Section	Ref no	Bibliographic citation	Study type	Ev lev	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Intro	1	Travis WD, Brambilla E, Noguchi M, et al: International association for the study of lung cancer/american thoracic society/european respiratory society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol 6:244-85, 2011		N/A								Evidence statement not needed
Intro	2	National Lung Screening Trial Research T, Aberle DR, Adams AM, et al: Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 365:395-409, 2011	Case series	3	53439	Asymptomatic men and women, 55 to 74 years of age, who had a history of at least 30 pack-years of cigarette smoking and who were either current smokers or had been smokers within the previous 15 years.	not applicable	not applicable	12 months	not applicable	not applicable	General comments: Describes baseline screen results, investingations and histology in the CT and CXR arms of the NLST. Nodule prevalence reported by size. Prevalence 4-30mm nodules 25.9% in CT arm and 6.9% in CXR arm. Lung cancer diagnosed in 1.1% CT and 0.7% CXR groups.
1 - Route to diagnosis	3	Greenberg AK, Lu F, Goldberg JD, et al: CT scan screening for lung cancer: Risk factors for nodules and malignancy in a high-risk urban cohort. PLoS ONE 7 (7), 2012	Case series	3	1182	Volunteers over age of 50 years with signficant smoking history.	not applicable	not applicable	Not recorded	not applicable	not applicable	General comments: Nodule prevalence 52.9%. Lung cancer prevalence 2.53%. Logistic regression analysis suggested increasing age, male gender and emphysema were significant predictors of nodule on baseline CT
1 - Route to diagnosis	4	Harthun NL, Lau CL: The incidence of pulmonary neoplasms discovered by serial computed tomography scanning after endovascular abdominal aortic aneurysm repair. Journal of Vascular Surgery 53:738-41, 2011	Case series	3	138	Consecutive patients undergoing CT follow up after endovascular repair abdominal aortic aneurysm.	not applicable	not applicable	2 years (average)	not applicable	not applicable	General comments: Age not reported. Lung nodule investigation and follow up not standardised. 7 patients underwent thoracic surgery. Nodule prevalence 18%. Lung cancer prevalence 4%.
1 - Route to diagnosis	5	Henschke CI, McCauley DI, Yankelevitz DF, et al: Early Lung Cancer Action Project: overall design and findings from baseline screening. Lancet 354:99-105, 1999	Case series	3	1000	Volunteers over age of 50 years with signficant smoking history fit enough to undergo thoracic surgery.	not applicable	not applicable	Not recorded	not applicable	not applicable	General comments: Confirmed low dose CT detects many more nodules than chest X-ray. Nodule prevalence 23%. Lung cancer prevalence 2.7%.
1 - Route to diagnosis	6	Iribarren C, Hlatky MA, Chandra M, et al: Incidental Pulmonary Nodules on Cardiac Computed Tomography: Prognosis and Use. American Journal of Medicine 121 (11):989-996, 2008	Case series	3	459	Control group ADVANCE study (population based determinants of coronary artery disease) age 60-69.	not applicable	not applicable	Not reported	not applicable	not applicable	General comments: Only healthy individuals included in this study. Nodule prevalence 18.0%.
1 - Route to diagnosis	7	Khokhar S, Vickers A, Moore MS, et al: Significance of non-calcified pulmonary nodules in patients with extrapulmonary cancers. Thorax 61:331-6, 2006	Case series	3	151	Consecutive oncology patients referred for nodule management. Lung cancer, haematological malignancy and non-melanoma skin cancer excluded.	not applicable	not applicable	Not recorded	not applicable	not applicable	General comments: Patients assigned to four groups according to risk of lung metastases. Nodule prevalence 100%. Lung cancer prevalence 21%.Nodule size and tobacco (not primary site group) were significant in multivariate analysis.
1 - Route to diagnosis	8	Margolis ML, Howlett P, Bubanj R: Pulmonary nodules in patients with esophageal carcinoma. Journal of Clinical Gastroenterology 26:245-8, 1998	Case series	3	116	Consecutive biopsy proven oesophageal cancer patients	not applicable	not applicable	Not recorded	not applicable	not applicable	General comments: Diagnosis established in 86% of SPNs. Included lesions up to 6cm. Multiple nodules not biopsied. Nodule prevalence 22%. Lung cancer prevalence 3.4%.
1 - Route to diagnosis	9	Markowitz SB, Miller A, Miller J, et al: Ability of low-dose helical CT to distinguish between benign and malignant noncalcified lung nodules. Chest 131:1028-34, 2007	Case series	3	4401	Active or retired workers at three Uranium plants.	not applicable	not applicable	Not recorded	not applicable	not applicable	General comments: Included significant proportion of never smokers. Nodule prevalence 22.3%. Lung cancer prevalence 0.75%.
1 - Route to diagnosis	10	Menezes RJ, Roberts HC, Paul NS, et al: Lung cancer screening using low-dose computed tomography in at-risk individuals: the Toronto experience. Lung Cancer 67:177-83, 2010	Case series	3	3352	Volunteers over age of 50 years with signficant smoking history in good health.	not applicable	not applicable	Not recorded	not applicable	not applicable	General comments: Nodule prevalence 18.0%. Lung cancer prevalence 1.9%.
1 - Route to diagnosis	11	Mery CM, Pappas AN, Bueno R, et al: Relationship between a history of antecedent cancer and the probability of malignancy for a solitary pulmonary nodule. Chest 125:2175-81, 2004	Case series	3	1104	Patients undergoind resection for solitary pulmonary nodules	not applicable	not applicable	Not recorded	not applicable	not applicable	General comments: Resected lung nodule malignancy rate 63% no previous cancer, 79% previous extrapulmonary cancer, 82% previous lung cancer. Age, smoking & histology predictive factors.
1 - Route to diagnosis	12	New York Early Lung Cancer Action Project I: CT Screening for lung cancer: diagnoses resulting from the New York Early Lung Cancer Action Project. Radiology 243:239-49, 2007	Case series	3	6295	Volunteers over age of 60 years with signficant smoking history fit enough to undergo thoracic surgery.	not applicable	not applicable	Not recorded	not applicable	not applicable	General comments: Nodule prevalence 41.8 %. Lung cancer prevalence 1.6%.
1 - Route to diagnosis	13	Quint LE, Park CH, Iannettoni MD: Solitary pulmonary nodules in patients with extrapulmonary neoplasms. Radiology 217:257-61, 2000	Case series	3	149	Consecutive patients with a solitary lung nodule and extra pulmonary malignancy	not applicable	not applicable	Not recorded	not applicable	not applicable	General comments: Demographics for overall study poplution not reported. Patients assigned to four groups according to risk of lung metastases. Nodule histology available in 96%. Lung cancer prevalence 50.3%.
1 - Route to diagnosis	14	Smyth EC, Hsu M, Panageas KS, et al: Histology and outcomes of newly detected lung lesions in melanoma patients. Annals of Oncology 23:577-82, 2012	Case series	3	229	Melanoma patients with a lung nodule that had undergone percutanous biopsy (database review)	not applicable	not applicable	Not recorded	not applicable	not applicable	General comments: Only includes melanoma patients with biopsied nodules so open to selection bias. 69% of the secondary cancers were melanoma. Multivariate analysis demonstrated that more advanced stage melanoma and multiple nodules predicted melanoma metastases.
1 - Route to diagnosis	15	Swensen SJ, Jett JR, Sloan JA, et al: Screening for lung cancer with low-dose spiral computed tomography. American Journal of Respiratory & Critical Care Medicine 165:508-13, 2002	Case series	3	1520	Volunteers over age of 50 years with signficant smoking history fit enough to undergo thoracic surgery.	not applicable	not applicable	Not recorded	not applicable	not applicable	General comments: Nodule prevalence 26%. Lung cancer prevalence 1.7%.
1 - Route to diagnosis	16	Wilson DO, Weissfeld JL, Fuhrman CR, et al: The Pittsburgh Lung Screening Study (PLuSS): outcomes within 3 years of a first computed tomography scan. American Journal of Respiratory & Critical Care Medicine 178:956-61, 2008	Case series	3	3642	Volunteers over age 50-79 years with signficant smoking history.	not applicable	not applicable	Not recorded	not applicable	not applicable	General comments: Nodule prevalence 41%. Lung cancer prevalence 1.46%.
1 - Route to diagnosis	17	Kasirajan K, Dayama A: Incidental findings in patients evaluated for thoracic aortic pathology using computed tomography angiography. Ann Vasc Surg 26:306-11, 2012	Case series	3	242	Consecutive patients undergoing endovascular repair or CT follow up of thoracic aortic disease.	not applicable	not applicable	Not reported	not applicable	not applicable	General comments: Lung nodules followed up as per Fleishner guidelines. Nodule prevalence 18.25. Lung cancer prevalence 1.1%.
1 - Route to diagnosis	18	Ekeh AP, Walusimbi M, Brigham E, et al: The prevalence of incidental findings on abdominal computed tomography scans of trauma patients. J Emerg Med 38:484-9, 2010	Case series	3	3113	Consecutive patients undergoing CT abdomen for trauma.	not applicable	not applicable	Not reported	not applicable	not applicable	General comments: Demographics not reported. Nodule prevalence 2.2%. Outcome of lung nodules not reported.

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1 - Route to diagnosis	19	Lehman SJ, Abbara S, Cury RC, et al: Significance of cardiac computed tomography incidental findings in acute chest pain. Am J Med 122:543-9, 2009	Case series	3	395	Patient undergoing CT coronary angiography as part of the Rule Out MI using CT study.	not applicable	not applicable	Not reported	not applicable	not applicable	General comments: Nodule prevalence 23.8%. Further investigation of lung nodules projected using Fleishner guidelines.
1 - Route to diagnosis	20	Machaalany J, Yam Y, Ruddy TD, et al: Potential clinical and economic consequences of noncardiac incidental findings on cardiac computed tomography. J Am Coll Cardiol 54:1533-41, 2009	Case series	3	966	Consecutive patients undergoing CT coronary angiograpy. 98% outpatients.	not applicable	not applicable	18.4 months	not applicable	not applicable	General comments: Lung nodule investigation and follow up not standardised. Nodule prevalence 6.4%. Lung cancer prevalence 0.2%.
1 - Route to diagnosis	21	Hall WB, Truitt SG, Scheunemann LP, et al: The prevalence of clinically relevant incidental findings on chest computed tomographic angiograms ordered to diagnose pulmonary embolism. Arch Intern Med 169:1961-5, 2009	Case series	3	589	Consecutive patients undergoing CTPA to rule out PE.	not applicable	not applicable	Not reported	not applicable	not applicable	General comments: Nodule prevalence 22%. Outcome of lung nodules not reported.
1 - Route to diagnosis	22	Barrett TW, Schierling M, Zhou C, et al: Prevalence of incidental findings in trauma patients detected by computed tomography imaging. Am J Emerg Med 27:428-35, 2009	Case series	3	3092	Consecutive patients admitted to major trauma centre	not applicable	not applicable	Not recorded	not applicable	not applicable	General comments: Nodule prevalence 6.3%. Lung nodule outcome not recorded.
1 - Route to diagnosis	23	National Lung Screening Trial Research T, Church TR, Black WC, et al: Results of initial low-dose computed tomographic screening for lung cancer. N Engl J Med 368:1980-91, 2013	Case series	3	53439	Asymptomatic men and women, 55 to 74 years of age, who had a history of at least 30 pack-years of cigarette smoking and who were either current smokers or had been smokers within the previous 15 years.	not applicable	not applicable	12 months	not applicable	not applicable	Describes baseline screen results, investingations and histology in the CT and CXR arms of the NLST. Nodule prevalence reported by size. Prevalence 4-30mm nodules 25.9% in CT arm and 6.9% in CXR arm. Lung cancer diagnosed in 1.1% CT and 0.7% CXR groups.
1 - Route to diagnosis	24	Bastarrika G, Garcia-Velloso MJ, Lozano MD, et al: Early lung cancer detection using spiral computed tomography and positron emission tomography. American Journal of Respiratory & Critical Care Medicine 171:1378-83, 2005	Case series	3	911	Volunteers over age of 40 years with signficant smoking history.	not applicable	not applicable	Not recorded	not applicable	not applicable	General comments: Study employed PET to reduce nodule follow up burden. Nodule prevalence 31%. Lung cancer prevalence 1.54%.
1 - Route to diagnosis	25	Blanchon T, Bréchot JM, Grenier PA, et al: Baseline results of the Depiscan study: a French randomized pilot trial of lung cancer screening comparing low dose CT scan (LDCT) and chest X-ray (CXR), Lung cancer (Amsterdam, Netherlands), 2007, pp 50-8	Case series	3	765	Volunteers over age 50-75 years with signficant smoking history.	not applicable	not applicable	Not recorded	not applicable	not applicable	General comments: Nodule prevalence 45.2%. Lung cancer prevalence 2.38%. Pilot trial demonstrating that non-calcified nodules are 10 [6.36—17.07] times more often detected from LDCT than from CXR.
1 - Route to diagnosis	26	Cardinale L, Cortese G, Borasio P, et al: Low dose CT in early lung cancer diagnosis: Prevalence data. RADIOLOGIA MEDICA 110:532-43, 2005	Case series	3	519	Volunteers over age of 55 years with signficant smoking history.	not applicable	not applicable	Not recorded	not applicable	not applicable	General comments: Patient demographics not reported. Nodule prevalence 22%. Lung cancer prevalence 1.1%.
1 - Route to diagnosis	27	Clin B, Luc A, Morlais F, et al: Pulmonary nodules detected by thoracic computed tomography scan after exposure to asbestos: Diagnostic significance. International Journal of Tuberculosis and Lung Disease 15 (12):1707-1713, 2011	Case series	3	5662	Retired asbestos exposed volunteers attending for CT scan.	not applicable	not applicable	Not recorded	not applicable	not applicable	General comments: Highly selected population. Non-smokers included. Nodule prevalence 17%.
1 - Route to diagnosis	28	Diederich S, Wormanns D, Semik M, et al: Screening for early lung cancer with low-dose spiral CT: prevalence in 817 asymptomatic smokers. Radiology 222:773-81, 2002	Case series	3	817	Volunteers over age of 40 years with signficant smoking history.	not applicable	not applicable	Not recorded	not applicable	not applicable	General comments: Nodule prevalence 43%. Lung cancer prevalence 1.2%.Higher incidence of nodule detection may be related to higher sensitivity CT protocol.
1 - Route to diagnosis	29	MacRedmond R, McVey G, Lee M, et al: Screening for lung cancer using low dose CT scanning: results of 2 year follow up. Thorax 61:54-6, 2006	Case series	3	449	Volunteers over age of 50 years with signficant smoking history.	not applicable	not applicable	Not recorded	not applicable	not applicable	General comments: Nodule prevalence 20.7%. Lung cancer prevalence 1.3%.Histology reported as NSCLC.
1 - Route to diagnosis	30	Novello S, Fava C, Borasio P, et al: Three-year findings of an early lung cancer detection feasibility study with low-dose spiral computed tomography in heavy smokers. Annals of Oncology 16:1662-6, 2005	Case series	3	520	Volunteers over age of 55 years with signficant smoking history.	not applicable	not applicable	5 years	not applicable	not applicable	General comments: Feasibility study. Nodule prevalence 46%. Lung cancer prevalence 1%.
1 - Route to diagnosis	31	Pedersen JH, Ashraf H, Dirksen A, et al: The danish randomized lung cancer ct screening trial- overall design and results of the prevalence round. Journal of Thoracic Oncology 4 (5):608-614, 2009	Case series	3	4104	Volunteer smokers age 50-70 with life expectancy of 10 years.	not applicable	not applicable	Not recorded	not applicable	not applicable	General comments: Reported incidence by age group and smoking history as cigarettes per day. Nodule prevalence 18.1%. Lung cancer prevalence 0.8%.Results planned to be pooled with NELSON trial.
1 - Route to diagnosis	32	Tiitola M, Kivisaari L, Huuskonen MS, et al: Computed tomography screening for lung cancer in asbestos-exposed workers. Lung Cancer 35:17-22, 2002	Case series	3	602	Volunteers over age 45 years with asbestos related lung disease.	not applicable	not applicable	Not recorded	not applicable	not applicable	General comments: Heterogenous patient group including pleural plaques and asbestosis. Nodule prevalence 18.4%. Lung cancer prevalence 8.8%.
1 - Route to diagnosis	33	van Klaveren RJ, Oudkerk M, Prokop M, et al: Management of lung nodules detected by volume CT scanning, The New England Journal of Medicine, 2009, pp 2221-9	Diagnostic accuracy	2+	7557	The mean (±SD) age of the screened participants was 59±6 years, and the mean number of pack-years smoked was 42±19; a total of 16% of the participants were women. Dutch Belgian	None		5 years	Proportion of patients with VDT <400 days who had cancer	The authors describe the early findings of the NELSON trial. This employed volumetry and provides evidence for the effectiveness of this as an observational approach to nodules. 2236 indeterminate nodules were discovered in 1451 patients at first line screening. Of those rescanned at 100+/-19 days, 129 nodules (5.8%) had VDT<400/7, 518 (23.2%) grew but with VDT>400/7, 1049 (46.9%) didn't grow and 486 (21.7%) resolved. One interval cancer with VDT>600/7 was seen between 1st and 2nd round - stage IV adeno. At second round, 71 (0.8%) existing nodules had VDT<400/7 - positive, 163 (1.8%) existing nodules had VDT 400-600/7, 2429 (26.2%) existing nodules had VDT>600/7, 3638 (39.2%) didn't grow and 2432 (26.2%) had resolved. 549 (5.9%) were not followed up.	
1 - Route to diagnosis	34	Veronesi G, Bellomi M, Mulshine JL, et al: Lung cancer screening with low-dose computed tomography: a non-invasive diagnostic protocol for baseline lung nodules. Lung Cancer 61:340-9, 2008	Case series	3	5201	Volunteers over age of 50 years with signficant smoking history.	not applicable	not applicable	Not recorded	not applicable	not applicable	General comments: Nodule prevalence 52.9%. Lung cancer prevalence 1.5%.
1 - Route to diagnosis	35	Keogan MT, Tung KT, Kaplan DK, et al: The significance of pulmonary nodules detected on CT staging for lung cancer. Clinical Radiology 48:94-6, 1993	Case series	3	551	Patients referred to tertiary centre for lung cancer staging.	not applicable	not applicable	24-48 months	not applicable	not applicable	General comments: Nodule prevalence 16%. Lung cancer prevalence 11%.Follow up data only available on 25 patients.
1 - Route to diagnosis	36	Chong S, Lee KS, Chung MJ, et al: Lung cancer screening with low-dose helical CT in Korea: experiences at the Samsung Medical Center. Journal of Korean Medical Science 20:402-8, 2005	Case series	3	6406	Volunteers over age 45 years.	not applicable	not applicable	Not recorded	not applicable	not applicable	General comments: Included non smokers. Nodule prevalence 35%. Lung cancer prevalence 0.57%.

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1 - Route to diagnosis	37	Hanamiya M, Aoki T, Yamashita Y, et al: Frequency and significance of pulmonary nodules on thin-section CT in patients with extrapulmonary malignant neoplasms. European Journal of Radiology 81:152-7, 2012	Case series	3	308	Consecutive patients undergoing staging CT for extrapulmonary carcinoma or sarcoma.	not applicable	not applicable	Not recorded	not applicable	not applicable	General comments: 28 nodules deemed malignant; 6 based on biopsy, 22 on interval increase on CT. Melanoma, sarcoma and testicular cancer more likely malignant (p<0.05), Nodule size and distance from pleura predictive of malignancy (P<0.001) in multivariate analysis.
1 - Route to diagnosis	38	Kim YH, Lee KS, Primack SL, et al: Small pulmonary nodules on CT accompanying surgically resectable lung cancer: likelihood of malignancy. Journal of Thoracic Imaging 17:40-6, 2002	Case series	3	141	Consecutive patients undergoing surgery for NSCLC with CT follow up available for 24 months.	not applicable	not applicable	33 months (average).	not applicable	not applicable	General comments: Nodule prevalence 44%. Lung cancer prevalence 3%. Reported nodule prevalence is in the non-primary lobe on the pre-op CT and was not resected at the time of surgery. Study subject to selection bias as only included patients with follow CT data (141 of 582 undergoing resection).
1 - Route to diagnosis	39	Nawa T, Nakagawa T, Kusano S, et al: Lung cancer screening using low-dose spiral CT: results of baseline and 1-year follow-up studies. Chest 122:15-20, 2002	Case series	3	7956	Employees at Hitachi undergoing CT as part of occupational lung cancer screening.	not applicable	not applicable	Not recorded	not applicable	not applicable	General comments: Highly selected population. Non-smokers included. Nodule prevalence 36%. Lung cancer prevalence 0.5%.
1 - Route to diagnosis	40	Yuan Y, Matsumoto T, Hiyama A, et al: The probability of malignancy in small pulmonary nodules coexisting with potentially operable lung cancer detected by CT. European Radiology 13:2447-53, 2003	Case series	3	223	Consecutive patients undergoing surgery for NSCLC and SCLC. Patients with more than 2 nodules excluded.	not applicable	not applicable	Not recorded	not applicable	not applicable	General comments: 50% malignant nodules in the tumour lobe. 43% benign nodules in the contralateral lobe. Does not report nodule malignant risk by site.
1 - Route to diagnosis	41	Bendix K, Jensen JM, Poulsen S, et al: Coronary dual source multi detector computed tomography in patients suspected of coronary artery disease: prevalence of incidental extra-cardiac findings. Eur J Radiol 80:109-14, 2011	Case series	3	1383	Consecutive patients referred for CT coronary angiograpy.	not applicable	not applicable	Not reported	not applicable	not applicable	General comments: Nodule prevalence 11%. Outcome of lung nodules not reported.
1 - Route to diagnosis	42	Foley PW, Hamaad A, El-Gendi H, et al: Incidental cardiac findings on computed tomography imaging of the thorax. BMC Res Notes 3:326, 2010	Case series	3	100	Consecutive patients undergoing CTPA.	not applicable	not applicable	Not reported	not applicable	not applicable	General comments: Demographics not reported. Nodule prevalence 14%. Outcome of lung nodules not reported.
1 - Route to diagnosis	43	Yorgun H, Kaya EB, Hazirolan T, et al: Prevalence of incidental pulmonary findings and early follow-up results in patients undergoing dual-source 64-slice computed tomography coronary angiography. J Comput Assist Tomogr 34:296-301, 2010	Case series	3	1206	Consecutive patients admitted for cardiovascular evaluation including cardiac CT.	not applicable	not applicable	Not reported	not applicable	not applicable	General comments: Lung nodule investigation and follow up not standardised. Nodule prevalence 7.5%. Lung cancer prevalence 1.2%.
1 - Route to diagnosis	44	Marchianò A, Calabrò E, Civelli E, et al: Pulmonary nodules: volume repeatability at multidetector CT lung cancer screening, Radiology, 2009, pp 919-25	Case series	3	101	Consecutive participants enrolled into screening study who underwent repeat low-dose CT after 3 months and had at least one indeterminate nodule with a volume of more than 60 mm(3) (diameter of 4.8 mm or greater). were considered	not applicable	Malignant and benign nodules.	12 months	not applicable	not applicable	One hundred one subjects (predominantly men) with 233 eligible nodules (mean volume, 98.3 mm(3)). The 95% confidence interval for difference in measured volumes was in the range of +/-27%.
2 - Initial assessment	45	de Hoop B, van Ginneken B, Gietema H, et al: Pulmonary perifissural nodules on CT scans: rapid growth is not a predictor of malignancy. Radiology 265:611-6, 2012	Prospective randomised trial of CT screening	2+	Patients with perifissural nodules (794 PFNs)	50-75 with smoking history	CT screening	No imaging		Risk of cancer	Nodules were classified as typical PFN (fissure-attached homogeneous, solid nodule with smooth margins and oval, lentiform or triangular shape) atypical PFN (as above but no fissure, or fissure-attached but convex on one side and rounded on other). None of 794 PFNs were malignant. 123 of 794 grew during f/u and 66 of these had VDT<400/7 - but were still not malignant. One was resected and was an intrapulmonary lymph node.	Identifies group of nodules that can be safely ignored and do not require ongoing follow-up
2 - Initial assessment	46	McWilliams A, Tammemagi MC, Mayo JR, et al: Probability of cancer in pulmonary nodules detected on first screening CT. N Engl J Med 369:910-9, 2013	RCT	1+	1871 and 1090	Consecutive patients enrolled into the PanCan and BCCA screening studies.	not applicable	Malignant and benign nodules.	12 months	Risk of cancer	Validationmodelof risk of malignancy showing PSN independent predictor and pGGN actually less like malignant when other factors such as size are included 1105 and 467 SSN respectively	Very large study of the predictors of malignancy in a wide range of nodule sizes. All patients had 3yr risk of cancer of at least 2%.
2 - Initial assessment	47	Ahn MI, Gleeson TG, Chan IH, et al: Perifissural nodules seen at CT screening for lung cancer. Radiology 254:949-56, 2010	Case series	3	146	Consecutive participants enrolled into screening study.	not applicable	Malignant and benign nodules.	7 years	not applicable	not applicable	Retrospective review of registry data. Participants at high risk of cancer (50-75 years; > 30 pack-year smoking history)
2 - Initial assessment	48	Franquet T, Muller NL, Gimenez A, et al: Infectious pulmonary nodules in immunocompromised patients: usefulness of computed tomography in predicting their etiology. Journal of Computer Assisted Tomography 27:461-8, 2003	Case series	3	78	Immunocompromised patients with lung nodules on CT	not applicable	Different infectious nodules	Not reported	not applicable	not applicable	Highly selected patient population.
2 - Initial assessment	49	Gould MK, Ananth L, Barnett PG, et al: A clinical model to estimate the pretest probability of lung cancer in patients with solitary pulmonary nodules. Chest 131:383-8, 2007	Case series	3	532	Veterans referred for investigation of pulmonary nodules	Risk prediction	Malignant and benign nodules.	2 years	not applicable	not applicable	Nodules identified on chest X-ray. Nearly all male, smoker or former smokers.
2 - Initial assessment	50	Gurney JW: Determining the likelihood of malignancy in solitary pulmonary nodules with Bayesian analysis. Part I. Theory. Radiology 186:405-13, 1993	literature review	3	Not reported	Not reported	Bayesian analysis	Malignant and benign nodules.	Not reported	not applicable	For malignant nodules the most important radiographic findings were thickness of cavity wall, spicular edge and size over 3cm. For benign nodules the most important characteristics were benign growth rate and pattern of calcification.	Theoretical study using previously reported clinical and radiological characteristics to derive liklihood ratios using Bayes theorum.
2 - Initial assessment	51	Gurney JW, Lyddon DM, McKay JA: Determining the likelihood of malignancy in solitary pulmonary nodules with Bayesian analysis. Part II. Application. Radiology 186:415-22, 1993	Case series	3	66	Not reported	Bayesian analysis	Malignant and benign nodules.	Not reported	Risk of cancer	The readers using Bayesian analysis performed significantly better than the expert readers (P < .05) when individual radiographs were considered and when all radiologic studies were combined. In addition, the readers using Bayesian analysis misclassified fewer malignant nodules as benign (mean, 6.5) than did the expert readers (mean, 6.5) than did the expert readers (mean, 16.5	4 radiologists in the non-baysian group and 2 in the baysian group.
2 - Initial assessment	52	Dewan NA, Shehan CJ, Reeb SD, et al: Likelihood of malignancy in a solitary pulmonary nodule: comparison of Bayesian analysis and results of FDG-PET scan. Chest 112:416-22, 1997	Retrospective analysis of prosectively collected cohort	2-	52 patients who had undergone both CT scan of the chest and a FDG-PET scan for evaluation of a solitary pulmonary nodule	43 patients were men and nine were women. Mean age was 63.6± 11.3. 37 had malignant and 15 benign nodules.	PET scan	Bayesian analysis using "standard criteria" and PET scan	n/a		likelihood ratios for malignancy in a solitary pulmonary nodule with an abnormal FDG-PET scan was 7.11 (95% confidence interval [CI], 6.36 to 7.96), suggesting a high probability for malignancy, and 0.06 (95% CI, 0.05 to 0.07) when the PET scan was normal, suggesting a high probability for benign nodule. FDG-PET scan can be a useful adjunct test in the evaluation of solitary pulmonary nodules.	This is an older paper confirming the utility of PET in the investigations useful for SPNs. The authors found PET to be highly predictive of a malignant nodule. This is, however, a retrospective analysis of prospectively collected data. Missing data are not mentioned and there is no validation in other PET cohorts.
2 - Initial assessment	53	Edinburgh KJ, Jasmer RM, Huang L, et al: Multiple pulmonary nodules in AIDS: usefulness of CT in distinguishing among potential causes. Radiology 214:427-32, 2000	Case series	3	60	AIDS patients with pulmonary nodules	not applicable	not applicable	Not reported	Aetiology of lung nodules	Nodules smaller than 1 cm, especially those with a centrilobular distribution, are typically infectious. Nodules larger than 1 cm are often neoplastic. A peribronchovascular distribution is suggestive of Kaposi sarcoma	Highly selected patient population.

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2 - Initial assessment	54	Harders SW, Madsen HH, Rasmussen TR, et al: High resolution spiral CT for determining the malignant potential of solitary pulmonary nodules: refining and testing the test. Acta Radiologica 52:401-9, 2011	Case series	3	213	Lung nodule patients undergoing HRCT	HRCT chest	not applicable	Not reported	Risk of cancer	Margin risk categories (P < 0.001), calcification patterns (P = 0.003), and pleural retraction (P < 0.001) were all statistically significantly associated to malignancy. Sensitivity, specificity, and overall diagnostic accuracy of HRCT were 98%, 23% and 87%, respectively.	90% histopathological confirmation of lung nodule aetiology.
2 - Initial assessment	55	Herder GJ, van Tinteren H, Golding RP, et al: Clinical prediction model to characterize pulmonary nodules: validation and added value of 18F-fluorodeoxyglucose positron emission tomography. Chest 128:2490-6, 2005	Cohort study	2+	106 eligible patients mean age was 64 years (age range, 32 to 85 years)	61 (57.5%) proved to have malignant nodules	PET	FDG uptake was scored using a 4-point scale (0, absent; 1, faint; 2, moderate; or 3, intense) and clinical prediction model.	203-925 days		Clinical prediction model ROCAUC was 0.79 (95% confidence interval [CI], 0.70 to 0.87). PET scan ROC-AUC value of 0.88 (95% CI, 0.77 to 0.91). PET scanning added to the predicted probability and improves the AUC by 13.6 (95% CI, 6 to 21; p =0.0003). The visual analysis of FDG-PET scans is a robust and accurate method in radiologically indeterminate SPNs. The combination of visually read FDG-PET scans and pretest factors appears to yield the best accuracy.	: The authors have performed a study to validate a previously published clinical prediction model for malignancy, compare this to PET (increased AUC but p=0.058) but a combined model wassignificantly better than either. PET significantly increasing the area under the receiver operating curve by 13% from 0.79 to 0.92. Therefore in some populations the use of such a model may be useful. This would need to validated in prospective cohorts and/or be integrated into a management of SPN trial
2 - Initial assessment	56	Kim H, Kang SJ, Suh GY, et al: Predictors for benign solitary pulmonary nodule in tuberculosis-endemic area. Korean Journal of Internal Medicine 16:236-41, 2001	Case series	3	201	Consecutive korean patients with nodules identified on chest X-ray	not applicable	Malignant and benign nodules.	Not reported	Risk of cancer	Patients with a older age (60.7 +/- 9.6 vs 56.2 +/- 13.1, p = 0.008) and more than 40-pack years smoking (27.8% vs 14.0%, p = 0.017) were more frequently related with malignant than benign SPN. On chest CT scans, spiculated margin, contrast enhancement more than 20 Hounsfield unit and presence of pleural tag and mediastinal LN enlargement were more frequently observed in malignant than benign SPNs. In contrast to previous studies, satellite lesions (21.5% vs 1.9%, p < 0.001) and cavitation (20.4% vs 5.6%, p = 0.001) were more frequently seen in benign than malignant SPN. Positive predictive values of benignity were 90.9% and 76.0%,	All patients underwent diagnostic testing with either bronchoscopy or lung biopsy.
2 - Initial assessment	57	Kui M, Templeton PA, White CS, et al: Evaluation of the air bronchogram sign on CT in solitary pulmonary lesions. Journal of Computer Assisted Tomography 20:983-6, 1996	Case series	3	132	Patients with solitary lung nodules	not applicable	Presence of air bronchus sign	Not reported	Risk of cancer	1 benign nodule (5.9%) had an air bronchogram; 33 (28.7%) lung cancers had this sign (p < 0.05).	Only 17 benign nodules. No other factors included.
2 - Initial assessment	58	Li F, Sone S, Abe H, et al: Malignant versus benign nodules at CT screening for lung cancer: comparison of thin-section CT findings. Radiology 233:793-8, 2004	Case series	3	222	Consecutive pateints enrolled into Japanese screening programme	not applicable	not applicable	Not reported	Risk of cancer	Among nodules with pure GGO, a round shape was found more frequently in malignant lesions (11 of 17, 65%) than in benign lesions (two of 12, 17%; P = .02; PPV, 85%); mixed GGO, a subtype with GGO in the periphery and a high-attenuation zone in the center, was seen much more often in malignant lesions (11 of 27, 41%) than in benign lesions (two of 29, 7%; P = .004; PPV, 85%). Among solid nodules, a polygonal shape or a smooth or somewhat smooth margin was present less frequently in malignant than in benign lesions (polygonal shape: 7% vs 38%, P = .02; smooth or somewhat smooth margin: 0% vs 63%, P < .001), and 98% (46 of 47) of polygonal nodules and 100% (77 of 77) of nodules with a smooth or somewhat smooth margin were benign.	Retrospective analysis of a highly selected patients group. Only 222 out of 672 had high resolution images available. High rate of malignancy for a screening study (26%).
2 - Initial assessment	59	Li Y, Chen K-Z, Wang J: Development and validation of a clinical prediction model to estimate the probability of malignancy in solitary pulmonary nodules in Chinese people. Clinical Lung Cancer 12:313-9, 2011	Case series	3	371	Nodules patients referred for surgical resection.	not applicable	not applicable	Not reported	Risk of cancer	gistic regression analysis identified six clinical characteristics (age, diameter, border, calcification, spiculation, and family history of tumor) as independent predictors of malignancy in patients with SPN. The area under the receiver operating characteristic (ROC) curve for our model (0.89; 50% confidence interval [CI], 0.78-0.99) was higher than those generated using another two reported models. In our model, sensitivity was 92.5%, specificity was 81.8%,positive predictive value was 90.2%, and negative predictive value was 85.7%	Highly selected patient population with high prevalence of malignancy (71%)
2 - Initial assessment	60	Malaisamy S, Dalal B, Bimenyuy C, et al: The clinical and radiologic features of nodular pulmonary sarcoidosis. Lung 187:9-15, 2009	Case series	3	33	Sarcoidosis patients with nodular disease	not applicable	not applicable	Not reported	Resolution of nodules	Nodules resolved in 70% of cases.	Small study. Not clear how patients were identified for inclusion.
2 - Initial assessment	61	Saito H, Minamiya Y, Kawai H, et al: Usefulness of circumference difference for estimating the likelihood of malignancy in small solitary pulmonary nodules on CT. Lung Cancer 58:348-54, 2007	Case series	3	214 nodules	Patients with solitary nodules referred for surgical resection	not applicable	not applicable	Not reported	Risk of cancer	Algorithm that included circumference difference had sensitivity of 96.6%, specificity of 86.1%, and positive predictive value of 94.1%	Highly selected patient population.
2 - Initial assessment	62	Schultz EM, Sanders GD, Trotter PR, et al: Validation of two models to estimate the probability of malignancy in patients with solitary pulmonary nodules. Thorax 63:335-41, 2008	Case series	3	151	Patients with solitary nodules referred for PET scanning	not applicable	not applicable	1 year	Performance of two cancer risk prediction models	The area under the ROC curve for the Mayo Clinic model (0.80; 95% CI 0.72 to 0.88) was higher than that of the VA model (0.73; 95% CI 0.64 to 0.82), but this difference was not statistically significant (Delta = 0.07; 95% CI -0.03 to 0.16). Calibration curves showed that the probability of malignancy was underestimated by the Mayo Clinic model and overestimated by the VA model.	Prevalence of malignancy high (44%). Multiple nodules excluded.
2 - Initial assessment	63	Swensen SJ, Silverstein MD, Edell ES, et al: Solitary pulmonary nodules: clinical prediction model versus physicians. Mayo Clinic Proceedings 74:319-29, 1999	Case series	3	100	Random sample from 629 patients with indeterminate SPN	not applicable	not applicable	Not applicable	Performance of prediciton model versus clinician opion	Receiver operating characteristic analysis showed no significant difference between the logistic model and the physicians' predictions. Calibration curves revealed that physicians overestimated the probability of a malignant lesion in patients with low risk of malignant disease by the prediction rule	Study peformed in a tertiary healthcare centre so clinicians may have had more expertise than the general physician.
2 - Initial assessment	64	Swensen SJ, Silverstein MD, Ilstrup DM, et al: The probability of malignancy in solitary pulmonary nodules. Application to small radiologically indeterminate nodules. Archives of Internal Medicine 157:849-55, 1997	Case series	3	629	Patients with indeterminate lung nodules	not applicable	not applicable	2 years	Derivation and validation of cancer prediction model	Three clinical characteristics (age, cigarette-smoking status, and history of cancer [diagnosis, > or = 5 years ago]) and 3 radiological characteristics (diameter, spiculation, and upper lobe location of the SPNs) were independent predictors of malignancy. The area (+/-SE) under the evaluated receiver operating characteristic curve was 0.8328 +/- 0.0226	Retrospective data collection. Potential for referral bias.
2 - Initial assessment	65	Yonemori K, Tateishi U, Uno H, et al: Development and validation of diagnostic prediction model for solitary pulmonary nodules. Respirology 12:856-62, 2007	Case series	3	452	Nodule patient referred for surgery	not applicable	not applicable	Not reported	Derivation and validation of cancer prediction model	The prediction model comprised the level of serum CRP, the level of carcinoembryonic antigen, the presence or absence of calcification, spiculation and CT bronchus sign. The areas under the receiver-operating characteristic curve in training and validation sets were 0.966 and 0.840, respectively. The diagnostic accuracies of the prediction model and the experienced chest radiologist for the validation set were 0.858 and 0.905, respectively.	Retrospective study in highly selected patient population with high prevalence of cancer (75%)
2 - Initial assessment	66	Copp DH, Godwin JD, Kirby KA, et al: Clinical and radiologic factors associated with pulmonary nodule etiology in organ transplant recipients. American Journal of Transplantation 6 (11):2759-2764, 2006	Case series	3	53	Solid organ transplant patients with SPN	not applicable	not applicable	Not reported	Clinical and radiological predictors of aetiology of lung nodules	18% malignant. Epstein-Barr virus seronegativity and lung transplant were each associated with PTLD (OR, 21.7, p < 0.01) and (OR, 36.6, p < 0.001), respectively. Diagnosis less than 90 days post-transplant was associated with Aspergillus infection (OR, 12.9, p = 0.007).	Retrospective analysis over 15 years. Small numbers and non standardised investigation/follow up protocol.
2 - Initial assessment	67	Wang CW, Teng YH, Huang CC, et al: Intrapulmonary lymph nodes: computed tomography findings with histopathologic correlations. Clin Imaging 37:487-92, 2013	Case series	3	26	Patients with IPLNs identified from review of histopathological cases (31 IPLNs)	not applicable	not applicable	Lesions were resected for entry into study. 15 patients had serial imaging with intervals of 1-20 months	Radiological features predictive of IPLNs on CT images	IPLNs were usually subpleural, frequently below level of carina, angular in shape. Most were solid but occasionally had ground glass morphology. For pleura-attached IPLNs, one or more linear opacities were identified. For pleura-separated IPLNs, 3 or more linear opacities extending from nodules were identified	Small numbers, but systematic analysis of radiological features suggestive of IPLNs

Section	Ref no	Bibliographic citation	Study type	Ev lev	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
2 - Initial assessment	68	Shaham D, Vazquez M, Bogot NR, et al: CT features of intrapulmonary lymph nodes confirmed by cytology. Clin Imaging 34:185-90, 2010	Case series	3	19	Patients with IPLNs on cytology identified from database of CT guided lung biopsies	not applicable	not applicable	Not stated	Radiological features of IPLNs on CT	All IPLNs were below carina, all but one were within 20mm of the chest wall. Nodules were oval, round, triangular, trapezoidal and had sharply defined borders. They were solid, homogenous, not calcified. One third has discrete tag extending to the pleura	Small numbers but consistent findings with previous study (ref 67)
2 - Initial assessment	69	Hyodo T, Kanazawa S, Dendo S, et al: Intrapulmonary lymph nodes: thin-section CT findings, pathological findings, and CT differential diagnosis from pulmonary metastatic nodules. Acta Med Okayama 58:235-40, 2004	Case series	3								
2 - Initial assessment	70	Oshiro Y, Kusumoto M, Moriyama N, et al: Intrapulmonary lymph nodes: thin-section CT features of 19 nodules. J Comput Assist Tomogr 26:553-7, 2002	Case series	3	16	Patients identified retrospectively from pathology database of resected nodules (19 nodules)	not applicable	not applicable	Not stated	Radiological features of IPLNs on CT	All nodules were in middle lobe, lingula or lower lobe. Nodules were either abutting visceral pleura or within 8mm of it. Most nodules were well circumscribed, homogenous, ovoid, round, and smaller than 12mm.	Very small series
2 - Initial assessment	71	Isbell JM, Deppen S, Putnam JB, Jr., et al: Existing general population models inaccurately predict lung cancer risk in patients referred for surgical evaluation. Annals of Thoracic Surgery 91:227-33; discussion 233, 2011	Case series	3	189	Patients referred for surgery for focal pulmonary lesion	not applicable	not applicable	Not reported	Peformance of two prediction models	73% nodules were malignant. The area under the receiver operating characteristic curve for the Mayo and solitary pulmonary nodules models was 0.79 and 0.80, respectively; however, the models were poorly calibrated (p<0.001).	Retrospective review of highly selected patient population.
2 - Initial assessment	72	Al-Ameri A, Thygesen H,Plant P K, Vaidyanathan S, Karthik S, Scarsbrook A, Callister MEJ: Risk of malignancy in pulmonary nodules: a validation study of four prediction models. Lung Cancer, 2015	Case series	3	244	Patients with pulmonary nodules identified from lung cancer MDT and nodule clinic	not applicable	not applicable	2 years stability for benign nodules	Performance of four risk prediction tools	Best performance was seen for Herder model in patients who underwent PET-CT (AUC 0.924). Mayo and Brock models perfomed similarly (AUC 0.89 and 0.90 respectively). Reasonable AUCs values seen for these three models even when patients were included outside the original inclusion criteria for the three scores. The VA model performed poorly. For small nodules (under 1cm diameter) the highest AUC was seen for the Brock model)	Validates the performance of these three nodules in a UK population. Brock model appears to perform best for small nodules, and Herder has highest accuracy in those nodules evaluated with PET-CT.
2 - Initial assessment	73	Aberle DR, DeMello S, Berg CD, et al: Results of the two incidence screenings in the National Lung Screening Trial. N Engl J Med 369:920-31, 2013	Case series	3	53454	Asymptomatic men and women, 55 to 74 years of age, who had a history of at least 30 pack-years of cigarette smoking and who were either current smokers or had been smokers within the previous 15 years.	not applicable	not applicable	12 months		nodules that were 4 to 6 mm in diameter accounted for roughly half the positive screening results with low-dose CT at both time points, but such nodules were associated with lung cancer in less than 1% of participants.	Largest case series of lung nodules in the liturature.
2 - Initial assessment	74	Horeweg N, van Rosmalen J, Heuvelmans MA, et al: Lung cancer probability in patients with CT-detected pulmonary nodules: a prespecified analysis of data from the NELSON trial of low-dose CT screening. Lancet Oncol, 2014	Case series	3	7155	Participants in Dutch-Belgian lung cancer screening trial. Age 50-75 with significant smoking history.	not applicable	not applicable	6.5 years	Volume-based predictors of malignancy	Lung cancer probability was low in participants with a nodule volume of 100 mm(3) or smaller (0·6% [95% CI 0·4-0·8]) or maximum transverse diameter smaller than 5 mm (0·4% [0·2-0·7]), and not significantly different from participants without nodules (0·4% [0·3-0·6], p=0·17 and p=1·00, respectively). Lung cancer probability was intermediate (requiring follow-up CT) if nodules had a volume of 100-300 mm(3) (2·4% [95% CI 1·7-3·5]) or a diameter 5-10 mm (1·3% [1·0-1·8]). Volume doubling time further stratified the probabilities: 0·8% (95% CI 0·4-1·7) for volume doubling times 600 days or more, 4·0% (1·8-8·3) for volume doubling times 400-600 days, and 9·9% (6·9-14·1) for volume doubling times of 400 days or fewer. Lung cancer probability was high for participants with nodule volumes 300 mm(3) or bigger (16·9% [95% CI 14·1-20·0]) or diameters 10 mm or bigger (15·2% [12·7-18·1]).	Large case series.
2 - Initial assessment	75	de Hoop B, Gietema H, van Ginneken B, et al: A comparison of six software packages for evaluation of solid lung nodules using semi-automated volumetry: what is the minimum increase in size to detect growth in repeated CT examinations. European Radiology 19:800-8, 2009	Case series	3	20	Consecutive patients with known pulmonary metastases (214 nodules analysed)	Volumetric analysis on 2 separate scans performed on same day with patient mobile between	Comparison between 6 software packages	Not applicable	Performance of 6 software tools for volumetry	Software packages provided adequate segmentation for 71-86% nodules. Variability in volumetry between scans was between 16.4% and 22.3% for various packages. Variability tended to be less for nodules >=8mm. When comparing difference systems, systematic volume differences detected in 11/15 comparisons	Where volumetry used to assess growth, this study suggests that essential to use the same software package to measure volume as too much variation between different software systems.
2 - Initial assessment	76	Zhao YR, van Ooijen PM, Dorrius MD, et al: Comparison of three software systems for semi-automatic volumetry of pulmonary nodules on baseline and follow-up CT examinations. Acta Radiol 55:691-8, 2014	Case series	3	25	50 patients randomly selected from NELSON screening trial - 25 had nodules persisting on follow-up scan	See next column	Comparison between 3 software packages	Not specifically stated, but probably 1 year interval scans as per NELSON protocol	Performance of 3 software tools	Segmentation at baseline was satisfactory for 84-93% nodules with three tools. Significant differences were found between measured volumes (38% and 50% between systems. At baseline, there was consensus on nodule size categorisation in 74-80% between systems. At follow-up, consensus on VDT was lower 47% and 44%.	Significant variability in performance of tools. Highlights need to standardise software for follow-up individual patients, and also suggests that some systems maybe more accurate than others.
3 - Surveillance	77	Revel MP, Bissery A, Bienvenu M, et al: Are Two-dimensional CT Measurements of Small Noncalcified Pulmonary Nodules Reliable? Radiology 231 (2):453-458, 2004	Case series	3	54 nodules	Retrospectively identified patients with pulmonary nodules on CT scan (sub 2cm)	Comparison of interobserver variation in 2-D diameter measurements between different reporters	Other reporters	Not applicable	Repeatability coefficients of diameter measurements	Repeatability coefficients were 1.70, 1.32 and 1.51 for readers 1, 2 and 3. 95% limits of agreement were -1.73 to +1.73. A change in size of under 1.7mm only having a 5% chance of corresponding to an actual change in nodule size	Authors conclude that 2D diameter measurements for small nodules are not reliable.
3 - Surveillance	78	Korst RJ, Lee BE, Krinsky GA, et al: The utility of automated volumetric growth analysis in a dedicated pulmonary nodule clinic. Journal of Thoracic & Cardiovascular Surgery 142:372-7, 2011	Prospective comparison of diagnostic accuracy	3	87 nodules in 69 patients comparing 2 sequential CT scans.	Patients referred to dedicated pulmonary nodule clinic (5-30mm) with 2 scans to compare. Mean age 62, 64% women	Interval CT with VDT by volumetry	Interval CT with 2D measurement to calculate VDT	Time between scans 0.5-32 months	Benign or malignant aetiology	Reasonable correlation between 2D and volumetry VDT (r=0.69, p<0.00001) - marginally better for sub-cm nodules (63% cases). For prospective cases (where volumetry only available subsequent to initial assessment) biopsy recommended in in 30 of 113 comparisons. 7 additional biopsies were prompted by volumetry (6.2% cases) of which 3 (43%) showed cancer. VDTs not quoted - used growth index instead (unable to extrapolate). Of 20 lung cancers, 11 (55%) exclusively enlarged, 8 had periods of enlargement and shrinking, and one progressively shrank over 3 scans.	Illustrates that some malignant nodules shrink during natural history. Volumetry seemed to be more sensitive for picking up malignancy than just 2D derived VDT
3 - Surveillance	79	Ko JP, Berman EJ, Kaur M, et al: Pulmonary Nodules: growth rate assessment in patients by using serial CT and three-dimensional volumetry. Radiology 262:662-71, 2012	Diagnostic accuracy	3	59	Screening study population US	Use of 3D volumetry	Radiological or clinical diagnosis			Growth rate precision increased with greater time between scans. Overall estimate for standard deviation of growth rate, on the basis of 939 growth rate determinations in clinically stable nodules, was 36.5% per year. Peripheral location (P = .01; 37.1% per year vs 25.6% per year) and adjacency to pleural surface (P = .05; 38.9% per year vs 34.0% per year) signifi cantly increased standard deviation of growth rate. All eight malignant nodules had an abnormally high growth rate detected. By using 3D volumetry, growth rate–based diagnosis of malignancy was made at a mean of 183 days, compared with radiologic or clinical diagnosis at 344 days.	Variability in growth rate estimate reduced with increasing time interval between scans

Section	Ref no	Bibliographic citation	Study type	Ev lev	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
3 - Surveillance	80	Revel M-P, Merlin A, Peyrard S, et al: Software volumetric evaluation of doubling times for differentiating benign versus malignant pulmonary nodules. AJR American Journal of Roentgenology. 187:135-42, 2006	Retrospective case series	3	45 patients with 27 SPNs, and 18 patients with MPNs (largest selected for analysis)	Solid NCN <20mm if second CT was available for retrospective VDT calculation	Retrospective computed aided VDT calculation	Benign vs malignancy nodules	Up to 2 years	Eventual diagnosis.	52 benign and 11 malignant nodules. Final diagnosis malignancy based on pathology. Final diagnosis of benign based on no growth for 2yrs no FDG avidity and >10mm (? why) or morphological criteria characteristic of benign. For malignant nodules, interscan change in diameter was >2mm for 6 nodules and <2mm for other 5. Sens VDT<500/7 for malignancy was 91% (95% CI 0.59-1.00) (one adenocarcinoma had VDT 646/7) whereas manual diameter change was 54% (95% CI 0.23-0.83). Mean and median VDT were 164/111 days respectively. 23/52 benign lesions grew with median VDT 947 days (unclear whether this is just those that grew). VDT<500 days in 5 false-positive cases thus specificity 90% (95%CI 0.79-0.97). If alter cut-off to VDT<700 days - sens and spec change to 100% and 85% respectively. Very short scan interval (<2 months). Weakness - small numbers, self-fulfilling diagnostic criteria, 4-detector CT scan.	Computer generated VDT useful, but 4-detector scan, small numbers, definition of benign nodules as VDT>500 days (may have missed some slow-growing cancers), and short interval duration between CTs (? How reliable is VDT calculation on such short intervals)
3 - Surveillance	81	de Hoop B, Gietema H, van de Vorst S, et al: Pulmonary ground-glass nodules: increase in mass as an early indicator of growth. Radiology 255:199-206, 2010	Diagnostic accuracy	3	Fifty-two GGNs were detected in 45 participants	(42 men, three women; Current or former heavy smokers, Recruite via NELSON. mean age, 62 years; range, 53 –73 years).	NONE	Agreement and time to agreeing on growth	up to 5 years	Time to agreement and measures of agreement Time for growth to exceed variability measures	Mass measurements show significant changes before diameter or volume measurements in GGO malignant nodules meaning the time to detection of malignant diagnosis is reduced. This could increase the confidence in observation protocols.	Shows that poor agreement for detection of the solid component - lower than expected. Mass measurement detects growth earlier than volume or diameter in GGOs. Low numbers so relaibility questionable (only 13 malignant nodules considered post resection)
3 - Surveillance	82	Xu DM, van Klaveren RJ, de Bock GH, et al: Role of baseline nodule density and changes in density and nodule features in the discrimination between benign and malignant solid indeterminate pulmonary nodules. European Journal of Radiology 70:492-8, 2009	Prospective randomised trial of CT screening	2+	Patients with indeterminate pulmonary nodules (312 patients 372 nodules)	50-75 with smoking history	CT screening	No imaging		Risk of cancer	Reviewed 372 solid purely intraparenchymal nodules. Baseline density (HU) was not signficantly different, but median change in density was significantly different between benign and malignant nodules (malignant nodules became denser during follow-up). Other baseline differences were that malignant nodules were more often non-spherical, irregular, lobulated or spiculated at baseline, 3/12 and 1 year follow-up. Nodules rarely changed morphology or shape (either benign or malignant).	:Density could be used as another parameter with which to monitor nodule progression, but there are no cut-offs to allow accurate delination of benign from malignant nodules
3 - Surveillance	83	Kostis WJ, Yankelevitz DF, Reeves AP, et al: Small Pulmonary Nodules, Reproducibility of Three-dimensional Volumetric Measurement and Estimation of Time to Follow-up CT. Radiology 231 (2):446-452, 2004	Retrospective case series	2+	115 patients	2 CT scans with nodule stability in between	Modelling reproducibility	N/a	N/A	Critical time to CT scan follow-up	Aimed to determine critical time to follow-up CT - earliest point at which reliable interval growth could be determined. This relates to reliably detected percentage volume change (taking into account artefact) and doubling time threshold between growing and stable nodules. Determined that critical time to follow-up CT for baseline screening/incidental nodules was 12/12 if 2mm, 5/12 if 5mm, 3/12 if 8mm, 1/12 if 10mm. Times shorter for	Technical support for Fleishner society recommendations.
3 - Surveillance	84	Xu DM, van der Zaag-Loonen HJ, Oudkerk M, et al: Smooth or attached solid indeterminate nodules detected at baseline CT screening in the NELSON study: cancer risk during 1 year of follow-up. Radiology 250:264-72, 2009	Prospective randomised trial of CT screening	2+	658 participants with 891 solid indeterminate nodules	50-75 with smoking history - NCNs 5-10mm in diameter	CT screening	No imaging		Risk of cancer	VDT at 3/12 showed 68 (8%) nodules to have VDT <400/7 - only 15% turned out to be malignant. At 1 year, 10 nodules had VDT<400/7 of which 50% were malignant. Predictors of malignancy at baseline were non-spherical morphology,	
3 - Surveillance	85	Zhao YR, Heuvelmans MA, Dorrius MD, et al: Features of resolving and nonresolving indeterminate pulmonary nodules at follow-up CT: the NELSON study. Radiology 270:872-9, 2014	Prospective randomised trial of CT screening	2+	750 participants with 964 nodules	50-75 with smoking history	CT screening	No imaging	2 years	Resolution of nodules - and features predictive of resolution	10.1% of nodules resolved. Features predictive of resolution were non-peripheral location, larger size and spiculate margins. 77.3% of nodules that would disappear had done so by 3 months	The majority of resolving nodules do so on 3 month scan. Factors that increase chance of resolution are the same factors that increase likelihood of malignancy (peripheral location and spiculation)
3 - Surveillance	86	Jennings SG, Winer-Muram HT, Tann M, et al: Distribution of stage I lung cancer growth rates determined with serial volumetric CT measurements. Radiology 241:554-63, 2006	Retrospective case series	3	149 patients	Stage I lung cancer having 2 pre-treatment CT scans >25 days apart	Manual 2D volume calculation		Post-cancer diagnosis - mean 3.4yrs	VDT	Tumour confirmed by CTgBx 92%, sputum analysis 3%, TBLBx in 2%, surgical excision in 0.7% and on growth alone in 1.3%. Median interval between CT was 130 days (range 25-2493). Median VDT was 207 days. 14% of tumours did not increase in size between scans (reduced to 5.7% when adjusted for length between scans). VDT were not significantly different by tumour types (adeno 215/7, squam 144/7, BAC 521/7). Calculated proportion of cancers with detectable growth (using 5-25% threshold for detection) showing 72-95% detectable growth at 3/12, 87-98% at 6/12, 95-98% at 12/12 and 98-99% at 24/12. Survival significantly lower in faster-growing tumours.	Relatively large numbers in study. Weaknesses are short time interval between some scans, no comparison with benign lesions, manual 2D volume calculation by single radiologist. Another paper suggesting that some tumours reduce in size. Gives some indication of optimum interval between scans for detecting growth
3 - Surveillance	87	Winer-Muram HT, Jennings SG, Tarver RD, et al: Volumetric growth rate of stage I lung cancer prior to treatment: serial CT scanning. Radiology 223:798-805, 2002	Retrospective case series	3	50 patients	Stage I lung cancers with 2 or more CTs able to compare tumour size		Different volumetric methods (perimeter - usualy volumetric technique, spherical, eliptical)	25-1,212 days pre-treatment of lung cancer	VDT by tumour type	VDTs (using perimeter method) median were 119 days (33-1,004) for squamous, 157 days (-26,711 to 64) for adeno, 370 days (40-6,960) for BAC. Negative growth was seen in differing numbers of patients by 3 different techniques. Overall median was 181 days	Largely technical paper comparing perimeter, spherical, and eliptical methods for volumetry. Showed very wide range of VDTs, negative growth of some cancers. No use of CXR dimensions. Again short time intervals for some scans.
3 - Surveillance	88	Hasegawa M, Sone S, Takashima S, et al: Growth rate of small lung cancers detected on mass CT screening. Br J Radiol 73:1252-9, 2000	Retrospective review from prospective CT screening trial	3	61 patients	Lung cancers identified by screening with more than one CT previously	None	VDT calculation by tumour characteristics (2D diameter measurements)		VDT.	Subdivided into GGO, GGO with solid component and solid nodule (G, GS,S). 95% of G, 95% of GS and 30% of S were invisible on CXR. Mean size 10,11,16mm. 80% tumours were adenos. Mean VDT values were 813, 457 and 149 days respectively. Range of VDTs was 52-1733. Mean VDT in smokers was lower than non-smokers (292 vs 607). VDT by tumour type was 97 SCLC, 129 Squamous, 533 adeno.	
3 - Surveillance	89	Henschke CI, Yankelevitz DF, Yip R, et al: Lung cancers diagnosed at annual CT screening: volume doubling times. Radiology 263:578-83, 2012	Retrospective evaluation of a prospectively enrolled screening population (ELCAP)	2+	111 cases of nodules with eventual diagnosis of lung cancer	Nodules with eventual diagnosis lung cancer for which VDT available, with negative screen 7-18/12 earlier (so not prevalence cancers).	Interval CT with VDT calculation (calculated by diameter measurement not volumetry)	Different histological and radiological subgroups of cancers	Not specified	VDT by eventual diagnosis	110 screen detected cancers and 1 symptom detected cancer studied. Median VDT (where able to measure due to previous nodule) for all cancers was 98 days (mean 136). 50% had VDT<100/7, 3% had VDT>400/7. NSCLC median/mean VDT were 121/154 days). Median VDTs by cell type were SCLC 43/7, Large cell neuroendocrine 82/7, Squamous 88/7, solid adenos 140/7, sub-solid adenos 251/7. All 99 solid nodules had VDT<400/7, and all 12 sub-solid nodules had VDT<900/7	Systematic evaluation of VDT for large number of screen detected (but not prevalence) cancers. Illustrates differences by cell type and morphology. Doesn't include benign nodules so don't allow comparison between cancer and benign
3 - Surveillance	90	Wilson DO, Ryan A, Fuhrman C, et al: Doubling times and CT screen-detected lung cancers in the Pittsburgh Lung Screening Study. Am J Respir Crit Care Med 185:85-9, 2012	Case series (non-randomised CT screening study)	3	63 lung cancers	Patients with lung cancers detected by CT screening suitable for volumetric analysis	Volumetric analysis	N/A	N/A	VDT and histological subtype of cancer.	For all lung cancers, median VDT was 357 days (IQR 236-630 days). Slower VDTs were seen for prevalent vs incident cancers (514 vs 237 days respectively), and for squamous vs adenocarcinomas/BAC (160 vs 387 days respectively)	Demonstrates relationship between method of detection (incident vs prevalent) and growth rate, and similarly between histology and growth rate. Long VDTs are seen for some adenocarcinoma/BAC lesions.
3 - Surveillance	91	MacMahon H, Austin JHM, Gamsu G, et al: Guidelines for management of small pulmonary nodules detected on CT scans: A statement from the Fleischner Society. Radiology 237 (2):395-400, 2005		N/A								Guidelines - no need for evidence statement
3 - Surveillance	92	Good CA, Wilson TW: The solitary circumscribed pulmonary nodule; study of seven hundred five cases encountered roentgenologically in a period of three and one-half years. J Am Med Assoc 166:210-5, 1958	Case series	3	705 patients	Patients with solitary nodules visible on CXR	Observation or exploration (surgical excision)	N/A	2-10 years for stable nodules	Eventual diagnosis (presumed for most stable nodules)	Of 705 patients with pulmonary nodules, 294 had evidence of calcification of which none turned out to be malignant. 37 nodules were unchanged over 2 years or more. Two were surgically excised - one benign, one adenocarcinoma. 35 kept under observation - some to 10 years and presumed benign.	Large series of CXR detected nodules. This is the first suggestion that 2yrs of stability is strongly suggestive of benign disease.
3 - Surveillance	93	Yankelevitz DF, Henschke CI: Does 2-year stability imply that pulmonary nodules are benign? AJR American Journal of Roentgenology. 168:325-8, 1997		N/A								Historical review of literature quoting 2 years of radiographic stability indicating benignity. Not suitable for evidence statement.

Section	Ref no	Bibliographic citation	Study type	Ev lev	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
3 - Surveillance	94	Ashraf H, Dirksen A, Loft A, et al: Combined use of positron emission tomography and volume doubling time in lung cancer screening with low-dose CT scanning, Thorax, 2011, pp 315-9	subset of randomised national screening trial	2+	Danish Lung Cancer Screening Trial, participants with indeterminate nodules who were referred for a 3-month rescan were investigated. 54 nodules were included. olid nodules with a diameter of 5-15 mm and non-solid nodules up to 20 mm not classified as benign were considered indeterminate and were rescanned after 3 months. Nodules >15mm referred for diagnostic intervention.	The prevalence of lung cancer was 37%	Patients underwent: initial scan, 3 month scan (and assessment of VDT) and in interim a PET scan.	PET was categorised as most likely benign to malignant (grades I-IV). VDT was calculated from volume measurements on repeated CT scans using semiautomated pulmonary nodule evaluation software	3 month intervention		Cut-off points for malignancy were PET >II and VDT <1 year. Multivariate model both PET (OR 2.63, p<0.01) and VDT (OR 2.69, p<0.01) were associated with lung cancer. PET and VDT predict lung cancer independently of each other.	The use of both PET and VDT in combination is recommended when screening for lung cancer with low-dose CT. This study suggests that a PET positive nodule with a VDT <1 year has a high probability of malignancy and invasive diagnostic investigation should be conducted.
3 - Surveillance	95	Heuvelmans MA, Oudkerk M, de Bock GH, et al: Optimisation of volume-doubling time cutoff for fast-growing lung nodules in CT lung cancer screening reduces false-positive referrals. Eur Radiol 23:1836-45, 2013	Retrospective modelling of prospective RCT of CT screening	2-	61 patients with 68 fast-growing nodules	50-75 with smoking history with VDT<400/7	Modelling to see if VDT could be reduced at 3/12 scan			Risk of cancer	Analysed VDT for 68 fast-growing nodules - 48 of which were judged to have VDT<400/7 at 3/12, the other 20 after 1 year. Lowering VDT cut-off to 223 days at 3/12 would not have missed any cancers, but would have reduced false-positive rate at 3/12. Not possible to reduce VDT at 1 year due to the wider range of VDTs for malignant nodules at this time cut-off.	Suggests that lower VDT can be used at 3/12 than 1 year but small numbers of nodules in analysis. Might reduce false positives from early screening round.
3 - Surveillance	96	Xu DM, Gietema H, de Koning H, et al: Nodule management protocol of the NELSON randomised lung cancer screening trial, Lung cancer (Amsterdam, Netherlands), 2006, pp 177-84		N/A								Trial protocol - no need evidence review
3 - Surveillance	97	Horeweg N, van der Aalst CM, Vliegenthart R, et al: Volumetric computed tomography screening for lung cancer: three rounds of the NELSON trial. Eur Respir J 42:1659-67, 2013	Prospective RCT of CT screening	2+	7582	50-75 with smoking history	CT screening (data only presented for screened group)	None (no data on control group presented)	5.5 years	Lung cancer diagnosis	6% of participants had positive screen result (nodule >500mm3) and 2.6% were diagnosed with lung cancer. Positive screen had PPV 40.6% and 1.2% of scans were false positives. Risk of cancer in 5.5 years of follow-up was 1% after negative baseline, 5.7% after indeterminate baseline and 48.3% after positive baseline	Description of outcomes from CT screening rounds in NELSON, although mortality data not yet available. Described low false negative rate compared to NLST.
4 - Subsolid	98	Matsuguma H, Yokoi K, Anraku M, et al: Proportion of ground-glass opacity on high-resolution computed tomography in clinical T1 N0 M0 adenocarcinoma of the lung: A predictor of lymph node metastasis. J Thorac Cardiovasc Surg 124:278-84, 2002		3	96	all malignant			not given		Showed that PGGN and PSN with u to 25% solid component had no nodal mets and after that nodal mets were present in 20-30% of cases, most for solid nodules. Small numbers once divided into 5 groups though	
4 - Subsolid	99	Hung JJ, Jeng WJ, Chou TY, et al: Prognostic value of the new International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society lung adenocarcinoma classification on death and recurrence in completely resected stage I lung adenocarcinoma. Ann Surg 258:1079-86, 2013	Retroseptive case series	3	283	Patients undergoing lung resection for stage 1 lung adenocarcinoma			5 years	survival and recurrence according to histological features	The solid predominant group was associated with male sex, smoking, size, and more poorly differentiated histological grade. Lepidic predominant group had significantly better overall survival (P = 0.002). Micropapillary and solid predominant groups had significantly lower probability of freedom from recurrence (P = 0.004). Older age (P = 0.039), visceral pleural invasion to the surface (PL2) (P = 0.009), and high grade (micropapillary/solid predominant) of the new classification (P = 0.028) were predictors of recurrence in multivariate analysis. The solid predominant group tends to have significantly worse postrecurrence survival (P = 0.074). .	The new adenocarcinoma classification has significant impact on death and recurrence in stage I lung adenocarcinoma. Patients with PL2 and micropapillary/solid predominant pattern have significant higher risk for recurrence. This information is important for patient stratification for aggressive adjuvant chemoradiation therapy
4 - Subsolid	100	Hung JJ, Yeh YC, Jeng WJ, et al: Predictive Value of the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society Classification of Lung Adenocarcinoma in Tumor Recurrence and Patient Survival. J Clin Oncol, 2014	Retrospective case series	3	573	Patients undergoing surgical resection for adenocarcinoma			not given	survival and recurrence according to histological features	The predominant histologic pattern was significantly associated with sex (P < .01), invasive tumor size (P < .01), T status (P < .01), N status (P < .01), TNM stage (P < .01), and visceral pleural invasion (P < .01). The percentage of recurrence was significantly higher in micropapillary- and solid-predominant adenocarcinomas (P < .01). Micropapillary- and solid-predominant adenocarcinomas had a significantly higher possibility of developing initial extrathoracic-only recurrence than other types (P < .01). The predominant pattern group (micropapillary or solid v lepidic, acinar, or papillary) was a significant prognostic factor in overall survival (OS; P < .01), probability of freedom from recurrence (P < .01), and disease-specific survival (P < .01) in multivariable analysis.	he new adenocarcinoma classification has significant impact on death and recurrence in stage I lung adenocarcinoma. Patients with PL2 and micropapillary/solid predominant pattern have significant higher risk for recurrence.
4 - Subsolid	101	Russell PA, Wainer Z, Wright GM, et al: Does lung adenocarcinoma subtype predict patient survival?: A clinicopathologic study based on the new International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary lung adenocarcinoma classification. J Thorac Oncol 6:1496-504, 2011	retrospective database analysis	3	210	Patents with stage 1-3 adenocarcinoma that had had surgical resection			not sepcified, last pt enetered in 2009 and published in 2011	survival and recurrence according to histological features	confirmed that the new subtypes of adenocarcinoma in situ, minimally invasive adenocarcinoma and lepidic-predominant adenocarcinoma had a 5-year survival approaching 100%, whereas micropapillary-predominant and solid with mucin-predominant adenocarcinomas were associated with particularly poor survival. Papillary-predominant and acinar-predominant adenocarcinomas had an intermediate prognosis. This effect persisted after controlling for stage.	Classification of lung adenocarcinoma according to the new International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification correlated with 5-year survival. These relationships persisted after controlling for known prognostic patient and tumor characteristics.
4 - Subsolid	102	Henschke CI, Yankelevitz DF, Mirtcheva R, et al: CT screening for lung cancer: frequency and significance of part-solid and nonsolid nodules. AJR American Journal of Roentgenology. 178:1053-7, 2002	case series	3	44	CT screenees					only 44 ssn but showed that ssn more likely to be malignant	
4 - Subsolid	103	Matsuguma H, Mori K, Nakahara R, et al: Characteristics of subsolid pulmonary nodules showing growth during follow-up with CT scanning. Chest 143:436-443, 2013	case series	2+	171	CT screenees	N/A		1 to 136 months		Reported on pathology of resected cases. 98 PSN and 76 pGGN. Resection or biopsy for >20mm SSN at start. All except 1 of 41 SSN that showed growth were malignant. No benign lesiosnwere resected. The cumulative frequency of growth was estimated at 2 and 5 years for pGGN and PSN	
4 - Subsolid	104	Ichinose J, Kohno T, Fujimori S, et al: Invasiveness and Malignant Potential of Pulmonary Lesions Presenting as Pure Ground-Glass Opacities. Ann Thorac Cardiovasc Surg, 2013	case series	3	160	resected cases ≤20 mm			not given		Pleural indentation was found in 5 of 21 PGGN that were malignant, but only another 9 were malignant. However SUV >0.8 on PET did discriminate. Numbers too small to make the conclusion. Reported on pathology.	
4 - Subsolid	105	Fan L, Liu SY, Li QC, et al: Multidetector CT features of pulmonary focal ground-glass opacity: differences between benign and malignant. Br J Radiol 85:897-904, 2012	case series	3	82	resected or clinically confrimed			not given		Pathologically or clincally confrimed fGGO. Concluded that lobulation, coarse interface and pleural indentation predicts malignancy	

Section	Ref no	Bibliographic citation	Study type	Ev lev	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
4 - Subsolid	106	Hiramatsu M, Inagaki T, Inagaki T, et al: Pulmonary ground-glass opacity (GGO) lesions-large size and a history of lung cancer are risk factors for growth. J Thorac Oncol 3:1245-50, 2008	case series	3	125	radiological database of SSN that were stable at 3 months follow up			median 1048 days		>10mm and history of lung cancer independent risk factors; 50 SSN under 10mm and with no history of lung cancer did not grow	
4 - Subsolid	107	Kim H, Park CM, Woo S, et al: Pure and part-solid pulmonary ground-glass nodules: measurement variability of volume and mass in nodules with a solid portion less than or equal to 5 mm. Radiology 269:585-93, 2013	cohort	2+	73	Patients with SSN detected on initial CT fro clinical indications			not given		Study just showing that mas measurements for smaller ≤5 mm solid port of PSN is reasonable reproducible GGN were 5 to 20mm	
4 - Subsolid	108	Kim HK, Choi YS, Kim J, et al: Management of multiple pure ground-glass opacity lesions in patients with bronchioloalveolar carcinoma. J Thorac Oncol 5:206-10, 2010	case series	3	23	resected cases of BAC with additional SSN			median 40.3 mo		Study of SSN in resceted BAC - small numbers as only 23 patients with 89 GGO and 5 pts had all resected and 18 had some resceted thus if not feasible to resected not important as outscome good	
4 - Subsolid	109	Kim TJ, Goo JM, Lee KW, et al: Clinical, pathological and thin-section CT features of persistent multiple ground-glass opacity nodules: comparison with solitary ground-glass opacity nodule. Lung Cancer 64:171-8, 2009	case series	2-	136	Patients with extra pulmonary malignancies					Muktiple vs single PSN	
4 - Subsolid	110	Kim TJ, Park CM, Goo JM, et al: Is there a role for FDG PET in the management of lung cancer manifesting predominantly as ground-glass opacity? AJR American Journal of Roentgenology. 198:83-8, 2012	case series	3	89	Patients identified from radiological database			30mo (10-65)		FDG uptake correlated with size and inversely with proportion of GGO. PET was of little use because of the low incidence of mets (none attrubtable to SSN in this study)	
4 - Subsolid	111	Kobayashi Y, Sakao Y, Deshpande GA, et al: The association between baseline clinical-radiological characteristics and growth of pulmonary nodules with ground-glass opacity. Lung Cancer 83:61-6, 2014	case series	3	67	Varaiety of sources - some from screening, some from CT for other reasons, not lung cancer some from surigical FU after lung resection			med 4.2 y		SSN observed without treatment werwe follwoed for time to 2mm growth or incidenc of 2mm growth. 34/120 (28%) grew by the median obs period of 4.2 years. Smoking and large size were predictors. Good graph showing that growth had occurred by 3 years approx	
4 - Subsolid	112	Lee SM, Park CM, Goo JM, et al: Transient part-solid nodules detected at screening thin-section CT for lung cancer: comparison with persistent part-solid nodules. Radiology 255:242-51, 2010	case series	3	93	screening			3 mo or longer		70% of PSN werwe transient and more comon in younger people, blood eosinophillia, larger solid portion and detection during FU 126 PSN	
4 - Subsolid	113	Lee SW, Leem CS, Kim TJ, et al: The long-term course of ground-glass opacities detected on thin-section computed tomography. Respir Med 107:904-10, 2013	case series	3	114	Patients with focal SSN that had persisted for >2 years			Median 45 mo		26% showed growth with size >10mm being most important. Mean VDT of 1041 days	
4 - Subsolid	114	Oh JY, Kwon SY, Yoon HI, et al: Clinical significance of a solitary ground-glass opacity (GGO) lesion of the lung detected by chest CT. Lung Cancer 55:67-73, 2007	case series	3	186	Majority identified by CT screening			Not specified		Rather confused paper as authors report of 186 subjects but say in methods that only 122 with 46 pGGN and 86 PSN werwe analysed, then go on to report on 186. All SSN wewre scanned at 3 months if <10mm or biopsied/reseceted if >10mm. New solid compnent or increase size - biosy or resect. 26/69 (38%) PGGN were transient and 57/117 (49%) of PSN Most of the rgression was at first follow up CT. Thus this applies ONLY to sub 10mm nodules. No difference in cancer incidence between PSN and pGGN (although rates were 30% and 19% respectively	
4 - Subsolid	115	Takahashi S, Ueda K, Kido S, et al: Long term follow-up for small pure ground-glass nodules: Implications of determining an optimum follow-up period and high-resolution CT findings to predict the growth of nodules. Japanese Journal of Radiology 30 (3):206-217, 2012	case series	3	111	75.7% FU of malignant disease			66mo		75% of CTs were done for follow up of malignant disease so a selected group. 12.7% increased after a long FU. Size > 10mm, lobulation and bubble like appearance assoc with growth 150 pGGN	
4 - Subsolid	116	Tamura M, Shimizu Y, Yamamoto T, et al: Predictive value of one-dimensional mean computed tomography value of ground-glass opacity on high-resolution images for the possibility of future change. J Thorac Oncol 9:469-72, 2014	case series	3	53	consecutive patients with pGGN			av 26.1 mo		attenuation, smoking and history of lung cacner independent factors 63 pGGN	
4 - Subsolid	117	Attina D, Niro F, Stellino M, et al: Evolution of the subsolid pulmonary nodule: a retrospective study in patients with different neoplastic diseases in a nonscreening clinical context. Radiol Med 118:1269-80, 2013	case series	3	97	Cancer patients with mainly pGGN			>2 years		Mainly pGGN. Cancer patients . Slow growth and most round <5mm were stable. Recommended longer than 3 year FU 68% were stable or resolved. Large and irregular ondules >10mm more likely to grow.	
4 - Subsolid	118	Chang B, Hwang JH, Choi YH, et al: Natural history of pure ground-glass opacity lung nodules detected by low-dose CT scan. Chest 143:172-8, 2013	case series	3	89	Screening			median 59 mo		90% of screen detect pGGN did not grow but growth was assoc with initial size and development of a solid portion median VDT 769 days for growing nodules. 40% of the original toal were not followed up 122 pGGN	
4 - Subsolid	119	Choi WS, Park CM, Song YS, et al: Transient subsolid nodules in patients with extrapulmonary malignancies: their frequency and differential features. Acta Radiol, 2014	case series	3	63	Patients with extra pulmonary maliganacy			not given		Patients with extra-pulmonary malignancies. SSNs that appeared on FU or ill-defined nodular margin predictive of malignancy. 46% were transient	
4 - Subsolid	120	Lee HY, Choi YL, Lee KS, et al: Pure ground-glass opacity neoplastic lung nodules: histopathology, imaging, and management. AJR Am J Roentgenol 202:W224-33, 2014	Review	N/a								Review article so N/A for e=vidence table
4 - Subsolid	121	Lee KH, Goo JM, Park SJ, et al: Correlation between the size of the solid component on thin-section CT and the invasive component on pathology in small lung adenocarcinomas manifesting as ground-glass nodules. J Thorac Oncol 9:74-82, 2014	case series	3	58	Resected cases			not given		Small numbers for this type of conclusion - solid component of 3mm or less predicted pre-invasive or MIA	
4 - Subsolid	122	Lee SM, Park CM, Goo JM, et al: Invasive pulmonary adenocarcinomas versus preinvasive lesions appearing as ground-glass nodules: differentiation by using CT features. Radiology 268:265-73, 2013	case series	2-	253	Pathologically confirmed SSN, resected			Not given		Highly selected group of PSN resected, 55 wewre not confirmed and excluded. 2 not resected wewre biosied and were both invasive. Showed that for pGGN ≤10mm cut off had 100% specificity for non-invasive lesion. For PSN the ROC of the logistic regression model was 0.9 for a combination of smaller size, smaller solid portion, non-lobulated border and non-spiculated border	
4 - Subsolid	123	Nakamura S, Fukui T, Taniguchi T, et al: Prognostic impact of tumor size eliminating the ground glass opacity component: modified clinical T descriptors of the tumor, node, metastasis classification of lung cancer. J Thorac Oncol 8:1551-7, 2013	case series	3	475	Clinical stage Lung Cancer patients with stage T1a to T2b N0M0 all resected			>2 years		Supports the other studies that show the solid component size is an important prognostic factor 113 probably as this was the number reclassified	

Section	Ref no	Bibliographic citation	Study type	Ev lev	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
4 - Subsolid	124	Silva M, Sverzellati N, Manna C, et al: Long-term surveillance of ground-glass nodules: evidence from the MILD trial. J Thorac Oncol 7:1541-6, 2012	RCT	1+	56	screening	Screening with CT	No screening	50.26 mo median		RCT review of GGNs. 39.3% pGGN resolved or decreased, 16.7% pregressed. PSN with solid component <5mm, 46.2% progressed Growth defined as 2mm or greater	
4 - Subsolid	125	Lee SH, Lee SM, Goo JM, et al: Usefulness of texture analysis in differentiating transient from persistent part-solid nodules(PSNs): a retrospective study. PLoS One 9:e85167, 2014	case series	3	77	Selected from radiological database			not given3 months was cutt off for transience		Study developed a logistic regression model with an ROC of 0.92 to predict transient nodules from persistent. However this was heavily influenced by eosinophillia and lesion multiplicity. Skewness for solid. Skewness was also an important actor for PSN. However, the clinical relevance to the UK population is doubtful as these lesions will be followed up in any case.	
4 - Subsolid	126	Nakao M, Yoshida J, Goto K, et al: Long-term outcomes of 50 cases of limited-resection trial for pulmonary ground-glass opacity nodules. J Thorac Oncol 7:1563-6, 2012	case series	3	50	SSN ≤2cm with no pleural indentation or vacsular convergence			median 10 years		Selected group of limited resection of SSN 16 had lobectomy and LN dissection and remaining 26 had limited resection with at least a 1cm margin. 4 of the 26 recurred after 5 years close to the resection. Same case series as Yoshida below	
4 - Subsolid	127	Gulati CM, Schreiner AM, Libby DM, et al: Outcomes of unresected ground-glass nodules with cytology suspicious for adenocarcinoma. J Thorac Oncol 9:685-91, 2014	case series	3	63	needle biopsies of GGN			45 resected 35 observed		Patients who had had a needle biopsy and confirmed early adeno. 16 of 47 elecetd to be observed, of these 6 grew and 5 were resected. The observed cases all did well. 2 of the 47 resceted cases developed mets and five devloped new cancers with thre progression nin existing GGN	
4 - Subsolid	128	Patz EF, Jr., Pinsky P, Gatsonis C, et al: Overdiagnosis in low-dose computed tomography screening for lung cancer. JAMA Intern Med 174:269-74, 2014	RCT	1+	53452	Subjects at high risk of lung cacner in an RCT of CT screeing vs CXR	CT screening	CXR	6.2 years	Overdiagnosis rate	Ovediagnosis rate was higher in BAC, a CT correlate of subsolid nodules	
4 - Subsolid	129	Maeyashiki T, Suzuki K, Hattori A, et al: The size of consolidation on thin-section computed tomography is a better predictor of survival than the maximum tumour dimension in resectable lung cancer. Eur J Cardiothorac Surg 43:915-8, 2013	case series	3	298	Stage 1A resected			not given probably a minumum of 1 year		Showed that the size of the solid component and the presense of air bronchogram wewre independednt predictors of lymph node mets. All pGGN did NOT have LN mets (30) and if solid compnent was ≤10mm. Part solid nodules had 16% had nodal mets. Solid, 32.6% mets. Some ?typos in paper but probably 233 PSN and 30 pGGN	
5 - PET	130	The Diagnosis and Treatment of Lung Cancer (Update). National Institute for Health and Clinical Excellence: Guidance. Cardiff (UK), 2011										Guideline - no need evidence reference
5 - PET	131	Gould MK, Maclean CC, Kuschner WG, et al: Accuracy of positron emission tomography for diagnosis of pulmonary nodules and mass lesions: a meta-analysis (Structured abstract), JAMA, 2001, pp 914-924	meta-analysis	1+	40 studies met inclusion criteria with 1474 nodules	Median prevelance of malignancy was 72.5%	meta-analysis with summary ROC				Sample sizes were small and blinding was often incomplete. For 1474 focal pulmonary lesions of any size, the maximum joint sensitivity and specificity of FDG-PET was 91.2% (95% confidence interval, 89.1%-92.9%). In current practice, FDG-PET operates at a point on the summary receiver operating characteristic curve that corresponds approximately to a sensitivity and specificity of 96.8% and 77.8%, respectively. There was no difference in diagnostic accuracy for pulmonary nodules compared with lesions of any size (P = .43), for semiquantitative methods of image interpretation compared with qualitative methods (P = .52), or for FDG-PET compared with FDG imaging with a modified gamma camera in coincidence mode (P = .19). Conclusions Positron emission tomography with 18-fluorodeoxyglucose is an accurate noninvasive imaging test for diagnosis of pulmonary nodules and larger mass lesions, although few data exist for nodules smaller than 1 cm in diameter. In current practice, FDG-PET has high sensitivity and intermediate specificity for malignancy.	This is a meta-analysis up to year 2000 of the diagnostic utility of PET for malignancy in patients with focal pulmonary abnormalities. The qualities of studies is commented on but the results show PET high sensitivity and good specificity for determining malignancy. They also found the methods of analysis of PET did not alter results. RECCOMENDATION: Patients with pulmonary nodules, especially >1cm should undergo PET scan and if suggestive of malignancy should undergo further investigation.
5 - PET	132	Cronin P, Dwamena BA, Kelly AM, et al: Solitary pulmonary nodules: meta-analytic comparison of cross-sectional imaging modalities for diagnosis of malignancy. Radiology 246:772-82, 2008	meta-analysis	1+	meta-analysis to estimate the diagnostic accuracy CT, MRI, PET and SPECT for evaluation of solitary pulmonary nodules (SPNs). studies published in PubMed between January 1990 and December 2005 involving at least 10 enrolled participants with histologic confirmation and having sufficient data to calculate contingency tables	Forty-four studies—10 dynamic CT, six dynamic MR, 22 FDG PET, and seven 99mTc-depreotide SPECT—met the inclusion criteria. studies involved 2867 patients with 2896 nodules. The trials were published between 1990 and 2005. 24 trials were prospective	meta-analysis of four imaging modalities	Sensitivities, specificities, positive predictive values, negative predictive values, diagnostic odds ratios, and areas under the ROC curve		Dynamic CT and MR, FDG PET, and 99mTc-depreotide SPECT are noninvasive and accurate in distinguishing malignant from benign SPNs; differences among these tests are nonsignificant		: Meta-analysis of four modalities to detect SPN. Detailed methodology and hetrogenicity accounted for. Showed similar Sensitivities, specificities, positive predictive values, negative predictive values, diagnostic odds ratios, and areas under the ROC curve for all four modalities. Publication bias evident.
5 - PET	133	Veronesi G, Bellomi M, Veronesi U, et al: Role of Positron Emission Tomography Scanning in the Management of Lung Nodules Detected at Baseline Computed Tomography Screening. Annals of Thoracic Surgery 84 (3):959-966, 2007	Case series	3	157	Patients in the COSMOS LDCT screening trial	CT-PET	Histological confirmation or follow-up	Not given	Test accuracy	PET-CT was psoitive in 51 of 58 lung cancers - see comment for sensitivity and specificty. For nodule < 1cm sensitivity was 83% and specificty 100%	Essentially showed that PET was 100% sensitive and 90% specific for nodules > 10mm that were solid or part solid. PET less good for nodule < 10mm and pure GGN
5 - PET	134	Pastorino U, Bellomi M, Landoni C, et al: Early lung-cancer detection with spiral CT and positron emission tomography in heavy smokers: 2-year results, Lancet, 2003, pp 593-597	non-randomised controlled trial	2++	1035 individuals aged 50 years or older who had smoked for 20 pack-years or more.	440 lung lesions were identified in 298 (29%) participants, 22 lung cancers diagnosed	All underwent low-dose CT annually with or without PET	For this question: Pet for patients with non-calcified nodule >7.0 mm and SUV max >2.0 to determine malignancy	2 years		PET scans were positive in 18 of 20 of the indentified cancer cases. Six patients underwent surgical biopsy for benign disease because of false-positive results (6% of recalls, 22% of invasive procedures). Negative contrast-enhanced CT and negative PET lesions were benign. Combined use of low-dose spiral CT and selective PET effectively detects early lung cancer. Lesions up to 5 mm can be checked again at 12 months without major risks of progression	The authors report the two year results of a non-randomised controlled trail aimed to be flexible in the management of pulmonary lesions detected by CT screening. The population is a high risk population. They found an overall lung cancer incidence of 2.1% but found lesions in 298 patients. Those with clearly benign features were considered benign. A sub-group went onto undergo PET scanning which correctly identified 18/20 cases(SUV max >2.0). They therefore recommend the use of Pet in algorithms to determine nodule malignancy (non-calcified and >7mm). RECCOMENDATION: In a high risk population (smokers, over 50) if a non-calcified nodule >7mm is found at CT then patients should undergo PET scan.

Section	Ref no	Bibliographic citation	Study type	Ev lev	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
5 - PET	135	Fletcher JW, Kymes SM, Gould M, et al: A comparison of the diagnostic accuracy of 18F-FDG PET and CT in the characterization of solitary pulmonary nodules.[Erratum appears in J Nucl Med. 2008 Mar;49(3):353]. Journal of Nuclear Medicine 49:179-85, 2008	prospective diagnostic trial	2+	532 participants with SPNs newly diagnosed on radiography and untreated. 60 excluded and 472 participated.	The prevalence of malignancy was 53% (184 malignant nodules, 35% were adenocarcinoma, 30% were squamous cell carcinoma, and 20% were other non–small cell lung cancer).	All patients underwent 18F-FDG PET and CT.	masked panel of 3 PET and 3 CT experts rated the studies on a 5-point scale (definitely benign to definitely malignant)	SPN tissue diagnosis or 2-y follow-up established the final diagnosis.		Likelihood ratios (LRs) for PET and CT results for combined ratings of either definitely benign (33% and 9% of patients), probably benign (27% and 12%) were 0.10 and 0.11, respectively. indeterminate (1% and 25%), probably malignant (21% and 39%), or definitely malignant (35% and 15%) were 5.18 and 1.61, respectively. Area under the receiver operating characteristic curve was 0.93 (95% confidence interval, 0.90–0.95) for PET and 0.82 (95% confidence interval, 0.77–0.86) for CT (P<0.0001 for the difference). PET inter- and intraobserver reliability was superior to CT.	: The authors report a large prospective, diagnostic trail of patients with SPN and the utility of PET scan. They seek to address some of the problems with other articles in the fiels including small sample size and bias patient selection. The study population did have a high prevelance of smokers (>90%) and male (97%). This may be due to the population enrolment from a veterens institute. However, they have sought to resuce bias in study design and image analysis. They have found PET to be superior to CT in predicting malignancy using a 5 point scale. They did not assess they utility of combined PET/CT.
5 - PET	136	Chang C-Y, Tzao C, Lee S-C, et al: Incremental value of integrated FDG-PET/CT in evaluating indeterminate solitary pulmonary nodule for malignancy. Molecular Imaging & Biology 12:204-9, 2010	cohort analysis	2+	One hundred seventeen patients (67 men and 50 women; mean age ± SD, 61.7± 13.6 years, range, 31– 86 years) with indeterminate solitary pulmonary nodules and no previous history of malignancy were analyzed.	A malignant diagnosis was based on histological findings or a clinical and radiological follow-up after at least 24 months. 43 had malignant disease, and 74 had benign lesions.	PET	PET/CT versus the companents in malignant and benign lesions	2 years		PET alone correctly classified 85% of nodules and integrated PET/CT interpretation increased the correct classification to 89%, with similar sensitivity and specificity of 88% and 89%, respectively. False-positive PET results mainly resulted from granulomatous disorders. Four (50%) of the eight cases deemed indeterminate on PET alone were resolved with combined PET/CT interpretation.	The authors conducted a study to determine the utility of PET in a cohort of patients we are addressing. They found using semi-quantitive analysis they PET was able to classify benign from malignant lesions ans a combined PET/Ct above either modality alone. The results are applicable to our population, the radiologists were blinded and cases were followed up for two years
5 - PET	137	Kim SK, Allen-Auerbach M, Goldin J, et al: Accuracy of PET/CT in characterization of solitary pulmonary lesions. Journal of Nuclear Medicine 48:214-20, 2007	Retrospective cohort study	2- (/+)	12 men and 30 women whose age ranged from 35 to 84 y (mean age +/- SD, 67 +/-11 y)	29 of the 42 lesions were malignant, 13 lesions were benign.	PET	visually scored on a 5-point scale from benign to malignant; the maximum standardized uptake value (SUVmax) was measured	up to 2 years		Comparison of CT versus PET versus PET/CT yielded accuracies of 74%, 74%, and 93%, respectively. The sensitivity and specificity for CT, PET, and PET/CT was 93%/31%, 69%/85%, and 97%/85%, respectively. There were significant differences (P , 0.05) between PET/CT and PET for accuracy, sensitivity, and specificity. Quantitative analysis does not improve accuracy of PET/CT for SPN characterization.	Although retrospective the authors have conducted and analysed the study with care. They found combined PET/CT to have improved diagnostic rate than either modality alone and that these is no difference between visual and quantative analysis. The study is limited by its retrospective design and small number and although had a – rating owing to these it should be considered towards a RECCOMENDATION. Combined PET/CT should be the investigation of choice over PET or CT alone.
5 - PET	138	Nie Y, Li Q, Li F, et al: Integrating PET and CT information to improve diagnostic accuracy for lung nodules: A semiautomatic computer-aided method. Journal of Nuclear Medicine 47:1075-80, 2006	Retrospective cohort study/case series	2-	92 consecutive cases of pulmonary nodules	Forty-two of the nodules were malignant and 50 benign	CT, 18F-FDG PET, and both CT and 18F-FDG PET. As well as clinical parameters.	Comparison of three computer aided diagnostic (CAD) schemes to determine benign from malignant nodules	2 year		Clinical parameters and CT features AUC of 0.83, for PET was 0.91 and for PET/CT was 0.95. Our CAD scheme based on both PET and CT was better able to differentiate benign from malignant pulmonary nodules than were the CAD schemes based on PET alone and CT alone	: The authors conducted a retrospective study to assess CAT to determine radiological differentiation (alongside clinical details) for determining a nodules chance of malignancy. The study is well conducted but is limited by the retrospective nature. However, it reinforces that a CT/PET combined is the optimal diagnostic tool, and computer aided image analysis is useful.
5 - PET	139	Herder GJ, Golding RP, Hoekstra OS, et al: The performance of(18)F-fluorodeoxyglucose positron emission tomography in small solitary pulmonary nodules. European Journal of Nuclear Medicine & Molecular Imaging 31:1231-6, 2004	Retrospective cohort study	2+	Thirty-five patients with 36 SPNs <10 mm in diameter	14 malignant and 22 benign nodules	FDG-PET	visual assessment of FDG PET	1.5 years		PET imaging correctly identified 30 of 36 small lesions. Specificity was 77% (17/22; 95% CI: 0.55–0.92), sensitivity 93% (13/14; 95% CI: 0.66–1.0), positive predictive value 72% (13/18; 95% CI: 0.46–0.90) and negative predictive value 94% (17/18; 95% CI: 0.73–1.0). PET imaging could be a useful tool in differentiating benign from malignant SPNs <10 mm	The authors studied the utility of PET in SPN <10mm. They found PET to be useful for small nodules. Retrospective study, risk of bias in patient selection. Analysis appropriate (PET) .
5 - PET	140	Nomori H, Watanabe K, Ohtsuka T, et al: Evaluation of F-18 fluorodeoxyglucose (FDG) PET scanning for pulmonary nodules less than 3 cm in diameter, with special reference to the CT images. Lung Cancer 45:19-27, 2004	prospective cohort analysis	2+	136 non-calcified nodules less than 3 cm	Eighty-one nodules were malignant and 55 were benign	PET scan	small (<1cm) and GGO nosules Vs others	2 years		Sensitivity and specificity for nodules with GGO images were 10 and 20%, respectively, which were significantly lower than 90 and 71% for nodules with solid images($P < 0.001$). Pulmonary noduleswhich are lessthan 1 cm in size or show GGO images on CT cannot be evaluated accurately by PET.	The authors conducted a prospective study for the utility of PET with nodule size and characteristics (GGO). They found PET to be less sensitive and specific for nodules under 1 cm and for GGO. RECCOMENDATION: PET is less sensitive and specific for nodules under 1 cm and for GGO.
5 - PET	141	Tsushima Y, Tateishi U, Uno H, et al: Diagnostic performance of PET/CT in differentiation of malignant and benign non-solid solitary pulmonary nodules. Annals of Nuclear Medicine 22:571-7, 2008	case series	3	53	screened			not given		benign PSN had higher FDG uptake than malignant	
5 - PET	142	Chun EJ, Lee HJ, Kang WJ, et al: Differentiation between malignancy and inflammation in pulmonary ground-glass nodules: The feasibility of integrated (18)F-FDG PET/CT. Lung Cancer 65:180-6, 2009	Retrospective cohort study	2-	68 GGNs in 45 patients (M:F = 24:21; mean age, 61)	criteria: (a) nodules composed of ≥50% ground-glass opacity, (b) patients who underwent integrated PET/CT within 1 week following dedicated chest CT, (c) definitive diagnosis determined by pathological specimen or at least 9 months of follow-up, and (d) lesions ≥10mmin diameter. 36 malignant GGNs and 32 inflammatory.	PET	PET criteria measured against final diagnosis. Furthermore, classification into Semi-solid and pure GG.	n/a		part-solid nodules, the maximum SUV was significantly higher in inflammation (2.00±1.18; range, 0.48–5.60) than in malignancy (1.26±0.71; range, 0.32–2.6) (P = 0.018). in pure GGNs, the maximum SUV of malignancy (0.64±0.19; range, 0.43–0.96) and inflammation (0.74±0.28; range, 0.32–1.00) showed no difference (P = 0.37)	The authors conducted a retrospective cohort analysis by searching their radiology database. They found PET to show higher uptake in inflammatory conditions (such as CAP) Vs malignancy in semi-solid nodules, and no differences in pure nodules. There is significant bias with patient selection and small patient numbers. In GGO there is limited utility of PET
5 - PET	143	Kinahan PE, Fletcher JW: Positron emission tomography-computed tomography standardized uptake values in clinical practice and assessing response to therapy. Semin Ultrasound CT MR 31:496-505, 2010	Review	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	This article reviews the theory of PET imaging SUV measurement and discusses the inherent inaccuracies
5 - PET	144	Evangelista L, Panunzio A, Polverosi R, et al: Indeterminate lung nodules in cancer patients: pretest probability of malignancy and the role of 18F-FDG PET/CT. AJR Am J Roentgenol 202:507-14, 2014	cohort	2+	59 consecutive oncologic patients (mean age ± SD, 67 ± 10 years)	Thirty-one patients had an SPN, and 28 had multiple lung lesions. The median diameter of the SPNs was 12 mm (range, 5–50 mm), and that of multiple lesions was 10 mm (range, 5–18 mm). 31 malignant and 28 benign.	PET/CT to investigate nodule. Incorporated Mayo clinic model and veteran affairs model.	performance chracteristics against finl diagnoses	pathology or radiology for 2 years		PET/CT improves stratification of cancer patients with indeterminate pulmonary nodules. A substantial number of patients considered at low and intermediate pretest likelihood of malignancy with histology-proven lung malignancy showed abnormal PET/CT findings.	The authors reviewed a single institution database and identified cancer patients with subsequent SMP/MPN. They assessed the utility of PET scan, and incorporated the mayo clinic and VA clinic models to assigh risk ccatagory. They found that the use of PET/CT was most importatnt in those with lo/intermediate risk of malignancy (pre-test).
5 - PET	145	Vansteenkiste JF, Stroobants SG, Dupont PJ, et al: FDG-PET scan in potentially operable non-small cell lung cancer: do anatometabolic PET-CT fusion images improve the localisation of regional lymph node metastases? The Leuven Lung Cancer Group. Eur J Nucl Med 25:1495-501, 1998	prospective cohort analysis	3	50	Patient with potentially operable NSCLC	all patients had CT, PET, and invasive surgical staging	all compared blind with surgical pathology results	N/A	Test accuracy	The sensitivity, specificity, and accuracy in detecting N2 disease of CT was 67%, 59%, and 64%, respectively. Results of PET blinded to CT were significantly better (p=0.004): 67%, 97%, and 88%, respectively. For PET visually correlated with CT, this was 93%, 97%, and 96%, respectively.	PET was significantly more accurate than CT in N2 staging in NSCLC. Both examinations were complementary.

Section	Ref no	Bibliographic citation	Study type	Ev lev	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
5 - PET	146	Matthies A, Hickeson M, Cuchiara A, et al: Dual time point 18F-FDG PET for the evaluation of pulmonary nodules. Journal of Nuclear Medicine 43:871-5, 2002	cohort	2-	Thirty-six patients (21 women, 15 men; mean age, 67 y; range, 36–88 y) with 38 known or suspected malignant pulmonary nodules	20 malignant tumors, 16 patients benign lesions.	Dual Time Point 18F-FDG PET	SUV values and the changes	18-26 months		The standardized uptake values (SUVs) were calculated for both time points. tumor SUVs (mean_SD) were 3.66_1.95 <(scan 1) and 4.43 _ 2.43 (scan 2) (20.5% _ 8.1% increase; *P* < 0.01). Four of 20 malignant tumors had SUVs of <2.5 on scan 1 (range, 1.12–1.69). Benign lesions had SUVs of 1.14 _ 0.64 (scan 1) and 1.11 _ 0.70 (scan 2) (*P* _ not significant). dual time point scanning with a threshold value of 10% increase between scan 1 and scan 2 reached a sensitivity of 100% with a specificity of 89%	The authors find that dual time point Pet is more accurate to distinguish malignant lesions. They present a small study and do not comment on radiologist blinding. They also have low/none BAC (a common form of false negative) and low incidence granulomatous disease (false positive). Their findings would need to be studied in a larger cohort. Furthermore the authors are not clear if this was a secondary analysis or a specifically designed study.
5 - PET	147	Cloran FJ, Banks KP, Song WS, et al: Limitations of dual time point PET in the assessment of lung nodules with low FDG avidity. Lung Cancer 68:66-71, 2010	retrospective database analysis	2-	113 patients underwent a total of 130 DTP PET/CT with 152 lesions assessed	Sixty-seven of the 128 lesions were able to be diagnosed as either benign (29) or malignant (38) in nature. Of these 67 42 had SUV <2.5	Dual time point (1h and 2h) PET scan if SUV<2.5	If dual time point could distinguish benign and malignant lesions	n/a		Utilizing a maximum SUV increase of 10%, which optimizes our sensitivity and specificity; our results demonstrate a sensitivity of 63% and a specificity of 59%, similar to other investigators evaluating lesions with low FDG avidity. Dual time point PET is unsatisfactory for assessing whether or not a non FDG-avid pulmonary nodule is malignant	the authos have conducted a retrospective database analysis of patients with low SUV values in assessing dual time point PET. They have shown no utility of such a method. There is a very large bulk of patiens missing/excluded as information was not available. This biased results.
5 - PET	148	Zhang L, Wang Y, Lei J, et al: Dual time point 18FDG-PET/CT versus single time point 18FDG-PET/CT for the differential diagnosis of pulmonary nodules: a meta-analysis. Acta Radiol 54:770-7, 2013	meta/sys review	1+/-	eight articles, with a total of 415 patients and 430 pulmonary nodules	PubMed (1966-2011.11), EMBASE (1974-2011.11), Web of Science (1972-2011.11), Cochrane Library (-2011.11), and four Chinese databases — CBM (1978-2011.11), CNKI (1994-2011.11), VIP (1989-2011.11), and Wanfang Database (1994-2011.11)	Dual Vs Single time point CT-PET	used dual time point 18FDG-PET/CT and single time point 18FDG-PET/CT as diagnostic tests for pulmonary, pathology or complete clinical follow up. Human studies and complete cperformance characteristics.	n/a		the summary sensitivity of dual time point 18FDG-PET/CT was 79% (95%CI, 74.0–84.0%), and its summary specificity was 73% (95%CI, 65.0–79.0%); the summary LRþ was 2.61 (95%CI, 1.96–3.47), and the summary LR– was 0.29 (95%CI, 0.21–0.41); the summary DOR was 10.25 95%CI, 5.79–18.14), and the area under the SROC curve (AUC) was 0.8244. Significant heterogeneity existed.	Meta analysis with significant heterogenicity and including 8 studies showed there may be an advantage in dual Vs dingle time point analysis. Larger studies needed.
5 - PET	149	Cao JQ, Rodrigues GB, Louie AV, et al: Systematic review of the cost-effectiveness of positron-emission tomography in staging of non-small-cell lung cancer and management of solitary pulmonary nodules. Clinical Lung Cancer 13 (3):161-170, 2012	sys review	1+	Eighteen studies in English Language from 10 different countries, with 5 studies specifically for SPNs	MEDLINE including PreMEDLINE (1950 to May 2010), EMBASE (1980 to Week 18, 2010), National Health Service (NHS) Economic Evaluation Database (2nd Quarter, 2010), and Health Technology Assessment Database (Issue 2, 2010)	mean PET costs, median average cost savings per patient, incremental cost-effectiveness ratio based on life years saved and quality-adjusted life years were calculated	mean cost of PET was $1478	n/a	PET imaging in the staging of NSCLC and diagnosis of SPNs is worth the cost in context of proper medical indications		The authors acknowledge that differences in healthcare management, health care costs, and disease prevalence mean that results from one country cannot always be applied another, However, with the limitations of the studies present, the heterogeneity there is a role in terms of cost-effectiveness for PET in the management of SPNs when assessed with a pre-test probability score.
5 - PET	150	Naalsund A, Maublant J: The solitary pulmonary nodule--is it malignant or benign? Diagnostic performance of Tc-depreotide SPECT. Respiration 73:634-41, 2006	non-randomised	2-	146 patients were enrolled in the study, with 118 following exclusions.	73 malignant, 45 benign	All had SPECT, 29 had SPECT and PET	performance chracteristics against finl diagnoses	pathological diagnosis		SPECT had sensitivity, specifi city and diagnostic accuracy of 89, 67 and 81%, respectively. SPECT was comparible to PET	The authors conclude spect has utility where PET is not available with moderate performance characteristics for nudule diagnosis
5 - PET	151	Schroeder T, Ruehm SG, Debatin JF, et al: Detection of pulmonary nodules using a 2D HASTE MR sequence: comparison with MDCT. AJR American Journal of Roentgenology. 185:979-84, 2005	non-RCT	2+	30 patients (19 men, 11 women; age range, 29–87 years; mean age, 53.3 years) with various pulmonary metastasizing malignancies	Breast cancer 6, Melanoma 2, Thyroid carcinoma 3, Gastric cancer 2, Colorectal carcinoma 3, Sarcoma 2,Testicular carcinoma 4, Hypernephroma 1, Lymphoma 1, Central bronchial carcinoma 3, Peripheral bronchial carcinoma 3	Study compared 4MDCT (reference standard) to MRI using HASTE sequence.	MDCT revealed 1,102 lung lesions in 30 patients that were located in 104 of 150 examined lobes. The HASTE MR sequence revealed a total of 1,031 pulmonary lesions that were distributed among all 30 patients.	n/a		Sensitivity values for the HASTE MR sequence were 73% for lesions smaller than 3 mm, 86.3% for lesions between 3 and 5 mm, 95.7% for lesions between 6 and 10 mm, and 100% for lesions bigger than 10 mm. The overall sensitivity for the detection of all pulmonary lesions was 85.4%.	the authors have correlated findings in patients with known metastatic disease to determine if HASTE MRI couls be usied with MDCT at reference. They found a good rate of detection of nodules using MR, especially for nodules >5mm. They conclude that MR HASTEcould be used in place of CT for further evaluation of nodules >5mm. The study is well conducted however there is little data about numbers considered but excluded.
5 - PET	152	Vogt FM, Herborn CU, Hunold P, et al: HASTE MRI versus chest radiography in the detection of pulmonary nodules: comparison with MDCT. AJR American Journal of Roentgenology. 183:71-8, 2004	cohort	2+	64 consecutive patients (34 men and 30 women; age range, 23–95 years; mean age, 56 years) with confirmed malignancy	breast cancer, *n* = 14; bronchial carcinoma, *n* = 9; colorectal cancer, *n* = 11; gastric cancer, *n* = 2; hypernephroma, *n* = 1; lymphoma, *n* = 4; melanoma, *n* = 6; prostate carcinoma, *n* = 2; testicular carcinoma, *n* = 4; thyroid carcinoma, *n* = 8; and sarcoma, *n* = 3	All patients underwent CxR, 4MDCT and 1.5T MRI. CT served as reference.	Ability of CxR and MRI with HASTE sequencing to determine pulmonary nodules	n/a		3 excluded because of claustrophobia. Data on 61 patients. The sensitivity values for HASTE MRI were 94.9% for lesions between 5 and 10 mm, 97.4% for lesions between 11 and 30 mm, and 100% for lesions exceeding 30 mm.	The authors performed a study to determine if HASTE MR could reliably detect nodules in patients with confirmed malignancy. They concluded that for nodules over 5 mm HASTE MR provides a alternative to CT. They have analysed the data in a blinded fasion and had clear aims. The total number of potentially eligible patients is unknown.
5 - PET	153	Wu LM, Xu JR, Hua J, et al: Can diffusion-weighted imaging be used as a reliable sequence in the detection of malignant pulmonary nodules and masses? Magn Reson Imaging 31:235-46, 2013	meta/sys review	1-	10 studies	MEDLINE and EMBASE databases were searched from January 2001 to August 2011	English articles, DWI used, DWI performance characteristics reported, quality of study design, >9 patients, pathology as gold standard.	performance characteristics to distinuish pulmonary nodules			Pooled sensitivity for DWI was 0.84 (95% CI, 0.76– 0.90) with significant heterogeneity (χ^2=34.66, P=.003) and a pooled specificity of 0.84 (95% CI, 0.64–0.94) with heterogeneity (χ^2=51.61, P=.002).	Significant hetrogenicity seen, multiple smaller retrospective studies included. threshold value for malignant/benign lesion classification could not be made

Section	Ref no	Bibliographic citation	Study type	Ev lev	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
5 - PET	154	Mori T, Nomori H, Ikeda K, et al: Diffusion-weighted magnetic resonance imaging for diagnosing malignant pulmonary nodules/masses: comparison with positron emission tomography. Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer 3:358-64, 2008	cohort	2+	114 patients with 165 pulmonary nodules/masses prospectively underwent FDG-PET and DWI within a 2-week interval.25 with a pure ground-glass opacity (GGO) appearance were excluded. 140 nodules/masses in 104 patients were entered in the study. 55 men and 49 women with their mean age of 68 _ 13-year-old (median, 70; range, 20–80- year-old).	Malignant (*n* =106; Primary lung cancer; Adenocarcinoma 66, Squamous-cell carcinoma 21, Adenosquamous carcinoma 3, Lymphoepithelioma-like carcinoma , Carcinoid 1, Metastatic lung tumor 14. Benign (*n* = 34); Hamartoma 1, Schwannoma 1, Active Inflammation 6, chronic inflammation 24, Intrapulmonary lymph node 1, Amyloid nodule 1	All patients had of diffusion-weighted magnetic resonance imaging (DWI) with apparent diffusion coefficient (ADC)calculation and FDGPET with SUV-CR calculation	Compare FDG EPT to DWI MRI in assessment of nodules prior to resection	n/a		Cutoff values of the ADC-min and the SUV-CR for benign/malignant discrimination to be 1.1 _ 10_3 mm2/s and 0.37, respectively. DWI and PET showed sensitivities of 0.70 and 0.72 and specificities of 0.97 and 0.79, respectively. DWI showed a significantly higher specificity than PET because of fewer falsepositives for active inflammatory lesions (p= 0.03). The ADC-min and SUV-CR values showed a significant reverse correlation (r=-0.504, p< 0.001).	The authors sought to compare the utility of PET Vs MRI for pre-operative assessment of nodules. They found the two modalities to be similar in diagnostic rates and similar false+ve and negative rates. They advocate Mri as it is cheaper and more readily available.
5 - PET	155	Ohba Y, Nomori H, Mori T, et al: Diffusion-weighted magnetic resonance for pulmonary nodules: 1.5 vs. 3 Tesla. Asian Cardiovascular & Thoracic Annals 19:108-14, 2011	cohort	2-	58 patients with 76 (58 malignant, 18 benign) pulmonary nodules	58 malignant tumors 42 tumors were resected by lobectomy, 8 by segmentectomy, and 9 by wedge resection).1 active inflammatory nodule were diagnosed histologically 17 chronic inflammatory nodules were diagnosed clinically without histology	1.5-Tand 3-Tesla imaging and 18F-fluorodeoxyglucose positron-emission tomography prior to surgery	Compared 1.5-T and 3-T MR modialities and each to PET			The sensitivities and specificities for discriminating benign and malignant lesions were similar among the 3 imaging techniques: 1.5-T imaging, 0.91 and 0.90; 3-T imaging, 0.88 and 0.94; positron-emission tomography, 0.94 and 0.94. 1.5-T and 3-T DWI are equally useful for imaging malignant pulmonary nodules, although the ADC values on 3-T DWI did not correlate with the FDG-uptake on PET as well as the ADC values on 1.5-T DWI.Both 1.5-T and 3-T diffusion-weighted magnetic resonance imaging modalities are equally useful for assessing malignant pulmonary nodules.	The authors compare the ability of two MR techniques in detection of nodules and find they are equally comparable. They also found 1.5T correlates with PET, whereas s-T does not (using PET SUV-CR). They conclude there may be a role for MRI in imaging malignant nodules. The study does not seek to determine benign from malignant nodules using these imagaing modalities.
5 - PET	156	Zou Y, Zhang M, Wang Q, et al: Quantitative investigation of solitary pulmonary nodules: dynamic contrast-enhanced MRI and histopathologic analysis. AJR American Journal of Roentgenology. 191:252-9, 2008	cohort	2-	68 patients (42 men, 26 women; mean age, 64.5 years; age range, 26–80 years) were consecutively enrolled in this study. All patients had definite SPNs 10–30 mm in diameter	40 nodules were malignant (17 adenocarcinomas, 15 squamous cell carcinomas, two small cell carcinomas, two large cell carcinomas, and one bronchial carcinoid and three metastatic lung tumors). Sixteen nodules were benign (five hamartomas, nine tuberculomas, and two granulomas). Twelve nodules were active inflammatory lesions (six, active tuberculosis; two, cryptococcosis infection; two, aspergillosis; two, organizing pneumonia).	MRI scan. All patients had surgical resection within a week	time–signal intensity curves generated after bolus injection of contrast material, steepest slope, peak height, and enhancement ratios of signal intensity at the first, second, and fourth minutes were calculated. Pathology was reviewed at resection for microvessel density and a score given.			The dynamic MRI values of benign SPNs were significantly lower than those of the other SPNs (p < 0.01). The enhancement ratio at the fourth minute for active inflammatory SPNs was significantly higher than that of malignant SPNs (p < 0.01). A high correlation coefficient (r = 0.87, p < 0.001) was found between steepest slope and microvessel density.	: The authors found areas of enhancement on MRI correlate with microvessel density and this can determine the liklihood of a benign Vs Malignant Vs actice inflammatory nodule. Potential patient enrollment is not clearly described. And it is not clear whether the image review process was blinded.
5 - PET	157	Satoh S, Nakaminato S, Kihara A, et al: Evaluation of indeterminate pulmonary nodules with dynamic MR imaging. Magn Reson Med Sci 12:31-8, 2013	Case series	2-	51 nodules in 51 patients (25 malignant, 12 inflammatory, 14 benign). Nodules were v large (up to 60mm)	As prev	MR images acquired at various intrewals	Dynamic MR	pathological	Morphologic enhancement, peak rate, time to peak enhancement, slope did not distinguish malignant from benign		Dynamic MR do not help distinguish benign from malignant nodules nut this study included many nodules > 30 mm.
5 - PET	158	Mamata H, Tokuda J, Gill RR, et al: Clinical application of pharmacokinetic analysis as a biomarker of solitary pulmonary nodules: dynamic contrast-enhanced MR imaging. Magn Reson Med 68:1614-22, 2012	cophort	2-	Thirty patients of 34 enrolled with SPNs	9 males, 25 females, 26–87 years old, average 65 years old. 25 malignant and 5 benign SPNs	T1 and T2-weighted structural images and 2D turbo FLASH perfusion images were acquired with shallow free breathing	perfusion indices and pharmacokinetic parameters assessed	Pathology		Using cut off of kep = 1.0 min−1 was 76%, specificity was 100%, positive predictive value (PPV) was 100%, negative predictive value (NPV) was 45%, and accuracy was 80%.	Small study, enrolment not clear, low numbers of benign SPNs. Study shows some encouraging results but given sample sixe there would need to be a larger study to confirm the results and as such there remains little to support this over PET.
5 - PET	159	Bai R-j, Cheng X-g, Qu H, et al: Solitary pulmonary nodules: comparison of multi-slice computed tomography perfusion study with vascular endothelial growth factor and microvessel density. CHINESE MEDICAL JOURNAL 122:541-7, 2009	cohort	2-	71 patients eligible. 68 included (38 men, 30 women, age range 28–79 years, mean age 52.8 years).	36 malignant nodules (16 adenocarcinoma, 14 squamous carcinoma, 2 adenosquamous carcinoma, 4 metastatic carcinoma), 16 inflammatory nodules (12 inflammatory granuloma, 4 suppurative pneumonia), and 16 benign nodules (12 tuberculoma, 4 harmatoma).	contrast enhanced CT scan	Contrast enhanced 64-slice spiral CT and histological specimens were assessed by immunohistochemistry.	n/a		The perfusion peak heights of malignant ((96.15±11.55) HU) and inflammatory ((101.15±8.41) HU) SPNs were significantly higher than those of benign ((47.24±9.15) HU) SPNs (P <0.05, P <0.05). The VEGF positive expressions appeared in 32 patients with malignant SPNs and 2 patients with benign SPNs, and the average value of the MVD was higher in patients with malignant SPNs (36.88±6.76) than in patients with either benign (4.51±0.60) or inflammatory (26.11±5.43) SPNs (P <0.05, P <0.05). Multi-slice CT perfusion has shown strong positive correlations with angiogenesis in SPNs.	: The authors have undertaken CT (with contrast) and found that contrast enhancement (measured in various ways) correlates with histopathological features to suggest angiogenesis. This has a weaker correlation with malignant vs inflammatory but there is a clearer difference between malignant Vs benign. The conclusion is limited with the small numbers, and method of analysis.
5 - PET	160	Yi CA, Lee KS, Kim EA, et al: Solitary pulmonary nodules: dynamic enhanced multi-detector row CT study and comparison with vascular endothelial growth factor and microvessel density. Radiology 233:191-9, 2004	cohort	3	One hundred thirty-one patients with solitary pulmonary nodules (82 men, mean age 56 years	701 malignant and 61 benign	unenhanced thin-section CT, followed by dynamic helical CT	measurement of peak attenuation, net enhancement, and enhancement dynamics and correlated with vascular endothelial growth factor (VEGF) staining	Final diagnosis by surgery of CT follow up for two years.	Using a cut off of 30 HU; sensitivity for malignant nodules was 99%, specificity was 54%, positive predictive value was 71%, negative predictive value was 97% and accuracy was 78%		The authors conclude that sensitivity remains high, but specificity is poor for DCE-CT
5 - PET	161	Sitartchouk I, Roberts HC, Pereira AM, et al: Computed tomography perfusion using first pass methods for lung nodule characterization. Investigative Radiology 43:349-58, 2008	cohort	3	Fifty-seven patients	25 men and 32 women, average age 63 years. 51 malignant and 6 benign nodules	first-pass, dynamic contrast-enhanced-CT	Paramaters measured on first pass CT with correlation of histology	histology	microvascular characterization in terms of BF, BV, or Kps allowed differentiation from benign and malignant nodules		: This study does demonstrate some parameters that may allow distinction of benign and malignant nodules. However, there are only 6 benign nodules and would therefore need to validated in larger cohorts.

Section	Ref no	Bibliographic citation	Study type	Ev lev	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
5 - PET	162	Li Y, Yang ZG, Chen TW, et al: First-pass perfusion imaging of solitary pulmonary nodules with 64-detector row CT: comparison of perfusion parameters of malignant and benign lesions. British Journal of Radiology 83:785-90, 2010	non-comparative	3	93 evaluated, 77 patients included (52 men and 25 women; age range 24–79 years; mean age 55.7 years)	46 malignant, 22 benign and 9 active inflammatory	first-pass perfusion imaging with a 64-detector row CT scanner	Perfusion, peak enhancement intensity (PEI), time to peak (TTP) and blood volume (BV) were measured			Authors found mean values higher in malignant from benign but not inflammatory. Using arbitrary cut offs for each they were able to demonstrate higher sens and PPV, however this was for benign Vs Malignant. They did find an absence of perfusion and relatively low blood volumes are predictors a lesion is benign.	. The study does not allow us to make recommendations based on thier paramaters as they are using mean values and found they are higher in malignant Vs benign but not inflammatory. Perfusion parameters do yield promising results to predict benignity but in practice it is not clear whether this would add little over other modalities.
5 - PET	163	Ohno Y, Koyama H, Matsumoto K, et al: Differentiation of malignant and benign pulmonary nodules with quantitative first-pass 320-detector row perfusion CT versus FDG PET/CT. Radiology 258:599-609, 2011	Cohort study	3	50 patients	Patients with pulmonary nodules (76 nodules) - malignant (43), benign with low biological activity (6), benign with high biological activity (27)	Quantitative first-pass perfusion CT	PET-CT	Not stated	Ability to discriminate benign from malignant lesions - judged by ROC curve	Nodule perfusion and extraction fraction performed significantly better than SUVmax (judged by ROC AUC). Sensitivity and specificity of Nodule perfusion and extraction fraction were higher than SUVmax	Conclude that dynamic first-pass area-detector perfusion CT has potential to be more specific and accurate than PET-CT. Tended to be large lesions (median 16mm), no assessment of intra-observer variability so may not perform as well in routine use,
5 - PET	164	Ohno Y, Nishio M, Koyama H, et al: Comparison of quantitatively analyzed dynamic area-detector CT using various mathematic methods with FDG PET/CT in management of solitary pulmonary nodules. AJR Am J Roentgenol 200:W593-602, 2013	cohort study	+	Fifty-two consecutive patients with 96 pulmonary nodules (84 referred)	29 men, mean age 72.4. Three groups: malignant nodules (n = 57), benign nodules with low biologic activity (n = 15), and benign nodules with high biologic activity (n = 24)	dynamic area-detector CT, PET/CT, and microbacterial or pathologic examinations	total, pulmonary arterial, and systemic arterial perfusions measured. SUV max for PET	pathology		Accuracy of total perfusion (83.3%) was significantly greater than the accuracy of the other indexes and over PET	Authors conclude this modality may have some better indices than other scanning methods but the SUVmax cut off was used. They conclude this may be complimentary to PET.
5 - PET	165	Louie AV, Senan S, Patel P, et al: When is a biopsy-proven diagnosis necessary before stereotactic ablative radiotherapy for lung cancer?: A decision analysis. Chest 146:1021-8, 2014	Descision tree analyis	3	N/A	N/A	PET-SABR and Biospy-SABR	Patholical diagnosis	N/A	Most QALYs	For prior malignancy probability of 65%, PET scan-biopsy-SABR was the preferred treatment strategy yielding 2.640 QALYs, compared with 2.563 and 2.086 for the PET scan-directed SABR and surveillance strategies, respectively . Consclude that PET-SABR better where probablity is 85%	I.e. minimal difference for PET and biopsy. The toxicty from biopsy may have been underestimated as if concern about morbidity, this implies lung disease that would increase toxicity. Thus a lower pre test probabilioty might be indicated
6- Biopsy	166	Chu X-Y, Hou X-B, Song W-A, et al: Diagnostic values of SCC, CEA, Cyfra21-1 and NSE for lung cancer in patients with suspicious pulmonary masses: a single center analysis. Cancer Biology & Therapy 11:995-1000, 2011	Cohort study	2-	659 patients with lung cancer vs 146 patients with benign pulmonary masses	Lung cancer patients with predominantly early stage disease (67.4% Stage I) vs benign group comprising TB, inflammatory pseudotumours, or other benign masses	Analysis of serum concentrations of 4 potential biomarkers	N/A	N/A	Ability to discriminate benign from malignant lesions	Most AUC values for individual tests were between 0.6 and 0.7 (i.e. poor) with highest value Cyfra21-1 but still only 0.72. When specifically looking at early stage cancer (of most relevance to nodules) sensitivity was low at 23.2%	Not sufficiently sensitive or accurate for use in clinical practice.
6- Biopsy	167	Shen J, Liu Z, Todd NW, et al: Diagnosis of lung cancer in individuals with solitary pulmonary nodules by plasma microRNA biomarkers. BMC CANCER 11:374, 2011	Cohort	2-	156	Patients with known benign and malignant solitary pulmonary nodules	Analysis of 5 plasma micro RNA markers	Logistic regression model	N/A	Accuracy of distinguishing benign and malignant nodules	Sensitivity of 75% and specificity of 85% for malignant nodule detectction	
6- Biopsy	168	Daly S, Rinewalt D, Fhied C, et al: Development and validation of a plasma biomarker panel for discerning clinical significance of indeterminate pulmonary nodules. J Thorac Oncol 8:31-6, 2013	Cohort	3	136 in discover set, 81 in test set	Patients with indeterminate nodules - 61 benign and 20 malignant in the test set	N/A	different biomarkers	N/A	Test accuracy in the cohort	& biomarkers out of 17 were selected and these achieved a 95% sens and 23% spec with a 93.8% NPV	Median size of nodules quite large: 14mm (3-50) for benogn in test set and 22mm (8-80) in validation set Thus may not relfect truly indeterminate nodules and some noduels are outside the definition for this guidelline.
6- Biopsy	169	Higgins G, Roper KM, Watson IJ, et al: Variant Ciz1 is a circulating biomarker for early-stage lung cancer. Proc Natl Acad Sci U S A 109:E3128-35, 2012	Cohort study	2-	170 in Set 1, 160 in Set 2	Patients with lung cancer (NSCLC, SCLC, various stages), COPD, asthma, anaemia, no known disease, benign lung nodules inflammatory lung disease, smokers	Measurement of plasma levels of CIZ1	N/A	N/A	Ability of Ciz-1 levels to discriminate between cancers and benign disease	AUC ROC was 0.958 for Set 1, and 0.913/0.905 for Set 2 (vs age-matched smokers or individuals with benign lung nodules respectively).	Reasonable performance in this cohort, but technology is not currently suitable for wider use, and needs prospective validation in larger cohort with control group of benign nodules before can be considered as biomarker to discriminate benign vs malignant nodules.
6- Biopsy	170	Emad A, Emad V: The value of BAL fluid LDH level in differentiating benign from malignant solitary pulmonary nodules. Journal of Cancer Research & Clinical Oncology 134:489-93, 2008	case control	2-	59 case (mal 42 and benign 17) and 21 control	solitary pulmonary lesion 1-4cm surrounded by aerated lung found by screening CXR	bronchoscopy and BAL	BAL (and serum) LDH	none	LDH in BAL and serum as measured in malignant vs benign nodules vs controls	BAL LDH was significantly higher in malignant than on benign or control serum/BAL LDH was significantly higher in control than malignant	control gp much younger// all patients were non smokers
6- Biopsy	171	Boyle P, Chapman CJ, Holdenrieder S, et al: Clinical validation of an autoantibody test for lung cancer. Ann Oncol 22:383-9, 2011	cohort	2-	145	Lung cancer stage 1 or 2 (nonsmall cell and small cell)	autoantibody panel	146 controls	unclear	sensitivity and specificity	sens 36% and specificity 91%	
6- Biopsy	172	Lam S, Boyle P, Healey GF, et al: EarlyCDT-Lung: an immunobiomarker test as an aid to early detection of lung cancer. Cancer Prev Res (Phila) 4:1126-34, 2011	cohort	2-	574 patients with cancer and unspecified number of benign controls (597	Patient populations with lung cancers (various histology and stage). No demographic	autoantibody panel	See previous	Not stated	sensitivity and specificity of 6 Ab panel	Sensitivity varied from 31% to 57% in 4 cohorts, and specificity from 84-89% where quoted	Little information presented about control populations, no benign nodules, variable histology and stage of lung cancer populations. Data does not support the use of this test in discriminating
6- Biopsy	173	Jett JR, Peek LJ, Fredericks L, et al: Audit of the autoantibody test, EarlyCDT(R)-lung, in 1600 patients: an evaluation of its performance in routine clinical practice. Lung Cancer 83:51-5, 2014	Case control	2-	1613 patients	Patients deemed high risk for lung cancer by their treating clinicians.	Measurement of 7 autoantibody panel	None	6 months	Development of lung cancer	CDT test had 41% sensitivity for predicting lung cancer development, with positive result increasing by 5.4 fold the chance of lung cancer diagnosis	Very high rate of lung cancer development in 6/12 (4%) suggesting that some may have had symptoms of lung cancer at the time the test was used. Not supportive of ability of test to discriminate benign from malignant nodules
6- Biopsy	174	van 't Westeinde SC, Horeweg N, Vernhout RM, et al: The role of conventional bronchoscopy in the workup of suspicious CT scan screen-detected pulmonary nodules. Chest 142:377-84, 2012	Case series	3	308 patients	Patients undergoing CT screening in NELSON study with abnormal findings on CT	Flexible bronchoscopy	None	At least 2 years	Diagnostic accuracy for diagnosing cancer	Sensitivity was 13.5%, specificity 100%, PPV 100% and NPV 47.6%. Of all cancers, 1% were detected by bronchoscopy alone and were retrospectively invisible on both low-dose CT and CT scan with IV contrast	Minimal yield from routine bronchoscopy for abnormal findings on CT screening
6- Biopsy	175	Baaklini WA, Reinoso MA, Gorin AB, et al: Diagnostic yield of fiberoptic bronchoscopy in evaluating solitary pulmonary nodules. Chest 117:1049-54, 2000	obs	3	177	solitary pulmonary lesion without endobronchial lesion	bronchoscopy with brush wash and transbronchial biopsy with fluoroscopic guidance	lesion size/ distance from the hilum/	4 years	diagnostic yield	151 malignant and 26 benign //diagnostic yield was 64% in malignant and 35% in benign// size of lesion <2cm 23% diagnosis, central 82% diag, vs peripheral 53%	all men// nodules >3cm included//yield of bronchoscopy is especially low in lesions<2cm which are peripheral (14%)
6- Biopsy	176	Aoshima M, Chonabayashi N: Can HRCT contribute in decision-making on indication for flexible bronchoscopy for solitary pulmonary nodules and masses? Journal of Bronchology 8 (3):161-165, 2001	obs	3	200	SPN/M who had an HRCT chest and no endobronchial lesion seen	HRCT chest	size distance from inlet of segmental bronchus Ct bronchus sign (bronchus runs into lesion)	2 year	Likelihood ratio of diagnosis from FFB	size >25mm <40mm from inlet of segmental bronchus and presence of CT bronchus sign likelhood ratio of positive FBB 1.13 to 4.08	fluoroscopic guidance used / included lesions>3cm/should fufill at least 2/3 conditions and will give diagnosis 68.6%
6- Biopsy	177	Schwarz C, Schonfeld N, Bittner RC, et al: Value of flexible bronchoscopy in the pre-operative work-up of solitary pulmonary nodules. Eur Respir J 41:177-82, 2013	Case series	3	225	Patients with solitary pulmonary nodule detected in routine clinical practice	Flexible bronchoscopy	None	Not quoted	Diagnostic yield and extent to which surgical management was altered	Unsuspected endobronchial involvement found in 4.4% of cases, bronchoscopy clarified aetiology in 41% cases. Surgery was cancelled in 4 cases	Surgical approach modified in a small proportion of cases
6- Biopsy	178	Oki M, Saka H, Kitagawa C, et al: Novel thin bronchoscope with a 1.7-mm working channel for peripheral pulmonary lesions. European Respiratory Journal 32:465-71, 2008	Case series	3	102	Patients with solitary pulmonary nodules, median size 30.5mm	Noval thin 3.5mm bronchoscope with 1.7mm working channel	N/A	18 months	Whether a diagnosis was obtained	A diagnosis was reached in 74% of malignant nodules and 60% of benign nodules	

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6- Biopsy	179	Lai RS, Lee SS, Ting YM, et al: Diagnostic value of transbronchial lung biopsy under fluoroscopic guidance in solitary pulmonary nodule in an endemic area of tuberculosis. Respiratory Medicine 90:139-43, 1996	obs	3	138	SPN <4cm on CXR	TBB and brush under fluorscopic guidnace	diagnosis of lung cancer vs TB	at least 2 months	sensitivity	Sens for lung cancer 68% (62/91)and TB 55% (22/45)	
6- Biopsy	180	Herth FJF, Eberhardt R, Becker HD, et al: Endobronchial ultrasound-guided transbronchial lung biopsy in fluoroscopically invisible solitary pulmonary nodules: a prospective trial. Chest 129:147-50, 2006	obs	3	138 of which 54 had lesion invisible to fluoroscopy	solitary pulmonary lesion (1.4-3.3cm) on Ct scan and referred for bronchoscopy	EBUS guided bronchoscopy	EBUS	diagnosis made at surgery	diagnosis	lesion identified in 48/54 (89%) diagnosismade in 38/54 (70%)	lesions unable to be visualsed by EBUS were in RUL or apical LUL// the 16 undiagnosed had surgery and 10 were malignant and 6 benign // 9 patients (17%) were saved a surgical procedure
6- Biopsy	181	Eberhardt R, Ernst A, Herth FJF: Ultrasound-guided transbronchial biopsy of solitary pulmonary nodules less than 20 mm. European Respiratory Journal 34:1284-7, 2009	obs	3	100	solitary pulmonary lesion <20mm detected on Ct scan but not visible under fluoroscopy	EBUS guided biopsy	diagnostic yield	not specified, rest had surg biopsy to establish Dx	diagnosis	nodules were detected by EBUS in 67/100 diagnosis made in 46/67 41 were malignant and 5 benign	size no difference in yield or ability to be detected by EBUS// overall diagiagnostic yield was 46/100// sensitivity 72%, specificity 100%, NPV 38 and PPV 100 in malignancy//no PET results//no control
6- Biopsy	182	Kurimoto N, Miyazawa T, Okimasa S, et al: Endobronchial ultrasonography using a guide sheath increases the ability to diagnose peripheral pulmonary lesions endoscopically. Chest 126:959-65, 2004	obs	3	150	peripheral SPN < 3cm detected on CXR or CT	bronchoscopy using EBUS guide sheath	none	until definate diagnosis made or lesions regressed on radiology	diagnostic yield	116/150)77%) diagnostic. // Malignant 82/101 (81%) and benign 34/49 (69%)// no signig diff in Dx rate depending on size inc <1cm lesions	121/150 probe was within lesion then diagnosis 87%, if probe adjacent 8/19 diagnosis (42%). There were poorer results from Left Upper lobe
6- Biopsy	183	Eberhardt R, Morgan RK, Ernst A, et al: Comparison of suction catheter versus forceps biopsy for sampling of solitary pulmonary nodules guided by electromagnetic navigational bronchoscopy. Respiration 79:54-60, 2010	obs	3	55 // 2 excluded as lost to follow up	peripheral SPN<3cm in patients referred for Ix of ?lung cancer	suction cather vs forceps Bx during EBUS and electromagnetic bronchoscopy	diagnostic yield	2 year or until diagnosis made	diagnosis	40/53 were diagnostic (75.5%)// catheter aspiration 36/40 vs 22/40 for forceps Bx	done under general anaesthetic// EBUS was used to verify position by electromagnetic// not clear what additional benefit EMB gave over EBUS as 30/55 lesions visualised with EBUS diagnosis obtained in 93% but in those not seen by EBUS diagnosis only 48%
6- Biopsy	184	Gildea TR, Mazzone PJ, Karnak D, et al: Electromagnetic navigation diagnostic bronchoscopy: a prospective study. American Journal of Respiratory & Critical Care Medicine 174:982-9, 2006	obs	3	58 (2 excluded equipment failure/not cooperative/ 2lost to follow up)//only **36** had no lymph nodes	solitary pulmonary lesion	electomagnetic navigation diagnostic bronchoscopy	EMV bronchoscopy	until diagnosis or 10 months	ability to navigate to correct area diagnostic yield safety	ability to steer to target area 58/58 40/54 (74%) of peripheral lesions positive Dx of these 31/54 (57%) were<2cm and there was no diff in yield for size// PTx 2 (3.5%)	no ROSE// size of lesions 22.8 -/+12.6mm // concious sedation used// fluoroscopy not used
6- Biopsy	185	Jensen KW, Hsia DW, Seijo LM, et al: Multicenter experience with electromagnetic navigation bronchoscopy for the diagnosis of pulmonary nodules. Journal of Bronchology and Interventional Pulmonology 19 (3):195-199, 2012	obs	3	92	SPN average size 2.61cm (SD1.42) average distance from pleural surface 1.81cm (SD 1.32)	bronchoscopy	electromagnetic navigation	Diagnosis or 6 months radiographic follow up	diagnostic yield	yield 60/92 (65%)// SPN <2cm 50%, >2cm 76%//	Distance from pleura did not affect yield after controlling for nodule size. There was only 6 month follow up and 8 excluded as inadequate follow up. The number or type of specimens did not affect yield
6- Biopsy	186	Lamprecht B, Porsch P, Wegleitner B, et al: Electromagnetic navigation bronchoscopy (ENB): Increasing diagnostic yield. Respiratory Medicine 106:710-5, 2012	Case series	3	112	Patients with solitary pulmonary nodules, median size 27mm	ENB bronchoscopy with Rapid on site evaluation	N/A	Further intervention by CT-guided biopsy or Surgery if diagnosis not reached	Whether a diagnosis was obtained	A diagnosis was reached in 80-87% of all nodules and in 76% of nodules <=20mm	
6- Biopsy	187	Seijo LM, de Torres JP, Lozano MD, et al: Diagnostic yield of electromagnetic navigation bronchoscopy is highly dependent on the presence of a Bronchus sign on CT imaging: results from a prospective study. Chest 138:1316-21, 2010	obs	3	51	SPN	electomagnetic navigational bronchoscopy	ct bronchus sign	unclear	diagnostic yield	Diagnostic yield in 30/38 (79%) with bronchus sign compared to 4/13 (31%) with no bronchus sign	some nodules >3cm (1.5-3.5)
6- Biopsy	188	Obata K, Ueki J, Dambara T, et al: Repeated ultrasonically guided needle biopsy of small subpleural nodules. Chest 116 (5):1320-1324, 1999	Case series	3	107	Patients with pulmonary nodules less than 2cm in size in contact with the pleura	Ultrasound guided biopsy	N/A	Surgical biopsy or clinical follow up	Diagnostic rate	39% of nodules were diagnosed.	
6- Biopsy	189	Baldwin DR, Eaton T, Kolbe J, et al: Management of solitary pulmonary nodules: how do thoracic computed tomography and guided fine needle biopsy influence clinical decisions? Thorax 57:817-22, 2002	obs	3	114	solitary pulmonary lesion <3cmin a specialist cardioresp hospital in NZ	successful management decisions	clinical data and CXR//plus Ct//plus CT biopsy result//results reviewed by 6 resp cons who estimated liklehood of malignancy and made management decisions	> 5 years	succesful management decision	31% nodules benign /31% malignant and curative surgery/40% malignant and non curative //intraclinicain decisin making was	PET/EBUS not used/available(NZ 2001). Patients with previous malignancy included. Intraclinician decision making was consistent when all 3 levels of information given. The greatest rise in successful decision making with addition of Ct and Bx was in those with a clinical test on intermediate probability. The most important effect was to avoid unnecessary surgery in benign lesions
6- Biopsy	190	Gupta S, Krishnamurthy S, Broemeling LD, et al: Small (<=2-cm) subpleural pulmonary lesions: Short-versus long-needle-path CT-guided biopsy - Comparison of diagnostic yields and complications. Radiology 234 (2):631-637, 2005	cross sectional study	3	176 Group A 48 (short) and Group B 128 (long)	solitary pulmonary lesion <1cm from pleura and <2cm wide	CT guided Bx	Gp A short /direct Bx route and Gp B transverse/ long/indirect route		diagnostic yield accuracy pneumothorax rate and need for chest drain	Gp A/B 71%/94% adequate tissue but when comparing 1-2cm lesions diagnosis was 4/10 vs 30/32 rate of Pneumothorax similar betweeen groups but more in Gp B needed drains A 8(17) B 49 (38)	Lesions >2cm were excluded as they are easier to biopsy. There was on site cytology technician. Gp A <1cm (mean was 0.4cm) Gp B >1cm (mean was 5.6cm) path for needle. Pleural surfaces transversed Gp A mean 1 Gp B mean 1.3. Mean number of pleural procedures in Gp A was 2.9 and in Gp B was 1.8.
6- Biopsy	191	Hayashi N, Sakai T, Kitagawa M, et al: CT-guided biopsy of pulmonary nodules less than 3 cm: usefulness of the spring-operated core biopsy needle and frozen-section pathologic diagnosis. AJR American Journal of Roentgenology. 170:329-31, 1998	obs	3	52	solitary pulmonary lesion <3cm on CT	CT guided biopsy using spring loaded core biopsy needle	nil	12m or until diagnosis made definitively	diagnosis rate	47/52 (90%) material was diagnostic 34/35 (97%) malignant and 13/17 (76%) benign	
6- Biopsy	192	Jin KN, Park CM, Goo JM, et al: Initial experience of percutaneous transthoracic needle biopsy of lung nodules using C-arm cone-beam CT systems. European Radiology 20:2108-15, 2010	obs	3	71	SPN <3cm 31male 40 female referred for CT guided Biopsy	CT guided biopsy	C arm cone beam CT system	until definate diagnosis or 2 year radiography	diagnostic yield safety	accuracy 98.4% (60/61), sens 97% (35/37), spec 100% (25/25) 18 Ptx (25.4%) 3 had drains (4.2%) and haemoptysis in 10 (14.1%)	It excluded indeterminate (no specific benign features and had no follow up) results from analysis. Less radiation tha fluoroscopy alone
6- Biopsy	193	Ohno Y, Hatabu H, Takenaka D, et al: Transthoracic CT-guided biopsy with multiplanar reconstruction image improves diagnostic accuracy of solitary pulmonary nodules. European Journal of Radiology 51:160-8, 2004	Cohort	2-	390	Patients with pulmonary nodules	CT-guided cutting biopsy or aspiration biopsy with or without fluoroscopy or multiplanar reconstruction(MPR)	CT-guided biopsy vs CT-guided biopsy with fluoroscopy vs CT-guided biopsy with MPR	Surgical confirmation or clinical follow up for 24months	Accuracy and pneumothorax rate	Biopsy with MPR was significantly better than the other two groups with an accuracy of 97%. The pneumothorax rate with MPR was 28% and not signifiantly different to the other two groups.	
6- Biopsy	194	Romano M, Griffo S, Gentile M, et al: CT guided percutaneous fine needle biopsy of small lung lesions in outpatients. Safety and efficacy of the procedure compared to inpatients. RADIOLOGIA MEDICA 108:275-82, 2004	obs	3	184	PN <15mm	CT guided Biopsy	diagnosis by another method	surgical diagnosis or 1 year	diagnostic rate	sensitivty 88.2% specificity 100% PPV 100% NPV 78.9% Diagnostic accuracy 91.8%	
6- Biopsy	195	Santambrogio L, Nosotti M, Bellaviti N, et al: CT-guided fine-needle aspiration cytology of solitary pulmonary nodules: a prospective, randomized study of immediate cytologic evaluation, Chest, 1997, pp 423-5	Cohort	2+	220	Patients with pulmonary nodules 1-3cm in size	Immediate cytological assessment of CT-guided needle aspirate	Immediate cytological assessment vs gross assessment only	Surgical biopsy or clinical follow up	Diagnostic accuracy	Cytological variation was more accurate (88% vs 81%)	

Section	Ref no	Bibliographic citation	Study type	Ev lev	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
6- Biopsy	196	Tsukada H, Satou T, Iwashima A, et al: Diagnostic accuracy of CT-guided automated needle biopsy of lung nodules. AMERICAN JOURNAL OF ROENTGENOLOGY 175 (1):239-243, 2000	Case series	3	103	Patients with pulmonary nodules less than 3cm in size	CT-guided automated needle biopsy	N/A	Surgical confirmation or clinical follow up for 24months	Accuracy and pneumothorax rate	Accuracy was between 66% and 87% depending on nodule size. 22.5% of patients had a pneumothorax	
6- Biopsy	197	Wagnetz U, Menezes RJ, Boerner S, et al: CT screening for lung cancer: implication of lung biopsy recommendations. AJR American Journal of Roentgenology. 198:351-8, 2012	Case series	3	110	Patients with nodules from a screening programme	CT-guided needle aspiration	N/A	Surgical confirmation or "long term" clinical follow up	Whether a diagnosis was obtained	Diagnosis was obtained in 76.4% of patients	
6- Biopsy	198	Westcott JL, Rao N, Colley DP: Transthoracic needle biopsy of small pulmonary nodules. Radiology 202 (1):97-103, 1997	obs	3	62 patients with 64 lesions and 75 biopsies performed	pulmonary nodules≤ 15mm	CT guided biopsy	diagnosis made by another method	2 years	diagnostic rate	sensitivity was 93%, specificity was 100% and accuracy 95%	
6- Biopsy	199	Fontaine-Delaruelle C, Souquet PJ, Gamondes D, et al: Negative predictive value of transthoracic core needle biopsy: a multicenter study. Chest, 2015	Case series	3	939	Patients undergoing CT guided lung biopsy at 3 French hospitals	CT guided biopsy	N/A	Not stated	Diagnostic yield (sensitivity, specificity, complication, yield of repeat biopsy)	Negative predictive value of 51%. Sens, spec and accuracy were 89%, 99%, 90%. Complication rate was 34% (life-threatening in 6%). Multivariate analysis showed predictors for false-negative result were radiologist experience and occurrence of complication during procedure Second biopsy performed in 24 cases with diagnosis in 95% cases and NPV of 67%	Nodules were large (median size 30mm, 72% >20mm) so unclear how generalisable findings are to smaller nodules where CT guided biopsy is often indicated.
6- Biopsy	200	Kothary N, Lock L, Sze DY, et al: Computed tomography-guided percutaneous needle biopsy of pulmonary nodules: impact of nodule size on diagnostic accuracy. Clinical Lung Cancer 10:360-3, 2009	obs for safety aspects	3	139	SPN <1.5 cm (37) and >1.5cm (132) (mean 2.8cm, range 1.6 - 8cm))	CT guided biopsy (either Fine needle aspiration or core Bx)	nodules<1.5 cm vs nodules>1.5cm	not clear - does not define the length of radiological FU	diagnostic yield accuracy safety	Diagnostic sample 94 (67.6%), (SPN<1.5cm 51.4% and SPN >1.5cm 73.5%) // 34.5% (48/139) PTx of which 7 (5%) needed a drain	decision to bx also included location of lesion and medical Hx (51.1% peripheral and 48.9% central). A cytopathologist present. 47 (37.8%) FNA only and 92 (66.2%) FNA and Core biopsy. There was no difference in pneumothorax rate depending on nodule size. Paper included for safety aspects only - observational
6- Biopsy	201	Wallace MJ, Krishnamurthy S, Broemeling LD, et al: CT-guided percutaneous fine-needle aspiration biopsy of small (< or =1-cm) pulmonary lesions. Radiology 225:823-8, 2002	Case series	3	61 patients	Patients with nodules <1cm in diameter	CT-guided FNA	None	2-18 months	Diagnostic accuracy (sens/spec)	FNA samples were adequate for diagnosis in 77% cases. Sensitivity 82%, specificity 100%, diagnostic accuracy 88%.	Suggested that Ctguided FNA performs well even for smaller nodules
6- Biopsy	202	Ohno Y, Hatabu H, Takenaka D, et al: CT-guided transthoracic needle aspiration biopsy of small (< or = 20 mm) solitary pulmonary nodules. AJR American Journal of Roentgenology. 180:1665-9, 2003	Case series	3	162	Patients with solitary pulmonary nodules <20mm	CT-guided needle aspiration	N/A	Surgical confirmation or clinical follow up for 24months	Diagnostic accuracy, pneumothorax rate and proportion requiring chest drains	The diagnostic accuracy was 77.2%, the pneumothorax rate was 28.4% and 2.5% required chest drains	
6- Biopsy	203	Choi SH, Chae EJ, Kim JE, et al: Percutaneous CT-guided aspiration and core biopsy of pulmonary nodules smaller than 1 cm: analysis of outcomes of 305 procedures from a tertiary referral center. AJR Am J Roentgenol 201:964-70, 2013	Case series	3	290	Patients with nodules <1cm diameter	CT guided FNA/core biopsy	N/A	2 years for benign lesions	Diagnostic accuracy (sens/spec)	Sensitivity 93%, specificity 99%, PPV 99%, NPV 88%. On multivariate analysis, aspiration alone (vs biopsy) was associated with diagnostic failure	Biopsy/aspiration performs well in small nodules, but aspiration had lower yield of 2 tests (may reflect confounding factors)
6- Biopsy	204	De Filippo M, Saba L, Concari G, et al: Predictive factors of diagnostic accuracy of CT-guided transthoracic fine-needle aspiration for solid noncalcified, subsolid and mixed pulmonary nodules. Radiol Med 118:1071-81, 2013	Case series	3	198	Patients undergoing trans-thoracic CT guided FNA for solid, subsolid and mixed pulmnoary nodules	CT guided FNA	N/A	N/A	Diagnostic accuracy	Accuracy was 95.1% for solid, 84.6% for mixed and 66.6% for subsolid nodules. Accuracy was higher for nodules adherent to pleura (95.6%) compared to central lesions (83.5%). In 75% of false negative and inadequate samples the needle was found to lie outside the lesion on MPR reconstructed images	Accuracy was reduced by size, distance from pleura and nature of lesion. The most common predictive factor is wrong position of needle tip, which can be potentially corrected using MPR reconstructions.
6- Biopsy	205	Choi JW, Park CM, Goo JM, et al: C-arm cone-beam CT-guided percutaneous transthoracic needle biopsy of small (</= 20 mm) lung nodules: diagnostic accuracy and complications in 161 patients. AJR Am J Roentgenol 199:W322-30, 2012	Case series	3	161 patients	Patients with pulmonary nodules (<20mm)	C-arm cone beam CT-guided percutaneous needle biopsy	N/A	Mean follow-up 575 days for benign lesions	Diagnostic accuracy (sens/spec)	Accuracy 98%, sensitivity 97%, specificity 100% Following multi-variate analysis, emphysema along needle path was risk factor for pneumothorax, haemoptysis was protective against pneumothorax, and GGN was risk factor for haemorrhage	Further evidence for test performance, and risk factors for pneumothorax and haemorrhage
6- Biopsy	206	Choo JY, Park CM, Lee NK, et al: Percutaneous transthoracic needle biopsy of small (</= 1 cm) lung nodules under C-arm cone-beam CT virtual navigation guidance. Eur Radiol 23:712-9, 2013	Case series	3	105	Patients with pulmonary nodules <=1cm undergoing percutaneous needle biopsy	Cone-beam CT guided percutaneous needle biopsy	N/A	N/A	Diagnostic accuracy (sens/spec)	Sensitivity 96.7%, specificity 100%, diagnostic accuracy 98%. Coplications occurred in 12.1% cases (pneumothorax in 6.5% and haemoptysis 5.6%)	Evidence for performance with cone-beam CT guidance
6- Biopsy	207	O'Neill AC, McCarthy C, Ridge CA, et al: Rapid needle-out patient- rollover time after percutaneous CT-guided transthoracic biopsy of lung nodules: Effect on pneumothorax rate. Radiology 262 (1):314-319, 2012	Cohort	2-	201	Patients with pulmonary nodules	Rapid roll-over following CT-guided biopsy	Conventional CT-guided biopsy vs Biopsy with rapid roll-over	Immediate assessment	Pneumothorax rate and proportion requiring chest drains	The rapid roll-over group had fewer pneumothoraces (23% vs 37%) and required fewer chest drains (4% vs 15%)	
6- Biopsy	208	Wiener RS, Schwartz LM, Woloshin S, et al: Population-based risk for complications after transthoracic needle lung biopsy of a pulmonary nodule: an analysis of discharge records. Annals of Internal Medicine 155:137-44, 2011	cross sectional analysis	3	15865	SPN	CT guided biopsy	none	unclear	adverse events	haemorrhage 1% pneumothorax 15% and 6.6% needed a chest drain	
6- Biopsy	209	Freund MC, Petersen J, Goder KC, et al: Systemic air embolism during percutaneous core needle biopsy of the lung: frequency and risk factors. BMC Pulm Med 12:2, 2012	Case series	3	610	Patients undergoing TTNB of pulmonary lesions	CT guided biopsy	None	N/A	Incidence of systemic air embolism and predictors thereof	3.8% of patients showed radiological features of SAE whereas clinically apparent incidence was 0.49%. 2 patients developed transient neurological symptoms, one died due to fatal SAE to coronoary arteries. Depth of needle, endotracheal intubation and prone position all increased risk of SAE	Description of risk of SAE.
7 - Surgery	210	Heo EY, Lee KW, Jheon S, et al: Surgical resection of highly suspicious pulmonary nodules without a tissue diagnosis. Japanese Journal of Clinical Oncology 41:1017-22, 2011	Case series	3	113	Patients undergoing resection for pulmonary nodules with high suspicion of malignancy without pre-operative pathological confirmation	Lung resection (not specified which operation)	Surgery for pulmonary nodules with pre-operative pathological confirmation of malignancy	Not quoted	Benign resection rate, costs, hospital days and waiting time	Compared features suggestive of benign vs malignant disease in the nodules without pre-op confirmation (but small numbers). Compared outcomes vs nodules confirmed as lung cancer pre-op, but likely multiple confounders and no information provided regarding patient characteristics, attempts made to identify or correct for confounding effects - e.g. LOS was 6/7 shorter in group without pre-op confirmation but very likely to reflect other differences between populations. Costs were lower $5830, but almost certainly relates to inpatient stay and therefore confounding effect.	One of few comparisons of pre-op vs no pre-op histology for surgical resection, but likely multiple unidentified confounders making use of findings questionable. No details provided about surgical strategy (sub-lobar, lobectomy, frozen section etc)
7 - Surgery	211	Sihoe AD, Hiranandani R, Wong H, et al: Operating on a suspicious lung mass without a preoperative tissue diagnosis: pros and cons. Eur J Cardiothorac Surg 44:231-7; discussion 237, 2013	Cohort study	2-	443	Patients undergoing resection for pulmonary nodules with high suspicion of malignancy without pre-operative pathological confirmation	Lung resection	Surgery for pulmonary nodules with pre-operative pathological confirmation of malignancy	Not quoted	Morbidity rate, survival, operating time, time to surgery	No differences in outcomes between those with or without pre-op tissue diagnosis. Confounding effects mentioned but not analysed in depth. Benign resection rate was 7.8%. Morbidity was low and mortality 0. All patients underwent frozen section analysis, and all patients with NSCLC confirmed at frozen section underwent lobectomy. No additional time for patients undergoing lobectomy without tissue vs with tissue. Survival similar between groups. Interval between first appt and surgery was higher with pre-op tissue (proportion waiting >28 days was 55% vs 42% - latter for no pre-op biopsy).	Better designed study than Heo et al. Some acknowledgement of potential confounders, but not analysed in depth. No effect on operation time or morbitidy from frozen section.
7 - Surgery	212	Mitruka S, Landreneau RJ, Mack MJ, et al: Diagnosing the indeterminate pulmonary nodule: percutaneous biopsy versus thoracoscopy. SURGERY 118:676-84, 1995	Case series	3	566	Patients undergiong either CTgBx or thoracoscopic wedge biopsy (some patients underwent both)	Thoracoscopic wedge biopsy	CTgBx	Not quoted	Diagnosis, complications	Of 312 patients undergoing CTgBx, 64% identified malignant disease, 6% specific benign disease, 29% had non-specific diagnosis. Of 91 non-specific benign diagnoses, 47 went onto surgical resection of which 32 (68%) were malignant. CTgBx had accuracy of 86% for malignant and 71% for benign lesions. Of 301 patients undergoing thoracoscopic biopsy - specific diagnosis were achieved in 97% cases (59% lung cancer, 15% metastases, 26% specific benign) with non-specific benign in 3%. Only 21% of lung cancers underwent lobectomy - the rest received wedge resections	: Thoracoscopic biopsy yields a definitive diagnosis in a greater proportion of cases than CTgBx (71% vs 97%) due to high rate of non-specific benign diagnoses (29%) in CTgBx group. Very low rates of lobectomy for lung cancer confirmed at frozen section

Section	Ref no	Bibliographic citation	Study type	Ev lev	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
7 - Surgery	213	Petersen RH, Hansen HJ, Dirksen A, et al: Lung cancer screening and video-assisted thoracic surgery. Journal of Thoracic Oncology 7 (6):1026-1031, 2012	Case series	3	58	CT screen detected nodules surgically removed	Surgical resection	Patients undergoing lung resection for non-screen detected cancers (in control arm of study	Not quoted	VATS vs open procedure, diagnosis	41/51 operations for screen-detected cancers were by VATS (80%). 7 operations for benign disease (benign resection rate 12%. Of 24 lung cancers in control group only 16 were suitable for surgery - 50% done by VATS. Zero 30 day mortality rate for all patients. 2 VATS procedures converted to open (4% cases)	12% benign resection rate from screening study. High use of VATS for screen detected lung cancers (80%)
7 - Surgery	214	Cardillo G, Regal M, Sera F, et al: Videothoracoscopic management of the solitary pulmonary nodule: a single-institution study on 429 cases. Annals of Thoracic Surgery 75:1607-11; discussion 1611-2, 2003	Case series	3	429	Patients with nodules undergoing thoracoscopic wedge excision	VATS resection	None	45 months	Diagnosis, demographic factors predicting malignancy, complications	No mortality, 3% morbidity. All cases had intraoperative frozen section. 52 cases were lung cancer (12%), 7 were metastases (2%) and 370 (86%) were benign. Benign lesions were hamartomas (83.5%), tuberculous lesions (7.3%), fibrous scars (5.7%) and granulomatous disease (1.9%). Conversion rate to mini-thoracotomy was 22% cases.	Large case series showing very high benign resection rate particularly related to resection of hamartomas (72% of all resected nodules were hamartomas)
7 - Surgery	215	Rubins JB, Rubins HB: Temporal trends in the prevalence of malignancy in resected solitary pulmonary lesions. Chest 109:100-3, 1996	Case series	3	360	Patients undergoing pulmonary mass resection (up to 6cm diameter)	Nodule resection	None	Not quoted	Benign resection rate	Evaluated benign resection rate over time period (1981 to 1994). Showed progressive increase in proportion of nodules with eventual malignant diagnosis (50-60% in 1981-3 cf 90-100% in 1990-94). Suggest that this is due to increased use of CT to evaluate nodules pre-operatively.	Historical perspective, although now very old data. Relates change in benign resection rate to advent of CT.
7 - Surgery	216	Kuo E, Bharat A, Bontumasi N, et al: Impact of video-assisted thoracoscopic surgery on benign resections for solitary pulmonary nodules. Annals of Thoracic Surgery 93:266-72; discussion 272-3, 2012	Case series	3	3217	Patients undergoing resection for focal pulmonary lesions 1995 - 2009	Surgical resection	Historical comparison	Not quoted	VATS vs open procedure, diagnosis	The proportion of lung resections performed by VATS increased from 6% (1995-2005) to 42.4% (2006-2009). Benign resection rate was 8.9% from 1995 - 2005, increasing to 14.8% by 2006-2009. 20.8% of VATS resections had benign diagnosis compared to 10.3% of open operations	: Large case series showing increase in benign resection rates alongside increase in proportion of lung resections performed by VATS. Authors links these events although confounding effects possible. If they are linked this would suggest alterations to clinical decision making due to advent of VATS perhaps reflecting differing rates of morbidity altering threshold for proceeding to surgical resection
7 - Surgery	217	Powell HA, Tata LJ, Baldwin DR, et al: Early mortality after surgical resection for lung cancer: an analysis of the English National Lung cancer audit. Thorax 68:826-34, 2013	Case series	3	10991	Patients undergoing lung resection for lung cancer in the UK	Lung resection	None	90 days	Death	90 day mortality was twice that at 30 days. Age was a strong predictor of early post-operative death. 30 day mortality from segmentectomy/wedge resections was 2.1% and at 90 days was 4.2%.	Illustrates operative risks with surgical resection of cancer - maybe useful for comparison against risks of cancer progression during nodule surveillance
7 - Surgery	218	Mohammed N, Kestin LL, Grills IS, et al: Rapid disease progression with delay in treatment of non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 79:466-72, 2011	Case series	3	46	Patients undergoing 2 CT scans during work-up for lung cancer treatment	None	None	Median interval between scans 13.4 weeks	Progression	48% of patients showed progression between, including progression within stage and upstaging. Median initial tumour dimension was 35mm	Difficult to directly extrapolate to risk of progression during nodule surveillance, as this is likely to happen at a much smaller size, with lower risks of progression accordingly.
7 - Surgery	219	Grogan EL, Weinstein JJ, Deppen SA, et al: Thoracic operations for pulmonary nodules are frequently not futile in patients with benign disease. Journal of Thoracic Oncology 6 (10):1720-1725, 2011	Case series	3	65	Patients undergoing nodule resection with eventual benign diagnosis	Nodule resection	None	Not quoted	Change in diagnosis or management plan	Benign diagnoses were granulomatous disease (57%), benign tumours (15%), fibrosis (12%), autoimmune or vascular disease (9%). Treatment changes occurred in 68% cases, Commonest single diagnosis was Histoplasmosis (23%) with commonest change in management being institution of antimicrobial treatment (esp anti-fungal treatment). 64% had pre-op PET imaging, with 62% of these having PET avidity. 15 patients (23% had pre-op CTgBx). 66% cases underwent VATS resection. Mean total cose was $25,518	Management plans changes in majority of cases, although may have been largely influenced by incidence of granulomatous disease (esp Histoplamosis) so applicability of findings to other geographical areas is less clear
7 - Surgery	220	Murasugi M, Onuki T, Ikeda T, et al: The role of video-assisted thoracoscopic surgery in the diagnosis of the small peripheral pulmonary nodule. Surgical Endoscopy 15:734-6, 2001	Case series	3	81	Patients with peripheral pulmonary nodules	Wedge excision by VATS	None	Not quoted	Diagnosis, mortality, morbidity	Definitive diagnosis in all patients. Lung cancer in 35%, metastases in 20% and benign disease in 45%. 75% of patients with lung cancer went on to lobectomy as definitive treatment. The remainder were left with wedge. No mortality or morbidity reported. Post-op LOS mean 9 days	Case series without comparator group - very high benign resection rate. Significant proportion of patients (20%) treated with wedge alone.
7 - Surgery	221	Mack MJ, Hazelrigg SR, Landreneau RJ, et al: Thoracoscopy for the diagnosis of the indeterminate solitary pulmonary nodule. Annals of Thoracic Surgery 56:825-30; discussion 830-2, 1993	Case series	3	242	Patients with nodules undergoing thoracoscopic wedge excision	VATS resection	None	Not quoted	Diagnosis, complications	Benign diagnosis in 52% and malignant in 48% (of which 44% primary lung cancer, 56% metastases). No mortality, limited morbidity. Average LOS 2.4 days. Only 29 of 51 patients with lung cancer went on to lobectomy at same anaesthetic (57%). Conversion rate to locate nodule was 1% (2 cases) but all lobectomies carried out as open procedures	High benign resection rate, relatively low rate of anatomical resection for confirmed lung cancer
7 - Surgery	222	Jimenez MF, Spanish Video-Assisted Thoracic Surgery Study G: Prospective study on video-assisted thoracoscopic surgery in the resection of pulmonary nodules: 209 cases from the Spanish Video-Assisted Thoracic Surgery Study Group. European Journal of Cardio-Thoracic Surgery 19:562-5, 2001	Case series	3	209	Patients with nodules undergoing VATS wedge excision	VATS resection	None	Not quoted	Diagnosis, mortality, morbidity, conversion rate	Diagnosis achieved in 100% cases. Benign 51.1%, malignant 48.8% (lung cancer 24.7%, metastatic 22.7%). Conversion rate 16.3%. Morbidity 9.6%, mortality 0.5%. Benign diagnoses were granuloma 24.7%, Hamartoma 13.5% and benign tumour 5.5%	Large series of VATS resection of nodules, high benign resection rate
7 - Surgery	223	Varoli F, Vergani C, Caminiti R, et al: Management of solitary pulmonary nodule. European Journal of Cardio-Thoracic Surgery 33:461-5, 2008	Case series	3	370	Patients with pulmonary nodules	Thoracoscopic surgical resection	None	Not quoted	Diagnosis	Nodule was suitable for wedge and frozen in 276 cases - of which 77 were lung cancer (proceeded to lobectomy in 50 cases), 61 were metastases, and 138 (50%) were benign. Nodule was too deep for wedge in 94 cases who proceeded straight for lobectomy - 65 were lung cancer, 10 metastases and 19 were benign. Overall benign resection rate was 42%	Algorithm advocating surgery for all nodules >1cm results in high benign resection rate (42%) including 20% of all lobectomies performed for benign disease. No reference to possibility of CT guided biopsy or surveillance
7 - Surgery	224	Infante M, Chiesa G, Solomon D, et al: Surgical procedures in the DANTE trial, a randomized study of lung cancer early detection with spiral computed tomography: comparative analysis in the screening and control arm, Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer, 2011, pp 327-35	Case series	3	72	CT screen detected nodules surgically removed (77 nodules in 72 patients)	Surgical resection	Procedures in control arm study	Not quoted	VATS, stage, complete resection	72 underwent surgery for 77 nodules in screened arm. 17 of 77 lesions were benign (22%). VATS in 17% resections. In control group, 28 patients underwent 31 surgical procedures - benign in 5 cases (benign resection rate 16%)	22% benign resection rate from screening study. Lower use of VATS
7 - Surgery	225	Scott WJ, Allen MS, Darling G, et al: Video-assisted thoracic surgery versus open lobectomy for lung cancer: a secondary analysis of data from the American College of Surgeons Oncology Group Z0030 randomized clinical trial, The Journal of thoracic and cardiovascular surgery, 2010, pp 976-81; discussion 981-3	Case series	3	964	Patients were participants in RCT comparing lymph node sampling vs dissection - VATS vs open was not subject of main trial, but outcomes were compared with propensity matching	VATS lobectomy (66)	Open lobectomy (686)	Not quoted	Operating time, lymph node sampling, R1/R2 resections, post-operative complications, mortality	For VATS procedures, operating time was shorter, node sampling similar, and there was less atelectasis requiring bronchoscopy, fewer chest drains beyond 7 days, shorter length of stay, and similar operating mortality	Not RCT of VATS vs open. The majority of VATS cases (82%) were performed by one surgeon so unclear how applicable to all operators, or do improved parameters just reflect competence of individual operator.
7 - Surgery	226	Paul S, Isaacs AJ, Treasure T, et al: Long term survival with thoracoscopic versus open lobectomy: propensity matched comparative analysis using SEER-Medicare database. BMJ 349:g5575, 2014	Cohort study	2++	2390	Patients undergoing lobectomy for lung cancer - propensity matched analysis from SEER database	VATS lobectomy (1195)	Open lobectomy (1195)	Median follow-up 40 months	Three year overall survial, disease free survival and cancer-specific survival. Perioperative complications and mortality	VATS lobectomy associated with shorter length of stay (5 vs 7 days, p<0.001), lower inpatient mortality (2.1% vs 3.6% p=0.03) but no differences in 3yr overall, disease free or cancer specific survival	Well designed propensity matched study with large numbers and robust outcomes.
7 - Surgery	227	Schuchert MJ, Abbas G, Awais O, et al: Anatomic segmentectomy for the solitary pulmonary nodule and early-stage lung cancer. Annals of Thoracic Surgery 93 (6):1780-1787, 2012	Retrospective cohort study	2-	785	Patients undergoing lung resection for pulmonary nodule or confirmed cancer	Anatomical segmentectomy	Survival and recurrence compared to lobectomy patients over same time period (432)	31.8 months	Survival, recurrence	Perfomed in peripheral lesions <2cm in size. Indications were 62.4% indeterminate pulmonary nodule (77% of these had lung cancer, 8.4% metastases, 13.9% benign disease) confirmed lung cancer , suspected mets. No difference in recurrence compared with separate group of lobectomy patients 14.5% vs 13.9% (same rates local recurrence 5.2% vs 5.3%). Morbidity was 34.9% with major morbidity in 9.3%.	: Recurrence rates similar, but no survival comparison included in the study

Section	Ref no	Bibliographic citation	Study type	Ev lev	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
7 - Surgery	228	Ginsberg RJ, Rubinstein LV: Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg 60:615-22; discussion 622-3, 1995	RCT	1+	276	Patient undergoing lung resection for T1N0M0 lung cancer	Lobectomy (n=125)	Limited resection (n=122) - wedge 40, segment 82	Not quoted although Kaplan Meier curves extend to 7 years	Survival, recurrence	Trend to increased mortality (cancer and all cause) with limited resection but not significant. Significant increase in locoregional recurrence with limited resection vs lobectomy (p=0.008), borderline when analysed on ITT basis (p=0.06). Localised recurrence was highest for wedge (0.086 per person year) less for segment (0.044) and lowest for lobectomy (0.022) - not stated whether significant difference between segment and wedge. Distant recurrence appeared the same. FEV1 remained significantly better in LR group than lobectomy to 1 year (incomplete data). No CT staging routinely performed	Old trial not using modern methods of staging, and not powered to show difference between wedge and segment. Main data not present on ITT basis. Effect on mortality only borderline, and on locoregional recurrence becomes borderline with ITT analysis. Despite flaws, still the most robust evidence to guide resection strategy for this group of patients.
7 - Surgery	229	Detterbeck FC: Lobectomy versus limited resection in T1N0 lung cancer. Ann Thorac Surg 96:742-4, 2013	RCT (amendment to 218)	1+	276	Patient undergoing lung resection for T1N0M0 lung cancer	Lobectomy (n=125)	Limited resection (n=122) - wedge 40, segment 82	As above	As above	See comments	Letter to journal highlighting alterations made to original paper by Ginsberg et al (in which data was unaccounte for one third of patients). Highlighted corrections made in response to Lederle letter below
7 - Surgery	230	Billmeier SE, Ayanian JZ, Zaslavsky AM, et al: Predictors and outcomes of limited resection for early-stage non-small cell lung cancer. Journal of the National Cancer Institute 103:1621-9, 2011	Retrospective cohort study	2-	679	Patients undergoing resection for early stage lung cancer	Sublobar resection (120 underwent wedge, 35 underwent segmentectomy)	Lobectomy	Up to 72 months. Median f/u 55 months	30 day and long term survival	155 patients undergoing sublobar resetion were more likely to have small tumour size, be uninsured, more severe lung disease. Unadjusted 30 day survival worse in limited resection (presumably relating to comorbidities - not significant once adjusted for covariables). Trend towards improved 5YS (57% vs 49% in both unadjusted and adjusted analyses	High quality retrospective cohort study with appropriate attempts to adjust for covariables. Non-significant trend towards worse long terms survival with limited resection - either relating to residual confounding factors even after adjustment, or to inferior outcomes for limited resection. Wedge and segmentectomy combined whereas may not be equivalent
7 - Surgery	231	Okami J, Ito Y, Higashiyama M, et al: Sublobar resection provides an equivalent survival after lobectomy in elderly patients with early lung cancer. Annals of Thoracic Surgery 90:1651-6, 2010	Retrospective cohort study	2-	764	Patients undergoing lung resetion for early stage lung cancer	Sublobar resection (90 segmentectomy, 56 wedge)	Lobectomy	5YS described	5YS, recurrence and post-op complications	Overall, limited resection associated with inferior survival HR 1.83 (1.26-2.67). When analysed by age subgroups, outcomes were similar for elderly subgroup (age>=75). Local recurrence higher in sublobar group (11.6% vs 1.5%). No significant difference in post-op complications.	Retrospective cohort with no attempt to correct for confounding factors. Equivalent survival in elderly populations suggests that some of advantages of lobectomy (shown in younger patients) maybe offset by other factors.
7 - Surgery	232	Miller DL, Rowland CM, Deschamps C, et al: Surgical treatment of non-small cell lung cancer 1 cm or less in diameter. Ann Thorac Surg 73:1545-50; discussion 1550-1, 2002	Retrospective cohort study	2-	100	Patients undergoing lung resection for NSCLC with primary tumour <=1cm	Lobectomy (n=71)	Segmentectomy (12) or wedge resection (13)	Median 43 months	Survival, recurrence	Overall 5YS for lobectomy was 71% vs 33% for limited resection (p=0.03), segment 57%, wedge 27% (wedge significantly worse than segment and lobe, no difference segment and lobe). 5 year cancer specific survival was 92% for lobectomy and 47% after limited resection (p=0.07), segment 75%, wedge 42% (wedge significantly worse than segment and lobe, no difference segment and lobe). Local recurrence rates were 13%, 8% and 30% respectively (lobe, segment, wedge - wedge worse than both others, no difference segment and lobe)	Small study and no propensity analysis, but worse survival and greater recurrence with limited resection vs lobectomy. Segment appeared intermediate between lobe and wedge, with no demonstrated significant difference vs lobe although numbers small, and study not powered to specifically address this question. On multivariate analysis, it appeared that limited resection no longer predicted poor survival, although not explicit about this
7 - Surgery	233	Altorki NK, Yip R, Hanaoka T, et al: Sublobar resection is equivalent to lobectomy for clinical stage 1A lung cancer in solid nodules. J Thorac Cardiovasc Surg 147:754-62; Discussion 762-4, 2014	Retrospective cohort study	2-	347	Patients undergoing lung resetion for early stage lung cancer (solid nodules) identified in I-ELCAP study	Sublobar resection (16 segmentectomy, 37 wedge)	Lobectomy	10 years	Survival (propensity matched), recurrence	No differences in survival for unadjusted, and propensity matched analysis between populations. Similarly no differences when small tumours analysed separately (<20mm). Non-significant trend to greate local recurrence in wedge vs segmentectomy	:Equivalent survival for unadjusted and propensity matched analyses in context of solid nodules identified in CT screening programme
7 - Surgery	234	Sienel W, Dango S, Kirschbaum A, et al: Sublobar resections in stage IA non-small cell lung cancer: segmentectomies result in significantly better cancer-related survival than wedge resections. Eur J Cardiothorac Surg 33:728-34, 2008	Retrospective cohort study	2+	87	Patients undergoing sublobar resections for stage IA NSCLC	Wedge resection	Anatomical segmentectomy	45 months	Local recurrence, distant recurrence and survival	Groups were well matched for pre-op parameters (although not randomised). Fewer lymph nodes resected with wedge. Significantly less locoregional recurrences (16% vs 55%) and less cancer related death (29% vs 52%) in segment group. Cancer related survival remained significantly better even after multivariate analysis	Retrosepctive cohort, but attempts to control for covariables, and good matching of groups pre-operatively.
7 - Surgery	235	Tsutani Y, Miyata Y, Nakayama H, et al: Oncologic outcomes of segmentectomy compared with lobectomy for clinical stage IA lung adenocarcinoma: propensity score-matched analysis in a multicenter study. J Thorac Cardiovasc Surg 146:358-64, 2013	Cohort study	2+	98	Patients undergoing segmentectomy for lung cancer (cIA)	Segmentectomy	Lobectomy	43 months	Recurrence free survival and overall survival	98 patients undergoing segmentectomy compared to 383 with lobectomy for stage IA disease. Lobectomy performed for large tumours, high SUV, pathogically invasive tumours and nodal involvement. 3 year OS was similar in both groups (but worse prognostic features in lobectomy group - so performed propensity analysis. In 81 propensity score matched patients, 3 year OS was 93.2% for lobectomy vs 95.7% for segmentectomy. Local recurrence occurred in 4.4% lobectomy group and 3.1% segmentectomy group	Large series of segmentectomy vs lobectomy with propensity matching showing equivalent OS and RFS at 3 years.
7 - Surgery	236	Landreneau RJ, Normolle DP, Christie NA, et al: Recurrence and survival outcomes after anatomic segmentectomy versus lobectomy for clinical stage I non-small-cell lung cancer: a propensity-matched analysis. J Clin Oncol 32:2449-55, 2014	Cohort study	2+	1192	Patients undergoing segmentectomy of lobectomy for stage I lung cancer	Segmentectomy	Lobectomy	Median f/u 5.4 years	Peri-operative mortality, locoregional, distant and overall recurrence, 5 year survival	Perioperative mortality was 1.2% in segmentectomy vs 2.5% in lobectomy. No signficant difference in locoregional or distant recurrence. Overall recurrence was 20.2% for segment vs 16.7% for lobectomy (p=NS). No significant differences in 5 year freedom from recurrence or survival. Segmentectomy was not an independent predictor of recurrence (HR 1.1, 95%CI 0.87-1.40)	Non significant increase in recurrence with segmentectomy, but no effect on survival. Propensity matching used to minimise confounding factors
7 - Surgery	237	Bao F, Ye P, Yang Y, et al: Segmentectomy or lobectomy for early stage lung cancer: a meta-analysis. Eur J Cardiothorac Surg 46:1-7, 2014	Meta-analysis	1-	22 studies	Patients undergoing segmentectomy or lobectomy for stage I lung cancers	Segmentectomy	Lobectomy	Not quoted	Overall survival and cancer specific survival	Hazard ratios of overall survival and cancer specific survival showed benefits of lobectomy for Stage I, IA and IA 2-3cm tumours (1.2, 1.24, 1.41 respectively - all significant). For tumours <2cm, segmentectomy showed equivlent survivival (HR 1.05, 95% CI 0.89-1.24).	Use of meta-analysis for observational studies is controversial. Significant heterogeneity in studies. However, large numbers of cases included and reasonable methodology given above reservations.
7 - Surgery	238	Harada H, Okada M, Sakamoto T, et al: Functional advantage after radical segmentectomy versus lobectomy for lung cancer. Ann Thorac Surg 80:2041-5, 2005	Retrospective cohort study	2-	83	Patients undergoing lung resection for small sized, early lung cancer (<2cm)	Radical segmentectomy	Lobectomy	6 months	Post-operative pulmonary physiology	Segmentectomy patients had better preserved lung function at 2 and 6 months. No significant effect on anaerobic threshold. Paper claims to demonstrate functional advantage over segment vs lobe	No follow-up for recurrence or survival - simply limited to pulmonary physiology analysis
7 - Surgery	239	Veronesi G, Maisonneuve P, Pelosi G, et al: Screening-detected lung cancers: is systematic nodal dissection always essential? Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer 6:525-30, 2011	Case series	3	290	Patients with screen detected lung cancers (n=97) or non-screen detected clinical stage I lung cancer (n=193)	Nodal dissection		Not quoted	Rate of nodal (>N0) disease	Considered patients with clinical stage I disease - assessed rates of occult nodal involvement according to size of pulmonary nodule and SUV of pulmonary nodule. Rates of nodal metastases were low if nodule was <10mm or SUV<2. Considering all nodules <10mm there were no cases of occult nodal disease in 48 screen detected cases and 23 non-screen detected cases (71 overall)	One case series showing low rates of nodal disease in 71 patients with nodules <10mm - needs repeating in other series before nodal sampling can be abandoned in this setting
7 - Surgery	240	Dendo S, Kanazawa S, Ando A, et al: Preoperative localization of small pulmonary lesions with a short hook wire and suture system: experience with 168 procedures. Radiology 225:511-8, 2002	Case series	3	150	Patients with pulmonary nodules where surgeons requested pre-op localisation	Hookwire insertion	None	N/A	Successful localisation, complications	Hookwire successfully placed without dislodgement in 97.6% of lesions. Asymptomatic pneumothorax occurred in 32.1%, 1.2% required chest drain placement. Pulmonary haemorrhage occurred in 14.9% but required no intervention. Nodule aetiology was lung cancer in 42.3%, metastasis in 17.8% and benign disease in 39.3%	Successful procedure, but surprisingly high rate of complications albeit not needing intervention
7 - Surgery	241	Ciriaco P, Negri G, Puglisi A, et al: Video-assisted thoracoscopic surgery for pulmonary nodules: rationale for preoperative computed tomography-guided hookwire localization. European Journal of Cardio-Thoracic Surgery 25:429-33, 2004	Case series	3	53	Patients undergoing VATS for pulmonary nodule where nodule >15mm from lung surface or 10mm diameter	Hookwire insertion	98 patients undergoing VATS without hookwire	N/A	Successful localisation, successful VATS procedure, complications	Hookwire successfully placed in all cases, but dislodged prior to surgery in 4 (7.5% cases). Hookwire facilitated VATS procedure in 58% cases (would not have been possible otherwise). Pneumothorax occurred in 7.5%. Surgery time significantly shorted in hookwire group (40 vs 75min p<0.001). Nodule aetiology in whole cohort was lung cancer in 5.9%, metastasis in 45.1% and benign disease in 41.1%	Shortened operation time (although possible other confounding factors between groups may have influenced difference in time)
7 - Surgery	242	Saito H, Minamiya Y, Matsuzaki I, et al: Indication for preoperative localization of small peripheral pulmonary nodules in thoracoscopic surgery. Journal of Thoracic & Cardiovascular Surgery 124:1198-202, 2002	Case series	3	61	Patients undergoing VATS for pulmonary nodule where nodule >10mm from lung surface or 10mm diameter	Hookwire insertion	59 patients undergoing VATS without hookwire	N/A	Requirement of hookwire for localisation. Conversion to open thoracotomy	Hookwire facilitated VATS resection in 85% cases (impalpable nodules). No conversions to open thoracotomy, but did occur in 12% cases where hookwire not used. Nodule aetiology was lung cancer in 51.6%, metastasis in 13.3% and benign disease in 23.3%	No complications recorded. Case series with comparator group but confounding factors

Section	Ref no	Bibliographic citation	Study type	Ev lev	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
7 - Surgery	243	Miyoshi K, Toyooka S, Gobara H, et al: Clinical outcomes of short hook wire and suture marking system in thoracoscopic resection for pulmonary nodules. European Journal of Cardio-Thoracic Surgery 36 (2):378-382, 2009	Case series	3	108	Patients undergoing VATS for pulmonary nodule where nodule <10mm, >5mm from lung surface or GGN	Hookwire insertion	None	N/A	Success of resection. Missing lesions (either nodules or hookwires in resected samples)	93.6% of nodules resected successfully. 4% cases where nodule was not resected at initial operation, and 2.4% where hookwire was not removed - requiring additional resection. 3.7% patients required chest drain for pneumothorax. Nodule aetiology was lung cancer in 54%, metastasis in 20% and benign disease in 26%	Successful in majority of cases. No comparator group
7 - Surgery	244	Yoshida Y, Inoh S, Murakawa T, et al: Preoperative localization of small peripheral pulmonary nodules by percutaneous marking under computed tomography guidance. Interactive Cardiovascular & Thoracic Surgery 13:25-8, 2011	Case series	3	57	Patients undergoing VATS for pulmonary nodule at request of surgeon	Hookwire insertion	None	N/A	Operation type, complications, positive surgical margin and recurrence	49.1% of cases developed pneumothorax although no treatment required, 29.8% had pulmonary bleeding, 7% experienced pain and 1.8% (1 patient) had dislodged hookwire.	Mainly reporting adverse events, which were frequent although not requiring intervention
7 - Surgery	245	Mayo JR, Clifton JC, Powell TI, et al: Lung nodules: CT-guided placement of microcoils to direct video-assisted thoracoscopic surgical resection. Radiology 250 (2):576-585, 2009	Case series	3	69	Patients undergoing VATS for excision of 75 nodules	Microcoil wire placement	None	N/A	Successful placement and removal. Complications	100% cases had microcoil successfully placed. 97% cases had successful removal of nodule. Microcoil was displaced in 3% cases at VATS. Pneumothorax requiring chest drain occurred in 3% and asymptomatic haemothorax in 1%	
7 - Surgery	246	Koyama H, Noma S, Tamaki Y, et al: CT localisation of small pulmonary nodules prior to thoracscopic resection: Evaluation of a point marker system. European Journal of Radiology 65:468-72, 2008	Case series	3	52	Patients undergoing VATS for pulmonary nodule where nodule <10mm, >10mm from lung surface or GGN	Point marker system	None	N/A	Successful resection. Complications	Successful placement without dislodgement in 98% cases (dislodged in one case). 19% cases developed asymptomatic pneumothorax. 10% cases developed pulmonary haemorrhage. Nodule aetiology was lung cancer in 54%, metastasis in 10% and benign disease in 35%	: Successful in majority of cases. No comparator group
7 - Surgery	247	Watanabe K-i, Nomori H, Ohtsuka T, et al: Usefulness and complications of computed tomography-guided lipiodol marking for fluoroscopy-assisted thoracoscopic resection of small pulmonary nodules: experience with 174 nodules. Journal of Thoracic & Cardiovascular Surgery 132:320-4, 2006	Case series	3	150	Patients undergoing VATS for pulmonary nodule where nodule <10mm, long distance from lung surface or GGN	Lipiodol marking with subseequent fluoroscopy intraoperatively	None	N/A	Successful resection. Complications	All nodules successfully resected. Complications were pain requiring analgesia (11%), pneumothorax requiring chest drain (6%), pneumothorax not requiring drain (11%), and haemopneumothorax requiring emergency operation in one patient (0.6%)	Successful procedure, but one significant adverse event
7 - Surgery	248	Kawanaka K, Nomori H, Mori T, et al: Marking of small pulmonary nodules before thoracoscopic resection: injection of lipiodol under CT-fluoroscopic guidance. Academic Radiology 16:39-45, 2009	Case series	3	65	Patients undergoing VATS for 107 pulmonary nodules	Lipiodol marking with subseequent fluoroscopy intraoperatively	None	N/A	Successful resection. Complications	All nodules successfully marked and resected. Complications were pneumothorax 31%, requiring drain in 4.6%, pulmonary haemorrhage in 15%. Nodule aetiology was lung cancer in 52%, metastasis in 21% and benign disease in 27%	
7 - Surgery	249	Kim YD, Jeong YJ, I H, et al: Localization of pulmonary nodules with lipiodol prior to thoracoscopic surgery. Acta Radiologica 52:64-9, 2011	Case series	3	67	Patients undergoing VATS for 68 pulmonary nodules.	Lipiodol marking with subseequent fluoroscopy intraoperatively	None	N/A	Successful marking. Complications	Lipoidal accumulation noted in 98% cases. Complications were pneumothorax 29%, pulmonary haemorrhage in 7% (more common for deeper nodules)	
7 - Surgery	250	Vandoni RE, Cuttat JF, Wicky S, et al: CT-guided methylene-blue labelling before thoracoscopic resection of pulmonary nodules. European Journal of Cardio-Thoracic Surgery 14:265-70, 1998	Case series	3	51	Patients undergoing VATS for 54 nodules <25mm and not in contact with pleura	Methylene blue injection to mark skin and pleura	None	N/A	Thoracoscopic resection and complications	91% patients had successful thoracoscopic removal of nodule. 25.4% developed small pneumothorax not requiring treatment. Nodule aetiology was lung cancer in 31%, metastasis in 28% and benign in 41%	
7 - Surgery	251	Grogan EL, Stukenborg GJ, Nagji AS, et al: Radiotracer-Guided Thoracoscopic Resection is a Cost-Effective Technique for the Evaluation of Subcentimeter Pulmonary Nodules. Annals of Thoracic Surgery 86 (3):934-940, 2008	Case series/decision analysis modeling	3	40	Modelling based on patients with 5-10mm suspicious pulmonary nodules	Radiotracer-guided thoracoscopic resection (RGTR) of pulmonary nodules	Thoracotomy	N/A	Cost-to-effectiveness ratio	Average cost-to-effectiveness ratio was $27,887 for RTGR vs $32,271 for thoracotomy.	Modelling evidence suggesting improved cost-effectiveness of RTGR vs thoracotomy, but no reference to alternative strategies for investigating nodules e.g. PET, CT surveillance, percutaneous biopsy
7 - Surgery	252	Ambrogi MC, Melfi F, Zirafa C, et al: Radio-guided thoracoscopic surgery (RGTS) of small pulmonary nodules. Surgical Endoscopy 26:914-9, 2012	Case series	3	211	Patients undergoing VATS resection for nodule smaller than 1cm and/or deeper than 1cm.	Radiotracer injection	None	N/A	Successful resection, complications	Successful localisation and resection in 99% cases. 10.4% cases developed pneumothorax but none required treatment. Nodule aetiology was 24.6% lung cancer, 28.9% metastasis, 46.4% benign.	: Largest case series, showing good performance and low complications.
7 - Surgery	253	Mattioli S, D'Ovidio F, Daddi N, et al: Transthoracic endosonography for the intraoperative localization of lung nodules. Annals of Thoracic Surgery 79:443-9; discussion 443-9, 2005	Case series	3	54	Patients undergoing VATS for nodules - surgical discretion based on dimeter and distance from pleura	Transthoracic sonography	None	N/A	Successful identification by US	Of 16 nodules deemed non-visible and non-palpable, US was able to identify 15 (94%). US more difficult when nodule surrounded by emphysema. No complications reported.	
7 - Surgery	254	Gonfiotti A, Davini F, Vaggelli L, et al: Thoracoscopic localization techniques for patients with solitary pulmonary nodule: hookwire versus radio-guided surgery, European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery, 2007, pp 843-7	RCT	2+	50	Patients undergoing nodule resection where nodule <2cm, and 1.5-3cm from pleura	Hookwire insertion	Radio-tracer injection	N/A	Successful removal nodule, operating time, complications	Hookwire located nodules in 84% cases, whereas radio-surgery in 96%. 6 (24%) pneumothoraces in hookwire compared to 1 (4%) in radio group (none needed draining). 1 case (4%) hookwire was displaced. No significant procedural or outcome differences	One of few randomised trials, but showed equivalence in outcomes, albeit with increased pneumothorax rate in hookwire group.
7 - Surgery	255	Grogan EL, Jones DR, Kozower BD, et al: Identification of small lung nodules: technique of radiotracer-guided thoracoscopic biopsy. Annals of Thoracic Surgery 85:S772-7, 2008	Case series	3	81	Patients undergoing VATS for nodules - at discretion of surgeon	Radiotracer injection (Tc MAA) then localised with gamma probe intraoperatively	None	N/A	Successful identification and removal. Complications	Lesion was localised and excised in 95.1% cases. Pneumothorax requiring drain insertion occurred in 10%. Nodule aetiology was lung cancer in 39%, metastasis in 10% and benign in 50%	Successful procedure. High rate of benign resection
7 - Surgery	256	Sugi K, Kobayashi S, Sudou M, et al: Long-term prognosis of video-assisted limited surgery for early lung cancer. European Journal of Cardio-Thoracic Surgery 37:456-60, 2010	Retrospective cohort study	2-	159	Patients undergoing lung resection for early NSCLC.	Wedge resection for GGN<15mm	Segmentectomy for solids <20mm, Lobectomy for others	5 years	Survival, recurrence	5YS was 95% for GGN, 83% for <20mm segmentectomy patients, 88% for lobectomy patients. No recurrence in GGN group. Localised recurrence in 6.3% of total population. No signficant differences in recurrence rates between segment and lobe	: Small numbers in GGN group, but no recurrence despite wedge for small GGNs. No difference between segments and lobes, but higher stage in lobes so maybe confounding factor
7 - Surgery	257	Nakata M, Sawada S, Saeki H, et al: Prospective study of thoracoscopic limited resection for ground-glass opacity selected by computed tomography. Ann Thorac Surg 75:1601-5; discussion 1605-6, 2003	Case series	3	96	Patients with GGO <=2cm (pure and mixed)	VATS wedge resection	Lobectomy	18 months	Mortality, recurrence, final histological diagnosis	Patients subdivided into pGGN and part-solid, and > and < 1cm. Patients with pGGN<1cm underwent wedge resection. 93% of these lesions were BAC or AAH (7% adeno). 31 underwent wedge with no recurrence reported (although relatively short f/u time. 4 of 13 pGGN >1cm were adenocarcinoma and underwent lobectomy in this series. No comment regarding nodal involvement.	: Low recurrence rates of wedge for pGGN <1cm correlating with high likelihood of BAC/AAH (93% in this group)
7 - Surgery	258	Tsutani Y, Miyata Y, Nakayama H, et al: Appropriate sublobar resection choice for ground glass opacity-dominant clinical stage IA lung adenocarcinoma: wedge resection or segmentectomy. Chest 145:66-71, 2014	Case series	3	239	Patients with GGO dominant tumours (>50% GGO component)	Segmentectomy	Wedge resection	42 months	Recurrence, recurrence free survival, OS	93 patients underwent wedge, 56 segmentectomy, 90 lobectomy. Sublobar resections were more likely for T1a (74.8%) vs T1b tumours (39.3%). Recurrences occurred in 1 patient undergoing segmentectomy (2%) and 1 undergoing lobectomy (1%). 3 year OS was same betweem groups (98.7%, 98.2%, 97.6% respectively). Lymph node metastases in 2 patients (0.8%)	Case series of lobectomy and sublobar resection for GGO dominant (i.e. pGGN + PSN) showing equivalent oncological outcomes for 3 operations.
7 - Surgery	259	Iwata H, Shirahashi K, Mizuno Y, et al: Feasibility of segmental resection in non-small-cell lung cancer with ground-glass opacity. Eur J Cardiothorac Surg 46:375-9, 2014	Case series	3	87	Patients undergoign segmentectomy for NSCLC (subgroup of 34 patients undergoing radical segmentectomy of which 28 were for pGGN + PSN)	Segmentectomy	Comparison within study of radical vs palliative segmentectomy	34 months	Survival, recurrence	28 patients with GGN/PSN underwent radical segmentectomy and 10 patients underwent palliative segmentectomy (amongst patients undergoing segmentectomy for other reasons). All patients operated for GGN (either radical or palliative segmentectomy) survived for the follow-up period (34 months)	Although other patients included, subgroup analysis for GGNs (mixed pGGN/PSN) showed good long term survival with no recurrence or mortality in patients undergoing segmentectomy.

Section	Ref no	Bibliographic citation	Study type	Ev lev	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
7 - Surgery	260	Kodama K, Higashiyama M, Takami K, et al: Treatment strategy for patients with small peripheral lung lesion(s): intermediate-term results of prospective study. Eur J Cardiothorac Surg 34:1068-74, 2008	Case series	3	179	Patients undergoing surgery for small peripheral lung lesions - of which 77 patients had pGGN or PSN	Sublobar resection	Lobectomy	92 months	Distant or local relapse	Of pGGN 22 were adenocarcinoma, 1 AAH, 4 lymphoproliferative disease and 2 inflammatory. Of PSN 46 were adenocarcinoma, 1 AAH, 1 benign. For 48 GGO type (pGGN+PSN) subsequently confirmed as lung cancer which underwent sublobar resection, there was 1 distant relapse (2%) and no local relapse with a median follow-up time of 92 months. Comparing sublobar and lobectomy for all patients (pGGN, PSN and solid nodules) 5 year OS was 96.6% and 80.0% respectively	: Case series of lobectomy and sublobar resection for small lung cancers. Subgroup analysis by pGGN/PSN for wedge resection showing good OS and low recurrence rates. When all cases considered, OS was much better for sublobar than lobar indicating confounding variables influencing decision to undergo sublobar resection in clinical practice.
7 - Surgery	261	Yano M, Yoshida J, Koike T, et al: Survival of 1737 lobectomy-tolerable patients who underwent limited resection for cStage IA non-small-cell lung cancer. Eur J Cardiothorac Surg, 2014	Case series	3	1737	Patients with clinical stage IA NSCLC - subgroup analysis for 810 patients with consolidation/tumour ratio <0.25 - i.e. pGGN and PSN	Segmentectomy/wedge resection	Various comparisons within study to those C/R >0.25	71 months	Survival, recurrence	810 patients with C/R ratio <=0.25 undergoing wedge/segment (approx 50% each) - OS 96.7% (95% CI 95.4-98.2) compared to 92.7 for C/R>0.25. Disease free survival was 96.5%. No data on nodal involvement	Large case series subdividing patients according to C/R ratio. For C/R<0.25 = pGGN and PSN - excellent long terms survival and very low recurrence following either wedge resection or segmentectomy.
8 - Non surg treatment	262	Takeda A, Kunieda E, Sanuki N, et al: Stereotactic body radiotherapy (SBRT) for solitary pulmonary nodules clinically diagnosed as lung cancer with no pathological confirmation: Comparison with non-small-cell lung cancer. Lung Cancer 77 (1):77-82, 2012	Case series	3	163	PS 0-2 patient treated with curative intent with SBRT 40-50 and more than 6 months follow up. Patient devided into 2 groups - 1 with histology and the other without. Reasons for no histology included negative biopsy, patient refused or too high risk	Stereotactic radiotherapy	n	Median 20 months (range 6-64)	3 yr local control, PFS, CSS and OS.	In no histology group sig less men (60% cf 74%) and sig less patients considered operable (12% vs 27%) but declined surgery.No acute toxicity in either group. Rates of pneumonitis similar and no sig dif in local control, regional control, distanct control, DFS, CSS and OS between the 2 groups. 3yr local control 80/87%, CSS 88%/91% and OS 54%/57%.	Case study of cases treated with SBRT with or without histological confirmation.
8 - Non surg treatment	263	Verstegen NE, Lagerwaard FJ, Haasbeek CJ, et al: Outcomes of stereotactic ablative radiotherapy following a clinical diagnosis of stage I NSCLC: comparison with a contemporaneous cohort with pathologically proven disease. Radiother Oncol 101:250-4, 2011	Retrospective cohort study	2+	591	PS 0-3 patients with stage I lung cancer treated with SABR in a single institution. Divided into 2 groups- one with pathological confirmation (206 -35.4%) and the second without pathological confirmation (383 - 64.6%)	Stereotactic radiotherapy	n/a	Median f/u was 32.8 months for group 1 (pathological confirmation) and 29.5 months for group 2(no pathology)	OS, Local, regional and distant control. Included a comparison of outcomes at 3 years.	Pathologically confirmed tumours were larger and had better lung function as measured by FEV1. No significant difference was seen in 3 year overall survival (53.7% versus 55.4% for clinical versus pathological diagnosis) or local control (91.2% versus 90.4% for clinical versus pathological diagnosis). Regional (88.1% versus 90.3% for clinical versus pathological diagnosis) and distant (73.0% versus 79.6% for clinical versus pathological diagnosis)recurrence rates were also not stastistically different.	Large cohort study in a large SABR centre with long follow and robust data collection. Used a risk calculation model to treat non-pathologically confirmed patients. Authors accepted that some patients had probable oligometastases rather than new primaries. Although outcomes are the same a potential confoudning factor is that non-pathologically treated patients had smaller lesions which could have improved their otucomes. However, this could be counter-ballanced by their worse lung function.
8 - Non surg treatment	264	Haidar YM, Rahn DA, 3rd, Nath S, et al: Comparison of outcomes following stereotactic body radiotherapy for non-small cell lung cancer in patients with and without pathological confirmation. Ther Adv Respir Dis 8:3-12, 2014	Retrospective cohort study	3	55	Reivew of 55 patients with presumed (23) or pathologically confirmed NSCLC. All PET positive and all had SABR 48 to 56GY in 4 to 5 fractions	Stereotactic radiotherapy	2 cohorts	Median follow up 26.2 months	OS, local control and toxicity	In non -pathologically confirmed patients Median OS 30.2 months and local failure rate 8.7% (2pts) and regional failure rate 13% (3pts). Low rates of acute toxicity 8.7% (2pts) and late toxicity 13% (3 pts). No difference in OS when compared with the pathologically confirmed group.	Small retrospective study showing no difference in outcome between pathologically confirmed and non-pathologically confirmed PET postive presumed NSCLC.
8 - Non surg treatment	265	Stephans KL, Djemil T, Reddy CA, et al: A comparison of two stereotactic body radiation fractionation schedules for medically inoperable stage I non-small cell lung cancer: the Cleveland Clinic experience. Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer 4:976-82, 2009	Retrospective cohort study	2-	86	Medically inoperable stage I NSCLC receiving SBRT. Patients cohorted from 10/03 - 02/06, and 03/06 - 08/07. 61 patients had histological diagnosis, 33 did not. Single institution	20Gy x 3	10Gy x 5	Median 15.3/12	1 year local control, nodal failure, distant metastasis and overall survival. Toxicity	For 50Gy vs 60Gy cohorts at 1 year, local control was 97.3 vs 100%, nodal failure 7.3 vs 3.4%, distant metastases 21.8 vs 29.5% and overal survival 83.1 vs 76.9% (no significant differences). 2 cases (2.2%) of Gd 2 pneumonitis and mild late chest wall toxicity in 9 patients (10%) commoner in 60Gy (18%) vs 50Gy group (4%, p=0.028)	Pre- and post- change in departmental policy in view of RTOG 0236 study. Well matched according to stage, size, histology, smoking, lung function and reason for inoperability. Significant increase in Lung V50 and in heterogeneity in dosimetry, with reduced % prescription isodose with 60Gy dose. Showed no difference in efficacy between the 2 doses, but increased chest wall toxicity with larger dose. Study probably underpowered to demonstrate difference in survival between dosing schedules (power not discussed). Increased toxicity may relate to increased dose, but non-blinded study with multiple possible confounders. Analysed survival of those with clinical vs pathological diagnoses and found no significant differences between groups. Suggests that radiographic criteria seem to be reasonable selection criteria in patients whose biopsy is medically contraindicated or non-diagnostic.
8 - Non surg treatment	266	Kashima M, Yamakado K, Takaki H, et al: Complications after 1000 lung radiofrequency ablation sessions in 420 patients: a single center's experiences. AJR American Journal of Roentgenology. 197:W576-80, 2011	Retrospective case series	3	420	137 patients with primary lung cancer confirmed with biopsy. 283 patients with metastases confirmed using either imaging or biopsy. Metastatic patients had 6 or fewer. Single institution.	Lung radio-frequency ablation	None	Mean 22.1 months (SD 17.9 months, range 3-84 months)	Procedural complications and mortality. Survival.	4 deaths (0.4% treatments). Common major complications (>1% Gd 3/4) and risk factors: aseptic pleuritis (2.3%, RFs >2 punctures and previous chemo), pneumonia (1.8%, RFs previous RT and age>65), lung abscess (1.6%, RF emphysema), bleeding (1.6%, RFs Plt<180, tumour >3cm), pneumothorax requiring pleural sclerosant (1.6%, RFs emphysema). 1,3,5 yr survival were 89.6%, 62.5%, 40.2% for lung cancer and 91.6%, 53.0%, 35.9% for metastases. Median survival 44.4 months and 36.0 months respectively. Total pneumothorax risk (all grades) 46.1%	No details of reasons for RFA vs other treatments. No staging information for lung cancer.
8 - Non surg treatment	267	Nour-Eldin N-EA, Naguib NNN, Saeed A-S, et al: Risk factors involved in the development of pneumothorax during radiofrequency ablation of lung neoplasms. AJR American Journal of Roentgenology. 193:W43-8, 2009	Retrospective case series	3	82	10 patients with NSCLC, and 72 patients with metastasesAll patients pathologically proven. Patients refused or were not candidates for surgery. Single institution	Lung radio-frequency ablation	None	No follow-up (CT at 1-6hrs)	Pneumothorax development	Incidence of PTx was 11.3% (14 of 124 sessions). 4 required intercostal tube. Risk factors were age>60, emphysema, tumour diameter<1.5cm, lower part of lung, >2.6cm traversed lung, traversal of major fissure.	
8 - Non surg treatment	268	Yan TD, King J, Sjarif A, et al: Treatment failure after percutaneous radiofrequency ablation for nonsurgical candidates with pulmonary metastases from colorectal carcinoma. Annals of Surgical Oncology 14:1718-26, 2007	Case series	3	55	Patients with lung metastases from colorectal carcinoma - either nonsurgical or >3/multiple lobe mets. Single institution.	Lung radio-frequency ablation	None	Median 24 months (range 6-40)	Local and overall progression free survival	Overall median survival 33 months. 1, 2, 3yr overall survival 85%, 64% and 46% respectively. 1, 2yr local PFS were 74% and 56%, and overall PFS were 61% and 34% respectively. Local and overall PFS reduced by lesion>3cm and local PFS alone reduced by CEA>5ng/ml following multivariate analysis	Not clear whether prospective or retrospective case identification.
8 - Non surg treatment	269	Yan TD, King J, Sjarif A, et al: Percutaneous radiofrequency ablation of pulmonary metastases from colorectal carcinoma: prognostic determinants for survival. Annals of Surgical Oncology 13:1529-37, 2006	Case series	3	55	Patients with lung metastases from colorectal carcinoma - either nonsurgical or >3/multiple lobe mets (same patients as previous study). Single institution.	Lung radio-frequency ablation	None	Median 24 months (range 6-40)	Overall survival	Overall median survival 33 months. 1, 2, 3yr overall survival 85%, 64% and 46% respectively. Lung metastasis >3cm associated with reduced OS following multivariate analysis	Same dataset as above. Not clear whether retrospective or prospective case identification.

Section	Ref no	Bibliographic citation	Study type	Ev lev	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
8 - Non surg treatment	270	Pennathur A, Abbas G, Gooding WE, et al: Image-guided radiofrequency ablation of lung neoplasm in 100 consecutive patients by a thoracic surgical service. Annals of Thoracic Surgery 88:1601-6; discussion 1607-8, 2009	Retrospective case series	3	100	46 primary lung cancer, 25 lung cancer recurrence, 29 metastases. Poor lung function/cardiac status or unresectable. Single institution.	Lung radio-frequency ablation	None	Median 12/12, mean 17/12. Range not stated	Time to progression, survival	Local progression occured in 35 (%) and overall progression in 60 (%). Median time to local progression was 15/12 and overall progression 7/12. Median survival was 23/12 (95% CI 18-37).	Heterogenous group including recurrence of local disease. Study specifically addressed RFA administered by thoracic surgeons
8 - Non surg treatment	271	Zhu JC, Yan TD, Glenn D, et al: Radiofrequency ablation of lung tumors: feasibility and safety. Annals of Thoracic Surgery 87:1023-8, 2009	Prospective case series	3	100	6 patients with lung cancer, 94 with metastases (majority colorectal). Single institution.	Lung radio-frequency ablation	None	Immediate complications assessed - no ongoing follow-up	Complications/morbidity	No procedural related mortality. Morbidity 43% - pneumothorax 33%, pleuritic chest pain 18%, pleural effusion 12% and chest drain insertion 20%. Ablation of more than 2 lesions and depth of lesion >3cm associated with increased morbidity in multivariate analysis	
8 - Non surg treatment	272	Nomura M, Yamakado K, Nomoto Y, et al: Complications after lung radiofrequency ablation: risk factors for lung inflammation. British Journal of Radiology 81:244-9, 2008	Case series	3	130	13% primary lung cancer, 16% lung cancer recurrence, 71% metastases. No information on pathology. Single institution.	Lung radio-frequency ablation	None	Short-term complications assessed - no ongoing follow-up	CRP as predictor of lung inflammation. Inflammation-related complications	Mortality in 0.6%. 17.7% major complications (pneumothorax, aseptic pleuritis, tumour dissemination, pyothorax), 29% minor pneumothorax. CRP rose from 1.3 to 3.4mg/dl. Large tumour size and previous RT significantly associated with increased CRP	Heterogenous group. No information on long-term follow-up
8 - Non surg treatment	273	Sano Y, Kanazawa S, Gobara H, et al: Feasibility of percutaneous radiofrequency ablation for intrathoracic malignancies: a large single-center experience. Cancer 109:1397-405, 2007	Case series	3	137	30 patients with primary lung cancer (8.2%), 336 with metastases (91.8%). No comment on pathological confirmation. Single institution.	Lung radio-frequency ablation	None	Short-term complications assessed - no ongoing follow-up	Complications/morbidity and mortality	2 patients (0.9%) died following RFA. Overall major complication rate was 17.1% (pneumothorax 25, pleuritis 6, pleural effusion requiring drain 4, lung abscess 1, intrapulmonary haemorrhage 1). Only age predicted major complication in multivariate analysis	
8 - Non surg treatment	274	Hiraki T, Sakurai J, Tsuda T, et al: Risk factors for local progression after percutaneous radiofrequency ablation of lung tumors: evaluation based on a preliminary review of 342 tumors. Cancer 107:2873-80, 2006	Case series	3	128	Primary lung cancer 24, metastatic 104. Adjuvant chemo for 193 tumours, but not for 98. Data regarding adjuvant treatment missing for 51 tumours. 3 patients RT post RFA. Single institution.	Lung radio-frequency ablation	None	Median 12/12 (mean 15/12, range 6-47)	Local control, primary and secondary technique effectiveness rates	Local progression occured in 94 tumors (27%) after first ablation session at a mean time of 7/12 (median 8). Some received a second ablation. Overall primary effectiveness rates were 72%, 60% and 58% at 1,2,3yrs. Risk factors for progression on multivariate analysis were larger tumor size, use of internally cooled electrode	Heterogenous treatment regimes (some with chemo, some without, few with adjuvant RT). Use of mutitined expandable electrode reduced recurrence (vs internally cooled electrode. Unclear definition of primary and secondary effectiveness
8 - Non surg treatment	275	Yoshimatsu R, Yamagami T, Terayama K, et al: Delayed and recurrent pneumothorax after radiofrequency ablation of lung tumors. Chest 135:1002-9, 2009	Case series	3	68	14 patients with primary lung cancer. 54 with metastatic disease. All patients unsuitable for surgery. Most had recieved other treatments e.g. chemo or RT. Single institution.	Lung radio-frequency ablation	None	Short-term complications assessed - no ongoing follow-up	Development of pneumothorax	PTx developed in 82 or 194 ablation sessions (42.3%). 20 were delayed, 13 were recurrent and 49 were non-progressive. Contact between post-RFA ground glass and pleura was only risk factor for delayed/recurrent PTx.	
8 - Non surg treatment	276	Choe YH, Kim SR, Lee KS, et al: The use of PTC and RFA as treatment alternatives with low procedural morbidity in non-small cell lung cancer. European Journal of Cancer 45:1773-9, 2009	Case series	3	65	All patients had primary lung cancer (biopsy proven). Single institution	Lung radio-frequency ablation (67 sessions) or percutaneous thoracic cryotherapy (9 sessions)	None	Mean 20.5/12, range 2.6-74.3, median 20.8	Overall survival and complications	Overall median survival 20.8/12. 1, 2, 3 year survival rates were 67%, 46%, 27%. Survival better in those patient achieving complete ablation post procedure. 17 cases haemoptysis - one requiring embolisation. 8 cases of pneumothorax - 2 requiring chest drain. 1 patient developed bronchopleural fistula, and 1 developed ARDS.	Analysed both RFA and PTC but no separate analyses for outcomes.
8 - Non surg treatment	277	Huang L, Han Y, Zhao J, et al: Is radiofrequency thermal ablation a safe and effective procedure in the treatment of pulmonary malignancies? European Journal of Cardio-Thoracic Surgery 39:348-51, 2011	Case series	3	329	237 primary lung cancer, 93 metastatic disease. A proportion of patients from both groups had received previous chemo/RT/surgery.	Lung radio-frequency ablation	None	Median 24/12.	Overall survival, progression-free survival, complications	Median progression-free survival 21.6/12. Overall survival at 1,2,5 years was 80.1, 45.8 and 24.3% respectively. Figures for NSCLC were 80.1, 45.8 and 24.3% respectively and for pulmonary metastases 50.6, 30.1 and 17.3% respectively. Tumors larger than 4cm had significantly greater risk of local progression. Complications 63 (19.1%) pneumothorax, 14 (4.2%) haemoptysis one death, 10 (3.0%) haemothorax, 15 (4.5%) pneumonia and 3 (0.9%) pericardial tamponade (one death). 30/7 mortality 0.6%	Large case series - heterogenous previous treatments.
8 - Non surg treatment	278	Ambrogi MC, Lucchi M, Dini P, et al: Percutaneous radiofrequency ablation of lung tumours: results in the mid-term. European Journal of Cardio-Thoracic Surgery 30:177-83, 2006	Case series	3	54	40 cases of NSCLC and 24 patients with metastases (not all biopsy proven). Single institution	Lung radiofrequency ablation	None	Mean 23.7/12 - median 24, range 6-50	Local disease free survival, overall survival, side-effects	Median OS 28.9 months (mean 17.3). Local progression-free survival was 24.1 (mean 12.9). 10 cases of pneumothorax (15.2%) 6 of which required pleural drainage. 1 pleural effusion and 1 chest wall haematoma. Overall radiological response rate was 61.9%. Local progression occurred significantly earlier in tumors >3cm, although no significant difference in OS between <3 and >3cm tumours	
8 - Non surg treatment	279	Hiraki T, Gobara H, Mimura H, et al: Does tumor type affect local control by radiofrequency ablation in the lungs? European Journal of Radiology 74:136-41, 2010	Case series	3	105	32 patients with primary lung cancer (pathologically proven), 73 with metastases (colorectal, renal, lung, HCC). Single institution.	Lung radiofrequency ablation	None	Not stated	Local control.	Overall local control rates were 86% at 1 year and 76% at 2 years. Metastatic colorectal cancer showed significantly better local control than other types, but multivariate analysis showed RR of progression same between all groups. Tumour size related to local control.	No data on overall survival. No indication of length of follow-up.
8 - Non surg treatment	280	Gadaleta C, Catino A, Mattioli V: Radiofrequency thermal ablation in the treatment of lung malignancies. In Vivo 20:765-7, 2006	Case series	3	54	9 patients with primary NSCLC, 45 with metastases from other solid tumours. Single institution	Lung radiofrequency ablation	None	18/12.	Local recurrence, complications	Complete ablation of lesion achieved in 88 out of 93 cases. Local recurrence in 5 cases (5%). Major complication pneumothorax requiring chest drain in 8 cases (12% of sessions). Other complications bronchopleural fistula (1 case), no treatment related mortality.	
8 - Non surg treatment	281	Hsie M, Morbidini-Gaffney S, Kohman LJ, et al: Definitive treatment of poor-risk patients with stage I lung cancer: a single institution experience. Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer 4:69-73, 2009	Retrospective cohort study	2-	96	Patients with stage IA/IB NSCLC not suitable for standard surgical resection (lobectomy/ pneumonectomy). Had to have pathological proof. Single institution	Limited surgical resection (45), RFA (12), Primary RT (39 - 70Gy median)	Other interventions	Median 30/12	Actuarial 3 year survival, median survival, 3 year local control	3 year survival was 62.7% for limited resection and 55% for RT. 3 year local control was 76.3% and 77.9% respectively. No analysis for RFA due to small numbers. No pre-treatment factors linked with survival following multi-variate analysis. Complicatiosn were subcutaneous emphysema in 1 surgical patients, Gd3/4 radiation pneumonitis in 2 RT patients and pneumothorax requiring drain in 3 RFA patients.	Patients not well matched pre-procedure - major confounder in assessing outcome. RT patients tended to have worse PS, lower FEV1 and more required oxygen (no statistics presented comparing these criteria). Some patients in surgical group were pathologically upstaged post-procedure. Overall paper demonstrates reasonable survival for patients with non-standard surgical treatment, but is unable to make meaningful comparison in outcomes between treatment groups.
8 - Non surg treatment	282	Beland MD, Wasser EJ, Mayo-Smith WW, et al: Primary non-small cell lung cancer: review of frequency, location, and time of recurrence after radiofrequency ablation. Radiology 254:301-7, 2010	Case series	3	79	Patients with NSCLC treated with RFA with follow-up imaging identified retrospectively. Excluded patients with mutliple cancers. Patients had stage I-IV disease and 24% underwent adjuvant RT, 11% brachytherapy. Single institution.	Lung radio-frequency ablation	None	Mean 16/12 (range 1-72/12)	Recurrence, median disease-free survival.	57% cases showed no evidence of recurrence. For 43% cases with recurrence, this was local in 38%, intrapulmonary in 18%, nodal in 18%, mixed in 6% and distant metastases in 21%. Increased tumour size and stage related to risk of recurrence by multivariate analysis. Median disease-free survival was 23/12	Heterogenous group by stage and treatment (some with RT/brachtherapy). Descriptive study of patterns of recurrence.

Section	Ref no	Bibliographic citation	Study type	Ev lev	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
8 - Non surg treatment	283	Hiraki T, Tajiri N, Mimura H, et al: Pneumothorax, pleural effusion, and chest tube placement after radiofrequency ablation of lung tumors: incidence and risk factors. Radiology 241:275-83, 2006	Case series	3	142	All patients undergoing RFA - 30 for primary lung cancer, 112 for metastatic disease (including lung). No details on pathological confirmation. Single institution.	Lung radio-frequency ablation	None	Short-term complications assessed - no ongoing follow-up	Complications - pneumothorax, pleural effusion, chest drain placement	Incidence of PTx was 52% (of sessions), incidence of pleural effusion was 19%, and requirement for chest drain (for PTx) was 11%. Risk factors (on univariate analysis) for PTx were male sex, no history pulmonary surgery, greater number of tumours ablated, involvement of middle/lower lobe, increased length of lung crossed. RFs for pleural effusion were cluster electrode, decreased distance to pleura and decreased length of lung crossed. RFs for chest drain placement were no history pulmonary surgery, use of cluster electrode and involvement of upper lobe.	No multivariate analysis performed of risk factors for complications. No survival or other outcome data
8 - Non surg treatment	284	de Baere T, Palussiere J, Auperin A, et al: Midterm local efficacy and survival after radiofrequency ablation of lung tumors with minimum follow-up of 1 year: prospective evaluation. Radiology 240:587-96, 2006	Prospective case series	3	60	9 (15%) patients with primary NSCLC, 51 (85%) with metastatic disease (including some patients with bilateral disease). 97 treatments (of 100 intended) given. Some patients also had RFA to liver metastases. 22 patient had chemotherapy in follow-up period. 2 trial centres	Lung radiofrequency ablation	None	Minimum 1 year - no mean/median/range given	Incomplete local treatment, overall survival, lung disease-free survival, complications	18/12 incomplete local treatment was 12% per patient (presumably local control 88%). Overall survival and lung disease-free survival at 18/12 were 71% and 34% respectively. Main adverse event was pneumothorax (54% procedures) but only 9% required chest drain. 18/12 OS was 76% for primary tumours and 71% for metastases.	Heterogeneity in patient characteristics (some patients had liver metastases) and treatment (some had liver RFA also, some had chemotherapy)
8 - Non surg treatment	285	Iguchi T, Hiraki T, Gobara H, et al: Percutaneous radiofrequency ablation of lung tumors close to the heart or aorta: evaluation of safety and effectiveness. JOURNAL OF VASCULAR & INTERVENTIONAL RADIOLOGY 18:733-40, 2007	Case Series	3	32	42 in 32 patients with tumours close to the heart (20) or aorta (22) were given RFA. Majority of tumours were metastases (37) with only 5 primary lung cancer. Tumours 1-9mm from critical structure were in subgroup A and B comprised of tumours adjacent to the structure.Treated between 2001-2005.	Lung radiofrequency ablation	None	Median 11 months (range 1-43)	Acute toxicity, local control which the authors call primary effectiveness	Group A: Local control 94.7% (6m), 69.3%(12m), 42.9%(24m). Group B Local Control 42.9% (6m) and 8.6% (12m) and no survivors at 24m. To note is that Group B tumours were larger than group A 32mm (+/-17) versus 21mm(+/-14). 7 tumours that progressed in group A 6 underwent re-ablation after local progression with an effectiveness rate of 81.%%(6m), 59.2%(12m) and 51.8%(24m). Complications 16 sessions (34%) mnor complications occured which included asymtomatic pleural effusion (5), pneumothorax (11). In 5 (10.6%) major complications included chest tube (4) and lung abscess (1). No grade 5 toxicity	
8 - Non surg treatment	286	Lencioni R, Crocetti L, Cioni R, et al: Response to radiofrequency ablation of pulmonary tumours: a prospective, intention-to-treat, multicentre clinical trial (the RAPTURE study). LANCET ONCOLOGY 9:621-8, 2008	Case series	3	106	106 pts with 183 lung tumours up 3.5cm (mean 1.7cm) treated with RFA in seven centres from around the world	Radiofrequency Ablation	None	Median Follow up not stated. Mean 15 months (SD 8) and range 1-30	Complications QoL, OS, CSS and LC as per RECIST.	Biopsy proven NSCLC or mets in patients that were medically inoperable having up to 3 lung tumours. Also considered unfit for RT or chemotherapy. Excluded central tumours (<1cm from mediastinum organs and major airways). Primary endpoints - Safety, technical success and confirmed CR. Treatment related complication defined with in 30 days of RFA. Performed QoL analysis. Only 1 of 106 pts did not manage RFA. 137 proceedures done. Large/symptomatic pneumothorax in 27 pts. Chest drain needed for large pleural effusions in 4 pts. Minor complications were pneumothorax (28pt) and pleural effusion (11pt) not needing intevention. Median hospital stay 3 days. No sig decline in PFTs. OS was 70% at 1 year and 48% at 2 years. CR rates at 1 year were 88% though only 80% were assessible. No longer term LC rates.	
8 - Non surg treatment	287	Ambrogi MC, Fanucchi O, Cioni R, et al: Long-term results of radiofrequency ablation treatment of stage I non-small cell lung cancer: a prospective intention-to-treat study. Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer 6:2044-51, 2011	Case series	3	59	80 percutaneous RFA performed in 57 patients with 59 tumours. All Stage I NSCLC	Radiofrequency Ablation	None	Median Follow Up 45.5 months (range 12-82)	Response rate, complications and PFTs at 6 months post RFA	Patient medically inoperable. Chose lesions <5cm and more than 1cm from large vessels and airways. 14 pts were treated up to 5 times in the same location for persistant or recurrent disease. Mean tumour size 2.6cm. Many stage 1a (75%). Major complications in 5% 4 pneumothorax requiring drains. Minor complications in 20% with lesions next to the pleural surface experiencing pain, 5 pneumothorax not needing drain, 3 pleural effusions, 2 minor haemoptysis and one haematoma. 1a did significantly better than 1b with CR rate 66 versus 40% (p=0.01). PFI was 30.2 versus 13.4 months for stage 1a and 1b respectively. Median OS was 33.4 months. OS and CSS were 83%/95% (1 year), 40%/59% (3 years) and 25%/40% at 5 years. Better for stage 1a vs 1b.	
8 - Non surg treatment	288	Hiraki T, Gobara H, Mimura H, et al: Percutaneous radiofrequency ablation of clinical stage I non-small cell lung cancer. Journal of Thoracic & Cardiovascular Surgery 142:24-30, 2011	Case series	3	50	56 Pts with stage I NSCLC treated with RFA were retrospecitvelly analyses 50 pts with histological confirmation.	Radiofrequency Ablation	None	Median Follow up 37 months range 2-88.	Response rate, complications, and survival rates	Complications: Pneumothorax G1 22 treatments. G2 6(12%) and G3 3(6%). No G4/5 events.G2 evenets included pneumothorax needing chest drain, pneumonitis. G3 included pleural fluid needing drainage, bronchopleural fistula needing surgery and empyema.No sig change in FEV1 1-3 months post but only 22 of 50. Local failure was 33% (<2cm) and 40% 2.1-3.0cm. OS was 94% (1yr), 86%(2yr),74%(3yr),67%(4yr),61%(5yr).	Single arm retrospective study on RFA in stage I NSCLC
8 - Non surg treatment	289	Simon CJ, Dupuy DE, DiPetrillo TA, et al: Pulmonary radiofrequency ablation: long-term safety and efficacy in 153 patients. Radiology 243:268-75, 2007	Case series	3	153	Primary or metastatic pulmonary tumours 189 tumours in 153 patients. 602 RFA proceedures performed in 183 sessions using either a single or cluster electrode.	Radiofrequency Ablation	None	Median 20.5 (range 3-74)	Local Control, Complications and Palliation	Feasible on 159 of 162. 21 patients had advanced disease and were Rx for palliation. 75pts had stage I NSCLC and 57 had lung metastases. Mean size was 3cm for stage 1 and 2.5 cm for mets. Complications Pneumothorax G1 18.6%, G2 9.8%. Haemoptysis G1 2.7%, Infection G3 2.2% and complication requiring admission 10.4%. OS for Stage 1 NSCLC 78% (1yr), 57% (2yr), 36% (3y) and 27% (5yrs). PFS rates 83% (1yr), 64% (2yr), 57% (3yr), 47% (4+5yr) FOR TUMOURS <3cm but 45% (1yr), 25% (2,3,4&5yrs) for >3cm.OVERALL PNEUMOTHORAX RATE 28.4% , CHEST DRAIN 9.8% and 30 day mortality of 3.9% of which 2.6% proceedure related (=G5!)	Retrospective Analysis of 153 patiente post pulmonary RFA
8 - Non surg treatment	290	Yamakado K, Hase S, Matsuoka T, et al: Radiofrequency ablation for the treatment of unresectable lung metastases in patients with colorectal cancer: a multicenter study in Japan. JOURNAL OF VASCULAR & INTERVENTIONAL RADIOLOGY 18:393-8, 2007	Case series	3	77	Good PS patients with unresectable lung mets, max size 6cm, 5 tumours or less, extrapulmonary mets ok if controlled on chemo.	RFA	None	Mean 19 months. Range 4-42	Primary End Point OS. Secondary End Points safety and intrapulmonary recurrence (local failure or new lesion)	Technical Success rate was high for all patients (89%). But in the small number of tumours > 3cm only 50% were covered by ground-glass opacity at the end of Rx. Fever developed in 20% and asymptomatic pleural effusion in 14%. Pneumothorax most frequent complication in 37% of which 20% required chest drain. This was removed 1-4 days post Rx (mean 2.4 days). Empyema 1%. No deaths due to the proceedure. Local control 83% and new lung tumours in 30%. 50% local control in tumours >3cm cf with 89% for tumours < 3cm. OS 84% (1yr), 62% (2yr) and 46% (3yr) Large tumour size and extrapulmonary disease sig prognostic factors.	Mutliple- centre study of RFA to lung mets from colorectal cancer

Section	Ref no	Bibliographic citation	Study type	Ev lev	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
8 - Non surg treatment	291	Bongers EM, Haasbeek CJA, Lagerwaard FJ, et al: Incidence and risk factors for chest wall toxicity after risk-adapted stereotactic radiotherapy for early-stage lung cancer. Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer 6:2052-7, 2011	Case series	3	500	530 tumours in 500 patients treated with risk adapted SBRT between 2003-2009. 36.4% confirmed histologically. Others had to be PET +ve and growing on CT. Mixture of T1 (307) and T2 (233). 74.8% medically inoperable and 25.% refused surgery.	Stereotactic radiotherapy	None	Median 33 months (range 13-86)	Local Control and chest wall toxicity.	Used CT to assess local control at 3,6 12, 18, 24 and 36 months. However scans only available for 86.2%(3m), 86.6%(6m), 83.4%(12m),58.3%(18m), 63.4%(24m) and 36.9%(36m). Rib toxicity score as per CTC 4.0. Further dosimetric analysis done on those patients with rib toxicity. Chest wall pain (CWP) reported in 57 pts (11.4%) and grade 3 [or severe] in 10 pts (2.0%). Early CWP (within 3 months of SBRT) was seen in 32 pts (6.4%) and late in 25 pts (5%) with a median onset of 8 months. CWP was significantly higher in patients in tumours closer to ribs and larger tumours. 95% with CWP had a distance <25mm from chest wall and all rib fractures occured in tumours <5mm from the chest wall.	
8 - Non surg treatment	292	Kawase T, Takeda A, Kunieda E, et al: Extrapulmonary Soft-Tissue Fibrosis Resulting From Hypofractionated Stereotactic Body Radiotherapy for Pulmonary Nodular Lesions. International Journal of Radiation Oncology Biology Physics 74 (2):349-354, 2009	Case series	3	379	379 consescutive patient who underwent SBRT at 4 separate institutions analysed. Treated T1-2 N0 lung cancers or mets <3cm.	Stereotactic radiotherapy	None	Median follow up 29 months (1-72)	Presence of a soft tissue mass outside the lung parenchyma.	2.4% (9 patients) had chest wall soft tissue masses post SBRT. Of those 9, 7 achieved local control of their primary treated lesion. Performed dosimetric analysis in those 9 patients. Of these 9 CT detected patients only 3 were symptomatic (no grading)	
8 - Non surg treatment	293	Lagerwaard FJ, Aaronson NK, Gundy CM, et al: Patient-reported quality of life after stereotactic ablative radiotherapy for early-stage lung cancer. Journal of Thoracic Oncology 7 (7):1148-1154, 2012	Case series	3	382	Cohort of 382 consecutive patients treated with SBRT in one institution from 2003-2008.	Stereotactic radiotherapy	None	Median Follow 23 months.	HRQOL Scores	Showed no significant change in HRQOL over 24 months except for a reduction in the physical domain. Although mean decrease in 2-3 points per year this is below the level that is considered clinically meaningful. Median OS 40 months with 66% 2 yr OS. Clinician reported toxicity of early effects in 38% mainly fatigue 27%, nausea (6%) cough and increase SOB (5%) and local chest pain (4%). G3 or higher in only 2.1%. Most common clinician reported late s/e was chest wall pain present at G3 or higher in 4% with 1% developiong rib fractures at 1-2 years .	Patient reported QoL after SBRT collective prospectively in 382 pts
8 - Non surg treatment	294	Crabtree TD, Denlinger CE, Meyers BF, et al: Stereotactic body radiation therapy versus surgical resection for stage I non-small cell lung cancer. Journal of Thoracic & Cardiovascular Surgery 140:377-86, 2010	Cohort	2+	538	Comparison of Stage I NSCLC patients who received Surgery or SBRT in a single instituion.	Surgery and SBRT	yes	Median follow up surgery 31 and SBRT 19	OS, treatment related morbidity	5 yr OS with surgery 55%. Lack of long term data for SBRT but 3 yrs OS 32% cf 68% for surgery. CSS the same and no sig dif in local control (surgery 94% vs SBRT 89%) at 3 years. Surgical patients were younger, lower Charlson CM scores, and better PFTs. 13.8% of surgical patients were found to have N1 nodes and 3.5% had N2. No treatment related SBRT deaths. I patient experienced G3 pneumonitis. In addtion there were 4 rib fractures, 3 pleural effusions, 2 lung collapse and haemoptyis 1 and pneumonia 1. In the match high risk surgical cohort operative mortaility was 7% and complication in 43.8% of this group including arrythmias 21%,resp failure 27%.	Unmatched cohort study of surgery versus SBRT in a single institution
8 - Non surg treatment	295	Timmerman R, McGarry R, Yiannoutsos C, et al: Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. Journal of Clinical Oncology 24:4833-9, 2006	Case series	3	70	Ph 2 study treating patients with medically inoperable stage I NSCLC with SBRT	Stereotactic radiotherapy	None	Median 17.5 months	Local control and toxicity	Local Control 95% at 2 yrs. Median OS was 32.6 months and 2 yr OS was 54.7%. Grade 3-5 toxicity was seen in 14 pts (20%). DSM committee felt that SBRT contributed to 6 deaths. There 2 year freedom from toxicity was 83% for peripheral lesion cf 54% for central/perihilar lesions. Patients with central lesions were found to have an 11 fold higher risk of toxicity.	Analysis of Prospective Case Study showing increased toxicity for central tumours treated with SBRT
8 - Non surg treatment	296	Uematsu M, Shioda A, Suda A, et al: Computed tomography-guided frameless stereotactic radiotherapy for stage I non-small cell lung cancer: a 5-year experience. INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY, BIOLOGY, PHYSICS 51:666-70, 2001	Case series	3	50	Single centre experience treating stage 1 NSCLC with SBRT (though 18 also received conventional RT_	Stereotactic radiotherapy	None	Median 36 months (range 22-66)	Local control and toxicity	Local control 94%. 3 ys OS was 66% (all patients) and 86% in those patient deemed medically OPERABLE. CSS 88% at 3 years. Minor G1/2 pain only.	Small early SABR study from Japan with some patient receiving SABR and conventional RT
8 - Non surg treatment	297	Widder J, Postmus D, Ubbels JF, et al: Survival and quality of life after stereotactic or 3D-conformal radiotherapy for inoperable early-stage lung cancer. INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY, BIOLOGY, PHYSICS 81:e291-7, 2011	Cohort	2-	229	202 patients treated with cyberknife SBRT compared to 27 patients treated with 3DCRT > 10 years previously in an earlier study	Stereotactic radiotherapy	3D-CRT	Median 13 months	OS, LC and QoL	Confouding factors: no PET for 3D CRT group. Better PS and lower age in 3D CRT group. Poorer planning and IGRT in 3D CRT group. No significant difference in QoL compliance at all time points 3,6,12+24months. More decline in physical functioning and worsening dyspnoea in 3DCRT cf to SBRT. Trend for improvment in GQOL with SABR but not significant.	Comparison of 2 cohorts- one treated with SABR 2006-2009 and conventional RT 1994-1996
8 - Non surg treatment	298	Timmerman R, Paulus R, Galvin J, et al: Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 303:1070-6, 2010	Case	3	55	Medically inoperable patients with histologically confirmed stage 1 NSCLC (T1 44pt T2 11) treated with 60Gy in 3 fractions. All patients turned down by a thoracic surgeon.	Stereotactic radiotherapy	None	34.4 months (4.8-49.9)	2yr actuarial local control. Secondary end points DFS, toxicity and OS	CR 51% at median of 6.5 months. PR in 21 patients and 89% in total responded. 1 local failure. 3 year LC was 97.6% and involved lobe control 90.6%. 2 regional failures with loco-regional control rate of 87.2% @ 3years. 14 patient died of cancer 1 primary alone, i involved lobe alone, 2 involved lobe and disseminated, 1 hilum alone, 1 nodes and disseminated and 8 disseminated alone. Higher dissemintated recurrence for T2 (47%) cf T1 14.7%. Note small numbers of T2 tumours. DFS 48.3% at 3 years and OS 55.8% @ 3 ys. Seven pts G3 and 2 pts G4 toxicity. No G5 toxicity.	Multi-centre study of SBRT for medically inoperble, histologically confirmed
8 - Non surg treatment	299	Atallah S, Cho BC, Allibhai Z, et al: Impact of pretreatment tumor growth rate on outcome of early-stage lung cancer treated with stereotactic body radiation therapy. Int J Radiat Oncol Biol Phys 89:532-8, 2014	Case Series	3	237	Medically inoperable patient with T1-2N0 tumours based on pahtological or radiological diagnosis. All treated with SABR at a single institution. 4 dose levels used.	Stereotactic radiotherapy	None	20.0 months	OS, Serial growth rate, local, regional and distant failure rate.	Patients were split into two groups based on their median serial growth rate (SGR). In the high SGR group the was a higher local failure rate (7.5%) versus 2.7% in the low SGR group- non signigicant (p=0.38). Regional failure was also higher in the high SGR group (19.2%) versus 6.0% in the low SGR group (p0.047). Distant failure was the were similar. ECOG performance status, GTV size and Male sex were also significant factors for OS and failure-free survival on univarible and multivariable analysis.	Single centre retrospective analysis of patients treated with stereotactic radiotherapy. Good quality analysis.
8 - Non surg treatment	300	Senthi S, Lagerwaard FJ, Haasbeek CJ, et al: Patterns of disease recurrence after stereotactic ablative radiotherapy for early stage non-small-cell lung cancer: a retrospective analysis. Lancet Oncol 13:802-9, 2012	Case Series	3	676	Medically inoperable patients with T1-2 tumours	Stereotactic radiotherapy	None	32.9 months	OS, acturarial 2 and 5 yr OS rates, patterns of recurence.	Histological confirmation was obtained in 35% (235pts). Crude local recurrence rate was 4% and median time to local recurrence was 14.9 months. Local recurrence was not related to the dose/fractionation schedule used. No difference in outcomes between patient with or without histological confirmation. Second primary lung cancer diagnosed in 6% (median of 18 months). 6% presented with regional recurrence with approx half being isolated regional recurrence (median time 13.1 months) Distant recurrence occured in 12% of which 70% of these had isolated distant recurrence (i.e. without local or regional recurrence) Median time to distant recurrence was 9.6 months.	Large single centre case series with good and robust long term follow up.
8 - Non surg treatment	301	Ricardi U, Frezza G, Filippi AR, et al: Stereotactic Ablative Radiotherapy for stage I histologically proven non-small cell lung cancer: an Italian multicenter observational study. Lung Cancer 84:248-53, 2014	Case series	3	196	Histologically confirmed stage I NSCLC treated with stereotactic radiotherapy	Stereotactic radiotherapy	None	Median f/u 30 months	Local control, overall survival, cancer specific survival and toxicity.	Median age 75 yrs. Median tumour size 2.48cm. Dose 48-60 Gy in 3-8 fractions. No 30/60 day post SABR mortality. Local control 89.7% at 3 years. 30.1% had one site of failure (local +/- nodal +/- distant) with DFS at 3 years 65.5%. Median time to recurrence was 15 months. Median OS 54 months. Stage IB was associated with decrease in OS, DFS and CSS on mulitvariate analysis.	Multi-centre study of pathologically confirmed stage I NSCLC. All deemed medically inoperable. Not all patients were staged with PET-CT which may account for slightly higher regional and distant recurrence rates though median OS higher than in many studies.

Section	Ref no	Bibliographic citation	Study type	Ev lev	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
8 - Non surg treatment	302	Haasbeek CJ, Palma D, Visser O, et al: Early-stage lung cancer in elderly patients: a population-based study of changes in treatment patterns and survival in the Netherlands. Ann Oncol 23:2743-7, 2012	Cohort study	2-	4605	Elderly patients (>74) with stage I lung cancer identified from the netherlands cancer registry over 3 time periods.	All treatment modalities including best supportive care	3 time periods; A (2001-2003), B (2004-2006) and C (2007-2009)	N/A	30/90 day mortality rates after surgery, date of diagnosis for RT, overall survival in all groups	Surgical rates remained constant over the 3 time periods (37%), radiotherapy rates went up 31.9% to 37.7% and best suportive care reduced from 31.9% to 24.9%. 30 day and 90 nday surgical mortality reduced from periods A to C (6.4% to 3.9% and 11.5% to 7.0% respectively. RT estimated mortality was 0.6% and 3.3% at 30 and 90 days. For the BSC group it was 17.9% and 33.3% respectively. Median OS for all patients was 19.6 months. Patients treated in time period C had a better survival than period A (16.4 to 24.4 months) with the largest reduction in death in the RT group when median OS improved from 16.8 to 26.1 months but also a significant reducton in the HR for death afer surgery (0.79). Two OS for surgery improved from 61.3% to 69.6% and RT from 35.7% to 69.6%. Median OS for untreated patients was 6.6 months.	3 time cohorts of stage I NSCLC patients 75 yrs and over. Increased use of RT, mostly SABR, over the 3 periods. Improvement on OS for surgery and RT groups with less patients getting BSC. Confouning factors better staging with PET/EBUS ovee the time periods and this may cause stage drift and improve OS on it own.
8 - Non surg treatment	303	McGarry RC, Song G, des Rosiers P, et al: Observation-only management of early stage, medically inoperable lung cancer: poor outcome. Chest 121:1155-8, 2002	Retrospective cohort study	2-	128	All patients with I/Iia NSCLC at single centre - stratified by no therapy, RT or surgery only. Single institution.	No intervention	Surgery or RT (curative or palliative)	Not stated	Survival	Median survival was 14.2/12 for no treatment compared to 19.9/12 for RT alone and 46.2/12 for surgery. Curative RT (>60Gy) had 20.8/12 median survival compared to 16.0/12 for palliative RT (non-significant difference). Cause of death wass lung cancer in 53% of untreated patients - maybe underestimate as many had unknown cause of death	Huge confounding factors related to comorbidities (acknowledged) - simply demonstrates poor outcome from BSC (and at that time RT also). Variability in RT regimes
8 - Non surg treatment	304	Vogl TJ, Naguib NNN, Gruber-Rouh T, et al: Microwave ablation therapy: clinical utility in treatment of pulmonary metastases. Radiology 261:643-51, 2011	Case series	3	80	80 patient underwent CT guided percutaneous microwave ablation of pulmonary mets (130 lesions). Pts not good surgical candidates (not resectable, high risk) 5 or fewer lesions, <5cm in axial dimensions, Exclude if nodal or extrathoracic disease or tumour infiltrating chest wall or mediastinum.	Microwave RFA	None	Range 6-24 months.	Local control, OS, and safety/complications	Safety and complications- no intraprocedural death. 8.5%(11pts) pneumothorax of which 5 needed chest drain. 6.2%(8pt) developed pulmonary haemorrhage which was self limiting. Haemoptysis in 4.6% (6pt) but self limiting. Overal local failute rate 26.9%. More effective for peripheral and tumours <3cm. Hepatocellular carcinomas responded best 80% but RCC least 40%. Reablation performed for 17 of 35 local failures with a secondary control tate of 52.9%	Prospective Single Centre Study of Microwave Ablation of Pulmonary Metastases
8 - Non surg treatment	305	Wolf FJ, Grand DJ, Machan JT, et al: Microwave ablation of lung malignancies: effectiveness, CT findings, and safety in 50 patients. Radiology 247:871-9, 2008	Case series	3	50	50 patients with 82 lesions treated with microwave RFA using CT guidance. All histologies allowed. Exclusion criteria were nodal disease, tumour abutting mediastinal structures or chest wall invasion.	Microwave RFA	none	Mean 10.8 months	Local control, complications, CSS and OS	26% recurred locally at 6 months. Tumours larger than 3 cm stat sig higher recurrence rates. 22% developed recurrence in a new site in the lung. Acturial OS were 65% (1yr), 55%(2y), 45% (3 yr). CSM was 83% (1yr), 73% (2yr) 61% (3ys). No comment of other treatment received. No 30 day deaths, 1 death due to Rx at 8 months due to an infected RFA cavity. Pneumothorax in 39% (22pt) and G2 or higher in 8pts. 2 pts experience skin burns one grade 3 (full thickness burn) and one patient had significant pain duing the procedure. 10 patients required hospital admission.	:Single centre preliminary results of microwave ablation for pulmonary tumours.
8 - Non surg treatment	306	Veronesi G, Szabo E, Decensi A, et al: Randomized phase II trial of inhaled budesonide versus placebo in high-risk individuals with CT screen-detected lung nodules, Cancer prevention research (Philadelphia, Pa.), 2011, pp 34-42	Phase 2 RCT	1+	202	Asymptomatic current/former smokers within last 15yrs (>20py). Persistent lung nodule (>4mm) on 2 serial yearly CT scans. Excluded clearly benign or known cancer (within 5yrs), or current ICS. Single institution.	Inhaled budesonide 800mcg bd	Placebo	1 year	Shrinkage of lung nodules on per-person analysis (reduction of 30% if >5mm, disappearance if less)	No significant effect on nodule progression/regression on per patient analysis. Non-significant trend towards regression of non/partially sold lesions after budesonide (although appearance of new lesions not different between groups).	Post-hoc subgroup analysis for non-significant trend of questionable importance. Essentially a well designed negative study. RCT checklist completed
8 - Non surg treatment	307	van den Berg RM, Teertstra HJ, van Zandwijk N, et al: CT detected indeterminate pulmonary nodules in a chemoprevention trial of fluticasone, Lung cancer (Amsterdam, Netherlands), 2008, pp 57-61	RCT	2	201 and then 108 in trial	Patient were eligible if they had 1. risk of lung cancer i.e. > 20 pack year histoty or previous history of lung or H+N cancer and 2. at lease one site of bronchial squamous meta/dysplasia. CT at baseline excluded those with pre-existing lung cancer	inhaled steroid	Yes- placebo	not clear	Change in existing and development of new nodules	No significant difference though study appears very underpowered.	RCT of inhaled steroids in patients with indeterminate pulmonary nodules
8 - Non surg treatment	308	Khokhar S, Mironov S, Seshan VE, et al: Antibiotic use in the management of pulmonary nodules. Chest 137:369-75, 2010	Retrospective cohort study	2-	114	Retrospectively analysed cohort of patients presenting to pulmonary/ thoracic surgery over 24/12. Single institution.	Antibiotics	No antibiotics	Variable - earlier follow-up for Abx treated patients. No figures given	Increase, stability, decrease or resolution of nodule on subsequent CT scan	No significant difference in nodule behavious comparing 24% of patients receiving antibiotics and 76% patients not receiving antibiotics. Larger nodules and those associated with bronchiectasis were more likely to be treated with antibiotics	Poorly designed retrospective cohort study with significant confounding factors. No demonstrated effect between antibiotic use and nodule resolution.
8 - Non surg treatment	309	Verstegen NE, Oosterhuis JW, Palma DA, et al: Stage I-II non-small-cell lung cancer treated using either stereotactic ablative radiotherapy (SABR) or lobectomy by video-assisted thoracoscopic surgery (VATS): outcomes of a propensity score-matched analysis. Ann Oncol 24:1543-8, 2013	Retrospective cohort study	2+	128	Restrospective surgery (VATS) and SABR cohorts	Surgery and SBRT	Surgery and SBRT	SABR (30months) and VATS (16months)	Local control and overall survival	Improved local control in the SABR arms at both 1 and 3 years. SABR 96.8% and 93.3% compared with VATS 86.9% and 82.6%. No difference in overall survival or distant recurrences.	Match cohrort using propensity score matched analysis. Small numbers and VATS surgery in the early stage so may have had a learning effect contributing to lower local control rates in their arm. No difference in OS supporting need for RCT of SABR versus Surgery
8 - Non surg treatment	310	Chang JY, Liu H, Balter P, et al: Clinical outcome and predictors of survival and pneumonitis after stereotactic ablative radiotherapy for stage I non-small cell lung cancer. Radiat Oncol 7:152, 2012	Retrospective case series	3	130	Stage I NSCLC treated with SABR at a single institution treated with 50Gy in 4 fractions	Stereotactic radiotherapy	None	Median 26 months	Overall survival, rates of radiation pneumonitis. Looked at association of these with performance status, SUV max on staging PET/CT, histology and disease operability.	2 year local control was 98.5%. Median OS was 60 months. OS at 1y (93%), 2yr(78.2%) and 3yr (65.3%). Performed univariate and mulitvariate analysis . Univariate OS was associated with PS, SUVmax, histology, operability but only SUVmax on multivariate. For radiation pneumontis mean ipsilateral lung dose >9.14Gy was significant on multivariate analysis.	Reasonable size case series showing that pre treatment SUVmax correlates with OS and ipsilated mean lung dose correlates with development of G2-3 radiation pneumonitis in patients treated with SABR.
8 - Non surg treatment	311	Baker R, Han G, Sarangkasiri S, et al: Clinical and dosimetric predictors of radiation pneumonitis in a large series of patients treated with stereotactic body radiation therapy to the lung. Int J Radiat Oncol Biol Phys 85:190-5, 2013	Case series	3	240 (263 tumours treated)	Mixture of T1-3 NSCLC (majority) and mets.	Stereotactic radiotherapy	None	15. 6 months	Development of radiation pneumonitis (RP)	Crude rate of RP was 11%. On univariate analysis female sex and Charlson co-morbidity index were siginficant predictors of RP. Dosimetric parameters were not signifcantly associated with RP though the doses were generally low. A PTV to lung volume ratio was sigificant for RP and on multivariate analysis female gender, larger ITV and smoking were predictors for RP.	Small numbers developed G3 RP with the majority getting grade 2 (ie not requiring oxygen but needed medical interventino eg steroids). No dosimetric parameter found to be significant.

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8 - Non surg treatment	312	Inoue T, Katoh N, Onimaru R, et al: Stereotactic body radiotherapy using gated radiotherapy with real-time tumor-tracking for stage I non-small cell lung cancer. Radiat Oncol 8:69, 2013	Case series	3	109 patients	T1 (79pts) and T2(30pts)	Stereotactic radiotherapy	None	25 months	5 yr local control rate, 5 yr overall survival rate, rates of radiation pneumonitis, dosimetric parameters (V20 and MLD)	Local control was 81% (3yrs) and 78% (5rs). Overall survival was 68%(3yrs) and 64%(5yrs). OS better for T1a compared with T1b/2 (75% vs 58%). Mean lung dose (MLD) and V20 were significantly higher in the patients that developed radiation pneumonitis; MLD 4.8Gy(+/-1.4) cf 3.8Gy(+/-1.3) for patients with G2/3 RP, V20 5.8%(+/-2.3) cf 7/6%(+/-3.3) for patients with G2/3 RP. Larger PTV soze correlated with MLD. Tumour motion larger in lower lobes but larger PTV size did not correlate with tumour motion amplitude. Importantly no complications were reported from gold marker insertion implanted near or in the tumour by bronchscopy.	Good size case series. Slightly lower local control rates than in other series and showed a difference between T1a and T1b/2. The dose used is a lower biological equivalent and this might explain these findings. Demostrates that tumour tracking is feasible and very low compliction rates from gold marker insertion.
8 - Non surg treatment	313	Stanic S, Paulus R, Timmerman RD, et al: No clinically significant changes in pulmonary function following stereotactic body radiation therapy for early- stage peripheral non-small cell lung cancer: an analysis of RTOG 0236. Int J Radiat Oncol Biol Phys 88:1092-9, 2014	Prospective case series	3	55	T1-3N0M0 medically inoperable NSCLC (pathologically confirmed)	Stereotactic radiotherapy	None	2 year follow up post SABR	FEV1, arterial blood gas, oxygen saturation and full pulmonary function tests taken before and post SABR. All patients required to be turned down by a thoracic surgeon and have histological confirmaiton.	At baseline mean FEV1 was 60.8% and DLCO 60.7%. At 2 years the mean FEV1 declined by 5.8% and DLCO by 6.3%, with minimal changes arterial blood gases in oxygen saturation and no significant delcine in oxygen saturation. There was no difference in dosimetric parameters between patient who developed radiation pneumonitis and those who did not. Poor baseline PFTs did not predict for worse overall surival. In addition patients that were inoperabe due to their poor lung function did better than those patients with normal pre-treatment PFTs and were inoperable for cardiac reasons.	High quality prospective phase II study with robust data collection. Poor pre-SABR PFTS did not predict for pulmonary toxicity or worse OS.
8 - Non surg treatment	314	Louie AV, Rodrigues G, Hannouf M, et al: Withholding stereotactic radiotherapy in elderly patients with stage I non-small cell lung cancer and co-existing COPD is not justified: outcomes of a Markov model analysis. Radiother Oncol 99:161-5, 2011	Case-control	2+	247	247 pts with COPD aged over 75 for T1/2N0 lung cancer treated with SABR	Stereotactic radiotherapy	treated at a single institution with SABR compared with a untreated population from the California Cancer Registry	N/A	Comparing predictive model to source data for OS.	Model correlated with source data for overall survival. Model predicted for 6.8-47.2% 5 yrs OS and 14.9-27.1 QALM (qaulity adjusted months) for patients treated with SABR. For untreated patients the model predicted for 9.0%(T1), 2.5%(T2) 5yr OS and 10.1(T1)/6.1(T2) QALMs. The benefit of SABR was the least for T2, GOLD III-IV patients.	Model paper comparing patients treated with SABR compared a untreated patient from historical cancer registry. Model suggests that SABR impoves both OS and QALMS in patients over 75yrs with COPD.
8 - Non surg treatment	315	Baumann P, Nyman J, Hoyer M, et al: Stereotactic body radiotherapy for medically inoperable patients with stage I non-small cell lung cancer - a first report of toxicity related to COPD/CVD in a non-randomized prospective phase II study. Radiother Oncol 88:359-67, 2008	Case series	3	60	T1 (65%) T2 (35%) with mean FEV1 64% and median Karnofsky index of 80	Stereotactic radiotherapy	none	Median 23 months	Local control, toxicity and serial FEV1 measurements	2 patients developed local failure (~3%). No grade 4-5 toxicity but grade 3 in 12pts (21%). No signficant decline in FEV1. No significant differences in rates of radiation pneumonits and fibrosis in patients with COPD or cardiovascular disease. Higher rates of pleural effusion were seen in the cardiac patients.	Conclusion is that stereotactic radiotherapy is safe for patients with COPD and cardiovascular morbidity (low rates of grade 3/4 toxicity) and high local control rates.
8 - Non surg treatment	316	Guckenberger M, Kestin LL, Hope AJ, et al: Is there a lower limit of pretreatment pulmonary function for safe and effective stereotactic body radiotherapy for early-stage non-small cell lung cancer? J Thorac Oncol 7:542-51, 2012	Case series	3	483 pts with 505 tumours	T1-3N0 (64% biopsy proven) with 423 pts with pre-treatment lung function and 270 pts with post treatment lung function	Stereotactic radiotherapy	none	N/A	Changes in pulmonary function test (PFTs) correlated with overall survival and radiation pneumonitis (RP)	Large range of pre-treatment PFTs. 90% range for (1) FEV1 and (2) DLCO was (1) 29-109% and (2) 5.5 to 19.1 ml.min/mmHg. PFTS were correlated with overall survival but not cause specific survival with a DLCO of 11.2 deferentiated between 3 yrs OS (66% vs 42%). RP rates were 7% and not increased in patients with poor PFTs. Significant and progressive decline in PFTs was seem post SABR by on average 3.6% at 6 months and 6.8% between 6-24 months. Bigger reductions in PFTs were seen for patients with better pre-treatment PFTs.	Conclusion Is that stereotactic radiothearpy is safe in terms of acute and late respiratory toxicity even in patients with poor pre-treatment PFTS.
8 - Non surg treatment	317	Bongers EM, Botticella A, Palma DA, et al: Predictive parameters of symptomatic radiation pneumonitis following stereotactic or hypofractionated radiotherapy delivered using volumetric modulated arcs. Radiother Oncol 109:95-9, 2013	Case series	3	79pts	Patients that received SABR using a VMAT RT technique with large PTVs or previous surgery (bi-lobectomy or pneumonectomy) were retrospectively analysed.	Stereotactic radiotherapy	none	N/A	Radiation dose, various lung parameters and compared with patients that devloped ≥ grade 3 radiation pneumonitis.	Grade ≥3 radiation pneumonitis in 8 pts. Multiple factors were predictive of RP in univariate analysis. In multivariate analysis the contralateral mean lung dose and ITV size were the strongest predictors of RP.	ITV size and contralteral MLD were strongest predictors for RP. Should aim to keep the MLD <3.6Gy. Small study and selected popluation so may not be applicable to all patients.
8 - Non surg treatment	318	Guckenberger M, Baier K, Polat B, et al: Dose-response relationship for radiation-induced pneumonitis after pulmonary stereotactic body radiotherapy. Radiother Oncol 97:65-70, 2010	Retrospective case series	3	59	Patients treated with image-guided SABR for primary NSCLC (21lesions) and Mets(54) with a variety of doses	Stereotactic radiotherapy	none	N/A	Dosemetric parameters were evaluated for all patients.	11 pts developed grade 2 RP. MLD was 12.5Gy(+/-4.3Gy) compared 9.9Gy(+/-5.8) for patients with RP.	Small study with only grade 2 RP seen. Higher MLD was associated with higher rates of RP.
9 - Information	319	Senthi S, Haasbeek CJ, Slotman BJ, et al: Outcomes of stereotactic ablative radiotherapy for central lung tumours: a systematic review. Radiother Oncol 106:276-82, 2013	Systematic Review	2++	315	Paper that had patients who rec	Stereotactic Radiotherapy	None	19 months (all 20 studies evaluated)	Overall survival, local control, treatment related mortality or grade 3/4 toxicity.	OS ranged from 50%(2 yrs) to 72% at 3 years. Local control rates at 2 years ranged from 60-94% and at 3 yrs from 64% to 94%. Treatment related mortality range from 0-18% though in some case was difficult to discern whether the death was trully SABR related eg pneumonia. From all studies the rate was 2.8% for treatment related mortality. Again with the caveats of defining treatment related versus non-related toxicity the rates of grade 3/4 toxicity were 8.6%.	Good review but compared a wide variety of dose scedules so with high rates of toxicity. Overall with dose adapted SABR regimes high rates of local control and acceptable levels of toxciity are seen though the rates of toxicity are higher than for peripheral tumours.
9 - Information	320	Lemonnier I, Baumann C, Jolly D, et al: Solitary pulmonary nodules: consequences for patient quality of life. Quality of Life Research 20:101-9, 2011	prospective single group with comparator group from the general population	Q3	171		Patients with diagnosis of SPN	French general population	6 months	HRQOL	HRQoL worse than French general population 6 months after diagnosis od SPN whether or not malignant	
9 - Information	321	van den Bergh KAM, Essink-Bot ML, Borsboom GJJM, et al: Short-term health-related quality of life consequences in a lung cancer CT screening trial (NELSON). British Journal of Cancer 102:27-34, 2010	Prospective qualitative study	Q3	733	screenees in the NELSON trial	CT screening	Control arm of CT screening study	3 months	HRQOL	Short trem QOL was worse in those people in the screening study that had a nodule than those that did not	
9 - Information	322	Wiener RS, Gould MK, Woloshin S, et al: What do you mean, a spot?: A qualitative analysis of patients' reactions to discussions with their physicians about pulmonary nodules. Chest 143:672-7, 2013	Observational qulaitative	Q2	22			none		HRQOL	Identified that patients preferred discussion of cancer risk and that patients assumed they had cancer. Lay terms were preferred and imaging viewing preferred	
10 - Technical	323	Fischbach F, Knollmann F, Griesshaber V, et al: Detection of pulmonary nodules by multislice computed tomography: improved detection rate with reduced slice thickness. European Radiology 13:2378-83, 2003	Diagnostic comparative	2+	100	Those with one or more pulmonary nodules	5mm slice thickness	1.25mm slice thickness	N/A	detection rate	for lesion <5mm, 88% and 86% detection rate vs 1.25 mm and K or agreement 0.56 for 5mm and 0.75 for 1.25 mm	Just two observers. Gold standar was the 1.25 mm.so potential for missed lesions with gold standard
10 - Technical	324	Lee HY, Goo JM, Lee HJ, et al: Usefulness of concurrent reading using thin-section and thick-section CT images in subcentimetre solitary pulmonary nodules. Clinical Radiology 64:127-32, 2009	Diagnostic comparative	2+	529	Patients with sub centimeter nodules	4 radiologists reading CTs with 1 and 5mm slice thickness in same patients	1mm and 5mm slice thickness	N/A	level of agreement on consistnecy; size of lesion	K 0.78 vs 0.67 for 1 vs 5mm slice on agreement for consistency of nodule	Nodules measured larger on the 1mm thickenss ; better agreement with tthink slice but authors conclude to use both 1 and 5mm

Section	Ref no	Bibliographic citation	Study type	Ev lev	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
10 - Technical	325	Sinsuat M, Saita S, Kawata Y, et al: Influence of slice thickness on diagnoses of pulmonary nodules using low-dose CT: potential dependence of detection and diagnostic agreement on features and location of nodule. Academic Radiology 18:594-604, 2011	Diagnostic comparative	2+	360	Patients with nodules	6 radiologists independent read CTs and classified as whether for further evaluation or not	2 vs 10mm slice thickness	N/A	Comparison of diagnosis on 2 or 10mm slices	67.6% same diagnosis on 2 and 10mm slices. 21% different. 10.6%missed on 10mm slices. Regarding detection and nondetection, NFE diagnoses were influenced by size (odds ratio [OR], 132.50; 95% confidence interval [CI], 4.77-4711) and the average CT value (OR, 27.20; 95% CI, 3.21-645.3), and INNFE diagnoses were influenced by size (OR, 16.10; 95% CI, 6.18-55.19) and the average CT value (OR, 7.67; 95% CI, 2.19-30.91). Regarding diagnostic agreement and disagreement, the NFE diagnoses were influenced by size (OR, 3.60; 95% CI, 1.29-11.04), nodule distance from the lung border (OR, 2.85; 95% CI, 1.27-6.65), and nodule location in the right upper lobe (OR, 0.07; 95% CI, 0.003-0.477), while the INNFE diagnoses were influenced by the average CT value (OR, 11.84; 95% CI, 3.33-55.86), size (OR, 0.42; 95% CI, 0.25-0.70), and nodule distance from the lung border (OR, 0.41; 95% CI, 0.25-0.66).	Assessed the influence of slice thickness on the ability of radiologists to detect or not detect nodules and to agree or disagree on the diagnosis
10 - Technical	326	Abe H, Ishida T, Shiraishi J, et al: Effect of temporal subtraction images on radiologists' detection of lung cancer on CT: results of the observer performance study with use of film computed tomography images. Academic Radiology 11:1337-43, 2004	Diagnostic comparative	3	30	patients with primary lung cancer and those with normal CT, from a screening programme of LDCT	7 radiologists independently read CTs	tempral subtraction images	N/A	AUC for detection of nodules that were cancer	AUC 0.868 improved to 0.93 with temporal subtraction	Low numbers for the conclusion made
10 - Technical	327	Cui Y, Ma D-Q, Liu W-H: Value of multiplanar reconstruction in MSCT in demonstrating the relationship between solitary pulmonary nodule and bronchus. Clinical Imaging 33:15-21, 2009	observational	4	148	patients with pulmonary nodules	multiplanar recon	without	n/a	dtection of air bronchus sign better with MPR	not given	
10 - Technical	328	Diederich S, Lentschig MG, Overbeck TR, et al: Detection of pulmonary nodules at spiral CT: Comparison of maximum intensity projection sliding slabs and single-image reporting. European Radiology 11 (8):1345-1350, 2001	Diagnostic comparative	3	18	patients with pulmonary nodules	each comparator	MIP 15, MIP 30 and single image with 10mm collimations	n/a	number of noduels detected and time to read CT	More nodule recorded by MIP 15mm than single image. Reduction in time to read CTs by 1.4-5.3 fold	Little difference between single image and 30mm MIP
10 - Technical	329	Gruden JF, Ouanounou S, Tigges S, et al: Incremental benefit of maximum-intensity-projection images on observer detection of small pulmonary nodules revealed by multidetector CT. AJR American Journal of Roentgenology. 179:149-57, 2002	Diagnostic comparative	3	25	patinets with metstatic disease with 2-9 nodules each	use of MIP, 10mm slab, 8mm interval	single image	n/a	detection of nodules	MIP increased reviewer detection and reduced the effect of experience of radiologists	
10 - Technical	330	Jankowski A, Martinelli T, Timsit JF, et al: Pulmonary nodule detection on MDCT images: evaluation of diagnostic performance using thin axial images, maximum intensity projections, and computer-assisted detection. European Radiology 17:3148-56, 2007	Diagnostic comparative	3	30	30 patients with 285 nodules ≥1mm from lung cancer screening	each comparator	axial 1mm vs. Axila MIP and CAD system	n/a	detection rates fo 3 independent observers	Both CAD and MIP increased nodule detection, MIP was less time-consuming	
10 - Technical	331	Kawel N, Seifert B, Luetolf M, et al: Effect of slab thickness on the CT detection of pulmonary nodules: use of sliding thin-slab maximum intensity projection and volume rendering. AJR American Journal of Roentgenology. 192:1324-9, 2009	Diagnostic comparative	3	88	Oncology patients with a total of 1058 nodules detected; 69.5% nodules ≤4mm	each comparator	MIP and VR with 3 different slab thicknesses, 5,8 and 11 mm	n/a	Sensitivty for detection of pulmonary nodules	80 to 85% with MIP 8mm vs 40-60% for other slab thickness and VR	MIP and slab thickness of 8mm clearly best. Two readers
10 - Technical	332	Matsumoto S, Ohno Y, Yamagata H, et al: Potential contribution of multiplanar reconstruction (MPR) to computer-aided detection of lung nodules on MDCT. European Journal of Radiology 81:366-70, 2012	Diagnostic comparative	3	60	Patients with suspected lung nodules	each comparator	MPR vs no MPR in CAD	n/a	detection rate, time to read CT	21 to 33% faster with MPR	Two readers
10 - Technical	333	Park EA, Goo JM, Lee JW, et al: Efficacy of computer-aided detection system and thin-slab maximum intensity porojection technique in the detection of pulmonary nodules in patients with resected metastases. Investigative Radiology 44 (2):105-113, 2009	Diagnostic comparative	3	49	Patients who had had pulmpnary metastectomy 514 nodules	each comparator	1mm section ct vs. thin slab MIP vs CAD	n/a	Sensitivty for detection of pulmonary nodules	sensitivity rose from 86-91% to 94-95% with MIP and 91-96% with CAD	CAD and MIP improve sensitivity for detection of nodules in people having metastatectomy
10 - Technical	334	Peloschek P, Sailer J, Weber M, et al: Pulmonary nodules: sensitivity of maximum intensity projection versus that of volume rendering of 3D multidetector CT data. Radiology 243:561-9, 2007	Diagnostic comparative (prospective)	3	20	Oncology patients	each comparator	VR vs MIP	n/a	sensitivity; reporting time		VR better for nodule <11mm diameter and for perihilar nodules and faster reporting time
10 - Technical	335	Valencia R, Denecke T, Lehmkuhl L, et al: Value of axial and coronal maximum intensity projection (MIP) images in the detection of pulmonary nodules by multislice spiral CT: comparison with axial 1-mm and 5-mm slices. European Radiology 16:325-32, 2006	Diagnostic comparative	3	60	Patients with suspected lung nodules	each comparator	10mm overlapping slices with axial and coronal MIP	N/A	ROC characterristics	Statistica difference only for 1mm slcine and MIP	3 radiologists. 1mm slices and MIP were better for sub 5mm nodules; all modalities the same for larger nodules
10 - Technical	336	Yoneda K, Ueno J, Nishihara S, et al: Postprocessing technique with MDCT data improves the accuracy of the detection of lung nodules. Radiation Medicine 25:511-5, 2007	Diagnostic comparative	3	164 segmented lung volumes	not given	each comparator	7 or 10 mm axial; 1mm axial; MIP 15mm; VR 15mm	N/A	Accuracy	not given	16 physicians more nodules detect with MIP and VR with thin section; thin section data essential
10 - Technical	337	Goo JM, Tongdee T, Tongdee R, et al: Volumetric measurement of synthetic lung nodules with multi-detector row CT: effect of various image reconstruction parameters and segmentation thresholds on measurement accuracy. Radiology 235:850-6, 2005	Diagnostic comparative	3	10	patients with asthma or chronic bronchitis	each comparator	inspiration vs expiration	n/a	difference in volume	28/33 nodules larger on expiration mean diff 23%	small study but large differences
10 - Technical	338	Honda O, Sumikawa H, Johkoh T, et al: Computer-assisted lung nodule volumetry from multi-detector row CT: influence of image reconstruction parameters. European Journal of Radiology 62:106-13, 2007	Diagnostic comparative	3	Not given - 39 nodules		each comparator	variable slice thickness	n/a	comparative nodule volume	Max difference in volume 16%	Showed volumetric measurements depend on the reconstruction
10 - Technical	339	Nietert PJ, Ravenel JG, Leue WM, et al: Imprecision in automated volume measurements of pulmonary nodules and its effect on the level of uncertainty in volume doubling time estimation. Chest 135:1580-7, 2009	Diagnostic comparative	3	Phantoms - no patients involved in study	N/A	Estimate of VDT based on differences in size		VDT estimates	Variability in estimate of VDT based on 2 nodule size measurements	Confidence intervals around VDT estimates were wide especially for 2.5 and 5mm slice thickness when growth was small (1 or 2mm growth in diameter)	Estimates of VDT need to consider slice thickness and degree of observed growth. Slice thickness od >2.5mm is inadequate for 1mm changes in nodule diameter
10 - Technical	340	Petrou M, Quint LE, Nan B, et al: Pulmonary nodule volumetric measurement variability as a function of CT slice thickness and nodule morphology. AJR American Journal of Roentgenology. 188:306-12, 2007	Diagnostic comparative	3	75 nodules		each comparator	different section thickness to measure volume	n/a	differences in volumes	N/a	Not all nodules have different methods applied. Variation in volume greater for smaller nodules and spiculated nodules
10 - Technical	341	Petkovska I, Brown MS, Goldin JG, et al: The effect of lung volume on nodule size on CT. Academic Radiology 14:476-85, 2007	Diagnostic comparative	3	41 patients	Patients with lung nodules	Scans at TLC	Scan at RV	N/A	Change in nodule volume comparing TLC and RV scans	Nodule diameter and volume varied non-uniformly between TLC and RV (some increasing in size, some decreasing). Mean value of volume changes were higher for non-calcified nodules (17%) vs calcified nodules (9%)	Highlights need to standardise protocols for performing surveillance scans where changes in size used to calculate VDT.

Section	Ref no	Bibliographic citation	Study type	Ev lev	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
10 - Technical	342	Honda O, Johkoh T, Sumikawa H, et al: Pulmonary nodules: 3D volumetric measurement with multidetector CT--effect of intravenous contrast medium. Radiology 245:881-7, 2007	Diagnostic comparative	3	60	17 men 43 women	each comparator	bone vs standard algorithm pre and post contrast	n/a	volume measurements	5.4 and 6.4% increase in volume post contrast	
10 - Technical	343	Gietema HA, Schaefer-Prokop CM, Mali WPTM, et al: Pulmonary nodules: Interscan variability of semiautomated volume measurements with multisection CT-- influence of inspiration level, nodule size, and segmentation performance. Radiology 245:888-94, 2007	Prospective controlled comparison	2+	20	15 men 5 women with known lung mets 218 nodules	LDCT	second LDCT		interscan variability	mean difference in nodule volume 1.3% 95% CI -21% to +24%	Segmentation most important factor. Change in inspiration only minmal effect
10 - Technical	344	Wang Y, van Klaveren RJ, van der Zaag-Loonen HJ, et al: Effect of nodule characteristics on variability of semiautomated volume measurements in pulmonary nodules detected in a lung cancer screening program. Radiology 248:625-31, 2008	Diagnostic comparative	3	82	Patients with 200 nodules 79 male and 3 female	Volumetry of nodules	Nodules meaured 3 times - 1mm soft kernel, 2mm soft kernel and 2mm sharp kernel	N/A	repeatabilty	1mm soft repeatability coefficient was 8.9%, 2mm soft and 2mm sharp was 22.5 and 37.5% respectively	1mm soft best reconstruction
10 - Technical	345	Goodman LR, Gulsun M, Washington L, et al: Inherent variability of CT lung nodule measurements in vivo using semiautomated volumetric measurements. AMERICAN JOURNAL OF ROENTGENOLOGY 186 (4):989-994, 2006	Diagnostic comparative	3	29 patients 50 nodules	Patients with pulmonary nodules <20mm diameter	quantitative evaluation of nodules (43)	3 observers, 3 CTs per patient	N/A	Variabilty bewtenn observers	Mean interobserver variabilty was 0.018% (SD 0.78%). SD of mean for each CT was 13%.	Conclude that interobserver variabilty is lower for volume measurements than diamtere measurements reported in the literature. Reproducibilty between CTs also better.
10 - Technical	346	Boll DT, Gilkeson RC, Fleiter TR, et al: Volumetric assessment of pulmonary nodules with ECG-gated MDCT. AJR American Journal of Roentgenology. 183:1217-23, 2004	Diagnostic observational	4	30	Patients with 73 small pulmonary nodules	ECG gated volumetry	3 separate assessments of nodule volume	N/A	Mulitvariate analysis of factros associated with nodule volume change between readings	Cardiac phase, nodule location and nodulear size were independently associated with volume change	Suggested accurate volumetry needs cardiac phase adjustment.
10 - Technical	347	Hein PA, Romano VC, Rogalla P, et al: Variability of semiautomated lung nodule volumetry on ultralow-dose CT: comparison with nodule volumetry on standard-dose CT. Journal of Digital Imaging 23:8-17, 2010	Diagnostic comparative	3	202 nodules		each comparator	Ultra LDCT vs CT for volume meaurements	n/a	variabilty in volume meaurement	similar variability for ULDCT	95% CI for variability was of the order of ±20%
10 - Technical	348	Christe A, Torrente JC, Lin M, et al: CT screening and follow-up of lung nodules: effects of tube current-time setting and nodule size and density on detectability and of tube current-time setting on apparent size. AJR American Journal of Roentgenology. 197:623-30, 2011	Diagnostic comparative	3	50		each comparator	different dose levels (simulated)	n/a	3 blinded readers ; logistic regerssion used to establish factors affecting sensitivity	sensitivity most affected by nodule density, size and then dose of CT	Conclude aslo that CAD reduces interobserver variability
10 - Technical	349	Gartenschlager M, Schweden F, Gast K, et al: Pulmonary nodules: detection with low-dose vs conventional-dose spiral CT. European Radiology 8:609-14, 1998	Diagnostic comparative	3	240 nodules		each comparator	30 vs 200 Ma	n/a	category of nodule by size and shape	not given; nodule size did not differ by more than one category	Discrepancies noted where nodule close to vessels
10 - Technical	350	Karabulut N, Toru M, Gelebek V, et al: Comparison of low-dose and standard-dose helical CT in the evaluation of pulmonary nodules. European Radiology 12:2764-9, 2002	Diagnostic comparative	3	25	referred for CT for assessment of pulmonary metastases	each comparator	LDCT vs CT	n/a		533 nodules with standard dose and 518 with LDCT. 491 detected by both.	Sensitivity of LDCT was 92.5%
10 - Technical	351	Rampinelli C, De Fiori E, Raimondi S, et al: In vivo repeatability of automated volume calculations of small pulmonary nodules with CT. AJR American Journal of Roentgenology. 192:1657-61, 2009	Diagnostic comparative	3	66		each comparator	Four consecutive CT datasets 2 LDCT and 2 Standard dose obtained in separate breath holds	n/a	volume measurements	The range of variation of the volumes of pulmonary nodules between two subsequent measurements was -38% +/- 60% for low-dose CT and -27% +/- 40% for standard-dose CT.	Recommended that a volume variation of greater than 30% for nodules between 5 and 10 mm should be confirmed by follow-up CT to be sure that a nodule is actually growing
10 - Technical	352	Kim H, Park CM, Song YS et al. Influence of radiation dose and iterative reconstruction algorithms for measurement accuracy and reproducibility of pulmonary nodule volumetry: a phantom study. Eur J Radiol 83(5);848-857, 2014	Diagnostic comparative	3	None (phantom study)	Phantoms with nodules (10 and 12mm)	Scaned with volumetric analysis at different radiation doses and with different reconstruction algorithms	As previous	N/A	Accuracy and reproducibility of nodule volume and mass measurements	These outcome measures were not significantly affected by radiation doses or reconstruction algorithms	Suggests that semi-automated volumetry can be applied to low-dose or ultra-low dose chest CT which is of relevance to follow-up surveillance CT.
10 - Technical	353	Yankelevitz DF, Reeves AP, Kostis WJ, et al: Small pulmonary nodules: volumetrically determined growth rates based on CT evaluation. Radiology 217:251-6, 2000	Diagnostic comparative	4	N/A Phantom plus 13 patients	n/a Phantom patients had diagnosis that was known		n/a	20 to 740 days		n/a	synthetic nodules study showed variability in volume to be ±3%
10 - Technical	354	Ashraf H, de Hoop B, Shaker SB, et al: Lung nodule volumetry: segmentation algorithms within the same software package cannot be used interchangeably. European Radiology 20:1878-85, 2010	Diagnostic comparative	3	188 baselien nodules	patients ina CT screening trial		agreement between readers	n/a	volume measurements	50% same volume between readers 4% >25% difference	essential to use the same algorithm for volume measurement.
10 - Technical	355	Das M, Ley-Zaporozhan J, Gietema HA, et al: Accuracy of automated volumetry of pulmonary nodules across different multislice CT scanners. European Radiology 17:1979-84, 2007	Diagnostic comparative	3	n/a phantom study	n/a		4 differet scanner volumetric software	n/a	absolute percentage volume errors	lowest APEs for diameter 5-10mm nodules and GE scanner had highest APE	concluded that variability could have an impact on foloww up studies
10 - Technical	356	Rampinelli C, Raimondi S, Padrenostro M, et al: Pulmonary nodules: Contrast-enhanced volumetric variation at different CT scan delays. AJR American Journal of Roentgenology. 195:149-54, 2010	Diagnostic comparative	3	53 nodules	n/a		IV contrast delays effect on nodule volume	n/a	Median volume ratios	4-7% increase with contrast; no effect if different delays	recommend that nodule volumes compared with both CTs either with or without contrast
10 - Technical	357	Gietema HA, Wang Y, Xu D, et al: Pulmonary nodules detected at lung cancer screening: interobserver variability of semiautomated volume measurements. Radiology 241:251-7, 2006	Diagnostic comparative	3	232	men aged 52-73 with 430 nodules frpm NELSON screening trial	each comparator	local and cenrtal observer evaluated same CT	n/a	Interobserver agreement.	no difference in volume in 89%. In 3.7% the discrepancy was greater than 10%	Good interobserver agreement in this RCT
10 - Technical	358	Revel M-P, Lefort C, Bissery A, et al: Pulmonary nodules: preliminary experience with three-dimensional evaluation. Radiology 231:459-66, 2004	Diagnostic comparative	3	24	Patients with 54 nodules aged 36 to 81	Volumetry of nodules	3 separate readers	N/A	Intra and inter observer agreement	CVs for all readers less than 3% in the 17 nodules where there was disagreement. 96% of all nodules yeiled repeatable results.	
10 - Technical	359	Wormanns D, Kohl G, Klotz E, et al: Volumetric measurements of pulmonary nodules at multi-row detector CT: in vivo reproducibility. European Radiology 14:86-92, 2004	Diagnostic comparative	3	10 (152 nodules)		each comparator	two consecutive LDCT within 10 mins	n/a	volume measurements	limits of agreement -5.5 to 6.6% for interobserver agreement and -3.9 to 5.75 for intraobserver agreement	