk of bias across the studies			
b. Some inconsistency across the specificities			

What is the diagnostic accuracy of imaging tests, and the optimal strategy for image utilisation, for diagnosing lung cancer in a solid pulmonary nodule?

Patient or population: Adults aged 18+ with solid pulmonary nodules

New test: Spiculation

Pooled sensitivity: 0.56 (95% CI: 0.44 to 0.67) | Pooled specificity: 0.74 (95% CI: 0.57 to 0.85)

Test result	Number of results per 1,000 patients tested (95% CI) Prevalence 5% Typically seen in	Number of participants (datasets)	Certainty of the Evidence (GRADE)
True positives	28 (22 to 33)	1328	⊕○○○ VERY LOW ^{a,b}
False negatives	22 (17 to 28)	(8)	
True negatives	699 (545 to 809)	2009	⊕○○○ VERY LOW ^{a,b}
False positives	251 (141 to 405)	(8)	
CI: Confidence interval			
Explanations			
a. Some risk of bias across the studies			
b. Inconsistency across the sensitivities and specificities			

FDG-avidity

What is the diagnostic accuracy of imaging tests, and the optimal strategy for image utilisation, for diagnosing lung cancer in a solid pulmonary nodule?

Patient or population: Adults aged 18+ with solid pulmonary nodules

New test: FDG-avidity

Pooled sensitivity: 0.84 (95% CI: 0.76 to 0.89) | Pooled specificity: 0.76 (95% CI: 0.66 to 0.83)

Test result	Number of results per 1,000 patients tested (95% CI) Prevalence 5% Typically seen in	Number of participants (datasets)	Certainty of the Evidence (GRADE)
True positives	42 (38 to 45)	1178	⊕⊕○○ LOW ^{a,b}
False negatives	8 (5 to 12)	(12)	
True negatives	719 (628 to 791)	720	⊕⊕○○ LOW ^{a,b}
False positives	231 (159 to 322)	(12)	
CI: Confidence interval			
Explanations			
a. Some risk of bias across the studies			
b. Some inconsistency across the sensitivities and specificities			

945 **Recommendation Table**

946 **Question Details**

POPULATION:	Adults (18+) with solid pulmonary nodules
INDEX TESTS:	Strategies for image utilisation for diagnosing lung cancer in a solid pulmonary nodule
GOLD STANDARD:	Pathological diagnosis of invasive lung cancer or clinical diagnosis of lung cancer
OUTCOME:	Diagnostic accuracy of strategies for image utilisation for diagnosing lung cancer

947

948

949 **FDG-avidity**

950 **SUMMARY OF JUDGEMENTS**

PROBLEM	JUDGEMENT						
	No	Probably no	Probably yes	Yes		Varies	Don't know
TEST ACCURACY	Very inaccurate	Inaccurate	Accurate	Very accurate		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	Does not favour the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know

951

952 **TYPE OF RECOMMENDATION**

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
☐	☐	☐	☒	☐

953

954 **CONCLUSIONS**

Recommendation

An FDG PET-CT ((fluorodeoxyglucose positron emission tomography computed tomography) scan should be considered for diagnosing lung cancer risk in solid pulmonary nodules ≥ 8 mm. (**Conditional**)

Justification

Solid nodule FDG-avidity appears to have a high sensitivity and moderate specificity for diagnosing lung cancer. (**Low**)

Subgroup considerations

There was not enough evidence to fully consider solid nodule subtypes ("without recent relevant imaging", "newly appeared since recent imaging", peri-cystic lesions and consolidation).

Research priorities

No further research priorities.

References

1. Avram C, Mederle AO, Mavrea A, Barata PI, Patrascu R. Comparison of Lung-RADS Version 2022 and British Thoracic Society Guidelines in classifying solid pulmonary nodules detected at lung cancer screening CT. *Life (Basel)*. 2024;15:27.
2. Gibson G, Kumar AR, Steinke K, et al. Risk stratification in the investigation of pulmonary nodules in a high-risk cohort: positron emission tomography/computed tomography outperforms clinical risk prediction algorithms. *Intern Med J*. 2017;47:1385–1392.
3. He C, Liu J, Li Y, et al. Quantitative parameters of enhanced dual-energy computed tomography for differentiating lung cancers from benign lesions in solid pulmonary nodules. *Front Oncol*. 2022; 12: 1027985.
4. He XQ, Huang XT, Luo TY, Liu X, Li Q. The differential computed tomography features between small benign and malignant solid solitary pulmonary nodules with different sizes. *Quant Imaging Med Surg*. 2024;14:1348–1358.
5. Zhu Y, Yip R, Zhang J, et al. Radiologic features of nodules attached to the mediastinal or diaphragmatic pleura at low-dose CT for lung cancer screening. *Radiology*. 2024;310:e231219.
6. Lee JH, Hwang EJ, Lim WH, Goo JM. Determination of the optimum definition of growth evaluation for indeterminate pulmonary nodules detected in lung cancer screening. *PLoS ONE*. 2022;17:e0274583.
7. Ji G, Liu F, Chen Z, et al. Application value of CT three-dimensional reconstruction technology in the identification of benign and malignant lung nodules and the characteristics of nodule distribution. *BMC Med Imaging*. 2025;25:7.
8. Jiang J, Lv FJ, Tao Y, et al. Differentiation of pulmonary solid nodules attached to the pleura detected by thin-section CT. *Insights Imaging*. 2023;14:146.
9. Qu BQ, Wang Y, Pan YP, Cao PW, Deng XY. The scoring system combined with radiomics and imaging features in predicting the malignant potential of incidental indeterminate small (<20 mm) solid pulmonary nodules. *BMC Med Imaging*. 2024;24:234.
10. Zhang R, Sun H, Chen B, Xu R, Li W. Developing of risk models for small solid and subsolid pulmonary nodules based on clinical and quantitative radiomics features. *J Thorac Dis*. 2021;13:4156–4168.
11. 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;68:347–52.
12. Zhao WH, Zhang LJ, Li X, Luo TY, Lv FJ, Li Q. Clinical and computed tomography characteristics of inflammatory solid pulmonary nodules with morphology suggesting malignancy. *Acad Radiol*. 2025; 32: 1067–1077.
13. Bailly P, Bouzerar R, Shields T, Meyer ME, Daouk J. Benefits of respiratory-gated 18F-FDG PET acquisition in lung disease. *Nucl Med Commun*. 2018;39:44–50.
14. Calcagni ML, Taralli S, Cardillo G, et al. Diagnostic performance of (18)F-Fluorodeoxyglucose in 162 small pulmonary nodules incidentally detected in subjects without a history of malignancy. *Ann Thorac Surg*. 2016;101:1303–9.
15. Evangelista L, Panunzio A, Polverosi R, Pommeri F, Rubello D. Indeterminate lung nodules in cancer patients: pretest probability of malignancy and the role of 18F-FDG PET/CT. *AJR Am J Roentgenol*. 2014; 202:507–14.

- 1007 16. Hashimoto Y, Tsujikawa T, Kondo C, et al. Accuracy of PET for diagnosis of solid pulmonary lesions with
1008 18F-FDG uptake below the standardized uptake value of 2.5. *J Nucl Med*. Mar 2006;47(3):426–31.
- 1009 17. Lee SH, Sung C, Lee HS, et al. Is ¹⁸F-FDG PET/CT useful for the differential diagnosis of solitary
1010 pulmonary nodules in patients with idiopathic pulmonary fibrosis? *Ann Nucl Med*. 2018;32:492–498.
- 1011 18. Ohba Y, Nomori H, Shibata H, et al. Evaluation of semiquantitative assessments of fluorodeoxyglucose
1012 uptake on positron emission tomography scans for the diagnosis of pulmonary malignancies 1 to 3 cm in
1013 size. *Ann Thorac Surg*. 2009;87:886–91.
- 1014 19. Susam S, Cinkooglu A, Ceylan KC, et al. Diagnostic success of transthoracic needle biopsy and PET-CT
1015 for 1 to 2 cm solid indeterminate pulmonary nodules. *Clin Respir J*. 2020;14:453–461.
- 1016 20. Veronesi G, Bellomi M, Veronesi U, et al. Role of positron emission tomography scanning in the
1017 management of lung nodules detected at baseline computed tomography screening. *Ann Thorac Surg*.
1018 2007;84:959–65.
- 1019 21. Zhao L, Tong L, Lin J, et al. Characterization of solitary pulmonary nodules with 18F-FDG PET/CT relative
1020 activity distribution analysis. *Eur Radiol*. 2015;25:1837–1844.
- 1021 22. Hammer MM, Nachiappan AC, Barbosa EJM, Jr. Limited utility of pulmonary nodule risk calculators for
1022 managing large nodules. *Curr Probl Diagn Radiol*. 2018;47:23–27.
- 1023 23. Susam S, Cinkooglu A, Ceylan KC, et al. Comparison of Brock University, Mayo Clinic and Herder models
1024 for pretest probability of cancer in solid pulmonary nodules. *Clin Respir J*. 2022;16:740–749.
- 1025 24. Perandini S, Soardi GA, Larici AR, et al. Multicenter external validation of two malignancy risk prediction
1026 models in patients undergoing 18F-FDG-PET for solitary pulmonary nodule evaluation. *Eur Radiol*.
1027 2017;27:2042–2046.
- 1028 25. Isbell JM, Deppen S, Putnam Jr JB, et al. Existing general population models inaccurately predict lung
1029 cancer risk in patients referred for surgical evaluation. *Ann Thorac Surg*. 2011;91:227–233.
- 1030 26. Perandini S, Soardi GA, Motton M, Dallaserra C, Montemezzi S. Limited value of logistic regression
1031 analysis in solid solitary pulmonary nodules characterization: a single-center experience on 288
1032 consecutive cases. *Clinical Trial. J Surg Oncol*. Dec 2014;110(7):883–7.
- 1033 27. Perandini S, Soardi GA, Motton M, Rossi A, Signorini M, Montemezzi S. Solid pulmonary nodule risk
1034 assessment and decision analysis: comparison of four prediction models in 285 cases. *Eur Radiol*. 2016;
1035 26:3071–6.
- 1036 28. Soardi GA, Perandini S, Larici AR, et al. Multicentre external validation of the BIMC model for solid solitary
1037 pulmonary nodule malignancy prediction. *Eur Radiol*. 2017;27:1929–1933.

Field	Content
Review Question	What is the diagnostic accuracy of imaging tests, and the optimal strategy for image utilisation* for diagnosing lung cancer in a solid pulmonary nodule? * Computer-aided measurement of specific nodule parameters (e.g. volume, mass) NOT artificial-intelligence tools where multiple parameters are computed to give an overall risk assessment.
Type of review question	Diagnostic accuracy review
Objective of the review	Solid pulmonary nodules are first assessed on non-invasive imaging tests – initially CT, sometimes supplemented by other imaging investigations. The way imaging tests are assessed (for example, how pulmonary nodules are measured) can vary. This question aims to clarify the optimal way to assess the likelihood of lung cancer using these various modalities and determine the overall diagnostic accuracy of these approaches.
Eligibility criteria – population / disease / condition / issue / domain	Adults with solid pulmonary nodules (18+ years of age)
Eligibility criteria – index test(s)	Nodule diameter Nodule volume Upper lobe location Spiculation FDG-avidity Brock score Mayo score Herder score VA UKLS
Eligibility criteria – gold standard	Pathological diagnosis of invasive lung cancer or clinical diagnosis of lung cancer
Outcomes and prioritisation	Diagnostic accuracy
Eligibility criteria – study design	RCTs, comparative studies, case series (>50 cases)

Other inclusion /exclusion criteria	Non-English language excluded unless full English translation Conference abstracts, Cochrane reviews, systematic reviews, reviews Cochrane reviews and systematic reviews can be referenced in the text, but CANNOT be used in a meta-analysis
Proposed sensitivity / subgroup analysis, or meta-regression	Adults with solid pulmonary nodules - Without previous cross-sectional imaging - Newly appeared since previous cross-sectional imaging - Peri-cystic lesions - Consolidation) Imaging types - Computed tomography (CT) - Positron emission tomography computed tomography (PET-CT) - Magnetic resonance imaging (MRI)
Selection process – duplicate screening / selection / analysis	Agreement should be reached between Guideline members who are working on the question. If no agreement can be reached, a decision should be made by the Guideline co-chairs. If there is still no decision, the matter should be brought to the Guideline group and a decision will be made by consensus
Data management (software)	RevMan5 Pairwise meta-analyses (if data in the correct format) Evidence review/considered judgement. Storing Guideline text, tables, figures, etc. MetaDTA Data meta-analyses GradePro Quality of evidence assessment
Information sources – databases and dates	MEDLINE, Embase, Central Register of Controlled Trials and Cochrane Database of Systematic Reviews Restricted to articles published from 1990 onwards
Methods for assessing bias at outcome / study level	RevMan5 diagnostic accuracy full review template (based on QUADAS2) (follow instructions in ' <i>BTS Guideline Process Handbook – Diagnostic Accuracy (June 2020)</i> ')
Methods for quantitative analysis – combining studies and exploring (in)consistency	If 3 or more relevant studies: RevMan5 for forest plots, summary ROC plots MetaDTA to combine studies (pooled specificity, sensitivity, likelihood ratios, diagnostic odds ratio and confidence intervals) and calculate RevMan parameters for summary ROC plot (follow instructions in '<i>BTS Guideline Process Handbook – Diagnostic Accuracy (June 2020)</i>')

Meta-bias assessment – publication bias, selective reporting bias	GRADEpro Diagnostic accuracy quality of evidence assessment for each index test (follow instructions in ' <i>BTS Guideline Process Handbook – Diagnostic Accuracy (June 2020)</i> ')
Rationale / context – what is known	The initial diagnostic assessment of a solid pulmonary nodule is made on the basis of CT images. Other imaging tests such as dynamic contrast-enhanced CT and PET-CT may provide additional information. This question aims to review the optimal way to assess pulmonary nodules using these imaging modalities, and the overall diagnostic accuracy of each of them for diagnosing lung cancer.

1041
1042
1043
1044
1045
1046
1047
1048
1049
1050
1051
1052
1053
1054
1055
1056
1057
1058
1059
1060
1061
1062
1063
1064
1065
1066
1067
1068
1069
1070

1072 **Q4** **In adults with solid pulmonary nodules, what is the diagnostic accuracy of strategies used to**
 1073 **detect change between interval computed tomography (CT) scans for diagnosing lung cancer?**

1074 **Contents**

1075	Question Evidence Review	52
1076	Background	52
1077	Outcomes	52
1078	Evidence Review	52
1079	Evidence Statements	53
1080	Recommendations	53
1081	Good Practice Points	54
1082	Research recommendations	54
1083	Algorithms	55
1084	Solid nodule follow-up pathway	55
1085	New solid nodule follow-up pathway	56
1086	Meta-analyses	57
1087	Volume doubling time (VDT)	57
1088	Volume change	60
1089	Risk of bias summary	61
1090	GRADE analyses	62
1091	Volume doubling time (VDT)	62
1092	Volume change	63
1093	Recommendation tables	64
1094	Volume doubling time (VDT)	64
1095	Volume change	66
1096	References	67
1097	Question Protocol	68

1098

1099 **Question 4 Evidence Review**

1100 **Q4** In adults with solid pulmonary nodules, what is the diagnostic accuracy of strategies used to
1101 detect change between interval computed tomography (CT) scans for diagnosing lung cancer?

1102 **Background**

1103 The assessment of interval change in solid pulmonary nodules is a key component of establishing the risk of
1104 malignancy and potential for a subsequent lung cancer diagnosis, in patients with a low initial probability of
1105 malignancy. In these patients, immediate invasive investigation may not be appropriate or feasible, and serial
1106 computed tomography (CT) surveillance is an established modality to help distinguish benign from malignant
1107 nodules. Several strategies have been proposed to define significant growth, and therefore the potential of a
1108 cancer diagnosis, including changes in diameter, volume, and volume doubling time (VDT). Accurate
1109 assessment of growth patterns is clinically important to avoid delaying cancer diagnosis, while minimising
1110 unnecessary imaging, procedures, and patient anxiety associated with benign nodules. This review aims to
1111 evaluate the diagnostic accuracy of CT-based strategies used to detect interval change suggestive of
1112 malignancy.

1113 **Outcomes**

1114 Visual analysis; diameter change; volume doubling time; mass doubling time; volume change

1115 **Evidence Review**

1116 The initial literature search identified 87 potentially relevant papers, and 8 papers were deemed relevant to the
1117 review.¹⁻⁸

1118 **Visual analysis**

1119 Only one study reported on the use of visual characteristics for diagnosing lung cancer in solid nodules at
1120 interval CT scans.¹ The data are shown in [Table Q4a](#).

1121 Table Q4a: Summary of visual analysis data for diagnosing cancerous solid nodules

Study	Visual change	n	Sensitivity [95 % CI]	Specificity [95 % CI]
Xu 2009 ¹	Margin *	372	0.00 [0.00, 0.21]	0.99 [0.97, 1.00]
Xu 2009 ¹	Morphology †	372	0.00 [0.00, 0.21]	0.99 [0.98, 1.00]
Xu 2009 ¹	Shape ‡	372	0.06 [0.00, 0.30]	0.86 [0.82, 0.89]

1122 * Spherical/non-spherical

1123 † Polygonal, round, irregular

1124 ‡ Smooth, lobulated, spiculated

1125 **Diameter change**

1126 Only one study reported on the use of diameter change for diagnosing lung cancer in solid nodules at interval
1127 CT scans.² The data are shown in [Table Q4b](#).

1128 Table Q4b: Summary of diameter change data for diagnosing cancerous solid nodules

Study	Diameter change	n	Sensitivity [95 % CI]	Specificity [95 % CI]
Lee 2022 ²	> 1.5 mm	93	0.55 [0.23, 0.83]	1.00 [0.96, 1.00]

1129

1130 **Volume doubling time (VDT)**

1131 Six studies reported on volume doubling time (VDT) for diagnosing lung cancer in solid nodules, with different
1132 studies using different VDT cut-off times.²⁻⁷ Meta-analysis showed a pooled sensitivity of [0.44 \[0.23, 0.67\]](#) and

1133 pooled specificity of 0.92 [0.87, 0.96] [95% confidence intervals] (Figure Q4a and Table Q4c). Although the
1134 specificities across the different VDT cut-off points showed consistency, there was much variation in the
1135 sensitivities across the different VDT cut-offs. Hence, to better address this question, meta-analyses were
1136 performed on two subgroups, VDT < 400 days and VDT < 600 days.

1137 *VDT < 400 days*

1138 Four studies assessed the diagnostic accuracy of a VDT of less than 400 days.^{2,4,5,7} Meta-analysis showed
1139 VDT < 400 days had a pooled sensitivity of 0.76 [0.59, 0.87] and a pooled specificity of 0.94 [0.79, 0.98] [95%
1140 confidence intervals] for diagnosing lung cancer in solid pulmonary nodules (Figure Q4b and Table Q4d).

1141 *VDT < 600 days*

1142 Five studies assessed the diagnostic accuracy of a VDT of less than 600 days.²⁻⁶ Meta-analysis showed VDT
1143 < 600 days had a pooled sensitivity of 0.87 [0.72, 0.94] and a pooled specificity of 0.84 [0.64, 0.93] [95%
1144 confidence intervals] for diagnosing lung cancer in a solid pulmonary nodule (Figure Q4c and Table Q4e).

1145 **Mass doubling time**

1146 No studies reported on mass doubling time for diagnosing lung cancer in solid pulmonary nodules at interval
1147 CT scans.

1148 **Volume change**

1149 *Volume change > 25%*

1150 Two studies reported on the use of volume change to diagnose lung cancer in a solid pulmonary nodule at
1151 interval CT scans.^{2,8} Meta-analysis showed a volume change of greater than 25% had a pooled sensitivity of
1152 0.62 [0.31, 0.86] and a pooled specificity of 0.81 [0.47, 0.91] [95% confidence intervals] (data shown in Figure
1153 Q4d and Table Q4f).

1154 **Evidence Statements**

1155 There is insufficient evidence to support the use of visual analysis to detect change between interval computed
1156 tomography (CT) scans for diagnosing lung cancer in solid pulmonary nodules.

1157 There is insufficient evidence to support the use of diameter change to detect change between interval
1158 computed tomography (CT) scans for diagnosing lung cancer in solid pulmonary nodules.

1159 A volume doubling time of < 400 days appears to have a moderate sensitivity and a very high specificity for
1160 detecting change between interval computed tomography (CT) scans for diagnosing lung cancer in solid
1161 pulmonary nodules. (**Very low**)

1162 A volume doubling time of < 600 days appears to have a high sensitivity and a high specificity for detecting
1163 change between interval computed tomography (CT) scans for diagnosing lung cancer in solid pulmonary
1164 nodules. (**Low**)

1165 There is insufficient evidence to support the use of mass doubling time (MDT) to detect change between
1166 interval computed tomography (CT) scans for diagnosing lung cancer in solid pulmonary nodules. (**Very low**)

1167 A volume change of > 25% between interval computed tomography (CT) scans appears to have a low
1168 sensitivity and a high specificity for detecting change between interval computed tomography (CT) scans for
1169 diagnosing lung cancer in solid pulmonary nodules. (**Low**)

1170 There is insufficient evidence to consider peri-cystic lesion and consolidated solid pulmonary nodule
1171 subgroups.

1172 **Recommendations**

1173 ➤ Comparison to the earliest available CT should be performed at each evaluation of solid pulmonary
1174 nodules.

- 1175 ➤ For adults with solid pulmonary nodules, a volume doubling time of less than 600 days should be
1176 considered suggestive of lung cancer. (**Conditional**)
- 1177 ➤ The **Solid nodule follow-up pathway** (Algorithm 2), incorporating solid pulmonary nodule changes at follow-
1178 up, should be used for determining lung cancer in progressing solid pulmonary nodules. (**Conditional** –
1179 by consensus)
- 1180 ➤ For new solid nodules, please use the **New nodule follow-up pathway** (Algorithm 3). (**Conditional** – by
1181 consensus)

1182 **Good Practice Points**

- 1183 ✓ Volumetry should be used when available and reliable, in preference to diameter, to calculate nodule size.
- 1184 ✓ A volume change of > 25% between interval CTs can be considered highly specific for detecting growth in
1185 a solid pulmonary nodule.
- 1186 ✓ In the absence of available or reliable volumetry, ≥ 2mm increase in diameter can be considered clear
1187 evidence of growth.

1188 **Research Recommendations**

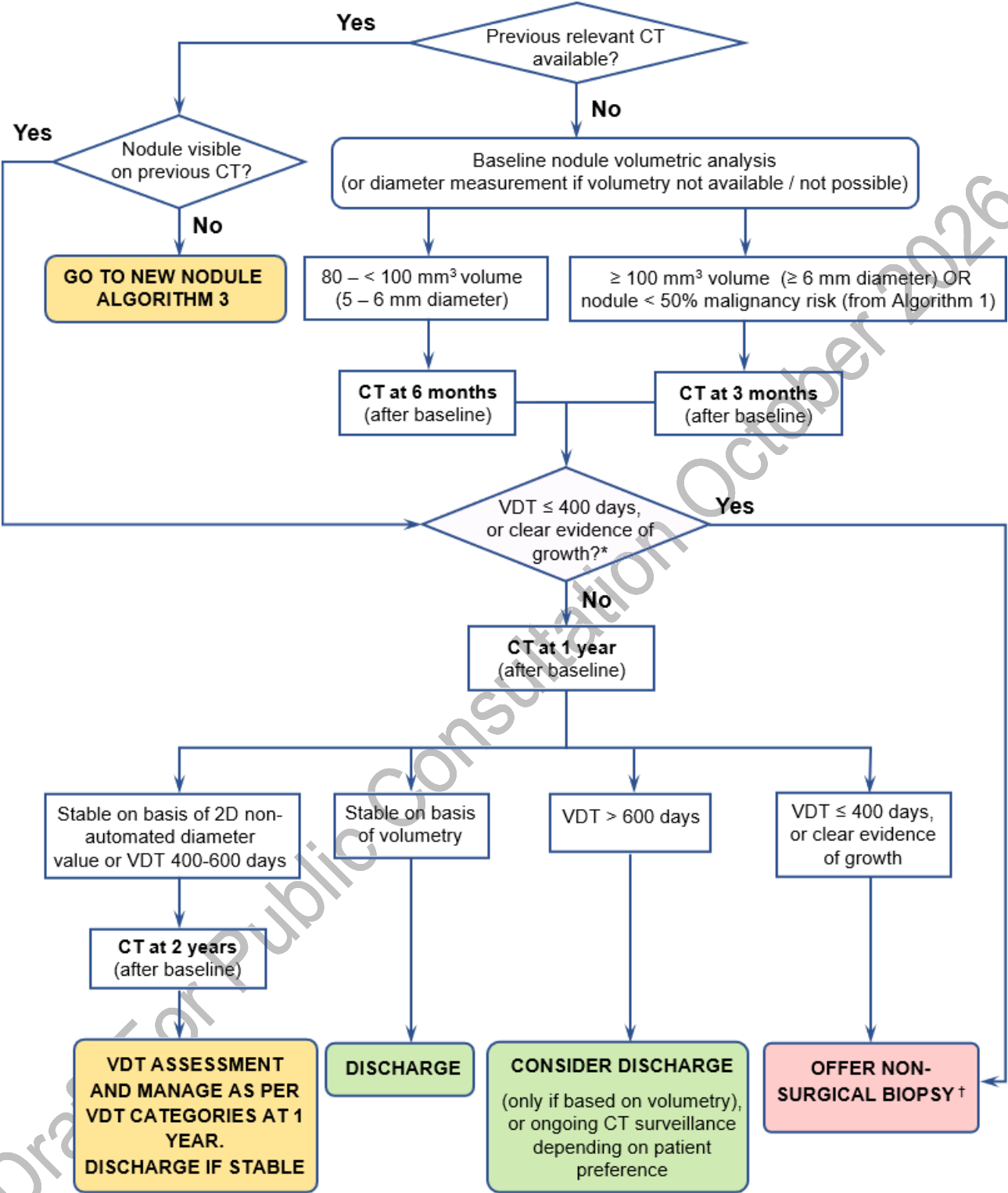
- 1189 ▪ Further research is needed to determine the optimal volume doubling time for identifying malignant solid
1190 pulmonary nodules.
- 1191 ▪ Further research is needed to determine the diagnostic accuracy of the optimal volume doubling time for
1192 identifying malignant solid pulmonary nodules.
- 1193 ▪ Further research is needed to determine the diagnostic accuracy of other strategies (visual characteristics,
1194 diameter change, mass doubling time and volume change) used to detect change between interval
1195 computed tomography (CT) for diagnosing lung cancer in solid pulmonary nodules.
- 1196 ▪ Research is needed to compare emerging AI methodologies with traditional volume doubling time
1197 thresholds for diagnosing lung cancer in solid pulmonary nodules.

1198

1199

1200

1201



1203

1204

1205 * ≥ 25% increase in volume, or ≥ 2mm in diameter

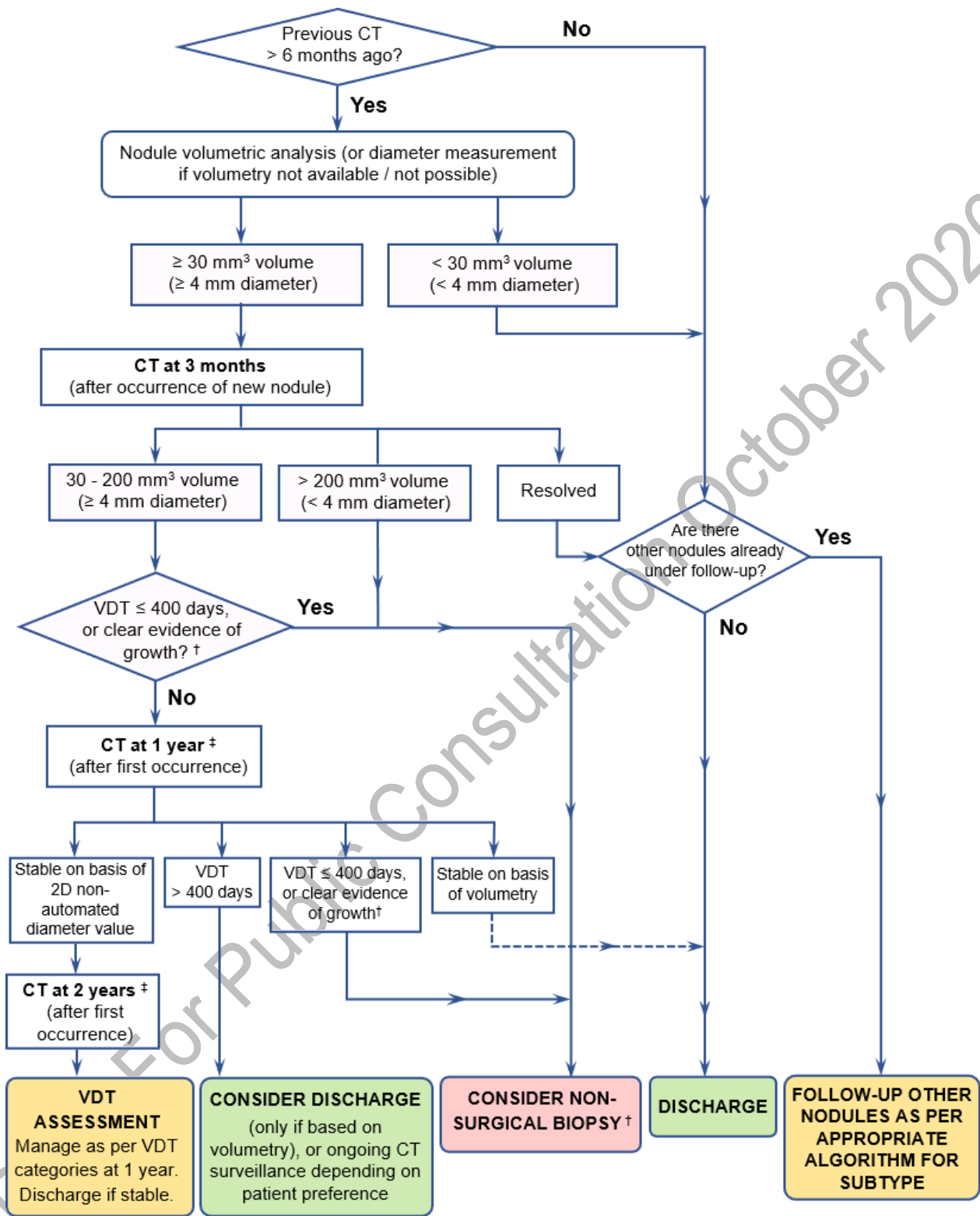
1206 † Consider further CT surveillance if nodule is < 200 mm³

1207 Brock and Herder models not to be used for nodule discrimination after baseline scan.

1208 CT – computed tomography; VDT – volume doubling time

1209 (for Algorithm 1 evidence please see ‘*BTS Guideline for pulmonary nodules – Online Appendix 3*’)

1210 **Algorithm 3 New solid nodule follow-up pathway***



1211
1212
1213

* Nodule must be confirmed to be truly new. If nodule is newly detected but visible in retrospect, follow Algorithm 2.

† ≥ 25% increase in volume, or ≥ 2mm in diameter.

‡ If the new nodule was discovered on follow-up CTs performed for other nodules, it is acceptable to modify the surveillance timepoints in this Algorithm and Algorithm 2 to ensure that both the nodule(s) originally under surveillance and the new nodule have sufficient time to permit reliable growth assessment.

1214 Brock and Herder models not to be used for nodule discrimination for new nodules.

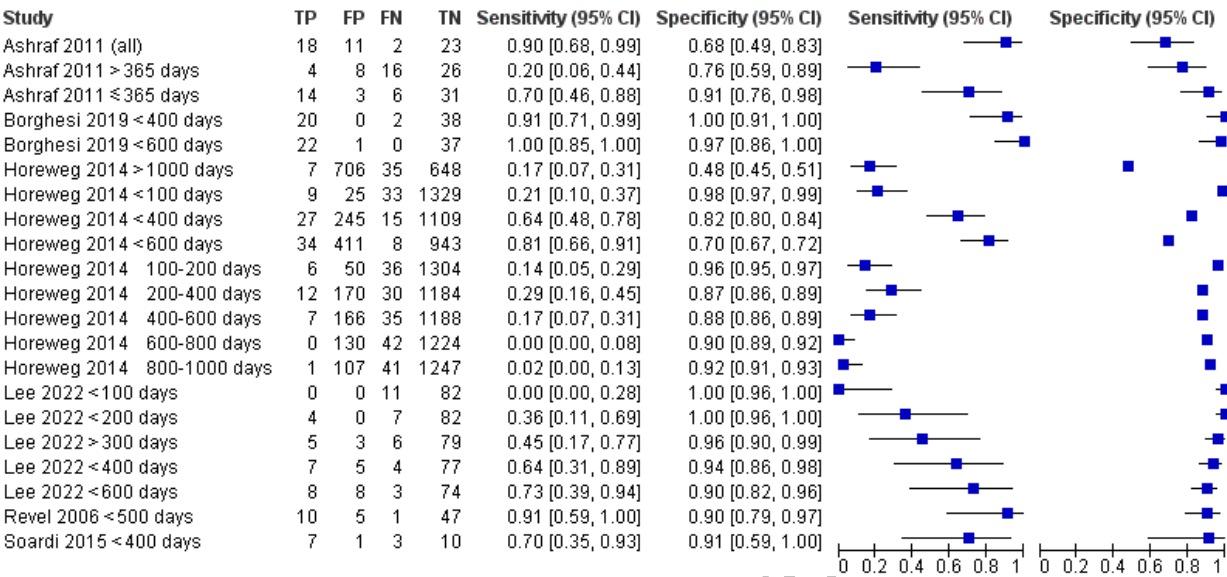
1215 CT – computed tomography; VDT – volume doubling time

1216 **Meta-analyses**

1217 **Volume doubling time (VDT)**

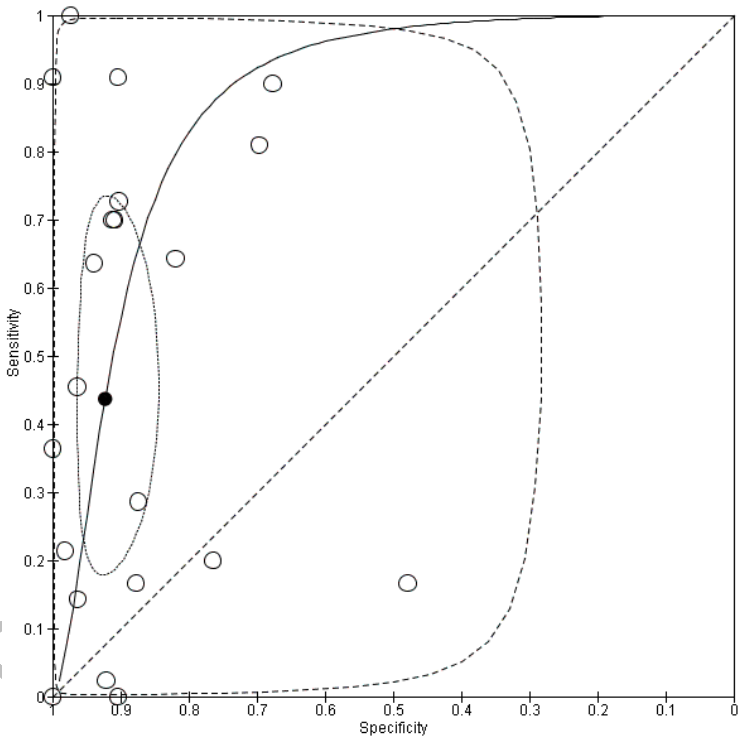
1218 Figure Q4a: Forest plot and SROC plot of VDT for diagnosing lung cancer in solid pulmonary nodules

1219 i) Forest plot



1220

1221 ii) SROC plot



1222

1223

1224

1225

1226 Table Q4c: Pooled results of VDT < 400 days for diagnosing lung cancer in solid pulmonary nodules

Pooled Sensitivity	0.437	[0.233, 0.665]
Pooled Specificity	0.923	[0.869, 0.956]
LR+	5.661	[2.718, 11.789]
LR-	0.610	[0.405, 0.920]
DOR	9.276	[3.158, 11.789]

1227

1228

1229 VDT < 400 days

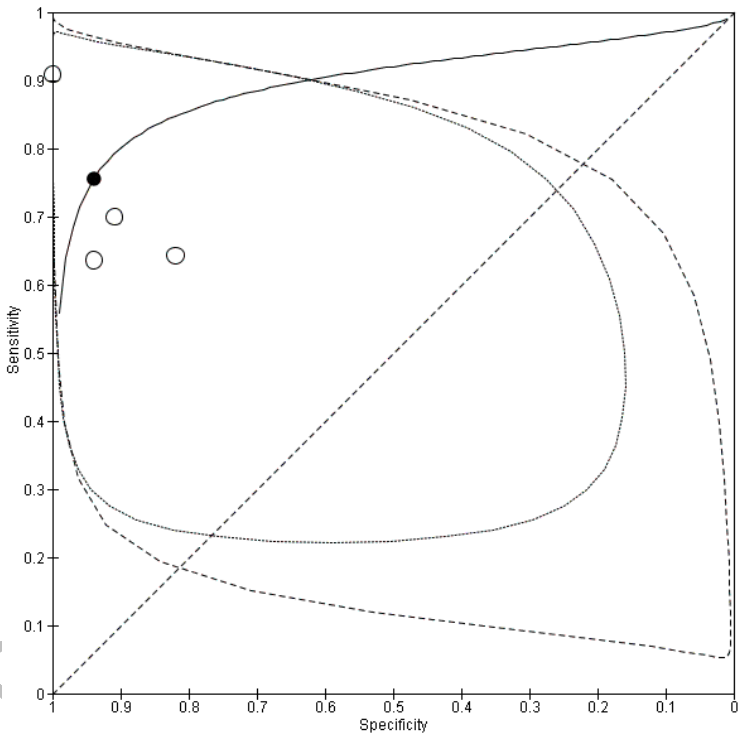
1230 Figure Q4b: Forest plot and SROC plot of VDT < 400 days for diagnosing lung cancer in solid pulmonary
1231 nodules

1232 i) Forest plot

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Borghesi 2019	20	0	2	38	0.91 [0.71, 0.99]	1.00 [0.91, 1.00]		
Horeweg 2014	27	245	15	1109	0.64 [0.48, 0.78]	0.82 [0.80, 0.84]		
Lee 2022	7	5	4	77	0.64 [0.31, 0.89]	0.94 [0.86, 0.98]		
Soardi 2015	7	1	3	10	0.70 [0.35, 0.93]	0.91 [0.59, 1.00]		

1233

1234 ii) SROC plot



1235

1236

1237

1238

1239

1240 Table Q4d: Pooled results of VDT < 400 days for diagnosing lung cancer in solid pulmonary nodules

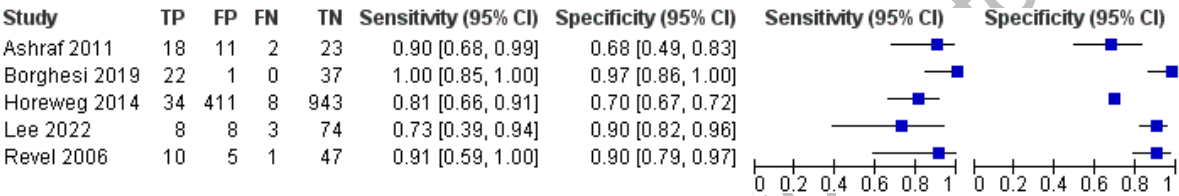
Pooled Sensitivity	0.756	[0.592, 0.868]
Pooled Specificity	0.939	[0.792, 0.984]
LR+	12.429	[2.995, 51.582]
LR-	0.260	[0.140, 0.485]
DOR	47.755	[7.018, 324.945]

1241

1242 VDT < 600 days

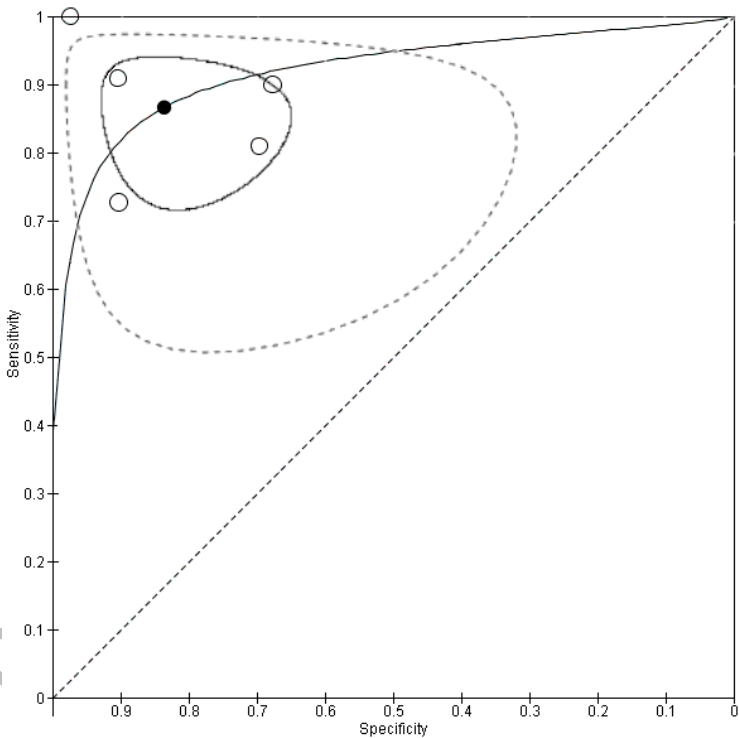
1243 Figure Q4c: Forest plot and SROC plot of VDT < 600 days for diagnosing lung cancer in solid pulmonary
1244 nodules

1245 i) Forest plot



1246

1247 ii) SROC plot



1248

1249

1250

1251

1252

1253 Table Q4e: Pooled results of VDT < 600 days for diagnosing lung cancer in solid pulmonary nodules

Pooled Sensitivity	0.866	[0.718, 0.942]
Pooled Specificity	0.836	[0.641, 0.931]
LR+	5.236	[2.312, 12.358]
LR-	0.077	[0.068, 0.359]
DOR	33.488	[7.896, 125.932]

Bayesian meta-analysis, data displayed as posterior median [95% posterior interval]

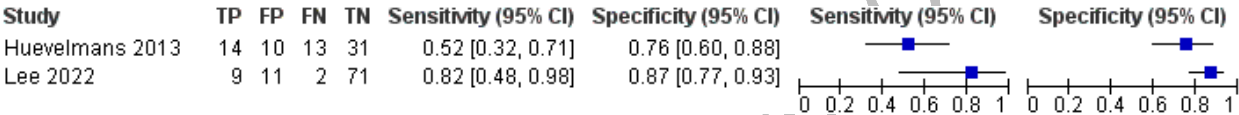
1260

1261 **Volume change**

1262 *Volume change > 25%*

1263 Figure Q4d: Forest plot and SROC plot of volume change for diagnosing lung cancer in solid pulmonary
1264 nodules

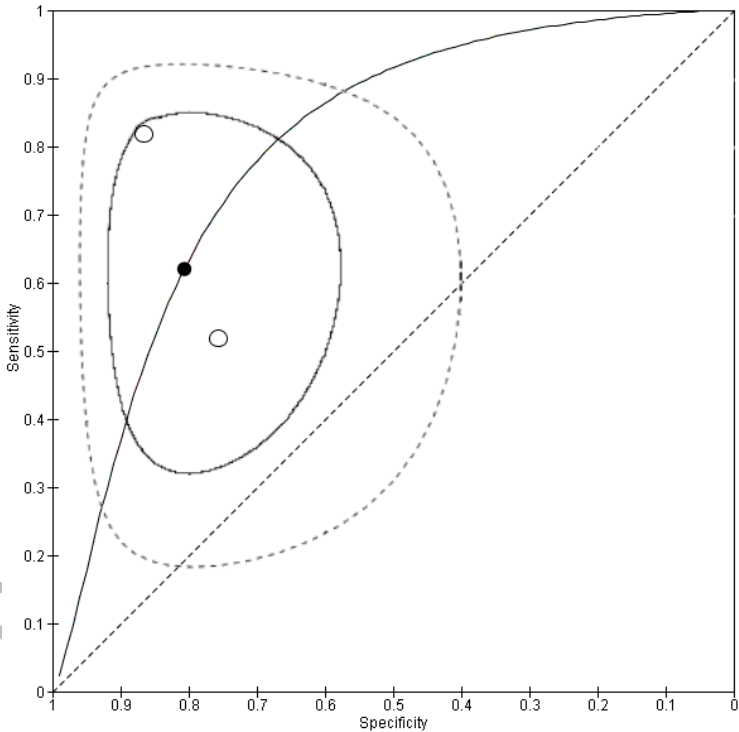
1265 i) Forest plot



1266

1267

1268 ii) SROC plot



1269

1270

1271

1272

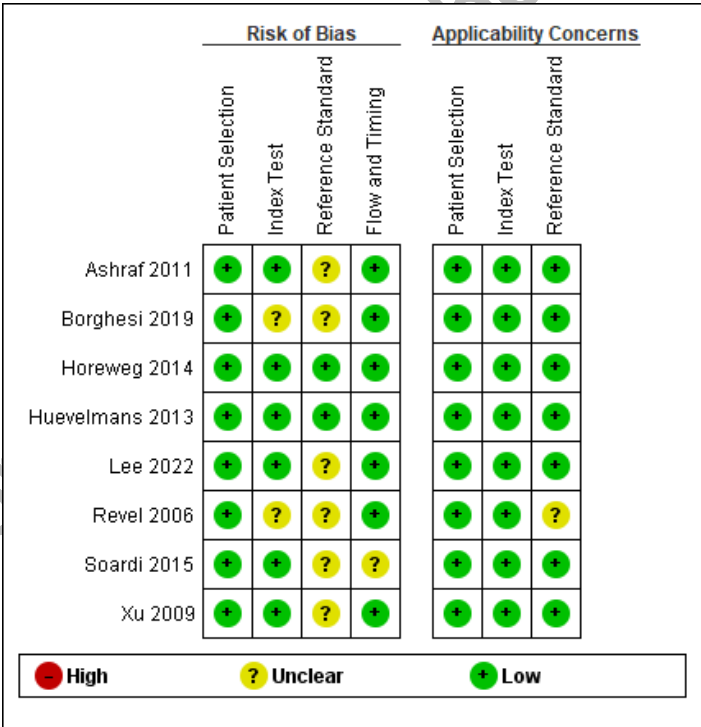
1273

1274 Table Q4f: Pooled results of volume change for diagnosing lung cancer in solid pulmonary nodules

Pooled Sensitivity	0.620	[0.314, 0.857]
Pooled Specificity	0.807	[0.471, 0.908]
LR+	3.144	[0.956, 7.082]
LR-	0.480	[0.187, 1.402]
DOR	6.689	[0.916, 30.326]

Bayesian meta-analysis, data displayed as posterior median [95% posterior interval]

1284 Risk of bias summary



1296 GRADE analyses

1297 Volume doubling time (VDT)

What is the diagnostic accuracy of pulmonary nodule volume doubling time between interval computed tomography (CT) scans for diagnosing lung cancer?

Patient or population: Adults aged 18+ with solid pulmonary nodules

New test: Pulmonary nodule volume doubling time

Pooled sensitivity: 0.44 (95% CI: 0.23 to 0.67) | Pooled specificity: 0.92 (95% CI: 0.87 to 0.96)

Test result	Number of results per 1,000 patients tested (95% CI) Prevalence 5% Typically seen in	Number of participants (studies)	Certainty of the Evidence (GRADE)
True positives	22 (12 to 33)	558	⊕○○○
False negatives	28 (17 to 38)	(21)	VERY LOW ^{a,b,c}
True negatives	877 (826 to 908)	12837	⊕○○○
False positives	73 (42 to 124)	(21)	VERY LOW ^{a,b,c}

CI: Confidence interval

Explanations

- a. Some risk of bias across studies
- b. Serious inconsistency across sensitivities
- c. Some imprecision across sensitivities

1298

1299 VDT < 400 days

What is the diagnostic accuracy of a pulmonary nodule volume doubling time of less than 400 days between interval computed tomography (CT) scans for diagnosing lung cancer?

Patient or population: Adults aged 18+ with solid pulmonary nodules

New test: Pulmonary nodule volume doubling time < 400 days

Pooled sensitivity: 0.76 (95% CI: 0.59 to 0.87) | Pooled specificity: 0.94 (95% CI: 0.79 to 0.98)

Test result	Number of results per 1,000 patients tested (95% CI) Prevalence 5% Typically seen in	Number of participants (studies)	Certainty of the Evidence (GRADE)
True positives	38 (30 to 43)	85	⊕⊕○○
False negatives	12 (7 to 20)	(4)	LOW ^{a,b}
True negatives	892 (752 to 935)	1485	⊕⊕○○
False positives	58 (15 to 198)	(4)	LOW ^{a,b}

CI: Confidence interval

Explanations

- a. Some risk of bias across studies
- b. Some inconsistency across sensitivities
- c. Some imprecision across sensitivities

1300

1301

1302

1303

1304

1305

1306 VDT < 600 days

What is the diagnostic accuracy of a pulmonary nodule volume doubling time of less than 600 days between interval computed tomography (CT) scans for diagnosing lung cancer?

Patient or population: Adults aged 18+ with solid pulmonary nodules

New test: Pulmonary nodule volume doubling time < 600 days

Pooled sensitivity: 0.87 (95% CI: 0.72 to 0.94) | Pooled specificity: 0.84 (95% CI: 0.64 to 0.93)

Test result	Number of results per 1,000 patients tested (95% CI) Prevalence 5% Typically seen in	Number of participants (studies)	Certainty of the Evidence (GRADE)
True positives	43 (36 to 47)	106	⊕○○○
False negatives	7 (3 to 14)	(5)	VERY LOW ^{a,b,c}
True negatives	794 (609 to 884)	1560	⊕○○○
False positives	156 (66 to 341)	(5)	VERY LOW ^{a,b,c}

CI: Confidence interval

Explanations

- a. Some risk of bias across studies
- b. Some inconsistency across sensitivities and specificities
- c. Some imprecision across sensitivities

1307

1308

1309 Volume change

1310 Volume change > 25%

What is the diagnostic accuracy of a pulmonary nodule volume change of greater than 25% between interval computed tomography (CT) scans for diagnosing lung cancer?

Patient or population: Adults aged 18+ with solid pulmonary nodules

New test: Pulmonary nodule volume change > 25%

Pooled sensitivity: 0.90 (95% CI: 0.84 to 0.94) | Pooled specificity: 0.88 (95% CI: 0.71 to 0.96)

Test result	Number of results per 1,000 patients tested (95% CI) Prevalence 5%* Typically seen in	Number of participants (studies)	Certainty of the Evidence (GRADE)
True positives	31 (16 to 43)	38	⊕⊕○○
False negatives	19 (7 to 34)	(2)	LOW ^{a,b}
True negatives	767 (447 to 863)	123	⊕⊕○○
False positives	183 (87 to 503)	(2)	LOW ^{a,b}

CI: Confidence interval

Explanations

- a. Some inconsistency across sensitivities
- b. Some imprecision across sensitivities

1311

1312

1313 **Recommendation Tables**

1314 **Question Details**

POPULATION:	Adults (18+) with solid pulmonary nodules
INDEX TESTS:	Strategies used to detect change between interval computed tomography (CT) scans
GOLD STANDARD:	Pathological diagnosis of invasive lung cancer or clinical diagnosis of lung cancer
OUTCOME:	Diagnostic accuracy of strategies used to detect change for diagnosing lung cancer

1315

1316 **Volume doubling time (VDT)**

1317 *VDT < 400 days*

1318 **SUMMARY OF JUDGEMENTS**

JUDGEMENT							
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
TEST ACCURACY	Very inaccurate	Inaccurate	Accurate	Very accurate		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	Does not favour the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know

1319

1320

1321 **TYPE OF RECOMMENDATION**

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
☐	☐	☐	☒	☐

1322

1323

1324 CONCLUSIONS

Recommendation

A solid pulmonary nodule volume doubling time of less than 400 days may indicate a diagnosis of lung cancer. (Conditional)

Justification

A solid pulmonary nodule volume doubling time of < 400 days provides a moderate sensitivity and a very high specificity for detecting change between interval computed tomography (CT) scans for diagnosing lung cancer in solid pulmonary nodules. (Low)

Subgroup considerations

There were not enough data to consider subgroups (consolidation and peri-cystic lesions)

Research priorities

Further research is needed to determine the optimal volume doubling time for diagnosing lung cancer in solid pulmonary nodules.

1328
1329 VDT < 600 days

1330 SUMMARY OF JUDGEMENTS

PROBLEM	JUDGEMENT						
	No	Probably no	Probably yes	Yes		Varies	Don't know
TEST ACCURACY	Very inaccurate	Inaccurate	Accurate	Very accurate		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	Does not favour the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know

1331
1332
1333 TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
☐	☐	☐	☒	☐

1334 **CONCLUSIONS**

Recommendation

A solid pulmonary nodule volume doubling time of less than 600 days may indicate a diagnosis of lung cancer. **(Conditional)**

Justification

A solid pulmonary nodule volume doubling time of < 600 days provides a high sensitivity and a high specificity for detecting change between interval computed tomography (CT) scans for diagnosing lung cancer in solid pulmonary nodules. **(Very low)**

Subgroup considerations

There were not enough data to consider subgroups (consolidation and peri-cystic lesions)

Research priorities

Further research is needed to determine the optimal volume doubling time for diagnosing lung cancer in solid pulmonary nodules.

1338

1339 **Volume change**

1340 *Volume change > 25%*

1341 **SUMMARY OF JUDGEMENTS**

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
TEST ACCURACY	Very inaccurate	Inaccurate	Accurate	Very accurate		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	Does not favour the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know

1342

1343 **TYPE OF RECOMMENDATION**

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
☐	☐	☐	☒	☐

1344 CONCLUSIONS

Recommendation

There is insufficient evidence to determine if a solid pulmonary nodule volume change of greater than 25% may indicate a diagnosis of lung cancer.

Justification

A solid pulmonary nodule volume change of 25% provides a low sensitivity and a high specificity for detecting change between interval computed tomography (CT) scans for diagnosing lung cancer in solid pulmonary nodules. (Low)

Subgroup considerations

Subgroups (consolidation and peri-cystic lesions) were not considered as there were not enough data.

Research priorities

Further research is needed to determine if solid pulmonary nodule volume change is a useful strategy for diagnosing lung cancer.

1348

1349

1350 References

- 1351 1. Xu DM, van Klaveren RJ, de Bock GH, et al. Role of baseline nodule density and changes in density and
1352 nodule features in the discrimination between benign and malignant solid indeterminate pulmonary
1353 nodules. *Eur J Radiol.* 2009;70(3):492-498.
- 1354 2. Lee JH, Hwang EJ, Lim WH, Goo JM. Determination of the optimum definition of growth evaluation for
1355 indeterminate pulmonary nodules detected in lung cancer screening. *PLoS ONE.* 2022;17(9):e0274583.
- 1356 3. Ashraf H, Dirksen A, Loft A, et al. Combined use of positron emission tomography and volume doubling
1357 time in lung cancer screening with low-dose CT scanning. *Thorax.* 2011;66(4):315-319.
- 1358 4. Borghesi AM, S.;Scrimieri, A.;Golemi, S.;Maroldi, R. Solid indeterminate pulmonary nodules of less than
1359 300 mm³: Application of different volume doubling time cut-offs in clinical practice. *Diagnostics (Basel).*
1360 2019;9(2) (no pagination).
- 1361 5. Horeweg N, van Rosmalen J, Heuvelmans MA, et al. Lung cancer probability in patients with CT-detected
1362 pulmonary nodules: a prespecified analysis of data from the NELSON trial of low-dose CT screening.
1363 *Lancet Oncol.* 2014;15(12):1332-1341.
- 1364 6. Revel MP, Merlin A, Peyrard S, et al. Software volumetric evaluation of doubling times for differentiating
1365 benign versus malignant pulmonary nodules. *AJR Am J Roentgenol.* 2006;187(1):135-142.
- 1366 7. Soardi GA, Perandini S, Motton M, Montemezzi S. Assessing probability of malignancy in solid solitary
1367 pulmonary nodules with a new Bayesian calculator: improving diagnostic accuracy by means of expanded
1368 and updated features. *Eur Radiol.* 2015;25(1):155-162.
- 1369 8. Heuvelmans MA, Oudkerk M, de Bock GH, et al. Optimisation of volume-doubling time cutoff for fast-
1370 growing lung nodules in CT lung cancer screening reduces false-positive referrals. *Eur Radiol.*
1371 2013;23(7):1836-1845.

1372

1373

Field	Content
Review Question	In adults with solid pulmonary nodules, what is the diagnostic accuracy of strategies* used to detect change between interval computed tomography (CT) scans for diagnosing lung cancer? * Computer-aided measurement of specific nodule parameters (e.g. volume, mass) NOT artificial-intelligence tools where multiple parameters are computed to give an overall risk assessment.
Type of review question	Diagnostic accuracy review
Objective of the review	Where the initial index of suspicion of cancer in a solid pulmonary nodule is low, the preferred strategy is often to repeat the CT scan after a defined interval to determine whether the nodule is changing. This question seeks to clarify the optimal strategy for measuring and defining that change in order to tell apart malignant from benign nodules.
Eligibility criteria – population / disease / condition / issue / domain	Adults with solid pulmonary nodules (18+ years of age)
Eligibility criteria – index test(s)	Visual analysis Diameter change Volume doubling time Mass doubling time Volume change
Eligibility criteria – gold standard	Pathological diagnosis of invasive lung cancer or clinical diagnosis of lung cancer
Outcomes and prioritisation	Diagnostic accuracy
Eligibility criteria – study design	RCTs, comparative studies, case series (>50 cases)

Other inclusion /exclusion criteria	Non-English language excluded unless full English translation Conference abstracts, Cochrane reviews, systematic reviews, reviews Cochrane reviews and systematic reviews can be referenced in the text, but CANNOT be used in a meta-analysis
Proposed sensitivity / subgroup analysis, or meta-regression	Adults with solid pulmonary nodules - Consolidation - Peri-cystic lesions
Selection process – duplicate screening / selection / analysis	Agreement should be reached between Guideline members who are working on the question. If no agreement can be reached, a decision should be made by the Guideline co-chairs. If there is still no decision, the matter should be brought to the Guideline group and a decision will be made by consensus
Data management (software)	RevMan5 Pairwise meta-analyses (if data in the correct format) Evidence review/considered judgement. Storing Guideline text, tables, figures, etc. MetaDTA Data meta-analyses Gradepro Quality of evidence assessment
Information sources – databases and dates	MEDLINE, Embase, Central Register of Controlled Trials and Cochrane Database of Systematic Reviews Restricted to articles published from 1990 onwards
Methods for assessing bias at outcome / study level	RevMan5 diagnostic accuracy full review template (based on QUADAS2) (follow instructions in ' <i>BTS Guideline Process Handbook – Diagnostic Accuracy (June 2020)</i> ')
Methods for quantitative analysis – combining studies and exploring (in)consistency	If 3 or more relevant studies: RevMan5 for forest plots, summary ROC plots MetaDTA to combine studies (pooled specificity, sensitivity, likelihood ratios, diagnostic odds ratio and confidence intervals) and calculate RevMan parameters for summary ROC plot (follow instructions in ' <i>BTS Guideline Process Handbook – Diagnostic Accuracy (June 2020)</i> ')

Meta-bias assessment – publication bias, selective reporting bias	GRADEpro Diagnostic accuracy quality of evidence assessment for each index test (follow instructions in '<i>BTS Guideline Process Handbook – Diagnostic Accuracy (June 2020)</i>')
Rationale / context – what is known	If the initial index of suspicion of cancer in a solid pulmonary nodule is low, surveillance is usually the preferred strategy, where the CT scan is repeated after a time interval (usually at least 3 months) to assess change in the nodule's appearance. The rationale is that malignant nodules will grow over time, benign scars tend to stay unchanged, and nodules that are due to inflammation or infection may resolve. In addition to growth, some nodules can alter their appearance (called morphological change) albeit without increasing in size. This question aims to determine the best way of measuring and defining what constitutes change in order to identify those nodules under surveillance that represent cancer.

1376

1377

1378

1379

1380

1381

1382

1383

1384

1385

1386

1387

1388

1389

1390

1391

1392

1393

1394

1395

1396

1397

1398

1399

1401 **Q5** **What is the diagnostic accuracy of imaging tests, and the optimal strategy for image utilisation**
 1402 **for diagnosing lung cancer in a sub-solid pulmonary nodule?**

1403 **Contents**

1404	Question Evidence Review	73
1405	Background	73
1406	Outcomes	73
1407	Evidence Review	73
1408	Evidence Statements	78
1409	Recommendations	79
1410	Good Practice Points	79
1411	Research recommendations	80
1412	Algorithms	81
1413	Ground-glass nodule pathway	81
1414	Part-solid nodule pathway	82
1415	Meta-analyses	83
1416	Nodule diameter	83
1417	Nodule volume	85
1418	Upper lobe location	85
1419	Spiculation	87
1420	FDG-avidity	89
1421	Air bronchogram	90
1422	Bubble-like lucency	92
1423	Clear lung/tumour interface	94
1424	CT density	95
1425	Size of solid component	97
1426	Area under the curve (AUC)	97
1427	Spiculation	97
1428	Air bronchogram	98
1429	Bubble-like lucency	98
1430	Risk of bias summaries	99

1431

1432

1433

1434	GRADE analyses	101
1435	Nodule diameter	101
1436	Nodule volume	102
1437	Upper lobe location	103
1438	Spiculation	104
1439	Air bronchogram	105
1440	Bubble-like lucency	106
1441	Clear lung/tumour interface	107
1442	CT density	107
1443	Size of solid component	108
1444	Recommendation tables	109
1445	Nodule diameter	109
1446	Upper lobe location	110
1447	Spiculation	111
1448	Air bronchogram	112
1449	Bubble-like lucency	113
1450	Clear lung/tumour interface	114
1451	CT density	115
1452	Size of solid component	116
1453	References	118
1454	Question Protocol	120
1455		
1456		
1457		
1458		
1459		
1460		
1461		
1462		
1463		
1464		
1465		
1466		
1467		
1468		
1469		
1470		

1471 Question 5 Evidence Review

1472 **Q5 What is the diagnostic accuracy of imaging tests, and the optimal strategy for image utilisation**
1473 **for diagnosing lung cancer in a sub-solid pulmonary nodule?**

1474 Background

1475 CT is the cornerstone imaging modality for assessment of sub-solid pulmonary nodules (SSN), while PET-CT
1476 may be considered in selected cases. However, there different methods for assessing imaging tests, and these
1477 can often vary, for example, how pulmonary nodules are measured. This review will determine the optimal
1478 strategy for image utilisation for diagnosing lung cancer in a sub-solid pulmonary nodule.

1479 Outcomes

1480 Nodule diameter; nodule volume; upper lobe location; spiculation; FDG-avidity; air bronchogram; bubble-like
1481 lucency; clear lung/tumour interface; size of solid component; Brock risk score; Herder risk score; Mayo risk
1482 score; Veterans Affairs (VA) risk score; UK Lung Cancer Screening (UKLS) risk score

1483 Evidence Review

1484 The initial literature search identified 640 potentially relevant papers, with 37 papers being deemed relevant to
1485 the review.¹⁻³⁷ However, relevant studies were heavily weighted to the study of adenocarcinoma spectrum
1486 lesions. Hence, for the purposes of this review, invasive adenocarcinoma (IAC) and minimally invasive
1487 adenocarcinoma (MIA) sub-solid pulmonary nodules were regarded as malignant; and adenocarcinoma in situ
1488 (AIS) and atypical adenomatous hyperplasia (AAH)) sub-solid pulmonary nodules regarded as benign. As a
1489 result, many studies had to be disregarded as AIS and/or AAH had been included in the malignant group.

1490 There were not enough data to consider all imaging types (computed tomography (CT), positron emission
1491 tomography computed tomography (PET-CT) and magnetic resonance imaging (MRI)) so the evidence review
1492 is focused on CT.

1493 Nodule diameter

1494 No studies reported on the diagnostic accuracy of diameter measurements for diagnosing lung cancer in sub-
1495 solid pulmonary nodules. Instead, 15 studies directly reported on maximal diameter measurements for IAC
1496 and MIA (malignant) and AIS and AAH (benign) sub-solid pulmonary nodules.¹⁻¹⁵ Twelve studies were
1497 excluded because:

- 1498 i) Mean diameter measurements were reported (6 studies),
- 1499 ii) The measurement type (e.g., mean $\pm$ standard deviation) was not defined (1 study),
- 1500 iii) The study involved less than five cases (one study); and
- 1501 iv) The study focused on a specific range of nodule size (4 studies).

1502 Meta-analyses were performed as detailed below.

1503 ***Malignant versus benign sub-solid pulmonary nodules***

1504 Meta-analysis showed that mean maximal nodule diameter was 4.01 (3.19 to 4.82) mm greater in malignant
1505 sub-solid pulmonary nodules (IAC + MIA) compared with benign sub-solid pulmonary nodules (AIS + AAH)
1506 (Figure Q5a and Table Q5a).¹⁻¹⁵

1507 ***Invasive adenocarcinoma (IAC) (malignant) versus benign sub-solid pulmonary nodules***

1508 Meta-analysis showed that mean maximal nodule diameter was 5.77 (4.23 to 7.30) mm greater in IAC sub-
1509 solid nodules (malignant) compared with benign sub-solid nodules (AIS + AAH) (Figure Q5a and Table Q5a).<sup>1-
1510 3,6,7,9-13,15</sup>

1511

1512 **Minimally invasive adenocarcinoma (MIA) (malignant) versus benign sub-solid pulmonary nodules**

1513 Meta-analysis showed that mean maximal nodule diameter was 2.34 (1.45 to 3.23) mm greater in MIA sub-
 1514 solid nodules (malignant) compared with benign sub-solid nodules (AIS + AAH) (Figure Q5a and Table Q5a).<sup>1-
 1515 3,6,7,10,12,13,15</sup>

1516 **Ground-glass nodules (GGN)**

1517 There were not enough data to consider all subgroup analyses (without recent relevant imaging, newly
 1518 appeared since recent imaging, ground-glass nodules (GGN) and part-solid nodules (PSN)), but GGN were
 1519 considered as a subgroup.^{1-3,11,12}

1520 The separate meta-analysis results for IAC and MIA GGN sub-solid nodules (malignant) versus benign GGN
 1521 sub-solid nodules (AIS + AAH) are summarised in Table Q5a and shown in Figure Q5b.

1522 Table Q5a: Summary of meta-analysis mean maximal diameter differences between malignant (IAC and MIA)
 1523 and benign (AIS + AAH) sub-solid pulmonary nodules and ground-glass sub-solid pulmonary nodules (GGN)

Sub-solid nodule type(s)	n	Mean maximal diameter difference (CI)
IAC + MIA (all) ¹⁻¹⁵	34	4.01 (3.19 to 4.82) mm greater than benign
IAC (all) ^{1-3,6,7,9-13,15}	16	5.77 (4.23 to 7.30) mm greater than benign
MIA (all) ^{1-3,6,7,10,12,13,15}	14	2.34 (1.45 to 3.23) mm greater than benign
IAC (GGN) ^{1-3,11,12}	7	3.96 (2.33 to 5.59) mm greater than benign
MIA (GGN) ^{1-3,12}	6	3.23 (1.46 to 4.99) mm greater than benign

1524 All – GGN and PSN; CI – 95% confidence intervals; GGN – ground-glass nodules (subgroup); IAC – invasive
 1525 adenocarcinoma; MIA – minimally invasive adenocarcinoma; n – number of datasets; PSN – part-solid nodules

1526 **Nodule volume**

1527 No studies reported on the diagnostic accuracy of nodule volume for diagnosing lung cancer in sub-solid
 1528 pulmonary nodules. Three studies reported on nodule volume measurements in malignant (invasive
 1529 adenocarcinoma (IAC) and minimally invasive adenocarcinoma (MIA)) and benign (adenocarcinoma in situ
 1530 (AIS) and atypical adenomatous hyperplasia (AAH)) sub-solid pulmonary nodules.^{4,15,16} Two studies were
 1531 excluded because the measurement type (e.g., mean ± standard deviation) was not defined. Meta-analyses
 1532 were performed as detailed below.

1533 **Malignant versus benign sub-solid pulmonary nodules**

1534 Meta-analysis showed that mean nodule volume was 0.86 (0.35 to 1.37) cm³ greater in malignant sub-solid
 1535 pulmonary nodules (IAC + MIA) (pooled result) compared with benign sub-solid pulmonary nodules (AIS +
 1536 AAH) (Figure Q5c).^{4,15,16}

1537 **Invasive adenocarcinoma (IAC) (malignant) versus benign sub-solid pulmonary nodules**

1538 Meta-analysis showed that mean nodule volume was 2.69 (1.89 to 3.49) cm³ greater in IAC (malignant) sub-
 1539 solid nodules compared with benign sub-solid nodules (AIS + AAH) (Figure Q5c).¹⁵

1540 **Minimally invasive adenocarcinoma (MIA) (malignant) versus benign sub-solid pulmonary nodules**

1541 Meta-analysis showed that mean maximal nodule diameter was 0.46 (0.10 to 0.83) cm³ greater in MIA
 1542 (malignant) sub-solid nodules compared with benign sub-solid nodules (AIS + AAH) (Figure Q5c).^{15,16}

1543 **Upper lobe location**

1544 Twelve studies reported on the diagnostic accuracy of upper lobe location for diagnosing lung cancer in sub-
 1545 solid pulmonary nodules.^{2,5,14,17-25} Meta-analysis of the results showed a pooled sensitivity of 0.63 [0.61, 0.65]
 1546 and pooled specificity of 0.43 [0.35, 0.51] [95% confidence intervals] (data shown in Figure Q5d, Table Q5j)

and summarised in [Table Q5b](#)). As there were not enough data to determine a full SROC curve ([Figure Q5d ii](#)), an estimated AUC could not be determined.

Ground-glass nodules (GGN)

There were not enough data to consider all subgroup analyses, but a subgroup analysis was performed on ground-glass nodules (GGN). Meta-analysis data are shown in [Figure Q5e](#), [Table Q5k](#) and summarised in [Table Q5b](#).

Table Q5b: Diagnostic accuracy of upper lobe location for diagnosing lung cancer in sub-solid nodules and ground-glass nodules (GGN) (subgroup)

Sub-solid nodule type	n	Sensitivity	Specificity
		Posterior median [95% PI]	Posterior median [95% PI]
All 2,5,14,17-25	12	0.63 [0.61, 0.65]	0.43 [0.35, 0.51]
GGN* 2,17,18,20,21,23	6	0.65 [0.60, 0.70]	0.41 [0.27, 0.60]

All – GGN and PSN; GGN – ground-glass nodule; n – number of studies; PI – posterior intervals; PSN – part-solid nodule

* Bayesian meta-analyses

Spiculation

Twenty-two studies reported on the diagnostic accuracy of spiculation for diagnosing lung cancer in sub-solid pulmonary nodules.^{2,5-8,10,11,14-16,18,19,21-30} Meta-analysis showed a pooled sensitivity of 0.28 [0.18, 0.39] and pooled specificity of 0.91 [0.86, 0.94] [95% confidence intervals] (data shown in [Figure Q5f](#), [Table Q5l](#) and summarised in [Table Q5c](#)). The estimated AUC was 0.755 ([Figure Q5q](#)).

Ground-glass nodules (GGN)

There were not enough data to consider all subgroup analyses, but a subgroup analysis was performed on ground-glass nodules (GGN). Meta-analysis data are summarised in [Table Q5c](#) (data shown in [Figure Q5g](#) and [Table Q5m](#)).

Table Q5c: Diagnostic accuracy of spiculation for diagnosing lung cancer in ground-glass nodules (GGN)

Sub-solid nodule type	n	Sensitivity [95% CI]	Specificity [95% CI]
All 2,5-8,10,11,14-16,18,19,21-30	22	0.28 [0.18, 0.39]	0.91 [0.86, 0.94]
GGN 2,11,16,18,21,23,27,29	8	0.17 [0.07, 0.36]	0.95 [0.87, 0.98]

All – GGN and PSN; CI – confidence intervals; GGN – ground-glass nodule; n – number of studies; PSN – part-solid nodules

FDG-avidity

No studies reported on the diagnostic accuracy of FDG-avidity for diagnosing lung cancer in sub-solid pulmonary nodules. However, one study compared FDG-avidity in malignant and benign sub-solid nodules, showing mean FDG-avidity was 2.80 (2.53 to 3.07) g/mL greater in malignant sub-solid nodules when compared with benign sub-solid nodules ([Figure Q5h](#)).⁹

Air bronchogram

Twelve studies reported on the diagnostic accuracy of the presence of air bronchogram for diagnosing lung cancer in sub-solid pulmonary nodules.^{6,7,10,11,15,17,18,23-25,29,30} Meta-analysis showed a pooled sensitivity of 0.27 [0.18, 0.40] and pooled specificity of 0.88 [0.79, 0.94] [95% confidence intervals] (data shown in [Figure Q5i](#), [Table Q5n](#) and summarised in [Table Q5d](#)). The estimated AUC was 0.634 ([Figure Q5r](#)).

1581 *Ground-glass nodules (GGN)*

1582 There were not enough data for all subgroup analyses, but a GGN subgroup meta-analysis was performed.
1583 Meta-analysis data are summarised in [Table Q5d](#) (data shown in [Figure Q5j](#) and [Table Q5o](#)).

1584 Table Q5d: Diagnostic accuracy of air bronchogram for diagnosing lung cancer in ground-glass nodules (GGN)

Sub-solid nodule type	n	Sensitivity [95% CI, or 95% PI]	Specificity [95% CI, or 95% PI]
All 6,7,10,11,15,17,18,23-25,29,30	12	0.27 [0.18, 0.40]	0.88 [0.79, 0.94]
GGN 11,17,18,29	4	0.38 [0.20, 0.61] *	0.84 [0.64, 0.93] *

1585 * Bayesian meta-analysis, posterior median [95% posterior intervals]

1586 All – GGN and PSN; CI – confidence intervals; GGN – ground-glass nodule; n – number of studies; PI – posterior
1587 intervals; PSN – part-solid nodules

1588 **Bubble-like lucency**

1589 Nineteen studies reported on the diagnostic accuracy of bubble-like lucency for diagnosing lung cancer in sub-
1590 solid pulmonary nodules.^{2,6-8,10,11,15,17-19,21,24-27,29-32} Meta-analysis showed a pooled sensitivity of 0.25 [0.19,
1591 0.31] and pooled specificity of 0.89 [0.85, 0.91] [95% confidence intervals] (data shown in [Figure Q5k](#), [Table](#)
1592 [Q5p](#) and summarised in [Table Q5e](#)). The estimated AUC was 0.704 ([Figure Q5s](#)).

1593 *Ground-glass nodules (GGN)*

1594 There were not enough data to consider all subgroup analyses, but a subgroup meta-analysis was performed
1595 for GGN. Meta-analysis data are summarised in [Table Q5e](#) (data shown in [Figure Q5l](#) and [Table Q5q](#)).

1596 Table Q5e: Diagnostic accuracy of bubble-like lucency for diagnosing lung cancer in ground-glass nodules
1597 (GGN)

Sub-solid nodule type	n	Sensitivity [95% CI]	Specificity [95% CI]
All 2,6-8,10,11,15,17-19,21,24-27,29-32	19	0.25 [0.19, 0.31]	0.89 [0.85, 0.91]
GGN 2,11,17,18,27,29,32	7	0.23 [0.13, 0.37]	0.90 [0.78, 0.95]

1598 All – GGN and PSN; CI – confidence intervals; GGN – ground-glass nodule; n – number of studies; PSN – part-solid
1599 nodules

1600 **Clear lung/tumour interface**

1601 Six studies reported on the diagnostic accuracy of a clear lung/tumour interface for diagnosing lung cancer in
1602 sub-solid pulmonary nodules.^{15,17,24-26,29} Meta-analysis showed a pooled sensitivity of 0.76 [0.52, 0.90] and
1603 pooled specificity of 0.25 [0.15, 0.38] [95% confidence intervals] (data shown in [Figure Q5m](#) and [Table Q5r](#)).
1604 As there were not enough data to determine a full SROC curve ([Figure Q5m ii](#)), an estimated AUC could not
1605 be determined.

1606 **CT density**

1607 No studies reported on the diagnostic accuracy of CT density. Instead, 14 studies reported on the mean CT
1608 densities of malignant and benign sub-solid pulmonary nodules.^{1,3,4,6,7,11,13,15,18,19,24-26,32} Three studies were
1609 excluded because: i) highest CT density measurements were reported (1 study); and ii) the measurement type
1610 (e.g., mean ± standard deviation) was not defined (2 studies). Meta-analyses were performed as detailed
1611 below.

1612 **Invasive versus non-invasive sub-solid pulmonary nodules**

1613 Meta-analysis showed that CT density was 104.11 (81.44 to 126.78) HU greater in malignant sub-solid
1614 pulmonary nodules (IAC + MIA) compared with benign sub-solid pulmonary nodules (AIS + AAH) ([Figure](#)
1615 [Q5n](#)).^{1,3,4,6,7,11,13,15,18,19,24-26,32}

1616 **Invasive adenocarcinoma (IAC) versus non-invasive sub-solid pulmonary nodules**

1617 Meta-analysis showed that mean maximal nodule diameter was 142.11 (94.96 to 189.25) HU greater in IAC
 1618 sub-solid nodules (malignant) compared with benign sub-solid nodules (AIS + AAH) (Figure Q5n and Table
 1619 Q5f).^{1,3,6,7,11,13,15,18,19,25,26,32}

1620 **Minimally invasive adenocarcinoma (MIA) versus non-invasive sub-solid pulmonary nodules**

1621 Meta-analysis showed that mean maximal nodule diameter was 59.23 (41.36 to 77.10) HU greater in MIA sub-
 1622 solid nodules (malignant) compared with benign sub-solid nodules (AIS + AAH) (Figure Q5n and Table
 1623 Q5f).^{1,3,6,7,13,15,18,19,25,26,32}

1624 **Ground-glass nodules (GGN)**

1626 There were not enough data to consider all subgroup analyses, but a subgroup analysis was performed on
 1627 ground-glass nodule (GGN). Meta-analysis data for IAC and MIA comparisons are summarised in Table Q5f
 1628 and shown in Figure Q5o.

1629 Table Q5f: Summary of meta-analysis mean CT density differences between malignant (IAC and MIA) and
 1630 benign (AIS + AAH) sub-solid pulmonary nodules and ground-glass sub-solid pulmonary nodules (GGN)

Invasive subsolid nodule subgroup	n	Mean CT density difference (CI)
IAC + MIA (all) ^{1,3,4,6,7,11,13,15,18,19,24-26,32}	39	104.11 (81.44 to 126.78) HU greater than benign
IAC (all) ^{1,3,6,7,11,13,15,18,19,25,26,32}	19	142.11 (94.96 to 189.25) HU greater than benign
MIA (all) ^{1,3,6,7,13,15,18,19,25,26,32}	18	59.23 (41.36 to 77.10) HU greater than benign
IAC (GGN) ^{1,3,11,18,25,32}	9	66.96 (49.12 to 84.80) HU greater than benign
MIA (GGN) ^{1,3,18,26,32}	6	46.05 (31.69 to 60.41) HU greater than benign

1631 All – GGN and PSN; CI – 95% confidence intervals; GGN – ground-glass nodules (subgroup); HU – Hounsfield units;
 1632 IAC – invasive adenocarcinoma; MIA – minimally invasive adenocarcinoma; n – number of datasets; PSN – part-solid
 1633 nodules

1634 **Size of solid component**

1635 No studies reported on the diagnostic accuracy of size of solid component for diagnosing lung cancer in sub-
 1636 solid pulmonary nodules. However, four studies reported on the mean size of solid component for malignant
 1637 and benign sub-solid nodules.^{4,8,9,33} Meta-analysis data are summarised in Table Q5g and data shown in
 1638 Figure Q5p.

1639 Table Q5g: Summary of meta-analysis mean size of solid component differences between malignant (IAC
 1640 and/or MIA) and benign (AIS + AAH) sub-solid pulmonary nodules (data from Figure Q5p)

Comparison	n	Mean size of solid component difference (CI)
Malignant versus benign ^{4,8,9,33}	7	Malignant 3.27 (3.02 to 3.53) mm greater
IAC (malignant) versus benign ^{9,33}	3	IAC 6.18 (5.52 to 6.84) mm greater
MIA (malignant) versus benign ³³	2	MIA 2.30 (0.53 to 4.06) mm greater

1641 CI – 95% confidence intervals; IAC – invasive adenocarcinoma; MIA – minimally invasive adenocarcinoma; n – number
 1642 of datasets

1643 **Risk calculator models (Brock, Herder, Mayo, VA and UKLS)**

1644 Seven studies reported data on the Brock, Mayo, VA and/or UKLS risk calculator models. There were no
 1645 available data for the Herder model; and sensitivity and specificity data were not available for the Herder, VA
 1646 and UKLS models. Available data are shown in Table Q5h.

1647 Table Q5h: Comparison of risk calculator models (Brock, Herder, Mayo, VA and UKLS) for identifying invasive
 1648 sub-solid nodules

Model	Study	AUC [95% CI]	Sensitivity (%)	Specificity (%)
Brock	Hammer 2019 ³⁴	0.78 [0.67, 0.85]	-	-
	Kim 2019 ³⁵	0.78	81.6	56.7
	Kim 2018 ⁵	0.75	82.3	53.8
Mayo	Maldonado 2020 ³⁶	0.89 [0.82, 0.99]	-	-
	Zhang 2021 ¹⁴	0.75	72.0	76.0
VA	Maldonado 2020 ³⁶	0.84 [0.76, 0.92]	-	-
UKLS	Maldonado 2020 ³⁶	0.58 [0.46, 0.70]	-	-
	Marcus 2019 ³⁷	0.89 [0.88, 0.89]	-	-

1649

1650 Risk calculator model comparison with other diagnostic tests

1651 The risk calculator model AUCs, sensitivities and specificities are compared with the other diagnostic tests
 1652 (upper lobe location, spiculation, air bronchogram and bubble-like lucency) in [Table Q5i](#).

1653

1654 Table Q5i: Area under the curve (AUC), sensitivity and specificity comparisons of risk calculator models (Brock,
 1655 Herder, Mayo, VA and UKLS) and other Guideline diagnostic tests for identifying invasive sub-solid nodules

Model / Test	AUC	Sensitivity (%)	Specificity (%)
Brock ^{5,34,35}	0.77 ± 0.02*	82.0 ± 0.49* ^{34,35}	55.2 ± 2.0* ^{34,35}
Mayo ^{14,36}	0.82 ± 0.10*	72.0 ¹⁴	76.0 ¹⁴
VA ³⁶	0.84	-	-
UKLS ^{36,37}	0.74 ± 0.22*	-	-
Upper lobe location ^{2,5,14,17-25}	-	63.1	42.8
Spiculation ^{2,5-8,10,11,14-16,18,19,21-30}	0.76	27.6	90.6
Air bronchogram ^{6,7,10,11,15,17,18,23-25,29,30}	0.68	27.3	88.5
Bubble-like lucency ^{2,6-8,10,11,15,17-19,21,24-27,29-32}	0.70	24.8	88.6
Clear lung/tumour interface ^{15,17,24-26,29}	-	76.3	24.8

1656 * Mean ± SD

1657 Evidence statements

1658 Malignant sub-solid pulmonary nodules (invasive adenocarcinoma (IAC) and minimally invasive
 1659 adenocarcinoma (MIA)) appear to have a greater maximal nodule diameter than benign sub-solid pulmonary
 1660 nodules (adenocarcinoma in situ (AIS), atypical adenomatous hyperplasia (AAH)) (**Very low**)

1661 Invasive adenocarcinoma (IAC) sub-solid pulmonary nodules appear to have a greater maximal nodule
 1662 diameter than minimally invasive adenocarcinoma (MIA) sub-solid pulmonary nodules (**Very low**)

1663 Invasive adenocarcinoma (IAC) sub-solid pulmonary nodules (malignant) may have a greater nodule volume
 1664 than benign sub-solid pulmonary nodules (adenocarcinoma in situ (AIS) and atypical adenomatous
 1665 hyperplasia (AAH)) (**Low**)

1666 Upper lobe location appears to have a low sensitivity and a low specificity for diagnosing lung cancer in sub-
 1667 solid pulmonary nodules (**Moderate**)

1668 Upper lobe location appears to have a moderate sensitivity and a low specificity for diagnosing lung cancer in
 1669 ground-glass pulmonary nodules (**Low**)

1670 Spiculation appears to have a low sensitivity and a very high specificity for diagnosing lung cancer in sub-solid
 1671 pulmonary nodules (**Very low**)

1672 Spiculation appears to have a low sensitivity and a very high specificity for diagnosing lung cancer in ground-
 1673 glass pulmonary nodules (**Low**)

1674 There is insufficient evidence to determine if FDG-avidity can determine lung cancer in sub-solid pulmonary
 1675 nodules.

1676 The presence of air bronchogram appears to have a low sensitivity and a high specificity for diagnosing lung
 1677 cancer in sub-solid pulmonary nodules (**Very low**)

1678 The presence of air bronchogram appears to have a low sensitivity and a high specificity for diagnosing lung
 1679 cancer in ground-glass pulmonary nodules (**Moderate**)

1680 The presence of bubble-like lucency appears to have a low sensitivity and a high specificity for diagnosing
 1681 lung cancer in sub-solid pulmonary nodules (**Low**)

1682 The presence of bubble-like lucency appears to have a low sensitivity and a very high specificity for diagnosing
 1683 lung cancer in ground-glass pulmonary nodules (**Low**)

1684 The presence of a clear lung/tumour interface appears to have a moderate sensitivity and a low specificity for
 1685 diagnosing lung cancer in sub-solid pulmonary nodules (**Very low**)

1686 Invasive sub-solid pulmonary nodules (invasive adenocarcinoma (IAC) and minimally invasive
 1687 adenocarcinoma (MIA)) appear to have a greater CT density than benign sub-solid pulmonary nodules
 1688 (adenocarcinoma in situ (AIS) and atypical adenomatous hyperplasia (AAH)) (**Very low**)

1689 Invasive adenocarcinoma (IAC) sub-solid pulmonary nodules appear to have a greater CT density than
 1690 minimally invasive adenocarcinoma (MIA) sub-solid pulmonary nodules (**Very low**)

1691 Invasive sub-solid pulmonary nodules (invasive adenocarcinoma (IAC) and minimally invasive
 1692 adenocarcinoma (MIA)) appear to have a greater size of solid component than benign sub-solid pulmonary
 1693 nodules (adenocarcinoma in situ (AIS) and atypical adenomatous hyperplasia (AAH)) (**Very low**)

1694 There is insufficient evidence to determine the diagnostic accuracy of risk calculator models (Brock, Herder,
 1695 Mayo, VA and UKLS) for diagnosing lung cancer in sub-solid nodules.

1696 **Recommendations**

- 1697 ➤ For adults with sub-solid pulmonary nodules, maximal nodule diameter (**Conditional**), increased CT
 1698 density (**Conditional**), spiculation (**Conditional**), size of solid component (**Conditional**), presence of air
 1699 bronchogram (**Conditional**) and presence of bubble-like lucency (**Conditional**) can be considered when
 1700 determining invasive lung cancer in a sub-solid pulmonary nodule.
- 1701 ➤ For adults with ground-glass pulmonary nodules (GGN), the **Ground-glass nodule pathway** (Algorithm 4)
 1702 should be used for determining lung cancer in GGN. (**Conditional** – by consensus)
- 1703 ➤ For adults with sub-solid pulmonary nodules with a solid component, the **Part-solid nodule pathway**
 1704 (Algorithm 5) should be used for determining lung cancer in part-solid pulmonary nodules. (**Conditional** –
 1705 by consensus)

1706 **Good Practice Points**

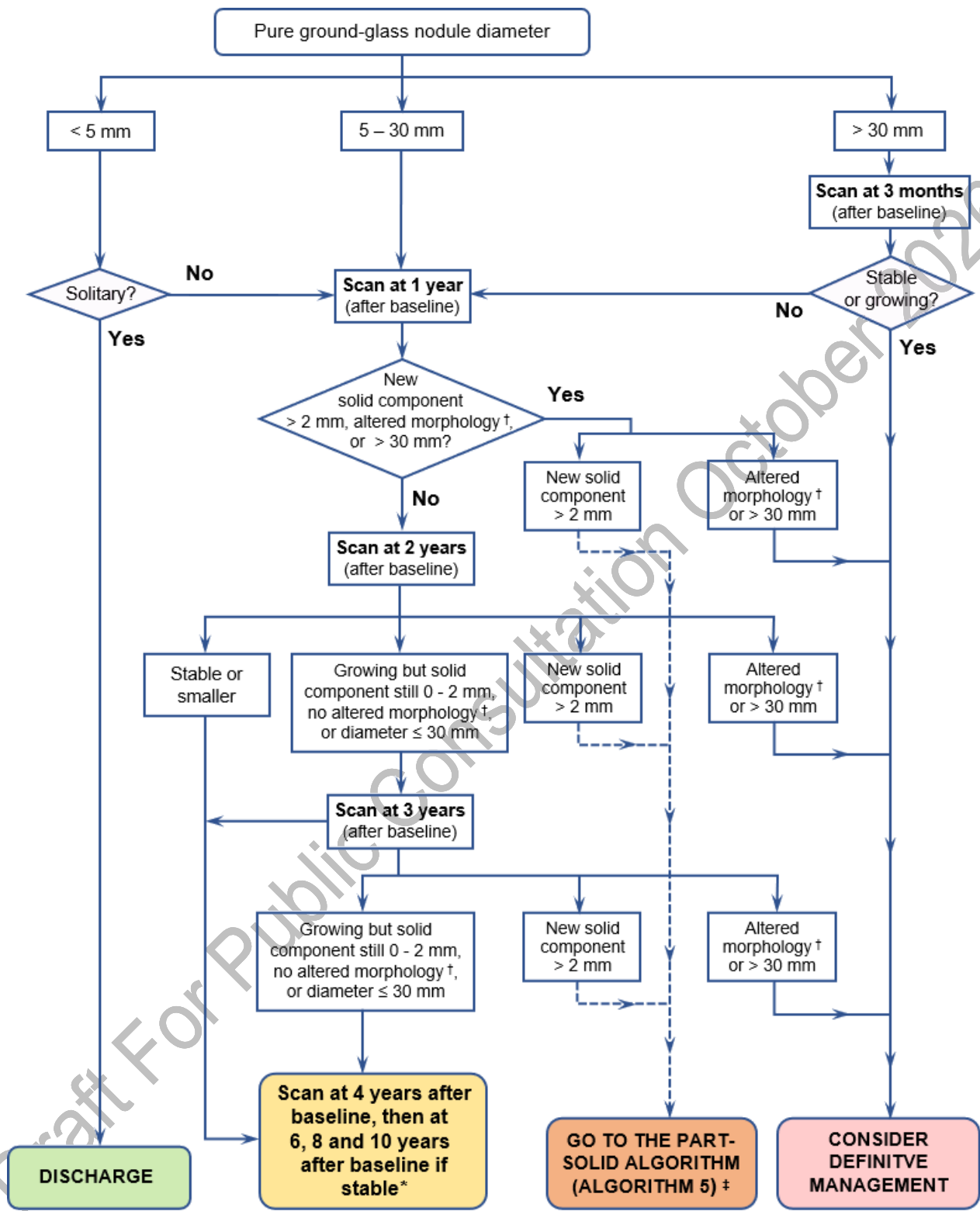
- 1707 ✓ Sub-solid pulmonary nodules should be reviewed on both mediastinal and lung windows to determine if
 1708 the nodule is of increased density.
- 1709 ✓ Diameter rather than volumetry should be used to determine the size of sub-solid pulmonary nodules.
- 1710 ✓ The maximum diameter of the solid component should be measured on lung windows and a lung kernel.

1711 **Research Recommendations**

- 1712 ▪ Further research is needed to determine the diagnostic accuracies of maximal nodule diameter, nodule
1713 volume and CT density for diagnosing lung cancer in sub-solid nodules and sub-solid nodule subtypes
1714 (ground glass nodules and part solid nodules)
- 1715 ▪ Further research is needed to determine the diagnostic accuracies of upper lobe location, spiculation and
1716 presence of bubble lucency for diagnosing lung cancer in part solid pulmonary nodules.
- 1717 ▪ Further research is needed to determine the diagnostic accuracy of the presence of air bronchogram for
1718 diagnosing lung cancer in part solid and ground glass pulmonary nodule subtypes.
- 1719 ▪ Further research is needed to determine the diagnostic accuracy of clear lung/tumour interface presence
1720 for diagnosing lung cancer in sub-solid pulmonary nodules and sub-solid nodule subtypes (ground glass
1721 nodules and part solid nodules)
- 1722 ▪ Further research is needed to determine the diagnostic accuracy of risk calculator models (Brock, Mayo,
1723 VA and/or UKLS) for diagnosing lung cancer in sub-solid pulmonary nodules.
- 1724 ▪ Further research is needed to determine if imaging-defined malignant sub-solid nodules represent clinically
1725 significant invasive lung cancer requiring intervention.
- 1726 ▪ Research is needed to determine the relative value of imaging biomarkers compared with clinical risk
1727 prediction models for guiding management decisions for sub-solid pulmonary nodules.

1728

1729



1731

1732 * Length of follow-up:

1733

- After 10 years of follow-up, consider CT every 5 years if patient remains suitable for definitive management.

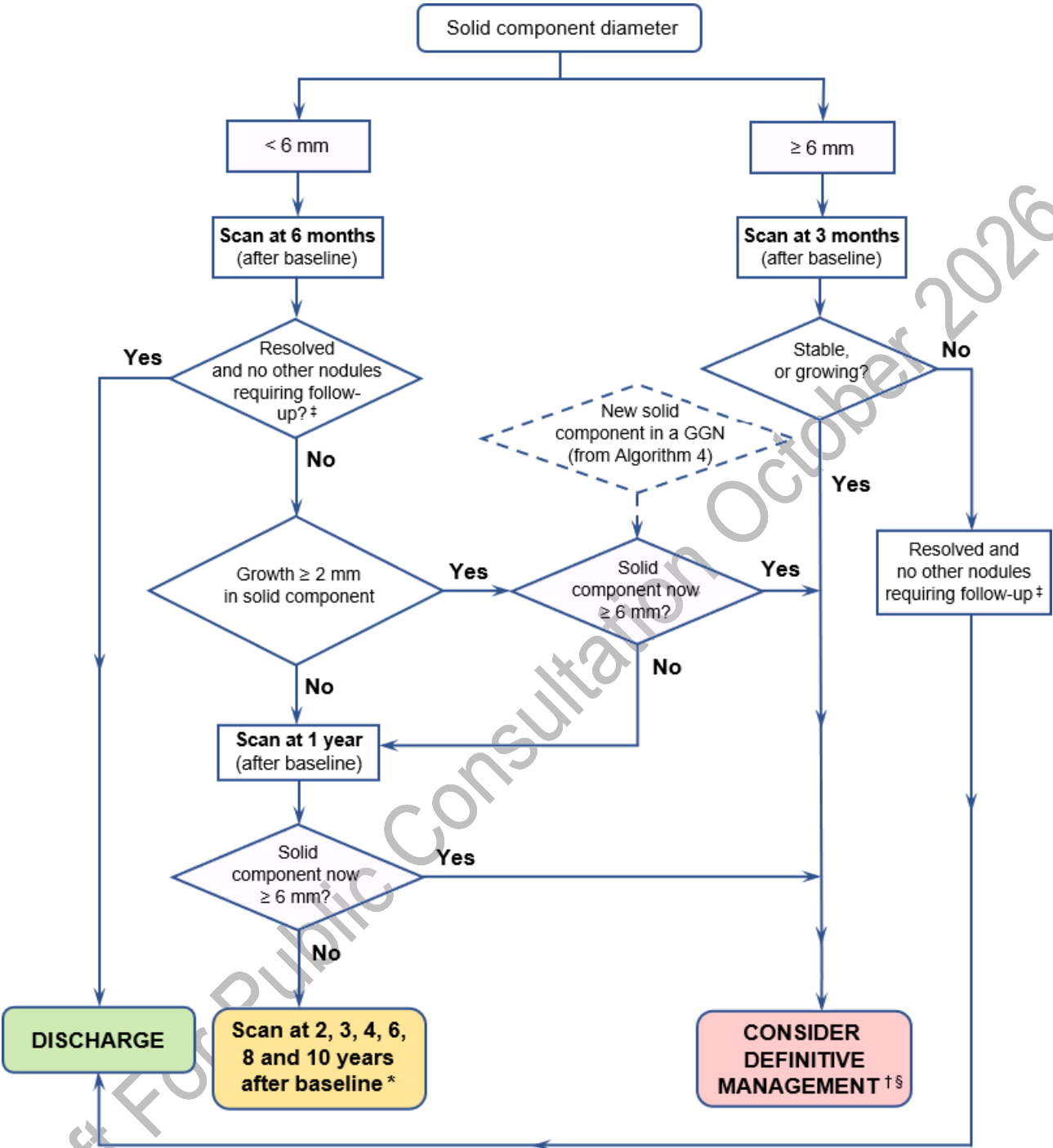
1734

- At any point at or after 4 years, if changes in the lesion occur, manage as per the steps for a scan at 2 years from baseline.

1735

† Altered morphology: air bronchograms, bubble-like lucency, increased CT density, distortion of fissure.

‡ Definitive management should be a shared decision-making process taking into account patient choice, age, co-morbidities, and fitness for treatment.



1737

1738 * Length of follow-up:

1739 - After 10 years of follow-up, consider CT every 5 years if patient remains suitable for definitive management.

1740 - At any point at or after 4 years, if changes in the lesion occur, manage as per the steps for a scan at 2 years from

1741 baseline.

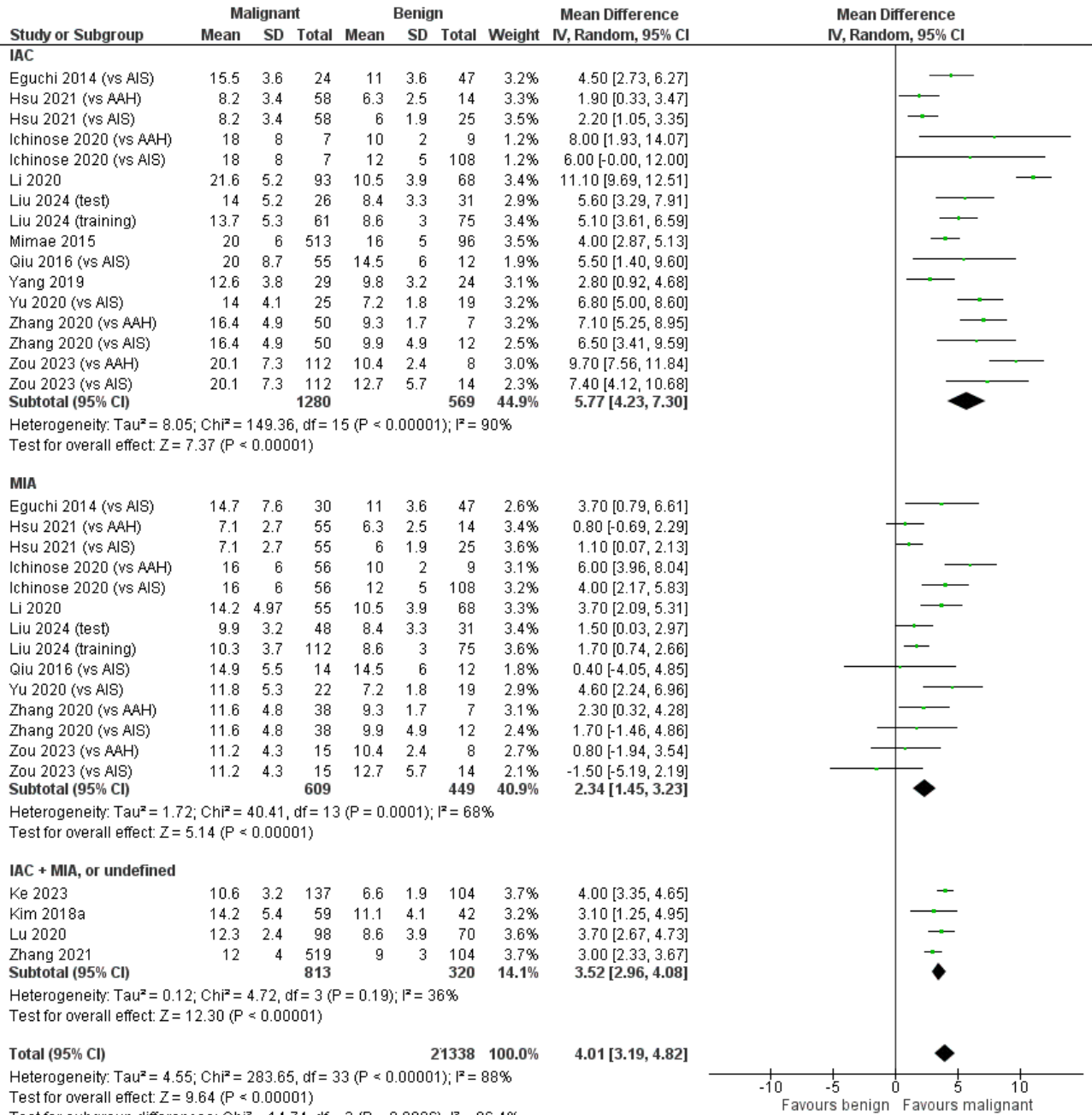
† PET-CT not required for further nodule characterisation or staging if solid component < 10 mm.

‡ If multiple GGNs and still persistent – see [Ground-glass nodule pathway](#) (Algorithm 4)

1742 Meta-analyses

1743 Nodule diameter

1744 Figure Q5a: Comparison of malignant versus benign sub-solid pulmonary nodule maximal diameter



1745

1746 AAH – atypical adenomatous hyperplasia; AIS – adenocarcinoma in situ; Benign – AAH and/or AIS; IAC – invasive
1747 adenocarcinoma; MIA – minimally invasive adenocarcinoma; undefined – study does not indicate malignant sub-solid
1748 nodule type(s); test – test set; training – training set

1749

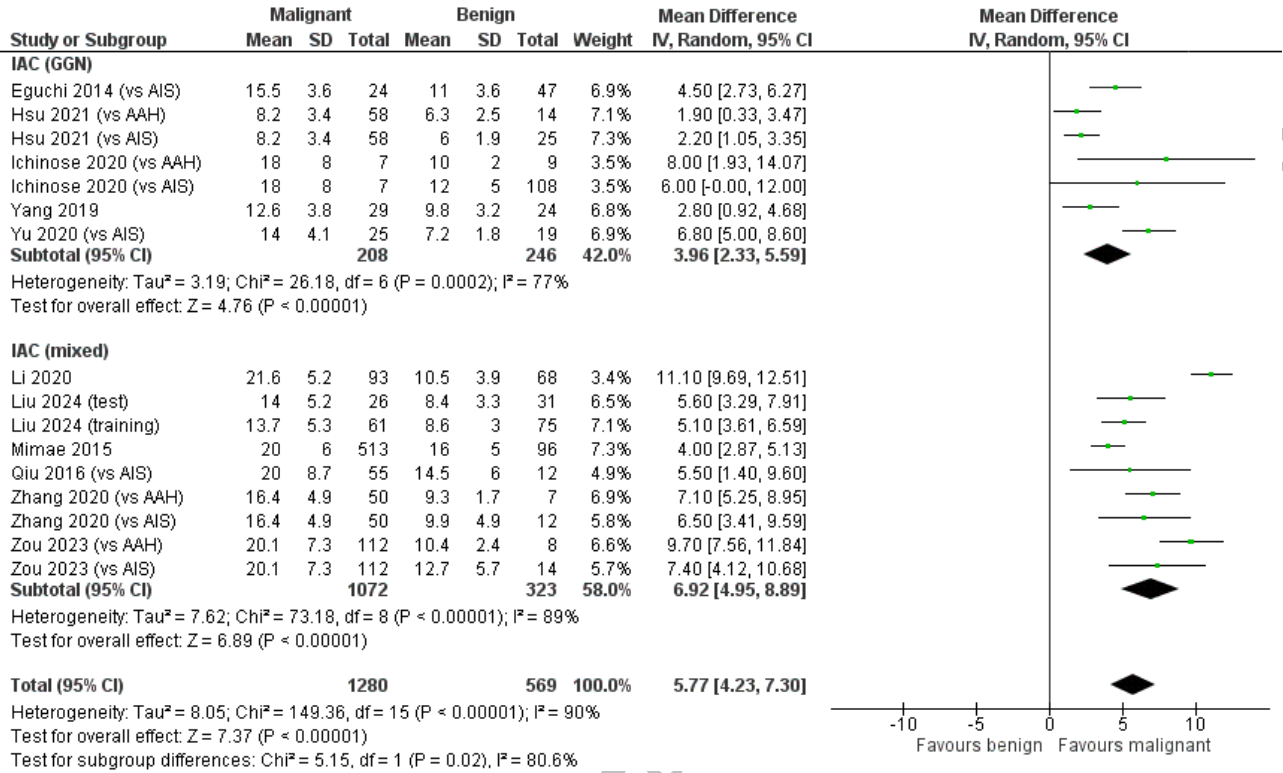
1750

1751

1752 **Ground-glass nodules (GGN)**

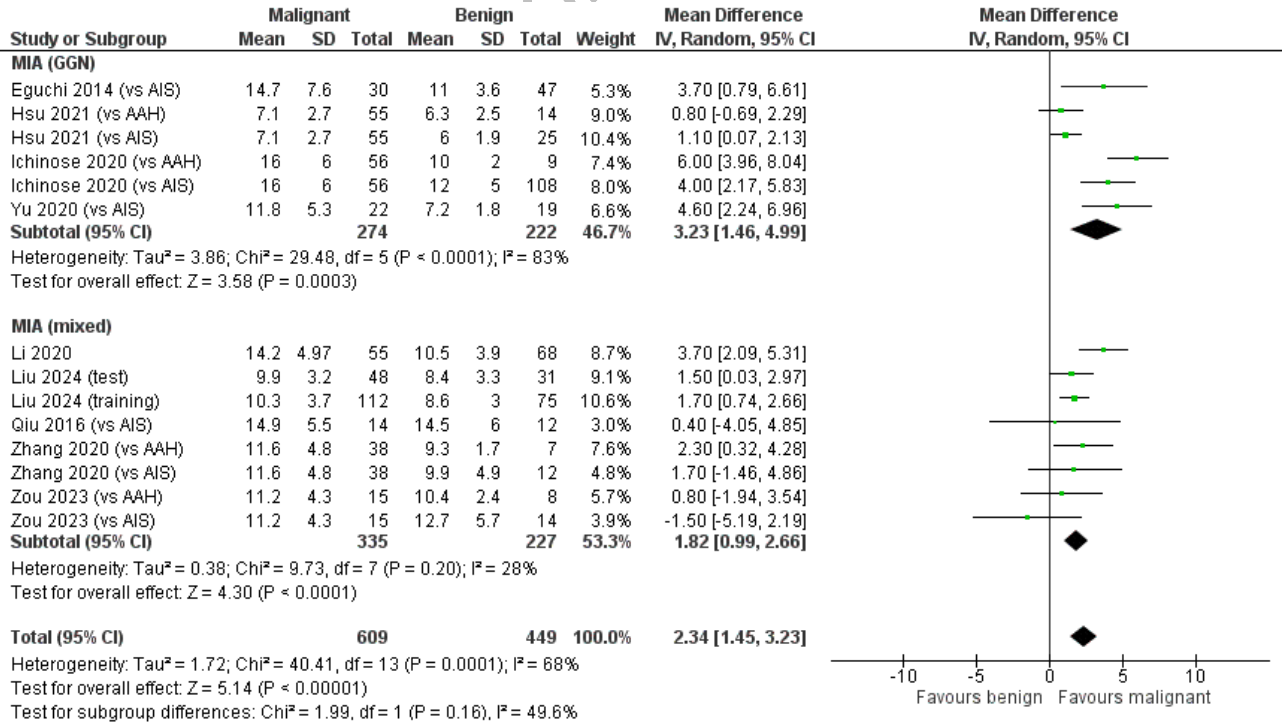
1753 Figure Q5b: Maximal diameter subgroup analyses of malignant versus benign ground-glass nodules (GGN)
1754 and mixed sub-solid nodules (GGN and part-solid nodules (PSN))

1755 i) IAC



1756

1757 ii) MIA

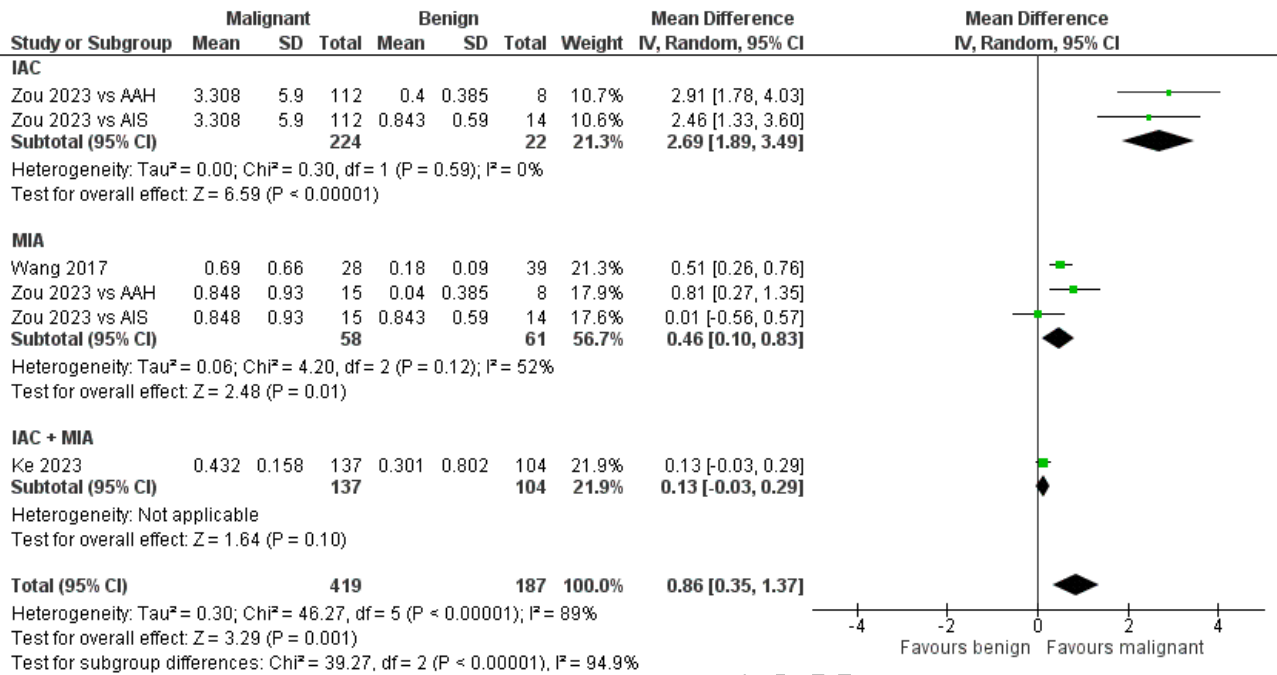


1758

1759 AAH – atypical adenomatous hyperplasia; AIS – adenocarcinoma in situ; Benign – AAH and/or AIS; GGN – ground-glass
1760 nodule; IAC – invasive adenocarcinoma; MIA – minimally invasive adenocarcinoma; mixed – PSN + GGN; PSN – part-
1761 solid nodule; test – test set; training – training set

1762 **Nodule volume**

1763 Figure Q5c: Comparison of malignant versus benign sub-solid pulmonary nodule volume



1764

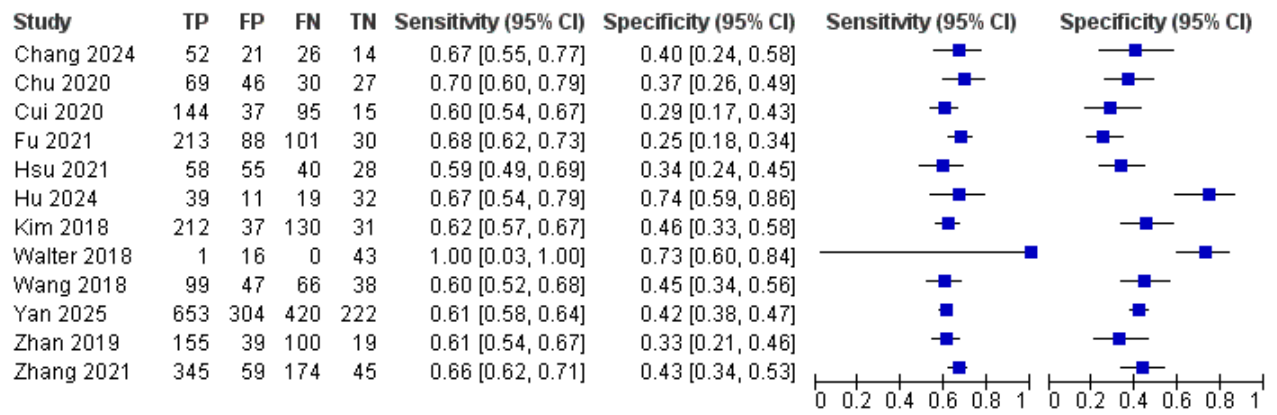
1765 (Please note data displayed as cm³ not mm³)

1766 AAH – atypical adenomatous hyperplasia; AIS – adenocarcinoma in situ; Benign – AAH and/or AIS; GGN – ground-glass
1767 nodule; IAC – invasive adenocarcinoma; MIA – minimally invasive adenocarcinoma; mixed – PSN + GGN; PSN – part-
1768 solid nodule; test – test set; training – training set
1769

1770 **Upper lobe location**

1771 Figure Q5d: Forest plot and SROC plot of upper lobe location for diagnosing lung cancer in sub-solid nodules

1772 iii) Forest plot



1773

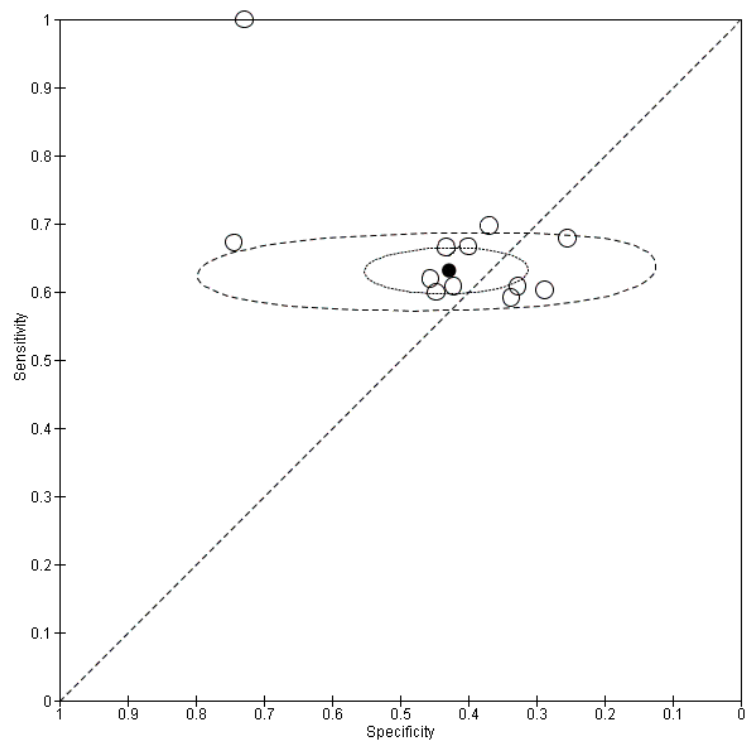
1774

1775

1776

1777

1778 iv) SROC plot (not enough data to determine curve)



1779

1780

1781 Table Q5j: Pooled results of upper lobe location for diagnosing lung cancer in sub-solid nodules

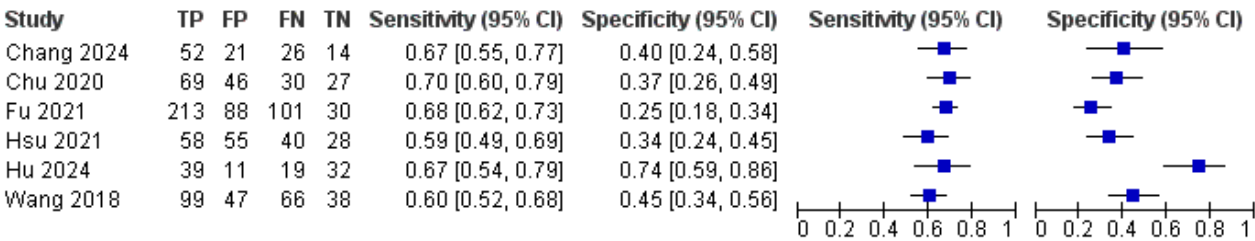
Pooled Sensitivity	0.631	[0.608, 0.654]
Pooled Specificity	0.428	[0.347, 0.514]
LR+	1.104	[0.950, 1.283]
LR-	0.861	[0.703, 1.055]
DOR	1.282	[0.901, 1.825]

1782

1783 **Ground-glass nodules (GGN)**

1784 Figure Q5e: Forest plot of upper lobe location for diagnosing lung cancer in ground-glass nodules (GGN)

1785 i) Forest plot



1786

1787

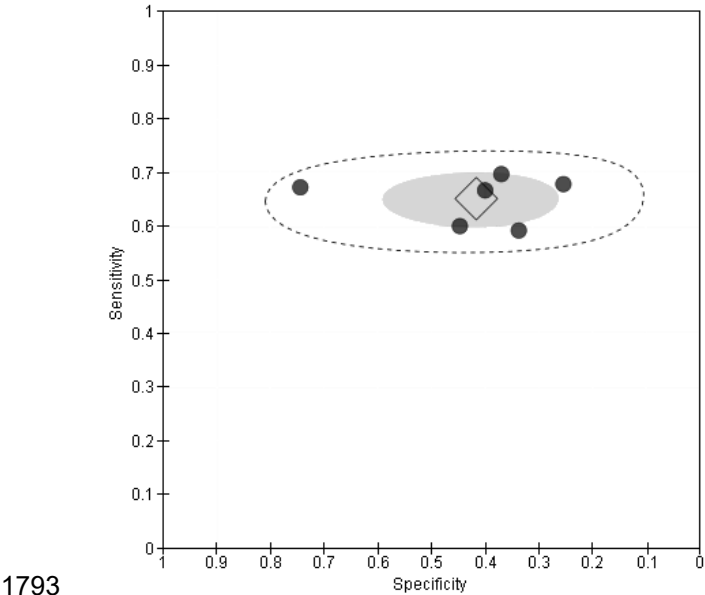
1788

1789

1790

1791

1792 ii) SROC plot (not enough data to determine curve)



1794 Table Q5k: Pooled results of upper lobe location for diagnosing lung cancer in ground-glass nodules (GGN)

Pooled Sensitivity	0.651	[0.596, 0.697]
Pooled Specificity	0.416	[0.272, 0.600]
LR+	1.114	[0.872, 1.637]
LR-	0.841	[0.573, 1.319]
DOR	1.328	[0.657, 2.826]

Bayesian meta-analysis, data displayed as posterior median [95% posterior interval]

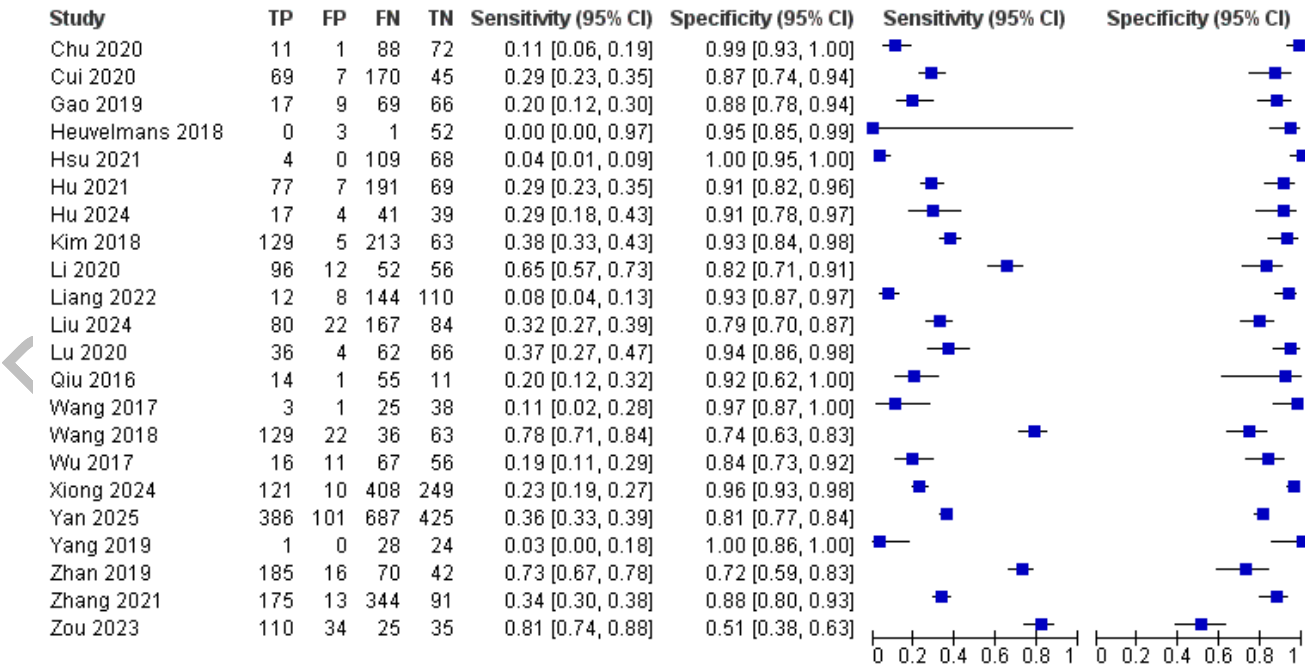
1795

1796

1797

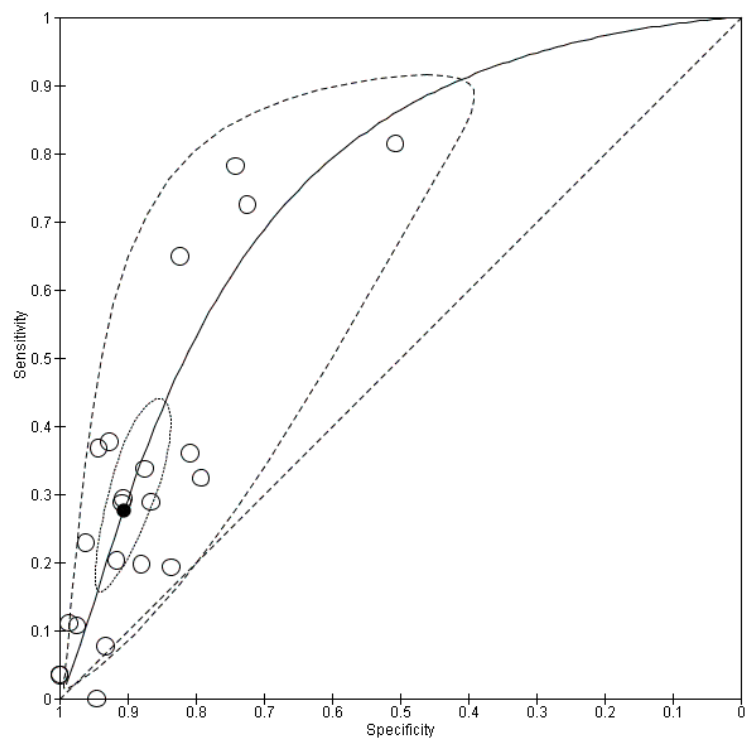
Spiculation

1798 Figure Q5f: Forest plot and SROC plot of spiculation for diagnosing lung cancer in sub-solid nodules



1799

1800 ii) SROC plot



1801

1802 Table Q5I: Pooled results of spiculation for diagnosing lung cancer in sub-solid nodules

Pooled Sensitivity	0.276	[0.182, 0.394]
Pooled Specificity	0.906	[0.858, 0.939]
LR+	2.926	[2.245, 3.812]
LR-	0.799	[0.712, 0.898]
DOR	3.659	[2.626, 5.099]

1803

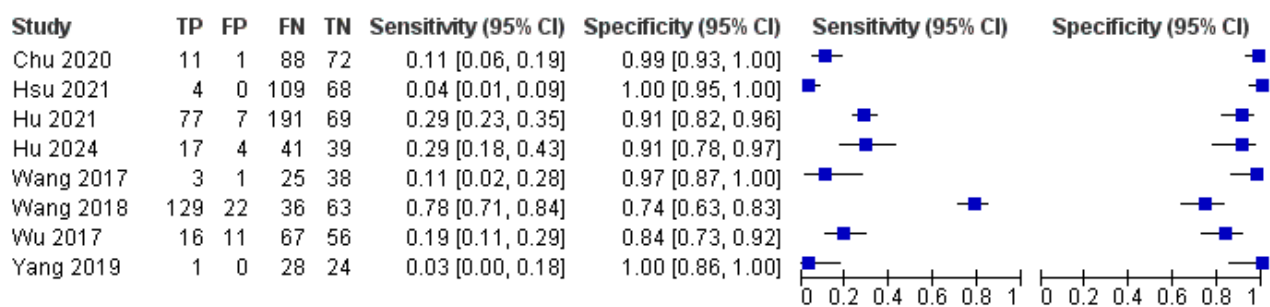
1804

1805 **Ground-glass nodules (GGN)**

1806 Figure Q5g: Forest plot and SROC plot of spiculation for diagnosing lung cancer in ground-glass nodules (GGN)

1807

1808 iii) Forest plot



1809

1810

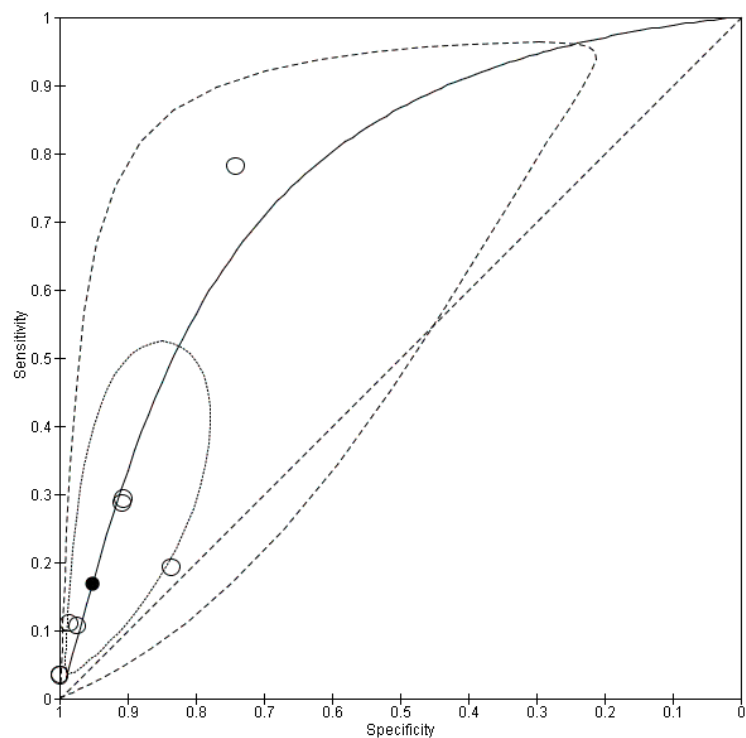
1811

1812

1813

1814

1815 iv) SROC plot



1816

1817 Table Q5m: Pooled results of spiculation for diagnosing lung cancer in ground-glass nodules (GGN)

Pooled Sensitivity	0.169	[0.067, 0.363]
Pooled Specificity	0.952	[0.873, 0.983]
LR+	3.482	[1.729, 7.010]
LR-	0.874	[0.758, 1.007]
DOR	3.985	[1.844, 8.613]

1818

1819

1820

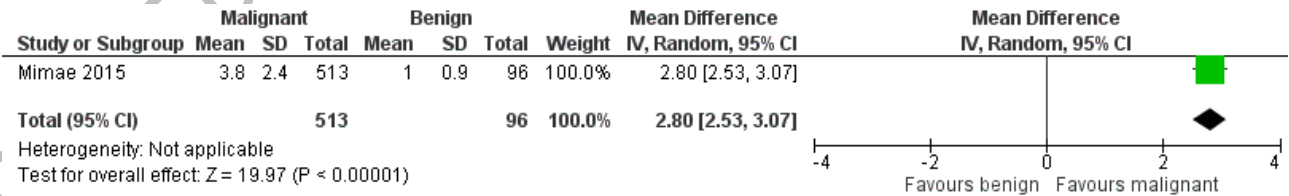
1821

1822

FDG-avidity

1823 Figure Q5h: Comparison of malignant versus benign sub-solid pulmonary nodule FDG-avidity

1824



1825

1826

1827

Benign – adenocarcinoma in situ (AIS); Malignant – invasive adenocarcinoma (IAC)

1828

1829

1830

1831

1832

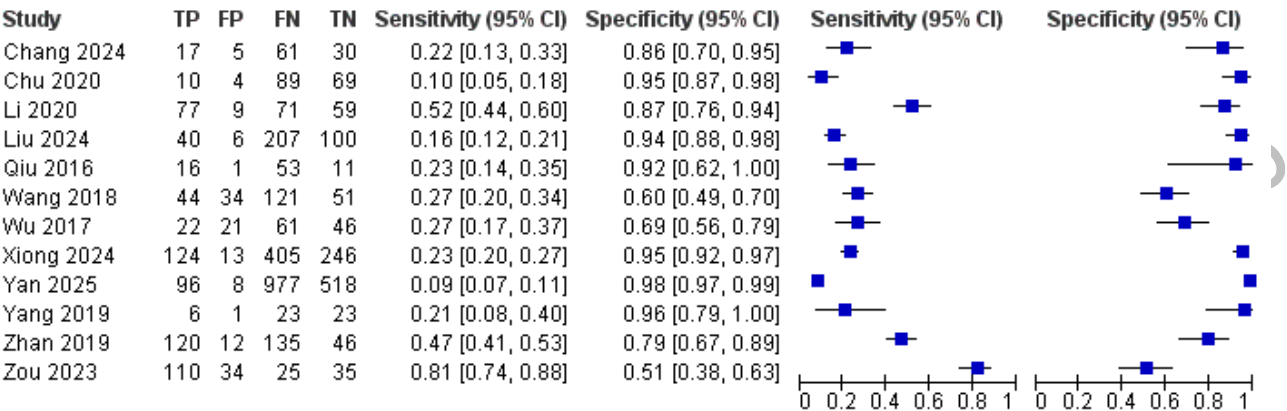
1833

1834

1835 **Air bronchogram**

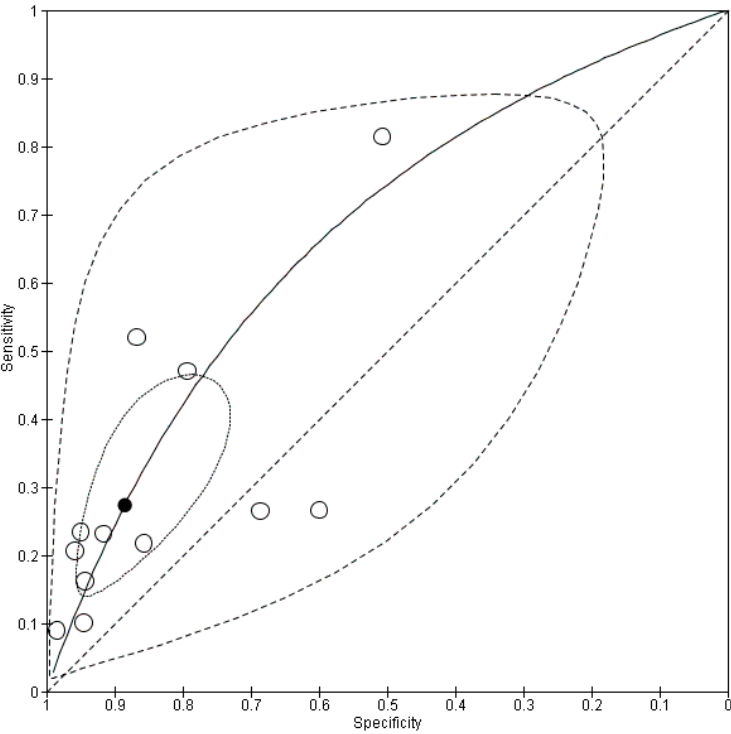
1836 Figure Q5i: Forest plot and SROC plot of air bronchogram for diagnosing lung cancer in sub-solid nodules

1837 i) Forest plot



1838

1839 ii) SROC plot



1840

1841 Table Q5n: Pooled results of air bronchogram for diagnosing lung cancer in sub-solid nodules

Pooled Sensitivity	0.273	[0.175, 0.400]
Pooled Specificity	0.885	[0.790, 0.940]
LR+	2.378	[1.514, 3.736]
LR-	0.821	[0.732, 0.921]
DOR	2.897	[1.733, 4.844]

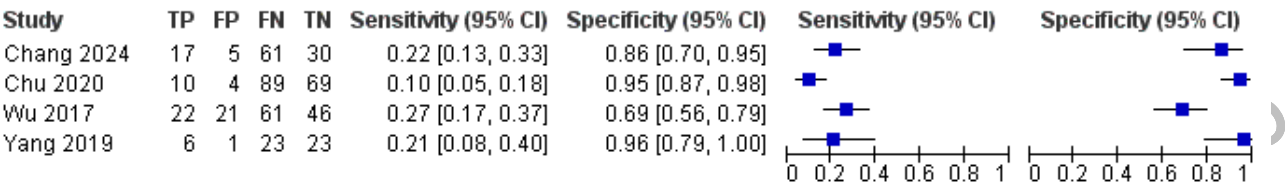
1842

1843

1844 **Ground-glass nodules (GGN)**

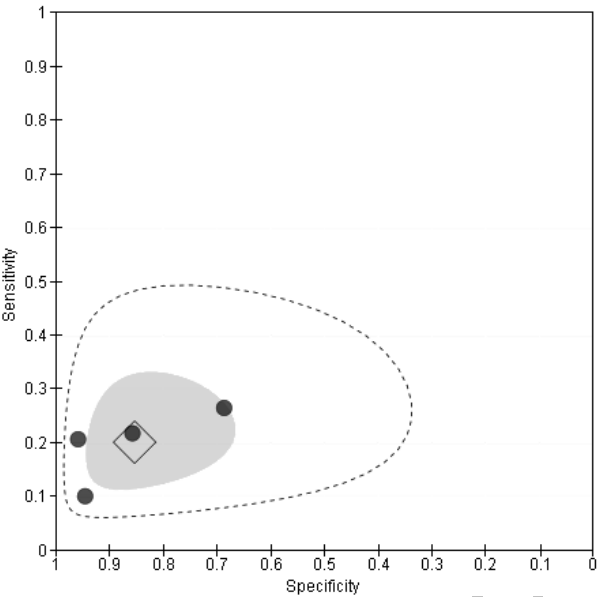
1845 Figure Q5j: Forest plot and SROC plot of air bronchogram for diagnosing lung cancer in ground-glass nodules
1846 (GGN)

1847 i) Forest plot



1848

1849 ii) SROC plot (not enough data to determine curve)



1850

1851 Table Q5o: Pooled results of air bronchogram for diagnosing lung cancer in ground-glass nodules (GGN)

Pooled Sensitivity	0.273	[0.175, 0.400]
Pooled Specificity	0.885	[0.790, 0.940]
LR+	2.378	[1.514, 3.736]
LR-	0.821	[0.732, 0.921]
DOR	2.897	[1.733, 4.844]

Bayesian meta-analysis, data displayed as posterior median [95% posterior interval]

1852

1853

1854

1855

1856

1857

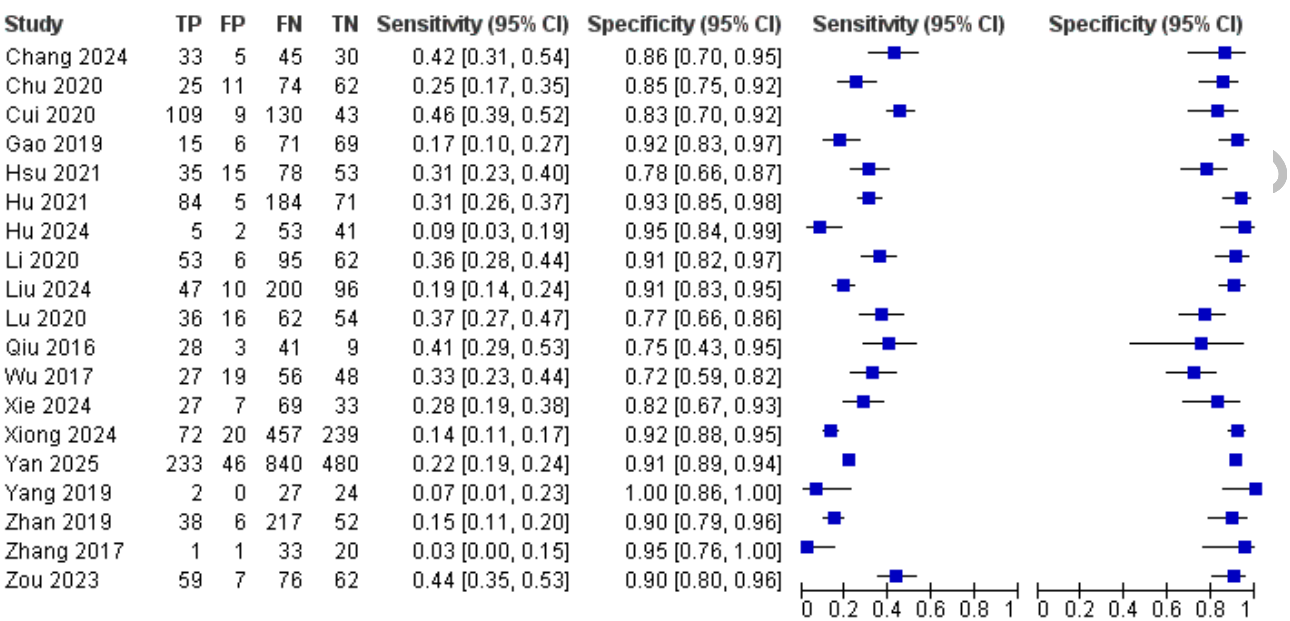
1858

1859

1860 **Bubble-like lucency**

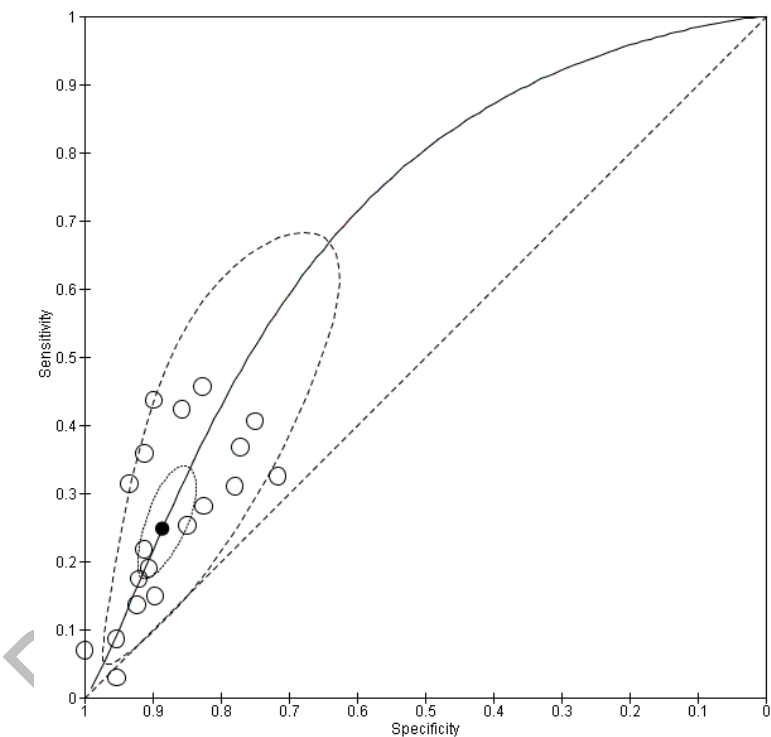
1861 Figure Q5k: Forest plot and SROC plot of bubble-like lucency for diagnosing lung cancer in sub-solid nodules

1862 i) Forest plot



1863

1864 ii) SROC plot



1865

1866

1867 Table Q5p: Pooled results of bubble-like lucency for diagnosing lung cancer in sub-solid nodules

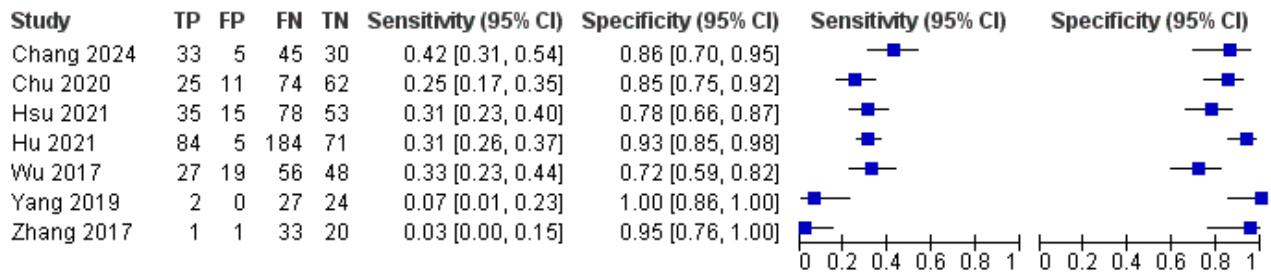
Pooled Sensitivity	0.248	[0.192, 0.314]
Pooled Specificity	0.886	[0.851, 0.913]
LR+	2.171	[1.746, 2.672]
LR-	0.849	[0.797, 0.904]
DOR	2.557	[1.985, 3.294]

1868
1869
1870

Ground-glass nodules (GGN)

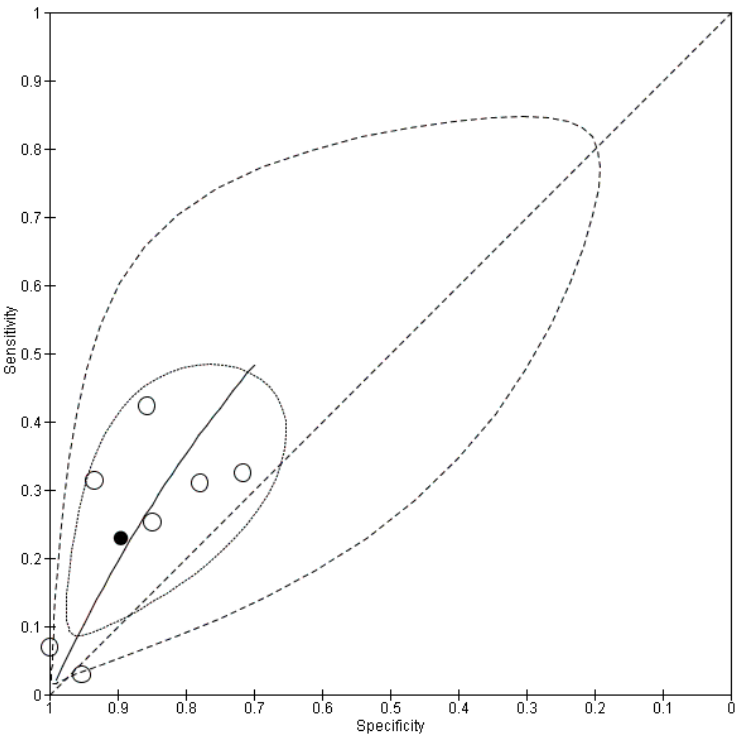
1871 Figure Q5l: Forest plot and SROC plot of bubble-like lucency for diagnosing lung cancer in ground-glass
1872 nodules (GGN)

1873 i) Forest plot



1874

1875 ii) SROC plot (not enough data to determine curve)



1876

1877

1878

1879

1880 Table Q5q: Pooled results of bubble-like lucency for diagnosing lung cancer in ground-glass nodules (GGN)

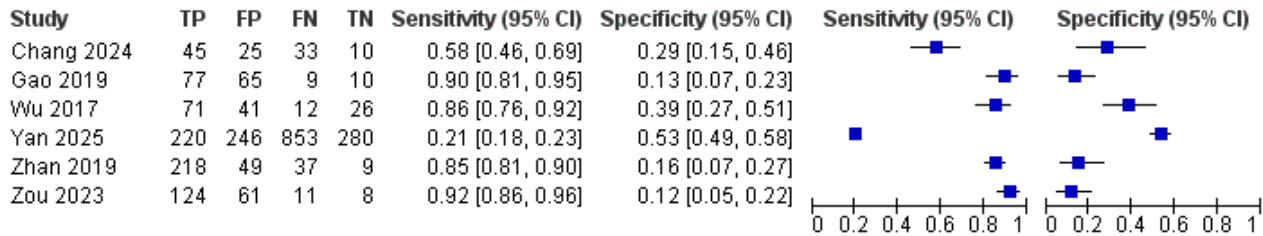
Pooled Sensitivity	0.229	[0.133, 0.336]
Pooled Specificity	0.895	[0.781, 0.953]
LR+	2.188	[1.201, 3.985]
LR-	0.861	[0.766, 0.967]
DOR	2.541	[1.291, 5.001]

1881

1882 **Clear lung/tumour interface**

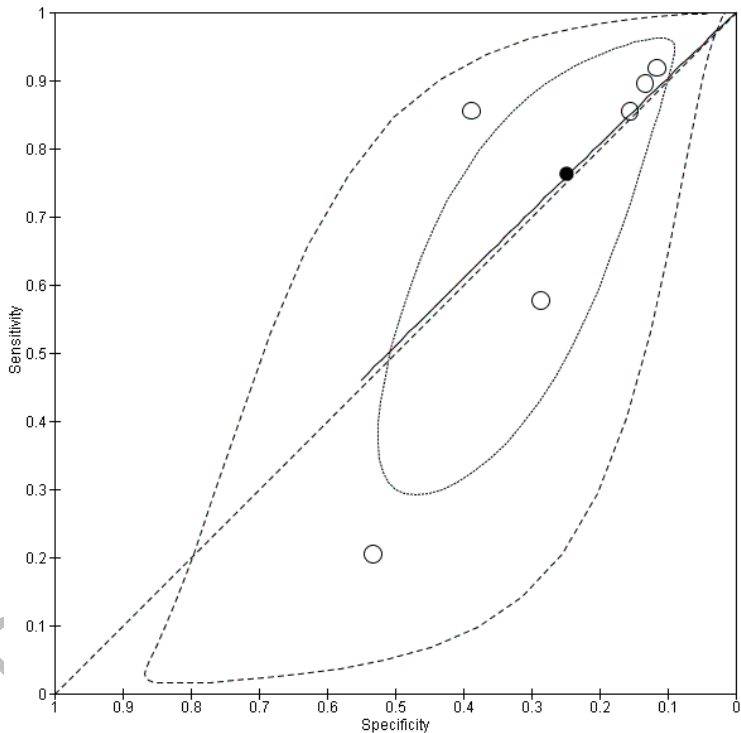
1883 Figure Q5m: Forest plot and SROC plot of clear lung/tumour interface for diagnosing lung cancer in sub-solid
1884 nodules

1885 i) Forest plot



1886

1887 ii) SROC plot (not enough data to determine full curve)



1888

1889

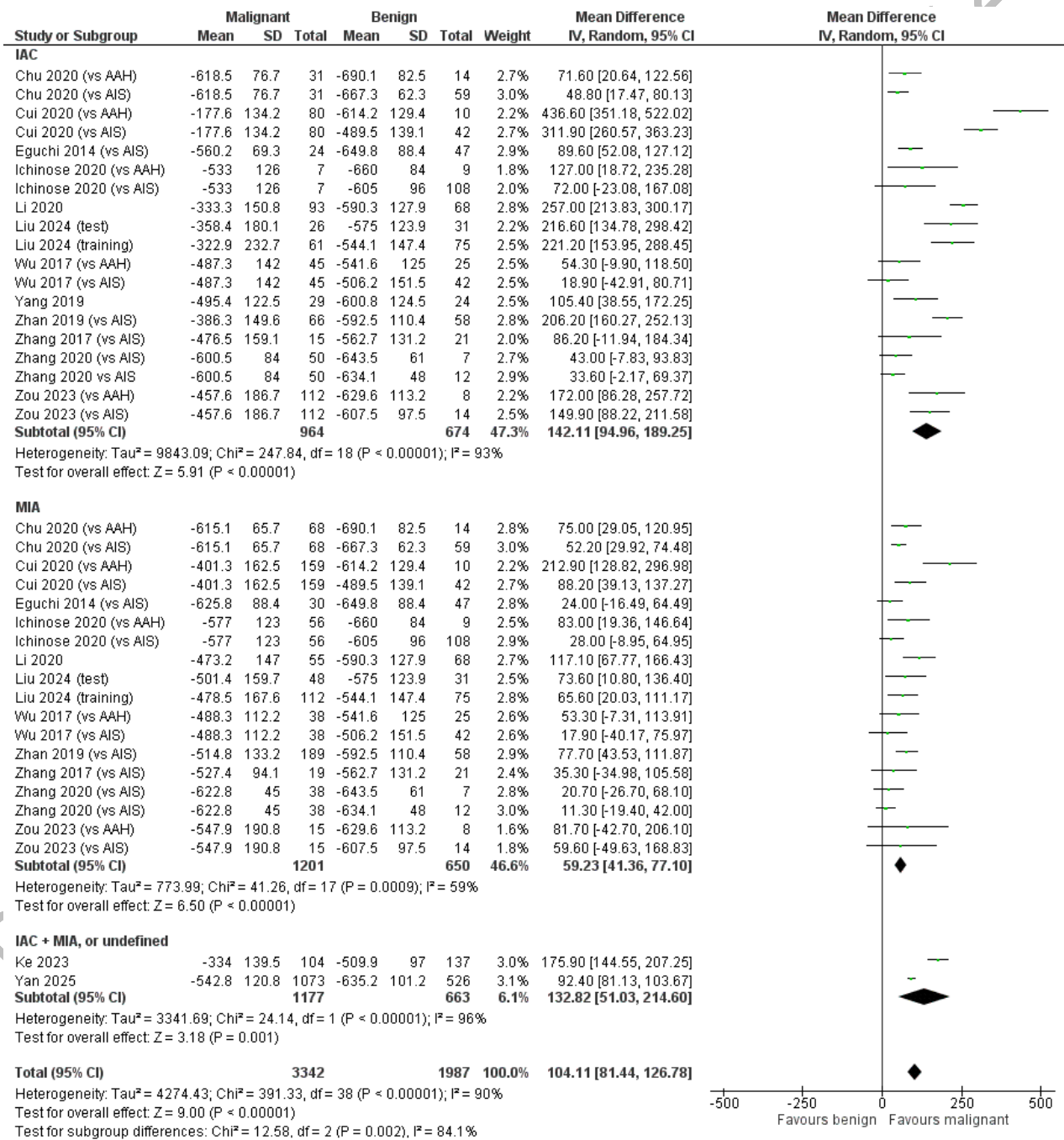
1890 Table Q5r: Pooled results of clear lung/tumour interface for diagnosing lung cancer in sub-solid nodules

Pooled Sensitivity	0.763	[0.522, 0.905]
Pooled Specificity	0.248	[0.149, 0.384]
LR+	1.015	[0.868, 1.188]
LR-	0.954	[0.569, 1.599]
DOR	1.064	[0.543, 2.087]

1891

1892 CT density

1893 Figure Q5n: Comparison of malignant versus benign sub-solid pulmonary nodule CT density



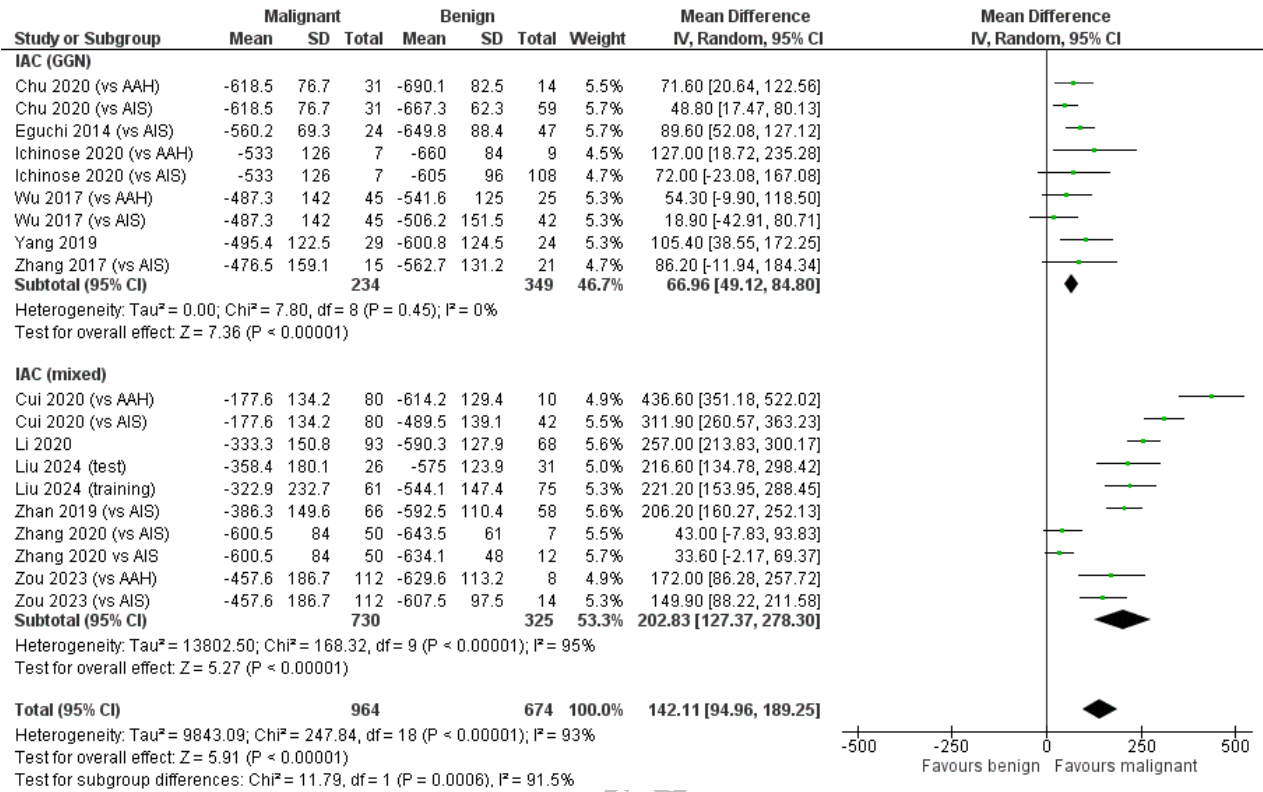
1894

1895 AAH – atypical adenomatous hyperplasia; AIS – adenocarcinoma in situ; Benign – AAH and/or AIS; IAC – invasive
1896 adenocarcinoma; MIA – minimally invasive adenocarcinoma; undefined – study does not indicate malignant sub-solid
1897 nodule type(s); test – test set; training – training set

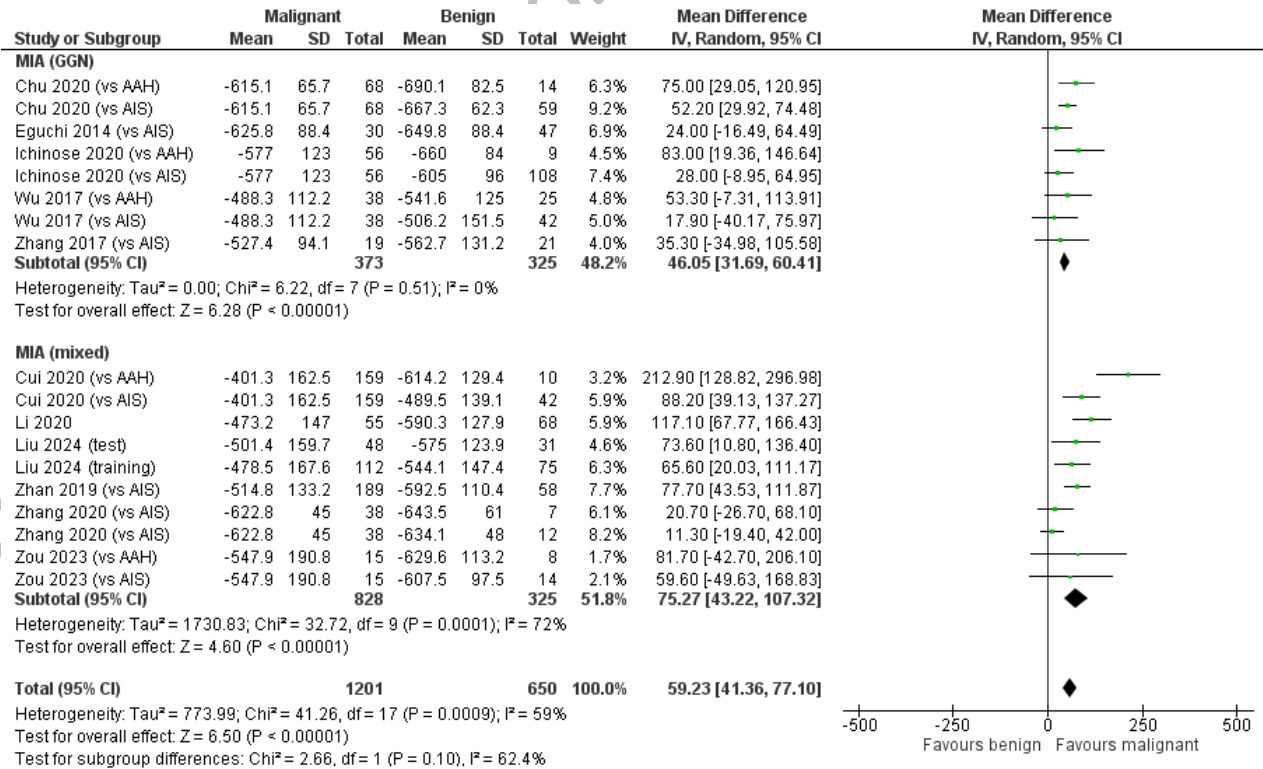
1898 **Ground-glass nodules (GGN)**

1899 Figure Q5o: CT density subgroup analyses of analyses of malignant versus benign ground-glass nodules
1900 (GGN) and mixed sub-solid nodules (GGN and part-solid nodules (PSN))

1901 i) IAC



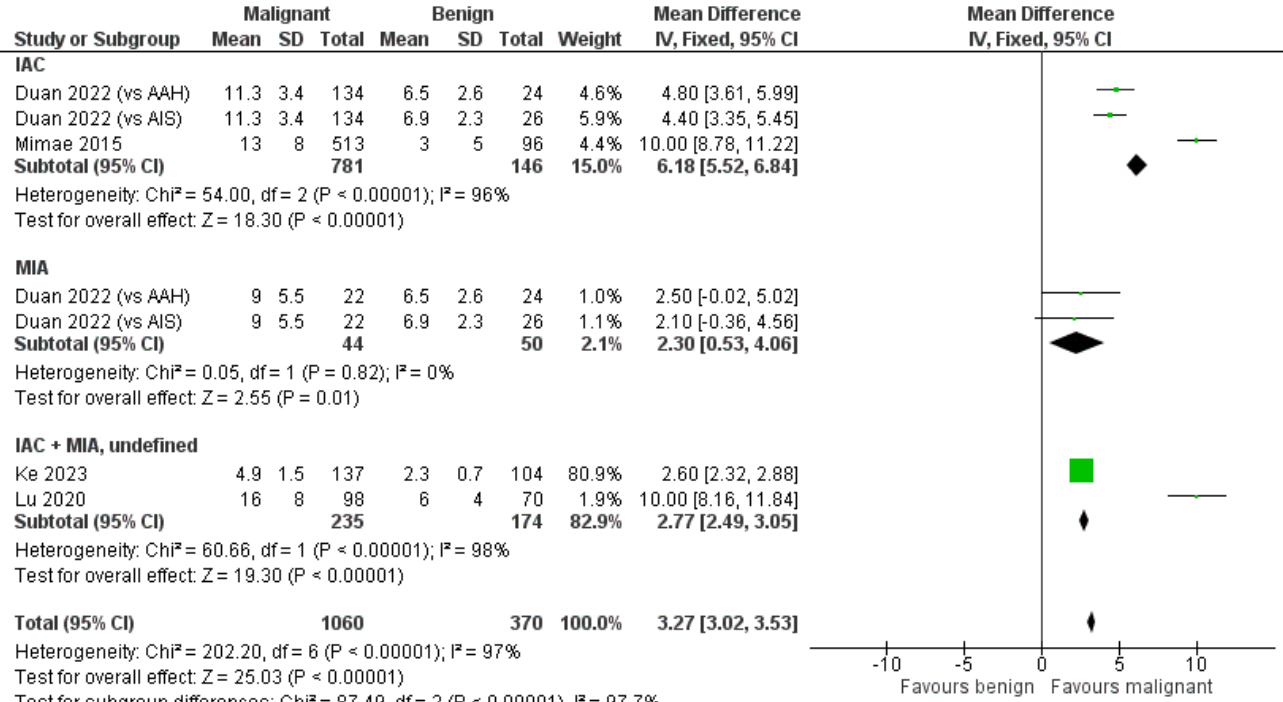
1902
1903
1904 ii) MIA



1905
1906 AAH – atypical adenomatous hyperplasia; AIS – adenocarcinoma in situ; Benign – AAH and/or AIS; GGN – ground-glass
1907 nodule; IAC – invasive adenocarcinoma; MIA – minimally invasive adenocarcinoma; mixed – PSN + GGN; PSN – part-
1908 solid nodule; test – test set; training – training set

1909 **Size of solid component**

1910 Figure Q5p: Comparison of malignant versus benign sub-solid pulmonary nodule size of solid component



1911

1912 AAH – atypical adenomatous hyperplasia; AIS – adenocarcinoma in situ; Benign – AAH and/or AIS; IAC – invasive
1913 adenocarcinoma; MIA – minimally invasive adenocarcinoma; undefined – study does not indicate malignant sub-solid
1914 nodule type(s); test – test set; training – training set

1915

1916 **Area under the curve (AUC)**

1917 **Spiculation**

1918 Figure Q5q: AUC of spiculation for diagnosing lung cancer in sub-solid nodules

1919

1920

1921

1922

1923

1924

1925

1926

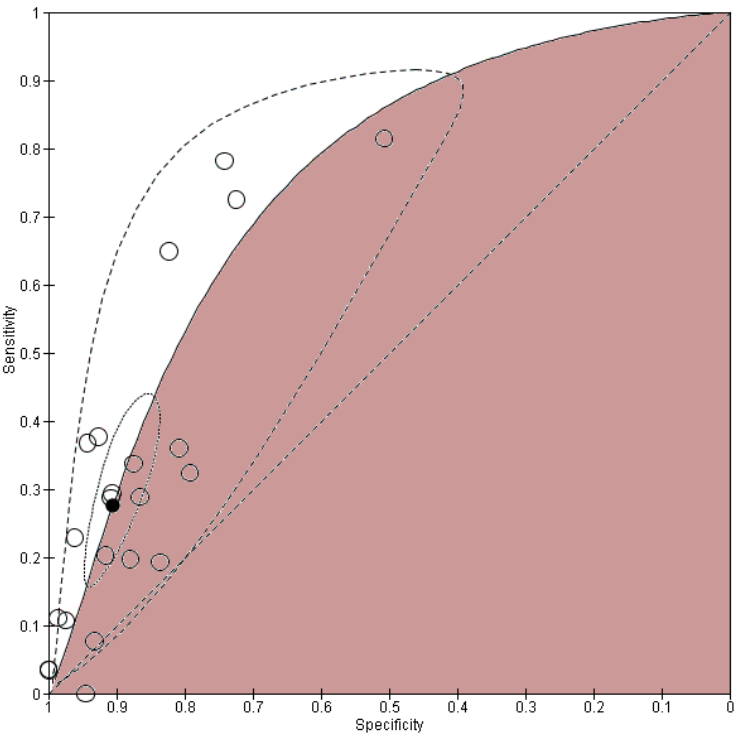
1927

1928

1929

1930

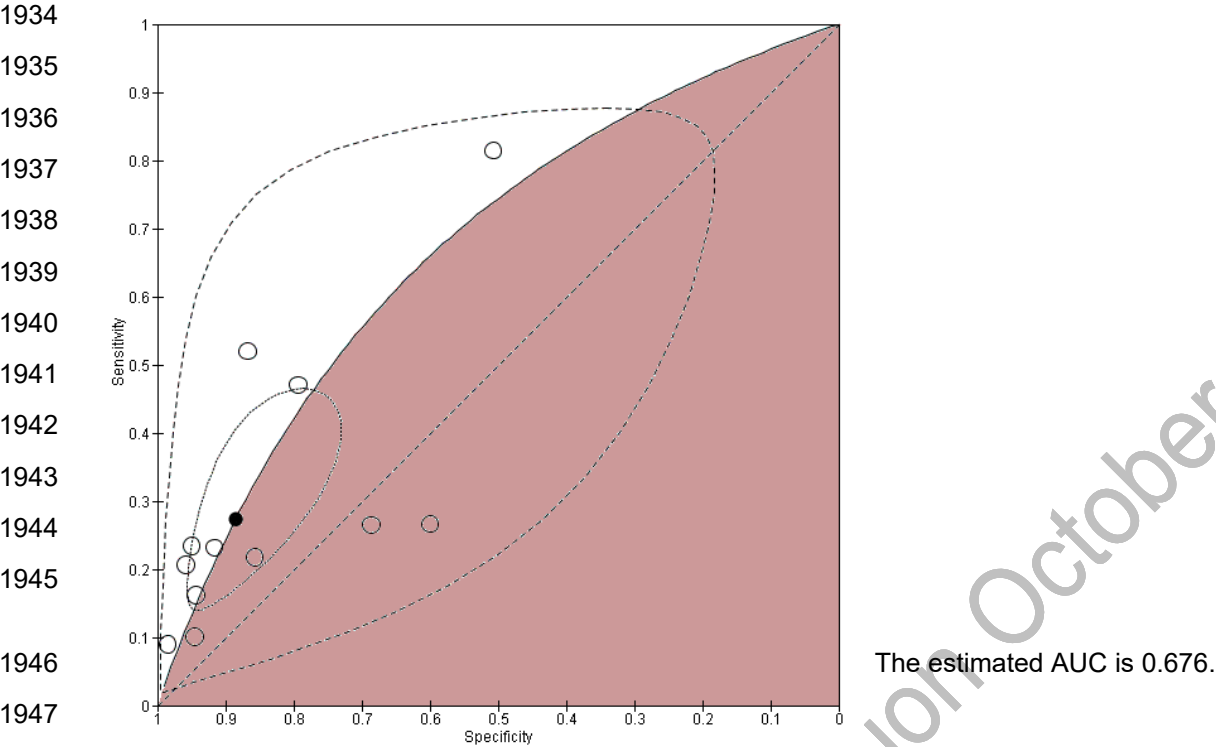
1931



The estimated AUC is 0.755.

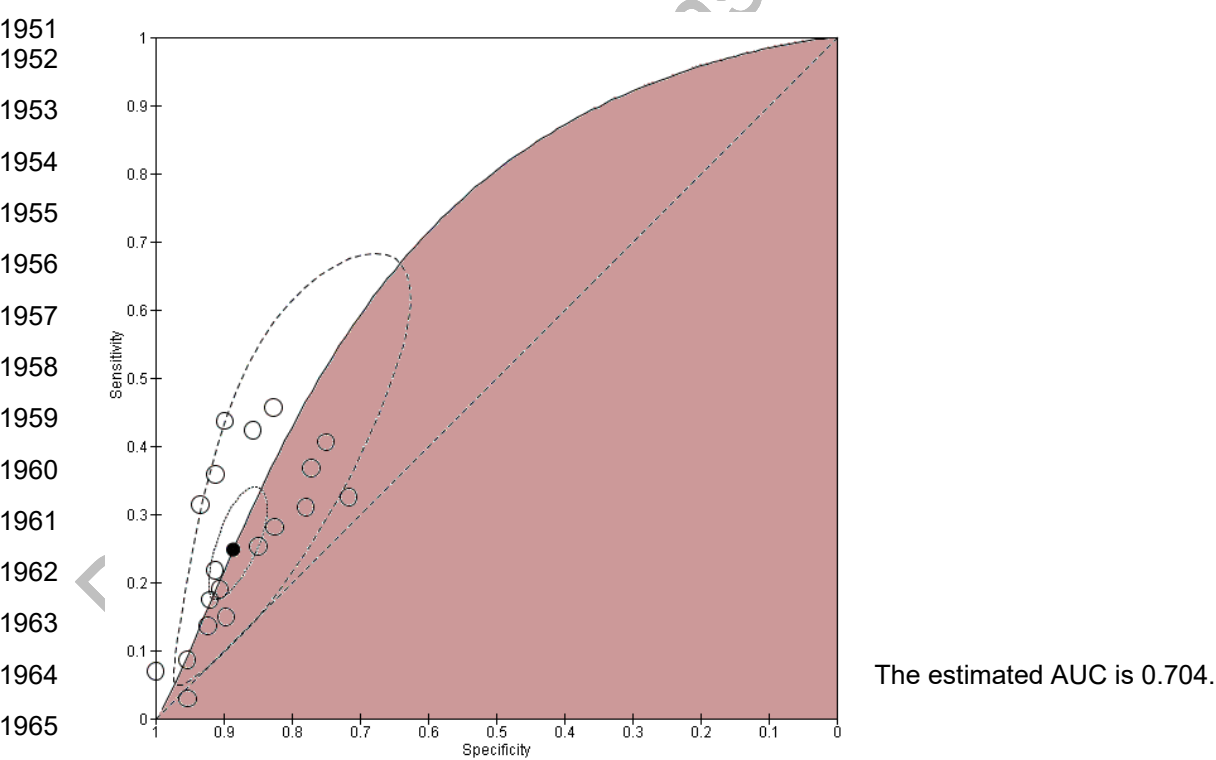
1932 **Air bronchogram**

1933 Figure Q5r: AUC of air bronchogram for diagnosing lung cancer in sub-solid nodules



1949 **Bubble-like lucency**

1950 Figure Q5s: AUC of bubble-like lucency for diagnosing lung cancer in sub-solid nodules



	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Chang 2024	+	+	+	+	+	+	+
Chu 2020	+	+	+	+	+	+	+
Cui 2020	+	+	+	+	+	+	+
Fu 2021	?	?	+	+	+	+	+
Gao 2019	+	+	+	+	+	+	+
Hsu 2021	+	+	+	+	+	+	+
Hu 2021	+	+	+	?	+	+	+
Hu 2024	+	+	+	+	+	+	+
Kim 2018b	+	?	?	+	+	+	+
Li 2020	?	+	?	+	+	+	+
Liang 2022	+	?	?	?	+	+	+
Liu 2024	+	?	?	?	+	+	+
Lu 2020	+	?	?	?	+	+	+
Qiu 2016	+	+	?	?	+	+	+
Walter 2018	+	?	?	+	+	+	?
Wang 2017	?	+	+	?	+	+	+
Wang 2018	+	+	?	?	+	+	+
Wu 2017	+	+	?	?	+	+	+
Xie 2024	+	+	+	+	+	+	+
Xiong 2024	+	+	?	+	+	+	+
Yan 2025	+	?	?	+	+	+	+
Yang 2019	?	+	?	?	+	+	+
Zhan 2019	+	?	?	?	+	+	+
Zhang 2017	+	+	+	+	+	+	+
Zhang 2021	+	+	+	+	+	+	+
Zou 2023	+	+	?	+	+	+	+

High

Unclear

Low

Intervention analyses

	Selection bias	Performance bias	Detection bias	Attrition bias	Publication bias
Chu 2020	?	+	+	+	+
Cui 2020	+	+	+	+	+
Duan 2022	+	+	+	+	+
Eguchi 2014	?	+	+	+	+
Hsu 2021	+	+	+	+	+
Ichinose 2020	?	+	?	+	+
Ke 2023	+	+	+	+	+
Kim 2018a	?	?	?	+	+
Li 2020	+	+	+	+	+
Liu 2024	+	?	?	+	+
Lu 2020	+	?	?	+	+
Mimae 2015	?	?	?	+	+
Qiu 2016	?	+	+	+	+
Wang 2017	?	+	+	+	+
Wu 2017	+	?	?	+	+
Yan 2025	+	?	?	+	+
Yang 2019	+	+	+	+	+
Yu 2020	+	?	?	+	+
Zhan 2019	+	?	?	+	+
Zhang 2017	+	?	?	+	+
Zhang 2020	?	?	?	+	+
Zhang 2021	?	+	+	+	+
Zou 2023	+	+	+	+	+

High

?

 Unclear

+

 Low

1970
1971
1972
1973
1974
1975
1976
1977
1978
1979
1980
1981
1982
1983

1984 GRADE analyses

1985 Nodule diameter

In adults with sub-solid pulmonary nodules, does maximal nodule diameter indicate lung cancer in sub-solid nodules?

Population: Adults aged 18+ with sub-solid pulmonary nodules
Intervention: Malignant sub-solid nodules, invasive adenocarcinoma (IAC), minimally invasive adenocarcinoma (MIA)
Comparator: Benign sub-solid nodules (adenocarcinoma in situ (AIS), atypical adenomatous hyperplasia (AAH))

Outcome	Number of participants (datasets)	Estimate of effect	Quality of the Evidence (GRADE)
Nodule diameter (IAC + MIA)	4040 (34 datasets)	4.01 (3.19 to 4.82) mm greater in the invasive nodule group	⊕○○○ VERY LOW ^{a,b}
Nodule diameter (IAC)	1849 (16 datasets)	5.77 (4.23 to 7.30) mm greater in the IAC nodule group	⊕○○○ VERY LOW ^{a,b}
Nodule diameter (MIA)	1058 (14 datasets)	2.34 (1.45 to 3.23) mm greater in the MIA nodule group	⊕○○○ VERY LOW ^{a,c,d}

- Explanations**
- a. Some risk of bias across the studies
 - b. Serious inconsistency across the studies
 - c. Some inconsistency across the studies
 - d. Some imprecision, CIs cross one MID

1986

1987

1988 *Ground-glass nodules (GGN)*

1989 *IAC (ground-glass nodules (GGN))*

In adults with sub-solid pulmonary nodules, does maximal nodule diameter indicate lung cancer in sub-solid nodules?

Population: Adults aged 18+ with sub-solid pulmonary nodules
Intervention: Invasive adenocarcinoma (IAC) (GGN) (malignant)
Comparator: Benign GGN (AIS, AAH)

Outcome	Number of participants (datasets)	Estimate of effect	Quality of the Evidence (GRADE)
Nodule diameter (IAC, GGN)	454 (7 datasets)	3.96 (2.33 to 5.59) mm greater in the IAC GGN group	⊕○○○ VERY LOW ^{a,b}

- Explanations**
- a. Some risk of bias across the studies
 - b. Serious inconsistency across the studies

1990

1991

1992

1993

1994

1995

1996

1997

1998

1999

In adults with sub-solid pulmonary nodules, does maximal nodule diameter indicate lung cancer in sub-solid nodules?

Population: Adults aged 18+ with sub-solid pulmonary nodules
Intervention: Minimally invasive adenocarcinoma (MIA) (GGN) (malignant)
Comparator: Benign GGN (AIS, AAH)

Outcome	Number of participants (datasets)	Estimate of effect	Quality of the Evidence (GRADE)
Nodule diameter (MIA, GGN)	496 (6 datasets)	3.23 (1.46 to 4.99) mm greater in the MIA GGN group	⊕○○○ VERY LOW ^{a,b,c}

- Explanations**
- a. Some risk of bias across the studies
 - b. Serious inconsistency across the studies
 - c. Some imprecision, CIs cross one MID

2001
2002
2003
2004

Nodule volume

In adults with sub-solid pulmonary nodules, does nodule volume indicate lung cancer in sub-solid nodules?

Population: Adults aged 18+ with sub-solid pulmonary nodules
Intervention: Malignant sub-solid nodules, invasive adenocarcinoma (IAC), minimally invasive adenocarcinoma (MIA)
Comparator: Benign sub-solid nodules (adenocarcinoma in situ (AIS), atypical adenomatous hyperplasia (AAH))

Outcome	Number of participants (datasets)	Estimate of effect	Quality of the Evidence (GRADE)
Nodule volume (IAC + MIA)	606 (6 datasets)	0.86 (0.35 to 1.37) cm ³ greater in the invasive nodule group	⊕○○○ VERY LOW ^{a,b}
Nodule volume (IAC)	246 (2 datasets)	2.69 (1.89 to 3.49) cm ³ greater in the IAC nodule group	⊕⊕○○ LOW ^{c,d}
Nodule volume (MIA)	119 (3 datasets)	0.46 (0.10 to 0.83) cm ³ greater in the MIA nodule group	⊕○○○ VERY LOW ^{b,c,d,e}

- Explanations**
- a. Serious inconsistency across the studies
 - b. Some imprecision, CIs cross one MID
 - c. Downgraded as data from single study
 - d. Downgraded as data from retrospective study/studies
 - e. Some inconsistency across the studies

2005
2006
2007
2008
2009
2010
2011
2012

What is the diagnostic accuracy of imaging tests, and the optimal strategy for image utilisation, for diagnosing lung cancer in a sub-solid pulmonary nodule?

Patient or population: Adults aged 18+ with sub-solid pulmonary nodules

New test: Upper lobe location

Pooled sensitivity: 0.64 (95% CI: 0.61 to 0.65) | Pooled specificity: 0.43 (95% CI: 0.35 to 0.51)

Test result	Number of results per 1,000 patients tested (95% CI) Prevalence 5% Typically seen in	Number of participants (datasets)	Certainty of the Evidence (GRADE)
True positives	32 (30 to 33)	3241	⊕⊕⊕○
False negatives	18 (17 to 20)	(12)	MODERATE ^a
True negatives	407 (330 to 488)	1304	⊕⊕⊕○
False positives	543 (462 to 620)	(12)	MODERATE ^a
CI: Confidence interval			

Explanations

a. Some risk of bias across the studies

2014
2015
2016
2017

Ground-glass nodules (GGN)

What is the diagnostic accuracy of imaging tests, and the optimal strategy for image utilisation, for diagnosing lung cancer in a sub-solid pulmonary nodule?

Patient or population: Adults aged 18+ with sub-solid pulmonary nodules

New test: Upper lobe location

Pooled sensitivity: 0.65 (95% CI: 0.60 to 0.70) | Pooled specificity: 0.41 (95% CI: 0.27 to 0.60)

Test result	Number of results per 1,000 patients tested (95% CI) Prevalence 5% Typically seen in	Number of participants (datasets)	Certainty of the Evidence (GRADE)
True positives	33 (30 to 35)	812	⊕⊕○○
False negatives	17 (15 to 20)	(6)	LOW ^{a,b}
True negatives	395 (258 to 570)	437	⊕⊕○○
False positives	555 (380 to 692)	(6)	LOW ^{a,b}
CI: Confidence interval			

Explanations

a. Some risk of bias across the studies

b. Some inconsistency across the specificities

2018
2019
2020
2021
2022
2023
2024
2025
2026
2027
2028
2029
2030

What is the diagnostic accuracy of imaging tests, and the optimal strategy for image utilisation, for diagnosing lung cancer in a sub-solid pulmonary nodule?

Patient or population: Adults aged 18+ with sub-solid pulmonary nodules

New test: Spiculation

Pooled sensitivity: 0.28 (95% CI: 0.18 to 0.39) | Pooled specificity: 0.91 (95% CI: 0.86 to 0.94)

Test result	Number of results per 1,000 patients tested (95% CI) Prevalence 5% Typically seen in	Number of participants (datasets)	Certainty of the Evidence (GRADE)
True positives	14 (9 to 20)	4740	⊕○○○
False negatives	36 (30 to 41)	(22)	VERY LOW ^{a,b}
True negatives	861 (815 to 892)	2115	⊕○○○
False positives	89 (58 to 135)	(22)	VERY LOW ^{a,b}
CI: Confidence interval			
Explanations			
c. Some risk of bias across the studies			
d. Serious inconsistency across the sensitivities			

2032
2033
2034

Ground-glass nodules (GGN)

What is the diagnostic accuracy of imaging tests, and the optimal strategy for image utilisation, for diagnosing lung cancer in a sub-solid pulmonary nodule?

Patient or population: Adults aged 18+ with sub-solid pulmonary nodules

New test: Spiculation

Pooled sensitivity: 0.17 (95% CI: 0.07 to 0.36) | Pooled specificity: 0.95 (95% CI: 0.87 to 0.98)

Test result	Number of results per 1,000 patients tested (95% CI) Prevalence 5% Typically seen in	Number of participants (datasets)	Certainty of the Evidence (GRADE)
True positives	8 (3 to 18)	843	⊕⊕○○
False negatives	42 (32 to 47)	(8)	LOW ^{a,b}
True negatives	904 (829 to 934)	475	⊕⊕○○
False positives	46 (16 to 121)	(8)	LOW ^{a,b}
CI: Confidence interval			
Explanations			
a. Some risk of bias across studies			
b. Some inconsistency across the sensitivities and specificities			

2035
2036
2037
2038
2039
2040
2041
2042
2043
2044
2045
2046
2047

What is the diagnostic accuracy of imaging tests, and the optimal strategy for image utilisation, for diagnosing lung cancer in a sub-solid pulmonary nodule?

Patient or population: Adults aged 18+ with sub-solid pulmonary nodules

New test: Air bronchogram

Pooled sensitivity: 0.27 (95% CI: 0.18 to 0.40) | **Pooled specificity:** 0.88 (95% CI: 0.79 to 0.94)

Test result	Number of results per 1,000 patients tested (95% CI) Prevalence 5% Typically seen in	Number of participants (datasets)	Certainty of the Evidence (GRADE)
True positives	14 (9 to 20)	2910	⊕○○○
False negatives	36 (30 to 41)	(12)	VERY LOW ^{a,b,c}
True negatives	841 (751 to 893)	1382	⊕○○○
False positives	109 (57 to 199)	(12)	VERY LOW ^{a,b,c}

CI: Confidence interval

Explanations

- c. Serious risk of bias across the studies
- d. Some inconsistency across the sensitivities and specificities
- e. Some imprecision across the specificities

2049
2050
2051
2052

Ground-glass nodules (GGN)

What is the diagnostic accuracy of imaging tests, and the optimal strategy for image utilisation, for diagnosing lung cancer in a sub-solid pulmonary nodule?

Patient or population: Adults aged 18+ with sub-solid pulmonary nodules

New test: Air bronchogram

Pooled sensitivity: 0.38 (95% CI: 0.20 to 0.61) | **Pooled specificity:** 0.84 (95% CI: 0.64 to 0.93)

Test result	Number of results per 1,000 patients tested (95% CI) Prevalence 5% Typically seen in	Number of participants (datasets)	Certainty of the Evidence (GRADE)
True positives	14 (9 to 20)	289	⊕⊕⊕○
False negatives	36 (30 to 41)	(4)	MODERATE ^a
True negatives	841 (751 to 893)	199	⊕⊕⊕○
False positives	109 (57 to 199)	(4)	MODERATE ^a

CI: Confidence interval

Explanations

- a. Some risk of bias across studies

2053
2054
2055
2056
2057
2058
2059
2060
2061
2062
2063
2064

What is the diagnostic accuracy of imaging tests, and the optimal strategy for image utilisation, for diagnosing lung cancer in a sub-solid pulmonary nodule?

Patient or population: Adults aged 18+ with sub-solid pulmonary nodules

New test: Bubble-like lucency

Pooled sensitivity: 0.25 (95% CI: 0.19 to 0.31) | Pooled specificity: 0.89 (95% CI: 0.85 to 0.91)

Test result	Number of results per 1,000 patients tested (95% CI) Prevalence 5% Typically seen in	Number of participants (datasets)	Certainty of the Evidence (GRADE)
True positives	12 (10 to 16)	3737	⊕⊕○○
False negatives	38 (34 to 40)	(19)	LOW ^{a,b}
True negatives	842 (808 to 867)	1742	⊕⊕○○
False positives	108 (83 to 142)	(19)	LOW ^{a,b}

CI: Confidence interval

Explanations

- a. Some risk of bias across the studies
- b. Some inconsistency across the sensitivities

Ground-glass nodules (GGN)

What is the diagnostic accuracy of imaging tests, and the optimal strategy for image utilisation, for diagnosing lung cancer in a sub-solid pulmonary nodule?

Patient or population: Adults aged 18+ with sub-solid pulmonary nodules

New test: Bubble-like lucency

Pooled sensitivity: 0.23 (95% CI: 0.13 to 0.37) | Pooled specificity: 0.90 (95% CI: 0.78 to 0.95)

Test result	Number of results per 1,000 patients tested (95% CI) Prevalence 5% Typically seen in	Number of participants (datasets)	Certainty of the Evidence (GRADE)
True positives	11 (7 to 17)	704	⊕⊕○○
False negatives	39 (33 to 43)	(7)	LOW ^{a,b}
True negatives	850 (742 to 905)	364	⊕⊕○○
False positives	100 (45 to 208)	(7)	LOW ^{a,b}

CI: Confidence interval

Explanations

- a. Some risk of bias across studies
- b. Some inconsistency across the sensitivities

What is the diagnostic accuracy of imaging tests, and the optimal strategy for image utilisation, for diagnosing lung cancer in a sub-solid pulmonary nodule?

Patient or population: Adults aged 18+ with sub-solid pulmonary nodules

New test: Clear lung/tumour interface

Pooled sensitivity: 0.76 (95% CI: 0.52 to 0.90) | Pooled specificity: 0.25 (95% CI: 0.15 to 0.38)

Test result	Number of results per 1,000 patients tested (95% CI) Prevalence 5% Typically seen in	Number of participants (datasets)	Certainty of the Evidence (GRADE)
True positives	38 (26 to 45)	1710	⊕○○○
False negatives	12 (5 to 24)	(6)	VERY LOW ^{a,b,c}
True negatives	236 (142 to 365)	830	⊕○○○
False positives	714 (585 to 808)	(6)	VERY LOW ^{a,b,c}

CI: Confidence interval

Explanations

- c. Some risk of bias across the studies
- d. Serious inconsistency across the sensitivities and specificities
- e. Some imprecision across the specificities

2084
2085
2086
2087

CT density

What is the diagnostic accuracy of imaging tests, and the optimal strategy for image utilisation, for diagnosing lung cancer in a sub-solid pulmonary nodule?

Population: Adults aged 18+ with sub-solid pulmonary nodules

Intervention: Malignant sub-solid nodules, invasive adenocarcinoma (IAC), minimally invasive adenocarcinoma (MIA)

Comparator: Benign sub-solid nodules (adenocarcinoma in situ (AIS), atypical adenomatous hyperplasia (AAH))

Outcome	Number of participants (datasets)	Estimate of effect	Quality of the Evidence (GRADE)
CT density (IAC + MIA)	5329 (39 datasets)	104.11 (81.44 to 126.78) HU greater in the invasive nodule group	⊕○○○ VERY LOW ^{a,b}
CT density (IAC)	1638 (19 datasets)	142.11 (94.96 to 189.25) HU greater in the IAC nodule group	⊕○○○ VERY LOW ^{a,b}
CT density (MIA)	1851 (18 datasets)	59.23 (41.36 to 77.10) HU greater in the MIA nodule group	⊕○○○ VERY LOW ^{a,c,d}

Explanations

- a. Some risk of bias across the studies
- b. Serious inconsistency across the studies
- c. Some inconsistency across the studies
- d. Some imprecision, CIs cross one MID

2088
2089
2090
2091
2092

2093

2094 **Ground-glass nodules (GGN)**2095 *IAC (ground-glass nodules (GGN))*

What is the diagnostic accuracy of imaging tests, and the optimal strategy for image utilisation, for diagnosing lung cancer in a sub-solid pulmonary nodule?

Population: Adults aged 18+ with sub-solid pulmonary nodules

Intervention: Invasive adenocarcinoma (IAC) (GGN) (malignant)

Comparator: Benign GGN (AIS, AAH)

Outcome	Number of participants (datasets)	Estimate of effect	Quality of the Evidence (GRADE)
CT density (IAC, GGN)	583 (9 datasets)	66.96 (49.12 to 84.80) HU greater in the IAC GGN group	⊕⊕○○ LOW ^{a,b}

Explanations

a. Some risk of bias across the studies

b. Downgraded as data from retrospective study/studies

2096

2097

2098

MIA (ground-glass nodules (GGN))

What is the diagnostic accuracy of imaging tests, and the optimal strategy for image utilisation, for diagnosing lung cancer in a sub-solid pulmonary nodule?

Population: Adults aged 18+ with sub-solid pulmonary nodules

Intervention: Minimally invasive adenocarcinoma (MIA) (GGN) (malignant)

Comparator: Benign GGN (AIS, AAH)

Outcome	Number of participants (datasets)	Estimate of effect	Quality of the Evidence (GRADE)
CT density (MIA, GGN)	698 (6 datasets)	46.05 (31.69 to 60.41) HU greater in the MIA GGN group	⊕○○○ VERY LOW ^{a,b}

Explanations

a. Serious risk of bias across the studies

b. Some imprecision, CIs cross one MID

2099

2100

2101

2102

Size of solid component

What is the diagnostic accuracy of imaging tests, and the optimal strategy for image utilisation, for diagnosing lung cancer in a sub-solid pulmonary nodule?

Population: Adults aged 18+ with sub-solid pulmonary nodules

Intervention: Invasive sub-solid nodules, invasive adenocarcinoma (IAC), minimally invasive adenocarcinoma (MIA)

Comparator: Benign sub-solid nodules (adenocarcinoma in situ (AIS), atypical adenomatous hyperplasia (AAH))

Outcome	Number of participants (datasets)	Estimate of effect	Quality of the Evidence (GRADE)
Solid component (IAC + MIA)	1430 (7 datasets)	3.27 (3.02 to 3.53) mm greater in the invasive nodule group	⊕○○○ VERY LOW ^{a,b}

Explanations

a. Serious inconsistency across the studies

b. Downgraded as data from retrospective study/studies

Recommendation Tables

Question Details

POPULATION:	Adults (18+) with sub-solid pulmonary nodules
INDEX TESTS:	Strategies for image utilisation for diagnosing lung cancer in a sub-solid pulmonary nodule
GOLD STANDARD:	Pathological diagnosis of invasive lung cancer or clinical diagnosis of lung cancer
OUTCOME:	Diagnostic accuracy of strategies for image utilisation for diagnosing lung cancer

Nodule diameter

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	Does not favour the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
☐	☐	☐	☒	☐

CONCLUSIONS

Recommendation

For adults with sub-solid pulmonary nodules, maximal nodule diameter can be considered when determining lung cancer risk. (**Conditional**)

Justification

Malignant sub-solid pulmonary nodules (invasive adenocarcinoma (IAC) and minimally invasive adenocarcinoma (MIA)) appear to have a greater maximal nodule diameter than benign sub-solid pulmonary nodules (adenocarcinoma in situ (AIS), atypical adenomatous hyperplasia (AAH)). (**Very low**)

Invasive adenocarcinoma (IAC) sub-solid pulmonary nodules appear to have a greater maximal nodule diameter than minimally invasive adenocarcinoma (MIA) sub-solid pulmonary nodules (**Very low**)

Subgroup considerations

Invasive adenocarcinoma (IAC) ground-glass nodules (malignant) appear to have a greater maximal nodule diameter than benign ground-glass nodules (adenocarcinoma in situ (AIS), atypical adenomatous hyperplasia (AAH)). (**Very low**)

There was not enough evidence to consider part-solid nodules and other sub-solid nodule subgroups.

Research priorities

Further research is needed to determine the diagnostic accuracy of maximal nodule diameter for diagnosing lung cancer in sub-solid nodules and sub-solid nodule subtypes (ground-glass nodules and part-solid nodules).

2116

2117

Upper lobe location

2118

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
TEST ACCURACY	Very inaccurate	Inaccurate	Accurate	Very accurate		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	Does not favour the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know

2119

2120

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
☐	☒	☐	☐	☐

2121

2122

2123

CONCLUSIONS

Recommendation

For patients with sub-solid pulmonary nodules, upper lobe location should not be considered for determining invasive lung cancer in sub-solid pulmonary nodules. (**Conditional**)

Justification

Upper lobe location appears to have a low sensitivity and a low specificity for diagnosing lung cancer in sub-solid pulmonary nodules. (**Moderate**)

Subgroup considerations

Upper lobe location appears to have a moderate sensitivity and a low specificity for diagnosing lung cancer in ground-glass pulmonary nodules. (**Low**)

There was not enough evidence to consider part-solid nodules and other sub-solid nodule subgroups.

Research priorities

Further research is needed to determine the diagnostic accuracy of upper lobe location for diagnosing lung cancer in sub-solid nodules and sub-solid nodule subtypes (ground-glass nodules and part-solid nodules).

Spiculation

SUMMARY OF JUDGEMENTS

PROBLEM	JUDGEMENT						
	No	Probably no	Probably yes	Yes		Varies	Don't know
TEST ACCURACY	Very inaccurate	Inaccurate	Accurate	Very accurate		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	Does not favour the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
☐	☐	☐	☒	☐

CONCLUSIONS

Recommendation

For adults with sub-solid pulmonary nodules, spiculation can be considered when determining invasive lung cancer in a sub-solid pulmonary nodule. (**Conditional**)

Justification

Spiculation appears to have a low sensitivity and a very high specificity for diagnosing lung cancer in sub-solid pulmonary nodules. (**Very low**)

Subgroup considerations

Spiculation appears to have a low sensitivity and a very high specificity for diagnosing lung cancer in ground-glass pulmonary nodules. (**Low**)

There was not enough evidence to consider part-solid nodules and other sub-solid nodule subgroups.

Research priorities

Further research is needed to determine the diagnostic accuracy of spiculation for diagnosing lung cancer in sub-solid nodules and sub-solid nodule subtypes (ground-glass nodules and part-solid nodules).

2138 **Air bronchogram**

2139 **SUMMARY OF JUDGEMENTS**

PROBLEM	JUDGEMENT						
	No	Probably no	Probably yes	Yes		Varies	Don't know
TEST ACCURACY	Very inaccurate	Inaccurate	Accurate	Very accurate		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	Does not favour the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know

2140

2141 **TYPE OF RECOMMENDATION**

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
☐	☐	☐	☒	☐

2142

2143

2144

2145

2146

Recommendation

For adults with sub-solid pulmonary nodules, the presence of air bronchogram can be considered when determining invasive lung cancer in a sub-solid pulmonary nodule. (Conditional)

Justification

The presence of air bronchogram appears to have a low sensitivity and a high specificity for diagnosing lung cancer in sub-solid pulmonary nodules. (Very low)

Subgroup considerations

The presence of air bronchogram appears to have a low sensitivity and a high specificity for diagnosing lung cancer in ground-glass pulmonary nodules. (Moderate)

There was not enough evidence to consider part-solid nodules and other sub-solid nodule subgroups.

Research priorities

Further research is needed to determine the diagnostic accuracy of the presence of air bronchogram for diagnosing lung cancer in sub-solid nodules and sub-solid nodule subtypes (ground-glass nodules and part-solid nodules).

2151
2152
2153 Bubble-like lucency

2154 SUMMARY OF JUDGEMENTS

JUDGEMENT							
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
TEST ACCURACY	Very inaccurate	Inaccurate	Accurate	Very accurate		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	Does not favour the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know

2155
2156 TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
☐	☐	☐	☒	☐

2157 **CONCLUSIONS**

Recommendation

For adults with sub-solid pulmonary nodules, presence of bubble-like lucency considered when determining invasive lung cancer in a sub-solid pulmonary nodule. (**Conditional**)

Justification

The presence of bubble-like lucency appears to have a low sensitivity and a high specificity for diagnosing lung cancer in sub-solid pulmonary nodules. (**Low**)

Subgroup considerations

The presence of bubble-like lucency appears to have a low sensitivity and a very high specificity for diagnosing lung cancer in ground-glass pulmonary nodules. (**Low**)

There was not enough evidence to consider part-solid nodules and other sub-solid nodule subgroups.

Research priorities

Further research is needed to determine the diagnostic accuracy of presence of bubble-like lucency for diagnosing lung cancer in sub-solid nodules and sub-solid nodule subtypes (ground-glass nodules and part-solid nodules).

2161
2162 **Clear lung/tumour interface**

2163 **SUMMARY OF JUDGEMENTS**

JUDGEMENT							
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
TEST ACCURACY	Very inaccurate	Inaccurate	Accurate	Very accurate		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	Does not favour the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know

2164
2165
2166
2167 **TYPE OF RECOMMENDATION**

Strong recommendation	Conditional recommendation	Conditional recommendation for	Conditional recommendation for the intervention	Strong recommendation for the intervention
-----------------------	----------------------------	--------------------------------	---	--

against the intervention	against the intervention	either the intervention or the comparison		
☐	☐	☒	☐	☐

2168
2169
2170

CONCLUSIONS

Recommendation

For patients with sub-solid pulmonary nodules, upper lobe location should not be considered for determining invasive lung cancer in sub-solid pulmonary nodules. (**Conditional**)

Justification

The presence of a clear lung/tumour interface appears to have a moderate sensitivity and a low specificity for diagnosing lung cancer in sub-solid pulmonary nodules. (**Very low**)

Subgroup considerations

There were not enough data to consider subgroups.

Research priorities

Further research is needed to determine the diagnostic accuracy of clear lung/tumour interface presence for diagnosing lung cancer in sub-solid pulmonary nodules and sub-solid nodule subtypes (ground-glass nodules and part-solid nodules).

2174

2175 **CT density**

2176 **SUMMARY OF JUDGEMENTS**

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	Does not favour the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know

2177

2178

2179 **TYPE OF RECOMMENDATION**

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
--	---	--	---	--

☐	☐	☐	☒	☐
--------------------------	--------------------------	--------------------------	-------------------------------------	--------------------------

2180

2181

CONCLUSIONS

Recommendation

For adults with sub-solid pulmonary nodules, increased CT density can be considered when determining invasive lung cancer in a sub-solid pulmonary nodule. (**Conditional**)

Justification

Invasive sub-solid pulmonary nodules (invasive adenocarcinoma (IAC) and minimally invasive adenocarcinoma (MIA)) appear to have a greater CT density than benign sub-solid pulmonary nodules (adenocarcinoma in situ (AIS) and atypical adenomatous hyperplasia (AAH)). (**Very low**)

Subgroup considerations

Invasive adenocarcinoma (IAC) ground-glass nodules (malignant) appear to have a greater CT density than benign ground-glass nodules (adenocarcinoma in situ (AIS), atypical adenomatous hyperplasia (AAH)). (**Low**)

Minimally invasive adenocarcinoma (MIA) ground-glass nodules (malignant) appear to have a greater CT density than benign ground-glass nodules (adenocarcinoma in situ (AIS), atypical adenomatous hyperplasia (AAH)). (**Very low**)

There was not enough evidence to consider part-solid nodules and other sub-solid nodule subgroups.

Research priorities

Further research is needed to determine the diagnostic accuracy of CT density for diagnosing lung cancer in sub-solid nodules and sub-solid nodule subtypes (ground-glass nodules and part-solid nodules).

2185

2186

Size of solid component

2187

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	Does not favour the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know

2188

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
--	---	--	---	--

☐	☐	☐	☒	☐
--------------------------	--------------------------	--------------------------	-------------------------------------	--------------------------

2189
2190
2191

CONCLUSIONS

Recommendation

For adults with sub-solid pulmonary nodules, size of solid component can be considered when determining invasive lung cancer in a sub-solid pulmonary nodule. **(Conditional)**

Justification

Invasive sub-solid pulmonary nodules (invasive adenocarcinoma (IAC) and minimally invasive adenocarcinoma (MIA)) appear to have a greater size of solid component than benign sub-solid pulmonary nodules (adenocarcinoma in situ (AIS) and atypical adenomatous hyperplasia (AAH)). **(Very low)**

Subgroup considerations

There were not enough data to consider subgroups.

Research priorities

Further research is needed to determine the diagnostic accuracy of the size of solid component for diagnosing lung cancer in sub-solid nodules and sub-solid nodule subtypes (ground-glass nodules and part-solid nodules).

2195
2196
2197
2198
2199
2200
2201
2202
2203

Draft For Public Consultation

2204 References

- 2205 1. Eguchi T, Yoshizawa A, Kawakami S, et al. Tumor size and computed tomography attenuation of
2206 pulmonary pure ground-glass nodules are useful for predicting pathological invasiveness. *PLoS ONE*.
2207 2014;9(5):e97867.
- 2208 2. Hsu WC, Huang PC, Pan KT, et al. Predictors of invasive adenocarcinomas among pure ground-glass
2209 nodules less than 2 cm in diameter. *Cancers (Basel)*. 2021;13(16) (no pagination) 3945.
- 2210 3. Ichinose J, Kawaguchi Y, Nakao M, et al. Utility of Maximum CT Value in Predicting the Invasiveness of
2211 Pure Ground-Glass Nodules. *Clin Lung Cancer*. 2020;21(3):281–287.
- 2212 4. Ke X, Hu W, Su X, Huang F, Lai Q. Potential of artificial intelligence based on chest computed tomography
2213 to predict the nature of part-solid nodules. *Clin Respir J*. 2023;17(4):320–328.
- 2214 5. Kim H, Park CM, Jeon S, et al. Validation of prediction models for risk stratification of incidentally detected
2215 pulmonary subsolid nodules: A retrospective cohort study in a Korean tertiary medical centre. *BMJ Open*.
2216 2018;8(5) (no pagination) e019996.
- 2217 6. Li X, Zhang W, Yu Y, et al. CT features and quantitative analysis of subsolid nodule lung adenocarcinoma
2218 for pathological classification prediction. *BMC Cancer*. 2020;20(1) (no pagination) 60.
- 2219 7. Liu M, Duan R, Xu Z, et al. CT-based radiomics combined with clinical features for invasiveness prediction
2220 and pathological subtypes classification of subsolid pulmonary nodules. *Eur J Radiol Open*. 2024;13 (no
2221 pagination) 100584.
- 2222 8. Lu J, Tang H, Yang X, Liu L, Pang M. Diagnostic value and imaging features of multi-detector CT in lung
2223 adenocarcinoma with ground-glass nodule patients. *Oncol Lett*. 2020;20(1):693–698.
- 2224 9. Mimae T, Miyata Y, Tsutani Y, et al. What are the radiologic findings predictive of indolent lung
2225 adenocarcinoma? *Jpn J Clin Oncol*. 2015;45(4):367–72.
- 2226 10. Qiu ZX, Cheng Y, Liu D, et al. Clinical, pathological, and radiological characteristics of solitary ground-
2227 glass opacity lung nodules on high-resolution computed tomography. *Ther Clin Risk Manag*. 2016; 12:
2228 1445–1453.
- 2229 11. Yang Y, Li K, Sun D, et al. Invasive Pulmonary Adenocarcinomas Versus Preinvasive Lesions Appearing
2230 as Pure Ground-Glass Nodules: Differentiation Using Enhanced Dual-Source Dual-Energy CT. *AJR Am J*
2231 *Roentgenol*. 2019;213(3):W114–W122.
- 2232 12. Yu Y, Cheng JJ, Li JY, et al. Determining the invasiveness of pure ground-glass nodules using dual-energy
2233 spectral computed tomography. *Transl Lung Cancer Res*. 2020;9(3):484–495.
- 2234 13. Zhang BW, Zhang Y, Ye JD, Qiang JW. Use of relative CT values to evaluate the invasiveness of
2235 pulmonary subsolid nodules in patients with emphysema. *Quant Imaging Med Surg*. 2021;11(1):204–214.
- 2236 14. Zhang R, Sun H, Chen B, Xu R, Li W. Developing of risk models for small solid and subsolid pulmonary
2237 nodules based on clinical and quantitative radiomics features. *J Thorac Dis*. 2021;13(7):4156–4168.
- 2238 15. Zou ZN, H.;Cha, Y.;Yang, J.;Han, W. Diagnostic Value of Combined High-resolution Computed
2239 Tomography and Artificial Intelligence-Aided Diagnosis System in Prediction of Benign and Malignant
2240 Pulmonary Ground-Glass Nodules. *IJ Radiology*. 2023;20(4) (no pagination) e135104.
- 2241 16. Wang X, Wang L, Zhang W, Zhao H, Li F. Can we differentiate minimally invasive adenocarcinoma and
2242 non-invasive neoplasms based on high-resolution computed tomography features of pure ground-glass
2243 nodules? *PLoS ONE*. 2017;12(7) (no pagination) e0180502.
- 2244 17. Chang Y, Xing H, Shang Y, Liu Y, Yu L, Dai H. Radiomics nomogram: distinguishing benign and malignant
2245 pure ground-glass nodules based on dual-layer spectral detector CT. *Clin Radiol*. 2024;79(10):e1205–
2246 e1213.
- 2247 18. Chu ZG, Li WJ, Fu BJ, Lv FJ. CT characteristics for predicting invasiveness in pulmonary pure ground-
2248 glass nodules. *AJR Am J Roentgenol*. 2020;215(2):351–358.
- 2249 19. Cui X, Fan S, Heuvelmans MA, et al. Optimization of CT windowing for diagnosing invasiveness of
2250 adenocarcinoma presenting as sub-solid nodules. *Eur J Radiol*. 2020;128 (no pagination) 108981.
- 2251 20. Fu F, Zhang Y, Wang S, et al. Computed tomography density is not associated with pathological tumor
2252 invasion for pure ground-glass nodules. *J Thorac Cardiovasc Surg*. 2021;162(2):451–459.

- 2253 21. Hu X, Gou J, Wang L, Lin W, Li W, Yang F. Diagnostic accuracy of low-dose dual-input computed
2254 tomography perfusion in the differential diagnosis of pulmonary benign and malignant ground-glass
2255 nodules. *Sci Rep*. 2024;14(1):17098.
- 2256 22. Walter JE, Heuvelmans MA, Yousaf-Khan U, et al. New Subsolid Pulmonary Nodules in Lung Cancer
2257 Screening: The NELSON Trial. *J Thorac Oncol*. 2018;13(9):1410–1414.
- 2258 23. Wang L, Shen W, Xi Y, Liu S, Zheng D, Jin C. Nomogram for Predicting the Risk of Invasive Pulmonary
2259 Adenocarcinoma for Pure Ground-Glass Nodules. *Ann Thorac Surg*. 2018;105(4):1058–1064.
- 2260 24. Yan B, Jiang Y, Fu S, Li R. PMILACG Model: A Predictive Model for Identifying Invasiveness of Lung
2261 Adenocarcinoma Based on High-Resolution CT-Determined Ground-glass Nodule Features. *Tohoku J*
2262 *Exp Med*. Mar 07 2025;265(1):13–20.
- 2263 25. Zhan Y, Peng X, Shan F, et al. Attenuation and morphologic characteristics distinguishing a ground-glass
2264 nodule measuring 5-10 mm in diameter as invasive lung adenocarcinoma on thin-slice CT. *AJR Am J*
2265 *Roentgenol*. 2019;213(4):W162–W170.
- 2266 26. Gao S, Li H, Zhou Y, Du C, Yang R, Wu Y. The predictive value of computed tomography value on high-
2267 resolution images in differentiating invasive from indolent lung adenocarcinoma. *Transl Cancer Res*.
2268 2024;13(1):268–277.
- 2269 27. Hu F, Huang H, Jiang Y, et al. Discriminating invasive adenocarcinoma among lung pure ground-glass
2270 nodules: A multi-parameter prediction model. *J Thorac Dis*. 2021;13(9):5383–5394.
- 2271 28. Liang L, Zhang H, Lei H, Zhou H, Wu Y, Shen J. Diagnosis of Benign and Malignant Pulmonary Ground-
2272 Glass Nodules Using Computed Tomography Radiomics Parameters. *Technol Cancer Res Treat*.
2273 2022;21:15330338221119748.
- 2274 29. Wu F, Tian SP, Jin X, et al. CT and histopathologic characteristics of lung adenocarcinoma with pure
2275 ground-glass nodules 10 mm or less in diameter. *Eur Radiol*. 2017;27(10):4037–4043.
- 2276 30. Xiong TW, Gan H, Lv FJ, Zhang XC, Fu BJ, Chu ZG. Artificial intelligence-measured nodule mass for
2277 determining the invasiveness of neoplastic ground-glass nodules. *Quant Imaging Med Surg*.
2278 2024;14(9):6698–6710.
- 2279 31. Xie B, Wang R, Fu K, Wang Q, Liu Z, Peng W. The value of predicting the invasiveness and degree of
2280 infiltration of pulmonary ground-glass nodules based on computed tomography features and enhanced
2281 quantitative analysis. *Quant Imaging Med Surg*. 2024;14(9):6767–6779.
- 2282 32. Zhang Y, Tang J, Xu J, Cheng J, Wu H. Analysis of pulmonary pure ground-glass nodule in enhanced dual
2283 energy CT imaging for predicting invasive adenocarcinoma: Comparing with conventional thin-section CT
2284 imaging. *J Thorac Dis*. 2017;9(12):4967–4978.
- 2285 33. Duan LS, W.;Bo, G.;Lu, G.;Guo, L. Qualitative (and Quantitative) Values of the Lung-RADS and Computed
2286 Tomography in Diagnosing Solitary Pulmonary Nodules. *Diagnostics (Basel)*. 2022;12(11) (no pagination)
2287 2699.
- 2288 34. Hammer MM, Palazzo LL, Kong CY, Hunsaker AR. Cancer risk in subsolid nodules in the National Lung
2289 screening Trial. *Radiology*. 2019;293(2):441–448.
- 2290 35. Kim H, Goo JM, Park CM. A simple prediction model using size measures for discrimination of invasive
2291 adenocarcinomas among incidental pulmonary subsolid nodules considered for resection. Observational
2292 Study. *Eur Radiol*. 2019;29(4):1674–1683.
- 2293 36. Gonzalez Maldonado S, Delorme S, Husing A, et al. Evaluation of Prediction Models for Identifying
2294 Malignancy in Pulmonary Nodules Detected via Low-Dose Computed Tomography. *JAMA Netw Open*.
2295 2020;3(2):e1921221.
- 2296 37. Marcus MW, Duffy SW, Devaraj A, et al. Probability of cancer in lung nodules using sequential volumetric
2297 screening up to 12 months: the UKLS trial. *Thorax*. 2019;74(8):761–767.

Field	Content
Review Question	What is the diagnostic accuracy of imaging tests, and the optimal strategy for image utilisation* for diagnosing lung cancer in a sub-solid pulmonary nodule? * Computer-aided measurement of specific nodule parameters (e.g. volume, mass) NOT artificial-intelligence tools where multiple parameters are computed to give an overall risk assessment.
Type of review question	Diagnostic accuracy review
Objective of the review	Sub-solid pulmonary nodules are first assessed on non-invasive imaging tests – initially CT, sometimes supplemented by other imaging investigations. The way imaging tests are assessed (for example, how pulmonary nodules are measured) can vary. This question aims to clarify the optimal way to assess the likelihood of lung cancer using these various modalities and determine the overall diagnostic accuracy of these approaches.
Eligibility criteria – population / disease / condition / issue / domain	Adults with solid pulmonary nodules (18+ years of age)
Eligibility criteria – index test(s)	Nodule diameter Nodule volume Upper lobe location Spiculation FDG-avidity Air bronchogram Bubble-like lucency Clear lung/tumour interface Size of solid component Brock score Mayo score Herder score VA UKLS

Eligibility criteria – gold standard	Pathological diagnosis of invasive lung cancer or clinical diagnosis of lung cancer	
Outcomes and prioritisation	Diagnostic accuracy	
Eligibility criteria – study design	RCTs, comparative studies, case series (>50 cases)	
Other inclusion /exclusion criteria	Non-English language excluded unless full English translation Conference abstracts, Cochrane reviews, systematic reviews, reviews Cochrane reviews and systematic reviews can be referenced in the text, but CANNOT be used in a meta-analysis	
Proposed sensitivity / subgroup analysis, or meta-regression	Adults with sub-solid pulmonary nodules - Without recent relevant imaging - Newly appeared since recent imaging - Ground-glass nodule (GGN)/non-solid nodule - Part-solid nodule (PSN) Imaging types - Computed tomography (CT) - Positron emission tomography computed tomography (PET-CT) - Magnetic resonance imaging (MRI)	
Selection process – duplicate screening / selection / analysis	Agreement should be reached between Guideline members who are working on the question. If no agreement can be reached, a decision should be made by the Guideline co-chairs. If there is still no decision, the matter should be brought to the Guideline group and a decision will be made by consensus	
Data management (software)	RevMan5	Pairwise meta-analyses (if data in the correct format) Evidence review/considered judgement. Storing Guideline text, tables, figures, etc.
	MetaDTA	Data meta-analyses
	Gradepro	Quality of evidence assessment

2301

2302

Information sources – databases and dates	MEDLINE, Embase, Central Register of Controlled Trials and Cochrane Database of Systematic Reviews Restricted to articles published from 1990 onwards
Methods for assessing bias at outcome / study level	RevMan5 diagnostic accuracy full review template (based on QUADAS2) (follow instructions in ' <i>BTS Guideline Process Handbook – Diagnostic Accuracy (June 2020)</i> ')
Methods for quantitative analysis – combining studies and exploring (in)consistency	If 3 or more relevant studies: RevMan5 for forest plots, summary ROC plots MetaDTA to combine studies (pooled specificity, sensitivity, likelihood ratios, diagnostic odds ratio and confidence intervals) and calculate RevMan parameters for summary ROC plot (follow instructions in ' <i>BTS Guideline Process Handbook – Diagnostic Accuracy (June 2020)</i> ')
Meta-bias assessment – publication bias, selective reporting bias	GRADEpro Diagnostic accuracy quality of evidence assessment for each index test (follow instructions in ' <i>BTS Guideline Process Handbook – Diagnostic Accuracy (June 2020)</i> ')
Rationale / context – what is known	As with solid nodules, the initial diagnostic assessment of a sub-solid pulmonary nodule is made on the basis of CT images, with other imaging tests sometimes providing additional information. Sub-solid nodules are morphologically different on CT scans, and when due to lung cancer can behave differently from cancers presenting as solid pulmonary nodules (in that they are often slower growing). This question aims to review the optimal way to assess sub-solid pulmonary nodules using these imaging modalities, and the overall diagnostic accuracy of each of them for diagnosing lung cancer.

2303
2304
2305
2306
2307
2308
2309
2310
2311
2312

2314 **Q6** **In adults with sub-solid pulmonary nodules, what is the diagnostic accuracy of strategies used**
 2315 **to detect change between interval computed tomography (CT) scans for diagnosing lung**
 2316 **cancer?**

2317 **Contents**

2318	Question Evidence Review	124
2319	Background	124
2320	Outcomes	124
2321	Evidence Review	124
2322	Evidence Statements	127
2323	Recommendations	127
2324	Good Practice Points	127
2325	Research recommendations	127
2326	Algorithms	128
2327	Ground-glass nodule pathway	128
2328	Part-solid nodule pathway	129
2329	Meta-analyses	130
2330	Diameter change	130
2331	MDT	131
2332	Volume change	132
2333	Risk of bias summaries	134
2334	GRADE analyses	135
2335	Diameter change	135
2336	MDT	136
2337	Volume change	136
2338	Recommendation tables	137
2339	Diameter change	137
2340	MDT	139
2341	Volume change	141
2342	References	142
2343	Question Protocol	143

2344

2345 Question 6 Evidence Review

2346 **Q6** In adults with sub-solid pulmonary nodules, what is the diagnostic accuracy of strategies used
2347 to detect change between interval computed tomography (CT) scans for diagnosing lung
2348 cancer?

2349 Background

2350 When the likelihood of invasive malignant tumour is felt to be low, CT surveillance of sub-solid nodules is
2351 favoured to determine if the nodule is changing (growing or changing in appearance). Sub-solid nodules differ
2352 from solid nodules in that they may consist of two distinct components: an outer ground-glass component and
2353 an inner solid component; and sometimes malignant sub-solid nodules can change their overall appearance
2354 (morphology) without necessarily getting larger. This review aims to determine the optimal strategies for
2355 detecting change in sub-solid pulmonary nodules between interval CT scans for diagnosing lung cancer.

2356 Outcomes

2357 Visual analysis; diameter change; volume doubling time; mass doubling time; volume change

2358 Evidence Review

2359 The initial literature search identified 123 potentially relevant papers, and 10 papers were deemed relevant to
2360 the review.¹⁻¹⁰ Relevant studies were heavily weighted to the study of adenocarcinoma spectrum lesions, so,
2361 for the purposes of this review, invasive adenocarcinoma (IAC) and minimally invasive adenocarcinoma (MIA)
2362 sub-solid pulmonary nodules were regarded as malignant; while adenocarcinoma in situ (AIS) and atypical
2363 adenomatous hyperplasia (AAH)) sub-solid pulmonary nodules were regarded as benign. As a result, many
2364 studies had to be disregarded as AIS and/or AAH had been included in the malignant group.

2365 Visual analysis

2366 There are currently no data to support a conclusion on changes in visual characteristics for diagnosing lung
2367 cancer in sub-solid nodules.

2368 Diameter change

2369 Four studies reported on the use of diameter change for identifying lung cancer in sub-solid nodules at interval
2370 CT scans.¹⁻⁴ Two studies defined an increase as ≥ 2 mm^{1,4}, one studied used ≥ 1.5 mm² and the final study
2371 was undefined³. Meta-analysis shows diameter change has a pooled sensitivity of 0.63 [0.37, 0.83] and a
2372 pooled specificity of 0.39 [0.22, 0.61] [95% confidence intervals] for diagnosing an invasive sub-solid
2373 pulmonary nodule (Figure Q6c and Table Q6e).

2374 Four studies also reported on baseline and follow-up diameter measurements in sub-solid nodules.^{2,4-6} Due to
2375 limited diagnostic accuracy data, an intervention type meta-analysis was also performed. Data are shown in
2376 Figure Q6b and summarised in Table Q6a.

2377 Table Q6a: Summary of diameter differences between baseline and follow-up CT scans in malignant and
2378 benign sub-solid pulmonary nodules (data from Figure Q6d)

Sub-solid nodule type	Follow-up time	n	Mean diameter difference (CI)
Malignant ^{2,4-6}	≤ 2 years	4	Follow-up 1.53 (-0.46 to 3.51) mm greater
Benign ^{4,6}	≤ 2 years	4	Follow-up 0.72 (-0.78 to 2.22) mm greater
Malignant ^{2,4-6}	> 2 years	2	Follow-up 2.48 (0.98 to 3.98) mm greater
Benign ^{4,6}	> 2 years	2	Follow-up 0.80 (-2.17 to 3.77) mm greater

2379

2380 **Volume doubling time (VDT)**

2381 No studies reported on the diagnostic accuracy of volume doubling time (VDT) for diagnosing lung cancer in
2382 sub-solid pulmonary nodules. Instead, two studies compared VDT between different sub-solid nodule types.
2383 The first study compared the MDT of malignant versus benign sub-solid nodules (Table Q6b).^{7,8} The malignant
2384 and benign datasets in Table Q6b included data from ground-glass nodules (GGN) and part-solid nodules
2385 (PSN).⁷

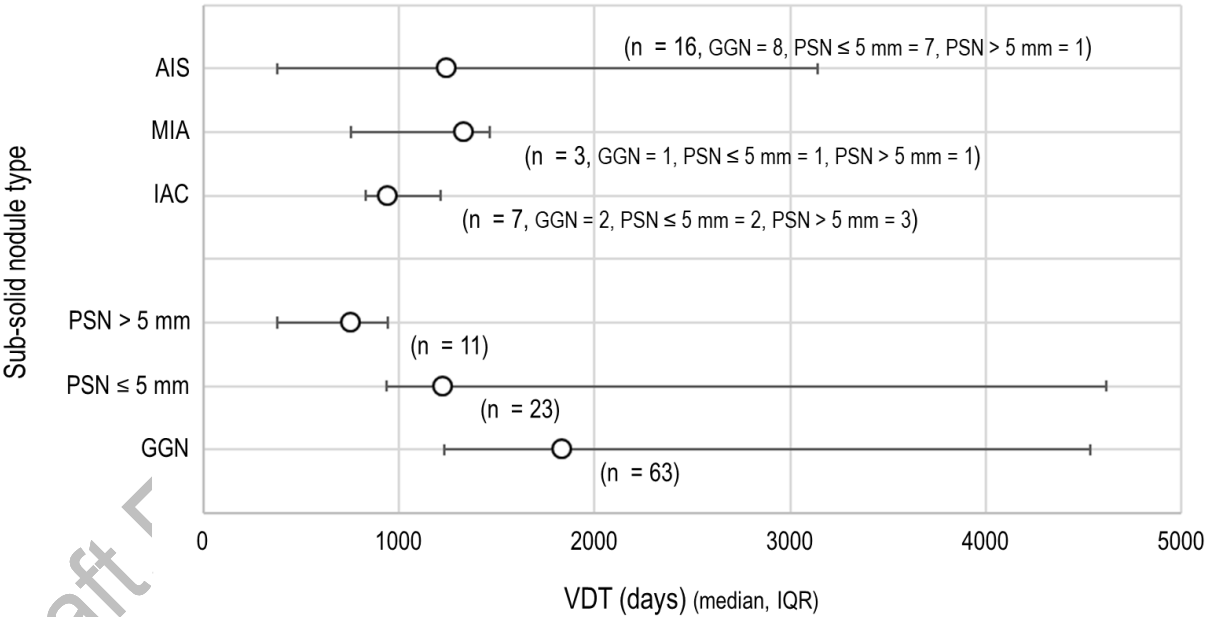
2386 Table Q6b: Comparison of volume doubling time (VDT) between malignant and benign sub-solid nodules

Sub-solid nodule type	n	VDT (days) (median, IQR)
Malignant*	187	552 (344, 725)
Benign*	2508	621 (458, 801)

2387 * Data from ground-glass nodules (GGN) and part-solid nodules (PSN)
2388 IQR – interquartile range; n – number of subjects; VDT – volume doubling time

2389 A more comprehensive study of VDT in sub-solid nodule types was done in the second study (Figure Q6a).⁸
2390 The bottom three rows in Figure Q6a plot shows the VDT median and interquartile range (IQR) of GGN, PSN
2391 with a solid component ≤5 mm and PSN with a solid component > 5mm; and the top three rows show the VDT
2392 (median and IQR) of invasive adenocarcinoma (IAC) (malignant) and minimally invasive adenocarcinoma
2393 (MIA) (malignant) and adenocarcinoma in situ (AIS) (benign) sub-solid nodules. Atypical adenomatous
2394 hyperplasia (AAH) sub-solid nodules (benign) were also assessed but there was no measurable difference in
2395 volume between baseline and follow-up CT scans.⁸

2396 Figure Q6a: Comparison of volume doubling times (VDT) between malignant and benign sub-solid nodules



2397
2398 AIS – adenocarcinoma in situ; GGN – ground-glass nodule; IAC – invasive adenocarcinoma; IQR – interquartile range;
2399 MIA – minimally invasive adenocarcinoma; n – number of nodules; PSN ≤ 5 mm – part-solid nodule with solid component
2400 less than, or equal to 5 mm; PSN > 5 mm – part-solid nodule with solid component greater than 5 mm; VDT – volume
2401 doubling time

2402 **Mass doubling time (MDT)**

2403 Only one study reported data that could be used to assess the diagnostic accuracy of mass doubling time
2404 (MDT) for diagnosing lung cancer in sub-solid pulmonary nodules.⁹ The study reported on MDT ≤400 days
2405 and >400 days for ground-glass nodules and part-solid nodules. Meta-analysis of the data is shown in Figure
2406 Q6e and Table Q6f and summarised in Table Q6c below.

2407 Table Q6c: Sensitivity and specificity of mass doubling time less than 400 days for diagnosing lung cancer in
 2408 sub-solid nodules

Sub-solid nodule type	n	Sensitivity [95% CI]	Specificity [95% CI]
GGN	1	0.50 [0.07, 0.93]	0.13 [0.00, 0.53]
PSN	1	0.93 [0.68, 1.00]	0.80 [0.28, 0.99]
Pooled results	2	0.76 [0.34, 0.94]	0.43 [0.14, 0.81]

2409 GGN – ground-glass nodule; PSN – part-solid nodule

2410 Two further studies compared MDT between different sub-solid nodule types.^{7,8} One study directly compared
 2411 the MDT of malignant versus benign sub-solid nodules (Table Q6d).⁸ The malignant and benign datasets in
 2412 Table Q6d included data from ground-glass nodules (GGN) and part-solid nodules (PSN).⁷

2413 Table Q6d: Comparison of volume doubling time (VDT) between malignant and benign sub-solid nodules

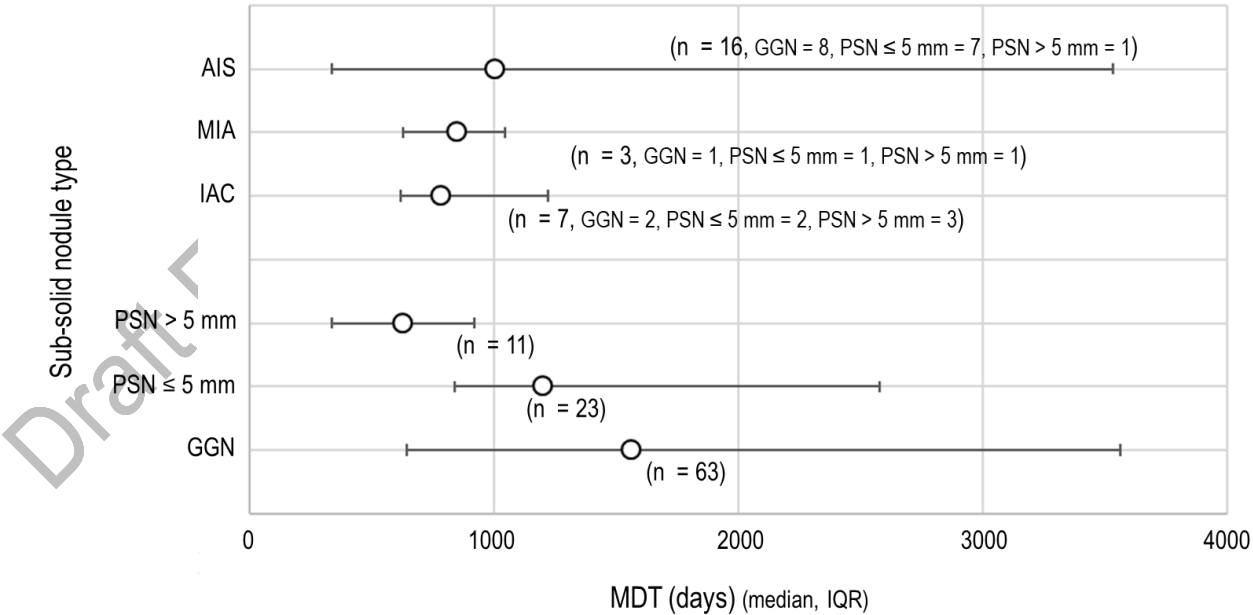
Sub-solid nodule type	n	VDT (days) (median, IQR)
Malignant*	187	488 (321, 630)
Benign*	2508	623 (463, 799)

2414 * Data from ground-glass nodules (GGN) and part-solid nodules (PSN)

2415 IQR – interquartile range; n – number of subjects; VDT – volume doubling

2416 The second study compared MDT in differing sub-solid nodule types (Figure Q6b).⁸ The MDT (median, IQR)
 2417 of GGN, PSN with a solid component ≤ 5 mm and PSN with a solid component > 5 mm is shown in the bottom
 2418 three rows of Figure Q6b; while the MDT (median, IQR) of invasive adenocarcinoma (IAC) and minimally
 2419 invasive adenocarcinoma (MIA) sub-solid nodules (both malignant) and adenocarcinoma in situ (AIS) sub-
 2420 solid nodules (benign) is shown in the top three rows. Atypical adenomatous hyperplasia (AAH) sub-solid
 2421 nodules (benign) were also assessed but there was no measurable difference in mass between baseline and
 2422 follow-up CT scans.⁸

2423 Figure Q6b: Comparison of mass doubling times (MDT) between malignant and benign sub-solid nodules



2424

2425 AIS – adenocarcinoma in situ; GGN – ground-glass nodule; IAC – invasive adenocarcinoma; IQR – interquartile range;
 2426 MDT – mass doubling time; MIA – minimally invasive adenocarcinoma; n – number of nodules; PSN ≤ 5 mm – part-solid
 2427 nodule with solid component less than, or equal to 5 mm; PSN > 5 mm – part-solid nodule with solid component greater
 2428 than 5 mm

2429 **Volume change**

2430 Two studies reported on the use of volume change to diagnose lung cancer in a sub-solid pulmonary nodule
2431 at interval CT scans. Meta-analysis shows volume change has a pooled sensitivity of 0.60 [0.32, 0.84] and a
2432 pooled specificity of 0.72 [0.34, 0.92] [95% confidence intervals] (data shown in [Figure Q6f](#) and [Table Q6g](#)).^{8,10}

2433 **Evidence Statements**

2434 There is insufficient evidence to support the use of visual analysis to detect change between interval computed
2435 tomography (CT) scans for diagnosing lung cancer in sub-solid pulmonary nodules.

2436 Diameter change may have a low sensitivity and low specificity for detecting change between interval
2437 computed tomography (CT) scans for diagnosing lung cancer in sub-solid pulmonary nodules. (**Very low**)

2438 A diameter change of ≥ 2 mm between interval CT scans may indicate lung cancer in a sub-solid pulmonary
2439 nodule. (**Very low**)

2440 There is insufficient evidence to support the use of volume doubling time (VDT) to detect change between
2441 interval computed tomography (CT) scans for diagnosing lung cancer in sub-solid pulmonary nodules.

2442 A mass doubling time (MDT) of ≤ 400 days may have a moderate sensitivity and a low specificity for detecting
2443 change between interval computed tomography (CT) scans for diagnosing lung cancer in sub-solid pulmonary
2444 nodules. (**Very low**)

2445 Volume change may have a low sensitivity and a low specificity for detecting change between interval
2446 computed tomography (CT) scans for diagnosing lung cancer in sub-solid pulmonary nodules. (**Very low**)

2447 There is insufficient evidence to consider ground-glass nodule (GGN) and part-solid nodule (PSN) subgroups.

2448 **Recommendations**

- 2449 ✓ For adults with pure ground-glass pulmonary nodules (GGN), the [Ground-glass nodule pathway](#) (Algorithm
2450 4) should be used for determining lung cancer in progressing GGN. (**Conditional** – by consensus)
- 2451 ➤ For adults with sub-solid pulmonary nodules with a solid component, the [Part-solid nodule pathway](#)
2452 (Algorithm 5) should be used for determining lung cancer in progressing part-solid pulmonary nodules.
2453 (**Conditional** – by consensus)

2454 **Good Practice Points**

- 2455 ✓ Comparison to the earliest available CT should be performed at each evaluation of sub-solid pulmonary
2456 nodule.
- 2457 ✓ The following changes on interval CT scans may be suggestive of invasive lung cancer in sub-solid
2458 pulmonary nodules: increase in the maximal diameter of the solid component, distortion of fissure,
2459 development of air bronchograms, development of bubble-like lucency, increased CT density.

2460 **Research Recommendations**

- 2461 ▪ Further research is needed to determine the diagnostic accuracy of visual characteristic changes between
2462 interval computed tomography (CT) for diagnosing lung cancer in sub-solid pulmonary nodules.
- 2463 ▪ Further research is needed to determine the diagnostic accuracy of volume doubling time for diagnosing
2464 lung cancer in sub-solid pulmonary nodules.
- 2465 ▪ Further research is needed to confirm the diagnostic accuracy of diameter change and volume change
2466 between interval computed tomography (CT) for diagnosing lung cancer in sub-solid pulmonary nodules.
- 2467 ▪ Further research is needed to confirm the diagnostic accuracy of mass doubling time for diagnosing lung
2468 cancer in sub-solid pulmonary nodules.
- 2469 ▪ Research is needed to determine the likelihood of invasive tumour in growing pure ground-glass nodules,
2470 with particular focus on the risk of overdiagnosis and overtreatment of these lesions.

2471

Algorithm 4 Ground-glass nodule (GGN) pathway



2474

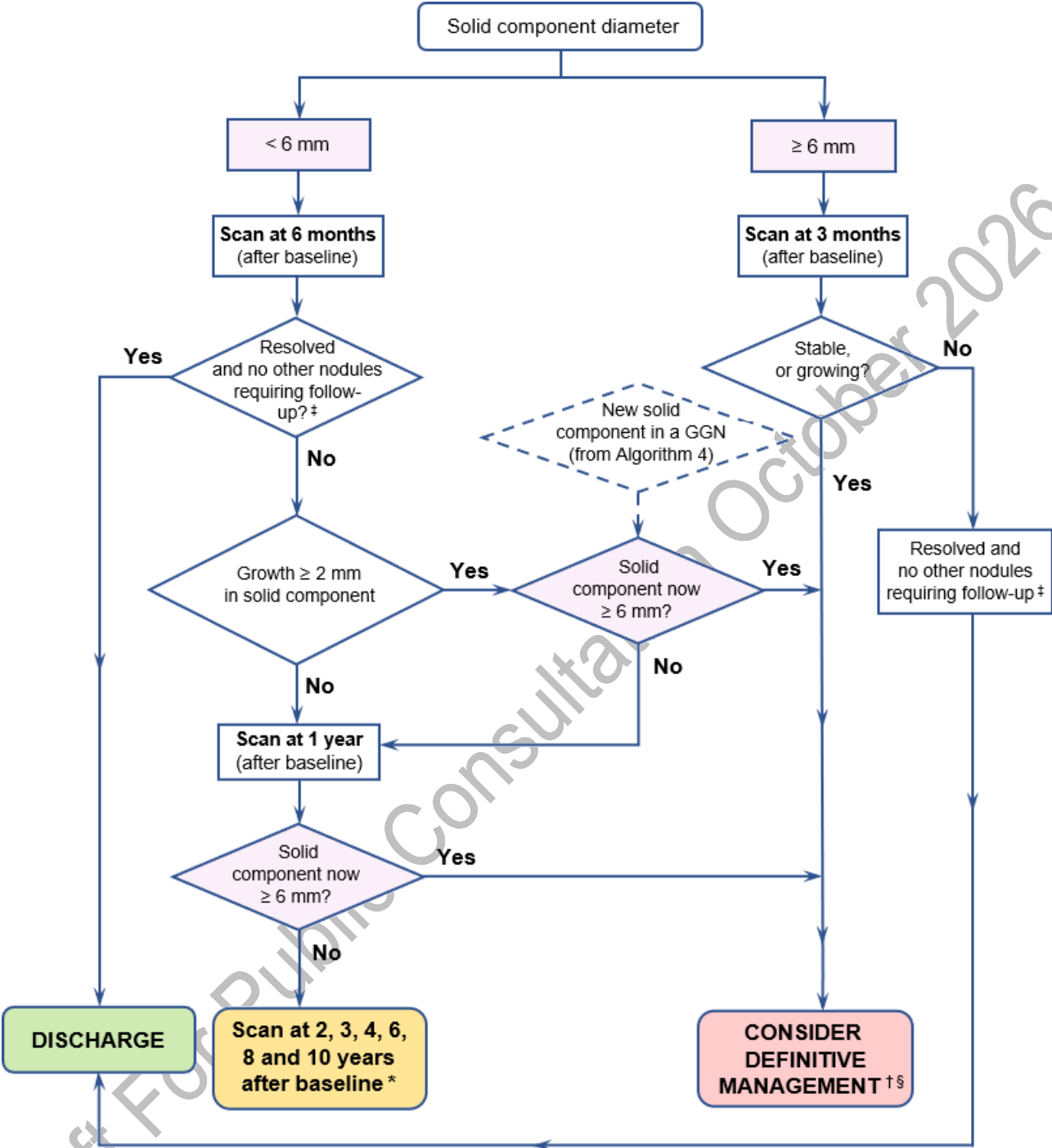
- 2475

- At any point at or after 4 years, if changes in the lesion occur, manage as per the steps for a scan at 2 years from

baseline.

† Altered morphology: air bronchograms, bubble-like lucency, increased CT density, distortion of fissure.

‡ Definitive management should be a shared decision-making process taking into account patient choice, age, comorbidities, and fitness for treatment.



2479

2480 * Length of follow-up:

- 2481 - After 10 years of follow-up, consider CT every 5 years if patient remains suitable for definitive management.
- 2482 - At any point at or after 4 years, if changes in the lesion occur, manage as per the steps for a scan at 2 years from
- 2483 baseline.

† PET-CT not required for further nodule characterisation or staging if solid component < 10 mm.

‡ If multiple GGNs and still persistent – see [Ground-glass nodule pathway](#) (Algorithm 4)

2484

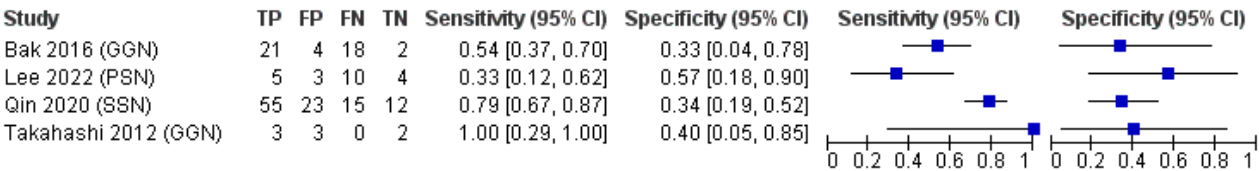
2485 **Meta-analyses**

2486 **Diameter change**

2487 *Diagnostic accuracy*

2488 Figure Q6c: Forest plot and SROC plot of diameter change for diagnosing lung cancer in sub-solid nodules

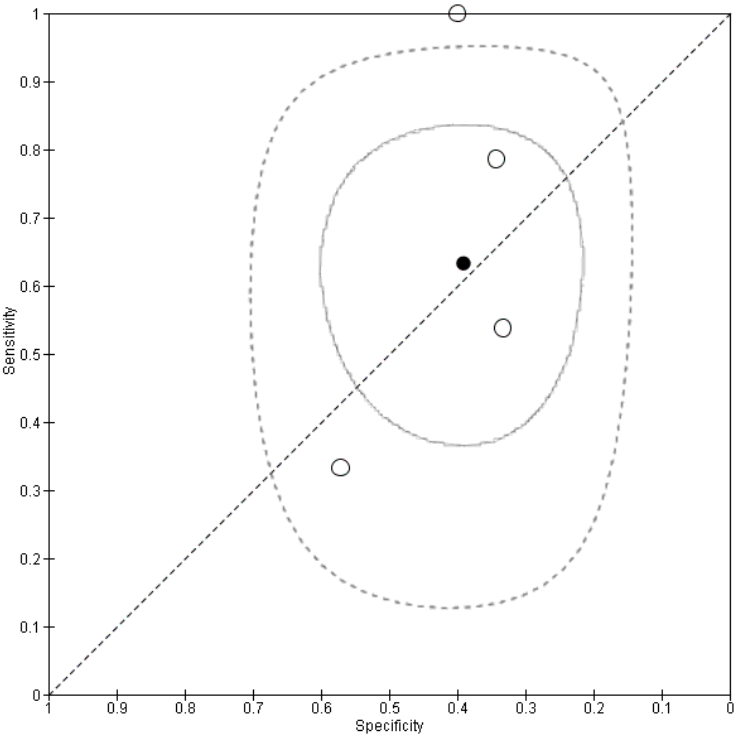
2489 i) Forest plot



2490

2491 GGN – ground-glass nodule; PSN – part-solid nodule; SSN – sub-solid nodule (GGN and PSN)

2492 ii) SROC plot (not enough data to determine curve)



2493

2494 Table Q6e: Pooled results of diameter change for diagnosing lung cancer in sub-solid nodules

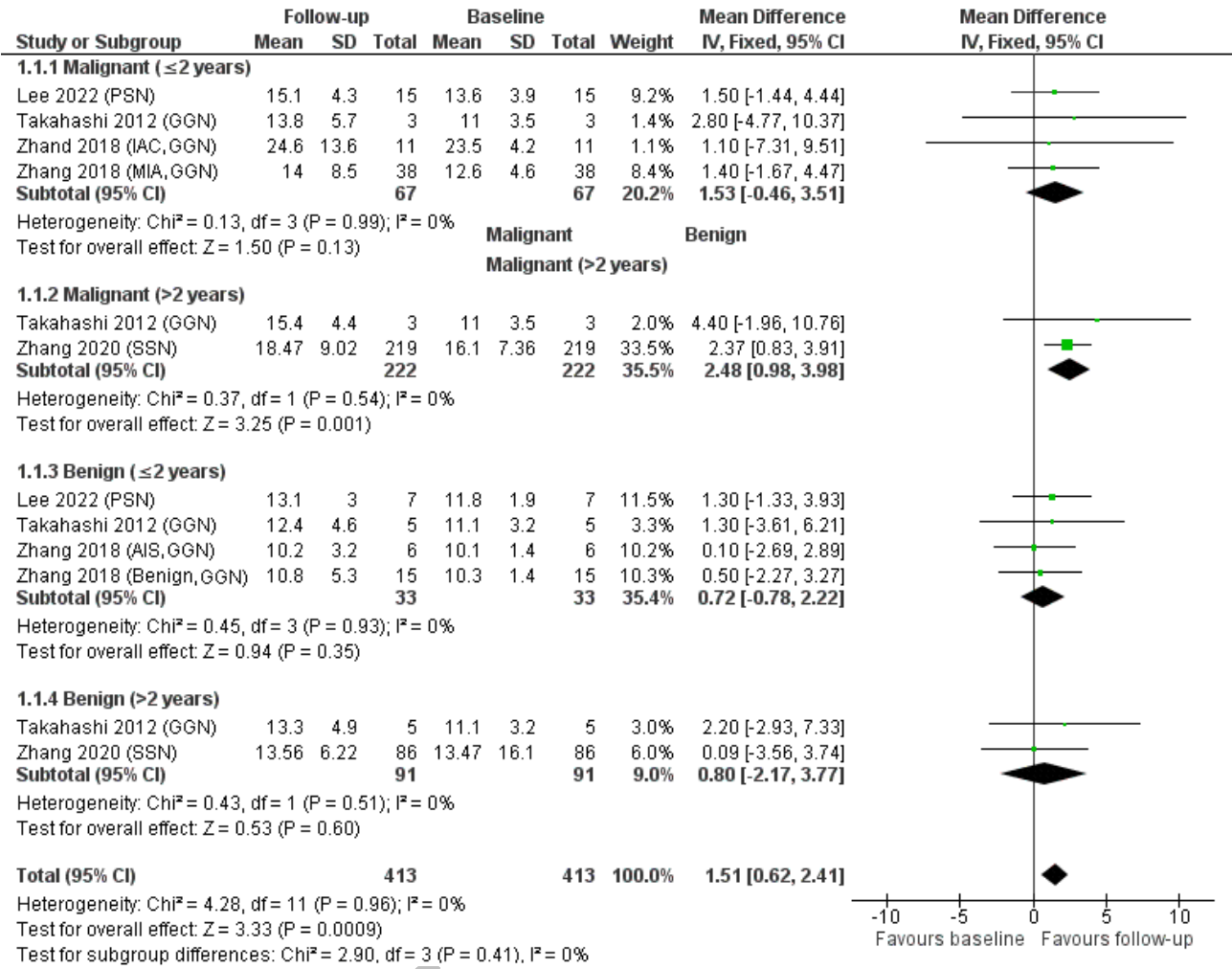
Pooled Sensitivity	0.633	[0.370, 0.834]
Pooled Specificity	0.391	[0.219, 0.666]
LR+	1.042	[0.583, 1.755]
LR-	0.937	[0.375, 2.025]
DOR	1.111	[0.295, 4.734]

Bayesian meta-analysis, data displayed as posterior median [95% posterior interval]

2501

2502 Intervention-type analysis

2503 Figure Q6d: Difference between baseline and follow-up diameter size in malignant and benign sub-solid
2504 nodules



2505

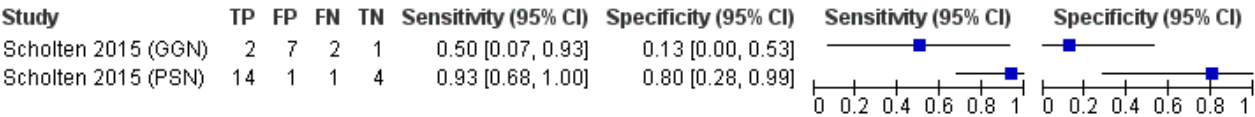
2506

2507 Mass doubling time (MDT)

2508 MDT ≤400 days

2509 Figure Q6e: Forest plot and SROC plot of MDT ≤400 days for diagnosing lung cancer in sub-solid nodules

2510 ii) Forest plot



2511

2512

2513

2514

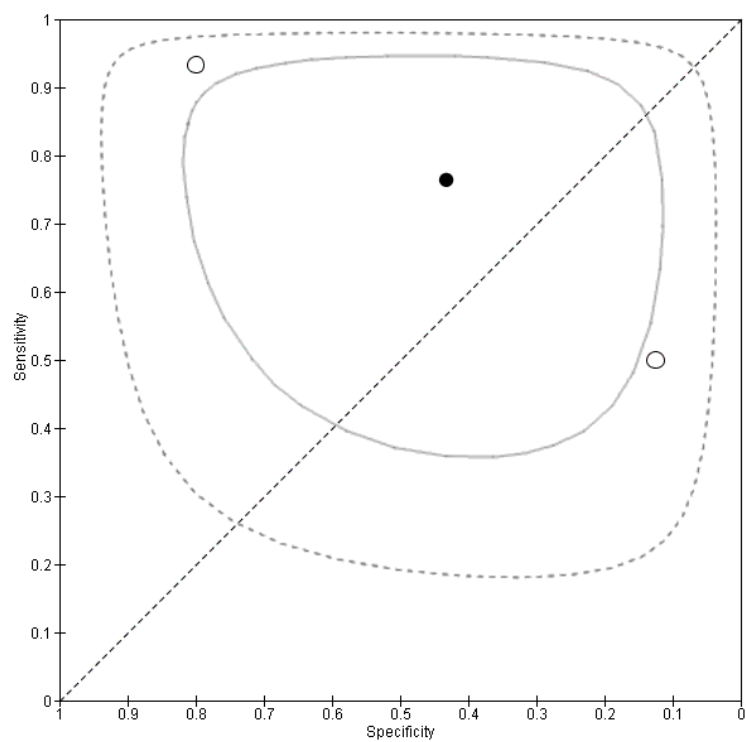
2515

2516

2517

2518

2519 ii) SROC plot (not enough data to determine curve)



2520

2521 Table Q6f: Pooled results of VDT <400 days for diagnosing lung cancer in solid nodules

Pooled Sensitivity	0.764	[0.339, 0.937]
Pooled Specificity	0.432	[0.138, 0.809]
LR+	1.284	[0.512, 4.190]
LR-	0.578	[0.116, 2.720]
DOR	2.399	[0.190, 27.380]

Bayesian meta-analysis, data displayed as posterior median [95% posterior interval]

2527

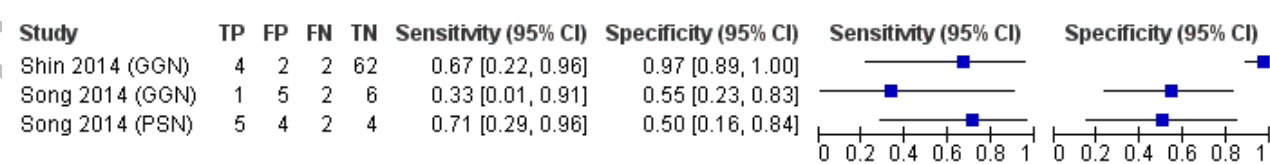
2528

2529

2530 **Volume change**

2531 Figure Q6f: Forest plot and SROC plot of volume change for diagnosing lung cancer in sub-solid nodules

2532 ii) Forest plot



2533

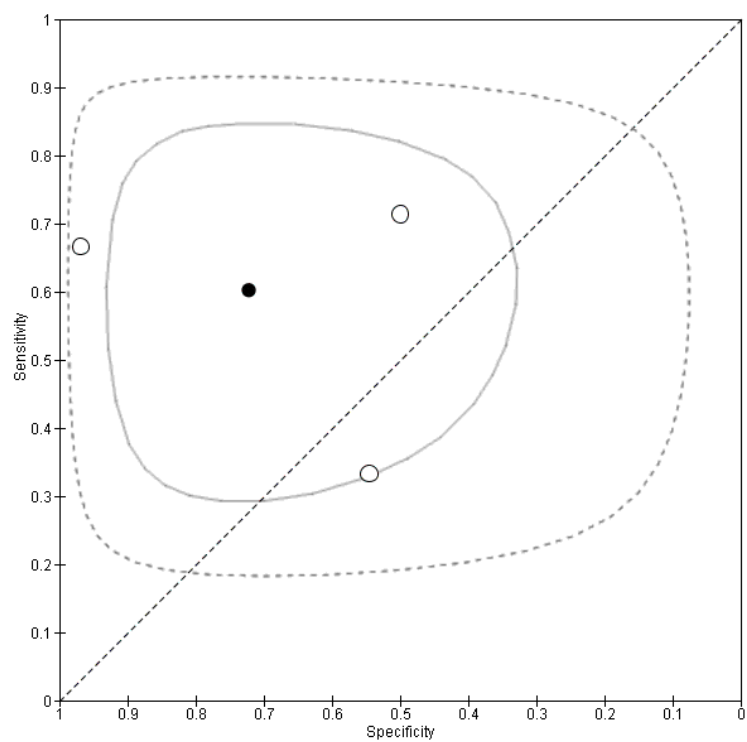
2534

2535

2536

2537

2538 ii) SROC plot (not enough data to determine curve)



2539
2540

2541 Table Q5g: Pooled results of volume change for diagnosing lung cancer in solid nodules

Pooled Sensitivity	0.602	[0.319, 0.839]	2542
Pooled Specificity	0.722	[0.341, 0.924]	2543
LR+	2.111	[0.741, 7.763]	2544
LR-	0.570	[0.233, 1.335]	2545
DOR	3.968	[0.544, 26.204]	2546

Bayesian meta-analysis, data displayed as posterior median [95% posterior interval]

2547
2548
2549
2550
2551
2552
2553
2554
2555
2556
2557
2558

	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Bak 2016	+	+	?	+	+	+	+
Lee 2022	+	+	+	?	+	+	+
Qin 2020	●	+	+	+	+	+	+
Scholten 2015	+	?	?	?	+	+	+
Shin 2014	+	?	+	+	+	+	+
Song 2014	+	?	?	+	+	+	+
Takahashi 2012	+	?	?	+	+	?	?
● High ? Unclear + Low							

Intervention analyses

	Selection bias	Performance bias	Detection bias	Attrition bias	Publication bias
Lee 2022	?	+	+	+	+
Takahashi 2012	?	+	?	+	+
Zhang 2018	+	+	?	+	+
Zhang 2020	?	+	+	+	+
● High ? Unclear + Low					

2560
2561
2562
2563
2564
2565
2566
2567
2568

2569 **GRADE analyses**

2570 **Diameter change**

2571 *Diagnostic accuracy*

What is the diagnostic accuracy of pulmonary nodule diameter change between interval computed tomography (CT) scans for diagnosing lung cancer?

Patient or population: Adults aged 18+ with solid pulmonary nodules

New test: Pulmonary nodule diameter change

Pooled sensitivity: 0.63 (95% CI: 0.37 to 0.83) | **Pooled specificity:** 0.39 (95% CI: 0.22 to 0.61)

Test result	Number of results per 1,000 patients tested (95% CI) Prevalence 5% Typically seen in	Number of participants (studies)	Certainty of the Evidence (GRADE)
True positives	32 (19 to 42)	127	⊕○○○ VERY LOW a,b,c
False negatives	18 (8 to 31)	(4)	
True negatives	371 (208 to 576)	53	⊕○○○ VERY LOW a,b,c
False positives	579 (374 to 742)	(4)	

CI: Confidence interval

Explanations

- a. Serious risk of bias across studies
- b. Serious inconsistency across sensitivities
- c. Serious imprecision across sensitivities and specificities

2572

2573

2574 *Intervention type analysis*

In adults with sub-solid pulmonary nodules, does nodule diameter change indicate malignant sub-solid nodules?

Population: Adults aged 18+ with sub-solid pulmonary nodules

Intervention: Malignant or benign sub-solid nodule baseline diameter

Comparator: Malignant or benign sub-solid nodule follow-up diameter

Outcome	Number of participants (datasets)	Estimate of effect	Quality of the Evidence (GRADE)
Nodule diameter change (all)	826 (12 datasets)	1.51 (0.62 to 2.41) mm greater in the follow-up group	⊕○○○ VERY LOW a,b,c
Nodule diameter change (malignant, ≤ 2-year follow-up)	134 (4 datasets)	1.53 (0.46 to 3.51) mm greater in the follow-up group	⊕○○○ VERY LOW a,c
Nodule diameter change (malignant, > 2-year follow-up)	444 (2 datasets)	2.48 (0.98 to 3.98) mm greater in the follow-up group	⊕○○○ VERY LOW a,c,d
Nodule diameter change (benign, ≤ 2-year follow-up)	66 (4 datasets)	0.72 (0.78 to 2.22) mm greater in the follow-up group	⊕○○○ VERY LOW a,c
Nodule diameter change (benign, > 2-year follow-up)	182 (2 datasets)	0.80 (2.17 to 3.77) mm greater in the follow-up group	⊕○○○ VERY LOW a,c,d

Explanations

- a. Serious risk of bias across the studies
- b. Serious inconsistency across the studies
- c. Serious imprecision, CIs within the MID
- d. Some inconsistency across the studies

2576

2577

2578

 $MDT \leq 400 \text{ days}$

New test: Pulmonary nodule mass doubling time ≤ 400 days

Pooled sensitivity: 0.76 (95% CI: 0.34 to 0.94) | **Pooled specificity:** 0.43 (95% CI: 0.14 to 0.81)

CI: Confidence interval

- a. Serious risk of bias across datasets
- b. Serious inconsistency across sensitivities and specificities
- c. Serious imprecision across sensitivities and specificities

2579

2580

2581

Volume change

Patient or population: Adults aged 18+ with solid pulmonary nodules

New test: Pulmonary nodule volume change

Pooled sensitivity: 0.60 (95% CI: 0.32 to 0.84) | **Pooled specificity:** 0.72 (95% CI: 0.34 to 0.92)

CI: Confidence interval

- a. Serious risk of bias across studies
- b. Serious inconsistency across sensitivities and specificities
- c. Serious imprecision across sensitivities and specificities

2582

2583

2584

2585

2586 **Recommendation Tables**

2587 **Question Details**

POPULATION:	Adults (18+) with sub-solid pulmonary nodules
INDEX TESTS:	Strategies used to detect change between interval computed tomography (CT) scans
GOLD STANDARD:	Pathological diagnosis of invasive lung cancer or clinical diagnosis of lung cancer
OUTCOME:	Diagnostic accuracy of strategies used to detect change for diagnosing lung cancer

2588

2589 **Diameter change**

2590 *Diagnostic accuracy*

2591 **SUMMARY OF JUDGEMENTS**

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
TEST ACCURACY	Very inaccurate	Inaccurate	Accurate	Very accurate		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	Does not favour the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know

2592

2593

2594 **TYPE OF RECOMMENDATION**

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
☐	☐	☒	☐	☐

2595

2596

Recommendation

There is insufficient evidence to determine if a sub-solid pulmonary nodule diameter change indicates a diagnosis of lung cancer.

Justification

Diameter change may have a low sensitivity and low specificity for detecting change between interval computed tomography (CT) scans for diagnosing lung cancer in sub-solid pulmonary nodules. (Very low)

Subgroup considerations

There was not enough evidence to consider ground-glass nodule/non-solid nodule and part-solid nodule subgroups.

Research priorities

Further research is needed to confirm the diagnostic accuracy of diameter change between interval computed tomography (CT) for diagnosing lung cancer in sub-solid pulmonary nodules.

2601

2602 Intervention-type analysis

2603 SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	Does not favour the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know

2604

2605 TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
☐	☐	☒	☐	☐

2606

2607

Recommendation

There is insufficient evidence to determine if a sub-solid pulmonary nodule diameter change indicates a diagnosis of lung cancer.

Justification

A diameter change of ≥ 2 mm between interval CT scans may indicate lung cancer in a sub-solid pulmonary nodule. (Very low)

Subgroup considerations

There was not enough evidence to consider ground-glass nodule/non-solid nodule and part-solid nodule subgroups.

Research priorities

Further research is needed to confirm the diagnostic accuracy of diameter change between interval computed tomography (CT) for diagnosing lung cancer in sub-solid pulmonary nodules.

2612

2613

2614 Mass doubling time (MDT)

2615 $MDT \leq 400$ days

2616 SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
TEST ACCURACY	Very inaccurate	Inaccurate	Accurate	Very accurate		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	Does not favour the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know

2617

2618

2619 **TYPE OF RECOMMENDATION**

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
☐	☐	☐	☒	☐

2620

2621 **CONCLUSIONS**

Recommendation

There is insufficient evidence to determine if a sub-solid pulmonary nodule mass doubling time of less than, or equal to 400 days indicates a diagnosis of lung cancer.

Justification

A mass doubling time (MDT) of ≤ 400 days may have a moderate sensitivity and a low specificity for detecting change between interval computed tomography (CT) scans for diagnosing lung cancer in sub-solid pulmonary nodules. (**Very low**)

Subgroup considerations

There was not enough evidence to consider ground-glass nodule/non-solid nodule and part-solid nodule subgroups.

Research priorities

Further research is needed to confirm the diagnostic accuracy of mass doubling time for diagnosing lung cancer in sub-solid pulmonary nodules.

2625

2626

2627 Volume change

2628 SUMMARY OF JUDGEMENTS

JUDGEMENT							
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
TEST ACCURACY	Very inaccurate	Inaccurate	Accurate	Very accurate		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	Does not favour the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know

2629

2630 TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
☐	☐	☒	☐	☐

2631

2632 CONCLUSIONS

Recommendation

There is insufficient evidence to determine if a sub-solid pulmonary nodule volume change indicates a diagnosis of lung cancer.

Justification

Volume change may have a low sensitivity and a low specificity for detecting change between interval computed tomography (CT) scans for diagnosing lung cancer in sub-solid pulmonary nodules. (Very low)

Subgroup considerations

There was not enough evidence to consider ground-glass nodule/non-solid nodule and part-solid nodule subgroups.

Research priorities

Further research is needed to confirm the diagnostic accuracy of volume change between interval computed tomography (CT) for diagnosing lung cancer in sub-solid pulmonary nodules.

2635

2636

- 2638 1. Bak SH, Lee HY, Kim JH, et al. Quantitative CT Scanning Analysis of Pure Ground-Glass Opacity Nodules
2639 Predicts Further CT Scanning Change. *Chest*. 2016;149(1):180–91.
- 2640 2. Lee JH, Hwang EJ, Lim WH, Goo JM. Determination of the optimum definition of growth evaluation for
2641 indeterminate pulmonary nodules detected in lung cancer screening. *PLoS ONE*. 2022;17(9):e0274583.
- 2642 3. Qin Y, Xu Y, Ma D, Tian Z, et al. Clinical characteristics of resected solitary ground-glass opacities:
2643 Comparison between benign and malignant nodules. *Thorac Cancer*. 2020;11(10):2767–2774.
- 2644 4. Takahashi S, Tanaka N, Okimoto T, et al. Long term follow-up for small pure ground-glass nodules:
2645 implications of determining an optimum follow-up period and high-resolution CT findings to predict the
2646 growth of nodules. *Jpn J Radiol*. 2012;30(3):206–17.
- 2647 5. Zhang YP, Heuvelmans MA, Zhang H, et al. Changes in quantitative CT image features of ground-glass
2648 nodules in differentiating invasive pulmonary adenocarcinoma from benign and in situ lesions:
2649 histopathological comparisons. *Clin Radiol*. 2018;73(5):504.e9–504.e16.
- 2650 6. Zhang R, Tian P, Qiu Z, Liang Y, Li W. The growth feature and its diagnostic value for benign and malignant
2651 pulmonary nodules met in routine clinical practice. *J Thorac Dis*. 2020;12(5):2019–2030.
- 2652 7. Liao RQ, Li AW, Yan HH, et al. Deep learning-based growth prediction for sub-solid pulmonary nodules
2653 on CT images. *Front Oncol*. 2022;12:1002953.
- 2654 8. Song YS, Park CM, Park SJ, et al. Volume and mass doubling times of persistent pulmonary subsolid
2655 nodules detected in patients without known malignancy. *Radiology*. 2014;273(1):276–84.
- 2656 9. Scholten ET, de Jong PA, de Hoop B, et al. Towards a close computed tomography monitoring approach
2657 for screen detected subsolid pulmonary nodules? *Eur Respir J*. 2015;45(3):765–73.
- 2658 10. Shin KE, Lee KS, Yi CA, et al. Subcentimeter lung nodules stable for 2 years at LDCT: long-term follow-
2659 up using volumetry. *Respirology*. 2014;19(6):921–8.

2660

2661

Field	Content
Review Question	In adults with sub-solid pulmonary nodules, what is the diagnostic accuracy of strategies* used to detect change between interval computed tomography (CT) scans for diagnosing lung cancer? * Computer-aided measurement of specific nodule parameters (e.g. volume, mass) NOT artificial-intelligence tools where multiple parameters are computed to give an overall risk assessment.
Type of review question	Diagnostic accuracy review
Objective of the review	Where the initial index of suspicion of cancer in a sub-solid pulmonary nodule is low, the preferred strategy is often to repeat the CT scan after a defined interval to determine whether the nodule is changing. This question seeks to clarify the optimal strategy for measuring and defining that change in order to tell apart malignant from benign nodules.
Eligibility criteria – population / disease / condition / issue / domain	Adults with sub-solid pulmonary nodules (18+ years of age)
Eligibility criteria – index test(s)	Visual analysis Diameter change Volume doubling time Mass doubling time Volume change
Eligibility criteria – gold standard	Pathological diagnosis of invasive lung cancer or clinical diagnosis of lung cancer
Outcomes and prioritisation	Diagnostic accuracy
Eligibility criteria – study design	RCTs, comparative studies, case series (>50 cases)

Other inclusion /exclusion criteria	Non-English language excluded unless full English translation Conference abstracts, Cochrane reviews, systematic reviews, reviews Cochrane reviews and systematic reviews can be referenced in the text, but CANNOT be used in a meta-analysis
Proposed sensitivity / subgroup analysis, or meta-regression	Adults with sub-solid pulmonary nodules - Ground-glass nodule (GGN)/non-solid nodule - Part-solid nodule (PSN)
Selection process – duplicate screening / selection / analysis	Agreement should be reached between Guideline members who are working on the question. If no agreement can be reached, a decision should be made by the Guideline co-chairs. If there is still no decision, the matter should be brought to the Guideline group and a decision will be made by consensus
Data management (software)	RevMan5 Pairwise meta-analyses (if data in the correct format) Evidence review/considered judgement. Storing Guideline text, tables, figures, etc. MetaDTA Data meta-analyses Gradepro Quality of evidence assessment
Information sources – databases and dates	MEDLINE, Embase, Central Register of Controlled Trials and Cochrane Database of Systematic Reviews Restricted to articles published from 1990 onwards
Methods for assessing bias at outcome / study level	RevMan5 diagnostic accuracy full review template (based on QUADAS2) (follow instructions in ' <i>BTS Guideline Process Handbook – Diagnostic Accuracy (June 2020)</i> ')
Methods for quantitative analysis – combining studies and exploring (in)consistency	If 3 or more relevant studies: RevMan5 for forest plots, summary ROC plots MetaDTA to combine studies (pooled specificity, sensitivity, likelihood ratios, diagnostic odds ratio and confidence intervals) and calculate RevMan parameters for summary ROC plot (follow instructions in ' <i>BTS Guideline Process Handbook – Diagnostic Accuracy (June 2020)</i> ')

Meta-bias assessment – publication bias, selective reporting bias	GRADEpro Diagnostic accuracy quality of evidence assessment for each index test (follow instructions in ‘<i>BTS Guideline Process Handbook – Diagnostic Accuracy (June 2020)</i>’)
Rationale / context – what is known	If the initial index of suspicion of cancer in a sub-solid pulmonary nodule is low, surveillance is usually the preferred strategy, where the CT scan is repeated after a time interval (usually at least 3 months) to assess change in the nodule’s appearance. Measurement of change in sub-solid nodules differs from solid nodules in that sub-solid nodules can have two components - an outer pure ground-glass component and an inner solid component. Sometimes, malignant sub-solid nodules can change their overall appearance (morphology) without necessarily getting larger. This question will determine how to assess change in these various components with the aim of identifying potentially harmful cancers.

2665

2666

2667

2668

2669

2670

2671

2672

2673

2674

2675

2676

2677

2678

2679

2680

2681

2682

2683

2684

2685

2686

2687

2688

2689

2691 **Q7** **In adults with pulmonary nodules, what is the diagnostic accuracy of biopsy of a pulmonary**
 2692 **nodule for diagnosing lung cancer?**

2693 **Contents**

2694	Question Evidence Review	147
2695	Background	147
2696	Outcomes	147
2697	Evidence Review	147
2698	Evidence Statements	150
2699	Recommendation	151
2700	Good Practice Points	151
2701	Research recommendation	151
2702	Meta-analyses	152
2703	Biopsy	152
2704	<i>Bronchoscopic biopsy</i>	153
2705	<i>Percutaneous biopsy</i>	155
2706	<i>Surgical biopsy</i>	156
2707	Risk of bias summary	157
2708	GRADE analyses	158
2709	Biopsy	158
2710	<i>Bronchoscopic biopsy</i>	158
2711	<i>Percutaneous biopsy</i>	159
2712	<i>Surgical biopsy</i>	159
2713	Recommendation tables	160
2714	Bronchoscopic biopsy	160
2715	Percutaneous biopsy	161
2716	Surgical biopsy	162
2717	References	163
2718	Question Protocol	165

2719
 2720
 2721
 2722
 2723
 2724

2725 **Question 7 Evidence Review**

2726 **Q7 In adults with pulmonary nodules, what is the diagnostic accuracy of biopsy of a pulmonary**
2727 **nodule for diagnosing lung cancer?**

2728 **Background**

2729 The decision to biopsy a pulmonary nodule is often complex. Deciding which modality to choose is based on
2730 both patient and nodule characteristics. There are several modalities available to clinicians to obtain a
2731 diagnostic biopsy, and these can be broadly categorised into:

- 2732 i) Bronchoscopic biopsy (flexible bronchoscopy, navigational bronchoscopy or robotic assisted
2733 bronchoscopy)
2734 ii) Percutaneous biopsy (USS or CT guided biopsy); and
2735 iii) Surgical biopsy.

2736 This review aims to assess the diagnostic accuracy of these biopsy modalities in diagnosing lung cancer in
2737 pulmonary nodules.

2738 **Outcomes**

2739 Diagnostic accuracy of biopsy (percutaneous, bronchoscopic, surgical)

2740 **Evidence Review**

2741 The initial literature search identified 430 potentially relevant papers, and 36 papers were deemed relevant to
2742 the review.¹⁻³⁶ A predominance of studies reporting percutaneous biopsies and low number reporting
2743 bronchoscopic biopsies is likely due to publication bias. There were also very few randomised studies
2744 assessing different pulmonary nodule biopsy modalities. Evidence for this question also primarily relied on
2745 observational real-world data.

2746 For all meta-analyses, there were not enough data to consider solid nodules and sub-solid nodules as separate
2747 subgroups. Details of the pulmonary nodule types, sizes and diagnostic yields within the included studies is
2748 shown in [Table Q7a](#).

2749 Table 7a: Nodule types, sizes and diagnostic yields

Study	Nodule types		Nodule sizes (mm)	Diagnostic yield (%)
Bronchoscopic biopsy				
Bondue 2023 ¹	SPN	76% Solid 14% PSN 10% GGN	< 30 16.3 ± 5.3*	61
Dibardino 2023 ²	SPN	Undefined	19.5 (7 to 47) [†]	87
Folch 2018 ³	SPN	Undefined	< 20 (49%) ≥ 20 (51%)	75
Herath 2023 ⁴	SPN	Undefined	23 (8 to 60) [‡]	85
Iwamoto 2023 ⁵	SPN	Undefined	< 5 (4%) 5-10 (28%) > 10 (74%)	100
Kim 2023 ⁶	PPL	84% Solid 14% PSN 2% GGN	≤ 30	79
Kunimasa 2016 ⁷	PPL	+GGN	Undefined	65
Pritchett 2018 ⁸	SPN	Undefined	16 (7 to 55) [†]	84

(continued on next page)

Pritchett 2024 ⁹	SPN	Undefined	19 (7 to 48) [†]	88
Styrvoky 2022 ¹⁰	SPN	Undefined	22.6 ± 13.3* 19 (7 to 73) [†]	91
Mean ± SD (bronchoscopic)				82 ± 12
<i>Percutaneous biopsy</i>				
Guralnik 2015 ¹¹	SPN	74% Solid 23% PSN 3% GGN	32 (6 to 149) [†]	100
He 2022 ¹²	SPN	90% Solid 9% PSN 1% GGN	≤ 20 (30%) 20-40 (34%) >40 (36%)	90
Hirose 2000 ¹³	SPN	Undefined	> 10	96
Huang 2019 ¹⁴	SPN	Undefined	Undefined	100
Huang 2021 ¹⁵	PPL	Undefined	≤ 20	83
Huang 2021 ¹⁶	SPN	>80% solid component	≤ 30	71
Hui 2022 ¹⁷	SPN	95% Solid 5% SSN	≤ 10 (47%) > 10 to 20 (53%)	100
Kim 2011 ¹⁸	SPN	Undefined	Undefined	84
Laurent 2000 ¹⁹	SPN	Undefined	< 20	94
Lee 2014 ²⁰	SPN	93% Solid 7% GGN	Undefined	80
Li 2013 ²¹	SPN	Undefined	< 20	89
Li 2017 ²²	SPN	Undefined	< 20	62
Li 2020 ²³	SPN	Undefined	2.9 ± 1.0*	42
Liu 2013 ²⁴	SPN	Undefined	5 to 10 (22%) >10 to 20 (78%)	95
Liu 2015 ²⁵	SPN	Undefined	Undefined	99
Liu 2017 ²⁶	SPN	Undefined	≤ 20 (48%) > 20 (52%)	97
Liu 2020 ²⁷	SPN	99% Solid 1% SSN	5 to < 20 16.6 ± 3.6*	92
Liu 2022 ²⁸	PPL	Undefined	2.5 ± 0.4* (52%) 3.4 ± 0.5* (48%)	86
Portela 2020 ²⁹	SPN	Undefined	≤ 10	93
Santambrogio 1997 ³⁰	SPN	Solid	< 30	90
Tsukada 2000 ³¹	Undefined	Undefined	23.0 ± 12.0 (6 to 70)	-
Xu 2018 ³²	SPN	Undefined	< 20	97
Zou 2024 ³³	SPN	Undefined	≤ 20 (30%) >20 to ≤ 30 (70%)	-
Mean ± SD (percutaneous)				88 ± 14
(continued on next page)				

Surgical biopsy				
Lin 2013 ³⁴	SPN	Undefined	18 ± 6*	100
Mack 1993 ³⁵	Undefined	Undefined	Undefined	100
Murasugi 2001 ³⁶	PPL	Undefined	14 (3 to 38)†	100
Mean ± SD (surgical)				100 ± 0

2750 +GGN – dataset includes ground-glass nodules; GGN – ground-glass nodules; PPL – peripheral pulmonary nodules;
2751 PSN – part solid nodules; Solid – solid pulmonary nodules; SPN – solitary pulmonary nodules; SSN – sub-solid nodule;
2752 Undefined – nodule type (solid, part solid or GGN) breakdown not defined

2753 * Mean ± SD

2754 † Median (range)

2755 ‡ Mean (range)

2756 Biopsy

2757 Thirty-six studies reported on the diagnostic accuracy of biopsy for diagnosing lung cancer in pulmonary
2758 nodules.¹⁻³⁶ Meta-analysis shows a pooled sensitivity of 0.93 [0.90, 0.95] and pooled specificity of 1.00 [0.99,
2759 1.00] [95% confidence intervals] (data shown in Figure Q7a and Table Q7b).

2760 Bronchoscopic biopsy

2761 Ten studies reported on the diagnostic accuracy of bronchoscopic biopsy for diagnosing lung cancer in
2762 pulmonary nodules.¹⁻¹⁰ Meta-analysis shows a pooled sensitivity of 0.91 [0.80, 0.96] and pooled specificity of
2763 1.00 [0.77, 1.00] [95% confidence intervals] (data shown in Figure Q7b and Table Q7c).

2764 Percutaneous biopsy

2765 Twenty-three studies reported on the diagnostic accuracy of percutaneous biopsy for diagnosing lung cancer
2766 in pulmonary nodules.¹¹⁻³³ Meta-analysis shows a pooled sensitivity of 0.93 [0.89, 0.95] and pooled specificity
2767 of 1.00 [0.96, 1.00] [95% confidence intervals] (data shown in Figure Q7c and Table Q7d).

2768 Three of these studies compared sensitivity and specificity across different nodule sizes. Data are summarised
2769 in Table Q7e.

2770 Table Q7e: Comparison of the diagnostic accuracies of percutaneous biopsy in different pulmonary nodule
2771 sizes

Study	n	Nodule size (mm)	Sensitivity	Specificity	p
Hui 2022 ¹⁷	105	≤ 10	0.79	1.00	> 0.05
	117	>10 to 20	0.90	1.00	
Liu 2013 ²⁴	25	5 to 10	0.94	1.00	0.08
	71	>10 to 20	0.96	1.00	
Liu 2017 ²⁶	31	≤ 20	0.96	1.00	> 0.05
	34	> 20	0.97	1.00	

2772 n – number of participants

2773 Surgical biopsy

2774 Three studies reported on the diagnostic accuracy of surgical biopsy for diagnosing lung cancer in pulmonary
2775 nodules.³⁴⁻³⁶ Meta-analysis shows a pooled sensitivity of 0.98 [0.78, 1.00] and pooled specificity of 0.98 [0.74,
2776 1.00] [95% confidence intervals] (data shown in Figure Q7d and Table Q7f).

2777 A summary of all meta-analysis data is shown in Table Q7g and distribution plots of the sensitivities and
2778 specificities across the three biopsy types is shown in Figure Q7e.

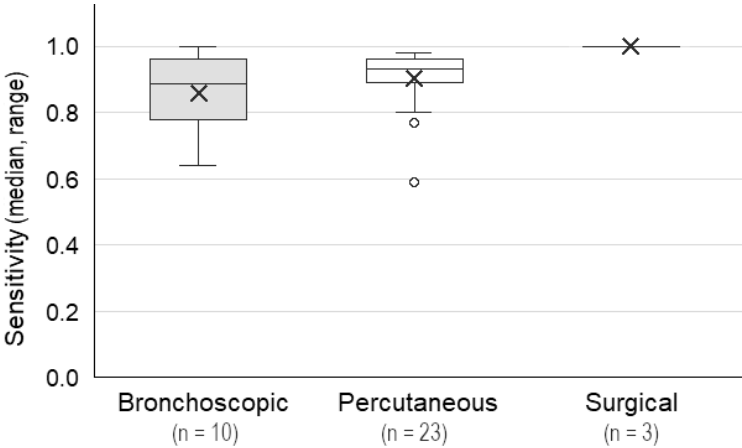
2779 Table Q7g: Comparison of the diagnostic accuracies of different biopsy techniques for diagnosing the
2780 invasiveness of pulmonary nodules

Biopsy type	n	Sensitivity [95% CI]	Specificity [95% CI]
All ¹⁻³⁶	36	0.93 [0.90, 0.95]	1.00 [0.99, 1.00]
Bronchoscopic ^{1-5,7-10}	10	0.91 [0.80, 0.96]	1.00 [0.77, 1.00]
Percutaneous ¹¹⁻³³	23	0.93 [0.89, 0.95]	1.00 [0.96, 1.00]
Surgical ³⁴⁻³⁶	3	0.98 [0.78, 1.00]	0.98 [0.74, 1.00]

2781 n – number of studies

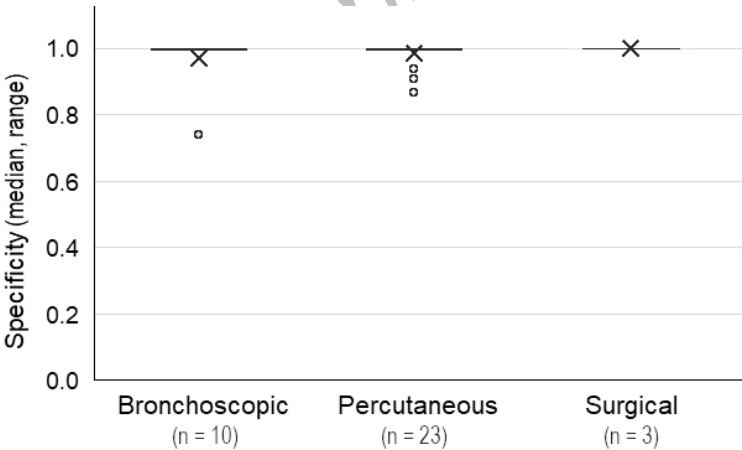
2782 Figure Q7e: Distribution plot comparison of the sensitivity and specificity data for bronchoscopic, percutaneous
2783 and surgical biopsies.

2784 i) **Sensitivities**



2785

2786 ii) **Specificities**



2787

2788 **Evidence Statements**

2789 Biopsy appears to have a very high sensitivity and very high specificity for determining invasive pulmonary
2790 nodules. (**Moderate**)

2791 Bronchoscopic biopsy appears to have a very high sensitivity and very high specificity for determining invasive
2792 pulmonary nodules. (**Low**) with a moderate interquartile range

2793 Percutaneous biopsy appears to have a very high sensitivity and very high specificity for determining invasive
2794 pulmonary nodules. (**High**) with a small interquartile range

2795 Surgical biopsy appears to have a very high sensitivity and very high specificity for determining invasive
2796 pulmonary nodules. (**Low**)

2797 There is insufficient evidence to consider solid and sub-solid nodule subgroups.

2798 **Recommendation**

2799 ➤ For patients with a suspected malignant pulmonary nodule, bronchoscopic (**Conditional**), percutaneous
2800 (**Strong**), or surgical (**Conditional**) biopsy can be considered for diagnosing lung cancer.

2801 **Good Practice Points**

- 2802 ✓ Modality for tissue acquisition should consider patient choice, nodule location, need for mediastinal
2803 staging, wait times and available services.
- 2804 ✓ All patients should be able to access peripheral bronchoscopy (including robotic-assisted bronchoscopy),
2805 endobronchial ultrasound (EBUS), percutaneous ultrasound/computed tomography (USS/CT) guided and
2806 surgical biopsy.

2807 **Research Recommendation**

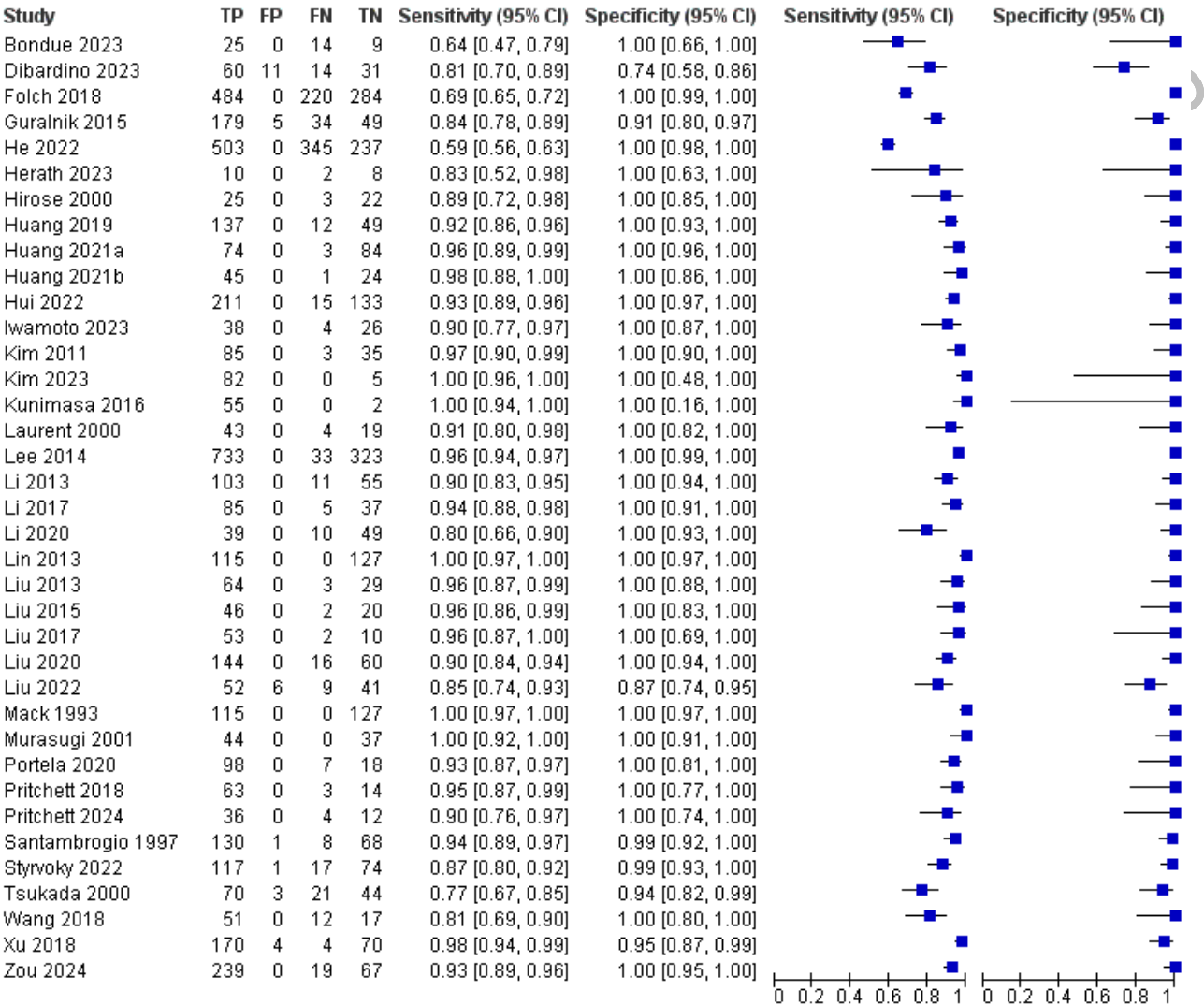
- 2808 ▪ Further research is needed to determine the diagnostic accuracies of biopsy (percutaneous,
2809 bronchoscopic, surgical) in solid and sub-solid pulmonary nodule subgroups.
- 2810 ▪ Randomised studies are needed to assess the diagnostic accuracy and yield of different pulmonary nodule
2811 biopsy modalities.
- 2812
- 2813
- 2814
- 2815

2816 **Meta-analyses**

2817 **Biopsy**

2818 Figure Q7a: Forest plot and SROC plot of biopsy for diagnosing invasive pulmonary nodules

2819 i) Forest plot



2820

2821

2822

2823

2824

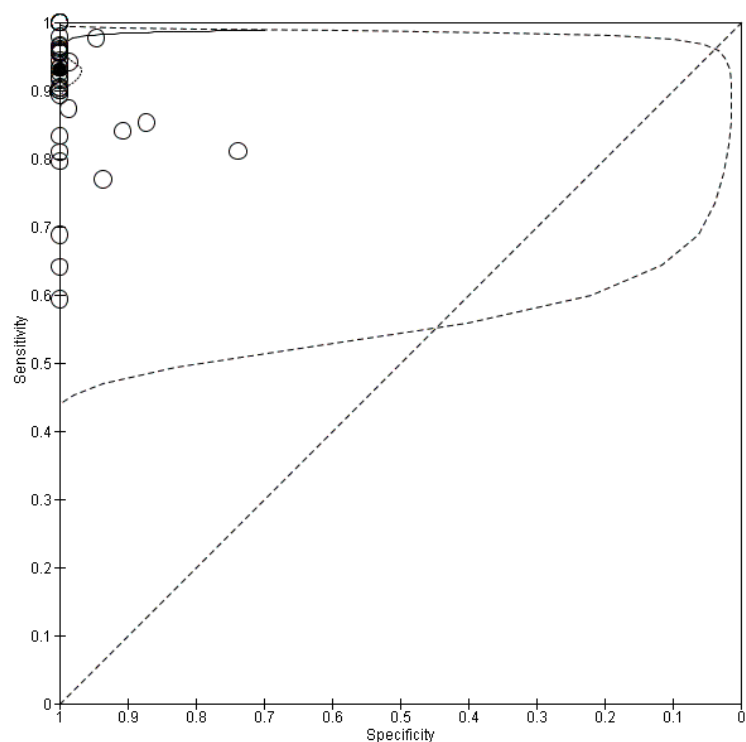
2825

2826

2827

2828

2829 ii) SROC plot



2830

2831 Table Q7b: Pooled results of biopsy for diagnosing invasive pulmonary nodules

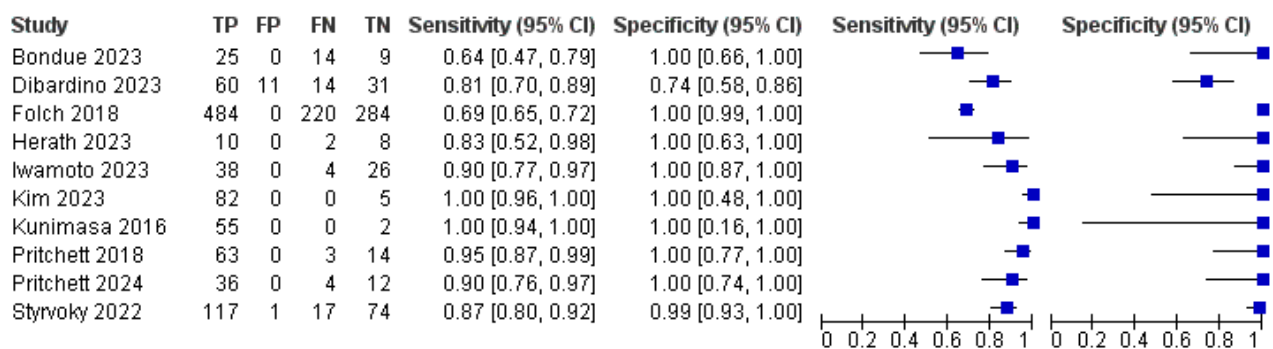
Pooled Sensitivity	0.930	[0.900, 0.952]
Pooled Specificity	1.000	[0.990, 1.000]
LR+	5308.716	[93.643, 300955.7]
LR-	0.070	[0.048, 0.101]
DOR	76208.53	[1288.609, 4506982]

2832

2833 *Bronchoscopic biopsy*

2834 Figure Q7b: Forest plot and SROC plot of bronchoscopic biopsy for diagnosing invasive pulmonary nodules

2835 i) Forest plot

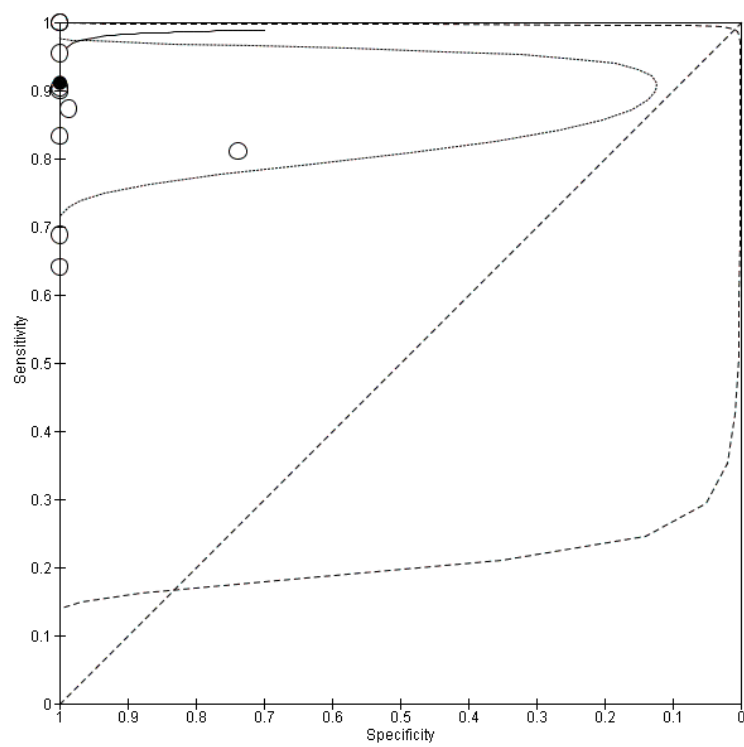


2836

2837

2838

2839 ii) SROC plot



2840

2841 Table Q7c: Pooled results of nodule diameter ≤ 8 mm for diagnosing invasive solid nodules

Pooled Sensitivity	0.911	[0.803, 0.963]
Pooled Specificity	0.999	[0.767, 1.000]
LR+	1262.689	[3.012, 529409.8]
LR-	0.089	[0.039, 0.206]
DOR	14174.62	[30.613, 6563145]

2842

2843

2844

2845

2846

2847

2848

2849

2850

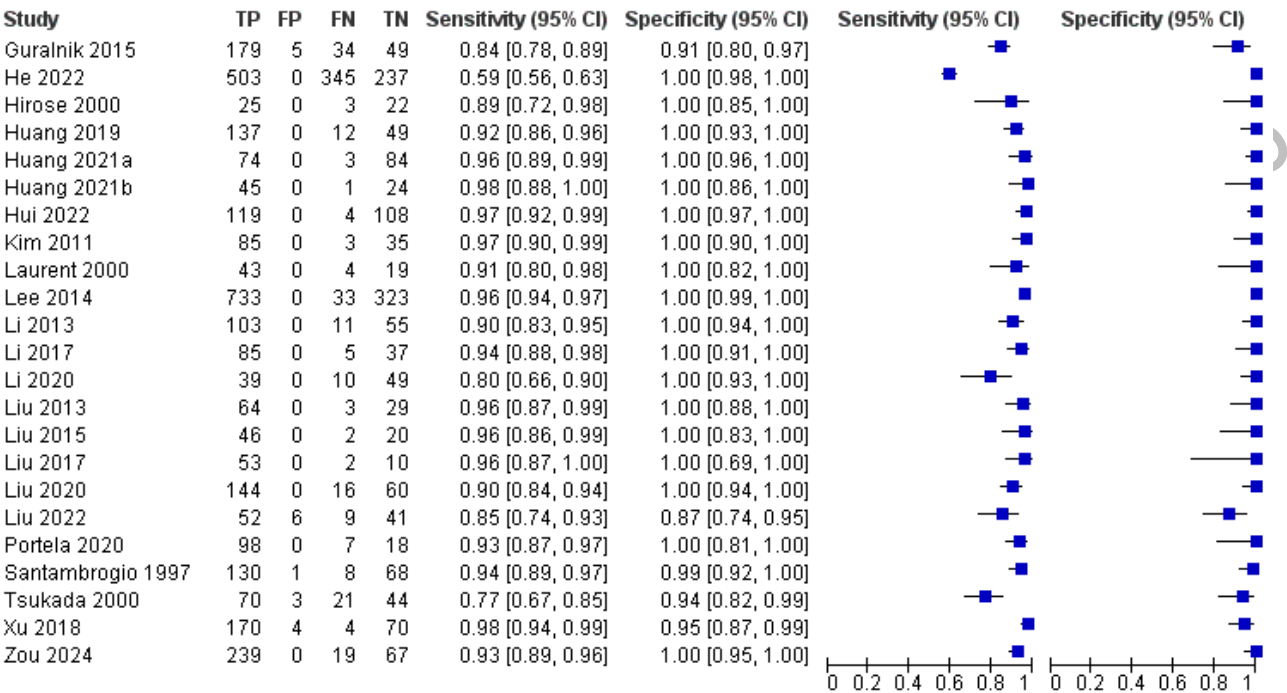
2851

2852

2853 Percutaneous biopsy

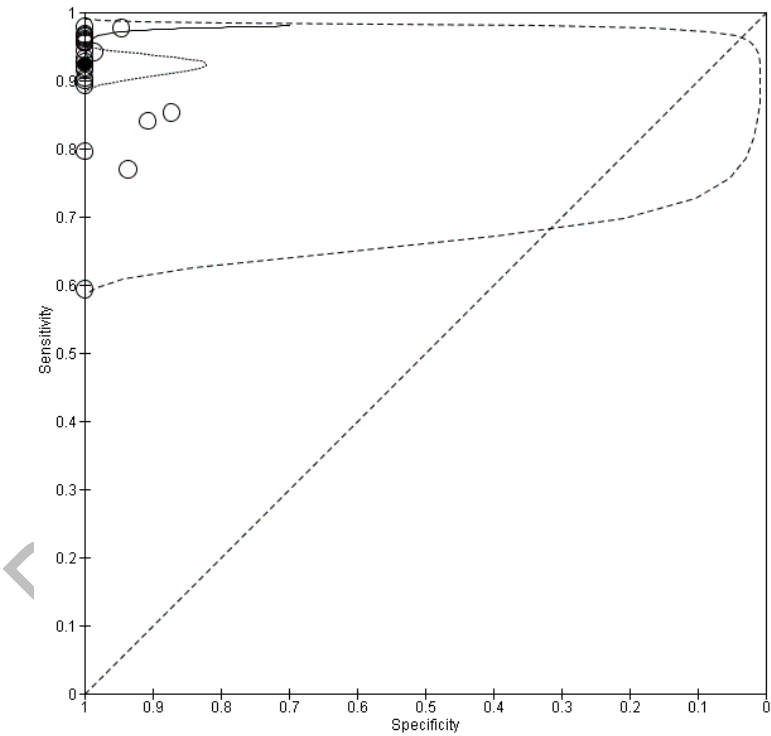
2854 Figure Q7c: Forest plot and SROC plot of percutaneous biopsy for diagnosing invasive pulmonary nodules

2855 i) Forest plot



2856

2857 ii) SROC plot



2858

2859

2860

2861 Table Q7d: Pooled results of percutaneous biopsy for diagnosing invasive pulmonary nodules

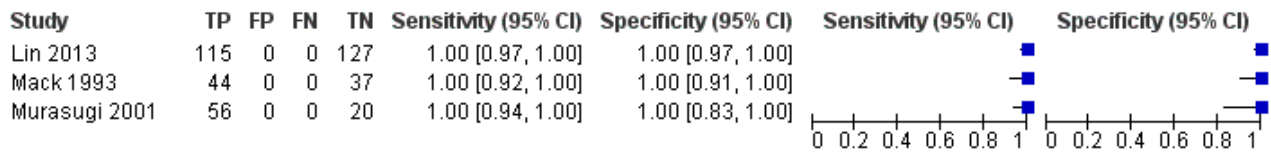
Pooled Sensitivity	0.925	[0.894, 0.947]
Pooled Specificity	1.000	[0.962, 1.000]
LR+	3399.816	[23.325, 495559.7]
LR-	0.075	[0.053, 0.107]
DOR	45044.09	[299.973, 6763846]

2862

2863 *Surgical biopsy*

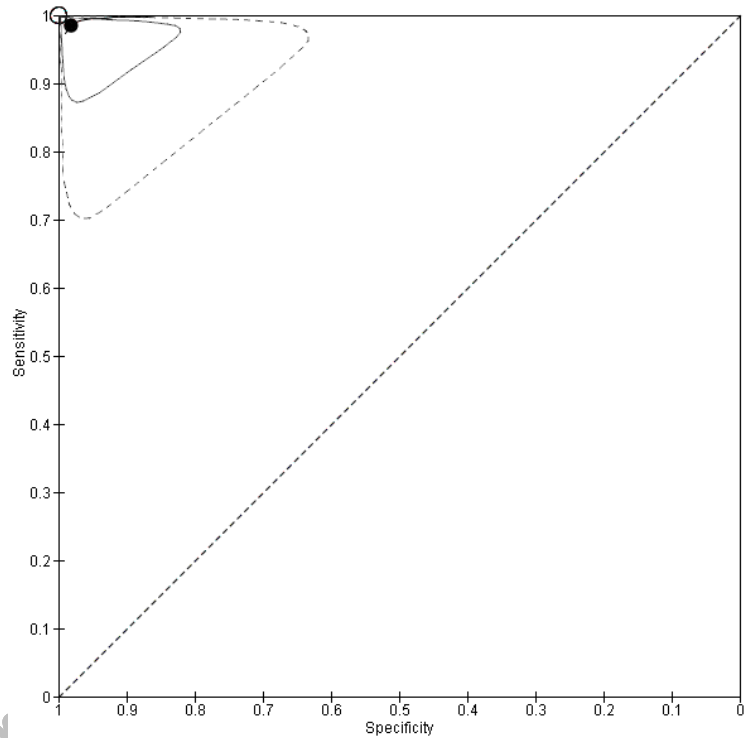
2864 Figure Q7d: Forest plot and SROC plot of surgical biopsy for diagnosing invasive pulmonary nodules

2865 i) Forest plot



2866

2867 ii) SROC plot



2868

2869 Table Q7f: Pooled results of surgical biopsy for diagnosing invasive pulmonary nodules

Pooled Sensitivity	0.985	[0.783, 0.998]
Pooled Specificity	0.982	[0.743, 0.997]
LR+	52.898	[3.639, 332.182]
LR-	0.016	[0.003, 0.241]
DOR	3414.015	[45.215, 48338.133]

Bayesian meta-analysis, data displayed as posterior median [95% posterior interval]

	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Bondue 2023	+	?	?	?	+	+	+
Dibardino 2023	+	+	+	+	+	+	+
Folch 2018	+	+	+	+	+	+	+
Guralnik 2015	+	+	+	+	+	+	+
He 2022	+	+	+	+	+	+	+
Herath 2023	?	?	?	?	+	+	+
Hirose 2000	+	+	+	+	+	+	+
Huang 2019	+	+	+	+	+	+	+
Huang 2021a	+	+	+	+	+	+	+
Huang 2021b	+	+	+	+	+	+	+
Hui 2022	+	+	?	+	+	+	+
Iwamoto 2023	?	?	?	?	+	+	+
Kim 2011	+	+	+	+	+	+	+
Kim 2023	+	+	+	+	+	+	+
Kunimasa 2016	+	+	+	+	+	+	+
Laurent 2000	+	+	?	?	+	+	+
Lee 2014	+	+	+	+	+	+	+
Li 2013	+	+	?	+	+	+	+
Li 2017	+	+	+	+	+	+	+
Li 2020	+	+	+	+	+	+	+
Lin 2013	?	+	+	+	+	+	+
Liu 2013	+	+	+	+	+	+	+
Liu 2015	?	+	+	+	+	+	+
Liu 2017	+	+	+	+	+	+	+
Liu 2020	+	+	+	+	+	+	+
Liu 2022	+	+	+	+	+	+	+
Mack 1993	?	?	?	?	+	+	+
Murasugi 2001	?	+	?	?	+	+	+
Portela 2020	+	+	+	+	+	+	+
Pritchett 2018	+	+	?	+	+	+	+
Pritchett 2024	?	+	?	+	+	+	+
Santambrogio 1997	+	+	+	+	+	+	+
Styvoky 2022	+	+	+	+	+	+	+
Tsukada 2000	+	+	+	+	+	+	+
Xu 2018	+	+	+	+	+	+	+
Zou 2024	+	+	?	?	+	+	+
High Unclear Low							

2871 GRADE analyses

2872 Biopsy

In adults with pulmonary nodules, what is the diagnostic accuracy of biopsy of a pulmonary nodule for diagnosing lung cancer?

Patient or population: Adults aged 18+ with pulmonary nodules

New test: Biopsy

Pooled sensitivity: 0.93 (95% CI: 0.90 to 0.95) | Pooled specificity: 1.00 (95% CI: 0.99 to 1.00)

Test result	Number of results per 1,000 patients tested (95% CI) Prevalence 5% Typically seen in	Number of participants (datasets)	Certainty of the Evidence (GRADE)
True positives	47 (45 to 48)	5483	⊕⊕⊕○ MODERATE ^a
False negatives	3 (2 to 5)	(37)	
True negatives	950 (941 to 950)	2347	⊕⊕⊕○ MODERATE ^a
False positives	0 (0 to 9)	(37)	
CI: Confidence interval			
Explanations			
a. Some risk of bias across the studies			

2873

2874

2875 Bronchoscopic biopsy

In adults with pulmonary nodules, what is the diagnostic accuracy of bronchoscopic biopsy of a pulmonary nodule for diagnosing lung cancer?

Patient or population: Adults aged 18+ with pulmonary nodules

New test: Bronchoscopic biopsy

Pooled sensitivity: 0.91 (95% CI: 0.80 to 0.96) | Pooled specificity: 1.00 (95% CI: 0.77 to 1.00)

Test result	Number of results per 1,000 patients tested (95% CI) Prevalence 5% Typically seen in	Number of participants (datasets)	Certainty of the Evidence (GRADE)
True positives	46 (40 to 48)	1248	⊕⊕○○ LOW ^{a,b}
False negatives	4 (2 to 10)	(10)	
True negatives	949 (729 to 950)	477	⊕⊕○○ LOW ^{a,b}
False positives	1 (0 to 221)	(10)	
CI: Confidence interval			
Explanations			
a. Some risk of bias across the studies			
b. Some imprecision across the specificities			

2876

2877

2878

2879

2880

2881

In adults with pulmonary nodules, what is the diagnostic accuracy of bronchoscopic biopsy of a pulmonary nodule for diagnosing lung cancer?

Patient or population: Adults aged 18+ with pulmonary nodules

New test: Percutaneous biopsy

Pooled sensitivity: 0.93 (95% CI: 0.89 to 0.95) | Pooled specificity: 1.00 (95% CI: 0.96 to 1.00)

Test result	Number of results per 1,000 patients tested (95% CI) Prevalence 5% Typically seen in	Number of participants (datasets)	Certainty of the Evidence (GRADE)
True positives	46 (45 to 47)	3795	⊕⊕⊕⊕
False negatives	4 (3 to 5)	(23)	HIGH
True negatives	950 (914 to 950)	1537	⊕⊕⊕⊕
False positives	0 (0 to 36)	(23)	HIGH
CI: Confidence interval			

2883

2884

2885 Surgical biopsy

In adults with pulmonary nodules, what is the diagnostic accuracy of bronchoscopic biopsy of a pulmonary nodule for diagnosing lung cancer?

Patient or population: Adults aged 18+ with pulmonary nodules

New test: Bronchoscopic biopsy

Pooled sensitivity: 0.98 (95% CI: 0.78 to 1.00) | Pooled specificity: 0.98 (95% CI: 0.74 to 1.00)

Test result	Number of results per 1,000 patients tested (95% CI) Prevalence 5% Typically seen in	Number of participants (datasets)	Certainty of the Evidence (GRADE)
True positives	49 (39 to 50)	215	⊕⊕○○
False negatives	1 (0 to 11)	(3)	LOW ^a
True negatives	933 (706 to 947)	184	⊕⊕○○
False positives	17 (3 to 244)	(3)	LOW ^a
CI: Confidence interval			

Explanations

a. Full study details not provided in two publications

2886

2887

2888

2889

2890

2891

2892

2893

2894

2895

2896

2897 Recommendation Tables

2898 Question Details

POPULATION:	Adults (18+) with pulmonary nodules
INDEX TESTS:	Biopsy (bronchoscopic, percutaneous or surgical)
GOLD STANDARD:	Pathological diagnosis of invasive lung cancer or clinical diagnosis of lung cancer
OUTCOME:	Diagnostic accuracy of biopsy

2899

2900 Bronchoscopic biopsy

2901 SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
TEST ACCURACY	Very inaccurate	Inaccurate	Accurate	Very accurate		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	Does not favour the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know

2902

2903 TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
☐	☐	☐	☒	☐

2904

2905 CONCLUSIONS

Recommendation
For patients with a suspected malignant pulmonary nodule, bronchoscopic biopsy can be considered for diagnosing lung cancer. (Conditional)
Justification
Bronchoscopic biopsy appears to have a very high sensitivity and very high specificity for determining invasive pulmonary nodules. (Low)
Subgroup considerations

There was not enough evidence to consider solid nodules and sub-solid nodules separately.

Research priorities

Further research is needed to determine the diagnostic accuracy of bronchoscopic in solid and sub-solid pulmonary nodule subgroups.

Percutaneous biopsy

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
TEST ACCURACY	Very inaccurate	Inaccurate	Accurate	Very accurate		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	Does not favour the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
☐	☐	☐	☐	☒

CONCLUSIONS

Recommendation

For patients with a suspected malignant pulmonary nodule, percutaneous biopsy can be considered for diagnosing lung cancer. (**Strong**)

Justification

Percutaneous biopsy appears to have a very high sensitivity and very high specificity for determining invasive pulmonary nodules. (**High**)

Subgroup considerations

There was not enough evidence to consider solid nodules and sub-solid nodules separately.

Research priorities

Further research is needed to determine the diagnostic accuracy of percutaneous biopsy in solid and sub-solid pulmonary nodule subgroups.

Surgical biopsy

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
TEST ACCURACY	Very inaccurate	Inaccurate	Accurate	Very accurate		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	Does not favour the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
☐	☐	☐	☒	☐

CONCLUSIONS

Recommendation

For patients with a suspected malignant pulmonary nodule, surgical biopsy can be considered for diagnosing lung cancer. (**Conditional**)

Justification

Surgical biopsy appears to have a very high sensitivity and very high specificity for determining invasive pulmonary nodules. (**Low**)

Subgroup considerations

There was not enough evidence to consider solid nodules and sub-solid nodules separately.

Research priorities

Further research is needed to determine the diagnostic accuracy of surgical biopsy in solid and sub-solid pulmonary nodule subgroups.

References

1. Bondue B, Taton O, Tannouri F, Van de Velde N, Remmelink M, Leduc D. High diagnostic yield of electromagnetic navigation bronchoscopy performed under cone beam CT guidance: results of a randomized Belgian monocentric study. Randomized Controlled Trial. *BMC pulm*. 2023;23(1):185.
2. DiBardino DM, Kim RY, Cao Y, et al. Diagnostic yield of cone-beam-derived augmented fluoroscopy and ultrathin bronchoscopy versus conventional navigational bronchoscopy techniques. *J Bronchology Interv Pulmonol*. 2022;03:03.
3. Folch EE, Pritchett MA, Nead MA, et al. Electromagnetic navigation bronchoscopy for peripheral pulmonary lesions: one-year results of the prospective, multicenter NAVIGATE study. *J Thorac Oncol*. 2019;14(3):445–458.
4. Herath S, Wong C, Dawkins P, et al. Cryobiopsy with radial-endobronchial ultrasound (Cryo-Radial) has comparable diagnostic yield with higher safety in comparison with computed tomography-guided transthoracic biopsy for peripheral pulmonary lesions: An exploratory randomised study. *Intern Med J*. 2022.
5. Iwamoto SK, Tsai WS. Novel approaches utilizing robotic navigational bronchoscopy: a single institution experience. *J Robot Surg*. 2023;17(3):1001–1006.
6. Kim SH, Mok J, Jo EJ, et al. The additive impact of transbronchial cryobiopsy using a 1.1-mm diameter cryoprobe on conventional biopsy for peripheral lung nodules. *Cancer Res*. 2023;55(2):506–512.
7. Kunimasa K, Tachihara M, Tamura D, et al. Diagnostic utility of additional conventional techniques after endobronchial ultrasonography guidance during transbronchial biopsy. *Respirology*. 2016;21(6):1100–5.
8. Pritchett MA, Schampaert S, de Groot JAH, Schirmer CC, van der Bom I. Cone-beam CT with augmented fluoroscopy combined with electromagnetic navigation bronchoscopy for biopsy of pulmonary nodules. *J Bronchology Interv Pulmonol*. 2018;25(4):274–282.
9. Pritchett MA, Williams JC, Schirmer CC, Langereis S. Cone-beam CT-based navigation with augmented fluoroscopy of the airways for image-guided bronchoscopic biopsy of peripheral pulmonary nodules a prospective clinical study. *J Bronchology Interv Pulmonol*. 2024;31(2):175–182.
10. Styrvoky K, Schwalk A, Pham D, et al. Shape-sensing robotic-assisted bronchoscopy with concurrent use of radial endobronchial ultrasound and cone beam computed tomography in the evaluation of pulmonary lesions. *Lung*. 2022;200(6):755–761.
11. Guralnik L, Rozenberg R, Frenkel A, Israel O, Keidar Z. Metabolic PET/CT-guided lung lesion biopsies: impact on diagnostic accuracy and rate of sampling error. *J Nucl Med*. 2015;56(4):518–22.
12. He JH, Ruan JX, Lei Y, et al. Supplementary benefits of CT-guided transthoracic lung aspiration biopsy for core needle biopsy. *Front Microbiol*. 2022;13:1005241.
13. Hirose T, Mori K, Machida S, Tominaga K, Yokoi K, Adachi M. Computed tomographic fluoroscopy-guided transthoracic needle biopsy for diagnosis of pulmonary nodules. *Jpn J Clin Oncol*. Jun 2000;30(6):259–62.
14. Huang MD, Weng HH, Hsu SL, et al. Accuracy and complications of CT-guided pulmonary core biopsy in small nodules: a single-center experience. *Cancer Imaging*. 2019;19(1):51.
15. Huang W, Ye J, Qiu Y, et al. Ultrasound-guided percutaneous core needle biopsy of peripheral pulmonary nodules <= 2 cm: diagnostic performance, safety and influence factors. *Front Oncol*. 2021;11:671884.
16. Huang YY, Cheng H, Li GC. Computed tomography-guided core needle biopsy for lung nodules: low-dose versus standard-dose protocols. *Wideochir Inne Tech Maloinwazyjne*. 2021;16(2):355–361.
17. Hui H, Yin HT, Wang T, Chen G. Computed tomography-guided core needle biopsy for sub-centimeter pulmonary nodules. *Kardiochir Torakochirurgia Pol*. 2022;19(2):65–69.

- 2975 18. Kim GR, Hur J, Lee SM, et al. CT fluoroscopy-guided lung biopsy versus conventional CT-guided lung
2976 biopsy: A prospective controlled study to assess radiation doses and diagnostic performance. *Eur Radiol.*
2977 2011;21(2):232–239.
- 2978 19. Laurent F, Latrabe V, Vergier B, Montaudon M, Vernejoux JM, Dubrez J. CT-guided transthoracic needle
2979 biopsy of pulmonary nodules smaller than 20 mm: results with an automated 20-gauge coaxial cutting
2980 needle. *Clin Radiol.* 2000;55(4):281–7.
- 2981 20. Lee SM, Park CM, Lee KH, Bahn YE, Kim JI, Goo JM. C-arm cone-beam CT-guided percutaneous
2982 transthoracic needle biopsy of lung nodules: clinical experience in 1108 patients. *Radiology.* 2014; 271(1):
2983 291–300.
- 2984 21. Li Y, Du Y, Yang HF, Yu JH, Xu XX. CT-guided percutaneous core needle biopsy for small (≤ 20 mm)
2985 pulmonary lesions. *Clin Radiol.* 2013;68(1):e43–8.
- 2986 22. Li GC, Fu YF, Cao W, Shi YB, Wang T. Computed tomography-guided percutaneous cutting needle biopsy
2987 for small (≤ 20 mm) lung nodules. *Medicine (Baltimore).* 2017;96(46):e8703.
- 2988 23. Li Y, Wang T, Fu YF, Shi YB, Wang JY. Computed tomography-guided biopsy for sub-centimeter lung
2989 nodules: technical success and diagnostic accuracy. *Clin Respir J.* 2020;20.
- 2990 24. Liu M, Lv Y, Wu L, Song J, Sequeiros RB, Li C. MRI-guided percutaneous coaxial cutting needle biopsy
2991 of small pulmonary nodules: feasibility. *Eur Radiol.* 2013;23(10):2730–8.
- 2992 25. Liu S, Li C, Yu X, et al. Diagnostic accuracy of MRI-guided percutaneous transthoracic needle biopsy of
2993 solitary pulmonary nodules. *Cardiovasc Intervent Radiol.* 2015;38(2):416–21.
- 2994 26. Liu M, Huang J, Xu Y, et al. MR-guided percutaneous biopsy of solitary pulmonary lesions using a 1.0-T
2995 open high-field MRI scanner with respiratory gating. *Eur Radiol.* 2017;27(4):1459–1466.
- 2996 27. Liu XL, Li W, Yang WX, et al. Computed tomography-guided biopsy of small lung nodules: diagnostic
2997 accuracy and analysis for true negatives. *J Int Med Res.* 2020;48(2):300060519879006.
- 2998 28. Liu W, Xu C, Li L, Yuan Q, Wang W, Zou J. The value of computed tomography-guided percutaneous lung
2999 biopsy combined with rapid on-site evaluation in diagnosis of peripheral pulmonary nodules. *Technol*
3000 *Cancer Res Treat* 2022;21:15330338221118718.
- 3001 29. Portela de Oliveira E, Souza CA, Inacio JR, et al. Imaging-guided percutaneous biopsy of nodules ≤ 1
3002 cm: Study of diagnostic performance and risk factors associated with biopsy failure. *J Thorac Imaging.*
3003 2020;35(2):123–128.
- 3004 30. Santambrogio L, Nosotti M, Bellaviti N, Pavoni G, Radice F, Caputo V. CT-guided fine-needle aspiration
3005 cytology of solitary pulmonary nodules: a prospective, randomized study of immediate cytologic evaluation.
3006 *Chest.* 1997;112(2):423–5.
- 3007 31. Tsukada H, Satou T, Iwashima A, Souma T. Diagnostic accuracy of CT-guided automated needle biopsy
3008 of lung nodules. *AJR Am J Roentgenol.* 2000;175(1):239–43.
- 3009 32. Xu C, Yuan Q, Chi C, et al. Computed tomography-guided percutaneous transthoracic needle biopsy for
3010 solitary pulmonary nodules in diameter less than 20 mm. *Medicine (Baltimore).* 2018;97(14):e0154.
- 3011 33. Zou X, Cui N, Ma Q, Lin Z, Zhang J, Li X. Conventional versus cone-beam computed tomography in lung
3012 biopsy: diagnostic performance, risks, and the advantages of tract embolization with gelfoam particle
3013 suspension. *Quant Imaging Med Surg.* 2024;14(9):6479–6492.
- 3014 34. Lin Y, Liu L, Pu Q. Mini-invasive diagnosis and synchronous treatment of solitary pulmonary nodule. *Asian*
3015 *Cardiovasc Thorac Ann.* 2013;21(3):306–12.
- 3016 35. Mack MJ, Hazelrigg SR, Landreneau RJ, Acuff TE. Thoracoscopy for the diagnosis of the indeterminate
3017 solitary pulmonary nodule. *Ann Thorac Surg.* 1993;56(4):825–30.
- 3018 36. Murasugi M, Onuki T, Ikeda T, Kanzaki M, Nitta S. The role of video-assisted thoracoscopic surgery in the
3019 diagnosis of the small peripheral pulmonary nodule. *Surg Endosc.* 2001;15(7):734–6.

Field	Content
Review Question	In adults with pulmonary nodules, what is the diagnostic accuracy of biopsy of a pulmonary nodule for diagnosing lung cancer?
Type of review question	Diagnostic accuracy review
Objective of the review	This question aims to determine the accuracy of percutaneous image-guided biopsy, bronchoscopic biopsy (including those using augmented techniques), and surgical biopsy in determining whether a nodule represents lung cancer. The diagnostic accuracy of these various biopsy techniques will be important determining whether and which type of biopsy is indicated in the investigative pathway, and the impact of a negative or non-diagnostic biopsy on further management.
Eligibility criteria – population / disease / condition / issue / domain	Adults with pulmonary nodules (18+ years of age)
Eligibility criteria – index test(s)	Biopsy
Eligibility criteria – gold standard	Pathological diagnosis of invasive lung cancer or clinical diagnosis of lung cancer
Outcomes and prioritisation	Diagnostic accuracy
Eligibility criteria – study design	RCTs, comparative studies, case series (>50 cases)
Other inclusion /exclusion criteria	Non-English language excluded unless full English translation Conference abstracts, Cochrane reviews, systematic reviews, reviews Cochrane reviews and systematic reviews can be referenced in the text, but CANNOT be used in a meta-analysis
Proposed sensitivity / subgroup analysis, or meta-regression	Adults with pulmonary nodules - Solid nodules - Sub-solid nodules Biopsy - Percutaneous - Bronchoscopic - Surgical

Selection process – duplicate screening / selection / analysis	Agreement should be reached between Guideline members who are working on the question. If no agreement can be reached, a decision should be made by the Guideline co-chairs. If there is still no decision, the matter should be brought to the Guideline group and a decision will be made by consensus	
Data management (software)	RevMan5	Pairwise meta-analyses (if data in the correct format) Evidence review/considered judgement. Storing Guideline text, tables, figures, etc.
	MetaDTA	Data meta-analyses
	Gradepro	Quality of evidence assessment
Information sources – databases and dates	MEDLINE, Embase, Central Register of Controlled Trials and Cochrane Database of Systematic Reviews Restricted to articles published from 1990 onwards	
Methods for assessing bias at outcome / study level	RevMan5 diagnostic accuracy full review template (based on QUADAS2) (follow instructions in ' <i>BTS Guideline Process Handbook – Diagnostic Accuracy (June 2020)</i> ')	
Methods for quantitative analysis – combining studies and exploring (in)consistency	If 3 or more relevant studies: RevMan5 for forest plots, summary ROC plots MetaDTA to combine studies (pooled specificity, sensitivity, likelihood ratios, diagnostic odds ratio and confidence intervals) and calculate RevMan parameters for summary ROC plot (follow instructions in ' <i>BTS Guideline Process Handbook – Diagnostic Accuracy (June 2020)</i> ')	
Meta-bias assessment – publication bias, selective reporting bias	GRADEpro	Diagnostic accuracy quality of evidence assessment for each index test (follow instructions in ' <i>BTS Guideline Process Handbook – Diagnostic Accuracy (June 2020)</i> ')
Rationale / context – what is known	For any test, the post-test probability of a diagnosis will be determined by the pre-test probability and the test performance. The biopsy techniques available to clinical teams investigating pulmonary nodules have different accuracy profiles. Furthermore, the diagnostic accuracy may vary with the location of the nodule within the lung (e.g. peripheral, adjacent to an airway) as well as with nodule type and size. Understanding test performance in these clinical situations is important in determining whether a biopsy is indicated, if so what type, and the impact of a non-cancer or non-diagnostic biopsy result on further management.	

3021

3022

3023

3024

3025

3026

3027

3029 **Q8** In adults with pulmonary nodules being considered for treatment for lung cancer with curative
 3030 intent, does pre-treatment biopsy provide the same clinical outcomes as no biopsy?

3031 **Contents**

3032	Question Evidence Review	168
3033	Background	168
3034	Outcomes	168
3035	Evidence Review	168
3036	Evidence Statements	171
3037	Recommendation	171
3038	Research recommendation	171
3039	Full tabulated data	172
3040	Risk of bias summary	173
3041	GRADE analyses	174
3042	Recommendation table	174
3043	References	175
3044	Question Protocol	176

3045
 3046

3047 **Question 8 Evidence Review**

3048 **Q8** In adults with pulmonary nodules being considered for treatment for lung cancer with curative
3049 intent, does pre-treatment biopsy provide the same clinical outcomes as no biopsy?

3050 **Background**

3051 In patients with pulmonary nodules considered at high risk of malignancy, treatment with curative intent may
3052 include surgical resection, stereotactic ablative radiotherapy, or other definitive therapies. While histological
3053 confirmation through pre-treatment biopsy is often recommended, biopsy procedures can carry risks
3054 associated with morbidity or may be technically not feasible. In some patients with a high clinical and
3055 radiological probability of lung cancer, treatment may proceed without tissue confirmation. This review
3056 examines whether obtaining a pre-treatment biopsy influences clinical outcomes compared with proceeding
3057 directly to curative-intent treatment without biopsy, balancing diagnostic certainty, treatment delay, procedural
3058 risk and overtreatment.

3059 **Outcomes**

3060 Benign resection; mortality; morbidity; quality of life; recurrence

3061 **Evidence Review**

3062 The initial literature search identified 416 potentially relevant papers, but only 12 papers were deemed relevant
3063 to the review.¹⁻¹²

3064 **Benign resection**

3065 Only two studies reported on benign resection following pre-treatment biopsy or no biopsy in adults with
3066 pulmonary nodules being considered for treatment for lung cancer with curative intent.^{1,2} Two further studies
3067 were excluded from the analysis because one had a high biopsy failure rate and the other included intra-
3068 operative biopsies in the pre-treatment biopsy group. Meta-analysis shows that benign resection was greater
3069 in the no pre-treatment biopsy group (371 per 1000 patients) compared with the pre-treatment biopsy group
3070 (63 per 1000 patients (33 to 119)) (Figure Q8a).

3071 Figure Q8a: Comparison of benign resection following pre-treatment biopsy or no pre-treatment biopsy



3072

3073 **Mortality**

3074 Nine studies reported on mortality following pre-treatment biopsy or no biopsy in adults with pulmonary nodules
3075 being considered for treatment for lung cancer with curative intent.³⁻¹¹ Seven reported on mortality during or
3076 post-biopsy, or surgical treatment (up to 30 days)³⁻⁹ and two studies reported on long-term mortality at 80
3077 months^{10,11}.

3078 *Short-term mortality*

3079 No studies directly compared short-term mortality following pre-treatment biopsy or surgical treatment. Two
3080 single arm studies reported on short-term mortality following pre-treatment biopsy^{4,5} and five single arm studies
3081 reported on short-term mortality following surgical treatment^{3,6-9}. Comparison of the pre-treatment biopsy and
3082 biopsy groups show no significant difference in mortality between the two groups ($p = 0.16$, unpaired t-test). A
3083 summary of the data is shown in Table Q8a and full data are shown in Table Q8d.

3084

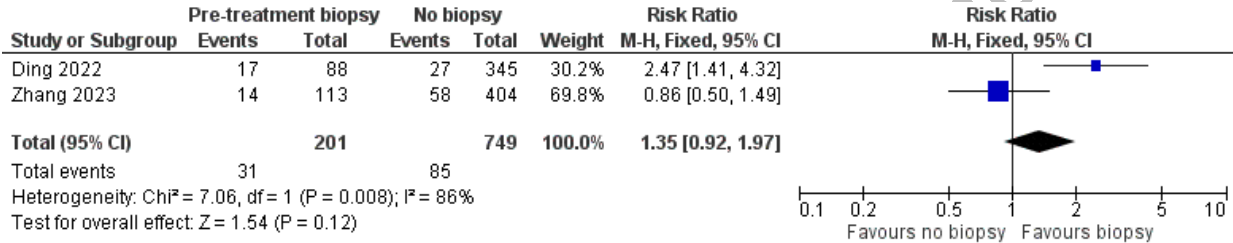
Table Q8a: Summary of percentage post-treatment mortality following pre-treatment biopsy or no biopsy

% Deaths within participant cohorts					
With pre-treatment biopsy			Without pre-treatment biopsy		p
Mean ± SD	Median [IQR]		Mean + SD	Median [IQR]	
0.0 (2) ^{4,5}	0.0 [0.0, 0.0]		0.8 ± 1.0 (5) ^{3,6-9}	0.7 [0.0, 0.9]	0.16*

(Study numbers in parentheses)
* Unpaired t-test

Longer-term mortality (80 months)

Two studies compared mortality at 80 months following pre-treatment biopsy or no pre-treatment biopsy.^{10,11} Meta-analysis shows no difference in mortality at 80 days between the pre-treatment biopsy group (153 per 1000 patients (104 to 224)) and the no pre-treatment biopsy group (113 per 1000 patients) (Figure Q8b).
Figure Q8b: Comparison of mortality at 80 days following pre-treatment biopsy or no pre-treatment biopsy



Morbidity

Eight studies reported on morbidity following pre-treatment biopsy or no pre-treatment biopsy in adults with pulmonary nodules being considered for treatment for lung cancer with curative intent.^{1,3,4,6-9,12} Two further study were excluded from the analysis. The first included participants in the “no biopsy” group that had undergone a pre-treatment biopsy but did not have a tissue diagnosis. The second reported surgical complications rather than biopsy related complication in the pre-treatment biopsy group. Only one study directly compared pre-treatment biopsy morbidity with no pre-treatment biopsy morbidity. Data are summarised in Table Q8b.¹²

Table Q8b: Comparison of morbidity following pre-treatment biopsy or no pre-treatment biopsy

Pretreatment biopsy		No biopsy		Risk Ratio [95% CI]	Morbidity per 1000 patients (CI)	
Events	Total	Events	Total		With biopsy	No biopsy
13	82	23	192	0.89 [0.48,1.65]	159 (86,294)	178

CI – confidence intervals

The remaining seven studies were single arm studies (six studies)^{1,3,4,6,8,9}, or intra-operative biopsy data had been included in the pre-treatment biopsy group, so only the “no pre-treatment biopsy” data were considered (one study)⁷. Adverse events in both groups included pneumothorax and bleeding, but adverse events in the no pre-treatment biopsy group also included air leak, pneumonia and arrhythmia.
Combining the two-arm study data from Table Q8b¹² and the “single” arm study data (n = 7)^{1,3,4,6-9}, a comparison of post-treatment morbidity in participants with or without a pre-treatment biopsy shows a significantly greater post-treatment morbidity in the pre-treatment biopsy group. Data are summarised in Figure Q8c and Table Q8c.^{1,3,4,6-9,12} Full data are shown in Table Q8e.

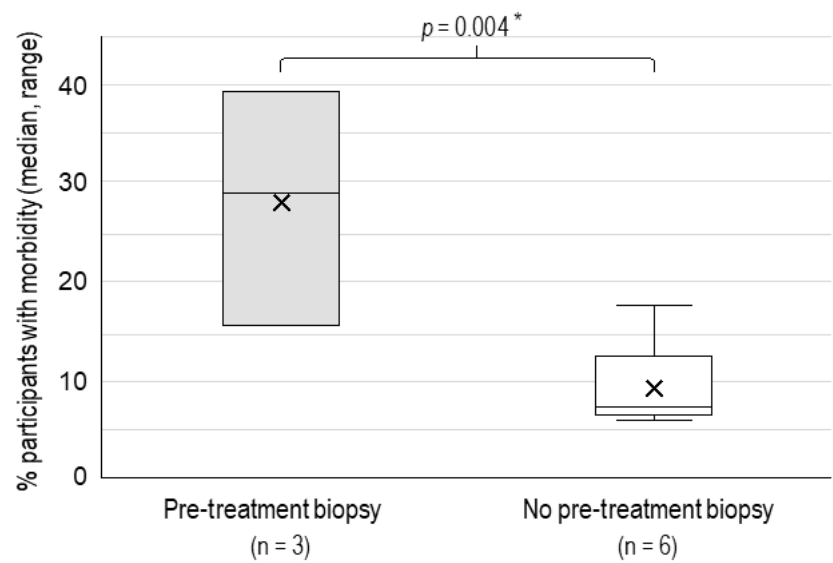
3114 Table Q8c: Morbidity comparison of pre-treatment biopsy versus no pre-treatment biopsy

Treatment group	% participants with post-treatment morbidity		n	p
	Mean ± SD	Median [IQR]		
Pre-treatment biopsy	28.1 ± 11.8	29.1 [15.8,39.4]	3 ^{1,4,12}	0.004*
No pre-treatment biopsy	9.2 ± 4.4	7.4 [6.7,12.6]	6 ^{3,6-9,12}	

3115 n – study numbers

3116 * Unpaired t-test

3117 Figure Q8c: Morbidity comparison of pre-treatment biopsy or no pre-treatment biopsy



3118

3119 * Unpaired t-test

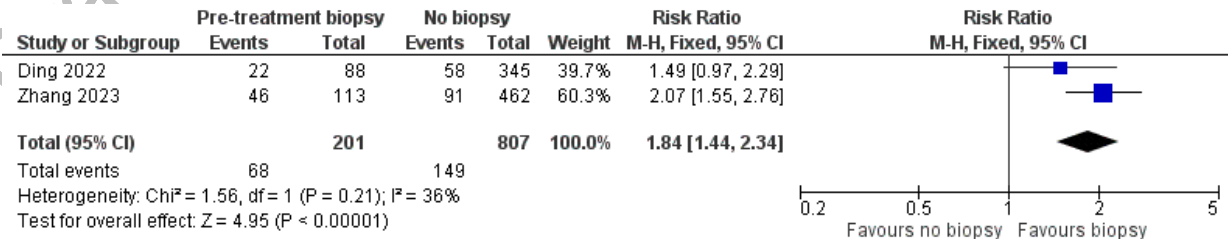
3120 **Quality of life**

3121 No studies reported on the effects of pre-treatment pulmonary nodule biopsy on quality of life.

3122 **Recurrence**

3123 Two studies reported on recurrence following pre-treatment biopsy or no pre-treatment biopsy in adults with
3124 pulmonary nodules being considered for treatment for lung cancer with curative intent.^{10,11} Both studies had
3125 an observation time of 80 months. Meta-analysis shows increased recurrence up to 80 months post-treatment
3126 in the pre-treatment biopsy group (340 per 1000 patients (266 to 432)) when compared with the no pre-
3127 treatment biopsy group (185 per 1000 patients). Data are shown in Figure Q8d.

3128 Figure Q8d: Comparison of the incidence of recurrence at 80 months following pre-treatment biopsy or no pre-
3129 treatment biopsy



3130

3131 **Evidence Statements**

3132 Pre-treatment biopsy may reduce the incidence of benign resection in adults with pulmonary nodules being
3133 considered for treatment for lung cancer with curative intent when compared with no pre-treatment biopsy.
3134 (**Very low**)

3135 Pre-treatment biopsy appears to have no effect on short-term mortality (up to 30-days post-treatment) in adults
3136 with pulmonary nodules being considered for treatment for lung cancer with curative intent when compared
3137 with no pre-treatment biopsy. (**Ungraded**)

3138 Pre-treatment biopsy appears to have no effect on longer-term mortality (up to 80 months post-treatment) in
3139 adults with pulmonary nodules when compared with no pre-treatment biopsy. (**Very low**)

3140 Pre-treatment biopsy appears to increase morbidity in adults with pulmonary nodules being considered for
3141 treatment for lung cancer with curative intent when compared with no pre-treatment biopsy. (**Ungraded**)

3142 Pre-treatment biopsy may increase recurrence (up to 80 months post-treatment) in adults with pulmonary
3143 nodules being considered for treatment for lung cancer with curative intent when compared with no pre-
3144 treatment biopsy (**Very low**)

3145 There was insufficient evidence to consider solid and sub-solid pulmonary nodule subgroups.

3146 There was insufficient evidence to consider bronchoscopic and percutaneous biopsy as separate subgroups.

3147 **Recommendation**

3148 ➤ For patients suitable for pre-treatment biopsy, a pre-treatment biopsy should be offered, where feasible,
3149 to patients who are suitable for curative-intent treatment. (**Conditional**)

3150 **Research Recommendation**

3151 ▪ Further specific research is needed to determine if pre-treatment biopsy improves clinical outcomes
3152 (benign resection, mortality, morbidity, quality of life, recurrence) in adults with pulmonary nodules being
3153 considered for treatment for lung cancer with curative intent.
3154

3155

3156

3157

3158

3159 **Full tabulated data**

3160 Table Q8d: Comparison of post-treatment mortality following pre-treatment biopsy or no biopsy

Study	With pre-treatment biopsy			Without pre-treatment biopsy			p
	Mortality (n)	Total (n)	Mortality (%)	Mortality (n)	Total (n)	Mortality (%)	
Cho 2014 ³				0	300	0.00	
Gilbert 2012 ⁴	0	330	0.00				
Rzyman 2013 ⁵	0	104	0.00				
Swanson 200 ⁷⁶				3	127	2.36	
Takeda 2006 ⁷				2	270	0.74	
Ueda 2015 ⁸				1	110	0.91	
Whooley 2023 ⁹				0	100	0.00	
Mean ± SD			0.0 ± 0.0			0.8 ± 1.0	0.16*
Median [IQR]			0.0 [0.0, 0.0]			0.7 [0.0, 0.9]	

3161 * Unpaired t-test

3162 IQR – interquartile range; n – number of participants; SD – standard deviation

3163

3164 Table Q8e: Comparison of post-treatment morbidity following pre-treatment biopsy or no biopsy

Study	With pre-treatment biopsy			Without pre-treatment biopsy			p
	Morbidity (n)	Total (n)	Morbidity (%)	Morbidity (n)	Total (n)	Morbidity (%)	
Barta 2017 ¹	53	182	29.12				
Cho 2014 ³				22	300	7.33	
Gilbert 2012 ⁴	130	330	39.39				
Kaaki 2018 ¹²	13	82	15.85	23	129	17.83	
Swanson 2007 ⁶				7	95	7.37	
Takeda 2006 ⁷				12	110	10.91	
Ueda 2015 ⁸				7	100	7.00	
Whooley 2023 ⁹				16	270	5.93	
Mean ± SD			28.1 ± 11.8			9.2 ± 4.4	0.004*
Median [IQR]			29.1 [15.8,39.4]			7.4 [6.7,12.6]	

3165 * Unpaired t-test

3166 IQR – interquartile range; n – number of participants; SD – standard deviation

3167

3168

3169

3170

	Selection bias	Performance bias	Detection bias	Attrition bias	Publication bias
Barta 2017	+	?	?	+	+
Ding 2022	?	?	?	+	+
Giles 2021	+	+	?	+	+
Isbell 2011	?	+	+	+	+
Kaaki 2018	+	?	?	+	+
Sihoe 2013	?	?	?	+	+
Yu 2023	+	?	?	+	+
Zhang 2023	+	+	+	+	+

High

Unclear

Low

3172
3173
3174
3175
3176
3177
3178
3179
GRADE analyses

Benign resection, longer-term mortality, recurrence

In adults with pulmonary nodules being considered for treatment for lung cancer with curative intent, does pre-treatment biopsy provide the same clinical outcomes as no biopsy?

Population: Adults (18+) being considered for treatment for lung cancer with curative intent

Intervention: Pre-treatment biopsy

Comparator: No pre-treatment biopsy

Outcome	Number of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects		Quality of the Evidence (GRADE)
			No biopsy	Pre-treatment biopsy	
Benign resection	386 (2 studies)	RR 0.17 (0.09 to 0.32)	371 per 1000	63 per 1000 (33 to 119)	⊕○○○ VERY LOW ^{a,b}
Longer-term mortality	950 (2 studies)	RR 1.35 (0.92 to 1.97)	113 per 1000	153 per 1000 (104 to 224)	⊕○○○ VERY LOW ^{a,c,d}
Recurrence	1008 (2 studies)	RR 1.84 (1.44 to 2.34)	185 per 1000	340 per 1000 (266 to 432)	⊕○○○ VERY LOW ^{a,c,d}

CI: Confidence interval

Explanations

- a. Some risk of bias across the studies
- b. Some inconsistency across the studies
- c. Serious inconsistency across the studies
- d. Some imprecision, CIs cross one MID

3181 Recommendation Table

3182 Question Details

POPULATION:	Adults (18+) with pulmonary nodules being considered for treatment for lung cancer with curative intent
INTERVENTION:	Pre-treatment biopsy
COMPARISON:	No pre-treatment biopsy
OUTCOMES:	Benign resection; mortality; morbidity; quality of life; recurrence

3183
3184
3185

SUMMARY OF JUDGEMENTS

PROBLEM	JUDGEMENT						
	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	Does not favour the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know

3186
3187
3188

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
☐	☐	☐	☒	☐

3189
3190

CONCLUSIONS

Recommendation
For patients suitable for pre-treatment biopsy, a pre-treatment biopsy should be offered, where feasible, to patients who are suitable for curative-intent treatment. (Conditional)
Justification
Pre-treatment biopsy appears to reduce the incidence of benign resection in adults with pulmonary nodules being considered for treatment for lung cancer with curative intent when compared with no pre-treatment biopsy. (Very low)
Pre-treatment biopsy appears to have no effect on short-term mortality (up to 30-days post-treatment) in adults with pulmonary nodules being considered for treatment for lung cancer with curative intent when compared with no pre-treatment biopsy. (Ungraded)
Pre-treatment biopsy appears to have no effect on longer-term mortality (up to 80 months post-treatment) in adults with pulmonary nodules when compared with no pre-treatment biopsy. (Very low)

Pre-treatment biopsy appears to increase morbidity in adults with pulmonary nodules being considered for treatment for lung cancer with curative intent when compared with no pre-treatment biopsy. (**Ungraded**)

Pre-treatment biopsy appears to increase recurrence (up to 80 months post-treatment) in adults with pulmonary nodules being considered for treatment for lung cancer with curative intent when compared with no pre-treatment biopsy. (**Very low**)

Subgroup considerations

There was not enough evidence to consider pulmonary nodule subgroups (solid or sub-solid) or different types of pre-treatment biopsy (percutaneous or bronchoscopic).

Research priorities

Further specific research is needed to determine if pre-treatment biopsy improves clinical outcomes (benign resection, mortality, morbidity, quality of life, recurrence) in adults with pulmonary nodules being considered for treatment for lung cancer with curative intent.

3194
3195
3196

References

- 3197 1. Barta JA, Henschke CI, Flores RM, Yip R, Yankelevitz DF, Powell CA. Lung cancer diagnosis by fine
3198 needle aspiration is associated with reduction in resection of nonmalignant lung nodules. *Ann Thorac Surg.*
3199 2017;103(6):1795-1801.
- 3200 2. Isbell JM, Deppen S, Putnam Jr JB, et al. Existing general population models inaccurately predict lung
3201 cancer risk in patients referred for surgical evaluation. *Ann Thorac Surg.* 2011;91(1):227-233.
- 3202 3. Cho J, Ko SJ, Kim SJ, et al. Surgical resection of nodular ground-glass opacities without percutaneous
3203 needle aspiration or biopsy. *BMC Cancer.* 2014;14:838.
- 3204 4. Gilbert S, Zhang H, Villeneuve PJ, et al. Optimizing health care resource utilization in the surgical
3205 management of patients with suspected lung cancer. *Ann Thorac Surg.* 2012;94(5):1667-1672.
- 3206 5. Rzyman W, Jelitto-Gorska M, Dziedzic R, et al. Diagnostic work-up and surgery in participants of the
3207 Gdansk lung cancer screening programme: the incidence of surgery for non-malignant conditions. *Interact*
3208 *Cardiovasc Thorac Surg.* 2013;17(6):969-973.
- 3209 6. Swanson SJ, Herndon JE, 2nd, D'Amico TA, et al. Video-assisted thoracic surgery lobectomy: report of
3210 CALGB 39802--a prospective, multi-institution feasibility study. *J Clin Oncol.* 2007;25(31):4993-4997.
- 3211 7. Takeda S, Koma M, Kadota Y, Funakoshi Y, Kusu T, Maeda H. Clinical impact of concomitant surgical
3212 diagnosis and subsequent lobectomy for preoperatively undiagnosed lung cancer. *Jpn J Thorac*
3213 *Cardiovasc Surg.* 2006;54(5):187-192.
- 3214 8. Ueda K, Hayashi M, Tanaka N, Hoshii Y, Tanaka T, Hamano K. Surgery for undiagnosed ground glass
3215 pulmonary nodules: decision making using serial computed tomography. *World J Surg.* 2015;39(6):1452-
3216 1459.
- 3217 9. Whooley J, Weedle R, Breen D, Soo A. Lung Cancer resection in the absence of pre-operative histology:
3218 The Accuracy of Multidisciplinary Team Consensus. *Eur J Surg Oncol.* 2023;15:15.
- 3219 10. Ding Y, Li J, Li X, Xu M, Geng H, Sun D. Impact of preoperative biopsy on tumor spread through air spaces
3220 in stage I non-small cell lung cancer: a propensity score-matched study. *BMC pulm.* 2022;22(1):293.
- 3221 11. Zhang Y, Hu Y, Zhang S, et al. Effects of pre-operative biopsy on recurrence and survival in stage I lung
3222 adenocarcinoma patients in China. *ERJ open res.* 2023;9(4).
- 3223 12. Kaaki S, Kidane B, Srinathan S, Tan L, Buduhan G. Is tissue still the issue? Lobectomy for suspicious lung
3224 nodules without confirmation of malignancy. *J Surg Oncol.* 2018;117(5):977-984.

Field	Content
Review Question	In adults with pulmonary nodules being considered for treatment for lung cancer with curative intent, does pre-treatment biopsy provide the same clinical outcomes as no biopsy?
Type of review question	Intervention review
Objective of the review	This question aims to determine the role of non-surgical biopsy in patients with nodules at higher risk of lung cancer in whom treatment with curative intent is being considered, by comparing clinical outcomes when pre-treatment biopsy is or is not performed.
Eligibility criteria – population / disease / condition / issue / domain	Adults with pulmonary nodules being considered for treatment with curative intent (18+ years of age)
Eligibility criteria – intervention(s)	Pre-treatment biopsy
Eligibility criteria – comparator(s)	No biopsy
Outcomes and prioritisation	Benign resection Mortality Morbidity Quality of life Recurrence
Eligibility criteria – study design	RCTs, comparative studies, case series (>50 cases)
Other inclusion /exclusion criteria	Non-English language excluded unless full English translation Conference abstracts, Cochrane reviews, systematic reviews, reviews Cochrane reviews and systematic reviews can be referenced in the text, but CANNOT be used in a meta-analysis
Proposed sensitivity / subgroup analysis, or meta-regression	Adults with pulmonary nodules being considered for treatment with curative intent Solid nodules Sub-solid nodules Pre-treatment biopsy Percutaneous Bronchoscopic

Selection process – duplicate screening / selection / analysis	Agreement should be reached between Guideline members who are working on the question. If no agreement can be reached, a decision should be made by the Guideline co-chairs. If there is still no decision, the matter should be brought to the Guideline group and a decision will be made by consensus	
Data management (software)	RevMan5	Pairwise meta-analyses Evidence review/considered judgement. Storing Guideline text, tables, figures, etc.
	Gradeprofiler	Quality of evidence assessment
Information sources – databases and dates	MEDLINE, Embase, PubMed, Central Register of Controlled Trials and Cochrane Database of Systematic Reviews Restricted to articles published from 1990 onwards	
Methods for assessing bias at outcome / study level	RevMan5 intervention review template and NICE risk of bias checklist (follow instructions in ' <i>BTS Guideline Process Handbook – Intervention Review (June 2020)</i> ')	
Methods for quantitative analysis – combining studies and exploring (in)consistency	If 3 or more relevant studies: RevMan5 for meta-analysis, heterogeneity testing and forest plots (follow instructions in ' <i>BTS Guideline Process Handbook – Intervention Review (June 2020)</i> ')	
Meta-bias assessment – publication bias, selective reporting bias	GRADEprofiler	Intervention review quality of evidence assessment for each outcome (follow instructions in ' <i>BTS Guideline Process Handbook – Intervention Review (June 2020)</i> ')
Rationale / context – what is known	Where a pulmonary nodule is considered high risk for lung cancer on the basis of non-invasive imaging tests, and the patient is considered suitable for treatment with curative intent, clinical teams can either seek to confirm the diagnosis of cancer with a non-surgical biopsy or alternatively proceed to treatment on the basis of imaging without pathological confirmation. Where that treatment is surgical, this will result in an eventual pathological diagnosis following lung resection, whereas for non-surgical treatments no pathological diagnosis will be available. This question seeks to compare these two approaches in terms of clinical outcomes.	

3226

3227

3228

3229

3230

3231

3232

3233

3235 **Q9** In adults with pulmonary nodules being considered for treatment with curative intent, does
 3236 **FDG positron emission tomography computed tomography (PET-CT) staging provide the same**
 3237 **clinical outcomes as no PET-CT staging?**

3238 **Contents**

3239	Question Evidence Review	179
3240	Background	179
3241	Outcomes	179
3242	Evidence Review	179
3243	Evidence Statements	182
3244	Recommendations	182
3245	Research recommendations	183
3246	Full tabulated data	183
3247	Risk of bias summary	184
3248	GRADE analyses	184
3249	Recommendation table	185
3250	References	186
3251	Question Protocol	187

3252 **Question 9 Evidence Review**

3253 **Q9** In adults with pulmonary nodules being considered for treatment with curative intent, does
 3254 **FDG positron emission tomography computed tomography (PET-CT) staging provide the same**
 3255 **clinical outcomes as no PET-CT staging?**

3256 **Background**

3257 FDG-PET-CT (fluorodeoxyglucose positron emission tomography computed tomography) staging aims to
 3258 determine whether a lung cancer has metastasised to lymph nodes or distant organs. Previous guidelines
 3259 have suggested that all patients with lung cancers being considered for curative treatment should undergo
 3260 PET-CT staging. This review aims to determine if FDG-PET-CT staging provides the same clinical outcomes
 3261 as no FDG-PET-CT staging in adults with pulmonary nodules being considered for treatment with curative
 3262 intent.

3263 **Outcomes**

3264 Nodal or distant metastases

3265 **Evidence Review**

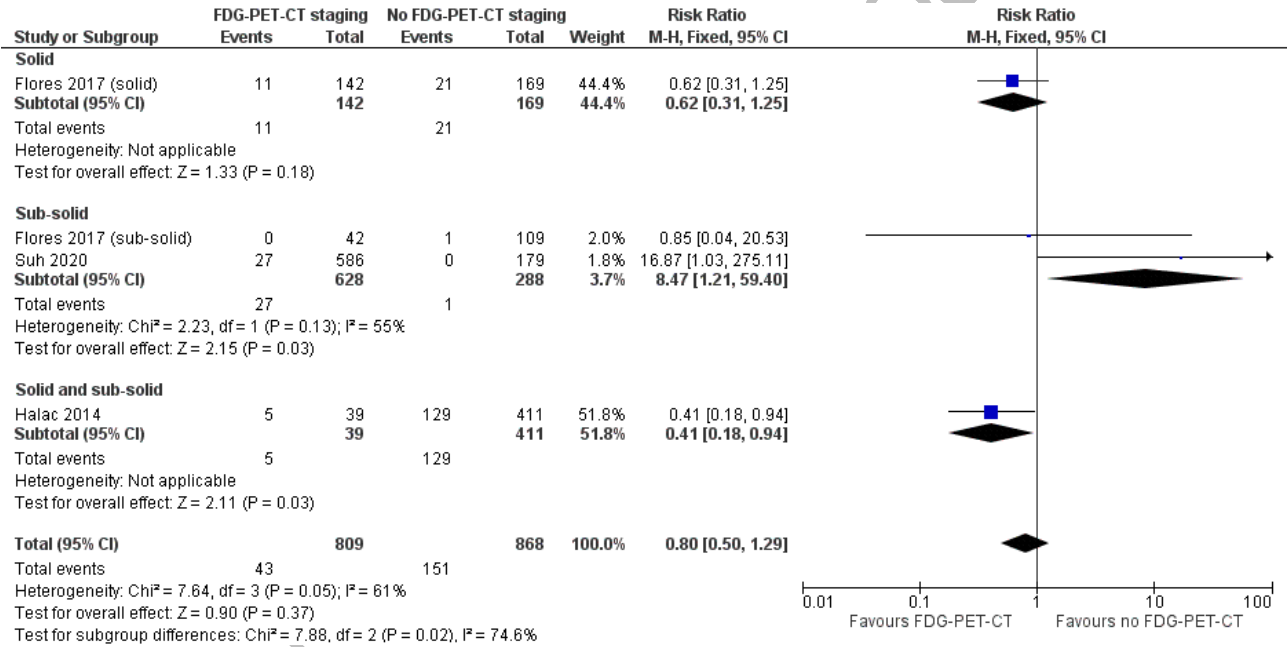
3266 The initial literature search identified 48 potentially relevant papers, and 8 papers were deemed relevant to the
3267 review.¹⁻⁸

3268 **Nodal/distant metastasis**

3269 *Pulmonary nodules*

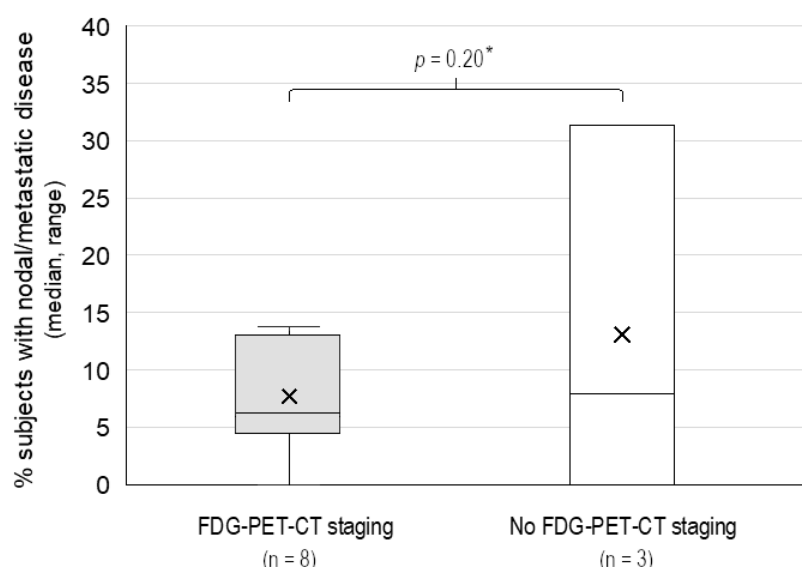
3270 Three studies compared FDG positron emission tomography computed tomography (FDG-PET-CT) staging
3271 against no FDG-PET-CT staging in subjects with pulmonary nodules being considered for treatment with
3272 curative intent.¹⁻³ Meta-analysis shows that the incidence of nodal or distant metastases is the same in the
3273 FDG-PET-CT staging group (**174 per 1000 patients**) when compared with the pre-treatment biopsy group (**139**
3274 **per 1000 patients (87 to 224)**) (Figure Q9a).

3275 Figure Q9a: Comparison of FDG-PET-CT staging versus conventional staging (no FDG-PET-CT) on incidence
3276 of nodal/metastatic disease in subjects with pulmonary nodules being considered for treatment with curative
3277 intent



3279 As two-arm study data were limited, single arm studies were also considered. Five studies reported on FDG-
3280 PET-CT staging in subjects with pulmonary nodules being considered for treatment with curative intent.⁴⁻⁸
3281 Comparing the percentage of participants with nodal or metastatic disease, there is no significant difference in
3282 the incidence of nodal/metastatic disease when comparing FDG-PET-CT staging or no FDG-PET-CT staging
3283 groups (7.7 ± 5.0 versus 13.1 ± 16.3 % (mean ± SD) respectively, *p* = 0.20, unpaired t-test). Data are shown
3284 in Figure Q9b and Table Q9a.

3285 Figure Q9b: Comparison of nodal/metastatic disease following FDG-PET-CT staging or no FDG-PET-CT
3286 staging of pulmonary nodules



* Unpaired t-test

(Studies with separate solid and sub-solid nodule data combined to give "all nodule" data)

Table Q9a: Summary of nodal/metastatic disease following FDG-PET-CT staging or no FDG-PET-CT staging single arm data in participants with pulmonary nodules

Nodule type	% participants with nodal/metastatic disease					p
	FDG-PET-CT staging		No FDG-PET-CT staging			
	Mean ± SD	Median [IQR]	Mean + SD	Median [IQR]		
All nodules	7.7 ± 5.0 ¹⁻⁸ (8)	6.2 [4.5, 13.1]	13.1 ± 16.3 ¹⁻³ (3)	7.9 [0.0, 31.4]	0.20*	

(study numbers in parentheses)

* Unpaired t-test

Solid nodules

Only one study compared FDG-PET-CT staging against conventional staging (no FDG-PET-CT) in subjects with solid pulmonary nodules.¹ Analysis suggests that the incidence of nodal or distant metastases may be greater in the FDG-PET-CT staging group (124 per 1000 patients) when compared with the pre-treatment biopsy group (77 per 1000 patients (39 to 155)) (data shown in Figure Q9a).

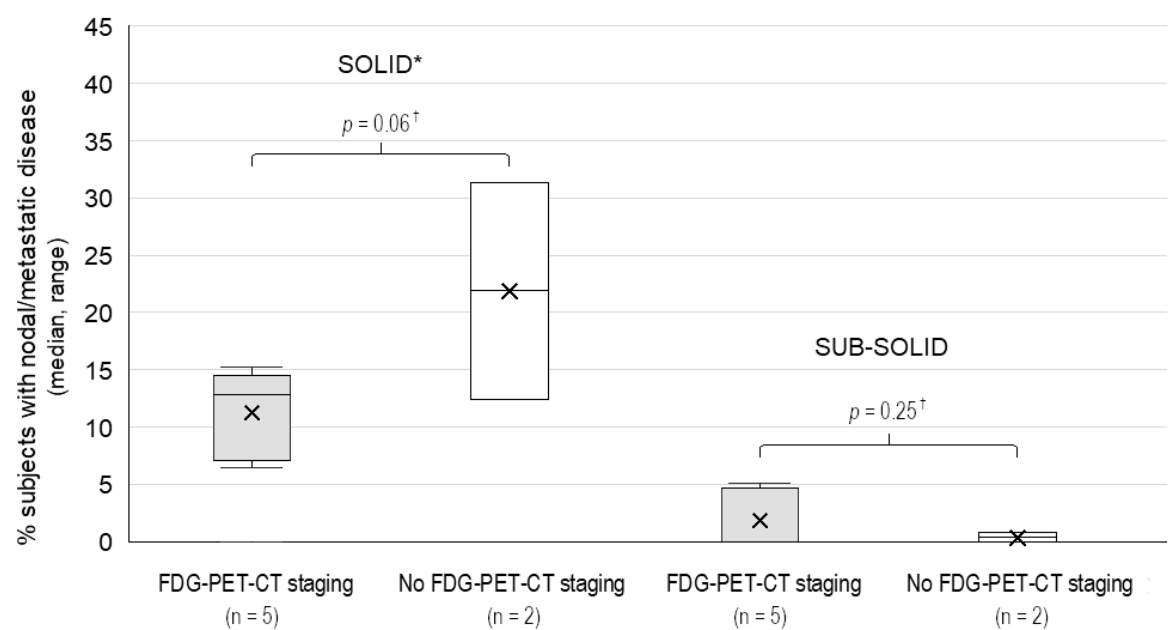
Sub-solid nodules

Two studies compared FDG-PET-CT staging against conventional staging (no FDG-PET-CT) in subjects with sub-solid pulmonary nodules.^{2,3} Meta-analysis suggests that the incidence of nodal or distant metastases may be less in the FDG-PET-CT staging group (3 per 1000 patients) when compared with the pre-treatment biopsy group (29 per 1000 patients (4 to 206)) (data shown in Figure Q9a).

Solid nodules versus sub-solid nodules

As there were limited solid nodule and sub-solid nodule direct comparison data (Figure Q9a), single arm solid pulmonary nodule only^{1,3,4,6,8} and sub-solid pulmonary nodule only¹⁻³ data were considered. Due to limited solid nodule only data, the solid nodule datasets in Figure Q9c included studies that defined their pulmonary nodule type as "solitary pulmonary nodule" (SPN) (one study)³; or ii) the nodule type was undefined (two studies)^{6,8,6,8}. Hence, these "assumed" solid nodule data may contain some sub-solid nodule data. Statistical comparison of the "assumed" solid nodules data (Figure Q9c) showed that nodal/metastatic disease incidence in the no FDG-PET-CT staging group was almost significantly greater than the FDG-PET-CT staging ($p = 0.06$, unpaired t-test). A summary of all data, including the "true" solid nodule data, is shown in Table Q9b. Full tabulated data are shown in Table Q9d.

Figure Q9c: Comparison of nodal/metastatic disease following FDG-PET-CT staging or no FDG-PET-CT staging of solid pulmonary nodules and sub-solid pulmonary nodules



3316

3317 * Solid nodule data included “solitary pulmonary nodule” data so may include sub-solid nodule data

3318 † Unpaired t-test

Table Q9b: Summary of nodal/metastatic disease following FDG-PET-CT staging or no FDG-PET-CT staging single arm data in participants with solid or sub-solid pulmonary nodules

Nodule type	% participants with nodal/metastatic disease						p
	FDG-PET-CT staging		No FDG-PET-CT staging				
	Mean ± SD	Median [IQR]	Mean + SD	Median [IQR]			
“True” solid	11.5 ± 5.3 ^{1,4}	(2)	11.5 [7.7, 15.3]	12.4 ¹	(1)	-	-
Solid*	11.2 ± 3.9 ^{1,3,4,6,8}	(5)	12.8 [7.1, 14.5]	21.9 ± 13.4 ^{1,3}	(2)	21.9 [12.4, 31.4]	0.06†
Sub-solid	1.9 ± 2.6 ^{1,2,4,5,7}	(5)	0.0 [0.0, 4.7]	0.5 ± 0.6 ^{1,2}	(2)	0.5 [0.0, 0.9]	0.25†

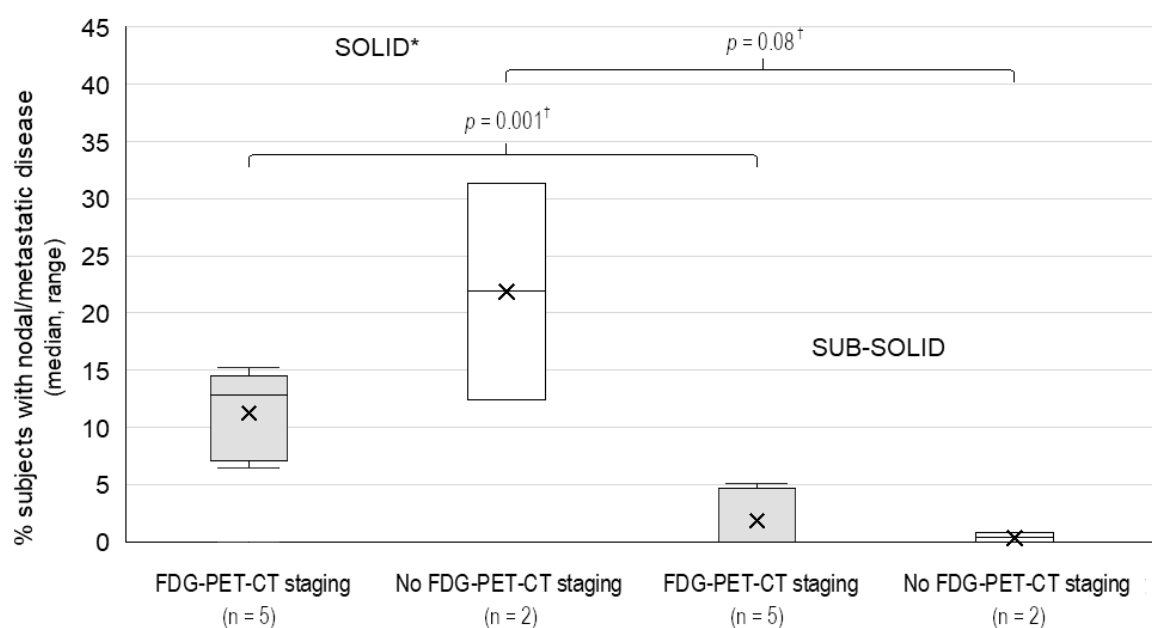
3321 (study numbers in parentheses)

3322 * ‘Solitary pulmonary nodules’, or undefined data included in datasets (FDG-PET-CT staging, n = 3; No FDG-PET-CT staging, n = 1)

3324 † Unpaired t-test

When comparing solid nodules versus sub-solid nodules in both groups (FDG-PET-CT staging or no FDG-PET-CT staging), nodal/metastatic disease is significantly greater in those with solid pulmonary nodules in the FDG-PET-CT staging group (11.2 ± 3.9 versus 1.9 ± 2.6 % (mean ± SD), solid nodules versus sub-solid nodules respectively, p = 0.001, unpaired t-test). For those in the no FDG-PET-CT staging group, a greater incidence of nodal/metastatic disease in those with solid nodules is nearing significance (21.9 ± 13.4 versus 0.5 ± 0.6 % (mean ± SD) solid nodules versus sub-solid nodules respectively, p = 0.08, unpaired t-test) (data summarised in Figure Q9d and Table Q9c).

Figure Q9d: Comparison of nodal/metastatic disease in participants with solid nodules versus participants with sub-solid nodules following FDG-PET-CT staging or no FDG-PET-CT staging



* Solid nodule data included "solitary pulmonary nodule" data so may include sub-solid nodule data

† Unpaired t-test

Table Q9c: Comparison of nodal/metastatic disease in solid nodules versus sub-solid following FDG-PET-CT staging or no FDG-PET-CT

Staging type	% participants with nodal/metastatic disease						p
	Solid* nodules			Sub-solid nodules			
	Mean ± SD	Median [IQR]		Mean + SD	Median [IQR]		
FDG-PET-CT	11.2 ± 3.9 ^{1,3,4,6,8}	(5)	12.8 [7.1, 14.5]	1.9 ± 2.6 ^{1,2,4,5,7}	(5)	0.0 [0.0, 4.7]	0.001†
No FDG-PET-CT	21.9 ± 13.4 ^{1,3}	(2)	21.9 [12.4, 31.4]	0.5 ± 0.6 ^{1,2}	(2)	0.5 [0.0, 0.9]	0.08†

(study numbers in parentheses)

* 'Solitary pulmonary nodules', or undefined data included in datasets (FDG-PET-CT staging, n = 3; No FDG-PET-CT staging, n = 1)

† Unpaired t-test

Sub-centimetre nodules

There was not enough evidence to consider sub-centimetre pulmonary nodules as a subgroup.

Evidence Statements

FDG-PET-CT staging appears to detect unexpected nodal/metastatic disease in patients with solid pulmonary nodules. (**Ungraded**)

The incidence of nodal/metastatic disease appears to be greater in patients with solid pulmonary nodules when compared with sub-solid pulmonary nodules. (**Ungraded**)

Recommendations

➤ For patients with solid pulmonary nodules being considered for treatment with curative intent, FDG PET-CT staging should be offered to detect occult nodal disease or metastases. (**Conditional**)

➤ Solid pulmonary nodules of ≥ 8 mm diameter should be offered FDG PET-CT staging (depending on PET-CT manufacturers' resolution specifications). (**Conditional** – by consensus)

- 3355 ➤ Sub-solid pulmonary nodules with a solid component ≥ 10 mm diameter should be offered FDG PET-CT
3356 staging. (**Conditional** – by consensus)

3357 **Research Recommendations**

- 3358 ▪ Further research is needed to confirm the effect of FDG-PET-CT on staging solid, sub-solid and sub-
3359 centimetre pulmonary nodules being considered for treatment with curative intent.
- 3360 ▪ Research is needed to determine the optimal size threshold at which PET-CT beneficial.

3361

3362

3363 **Full tabulated data**

3364 Table Q9d: Nodal/metastatic disease data following i) FDG-PET-CT staging, or ii) no FDG-PET-CT staging in
3365 pulmonary nodules being considered for treatment with curative intent

3366 i) FDG-PET-CT staging

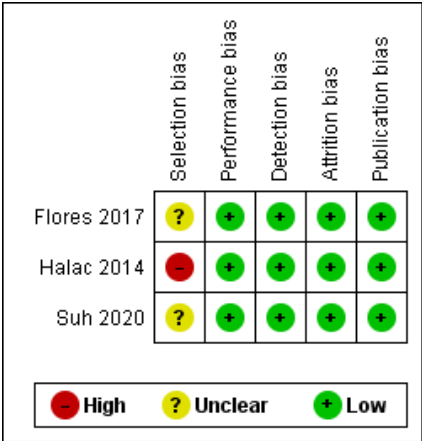
Study	Nodule type	FDG PET-CT staging		
		Total subjects	Subjects with nodal/metastatic disease	% with nodal/metastatic disease
Casiraghi 2011 ⁴	Solid	190	29	15.3
Casiraghi 2011 ⁴	SSN	26	0	0.0
Chen 2021 ⁵	SSN	217	11	5.1
Flores 2017 ¹	Solid	142	11	7.7
Flores 2017 ¹	SSN	42	0	0.0
Halac 2014 ³	SPN	39	5	12.8
Lee 2007 ⁶	Undefined	156	10	6.4
Song 2017 ⁷	SSN	72	0	0.0
Suh 2020 ²	SSN	629	27	4.3
Veronesi 2011 ⁸	Undefined	290	40	13.8

3367 SPN – solitary pulmonary nodule; SSN – sub-solid nodule

3368 ii) No FDG-PET-CT staging

Study	Nodule type	No FDG PET-CT staging		
		Total subjects	Subjects with nodal/metastatic disease	% with nodal/metastatic disease
Flores 2017 ¹	Solid	169	21	12.4
Flores 2017 ¹	SSN	109	1	0.9
Halac 2014 ³	SPN	226	0	0.0
Suh 2020 ²	SSN	411	129	31.4

3369 SPN – solitary pulmonary nodule; SSN – sub-solid nodule



3371
3372
3373
3374
3375
3376
3377
3378

3379 GRADE analyses

3380 Pulmonary nodules, solid pulmonary nodules and sub-solid pulmonary nodules

In adults with pulmonary nodules being considered for treatment for lung cancer with curative intent, does FDG positron emission tomography computed tomography (PET-CT) staging provide the same clinical outcomes as no PET-CT staging?

Population: Adults (18+) being considered for treatment for lung cancer with curative intent

Intervention: FDG-PET-CT staging

Comparator: No FDG-PET-CT staging

Outcome	Number of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects		Quality of the Evidence (GRADE)
			FDG-PET-CT staging	No FDG-PET-CT staging	
Pulmonary nodules	1677 (4 studies)	RR 0.80 (0.50 to 1.29)	174 per 1000	139 per 1000 (87 to 224)	⊕○○○ VERY LOW ^{a,b,c}
Solid nodules	311 (1 study)	RR 0.62 (0.31 to 1.25)	124 per 1000	77 per 1000 (39 to 155)	-
Sub-solid nodules	916 (2 studies)	RR 8.47 (1.21 to 59.4)	3 per 1000	29 per 1000 (4 to 206)	⊕○○○ VERY LOW ^{a,b,c}

CI: Confidence interval

Explanations

- a. Some risk of bias across the studies
- b. Serious inconsistency across the studies
- c. Serious imprecision, CIs cross both MIDs

3381

3382 **Recommendation Table**

3383 **Solid pulmonary nodules**

3384 **Question Details**

POPULATION:	Adults (18+) with pulmonary nodules being considered for treatment for lung cancer with curative intent
INTERVENTION:	FDG-PET-CT staging
COMPARISON:	No FDG-PET-CT staging
OUTCOMES:	Nodal/metastatic disease

3385

3386 **SUMMARY OF JUDGEMENTS**

JUDGEMENT							
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
TEST ACCURACY	Very inaccurate	Inaccurate	Accurate	Very accurate		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	Does not favour the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know

3387

3388 **TYPE OF RECOMMENDATION**

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
☐	☐	☐	☒	☐

3389

3390 **CONCLUSIONS**

Recommendation

For patients with solid pulmonary nodules being considered for treatment with curative intent, FDG-PET-CT staging can be considered for aiming to reduce the incidence of nodal/metastatic disease. **(Conditional)**

Justification

FDG-PET-CT staging appears to detect unexpected nodal/metastatic disease in patients with solid pulmonary nodules. (**Ungraded**)

The incidence of nodal/metastatic disease appears to be greater in patients with solid pulmonary nodules. (**Ungraded**)

Subgroup considerations

No subgroups to consider.

Research priorities

Further research is needed to confirm the effect of FDG-PET-CT staging on solid, sub-solid and sub-centimetre pulmonary nodules being considered for treatment with curative intent.

References

1. Flores RM, Nicastrì D, Bauer T, et al. Computed tomography screening for lung cancer: mediastinal lymph node resection in Stage IA nonsmall cell lung cancer manifesting as subsolid and solid nodules. *Ann Surg.* 2017;265(5):1025-1033.
2. Suh YJ, Park CM, Han K, et al. Utility of FDG PET/CT for preoperative staging of non-small cell lung cancers manifesting as subsolid nodules with a solid portion of 3 cm or smaller. *American Journal of Roentgenology.* 2020;214(3):514-523.
3. Halac M, Ozhan M, Yilmaz Aksoy S, et al. The role of FDG-PET/CT in detecting unsuspected and unknown distant metastasis in the initial staging of NSCLC. *Turk.* 2014;44(6):1029-1040.
4. Casiraghi M, Travaini LL, Maisonneuve P, et al. Lymph node involvement in T1 non-small-cell lung cancer: could glucose uptake and maximal diameter be predictive criteria? *Eur J Cardiothorac Surg.* 2011;39(4):e38-43.
5. Chen YC, Lin YH, Chien HC, et al. Preoperative consolidation-to-tumor ratio is effective in the prediction of lymph node metastasis in patients with pulmonary ground-glass component nodules. *Thorac Cancer.* 2021;12(8):1203-1209.
6. Lee ST, Berlangieri SU, Poon AM, et al. Prevalence of occult metastatic disease in patients undergoing 18F-FDG PET for primary diagnosis or staging of lung carcinoma and solitary pulmonary nodules. *Intern Med J.* 2007;37(11):753-759.
7. Song JU, Song J, Lee KJ, et al. Are there any additional benefits to performing positron emission tomography/computed tomography scans and brain magnetic resonance imaging on patients with ground-glass nodules prior to surgery? *Tuberculosis and Respiratory Diseases.* 2017;80(4):368-376.
8. Veronesi G, Maisonneuve P, Pelosi G, et al. Screening-detected lung cancers: is systematic nodal dissection always essential? *J Thorac Oncol.* 2011;6(3):525-530.

Field	Content
Review Question	In adults with pulmonary nodules being considered for treatment with curative intent, does FDG positron emission tomography computed tomography (PET-CT) staging provide the same clinical outcomes as no PET-CT staging?
Type of review question	Intervention review
Objective of the review	This question aims to determine the impact on clinical outcomes of undertaking PET-CT staging for different types and sizes of pulmonary nodules being considered for treatment with curative intent.
Eligibility criteria – population / disease / condition / issue / domain	Adults with pulmonary nodules being considered for treatment with curative intent (18+ years of age)
Eligibility criteria – intervention(s)	FDG PET-CT
Eligibility criteria – comparator(s)	No FDG PET-CT
Outcomes and prioritisation	Nodal or distant metastases
Eligibility criteria – study design	RCTs, comparative studies, case series (>50 cases)
Other inclusion /exclusion criteria	Non-English language excluded unless full English translation Conference abstracts, Cochrane reviews, systematic reviews, reviews Cochrane reviews and systematic reviews can be referenced in the text, but CANNOT be used in a meta-analysis
Proposed sensitivity / subgroup analysis, or meta-regression	Adults with pulmonary nodules being considered for treatment with curative intent - Solid nodules - Sub-solid nodules - Sub-centimetre nodules
Selection process – duplicate screening / selection / analysis	Agreement should be reached between Guideline members who are working on the question. If no agreement can be reached, a decision should be made by the Guideline co-chairs. If there is still no decision, the matter should be brought to the Guideline group and a decision will be made by consensus

Data management (software)	RevMan5 Pairwise meta-analyses Evidence review/considered judgement. Storing Guideline text, tables, figures, etc. Gradeprofiler Quality of evidence assessment
Information sources – databases and dates	MEDLINE, Embase, Central Register of Controlled Trials and Cochrane Database of Systematic Reviews Restricted to articles published from 1990 onwards
Methods for assessing bias at outcome / study level	RevMan5 intervention review template and NICE risk of bias checklist (follow instructions in ' <i>BTS Guideline Process Handbook – Intervention Review (June 2020)</i> ')
Methods for quantitative analysis – combining studies and exploring (in)consistency	If 3 or more relevant studies: RevMan5 for meta-analysis, heterogeneity testing and forest plots (follow instructions in ' <i>BTS Guideline Process Handbook – Intervention Review (June 2020)</i> ')
Meta-bias assessment – publication bias, selective reporting bias	GRADEprofiler Intervention review quality of evidence assessment for each outcome (follow instructions in ' <i>BTS Guideline Process Handbook – Intervention Review (June 2020)</i> ')
Rationale / context – what is known	PET-CT staging aims to determine whether a lung cancer has metastasised to lymph nodes or distant organs. Previous guidelines (e.g. NICE) have suggested that all patients with lung cancers being considered for curative treatment should undergo PET-CT staging. This question seeks to determine whether this approach is appropriate for all pulmonary nodules being considered for curative treatment, or whether there are some nodules for which the pre-test probability of metastatic spread is so low that PET-CT is not indicated.

3424

3425

3426

3427

3428

3429

3430

3431

3432

3433

3434

3435

3436

3437	Online Supplementary Appendix 10	Literature Search Strategy and PRISMA diagram
3438	Contents	
3439	Databases used	190
3440	Summary of records retrieved	190
3441	Database search strategies	191
3442	MEDLINE	191
3443	Search 1	191
3444	Search 2	192
3445	Additional Search	193
3446	EMBASE	194
3447	Search 1	194
3448	Search 2	195
3449	Additional Search	197
3450	Cochrane Central Register of Controlled Trials (CENTRAL)	198
3451	Search 1	198
3452	Cochrane Database of Systematic Reviews (CDSR)	199
3453	Search 1	199
3454	PRISMA diagram	200
3455		

3456 **Databases used**

- 3457 MEDLINE
3458 EMBASE
3459 Central Register of Controlled Trials (CENTRAL)
3460 Cochrane Database of Systematic Reviews (CDSR)
3461
3462 MEDLINE and EMBASE via Ovid for Search 1 and Search 2 and Additional search
3463 CENTRAL and CDSR Search 1 via Ovid

3464
3465
3466
3467
3468

Summary of records retrieved

Database	Search 1 Records		Search 2 Records		Additional Search Records	
	Retrieved	Deduplicated	Retrieved	Deduplicated	Retrieved	Deduplicated
MEDLINE	5482	-	919	-	1282	-
EMBASE	6385	-	1728	-	2271	-
CENTRAL	334	-	-	-	-	-
CDSR	0	-	-	-	-	-
Total	12201	9041	2647	1934	3553	2332

- 3469 **Total records retrieved after individual search deduplication** **13307**
3470 **Total records retrieved after across-search deduplication** **11740**

3471

3472
3473

3474 **Database search strategies**

3475 **MEDLINE**

3476 **Search 1**

3477 **Search via OVID**

3478 **Search date 23 May 2023**

3479 **Records identified = 5482**

3480 Database: Ovid MEDLINE(R) ALL <1946 to May 23, 2023>

3481 **Search Strategy**

3482 -----

3483 1 exp multiple pulmonary nodule/ (1721)

3484 2 exp solitary pulmonary nodule/ (4681)

3485 3 lung nodul\$.ti,ab,kw. (4953)

3486 4 pulmonary nodul\$.ti,ab,kw. (9147)

3487 5 or/1-4 (14677)

3488 6 exp tomography, x-ray computed/ (490286)

3489 7 (CT\$ or computed tom\$ or computed-tom\$).ti,ab,kw. (830112)

3490 8 6 or 7 (1029857)

3491 9 exp tomography, emission-computed/ (132225)

3492 10 (PET-CT or PET CT).ti,ab,kw. (38169)

3493 11 ((positron emission or positron-emission) adj2 (computed tomography or computed-

3494 tomography)).ti,ab,kw. (12052)

3495 12 or/9-11 (145423)

3496 13 exp magnetic resonance imaging/ (531117)

3497 14 (magnetic resonance imag\$ or MRI or MR imag\$).ti,ab,kw. (510001)

3498 15 13 or 14 (719345)

3499 16 8 or 12 or 15 (1650025)

3500 17 exp lung neoplasm/ (273038)

3501 18 (lung and (neoplasm\$ or cancer\$)).ti,ab,kw. (264005)

3502 19 (pulmonary and (neoplasm\$ or cancer\$)).ti,ab,kw. (46566)

3503 20 (lung adj (cancer or tumor\$ or tumour\$ or neoplasm\$)).ti,ab,kw. (204891)

3504 21 (pulmonary adj (cancer or tumor\$ or tumour\$ or neoplasm\$)).ti,ab,kw. (4505)

3505 22 or/17-21 (398514)

3506 23 "sensitivity and specificity"/ (368472)

3507 24 "predictive value of tests"/ (222830)

3508 25 roc curve/ (70901)

3509 26 false negative reactions/ (18296)

3510 27 false positive reactions/ (28595)

3511 28 (sensitivity or specificity or diagnostic\$).ti,ab,kw. (2033353)

3512 29 (predictive adj3 value\$).ti,ab,kw. (137266)

3513 30 (roc adj (curve\$ or analy\$)).ti,ab,kw. (68499)

3514 31 receiver operating characteristic\$.ti,ab,kw. (108238)

3515 32 (true adj (positiv\$ or negativ\$)).ti,ab,kw. (11039)

3516 33 (false adj (positiv\$ or negativ\$)).ti,ab,kw. (89704)

3517 34 or/23-33 (2516868)

3518 35 exp metastases/ (221227)

3519 36 metast\$.ti,ab,kw. (617909)

3520 37 secondary.ti,ab,kw. (848589)

3521 38 (node or nodal\$).ti,ab,kw. (252239)

3522 39 or/35-38 (1646465)

3523 40 (low dose or low-dose).ti,ab,kw. (113477)

3524 41 5 and 8 and 40 (805)
 3525 42 incident\$.ti,ab,kw. (175435)
 3526 43 5 and 42 (779)
 3527 44 41 or 43 (1523)
 3528 45 (previous adj (history or occurrence)).ti,ab,kw. (13063)
 3529 46 (prior adj (history or occurrence)).ti,ab,kw. (7868)
 3530 47 (earlier adj (history or occurrence)).ti,ab,kw. (391)
 3531 48 or/45-47 (21156)
 3532 49 5 and 48 (55)
 3533 50 5 and 16 and 22 and 34 (3006)
 3534 51 biops\$.ti,ab,kw. (459552)
 3535 52 5 and 51 (2877)
 3536 53 5 and 12 and 39 (531)
 3537 54 44 or 49 or 50 or 52 or 53 (6333)
 3538 55 exp animals/ not humans/ (5123796)
 3539 56 54 not 55 (6287)
 3540 57 limit 56 to english language (5618)
 3541 58 limit 57 to yr="1990-Current" (5482)
 3542

3543 **Search 2**

3544 **Search via OVID**

3545 **Search date 24 March 2025**

3546 **Records identified = 919**

3547 Database: Ovid MEDLINE(R) ALL <1946 to March 24, 2025>

3548 **Search Strategy**

3549 -----

3550 1 exp multiple pulmonary nodule/ (2118)
 3551 2 exp solitary pulmonary nodule/ (5068)
 3552 3 lung nodul\$.ti,ab,kw. (5822)
 3553 4 pulmonary nodul\$.ti,ab,kw. (10504)
 3554 5 or/1-4 (16723)
 3555 6 exp tomography, x-ray computed/ (520234)
 3556 7 (CT\$ or computed tom\$ or computed-tom\$).ti,ab,kw. (943217)
 3557 8 6 or 7 (1146860)
 3558 9 exp tomography, emission-computed/ (141509)
 3559 10 (PET-CT or PET CT).ti,ab,kw. (45534)
 3560 11 ((positron emission or positron-emission) adj2 (computed tomography or computed-
 3561 tomography)).ti,ab,kw. (14253)
 3562 12 or/9-11 (158372)
 3563 13 exp magnetic resonance imaging/ (569730)
 3564 14 (magnetic resonance imag\$ or MRI or MR imag\$).ti,ab,kw. (575537)
 3565 15 13 or 14 (794655)
 3566 16 8 or 12 or 15 (1832246)
 3567 17 exp lung neoplasm/ (294625)
 3568 18 (lung and (neoplasm\$ or cancer\$)).ti,ab,kw. (300779)
 3569 19 (pulmonary and (neoplasm\$ or cancer\$)).ti,ab,kw. (52152)
 3570 20 (lung adj (cancer or tumor\$ or tumour\$ or neoplasm\$)).ti,ab,kw. (233182)
 3571 21 (pulmonary adj (cancer or tumor\$ or tumour\$ or neoplasm\$)).ti,ab,kw. (4704)
 3572 22 or/17-21 (441517)
 3573 23 "sensitivity and specificity"/ (378274)

3574 24 "predictive value of tests"/ (232510)
 3575 25 roc curve/ (78476)
 3576 26 false negative reactions/ (18392)
 3577 27 false positive reactions/ (28795)
 3578 28 (sensitivity or specificity or diagnostic\$.ti,ab,kw. (2290655)
 3579 29 (predictive adj3 value\$.ti,ab,kw. (156598)
 3580 30 (roc adj (curve\$ or analy\$)).ti,ab,kw. (88261)
 3581 31 receiver operating characteristic\$.ti,ab,kw. (138061)
 3582 32 (true adj (positiv\$ or negativ\$)).ti,ab,kw. (12390)
 3583 33 (false adj (positiv\$ or negativ\$)).ti,ab,kw. (97446)
 3584 34 or/23-33 (2808730)
 3585 35 exp metastases/ (229427)
 3586 36 metast\$.ti,ab,kw. (688851)
 3587 37 secondary.ti,ab,kw. (968039)
 3588 38 (node or nodal\$.ti,ab,kw. (277300)
 3589 39 or/35-38 (1847767)
 3590 40 (low dose or low-dose).ti,ab,kw. (123396)
 3591 41 5 and 8 and 40 (978)
 3592 42 incident\$.ti,ab,kw. (199604)
 3593 43 5 and 42 (938)
 3594 44 41 or 43 (1836)
 3595 45 (previous adj (history or occurrence)).ti,ab,kw. (14268)
 3596 46 (prior adj (history or occurrence)).ti,ab,kw. (9041)
 3597 47 (earlier adj (history or occurrence)).ti,ab,kw. (431)
 3598 48 or/45-47 (23547)
 3599 49 5 and 48 (64)
 3600 50 5 and 16 and 22 and 34 (3453)
 3601 51 biops\$.ti,ab,kw. (500112)
 3602 52 5 and 51 (3286)
 3603 53 5 and 12 and 39 (598)
 3604 54 44 or 49 or 50 or 52 or 53 (7285)
 3605 55 exp animals/ not humans/ (5320597)
 3606 56 54 not 55 (7235)
 3607 57 limit 56 to english language (6534)
 3608 58 limit 57 to dt=20230526-20250325 (919)
 3609

3610 **Additional search**

3611 **Search via OVID**

3612 **Search date 28 March 2025**

3613 **Records identified = 1282**

3614 Database: Ovid MEDLINE(R) ALL <1946 to March 28, 2025>

3615 **Search Strategy**

3616 -----

3617 1 exp multiple pulmonary nodule/ (2119)
 3618 2 exp solitary pulmonary nodule/ (5070)
 3619 3 lung nodul\$.ti,ab,kw. (5807)
 3620 4 pulmonary nodul\$.ti,ab,kw. (10482)
 3621 5 or/1-4 (16689)

3622 6 (volume or diameter or upper or spiculation or FDG-avidity or Brock or Herder or Mayo or VA or
3623 UKLS or size or bubble or density or mass or bronchogram or visual or morphology).ti,ab,kw.
3624 (5151188)
3625 7 malignant.ti,ab,kw. (471111)
3626 8 benign.ti,ab,kw. (278950)
3627 9 7 and 8 (87478)
3628 10 5 and 6 and 9 (907)
3629 11 (previous adj (history or occurrence)).ti,ab,kw. (14244)
3630 12 (prior adj (history or occurrence)).ti,ab,kw. (9012)
3631 13 11 or 12 (23071)
3632 14 5 and 13 (64)
3633 15 (PET-CT or PET CT).ti,ab,kw. (45316)
3634 16 ((positron emission or positron-emission) adj2 (computed tomography or computed-
3635 tomography)).ti,ab,kw. (14215)
3636 17 15 or 16 (50045)
3637 18 staging.ti,ab,kw. (104336)
3638 19 5 and 17 and 18 (155)
3639 20 percutaneous.ti,ab,kw. (181236)
3640 21 bronchoscopic.ti,ab,kw. (8540)
3641 22 20 or 21 (189463)
3642 23 treatment.ti,ab,kw. (5750518)
3643 24 5 and 22 and 23 (198)
3644 25 10 or 14 or 19 or 24 (1304)
3645 26 limit 25 to yr="1990-Current" (1282)
3646

3647 EMBASE

3648 Search 1

3649 Search via OVID

3650 Search date 25 May 2023

3651 Records identified = 6384

3652 Database: Embase <1974 to 2023 May 25>

3653 Search Strategy

3654 -----
3655 1 exp pulmonary nodule/ (27909)
3656 2 lung nodul\$.ti,ab,kw. (9031)
3657 3 pulmonary nodul\$.ti,ab,kw. (15181)
3658 4 or/1-3 33830
3659 5 exp computer assisted tomography/ (1360605)
3660 6 (CT\$ or computed tom\$ or computed-tom\$).ti,ab,kw. (1302947)
3661 7 5 or 6 (1980808)
3662 8 exp positron emission tomography/ (226993)
3663 9 (PET-CT or PET CT).ti,ab,kw. (79850)
3664 10 ((positron emission or positron-emission) adj2 (computed tomography or computed-
3665 tomography)).ti,ab,kw. (15724)
3666 11 or/8-10 (254189)
3667 12 exp magnetic resonance imaging/ (1227572)
3668 13 (magnetic resonance imag\$ or MRI or MR imag\$).ti,ab,kw. (798965)
3669 14 12 or 13 (1305532)
3670 15 7 or 11 or 14 (2880313)
3671 16 exp lung neoplasm/ (478134)

3672 17 (lung and (neoplasm\$ or cancer\$)).ti,ab,kw. (414492)
 3673 18 (pulmonary and (neoplasm\$ or cancer\$)).ti,ab,kw. (76691)
 3674 19 (lung adj (cancer or tumor\$ or tumour\$ or neoplasm\$)).ti,ab,kw. (314952)
 3675 20 (pulmonary adj (cancer or tumor\$ or tumour\$ or neoplasm\$)).ti,ab,kw. (4957)
 3676 21 or/16-20 (628877)
 3677 22 "sensitivity and specificity"/ (483054)
 3678 23 predictive value/ (243328)
 3679 24 receiver operating characteristic/ (206311)
 3680 25 false negative result/ (25076)
 3681 26 false positive result/ (40137)
 3682 27 diagnostic test accuracy study/ (228515)
 3683 28 (sensitivity or specificity or diagnostic\$).ti,ab,kw. (2723155)
 3684 29 (predictive adj3 value\$).ti,ab,kw. (210092)
 3685 30 (roc adj (curve\$ or analy\$)).ti,ab,kw. (119752)
 3686 31 receiver operating characteristic\$.ti,ab,kw. (142153)
 3687 32 (true adj (positiv\$ or negativ\$)).ti,ab,kw. (16992)
 3688 33 (false adj (positiv\$ or negativ\$)).ti,ab,kw. (125631)
 3689 34 or/22-33 (3194736)
 3690 35 exp metastases/ (785358)
 3691 36 metast\$.ti,ab,kw. (914646)
 3692 37 secondary.ti,ab,kw. (1216957)
 3693 38 (node or nodal\$).ti,ab,kw. (366479)
 3694 39 or/35-38 (2434904)
 3695 40 (low dose or low-dose).ti,ab,kw. (168795)
 3696 41 4 and 7 and 40 (1654)
 3697 42 incident\$.ti,ab,kw. (248144)
 3698 43 4 and 42 (2090)
 3699 44 41 or 43 (3573)
 3700 45 (previous adj (history or occurrence)).ti,ab,kw. (23403)
 3701 46 (earlier adj (history or occurrence)).ti,ab,kw. (549)
 3702 47 or/45-46 (23949)
 3703 48 4 and 47 (119)
 3704 49 4 and 15 and 21 and 34 (4959)
 3705 50 biops\$.ti,ab,kw. (754928)
 3706 51 4 and 50 (8061)
 3707 52 4 and 11 and 39 (2858)
 3708 53 44 or 48 or 49 or 51 or 52 (14841)
 3709 54 exp animals/ not humans/ (11679073)
 3710 55 53 not 54 (10729)
 3711 56 limit 55 to english language (9903)
 3712 57 limit 56 to conference abstracts (3360)
 3713 58 56 not 57 (6543)
 3714 59 limit 58 to yr="1990-Current" (6385)

3715 **Search 2**

3716 **Search via OVID**

3717 **Search date 21 March 2025**

3718 **Records identified = 1728**

3719 Database: Embase <1974 to 2025 March 21>

3720 **Search Strategy**

3721

3722 1 exp pulmonary nodule/ (32811)

3723 2 lung nodul\$.ti,ab,kw. (10592)
 3724 3 pulmonary nodul\$.ti,ab,kw. (17524)
 3725 4 or/1-3 (39248)
 3726 5 exp computer assisted tomography/ (1580292)
 3727 6 (CT\$ or computed tom\$ or computed-tom\$).ti,ab,kw. (1453338)
 3728 7 5 or 6 (2251761)
 3729 8 exp positron emission tomography/ (264881)
 3730 9 (PET-CT or PET CT).ti,ab,kw. (91779)
 3731 10 ((positron emission or positron-emission) adj2 (computed tomography or computed-
 3732 tomography)).ti,ab,kw. (18039)
 3733 11 or/8-10 (292433)
 3734 12 exp magnetic resonance imaging/ (1383009)
 3735 13 (magnetic resonance imag\$ or MRI or MR imag\$).ti,ab,kw. (877513)
 3736 14 12 or 13 (1464201)
 3737 15 7 or 11 or 14 (3244104)
 3738 16 exp lung neoplasm/ (593210)
 3739 17 (lung and (neoplasm\$ or cancer\$)).ti,ab,kw. (464763)
 3740 18 (pulmonary and (neoplasm\$ or cancer\$)).ti,ab,kw. (85853)
 3741 19 (lung adj (cancer or tumor\$ or tumour\$ or neoplasm\$)).ti,ab,kw. (352316)
 3742 20 (pulmonary adj (cancer or tumor\$ or tumour\$ or neoplasm\$)).ti,ab,kw. (5249)
 3743 21 or/16-20 (719106)
 3744 22 "sensitivity and specificity"/ (541874)
 3745 23 predictive value/ (288303)
 3746 24 receiver operating characteristic/ (265463)
 3747 25 false negative result/ (28746)
 3748 26 false positive result/ (46316)
 3749 27 diagnostic test accuracy study/ (284940)
 3750 28 (sensitivity or specificity or diagnostic\$).ti,ab,kw. (3003325)
 3751 29 (predictive adj3 value\$).ti,ab,kw. (233099)
 3752 30 (roc adj (curve\$ or analy\$)).ti,ab,kw. (143530)
 3753 31 receiver operating characteristic\$.ti,ab,kw. (171182)
 3754 32 (true adj (positiv\$ or negativ\$)).ti,ab,kw. (18726)
 3755 33 (false adj (positiv\$ or negativ\$)).ti,ab,kw. (134692)
 3756 34 or/22-33 (3549982)
 3757 35 exp metastases/ (884701)
 3758 36 metast\$.ti,ab,kw. (1005661)
 3759 37 secondary.ti,ab,kw. (1359799)
 3760 38 (node or nodal\$).ti,ab,kw. (398681)
 3761 39 or/35-38 (2702651)
 3762 40 (low dose or low-dose).ti,ab,kw. (182218)
 3763 41 4 and 7 and 40 (1990)
 3764 42 incident\$.ti,ab,kw. (276418)
 3765 43 4 and 42 (2592)
 3766 44 41 or 43 (4360)
 3767 45 (previous adj (history or occurrence)).ti,ab,kw. (25660)
 3768 46 (earlier adj (history or occurrence)).ti,ab,kw. (593)
 3769 47 45 or 46 (26250)
 3770 48 4 and 47 (137)
 3771 49 4 and 15 and 21 and 34 (6125)
 3772 50 biops\$.ti,ab,kw. (824628)
 3773 51 4 and 50 (9675)
 3774 52 4 and 11 and 39 (3592)
 3775 53 44 or 48 or 49 or 51 or 52 (17870)
 3776 54 exp animals/ not humans/ (5878923)
 3777 55 53 not 54 (17768)

3778 56 limit 55 to english language (16621)
 3779 57 limit 56 to conference abstracts (6419)
 3780 58 56 not 57 (10202)
 3781 59 limit 58 to dc=20230526-20250324 (1728)

3782 **Additional search**

3783 **Search via OVID**

3784 **Search date 28 March 2025**

3785 **Records identified = 2271**

3786 Database: Embase <1974 to 2025 March 28>

3787 **Search Strategy**

3788 -----

3789 1 exp pulmonary nodule/ (32851)
 3790 2 lung nodul\$.ti,ab,kw. (10600)
 3791 3 pulmonary nodul\$.ti,ab,kw. (17545)
 3792 4 or/1-3 (39291)
 3793 5 (volume or diameter or upper or spiculation or FDG-avidity or Brock or Herder or Mayo or VA or
 3794 UKLS or size or bubble or density or mass or bronchogram or visual or morphology).ti,ab,kw.
 3795 (6568179)
 3796 6 malignant.ti,ab,kw. (632363)
 3797 7 benign.ti,ab,kw. (386521)
 3798 8 6 and 7 (124737)
 3799 9 4 and 5 and 8 (1744)
 3800 10 (previous adj (history or occurrence)).ti,ab,kw. (25699)
 3801 11 (prior adj (history or occurrence)).ti,ab,kw. (19273)
 3802 12 10 or 11 (44578)
 3803 13 4 and 12 (268)
 3804 14 (PET-CT or PET CT).ti,ab,kw. (91925)
 3805 15 ((positron emission or positron-emission) adj2 (computed tomography or computed-
 3806 tomography)).ti,ab,kw. (18070)
 3807 16 14 or 15 (97289)
 3808 17 staging.ti,ab,kw. (172387)
 3809 18 4 and 16 and 17 (503)
 3810 19 percutaneous.ti,ab,kw. (276440)
 3811 20 bronchoscopic.ti,ab,kw. (13555)
 3812 21 19 or 20 (289436)
 3813 22 treatment.ti,ab,kw. (7951213)
 3814 23 4 and 21 and 22 (577)
 3815 24 9 or 13 or 18 or 23 (2976)
 3816 25 case report.ti,ab. (606710)
 3817 26 24 not 25 (2662)
 3818 27 review.ti,ab. (2986128)
 3819 28 26 not 27 (2296)
 3820 29 limit 28 to yr="1990-Current" (2271)
 3821 30 limit 29 to dc=19891231-20250324 (2271)

3822

3823

3824 **Cochrane Central Register of Controlled Trials (CENTRAL)**

3825 **Search 1**

3826 **Search via OVID**

3827 **Search date 26 May 2023**

3828 **Records identified = 334**

3829 Database: Cochrane Central Register of Controlled Clinical Trials

3830 **Search Strategy**

3831 -----

- 3832 1 exp multiple pulmonary nodule/ (91)
3833 2 exp solitary pulmonary nodule/ (121)
3834 3 lung nodul\$.ti,ab,kw. (391)
3835 4 pulmonary nodul\$.ti,ab,kw. (364)
3836 5 or/1-4 (625)
3837 6 exp tomography/ (22037)
3838 7 (CT\$ or computed tom\$ or computed-tom\$).ti,ab,kw. (70888)
3839 8 6 or 7 (85753)
3840 9 exp positron emission tomography/ (1907)
3841 10 (PET-CT or PET CT).ti,ab,kw. (2438)
3842 11 ((positron emission or positron-emission) adj2 (computed tomography or computed-
3843 tomography)).ti,ab,kw. (1258)
3844 12 or/9-11 (4012)
3845 13 exp magnetic resonance imaging/ (10820)
3846 14 (magnetic resonance imag\$ or MRI or MR imag\$).ti,ab,kw. (38413)
3847 15 13 or 14 (41092)
3848 16 8 or 12 or 15 (109338)
3849 17 exp lung neoplasm/ (10300)
3850 18 (lung and (neoplasm\$ or cancer\$)).ti,ab,kw. (28155)
3851 19 (pulmonary and (neoplasm\$ or cancer\$)).ti,ab,kw. (4178)
3852 20 (lung adj (cancer or tumor or tumour or neoplasm)).ti,ab,kw. (23085)
3853 21 (pulmonary adj (cancer or tumor\$ or tumour\$ or neoplasm\$)).ti,ab,kw. (59)
3854 22 or/17-21 (31325)
3855 23 "sensitivity and specificity"/ (10779)
3856 24 "predictive value of tests"/ (8745)
3857 25 roc curve/ (1678)
3858 26 false negative reactions/ (340)
3859 27 false positive reactions/ (522)
3860 28 (sensitivity or specificity or diagnostic\$).ti,ab,kw. (106126)
3861 29 (predictive adj3 value\$).ti,ab,kw. (8879)
3862 30 (roc adj (curve\$ or analy\$)).ti,ab,kw. (2811)
3863 31 receiver operating characteristic\$.ti,ab,kw. (5424)
3864 32 (true adj (positiv\$ or negativ\$)).ti,ab,kw. (455)
3865 33 (false adj (positiv\$ or negativ\$)).ti,ab,kw. (3273)
3866 34 or/23-33 (125178)
3867 35 exp metastases/ (6518)
3868 36 metast\$.ti,ab,kw. (48166)
3869 37 secondary.ti,ab,kw. (346277)
3870 38 (node or nodal\$).ti,ab,kw. (16221)
3871 39 or/35-38 (388235)
3872 40 (low dose or low-dose).ti,ab,kw. (29863)
3873 41 5 and 8 and 40 (125)
3874 42 incident\$.ti,ab,kw. (8513)

3875 43 5 and 42 (31)
 3876 44 41 or 43 (149)
 3877 45 (previous adj (history or occurrence)).ti,ab,kw. (1683)
 3878 46 (prior adj (history or occurrence)).ti,ab,kw. (1116)
 3879 47 (earlier adj (history or occurrence)).ti,ab,kw. (32)
 3880 48 or/45-47 (2814)
 3881 49 5 and 48 (1)
 3882 50 5 and 16 and 22 and 34 (203)
 3883 51 biops\$.ti,ab,kw. (34436)
 3884 52 5 and 51 (120)
 3885 53 5 and 12 and 39 (7)
 3886 54 44 or 49 or 50 or 52 or 53 (348)
 3887 55 limit 54 to english language (334)
 3888

3889 **Cochrane Database of Systematic Reviews (CDSR)**

3890 **Search 1**

3891 **Search via OVID**

3892 **Search date 26 May 2023**

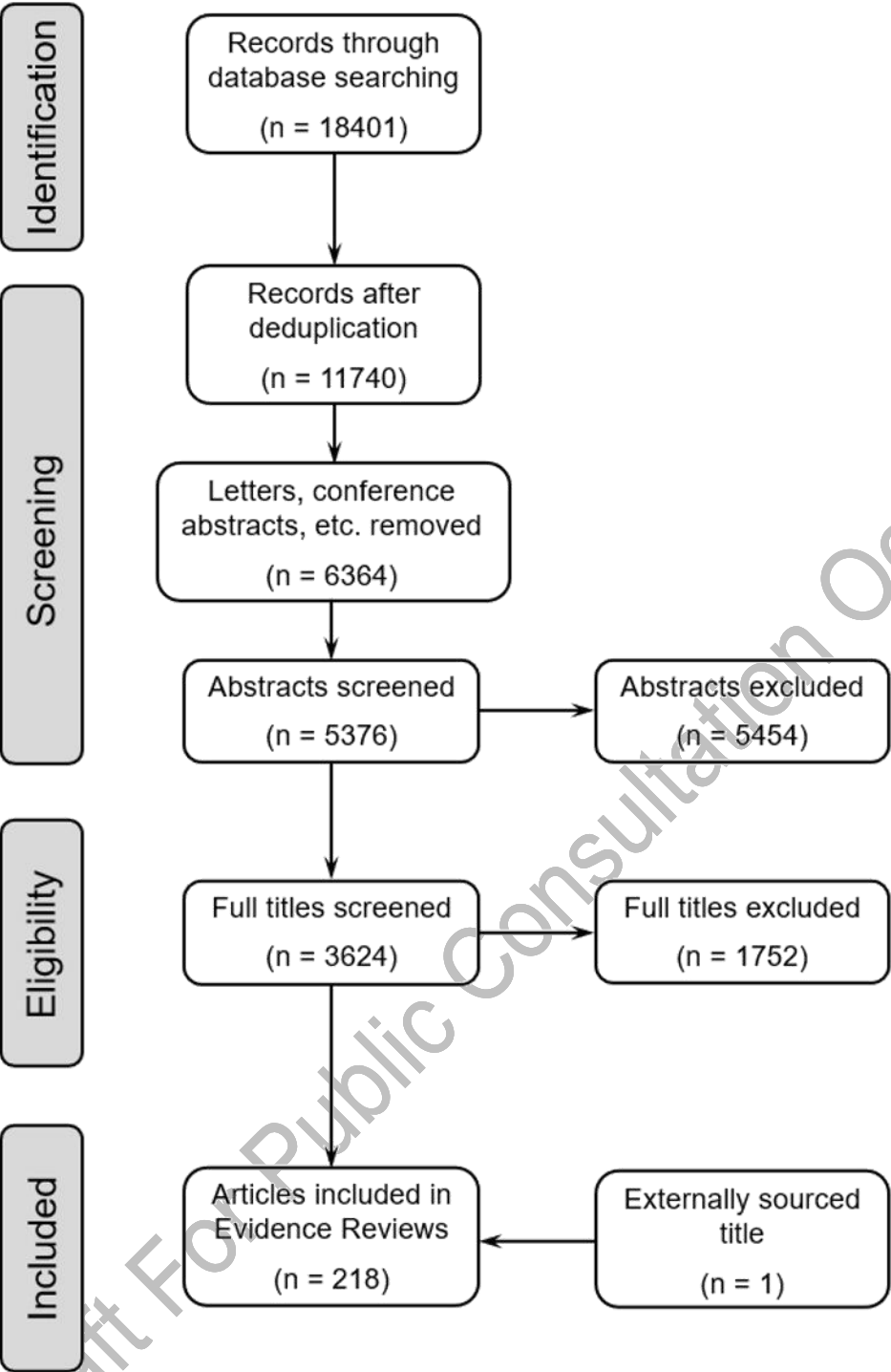
3893 **Records identified = 0**

3894 Database: Cochrane Central Register of Controlled Clinical Trials

3895 **Search strategy**

3896 The Cochrane Central Register of Controlled Clinical Trials (CENTRAL) Search 1 strategy was used.

3897



3899
3900
3901
3902
3903
3904
3905
3906

3908 **Contents**

3909	Research recommendations (per Questions 1 – 9)	202
3910	Q1 Investigative approach following LDCT screening or incidental detection	202
3911	Q2 Likelihood of lung cancer following a previous history of non-lung cancer	202
3912	Q3 Baseline diagnostic approach – solid nodules	202
3913	Q4 Surveillance – solid nodules	202
3914	Q5 Baseline diagnostic approach – sub-solid nodules	202
3915	Q6 Surveillance – sub-solid nodules	203
3916	Q7 Pulmonary nodule biopsy for diagnosing lung cancer	203
3917	Q8 Pre-treatment biopsy versus no pre-treatment biopsy	203
3918	Q9 FDG PET-CT staging	203
3919	Further research recommendations (across the questions)	203

3920

3921

3922

3923

3924

3925

3926

3927

3928

3929

3930 **Research recommendations** (per Questions 1 – 9)

3931 **Question 1 Investigative approach following low dose computed tomography (LDCT) screening or**
3932 **incidental detection**

- 3933 ▪ Further research is needed to determine whether the risk of malignancy differs between screening-
3934 detected and incidentally detected pulmonary nodules.

3935 **Question 2 Likelihood of lung cancer following a previous history of non-lung cancer**

- 3936 ▪ Further research is needed to determine whether a previous history of non-lung cancer is an independent
3937 predictor of primary lung cancer in patients with pulmonary nodules.

3938 **Question 3 Baseline diagnostic approach – solid nodules**

- 3939 ▪ Further research is needed to establish the diagnostic accuracy of nodule diameter, nodule volume, and
3940 the Brock risk prediction model for identifying lung cancer in solid pulmonary nodules.
- 3941 ▪ Further research is needed to identify the most informative PET-CT and MRI imaging biomarkers for
3942 diagnosing lung cancer in solid pulmonary nodules.
- 3943 ▪ Further research is needed to identify imaging biomarkers associated with malignancy in the following
3944 solid nodule subgroups: nodules without recent relevant imaging, newly appeared nodules since recent
3945 imaging, peri-cystic lesions, and nodules presenting as consolidation.

3946 **Question 4 Surveillance – solid nodules**

- 3947 ▪ Further research is needed to determine the optimal volume doubling time (VDT) threshold and evaluate
3948 its diagnostic accuracy for identifying malignant solid pulmonary nodules.
- 3949 ▪ Further research is needed to evaluate the diagnostic accuracy of interval CT changes (morphological
3950 features, diameter change, mass doubling time (MDT), and volume change) for identifying lung cancer in
3951 solid pulmonary nodules.
- 3952 ▪ Research is needed to compare emerging artificial intelligence (AI)-based approaches with conventional
3953 VDT thresholds for diagnosing lung cancer in solid pulmonary nodules.

3954 **Question 5 Baseline diagnostic approach – sub-solid nodules**

- 3955 ▪ Further research is needed to determine the diagnostic accuracy of maximal nodule diameter, nodule
3956 volume, CT density, air bronchograms, and a clear lung-tumour interface for identifying lung cancer in
3957 ground-glass pulmonary nodules.
- 3958 ▪ Further research is needed to determine the diagnostic accuracy of maximal nodule diameter, nodule
3959 volume, CT density, upper-lobe location, spiculation, bubble lucencies, air bronchograms, and a clear lung-
3960 tumour interface for identifying lung cancer in part-solid pulmonary nodules.
- 3961 ▪ Further research is needed to establish the diagnostic accuracy of risk prediction models (Brock, Mayo,
3962 VA and/or UKLS) for diagnosing lung cancer in sub-solid pulmonary nodules.
- 3963 ▪ Further research is needed to determine whether imaging-defined malignant sub-solid nodules represent
3964 clinically significant invasive lung cancer requiring treatment.
- 3965 ▪ Research is needed to evaluate the relative contribution of imaging biomarkers and clinical risk prediction
3966 models in guiding management decisions for sub-solid pulmonary nodules.

3967 **Question 6 Surveillance – sub-solid nodules**

- 3968 ▪ Further research is needed to evaluate the diagnostic accuracy of interval CT changes (morphological
3969 features, diameter growth, volume doubling time (VDT), mass doubling time (MDT), and volume change)
3970 for identifying lung cancer in sub-solid pulmonary nodules.
- 3971 ▪ Research is needed to determine the likelihood of invasive disease in growing pure ground-glass nodules,
3972 with particular emphasis on the risks of overdiagnosis and overtreatment.

3973 **Question 7 Pulmonary nodule biopsy for diagnosing lung cancer**

- 3974 ▪ Further research is needed to establish the diagnostic accuracy of percutaneous and bronchoscopic
3975 biopsy techniques across solid and sub-solid pulmonary nodule subgroups.
- 3976 ▪ Randomised studies are needed to assess the diagnostic accuracy and diagnostic yield of different
3977 pulmonary nodule biopsy modalities.

3978 **Question 8 Pre-treatment biopsy versus no pre-treatment biopsy**

- 3979 ▪ Further research is needed to determine whether pre-treatment biopsy improves clinical outcomes,
3980 including rates of benign resection, mortality, morbidity, quality of life, and recurrence, in adults with
3981 pulmonary nodules being considered for curative-intent treatment.

3982 **Question 9 FDG PET-CT staging**

- 3983 ▪ Further research is needed to determine the impact of FDG PET-CT on staging and treatment decision-
3984 making in patients with solid, sub-solid, and sub-centimetre pulmonary nodules being considered for
3985 curative-intent treatment.
- 3986 ▪ Research is needed to establish the minimum nodule size threshold at which FDG PET-CT provides
3987 clinically meaningful benefit.

3988

3989

3990 **Further research recommendations** (across the questions)

- 3991 ▪ What are the outcomes for solid nodules with a Herder risk <50%, managed with CT surveillance?
- 3992 ▪ What is the risk of lung cancer in new nodules that appear within 6 months, compared to those at 3 and
3993 12 months?
- 3994 ▪ What is the optimal management of pericystic lesions?
- 3995 ▪ What is the accuracy of altered morphology (bubble lucency, air bronchogram, increased density) for
3996 diagnosing invasive lung cancer in sub-solid nodules without a solid component?
- 3997 ▪ Does the combination of growth and FDG avidity for solid nodules improve discrimination for invasive lung
3998 cancer over growth alone?
- 3999 ▪ What is the incremental clinical utility of using artificial intelligence algorithms for predicting malignancy in
4000 nodule management?
- 4001 ▪ What is the diagnostic accuracy of mass doubling time for diagnosing lung cancer in sub-solid pulmonary
4002 nodules?
- 4003 ▪ Can nodule follow-up intervals be further personalised?
- 4004 ▪ What is the clinical utility of early biopsy, compared to existing surveillance strategies, in diagnosis and
4005 management of pulmonary nodules?
- 4006 ▪ Randomised studies are needed to assess the diagnostic accuracy and yield of different pulmonary nodule
4007 biopsy modalities.

- 4008
4009
- Does pre-treatment biopsy improve clinical outcomes in adults with persistent sub-solid pulmonary nodules?
- 4010
4011
- What is the optimal size threshold at which PET-CT is beneficial, for solid and sub-solid pulmonary nodules?
- 4012
4013
4014
- Decision-support studies are required to optimise how clinicians explain uncertain cancer risk, surveillance and competing harms.

Draft For Public Consultation October 2026