

British Thoracic Society guidelines for the investigation and management of pulmonary nodules

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SUMMARY OF RECOMMENDATIONS

This guideline is based on a comprehensive review of the literature on pulmonary nodules and expert opinion. Although the management pathway for the majority of nodules detected is straightforward it is sometimes more complex and this is helped by the inclusion of detailed and specific recommendations and the 4 management algorithms below. The Guideline Development Group (GDG) wanted to highlight the new research evidence which has led to significant changes in management recommendations from previously published guidelines. These include the use of two malignancy prediction calculators (section 'Initial assessment of the probability of malignancy in pulmonary nodules', algorithm 1) to better characterise risk of malignancy. There are recommendations for a higher nodule size threshold for follow-up (≥ 5 mm or ≥ 80 mm 3) and a reduction of the follow-up period to 1 year for solid pulmonary nodules; both of these will reduce the number of follow-up CT scans (sections 'Initial assessment of the probability of malignancy in pulmonary nodules' and 'Imaging follow-up', algorithms 1 and 2). Volumetry is recommended as the preferred measurement method and there are recommendations for the management of nodules with extended volume doubling times (section 'Imaging follow-up', algorithm 2). Acknowledging the good prognosis of sub-solid nodules (SSNs), there are recommendations for less aggressive options for their management (section 'Management of SSNs', algorithm 3).

The guidelines provide more clarity in the use of further imaging, with ordinal scale reporting for PET-CT recommended to facilitate incorporation into risk models (section 'Further imaging in management of pulmonary nodules') and more clarity about the place of biopsy (section 'Non-imaging tests and non-surgical biopsy', algorithm 4). There are recommendations for the threshold for treatment without histological confirmation (sections 'Surgical excision biopsy' and 'Non-surgical treatment without pathological confirmation of malignancy', algorithm 4).

Finally, and possibly most importantly, there are evidence-based recommendations about the information that people need and which should be provided. This document is intended to be used both as a summary in the day to day management of a person with a pulmonary nodule and a comprehensive reference text.

RECOMMENDATIONS

Route of detection of pulmonary nodules

- Use the same diagnostic approach for nodules detected incidentally as those detected through screening. Grade D
- Consider using the presence of previous malignancy as a factor in the risk assessment for further investigation. Grade D
- Do not prioritise management of pulmonary nodules according to the route of presentation. Grade D
- Evaluate coexistent lung nodules detected in patients with known lung cancer otherwise suitable for radical treatment in their own right; they should not be assumed to be malignant. Grade D

Initial assessment of the probability of malignancy in pulmonary nodules

- Do not offer nodule follow-up or further investigation for people with nodules with diffuse, central, laminated or popcorn pattern of calcification or macroscopic fat. Grade C
- Do not offer nodule follow-up or further investigation for people with typical perifissural or subpleural nodules (homogeneous, smooth, solid nodules with a lentiform or triangular shape either within 1 cm of a fissure or the pleural surface and <10 mm). Grade C
- Consider follow-up of larger intrapulmonary lymph nodes, especially in the presence of a known extrapulmonary primary cancer. Grade D
- Do not offer nodule follow-up for people with nodules <5 mm in maximum diameter or <80 mm 3 volume. Grade C
- Offer CT surveillance to people with nodules ≥ 5 mm to <8 mm maximum diameter or ≥ 80 mm 3 to <300 mm 3 . Grade C
- Use composite prediction models based on clinical and radiological factors to estimate the probability that a pulmonary nodule (≥ 8 mm or ≥ 300 mm 3) is malignant. Grade C
- Use the Brock model (full, with spiculation) for initial risk assessment of pulmonary nodules (≥ 8 mm or ≥ 300 mm 3) at presentation in people aged ≥ 50 who are smokers or former smokers. Grade C
- Consider the Brock model (full, with spiculation) for initial risk assessment of pulmonary nodules (≥ 8 mm or ≥ 300 mm 3) in all patients at presentation. Grade D

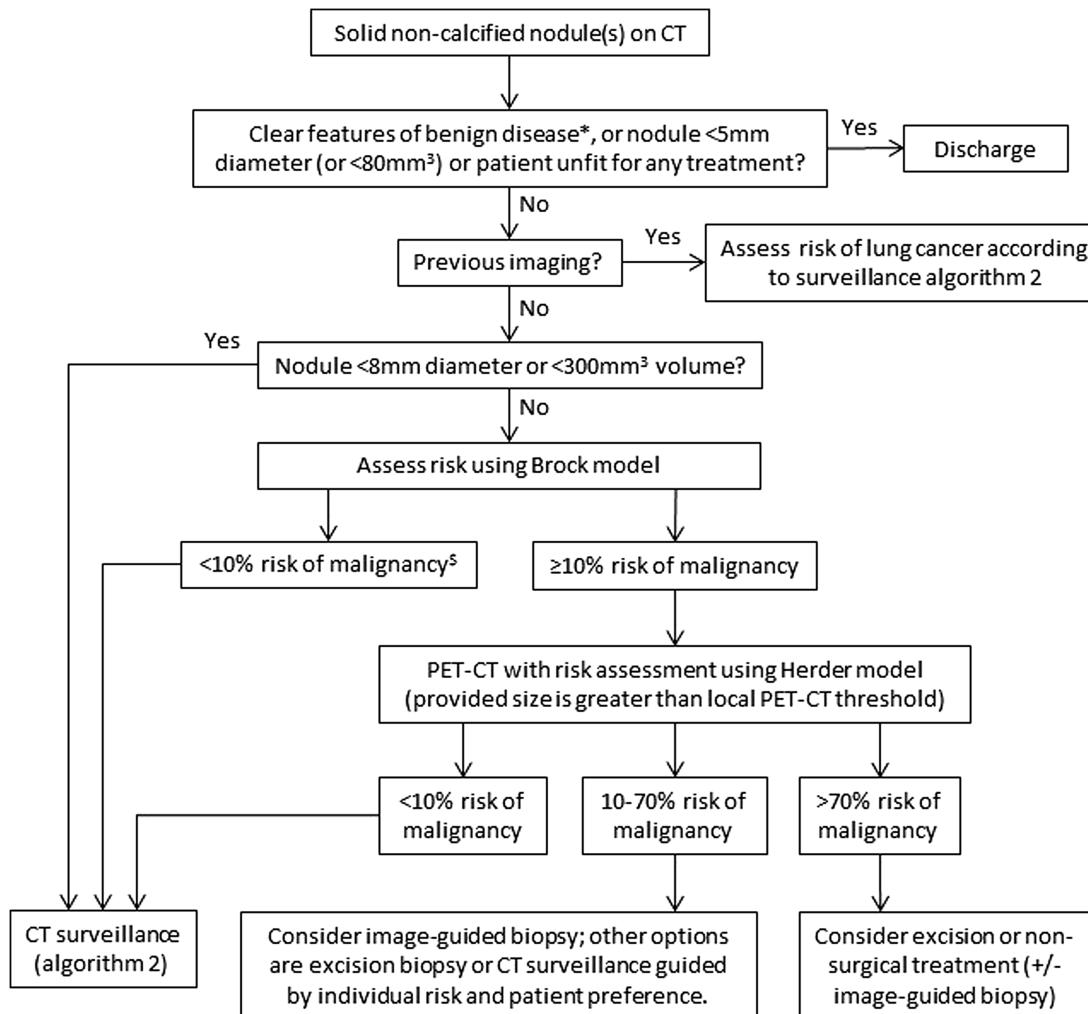


Figure 1 Initial approach to solid pulmonary nodules.

- Base the risk assessment of people with multiple pulmonary nodules on that of the largest nodule. **Grade C**
- Nodule malignancy risk prediction models should be validated in patients with known extrapulmonary cancer. **RR**
- Further analysis of variation in volumetry measurements by different software packages should be undertaken and methods developed for standardisation. **RR**

Imaging follow-up

- Where initial risk stratification assigns a nodule a chance of malignancy of <10%, assess growth rate using interval CT with capability for automated volumetric analysis. **Grade C**
- Assess growth for nodules $\geq 80 \text{ mm}^3$ or $\geq 6 \text{ mm}$ maximum diameter by calculating volume doubling time (VDT) on the basis of repeat CT at 3 months and 1 year. **Grade C**
- Use a $\geq 25\%$ volume change to define significant growth. **Grade C**
- Assess growth for nodules of ≥ 5 to $< 6 \text{ mm}$ maximum diameter by calculating VDT on the basis of repeat CT at 1 year. **Grade C**
- Offer further diagnostic investigation (biopsy, imaging or resection) for patients with nodules showing clear growth or

a VDT of < 400 days (assessed after 3 months, and 1 year). **Grade C**

- Discharge patients with solid nodules that show stability ($< 25\%$ change in volume) on CT after 1 year. **Grade C**
- If two-dimensional diameter measurements are used to assess growth, follow-up with CT for a total of 2 years. **Grade D**
- Consider ongoing yearly surveillance or biopsy for people with nodules that have a VDT of 400–600 days, according to patient preference. **Grade C**
- Consider discharge or ongoing CT surveillance for people who have nodules with a VDT of > 600 days, taking into account patient preference and clinical factors such as fitness and age. **Grade C**
- Where nodules are detected in association with an extrapulmonary primary cancer, consider the growth rate in the context of the primary and any treatment thereof. **Grade D**

Management of sub-solid nodules (SSNs)

- Do not follow-up SSNs that are $< 5 \text{ mm}$ in maximum diameter at baseline. **Grade C**
- Reassess all SSNs with a repeat thin-section CT at 3 months. **Grade D**

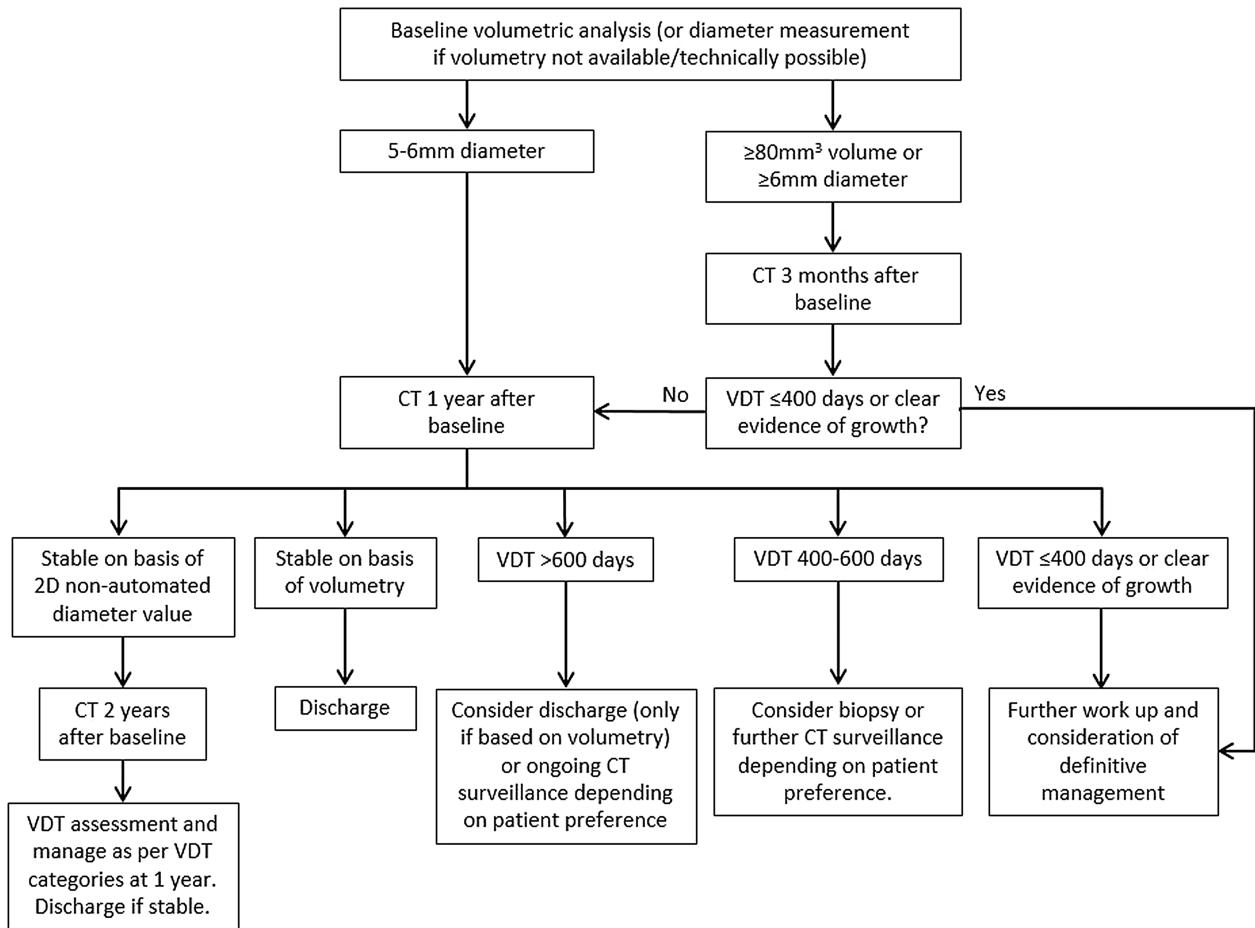


Figure 2 Solid pulmonary nodule surveillance algorithm. VDT, volume doubling time.

- Use the Brock risk prediction tool to calculate risk of malignancy in SSNs ≥ 5 mm that are unchanged at 3 months. **Grade C**
- Consider using other factors to further refine the estimate of risk of malignancy, including smoking status, peripheral eosinophilia, history of lung cancer, size of solid component, bubble-like appearance and pleural indentation. **Grade D**
- Offer repeat low-dose, thin-section CT at 1, 2 and 4 years from baseline where the risk of malignancy is approximately $<10\%$. **Grade D**
- Discuss the options of observation with repeat CT, CT-guided biopsy, or resection/non-surgical treatment with the patient where the risk of malignancy is approximately $>10\%$; consider factors such as age, comorbidities and risk of surgery. **Grade D**
- Consider using changes in mass of SSNs to accurately assess growth. **Grade D**
- Consider resection/non-surgical treatment or observation for pure ground-glass nodules (pGGNs) that enlarge ≥ 2 mm in maximum diameter; if observed, repeat CT after a maximum of 6 months. Take into account patient choice, age, comorbidities and risk of surgery. **Grade D**
- Favour resection/non-surgical treatment over observation for part-solid nodules (PSNs) that show enlargement of the solid component, or for pGGNs that develop a solid component. Take into account patient choice, age, comorbidities and risk of surgery. **Grade D**
- Favour resection/non-surgical treatment over observation where malignancy is pathologically proven. Take into account patient choice, age, comorbidities and risk of surgery. **Grade D**

Further imaging in management of pulmonary nodules

- Offer a PET-CT scan to patients with a pulmonary nodule with an initial risk of malignancy of $>10\%$ (Brock model) where the nodule size is greater than the local PET-CT detection threshold. **Grade B**
- Ensure that PET-CT reports include the method of analysis. **Grade D**
- Use qualitative assessment with an ordinal scale to define FDG uptake as absent, faint, moderate or high using the following guide:
 - Absent—uptake indiscernible from background lung tissue
 - Faint—uptake less than or equal to mediastinal blood pool
 - Moderate—uptake greater than mediastinal blood pool
 - Intense—uptake markedly greater than mediastinal blood pool. **Grade D**
- Reassess risk after PET-CT using the Herder prediction tool. **Grade B**
- After reassessment of risk:
 - Consider CT surveillance for people who have nodules with a chance of malignancy of $<10\%$.
 - Consider image-guided biopsy where the risk of malignancy is assessed to be between 10 and 70%; other options are excision biopsy or CT surveillance guided by individual risk and patient preference.
 - Offer people surgical resection as the favoured option where the risk that the nodule is malignant is $>70\%$; consider non-surgical treatment for people who are not fit for surgery. **Grade C**
- Do not use MRI, single photon emission CT (SPECT) or dynamic contrast-enhanced CT to determine whether a

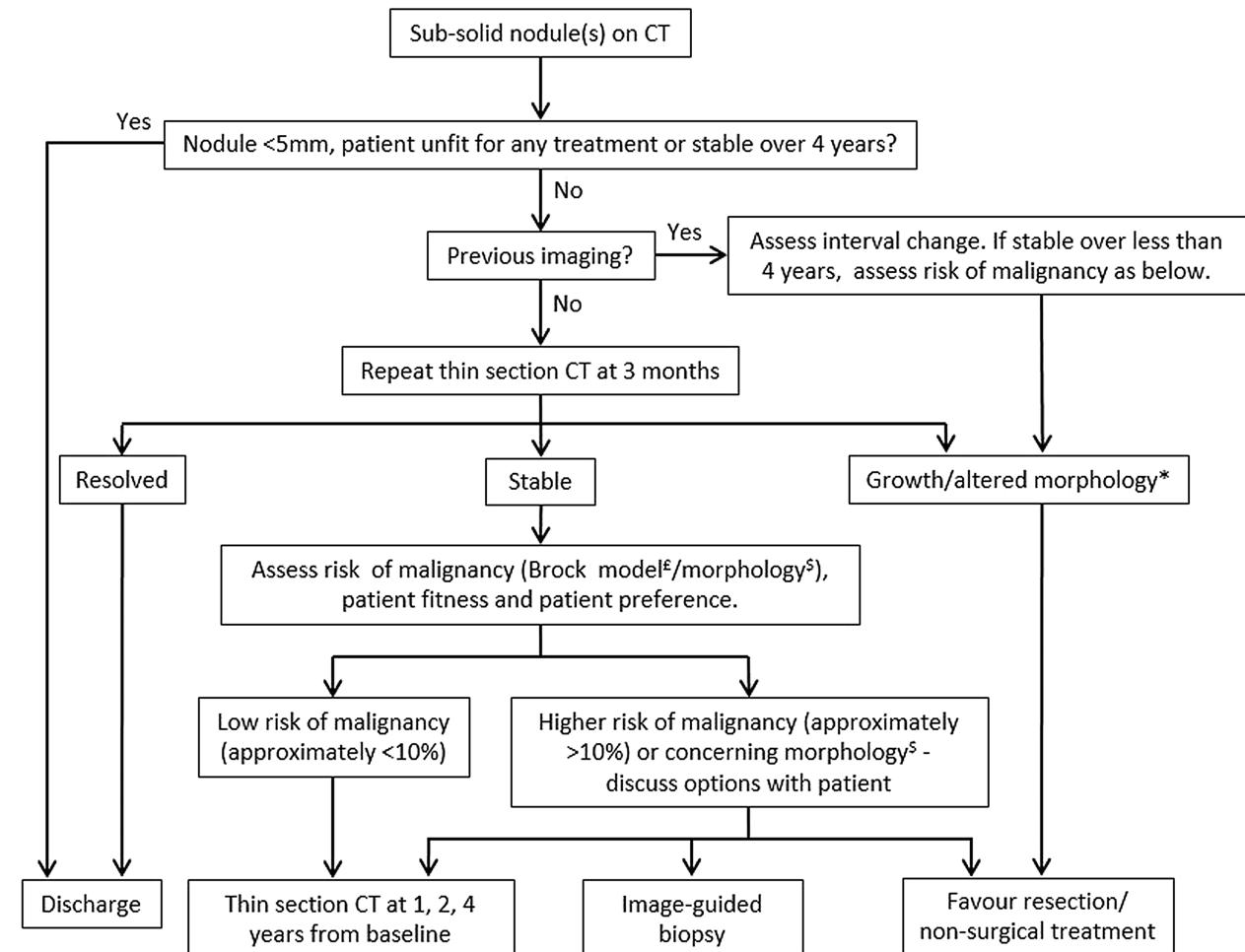


Figure 3 Sub-solid pulmonary nodules algorithm. PSNs, part solid nodules; SSN, sub-solid nodules.

nodule is malignant where PET-CT is an available alternative. **Grade D**

- Further research is needed into the most effective follow-up pathway in low to medium risk patients and for those with pGGNs. **RR**
- Further research should be undertaken into the use of PET-CT in the evaluation of pGGNs using lower standardised uptake value (SUV) cut-off values. **RR**

Non-imaging tests and non-surgical biopsy

- Do not use biomarkers in the assessment of pulmonary nodules. **Grade D**
- Consider bronchoscopy in the evaluation of pulmonary nodules with bronchus sign present on CT. **Grade D**
- Consider augmenting yield from bronchoscopy using either radial endobronchial ultrasound, fluoroscopy or electromagnetic navigation. **Grade D**
- Offer percutaneous lung biopsy where the result will alter the management plan. **Grade C**
- Consider the use of other imaging techniques such as C-arm cone beam CT and multiplanar reconstruction to improve diagnostic accuracy. **Grade D**

► Consider the risk of pneumothorax when deciding on a transthoracic needle biopsy. **Grade C**

- Interpret negative lung biopsies in the context of the pre-test probability of malignancy. **Grade D**
- Consider repeating percutaneous lung biopsies where the probability of malignancy is high. **Grade D**
- Undertake research into the application of new and existing biomarkers in the evaluation of pulmonary nodules. **RR**

Surgical excision biopsy

- Surgical resection of pulmonary nodules should preferentially be by video-assisted thoracoscopic surgery (VATS) rather than by an open approach. **Grade C**
- Offer lobectomy (to patients fit enough to undergo the procedure) as definitive management of a pulmonary nodule confirmed as lung cancer preoperatively or after wedge resection and intraoperative frozen section analysis during the same anaesthetic procedure. **Grade C**
- Consider anatomical segmentectomy where preservation of functioning lung tissue may reduce the operative risk and improve physiological outcome. **Grade D**
- Consider a diagnostic anatomical segmentectomy for nodules <2 cm in diameter without nodal disease when there has

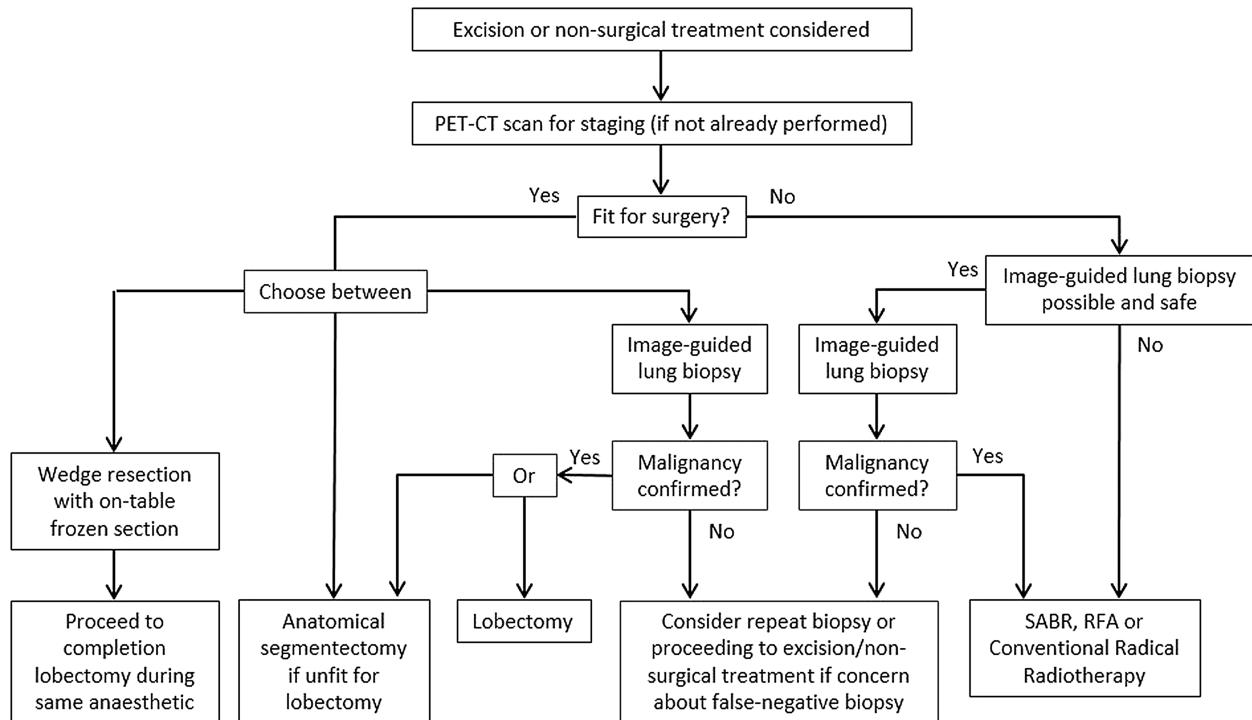


Figure 4 Pulmonary nodule treatment algorithm. RFA, radiofrequency ablation; SABR, stereotactic ablative body radiotherapy.

been no pathological confirmation and frozen section analysis is not possible. **Grade D**

- Use localisation techniques depending on local availability and expertise to facilitate limited resection of pulmonary nodules. **Grade D**
- Consider sublobar resection for pGGNs deemed to require surgical resection owing to the excellent long-term prognosis and low risk of local relapse. **Grade D**
- Prospective trials should compare complications and oncological outcomes from lobectomy versus anatomical segmentectomy in appropriately selected patients. **RR**

Non-surgical treatment without pathological confirmation of malignancy

- Consider people who are unfit for surgery who have pulmonary nodule(s) with high probability of malignancy, where biopsy is non-diagnostic or not possible, for treatment with stereotactic ablative body radiotherapy

(SABR) or radiofrequency ablation (RFA) if technically suitable. **Grade C**

- Consider people who are unfit for surgery who have pulmonary nodule(s) with high probability of malignancy, where biopsy is non-diagnostic or not possible, for treatment with conventional radical radiotherapy if not suitable for SABR or RFA. **Grade D**
- Do not use inhaled corticosteroids in the management of indeterminate pulmonary nodules. **Grade B**
- Do not use antibiotics in the management of indeterminate pulmonary nodules. **Grade D**
- Consider prospective randomised trials of local treatments for pathologically proven or clinically diagnosed early-stage lung cancer and pulmonary oligometastases. **RR**
- Prospective randomised trials of interventions for pathologically proven or clinically diagnosed early-stage lung cancer should include assessment of harms. **RR**

Information and support

- Offer accurate and understandable information to patients and carers about the probability of malignancy of the pulmonary nodule. **Grade D**
- Ensure patients have the opportunity to discuss concerns about lung cancer and surveillance regimens. **Grade D**

Table 1 Definition and terms relating to pulmonary nodules (see also figures 5 and 6)	
Pulmonary nodule	Focal, rounded opacity ≤ 3 cm diameter, mostly surrounded by aerated lung, including contact with pleura, but without potentially related abnormalities in the thorax
Sub-solid nodule (SSN)	A part-solid or pGGN
Part-solid nodule (PSN) (b)	A focal opacity that has both solid and ground-glass component ≤ 3 cm diameter
pGGN (c) (synonymous with non-solid nodule)	A focal ground-glass opacity ≤ 3 cm diameter that does not obscure vascular pattern
Solid component	The part of a nodule that obscures the underlying bronchovascular structure
Ground glass	Opacification that is greater than that of the background but through which the underlying vascular structure is visible

pGGN, pure ground-glass nodule.

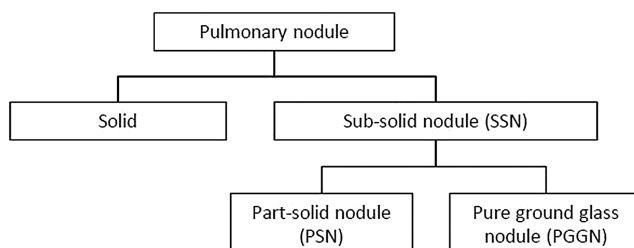


Figure 5 Classification of pulmonary nodules.

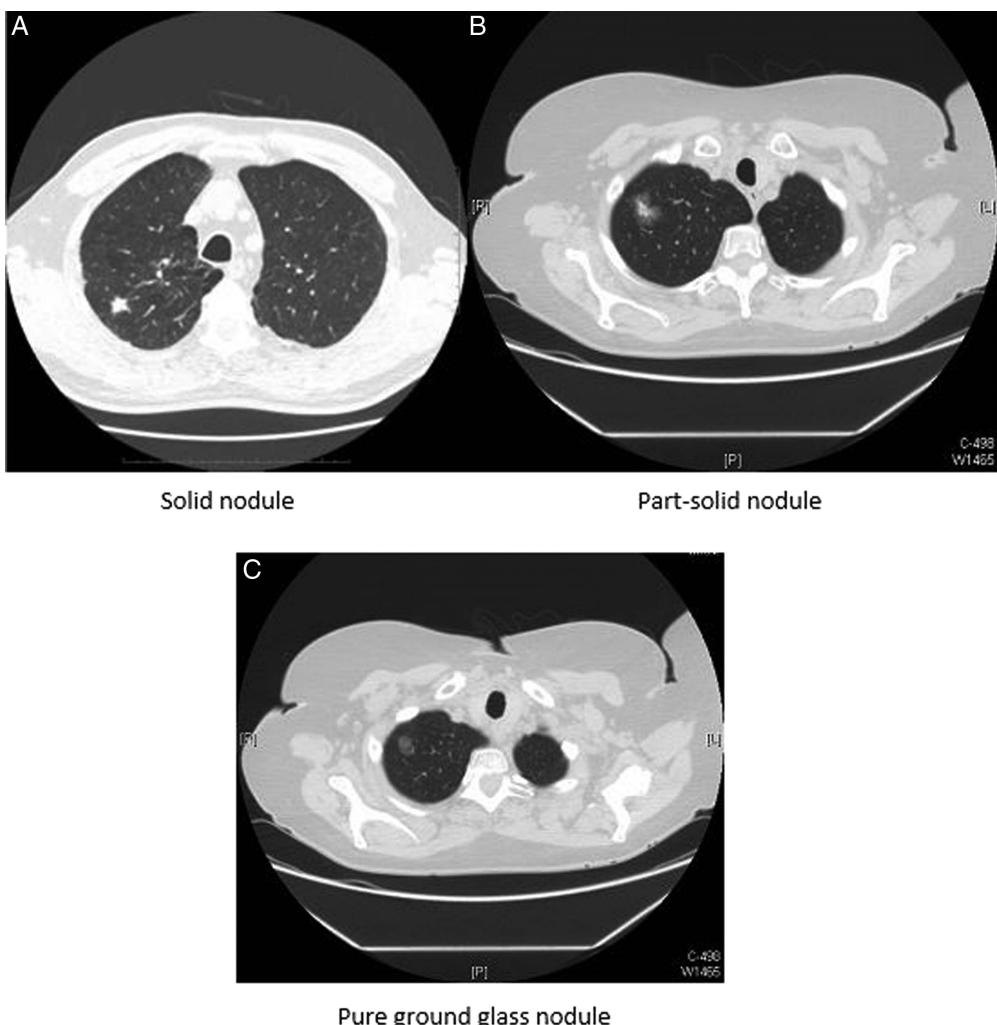


Figure 6 Images of nodules.

- ▶ Offer patients the choice of seeing a lung cancer nurse specialist where the probability of malignancy is high or when patients are anxious about the possibility of having lung cancer. **Grade D**
- ▶ Ensure that clear written and verbal information is available on follow-up schedules and the number of repeat CT scans required. **Grade D**

- ▶ Explain the risks and benefits of investigations and treatment. Where appropriate, offer a choice of management. **Grade D**
- ▶ Inform patients who remain at high risk of developing malignancy about the warning symptoms of lung cancer at the start of observation and at discharge from follow-up. **Grade D**
- ▶ Emphasise to patients the importance of smoking cessation and offer referral to smoking cessation services. **Grade D**

Technical aspects of the imaging of pulmonary nodules

- ▶ Where CT scans are performed that include the chest where nodule detection is of potential importance, use a maximum section thickness of 1.25 mm. **Grade C**
- ▶ Use low radiation dose CT with a maximum section thickness of 1.25 mm in follow-up imaging. **Grade C**
- ▶ Use maximum intensity projection (MIP) or volume rendering (VR) to improve nodule detection and characterisation. **Grade C**
- ▶ Use diameter measurements where volumetry is not possible or where there is clear evidence of marked growth. **Grade D**
- ▶ When reporting on growth, take into account factors that may reduce accuracy such as nodule shape and position and interval between scans. **Grade D**
- ▶ Ensure a radiologist or radiographer checks that the nodule has been accurately segmented. **Grade D**

Table 2 Aspects of the new classification of adenocarcinoma in relation to nodule type

Term	Malignant potential	CT correlate
Atypical adenomatous hyperplasia (AAH)	Premalignant	pGGN <5 mm
Adenocarcinoma in situ (AIS)	Premalignant	pGGN >5 mm up to 30 mm
Minimally invasive adenocarcinoma (MIA)	Invasive	PSN, solid area <5 mm
Invasive adenocarcinoma	Invasive	Larger PSN or solid nodule

pGGN, pure ground-glass nodule; PSN, part-solid nodule.

INTRODUCTION

Pulmonary nodules are well or poorly circumscribed, approximately rounded structures that appear on imaging as focal opacities and by traditional definition are ≤ 3 cm in diameter and surrounded by aerated lung (table 1). They may be single or multiple and do not have associated abnormalities in the thorax, such as lymphadenopathy or pleural disease. This definition is now commonly extended to include nodules in contact with the pleura. The now widespread use of helical multi-detector row CT has made it commonplace to detect, incidentally, nodules <1 cm in diameter as well as SSNs that are partly or wholly ground-glass opacities. These smaller nodules arguably present a greater clinical challenge than their larger counterparts and are therefore included in the scope of this guideline. Where appropriate, guidance is tailored to these distinct groups although it should be noted that in the literature precise definitions are not always given and a variety of terms are used. This is highlighted in the evidence review sections where necessary. This guideline proposes to standardise definitions and terms and these are shown in table 1 and figure 5, with images of the types of nodules shown in figure 6.

Classification of adenocarcinoma and the relationship to nodule characteristics

In the current classification of lung adenocarcinoma,¹ two preinvasive lesions and one early invasive lesion are defined (see also section ‘Management of SSNs’). Atypical adenomatous hyperplasia (AAH) is a premalignant lesion that typically measures <5 mm in diameter and may appear as a pure ground-glass nodule (pGGN) or may not be apparent on CT. Adenocarcinoma *in situ* (AIS) is a preinvasive lesion that may measure up to 30 mm in diameter and typically appears as a pGGN on CT. AAH is a relatively common incidental finding, present in the lung tissue adjacent to resected adenocarcinomas in up to 23% of cases. A small but unknown proportion of AAH lesions may evolve (often slowly) into AIS, and AIS may progress to become invasive adenocarcinoma. The first stage of AIS becoming invasive adenocarcinoma is termed minimally invasive adenocarcinoma (MIA). MIA is defined as a lesion of AIS within which there is an area of invasive adenocarcinoma that measures ≤ 5 mm in diameter. MIA may correlate with an appearance on CT as a ground-glass opacity within which there is a solid area measuring <5 mm (see table 2).

Aim of the guideline

The detection of pulmonary nodules is common. In populations undergoing CT screening and at high risk of lung cancer, nodules are detected in 20–50% of individuals, depending on the size of the cut-off point for reporting a nodule. The majority of these nodules are small and benign but some will be malignant and, according to the National Lung Screening Trial (NLST), effective treatment will result in a reduction in mortality.² It is important to have clear guidance about the most effective way to manage these nodules and an assessment of how data from screening studies can be used to guide the approach on other populations and individuals. It is acknowledged that the majority of the evidence reviewed for this guideline comes from countries outside the UK and that there are potentially important differences in populations as a result of their geographical location.

The aim of this guideline is therefore to provide comprehensive recommendations for the management of pulmonary nodules in the UK according to the definitions given above. The recommendations will apply to the UK healthcare system making clear where evidence may have limited applicability.

Target audience

The BTS guideline for the investigation and management of solitary and multiple pulmonary nodules is aimed primarily at practitioners within the UK. This will include physicians, general practitioners, nurses, radiologists, surgeons and other healthcare professionals. It may be of relevance to other healthcare systems.

Groups covered

- A. Adults (≥ 18 years) with pulmonary nodules
- B. Adults with single and multiple pulmonary nodules
- C. Adults with nodules that are detected in the context of current or previously treated malignancy (either pulmonary or extrapulmonary)
- D. Adults with nodules detected in routine clinical practice, as part of radiological surveillance after a previous malignancy, or by CT screening for lung cancer
- E. Adults with nodules of different morphologies including pGGNs and part-solid nodules (PSNs)

Groups not covered

- A. Children (younger than 18) with pulmonary nodules
- B. Adults where the nodule in question has been pathologically shown to represent lung cancer or a pulmonary metastasis from another cancer

Topics covered

- A. The route of detection of pulmonary nodules
- B. Risk assessment for malignancy based on clinical and radiological factors
- C. Imaging follow-up
- D. SSNs
- E. Further imaging of pulmonary nodules
- F. Biopsy techniques, indications, interpretation and risks
- G. Surgical excision
- H. Indications for recommending curative treatment in the absence of a pathological diagnosis
- I. Information and support for patients and carers
- J. Technical aspects of imaging pulmonary nodules

Topics not covered

The guidelines will cross-reference to the NICE Guideline CG121 Lung Cancer: the diagnosis and treatment of lung cancer. Service organisation was not included as part of the literature review, but following stakeholder comments a suggested approach to service organisation is given in appendix 3.

Methodology

This guideline is based on the best available evidence. The methodology used to write the guideline adheres strictly to the criteria as set out by the AGREE collaboration, which is available online <http://www.agreetrust.org/resource-centre/agree-ii/>. The British Thoracic Society Standards of Care Committee guideline production manual is available at: <https://www.brit-thoracic.org.uk/guidelines-and-quality-standards/>.

Clinical questions and literature search

Clinical questions were structured in the PICO (Patient, Intervention, Control, Outcome) format, to define the scope of the guideline and inform the literature search (see online supplementary appendix 1).

Systematic electronic database searches were conducted to identify potentially relevant studies for inclusion in the guideline. For each topic area the following databases were searched: Ovid MEDLINE (including MEDLINE In Process), Ovid EMBASE and the Cochrane Library (including the Cochrane

Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects) from 1980.

The searches were first run in November 2012 and updated in June 2014, (see online supplementary appendix 2 for search strategy). Searches included a combination of indexed terms and free text terms and were limited to English language publications only. The initial search identified 6819 potential abstracts and the second search 2739.

Appraisal of literature

Appraisal was performed to be compliant with the AGREE collaboration. Two individuals (DRB and MEJC) read the title and abstract of each article retrieved by the literature searches and decided whether the paper was definitely relevant, possibly relevant or not relevant to the project. Criteria formulated for categorising the abstracts into these three groups were:

- ▶ Whether the study dealt with the clinical question.
- ▶ Whether the appropriate study type was used to produce the best evidence to answer the clinical question.
- ▶ Review articles were excluded.
- ▶ Abstract was in English.
- ▶ Abstracts were reviewed irrespective of the journal of publication, country in which the research was performed or published and the date of publication.

The full paper was obtained for all relevant or possibly relevant abstracts and allocated to the relevant section(s) of the guideline.

The first screening process identified 2021 of the initial 6819 reference abstracts to be definitely or possibly relevant to the guideline. Two guideline reviewers for each section independently reviewed the abstracts to identify papers to be appraised for the guideline. The two reviewers for each section then independently appraised each paper assigned to them using the Scottish Intercollegiate Guidelines Network (SIGN) critical appraisal checklists. The reliability of the evidence in each individual study was graded using the SIGN critical appraisal checklists. The body of evidence for each recommendation was summarised into evidence statements and graded using the SIGN grading system (see table 3).

Disagreements were resolved by discussion with the section partner. The second literature search in June 2014 yielded 2739

Table 3 Key to evidence statements

Grade	Evidence
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case-control or cohort studies or high-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2-	Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies—for example, case reports, case series
4	Expert opinion

RCT, randomised controlled trial.

abstracts of which 1611 were possibly definitely or relevant. Four members of the group (DRB, MEJC, KR and IW) sorted the references into subject groups and these were forwarded to the pairs of reviewers for each group.

Considered judgement and grading of evidence

The GDG used the evidence tables to judge the body of evidence and grade recommendations for this guideline. Evidence tables are available in online supplementary appendix 3. Where evidence was lacking to answer the formulated clinical questions, expert opinions were obtained through consensus. The following were considered in grading of the recommendations:

- ▶ The available volume of the body of evidence.
- ▶ How applicable the obtained evidence was in making recommendations for the defined target audience of this guideline.
- ▶ Whether the evidence was generalisable to the target population for the guideline.
- ▶ Whether there was clear consistency in the evidence obtained to support recommendations.
- ▶ What the implications of recommendations would be on clinical practice in terms of resources and skilled expertise.
- ▶ Cost-effectiveness was not reviewed in detail as in-depth economic analysis of recommendations fell beyond the scope of this guideline.

Recommendations were graded from A to D according to the strength of the evidence as shown in table 4. In line with SIGN guidance, ‘minus’ evidence was considered in context but in the absence of other ‘plus’ supporting evidence, it was discussed by the GDG and any recommendation hence made was grade D. Important practical points lacking any research evidence, and not likely to be obtained by research evidence were highlighted as ‘good practice points’. Recommendations for further research are designated ‘RR’.

Drafting the guideline

The GDG corresponded regularly by email, and meetings of the full group were held in February, May and November 2012, February, April, June and October 2013, February and June 2014. The BTS Standards of Care Committee (SOCC) reviewed the draft guideline in September 2014. The draft guideline was

Table 4 Grades of recommendations

Grade	Type of evidence
A	At least one meta-analysis, systematic review or RCT rated as 1++ and directly applicable to the target population or A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4 or Extrapolated evidence from studies rated as 2+
✓	Important practical points for which there is no research evidence, nor is there likely to be any research evidence. The guideline committee wishes to emphasise these as good practice points

RCT, randomised controlled trial.

made available online in January 2015 for public consultation. A draft guideline document was circulated to all the relevant stakeholders for consultation in January 2015. The BTS SOCC re-reviewed the revised draft guideline and granted final approval in March 2015.

Updating the guideline

It is intended that the recommendations in this guideline will remain valid for 5 years. The need for an update will be reviewed 3 years after publication and an update planned if important new evidence emerges. The GDG also has a specific recommendation to clinicians in respect of managing pulmonary nodules. This is to maintain a database of patients with nodules for at least the life of this guideline. This is required because some of the recommendations state that patients can be discharged from follow-up on the basis of current evidence and UK policy on screening. If longer surveillance periods are recommended in the future, a database will allow identification of patients who may be offered extended follow-up.

✓Good practice point: Maintain a database of patients with pulmonary nodules for the purpose of monitoring outcomes and facilitating recall for further surveillance if required.

Declaration of interests

The GDG members adhered to the BTS policy for the declaration of interests (available on the BTS website or by contacting BTS head office).

Guideline development group members

GDG member	Contribution	Representing
D R Baldwin Consultant respiratory physician, Nottingham	Co-chair, editing, sub-solid section, information section, definitions, summary conclusion, service organisation and algorithms	BTS
M E J Callister Consultant respiratory physician, Leeds	Co-chair, editing, observation, surgery, non-surgical treatment sections and algorithms	BTS
A R Akram Respiratory specialty trainee, Edinburgh	Further imaging section	BTS
S Barnard Consultant thoracic surgeon, Newcastle	Surgery section	BTS
P Cane Consultant pathologist, London	Non-surgical biopsy and biomarker sections	
J Draffan Respiratory nurse specialist, Darlington	Information section	NLCFN
K Franks Consultant clinical oncologist, Leeds	Non-surgical treatments section	
F Gleeson Consultant radiologist, Oxford	Technical radiology section	RCR
R Graham Consultant radiologist, Bath	Further imaging section	BNMS
P Malhotra Respiratory specialty trainee, Prescott	Route of presentation and initial assessment sections	BTS
M Prokop Consultant radiologist, Nijmegen	Technical radiology section	
K A Rodger Consultant respiratory physician, Leeds	Non-surgical biopsy and biomarker sections	BTS

M Subesinghe Consultant radiologist, Oxford	Further imaging section	
D Waller Consultant thoracic surgeon, Leicester	Surgery section	SCTS
I Woolhouse Consultant respiratory physician, Birmingham	Route of presentation and initial assessment sections	RCP London
Ms A Biagioli		Patient representative
Ms C Paterson		Patient representative

The GDG would also like to acknowledge Dr Anand Devaraj and Dr Sue Copley for their extensive and very helpful comments as stakeholders on behalf of the British Society of Thoracic Imaging.

Stakeholder organisations

The draft guideline was made available for public consultation in January 2015 and feedback was invited from the following organisations:

- Royal College of Physicians, London
- Royal College of Physicians, Edinburgh
- Royal College of Physicians and Surgeons of Glasgow
- Royal College of Radiologists
- Royal College of Pathologists
- Royal College of General Practitioners
- The Society for Cardiothoracic Surgery in Great Britain and Ireland (SCTS)
- British Thoracic Oncology Group
- British Society of Thoracic Imaging
- British Nuclear Medicine Society (BNMS)
- National Lung Cancer Forum for Nursing (NLCFN)
- Primary Care Respiratory Society—UK
- Association of Respiratory Nurse Specialist
- Association for Chartered Physiotherapists in Respiratory Care

The pulmonary nodule pathway

In developing the PICO questions, the GDG considered the pathway that patients take from detection through diagnosis, treatment and follow-up. Figure 7 shows the pathway used with the PICO questions (modified from the original after a revision following the initial literature review).

ROUTE OF DETECTION OF PULMONARY NODULES

Key question: Are there important differences in nodule characteristics according to the route of presentation and clinical context?

The detection of lung nodules and the subsequent risk of malignancy may be influenced by the route of presentation and clinical context. The routes to presentation can be broadly divided into:

1. Patients with respiratory symptoms referred for chest X-ray (CXR) examination or CT chest scan.
2. Incidental finding on CXR, CT chest scan, or cross-sectional imaging for other purposes.
3. Patients participating in lung cancer screening studies or programmes.
4. Patients with known cancer undergoing staging investigations or follow-up imaging.

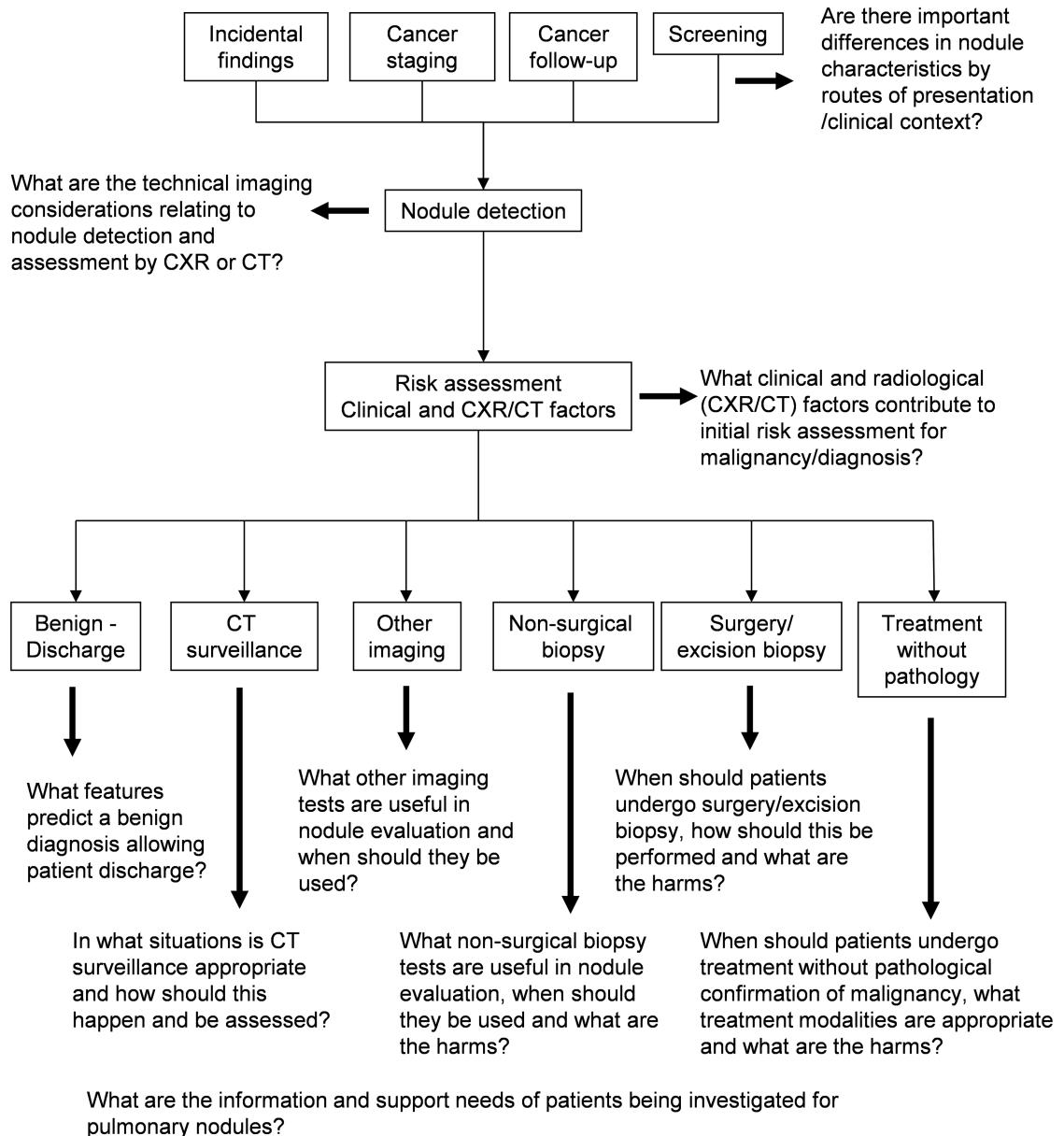


Figure 7 Nodule pathway use to generate key questions, with modified PICO (Patient, Intervention, Control, Outcome) questions after literature review.

Evidence review

No studies directly comparing lung nodules by the route of presentation/clinical context were found. The prevalence and aetiology of lung nodules in different contexts have been described in a number of case series. There were no studies of sufficient size in patients with respiratory symptoms referred for chest imaging (group 1 above). Eleven case series were identified reporting incidental findings on thoracic imaging performed for other purposes (five cardiac CT, three CT angiogram, two trauma CT, one CT abdomen). There were 21 case series of lung cancer screening (17 population based and four occupational studies), and eight case series reporting pulmonary nodules diagnosed on CT to stage a known cancer (two studies relating to lung cancer, six to extra-thoracic cancers). For the purposes of the evidence review, series of incidental and screen-detected nodules were considered together.

Incidental finding of pulmonary nodules and lung cancer screening studies

Only one study was undertaken in the UK (incidental findings on CT angiogram).³ Sixteen studies were from North America and Canada,^{4–19} 13 from Europe^{20–32} and two from Korea and Japan.^{33,34} Nodule and lung cancer prevalence by country/continent in which the study was performed is shown in table 5.

Nodule prevalence in the largest screening study of 53 439 participants aged 55–74 years, with a history of at least 30 pack-years of smoking² was 25.9% with a lung cancer prevalence of 1.1%. The prevalence of nodules and lung cancer in the screening and incidental finding studies are shown in table 6. Screening studies recruit asymptomatic people at higher risk of lung cancer, whereas studies of the incidental finding of pulmonary nodules include a mixture of younger patients at low risk of lung cancer (trauma studies) and people at higher risk who may have similar risk factors for lung cancer (cardiac CT).

Table 5 Prevalence of lung nodules and cancer by geographical area

Geographical area	Studies (n)	Patients (n)	Nodule prevalence (%), mean (range)	Lung cancer prevalence (%), mean (range)
N America	16	83 825	23 (2–53)	1.7 (0–4.0)
Europe	13	29 696	29 (8–53)	1.2 (0.2–2.4)
East Asia	2	14 362	35.5 (35–36)	0.54 (0.50–0.57)
UK	1	100	14	N/A

Studies in patients with known cancer

A number of case series have examined the prevalence of malignant nodules in patients with known cancer. Interpretation of these studies is limited by their heterogeneous nature—in particular, reporting of the stage of the primary tumour, the time from diagnosis of the primary tumour in relation to the CT scan demonstrating nodules, the definition of nodule size and selection criteria for further investigation or follow-up.

Three studies grouped the primary sites according to predicted likelihood of metastasising to the lung based on the following groups:

1. Patients with squamous cell cancers of the head and neck.
2. Patients with lymphoma or leukaemia.
3. Patients with carcinomas of the urinary bladder, breast, uterine cervix, biliary tree, oesophagus, ovary, prostate or stomach.
4. Patients with carcinomas of the salivary glands, adrenal gland, colon, parotid gland, kidney, thyroid gland, thymus or uterus.
5. Patients with melanoma, sarcoma or testicular carcinoma.

Using multivariate analysis, one study³⁶ found an association between the type of extrapulmonary cancer and the proportion of lung cancer/metastatic nodules. Groups 1–3 were more likely to have a lung primary and group 5 more likely to be metastatic, although numbers in each group were small. Another study³⁷ did not find this association or an association with stage (III or IV) of the primary tumour. A third study³⁸ found that group 4 patients were more likely to have a malignant nodule. A further study³⁹ of patients with known extrapulmonary cancer referred for resection of a lung nodule found that 68% of resected nodules were malignant, of which 58% were non-small cell lung cancer (NSCLC); 113 nodules (10%) were metastases. Logistic regression analysis suggested that nodules were more likely to be NSCLC in patients aged >55 years, smokers and if the known cancer was breast or prostate.

Two case series reported subcentimetre lung nodules detected preoperatively on CT in patients who had undergone curative surgery for lung cancer in Asia. One study⁴⁰ of 223 patients found that 26% of patients had nodules, of which 6% were malignant. Half of the malignant nodules were found in the primary tumour lobe. The second study⁴¹ reported nodule prevalence in 582 patients in the non-primary lobe which was not resected at the time of surgery. This study group included

only patients with 24 months' follow-up CT data (141 of 582 undergoing resection); 62 (44%) patients had a nodule and 3% were malignant. A study from the UK⁴² included 551 patients with lung cancer who had a staging CT scan and who were considered operable. Eighty-eight patients (16%) were found to have small non-calcified pulmonary nodules (size range 4–12 mm). Adequate follow-up (histological confirmation or CT follow-up for 24–48 months) was possible only in 25 patients who had a total of 36 nodules. Twenty-five nodules (70%) were subsequently confirmed to be benign, four (11%) were malignant and the nature of seven (19%) could not be determined.

Smyth *et al*⁴³ reported histological findings from biopsy of suspicious lesions in 229 patients with previous malignant melanoma. They found that 88% of the biopsies were malignant; 69% were metastatic melanoma, 14% were new primary NSCLC and 5% were recurrent metastatic non-melanoma cancer. Multivariate analysis of predictive factors for melanoma metastases demonstrated ORs of 9.0 for stage III/IV disease, 3.44 for multiple nodules, 0.21 for smoking and 0.26 for previous non-melanoma cancer. Margolis *et al*⁴⁴ retrospectively reviewed 116 patients with oesophageal cancer and found that 19% had solitary nodules and 3% had multiple nodules. Diagnosis was established in 19 of the 22 solitary pulmonary nodules (SPNs). None were metastases but 4 of 22 were lung cancer. All four cases of multiple nodules were classed as metastases without biopsy.

Summary

No studies were found that compared the features of pulmonary nodules according to the route of presentation. Thus the differences found will be influenced by selection bias and study protocol. The best evidence came from extrapolated evidence from CT screening trials where entry criteria were clearly defined. Thus the overall conclusion has to be that the route of presentation should not be an important factor in the management of pulmonary nodules.

Evidence statement

- The reported prevalence of non-calcified lung nodules is higher in screening studies than in studies reporting nodules as incidental findings on non-staging CT scans, but these differences are likely to reflect selection bias and protocol differences. **Evidence level 3**
- The reported prevalence of malignant nodules is similar in screening studies and in studies reporting nodules as incidental findings. **Evidence level 3**
- In screening studies, the prevalence of malignant nodules varies according to the screened population. **Evidence level 2+**
- The prevalence of malignant nodules may be higher in patients with extrapulmonary cancer, but studies are small and subject to selection bias. The relationship between the risk of nodule malignancy and the time from diagnosis of the primary tumour is not known owing to inconsistent reporting of this variable. **Evidence level 3**
- In patients with known extrapulmonary cancer there is conflicting evidence as to whether the primary site predicts

Table 6 Lung nodule and cancer prevalence in series of incidentally detected nodules and screening trials

	Studies (n)	Patients (n)	Nodule prevalence (%), mean (range)	Lung cancer prevalence (%), mean (range)
Incidental	11 ^{3 5 7 13–18 31 32}	11 683	13 (2–24)	1.5 (0–4.0)
Screening	21 ^{4 6 8–12 19–30 34 35}	116 300	33 (17–53)	1.4 (0.5–2.7)

whether the lung nodule is malignant or whether it is a metastasis or lung primary. Evidence level 3

- There is limited evidence relating to the aetiology of coexistent lung nodules in patients with known primary lung cancer. The reported prevalence of malignancy in sub-12 mm coexistent nodules in patients selected to undergo curative surgery is 3–11%. Evidence level 3

Recommendations

- Use the same diagnostic approach for nodules detected incidentally as those detected through screening. Grade D
- Consider using the presence of previous malignancy as a factor in the risk assessment for further investigation. Grade D
- Do not prioritise management of pulmonary nodules according to the route of presentation. Grade D
- Evaluate coexistent lung nodules detected in patients with known lung cancer otherwise suitable for radical treatment in their own right; these nodules should not be assumed to be malignant. Grade D

INITIAL ASSESSMENT OF THE PROBABILITY OF MALIGNANCY IN PULMONARY NODULES

Key question: What clinical and radiological factors contribute to the initial risk assessment for malignancy?

Management strategies can be guided by an accurate assessment of the risk of a nodule being malignant with the lowest risk favouring the least invasive approach and vice versa. This section relates to individual nodule risk assessment rather than population risk.

Evidence review

Thirty studies were identified that evaluated clinical and radiological characteristics of nodules in relation to probability of malignancy.^{4 36–39 43 45–68} Twenty-eight were retrospective case series, one was a screening study and one was based on a retrospective literature review. Eleven studies included patients with multiple pulmonary nodules.^{36–39 43 46 48 53 60 66 68} Only one study was conducted and validated in a UK population.⁶⁸ Six studies included patients with known extrapulmonary cancer.^{36–39 43 68}

The studies can be grouped into four categories:

1. Studies that evaluated clinical and radiological characteristics and/or described prediction models (n=18).
2. Studies that externally validated prediction models from category 1 (n=5).
3. Studies that compared prediction models with clinical judgement (n=2).
4. Studies that evaluated predictors of metastases versus primary lung cancer (n=5).

Studies that evaluated clinical and radiological characteristics and/or described prediction models

These studies had a wide range of inclusion criteria, differing demographic profiles, different criteria for labelling nodules as benign or malignant, and a wide variation in the prevalence of malignancy (1.8–75%).^{4 37 45–48 50 53 54 56–61 64–66} Overall these studies identified:

1. Eight clinical predictors of malignancy: age, current or ever smokers, time since quitting smoking, pack-years, family history of lung cancer, history of cancer >5 years before nodule detection, any history of previous cancer and haemoptysis.
2. Thirteen radiological predictors of malignancy: diameter, distance from pleura >10 mm, spiculation, ground-glass

appearance, pleural indentation, vascular convergence, circumference diameter ratio, upper lobe location, volume, growth, air bronchogram, lymphadenopathy and cavity wall thickness.

3. Five radiological predictors for benign aetiology: calcification, smooth border, cavitation, satellite lesions and perifissural location.

4. Two biochemical predictors of malignancy (C reactive protein (CRP) and carcinoembryonic antigen (CEA))

Of these, nine predictors of malignancy (four clinical and five radiological) were identified consistently in two or more studies which reported multivariate analysis:

1. Age (OR=1.04–2.2 for every 10-year increment)
2. Current or former smoking status (OR=2.2–7.9)
3. Pack-years of smoking
4. Previous history of extrapulmonary cancer
5. Nodule diameter (OR approximately 1.1 for each 1 mm increment)
6. Spiculation (OR=2.1–5.7)
7. Upper lobe location
8. Pleural indentation
9. Volume doubling time <400 days.

Predictors of a benign aetiology included presence of a diffuse, central, laminated or popcorn pattern of calcification (OR=0.07–0.20) and perifissural location.

de Hoop *et al*⁴⁵ specifically assessed perifissural nodules (PFNs) detected on CT screening in the NELSON study. These are homogeneous solid nodules, attached to a fissure with a lentiform or triangular shape and may be subpleural (figure 8). Seven hundred and ninety-four of the 4026 nodules (19.7%) detected at baseline screening were classified as PFNs, and were followed up according to the standard protocol. At first follow-up 66 PFNs (8.3% of all PFNs) grew with a volume doubling time (VDT) <400 days. One was resected and was proved to be a lymph node. None of the other PFNs turned out to be malignant after 5 years of follow-up. In a similar retrospective review, Ahn *et al*⁴⁷ found 234 PFNs (28% of all non-calcified nodules) in 98 subjects participating in a CT screening study. None of the PFNs developed into cancer during the study 2-year follow-up period, or during 7½ years of follow-up thereafter. PFNs are thought to be intrapulmonary lymph nodes on the basis of their CT features and histological correlates. Four studies examined histologically confirmed intrapulmonary lymph nodes (n=38, 19, 18 and 11, respectively) and characterised their CT features.^{69–72} In all these studies and that of de Hoop, the nodules were relatively small (<10 mm). Caution may be required in larger PFNs (>10 mm) in the presence of known non-lung primary cancers as there is anecdotal evidence of malignancy in these nodules.

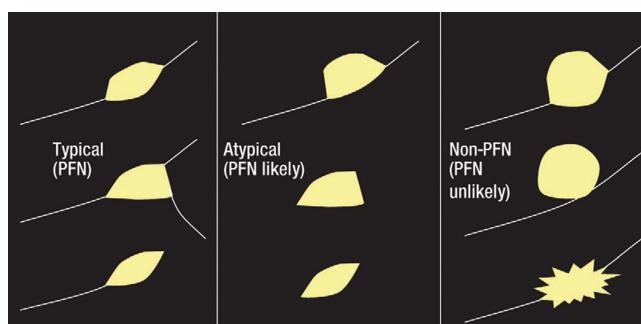


Figure 8 Appearance of perifissural nodules (PFN) as defined in de Hoop *et al*. (Reproduced with permission.)

Gurney (Bayesian method)⁵⁰ performed a retrospective literature review and applied the odds-likelihood ratio form of the Bayes theorem to calculate the probability of a nodule being benign or malignant. Only studies that included >100 patients were analysed but there was a wide variation in average nodule size and prevalence of malignancy, and studies were subject to methodological bias. A total of 15 malignant and 19 benign findings were identified for nodules. The most important predictors of malignancy were spiculation, diameter and cavity wall thickness, while predictors of a benign aetiology were VDT >465 days and calcification.

Five studies derived composite prediction models based on a combination of clinical and radiological factors using multivariate logistic regression analysis:

Swensen *et al*⁶⁴ (Mayo Clinic model) evaluated, at a single centre in the USA, the probability of malignancy in 419 radiologically indeterminate SPNs that measured between 4 and 30 mm in diameter on CXR. Patients with a diagnosis of cancer within 5 years before the discovery of the nodule, and any history of lung cancer were excluded. Mean age of the patients was 62 years, 51% were male and 67% were current or past smokers. Sixty-five per cent of nodules were benign, 23% malignant and 12% were indeterminate. Three clinical characteristics (age, smoking status and history of cancer more than 5 years previously) and three radiological characteristics (diameter, spiculation and upper lobe location) were independent predictors of malignancy. The area under the receiver operating characteristic (ROC) curve (\pm SE) for the prediction model was 0.83 (\pm 0.02). The model was validated on data from a separate group of 210 patients. The area under the ROC curve (\pm SE) for the validation set was 0.80 (\pm 0.03). Calibration curves for the derivation and validation sets showed a good agreement between the predicted probability and the observed frequency of malignant SPNs.

Gould *et al*⁴⁹ (Veterans Administration (VA) model) studied 375 patients enrolled from multiple centres in USA with SPNs measuring between 7 and 30 mm on CXR. Patients with a history of cancer, including lung cancer within 5 years were included but the authors were unable to identify patients who had a history of cancer more than 5 years before nodule detection. Mean (\pm SD) age of the patients was 65.9 (\pm 10.7) years, 98% were male and 94% were current smokers or former smokers. Fifty-four per cent of SPNs were malignant and 46% benign. Independent predictors of malignant SPNs included a positive smoking history (OR=7.9; 95% CI 2.6 to 23.6), older age (OR=2.2 per 10-year increment; 95% CI 1.7 to 2.8), larger nodule diameter (OR=1.1 per 1 mm increment; 95% CI 1.1 to 1.2) and time since quitting smoking (OR=0.6 per 10-year increment; 95% CI 0.5 to 0.7). The area under the ROC curve (\pm SE) was 0.79 (\pm 0.05) and the model was well calibrated.

Li *et al*⁵⁹ studied 371 surgically resected SPNs \leq 30 mm in diameter at a single centre in China. Median patient age was 57.1 years, 53% were male and 42% had a history of smoking. Patients with a diagnosis of cancer within 5 years before the discovery of the nodule were excluded. Fifty-three per cent of the nodules were malignant and 46% were benign. Independent predictors of malignancy included age (OR=1.07; 95% CI 1.05 to 1.09), diameter (OR=1.96; 95% CI 1.38 to 2.60), clear border (OR=0.25; 95% CI 0.13 to 0.45), calcification (OR=0.20; 95% CI 0.07 to 0.59), spiculation (OR=2.09; 95% CI 1.06 to 4.14) and family history of cancer (OR=3.55; 95% CI 1.26 to 9.97). The area under the ROC curve for the model (0.89; 95% CI, 0.78 to 0.99) was higher than those derived by Swensen *et al* and Gould *et al*. Although a history of smoking

was a significant predictor of malignancy on univariate analysis, this was not significant on multivariate analysis. The authors hypothesised that this might have been owing to the high prevalence of adenocarcinoma in their population (67% of all malignant SPNs were adenocarcinomas). Data from an additional 62 patients were used to validate this model but the authors did not give any further details about ROC curves in the validation set. In addition, calibration curves were not reported for either the development or validation sets.

Yonemori *et al*⁶⁵ studied 452 surgically resected SPNs \leq 30 mm in diameter at a single centre in Japan. Mean patient age was 62 years, 55% were male and 49% had a history of current or past smoking. Any SPN diagnosed as metastatic extra-pulmonary cancer was excluded. Patients with a history of cancer more than 5 years previously were included, but it was unclear if those with cancer within 5 years of nodule detection were also included. Seventy-five per cent of the nodules were malignant and 25% were benign. Independent predictors of malignancy identified were level of serum CRP, level of CEA, presence of spiculation, the CT bronchus sign (where a bronchus is seen to enter the nodule) and the absence of calcification; ORs and 95% CIs were not reported. The area under the ROC curve for the prediction model was 0.96, and 0.94 if biochemical variables (CRP and CEA) were not included. The model was validated on data from a separate group of 148 patients. The area under the ROC curve for the validation set was 0.84. CIs for the development and validation sets were not reported.

McWilliams *et al*⁴⁶ (Brock University model) analysed data from two cohorts of participants undergoing low-dose CT screening. The development dataset included participants in the Pan-Canadian Early Detection of Lung Cancer Study (PanCan) while the validation dataset included participants involved in chemoprevention trials at the British Columbia Cancer Agency (BCCA). All participants were current or former smokers between 50 and 75 years of age without a history of lung cancer. The final outcomes of all nodules of any size that were detected on baseline low-dose CT scans were tracked. Parsimonious and fuller multivariate logistic regression models were prepared to estimate the probability of lung cancer. In the PanCan dataset, 1871 people had 7008 nodules, of which 102 were malignant, and in the BCCA dataset, 1090 people had 5021 nodules, of which 42 were malignant. Among those with nodules, the rates of cancer in the two datasets were 5.5% and 3.7%, respectively. Predictors of cancer in the model included older age, female sex, family history of lung cancer, emphysema, larger nodule size, location of the nodule in the upper lobe, PSN type, lower nodule count and spiculation. The final parsimonious and full models demonstrated areas under the ROC curve of more than 0.91 to 0.98 with good calibration, even for nodules that were \leq 10 mm.

Herder *et al*⁵⁵ performed an external validation of the Mayo clinic model and quantified the potential added value of fluorodeoxyglucose-positron emission tomography (FDG-PET) scanning in a population of patients with radiologically indeterminate pulmonary nodules. They demonstrated improved accuracy of the Mayo model by addition of a factor relating to a four-point intensity scale of FDG avidity. This model is described in greater detail in the section 'FDG PET-CT and clinical risk prediction models'.

Studies that externally validated prediction models

Four studies externally validated the Mayo model, two validated the Bayesian method,⁵⁰ two validated the VA model, and one study validated the Brock and Herder models. Three studies

included patients referred for PET scan, and one included patients who had surgically resected nodules. The prevalence of malignancy varied from 40.6% to 73%. The area under the ROC curve (AUC) results for the Mayo model were 0.79–0.90, for the VA model 0.73 to 0.74 and for the Bayesian method 0.80 (one study did not quote the AUC for the Bayesian method).

Dewan *et al*⁵² compared the accuracy of predicting the probability of cancer in 52 patients with SPNs using Bayesian analysis and PET. Three patients with extrapulmonary malignancy were included. PET, as a stand-alone test, was better at classifying nodules as malignant or benign than either Bayesian analysis alone or Bayesian analysis plus PET scan.

Herder *et al*⁵³ validated the Mayo model in conjunction with PET scanning in 106 patients referred for PET evaluation of an indeterminate lung nodule. Patients with prior malignancy within the past 5 years were excluded. The addition of PET scan findings (classified using a four-point scale) increased the AUC by 13% from 0.79 to 0.92.

Schultz *et al*⁶² compared the Mayo and VA models in 151 patients undergoing PET evaluation of lung nodules (maximum one on CXR and six on CT). 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. Calibration curves showed that the Mayo model underestimated, while the VA model overestimated, the probability of malignancy.

Isbell *et al*⁶⁷ evaluated the Mayo and Bayesian models in patients with pulmonary nodules referred for surgical resection. Area under the ROC curve was 0.78 (95% CI 0.70 to 0.85) for the Mayo model, and 0.80 (95% CI 0.73 to 0.87) for the Bayesian model. The Mayo model was well calibrated for the two highest quintiles of probabilities but underestimated the probability of malignancy for the lower quintiles. The Bayesian model underestimated probability for the lower quintiles and overestimated for the higher quintiles.

Al-Ameri *et al*⁶⁸ compared the performance of four prediction models (Mayo, VA, Brock University and the model described by Herder *et al*) in a cohort of 244 patients with pulmonary nodules detected in routine clinical practice in a UK teaching hospital. Of the three CT based scores, the Mayo and Brock models performed similarly, and both were significantly more accurate than the VA model. The AUCs were 0.89 (95% CI 0.85 to 0.94) for the Mayo model, 0.90 (95% CI 0.86 to 0.95) for the Brock model, and 0.74 (95% CI 0.67 to 0.80) for the VA model. In patients undergoing FDG PET-CT, the Herder model had significantly higher accuracy than the other three models (AUC 0.92; 95% CI 0.87 to 0.97). When analysis was extended to include patients outside the original described inclusion criteria for each model, the accuracy remained high, especially for the Herder score (AUC 0.92). For subcentimetre nodules, AUC values for Mayo and Brock models were 0.79 (95% CI 0.63 to 0.95) and 0.85 (95% CI 0.77 to 0.94), respectively.

Studies that compared prediction models with clinical judgement

Swensen *et al*⁶³ compared four physicians' clinical judgements with the Mayo model in 100 patients with indeterminate pulmonary nodules. Although ROC analysis showed no statistically significant difference between the two, calibration curves revealed that physicians overestimated the probability of malignancy in patients with a low risk of malignant disease. Gurney compared the accuracy of four expert radiologists using clinical judgement with two other radiologists using Bayesian analysis in 66 patients with pulmonary nodules.⁵¹ The latter performed

significantly better than the former ($p<0.05$) and misclassified fewer malignant nodules as benign.

Studies that specifically evaluated predictors of metastases versus primary lung cancer

A number of case series have examined the prevalence of malignant nodules in patients with known extrapulmonary cancer—these are described in the section on route of detection of pulmonary nodules.^{36–44} Because of their heterogeneous nature, these studies provide conflicting evidence as to whether the primary site predicts whether the lung nodule is malignant or whether it is a metastasis or lung primary.

Patients with multiple pulmonary nodules

The Brock model is the only multivariate model that included an analysis of multiple pulmonary nodules.⁴⁶ In this model the presence of multiple nodules had a small negative effect on the likelihood of malignancy in any one nodule. The remaining studies were small case series^{48 53 60 66} which did not report multivariable analysis, and were based on specific patient populations which can broadly be divided into three groups:

1. Immunosuppressed patients including those with AIDS and post-transplant settings.
2. Nodules in patients with suspected or proven pulmonary infections (eg, TB, histoplasmosis and other fungal diseases).
3. Nodules in the setting of known diffuse parenchymal disease.

In the NELSON trial the nodule management algorithm was determined according to the largest nodule when more than one nodule was present. This is the best evidence for the effectiveness of this approach.²⁹

Limitations and choice of predictive models

The accuracy and clinical utility of predictive models depend on the case mix of the population in which it was derived and the prevalence of malignancy in that population. The applicability of the predictors identified will depend on the methods used to identify the events (ie, nodules) and the method of evaluation (essentially CT or CXR). The clinical characteristics and results of the studies that developed predictive models are summarised in table 7.

The Mayo model was developed in a cohort of patients with lung nodules who were originally managed in the 1980s at a single tertiary care centre in the USA.⁶⁴ The investigators excluded patients with a history of lung cancer or a history of extrathoracic cancer within 5 years, and 12% of the patients did not have a final diagnosis. The VA model did include patients with a history of lung cancer or a history of extrathoracic cancer within 5 years but evaluated a relatively smaller number of clinical predictors.⁴⁹ The population in the VA model comprised mainly older male smokers, and nodule size range was 7–30 mm, hence the accuracy of this model is unknown in nodules that are smaller than 7 mm in diameter.

Herder *et al*⁵³ validated the Mayo model in 106 patients referred for PET evaluation of an indeterminate lung nodule. Patients with prior malignancy within the past 5 years were excluded. The addition of PET scan findings (classified using a four-point scale) increased the AUC by 13% from 0.79 to 0.92. In a non-screening population, this score demonstrates the highest accuracy.

The Brock model has the highest AUC but was based on a screening population.⁴⁶ All participants were current or former smokers, hence smoking status was not included as a variable in the final predictive models. In addition, this model did not

Table 7 Summary of studies that developed composite prediction models

Reference	Subjects	Study setting	Age (years), mean (range)	Male (%)	Current/ former smokers (%)	Nodule size (mm), mean (range)		Nodule count (mm),		Prevalence of malignancy (%)	Predictors of malignancy or benignity	Odds ratio (95% CI)	AUC (95% CI)
						Benign	Malignant	Benign	Malignant				
McWilliams et al ⁴⁶ Parsimonious model	2961 (1871 developed 1090 tested)	Multicentre screening study, Canada	62 (50–75)	53	100	4.1 (1–70)	15.7 (2–86)	6.2 (1–31)	4.8 (1–19)	5.5	Female sex Nodule size Upper lobe Nodule count per scan, per each additional nodule Spiculation	1.91 (1.19 to 3.07) - (non-linear) 1.82 (1.12 to 2.98) 0.92 (0.85 to 1.00)	0.94 (0.91 to 0.96) 0.91 for nodules <10 mm
McWilliams et al ⁴⁶ Full model	2961 (1871 developed 1090 tested)	Multicentre screening study, Canada	62 (50–75)	53	100	4.1 (1–70)	15.7 (2–86)	6.2 (1–31)	4.8 (1–19)	4.8 (1–19)	Age per year Female sex Family history Emphysema Nodule size Ground glass Part solid Upper lobe Nodule count per scan, per each additional nodule Spiculation	1.03 (0.99 to 1.07) 1.82 (1.12 to 2.97) 1.34 (0.83 to 2.17) 1.34 (0.78 to 2.33) Non-linear 0.88 (0.48 to 1.62) 1.46 (0.74 to 2.88) 1.93 (1.14 to 3.27) 0.92 (0.85 to 1.00)	0.97 0.93 for nodules <10 mm
Gould et al ⁴⁹	375	Newly detected SPNs on CXR 7–30 mm referred for PET, multicentre, USA	66 (range not given)	98	94	14.8 (7–30)	18.9 (7–30)	Not applicable		54	Smoking Age (per 10 years) Diameter (per mm) Time since quitting (per 10 years)	7.9 (2.6 to 23.6) 2.2 (1.7 to 2.8) 1.1 (1.1 to 2.2) 0.6 (0.4 to 0.7)	0.79 (0.74 to 0.84)
Swensen et al ⁶⁴	639	Newly detected SPNs on CXR 4–30 mm, single centre, USA	62 (15–82)	51	68	11.6 (4–30)	17.8 (5–30)	Not applicable		23	Age Ever smoker Cancer ≥5 years Diameter Spiculation Upper lobe	1.04 (1.01 to 1.07) 2.21 (1.17 to 4.16) 3.8 (1.39 to 10.5) 1.14 (1.09 to 1.19) 2.83 (1.47 to 5.45) 2.19 (1.27 to 3.79)	0.83 (0.81 to 0.85)
Herder et al ⁵⁵	106	Patients with indeterminate SPNs <30 mm referred for PET	64 (32–85)	58	75	<10 mm 49% 11–20 mm 36% 21–30 mm 16%	<10 mm 18% 11–20 mm 43% 21–30 mm 39%	Not applicable		57	Same as Swensen	Not applicable	Validated Mayo model—AUC 0.79 (0.70 to 0.87) Addition of PET results increased AUC to 0.92 (0.87 to 0.97)

AUC, area under the receiver operating characteristic curve; CXR, chest X-ray; PET, positron emission tomography; SPNs, solitary pulmonary nodules.

incorporate PET scan findings as an additional predictive variable. The prevalence of malignancy (5.5% in the PanCan cohort, and 3.7% in the BCCA cohort) was significantly lower than that reported by Swensen (23%), Gould (54%) and Herder (57%).

Figure 9 shows how the various models compare for a 70-year-old man with a spiculated upper lobe nodule according to nodule diameter. The models perform very differently across the whole range of diameters. The Brock model shows a much lower probability of malignancy for smaller nodules and is the only model with a large number of smaller nodules in the derivation population. Despite being developed in an exclusively smoking or ex-smoking population, the likelihood of malignancy using the Brock tool is consistently below the likelihood of the Mayo tool even when the latter was calculated for a non-smoking patient.

The validation study by Al-Ameri *et al*⁶⁸ is the only study to validate the Brock and Herder models, and the only analysis of the performance of any models in a UK population. In patients undergoing FDG PET-CT, the Herder model was clearly the most accurate in predicting malignant risk, even when used in a cohort not restricted by the inclusion criteria of the model (ie, including patients with a previous history of lung cancer or an extra-thoracic cancer within the past 5 years). For smaller subcentimetre nodules, the highest accuracy was seen for the Brock score.

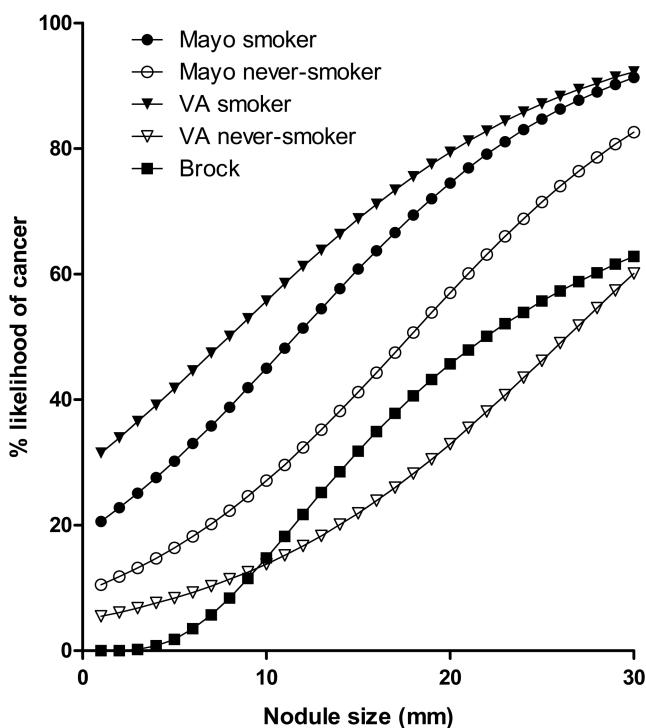


Figure 9 Predicted probability of malignancy according to nodule size in a 70-year-old man (spiculate nodule in upper lobe). VA, Veterans Administration.

Patients with smaller pulmonary nodules

A consistent finding from the studies considered in the section 'Risk prediction models' is the strong effect of size on predicting malignancy in a nodule. However, as discussed above, the prediction tools vary considerably in their estimates of malignant risk for very small nodules. Thus a non-spiculated 4 mm upper lobe nodule in a 70-year-old smoking woman has a malignant probability of 0.3% according to the Brock model, 11.9% according to the Mayo model and 39.1% according to the VA model.

The largest body of data relating to small nodules comes from the CT screening studies. Both NLST and NELSON studies have published rates of malignancy by nodule size alone in screened populations.

In a report of the initial CT findings (prevalence screen) from 26 309 patients randomised to the CT screening arm of NLST, 3668 patients were found to have a nodule of between 4 and 6 mm in diameter, of which only 18 were subsequently confirmed as lung cancer (positive predictive value (PPV) 0.5%; 95% CI 0.3% to 0.7%).¹⁹ In a subsequent report, Aberle *et al*⁷³ described the results of the two incidence screenings in NLST. Of 24 715 patients undergoing low-dose CT at the first incidence screening round, 3822 were found to have a nodule of 4–6 mm in diameter, of which 12 were subsequently confirmed as lung cancer (PPV 0.3%; 95% CI 0.2% to 0.5%). Of 24 102 patients undergoing low-dose CT at the second incidence screen, 2023 were found to have a nodule of 4–6 mm in diameter, of which 15 were subsequently confirmed as lung cancer (PPV 0.7%; 95% CI 0.4% to 1.1%).

Horeweg *et al*⁷⁴ reported results from 7155 Dutch participants in the NELSON study who underwent CT in the first or second rounds. The risk of developing lung cancer over a 2-year period was quantified for ranges of nodule size (volume/diameter) and VDT. Lung cancer probabilities were calculated using both screen-detected lung cancers, and interval cancers identified through linkages to the Dutch Cancer Registry. Over two rounds of screening, 6394 nodules were detected on 14 024 scans. The 2-year lung cancer probability was 1.3% for all participants (95% CI 1.2% to 1.5%). Participants without any pulmonary nodule (54.4%) had a lung cancer probability of 0.4% (95% CI 0.3% to 0.6%).

Patients with a nodule with a volume of $\geq 100 \text{ mm}^3$ had a significantly higher chance of being diagnosed with lung cancer than those patients without nodules. However, there was no difference in risk of lung cancer between patients with smaller nodules ($< 100 \text{ mm}^3$) and patients with no nodules. Similar findings were shown by nodule diameter, with the smallest nodule size associated with a significantly increased risk compared with patients with no nodules being 5–6 mm (PPV 0.9%; 95% CI 0.5% to 1.6%, $p=0.03$). Patients with smaller nodules ($< 5 \text{ mm}$ diameter) had no increased risk compared with patients with no nodules. By subdividing the population by nodule volume and diameter, and comparing risk with that in patients without nodules, Horeweg *et al*⁷⁴ were able to define an appropriate size cut-off point for discharging small nodules without any follow-up. They concluded that nodules $< 5 \text{ mm}$ in diameter or $< 100 \text{ mm}^3$ volume do not require any CT surveillance, as they are not associated with a significantly increased risk of lung cancer. However, two other studies have reported variation in absolute volume measurement between volumetric software packages.^{75 76} Therefore, until there is better agreement confirmed between packages it might be safer to reduce the threshold to 80 mm^3 . Subjects entered into screening trials have a greater baseline risk of malignancy than the general population but these findings probably apply to lower risk populations as well since the nodules below the stated size and volume cut-off point conferred no extra risk of malignancy and may therefore confer no extra risk irrespective of baseline risk. Horeweg *et al* also found that the chance of developing lung cancer after two screening rounds was 2.4% for nodules between 100 and $< 300 \text{ mm}^3$ in volume and 16.9% for nodules $\geq 300 \text{ mm}^3$. The corresponding chance of lung cancer for a diameter of 5 to $< 8 \text{ mm}$ was 1.0% and for $\geq 8 \text{ mm}$, 9.7%. Thus it might be

argued that at least for nodules $<300 \text{ mm}^3$ or $<8 \text{ mm}$ diameter, where PET-CT is less valuable (see section ‘Further imaging in management of pulmonary nodules’), CT follow-up is indicated without further risk assessment.

The sample size contributing to these estimates is considerably larger than those used to produce the risk prediction tools described above. The higher risks assigned to these small nodules from the Mayo and VA models are likely to be erroneous in this context, and so the Brock model is preferred.

Summary

There have been several validated risk prediction models developed to assist in the management of pulmonary nodules. Earlier risk models have been improved considerably by the addition of PET findings while new models based on larger datasets and using more modern imaging have generated more reliable data to inform the recommendations on risk prediction and subsequent management (see also algorithm 1, initial assessment). The best evidence to guide recommendations comes from CT screening trials that selected subjects at relatively high risk of lung cancer.

Evidence statement

- Clinical predictors of lung cancer in patients presenting with pulmonary nodules include:
 - A. increasing age
 - B. history of smoking
 - C. number of pack years smoked. **Evidence level 2+**
- Radiological (CT) predictors of lung cancer in patients presenting with pulmonary nodules include:
 - A. increasing nodule diameter
 - B. spiculation
 - C. pleural indentation
 - D. upper lobe location. **Evidence level 2+**
- Nodules with diffuse, central, laminated or popcorn pattern of calcification or macroscopic fat can be considered benign. **Evidence level 2+**
- A homogeneous, smooth, solid nodule with a lentiform or triangular shape either within 1 cm of a fissure (perifissural) or the pleural surface (subpleural) can be considered benign. **Evidence level 2+**
- In the NLST and NELSON, the prevalence of lung cancer among patients with 4–6 mm nodules was 0.5% and in NELSON, malignancy risk was no different from the subjects without nodules where nodules measured $<5 \text{ mm}$ or $<100 \text{ mm}^3$, with better accuracy for volume measurements. **Evidence level 2+**
- There is variation between different volumetry software packages such that the threshold of 100 mm^3 found in NELSON could be as low as 80 mm^3 depending on the software. **Evidence level 3**
- In NELSON, the risk of lung cancer among nodules of 100 mm^3 to $<300 \text{ mm}^3$ and 5 to $<8 \text{ mm}$ diameter was found to be 2.4% and 1.0%, respectively. **Evidence level 2+**
- Prediction models for pulmonary nodules based on clinical and radiological parameters have been externally validated. In the only validation study performed in a UK population, the Herder model (incorporating nodule FDG avidity) performed significantly better than other models (Mayo, Brock, Veterans Administration). In subcentimetre nodules, the Brock score had the highest accuracy (AUC value). **Evidence level 2+**
- The use of clinical prediction models is more accurate than clinicians’ individual clinical judgement in estimating the probability of malignancy in patients with pulmonary nodules. **Evidence level 3**

► In patients with known extrapulmonary cancer who have pulmonary nodules at presentation, there is limited evidence for the role of clinical and radiological factors in differentiating nodules that are primary lung cancer or metastases. **Evidence level 3**

► There is limited evidence outside the screening population for determining aetiology and management in patients with multiple pulmonary nodules. **Evidence level 3 supported by 2+**

► In a screening population the presence of multiple pulmonary nodules was found to indicate a lower risk of malignancy. **Evidence level 2+**

► In the NELSON screening trial, effective management of subjects with multiple nodules was achieved as determined by the management of the largest nodule. **Evidence level 2+**

Recommendations

- Do not offer follow-up or further investigation for people with nodules with diffuse, central, laminated or popcorn pattern of calcification or macroscopic fat. **Grade C**
- Do not offer nodule follow-up or further investigation for people with perifissural or subpleural nodules (homogeneous, smooth, solid nodules with a lentiform or triangular shape either within 1 cm of a fissure or the pleural surface and $<10 \text{ mm}$). **Grade C**
- Consider follow-up of larger intrapulmonary lymph nodes, especially in the presence of a known extrapulmonary primary cancer. **Grade D**
- Do not offer nodule follow-up for people with nodules $<5 \text{ mm}$ in maximum diameter or $<80 \text{ mm}^3$ volume. **Grade C**
- Offer CT surveillance to people with nodules $\geq 5 \text{ mm}$ to $<8 \text{ mm}$ maximum diameter or $\geq 80 \text{ mm}^3$ to $<300 \text{ mm}^3$ volume. **Grade C**
- Use composite prediction models based on clinical and radiological factors to estimate the probability that a pulmonary nodule ($\geq 8 \text{ mm}$ or $\geq 300 \text{ mm}^3$) is malignant. **Grade C**
- Use the Brock model (full, with spiculation) for initial risk assessment of pulmonary nodules ($\geq 8 \text{ mm}$ or $\geq 300 \text{ mm}^3$) at presentation in people aged ≥ 50 or who are smokers or former smokers. **Grade C**
- Consider the Brock model (full, with spiculation) for initial risk assessment of pulmonary nodules ($\geq 8 \text{ mm}$ or $\geq 300 \text{ mm}^3$) in all patients at presentation. **Grade D**
- Base the risk assessment of people with multiple pulmonary nodules on that of the largest nodule. **Grade C**
- Nodule malignancy risk prediction models should be validated in patients with known extrapulmonary cancer. **RR**
- Further analysis of variation in volumetry measurements by different software packages should be undertaken and methods developed for standardisation. **RR**

IMAGING FOLLOW-UP

Key question: In what situations is CT surveillance appropriate and how should this happen and be assessed?

After assessment of the risk of malignancy on the basis of clinical and initial radiological characteristics, some people will have pulmonary nodules with a low risk of malignancy and will therefore be suitable for CT surveillance rather than further imaging or biopsy. The overall aim of this approach is to use assessment of nodule growth to discriminate between benign and malignant nodules. Technical considerations regarding the measurement of nodule size and the threshold for determining change in size are given in section ‘Technical aspects of the imaging of pulmonary nodules’. Here the GDG considered the timing of surveillance CT scans to assess growth, and the range of growth rates considered predictive of malignant or benign disease.

Evidence review

How should nodule change be assessed?

Pulmonary nodule size has traditionally been assessed by measuring the largest transverse cross-sectional diameter. The VDT of a nodule can then be estimated from the difference in nodule diameter between baseline and follow-up CT and the time interval between these two scans, using a simple exponential growth model that assumes uniform three-dimensional (3D) tumour growth. Within the past 15 years, volumetric analysis (calculated either manually or by a semiautomated/automated method) has been increasingly reported as an alternative tool with which to assess nodule growth.

In a retrospective case series, Revel *et al*⁷⁷ assessed variability in 2D CT measurements of 54 pulmonary nodules in 24 patients both between readers and in the same reader's measurements at different times. Both intra- and inter-reader agreement for 2D measurements were found to be poor, with a change in size of <1.7 mm only having a 5% chance of corresponding to an actual change in nodule size. Korst *et al*⁷⁸ compared automated 3D volumetric estimates of pulmonary nodule growth rate with those derived from 2D measurement of nodule diameter in a retrospective case series of 87 nodules in 69 patients seen in a routine review clinic. Although correlation overall between these measurements was good, greater divergence was seen between these two methods for irregular nodules, or where the time interval between scans was shorter (<100 days). Of the cases where volumetric analysis would have changed management and prompted a biopsy (6.2% of all cases), 43% of nodules had an eventual malignant diagnosis.

Ko *et al*⁷⁹ compared semiautomated 3D volumetric analysis against standard calliper cross-sectional diameter measurement of 123 lung nodules in a retrospective analysis of 59 patients recruited through a CT lung cancer screening programme. Abnormal growth was detected in nodules subsequently proved to be malignant at a much shorter time interval (183 ± 158 days) by 3D volumetry than by standard radiological diagnosis (344 ± 284 days), suggesting greater sensitivity of the volumetric technique. Similarly, Revel *et al*⁸⁰ compared automated 3D volumetric analysis against 2D calliper measurement of 63 solid lung nodules in a retrospective case series. The sensitivity for volumetric-calculated doubling time for malignancy (with a 2-month median interval for rescan) was 91% (95% CI 0.59 to 1.00) compared with a sensitivity of manual diameter-change measurement of 54% (95% CI 0.23 to 0.83).

In addition to growth in the size of a nodule, changes in other parameters have been evaluated. de Hoop *et al*⁸¹ retrospectively compared diameter, volume and mass measurements of 52 GGNs detected in a lung cancer screening trial. Of the three parameters, mass measurements showed the least intra- and interobserver variation. Furthermore, in a subgroup of 13 malignant GGNs subsequently resected, changes in mass were seen significantly earlier than changes in volume or diameter (mean time 425, 673 and 713 days, respectively, $p=0.02$).

Xu *et al*⁸² retrospectively analysed 372 indeterminate solid intraparenchymal nodules in 312 patients recruited to the NELSON lung cancer screening trial. Although baseline density did not differ between nodules with an eventual benign or malignant diagnosis, malignant nodules showed a statistically significant increase in density during CT follow-up compared with benign nodules (median change 12.8 Hounsfield units (HU) vs -0.1 HU, respectively, $p<0.05$). However, there was significant overlap in density changes between benign and malignant nodules, indicating that density change alone is unlikely to be sufficiently specific or sensitive to accurately identify malignant nodules.

What is the appropriate time interval between surveillance scans?

In seeking to discriminate between benign and malignant nodule growth patterns, CT surveillance aims to have a high sensitivity for detecting nodule growth consistent with malignancy at the earliest opportunity, while maintaining high specificity and minimising false-positive referrals (nodules deemed to have grown but which have a subsequent benign diagnosis). The optimal interval between surveillance scans will relate to the reliability of detecting percentage volume change taking into account artefact, and the doubling time threshold between growing and stable nodules.

In a retrospective analysis of patients recruited to a lung cancer screening programme, Kostis *et al*⁸³ reviewed 115 pulmonary nodules deemed stable over 2 years' observation. They assessed error in 3D volumetric assessment of nodule size due to artefact and other factors, to determine whether apparent growth might simply reflect measurement errors in stable nodules. They then derived the critical time to follow-up CT—that is, the earliest point at which growth in a nodule of a given size can be reliably identified with repeat CT. As expected, the percentage SD of nodule size estimate increased with decreasing nodule size. The critical time to follow-up CT was calculated as 12 months for nodules with initial diameter 2–5 mm, 5 months for nodules 5–8 mm and 3 months for nodules 8–10 mm.

Although detecting nodule growth at the earliest opportunity is preferable enabling prompt treatment to be offered, there is evidence that the accuracy of growth rate measurement and assessment of malignant risk improves with a greater time interval between surveillance scans. Thus Ko *et al*⁷⁹ demonstrated a reduction in SD of growth rate estimate with increasing time between scans (SD of 47% at 6 months, 30% at 1 year and 20% at 2 years).

Xu *et al*⁸⁴ retrospectively evaluated 891 indeterminate nodules detected during the NELSON CT screening trial. VDT was assessed at 3-month and 12-month interval scans, and nodules with a VDT of <400 days at either time point were referred for further investigation. Overall, 78 nodules were referred owing to a VDT of <400 days—68 nodules at 3 months and 10 at 12 months. The proportions of nodules with an eventual malignant diagnosis referred at 3 months and 12 months were 15% and 50%, respectively, indicating greater specificity for assessment of malignant risk at the later time point.

Zhao *et al*⁸⁵ retrospectively reviewed characteristics of resolving pulmonary nodules detected at initial scan in a CT screening programme. Of a total of 964 indeterminate nodules initially detected, 10.1% (97) disappeared at subsequent screening. The majority of resolving nodules (75/97 (77%)) had disappeared by 3 months. Features predicting resolution were non-peripheral location, spiculation and larger nodule size (≥ 8 mm vs <8 mm). The last two factors are also predictors of malignancy, therefore limiting the extent to which baseline features can be used to predict which nodules will subsequently resolve.

What growth rates are reported for malignant pulmonary nodules?

A number of studies describing VDTs for malignant pulmonary nodules were reviewed. Considering only studies with 50 or more cases, five reports of doubling times for nodules subsequently confirmed as lung cancer were identified and details of their findings are shown in table 8. Two studies retrospectively reviewed growth rates of lung cancers detected in routine clinical practice^{86 87} and three studies reviewed cancers detected by CT screening.^{88–90} Of the studies reviewed, two used 2D diameter assessment of size only, two used manual volumetric analysis and one used automated/semautomated volumetric analysis.

All studies showed a wide range of growth rates for lung cancers. VDTs were reported by histological subtype of tumour and the mean/median values are shown in table 9. Direct comparison of these studies is limited by differences in the methods of volume estimation (2D diameter measurement vs manual or automated 3D volumetry), histological definitions (two studies grouped adenocarcinomas and bronchoalveolar cell carcinoma (BAC)/AIS together) and presentation of data (parametric or non-parametric variables). Despite these limitations, consistent patterns were seen between histological subtypes with progressively longer VDTs quoted for small cell carcinoma, squamous cell carcinoma, adenocarcinoma, BAC/AIS, respectively.

Two studies^{88 89} compared VDT by radiological appearance of the nodule, and showed shorter VDTs for solid versus SSNs or pGGNs. In one of the largest series of malignant nodules, Henschke *et al* reported that all lung cancers detected as solid nodules in the International Early Lung Cancer Action Program (I-ELCAP) screening programme had VDTs of <400 days (n=99), whereas 3 of the 12 SSNs detected had VDTs of >400 days (413, 531, 884 days).⁸⁹

The upper limit of VDT for malignant nodules was high in some series owing to the presence of very slow growing nodules that turned out to be lung cancers: 884, 1435 and 1733 days.^{88–90} Cancers with long VDTs tended to present as SSNs and were associated with BAC/AIS on eventual histology. In two studies, regression on nodules subsequently diagnosed as cancer was described (leading to negative VDTs).

What is an appropriate cut-off point for nodule growth rate to allow discrimination of benign and malignant nodules?

The presence of extremely long VDTs for some lung cancers, and the observation that a proportion of malignant nodules reduce in size on interval screening, indicates that there is no upper limit of VDT above which nodules can be guaranteed to be benign. Similarly, the observation that some malignant nodules show a long period of radiological stability before growing means that it is not possible to define a period of surveillance during which stability will completely exclude the possibility of malignancy. Current practice is guided by recommendations from the Fleishner Society which recommend follow-up for either 12 or 24 months depending on initial nodule size and patient risk.⁹¹ Stability over 2 years of follow-up has traditionally been regarded as indicative of benign disease, having first been proposed on the basis of CXR follow-up of nodules in the 1950s,⁹² although the evidence underlying this assumption has been questioned.⁹³

Although some cancers grow very slowly, or grow after a prolonged period of stability, it is not practical to follow up every nodule indefinitely for fear of missing an occasional cancer. Studies reporting growth rate of lung cancers will obviously consider only nodules with an eventual malignant diagnosis and are therefore all retrospective in nature. These data do not facilitate a prospective assessment of risk in any given pulmonary nodule with a known growth rate. Instead, studies of populations of all nodules (both benign and malignant) by growth rate

Table 8 Reported growth rates of pulmonary nodules subsequently diagnosed as lung cancer cases on previous surveillance CT

Authors	Number of subjects	Study setting/patient population	Method of growth rate assessment	VDT and comments
Hasegawa <i>et al</i> ⁸⁸	61	Retrospective case series of lung cancers detected through CT screening	2D Calliper measurement	Overall mean 452 days (SD 381 days, range 52–1733 days) pGGN mean±SD 813±375 days (n=19), PSN mean 457±260 days (n=19) Solid mean 149±125 days (n=223) (p<0.05)
Winer-Muram <i>et al</i> ⁸⁷	50	Retrospective case series of lung cancer cases detected in routine clinical practice with at least 2 evaluable chest CT scans before resection (>25 days apart)	2D Calliper measurements and manual 2D volume measurements	Overall median 147 days for 2D diameter assessment 174 Days for elliptical volume method 181 Days for perimeter volume method
Jennings <i>et al</i> ⁸⁶	149	Retrospective case series of patients with resected stage I lung cancer detected in routine clinical practice	Manual 2D volume measurement	Median 207 days (mean=161 days, SD 117 days) 21 of 149 tumours reduced in size between scans
Henschke <i>et al</i> ⁸⁹	111	Retrospective case series of 110 interval lung cancers detected through CT screening and 1 symptom-detected cancer between screens	2D Calliper measurement	Overall median 98 days (mean 136 days) Malignant solid nodules all VDT<400 days
Wilson <i>et al</i> ⁹⁰	63	Retrospective case series of lung cancers detected through CT screening	Automated 3D volumetry	Overall median 357 days (IQR 236–630)

pGGN, pure ground-glass nodule; PSN, part-solid nodule; VDT, volume doubling time.

Table 9 Volume doubling time (VDT) according to histological subtype

	VDT (days)				
	All lung cancer	Small cell	Squamous cell	Adenocarcinoma	Bronchoalveolar cell carcinoma/AIS
Hasegawa <i>et al</i> ⁸⁸	452 (mean) n=61	97 (mean) n=4	129 (mean) n=8	533 (mean) n=49	N/A
Winer-Muram <i>et al</i> ⁸⁷	174 (median) n=50	N/A	119 (median) n=16	157 (median) n=15	370 (median) n=9
Jennings <i>et al</i> ⁸⁶	207 (median) n=149	N/A	144 (median) n=48	216 (median) n=51	521 (median) n=19
Henschke <i>et al</i> ⁸⁹	98 (median) n=111	43 (median) n=21	88 (median) n=21	140 (median) n=43	251 (median) n=12
Wilson <i>et al</i> ⁹⁰	357 (median) n=63	N/A	160 (median) n=8	387 (median) n=46	N/A

AIS, adenocarcinoma in situ.

are of more use in providing clinicians and patients with accurate information on malignant risk on which to base decisions about management and follow-up.

Ashraf *et al*⁹⁴ reported a series of 54 indeterminate pulmonary nodules identified through the Danish Lung Cancer Screening Trial. They classified nodules according to VDT derived by automated 3D volumetric analysis on repeat CT scanning at 3 months, and FDG avidity of nodules at PET-CT. Nodules were grouped into those with a VDT <1 year, and those with a VDT >1 year or regressing. Seventeen nodules had a VDT <1 year (31% of total group), of which 14 were malignant (82%). Six of the remaining 37 nodules which either regressed or had a VDT >1 year were malignant (16%). The VDTs of these slow-growing malignant nodules were not reported. The VDT estimates were made on the basis of a 3-month interval scan. As discussed above, there appears to be greater error in VDT estimates made at 3 months compared with 12 months, and it is unclear to what extent this affected the sensitivity of 3-month VDT assessment for detecting malignant nodules.^{79 84 95}

By far the largest series of pulmonary nodules followed up by volumetric analysis comes from the NELSON study. The trial used VDT (calculated by automated volumetric analysis after a 3-month or 12-month interval) to guide management of indeterminate pulmonary nodules (50–500 mm³) so that patients with nodules with a VDT of <400 days were referred to a chest physician for investigation and diagnosis, whereas those with nodules with a VDT >400 days were considered benign and re-entered the screening programme.⁹⁶ At least a 25% change in volume was required to indicate a significant change.⁹⁷ It should be noted that where the automated software was unable to calculate volume, VDT was measured by manually measuring maximum diameter in three perpendicular planes. Thus any conclusions about follow-up periods relying on diameter measurements can only apply when VDT is calculated using this method.

Horeweg *et al*⁷⁴ reported the follow-up of 2500 nodules where VDT was calculated. As discussed in the section 'Patients with smaller pulmonary nodules', the 2-year lung cancer probability was 1.3% for all participants (95% CI 1.2% to 1.5%) in the screening programme, whereas participants without any pulmonary nodules (54.4%) had a 2-year lung cancer probability of 0.4% (95% CI 0.3% to 0.6%). Participants with slowly growing nodules (VDT >600 days), stable, shrunken or resolved nodules had a low probability of lung cancer (0.0–1.0%). Lung cancer probability was not significantly increased for participants with nodule VDTs of ≥600 days (0.8%; 95% CI 0.4% to 1.7%) compared with participants without nodules ($p=0.06$). Lung cancer probability was significantly increased for participants with nodule VDTs of 400–600 days (4.0%; 95% CI 1.8% to 8.3%, $p<0.0001$) and was even higher in participants with nodule VDTs of ≤400 days (9.9%; 95% CI 6.9% to 14.1%, $p<0.0001$). Analysis was not presented by nodule morphology (solid vs sub-solid, etc).

Although there is a trend to increased cancer risk in patients with slowly growing nodules (with VDT >600 days), the risk of malignancy in this situation is very small (0.8%). In considering more aggressive management in this situation, this risk must be considered alongside the operative mortality of thoracoscopic wedge resection (0.4% inpatient mortality according to the Society for Cardiothoracic Surgery in Great Britain and Ireland, with possible higher 90-day mortality) (www.bluebook.scts.org).

The NELSON trial is the only screening study to date to have prospectively assessed growth using automated volumetry in a defined protocol. Thus despite this being a single publication, it

is unlikely that any future studies will be able to provide this level of prospective data for such a large number of patients with pulmonary nodules.

There is little evidence for the management of new nodules that appear in follow-up CTs. Here, the risk of malignancy will depend on the growth rate and it should be noted that rapid growth may imply an inflammatory process rather than malignancy.

Summary

A repeat CT at 3 months will reliably detect growth in larger nodules, and will also demonstrate resolution in the majority of resolving nodules. Automated or semiautomated volumetry is more accurate than diameter measurements and accuracy of VDT assessment is better after 1 year than 3 months, especially for small nodules (<6 mm). Some lung cancers have very long VDTs, show prolonged periods of stability or even reduce in size on interval screening so that there is no upper limit of VDT above which nodules can be guaranteed to be benign. The approach to this problem, as recently suggested in a NELSON publication, may be to compare the risk of malignancy with that of the baseline risk of malignancy to define a point where follow-up is no longer indicated, given the absence of national screening programmes. A consistent finding in the studies quoted above is the slow rate of growth for SSNs, and therefore recommendations for duration of follow-up are distinct for this subgroup and are considered in the next section of the guideline. The evidence quoted for assessment of VDT and duration of follow-up relates to assessment of the risk of lung cancer. There is no published evidence informing assessment of the likelihood of lung metastasis from extrapulmonary malignancy according to VDT, and no evidence to guide appropriate duration of surveillance follow-up to exclude malignancy in this setting.

Evidence statement

- ▶ Repeat CT scans to assess interval growth have greater sensitivity and specificity for detecting malignancy at 1 year than scans at earlier time points. **Evidence level 2+**
- ▶ The majority of pulmonary nodules that eventually resolve have done so after a 3-month interval. **Evidence level 3**
- ▶ Accuracy of growth detection at 3 months reduces with smaller nodule size. **Evidence level 3**
- ▶ The growth rate of malignant nodules differs by histological subtypes and CT morphology. Small cell and squamous cell carcinomas tend to have shorter VDTs than adenocarcinoma. **Evidence level 3**
- ▶ Malignant nodules show wide ranges of growth rates, with some demonstrating regression at times. There is therefore no growth rate threshold beneath which, nor duration of radiological stability beyond which, malignancy is definitely excluded. **Evidence level 3**
- ▶ In the NELSON screening study, patients with nodules with a VDT <400 days and 400–600 days measured after a 3- or 12-month interval, had 2-year cancer probabilities of 9.7% and 4.1%, respectively, significantly greater than the cancer risk of subjects without nodules (0.4%) and the screened population as a whole (1.3%). **Evidence level 2+**
- ▶ The same study showed that the 2-year risk of lung cancer was 0.8% when the VDT was >600 days, not significantly higher than for subjects without nodules. **Evidence level 2+**
- ▶ In NELSON, where diameter measurements were used to calculate VDT, maximum diameter was measured in three planes. **Evidence level 2+**
- ▶ At least a 25% change in volume is required before the change can be regarded as significant. **Evidence level 2+**

- Duration of follow-up to ensure stability of nodules is not known for 2D diameter measurements. Evidence level 3

Recommendations

- Where initial risk stratification assigns a nodule a chance of malignancy of <10%, assess growth rate using interval CT with capability for automated volumetric analysis. Grade C
- Assess growth for nodules $\geq 80 \text{ mm}^3$ or $\geq 6 \text{ mm}$ maximum diameter by calculating VDT by repeat CT at 3 months and 1 year. Grade C
- Use a $\geq 25\%$ volume change to define significant growth. Grade C
- Assess growth for nodules of $\geq 5 \text{ mm}$ to $<6 \text{ mm}$ maximum diameter by calculating VDT by repeat CT at 1 year. Grade C
- Offer further diagnostic investigation (biopsy, imaging or resection) for patients with nodules showing clear growth or a VDT of <400 days (assessed after 3 months, and 1 year). Grade C
- Discharge patients with solid nodules that show stability (<25% change in volume) on CT after 1 year. Grade C
- If 2D diameter measurements are used to assess growth, follow-up with CT for a total of 2 years. Grade D
- Consider ongoing yearly surveillance or biopsy for people with nodules that have a VDT of 400–600 days, according to patient preference. Grade C
- Consider discharge or ongoing CT surveillance for people who have nodules with a VDTs of >600 days, taking into account patient preference and clinical factors such as fitness and age. Grade C
- Where nodules are detected in the context of an extrapulmonary primary cancer, consider the growth rate in the context of the primary and any treatment thereof. Grade D

MANAGEMENT OF SSNs

Key question: What are the features of SSNs and how should these nodules be managed?

SSNs merit special consideration because evidence is emerging that they require a different management approach than that required for solid nodules and have potentially different implications for prognosis. The pathological correlates have been described in the introduction in relation to the new classification of adenocarcinoma.¹ SSNs may represent preinvasive and invasive lesions and there are imaging predictors of progression to invasive disease, especially the development of a solid component (which is usually small in relation to the ground-glass component).⁹⁸ However, there is some debate about how these

lesions should be managed because surgical series have reported a 100% cure rate in nodules that are $>50\%$ ground glass.^{99–101}

Evidence review

The evidence consisted of case series, some collected prospectively as part of well-designed randomised controlled trials (RCTs) of CT screening. There were 40 publications reporting 50 or more SSNs retrieved by the search protocol (19 reported on more than 100). Fifteen reported only on resected or pathologically confirmed nodules, eight on nodules detected by CT screening (including three from RCTs) and 22 on nodules detected from a mixture of populations. Most series were from eastern Asia (Korea 16, Japan 17, China 2, USA 1, Canada 1, Italy 2, Netherlands 1). The majority of studies employed thin-section CT to evaluate SSNs.

Prevalence of SSNs

The prevalence of SSNs is difficult to extract from most studies as it is not directly reported. In the PanCan dataset 1871 of 2537 subjects had nodules detected over the screening rounds, and 15.9% of nodules were pGGNs and 4.3% PSNs. In the BCCA dataset the proportions were 9.3% and 0.9%, respectively.⁴⁶ If these proportions are applied to the prevalence of nodules in the much larger NLST² (over 27 000 subjects), where the average proportion of subjects with nodules $\geq 4 \text{ mm}$ was 24%, the prevalence of pGGNs detected will lie in the range 2.2–3.8% and PSNs would be found in 0.2–1% of CTs. This broadly agrees with the original report from ELCAP¹⁰² (1000 subjects), where it was found that 2.8% of baseline CTs detected pGGNs and 1.6% detected PSNs. In a review of 60 000 CTs Matsuguma *et al* found only 98 pGGNs (0.16%) and 76 (0.13%) PSNs¹⁰³; this may reflect the different population including a higher proportion of non-smokers.

Histopathological correlates of SSNs

Only six studies were identified where consecutive cases were resected and most of these reported histology according to the previous classification of adenocarcinoma. Two more recent studies that reported on SSNs $\leq 20 \text{ mm}$ diameter are shown in table 10.^{103 104} One study looked at a CT-detected series and the other resected all lesions. Amongst the resected lesions the spectrum of pathology was similar, although the overall rates of invasive carcinoma were much lower in the CT-detected series, probably reflecting selection bias in the resected series.

Table 10 Histopathological correlates of SSNs ($\leq 20 \text{ mm}$) reported according to the new international classification of adenocarcinoma

	pGGN		PSN	
Study	Matsuguma ¹⁰³	Ichinose ¹⁰⁴	Matsuguma ¹⁰³	Ichinose ¹⁰⁴
Selection	Detected on CT	Resected lesions	Detected on CT	Resected lesions
Total N (%)	98 (100)	114 (100)	76 (100)	77 (100)
Pathological diagnosis N (%)	19 (19)	114 (100)	37 (49)	77 (100)
AAH (% of pathologically confirmed)	3 (16)	6 (5)	0	
AIS N (%)	12 (63)	70 (61)	24 (65)	7 (9)
MIA N (%)	4 (21)	16 (14)	7 (19)	58 (75) (MIA and adenocarcinoma)
Invasive adenocarcinoma	0	13 (11)	6 (8)	
Benign tumour		8 (7)		7 (9)
Lymphoma				5 (6)
Proportion malignant (%)	4	27	35	80

AAH, atypical adenomatous hyperplasia; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma; pGGN, pure ground-glass nodule; PSN, part-solid nodule; SSN, sub-solid nodule.

Proportion malignant

The best evidence for the proportion of SSNs malignant, when detected by CT, comes from the screening trials, although again most report the previous classification of adenocarcinoma. In the PanCan dataset,⁴⁶ 1.9% (21/1105) of pGGNs and 6.6% (20/303) of PSNs were malignant and in the BCCA the numbers were lower but the rates were 1.3% (6/467) and 22.2% (10/45), respectively.

Predictors of malignancy and growth pattern

Twenty-four studies with 50 or more cases looked at predictors of malignancy.^{46 81 103–124} Initial size of lesion and growth are predictive of malignancy. A previous history of lung cancer was also found to be an independent predictor in three studies.^{103 106 116} McWilliams *et al*⁴⁶ were able to show that pGGNs, although more often malignant than solid nodules, actually conferred a lower chance of being malignant when adjusted for other factors in the risk prediction model. This was not the case for PSNs, where the part solid nature was an independent predictor of malignancy. Despite this, even PSNs ≤5 mm in maximum diameter, with other adverse factors added, had no more than a 1% risk of being malignant over 2–4 years for people aged <78. Two further studies noted that older age was associated with an increased risk of malignancy.^{113 114} Three studies showed that a peripheral eosinophilia was predictive of benignity.^{112 114 125} Morphological features predictive of malignancy, other than initial size, were pleural retraction or indentation and a bubble-like appearance in a pGGN.

Some studies evaluated the outcome of nodules that were persistent. Lee *et al* analysed the long-term progression of 175 SSNs that persisted for more than 2 years in 114 patients.¹¹³ The mean initial size was 7.8 ± 4.4 mm and median follow-up duration was 45 months. Forty-six (26.3%) SSNs showed significant size increases (≥ 2 mm in the longest diameter) with a mean VDT of 1041 days. In a multivariate analysis, large size (≥ 10 mm), PSNs and old age (≥ 65 years) were risk factors for significant size increase, with ORs (95% CI) of 6.46 (2.69 to 15.6), 2.69 (1.11 to 6.95) and 2.55 (1.13 to 5.77), respectively. SSNs with character changes from pure to mixed or mixed to solid showed more rapid volume expansion. The authors concluded that SSNs which persisted for several years showed an indolent course but noted that larger lesions with a solid portion in male or elderly individuals may be cause for more concern. In a retrospective study of 93 individuals with 126 PSNs identified from 16 777 individuals who underwent chest CT, 69.8% of PSNs were transient. Multivariate analysis showed that young patient age, detection of the lesion at follow-up, blood eosinophilia, lesion multiplicity, ill-defined border and large solid portion (the latter OR was only 1.05) were significant independent predictors of transient PSNs.¹¹² A further study followed up 120 SSNs (91 pGGNs) for a median of 4.2 years that had been observed without treatment for a minimum of 6 months.¹¹¹ Of these SSNs 28% grew by ≥ 2 mm and all of these had grown by 3 years. Independent predictors of growth were smoking history (OR=6.51) and initial size >10 mm (OR=4.06).

Two studies have developed logistic regression models specifically for PSNs. One found an ROC of 0.93 for distinguishing transient from persistent SSNs; however, the model was strongly influenced by eosinophilia and lesion multiplicity.¹²⁵ The other developed a model to predict invasive versus non-invasive adenocarcinoma confirmed by resection. This showed an ROC

of 0.9 but was strongly influenced by whether the lesion had a spiculated margin or not (OR=26.8) or a lobulated border (OR=2.9).¹²²

In the review by Matsuguma *et al*¹⁰³ of more than 60 000 CTs it is stated that the usual policy of the institution was to offer patients resection for all sub-solid lesions >15 mm diameter and lesions showing >2 mm growth or development of a ≥ 2 mm solid area in a pGGN. Some patients did not have resection in view of comorbidities. The authors found that 18 (10%) of 174 nodules reduced in size and 41 (24%) showed growth. All except one SSN that showed growth was malignant. Estimates were made of cumulative percentages of growing nodules at 2 and 5 years (13% and 23% in pGGNs and 38% and 55% in PSNs). The multivariate analysis showed that size >10 mm and history of lung cancer were independent predictors of malignancy in SSNs. The authors reported that none of the pGGNs were invasive adenocarcinoma, with only 4% MIA.

Hiramatsu *et al*, again in the setting of a large Japanese thoracic surgical centre, studied 184 patients referred with SSNs.¹⁰⁶ Of these, 17 underwent immediate investigation and 10 were lost to follow-up. Of the remaining 157, at the initial 3-month follow-up CT, six nodules had resolved but six had already shown obvious growth, while another three showed metastases and four progression of another malignancy. Fifty SSNs that were ≤ 10 mm in patients with no history of lung cancer did not grow at 3.5 years.

Ichinose *et al*,¹⁰⁴ again from Japan, looked at 191 resected lesions in 160 patients. They found that the proportion of lesions that were malignant was higher, probably owing to the different selection criteria. They noted that eight of 14 pGGNs with an standardised uptake value (SUV) max of 0.8 were malignant compared with four of 52 that were below this threshold.

In a third study from Japan, Takahashi *et al*¹¹⁵ followed up 150 pGGNs in 111 patients. Patients had high-resolution CT (HRCT) at various intervals but scans were evaluated at first detection, 2 years later and at final follow-up. After a mean of 66 months 19 (12.7%) nodules increased in size by ≥ 2 mm. Six of the 19 nodules that increased were stable at 2 years. The time to growth was 39.9 months in these nodules and 16.9 months in those 13 nodules deemed to have grown at 2 years. The authors concluded that more than 2 years' follow-up was necessary to detect growth. The final diagnosis of the growing nodules was determined in seven of 19 (and one further nodule that was stable at 2 years and decreased at follow-up). These were BAC in four and mixed subtype adenocarcinoma in three. All resected patients were alive after a mean of 32 months.

Lee *et al*¹¹³ followed up 175 SSNs that had been stable on HRCT for 2 years and found that after a median follow-up period of 45 months, 26% had enlarged by ≥ 2 mm. Large size, part-solid type and increasing age were predictors of growth. Kobayashi *et al*¹¹¹ followed up 120 SSNs and found that after a median of 4.2 years, 28% had enlarged by ≥ 2 mm. Smoking and large size were the most important predictors of growth. Chang *et al*¹¹⁸ found that 12 (9.8%) of 122 pGGN lesions that were followed up for more than 2 years grew and that the 11 that were surgically biopsied were lung cancer. Larger size and the development of a solid component were predictors of growth. The mean VDT of growing pGGNs was 769 days. Most studies used linear measurements to assess growth, but another study showed that change in mass was a more reliable measure.⁸¹

Nakao *et al*¹²⁶ performed a prospective trial of limited resection of 50 SSNs ≤ 2 cm with no pleural indentation or vascular convergence; 40 were adenocarcinoma. There were no recurrences before 5 years but four after 10 years. The authors

concluded that long-term follow-up was indicated after limited resection and that the latter should only be done in a trial setting. Silva *et al*¹²⁴ reported the experience from the Italian Multicentric Italian Lung Detection (MILD) trial—lung cancer randomised controlled CT screening trial. Seventy-six SSNs were found in 56 participants. Of 48 pGGNs, 31% resolved, 8.3% reduced in size, 43.8% remained stable and 16.7% progressed over an average follow-up period of 50 months. Of these pGGNs, 81% were <10 mm. For PSNs, with a solid component <5 mm, 11.5% resolved, 42.3% remained stable and 46.2% progressed. Lung cancer was found in one pGGN and three PSNs.

Prognosis

The reported prognosis of SSNs is very good, irrespective of the selection criteria. Case series of more than 100 SSNs, whether all resected or managed by follow-up and resection of selected nodules, report few deaths due to cancer^{109 110 115}. One study found that even when SSNs with suspicious cytology are observed, the outcome is still good.¹²⁷ These observations have led some authors to suggest that less aggressive treatment is more appropriate. Patz *et al*¹²⁸ reported overdiagnosis in the NLST to be a maximum of 18.5% overall, but found this rose to 79% (62%–94%) when BAC was detected by CT screening. Many of these tumours, in the new international classification, would have been designated MIA. The CT correlate would be mostly SSNs. Careful evaluation to identify more indolent tumours has been advocated as a way to reduce overdiagnosis and the associated potential harms by the use of imaging follow-up and minimally invasive surgery.¹²⁸

Lymph node metastases

Maeyashiki *et al*¹²⁹ looked at 398 consecutive clinical stage 1A lung cancers undergoing resection with 263 SSNs. They found that the size of the consolidation (solid component) and the presence of an air bronchogram were independent predictors of lymph node metastases and that 16% of PSNs had nodal metastases. Node metastases occurred in 9.8% of lesions <20 mm diameter and in 22.1% of lesions ≥20 mm (including solid lesions). None of the pGGNs (n=30) or PSNs (number not given) with solid component ≤10 mm had nodal metastases. Ichinose *et al*¹⁰⁴ reported that one of 114 pGGNs showed lymph node involvement. A further study of 57 SSNs showed that the proportion of the solid component was predictive of nodal metastases and that there were no metastases in the 15 SSNs where the solid component was ≤25% of the total diameter.⁹⁸

Multiple SSNs

SSNs are frequently multiple. One study of 193 SSNs compared the features of single versus multiple nodules.¹⁰⁹ Multiple SSNs were more frequently AAH or BAC, and occurred more often in women and non-smokers. However, the authors did not think the differences were enough to recommend a different approach to management. Another study looked at multiple pGGNs in 73 patients undergoing resection for BAC and found that all but one remained stable over a 40-month median follow-up.¹⁰⁸ In a study of PSNs, nodules were more likely to be benign if multiple.¹¹²

SSNs and staging

Two recent studies have shown that measurement of the solid component of malignant PSNs is a better predictor of prognosis than total diameter,^{123 129} one study suggesting a change to the

T descriptor of the Tumour Node Metastasis (TNM)—staging system for lung cancer (table 11).¹²³

Summary

SSNs merit separate consideration from solid nodules because they represent lesions that confer a better prognosis but paradoxically are more likely to be malignant than their pure solid counterparts, with part-solid nature being an independent predictor of malignancy. There are now well-established baseline predictors of malignancy, and growth or the development of a solid component in pGGNs are strong predictors. Many SSNs have slow growth rates and may remain stable for years. The management of these nodules is therefore uncertain as the prognosis may be good even when confirmed adenocarcinomas are seen. This may suggest that a less aggressive approach is indicated for these lesions.

Evidence statement

- The prevalence of pGGNs and PSNs in high-risk screening cohorts is 2–4% and 0.2–1%, respectively. This may be less in some populations that have more non-smokers. Evidence level 2++
- The pathological correlates of SSNs are AAH, AIS, MIA and invasive adenocarcinoma. pGGNs are more often AAH, AIS and MIA and PSNs more often invasive adenocarcinoma. Evidence level 3
- The majority of studies have assessed SSNs by high-resolution (thin-section) CT. Evidence level 3
- Baseline factors consistently associated with malignancy in SSNs are older age, previous history of lung cancer, size of nodule and part-solid nature. Evidence level 2++
- Other baseline factors that may be predictive of malignancy are size of the solid component in PSNs, pleural indentation and bubble-like appearance. Evidence level 3
- SSNs are more likely to be malignant than solid nodules; however, only PSNs are independent predictors of malignancy. Evidence level 2++
- SSNs may resolve after initial follow-up at 3 months. Factors predictive of resolution of PSNs are younger age, peripheral eosinophilia, lesion multiplicity and an ill-defined border. Evidence level 3
- About a quarter of SSNs will show growth; PSNs grow more often than pGGNs. Around a quarter of SSNs may grow after being stable for ≥2 years. Evidence level 3
- Growth of SSNs is strongly predictive of malignancy; defined as ≥2 mm in maximum diameter. Larger size, current smoking and part solid nature are predictors of growth. Change in mass of SSNs, measured on CT, may be an early indicator of growth. Evidence level 3
- The appearance of a new solid component in a pGGN or enlargement of a solid component (≥2 mm in maximum diameter) is predictive of malignancy. Evidence level 3
- The prognosis of resected SSNs is excellent (95–100% 5-year survival) and may remain good even when resection is delayed following imaging follow-up. Evidence level 3
- PET-CT may have a role in the management of SSNs using lower SUV thresholds. Evidence level 3
- The rate of lymph node metastases in SSNs is related to the size of the solid component; the rate is <1% for pGGNs and where the solid component is <10 mm. Evidence level 3

Recommendations

- Do not follow-up SSNs that are <5 mm in maximum diameter at baseline. Grade C
- Reassess all SSNs with a repeat thin-section CT at 3 months. Grade D

Table 11 Case series of more than 100 SSNs reporting predictors of growth or malignancy

Study	Number of SSNs	Predictors of malignancy or growth	OR in multivariate analysis
McWilliams et al ⁴⁶	1672	Predictive models for all nodules including age, sex, size, spiculation, location, emphysema, family history of lung cancer	PSN 1.16 pGGN 0.86
Lee et al ¹²²	272	CT features only; predictors of non-invasive disease: Size Solid proportion Non-lobulated border Non-spiculated border	0.819 0.953 2.856 26.80
Ichinose et al ¹⁰⁴	191	Pleural indentation PET SUVmax >0.8	2.64 (pGGN) 16.0 (pGGN)
Oh et al ¹¹⁴	186	Female sex Spiculated border Eosinophilia (-ve)	
Lee et al ¹¹³	175	Size ≥10 mm Solid component Age ≥65 years	6.46 (2.69–15.6) 2.69 (1.11–6.95) 2.55 (1.13–5.77)
Matsuguma et al ¹⁰³	174 (98 pGGN)	Size ≥10 mm History of lung cancer	pGGN only 13.7
Takahashi et al ¹¹⁵	150	Size ≥10 mm Lobulated margin Bubble-like	4.03
Attina et al ¹¹⁷	146	Age Smoking	
Lee et al ¹¹²	126	Young age (-ve) Eosinophilia (-ve) Large solid portion (-ve) Multiplicity (-ve) Ill-defined border (-ve)	
Hiramatsu et al ¹⁰⁶	125	Initial size >10 mm History of lung cancer	1.42 3.51
Kobayashi et al ¹¹¹	120	Smoking Size 10 mm 11–30 mm	6.51 (p<0.01) 1.0 4.06

PET, positron emission tomography; pGGN, pure ground-glass nodule; PSN, part-solid nodule; SSN, sub-solid nodule; SUV, standardised uptake value.

- ▶ Use the Brock risk prediction tool to calculate risk of malignancy in SSNs ≥5 mm that are unchanged at 3 months. **Grade C**
- ▶ Consider using other factors to further refine the estimate of risk of malignancy, including smoking status, peripheral eosinophilia, history of lung cancer, size of solid component, bubble-like appearance and pleural indentation. **Grade D**
- ▶ Offer repeat low-dose, thin-section CT at 1, 2 and 4 years from baseline where the risk of malignancy is approximately <10%. **Grade D**
- ▶ Discuss the options of observation with repeat CT, CT-guided biopsy, or resection/non-surgical treatment with the patient where the risk of malignancy is approximately >10%; consider factors such as age, comorbidities and risk of surgery. **Grade D**
- ▶ Consider using changes in mass of SSNs to accurately assess growth. **Grade D**
- ▶ Consider resection/non-surgical treatment or observation for pGGNs that enlarge ≥2 mm in maximum diameter; if observed, repeat CT after a maximum of 6 months. Take into account patient choice, age, comorbidities and risk of surgery. **Grade D**
- ▶ Favour resection/non-surgical treatment over observation for PSNs that show enlargement of the solid component, or for pGGNs that develop a solid component. Take into account patient choice, age, comorbidities and risk of surgery. **Grade D**
- ▶ Favour resection/non-surgical treatment over observation where malignancy is pathologically proven. Take into

account patient choice, age, comorbidities and risk of surgery. **Grade D**

FURTHER IMAGING IN MANAGEMENT OF PULMONARY NODULES

Key question: What other imaging tests are useful in nodule evaluation and when should they be used?

Once a pulmonary nodule has been detected by CT, a number of imaging modalities can be used to help further determine the likelihood of malignancy. The majority of evidence involves FDG PET with or without CT. Studies have also assessed the utility of scintigraphic techniques using ^{99m}-technetium (^{99m}Tc)-labelled compounds with single photon emission CT (SPECT), MRI including diffusion weighted (DW) and dynamic contrast-enhanced (DCE) imaging and DCE-CT.

Evidence review

PET and PET-CT

PET-CT is a cross-sectional imaging technique that provides both anatomical and functional information. It has become firmly established in the management pathways of several malignancies, including lung cancer.¹³⁰ FDG is the preferred radiopharmaceutical agent for oncological PET-CT. It is a glucose analogue that is injected and taken up and trapped within metabolically active cells; tumour cells have differentially increased glucose use and display increased tracer uptake. However, false-positive uptake is

seen in both infective and inflammatory conditions, such as TB and sarcoidosis, whereas false-negative observations are associated with certain types of malignancy, including adenocarcinomas with a significant bronchoalveolar or mucinous component and well-differentiated carcinoid tumours.

A large proportion of the literature focuses on FDG PET alone before the introduction of integrated PET-CT scanners, which are now widely available throughout the UK. The CT component of the examination improves anatomical localisation and can provide additional growth/morphological information that may strengthen a diagnosis of lung malignancy or raise the possibility of alternative benign diagnoses. Nevertheless, the GDG considered the FDG PET only literature still relevant to current practice with FDG PET-CT.

Meta-analyses

Gould *et al*¹³¹ performed the first meta-analysis to determine the accuracy of FDG PET in diagnosing malignancy in patients with pulmonary nodules and masses. A pooled analysis limited to pulmonary nodules identified 13 studies with a total of 450 nodules with an overall sensitivity and specificity of FDG PET of 93.9% and 85.8%, respectively. A variable size cut-off point defining the upper range of nodule size was used (either 3 or 4 cm depending on the studies quoted) meaning that some lesions between 3 and 4 cm in size were included in the nodule analysis and were outside the size definition used in this guideline. Cronin *et al*¹³² performed a meta-analytic comparison of the cross-sectional imaging modalities for the diagnosis of malignancy in SPNs (up to 3 cm diameter). A pooled analysis of 1008 nodules from 22 eligible studies reported a similar sensitivity and specificity of FDG PET of 95% and 82%, respectively.

Lung cancer screening studies

Several studies have assessed the utility of PET-CT within lung cancer screening studies, where patients have a higher risk of malignancy than the general population, mostly attributable to their smoking history and age. Veronesi *et al*¹³³ analysed a subset of 157 patients from the COSMOS early detection trial for lung cancer, who underwent FDG PET-CT for indeterminate nodules >8 mm (or growing lesions <8 mm) in size. The sensitivity, specificity and accuracy of FDG PET-CT were 88%, 93% and 91%, respectively, with optimal performance for solid nodules ≥10 mm. Ashraf *et al*¹³⁴ reviewed a subset of the Danish Lung Cancer Screening Trial comprising 53 patients with indeterminate nodules between 5 and 20 mm, who underwent a FDG PET-CT scan alongside a baseline and 3-month follow-up CT scan. The finding of a VDT of <1 year, or FDG avidity at the same level or higher than the mediastinum, both had a similar accuracy for diagnosing malignancy. When these criteria were used in combination, sensitivity and specificity increased (90% and 82%, respectively). Pastorino *et al*¹³⁴ reported the 2-year results of a screening trial looking at the efficacy of yearly CT and selective use of FDG PET for nodules ≥7 mm in 42 patients. The sensitivity and specificity of FDG PET were 90% and 82%, respectively. Bastarrika *et al*²⁰ reported on 24 patients who underwent FDG-PET for nodules ≥10 mm or smaller (>7 mm) growing nodules with a sensitivity, specificity, PPV and negative predictive value (NPV) of FDG PET of 69%, 91%, 90% and 71%, respectively. Four false-negative lesions (ie, PET negative) which reduced the sensitivity and NPV of FDG PET, showed interval growth on 3-month follow-up CT, increasing the sensitivity of the combined diagnostic algorithm to 100%.

The screening studies demonstrate that in high-risk populations, a positive PET-CT scan warrants progression to more

invasive diagnostic tests to confirm or refute malignancy, whereas a negative scan has a lower exclusion value for malignancy and requires continued surveillance with CT.

Other PET and PET-CT studies

Outside screening trials, the results for PET-CT for predicting malignancy are broadly consistent. Fletcher *et al*¹³⁵ conducted a large head-to-head prospective trial comparing the diagnostic accuracy of FDG PET with CT. Accuracy estimates of FDG PET and CT were based on 344 patients who had a definitive benign or malignant (53%) diagnosis established on histology or follow-up. Using qualitative visual assessment of FDG uptake linked to a five-point ordinal scale, FDG PET had a similar sensitivity to CT (91.7% vs 95.6%) but a greater specificity (82.3% vs 40.6%) and overall, was more accurate than CT in predicting malignancy with an area under the ROC curve of 0.93 and 0.82 ($p<0.001$), respectively. Smaller retrospective studies assessing the relative accuracies of FDG PET-CT, FDG PET and CT for the diagnosis of malignancy in SPNs have reported similar results with the accuracy of FDG PET-CT better than FDG PET or CT alone.^{136 137} The synergistic combination of anatomical and functional information preserves the sensitivity of CT and favourable specificity of FDG PET to improve diagnostic accuracy. Nie *et al*¹³⁸ in a retrospective study of 92 consecutive patients with indeterminate pulmonary nodules (<3 cm) used computer-aided diagnosis with 4 clinical, 16 CT and 4 PET input parameters to illustrate this. A computer-aided detection (CAD) scheme based on both CT and PET input parameters provided better discrimination between benign and malignant nodules with an area under the ROC curve of 0.95 compared with 0.91 for PET alone or 0.83 for CT alone.

Nodules <10 mm

The utility of PET for characterising nodules <10 mm is not clear with sparse data available in both meta-analyses. Gould *et al*¹³¹ noted a paucity of data on nodules <1 cm; the eight instances where results were available showed three true-positive, two true-negative and three false-negative observations. Cronin *et al* included seven studies not part of the prior meta-analysis from which information on only nine nodules was available;¹³² eight of these nodules were from one study detailed below.¹³⁹

Two of the lung cancer screening studies provide data on SPNs <1 cm. Veronesi *et al*¹³³ in a subgroup analysis of 44 nodules of <1 cm reported a sensitivity, specificity and accuracy of FDG PET-CT for malignancy of 83%, 100% and 95%, respectively. Diederich *et al*²⁴ had three nodules <1 cm in their cohort, all of which were PET negative, including two false-negative lesions, which were adenocarcinomas on histology.

Nomori *et al*¹⁴⁰ in a prospective trial evaluating FDG PET for pulmonary nodules <3 cm, assessed 136 non-calcified nodules, of which 20 nodules were <1 cm. All subcentimetre nodules were negative on FDG PET, including 12 malignant nodules, leading to the authors' conclusion that FDG PET was not suitable for nodules <1 cm. Herder *et al*¹³⁹ undertook a small retrospective study addressing the same question, with conflicting results. Eight out of 36 nodules in their cohort were <1 cm with four true-positive, three true-negative and one false-positive observations with a sensitivity and specificity of FDG PET for nodules <1 cm of 90% and 78%, respectively.

PET-CT scanners have a finite ability to resolve small objects, which is dependent on the spatial resolution of the system and image pixel size. Assuming a standard scanner bore width of 80 cm and a 192×192 image matrix, a pixel size of 4.2 mm

(800 mm/192), will in theory, permit objects of at least 8.4 mm to be resolved. Tracer uptake related to lesions smaller than this will be underestimated owing to partial volume errors. In addition, for a lesion to be visualised, tracer uptake must be clearly depicted above background activity, which is problematic for lesions with minimal tracer uptake or areas with increased background activity such as the dependent lower lobes. Lesion detection is also adversely affected by breathing artefact, particularly peripheral lesions and those just above the diaphragm, the latter additionally affected by scatter artefact from the liver.

Sub-solid nodules

FDG PET-CT may be suboptimal at characterising SSNs as benign or malignant using conventional criteria. Veronesi *et al*¹³³ found from a cohort of 157 patients that five of six pGGNs (1.4–1.8 cm) were falsely negative on FDG PET-CT and concluded that PET was not helpful. However, the sensitivity, specificity and accuracy of FDG PET-CT were much higher for the subset of 30 PSNs (no information on the size of the solid component). Nomori *et al*¹⁴⁰ reported 15 pGGNs (10 malignant, 5 benign) from a cohort of 136 nodules; nine malignant nodules were falsely negative on FDG PET, whereas four benign nodules were falsely positive and similarly concluded that FDG PET could not evaluate ground-glass nodules accurately. Ichinose used an SUV cut off point of 0.8 and found that for 64 pGGNs that had PET, the sensitivity was 67% and specificity 89% for detection of invasive lung cancer.¹⁰⁴ Smaller retrospective studies have suggested that SSNs with increased FDG uptake may have a potential benign infective/inflammatory aetiology and should therefore be followed-up with CT rather than with more invasive investigations.^{141 142}

Qualitative versus quantitative analysis

Gould *et al*¹³¹ in their meta-analysis found that semiquantitative analysis of FDG uptake provided no additional benefit to the diagnostic accuracy achieved through qualitative visual assessment. SUV is a relative measure of FDG uptake, which is prone to variability as a result of scanner features (spatial resolution, image scatter and noise), patient factors (blood glucose, renal function, biological variability), imaging protocols (injected activity, duration of uptake period, respiratory motion) and reconstruction algorithms (attenuation and scatter correction).¹⁴³ Multiple sources of potential error make reproducibility of SUV measurements and application of SUV cut-off points to determine malignancy difficult, owing to a lack of standardisation across imaging centres, resulting in an estimated greater than 15–20% variability in SUV_{max} measurements.¹⁴³ The advantage of SUV is that it is less variable across individuals than subjective assessments, and may be used for follow-up scanning, provided that the same scanner is used. Early FDG PET studies suggesting that an SUV <2.5 is in keeping with a benign nodule have been proved incorrect with a significant chance of malignancy remaining in such nodules. For these reasons, either qualitative visual assessment of FDG uptake of SPNs (\pm linked ordinal scale) and/or SUV measurements may be used.

FDG PET-CT and clinical risk prediction models

Gould *et al*¹³¹ suggested that the best use of FDG PET was in conjunction with an estimation of the pre-test probability of malignancy. Herder *et al*⁵⁵ confirmed this in a retrospective study of 106 patients with indeterminate SPNs evaluated with FDG PET. They validated the Mayo clinical risk prediction model and reported a high diagnostic accuracy (86%) of FDG

PET for malignancy. Importantly, combined information gained from both clinical assessment and FDG PET resulted in the best diagnostic accuracy, with FDG PET significantly increasing the area under the ROC by 13% from 0.79 to 0.92. More recently, Evangelista *et al*¹⁴⁴ retrospectively reviewed 59 patients with cancer with indeterminate solitary or multiple lung nodules who underwent FDG PET-CT. They used the Mayo clinic and VA clinic risk prediction models to assign risk categories and assessed the additional role of FDG PET-CT. They found that the use of FDG PET-CT was most efficacious and improved risk stratification in those with a low to intermediate pre-test probability of malignancy. In the Herder model, FDG uptake was classified as absent, faint, moderate or intense. The authors did not provide objective measures or definitions but others have.^{135 145} The last two studies used a five-point scale that can be adapted to a four-point scale to facilitate consistency in reporting and use with the Herder model. Table 12 shows the two scales. From these, the GDG derived a four-point qualitative scale to be used with the Herder model (see recommendations).

Dual time point imaging

Dual time point imaging involves image acquisition at two time points rather than a single time point after the injection of tracer. The technique is reliant upon the observation that malignant nodules continue to accumulate tracer with time, whereas benign nodules either remain stable or display reduced tracer uptake, which aids differentiation. Individual studies have shown conflicting results for FDG PET,^{146 147} but a recent meta-analysis of dual time point FDG PET-CT by Zhang *et al*¹⁴⁸ showed that dual time point imaging offered slightly improved specificity in comparison with single time point FDG PET-CT, although they had similar diagnostic accuracies for diagnosing malignancy. However, only eight studies (415 nodules) were included in this meta-analysis and it was limited by significant between-study heterogeneity; larger prospective studies are required for further evaluation. From a practical aspect, the additional time required to perform dual time point imaging and resultant reduction in patient throughput makes routine adoption of this technique unrealistic.

Cost-effectiveness

Cao *et al*¹⁴⁹ published a systematic review of the cost-effectiveness of FDG PET in the staging of NSCLC and the

Table 12 Two ordinal scales with definitions for reporting fluorodeoxyglucose uptake

Scale	Vansteenkiste <i>et al</i> ¹⁴⁵	Fletcher <i>et al</i> ¹³⁵
1	Absent	Benign—no uptake, same as reference lung tissue (SUV 0.6–0.8)
2	Less than mediastinal blood pool (MBP)	Probably benign—uptake greater than reference lung tissue but less than MBP (SUV greater than 0.6–0.8 but less than 1.5–2.0)
3	Comparable with MBP	Indeterminate—2–3 times greater than reference lung but less than MBP (SUV 1.5–2.0 but less than 2.5)
4	Greater than MBP	Probably malignant—greater than MBP (where MBP corresponds to 2.5)
5	Much greater than MBP	Definitely malignant—much greater than MBP (substantially greater than 2.5)

SUV, standardised uptake value.

management of SPNs. Five studies assessed the utility of PET for pulmonary nodule management, none from a UK setting. The studies were heterogeneous and the conclusions varied depending on factors such as the sensitivities and specificities assigned to FDG PET, the pre-test probabilities of malignancy and the healthcare setting. Nevertheless, the overall conclusion was that the additional information gained from FDG PET imaging in the diagnosis and management of indeterminate of SPNs is of value in the appropriate clinical context.

Single-photon emission CT

SPECT imaging using 99m Tc-labelled radiopharmaceutical agents is similar in principle to PET imaging, where the distribution of injected radiopharmaceutical agent and emission of gamma photons is used to create representative cross-sectional images. This permits more accurate localisation of tracer uptake in comparison with planar imaging, but the spatial resolution of SPECT remains lower than PET. Studies have assessed the utility of 99m Tc-depreotide SPECT, a somatostatin analogue, as an alternative to FDG PET for the evaluation of SPNs given that malignant nodules have a greater expression of somatostatin receptors than benign nodules. Cronin *et al*¹³² in a pooled analysis of seven studies (439 nodules), reported a sensitivity, specificity and area under the ROC curve of 95%, 82% and 0.94, respectively, which was not significantly different from the results obtained with FDG PET. Naalsund and Maublant¹⁵⁰ in a multicentre prospective study analysing 118 nodules, reported slightly inferior results with a sensitivity, specificity and diagnostic accuracy of 89%, 67% and 81%, respectively. However, since October 2010, 99m Tc-depreotide is no longer commercially available in Europe.

MRI

MRI is a non-ionising cross-sectional imaging technique which is reliant upon the variable excitation and relaxation of hydrogen atoms—that is, protons, in response to a radiofrequency pulse, while in a static magnetic field. Imaging the lungs is problematic owing to inherent low proton density, resulting in poor image contrast, numerous air–soft tissue interfaces which result in signal loss and distortion and cardiac and respiratory motion, causing image blur. However, technological advances incorporating faster image sequences and functional imaging sequences including DW-MRI and DCE-MRI have changed this.

Studies assessing the accuracy of ultrafast MRI techniques using a HASTE sequence for the detection of pulmonary nodules, in comparison with the ‘gold standard’ of CT, have reported reliable detection of pulmonary nodules >5 mm.^{151 152} However, no studies have assessed the ability of HASTE MRI to differentiate between benign and malignant SPNs.

DWI-MRI

DWI-MRI is based on the free diffusion of water molecules (Brownian motion) with areas of restricted diffusion—that is, tissues with increased cellularity, returning a high signal which can be quantified with the apparent diffusion coefficient value. Wu *et al*¹⁵³ performed a meta-analysis of 10 studies (712 nodules) assessing the diagnostic accuracy of DWI-MRI in differentiating benign from malignant lesions (pulmonary nodules and masses) and reported a pooled sensitivity and specificity of 84% and area under the summary ROC curve of 0.9. The authors noted significant between-study heterogeneity with a high proportion of retrospective studies with significantly higher and potentially confounding pooled sensitivity and specificity estimates. Consequently, they concluded that high-quality

prospective studies are required to further assess the utility of DWI-MRI. Mori *et al*¹⁵⁴ prospectively compared DWI-MRI and FDG PET-CT to diagnose malignancy in 140 lesions and reported similar sensitivities (70% vs 72%) and diagnostic accuracies (76% vs 74%), although specificity was significantly better with DWI-MRI (97% vs 79%). Ohba *et al* in a prospective comparative study between 1.5 T and 3 T DWI-MRI and FDG PET-CT assessing 76 lesions reported similar sensitivities and specificities between the two techniques, although importantly both studies included both pulmonary nodules and masses.¹⁵⁵

Dynamic contrast-enhanced MRI

DCE-MRI provides information related to the underlying perfusion and permeability of the tissue microenvironment based upon the degree of uptake of gadolinium-based contrast material. Cronin *et al*¹³² in a pooled analysis of six studies (284 nodules) reported no significant difference in the diagnostic performance of DCE-MRI compared with FDG PET and other imaging techniques. Smaller single-centre prospective studies have produced conflicting results; some have confirmed a high accuracy of DCE-MRI for diagnosing malignancy in SPNs,¹⁵⁶ whereas Satoh *et al*¹⁵⁷ suggested that DCE-MRI is inadequate for distinguishing between benign and malignant SPNs. Mamata *et al*¹⁵⁸ undertook a small study of 30 patients, using more complex analysis of DCE-MRI studies (perfusion indices and pharmacokinetic parameters) to help differentiate between benign and malignant SPNs. Using a parameter that focuses specifically on the dynamics of contrast material transport into and out of the extravascular extracellular space (k_{ep}) with a cut-off point of 1.0 min^{-1} , they reported a sensitivity, specificity and accuracy for diagnosing malignancy of 76%, 100% and 80%, respectively. Overall, despite technological advances in MRI and some potentially promising results in small individual studies, there remains little evidence to support its use over FDG PET-CT.

Dynamic contrast-enhanced CT

DCE-CT provides similar information to that obtained with DCE-MRI using iodinated contrast material, with the overall contrast enhancement of malignant nodules usually higher than that of benign nodules. Cronin *et al*¹³² in a pooled analysis of 10 studies (1167 nodules) reported a sensitivity, specificity and area under the ROC curve of 93%, 76% and 0.93, respectively, which was comparable with the diagnostic performance of FDG PET. Smaller prospective studies have reported similar results but with lower specificities and differing cut-off values, probably attributable to varying image acquisition parameters.^{159 160} Single-centre prospective studies have also looked at the first-pass perfusion DCE-CT assessing tissue haemodynamics based on perfusion parameters to differentiate between benign and malignant nodules. Sitartchouk *et al*¹⁶¹ in a single-centre study of 57 nodules, first reported the utility of perfusion parameters in differentiating between benign and malignant SPNs. Li *et al*¹⁶² in a similar sized study of 77 nodules confirmed this potential with sensitivities, specificities and accuracies to diagnose malignancy of 91.3–93.5%, 81.8–90.9% and 88.2–92.6%, respectively. More recently, Ohno *et al* in two prospective comparative studies between perfusion DCE-CT and FDG PET-CT have suggested that perfusion CT is more specific and accurate than FDG PET-CT.^{163 164} However, in both studies an SUV_{max} cut-off point was used to determine malignancy on FDG-PET-CT with nodule characteristics on the CT component of the examination not obviously used to make this decision. Further comparative studies with FDG PET-CT using optimal

image interpretation are required before considering DCE-CT as a viable alternative for diagnosing malignancy in SPNs.

Risk thresholds for further investigation of risk of malignancy
 Louie *et al*¹⁶⁵ developed a Markov model to determine appropriate thresholds for deciding between management strategies in patients unfit for surgical resection. They modeled the pre-test probability of malignancy below which CT surveillance was appropriate and above which PET-CT should be performed, and proposed 17% as an appropriate cut-off between these two strategies. The GDG assessed the effect of increasing the threshold for PET-CT from 10% (as proposed previously) to 17% in a cohort of British patients with incidentally detected pulmonary nodules (unpublished data) and found that a malignant diagnosis would have been delayed for 23% of patients affected by this change. Thus a 10% threshold for proceeding to PET-CT was preferred. Louie *et al* also modeled the threshold above which it was appropriate to proceed to treatment without biopsy confirmation of malignancy, suggesting 85% probability of malignancy as an appropriate cut-off. Again, when these thresholds were used in a UK population, use of a 70% cut-off for treatment resulted in only a small increase in treatment of benign disease and reduced the chance of treatment delay, so the GDG considered that a lower threshold was appropriate (see further discussion in ‘Non-surgical treatment without pathological confirmation section.’) Thus figure 1 specifies a range of 10–70% where biopsy is preferred.

Summary

PET-CT remains the preferred investigation in the further evaluation of pulmonary nodules, partly because it is widely available and no alternative investigation shows superiority. Further research is required to evaluate alternative techniques, such as DCE-CT, which may be more cost-effective. PET-CT is less useful in smaller nodules but these have a lower risk of malignancy and can be managed by further imaging follow-up. In the assessment of risk, the Mayo model is substantially improved by the addition of PET-CT as described by Herder *et al* and when used with an ordinal scale to categorise FDG uptake.

Evidence statement

- ▶ Pre-test probability of malignancy influences interpretation of PET-CT, with high-risk individuals at risk of false-negative results, and low-risk individuals at risk of false-positive results. **Evidence level 3**
- ▶ In a meta-analysis PET has shown a sensitivity of 93.9% and specificity of 88.5% for determining malignancy from a pooled cohort of studies including patients with low to high risk. **Evidence level 2++**
- ▶ PET has a good sensitivity and moderate specificity for determining a malignant nodule in patients with a high risk of malignancy with a pulmonary nodule of uncertain aetiology of ≥ 10 mm, with more limited evidence for nodules < 10 mm. Further imaging to assess growth increases the sensitivity of determining malignancy. **Evidence level 1 – supported by 2++**
- ▶ PET has a lower sensitivity and higher false-negative rate in SSNs. **Evidence level 2++ and 3**
- ▶ Methods of assessing FDG uptake include qualitative visualisation, semiquantitative analysis and the measurement of SUVs; all have similar accuracy. The Herder model employed an ordinal scale. **Evidence level 3**
- ▶ Risk prediction models are improved by the addition of information from PET-CT; the Herder model AUC improved from 0.79 to 0.92. **Evidence level 3**
- ▶ MRI does not have a routine place in assessing pulmonary nodules outside of research studies. **Evidence level 2++ and 3**

- ▶ SPECT does not show any advantage over PET-CT in the assessment of pulmonary nodules. **Evidence level 2++ and 3**
- ▶ DCE-CT has a high sensitivity but low specificity for determining malignancy. **Evidence level 2++ and 3**

Recommendations

- ▶ Offer a PET-CT to patients with a pulmonary nodule with an initial risk of malignancy of $> 10\%$ (Brock model) where the nodule size is greater than the local PET-CT detection threshold. **Grade B**
- ▶ Ensure that PET-CT reports include the method of analysis. **Grade D**
- ▶ Use a qualitative assessment with an ordinal scale to define FDG uptake as absent, faint, moderate or high using the following guide:
 - Absent—Uptake indiscernible from background lung tissue
 - Faint—Uptake less than or equal to mediastinal blood pool
 - Moderate—Uptake greater than mediastinal blood pool
 - Intense—Uptake markedly greater than mediastinal blood pool. **Grade D**
- ▶ Reassess risk after PET-CT using the Herder prediction tool. **Grade B**
- ▶ After reassessment of risk:
 - Consider CT surveillance for people who have nodules with a chance of malignancy $< 10\%$
 - Consider image-guided biopsy where the risk of malignancy is assessed to be between 10 and 70%; other options are excision biopsy or CT surveillance guided by individual risk and patient preference
 - Offer people surgical resection as the favoured option where the risk that the nodule is malignant is $> 70\%$; consider non-surgical treatment for people who are not fit for surgery. **Grade C**
- ▶ Do not use MRI, SPECT or DCE-CT to determine whether a nodule is malignant where PET-CT is an available alternative. **Grade D**
- ▶ Further research is needed into the most effective follow-up pathway in low-to-medium risk patients and for those with pGGNs. **RR**
- ▶ Further research should be undertaken into the use of PET-CT in the evaluation of pGGNs using lower SUV cut-off values. **RR**

NON-IMAGING TESTS AND NON-SURGICAL BIOPSY

Key question: What non-surgical biopsy/non-imaging tests are useful in nodule evaluation, when should they be used and what are the harms?

Non-surgical biopsy or further non-imaging tests are used where there is insufficient certainty about the diagnosis to allow definitive management. The choice of test may depend on the preferences of the patient and so it is especially important to ensure the balance of accuracy and safety has been explained and that this is acceptable to the patient (see section ‘Information and support’).

Evidence review

Biomarkers

Five studies were identified assessing the role of biomarkers in determining the likelihood of a pulmonary nodule being malignant. Four of these studies measured circulating markers, and one involved analysis of bronchoalveolar lavage fluid.

Chu *et al*¹⁶⁶ described a cross-sectional study that looked at combining tumour markers (squamous cell carcinoma antigen, CEA, cytokeratin 19 fragment antigen and neuron-specific enolase) in 805 patients with suspicious pulmonary masses, of

whom 444 were found to have stage I lung cancer. The test performed poorly, with a demonstrated sensitivity of only 23.2%. Shen *et al*¹⁶⁷ reported a cross-sectional study looking at the role of plasma microRNAs in 156 patients with SPNs found that plasma microRNA could distinguish between malignant and benign nodules with 75% sensitivity and 85% specificity (ROC AUC 0.86). Daly *et al*¹⁶⁸ looked at a panel of seven biomarkers (interleukin (IL) 6, IL-10, IL-1ra, sIL-2R α , stromal cell-derived factor-1 $\alpha+\beta$, tumour necrosis factor α and macrophage inflammatory protein 1 α) in a validation cohort of 81 patients (61 with benign nodules, 20 with malignant nodules). They found that the sensitivity and specificity for diagnosing malignancy were 95% and 23.3%, respectively, with a negative predictive value of 93.8%.

Higgins *et al* assessed the performance of a variant form of Ciz1 (a nuclear matrix protein) as a circulating biomarker for stage 1 lung cancer. In a validation cohort of 160 individuals comprising patients with stage I lung cancer, benign pulmonary nodules, inflammatory lung disease and age-matched smoking controls, the test performed well with 95% sensitivity and 74% specificity. Currently, however, measurement requires Western blot analysis which is not easily applied outside a research laboratory, and the authors acknowledge that the assay would need to switch platforms and be validated further before widespread use.¹⁶⁹

The value of lactate dehydrogenase (LDH) in bronchoalveolar lavage fluid for discriminating between benign and malignant pulmonary nodules was assessed in a prospective case-control trial with 21 controls, 17 patients with benign SPNs and 42 with malignant lesions.¹⁷⁰ LDH levels were significantly higher in those with malignant SPNs than in those with benign lesions or controls, although this study excluded those with a smoking history.

Three studies evaluated the performance of a panel of circulating autoantibodies in predicting patients with lung cancer. This test is commercially available (EarlyCDT-Lung) and is marketed as a tool to risk stratify patients with pulmonary nodules. Boyle *et al*¹⁷¹ described use of a panel of six circulating autoantibodies in three cohorts of patients with newly diagnosed lung cancer ($n=145, 241, 269$), each matched to control individuals (although little clinical information was supplied about the control groups). Sensitivities of 36–39% and specificities of 89–91% were reported for the three cohorts. Lam *et al* reported a similar study with the same panel of autoantibodies measured in four cohorts of patients with newly diagnosed lung cancer from Europe and North America.¹⁷² Results were compared with control populations for three of the four cohorts, with control populations matched by age, sex and (in two cohorts) smoking history. Overall, results were similar to those of the study by Boyle *et al*,¹⁷¹ with sensitivities of 34–43% and specificities of 87–89% for lung cancer.

A subsequent report described the addition of a seventh autoantibody to the panel and assessed performance in routine clinical practice in 1613 patients for whom US physicians ordered the EarlyCDT-Lung test.¹⁷³ Sensitivity and specificity for lung cancer were 37% and 91%, respectively, with a positive test increasing the chance of lung cancer diagnosis by a factor of 5.4. No data are presented for baseline clinical or demographic data for the whole population. Of all patients tested (irrespective of test results), 3.8% were diagnosed with lung cancer within 6 months, which is considerably in excess of the rates of lung cancer seen in CT screening studies. From the information provided in the study, it is impossible to comment on the reasons for such a high rate of lung cancer diagnosis. To date, there are no published studies reporting the performance of the Early

CDT-Lung test in prospectively recruited populations at high risk of developing lung cancer according to predefined criteria. Trials are ongoing, including a study in the UK using the test as a pre-CT screening tool. Of relevance to this guideline, there are no reports evaluating the performance of this test in a cohort of patients with pulmonary nodules, and thus its efficacy in discriminating malignant from benign nodules is unknown.

Flexible bronchoscopy

van't Westeinde *et al*¹⁷⁴ evaluated the use of conventional bronchoscopy in the investigation of 308 consecutive patients with a positive CT screen enrolled in the NELSON trial. There were 318 suspicious lesions, with mean diameter of 14.6 mm (only 2.8% were >3 cm). The sensitivity of bronchoscopy was only 13.5% (95% CI 9.0% to 19.6%) with a negative predictive value of 47.6%. The authors do not recommend routine use of bronchoscopy for positive test results in a screening programme.

Bronchoscopy with guidance

Several case series have reported the yield of bronchoscopy under fluoroscopic guidance. Baaklini *et al*¹⁷⁵ described a retrospective analysis of 177 patients undergoing bronchoscopy with fluoroscopy for pulmonary nodules without endobronchial abnormality. Diagnostic yield fell for progressively distal lesions (yield 82% for central, 61% for intermediate and 53% for peripheral), with particularly low yield for lesions <2 cm in the outer third of the lung (14%). Aoshima *et al*¹⁷⁶ reported results from a cohort of 208 procedures carried out with fluoroscopy. Diagnostic yield was 62% for malignant lesions and 12% for benign lesions. Factors associated with reduced yield were diameter <25 mm, distance >40 mm from inlet of segmental bronchus and absence of CT bronchus sign ($p<0.05$ for each factor). The CT bronchus sign refers to the finding that the third- or fourth-order bronchus leads to the lesion. Schwarz *et al*¹⁷⁷ performed flexible bronchoscopy with fluoroscopy in 225 patients with nodules <3 cm. Unsuspected endobronchial involvement was found in 4.4% of cases, and bronchoscopy confirmed aetiology of the nodule in 41% cases. Oki *et al*¹⁷⁸ described a case series of patients with peripheral pulmonary lesions undergoing fluoroscopic guided bronchoscopy with a 3.5 mm thin bronchoscope in the absence of endobronchial lesion seen with standard scope. Of the 98 patients with appropriate follow-up data, thin bronchoscopy yielded diagnostic information in 69% of patients overall (median lesion size 30.5 mm). The thin bronchoscope could be inserted into more distal bronchi (mean 4.3 generations vs 2.3 with standard bronchoscope, $p<0.001$) and allowed visualisation of an endobronchial lesion in 14% patients. Lai *et al*¹⁷⁹ reported the diagnostic yield of bronchoscopy with transbronchial biopsy under fluoroscopy for pulmonary nodules in an area endemic for TB. The diagnostic sensitivity was 70% in patients with lung cancer and 55% in patients with TB. Yield fell for smaller nodules (35% diagnostic rate for nodules <2 cm vs 65% for nodules >2 cm).

Radial endobronchial ultrasound

Several further case series have looked at the role of radial endobronchial ultrasound (rEBUS) to increase the diagnostic rate of bronchoscopy.^{180–182} Herth *et al*¹⁸⁰ described a prospective crossover study comparing fluoroscopy with rEBUS in 54 patients with pulmonary nodules not visualised with fluoroscopy (mean nodule diameter 2.2 cm). Radial EBUS located 89% of the nodules, and in 70% a biopsy yielded a diagnosis. Pneumothorax occurred in one patient. Eberhardt *et al*¹⁸¹ reported a similar study from the same group, using rEBUS to sample 100 small

pulmonary nodules <2 cm not visualised by fluoroscopy. A lesion was visualised by rEBUS in 67% of cases, and biopsies established a diagnosis in 46% of patients. Pneumothorax occurred in 3% cases. Kurimoto *et al*¹⁸² reported the yield of rEBUS in 150 consecutive patients with pulmonary nodules. Biopsies were diagnostic in 77% of cases, and yield did not appear to vary with nodule size (76% diagnosis rate for 21 nodules <10 mm diameter). Moderate bleeding occurred in two patients (1%) with no reported pneumothoraces.

Electromagnetic navigation

Electromagnetic navigation bronchoscopy (ENB) creates a virtual bronchoscopic image of patients' airways derived from a CT scan of their chest. Patients are then placed on a board which generates an electromagnetic field. The virtual and actual anatomy are aligned, which allows a steerable sensor probe to navigate to the lesion under virtual real-time guidance. Four case series were identified evaluating this technique.^{183–186}

Eberhardt *et al*¹⁸³ assessed performance of ENB in 54 patients with pulmonary nodules <3 cm diameter. Of 53 lesions with follow-up data, 75.5% of samples were diagnostic (sensitivity 72.3% for malignancy). The study also compared yields of catheter aspiration with forceps biopsy with this technique, finding this former to have a greater diagnostic yield.

Gildea *et al*¹⁸⁴ reported results from a series of patients with pulmonary nodules and lymph nodes sampled by ENB. Of 54 procedures for peripheral lesions with mean diameter 22 mm, 40 (74%) were diagnostic. Efficacy did not differ by size of lesion with similar yield for nodules >2 cm and <2 cm (73.9% vs 74.1%, respectively). Pneumothorax occurred in two patients (3%).

Jensen *et al*¹⁸⁵ performed a retrospective analysis of the performance of ENB across five centres. Ninety-two patients underwent the procedure (mean nodule size 2.6 cm), with an overall diagnostic yield of 65%. Unlike the previous report, they did find a significant reduction in yield for nodules <2 cm compared with those >2 cm (50% vs 76% respectively, p=0.01). Pneumothorax occurred in 3% of patients.

Lamprecht *et al*¹⁸⁶ reported results from ENB in conjunction with rapid on-site cytological evaluation. In 112 patients, ENB was diagnostic in 83.9%, with a trend towards better results for large nodules (yield for lesions <2 cm vs >2 cm were 75.6%

and 89.6%, respectively, p=0.06). Pneumothoraces occurred in two cases (1.8%).

Finally, Seijo *et al*¹⁸⁷ described results of ENB in 51 consecutive patients with pulmonary nodules (mean size 2.5 cm). Overall diagnostic yield was 67%, but this was significantly higher in patients with the CT bronchus sign than in those without (79% vs 31%, p=0.04). The CT bronchus sign was the only variable predicting yield on multivariate analysis (OR=7.6, 9% CI 1.8 to 31.7). There were no procedure-related complications.

Image-guided biopsy

Ultrasound

The only large case series (>50 cases) reviewed for ultrasound-guided biopsy of nodules was that from Obata *et al*,¹⁸⁸ describing results from 107 nodules sampled. All nodules were ≤2 cm in diameter, and all were in contact with the pleura. The yield from the first biopsy was only 39% (56% for malignant lesions and 16% for benign lesions). A proportion of those with negative initial procedures underwent a repeat attempt and of those, 49% were diagnostic. No further studies were identified meriting inclusion, presumably reflecting the more common practice to biopsy peripheral nodules under CT guidance (see following section).

CT-guided biopsy

Eleven retrospective case series were identified assessing the performance of CT-guided percutaneous biopsy of pulmonary nodules/masses.^{189–199} Case series were only considered if more than 50 patients were included and where patient level data was available to allow cases to be pooled to allow calculation of overall test performance. Other case series discussed below were excluded from this combined analysis if the authors limited inclusion to specific groups (eg, nodules <1 cm diameter). There was wide heterogeneity in the inclusion criteria of the various reports (eg, difference in size of nodules included, use of rapid on-site cytology, use of multiplanar reconstruction (MPR)). Although we acknowledged these variables, papers were reviewed for test performance (true positive, true negative, false positive, false negative) in order to determine overall sensitivity, specificity and negative likelihood ratio. Data from these case reports are shown in table 13. Sensitivities in individual

Table 13 Case series of CT-guided biopsy of pulmonary nodules

	Total no cases	Follow-up data available	Useful sample obtained	True +ve	True -ve	False +ve	False -ve	Sensitivity (%)	Specificity (%)	Negative LR
Baldwin <i>et al</i> ¹⁸⁹	114	114	98	71	23	1	3	96	96	0.042
Gupta <i>et al</i> ¹⁹⁰	176	176	143*	104	34	0	5	95	100	0.046
Hayashi <i>et al</i> ¹⁹¹	52	52	50	34	15	0	1	97	100	0.029
Jin <i>et al</i> ¹⁹²	71	61	61	35	25	0	1	97	100	0.028
Ohno <i>et al</i> ¹⁹³	396	396	396	266	80	20	30	90	72	0.141
Romano <i>et al</i> ¹⁹⁴	229	184	184	113	56	0	15	88	100	0.117
Santambrogio <i>et al</i> ¹⁹⁵	220	220	207	130	68	1	8	94	99	0.059
Tsukada <i>et al</i> ¹⁹⁶	138†	138	138	70	44	3	21	77	94	0.245
Wagnetz <i>et al</i> ¹⁹⁷	108	104	104	79	16‡	0	9	90	100	0.102
Westcott <i>et al</i> ¹⁹⁸	64	64	64	40	21	0	3	93	100	0.070
Total	1568	1509	1445	942	382	25	96	91	94	0.10 (95% CI 0.08 to 0.12)

*155 cases reported in paper, but data only presented for 143 cases.

†Includes results from repeat biopsies of same nodules.

‡Calculated from information provided in text.

LR, likelihood ratio.

reports varied from 77% to 97%, and specificities from 72% to 100%. Considering the data together (accepting the significant heterogeneity of studies) the overall sensitivity was 90% and specificity 95% with a negative likelihood ratio of 0.10 (95% CI 0.08 to 0.12).

A number of case series examined the effect of specific variables on the CT-guided biopsy performance—namely, nodule size, nodule morphology, needle path length, C-arm cone beam system, MPR, immediate cytological assessment and aspiration versus cutting needle.

Four case reports assessed the effect of nodule size on test outcome. Kothary *et al*²⁰⁰ described a retrospective case series of 139 patients who underwent a CT-guided biopsy and compared test performance and complication rate by nodule size (37 nodules ≤1.5 cm vs 102 nodules >1.5 cm). Larger nodules were statistically more likely to result in diagnostic specimens than smaller nodules (73.5% vs 51.4%, p=0.012), although there was no significant difference in diagnostic accuracy for malignancy (81.3% vs 69.6%, respectively, p=NS). Wallace *et al* reported performance of CT-guided biopsy in 61 patients with nodules ≤1 cm diameter, and found an overall sensitivity of 82%, specificity of 100% and accuracy of 88%.²⁰¹ When results for 8–10 mm and 5–7 mm nodules were compared, sensitivity was lower for smaller nodules (88% vs 50%, respectively, p=0.026), although there were only 10 cases in the smaller nodule group. Ohno *et al* described a retrospective case series of 162 patients undergoing CT-guided biopsy of pulmonary nodules ≤20 mm in diameter.²⁰² Overall diagnostic accuracy was 77.2%, and varied with nodule size (52% for lesions ≤10 mm, 74.4% for 11–15 mm, 91.5% for 16–20 mm, p<0.05). Tsukada *et al*¹⁹⁶ reported performance of CT-guided biopsy in 138 patients with nodules of mean diameter 23 mm (range 6–70 mm). Overall diagnostic accuracy was 82.6%, but decreased significantly with reducing size of lesion (86.7% for 20–30 mm, 78.9% for 10–20 mm, 66.7% for ≤10 mm). Choi *et al*²⁰³ conducted a retrospective analysis of outcomes in CT-guided aspiration and core biopsy of 305 pulmonary nodules <1 cm in a tertiary referral centre. The sensitivity, specificity and accuracy were 93.1%, 98.8% and 95.0%, respectively. No comparison was made between nodules of different sizes, but the data show good performance of the technique even with small subcentimetre nodules.

De Filippo *et al* retrospectively reviewed 198 CT-guided biopsies of pulmonary nodules. They demonstrated differences in diagnostic accuracy on the basis of nodule morphology, with solid nodules demonstrating highest accuracy (95.1%) with progressively lower accuracy for PSNs (84.6%) and pGGNs (66.6%).²⁰⁴ Choi *et al*²⁰³ described similarly differing accuracy by nodule morphology (solid 96.7%, part-solid 95.8%, pure ground glass 85.3%), although nodule morphology was not a significant predictor of diagnostic failure by univariate analysis.

Two case series described effects of needle path length on performance. Ohno *et al*²⁰² showed that diagnostic accuracy fell with increased needle path length, with statistically lower accuracy where needle path length was >40 mm compared with shorter path lengths (p<0.05). Gupta *et al*¹⁹⁰ reported the relationship between needle path length and test performance for subpleural pulmonary nodules. In 48 patients, a short direct path was selected (mean 0.4 cm path) and results compared with 128 patients where a longer indirect path was used (mean 5.6 cm path). Fewer diagnostic samples were obtained using the shorter path, although sensitivity, specificity and accuracy (limited to cases with diagnostic sample) did not differ between approaches. This latter report is likely to reflect the specific

challenge of sampling lesions immediately beneath the pleura, thereby explaining the apparently conflicting results of these two case series.

Three case series describe results with C-arm cone beam CT (CBCT) guidance which allows real-time fluoroscopic and 3D-CT capabilities. Jin *et al* reported results of CBCT-guided biopsy of 71 patients with pulmonary nodules ≤30 mm diameter.¹⁹² Sensitivity was 97%, specificity 100% and accuracy 98.4%. Choi *et al*²⁰⁵ reported a similar cohort of 161 consecutive patients undergoing CBCT-guided biopsy, with very similar outcomes (sensitivity 96.8%, specificity 100%, accuracy 98.2%). Finally, Choo *et al*²⁰⁶ reported use of a CBCT virtual navigation system in 105 consecutive patients with nodules ≤10 mm undergoing image-guided biopsy. Again almost identical performance was reported (sensitivity 96.7%, specificity 100%, accuracy 98%) despite the small size of the lesions. CBCT guidance does involve an additional radiation dose for operator and patient (radiation dose in Jin *et al* was 272±116 mGy). No studies compared performance of CBCT with conventional CT guidance (neither randomised nor cohort studies), so the additional value of CBCT guidance remains unclear. However, performance particularly for smaller nodules (≤1 cm) does appear impressive.

One retrospective cohort study assessed the utility of MPR during CT-guided biopsy of indeterminate pulmonary nodules, comparing test performance with conventional CT-guidance. Sixty-five patients underwent nodule biopsy by CT with MPR, compared with 250 undergoing conventional biopsy. The populations were well-matched, albeit non-randomised. Diagnostic accuracy was higher in the MPR group than in conventional group both for aspiration biopsy (96.9% vs 82.4%, respectively, p<0.05) and cutting biopsy (97.0% vs 81.3%, respectively, p<0.05). The MPR technique was particularly useful for small nodules (<20 mm).

Santambrogio *et al*¹⁹⁵ describe a randomised controlled trial of on-site cytological evaluation of CT-guided biopsy samples. Two hundred and twenty patients with nodules 1–3 cm underwent CT fine needle aspiration by a thoracic surgeon. Samples from 110 patients were immediately assessed by a cytologist for sample adequacy (with repeat aspiration if inadequate). For the other 110 samples a gross assessment was made by the operator only. Diagnostic accuracy was 99% in the group with immediate cytological examination compared with 88% in the control group (p<0.001), with a small but significant increase in the number of aspirates in the intervention group (1.22 vs 1.10, p=0.015). There was no difference in complications. Although clearly improving yield from this procedure in this study, these findings are not relevant to analysis of core needle biopsies taken by cutting needles, which are increasingly favoured as they provide larger histological samples.

Only one report of those reviewed specifically compared the performance of aspiration and core biopsy. Choi *et al*²⁰³ included a biopsy method (aspiration vs core biopsy vs combined procedure) in univariate and multivariate analysis of factors predicting diagnostic failure. Of 94 aspiration procedures, a non-diagnostic sample occurred in 19.1% compared with only 4.6% of 153 core biopsy procedures. Sensitivity and accuracy (only calculated on the basis of diagnostic samples) were 89.2% and 93.4% for aspiration vs 93.6% and 95.2% for core biopsy, with aspiration being an independent risk factor for diagnostic failure (OR=3.19, p=0.001).

Interpretation of CT-guided biopsy results

Whilst there is clear heterogeneity in the studies considered together in table 13, the pooled data gives an overall assessment

of the performance of CT-guided biopsy in reported clinical practice. Overall sensitivity is 90.7% (95% CI 88.8% to 92.4%), specificity 93.9% (95% CI 91.1% to 96.0%), PPV 97.4% (95% CI 96.2% to 98.3%) and NPV 79.9% (95% CI 76.0% to 83.4%). The negative predictive value is of particular importance, as clinicians often have to make a decision about management of a non-malignant biopsy result, mindful of the possibility of a false-negative result.

As with any diagnostic test, the post-test probability of malignancy (after a non-malignant CT biopsy) will depend on the pre-test probability and the negative likelihood ratio (calculated here as 0.10, 95% CI 0.08 to 0.12). The effect of a negative (ie, non-malignant) biopsy on the post-test probability of cancer is shown in figure 10. Where the pre-test probability is high (eg, 90%) there is still approximately a 50% chance of malignancy even after a non-malignant biopsy (exact value 47.0%, 95% CI 41.9% to 51.9%). This has recently been confirmed in the largest retrospective series, where there was a 90% prevalence of malignancy. However, in this series half of the lesions were outside the definition of pulmonary nodules as they were greater than 30 mm. The authors emphasised the importance of considering repeat biopsies as they showed that repeat biopsies usually confirm the diagnosis of malignancy.¹⁹⁹ However, if the pre-test probability of cancer is only 50%, then the chance of malignancy drops to about 10% after a non-malignant biopsy (exact value 9.0%, 95% CI 7.4% to 10.7%).

The impact of CT-guided biopsy findings on clinical decision-making was investigated by Baldwin *et al.*¹⁸⁹ Clinicians were presented with 114 patient scenarios with and without the results of CT-guided biopsy of pulmonary nodules, and asked to specify management. The proportion of successful decisions (against known outcomes) was assessed. Agreement between clinicians on the need for surgery increased with biopsy result information compared with CT findings alone (κ value 0.57 vs 0.44, respectively). The major benefit of knowing the CT-guided biopsy result was a reduction in unnecessary surgery, especially when the clinical perception of pre-test probability of malignancy was intermediate (31–70%).

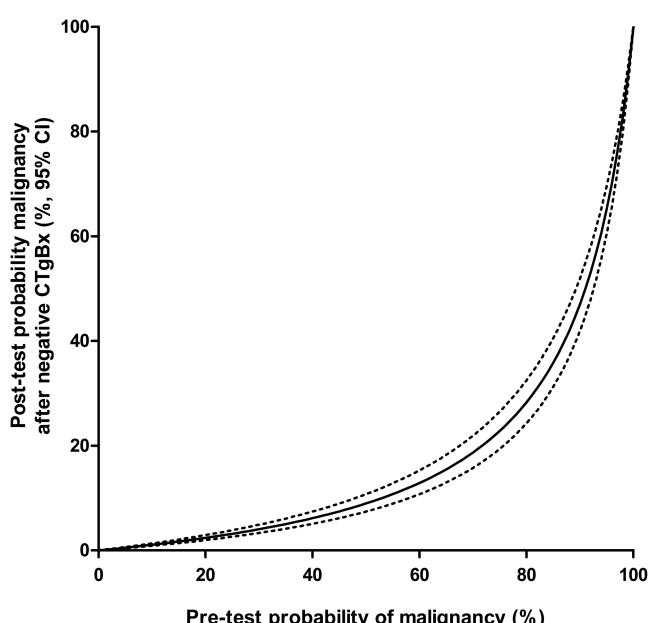


Figure 10 The effect of a negative CT-guided percutaneous biopsy (CTgBx) on the probability of a pulmonary nodule being malignant.

Safety

The most commonly reported complication was pneumothorax. Rates were quoted in 11 studies and varied widely between 6.5% and 69% of cases.^{190 192–198 201 205 206} The frequency of chest drain insertion varied similarly (2.5–32.3%). Factors reported as increasing the risk of pneumothorax were lower FEV₁,^{193 202} the presence of emphysema along the needle tract^{205 207} longer needle path length,²⁰² number of punctures,¹⁹³ upper lobe location of nodule²⁰¹ and core biopsy versus aspiration.¹⁹³

The most comprehensive data about complications after CT-guided biopsy of pulmonary nodules comes from Wiener *et al*²⁰⁸ who conducted a cross-sectional analysis of 15 865 patients undergoing biopsies across four US states. Discharge records were reviewed and the percentage of patients with complications was calculated. Pneumothorax risk was 15.0% (95% CI 14.0% to 16.0%), and 6.6% (95% CI 6.0% to 7.2%) of all biopsies resulted in insertion of a chest drain. Haemorrhage was rare, complicating only 1.0% of cases (95% CI 0.9% to 1.2%), although 17.8% of patients with haemoptysis required a blood transfusion. Smoking patients and those with COPD had a higher risk of complications. Clinically apparent systemic air embolism was also identified in three patients out of 610 (0.49%) and resulted in death in one patient (0.16%).

O'Neill *et al*²⁰⁷ described a non-randomised comparison of patients undergoing CT-guided lung biopsy with a 'rapid needle-out patient rollover time' approach compared with standard technique (n=120 and 81, respectively). Fewer pneumothoraces were found in patients where this technique was used (23% vs 37%, p=0.04) and fewer cases needed chest drain placement (4% vs 15%, p=0.029).

Summary

Although some biomarkers show interesting early results, further studies are required to validate their performance prospectively in clearly defined patient populations before they can be recommended for clinical use. Standard bronchoscopy has a very low yield but this can be increased with the image-guidance techniques described (fluoroscopy, rEBUS and ENB). However, no studies compared performance between these various techniques, and direct comparison between yields described in these series is limited by significant heterogeneity in inclusion criteria, and multiple confounding factors. The reported yields (65–84% for ENB and 46–77% for rEBUS) were less than those for CT-guided percutaneous transthoracic biopsy (pooled 91%), although the latter has a much higher pneumothorax rate (6.6% requiring chest drain in the largest series). The latter may be important for some patients although ENB and to a lesser extent rEBUS may be very time-consuming and are not as widely available as percutaneous biopsy. Figure 10 shows how in a percutaneous biopsy, the pre-test probability of malignancy is altered by a negative biopsy. This may be important when explaining the possible implications to patients.

Evidence statements

- Biomarkers do not offer sufficient accuracy to differentiate malignant from benign nodules. Evidence level 3
- The diagnostic yield of bronchoscopy in the investigation of pulmonary nodules is low. Evidence level 3
- Diagnostic yield of bronchoscopy may be increased by the use of fluoroscopy, electromagnetic navigation and radial endobronchial ultrasound and in the presence of a CT bronchus sign. However, yield remains relatively low for lesions <2 cm in the peripheral third of the lung. Evidence level 3

- The diagnostic yield from CT-guided biopsy of pulmonary nodules decreases with decreasing size of the lesion. **Evidence level 2+**
- Techniques such as multiplanar reconstructed images and C-arm cone-beam CT may increase the yield. **Evidence level 3**
- Pneumothorax is the most common complication of CT-guided biopsies; by far the largest study showed an incidence of 15%, with 6.6% of patients requiring an intercostal drain insertion. Consistent factors that increase the risk are lower FEV₁ and presence of emphysema along the needle tract. **Evidence level 3**
- The post-test probability of malignancy after a negative lung biopsy depends on the pre-test probability. **Evidence level 3**
- Repeating biopsies in patients with nodules with a high probability of malignancy showed a high confirmation rate of malignancy. **Evidence level 3**

Recommendations

- Do not use biomarkers in the assessment of pulmonary nodules. **Grade D**
- Consider bronchoscopy in the evaluation of pulmonary nodules with bronchus sign present on CT. **Grade D**
- Consider augmenting the yield from bronchoscopy using either radial endobronchial ultrasound, fluoroscopy or electromagnetic navigation. **Grade D**
- Offer percutaneous lung biopsy in cases where the result will alter the management plan. **Grade C**
- Consider the use of other imaging techniques such as C-arm cone beam CT and MPR to improve diagnostic accuracy. **Grade D**
- Consider the risk of pneumothorax when deciding on a transthoracic needle biopsy. **Grade C**
- Interpret negative lung biopsies in the context of the pre-test probability of malignancy. **Grade D**
- Consider repeating percutaneous lung biopsies where the probability of malignancy is high. **Grade D**
- Research should be undertaken into the application of new and existing biomarkers in the evaluation of pulmonary nodules. **RR**

SURGICAL EXCISION BIOPSY

Key questions:

1. When should patients undergo excision biopsy?
2. What is the optimal surgical management for nodules confirmed to represent lung cancer (either preoperatively or at intraoperative frozen section pathological analysis)?
3. How do localisation techniques for pulmonary nodules compare?
4. Are there specific recommendations for surgical management of SSNs

Evidence review

Timing and method of excision biopsy of pulmonary nodules

When should excision biopsy be performed?

Excision biopsy of pulmonary nodules is performed in two situations—first, where clinical suspicion of malignancy remains high despite a benign or indeterminate preoperative biopsy, and second, where a nodule is considered of sufficiently high risk for malignancy to merit the option of excision without attempt at preoperative biopsy. Evidence for the performance of non-surgical biopsy is reviewed in the previous section. Two case series specifically comparing strategies of proceeding to excision biopsy with or without preoperative confirmation of malignancy were identified.

Heo *et al*²¹⁰ reviewed 113 patients undergoing lung resection for nodules without biopsy proof of malignancy (of whom 15%

eventually had a benign diagnosis) with 129 patients with nodules with preoperative confirmation of malignancy. Patients without preoperative confirmation of malignancy had shorter waiting times (from admission for investigation to day of surgery), lower total hospital costs and shorter length of stay in hospital. Sihoe *et al*²¹¹ compared outcomes in 206 patients without preoperative confirmation of malignancy (109 with inconclusive preoperative biopsy, 97 without attempt at preoperative biopsy) with 237 patients with preoperative confirmation of malignancy. Benign disease was found in 16 patients without preoperative diagnosis (7.8%). The interval between first presentation and acceptance for surgery was shorter for patients without preoperative diagnosis (although time to operation was not presented). Patients diagnosed with lung cancer at frozen section proceeded to lobectomy, and performing intraoperative frozen section did not increase mean operation time or morbidity compared with patients with preoperation confirmation of malignancy. No other clinical differences were seen between the groups. In both cases series, the decision to attempt preoperative biopsy or to proceed directly to lung resection was made at the clinician's discretion, therefore introducing multiple confounding variables that are poorly identified and not controlled for in the analyses. This limits the usefulness of the comparisons drawn between these patient populations.

The relative performance of thoracoscopic excision wedge biopsy and CT-guided percutaneous lung biopsy were compared in a case series by Mitruka *et al*.²¹² Of 312 patients undergoing CT-guided biopsy, 64% had a malignant diagnosis, 6% had a specific benign diagnosis, and 29% (91) had a non-specific benign diagnosis. Of the last group, 47 went on to excision biopsy and 32 (68%) of these were malignant. Percutaneous biopsy had an accuracy of 86% for malignant disease and 71% for benign disease, whereas specific diagnoses were achieved for 97% of patients undergoing excision biopsy.

The clinical threshold at which a decision is made to surgically excise a pulmonary nodule will affect an institution's (or clinician's) benign resection rate. Benign resection rates in case series of indeterminate pulmonary nodules undergoing surgical excision vary widely from 12%²¹³ to 86%.²¹⁴ Two case series reported changing benign resection rates over times, albeit with differing findings. Thus Rubins and Rubins²¹⁵ described a progressive reduction in the proportion of resected pulmonary nodules (<3 cm in diameter) with an eventual benign diagnosis from 44% in 1981 to 8% in 1994—a change which they relate to the advent of CT imaging, allowing better preoperative assessment of malignant features. Kuo *et al* documented a significant rise in benign resection rate from 8.9% in 1995–2005 to 14.8% in 2006–2009 associated with an increase in VATS wedge resections over the same time period.²¹⁶

No studies have specifically examined what constitutes an optimal or acceptable benign resection rate. Factors that influence the threshold for surgical resection include the risk of morbidity and mortality for excision (particularly if the nodule turns out to be benign) compared with the possibility of stage progression during a period of radiological surveillance. Outcome data from the Society for Cardiothoracic Surgery in Great Britain and Ireland (2010) report an inpatient mortality rate of 0.4% for wedge resection/segmentectomy in 2010 (eight deaths from 1713 cases) (bluebook.scts.org). A review of early mortality following surgical resection for lung cancer from the UK National Lung Cancer Audit between 2004 and 2010 reported a 30-day mortality of 2.1% and a 90-day mortality of 4.2% (35 deaths and 70 deaths, respectively) from 1671 patients undergoing wedge resection or segmentectomy.²¹⁷ No accurate

estimate of the risk of stage progression during surveillance is available. There are only minimal data published describing the natural history of untreated lung cancer, with one case series including larger T2 tumours and patients with N1 nodal disease where the rate of disease progression is likely to be significantly faster than for small pulmonary nodules.²¹⁸

One case series documented the effects of a benign diagnosis at resection on patient management.²¹⁹ A treatment change was reported in response to the biopsy result in 68% of benign cases, with mean total costs of US\$25 515 (£15 870) per patient. The commonest diagnosis was histoplasmosis (23% of all cases) prompting initiation of anti-fungal treatment, and thus these findings may not be generalisable to other geographical areas with lower rates of granulomatous disease.

How should excision biopsy be performed?

Once a decision is made to proceed with surgical excision of a pulmonary nodule, two subsequent choices are the surgical approach (VATS vs thoracotomy) and the extent of the initial lung resection (wedge resection/segmentectomy/lobectomy).

Five case series were identified describing initial VATS wedge resection with intraoperative frozen section pathological analysis for indeterminate pulmonary nodules and summary details are shown in table 14.^{214 220–223} All reported high sensitivity and specificity with a definitive diagnosis achieved in all cases, and low rates of morbidity and mortality (one patient death from 1331 combined cases). The rates of conversion to thoracotomy varied as indicated below, although several of the earlier studies reported routine conversion to thoracotomy whenever primary lung cancer was confirmed.

Two case series of surgical resection of nodules detected by CT screening (from Denmark and Italy) reported lower rates of VATS resection (50% and 17%, respectively) and lower benign resection rates (12% and 22%, respectively).^{213 224} No deaths were reported in the Danish series, but the series from the DANTE trial had a 4% postoperative mortality.

No studies have directly compared a VATS approach with an open approach specifically for resection of indeterminate pulmonary nodules. Cohort studies have compared outcomes for resection of lung cancer cases, although there are no prospective randomised trials. In a propensity matched analysis, Scott *et al*²²⁵ showed that VATS lobectomy for lung cancer was associated with fewer respiratory complications and shorter hospital stay than open surgery with similar operative mortality, although there were significant confounding effects related to surgical operator. Recently, a large propensity matched analysis using the

US SEER-Medicare database has compared thoracoscopic versus open lobectomy.²²⁶ In matched analysis of 1195 patients in each treatment category, those undergoing thoracoscopic resection had significantly lower rates of postoperative pneumonia, atelectasis and sepsis, and lower in-hospital mortality (2.1% vs 3.6%, p=0.029). There were no statistical differences in 3-year overall survival and disease-free survival, although there was a trend towards improved 3-year cancer-specific survival with the thoracoscopic approach (HR=0.74, 95% CI 0.56 to 0.97). The authors comment that this trend might be due to the early mortality benefit of thoracoscopic lobectomy, or unknown confounders not controlled for in the propensity matching.

The extent of lung resection will depend on the location of the nodule, and whether or not there is preoperative pathological confirmation of malignancy. In the absence of preoperative pathology, nodules in the lung periphery are suitable for wedge resection and intraoperative frozen section pathological analysis as described in the above case series. This approach has the obvious advantage of limiting the extent of lung resection for benign disease, thereby avoiding the unnecessary additional mortality and morbidity associated with lobectomy. If intraoperative frozen section confirms lung cancer, then a decision must be taken about proceeding to an anatomical lung resection. The evidence comparing oncological outcomes from lobectomy with those from sublobar resection are considered below.

Wedge resection may not be possible for more centrally situated nodules. Varoli *et al*²²³ describe 94 patients undergoing diagnostic lobectomies for indeterminate pulmonary nodules deemed unsuitable for wedge resection, of which 20% were benign. Schuchert *et al*²²⁷ describe a case series of 490 patients with indeterminate pulmonary nodules or mass lesions undergoing anatomical segmentectomy as a definitive diagnostic and management procedure. The benign resection rate was 14%. Among those patients with a pulmonary nodule found to represent NSCLC, no significant difference in time to recurrence was seen in comparison with an unmatched population of patients undergoing lobectomy for the same indication over the same time period. Only limited patient characteristics are presented for the lobectomy cohort, and no correction is made for confounding variables.

Optimal surgical management for nodules confirmed to represent lung cancer

Lobectomy versus sublobar resection

In the only prospective randomised controlled trial of lobectomy versus sublobar resection for early-stage lung cancer, 276

Table 14 Case series of video-assisted thoracoscopic surgery wedge resections for pulmonary nodules

Author	Number of patients	Diagnostic outcome	Rates of conversion to thoracotomy	Morbidity/mortality
Cardillo <i>et al</i> ²¹⁴	429	Definitive diagnosis in 100% of cases; 86% benign	22% to identify lesion	No mortality Morbidity 4.4%
Murasugi <i>et al</i> ²²⁰	81	Definitive diagnosis in 100% of cases; 45% benign	8% to identify lesion, 26% to facilitate lobectomy for confirmed lung cancer	No mortality No reported morbidity
Mack <i>et al</i> ²²¹	242	Definitive diagnosis in 100% of cases; 52% benign	1% to identify lesion, 12% to facilitate lobectomy for confirmed lung cancer	No mortality Morbidity 3.7%
Jimenez ²²²	209	Definitive diagnosis in 100% of cases; 51% benign	16% conversion to thoracotomy	Mortality 0.5% (1 case) Morbidity 9.6%
Varoliet <i>et al</i> ²²³	370	Definitive diagnosis in 100% of cases; 51% benign	10% to facilitate lobectomy for confirmed lung cancer	No mortality Morbidity 3.3%

patients with T1N0M0 lung cancer were randomised to lobectomy or sublobar resection.²²⁸ Twenty-nine patients had a major protocol violation, and analyses are presented for the remaining 247 eligible patients (lobectomy 125, segmentectomy 82, wedge resection 40). A correction, highlighted by Detterbeck in 2013²²⁹ was published in a letter in 1996 that altered the results but not the conclusion of the original paper. A significantly smaller reduction in FEV₁ after sublobar resection compared with lobectomy was apparent at 6 and 12–18 months. Using the corrected data, there was a trend towards survival benefit in the lobectomy group (5-year actuarial survival, 73% vs 56%; log-rank p=0.062) and a decrease in the rate of recurrence (5-year actuarial rate of 63% vs 78%; p=0.042). The rate of distant recurrences was the same in both groups, but the patients undergoing limited resection had a threefold higher rate of locoregional recurrence (5.4% vs 1.9% per person per year; p=0.009) (although less when analysed on an intention-to-treat basis).

It is now more than 30 years since this study opened, and the lack of requirement for staging CT before surgery illustrates the changes in practice over the intervening period. Nevertheless, this remains the only randomised study examining this issue to date. Several subsequent retrospective cohort studies have looked at the same question, with differing conclusions.

Billmeier *et al*²³⁰ report a population and health system-based sample of patients with stage I or II NSCLC. Outcomes in 524 patients undergoing lobectomy were compared with those for 155 patients undergoing limited resection (120 wedge resection, 35 segmentectomy). Patients undergoing limited resection were more likely to have small tumour size, worse lung function and be uninsured/covered by Medicare. Thirty-day survival was worse in the limited resection group (presumably relating to comorbidities) with no difference seen when adjusted for covariates. After a median follow-up of 55 months, a trend towards improved long-term survival was evident for lobectomy versus limited resection (HR=1.35, 95% CI 0.99 to 1.84, p=0.05). Okami *et al*²³¹ report a single-centre, retrospective cohort study comparing lobectomy (n=672) and sublobar resection (n=146, segmentectomy n=90, wedge resection n=56) for stage IA NSCLC. Sublobar resection was associated with worse 5-year survival (HR=1.83, 95% CI 1.26 to 2.67, p=0.0015) after multivariate analysis. When the cohort was subdivided by age, survival of younger patients (<75 years) was significantly worse after sublobar resection (5-year survival 64.0% vs 90.9% p<0.0001), but there was no significant difference in survival after lobectomy and sublobar resection for those aged ≥75 years (74.3% vs. 67.6%, p=0.92).

Miller *et al*²³² reviewed outcomes of 100 patients undergoing surgical resection for NSCLC ≤1 cm in diameter in a single-centre retrospective cohort study. Seventy-five patients underwent lobectomy/bilobectomy, 12 segmentectomy and 13 wedge resection. Comparing lobectomy with sublobar resection, overall 5-year survival was 71% vs 33% (p=0.03) and cancer-specific survival was 92% vs 47% (p=0.07). Altorki *et al*²³³ reported a retrospective cohort series of patients undergoing lung resection for NSCLC identified as a solid nodule in the International Early Lung Cancer Action Program, comparing patients undergoing lobectomy (n=294) and sublobar resection (n=53, segmentectomy n=16, wedge resection n=37). In both unadjusted and propensity matched analysis, 10-year survival was similar between the two groups, and remained so when analysis was limited to cancers ≤20 mm diameter.

In the original RCT and these four subsequent cohort studies, the inclusion of both non-anatomical wedge resection and

anatomical segmentectomy within the same sublobar group has been questioned, as outcomes from these two procedures may not be equivalent. Sienel *et al*²³⁴ compared outcomes from patients undergoing segmentectomy (n=56) or wedge resection (n=31) for stage IA NSCLC in a single-centre cohort study. Groups were well matched preoperatively. Less locoregional recurrence (16% vs 55%, p=0.001) and fewer cancer-related deaths (29% vs 52%, p=0.016) were seen in the segmentectomy group, and this type of resection showed a prognostic benefit after multivariate analysis (OR=1.16, 95% CI 1.13 to 1.20, p=0.039).

In the previously discussed cohort study by Miller *et al*, a subgroup analysis comparing wedge resection and segmentectomy showed that the former was associated with lower overall survival (27% vs 57%, p=0.03) and more local recurrence (p=0.05). There was no significant difference in either parameter when segmentectomy and lobectomy were compared, although the study might have been underpowered to show such a difference. Furthermore, a similar trend towards increased local recurrence with wedge resection compared with segmentectomy was demonstrated by Ginsberg *et al* (recurrence rates per person per year were 0.086 for wedge resection, 0.044 for segmentectomy and 0.022 for lobectomy).²²⁸ There is therefore limited low-quality evidence to suggest that wedge resection is inferior to segmentectomy in oncological outcomes, and therefore poor outcomes for patients undergoing wedge resection will have contributed to overall outcomes for the combined sublobar resections groups referenced above.^{228 230–232}

Whether segmentectomy is equivalent or inferior to lobectomy is a subject open for debate. In a large retrospective cohort study, Schuchert *et al*²²⁷ reported outcomes for patients with stage IA NSCLC undergoing segmentectomy (n=325) or lobectomy (n=432) (non-randomised). The segmentectomy patients were a subgroup of a larger cohort comprising patients with indeterminate pulmonary nodules and confirmed lung cancers (n=785). No difference in overall or local recurrence was demonstrated (5.2% for lobectomy vs 5.3% for segmentectomy), although data for overall and cancer-specific survival were not reported. Tsutani *et al*²³⁵ reported a case series of 98 patients undergoing segmentectomy and 383 undergoing lobectomy for clinically diagnosed stage IA disease. The lobectomy patients had worse prognostic factors (large tumours, high SUV) so propensity matching analysis was performed. Three-year overall survival was 93.2% in the lobectomy group versus 95.7% in the segmentectomy group. From a retrospective dataset of 392 patients who underwent segmentectomy and 800 patients who underwent lobectomy, Landreneau *et al* selected 312 patients with clinical stage I NSCLC who had anatomical segmentectomy and propensity matched them for preoperative variables with 312 who had undergone lobectomy.²³⁶ No significant differences were seen in locoregional recurrence (5.5% vs 5.1%, respectively, p=1.00), overall recurrence (20.2% vs 16.7%, p=0.30) or 5-year survival (54% vs 60%, p=0.258). Bao *et al*²³⁷ performed a meta-analysis of 22 studies comparing lobectomy and segmentectomy for stage I lung cancer. The authors acknowledged the small retrospective nature of many of the included studies, and significant heterogeneity in the various indications for segmentectomy (poor cardiopulmonary function, elderly patients, small lesions). HRs for overall and cancer-specific survival were determined for all stage I tumours, stage IA tumours, and tumours of ≤2 cm diameter. Segmentectomy was associated with significantly worse survival for stage I tumours (HR=1.2, 95% CI 1.04 to 1.38) and stage IA tumours (HR=1.24, 95% CI 1.08 to 1.42). However, no difference in

survival was seen between these surgical techniques for tumours of ≤ 2 cm (HR=1.05, 95% CI 0.89 to 1.24). Harada *et al* described a retrospective cohort study comparing lung function and other physiological parameters after segmentectomy and lobectomy for early-stage cancer, demonstrating better preserved lung function at 2 and 6 months postoperatively in patients receiving segmentectomy, although no effect was seen on anaerobic threshold.²³⁸

Nodal dissection

One case series assessed predictive factors for nodal involvement in clinical stage I lung cancers identified through CT screening or in a control population.²³⁹ Of 71 cases where the primary tumour was ≤ 10 mm (48 identified through CT screening, 23 in a control population), there were no cases of nodal metastases. The authors suggest that in certain early-stage lung cancers (tumour size ≤ 10 mm or SUVmax <2.0) nodal dissection is not required. These findings need replicating in other studies before this can be routinely recommended.

Localisation techniques for pulmonary nodules

If limited resection is planned, nodules that are either of small size, located deep to the visceral pleura, or of ground-glass morphology may be difficult to locate at thoracoscopic surgery. A number of techniques have been developed to facilitate localisation of these nodules. Some techniques involve preoperative marking of nodules and include CT-guided hookwire/needle/microcoil insertion, Lipiodol injection (lipid-soluble contrast medium with subsequent intraoperative fluoroscopy), methylene blue injection (to identify the overlying visceral pleura to guide resection) or radio-tracer injection (using ^{99m}Tc macro-aggregated albumin with subsequent use of intraoperative gamma probe). An alternative approach has been to use intraoperative ultrasonography to identify the nodule in a collapsed lung during single lung ventilation.

Considering only reports with 50 or more patients, seven case series were identified for CT-guided wire localisation or equivalent,^{240–246} three for Lipiodol marking,^{247–249} one for methylene blue injection,²⁵⁰ two for radio-tracer injection^{251 252} and one for transthoracic ultrasonography.²⁵³ One small randomised trial comparing hookwire and radiotracer was identified.²⁵⁴ A summary of these reports is shown in table 15.

The inclusion criteria whereby localisation was deemed necessary varied between case studies. Some studies stipulated a maximum size of nodule (usually 10 mm but 25 mm in one study), or distance from visceral pleura (range 5–15 mm). Some studies included SSNs, whereas others left requirement for localisation to the discretion of the surgeon. The outcome measures varied also, with some reporting successful localisation, whereas others required thoracoscopic resection for success. Success rates according to these disparate criteria range from 84% to 100%. Accepting the limitations of comparison between these series, no one technique appeared more efficacious than any other.

Thirteen of the 14 studies of preoperative localisation reported complications. The remaining study did not discuss complications at all.²⁴² Pneumothorax was reported in all 13 series, with rates of 4–49.1%, although most of these were asymptomatic and did not require treatment. Five studies quoted the rate of pneumothorax requiring chest drain (1.2–6%), and pulmonary haemorrhage (7–29.8%). Pain was reported in two series (7, 11%) and dislodgement of wire/coil in four series (1.8–7.5%). One patient (0.6%) undergoing Lipiodol injection developed a haemopneumothorax requiring immediate operation.²⁴⁷ The one report of intraoperative ultrasound localisation

described no complications.²⁵³ Ultrasound successfully localised 94% of nodules, but this was more difficult when the surrounding lung was emphysematous.

Gonfianti *et al*²⁵⁴ reported a small randomised trial of hook-wire versus radiotracer localisation for resection of nodules <2 cm in diameter (n=25 in each arm). The hookwire technique successfully located 84% of nodules compared with 96% with radiolabelling. Twenty-four per cent of patients in the hookwire group developed a pneumothorax compared with 4% in the radiolabelling group (none needed insertion of chest drain). No specific details were given of the randomisation process. No significant differences were reported between the two groups, reflecting the small sample size.

Surgical management of SSNs

Six case series (all from Japan) were identified specifically reporting outcomes for patients with SSNs undergoing surgical resection.^{256–261} The studies differed in their inclusion criteria, with some reporting outcomes for a combined sub-solid cohort (pGGNs and PSNs), other reports subdividing these two populations or reporting outcomes according to the ratio between consolidation and solid tumour, and other studies considering only small nodules (<15 or <20 mm). The surgical management differed also, with some case series reporting outcomes for lobectomy versus sublobar resection, whereas others compared segmentectomy and wedge resection.

The consistent finding between all case series was excellent long-term prognosis from sublobar resection with low rates of local recurrence. Thus Tsutani *et al*²⁵⁸ reported 3-year overall survival of 98.7% and 98.2% for ground-glass opacity dominant tumours (>50% ground-glass component) undergoing wedge resection (n=93) or segmentectomy (n=56), respectively. Three-year recurrence-free survival was 98.1% and 96.7%, respectively. Iwata *et al*²⁵⁹ described a case series of patients undergoing segmentectomy for NSCLC, which included 38 patients with ground-glass opacity dominant tumours (>50% ground-glass component), none of whom died in the follow-up period (mean follow-up 34.6 months). Yano *et al*²⁶¹ described a case series of 810 patients with stage IA lung cancer with a consolidation/tumour ratio <0.25 , reporting 5-year overall survival of 96.7% and disease-free survival of 96.5%.

Summary

Lobectomy appears to be associated with improved outcomes compared with sublobar resection in one RCT and three retrospective cohort studies of early-stage lung cancer, with one cohort study, part of a screening programme, showing equivalence. Anatomical segmentectomy was found to be oncologically equivalent to lobectomy in one retrospective cohort study and two retrospective propensity matched analyses. In a meta-analysis of observational studies, segmentectomy had worse survival for stage I and stage IA tumours, but equivalent survival for tumours ≤ 2 cm in diameter. One cohort study and two subgroup analyses have suggested worse outcome for wedge resection than for segmentectomy. Further prospective, randomised evidence would clarify the relative oncological performance of anatomical segmentectomy and lobectomy.

Localisation techniques seem to be a necessary aid for resection of smaller nodules and no one technique was identified as better than the others.

There is very limited evidence to suggest nodal dissection may not be necessary for nodules <10 mm, or for PSNs with a solid component <10 mm.

Table 15 Case series reporting localisation techniques for surgical resection of pulmonary nodules

Authors	Localisation technique	Patient population	Efficacy	Complications
Dendo <i>et al</i> ²⁴⁰	CT-guided hookwire	150 Patients undergoing VATS resection of 168 nodules	97.6% Hookwire placed successfully	32.1% Pneumothorax (chest tube in 1.2%) 14.9% Pulmonary haemorrhage
Ciriaco <i>et al</i> ²⁴¹	CT-guided hookwire	53 Patients undergoing VATS nodule resection	92.5% Hookwire remained in situ facilitating VATS in 58%.	7.5% Pneumothorax
Saito <i>et al</i> ²⁴²	CT-guided hookwire	61 Patients undergoing VATS nodule resection	85% Hookwire facilitated VATS	None reported
Miyoshi <i>et al</i> ²⁴³	CT-guided hookwire	108 Patients undergoing VATS nodule resection	93.6% Successful resection 4% Nodule not in resection specimen, 2.4% Hookwire left in situ	3.7% of patients, chest drain for pneumothorax
Yoshida <i>et al</i> ²⁴⁴	CT-guided hookwire	57 Patients undergoing VATS nodule resection	One hookwire dislodged by time of surgery. Successful surgery for all cases	49.1% Pneumothorax (no chest drain) 29.8% Pulmonary haemorrhage 7% Pain
Koyama <i>et al</i> ²⁴⁶	CT-guided point marker system	52 Patients undergoing VATS nodule resection	Successful placement in 98% cases (one dislodged) and resection	19% Asymptomatic pneumothorax 10% Pulmonary haemorrhage
Mayo <i>et al</i> ²⁴⁵	CT-guided microcoil wire	69 Patients undergoing VATS resection of 75 nodules	Successful placement in all cases, but dislodged in 3%. 97% of nodules removed	3% Pneumothorax requiring drain 1% Asymptomatic haemothorax
Watanabe <i>et al</i> ²⁴⁷	Lipiodol marking	150 Patients undergoing VATS nodule resection	All nodules successfully resected	11% Pain requiring analgesia 17% Pneumothorax (6% drain) 0.6% Haemopneumothorax (emergency operation)
Kawanaka <i>et al</i> ²⁴⁸	Lipiodol marking	65 Patients undergoing VATS resection of 107 nodules	All nodules successfully marked and resected	31% Pneumothorax (5% drain) 15% Pulmonary haemorrhage
Kim <i>et al</i> ²⁴⁹	Lipiodol marking	67 patients undergoing VATS resection of 68 nodules	Marking successful in 98%	29% Pneumothorax 7% Pulmonary haemorrhage
Vandoni <i>et al</i> ²⁵⁰	Methylene blue marking	51 Patients undergoing VATS resection of 54 nodules	Successful thoracoscopic resection in 91% of patients	25.4% Pneumothorax (no drain)
Grogan <i>et al</i> ²⁵⁵	Radiotracer injection	81 Patients undergoing VATS nodule resection	Successful localisation and excision in 95.1% of cases	10% Pneumothorax with drain
Ambrogi <i>et al</i> ²⁵²	Radiotracer injection	211 Patients undergoing VATS nodule resection	Successful localisation and resection in 99% of cases	10.4% Pneumothorax no drain
Mattioli <i>et al</i> ²⁵³	Transthoracic ultrasound	54 Patients undergoing VATS resection of 65 nodules	Successful identification of 15/16 non-visible or palpable nodules (94%)	None
Gonfiotti <i>et al</i> ²⁵⁴	Hookwire vs radiotracer	50 Patients randomised to each procedure for VATS resection	Successful localisation: 84% hookwire 96% for radiotracer (not significant)	24% Pneumothorax no drain hookwire 4% Pneumothorax radiotracer. 4% (n=1) Hookwire displacement

VATS, video-assisted thoracoscopic surgery.

The evidence comparing lobar and sublobar resection in SSNs was limited to case series, but the excellent survival and low rates of recurrence from sublobar resections in these series suggest that there may be little to be gained by extending to a lobectomy. Unfortunately, there was inconsistency in the inclusion criteria reported relating to the cut-off point or inclusion of PSNs (eg, >50% ground-glass component vs consolidation/tumour ratio <0.25). Therefore the recommendation for sublobar resection can only be confidently made for pGGNs. In the absence of specific evidence for PSNs with consistent definitions, these should probably be surgically managed in the same way as solid nodules.

From the limited evidence available, the rate of lymph node metastases is low and related to size of the solid component in PSNs. The rate in pGGNs is negligible (see section Management of SSNs, sub-section lymph node metastases).

Evidence statements

- ▶ VATS wedge resection with intraoperative frozen section has a high diagnostic sensitivity and specificity and generally low complication/mortality rates. **Evidence level 3**
- ▶ Case series dealing with the problem of whether to proceed to surgical resection without preoperative biopsy are limited by confounding factors. **Evidence level 3**
- ▶ Benign resection rates vary considerably between published case series. **Evidence level 3**
- ▶ Excision biopsy of benign lesions has been shown to lead to change in treatment. **Evidence level 3**
- ▶ Lobectomy for early-stage lung cancer was associated with reduced locoregional recurrence and probable improved survival compared with combined results for wedge resection and segmentectomy, in a randomised controlled trial. Patients were not diagnosed or staged contemporarily. **Evidence level 2+**

- ▶ Anatomical segmentectomy is associated with reduced locoregional recurrence and possibly improved survival compared with non-anatomical wedge resection for early-stage lung cancer. **Evidence level 2+**
- ▶ There is emerging evidence to demonstrate oncological equivalence of segmentectomy and lobectomy for tumours ≤2 cm in diameter. **Evidence level 2+**
- ▶ There is no evidence to suggest superiority of any particular localisation technique for impalpable nodules, and no consistent criteria for when these should be used. Complications rates in some case series are high, although mostly relate to asymptomatic pneumothorax or pulmonary haemorrhage not requiring specific treatment. **Evidence level 3**
- ▶ Despite heterogeneity in inclusion criteria and details of surgical management, case series of SSNs undergoing predominantly sublobar resection report very good long-term prognosis. **Evidence level 3**

Recommendations

- ▶ Surgical resection of pulmonary nodules should preferentially be by VATS rather than by an open approach. **Grade C**
- ▶ Offer lobectomy (to patients fit enough to undergo the procedure) as definitive management of a pulmonary nodule confirmed as lung cancer preoperatively or after wedge resection and intraoperative frozen section analysis during the same anaesthetic procedure. **Grade C**
- ▶ Consider anatomical segmentectomy where preservation of functioning lung tissue may reduce the operative risk and improve physiological outcome. **Grade D**
- ▶ Consider a diagnostic anatomical segmentectomy for nodules <2 cm in diameter without nodal disease when there has

been no pathological confirmation and frozen section is not possible. **Grade D**

- ▶ Use localisation techniques, depending on local availability and expertise, to facilitate limited resection of pulmonary nodules. **Grade D**
- ▶ Consider sublobar resection for pGGNs deemed to require surgical resection owing to the excellent long-term prognosis and low risk of local relapse. **Grade D**
- ▶ Prospective trials should compare complications and oncological outcomes from lobectomy versus anatomic segmentectomy in appropriately selected patients. **RR**

NON-SURGICAL TREATMENT WITHOUT PATHOLOGICAL CONFIRMATION OF MALIGNANCY

Key question: When should patients undergo non-surgical treatment without pathological confirmation of malignancy, what treatment modalities are appropriate and what are the harms?

The clinical and radiological factors that predict the likelihood of a pulmonary nodule being malignant are considered elsewhere in this guideline. The decision to refer a patient with a pulmonary nodule for biopsy (CT-guided, bronchoscopic or excision) reflects the pre-test likelihood of malignancy in addition to the potential risks associated with the biopsy techniques and patient preference. In some situations, patients with pulmonary nodules are referred for non-surgical treatments for presumed malignancy in the absence of pathological confirmation, either owing to clinical factors which preclude biopsy (such as severe emphysema), a previously inconclusive biopsy or patient choice. Evidence for when patients should undergo such treatments without pathological confirmation of malignancy was reviewed.

Evidence review

Outcome of patients treated without pathological confirmation
Four retrospective cohort studies specifically compared outcomes in patients with clinically diagnosed lung cancer (CDLC) versus patients with pathologically proven NSCLC.^{262–265} Summary details of the studies are shown in table 16. In all four studies, a clinical diagnosis of lung cancer was made on the basis of clinical characteristics, CT findings (including progressive enlargement) and FDG avidity on PET-CT scan, and three studies explicitly recorded the decision being made by multidisciplinary team consensus.^{262–264}

Takeda *et al*²⁶² reported similar 3-year local control, progression-free survival, cause-specific survival and overall survival rates between CDLC and pathologically proven NSCLC, suggesting that few benign lesions were likely to have been included in the CDLC group. Patients with CDLC did not undergo histological confirmation because of negative biopsy results, increased risk of biopsy or patient choice. No quantitative model was used to define the CDLC group, limiting direct comparison with other studies. Verstegen *et al*²⁶³ reported a retrospective analysis from a prospectively collected institutional database for patients undergoing stereotactic ablative body radiotherapy (SABR) for proven or suspected stage I NSCLC. Outcomes (shown in table 16) were similar between the two groups. No quantitative prediction model was prospectively used to define the CDLC population, but retrospective use of prediction models from Swensen *et al*⁶⁴ and Herder *et al*⁵⁵ indicated a mean probability of malignancy of 92.5% (95% CI 91.8% to 93.3%) in the CDLC group and 94.8% (95% CI 94.2% to 95.4%) in the NSCLC group. Potential confounders included lower FEV₁ and a higher proportion of T1 tumours in

Table 16 Case series comparing outcomes in clinically diagnosed versus pathologically proven non-small cell lung cancer (NSCLC) treated with Stereotactic Ablative Body Radiotherapy

Author	Number of patients	Follow-up period	Outcome	Potential confounding factors
Takeda <i>et al</i> ²⁶²	58 CDLC vs 115 pathologically proven NSCLC	20.2 Months CDLC (range 6–59) vs 21.2 months NSCLC (range 6–64)	3 Year local control 80% vs 87% (p=0.73) and OS 54% vs 57% (p=0.48)	Fewer operable tumours in CDLC group
Verstegen <i>et al</i> ²⁶³	382 CDLC vs 209 pathologically proven NSCLC	Not supplied	3 Year local control 91% vs 90% (p=0.98) and OS 54% vs 55% (p=0.99)	Lower FEV ₁ and smaller tumour size in CDLC group
Haidar <i>et al</i> ²⁶⁴	23 CDLC vs 32 pathologically proven NSCLC	24.2 Months CDLC (range 2–65) vs 25.8 months NSCLC (range 4–53)	Local control at last follow-up 91% vs 94% (p=NS) and actuarial 2 year OS 65% vs 64% (p=NS)	Smaller tumour size in CDLC group
Stephans <i>et al</i> ²⁶⁵	33 CDLC vs 61 pathologically proven NSCLC	15.3 Months (range 2–48) for whole cohort	No significant difference in OS (p=0.37)—actual rates not supplied	Probably multiple, but patient characteristics not reported by CDLC/NSCLC

CDLC, clinically diagnosed lung cancer; FEV₁, forced expiratory volume in one second; NSCLC, non-small cell lung cancer; OS, overall survival.

the CDLC group (although subgroup analysis was performed by T stage showing no differences in outcome). Additionally, the high proportion of patients with other previous malignancy (34%) raised the possibility that some presumed primary lung cancers were instead metastatic recurrence. A third retrospective cohort by Haidar *et al*²⁶⁴ reported outcomes for 55 patients undergoing SABR for early-stage lung cancer. The groups were well matched according to the limited clinical information supplied, and over a mean follow-up of 24 months, local control, actuarial 1- and 2-year survival and toxicities did not differ between the two groups. Finally, a retrospective cohort study by Stephans *et al*²⁶⁵ was identified which compared outcomes after two different SABR protocols for patients with stage I NSCLC. As a secondary analysis, outcomes were compared between clinically and pathologically diagnosed lung cancers, with no significant difference shown in overall survival (p=0.37). Patient characteristics for the NSCLC and CDLC groups were not reported, thereby limiting the ability to identify and assess possible confounding variables.

Of the four studies considered, three were explicit about potential confounding variables (and in Verstegen *et al*, attempted to minimise one confounding factor). All four studies were consistent in reporting similar outcomes between pathologically confirmed and CDLC treated with SABR, thereby tending to support the accuracy of clinically diagnosed cases when made by a multidisciplinary assessment of clinical and radiological criteria.

A recent study developed a decision tree and Markov model comparing the relative merits of surveillance, a PET-CT scan directed SABR strategy without histological confirmation and a PET-CT scan–biopsy–SABR strategy. The authors concluded that when there are concerns about biopsy-related morbidity, a PET scan–SABR policy is warranted when the pre-test probability of malignancy in pulmonary nodules exceeds 85%.¹⁶⁵ However, the estimated complication rate might have been below that expected in people with comorbidities sufficient to make percutaneous biopsy a concern.

Treatment modalities

Publications relating to non-surgical treatment modalities for pulmonary nodules largely comprised case series and poor-quality retrospective cohort studies for patient populations with presumed or pathologically proved malignancy. The majority of studies considered RFA (n=25 studies)^{266–290} and SABR (n=14)^{262 265 291–302}. Other publications reported outcomes

from conventional radiotherapy (n=3),^{281 297 303} percutaneous cryotherapy (n=1),²⁷⁶ microwave ablation (n=2)^{304 305} inhaled corticosteroids (n=2)^{306 307} and antibiotics (n=1).³⁰⁸

Comparison of outcomes between the case series and cohort studies reviewed was severely limited by a number of problems. First, the reviewed studies considered heterogeneous populations, with some reporting outcomes from early-stage lung cancer only, the majority of reports considering a mixed population of lung cancer and metastases from other solid tumours, and two series considering metastases alone. Second, for case series of pulmonary metastases, there was significant variability in the tissue types considered and the number of metastatic lesions treated. Third, there was variability between studies in the proportion of patients with pathologically proven malignancy (lung cancer or other metastatic disease) and those where malignancy was presumed on the basis of clinical and radiological criteria. Fourth, where patients were treated for presumed malignancy without pathological confirmation, the criteria on which these presumed diagnoses were made were often not explicitly defined, and in the reports where they were defined often varied between cases series. Fifth, patients in some case series received systemic treatment together with local ablative treatment, thus confounding comparison of overall survival. Sixth, some series reported repeated treatments with ablative therapy after disease progression. Finally, the length of follow-up and the outcome parameters reported (which included overall survival, progression-free survival and disease-specific survival) varied between studies. Overall median survival was the most frequently reported parameter. For patients treated for presumed or proven lung cancer, overall median survival after RFA varied between 21 and 44 months, and after stereotactic radiotherapy varied between 24 and 54 months. However for the reasons described above direct comparison between these quoted figures is not appropriate.

While most studies reported outcomes from just one treatment modality, one multicentre and four single-centre retrospective cohort studies compared different treatment modalities for patients with pulmonary nodules presumed or pathologically proved to be early-stage NSCLC.

Verstegen *et al*³⁰⁹ performed a retrospective cohort analysis of patients treated for stage I-II NSCLC treated with VATS in six hospitals or SABR at a central hospital. Sixty-four cases of each (from 86 VATS and 527 SABR patients) were selected for analysis by investigators who were blinded to the outcome using a

propensity score-matched analysis to reduce bias and confounding by matching on multiple variables. This excluded patients with severe COPD (GOLD score 4), previous or synchronous lung malignancy. Outcomes were analysed on an intention-to-treat basis with cases with an eventual benign diagnosis after VATS included. There was no difference in 3-year overall survival and freedom from progression rate. Local/regional control appeared to be better in the SABR group ($p=0.037$) and treatment-related toxicity appeared to be less in the SABR group. Shorter median follow-up in the VATS arm (16 vs 32 months) and operator experience with the VATS technique are both possible confounding factors.

Hsie *et al*²⁸¹ retrospectively compared outcomes in 96 patients with pathologically confirmed stage I NSCLC not suitable for standard surgical resection (lobectomy/pneumonectomy) and treated with either limited surgical resection, RFA or conventional radical radiotherapy. Patients were assigned to treatment groups by clinician preference and the cohorts were not well matched. Significant confounding factors were worse performance status, lower FEV₁ and greater use of long-term oxygen treatment in the radiotherapy group. Three-year survival was 63% for limited resection and 55% for radiotherapy (no quoted figure for RFA owing to small patient numbers), leading the authors to conclude that survival is reasonable for patients not suitable for standard surgical resection.

Crabtree *et al*²⁹⁴ retrospectively compared outcomes from 538 patients with stage I NSCLC treated with surgery or SABR in a single-centre study. Treatments were assigned by clinical preference and major confounders were differences between the cohorts in age, comorbidity, pulmonary function tests and the proportion of patients with pathological confirmation of malignancy (100% vs 80% for surgery vs SABR). Three-year overall survival was 68% and 32% for patients receiving surgery and SABR, respectively. Propensity analysis matching 57 high-risk surgical patients with 57 patients undergoing SABR showed no significant difference in disease-free survival (77% vs 86%) or overall survival (54% vs 38%) at 3 years.

Widder *et al*²⁹⁷ reported survival and quality of life data for two cohorts of patients treated with radiotherapy for inoperable stage I lung cancer. Twenty-seven patients treated with 3D conformal radiotherapy (CR) between 1994 and 1996 were compared with 202 patients treated with SABR between 2006 and 2009. Confounding factors included a lack of PET-CT imaging for the CR radiotherapy group, differences in rates of pathological confirmation (74% for the CR group vs 29% for the SABR group), and differences in performance status and age. Two-year overall survival was significantly better in the SABR than CR group (72% vs 48%, HR=2.6, 95% CI 1.5 to 4.8, $p<0.01$).

McGarry *et al*³⁰³ retrospectively compared outcomes for 128 patients with stage I/Ia NSCLC treated with surgery, radiotherapy (curative or palliative) and observation only, reporting median survival times of 46.2 months, 19.9 months and 14.2 months, respectively. The study demonstrates poor outcome from observation only for lung cancer, but the substantial confounding factors prevent meaningful comparison among groups. These confounders were not explicitly described in the report and no attempt was made to correct for them.

All five cohort studies are subject to selection bias and confounders. However, Verstegen *et al* made substantial efforts to try to compensate for these factors. Propensity score matching was used to reduce bias by matching patients according to numerous baseline variables, and analysis was performed on an intention-to-treat basis of clinical diagnosis, irrespective of the

final histological result. The four single-centre cohort studies^{281 294 297 303} have significant selection bias and major confounding factors, which preclude direct comparison between outcomes in the groups studied.

Two RCTs assessed the effect of inhaled corticosteroids on nodule size in patients with persistent indeterminate pulmonary nodules. Veronesi *et al*³⁰⁶ randomised 202 patients to inhaled budesonide 800 µg twice a day or placebo for 12 months and showed no effect on pre-existing nodule size or the development of new nodules. van der Berg *et al*³⁰⁷ randomised patients with evidence of bronchial squamous metaplasia/dysplasia and either >20 pack-year history of smoking or previous history of lung or head and neck cancer to inhaled fluticasone. Again no effect was seen on either previously detected nodules or the development of new nodules.

Khokhar *et al*³⁰⁸ retrospectively reviewed patients with pulmonary nodules to see whether antibiotic prescription was associated with a change in CT appearance of nodules on a follow-up scan. No significant difference was seen in nodule appearance between 34 patients who received antibiotics and 109 patients who did not. The authors concluded that their data did not support routine use of antibiotics in patients found to have pulmonary nodules on CT scan. Significant selection bias and confounding variables were present.

Harms of treatments

The potential harms of treatments for presumed or proven malignant nodules have been reported in a number of case series. There was wide variability between studies in the frequency of reported complications, which related in part to the different criteria used to define/grade these complications. For example, some case series reported any haemoptysis following RFA treatment, whereas others reported only significant or major bleeding without specifically defining the relevant criteria. Similarly, pneumothoraces were classed as minor, major or sometimes only reported if intercostal drain insertion was required.

The frequency of complications in case series of patients treated with RFA^{266 267 271–273 275–278 280 281 283–287 289 290 304 305} was as follows: pneumothorax was the most commonly reported complication with rates varying from 9% to 54% in 19 case series. Other reported complications after RFA were bleeding (0.7–26%), pleural effusion (1.8–19%), pneumonia (1.8–12%), pleuritis (0.6–4.3%), lung abscess (0.3–3.1%), haemothorax (3.0%), severe pain (2%), bronchopleural fistula (1.5–1.8%), acute respiratory distress syndrome (1.5%) and pericardial tamponade (0.9%). Procedure-related mortality varied from 0% to 0.9% in seven case series, although one series reported a 30-day procedure-related mortality of 2.6%.²⁸⁹

Currently, in the UK, lung SABR is used only for peripheral lesions, and treatment is generally very well tolerated provided that organ at risk tolerances are adhered to. The main acute toxicities are fatigue, chest pain, skin erythema and cough, but these side effects are almost always mild (<grade 3) and self-limiting. Severe radiation pneumonitis—that is, grade 3 (requiring oxygen, severe symptoms±limiting self-care), is uncommon (range 1–2.8%) and grade 2 (symptomatic requiring medical intervention±limiting activities of daily living) or less ranges from 1% to 11%.^{310–312} The incidence of radiation pneumonitis does not appear to be higher in patients with poor pulmonary function.^{313–316} There is no strong evidence for absolute dose constraints, though in one large institutional series the risk of pneumonitis was higher in tumours with a large radiotherapy volume (internal target volume >145 ml) and when the

contralateral lung receives a mean dose of >3.6 Gy.³¹⁷ Guckenberger *et al*³¹⁸ observed a dose relationship between ipsilateral lung dose and the development of radiation pneumonitis. Patients developing pneumonitis had an ipsilateral mean lung dose of 12.5 ± 4.3 Gy compared with a mean dose of 9.9 ± 5.8 Gy in unaffected patients. Ideally, the mean lung doses should be low in SABR and these figures are only a guide as they are based on relatively small numbers of patients and events. To minimise the risk of pneumonitis the UK SABR consortium has produced strict planning guidelines, which include limits for lung doses. Rib fracture and chest wall pain are the main late side effects with varying incidence depending on the dose fractionation scheme used. In one large single institutional series of >500 patients using a risk adaptive dose schedule with reduced doses for lesions close to or involving the chest wall, severe (grade 3 or higher) chest wall toxicity was rare $\leq 2\%$ and grade 2 or less toxicity was $<10\%$.²⁹¹

Currently, SABR is not routinely used for lesions close to central mediastinal structures. This practice is based on a phase II study by Timmerman *et al* which showed that for central lesions treated with SABR the rates of severe toxicity (grade 3 or higher) were 46% at 2 years compared with 17% for peripheral lesions. Toxicities included decline in pulmonary function tests, pneumonias, pleural effusions, apnoea, skin reaction and treatment-related deaths.²⁹⁵ A more recent systematic review of SABR for central lesions showed lower rates of toxicity³¹⁹ and a European Organisation for Research and Treatment of Cancer (EORTC) study started in November 2014 (trial reference EORTC-222113-08113-ROG-LCG) to evaluate SABR for central lesions.

Summary

Four retrospective case series provide evidence that for SABR, outcomes are similar for people with nodules that are not pathologically confirmed as malignant and for those with prior confirmation. Most evidence found was for SABR and RFA, although the variability in case definition, pathological confirmation, proportion of primary and secondary cancer, selection criteria and concomitant treatment made comparison inappropriate. One study used propensity score matching in a comparison of SABR and VATS for stage I-II lung cancer and showed a similar 3-year outcome. Non-surgical treatments show marked variation in the frequency of harms, something that is likely to be strongly influenced by case selection and the technique employed.

Evidence statements

- Where biopsy of a pulmonary nodule is either non-diagnostic or not possible, patients diagnosed with clinical lung cancer by a multidisciplinary assessment on the basis of clinical and radiological criteria appear to have similar outcomes to patients with pathological confirmation of malignancy following SABR. **Evidence level 2+**
- Inhaled corticosteroids have no effect on pre-existing nodule size or on the development of new pulmonary nodules on CT scan. **Evidence level 1+**
- There is no evidence to support routine use of antibiotics in the management of indeterminate pulmonary nodules. **Evidence level 3**
- Treatment of central lesions with SABR has been associated with higher rates of toxicity than with SABR for peripheral lesions. This may be alleviated by using risk-adapted dose schedules and is the subject of ongoing clinical trials. **Evidence level 3**
- In the treatment of pulmonary nodules, proved or presumed to be malignant, SABR and RFA have low rates of acute

mortality. Reported rates of morbidity are highly variable. **Evidence level 3**

Recommendations

- For people who are unfit for surgery who have pulmonary nodule(s) with a high probability of malignancy, where biopsy is non-diagnostic or not possible, consider treatment with SABR or RFA, if technically suitable. **Grade C**
- For people who are unfit for surgery who have pulmonary nodule(s) with a high probability of malignancy, where biopsy is non-diagnostic or not possible, consider treatment with conventional radical radiotherapy if not suitable for SABR or RFA. **Grade D**
- Do not use inhaled corticosteroids in the management of indeterminate pulmonary nodules. **Grade B**
- Do not use antibiotics in the management of indeterminate pulmonary nodules. **Grade D**
- Consider prospective randomised trials of local treatments for pathologically proved or clinically diagnosed early-stage lung cancer and pulmonary oligometastases. **RR**
- For prospective randomised trials of interventions for pathologically proved or clinically diagnosed early-stage lung cancer include assessment of harms. **RR**

INFORMATION AND SUPPORT

Key question: What are the information and support needs of patients with pulmonary nodules?

Patients who have pulmonary nodules detected by whatever method may be concerned or anxious about the implications for their health. A clear understanding is essential for patients and their carers to make informed choices about the options for management. They may need professional support when interpreting information. The NICE guideline on the management of lung cancer (CG121) made detailed recommendations on the information and support needs of patients, some of which will be applicable to pulmonary nodules, especially those that have a high probability of being malignant. The National Lung Cancer Forum for Nurses has emphasised the key role of the lung clinical nurse specialist in providing information and support to patients and has produced specific guidance for managing patients with lung nodules (available at: <http://www.nlcfn.org.uk>).

Evidence review

The search retrieved four papers on the psychological consequences of finding pulmonary nodules but only three were of sufficient quality to be included in the review. Lemonnier *et al* compared health-related quality of life measures in 171 patients with pulmonary nodules 1–3 cm in diameter with those of the general population with a similar age.³²⁰ They found that patients with pulmonary nodules had worse self-reported health status (as measured by a reduction in score on the Short Form 36 Health Survey of between 11 and 30 points), which was most marked for older people and those who were smokers. Furthermore, patients with malignant nodules had scores that were 5–15 points lower than those with non-malignant nodules. The study did not examine intervention for the lower scores. van den Bergh *et al*,³²¹ in the context of the NELSON study, compared health-related quality of life measures in subjects who had CTs with those who did not and in those within the CT screen group who had nodules detected with those who did not. They found that there was no difference in scores before the screen compared with the second annual screen time-point but that after 1 year there was a transient increase in the impact of event scale in subjects with an indeterminate nodule. This

limited evidence demonstrates in two different settings that the finding of pulmonary nodules does affect quality of life, but appeared to be minimal in the highly organised environment of NELSON where there were clear protocols and detailed patient information. Wiener *et al.*³²² in a qualitative study involving 22 patients with indeterminate pulmonary nodules from Boston USA, found that almost all patients, when first informed about a pulmonary nodule thought that they had cancer. This perception, and the distress caused, was strongly influenced by the information given. Patients were frustrated not to be given adequate information and noted that many healthcare providers did not inform them about cancer risk. The authors set out seven patient-endorsed communication strategies as a suggested guide for communication. This included directly addressing the risk of cancer, ensuring there is a verbal explanation (not just a letter) and avoiding minimising or dismissive language.

Evidence statements

- ▶ The finding of a pulmonary nodule has an adverse impact on quality of life. **Evidence level 2+**
- ▶ Patients commonly assume that the finding of a nodule means that they have cancer. **Evidence level Qualitative**
- ▶ Patients may be frustrated if healthcare providers fail to deal with their concerns about cancer or potential adverse effects of surveillance. **Evidence level Qualitative**
- ▶ Effective communication by the healthcare team can reduce the impact on quality of life after diagnosis of a pulmonary nodule. **Evidence level Qualitative**

Recommendations

- ▶ Offer accurate and understandable information to patients and carers about the probability of malignancy of the pulmonary nodule. **Grade D**
- ▶ Ensure patients have the opportunity to discuss concerns about lung cancer and surveillance regimens. **Grade D**
- ▶ Offer patients the choice of seeing a lung cancer nurse specialist where the probability of malignancy is high or when patients are anxious about the possibility of having lung cancer. **Grade D**
- ▶ Ensure that clear written and verbal information is available on follow-up schedules and the number of repeat CT scans required. **Grade D**
- ▶ Explain the risks and benefits of investigations and treatment. Where appropriate offer a choice of management. **Grade D**
- ▶ Inform patients who remain at high risk of developing malignancy about the warning symptoms of lung cancer at the start of observation and at discharge from follow-up. **Grade D**
- ▶ Emphasise to patients the importance of smoking cessation and offer referral to smoking cessation services. **Grade D**

TECHNICAL ASPECTS OF THE IMAGING OF PULMONARY NODULES

Key question: What are the technical imaging considerations relating to nodule detection and assessment by CXR, CT and PET-CT?

Evidence review

Advances in imaging technology

Imaging technology is improving rapidly and evidence reviewed for the purposes of guideline development often reports on technology that has effectively become out of date, although may still be in use clinically. Thus recommendations have to be interpreted in the light of current technology.

The most significant technological changes over the lifetime of this guideline may be:

1. The introduction of CT scanners using iterative reconstruction that will substantially reduce the effective radiation

dose. Possible consequences are a lowering of the threshold for performing CT scans, thus increasing the number of incidentally detected nodules, and a more permissive approach to follow-up examinations.

2. The increased use of perfusion CT to assess nodule vascularity and perfusion. This may have implications for prognostication, and differentiation between benign and malignant nodules
3. Improved image data reconstruction, such as nodule surface textural analysis. This may aid differentiation of benign from malignant nodules.
4. Changes in PET-CT scanner construction and image processing. This is likely to produce substantial improvements in the accuracy of characterisation of pulmonary nodules. Appendix 2 shows specific likely future developments in PET-CT.
5. The method of reporting positivity in PET-CT may be optimised; methods may include modification of absolute SUV cut-off points according to nodule type. There may be different values for solid and SSNs and nodule size with lower levels for nodules with greater ground-glass components and for smaller nodules.

Method of detection

Extensive publications on the detection of pulmonary nodules using CXR and CT scan are available. These include new techniques to improve detection by CXR, such as subtraction methods and computer-aided detection (CAD), as well as improved detection by CT in comparison with CXR. The latter includes CAD in CT and reconstruction algorithms such as MPR, maximum intensity projection (MIP), and volume rendering (VR). Aside from the reconstruction algorithms none of these techniques are in use in routine clinical practice and remain areas for research. These guidelines focus on nodule characterisation once detected but it is known that nodules are better detected and characterised if a CT scan maximum section thickness of 1.25 mm^{323–325} is used and if they are reported using software reconstruction algorithms including MPR, or MIP or VR review.^{326–337}

Factors influencing the accuracy of measurements

Nodule measurement

Eight studies investigated a variety of technical scanning parameters that affect nodule measurement: section thickness, reconstruction algorithms, scan dose, the use of intravenous contrast, and nodule size and shape. **Table 17** illustrates some of the technical factors and a more detailed review of the studies can be found in appendix 2.

Growth measurement

Growth measurement is dependent on the technical factors shown in **table 17**. Volume measurements have been shown to be more reproducible than manual calliper measurements as reviewed in the section ‘Imaging follow-up’. In addition to these, a number of software packages have achieved high levels of reproducibility in synthetic nodules and are therefore potentially used for assessment of growth. A key factor is the ability of the software to correctly segment the nodule. Volume is calculated using a series of ‘segments’ of the total volume added together and it is important that these accurately reflect the borders of the nodule. A number of algorithms have been shown to do this accurately but reproducibility decreases as the nodule size decreases. As noted above the use of intravenous contrast can increase volume measurement and therefore may alter growth estimates. The influence of the duration of

Table 17 Selected technical factors affecting pulmonary nodule measurement

Study author and year	Technical factor	Effect on nodule measurement
Honda <i>et al</i> (2007) ³³⁸ Nietert <i>et al</i> (2009) ³³⁹ Petrou <i>et al</i> (2007) ³⁴⁰ Sinsuat <i>et al</i> (2011) ³²⁵ Goo <i>et al</i> (2015) ³³⁷	Section thickness	Thin section (0.625, 1.25 mm) more reproducible than 2.5 mm and 5 mm Radiologists more likely to miss nodules <5 mm on 10 mm sections than 2 mm
Honda <i>et al</i> (2007) ³³⁸ Honda <i>et al</i> (2007) ³³⁸ Petkovska <i>et al</i> (2007) ³⁴¹	Reconstruction algorithm Overlapping reconstruction Lung volume	High spatial frequency algorithm and bone algorithm increased volume Non-overlapping increased measured volume Nodule diameter and volume varied non-uniformly (some increased and some decreased with increasing lung volume from RV to TLC)
Honda <i>et al</i> (2007) ³⁴²	Intravenous contrast	Minimal increase in measured volume after contrast

RV, residual volume; TLC, total lung capacity.

follow-up has already been reviewed in the section ‘Imaging follow-up’. A more detailed review is given in appendix 2.

Nodule size, shape and position

Table 18 summarises the important factors that influence the accuracy of measurements at baseline and when measuring growth. As expected, nodules that are smaller or have a more complex shape are more difficult to measure and therefore growth detection is more challenging. This is also the case if they are next to other structures such as blood vessels and the pleura. Similarly, if the nodule is moving it is more difficult to measure. A more detailed description of studies reviewed appear in appendix 2 and the section ‘Imaging follow-up’.

Low-dose CT

Hein *et al*,³⁴⁷ using ultra-low-dose and standard-dose CT scans in 20 patients with 202 nodules with a mean diameter of 11 mm, demonstrated no difference in interscan or interobserver variability in measured nodule volumes, suggesting that low-dose CT scans used to follow up nodules are acceptable and will not result in false changes in nodule volumes. Other studies have confirmed this finding and shown that the use of low-dose CT does not affect nodule detection or volumetric measurement.^{348–350}

Evidence statement

- Nodule detection and characterisation is best achieved using a maximum section thickness of 1.25 mm, contiguous section CT, and use should be made of MPR, or MIP or VR. **Evidence level 2+**
- Different software programmes use different algorithms to segment and calculate nodule volumes, and the measurements from each are not interchangeable. **Evidence level 2+**
- Nodule volume measurement success and accuracy are affected by nodule position (juxtapleural, juxtapacardiac) and the depth of inspiration. **Evidence level 2+**
- The reliability of detection of nodule growth is increased with greater time between scans. **Evidence level 2+**
- The data from different scanners are comparable when volumes are calculated using the same software. **Evidence level 3**

Recommendations

- When CT scans are performed that include the chest, where nodule detection is of potential importance, use a maximum section thickness of 1.25 mm. **Grade C**
- Use low radiation dose CT with a maximum section thickness of 1.25 mm in follow-up imaging. **Grade C**
- Use MIP or VR to improve nodule detection and characterisation. **Grade C**
- Use diameter measurements where volumetry is not possible or where there is clear evidence of marked growth. (Grade D)

- When reporting growth, take into account factors that may reduce accuracy, such as nodule shape and position and interval between scans. **Grade D**
- Ensure a radiologist or radiographer checks that the nodule has been accurately segmented. **Grade D**

Table 18 Patient related factors that may influence accuracy of nodule measurement

Study author and year	Patient or nodule factor	Effect on nodule measurement
Gietema <i>et al</i> (2007) ³⁴³ Korst <i>et al</i> (2011) ⁷⁸ Wang <i>et al</i> (2008) ³⁴⁴	Non-spherical or irregular nodule shape	Less accurate segmentation for volume measurement
Ko <i>et al</i> (2012) ⁷⁹	Juxta pleural position	Less reliable volumetry
Goodman <i>et al</i> (2006) ³⁴⁵	Smaller nodule size	Less reproducible measurements
Kostis <i>et al</i> (2004) ⁸³		
Wang <i>et al</i> (2008) ³⁴⁴	Juxta vascular position	Less reliable volumetry
Boll <i>et al</i> (2004) ³⁴⁶	Cardiac motion	Less reliable volumetry

Summary of research recommendations

- Nodule malignancy risk prediction models should be validated in patients with known extra pulmonary cancer.
- Further analysis of variation in volumetry measurements by different software packages should be undertaken and methods developed for standardisation.
- Further research is needed into the most effective follow-up pathway in low to medium risk patients and for those with pGGNs.
- Further research should be undertaken into the use of PET-CT in the evaluation of pGGNs using lower SUV cut-off values.
- Research should be undertaken into the application of new and existing tumour markers in the evaluation of pulmonary nodules.
- Prospective trials should compare complications and oncological outcomes from lobectomy versus anatomic segmentectomy in appropriately selected patients.
- Prospective randomised trials of local treatments for pathologically proved or clinically diagnosed early-stage lung cancer and pulmonary oligometastases should be considered.
- Prospective randomised trials of interventions for pathologically proved or clinically diagnosed early-stage lung cancer should include assessment of harms.

Conclusion

This guideline is based on an extensive and detailed review of the published literature relating to the management of pulmonary nodules. Until the turn of this century there were relatively few research studies on this subject with most publications being review articles and expert opinion pieces. More recently, there have been many more studies and this is reflected by the fact that half of the articles referenced were published from 2010 onwards and almost a third since 2012. This has enabled evidence-based development of algorithms for the management of pulmonary nodules that should lead to more efficient use of resources and consistent outcomes for patients. The GDG recognised that there remain uncertainties about the merits of longer term follow-up of some pulmonary nodules and have therefore recommended that a record of people with nodules is kept in case new evidence suggests benefit from longer term follow-up, particularly those nodules that may represent more indolent cancers.

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APPENDIX 1: PREDICTION MODELS AND VOLUME DOUBLING TIME (VDT) CALCULATION

Risk prediction calculators and a VDT calculator are available on the BTS website at:

<https://www.brit-thoracic.org.uk/guidelines-and-quality-standards/pulmonary-nodules/>

These risk prediction calculators are provided to assist clinicians in the diagnosis and management of pulmonary nodules—the information provided should be used in conjunction with the BTS guideline for the investigation and management of pulmonary nodules.

Probability of malignancy following CT (Brock model): This calculator estimates the probability that a lung nodule described above will be diagnosed as cancer within a 2–4-year follow-up period.⁴⁶

Probability of malignancy following PET-CT (Herder model): This calculator estimates the probability that a lung nodule described above will be diagnosed as cancer.⁵⁵

DISCLAIMER

The risk prediction calculator tool ('RPCT') functionality made available on the above webpage is provided 'as is' with no warranties whatsoever.

The British Thoracic Society, on its own behalf and on behalf of all of its service providers associated with the RPCT ('BTS') and its licensors, hereby expressly exclude to the fullest extent permitted by law all express, implied, and statutory warranties and conditions including, without limitation, warranties and conditions of merchantability, fitness for any particular purpose, non-infringement of proprietary rights, security, reliability, timeliness and performance.

Users hereby acknowledge and agree that (a) their use of the RPCT is entirely at their own discretion and risk; (b) BTS excludes all liability for any loss or damage arising from such use to the fullest extent permissible by law; (c) the RPCT is for information purposes only, you are not entitled to base any treatment or other medical decision on information obtained from the RPCT and you agree to be solely responsible for, and to indemnify BTS and hold BTS harmless against, any loss or damage arising from any such decision.

Risk prediction calculators for use on a smartphone/tablet may be available in due course.

APPENDIX 2: DETAIL OF TECHNICAL CONSIDERATIONS IN RADIOLOGY

LIKELY CHANGES IN PET-CT TECHNOLOGY

1. Improved detectors used for the PET component (potentially bismuth germinate $\text{Bi}_4\text{Ge}_3\text{O}_{12}$, lutetium oxyorthosilicate doped with cerium $\text{Lu}_2\text{SiO}_5:\text{Ce}$, or solid state).
2. Smaller crystal sizes in non-solid state detectors, providing increased spatial resolution.
3. Solid state detectors, although not currently in use in clinical practice, have the potential advantage of increased spatial and signal timing resolution with improved signal-to-noise ratio.
4. 3D acquisition that means detection is no longer restricted to a single slice but is performed over the whole detector length, resulting in substantially increased sensitivity, but with increased scatter detection.
5. Image processing algorithms. Currently and historically, image reconstruction algorithms have used flight-ordered subsets expectation maximisation (time of flight-OSEM) reconstruction, but new algorithms such as Bayesian penalised likelihood reconstruction algorithms and others

including spatial point-spread correction, appear able to detect smaller nodules and provide more accurate measures of metabolic activity.

6. The use of respiratory gating. Although not widely used, owing to its complexity and time required for set-up, respiratory gating may provide a more accurate assessment of the metabolic activity of small nodules by effectively reducing the effect of partial voluming secondary to respiratory motion.

REVIEW OF SELECTED STUDIES OF TECHNICAL FACTORS IN NODULE MEASUREMENT

Honda *et al*³³⁸ investigated changes in volumetric measurement using different reconstruction parameters in 39 nodules of <20 mm. Variable slice thickness, field of view, reconstruction algorithm and reconstruction intervals were investigated. The nodules ranged from 4 to 16 mm in diameter. High spatial frequency and bone algorithms increased the nodule volumes, as did non-overlapping reconstruction.

Nietert *et al*³³⁹ using a lung phantom assessed the accuracy of automated volumetry on 1624 estimates using section thicknesses of 0.625, 1.25, 2.50 and 5.00 mm. The artificial nodules ranged in diameter from 3.00 to 15.9 mm in average diameter. They simulated growth scenarios of 4–5 mm, 4–6 mm, 4–8 mm, 5–6 mm and 9–10 mm. The CIs around growth and VDT were extremely wide for 2.50 mm and 5.00 mm.

Petrou *et al*³⁴⁰ analysed the effect of different section thicknesses, 1.25 mm, 2.5 mm and 5.00 mm, and reconstruction intervals on volumetry measurements for 75 nodules. Volume variability between the different section thicknesses was correlated with nodule diameter, shape and margin. There was substantial variation on individual nodules, with significant variation for nodules ≤10 mm, and spiculated nodules compared with smooth nodules.

Rampinelli *et al*³⁵¹ assessed the reliability of automated volume calculation on 83 nodules scanned during the same session using two low-dose and two standard-dose CT scans on two separate breath holds. They correlated nodule volume change with diameter, percentage of emphysema, nodule site and morphology. The variation in nodule volume was greatest for low-dose scans ($-38\% \pm 60\%$) compared with standard-dose CT scans ($-27\% \pm 40\%$). No significant differences were obtained for nodule site, diameter, morphology or degree of emphysema. Kim *et al*, in a more recent study found no influence of radiation dose on the accuracy of volume measurement.³⁵²

Sinsuat *et al*³²⁵ analysed the ability of six radiologists to both detect pulmonary nodules and agree a diagnosis on CT sections of 2 mm and 10 mm. Nodules were more likely not to be detected when small (<5 mm) on the thicker sections, and were more likely to be misdiagnosed on the 10 mm sections.

Goo *et al* assessed the effect of various reconstruction parameters and segmentation thresholds on four acrylic spheres of 3.2 mm, 4.8 mm, 6.4 mm and 12.7 mm.³³⁷ Images were reconstructed at section thicknesses of 0.75, 1.0, 2.0, 3.0 and 5.0 mm, and different reconstruction intervals. Nodules were segmented using different segmentation thresholds. The absolute percentage error of volume measurement is lowest using thin sections, with errors progressively increasing with decreasing nodule size.

Honda *et al*³⁴² imaged 60 nodules in 60 patients before and after intravenous contrast, and used both bone and soft tissue reconstruction algorithms. They showed that the measured volumes were greatest using the bone algorithm and after

contrast. The mean difference between the reconstruction algorithms before contrast was 33 mm³ with the median volumes being 817 mm³ and 812 mm³, respectively, and 24 mm³ with the median volumes after contrast being 887 mm³ and 855 mm³, respectively.

Petkovska *et al*³⁴¹ assessed the effect of lung volume on nodule size measured using automated volumetry in 75 indeterminate nodules scanned at total lung capacity and residual volume. Both nodule diameter and volumetry varied non-uniformly between total lung capacity and residual volume, with a 16.8% mean change in absolute volume across all nodules, with no significant difference between nodules <5 mm and ≥5 mm.

REVIEW OF SELECTED STUDIES ON THE TECHNICAL FACTORS INFLUENCING NODULE GROWTH

Yankelevitz *et al*³⁵³ assessed the accuracy of automated volumetric measurements of synthetic nodules, and then nodules in 13 patients, to estimate growth rates. Synthetic spheres were scanned twice as pairs of different sizes, before and after being altered in shape, and then spheres of varying diameters. In 13 patients, nodules with diameters <10 mm, range 3.9–9.3 mm, were scanned twice at different intervals. The software could accurately measure the volumes in the synthetic nodules to within ±3%. Five of the 13 nodules were proved to be malignant and all had doubling times <177 days, with the benign nodules having doubling times of >396 days.

Ashraf *et al*³⁵⁴ assessed the impact of using different segmentation algorithms within the same software to calculate nodule growth. Using 188 nodules >5 mm in diameter from a lung cancer screening study, baseline and follow-up scans were independently read by two readers. Nodules were correctly segmented and measured in 72% of nodules, with 80% of these cases occurring when the same algorithms were chosen. The volumetric measurements were identical in 50% using the same algorithm, with a difference of >25% in 4%. Using different algorithms, 83% of measurements resulted in a difference of >5%.

Das *et al*³⁵⁵ scanned a lung phantom with nodules of different size using scanners from the four main CT vendors (Siemens, GE, Philips, Toshiba); different doses—routine and low dose—and thin and thick collimations were used. Average percentage volume errors (APEs) were calculated and compared. The mean APE for all nodules was 8.4%, and did not differ significantly amongst the scanners.

de Hoop *et al*⁷⁵ evaluated 214 nodules in 20 patients with pulmonary metastases, using six semiautomated volume software packages. Each patient underwent two low-dose CT scans separated by the time it takes to get on and off a CT scanner, to enable zero growth to be simulated. Adequate segmentation was achieved in 71–86% of nodules, with variability in volumetry between 16.4% and 22.3%. Rampinelli *et al*³⁵⁶ assessed the effect of intravenous contrast on volumetric calculation on 35 pulmonary nodules, comparing scans performed without contrast (unenhanced) with scans performed after injected contrast at 30, 60, 120, 180 and 300 s delays. Contrast-enhanced scans resulted in significantly larger volumes than unenhanced scans, with variations in volume of 4–7%.

CHARACTERISTICS OF NODULES THAT MAY INFLUENCE THE ACCURACY OF MEASUREMENT AND GROWTH ESTIMATION

Gietema *et al* assessed 218 nodules in 20 patients.³⁴³ Non-calcified nodules between 15 mm³ and 500 mm³ not abutting the pleura or a vessel were measured on two occasions by

low-dose CT using the standard method for simulating zero growth of scanning the patient after they have got on and off the scanner. They showed that accurate segmentation is more difficult for nodules that are non-spherical and of irregular shape. They also confirmed that the degree of inspiration affects the measured volume, with an increase in inspiratory effort leading to a decrease in lung nodule volume. They suggest that the threshold for determining a genuine increase in nodule volume is 15% for a spherical lesion, and 30% for an irregular nodule.

Ko *et al*⁷⁹ examined the problem of reliability of growth rate detection using semiautomated software. In 123 nodules presumed to be stable in 59 patients followed up over 2.0–8.5 years, in comparison with eight nodules proved to be malignant, they found that longer duration improved the reliability of the volumetric measures, with less reliable volumetry for peripheral and juxtapleural lesions. pGGNs and PSNs were measured as reliably as solid nodules, as were nodules of < or >5 mm.

Korst *et al*⁷⁸ compared the effect on the decision to biopsy using 2D measurements of pulmonary nodule growth in comparison with automated volumetric measurement on 87 nodules in 69 patients over a 27-month period. Fifty-five of the nodules were <1 cm, 55 were irregular and 7 part solid. Volumetric growth rates correlated with 2D measurements, $r=0.69$, with correlation worsening in irregular nodules and those assessed with an interval <100 days. Twenty lung cancers were diagnosed, and eight of these had periods of enlargement and shrinkage over time. Of the seven patients for whom biopsy was recommended on the basis of volumetric growth, three had cancer.

Kostis *et al*⁸³ assessed the reliability of automated nodule volumetry in 115 solid nodules, 75 < 5 mm in diameter, from a lung cancer screening programme that were stable when assessed subjectively and on bidimensional measurement. They excluded juxtapleural nodules. They found that apparent growth was greatest in small nodules <5 mm in diameter, those with shorter follow-up and those with artefacts affecting image quality.

Marchianò *et al*³⁵ analysed the reliability of semiautomated volumetry in 233 nodules >4.8 mm in diameter from a lung cancer screening programme. Non-solid, part solid and juxtapleural nodules were excluded. They assumed that all nodules that appeared stable on three consecutive scans with a follow-up of 12 months were benign. They showed that 95% of the nodules volumes fluctuated in the ±27% range, with 70% of all measurements having a volume variation range <10%, and only two nodules had an increase of >25%.

Gietema *et al*³⁵⁷ in a study assessing interobserver variability in nodules detected in the NELSON lung cancer screening trial, showed that two observers independently measuring the volume of nodules detected had good correlation for most nodules, with discrepant results obtained in 11%. In 3.7% the volume discrepancy was >10%, with the most common cause being incomplete segmentation.

Goodman *et al*³⁴⁵ evaluated volumetric nodule software in 50 nodules scanned using a zero growth model on three occasions, with nodules up to 20 mm in diameter included. They demonstrated minimal interobserver variability, but segmentation failed in six patients, eight patients had completely calcified nodules and variability in nodule volume was greatest in small nodules <9 mm.

Revel *et al*³⁵⁸ assessed the percentage of successful segmentation, intraobserver variability, inter-reader agreement among three readers and the repeatability of volume calculation using

automated volumetry software in 54 solid non-calcified nodules measuring 5–18 mm in diameter, with 12 nodules <5 mm. Nodule segmentation was successful in 96%, failing in two juxtapleural nodules, with excellent repeatability. There was no variation in measurements in 67% of the nodules, with minimal variation in the remaining nodules, and excellent inter-reader agreement.

Wang *et al*³⁴⁴ retrospectively assessed the effect of nodule morphology, size and location on semiautomated volume measurement variability in 4225 nodules in 2239 patients scanned in a lung cancer screening programme performed by two readers. There was complete agreement for the calculated volume in 86% of the nodules, with large disagreement, demonstrating a relative volume difference of ≥15% in only 4% of the nodules. The greatest disagreement was seen in irregular and juxtapulmonary nodules. There was complete agreement in 91% of purely intraparenchymal nodules but only 70% for juxtapulmonary nodules, and 90% for smooth nodules but only 34% for irregular nodules.

Wormanns *et al*³⁵⁹ assessed the repeatability of automated volumetric software in 151 nodules scanned using a zero growth model in 10 patients. Two observers performed measurements on 50 randomly selected nodules. Segmentation was possible in all nodules. Interobserver agreement, −5.5% to 6.6% and intraobserver agreement, −3.9% to 5.7%, were excellent. The mean volume measurement error was 0.7%, with a 95% range of observed errors of −20.4% to 21.9%. Jennings *et al* compared diameter and cross-sectional area with volumetric measurements to assess nodule growth in 63 patients with stage 1 lung cancer, with a median nodule diameter of 19.3 mm.⁸⁶ Each nodule was measured on their first and second CT scans as a minimum. Diameter and area were highly correlated with volume measurements, but nodule diameter was inaccurately assessed when compared with growth on 37% of occasions. Manual diameter measurements were more inaccurate than automated measurement.

Revel *et al*³⁵⁸ evaluated the intra- and interobserver variability of 2D CT measurements of 54 pulmonary nodules ranging in size from 3 to 18 mm. Three radiologists independently measured each nodule on three occasions. There were significant variations in the diameters measured. The variations were of sufficient size, that to be 95% sure that a nodule had genuinely

increased in size, an increase in diameter of a nodule would have to be >1.70 mm.

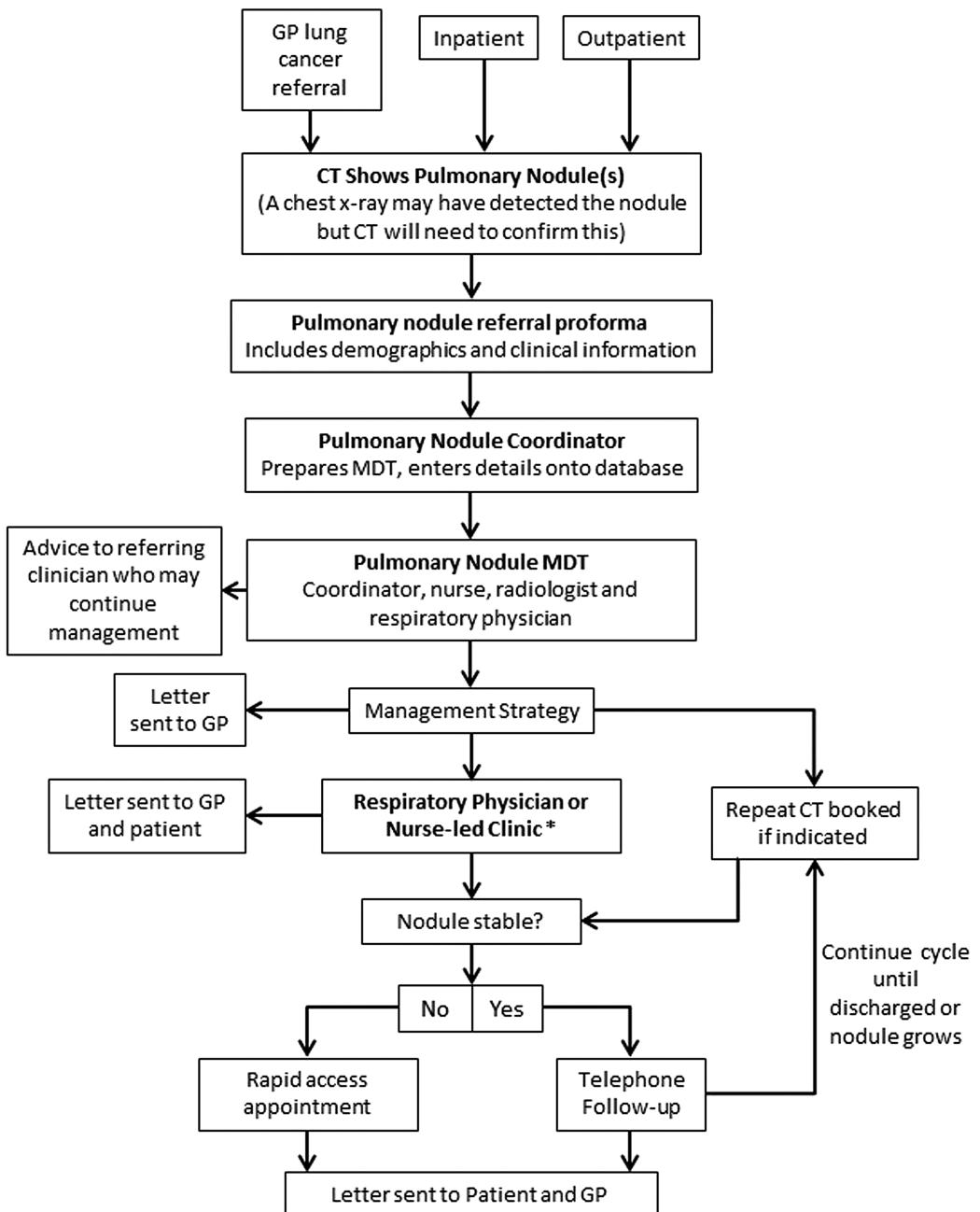
Boll *et al*³⁴⁶ assessed 73 nodules in 30 patients during the cardiac cycle, repeating the assessment three times, and compared the results with measurements from phantoms. Cardiac motion causes variation in nodule volume estimation, with small nodules and those closest to the heart most affected.

APPENDIX 3: SERVICE ORGANISATION

Effective management of people with pulmonary nodules is best achieved by professionals familiar with the latest recommendations, as provided in this guideline. Nodules are common and therefore justify a systematic approach. The majority of nodules detected will have a low probability of malignancy and will be suitable for imaging follow-up. People with these nodules will require a clear explanation about what a pulmonary nodule may be and the way in which it will be followed up. The GDG recommends that when a nodule is detected, a CT should be performed where it has not already been done. The findings should be managed according to this guideline in a structured fashion suited to the local institution. The GDG did not want to be prescriptive about the design of the service but noted that a structured approach may be achieved by reviewing the CT findings at an imaging meeting with recommendations made directly to the referring clinician or at a dedicated nodule multidisciplinary team (MDT).

Figure 11 shows an example of a dedicated nodule service where the nodule MDT provides central coordination of management of people with nodules. The advantages of this include greater efficiency, use of expert clinicians, data collection, a greater chance of using the latest guidance and potentially, a reduction in disruption of other meetings and the need for informal discussion. The principal disadvantage is the cost associated with the extra MDT meeting and staff time.

Whichever service design is employed it is important that it facilitates accurate implementation of the guideline, including the important elements of communication with the patient. This may be by a face-to-face appointment or by the telephone when patients are offered appointments according to their needs. The service should include the radiological standards of volumetry, low radiation dose and thin-section (1.25 mm) CT for SSN follow-up. There should be written communication with primary care.



* Some services may elect to conduct this element via telephone or see patients face to face according to their individual preferences

Figure 11 An example of a pulmonary nodule service pathway. MDT, multidisciplinary team.

Correction

Callister ME, Baldwin DR, Akram AR, *et al.* British Thoracic Society guidelines for the investigation and management of pulmonary nodules. *Thorax* 2015;70(Suppl 2):ii1-ii54.

Reference 74 is incorrect. It should read 'Horeweg N, van Rosmalen J, Heuvelmans MA, *et al.* Lung cancer probability in patients with CT-detected pulmonary nodules: a pre-specified analysis of data from the NELSON trial of low-dose CT screening. *Lancet Oncol* 2014;15:1332-41.'

Initial assessment of the probability of malignancy in pulmonary nodules

The Guideline Development Group wishes to clarify evidence and recommendations concerning the threshold for discharging patients with previous or active cancer. Screening studies that provide data on risk of malignancy in pulmonary nodules excluded patients with previous cancer (specifically any diagnosis of melanoma, renal, breast or lung cancer within 5 years in NELSON) or active cancer. As stated in the guideline, there is limited and conflicting evidence about the rate of malignancy of nodules in people with extra-thoracic cancer. The GDG wanted to ensure there was caution regarding discharging patients with very small nodules in the context of previous or active cancer where the risk of malignancy may be higher. Thus nodule follow-up below the threshold of <5mm maximum diameter or <80 mm³ volume for people with a history of previous or active cancer should be considered according to clinical judgement.

The recommendations that relate to this are:

Consider using the presence of previous malignancy as a factor in the risk assessment for further investigation (Grade D) *Thorax* 2015;70(Suppl 2):ii1-ii12.

Do not prioritise management of pulmonary nodules according to the route of presentation (Grade D) *Thorax* 2015;70(Suppl 2):ii1-ii12.

Do not offer nodule follow-up for people with nodules <5 mm in maximum diameter or <80 mm³ volume (Grade C) *Thorax* 2015;70(Suppl 2):ii1-ii17.

Thorax 2015;70:1188. doi:10.1136/thoraxjnl-2015-207168corr1



Online Appendix 1

BTS Guideline for the investigation and management of pulmonary nodules

PICO questions

1. Are there important differences in nodule characteristics according to the route of presentation and clinical context?
2. What clinical and radiological factors contribute to initial risk assessment for malignancy?
3. In what situations is CT surveillance appropriate and how should this happen and be assessed?
4. What are the features of sub-solid nodules and how should these nodules be managed?
5. What other imaging tests are useful in nodule evaluation and when should they be used?
6. What non-surgical biopsy/non-imaging tests are useful in nodule evaluation, when should they be used and what are the harms?
7. When should patients undergo excision biopsy and proceed to resection?
8. What is the optimal surgical management for nodules confirmed to represent lung cancer (either pre-operatively or at intra-operative frozen section pathological analysis)?
9. How do localisation techniques for pulmonary nodules compare?
10. Are there specific recommendations for surgical management of pure ground glass nodules (pGGN)
11. When should patients undergo non-surgical treatment without pathological confirmation of malignancy, what treatment modalities are appropriate and what are the harms?
12. What are the information and support needs of patients with pulmonary nodules?
13. What are the technical imaging considerations relating to nodule detection and assessment by CXR, CT and PET-CT?

April 2015

BTS Pulmonary Nodule Guideline

Literature search details

July 2012:

Sources to be searched;

Cochrane Database of Systematic Reviews (CDSR)
Database of Abstracts of Reviews of Effects (DARE)
Cochrane Central Register of Controlled Trials (CENTRAL)
Health Technology Assessment Database (HTA)
NHS Economic Evaluations Database (NHSEED)
MEDLINE and MEDLINE In-Process
EMBASE

Search Strategy:

- 1 *multiple pulmonary nodules/ or *solitary pulmonary nodule/ (2276)
- 2 ((multiple or solitary) adj (pulmonary or lung or "ground-glass opacity" or "ground-glass" or GGO or part-solid) adj (nodule\$ or lesion\$ or mass or masses)).ti,ab. (1774)
- 3 "coin lesion".ti,ab. (257)
- 4 (((radiofrequency adj ablation) or RFA) and (pulmonary or lung\$)).ti,ab. (1063)
- 5 (early adj2 "lung cancer").ti,ab. (1060)
- 6 1 or 2 or 3 or 4 or 5 (5563)
- 7 limit 6 to (english language and humans) (4010)
- 8 limit 7 to yr="1990 - 2012" (3534)
- 9 (8 not (comment or editorial or letter)).pt. (3354)

PULMONARY_NODULE_BTS Update 2014 search

Sources to be searched;

Cochrane Database of Systematic Reviews (CDSR)
Database of Abstracts of Reviews of Effects (DARE)
Cochrane Central Register of Controlled Trials (CENTRAL)
Health Technology Assessment Database (HTA)
NHS Economic Evaluations Database (NHSEED)
MEDLINE and MEDLINE In-Process
EMBASE

Date range searched: Limit years "1985 - 2014" in Medline and Embase
All kind of studies in MEDLINE and EMBASE

English language only

Human studies only

Cochrane Library (includes CDSR, DARE, CENTRAL, HTA and NHSEED)

<http://www.thecochranelibrary.com>

Searched online 25/04/14

Strategy saved as: PULMONARY_NODULE_BTS

#1	MeSH descriptor: [Multiple Pulmonary Nodules] explode all trees	6
#2	MeSH descriptor: [Solitary Pulmonary Nodule] explode all trees	70
#3	#1 or #2	74
#4	((multiple or solitary) next (pulmonary or lung or "ground-glass opacity" or "ground-glass" or GGO or part-solid) next (nodule* or lesion* or mass or masses)):ti or ((multiple or solitary) next (pulmonary or lung or "groundglass opacity" or "ground-glass" or GGO or part-solid) next (nodule* or lesion* or mass or masses)):ab	32
#5	((benign or malignant or indolent or resected or indeterminate) next nodule*):ti or ((benign or malignant or indolent or resected or indeterminate) next nodule*):ab	29
#6	"coin lesion":ti or "coin lesion":ab	0
#7	(lung or pulmonar*):kw	22939
#8	MeSH descriptor: [Catheter Ablation] explode all trees	1173
#9	#7 and #8	187
#10	((radiofrequency next ablation) or RFA) and (pulmonary or lung*):ti or (((radiofrequency next ablation) or RFA) and (pulmonary or lung*)):ab	67
#11	(early near/2 "lung cancer"):ti or (early near/2 "lung cancer"):ab	45
#12	#3 or #4 or #5 or #6 or #9 or #10 or #11	363

Of 363 total results in Cochrane Library 2 were from CDSR, 23 from DARE, 309 from CENTRAL, 16 from HTA and 13 from NHSEED. Results saved to Endnote library marked CDSR 25/04/14, DARE 25/04/14, CENTRAL 25/04/14, HTA 25/04/14 and NHSEED 25/04/14 in Custom 4 field.

MEDLINE and MEDLINE In-Process

Searched 25/04/14 via OVID interface

Strategy saved as: PULMONARY_NODULE_BTS_MEDLINE

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

1 *multiple pulmonary nodules/ or *solitary pulmonary nodule/ (2573)

- 2 ((multiple or solitary) adj (pulmonary or lung or "ground-glass opacity" or "ground-glass" or GGO or part-solid) adj (nodule\$ or lesion\$ or mass or masses)).ti,ab. (1937)
- 3 ((benign or malignant or indolent or resected or indeterminate) adj nodule\$).ti,ab. (1387)
- 4 "coin lesion".ti,ab. (255)
- 5 *Catheter Ablation/ and (lung or pulmonar*).hw. (2145)
- 6 (((radiofrequency adj ablation) or RFA) and (pulmonary or lung\$)).ti,ab. (1269)
- 7 (early adj2 "lung cancer").ti,ab. (1250)
- 8 1 or 2 or 3 or 4 or 5 or 6 or 7 (8982)
- 9 limit 8 to (english language and humans) (6832)
- 10 9 not (comment or editorial or letter).pt. (6379)
- 11 limit 10 to yr="1985 - 2014" (6060)

6060 total results saved to Endnote library marked 'MEDLINE 25/04/14' in Custom 4 field.

EMBASE

Searched 25/04/14 via OVID interface

Strategy saved as: PULMONARY_NODULE_BTS_EMBASE

EMBASE 1974 to 2014 April 24

- 1 *lung nodule/ (3461)
- 2 ((multiple or solitary) adj (pulmonary or lung or "ground-glass opacity" or "ground-glass" or GGO or part-solid) adj (nodule\$ or lesion\$ or mass or masses)).ti,ab. (2603)
- 3 ((benign or malignant or indolent or resected or indeterminate) adj nodule\$).ti,ab. (1852)
- 4 "coin lesion".ti,ab. (293)
- 5 *"radiofrequency ablation"/ and (lung or pulmonar*).hw. (1098)
- 6 (((radiofrequency adj ablation) or RFA) and (pulmonary or lung\$)).ti,ab. (2131)
- 7 (early adj2 "lung cancer").ti,ab. (1923)
- 8 1 or 2 or 3 or 4 or 5 or 6 or 7 (11080)
- 9 limit 8 to (english language and humans) (7757)
- 10 9 not (comment or editorial or letter).pt. (7521)
- 11 limit 10 to yr="1985 - 2014" (7385)

7385 total results saved to Endnote library marked 'EMBASE 25/04/14' in Custom 4 field.

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. <i>J Thorac Oncol</i> 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. <i>N Engl J Med</i> 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, investigations 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. <i>PLoS ONE</i> 7 (7), 2012	Case series	3	1182	Volunteers over age of 50 years with significant 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. <i>Journal of Vascular Surgery</i> 53:738-41, 2011	Case series	3	138	Consecutive patients undergoing CT follow up after endovascular abdominal aortic aneurysm repair.	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, Yankelitz DF, et al: Early Lung Cancer Action Project: overall design and findings from baseline screening. <i>Lancet</i> 354:99-105, 1999	Case series	3	1000	Volunteers over age of 50 years with significant 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. <i>American Journal of Medicine</i> 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-calciified pulmonary nodules in patients with extrapulmonary cancers. <i>Thorax</i> 61:351-1, 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. <i>Journal of Clinical Gastroenterology</i> 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. <i>Chest</i> 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. <i>Lung Cancer</i> 67:177-83, 2010	Case series	3	3352	Volunteers over age of 50 years with significant 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. <i>Chest</i> 125:2175-81, 2004	Case series	3	1104	Patients undergoing 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. <i>Radiology</i> 243:239-49, 2007	Case series	3	6295	Volunteers over age of 60 years with significant 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. <i>Radiology</i> 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 population 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. <i>Annals of Oncology</i> 23:577-82, 2012	Case series	3	229	Melanoma patients with a lung nodule that had undergone percutaneous 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. <i>American Journal of Respiratory & Critical Care Medicine</i> 165:508-13, 2002	Case series	3	1520	Volunteers over age of 50 years with significant 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 (PLUS): outcomes within 3 years of a first computed tomography scan. <i>American Journal of Respiratory & Critical Care Medicine</i> 178:956-61, 2008	Case series	3	3642	Volunteers over age 50-79 years with significant 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. <i>Ann Vasc Surg</i> 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 18.2%. 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. <i>J Emerg Med</i> 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.

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
1 - Route to diagnosis	19	Lehman SI, Abbara S, Cury RC, et al: Significance of cardiac computed tomography incidental findings in acute chest pain. <i>Am J Med</i> 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 Fleischner guidelines.
1 - Route to diagnosis	20	MacAulay J, Yam Y, Ruddy TD, et al: Potential clinical and economic consequences of noncardiac incidental findings on cardiac computed tomography. <i>J Am Coll Cardiol</i> 54:1533-41, 2009	Case series	3	966	Consecutive patients undergoing CT coronary angiography. 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. <i>Arch Intern Med</i> 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. <i>Am J Emerg Med</i> 27:428-35, 2009	Case series	3	3052	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 spiral computed tomographic screening for lung cancer. <i>N Engl J Med</i> 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, investigations 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-Vellosa MJ, Lozano MD, et al: Early lung cancer detection using spiral computed tomography and positron emission tomography. <i>American Journal of Respiratory & Critical Care Medicine</i> 171:1378-83, 2005	Case series	3	911	Volunteers over age of 40 years with significant 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 Depiccan study: a French randomized pilot trial of lung cancer screening comparing low dose CT scan (LDCT) and chest X-ray (CXR). <i>Lung Cancer</i> (Amsterdam, Netherlands), 2007, pp 50-8	Case series	3	765	Volunteers over age 50-75 years with significant 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-calified 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. <i>RADIOLOGIA MEDICA</i> 110:532-43, 2005	Case series	3	519	Volunteers over age of 55 years with significant 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. <i>International Journal of Tuberculosis and Lung Disease</i> 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, Wörmann D, Semik M, et al: Screening for early lung cancer with low-dose spiral CT: prevalence in 817 asymptomatic smokers. <i>Radiology</i> 222:773-81, 2002	Case series	3	817	Volunteers over age of 40 years with significant 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. <i>Thorax</i> 61:54-6, 2006	Case series	3	449	Volunteers over age of 50 years with significant 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. <i>Annals of Oncology</i> 16:1662-6, 2005	Case series	3	520	Volunteers over age of 55 years with significant 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. <i>Journal of Thoracic Oncology</i> 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%. Lung cancer prevalence 0.8%. Results planned to be pooled with NELSON trial.
1 - Route to diagnosis	32	Tiltola M, Kivisaari I, Huuskonen MS, et al: Computed tomography screening for lung cancer in asbestos-exposed workers. <i>Lung Cancer</i> 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 asbestos. 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. <i>The New England Journal of Medicine</i> , 2009, pp 2221-9	Diagnostic accuracy	2+	7557	The mean ($\pm SD$) age of the screened participants was 59 \pm 6 years, and the mean number of pack-years smoked was 42 \pm 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 rescreened 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. <i>Lung Cancer</i> 61:340-9, 2008	Case series	3	5201	Volunteers over age of 50 years with significant 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	Keegan MT, Tung KT, Kaplan DK, et al: The significance of pulmonary nodules detected on CT staging for lung cancer. <i>Clinical Radiology</i> 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. <i>Journal of Korean Medical Science</i> 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%.

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
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 angiography.	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, Hamada 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, Calabro 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, Tammeimagi 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	Validation model of risk of malignancy showing PSN independent predictor and pGNN 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 ED, et al: A clinical model to estimate the pretest probability of lung cancer in patients with solitary pulmonary nodules. Chest 131:183-8, 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 likelihood ratios using Bayes theorem.
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 ($P < 0.05$) 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-bayesian group and 2 in the bayesian 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 prospectively collected cohort	2-	S2 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.

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	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. <i>Acta Radiologica</i> 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 ^{18}F -fluorodeoxyglucose positron emission tomography. <i>Chest</i> 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 ROC-AUC 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 was significantly 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 be 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. <i>Korean Journal of Internal Medicine</i> 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. <i>Journal of Computer Assisted Tomography</i> 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. <i>Radiology</i> 233:793-8, 2004	Case series	3	222	Consecutive patients 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. <i>Clinical Lung Cancer</i> 12:313-9, 2011	Case series	3	371	Nodules patients referred for surgical resection.	not applicable	not applicable	Not reported	Risk of cancer	Logistic 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, Bimbeny C, et al: The clinical and radiologic features of nodular pulmonary sarcoidosis. <i>Lung</i> 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. <i>Lung Cancer</i> 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. <i>Thorax</i> 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. <i>Mayo Clinic Proceedings</i> 74:319-29, 1999	Case series	3	100	Random sample from 629 patients with indeterminate SPN	not applicable	not applicable	Not applicable	Performance of predicton model versus clinician opinion	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 performed in a tertiary healthcare centre so clinicians may have had more expertise than the general physician.
2 - Initial assessment	64	Swensen SJ, Silverstein MD, Istrup DM, et al: The probability of malignancy in solitary pulmonary nodules. Application to small radiologically indeterminate nodules. <i>Archives of Internal Medicine</i> 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, > 0 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. <i>Respiratory</i> 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. <i>American Journal of Transplantation</i> 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. <i>Clin Imaging</i> 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

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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 58:335-40, 2004	Case series	3								
2 - Initial assessment	70	Oshiro Y, Kusumoto M, Moriyma 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	Performance 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-Amen A, Thygesen H, Plant P K, Vaideyanathan S, Karthik S, Scarbrook A, Calister ME: 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 performed similarly (AUC 0.89 and 0.90 respectively). Reasonable AUC 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 literature.
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 0-40.8]) 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 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 JP, Bissery A, Bienvienu 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 chance of 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	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 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) significantly 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, Peyrand 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, Recruit 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 reliability 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 significantly 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 delineation 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 Fleischner 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, Heuveldmans 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 120 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 125/7, 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 - usually volumetric technique, spherical, elliptical)	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, 26-711 to 64) for adenoc, 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 elliptical 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, 53 aden.	Largely technical paper comparing perimeter, spherical, and elliptical 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	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. solid 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%	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 >11 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		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 >500mm ³) 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 NO MO 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 JW, 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	Retrospective case series	3	283	Patients undergoing lung resection for stage I 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) in 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 chemotherapy
4 - Subsolid	100	Hung JJ, Yeh YC, Jeng JW, 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), 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.		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.
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. 6:496-504, 2011	retrospective database analysis	3	210	Patients with stage 1-3 adenocarcinoma that had had surgical resection		not specified, last pt entered 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 lesions were 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 confirmed			not given		Pathologically or clinically confirmed 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. <i>J Thorac Oncol</i> 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. <i>Radiology</i> 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. <i>J Thorac Oncol</i> 5:206-10, 2010	case series	3	23	resected cases of BAC with additional SSN			median 40.3 mo		Study of SSN in resected BAC - small numbers as only 23 patients with 89 GGO and 5 pts had all resected and 18 had some resected thus if not feasible to resected not important as outcome 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. <i>Lung Cancer</i> 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? <i>AJR American Journal of Roentgenology</i> , 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 attributable 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. <i>Lung Cancer</i> 83:61-6, 2014	case series	3	67	Variety of sources - some from screening, some from CT for other reasons, not lung cancer some from surgical FU after lung resection			med 4.2 y		SSN observed without treatment werwe followed for time to 2mm growth or incidec 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. <i>Radiology</i> 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 eosinophilia, 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. <i>Respir Med</i> 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. <i>Lung Cancer</i> 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 werwe scanned at 3 months if <10mm or biopsied/resected if >10mm. New solid component or increase size - biopsy or resect. 26/69 (38%) PGGN were transient and 57/117 (49%) of PSM. Most of the regression 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. <i>Japanese Journal of Radiology</i> 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. <i>J Thorac Oncol</i> 9:469-72, 2014	case series	3	53	consecutive patients with pGGN			av 26.1 mo		attenuation, smoking and history of lung cancer 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. <i>Radiol Med</i> 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. <i>Chest</i> 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 69 days for growing nodules. 40% of the original tool 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. <i>Acta Radiol</i> , 2014	case series	3	63	Patients with extra pulmonary malignancy			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. <i>AJR Am J Roentgenol</i> 202:W224-33, 2014	Review	N/a							Review article so N/A for evidence 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. <i>J Thorac Oncol</i> 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. <i>Radiology</i> 268:265-73, 2013	case series	2-	253	Pathologically confirmed SSN, resected			Not given		Highly selected group of PSN resected, 55 werwe not confirmed and excluded. 2 not resected werwe biopsied 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. <i>J Thorac Oncol</i> 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. <i>J Thorac Oncol</i> 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% progressed. 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. <i>PLoS One</i> 9:e85167, 2014	case series	3	77	Selected from radiological database			not given3 months was cut 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 eosinophilia and lesion multiplicity. Skewness for solid. Skewness was also an important factor 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. <i>J Thorac Oncol</i> 7:1563-6, 2012	case series	3	50	SSN ≤2cm with no pleural indentation or vascular 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 nodule with cytology suspicious for adenocarcinoma. <i>J Thorac Oncol</i> 9:685-91, 2014	case series	3	63	needle biopsies of GGN			45 resected 35 observed		Patients who had a needle biopsy and confirmed early adenoc. 16 of 47 elected to be observed, of these 6 grew and 5 were resected. The observed cases all did well. 2 of the 47 resected cases developed mets and five developed new cancers with the progression in non existing GGN	
4 - Subsolid	128	Patz EF, Jr., Pinsky P, Gatsoulis C, et al: Overdiagnosis in low-dose computed tomography screening for lung cancer. <i>JAMA Intern Med</i> 174:269-74, 2014	RCT	1+	53452	Subjects at high risk of lung cancer in an RCT of CT screening vs CXR	CT screening	CXR	6.2 years	Overdiagnosis rate	Overdiagnosis rate was higher in BAC, a CT correlate of subsolid nodules	
4 - Subsolid	129	Maeyashiki T, Suzuki K, Hatton 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. <i>Eur J Cardiothoracic Surg</i> 43:915-8, 2013	case series	3	298	Stage 1A resected			not given probably a minimum of 1 year		Showed that the size of the solid component and the presence of air bronchogram were independent predictors of lymph node mets. All pGGN did NOT have LN mets (30) and if solid component 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). <i>JAMA</i> , 2001, pp 914-924	meta-analysis	1+	40 studies met inclusion criteria with 1474 nodules	Median prevalence 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. RECOMMENDATION: Patients with pulmonary nodules, especially >1cm should undergo PET scan and if suggestive of malignancy should undergo further investigation.
5 - PET	132	Crönin P, Dwamena BA, Kelly AM, et al: Solitary pulmonary nodules: meta-analytic comparison of cross-sectional imaging modalities for diagnosis of malignancy. <i>Radiology</i> 246:772-82, 2008	meta-analysis	1+	meta-analysis to estimate the diagnostic accuracy of 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 heterogeneity 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. <i>Annals of Thoracic Surgery</i> 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 positive in 51 of 58 lung cancers - see comment for sensitivity and specificity. For nodule < 1cm sensitivity was 83% and specificity 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. <i>Lancet</i> , 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 identified 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 trial 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). RECOMMENDATION: 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 trial of patients with SPN and the utility of PET scan. They seek to address some of the problems with other articles in the field including small sample size and bias patient selection. The study population did have a high prevalence of smokers (~90%) and male (97%). This may be due to the population enrollment from a veterans institute. However, they have sought to reduce 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 their 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 \pm SD, 61.7 \pm 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 components 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-quantitative analysis they PET was able to classify benign from malignant lesions and 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 \pm SD, 67.7 \pm 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 (SUV _{max}) 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 quantitative 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 RECOMMENDATION. 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 CAD to determine radiological differentiation (alongside clinical details) for determining a nodule's 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 18F-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, Ohsuka 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 nodules 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 nodules which are less than 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. RECOMMENDATION: 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 \geq 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 \geq 10mm in 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 \pm 1.18; range, 0.48–5.60) than in malignancy (1.26 \pm 0.71; range, 0.32–2.6) ($P = 0.018$). In pure GGNs, the maximum SUV of malignancy (0.64 \pm 0.19; range, 0.43–0.96) and inflammation (0.74 \pm 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		This article reviews the theory of PET imaging SUV measurement and discusses the inherent inaccuracies
5 - PET	144	Evangelista L, Panizzon 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 \pm SD, 67 \pm 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 characteristics against final 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 assign risk category. They found that the use of PET/CT was most important in those with low/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 anatomic metabolic 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, Cuchara A, et al: Dual time point 18F-FDG PET for the evaluation of pulmonary nodules. <i>Journal of Nuclear Medicine</i> 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 ($\text{mean} \pm \text{SD}$) 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/no 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. <i>Lung Cancer</i> 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 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 authors 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 patients 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 18F-DG-PET/CT for the differential diagnosis of pulmonary nodules: a meta-analysis. <i>Acta Radiol</i> 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 performance 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 LR _b 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 heterogeneity and including 8 studies showed there may be an advantage in dual Vs single 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. <i>Clinical Lung Cancer</i> 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. <i>Respiration</i> 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 characteristics against final diagnoses		pathological diagnosis		SPECT had sensitivity, specificity and diagnostic accuracy of 89, 67 and 81%, respectively. SPECT was comparable to PET	The authors conclude spect has utility where PET is not available with moderate performance characteristics for nodule 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. <i>AJR American Journal of Roentgenology</i> . 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 could be used with MDCT at reference. They found a good rate of detection of nodules using MR, especially for nodules >5mm. They conclude that MR HASTE could 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. <i>AJR American Journal of Roentgenology</i> . 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 an alternative to CT. They have analysed the data in a blinded fashion 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? <i>Magn Reson Imaging</i> 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 distinguish pulmonary nodules			Pooled sensitivity for DWI was 0.84 (95% CI, 0.76–0.90) with significant heterogeneity ($\chi^2=34.66$, $P=.003$) and a pooled specificity of 0.84 (95% CI, 0.64–0.94) with heterogeneity ($\chi^2=51.61$, $P=.002$).		Significant heterogeneity 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 , Carcioid 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 diffusion-weighted MRI in assessment of nodules prior to resection	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 (38 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-T and 3-Tesla imaging	Compared 1.5-T and 3-T MR modalities 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 3-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 imaging 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 likelihood of a benign Vs Malignant Vs active 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 intervals	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 but this study included many nodules > 30 mm.
5 - PET	158	Marmata 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	cohort	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 $k_{ep} = 1.0 \text{ min}^{-1}$ 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 size 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 hamartoma).	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	Sitarchouk 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	Parameters measured on first pass CT with correlation of histology	histology	microvascular characterization in terms of BP, 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 be validated in larger cohorts.

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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. <i>British Journal of Radiology</i> 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 (PE), 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 their parameters 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. <i>Radiology</i> 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	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 mathematical methods with FDG PET/CT in management of solitary pulmonary nodules. <i>AJR Am J Roentgenol</i> 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 microbial 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. <i>Chest</i> 146:1021-8, 2014	Decision tree analysis	3	N/A	N/A	PET-SABR and Biopsy-SABR	Pathological 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 . Conclude that PET-SABR better when probability is 85%	i.e. minimal difference for PET and biopsy. The toxicity from biopsy may have been underestimated as if concern about morbidity, this implies lung disease that would increase toxicity. Thus a lower pre-test probability 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. <i>Cancer Biology & Therapy</i> 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. <i>BMC Cancer</i> 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 detection	
6- Biopsy	168	Daly S, Renwalt D, Fried C, et al: Development and validation of a plasma biomarker panel for discerning clinical significance of indeterminate pulmonary nodules. <i>J Thorac Oncol</i> 3:81-6, 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 benign in test set and 22mm (8-80) in validation set This may not reflect truly indeterminate nodules and some nodules are outside the threshold for this guideline	
6- Biopsy	169	Higgins G, Roper KM, Watson J, et al: Variant Ciz1 is a circulating biomarker for early-stage lung cancer. <i>Proc Natl Acad Sci U S A</i> 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. <i>Journal of Cancer Research & Clinical Oncology</i> 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. <i>Ann Oncol</i> 22:383-9, 2011	cohort	2-	145 Lung cancer stage 1 or 2 (non small cell and small cell)	autoantibody panel	146 controls	unclear		sensitivity and specificity	sens 36% and specificity 91%	
6- Biopsy	172	Lam C, Boyle P, Healey GF, et al: EarlyCDT-Lung: an immunoassay test as an aid to early detection of lung cancer. <i>Cancer Prev Res (Phila)</i> 4:1126-34, 2011	cohort	2-	574 patients with cancer and unspecified number of benign controls (597) 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 screening
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. <i>Lung Cancer</i> 83:S1-5, 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 Westeninde SC, Horwedge N, Vermhout RM, et al: The role of conventional bronchoscopy in the workup of suspicious CT scan screen-detected pulmonary nodules. <i>Chest</i> 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. <i>Chest</i> 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? <i>Journal of Bronchology</i> 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 likelihood ratio of positive FFB 1.13 to 4.08	fluoroscopic guidance used // included lesions>3cm/should fulfil 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. <i>Eur Respir J</i> 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. <i>European Respiratory Journal</i> 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	

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	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. <i>Respiratory Medicine</i> 90:139-43, 1996	obs	3	138	SPN <4cm on CXR	TBB and brush under fluoroscopic guidance	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. <i>Chest</i> 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%) diagnosis made in 38/54 (70%)	lesions unable to be visualised 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. <i>European Respiratory Journal</i> 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 malignant and 5 benign	size no difference in yield or ability to be detected by EBUS// overall diagnostic 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. <i>Chest</i> 125:959-65, 2004	obs	3	150	peripheral SPN <3cm detected on CXR or CT	bronchoscopy using EBUS guide sheath	none	until definite diagnosis made or lesions regressed on radiology	diagnostic yield	116/150 (77%) diagnostic. // Malignant 82/101 (81%) and benign 34/49 (69%)// no signif 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. <i>Respiration</i> 79:54-60, 2010	obs	3	55 // 2 excluded as lost to follow up	peripheral SPN<3cm in patients referred for bx of ?lung cancer	suction catheter 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. <i>American Journal of Respiratory & Critical Care Medicine</i> 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	electromagnetic 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 // conscious 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. <i>Journal of Bronchology and Interventional Pulmonology</i> 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, Wegleinert B, et al: Electromagnetic navigation bronchoscopy (ENB): increasing diagnostic yield. <i>Respiratory Medicine</i> 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. <i>Chest</i> 138:1316-21, 2010	obs	3	51	SPN	electromagnetic 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. <i>Chest</i> 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? <i>Thorax</i> 57:817-22, 2002	obs	3	114	solitary pulmonary lesion <3cm in a specialist cardiorespiratory hospital in NZ	successful management decisions	clinical data and CXR/+plus Ct/+plus CT biopsy result/ results reviewed by 6 resp cons who estimated likelihood of malignancy and made management decisions	> 5 years	successful management decision	31% nodules benign /31% malignant and curative surgery/40% malignant and non curative //intraclinician decision 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 (<2cm) subpleural pulmonary lesions: Short-versus long-needle-path CT-guided biopsy - Comparison of diagnostic yields and complications. <i>Radiology</i> 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 between 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. <i>AJR American Journal of Roentgenology</i> , 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. <i>European Radiology</i> 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 definite diagnosis or 2 year radiography	diagnostic yield safety	accuracy 98.4% (60/61), sens 97% (35/37), spec 100% (25/25) 3 had drains (4.2%) and haemoptysis in 10 (14.1%) 18 Pt x (25.4%)	it excluded indeterminate (no specific benign features and had no follow up) results from analysis. Less radiation than fluoroscopy alone
6- Biopsy	193	Ohno Y, Hatabu H, Takenaka D, et al: Transthoracic CT-guided cutting biopsy or aspiration biopsy with or without fluoroscopy or multiplanar reconstruction image Improves diagnostic accuracy of solitary pulmonary nodules. <i>European Journal of Radiology</i> 51:160-8, 2004	Cohort	2-	350	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 MPR	Surgical confirmation or clinical follow up for 24months	Accuracy and pneumothorax rate	Biopsies with MPR was significantly better than the other two groups with an accuracy of 97%. The pneumothorax rate with MPR was 28% and not significantly different to the other two groups.	
6- Biopsy	194	Romano M, Griffi 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. <i>RADIOLOGIA MEDICA</i> 108:275-82, 2004	obs	3	184	PN <15mm	CT guided Biopsy	diagnosis by another method	surgical diagnosis or 1 year	diagnostic rate	sensitivity 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. <i>Chest</i> , 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 =1cm) 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, Choi EJ, Kim JE, et al: Percutaneous CT-guided aspiration and core biopsy of pulmonary nodules smaller than 1 cm: analysis of outcome of 305 procedures from a tertiary referral center. AJR Am J Roentgenol 201:96-70, 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, Concaro 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 pulmonary 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%. Complications 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: roll-over 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 TTN 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 coronary 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 no 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-confirmation but very likely to reflect other differences between populations. Costs were lower \$5830, but almost certainly relate 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	Silhoe AD, Hirandani 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 apt 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 morbidity 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 undergoing 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	Rubin JB, Rubin 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	Evaluative 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 dose was \$25,518	Management plans change in majority of cases, although may have been largely influenced by incidence of granulomatous disease (esp Histoplasmosis) 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, Hazenberg 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 Group: 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 nodules. 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 227-35	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 afelectasis 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 for lung cancer - 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 survival, 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	Performed 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 metas. 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 NO 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 T1NOMO 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. Design 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 T1NO lung cancer. Ann Thorac Surg 96:742-4, 2013	RCT (amendment to 218)	1+	276	Patient undergoing lung resection for T1NOMO 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 unaccouente for one third of patients). Highlighted corrections made in response to Lederle letter below
7 - Surgery	230	Billmeier SE, Avanian 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 resection 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 covariates). Trend towards improved S5Y (57% vs 49% in both unadjusted and adjusted analyses)	High quality retrospective cohort study with appropriate attempts to adjust for covariates. 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 resection for early stage lung cancer	Sublobar resection (90 segmentectomy, 56 wedge)	Lobectomy	S5Y described	S5Y, 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 S5Y 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, Hanecka T, et al: Sublobar resection is equivalent to lobectomy for clinical stage IA lung cancer in solid nodules. J Thorac Cardiovasc Surg 147:754-62; Discussion 762-4, 2014	Retrospective cohort study	2-	347	Patients undergoing lung resection 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 greater 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	Siemel 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	Retrospective cohort, but attempts to control for covariabes, 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 tumors, high SUV, pathologically 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 significant 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 equivalent survival (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	Ciriacò 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 shortened 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, Nomia S, Tamaki Y, et al: CT localisation of small pulmonary nodules prior to thorascopic 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 subsequent 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 subsequent 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, JH, 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 subsequent 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, Curtat 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 (RTGR) 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 endoscopy 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 diameter 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	Gonfiantini 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, Ozkower BD, et al: Identification of small lung nodules: technique of radiotracer-guided thoracoscopic biopsy. Annals of Thoracic Surgery 85:S727-7, 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 resection 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 significant 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% aden). 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 between 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 undergoing 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, Tamaki 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 deviated 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, distant 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 SBRT 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 statistically 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 confounding factor is that non-pathologically treated patients had smaller lesions which could have improved their outcomes. However, this could be counter-balanced 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	Review 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 positive 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 overall survival 83.1 vs 76.9% (no significant difference). 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 VSD and in heterogeneity in dosimetry, with reduced % prescription isodosimetry 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: asept 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 PI <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, Sjafri 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, Sjafri 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.

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8 - Non surg treatment	270	Pennathur A, Abbas G, Gooding WE, et al: Image-guided radiofrequency ablation of lung neoplasms 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 occurred 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, intraparenchymal 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 tumors, but not for 98. Data regarding adjuvant treatment missing for 51 tumors. 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 occurred 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 1,2,3 yrs. 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 multifilament 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 received 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 patients 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 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%) haemotorax, 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. Complications 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 multiple 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/brachytherapy). Descriptive study of patterns of recurrence.

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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 3.2mm (+/-1.7) versus 21mm(+/-14). 7 tumours that progressed in group A 6 underwent re-ablation after local progression with an effectiveness rate of 81.1% (6m), 59.2% (12m) and 51.8% (24m). Complications 16 sessions (34%) minor complications occurred which included asymptomatic 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 mediastinal 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 procedures 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 intervention. Median hospital stay 3 days. No sig decline in PTx. 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. Close 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 retrospectively 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 events included pneumothorax needing chest drain, pneumonitis. G3 included pleural fluid needing drainage, bronchopleural fistula needing surgery and empyema. No sig change in FEV1 3-1 months post but only 22 of 50. Local failure was 33% (<2cm) and 40% 2-3.0cm. 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 procedures 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+yr) FOR TUMOURS <3cm but 45% (1yr), 25% (2,3&4yrs) for >3cm.OVERALL PNEUMOTHORAX RATE 28.4%, CHEST DRAIN 9.8% and 30 day mortality of 3.9% of which 2.6% procedure related (=G5)	Retrospective Analysis of 153 patient post pulmonary RFA
8 - Non surg treatment	290	Yamakado K, Hase S, Matsuo 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 procedure. Local control 83% and new lung tumours in 30%. 50% local control in tumours >3cm with 89% for tumours < 3cm. OS 84% (1yr), 62% (2yr) and 46% (3yr) Large tumour size and extrapulmonary disease sig prognostic factors.	Multiple- 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 CJ, Lagerwaard FJ, et al: Incidence and risk factors for chest wall toxicity after risk-adapted stereotactic radiotherapy for early-stage lung cancer. <i>Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer</i> 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 25.2% 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 occurred 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. <i>International Journal of Radiation Oncology Biology Physics</i> 74 (2):349-354, 2009	Case series	3	379	379 consecutive 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. <i>Journal of Thoracic Oncology</i> 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% developing 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. <i>Journal of Thoracic & Cardiovascular Surgery</i> 140:377-86, 2010	Cohort	2+	538	Comparison of Stage I NSCLC patients who received Surgery or SBRT in a single institution.	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 diff 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. 1 patient experienced G3 pneumonitis. In addition there were 4 rib fractures, 3 pleural effusions, 2 lung collapse and haemoptysis 1 and pneumonia 1. In the match high risk surgical cohort operative mortality was 7% and complication in 43.8% of this group including arrhythmias 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. <i>Journal of Clinical Oncology</i> 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/peripheral 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. <i>INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY, BIOLOGY, PHYSICS</i> 51:666-70, 2001	Case series	3	50	Single centre experience treating stage I 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 yrs 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. <i>INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY, BIOLOGY, PHYSICS</i> 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	Confounding 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 improvement in QoL 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. <i>JAMA</i> 303:1070-6, 2010	Case	3	55	Medically inoperable patients with histologically confirmed stage I 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 6.6 months. PR in 21 patients and 89% in total responded. 1 local failure. 2 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, 1 involved lobe alone, 2 involved lobe and disseminated, 1 hilum alone, 1 nodes and disseminated and 8 disseminated alone. Higher disseminated 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 yrs. Seven pts G3 and 2 pts G4 toxicity. No G5 toxicity.	Multi-centre study of SBRT for medically inoperable, histologically confirmed
8 - Non surg treatment	299	Atallah S, Cho BC, Alibhai Z, et al: Impact of pretreatment tumor growth rate on outcome of early-stage lung cancer treated with stereotactic body radiation therapy. <i>Int J Radiat Oncol Biol Phys</i> 89:532-8, 2014	Case Series	3	237	Medically inoperable patient with T1-2N0 tumours based on pathological 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 was a higher local failure rate (7.5% versus 2.7% in the low SGR group, non significant (p=0.38). Regional failure was also higher in the high SGR group (19.2%) versus 6.0% in the low SGR group (p=0.047). 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 univariable and multivariable analysis.	Single centre retrospective analysis of patients treated with stereotactic radiotherapy. Good quality analysis.
8 - Non surg treatment	300	Senthil 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. <i>Lancet Oncol</i> 13:802-9, 2012	Case Series	3	676	Medically inoperable patients with T1-2 tumours	Stereotactic radiotherapy	None	32.9 months	OS, actuarial 2 and 5 yr OS rates, patterns of recurrence.	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 occurred 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	Riccardi 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. <i>Lung Cancer</i> 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 multivariate analysis.	Multicentre 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.

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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 supportive care reduced from 31.9% to 24.9%. 30 day and 90 day 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 reduction in the HR for death after 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. Confounding factors better staging with PET/EBUS over the time periods and this may cause stage drift and improve OS on its 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 was 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. Overall local failure 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 rate 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. Actuarial OS were 65% (1yr), 55%(2y), 45% (3 yr). CSS 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 during 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 solid 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 history or previous history of lung or H+N cancer and 2. at least 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 behaviours 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	Retrospective 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 cohort 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 multivariate analysis . Univariate OS was associated with PS, SUVmax, histology, operability but only SUVmax on multivariate. For radiation pneumonitis mean ipsilateral lung dose >9.4Gy was significant on multivariate analysis.	Reasonable size case series showing that pre treatment SUVmax correlates with OS and ipsilateral 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 significant predictors of RP. Dosimetric parameters were not significantly associated with RP though the doses were generally low. A PTV to lung volume ratio was significant 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 intervention 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. <i>Radiat Oncol</i> 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% (5yrs). 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 5.8Gy(+/-2.3) cf 7.6Gy(+/-3.3) for patients with G2/3 RP. Larger PTV size 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 bronchoscopy.	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. Demonstrates that tumour tracking is feasible and very low complication 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. <i>Int J Radiat Oncol Biol Phys</i> 88:109-9, 2014	Prospective case series	3	55	T1-3N0MO 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 confirmation.	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 decline 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 survival. In addition patients that were inoperable 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. <i>Radiat Oncol</i> 99:161-5, 2011	Case-control	2+	247 pts with COPD aged over 75 for T1/2NO 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 6.4-47.2% 5 yrs OS and 14.9-27.1 QALM (quality 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 improves 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 and co-existing COPD is not justified: outcomes of a Markov model analysis. <i>Radiat Oncol</i> 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 significant decline in FEV1. No significant differences in rates of radiation pneumonitis 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? <i>J Thorac Oncol</i> 7:542-51, 2012	Case series	3	483 pts with 505 tumours	T1-3NO (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) 29-100% 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 deferrated 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 seen 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 radiotherapy 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. <i>Radiat Oncol</i> 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 developed ≥ 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 contralateral MLD were strongest predictors for RP. Should aim to keep the MLD <3.6Gy. Small study and selected population 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. <i>Radiat Oncol</i> 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	Senthil S, Haasbeek CJ, Slotman BJ, et al: Outcomes of stereotactic ablative radiotherapy for central lung tumours: a systematic review. <i>Radiat Oncol</i> 106:276-82, 2013	Systematic Review	2++	315	Paper that had patients who received SABR	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 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 truly 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 schedules so with high rates of toxicity. Overall with dose adapted SABR regimes high rates of local control and acceptable levels of toxicity 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. <i>Quality of Life Research</i> 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 Berg KAM, Essink-Bot ML, Borsboom GJM, et al: Short-term health-related quality of life consequences in a lung cancer CT screening trial (NELSON). <i>British Journal of Cancer</i> 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 physician about pulmonary nodules. <i>Chest</i> 143:672-7, 2013	Observational qualitative	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, Grieshaber V, et al: Detection of pulmonary nodules by multislice computed tomography: improved detection rate with reduced slice thickness. <i>European Radiology</i> 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. <i>Clinical Radiology</i> 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 consistency; 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 thickness; better agreement with thin 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	Sirsut M, Saito 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 vs 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, Shirakishi 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	temporal 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 solid pulmonary nodule and bronchus. Clinical Imaging 33:15-21, 2009	observational	4	148	patients with pulmonary nodules	multiplanar recon	without	n/a	detection 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 nodules 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	patients with metastatic 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, Timtit 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	sensitivity 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 projection 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 pulmonary metastectomy 514 nodules	each comparator	1mm section ct vs. thin slab MIP vs CAD	n/a	sensitivity 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 metastectomy	
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, Lehmkohl 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 characteristics	Statistica difference only for 1mm slice 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	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-calciified 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. <i>Radiology</i> 245:881-7, 2007	Diagnostic comparative	3	60	17 men 43 women	each comparator	bone vs standard algorithm pre and post contrast	n/a	volumne 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 multislice CT— influence of inspiration level, nodule size, and segmentation performance. <i>Radiology</i> 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 minimal 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. <i>Radiology</i> 248:625-31, 2008	Diagnostic comparative	3	82	Patients with 200 nodules 79 male and 3 female	Volumetry of nodules	Nodules measured 3 times -1mm soft kernel, 2mm soft kernel and 2mm sharp kernel	N/A	repeatability	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. <i>AMERICAN JOURNAL OF ROENTGENOLOGY</i> 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	Variability bewtenn observers	Mean interobserver variability was 0.018% (SD 0.78%). SD of mean for each CT was 13%	Conclude that interobserver variability is lower for volume measurements than diamtere measurements reported in the literature. Reproducibility between CTs also better.
10 - Technical	346	Boll DT, Gilkeson RC, Fleiter TR, et al: Volumetric assessment of pulmonary nodules with ECG-gated MDCT. <i>AJR American Journal of Roentgenology</i> , 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	Multivariate analysis of factros associated with nodule volume change between readings	Cardiac phase, nodule location and nodular 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 in ultra-low-dose CT: comparison with nodule volumetry on standard-dose CT. <i>Journal of Digital Imaging</i> 23:8-17, 2010	Diagnostic comparative	3	202 nodules		each comparator	Ultra LDCT vs CT for volume measurements	n/a	variability in volume measurement	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. <i>AJR American Journal of Roentgenology</i> , 197:223-30, 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. <i>European Radiology</i> 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. <i>European Radiology</i> 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. <i>AJR American Journal of Roentgenology</i> , 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. <i>Eur J Radiol</i> 83(S):848-857, 2014	Diagnostic comparative	3	None (phantom study)	Phantoms with nodules (10 and 12mm)	Scanned 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. <i>Radiology</i> 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. <i>European Radiology</i> 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-Zaporojzan J, Gietema HA, et al: Accuracy of automated volumetry of pulmonary nodules across different multislice CT scanners. <i>European Radiology</i> 17:1979-84, 2007	Diagnostic comparative	3	n/a phantom study	n/a		4 different 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. <i>AJR American Journal of Roentgenology</i> , 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. <i>Radiology</i> 241:251-7, 2006	Diagnostic comparative	3	232	men aged 52-73 with 430 nodules frpm NELSON screening trial	each comparator	local and central 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. <i>Radiology</i> 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 yeield repeatable results.	
10 - Technical	359	Wormann D, Kohl G, Klötz E, et al: Volumetric measurements of pulmonary nodules at multi-row detector CT: In vivo reproducibility. <i>European Radiology</i> 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	

Online Appendix 4

BTS Guideline for the investigation and management of pulmonary nodules

Patient Information

Patient information can be found on the National Lung Cancer Forum for Nurses website:
<http://www.nlcfn.org.uk/>

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