Risk stratification in the investigation of pulmonary nodules in a high risk cohort – PET/CT outperforms clinical risk prediction algorithms.

Authors *(all authors meet authorship criteria as per the ICMJE guidelines)*

[1]Glenna Gibson - Radiology registrar.

[2]Aravind Ravi Kumar - Nuclear medicine physician.

[3]Karin Steinke - Thoracic radiologist.

[4]Farzad Bashirzadeh - Respiratory physician.

[5]Rebecca Roach - Medical registrar.

[6]Morgan Windsor - Thoracic surgeon.

[7]Robert Ware - Statistician.

[8]David Fielding - Respiratory physician.

Affiliations

[1,3] Department of Radiology, Royal Brisbane and Women's Hospital, QLD

[2] Department of Nuclear Medicine, Royal Brisbane and Women's Hospital, QLD

[4,5,6,8] Department of Thoracic Medicine, Royal Brisbane and Women's Hospital, QLD

[7] School of Population Health, University of Queensland, QLD

Corresponding Author

Dr. David Fielding

Address: Department of Thoracic Medicine, Level 3 Ned Hanlon Building, Royal Brisbane and Women's Hospital, Butterfield Street, Herston, QLD, Australia, 4029

Phone: (07) 3646 8111

E-mail: David.Fielding@health.qld.gov.au

Acknowledgements

Royal Brisbane and Women's Hospital

Word Count

Abstract: 246

Main text: 2947

Abstract

Background:

Clinical prediction models and 18F-FDG-PET/CT are used for assessment of solitary pulmonary nodules (SPNs) however biopsy is still required before treatment which carries risk.

Aim:

To determine combined predictive benefit of one such model combined with modern PET/CT data to improve decision making about biopsy prior to treatment and possibly reduce costs.

Method:

Patients with a SPN undergoing 18F-FDG-PET/CT from January 2011-December 2012 were retrospectively identified. 143 patients met inclusion criteria. PET/CT studies were rated (5-point visual scale), and CT characteristics were determined. Tissue was obtained by EBUS-GS, CT-guided biopsy and/or surgery. EBUS-TBNA was used instead of nodule biopsy if there were PET-positive subcentimeter lymph nodes.

Results:

The prediction model yielded an AUC-ROC curve of 64% (95% CI 0.55-0.75). PET/CT increased this to 75% (95% CI 0.65-0.84). The 11% improvement is statistically significant. PET/CT score was the best single predictor for malignancy. A PET score of 1-2 had a specificity of 100% (CI 0.73-1.0) whereas a score of 4-5 had a sensitivity of only 76% (CI 0.68-0.84). No significant difference in clinical prediction scores between groups was noted. PET/CT showed greatest benefit in true negatives and in detecting small mediastinal lymph nodes to allow EBUS-TBNA with higher diagnostic rate. Cost analysis didn't support a policy of resection-without-tissue-diagnosis.

Conclusion:

PET/CT improves clinical prediction of SPNs, but its greatest use is in proving benignity. High PET scores had high false positive rates and didn't add to clinical prediction. PET should be incorporated early in decision making to allow more effective biopsy strategies.

Key Words:

Solitary pulmonary nodule, FDG-PET/CT, clinical prediction model.

Figure 1

Probability of malignancy = $1/(1 + e^{-x})$

where x = -6.8272 + (0.0391 x age) + (0.7917 x cigarettes) + (1.3388 x cancer) + (0.1274 x diameter) + (1.0407 x spiculation) + (0.7838 x upper),

where e is the base of natural logarithms; age is the patient's age in years; cigarettes is 1 if the patient is a current or former smoker and 0 if a never smoker; cancer is 1 if the patient has a personal history of extrathoracic cancer that had been diagnosed > 5 years ago, otherwise 0; diameter is the diameter of the SPN in millimeters; spiculation is 1 if the edge of the lesion has spiculation, otherwise 0; and upper is 1 if the SPN is located in either upper lobe, otherwise 0.

Figure1.jpg

Figure 3

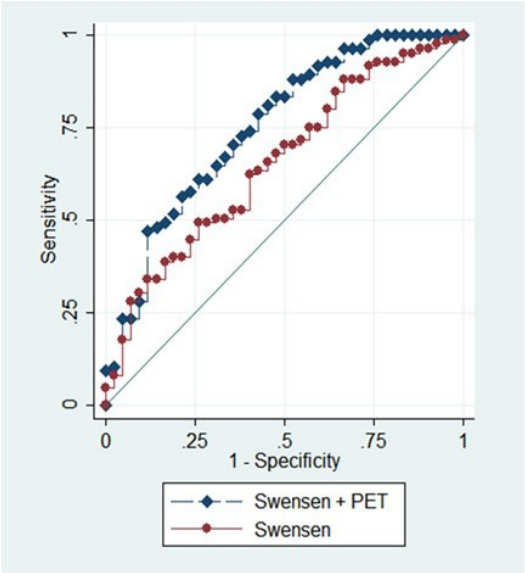
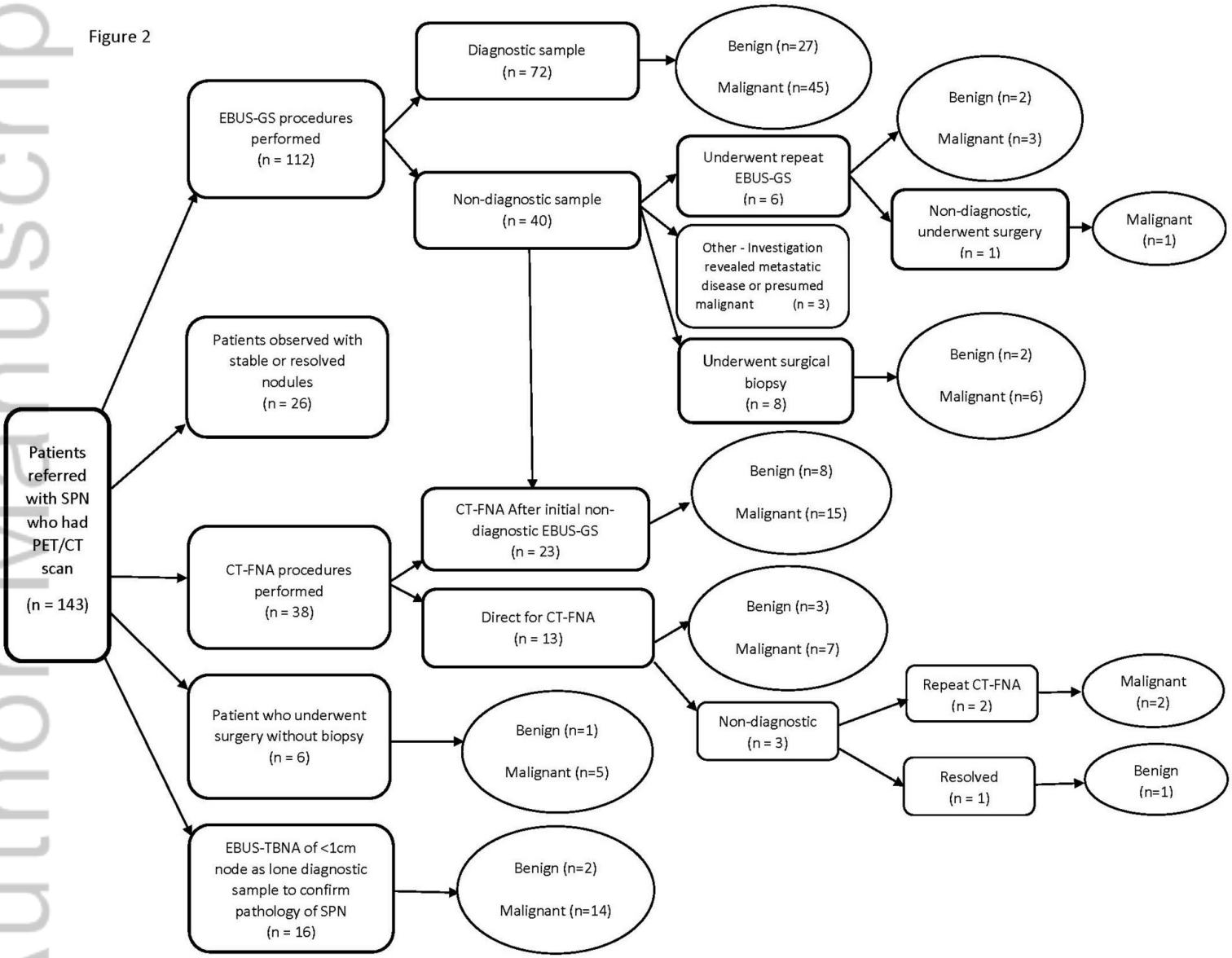


Figure3.jpg

Figure 2



NewFigure2Flowchart.jpg

Risk stratification in the investigation of pulmonary nodules in a high risk cohort – PET/CT outperforms clinical risk prediction algorithms.

INTRODUCTION

The discovery of a solitary pulmonary nodule (SPN) on chest imaging is a common occurrence within the community and hospital setting.[1] This results in a large number of referrals to tertiary/quaternary Thoracic Medicine Clinics for further investigation and management. The most appropriate management pathway for an indeterminate SPN remains controversial despite extensive research and literature,[2,3] and likely varies between centers depending on relevant patient demographics and underlying probability of malignancy.

The widely accepted radiological definition of a SPN is of an entirely intraparenchymal lung lesion with a diameter of between 8-30 mm with no associated atelectasis or adenopathy.[1,4,5] The prevalence of lung cancer in patients with these lesions varies widely in studies from 5% to 70%.[6] This variation likely stems from differences in patient demographics, geography (eg. endemicity of infections such as tuberculosis and coccidioidomycosis) and prevalence of inflammatory lung disease.[6]

Lesion evaluation at our institution will usually consist of a CT, bronchoscopy using endobronchial ultrasonography with guide sheath (EBUS-GS), and 18-fluorine-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT). Patients then proceed to repeat EBUS-GS biopsy and/or CT-guided percutaneous biopsy if the initial sample was non-diagnostic, and surgical biopsy considered under exceptional circumstances. Complication rates for EBUS-GS are extremely low.[3,7] CT-guided

biopsy is known to be associated with risks such as pneumothorax (median 25%, range 4 – 60%), haemorrhage (median 12%, range 2 – 66%), and rare entities such as tumour seeding and air embolism.[8,9] In skilled hands the rate and severity of complications is low and the diagnostic accuracy, sensitivity and specificity lie around 95%.[10] Negative biopsies and complications mean we continue to search for clinical and radiologic identifiers of malignancy which could obviate the need for invasive investigations.

Clinical prediction models have been developed to accurately characterize SPNs. The most well-known model was developed in the 1990's at the Mayo Clinic by Swensen and colleagues, who found that three clinical characteristics (age, cigarette-smoking status, and history of cancer [diagnosed >= 5 years ago]), and three radiological characteristics (diameter, spiculation and upper lobe location) were independent predictors of malignancy.[11] Herder and colleagues subsequently demonstrated that a clinical prediction model alone may underestimate the actual probability of malignancy, and that adding FDG-PET scan results improves diagnostic accuracy.[12]

CT is the mainstay for detection and localization of pulmonary lesions,[13] however it has poor specificity (57%) for characterization of the nodule[14] and reduced sensitivity for detection of metastases when compared with PET/CT.[15]

The utility of PET for predicting malignancy was found in a large meta-analysis to have sensitivity of 96.8% and specificity of 77.8%.[16] PET adds invaluable clinical information but is not able to be used as a stand-alone test.[13,15] Fletcher and others have published on the benefits of using a global rating score for PET/CT as opposed to using only SUV values, which incorporates comparison of tracer uptake of the lung nodule against the background blood pool appearance rather than SUVmax.[4,14,17]

The study purpose was to integrate a validated clinical prediction model with a PET/CT scoring system to obtain an overall likelihood of a SPN being malignant. This was achieved by using the clinical prediction model described by Swensen et al combined with a modified PET scoring system in a manner similar to that proposed by Herder et al, using PET/CT visual interpretation criteria based on a study performed by Fletcher et al.[11,12,14] Importantly these methods require more than simple reporting of SUV values. Given the improvements in scanning technology since these earlier studies we considered that our PET/CT data would be more specific than previous studies.

We wanted to consider the potential impact of using an improved clinical/PET prediction algorithm in a clinic where there were a large number of referrals for small and sometimes difficult to biopsy nodules. This data was applied retrospectively to our patient cohort to better understand whether non-invasive investigation methods could accurately characterise lesions. Many authors advocate for a "surgery without tissue diagnosis" approach for appropriate patients.[13,18,19] However, an accurate algorithm would mean that we might safely send appropriate patients for surgery without the need for invasive biopsy, thus reducing waiting times, costs and complications.

MATERIALS AND METHODS

Approval from the RBWH Human Research Ethics Committee was obtained. This retrospective study was performed in a quaternary thoracic referral center on all patients who presented to our Thoracic Medicine Department with a SPN who underwent 18F-FDG-PET/CT. Patients between January 2011 and December 2012 were analysed.

The primary inclusion criteria was the presence of a new, untreated, solitary pulmonary lesion measuring 8-30 mm. Inclusion was dependent on tissue diagnosis obtained by EBUS-GS or CT-guided biopsy and/or surgery, or, 2-year imaging follow up to confirm benignity. In addition, where there were sub-centimetre regional lymph nodes in a patient referred for

investigation of a nodule with suspicious clinical or PET/CT features, EBUS-TBNA was performed instead of sampling the nodule. Reasons for exclusion included sub-solid and ground glass nodules, pleural involvement, multiple lesions, > 1cm CT lymphadenopathy or other suspected metastatic disease seen on CT or PET/CT, adjacent parenchymal changes suspicious for pneumonia or atelectasis, benign calcifications, and inability to obtain a full set of clinical data. Demographic and clinical data were collected from medical histories and progress notes in medical charts. This included age, sex, smoking status and history of extrathoracic malignancy greater than 5 years ago, for inclusion in modelling as per Swensen et al.[11] Costs of biopsy and surgery were estimated using costs from a similar institution.[20]

CT Image Acquisition and Interpretation

CT scans were reviewed under the supervision of an experienced thoracic radiologist (KS) for the spiculation, size (millimeters), and whether or not the lesion was in an upper lobe. These parameters were chosen based on the validated clinical prediction model described by Swensen et al.[11]

PET/CT Image Acquisition and Interpretation

PET/CT scans were performed on a Phillips Gemini GXL 16 PET/CT scanner (Philips Medical Systems, Cleveland Ohio USA). Patients fasted for a minimum of 4 hours pre-scan and blood sugar levels were checked to ensure levels below 10 mmol/L. Patients received an IV injection of 4.5 MBq/kg of 18F-FDG and underwent a 60 minute uptake period. Emission images were obtained from skull base to mid-thigh with arms up over 10-13 bed positions with 2 minutes (<90kg;) or 2.5 minutes (weight >90 kg) for each bed position. Non-contrast CT scan was acquired during tidal breathing to correlate with emission images. Tube voltage was set at 140kV with current variation according to weight (<60kg:20mA, 60-90kg:30mA, >90kg:50mA).

PET/CT scans were reviewed and rated by a single experienced nuclear medicine physician (ARK) and categorised according to the system used by Fletcher et al as definitely benign(no increased uptake)/probably benign(uptake substantially less than blood pool but greater than lung tissue)/indeterminate(uptake 2-3 times that in reference lung but less than blood pool)/probably malignant(uptake greater than blood pool)/definitely malignant(uptake much greater than blood pool).[14] A visual subjective scale was used as this has been shown to be equal or superior to methods requiring measurement of SUV etc.[4,14,17] For analyses PET/CT scores were coded as a three-level variable (definitely malignant/probably malignant/intermediate to benign).

Clinical Prediction Model According to Swensen et al.[11]

The clinical and radiographic variables used in this established and validated clinical prediction model were the primary focus of our data collection. The model expresses the probability of these variables using a logistic model with parameter values as shown in Figure 1.

Statistical Analysis

Patient characteristics are summarised using mean(standard deviation) for continuous variables and frequency(percentage) for categorical variables. Initial analysis involved assessing the goodness-of-fit of the data from this sample against the model developed by Swensen and colleagues using the Pearson test, where a high p-value implies a well-calibrated model. PET/CT scores were added to the model of Swensen et al and the models were compared. The patients with suspicious regional subcentimeter lymph nodes who had EBUS-TBNA as a first diagnostic test were not used for this part of the analysis, because interpretation of the PET nodule appearance was thought potentially confounded by this regional lymphadenopathy. The predictive ability of models is expressed using the area under the receiver operating characteristic (ROC-AUC) curve. The extra model information due to the addition of PET/CT was assessed using the Bayesian information criterion (BIC).

The BIC identifies the model with the most explanatory power relative to its complexity. By convention a variable added to a model was considered to improve the model if the BIC was at least two units smaller in the new model. Each variable was assessed individually both with and without PET/CT. Analyses were conducted using Stata statistical software v13.1 (StataCorp, College Station, TX, USA).

RESULTS

Final analysis included 143 patients, 127 patients who had a SPN alone and 16 patients with a SPN and a locoregional FDG-avid subcentimeter lymph node on PET/CT. Baseline demographic data and PET/CT scores of SPN only patients are presented in Table 1. One hundred fourteen (89.8%) patients were active smokers or had a history of smoking. Overall 86 (67.7%) of SPN's were characterised as definitely malignant on PET/CT.

Biopsies were performed in 117 patients (26 patients were monitored for progress/resolution rather than biopsied). Figure 2 shows distribution and subsequent outcomes for all patients. Thirty-one biopsies were repeat biopsy episodes due to non-diagnostic initial biopsy. Diagnostic yield and non-diagnostic biopsies are presented in Table 2. Of the EBUS-GS performed, a total of six patients had a second EBUS-GS and 23 proceeded to CT-FNA. The total number of EBUS-GS procedures was therefore 112 and CT-FNA was 38. Sixteen patients underwent EBUS-TBNA instead of SPN biopsy, six of which had a PET/CT scan prior to biopsy.

The most common malignant diagnosis was non-small cell lung carcinoma (adenocarcinoma [n = 34], squamous cell carcinoma [n = 16], unspecified non-small cell lung carcinoma [n = 14]). A benign pulmonary nodule was diagnosed in 42 of 127 (33%) patients with tissue diagnosis obtained in 16 patients. Ten nodules resolved within the follow-up period of two

years, and 16 nodules were shown to be stable on CT in this timeframe and were thus classified as benign (Table 3).

Model Validation and Operating Characteristics

The Pearson goodness-of-fit statistic (P=0.44) indicated the observed proportion of malignancies did not differ from the proportion predicted by the model described by Swensen and colleagues. The probability of malignancy was calculated using the complete model (i.e. using the six variables with the specified coefficients) of Swensen and the ROC-AUC= 0.58 (95% CI= 0.48–0.69). When the six variables were re-specified according to the study data the ROC-AUC improved to 0.65 (95% CI = 0.55–0.75). When PET/CT scan scores were included in the re-specified model the ROC-AUC rose to 0.75 (95% CI = 0.65–0.84), a significant improvement over the model that did not include PET/CT scores (P=0.02). The two ROC curves are displayed in Figure 3.

Variables were subsequently analyzed to determine which were the most significantly associated with malignancy. Size was the only variable shown to be statistically significant, whereas age, smoking, history of cancer, spiculation and upper lobe location were not. When PET/CT scores were added, BIC values suggest that PET/CT scores alone provides a better model than PET/CT score with any other variable. Results are presented in Table 4.

As shown in Table 1, PET/CT was reported as “definitely malignant” in 86 cases however only 69 of these cases were malignant (80%) compared to 17 cases (20%) which were benign. Conversely there were 10 lesions reported on PET/CT as either “Definitely benign” or “Probably benign” and all of these were shown to truly be benign (see Table 5).

Because PET/CT out-performed all other clinical indices, we further explored the potential relative costs of an operate-without-tissue-diagnosis strategy in these 86 cases. Table 6 shows the costs of two different hypothetical management strategies, one electing to only

operate on confirmed malignancy cases and the other to operate on all cases with PET/CT reported as showing “Definitely malignant”. It shows that for the 24 month period there is a cost saving of over $100,000, as well as the fact that for the no-biopsy strategy there are 17 cases who have had an unnecessary thoracotomy.

DISCUSSION

Our results demonstrate that PET/CT characterisation of a SPN improves the ability to predict malignancy in our patient group by 10%. While this is statistically significant, this modest improvement is unlikely to strongly impact the way a clinician chooses to manage their patients over and above what they already consider to be the patient’s likelihood of malignancy based on clinical history and pre-test probability. The six clinical and radiologic characteristics shown to be most strongly associated with malignancy were analysed in our cohort, with only size of the lesion shown to be significantly associated with malignancy. However, PET/CT results were shown to be the single most significant variable when it came to predicting the likelihood of malignancy.

Overall specificity of our PET/CT results were much lower than reported in other studies (29% compared to an average of 77.8%).[16] A large number of benign lesions were considered likely malignant due to strongly avid FDG uptake. This correlates with the well-described finding that false positive results are one of the major factors which limit the accuracy of PET/CT.[6,12,15] We hypothesize that our higher-than-average number of false positive results may stem from the often complicated nature of referrals to our quaternary referral center. Indeed many patients sent for management in our clinic have had lesions with strong radiological suspicion for malignancy, (hence their referral having undergone variable periods of observation and/or attempts at biopsy) on lesions which ultimately were found to be benign (i.e. many patients with benign lesions were pre-selected out of our patient cohort). This creates a selection bias in our patient group and is predicted to have increased the number of false positive lesions we encountered. This has likely resulted in a

falsely low representation of the true specificity of PET/CT and our results may not be able to be applied to all patient groups in all centers.

Secondly, prevalence of malignancy in our patient group, again likely due to the complex nature of our referrals and pre-selection, is higher than that described in most centers (67 % compared to 20 – 57%).[11,14,21,22] By the time patients are referred to us most lesions have strong radiologic features of malignancy and/or have had observation showing lesion growth or other worrisome features. The performance of the clinical algorithm in our study was probably limited by this very high prevalence of malignancy. Most clinical risk prediction algorithms are individualised toward particular patient groups and directed toward the detection of early lung cancers.[23] This study is focused on larger lesions (> 8mm) which may account for the comparatively poor performance of our clinical predictors.

The complete absence of false negative results (sensitivity = 100%) does however, highlight one of the foremost advantages of PET/CT; lack of FDG uptake is an accurate predictor of benignity. This highlights a subgroup of patients who could be spared invasive biopsy in the pursuit for a diagnostic tissue sample if PET/CT was done before any form of biopsy, as it is unlikely to change management. Unfortunately, current Australian Medicare guidelines do not allow funded PET/CT scans before tissue diagnosis in most cases and this may limit access of this valuable investigation to a significant patient population.[24]

Whilst this method of PET/CT interpretation results in clinically useful low false negative results, the true ability of nuclear medicine physicians in interpreting the clinical significance of an FDG avid lesion is underestimated using the Fletcher method as there is no consideration given for benign causes of FDG-avidity. Real-life reporting will take into account the clinical history, pattern of abnormality, radiological appearance and other imaging/laboratory tests, which would likely result in higher positive predictive values and specificity.

A subgroup of 16 patients had possible metastatic subcentimeter nodal disease on PET/CT. In 14 of 16 patients (87.5%) a diagnosis of malignancy was provided by EBUS-TBNA, thereby avoiding the need for other form of biopsy. PET/CT expert visual interpretation of mediastinal nodes has been shown to have an accuracy of greater than 95% in a recent study.[25]

Sensitivity and specificity of EBUS-TBNA were both 100%. These positive results are well published elsewhere, with a 2009 meta-analysis revealing a sensitivity of 93% and specificity of 100%,[26] and negligible complications reported.[27,28] Subcentimeter nodes are rarely reported to be biopsied for tissue diagnosis of cancer, and this method has clear potential for greater uptake, particularly as a substitute for the more difficult biopsy of the peripheral lesion. None of our patients who had EBUS-TBNA in this way experienced a procedure-related complication and none required a repeat biopsy due to non-diagnostic specimen. This is another reason patients would benefit from undergoing PET/CT scan before any form of invasive investigation, as the most appropriate biopsy technique (EBUS-TBNA versus EBUS-GS) can be selected.

Guidelines for decision making regarding management in patients with SPN has been updated recently,[18] and surgical resection without prior tissue diagnosis remains an acceptable and recommended pathway in some patients with a very high probability of cancer.[13] In our cohort, 7 patients with malignancy not treatable by surgical resection (2 with small cell lung carcinoma and 5 with metastases) could have been deemed appropriate for surgery as a first line management. This brings to point that while surgery before tissue diagnosis remains a valid option in certain cases, this approach continues to fall out of favour in many institutions despite the advances in functional imaging such as PET/CT. The morbidity and mortality of performing surgery in these patients would need to be individually assessed, but could be deemed unacceptable in many cases. In our experience, the

decision to observe lesions or obtain tissue diagnosis before referring for surgical management did not result in any patients having missed diagnoses or clinically significant delay in treatment. These findings strongly support a tissue-diagnosis-before-surgery pathway.

ACKNOWLEDGEMENTS

Royal Brisbane and Women's Hospital and the University of Queensland, School of Population Health.

CONCLUSION

While PET/CT results improve upon the predictive ability of this clinical prediction model in the characterization of SPNs, the degree of improvement may not be clinically significant, particularly in a complex patient group seen at a quaternary referral center with a high pre-test probability of malignancy. PET/CT outperformed all other clinical factors, however, could not be relied on to accurately discriminate nodules even when reported as "Definitely malignant" by the Fletcher criteria. The true value of PET/CT in our patient cohort lies firstly in the confident identification of benign nodules, and secondly, in the identification of unexpected mediastinal and hilar nodal disease. This finding identifies a subgroup of patients who can undergo safe and accurate tissue diagnosis via EBUS-TBNA in lieu of biopsy of the SPN, therefore decreasing exposure to biopsy techniques with higher complication and repeat biopsy rates. Our data therefore supports the use of pre-procedure PET/CT. Overall the combination of EBUS-GS and EBUS-TBNA, with subsequent CT-FNA for negative samples remains a sensitive and cost effective approach. Until PET/CT results and/or clinical predictors can accurately predict malignancy in all patient cohorts, obtaining tissue diagnosis via invasive biopsy remains a necessary step before sending patients to surgery.

REFERENCES

1 - Ost D, Fein AM, Feinsilver SH. Clinical practice. The solitary pulmonary nodule. N Engl J Med 2003; 348: 2535-42.

2 - Callister ME, Baldwin DR, Akram AR, Barnard S, Cane P, Draffan J, et al; British Thoracic Society Pulmonary Nodule Guideline Development Group; British Thoracic Society Standards of Care Committee. British Thoracic Society guidelines for the investigation and management of pulmonary nodules. Thorax 2015 Aug; 70 Suppl 2: ii1-ii54. doi: 10.1136/thoraxjnl-2015-207168.

3 - Gould MK, Donington J, Lynch WR, Mazzone PJ, Midthun DE, Naidich DP, et al. Evaluation of individuals with pulmonary nodules: when is it lung cancer? Chest 2013; 143(Suppl): e93S–e120S

4 - Kim SK, Auerbach BD, Goldin J, Fueger BJ, Dahlbom M, Brown M, et al. Accuracy of PET/CT in characterization of solitary pulmonary lesions. J Nucl Med 2007; 48: 214–20.

5 - Tan BB, Flaherty KR, Kazerooni EA, Iannettoni MD. The solitary pulmonary nodule. Chest 2003; 123(1 suppl): 89S–96S.

6 - Sharma P, Singh H, Basu S, Kumar R. Positron emission tomography-computed tomography in the management of lung cancer: An update. South Asian Journal of Cancer 2013; 2: 171-78.

7 - Hayama M, Izumo T, Matsumoto Y, Chavez C, Tsuchida T, Sasada S. Complications with Endobronchial Ultrasound with a Guide Sheath for the Diagnosis of Peripheral Pulmonary Lesions. Respiration 2015; 90: 129-35.

8 - Loh SE, Wu DD, Venkatesh SK, Ong CK, Liu E, Seto KY, et al. CT-guided thoracic biopsy: evaluating diagnostic yield and complications. Ann Acad Med Singapore 2013; 42: 285-90.

9 - Wiener RS1, Wiener DC, Gould MK. Risks of Transthoracic Needle Biopsy: How High? Clin Pulm Med 2013; 20: 29-35.

10 - Yang W, Sun W, Li Q, Yao Y, Lv T, Zeng J, et al. Diagnostic Accuracy of CT Guided Transthoracic Needle Biopsy for Solitary Pulmonary Nodules. PLoS One 2015.10: doi:10.1371/ journal.pone.0131373

11 - Swensen SJ, Silverstein MD, Ilstrup DM, Schleck CD, Edell ES. The probability of malignancy in solitary pulmonary nodules. Application to small radiologically indeterminate nodules. Arch Intern Med 1997; 157: 849-55.

12 - Herder GJ, van Tinteren H, Golding RP, Kostense PJ, Comans EF, Smit EF, et al. Clinical prediction model to characterize pulmonary nodules: validation and added value of 18F-fluorodeoxyglucose positron emission tomography. Chest. 2005; 128: 2490-6.

13 - Ost DE, Gould MK. Decision making in patients with pulmonary nodules. Am J Respir Crit Care Med 2012; 185: 363-72.

14 - Fletcher JW, Kymes SM, Gould M, Alazraki N, Coleman RE, Lowe VJ, et al. A comparison of the diagnostic accuracy of 18F-FDG PET and CT in the characterization of solitary pulmonary nodules. J Nucl Med 2008; 49: 179-85.

15 - Jeong YJ, Yi CA, Lee KS. Solitary pulmonary nodules: detection, characterization, and guidance for further diagnostic workup and treatment. AJR Am J Roentgenol. 2007; 188: 57-68.

16 - Gould MK, Maclean CC, Kuschner WG, Rydzak CE, Owens DK. Accuracy of Positron Emission Tomography for diagnosis of pulmonary nodules and mass lesions: a meta-analysis. JAMA 2001; 285: 914–24.

17 - van Gómez López O, García Vicente AM, Honguero Martínez AF, Londono GAJ, Caicedo CHV, Atance PL, et al. (18)F-FDG-PET/CT in the assessment of pulmonary solitary nodules: comparison of different analysis methods and risk variables in the prediction of malignancy. Transl Lung Cancer Res 2015; 4: 228-35.

18 - Detterbeck FC, Lewis S, Diekemper R, Addrizzo-Harris D, Alberts W. Executive Summary: Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2013; 143(5 Suppl):7S-37S.

19 - Rivera MP, Mehta AC, Wahidi MM. Establishing the diagnosis of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013; 143(5 Suppl): e142S-65S.

20 - Steinfort, DP. Endobronchial ultrasound in the management of lung cancer: integration of a new technology into clinical care. PhD thesis, Medicine, Dentistry & Health Sciences - Medicine (RMH & WH), The University of Melbourne. 2012: http://hdl.handle.net/11343/37699

21- Gould MK, Ananth L, Barnett PG, Veterans Affairs SNAP Cooperative Study Group. A clinical model to estimate the pretest probability of lung cancer in patients with solitary pulmonary nodules. Chest 2007; 131: 383-8.

22 - Dabrowska M, Krenke R, Korczynski P, Maskey-Warzechowska M, Zukowska M, Kunikowska J, et al. Diagnostic accuracy of contrast-enhanced computed tomography and positron emission tomography with 18-FDG in identifying malignant solitary pulmonary nodules. Medicine (Baltimore). 2015; 94: e666.

23- Adamek M, Wachuła E, Szabłowska-Siwik S, Boratyn-Nowicka A, Czyzewski D. Risk factors assessment and risk prediction models in lung cancer screening candidates. Ann Trans Med 2016; 4:151.

24 - Medicare Benefits Schedule Book Category 5. Australian Government Department of Health [updated 01 Mar 2014]; cited 09 Feb 2017. Available from: http://www.health.gov.au/mbsonline.

25 - Nguyen P, Bhatt M, Bashirzadeh F, Hundloe J, Ware R, Fielding D, et al. Comparison of objective criteria and expert visual interpretation to classify benign and malignant hilar and mediastinal nodes on 18-F FDG PET/CT. Respirology 2015; 20: 129-37.

26 - Gu P, Zhao YZ, Jiang LY, Zhang W, Xin Y, Han BH. Endobronchial ultrasound-guided transbronchial needle aspiration for staging of lung cancer: a systematic review and meta-analysis. Eur J Cancer 2009; 45:1389–96.

27 - Guarize J, Pardolesi A, Donghi S, Filippi N, Casadio C, Midolo V, et al. Endobronchial ultrasound for mediastinal staging in lung cancer patients. Multimed Man Cardiothorac Surg 2014; doi: 10.1093/mmcts/mmu021.

28 - Steinfort, DP, Hew, MJ, Irving, LB. Bronchoscopic evaluation of the mediastinum using endobronchial ultrasound: a description of the first 216 cases carried out at an Australian tertiary hospital. Intern Med J 2011; 41: 815–24.

Figure Legends

Figure 1

Clinical Prediction Model according to Swensen et al.[11]

Figure 2

Investigation pathway and pathology (benign vs malignant).

Figure 3

ROC curves for the prediction model of Swensen et al,[11] and for the combined model of Swensen and FDG-PET/CT scores.

Tables

Table 1 – Baseline Demographic Data and PET/CT Scores of SPN

			Malignant (n = 85)	Benign (n = 42)
Clinical Prediction Model[11]	Mean age yrs (SD)		68.7 (10.4)	66.5 (9.3)
	Smoker		77 (90%)	37(88%)
	Cancer > 5 yrs ago		39 (46%)	16 (38%)
	Spiculation		37 (44%)	22 (52%)
	Location	Upper lobe	47 (55%)	27 (64%)
		Elsewhere	39 (46%)	15 (36%)
	Diameter	8 – 10 mm	9 (10%)	7 (17%)
		11 - 20 mm	33 (39%)	20 (47%)
		21 - 30 mm	44 (51%)	15 (36%)
PET/CT Score[12]	1	Definitely benign	0 (0%)	1 (2%)
	2	Probably benign	0 (0%)	9 (21%)
	3	Indeterminate	7 (8%)	8 (18%)
	4	Probably malignant	10 (12%)	7 (18%)
	5	Definitely malignant	69 (80%)	17 (41%)

Table 2 – Biopsy Data

	EBUS-GS (n = 112)	EBUS-TBNA (n = 16)	CT-guided FNA (n = 38)
Diagnostic Yield	72 (64%)	14 (87.5%)	34 (90%)
Repeat Biopsy	31 (29%)	0 (0%)	2 (5%)

Where n = total number of cases, numbers in cells = numbers of patients with respective percentages in brackets

Table 3 – Pathology of peripheral pulmonary nodules

Type	Diagnosis	n	%
Malignant	Adenocarcinoma	34	67
	Squamous cell carcinoma	16	
	Unspecified NSCLC	14	
	Metastatic disease	5	
	Undifferentiated malignancy	4	
	Carcinoid	3	
	Adenosquamous carcinoma	3	
	Carcinoma in situ	2	
	Small cell carcinoma	2	
	Basaloid	1	
	Poorly differentiated carcinoma	1	
Benign	Fibrosis/scar	5	*33
	Inflammation	4	
	Benign lymphoid	2	
	Cryptococcus	1	
	Pneumonia	1	
	Hamartoma	1	
	Anthracotic scar	1	
	Fungus ball	1	
	Resolved or stable for 2 years	26	

Table 4

Variable	Univariable	BIC	Adjusted by PET/CT	BIC
Age	1.02 (0.98, 1.06); 0.30	169.8	1.01 (0.97, 1.06); 0.49	159.1
History of smoking	1.02 (0.98, 1.06); 0.30	170.8	0.90 (0.25, 3.29); 0.88	159.6
Cancer > 5 yrs ago	1.38 (0.65, 2.93); 0.41	170.2	1.69 (0.72, 3.94); 0.22	158.1
Size	1.06 (1.00, 1.12); 0.04	166.3	1.02 (0.96, 1.09); 0.43	159.0
Spiculation	0.70 (0.33, 1.47); 0.35	170.0	0.83 (0.37, 1.89); 0.66	159.4
Upper lobe	0.66 (0.31, 1.40); 0.28	169.7	0.89 (0.38, 2.07); 0.79	159.6
PET/CT				
Def. malignant	1.00 (ref)	154.8		
Prob. malignant	0.38 (0.13, 1.13); 0.08			
Indeterminate/Benign	0.11 (0.04, 0.30); <0.001			

Univariable logistic regressions show size is statistically significant, however PET/CT has the lowest BIC value for all variables and is therefore the single best predictor as a stand-alone model. Adding PET/CT to each variable results in all variables being statistically insignificant.

Table 5 – Final pathology vs PET/CT characterisation

	Malignant (85)	Benign (42)
Pet Score 1,2	0	10
Pet Score 3*,4,5	85	32

*A PET score of 3 (indeterminate) was included in positive scores as these lesions were likely to be investigated as potentially malignant.

Sn=100%, Sp=29%, NPV=100%, PPV=73%

Table 6 - **Results of costs for differing biopsy strategies for 86 patients with PET/CT scores showing "Definitely malignant".**

	Surgery for biopsy confirmed primary lung malignancy		Surgery only for all "definitely malignant" on PET without biopsy	
	Number	Total cost	Number	Total cost
EBUS-GS	81	81 x $2,748 = $222,588	0	0
CT-FNA	23	23 x $2,724 = $62,652	0	0
Surgery	69	69 x $23,327 = $1,609,563	86	86 x $23,327 = $2,006,122
Total		$1,894,803		$2,006,122