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ONCOLOGY

Predicting EGFR mutation status in lung cancer:Proposal for a scoring model using imaging and demographic characteristics

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Abstract
Objective To determine if a combination of CT and demographic features can predict EGFR mutation status in bronchogenic carcinoma.
Methods We reviewed demographic and CT features for patients with molecular profiling for resected non-small cell lung carcinoma. Using multivariate logistic regression, we identified features predictive of EGFR mutation. Prognostic factors identified from the logistic regression model were then used to build a more practical scoring system.
Results A scoring system awarding 5 points for no or minimal smoking history, 3 points for tumours with ground glass component, 3 points for airbronchograms, 2 points for absence of preoperative evidence of nodal enlargement or metastases and 1 point for doubling time of more than a year, resulted in an AUROC of 0.861. A total score of at least 8 yielded a specificity of 95 %. On multivariate analysis sex was not found to be predictor of EGFR status.
Conclusions A weighted scoring system combining imaging and demographic data holds promise as a predictor of EGFR status. Further studies are necessary to determine reproducibility in other patient groups. A predictive score may help determine which patients would benefit from molecular profiling and may help inform treatment decisions when molecular profiling is not possible.
Key points
- *EGFR mutation-targeted chemotherapy for bronchogenic carcinoma has a high success rate.*
- *Mutation testing is not possible in all patients.*
- *EGFR associations include subsolid density, slow tumour growth and minimal/no smoking history.*
- *Demographic or imaging features alone are weak predictors of EGFR status.*
- *A scoring system, using imaging and demographic features, is more predictive.*

Keywords EGFR · Lung cancer · Gene mutation · Scoring model · Adenocarcinoma

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Introduction

Despite improvements in early detection and surgical techniques, the 5-year survival for lung cancer in North America is only 17 % [1]. The majority of patients present with advanced disease and lung cancer remains the leading cause of cancer death [2, 3]. However, the introduction of oncogene-specific targeted chemotherapy and opportunities for personalised medicine has ushered in a promising new era in the battle against lung cancer.

Epidermal growth factor receptor (EGFR) mutation is the most common mutation for which there is US Food and Drug Administration (FDA)-approved targeted chemotherapy (gefitinib and erlotinib). Several phase III trials have shown a marked improvement in progression-free survival when

patients with EGFR mutation-positive tumours are treated with targeted chemotherapy rather than traditional chemotherapy [4].

As a group, patients with EGFR mutation-positive tumours demonstrate different demographics than those without the mutation. Patients with EGFR-positive tumours are more likely to be never smokers, female and of Asian descent [5–7]. While sex has been shown to be associated with EGFR mutation status in univariate analysis, recently the association has been questioned with some data showing that sex loses any significance when results are stratified by smoking status [8, 9]. The prevalence of EGFR mutation in adenocarcinoma is variable geographically, ranging from 60 % in some East Asian countries to 10 % in North America [9–11].

The relationship between EGFR status and imaging appearance on computed tomography (CT) is less clear. Some studies have found that ground glass tumours are more likely to be EGFR positive [12, 13] and others have found no statistically significant relationship or have found an inverse relationship [14, 15]. Other CT characteristics found to be associated with EGFR mutation include air bronchograms and small tumour size [16, 17].

While individual demographic and imaging variables appear to be associated with an increased likelihood of EGFR mutation, no one variable is adequately predictive [9]. There is a suggestion that some centres may use EGFR inhibitors to treat non-smokers with adenocarcinoma even when molecular profiling has not been performed [4]. However, even in large studies performed in areas with a high prevalence of EGFR mutation, only 60 % of never smokers with adenocarcinoma will have EGFR-positive tumours [9]. It is cost-prohibitive to use EGFR-targeted treatment for tumours without the mutation. The International Association for the Study of Lung Cancer recommends molecular testing for adenocarcinomas prior to chemotherapy regardless of sex or smoking status [18]. Nonetheless, there are some patients for whom tissue sampling is not possible. We sought to determine if a scoring system using multiple demographic and imaging characteristics may predict EGFR mutation status.

Materials and methods

In 2005 a lung tumour tissue bank was begun at our institution. This included tissue samples from patients undergoing resection at our institution or at any other institution in the province. Patients with bronchogenic carcinoma who had valid signed consent to participate in the tissue bank between 2005 and 2014, had sufficient tissue for molecular analysis, and had at least one pre-surgical CT available for review were eligible for our study. From the tumour bank database, we retrieved demographic information including patient sex and smoking history (in pack-years). Surgical staging information was also retrieved. Patient ethnicity was not recorded. Institutional Research Ethics Board approval was obtained.

Radiology

We searched the Imaging Archive for all CTs (16- and 64-slice multidetector CTs) as well as positron emission tomography (PET) performed prior to surgical resection. CTs were performed on 15 different CT scanners in 13 different institutions. CTs reviewed were performed with section thickness reconstruction of 3 mm or less in at least one plane. All CTs included high spatial frequency images (lung algorithm) and intermediate spatial frequency images (mediastinal algorithm). CT acquisition technique was variable with a range of doses and a range of dose-saving techniques. We included examinations performed both with and without administration of intravenous (IV) contrast.

CTs were reviewed by two board-certified radiologists (one fellowship-trained thoracic radiologist with 8 years of subspecialty experience and one current thoracic imaging fellow with 4 years general post-residency CT experience). The radiologists were blinded to molecular analysis results. In order to ensure uniform application of scoring criteria, 42 cases were reviewed independently by both radiologists. Discordant scoring was discussed in a conference setting at which time the images were reviewed again. Disagreements in CT scoring were settled by consensus, with a third chest fellowship trained radiologist consulted when necessary. Once we were satisfied that CT review was performed in a uniform manner, cases were scored by only one radiologist. One radiologist reviewed a total of 42 cases and the other radiologist a total of 109 cases.

We recorded tumour size (mean of maximum tumour diameter and perpendicular diameter) on a single thin section high frequency reconstruction image viewed on lung windows (window width 1200, window length 600), presence of ground glass component, presence of any internal air bronchograms, tumour margin (whether smooth, spiculated, lobulated or ground glass halo), the presence on imaging of local or distant metastasis and the presence on imaging of metastatic lymph nodes. Metastatic lymph node was defined as either larger than 1 cm in short axis, enlarging relative to prior imaging or positive on PET without benign explanation. For patients with more than one pre-surgical CT, doubling time was calculated using volume doubling of a sphere (with diameter estimated by mean tumour diameter as described above). In the event of three or more pre-surgical CTs, the most remote and the most recent CTs were used to measure volume doubling time.

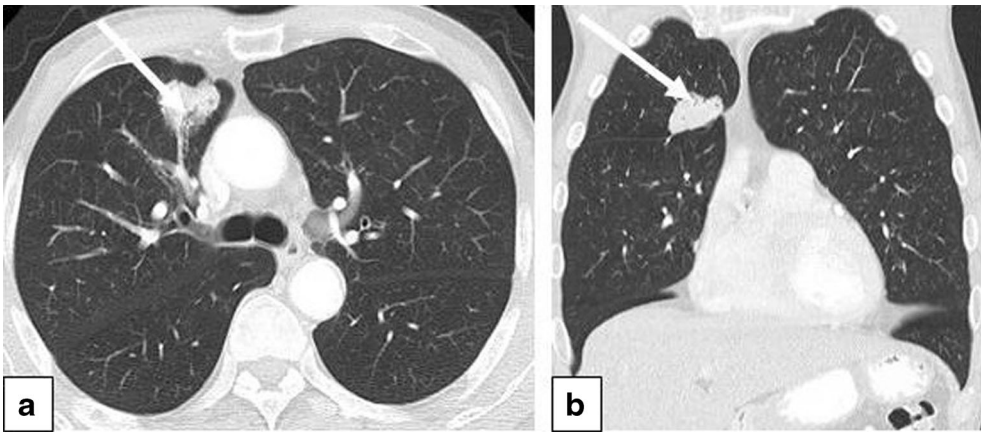

Fig. 1 Axial 5-mm section thickness reconstruction (**A**) and coronal 2-mm section thickness reconstruction (**B**) computed tomography demonstrating air bronchograms (arrows) in an adenocarcinoma with epidermal growth factor receptor (EGFR) mutation

Molecular profiling

DNA extraction from formalin-fixed and paraffin-embedded samples was performed using the MagnaPur Robotic system with the MagnPur2 Compact Nucleic Acid Isolation Kit as described by the manufacturer. SNaPshot system was used to detect single nucleotide polymorphisms (SNPs) in exon 20 (T790M) and exon 21 (L858R). Quadruplex Sizing Genotyping was used to identify insertions and deletions in exons 19 and 20 of EGFR gene.

Statistical methods

The patient sample characteristics were described using means, frequencies and proportions as appropriate to the type of measure being numerical or categorical.

Univariate logistic regression analysis was conducted, modelling the probability of EGFR positive as a function of prognostic factors that included presence of air bronchogram, presence of ground glass component, absence of metastasis or lymphadenopathy, no significant smoking history (less than 20 pack-years), doubling time, margin of the lesion (spiculated), sex and tumour size (less than 3 cm). Odds ratios and associated 95 % confidence intervals (CIs) were calculated. Prognostic factors with odds ratios deemed to be clinically significant when exhibiting greater than 50 % increase in odds of EGFR positive in the univariate analysis were included in a multivariate logistic regression analysis. Backward stepwise regression analysis was conducted to determine the final set of prognostic factors that constituted the optimal prognostic model; the criteria for retention of the prognostic factors in the model was based on the drop in the area under the receiver operating characteristic (AUROC) curve associated with the exclusion of the prognostic factor, using a p-value of < 0.05 as the retention criteria. The linear combination of the regression coefficients of the exponential component of the final multiple logistic regression model was used to compute a prognostic score, from this point onward referred to as the statistically determined prognostic score.

The set of prognostic factors comprising the final multiple logistic regression model were also selected to develop a clinically determined prognostic score using a simpler and more easily applied scoring scheme for practical in-clinic use. Doubling time was included with these prognostic factors in

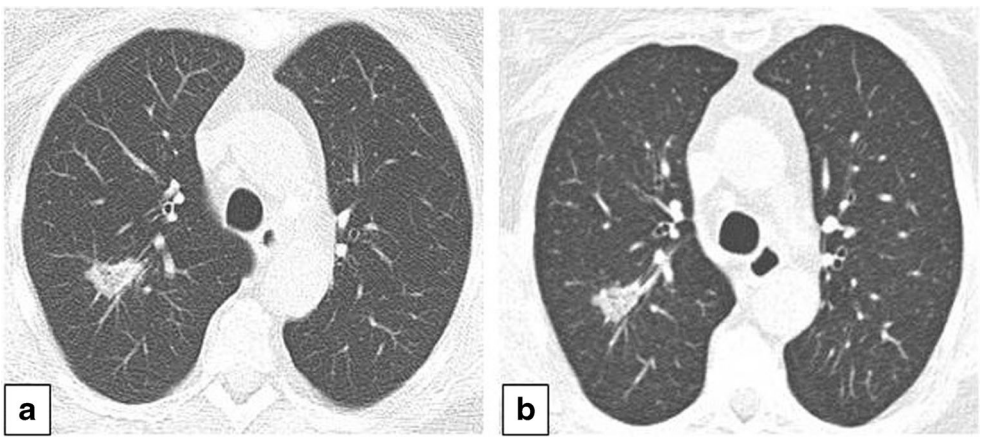

Fig. 2 Axial computed tomography at baseline (**A**) and 13 months later (**B**) demonstrating very slow growth in an adenocarinoma with epidermal growth factor receptor (EGFR) mutation. The baseline examination was reconstructed at 2-mm section thickness. The follow-up examination was performed for another indication and was reconstructed at 5-mm section thickness

Table 1 Prevalence of CT and demographic features in epidermal growth factor receptor positive (EGFR+) versus epidermal growth factor receptor negative (EGFR-) patients

	EGFR+ (% of 21)	EGFR- (% of 98)	Odds ratio* (95 % CI)	Adjusted odds** ratio (95 % CI)
Ground glass component	47.62	14.29	5.455 (1.945–15.224)	2.668 (0.611–11.655)
Tumour size < 3 cm	66.67	59.18	1.397 (0.511–3.722)	1.029 (0.267–3.973)
Air bronchogram	61.9	23.47	5.299 (1.955–14.360)	4.506 (1.076–18.876)
No or low smoking history (<20 PY)	57.14	14.29	8.000 (2.848–22.475)	10.891 (2.748–43.172)
No metastasis or lymph nodes on preoperative imaging	100	70.41	–	–
Doubling time ≥ 365 days (data available for 34 patients)	28.57 (6 of 8)	5.1 (5 of 26)	–	–
Female	71.43	45.92	2.944 (1.055–8.221)	1.694 (0.456–6.298)
Absence of spiculated margin	61.9	41.9	2.259 (0.858–5.947)	2.247 (0.632–8.097)

*Odds ratios from univariate logistic regression analyses; indicating the odds of being EGFR positive (vs. EGFR negative) modelling the probability of being EGFR positive as a function of each prognostic factor independently

**Odds ratios from a multivariate logistic regression modelling the probability of being EGFR positive

specifying the clinically determined prognostic score; doubling time could not be included in the logistic regression modelling due to missing values for those who did not receive serial CTs.

The ROC curves for the statistically determined prognostic scoring model and the clinically specified prognostic scoring model were plotted together on the same graph. The respective AUROC curve values were also calculated and statistical significance of the difference between the two AUROC curve values was evaluated.

The sensitivity, specificity, positive predictive value and negative predictive value were computed for various cut-off values of the prognostic score determined by the clinically specified scoring model.

Results

A total of 492 patients with non-small cell lung cancer were included in the molecular analysis tissue bank; 4.2 % of the samples were EGFR positive. We obtained demographic and CT data for a total of 119 patients, 18 % of whom had EGFR-positive tumours. (All EGFR-positive patients who had demographic and CT data available and a random sample of the EGFR negative patients were reviewed.)

The mean size of the EGFR-positive tumours was 22.1 mm (SD 8.9 mm) and the mean size of EGFR-negative tumours was 26 mm (SD 14.7 mm). 106 of the 119 cases were stage I or II at the time of resection. There was comparable distribution of low- and high-stage cancers among EGFR-positive

Table 2 Clinical scoring model. Higher score is associated with an increased likelihood of epidermal growth factor receptor (EGFR) mutation

Feature	Points awarded	AUROC curve
Ground glass component	3	0.67
Air bronchogram	3	0.69
No or low smoking history (<20 PY)	5	0.75
No metastasis or lymph nodes on preoperative imaging	2	0.65
Doubling time	+1	0.63
≥365 days	0	
No data	-1	
<365 days		
Maximum total score	14	

AUROC area under the receiver operating characteristic, *CT* computed tomography, *PY* pack-year

and EGFR-negative tumours. Four patients in total had metastasis, one of those had an EGFR-positive tumour. Of the EGFR-positive tumours, 16.7 % were advanced stage (III or higher) versus 19 % of EGFR-negative tumours. None of the EGFR-positive tumours demonstrated any evidence of metastatic disease or nodal involvement on preoperative imaging.

EGFR-positive tumours were more common in women than in men (71 % of the EGFR-positive tumours were found in women vs. 46 % of the EGFR-negative tumours). However, smoking was the most important single predictor. 86 % of patients with EGFR-negative tumours were heavy (more than 20 pack-years) smokers compared to only 43 % of the patients with EGFR-positive tumours.

Spiculated margins were seen in only 38 % of EGFR-positive cases compared to 58 % of tumours without the mutation. Air bronchograms (Fig. 1) were present in 62 % of EGFR-positive tumours but present in only 23 % of EGFR-negative tumours. 48 % of the EGFR tumours contained a ground glass component while ground glass was present in only 14 % of tumours without EGFR mutation. Serial CTs were available for 34 patients. 91 % of lesions with a short doubling time (less than 365 days) were EGFR negative (Fig. 2). Of the 42 cases reviewed by both radiologists, there was disagreement in seven of 210 (3 %) CT observations. All disagreements were settled by consensus.

Univariate logistic regression analysis identified prognostic factors for which the odds of being EGFR positive was more than 50 % higher than being EGFR negative . These results are summarized in Table 1.

Multivariate logistic regression analysis was used, based on associated AUROC curve values, to identify the final set of prognostic factors that included presence of air bronchogram, presence of ground glass, absence of metastasis or lymphadenopathy, absence of significant smoking history (less than 20 pack-years) and doubling time; tumour size, sex and spiculated margins were eliminated from the model as they did not contribute to the improved performance of the model.

Using the results of our multivariate logistic regression analysis to model the presence of EGFR mutation, we were able to build a statistically determined prognostic model specified by the following equation:

$$\begin{aligned} Score &= -7.34 + 0.63*(GG\ present) + 0.77*(air\ bronchogram\ present) \\ &\quad + 6.92*(no\ mets) + 1.23*(smoking\ Hx\ less\ than\ 20\ pack{-}years) \end{aligned}$$

These results were then used to guide the creation of a clinical scoring model to allow easier and more practical use. The clinical scoring model assigns 3 points for a tumour with a ground glass component, 3 points for the presence of air bronchograms and 2 points if preoperative imaging demonstrates no evidence of metastasis or nodal enlargement. Patients who are non-smokers or who have a smoking history of less than 20 pack-years are assigned 5 points. If serial CTs have been performed and doubling time is available, 1 point is awarded for a doubling time of at least 365 days, and 1 point is deducted if the doubling time is less than 365 days. These scores for each prognostic factor yield a clinically determined prognostic model specified by the following equation:

$$\begin{aligned} Score &= 3*(GG\ present) + 3*(air\ bronchogram\ present) \\ &\quad + 2(no\ mets) + 5*(smoking\ Hx\ less\ than\ 20\ pack{-}years) \\ &\quad + 1*(doubling\ time\ at\ least\ 365\ days) \\ &\quad + 0*(doubling\ time\ not\ available) \\ &\quad - 1*(doubling\ time\ less\ than\ 365\ days) \end{aligned}$$

Table 2 presents the clinical scoring model and the associated AUROC curve for each of the prognostic factors independently. Figure 3 presents the ROC curves for the statistically determined scoring model and the clinical scoring model, with AUROC curve values of 0.874 and 0.861 respectively (p=0.2921).

A total clinical score of 8 or more yielded a specificity of 95 %, a sensitivity of 57 %, a negative predictive value of 91 % and a positive predictive value of 71 % for the presence of EGFR mutation. A total clinical score of 7 or more results in a more sensitive (76 %) but less specific (84 %) test with a negative predictive value of 94 % and positive predictive value of 50 %.

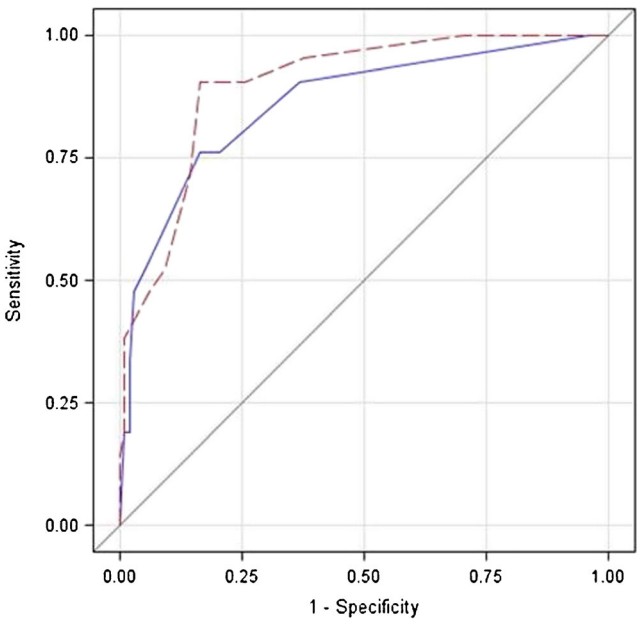

Fig. 3 Receiver operating characteristic (ROC) curves for the statistically determined model (red dashed line) versus the clinical scoring model (blue line)

Discussion

In our sample, the clinical scoring model performed better than individual demographic or imaging characteristics in predicting EGFR mutation status. Based on the statistical analysis conducted, the derived weighting scheme for the scoring model assigns greater importance to certain features than to other features. The scoring model is simple enough to be performed during a clinic visit without additional resources or testing.

We found bronchogenic carcinoma with EGFR mutation was more likely to demonstrate specific CT characteristics (ground glass component, air bronchogram and long doubling time) than tumours without EGFR mutations status. Our findings regarding the increased incidence of ground glass component in EGFR-positive tumours supports the conclusions of prior studies including a recent study by Choi et al. [19] comparing the CT characteristics of tumours with EGFR mutation with those with Anaplastic Lymphoma Kinase Gene Rearrangement.

Very little is known about the relationship between change on serial CT and EGFR mutation status. Although we could calculate tumour doubling time for only 29 % of our patients, a doubling time of over 365 days was strongly associated with the presence of EGFR mutation. Adenocarcinoma with a ground glass component is known to grow slowly [20, 21], and our results may reflect the association between EGFR mutation and subsolid tumours. However, we were unable to determine if these two features held any independent value.

As in other demographic studies [5–7], heavy smokers were less likely to have EGFR-positive tumours. It is interesting that although female sex is commonly considered a factor associated with EGFR mutation status, our multivariate analysis suggested that female sex is not a strong independent predictor of EGFR mutation. Our results are similar to those obtained by the large PIONNEER study that showed sex loses its significance when results are stratified by smoking status [9]. The prevalence of EGFR-positive tumours has been shown to be heavily influenced by ethnicity [5–7, 9–11]. Unfortunately our database did not include information on ethnic origin. The study was performed in a region with an overwhelmingly Caucasian population. The most recent census data shows that only 1 % of the population identified themselves as of East or Southeast Asian origin.

While molecular analysis will always be preferable, the ability to predict EGFR mutation status has important clinical implications. Tissue analysis is not possible for all patients. Some centres may not have access to molecular profiling technology, patients may not be able or willing to undergo biopsy and some tissue samples may be insufficient to test [22, 23]. Given the potential for some patients to demonstrate excellent response to targeted therapy, it is problematic to withhold treatment because molecular studies cannot be performed. However, it is also difficult to justify the high financial cost of targeted chemotherapy without a reasonable expectation that it might be successful.

There is at least one report that never-smokers with bronchogenic carcinoma may be treated with EGF inhibitors without molecular confirmation [4]. However, 54 % of light or never smokers in our study did not have EGFR-positive tumours. Predictive accuracy was improved in our study when CT characteristics were also considered. In health-care settings where access to molecular profiling is limited, a validated predictive method may help determine which patients receive molecular profiling.

To our knowledge this study is the first to propose a multivariable scoring system to predict EGFR mutation status. Because the study was performed in a region with relatively little ethnic variation and included only patients treated surgically, the results should be interpreted with caution. Nonetheless, our data suggest that a multivariable scoring system using both demographic and CT features is likely to be a better predictor than smoking history alone. Prospective studies including non-surgical candidates and in different geographic regions will be required to determine if the proposed clinical tool can be used to inform treatment decisions when molecular profiling is not possible.

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