RESEARCH

Clinical and radiological features associated with EGFR mutation in non-small-cell lung cancer: a study of 149 cases

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Abstract

Background Lung cancer is the leading cause of cancer death in the world. Non-small-cell lung cancer (NSCLC) accounts for 85% of primary lung tumors. Epidermal growth factor receptors (EGFRs) are found on the surface of tumor cells, and their role is to send a growth signal to the cell nucleus. Tumor cells with EGFR mutations are very sensitive to cancer treatments called "Targeted Therapies." The search for EGFR mutations requires lung biopsies. Some studies have shown a correlation between clinico-radiological characteristics and the EGFR mutation. In this study, an attempt was made to identify the relevant clinico-radiological characteristics associated with the EGFR mutation in patients with NSCLC.

Objectives The main objective of this study was to evaluate the clinico-radiological characteristics useful for predicting the risk of EGFR mutation in patients with NSCLC.

Materials and methods This is a retrospective cross-sectional study, carried out in 149 patients followed up for lung adenocarcinoma who benefited from an EGFR mutation study at the anatomopathology department of the University Hospital of Fez, spread over a period of 4 years (between January 2018 and December 2021). A database was compiled from this study, including sociodemographic, clinical, anatomopathological and radiological data. A statistical analysis was carried out in order to identify the factors associated with EGFR mutation.

Results According to the inclusion and exclusion criteria, of the 149 patients included, the mean age was $61.05 +/- 11.095$ years. Males predominated with a percentage of 70.5% ($n = 105$). Fifty-seven point seven percent of patients were smokers or ex-smokers. Forty-one patients had an EGFR mutation, representing a percentage of 27.5%. Multivariate analysis by logistic regression revealed an association of the EGFR mutation with irregular contours (ORA = 6.43; CI95% 1.26;32.78), with the presence of spiculations (ORA = 5.81; CI95% 1.96;17.22), with pleural attachment (ORA = 3.53; CI95% 1.32;9.42), with heterogeneous enhancement (ORA = 30.679; CI95% 5.149;182.778), with absence of emphysema (ORA = 4.815; CI95% 1.966;17.220) and with presence of distant metastasis (ORA = 4.123; CI95% 1.373;12.383).

Conclusions This study provides substantial evidence to support the assertion that irregular contours, the presence of spiculations, pleural attachment, heterogeneous enhancement, the absence of emphysema and the presence of distant metastasis are statistically correlated with EGFR mutations. The model developed within this study,

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Mourabiti *et al. Egypt J Radiol Nucl Med*   (2023) 54:171

Page 2 of 11

encompassing all relevant clinical and CT characteristics, has demonstrated its effectiveness as a reliable predictor for EGFR mutations (AUC: 0.7659) and consequently as a key determinant of EGFR-TKI treatment response.

Keywords Non-small-cell lung cancer, EGFR mutation, Clinical and CT characteristics

Background

Lung cancer is a common neoplastic malignancy representing 18% of all tumors, affecting mostly men with an average age of 70 years, and representing the first cause of cancer-related mortality in 2020 [1, 2]. Lung cancers are classified as non-small-cell lung carcinoma (NSCLC) and small-cell lung carcinoma [3]. Approximately 85% of lung neoplasms are NSCLC. These types can be affected by mutations in the epidermal growth factor receptor (EGFR), the Kirsten rat sarcoma viral oncogene homolog (KRAS), the anaplastic lymphoma kinase mutation (ALK) or other rarer mutations (ROS1, BRAF, V600E, NTRK…) [4, 5]. Over the last decade, the treatment of NSCLC has evolved from cytotoxic chemotherapy to targeted therapy based on molecular mutations, in the face of significant developments in molecular biology [6, 7]. Small molecule tyrosine kinase inhibitors (TKIs) targeting specific EGFR mutations are the first targeted drugs for the treatment of NSCLC. Riley et al. [8] reported that the response of EGFR-TKIs in patients with EGFR mutations (60–80%) was significantly higher than in patients with negative or unknown EGFR mutation status (10–20%). As well as a large number of clinical trials, Schuler et al. [9] found that treatments based on eroltinib, gefitinib or afatinib in EGFR-mutated NSCLC had a longer (progression-free) survival and a higher response rate compared with standard first-line chemotherapy. However, they also found that if a patient with EGFR non-mutant lung cancer is treated with targeted drugs such as gefitinib, survival was significantly shorter than that of patients receiving standard first-line chemotherapy [7]. These results underline the importance of precisely identifying a patient's genetic mutation status in order to guide treatment. In this context, the detection of useful clinico-scanographic features could help characterize tumors and predict the risk of mutation [5].

The main objective of this study was to evaluate the clinico-radiological characteristics useful for predicting the risk of EGFR mutation in patients with NSCLC.

Methods

Ethics

Ethics committee approval for this study was approved by the Ethics Committee for Biomedical Research Casablanca, Morocco, in accordance with the Declaration of Helsinki, under reference 17/15. Written informed consent was obtained for all patients.

Anonymity and confidentiality were respected for all participants.

Study design

This is a retrospective cross-sectional study of 149 patients with lung cancer who underwent an EGFR mutation study at the anatomopathology department of the University Hospital of Fez, spread over a period of 4 years, between January 2018 and December 2021 (Fig. 1).

Inclusion and exclusion criteria

1. Inclusion criteria

Our study included all patients with lung adenocarcinoma who underwent EGFR mutation testing and received imaging at the radiology department of HASSAN II University Hospital in Fez over a four-year period.

2. Exclusion criteria

Patients without pre-treatment imaging.
Patients with large tumors causing bronchial invasion with downstream atelectasis.
Patients with no imaging in our department.
Patients with improper EGFR test results or indeterminate results.

CT protocol used

CT examinations were performed with a 64-section scanner (GE medical system). Acquisitions were done in the supine position at the end of inspiration. The scanning parameters were as follows: slice thickness of 5 mm with reconstruction of 1,25 mm; tube voltage of 120 kV; tube current of 100–200 mAs; collimation of 3 mm; pitch of 1–1.5; matrix size of 512×512, FOV of 35 cm.

All CT scan were done before and after contrast with doses up to 2 ml/kg with flow rate of 4ml/sec.

All CT images were transmitted to the postprocessing workstation.

Data collection methods

Data were collected using a computerized patient record form from the HOSIX clinical data archiving system.

```
225 patients
recruited
        │
        │
        ├──── 76 patients ────── - Absence of pre-treatment imaging (N=23).
        │      excluded
        │                        - Large tumors with atelectasis downstream
        │                          (N=16).
        │
        │                        - No imaging in our training (22).
        │
        │                        - Improper or indeterminate EGFR test
        │                          results (N=15).
        │
149 patients
included
        │
        ├──── CT scan study
```

24 Characteristics:

Localisation, lobe affected, contours, spiculation, form, limits, density, air bronchogram, scissural attachment, pleural attachment, scissural retraction, pleural retraction, enhancement, cavitation, emphysema, calcifications, fibrosis, size, pulmonary nodule in the same lobe, pulmonary nodule in another lobe, mediastinal PDA, homolateral pleural effusion, contralateral PE and distant metastasis.

Chi 2 Test ⟱

6 pertinent characteristics :

irregular contours

spiculations

pleural attachment

heterogeneous enhancement

absence of emphysema

distant metastases

Fig. 1 Study design diagram

Mourabiti *et al. Egypt J Radiol Nucl Med*   (2023) 54:171

Page 4 of 11

CT scan data were collected using the PACS radiology data archiving system (Agfa Impax, version 6.6.1.3004, Agfa-Gevaert).

A database was created from this data, including sociodemographic, clinical, anatomopathological and radiological results.

The CT data have been validated by an associate professor of radiology.

Sociodemographic characteristics

Age at time of study, sex and smoking status.

Anatomopathological results immunohistochemical study and search for EGFR mutation.

CT scan results

Analysis of CT scans includes central or peripheral localization, lobe affected, contours, presence of spiculation, form, borders, density (solid or mixed), presence of air bronchogram, scissural attachment, pleural attachment, scissural retraction, pleural retraction, heterogeneous or homogeneous enhancement, presence or absence of cavitation, emphysema, calcifications, fibrosis, size of tumor, pulmonary nodule in the same lobe, pulmonary nodule in another lobe, mediastinal lymphadenopathy, homolateral pleural effusion, contralateral pleural effusion and presence or absence of distant metastases.

Statistical analysis

Firstly, a descriptive analysis of the sociodemographic, clinical and radiological characteristics of the patients was conducted. Quantitative variables were expressed as means and standard deviations, and qualitative variables were expressed as percentages.

A univariate analysis was then performed to investigate the association between the EGFR mutation and the various parameters. For group comparisons, we used standard parametric tests (Student's t test, Chi-2) depending on the nature of the variables to be compared.

Finally, a multivariate analysis using binary logistic regression was used to determine the factors associated with the EGFR mutation after adjustment for the different factors that had a significance level of $p < 0.20$ in the univariate analysis.

For each statistical test used, the test was considered significant when p (significance level) was less than 0.05. Statistical analysis was performed using SPSS version 26 software.

Results

Based on the inclusion and exclusion criteria, of the 149 patients included, the mean age was $61.05 +/- 11.09$ years. Males predominated with a percentage of 70.5% ($n = 105$). The M/F sex ratio was 2.38. 57.7% ($N = 86$) of

patients were smokers or ex-smokers. Forty-one patients had an EGFR mutation (27.5%).

All patients underwent a CT scan with ICM injection. The clinical and CT features of the patients are summarized in Tables 1 and 2. As shown in Table 1, univariate analysis of sociodemographic parameters showed that older age, male gender and non-smoking patients had more EGFR mutations, and this difference was statistically significant ($p = 0.030$, $p = 0.026$ and $p < 0.001$, respectively).

The univariate analysis of the CT parameters is summarized in Table 2, showing 5 characteristics associated with an EGFR mutation, with a statistically significant association including spiculated contours ($p = 0.007$), presence of pleural attachment ($p = 0.006$), heterogeneous enhancement ($p < 0.001$), absence of emphysema ($p = 0.001$) and presence of a pulmonary nodule in the same lobe as the primary tumor ($p = 0.02$).

Multivariate analysis by logistic regression revealed an association of the EGFR mutation with irregular contours (ORA = 6.43; CI95% 1.26;32.78), with the presence of spiculations (ORA = 5.81; CI95% 1.96;17.22) Fig. 2, with pleural attachment (ORA = 3.53; CI95% 1.32;9.42), with heterogeneous enhancement (ORA = 30.679; CI95% 5.149;182.778) Fig. 3, with the absence of emphysema (ORA = 4.815; CI95% 1.966;17.220) and with the presence of distant metastasis (ORA = 4.123; CI95% 1.373;12.383) Fig. 4. These characteristics were significant predictors of EGFR mutation (Table 3).

To illustrate the predictive capacity of the EGFR mutation, we compared the models developed on the basis of clinico-radiological features and the pertinent clinico-radiological features.

We used the performance measures precision (PR), recall (RE), F1 score and accuracy (CA).

Model 1 (Fig. 5) shows the model developed from all the clinical characteristics. In 33 non-mutated patients, we obtained 27 correct estimates with an accuracy of

Table 1 Sociodemographic factors associated with EGFR mutation

Variable	EGFR		p
	No mutation	**Mutation**	
Age	59.84 ± 11.09	64.24 ± 10.51	0.030
Sex			0.026
Male	82 (75.9)	23 (56.1)	
Female	26 (24.1)	18 (43.9)	
Smoking status			< 0.001
Non smoker	36 (33.3)	27 (65.9)	
Smoker	72 (66.7)	14 (34.1)	

Mourabiti *et al. Egypt J Radiol Nucl Med*   (2023) 54:171

Page 5 of 11

Table 2 Scanographic features associated with EGFR mutation by univariate analysis

Variable	EGFR		p
	No mutation	**Mutation**	
Location			0.78
Central	63 (58.3)	23 (56.1)	
Peripheral	45 (41.7)	18 (43.9)	
Lobes			0.35
Lower Lobe	26 (24.1)	15 (36.6)	
Middle Lobe	1 (0.9)	0	
Upper Lobe	78 (72.2)	24 (58.5)	
UL + LL	3 (2.8)	2 (4.9)	
Borders			0.091
Irregular	102 (94.4)	35 (85.4)	
Regular	6 (5.6)	6 (14.6)	
Spiculations			0.007
No	79 (73.1)	20 (48.8)	
Yes	29 (26.9)	21 (51.2)	
Shape			0.26
Round	26 (24.1)	15 (36.6)	
Oval	29 (26.9)	6 (14.6)	
Undefined	53 (49)	20 (48.8)	
Limit			0.85
Well limited	55 (50.9)	22 (53.7)	
Mal limited	53 (49.1)	19 (46.3)	
Density			1
Solid	97 (89.8)	37 (90.2)	
Mixed	11 (10.2)	4 (9.8)	
Air bronchogram			0.71
Yes	43 (39.8)	18 (43.9)	
No	65 (60.2)	23 (56.1)	
Scissural attachment			0.44
Yes	71 (65.7)	24 (58.5)	
No	37 (34.3)	17 (41.5)	
Pleural attachment			0.006
Yes	88 (81.5)	24 (58.5)	
No	20 (18.5)	17 (41.5)	
Scissural retraction			1
Yes	24 (22.2)	9 (22)	
No	84 (77.8)	32 (78)	
Pleural retraction			0.85
Yes	39 (36.1)	16 (39)	
No	69 (63.9)	25 (61)	
Enhancement			< 0.001
Homogenous	2 (1.9)	14 (34.1)	
Heterogeneous	106 (98.1)	27 (65.9)	
Cavitation			1
Yes	10 (9.3)	4 (9.8)	
No	98 (90.7)	37 (90.2)	
Emphysema			0.001
Yes	56 (51.9)	9 (22)	

Table 2 (continued)

Variable	EGFR		p
	No mutation	**Mutation**	
No	52 (48.1)	32 (78)	
Calcifications			0.27
Yes	22 (20.4)	12 (19.3)	
No	86 (79.6)	29 (70.7)	
Fibrosis			0.5
Yes	7 (6.5)	1 (2.4)	
No	101 (93.5)	40 (97.6)	
Maximum size			0.78
< 3cm	13 (12.3)	4 (9.8)	
> 3cm	95 (87.7)	37 (90.2)	
Lung nodule in the same lobe			0.02
Yes	41 (38)	24 (58.5)	
No	67 (62)	17 (41.5)	
Lung nodule in another lobe			0.2
Yes	45 (41.7)	22 (53.7)	
No	63 (58.3)	19 (46.3)	
Mediastinal lymphadenopathy			1
Yes	70 (64.8)	27 (65.9)	
No	38 (35.2)	14 (34.2)	
Homolateral pleural effusion			0.58
Yes	44 (40.7)	19 (46.3)	
No	64 (59.3)	22 (53.7)	
Contralateral pleural effusion			0.39
Yes	4 (3.7)	3 (7.3)	
No	104 (96.3)	38 (92.7)	
Distant metastasis			0.13
Yes	58 (53.7)	28 (68.3)	
No	50 (46.3)	13 (31.7)	

82%. However, in 14 mutated patients, there were only 8 correct estimates with an accuracy of 57%.

The accuracy score in this case was 0.7446.

Model 2 (Fig. 6) shows the model developed from the pertinent clinical features using the χ 2 test, in 33 non-mutated patients, there were 30 correct estimates with an accuracy of 79%. However, in 14 mutated patients, there were only 6 correct estimates with an accuracy of 67%.

The accuracy score in this case was 0.7659.

From these two models, we concluded that the model developed on the pertinent clinical characteristics is the most accurate for predicting EGFR gene mutations.

Discussion

In this retrospective study, we attempted to explore the relationships between clinical features and EGFR mutation in patients with NSCLC. Clinical characteristics are readily available for NSCLC patients and are generally expected to be used as predictors of EGFR mutation.

Mourabiti *et al. Egypt J Radiol Nucl Med*   (2023) 54:171

Page 6 of 11
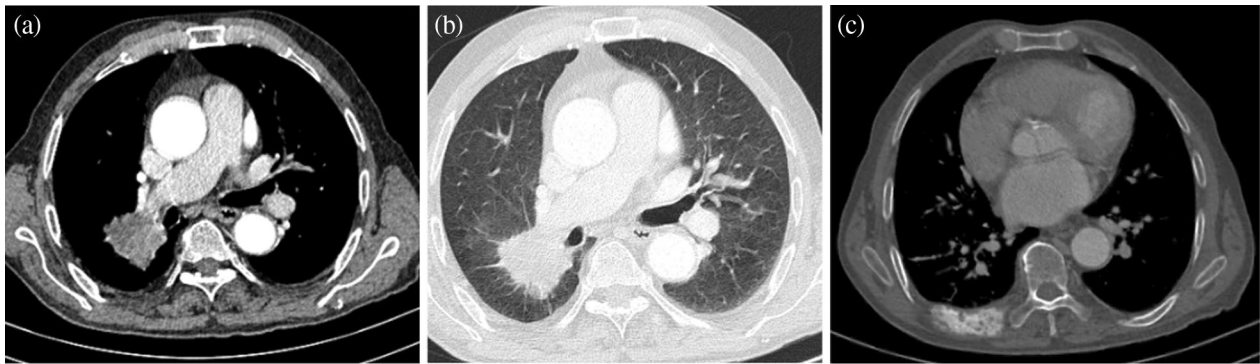
Fig. 2 An 81-year-old non-smoking man with a CT scan of the mediastinum (**a**), parenchymal (**b**) and bone (**c**) windows showing a centrally distributed LID lung parenchymal mass with solid density, spiculated contours, heterogeneous enhancement and secondary location in the costal bone
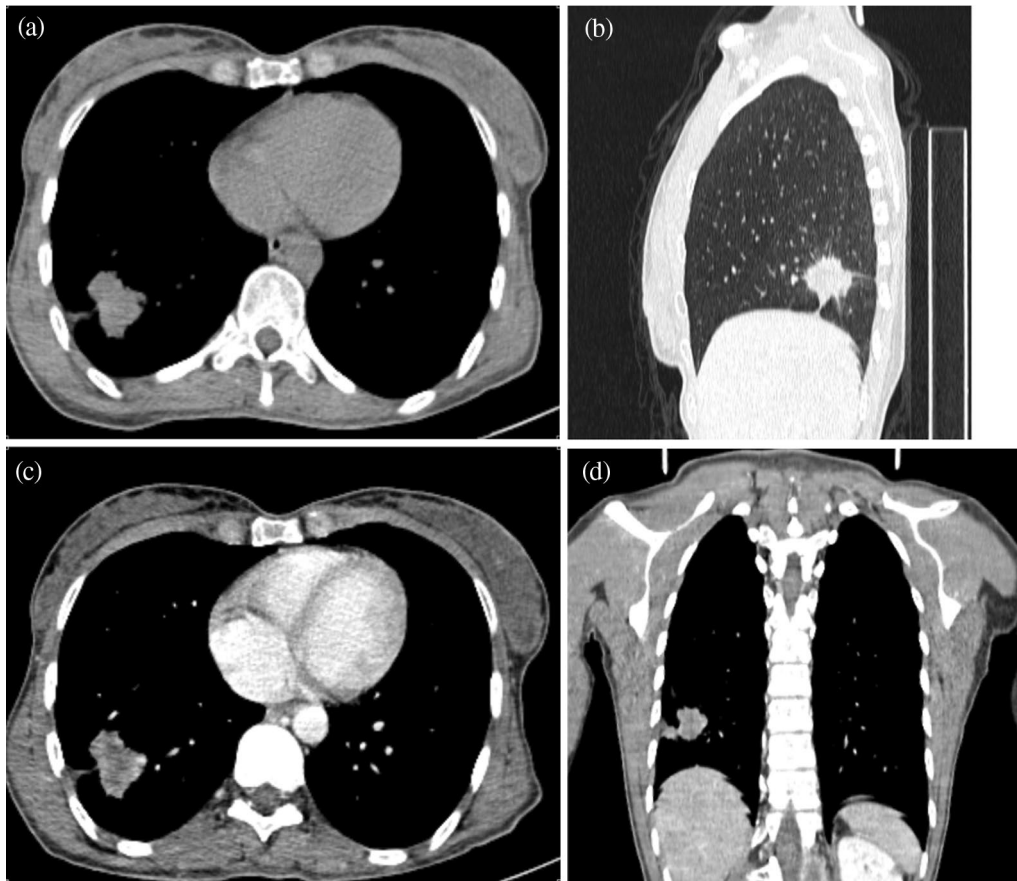
Fig. 3 A 47-year-old woman, non-smoker, with a thoracic CT scan in the mediastinal window before injection (**a**) and after injection of the ICM in axial (**c**) and coronal (**d**) sections and in the parenchymal window (**b**): a peripheral LID lung parenchymal mass with solid density, spiculated contours, heterogeneously enhanced after contrast (**c**, **d**), associated with pleural retraction and attachment

Cumulative studies have reported that several clinical factors such as female gender, non-smokers, adenocarcinoma histology and Asian origin were frequently associated with EGFR mutation [10]. Consequently, in clinical practice, these factors are the main parameters used to predict EGFR mutation, and confirmation is carried out by molecular biology mutation testing. In our study, and in line with most previous findings, we found that EGFR

Mourabiti *et al. Egypt J Radiol Nucl Med*   (2023) 54:171

Page 7 of 11
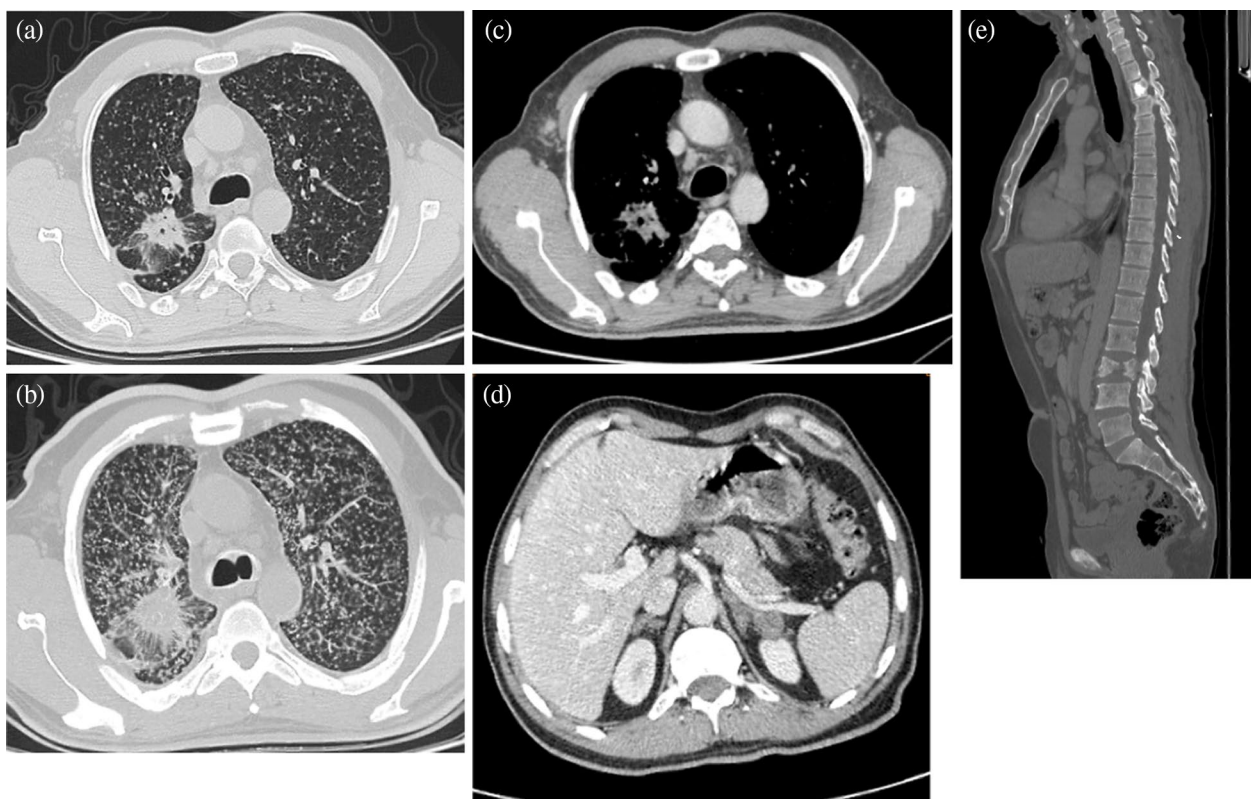
Fig. 4 A 58-year-old man, non-smoker, with a chest CT scan in the parenchymal (**a**, **b**) and mediastinal (**c**) windows, showing an LSD lung parenchymal mass, centrally distributed, of solid density, with spiculated contours, with an air bronchogram and pleural retraction with carcinomatous miliary (**b**), secondary localizations on the left adrenal on the abdominal scan (**d**) and bone (lytic lesion with vertebral compression of L3) on the bone window (**e**)

mutation rates were higher in non-smoking patients, however we found that the mutation rate is discretely higher in males, and this could be explained by the clear male predominance in our study population.

Early studies showed conflicting results regarding the correlation between CT findings and EGFR mutation status in patients with NSCLC [11, 12]. According to a study by Zhou et al. [10], there was no difference in the CT morphological characteristics of lung tumors between mutated and non-mutated patients. However, Rizzo et al. [13] demonstrated that EGFR mutations are closely associated with a number of scanographic features such as air bronchogram, pleural retraction, lesion size and the presence or absence of pulmonary fibrosis. In recent years, a number of studies involving large cohorts with a good level of evidence have demonstrated a significant correlation between certain scanographic features and EGFR mutation status.

In our study, we used 24 CT features that exceed the majority of subsequent studies. Multivariate analysis of the data showed an association of EGFR mutation with irregular contours, with the presence of spiculations, with pleural attachment, with heterogeneous enhancement, with the absence of emphysema and with the presence of distant metastasis.

The association with the other characteristics was not significant in our study.

A meta-analysis, including 21 different studies on 5871 patients [14], showed a significant association between the presence of spiculations and EGFR mutation in the majority of studies with an overall OR of 1.42 (95% CI 1.19–1.70). In our study, spiculated contours were significantly more frequent in mutated patients (ORA = 5.81; CI95% 1.96;17.22), which is consistent with the majority of studies.

Few studies have evaluated the correlation between EGFR mutation and tumor enhancement. Among them, an interesting study by Liu et al. [15] involving 385 patients with NSCLC showed a significant association ($p = 0.001$) between heterogeneous tumor enhancement and EGFR mutation (OR, 0.23; 95% CI: 0.10, 0.53). In our study, we found that heterogeneous enhancement was significantly more frequent in mutated patients (ORA = 30.679; CI95% 5.149;182.778).
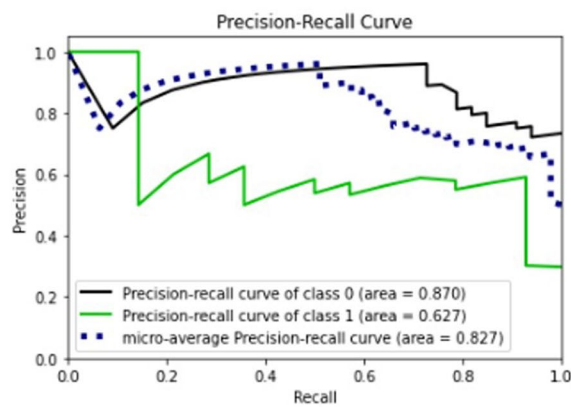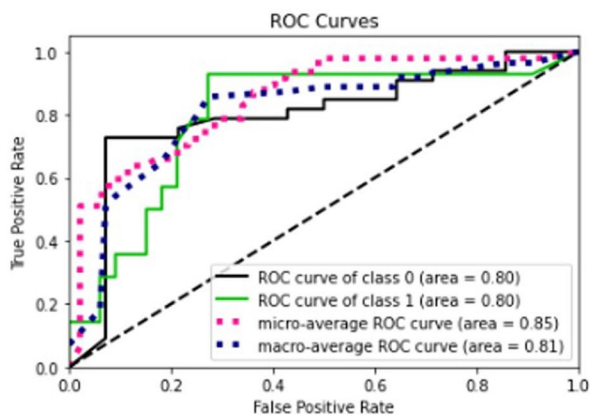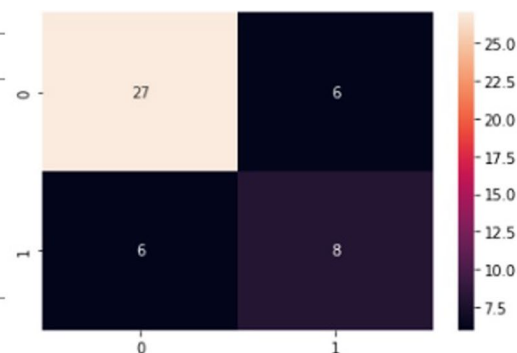
Mourabiti *et al. Egypt J Radiol Nucl Med*   (2023) 54:171

Page 8 of 11

Table 3 Factors associated with EGFR mutation by multivariate analysis

	p	OR adjusted	95% confidence interval for ORA	
			Lower	Superior
Borders				
Regular	–	1	–	–
Irregular	0.025	6.438	1.264	32.785
Spiculation				
No	–	1	–	–
Yes	0.001	5.819	1.966	17.220
Pleural attachment				
No	–	1	–	–
Yes	0.012	3.535	1.327	9.421
Enhancement				
Homogenous	–	1	–	–
Heterogeneous	0.000	30.679	5.149	182.778
Distant metastasis				
No	–	1	–	–
Yes	0.012	4.123	1.373	12.383
Emphysema				
Yes	–	1	–	–
No	0.005	4.815	1.966	17.220

The majority of studies found a significant association between the EGFR mutation and the absence of emphysema, which could be explained by the clear predominance of the EGFR mutation in non-smoking patients. Rizzo et al. [13] found a significant association between the EGFR mutation and the absence of emphysema ($p = 0.03$) in both univariate and multivariate analysis. Usui et al. [16] found that the frequency of EGFR mutation was low in patients with underlying lung diseases such as emphysema and pulmonary fibrosis. Another study by Liu et al. [15] found that EGFR mutation was elevated in smoking patients without extensive emphysema on CT, suggesting that EGFR mutations could be predicted in smokers with little or no emphysema bullae on CT. In our study, we found that the absence of emphysema was significantly more frequent in patients with EGFR mutation.

Few studies in the literature have evaluated the association between pleural attachment and EGFR mutation, with discordant results. Zhang Shi et al. [17] found no significant correlation between these two parameters. Zhou et al. [10] found that lung tumors with pleural attachment were more likely to be non-mutated tumors. However, a more recent study by Liu et al. [15] found a small but significant association between pleural attachment and EGFR mutation, ($p = 0.004$), with an

Statut	Precision	Recall	F1-score	Support
No Mutation	0.82	0.82	0.82	33
Mutation	0.57	0.57	0.57	14
accuracy			0.74	47
macro avg	0.69	0.69	0.69	47
weighted avg	0.74	0.74	0.74	47

Fig. 5 Model developed from all the clinical characteristics

Mourabiti *et al. Egypt J Radiol Nucl Med* (2023) 54:171

Page 9 of 11

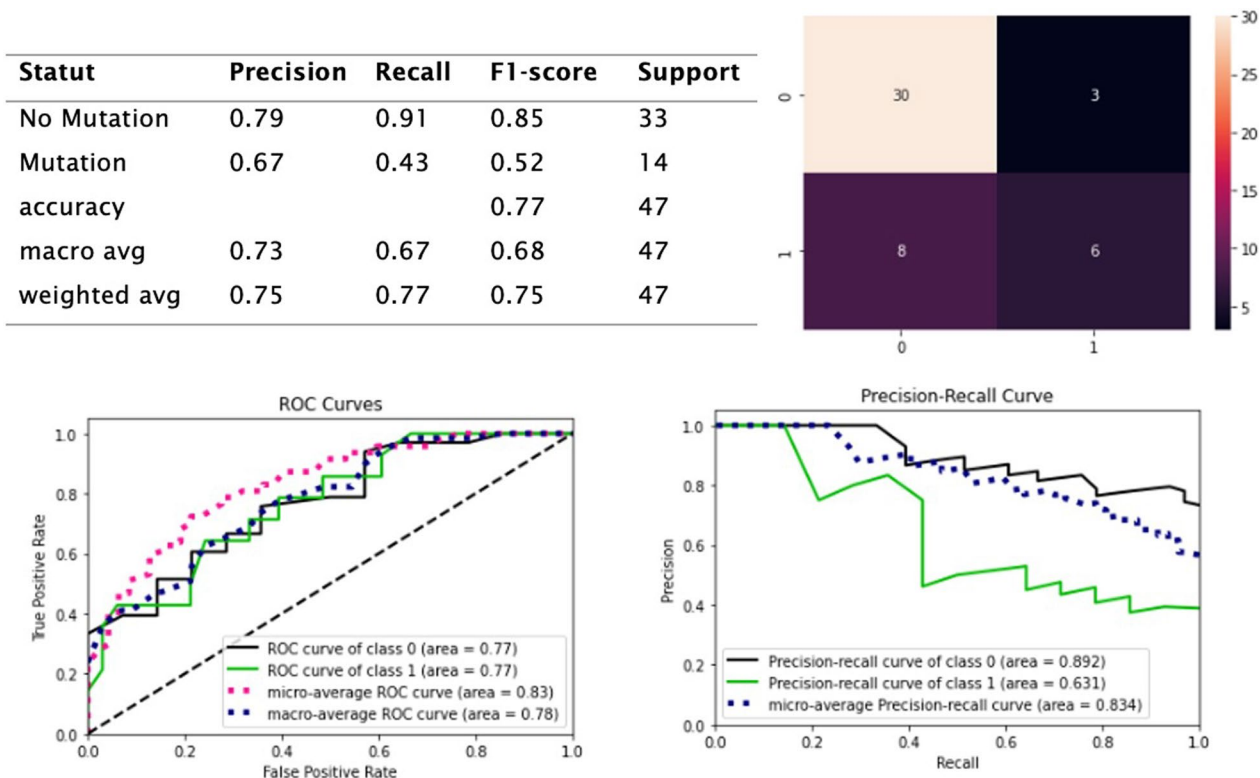| Statut	Precision	Recall	F1-score	Support
No Mutation	0.79	0.91	0.85	33
Mutation	0.67	0.43	0.52	14
accuracy			0.77	47
macro avg	0.73	0.67	0.68	47
weighted avg	0.75	0.77	0.75	47

Fig. 6 Model developed on the basis of pertinent clinical characteristics

OR = 0.54 (95% CI, 0.35–0.83). In our study, we found that the presence of pleural attachment was significantly more frequent in patients with EGFR mutation (ORA = 3.53; CI95% 1.32;9.42).

The association between distant metastases and EGFR mutation has been assessed in very few studies in the literature, and this could be explained by the fact that the majority of tumors studied were diagnosed at an early stage. Zhang Shi et al. [17] found no significant correlation between the two parameters. Another study by Rizzo et al. [13] found that there was no significant association between these two parameters ($p = 0.64$). In our study and contrary to previous studies, we found that the presence of distant metastases was significantly more frequent in mutated patients.

Wenting Tu et al. [18] found in a recent study that the maximum tumor diameter of the EGFR mutation group was significantly smaller than that of the non-mutant type, therefore, according to these authors, the smaller tumors suggest an EGFR mutation, which is discordant with our study, where we found that the majority of mutated patients were > 3cm in size, this could be due to the delay in diagnosis and the absence of screening in our context.

Regarding the association between EGFR mutation and the presence of ground-glass lesions (GGO), a meta-analysis, including 23 different studies on 6893 patients [14], showed a significant association between the presence of ground-glass and EGFR mutation, with an overall OR of 1.86 (95% CI 1.34–2.57). In our study, the majority of mutated and non-mutated tumors had a solid density. We therefore found no significant correlation between tumor density and EGFR mutation.

This study has some limitations: firstly, it is cross-sectional and concerns only one institution. A prospective multi-institutional study should be conducted to generalize the model and verify our results on a large scale. In the future, we propose complementing this study with a prospective cohort to better investigate EGFR mutation status in patients with non-small-cell lung cancer.

Conclusions

In conclusion, lung cancer is the world's most common cause of death from cancer. Non-small-cell lung carcinoma (NSCLC), and in particular adenocarcinoma, is the most common histological type. This study provides substantial evidence to support the assertion that irregular contours, the presence of spiculations, pleural

Mourabiti *et al. Egypt J Radiol Nucl Med*   (2023) 54:171

Page 10 of 11

attachment, heterogeneous enhancement, the absence of emphysema and the presence of distant metastasis are statistically correlated with EGFR mutations. The model developed within this study, encompassing all relevant clinical and CT characteristics, has demonstrated its effectiveness as a reliable predictor for EGFR mutations (AUC: 0.7659) and consequently as a key determinant of EGFR-TKI treatment response.

In the future, we hope to obtain more complete data to predict EGFR mutation subtypes (exons 18, 19, 20 and 21) and mutations such as K-RAS and ALK. We are looking forward to more comprehensive studies that will involve the development of therapies targeted at the different EGFR mutation subtypes.

Abbreviations

NSCLC	Non-small-cell lung cancer
EGFR	Epidermal growth factor receptor
KRAS	Kirsten Rat Sarcoma Viral Oncogene Homolog
ALK	Anaplastic lymphoma kinase
CT	Computed tomography
ICM	Iodinated contrast media
ROC	Receiver operating characteristic
PR	Precision
RE	Recall
CA	Accuracy
PACS	Picture Archiving and Communicating System

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Author contributions
All authors read and approved the final manuscript.

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Not applicable.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Ethics committee approval for this study was approved by the Ethics Committee for Biomedical Research Casablanca, Morocco, in accordance with the Declaration of Helsinki, under reference 17/15. Written informed consent was obtained for all patients. Anonymity and confidentiality were respected for all participants.

Consent for publication
Yes, I have the consent of all patients.

Competing interests
The authors declare that they have no competing interests.

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