

A Retrospective Validation Study of 3 Models to Estimate the Probability of Malignancy in Patients with Small Pulmonary Nodules from a Tertiary Oncology Follow-up Centre

Introduction

The management of patients with small pulmonary nodules (PNs) is clinically challenging. With the widespread availability of multi-detector row CT scanners and the significant increase in the number of scans performed¹, this scenario is likely to increase in clinical practice, and clear evidence is required to guide management strategies.

Data from published case series in Europe^{2 3}, Asia^{4 5}, and America^{6 7 8} report the prevalence of PNs from 2% to 24% (mean 13%) with a mean lung cancer prevalence of 1.5%. The prevalence of PNs in a screening population is higher (mean 33%)⁹ but management of nodules in this scenario is predetermined for the majority of screening programmes.

The effective management of PNs requires knowledge of the “pre-test” probability of malignancy in each individual patient, prior to conducting further investigation¹⁰. The British Thoracic Society Guidelines for the management of pulmonary nodules recommends the use of prediction models when evaluating these patients.

Twenty-eight studies ¹¹⁻³³ in the literature have evaluated the clinical and radiological characteristics of PNs in relation to the probability of malignancy. Four studies have developed composite prediction models that can be used in clinical practice and are easily accessible.

Swensen et al¹¹ (Mayo model) and Gould et al ¹² (VA model) identified independent clinical and radiological predictors of malignancy and used this to create and validate models with an AUC of 0.8.

The Mayo model was validated with the additional parameter of PET avidity by Herder et al ¹³, increasing the AUC to 0.92 (the Herder model).

McWilliams et al¹⁴ developed a model based on a lung cancer screening population. The AUC for this model was 0.94 and specifically 0.91 for nodules $\leq 10\text{mm}$.

A number of case series have attempted to address the likelihood of malignancy in patients with known extra-thoracic cancer ³⁴⁻³⁵. However due to their heterogeneity, and small patient numbers these studies do not provide sufficient data to distinguish benign from malignant nodules or a metastasis from a primary lung cancer.

The aim of this study was to validate three existing composite prediction models in a non-screening clinically referred patient population with small, predominantly sub-centimeter PNs.

Materials and Methods

The Research and Development department at our Trust approved the study and waived requirements for informed consent.

Case Identification and Data Collection

The electronic medical records of all patients with PNs reported on CT imaging, between January 2012 to January 2013 at our centre were identified by a word search on the Radiology Information System (RIS) using the phrase “pulmonary nodule(s)” and/or “lung nodule(s)”. Once identified, each report was reviewed and patients with nodules of less than 12 mm identified. A 12mm nodule diameter was used as a cut-off to maximize the number of primary lung cancers (which often present above 10mm diameter at initial presentation) included with the data-set.

Patient demographics, the clinical indication for CT imaging, radiological characteristics of the pulmonary nodules and the final diagnosis were recorded.

The patients were divided into two groups:

1. Incidental finding on a chest CT in patients with or without respiratory symptoms with any history of malignancy within 5 years.

2. Patients with either a known or prior cancer within the last 5 years, scanned either as a staging or follow up scan, or scanned for another reason.

The distribution of patients in each group is shown in Table 1.

Ground truth diagnosis of the pulmonary nodule was determined as:

- a) Malignant when histopathology revealed a specific malignant diagnosis.
- b) Pulmonary metastasis without histology was defined as a non-calcified nodule with a smooth regular border, demonstrating either growth (percentage volume change of $\geq 25\%^{34}$), or a reduction in size due to chemotherapy treatment, assessed by a chest radiologist.
- c) Benign diagnosis by either benign histopathology or nodule stability over 2 years of CT follow-up, defined as a percentage volume change of $\leq 25\%$.

Patients

The initial electronic search of the radiology information search system identified 2256 CT scans performed in 1209 patients.

The CT image was reviewed to confirm the presence of the nodule, confirm nodule size (using 2D caliper measurements) and to collect information about nodule morphology. In the case of nodules not diagnosed as malignant on histology, volume growth was recorded using the Lung VCAR application (GE Healthcare systems).

The electronic patient records were reviewed for patient age, gender, smoking history, history of active or previous cancer, and family history of cancer. Histology reports were reviewed to confirm the diagnosis of the resected nodule.

Patients were excluded for the following reasons: incomplete demographic data, no nodule identifiable on the CT, nodule size > 12 mm, CT follow up of < 2 years in the case of likely benign nodules or if no histology was available.

Figure 1 summarises study eligibility and reasons for patient exclusion.

Data Analysis

A comparison of final diagnosis to the probability of malignancy predicted by each of the Mayo Model, the VA model and the McWilliams model was calculated (see Appendix A for links to each prediction model calculator). Model accuracy was assessed by calculating the area under the receiver operating characteristic (ROC) curve, comparing the model probability of malignancy with the actual patient diagnosis. Calibration curves were calculated between the observed and predicted probabilities of the models (see Appendix B).

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123 Attempted assessment of the Herder model was limited by the small number of
124 patients undergoing PET-CT for sub-centimeter PNs (required in the model). The
125 results of this analysis are presented in Appendix B only.

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127 Analyses were performed using SPSS for Mac Version 22.0.

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Results

702 of 1209 patients met the inclusion criteria for the study.

Baseline demographics of the population are presented in Table 1. Current or former smokers accounted for 457 (65%) patients and 306 (43.6%) patients had an active or previous history of lung or extra-thoracic cancer.

Of 702 nodules identified, 379 (54%) were benign, 303 (43%) pulmonary metastases and 20 (3%) primary lung cancers. The overall prevalence of malignancy in this cohort was 46%.

Size of the nodule was not associated with a malignant diagnosis ($p=0.076$). The majority of nodules were solid (95.7%) and all perifissural nodules were benign. Nodules in upper lobes were more likely to be malignant in comparison to nodules found in the lower lobes ($p=0.021$), but there was no significant difference in the number of malignant nodules seen in the right lung.

7 of the 379 patients (%) with a benign PN had a diagnosis of fungal infection confirmed by histopathology.

Of the 20 primary lung cancers, 16 were adenocarcinomas and 4 squamous cell carcinomas. Patients with a prior history of malignancy were more likely to present with a malignant nodule ($p=0.001$). The diagnosis of the primary cancer in patients with pulmonary metastases is shown in Figure 2.

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169 A summary of the other characteristics and method of nodule diagnosis is shown

170 in Table 2.

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Validation of Prediction Models

The probability of malignancy score was calculated by each model using online published calculators (Appendix A). Probability scores were compared to the actual patient diagnosis determined by histopathology or 2 year CT thorax follow-up of the pulmonary nodule.

Comparison Between Models

The area under the ROC curve (AUC) was highest for the McWilliams Model (0.82; 95%CI 0.78-0.91) and lowest for the Mayo Model (0.58; 95% CI 0.55-0.59). The VA Model had an AUC of (0.62; 95%CI 0.47-0.64).

The ROC curves for each of the models are shown in Figure 3.

The AUC for each of the models was calculated separately for patients with a prior history of malignancy (within 5 years) and for those without a prior history of malignancy. This analysis showed that the McWilliams model performed less well in patients with a prior history of malignancy, whilst the Mayo and VA performed slightly better in this group.

The results are shown in Table 3.

The calibration of the models is shown in Figure 4, Appendix B.

Discussion

This is the largest study to our knowledge to validate predictive models for PNs in a non-screening clinically referred patient population. All three of the validated models in this study were not specifically designed for use in patients with a previous history of malignancy within 5 years of presentation with a PN. However in clinical practice, it is often this group of patients where it is challenging to differentiate between primary lung cancer, pulmonary metastases or benign nodules, and this is particularly the case with sub-centimeter nodules. In this study population, 12.1% of patients with a prior history of malignancy were subsequently diagnosed with a benign nodule.

Our findings indicate that the accuracy of all models is lower in patients with prior malignancy than that reported in the papers that described their development. The McWilliams model was the most accurate overall; this may be due to this model having a high percentage of sub-centimeter pulmonary nodules in both development and validation datasets.

The accuracy of the Mayo and VA models was higher in patients with a prior history of malignancy. This may be due to the higher prevalence of nodule malignancy in the models' development datasets, similar to our population. Conversely, the McWilliams model (based on a lung cancer screening population) had a greater accuracy amongst patients without a previous history of cancer.

All models underestimated the probability of malignancy from the first up to at least the third quintile. This may be due to the prevalence of nodule malignancy in our patient sample being higher (46%) than the development data set of the Mayo (23%) and McWilliams (5.5%) model. In contrast, the VA model was developed from patient cohorts with a relatively high prevalence of malignancy (54%). Hence the highest overestimation for malignancy was seen in this model, in those with a high pre-test probability.

The calibration plots (Appendix B, Figure 4) demonstrate variability in the predictive ability of each model according to malignant nodule prevalence. This implies that before widespread use of predictive models as suggested by the current evidence based guidelines, the characteristics of the local population should be assessed. The overall appearance of the McWilliams model calibration plot showed a greater spread between each quintile in comparison to the other models, demonstrating it to be the most accurate at predicting malignancy for nodules with both a high, intermediate and low probability.

Combining information from the ROC analysis and calibration data, the McWilliams model has the best discriminative ability between benign and malignant nodules using these validation methods. It performs best overall in patients without a prior history of malignancy (Table 3).

The first study to validate prediction models in the UK by Al-Ameri et al³⁶ found the Herder to be the most accurate in predicting malignant risk, even in patients

with a prior history of cancer. For smaller sub-centimeter nodules, the highest accuracy was seen for the McWilliams model, as seen in this study.

The BTS pulmonary nodule guidelines 2015 recommend the validation of composite prediction models in patients with a prior history of extra-thoracic malignancy. Our results demonstrate the limitations of these composite models when utilised in a population with a high prevalence of such patients and in particular in PNs ≤ 12 mm. Further research is needed to risk stratify patients according to the patient's mode of presentation, irrespective of nodule size. Obtaining data from multiple centres may reduce bias in the distribution and prior diagnoses of patients.

This study has several limitations. There was an under-representation of primary lung cancers within the population of patients presenting with small (particularly sub-centimeter) pulmonary nodules. This is representative of a non-screening clinical practice, with most patients with clinically diagnosed primary lung cancer presenting at a later stage. The population had a high proportion of patients with pulmonary metastases, as patients were included with a current or prior history of cancer which is a common and difficult clinical scenario. There was therefore a bias towards these diagnoses which may be underrepresented in other centres. The majority of patients with pulmonary metastases did not have a histological diagnosis. In addition, there were no patients from a lung cancer screening population, as this is yet to be established in the UK. However, the selected population reflects clinical practice in whom there is likely to be a mix of patients with and without a prior history of cancer,

suggesting that our results are likely to be applicable to a broad range of UK practice.

In conclusion, our study demonstrates that all three prediction models assessed had a lower predictive value than published in the original papers. The McWilliams model appears to be the most clinically useful tool to establish the pre-test probability of malignancy in an unselected population that includes patients with a prior history of malignancy.

Further studies are now needed to create and validate prediction models tailored specifically for patients with a prior history of extra-thoracic malignancy.

Figure Legends:

Figure 1: Study Eligibility and Reasons for Patient Exclusion

Figure 2: Primary Cancer Site of Patients with Pulmonary Metastases

Figure 3: Receiver Operator Characteristic Curves for Validation of 4 Composite Prediction Models

Figure 4: Calibration Curves for Validation of Composite Prediction Models (in Appendix B)

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