Title	Metabolic Phenotype of Stage IV Lung Adenocarcinoma: relationship with epidermal growth factor receptor mutation
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Title

Metabolic phenotype of stage IV lung adenocarcinoma: relationship with epidermal growth factor receptor mutation

Abstract

Purpose Epidermal growth factor receptor (EGFR) mutation status is important in treatment stratification of stage IV lung adenocarcinoma. We evaluated the relationship between the maximum standardized uptake value (SUVmax) measured on PET/CT and EGFR mutations; and the value of SUVmax in predicting EGFR mutations.

Patients and methods: Seventy-one stage IV lung adenocarcinoma patients with verified EGFR mutations (48 EGFR-mutant, 23 EGFR-wild type) having pre-treatment PET/CT were retrospectively reviewed. SUVmax of the primary tumors (n=71), nodal (n=246) and distant metastases (n=618) were compared between EGFR-mutant and EGFR-wild type adenocarcinoma by Mann-Whitney U-test. The receiver operating characteristics (ROC) curve and logistic regression were performed for factors, SUVmax, age, sex and smoking status. The significant predictors were assessed individually and in combination in discriminating EGFR mutation status. Statistical significance was assumed at $p<0.05$

Results: The metastases in EGFR-mutant adenocarcinoma had lower SUVmax than EGFR-wild type adenocarcinoma (nodal SUVmax 3.4 vs. 5.5, distant metastasis SUVmax 3.4 vs. 4.7 respectively; both $p<0.001$). No statistical significant difference was observed in the primary tumors SUVmax between the two groups (SUVmax 7.4 vs. 8.1, $p=0.311$). A ROC-derived SUVmax $\leqq 7.2$ in metastasis could separate EGFR-mutant from EGFR-wild type adenocarcinoma (area under the curves, AUC, 0.71-0.74, $p<0.05$). SUVmax was a significant independent predictor and when combined with age, sex and smoking status, were highly predictive of EGFR mutation status (AUC 0.90)

Conclusion: Low SUVmax in the metastasis favors the presence of EGFR mutations in stage IV lung adenocarcinoma and SUVmax is an independent predictor of EGFR mutations.

Keywords: EGFR mutations; adenocarcinoma; stage IV; PET/CT; SUVmax

Introduction

Tyrosine kinase inhibitors (TKIs) have revolutionized the treatment of stage IV non-small cell lung cancer (NSCLC), especially in adenocarcinoma. The drug efficacy is dependent on the presence of epidermal growth factor receptor (EGFR) mutations that confer favorable response to TKIs. Though demographic characteristics such as age, sex and smoking status were correlated factors with the presence of EGFR mutations, they were insufficiently sensitive to select individual for TKI therapy. Hence, the current recommendation remains in prioritizing EGFR mutation testing over other molecular predictive tests in all advanced stage lung adenocarcinoma [1]. Obtaining sufficient tumor material of good quality to allow for EGFR mutations testing remains challenging in advanced disease when the primary tumor is not resectable [2].

18-fluoro-deoxyglucose (^{18}F-FDG) positron-emission tomography/computed tomography (PET/CT) forms an essential staging tool for NSCLC. The glucose metabolism has been found to be associated with disease aggressiveness and cell proliferation [3]. Given that EGFR signaling transduction pathway is responsible for cell survival and proliferation [4], previous studies have explored the relationship between the metabolic uptake and EGFR mutations. These studies showed correlations of opposite trends between pre-treatment maximum standardized uptake value (SUVmax) of the primary tumor and the presence of EGFR mutations and one reported no correlation [5-9]. There was significant design heterogeneity among these studies, which included patients with different stages of disease and of various histological subtypes, thus difficult to draw conclusive results from these studies.

Herein, we aim to evaluate the metabolic signatures of the primary tumors and metastases in a Chinese cohort of stage IV lung adenocarcinoma in association to their EGFR mutation status and the value of SUVmax in predicting EGFR mutations.

Materials and methods

Patients

EGFR mutations testing started at our hospital in 2009. We retrospectively identified all newly diagnosed therapy-naive patients with NSCLC who underwent staging PET/CT from January 2009 to January 2014. Inclusion criteria were (a) patients with histological confirmation of adenocarcinoma, (b) stage IV (both M1a and M1b) disease demonstrated either by PET/CT or proven by histology and (c) EGFR mutation status determined. Staging was based on the new 7th revised edition for lung cancer staging by the International Staging Committee of the International Association of the Study of Lung Cancer (IASLC) [10]. The study was approved by the institutional review board and the need for written informed consent was waived.

Eighty-nine stage IV NSCLC patients were identified but EGFR mutation status was not verified in 17 of them due to insufficient tissue material. One PET/CT was excluded due to technical error that prevented retrospective quantitative analysis. Thus, the study population comprised of 71 patients. The patients' demographics characteristics; age, sex and smoking history were collected. Non-smokers were defined as those who never smoked or smoked less than 100 cigarettes in their lifetime, while patients who gave up smoking more than one year at the time of diagnosis were considered ex-smokers. The rest were categorized as current smokers[5].

EGFR mutation status

EGFR mutations were tested on genomic DNA from frozen tumor tissues using Sanger sequencing of exons 18 to 21, or DNA extracted from formalin-fixed, paraffin-embedded tumors using allele-specific PCR (amplification refractory mutation system) (EGFR RGQ PCR Kit, Qiagen) according to previously described protocols [11, 12]. Tumors harboring EGFR mutations on these exons were labeled as EGFR-mutant and those without were labeled as EGFR-wild type.

PET/CT acquisition and analysis

PET/CT examinations were performed using dedicated PET/CT scanner (Discovery VCT, 64-multislice CT, GE Healthcare Bio-Sciences Corp., Piscataway, New Jersey, USA). Patients were required to fast 6 hours prior to the examination and serum glucose was maintained below 180mg/dl before 370MBq ^{18}F-FDG injection. An hour following ^{18}F-FDG injection, either a low-dose CT (field of view, 50 cm; pixel size, 3.91 mm; 0.5 s/CT rotation, pitch 0.984:1; 2.5 mm intervals; 120 kVp; 80–200 mA) or contrast enhanced CT (same parameters but with 200-400mA, 1.5ml/kg intravenous contrast at a rate of 2.0 ml/sec) was performed for anatomical correlation and attenuation correction, covering from skull base to the upper thighs. This was followed by PET emission scan, taking approximately 3-4 min per bed position and 5-6 bed positions per patient. PET images were reconstructed using 14 subsets and two iterations based on an ordered-subset expectation maximization iterative algorithm.

All the examinations were retrospectively reviewed on dedicated ADW4.3 workstation (GE Healthcare, Milwaukee, Wisconsin, USA). Reviewers were blinded to the EGFR mutations at the time of review. Volume of interest (VOI) was placed to encompass the entire primary tumor, lymph node or metastasis, but carefully excluding tissue outside of the measured lesion by WSQ and XY to derive the SUVmax. Radiologist EL (3 years experience in PET/CT with special interest in thoracic imaging) subsequently verified all lesions and VOI contoured. Metastatic lymph nodes were defined as lymph nodes with increased metabolic activity compared to background mediastinal blood pool based on visual qualitative analysis. Only lesions with the longest axis equal or more than 1.0 cm were included in the analysis to avoid partial volume effect. The SUVmax was corrected based on lean body mass. In the presence of multiple metastatic lesions, one lymph node and one distant metastasis with the highest SUVmax in each patient were selected for subgroup analyses. The lesions that were not biopsied were verified by follow-up imaging by either PET/CT or CT based on EORTC and RECIST 1.1 criteria respectively[13, 14]. Tumors that responded in concordant fashion as the overall disease in the form of complete response, partial response, stable disease or disease progression were considered true positive tumors; whereas tumors that responded different from the

overall disease were considered false positive tumors and would be excluded from analysis.

Statistics

Descriptive statistics were used for demographic data. Median value was expressed with ranges. Non-parametric Mann-Whitney U test was used to compare the difference in SUVmax between EGFR-mutant and EGFR-wild type adenocarcinoma. Receiver operating characteristics (ROC) curve was constructed to derive the optimal cut-off value for SUVmax in predicting EGFR mutation status. Demographic features (age, sex, smoking status) and SUVmax with *p*-value <0.05 in the univariate analysis were further analyzed by multivariate logistic regression to identify significant predictors for EGFR mutations. The SUVmax was dichotomized by the ROC-derived cut-off value and age was treated as continuous variable for both univariate and multivariate analyses. ROC curves were constructed for individual predictor and combined factors in predicting EGFR mutations. Null hypothesis was rejected when *p*-value <0.05 and statistical significance was assumed. All analyses were performed using SPSS (version 20.0, Chicago, IL, USA).

Results

Patients and disease characteristics

The median age of the study population was 65 years old (range 35-85 years-old). The median age of patients with EGFR-mutant adenocarcinoma (median 70 years-old, range 41-85 years-old) was higher than patients with EGFR-wild type adenocarcinoma (median 57 years-old, range 35-79 years-old) ($p<0.001$). Further clinical characteristics were tabulated in Table 1. The follow-up PET/CT or CT was performed at a median of 9.2 months (1.1-44.8 months). Five patients had shorter follow-up period of less than 3 months due to rapid disease progression given that our study cohort was stage IV adenocarcinoma with poor prognosis.

There were 48 patients with EGFR-mutant adenocarcinoma (with 4 patients having double EGFR mutations, Table 1) and 23 patients with EGFR-wild type adenocarcinoma (Figures 1A and 1B). Forty-eight patients (30 EGFR-mutant and 18 EGFR-wild type) had nodal metastases with 246 metastatic lymph nodes evaluated. There were 618 distant metastases evaluated in 68 patients (45 EGFR-mutant and 23 EGFR-wild type). Three patients had their brain metastases resected at the time of initial diagnosis of underlying NSCLC prior to staging PET/CT, therefore not evaluated.

^{18}F-FDG avidity of tumors

There was no difference in the SUVmax between the EGFR-mutant and EGFR-wild type primary tumors (p=0.311) (Figure 2, Table 2).

The SUVmax of the EGFR-mutant lymph nodes was lower than EGFR-wild type adenocarcinoma (p<0.001) (Table 2). In subgroup analysis based on the highest nodal SUVmax, the metabolic uptake remained significantly lower in the EGFR-mutant lymph nodes, SUVmax 3.5 (1.1-10.5) than EGFR-wild type lymph nodes, SUVmax 7.1 (2.4-19.1) (p=0.005, Figure 3A).

The EGFR-mutant distant metastases had lower ^{18}F-FDG avidity (p<0.001) (Table 2). The SUVmax of the most avid distant metastasis was lower in EGFR-mutant adenocarcinoma, SUVmax 5.8 (2.6-16.6) than EGFR-wild type metastasis, 8.4 (3.0-18.1) (p=0.006, Figure 3B).

ROC curve analysis based on the most ^{18}F-FDG-avid metastases

When attempting to optimize the sensitivity and maintaining a high specificity (>80%), SUVmax $\leqq$7.2 in both nodal and distant metastases could predict EGFR-mutant status. In lymph node categorization, the accuracy (Acc) 73%, sensitivity (Sen) 50%, specificity (Spec) 87%, positive predictive value (PPV) 69%, negative predictive value (NPV) 74%, area under the curve (AUC) 0.74, p=0.005 were achieved; whereas in distant metastasis, the diagnostic characteristics were Acc 72%, Sen 57%, Spec 80%, PPV 59%, NPV 78%, AUC 0.71, p=0.006 (Figure 4).

Prediction of EGFR mutation status

The SUVmax was dichotomized at SUVmax 7.2. In the univariate analysis, all factors tested (age, sex, smoking status and SUVmax) were significantly correlated with EGFR mutation status (all $p<0.001$). Subsequent multivariate logistic regression analysis demonstrated all factors were significant predictors (all $p<0.001$). ROC curves analysis showed that each individual factor could predict EGFR mutation status with AUC ranging from 0.58-0.74. When combining all 4 factors, they were highly predictive of EGFR mutations (AUC 0.90, Sen 82%, Spec 79%, PPV 85%, NPV 76%) (Figure 5) [15, 16].

Discussion

In this study, we demonstrated that the metastases, but not the primary tumor, from stage IV EGFR-mutant adenocarcinoma had significantly lower SUVmax than EGFR-wild type adenocarcinoma and that SUVmax was a significant independent predictor for EGFR mutations. When SUVmax was combined with easily accessible demographic parameters, namely age, sex and smoking status, these were highly predictive of EGFR mutations with an AUC 0.90 [15, 16].

The EGFR mutation status is important in selecting NSCLC for TKI therapy. The clinical challenge remains with obtaining adequate tumor tissue of good quality, often from small samples acquired from bronchoscopic fine needle aspiration or core needle biopsies, for EGFR mutation analysis. Even with sensitive PCR approaches, insufficient DNA extraction from these small samples can result in artifacts that preclude confident interpretation [17], as shown in 19% of our patients whom could not have their EGFR status verified and had to be excluded from the study cohort. This is often the limiting step in initiation of personalized treatment with TKIs.

The low SUVmax in EGFR-mutant adenocarcinoma in our study may seem counterintuitive, given the role of EGFR in modulating cell survival. We propose that the cellular metabolism of the metastasis may have been altered following a series of complex cell-biological events, forming the invasion-metastasis cascade [18]. It is plausible

that the metabolic phenotype of EGFR-mutant primary tumor may differ from that of metastases. This biological adaptation supports our results in that the nodal and distant metastases from EGFR-mutant adenocarcinoma had lower SUVmax but not the primary tumor. The lower metabolic uptake in EGFR-mutant adenocarcinoma could be related to the lower proportion of GLUT-1 overexpression in mutant-EGFR adenocarcinoma, 23% compared to 58% in EGFR-wild type adenocarcinoma [19].

Our study cohort was made up of all stage IV lung adenocarcinoma when compared to others published studies that included various stages and different histological subtypes of NSCLC (Table 3) [5-9]. The inclusion of different histological subtypes is likely going to impact upon the semi-quantification of SUVmax, as squamous cell carcinoma is known to be more FDG avid than adenocarcinoma [20]. Some studies concentrated in analyzing the primary tumors but not the metastases, therefore potentially masking the different metabolic phenotypes expressed by the EGFR-mutant and EGFR-wild type metastases [6, 9]. Huang et al. drew different conclusion from ours and suggested that SUVmax > 9.5 was more likely to harbor EGFR mutations in 77 patients [5]. The discrepancy maybe related to the evaluation protocol that only included SUVmax from the primary tumors and mediastinal nodal metastases but not distant metastases. Furthermore, the number of metastases per patient may have also affected the results. Higher SUVmax in NSCLC with EGFR-overexpression was observed in stage I resected primary tumors but the results could be again confounded by high proportion (24.3%) of squamous cell origin in the cohort [9].

Despite statistical significant difference in the SUVmax between the two groups, substantial overlap was observed in the lower ranges of SUVmax of the metastases (Figure 3A and 3B) and tissue molecular confirmation should be performed whenever possible. In our study, identifying the EGFR mutation status was not feasible in 19% of the identified cases, indicating the clinical challenge in determining EGFR based on tissue molecular testing. Thus, SUVmax maybe a useful adjunct to demographic features in predicting EGFR mutations.

This was a retrospective study that may introduce selection bias, likely explaining a high proportion of EGFR-mutant adenocarcinoma (68%) in our cohort. Our findings may be

less applicable to populations that have lower incidence of EGFR mutation. The study only evaluated stage IV lung adenocarcinoma and would require further validation of our results in less advanced stage NSCLC. As clinically impractical and unethical, not all lesions were biopsied and analyzed individually for EGFR mutation status; this may introduce bias in the molecular analysis given disease heterogeneity and validation through follow-up imaging could be imprecise. Thus, we could have included inflammatory and reactive lymph nodes.

Conclusion

In conclusion, the metastases of EGFR-mutant stage IV adenocarcinoma have lower metabolic phenotype compared to EGFR-wild type metastases and SUVmax is a significant independent predictor of EGFR mutations.

Disclosure

No conflict of interest is reported with this article.

Acknowledgments

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Legends

Figure 1 Maximum intensity projection of PET data in stage IV lung adenocarcinoma. A, EGFR-wild type primary tumor in the collapsed right lower lobe (SUVmax 16.9) with pleural, osseous and peritoneal metastases (SUVmax 1.8-6.8). FDG uptake in the right parotid gland was related to concurrent sialadenitis. B, EGFR-mutant primary tumor in the consolidated right lower lobe (SUVmax 8.5) with nodal and widespread osseous metastases (SUVmax 1.7-5.2).

Figure 2. Box-plot of SUVmax of primary tumors of EGFR-mutant and EGFR-wild type adenocarcinoma. There was no statistical significant difference in the SUVmax of the primary tumors between EGFR-mutant (*N=48*) and EGFR-wild type (*N=23*) adenocarcinoma (p=0.311). The boxes represent the 25^{th}-75^{th} percentiles of the SUVmax and the crossbars denote the minimum and maximum values that were not outliers. The circle represents the mild outlier.

Figure 3. Box-plots of SUVmax of metastases of EGFR-mutant and EGFR-wild type adenocarcinoma. A, The highest nodal SUVmax from each patient in EGFR-mutant (*N=30)* and EGFR-wild type adenocarcinoma (*N=18)* was selected, and the difference was statistically significant (p=0.005). B, The distant metastasis with highest SUVmax from each patient in EGFR-mutant (*N=45)* and EGFR-wild type adenocarcinoma (*N=23)* was selected, and the difference was statistically significant (p=0.006). The boxes represent the 25^{th}-75^{th} percentiles of the SUVmax and the crossbars denote the minimum and maximum values that were not outliers. The circle represents the mild outlier and the asterisk is the extreme outlier. SUVmax: maximum standardized uptake value; EGFR: epidermal growth factor receptor.

Figure 4. ROC curves of nodal and metastasis SUVmax in predicting EGFR mutations. A SUVmax ≦7.2 would predict EGFR mutations with high specificity. A, In nodal metastasis, Acc 73%, AUC 0.74, p=0.005. B, In distant metastasis, Acc 72%, AUC 0.71, p=0.006. ROC: receiver operating characteristics; SUVmax: maximum standardized uptake value; EGFR: epidermal growth factor receptor; Acc: accuracy; AUC: area under the curve.

Figure 5. ROC curves of individual predictors and combined predictive factors (SUVmax, age, sex and smoking status) in determining EGFR mutation status. ROC: receiver operating characteristics; AUC: area under the curve, followed by 95% confidence intervals in brackets.

Table 1. The clinical characteristics of the study population in respect to EGFR mutation status and the frequencies of EGFR mutation types. EGFR: epidermal growth factor receptor; *N*: number of patients.

Table 2. The metabolic parameters of the primary tumors and metastases in association with EGFR mutation status. EGFR: epidermal growth factor receptor; *n*: number of lesions; *: statistical significance.

Table 3. Summary of the studies evaluated the relationship between metabolic uptake and EGFR mutation status. *N*: total number; *n*: number in subgroups; ADC: adenocarcinoma; EGFR: epidermal growth factor receptor; LN: lymph node; SUV: standardized uptake value; †only mutations in exons 19 and 21; ‡EGFR status determined by EGFR-overexpression on immunohistochemistry.

TABLE 1. The clinical characteristics of the study population in respect to EGFR mutation status and the frequencies of EGFR mutation types. EGFR: epidermal growth factor receptor; *N*: number of patients.

		EGFR-mutant (*N*)	EGFR-wild type (*N*)	Total (*N*)
Smoking status	Non-smoker	39	12	51
	Smoker/ ex-smoker	8	11	19
	Undetermined	1	0	1
Sex	Female	31	7	38
	Male	17	16	33
EGFR mutations	Exon 21	27		52
	Exon 20	5		
	Exon 19	15		
	Exon 18	5		
	Negative		23	23

TABLE 2. The metabolic parameters of the primary tumors and metastases in association with EGFR mutation status. EGFR: epidermal growth factor receptor; *n*: number of lesions; *: statistical significance.

	EGFR-mutant	EGFR-wild type	*p*-value
Primary tumor SUVmax	*n*=48	*n*=23	
Median (range)	7.4 (2.5-15.2)	8.1 (1.3-22.5)	0.311
Nodal metastasis	*n*=118	*n*=128	
SUVmax Median (range)	3.4 (1.1-10.5)	5.5 (1.3-19.1)	<0.001*
Distant metastasis	*n*=389	*n*=229	
SUVmax Median (range)	3.4 (0.9-16.6)	4.7 (1.4-18.1)	<0.001*

TABLE 3. Summary of the studies evaluated the relationship between metabolic uptake and EGFR mutation status. *N*: total number; *n*: number in subgroups; ADC: adenocarcinoma; EGFR: epidermal growth factor receptor; LN: lymph node; SUV: standardized uptake value; †only mutations in exons 19 and 21; ‡EGFR status determined by EGFR-overexpression on immunohistochemistry.

Studies	*N*	Disease stage (*n*)	Histology	EGFR mutant: wild type (*n*)	Lesions measured	Metabolic parameters	Findings
Huang et al.[5]	77	IIIB/IV (15/62)	ADC	49:28	Primary tumor, mediastinal LN	SUVmax	High SUVmax was predictive of EGFR mutations
Na et al.[6]	100	I/II/III/IV (39/18/38/5)	ADC, non-ADC	21:79†	Primary tumor	SUVmax	Low SUV was predictive of EGFR mutations
Mak et al.[7]	100	I-IV (32/8/18/42)	ADC, non-ADC	24:76	Primary tumor, one LN, one metastasis	SUVmax	Low SUV was associated with EGFR mutations
Chung et al.[8]	106	I-IV (12/7/27/60)	ADC	42:64	Primary tumor, one metastasis	SUVmax	Not predictive of EGFR mutations
					All	MTV, TLG	
Lee et al.[9]	167	I (167)	ADC, non-ADC	42:125‡	Primary tumor	SUVmax	High SUVmax was associated with EGFR overexpression

Figure 1

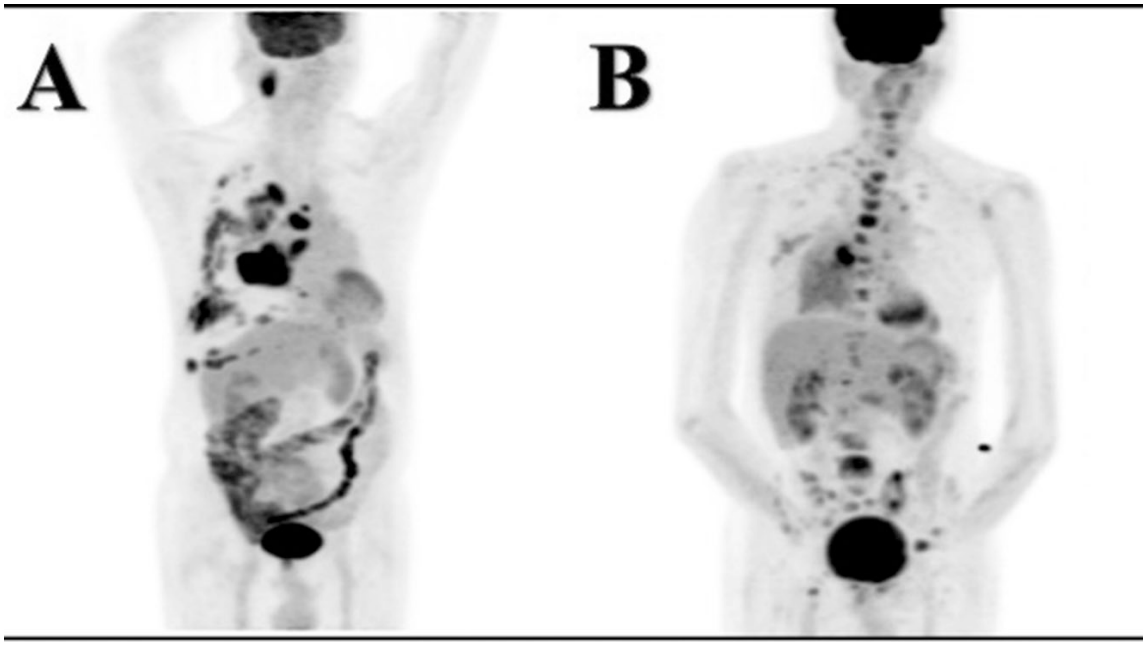


Figure 2

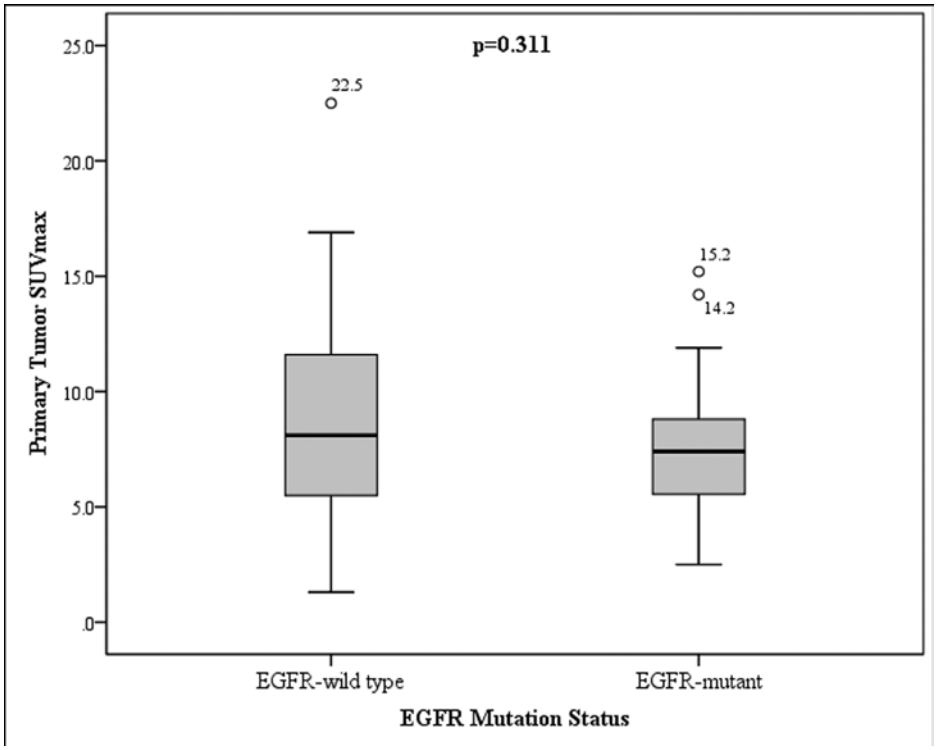


Figure 3

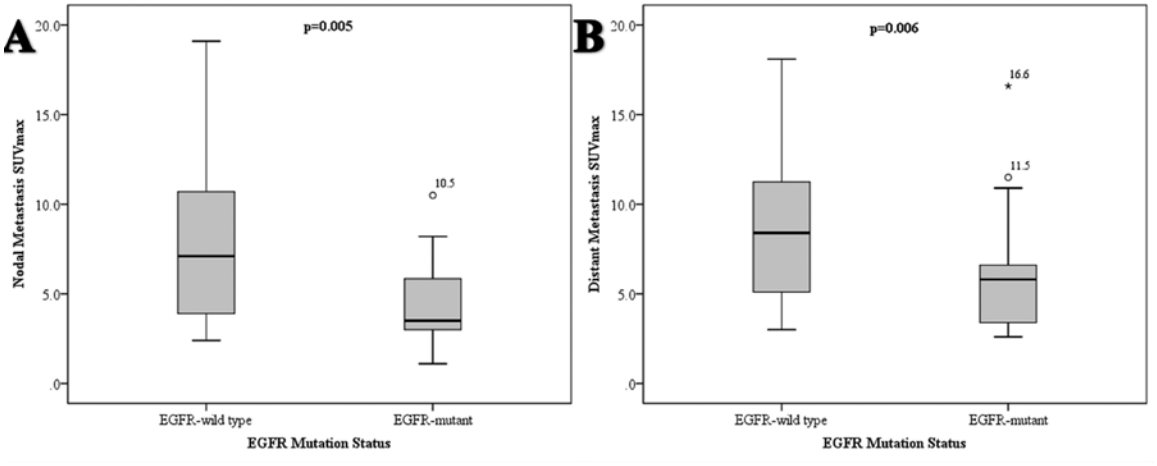


Figure 4

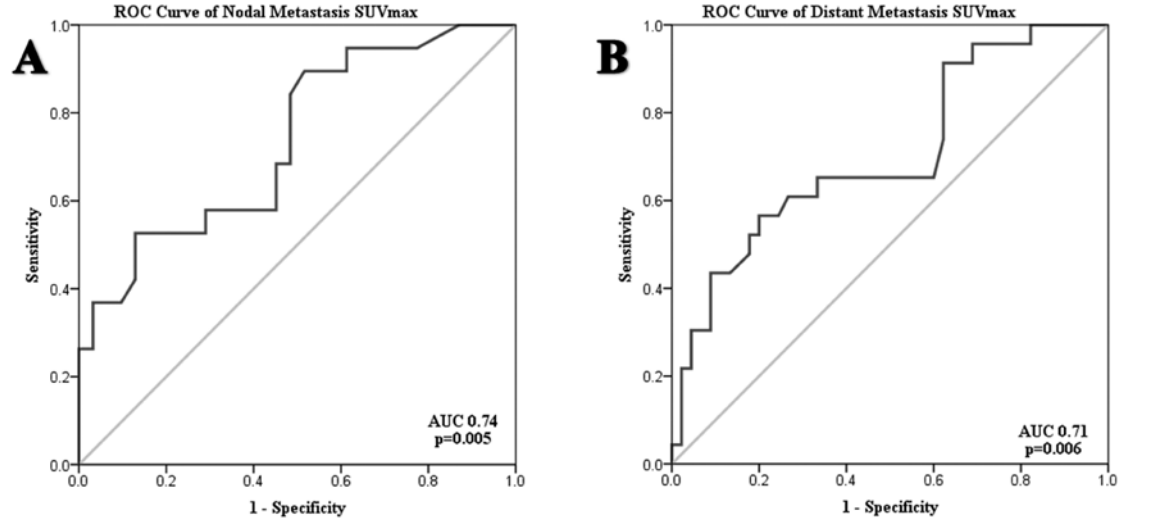
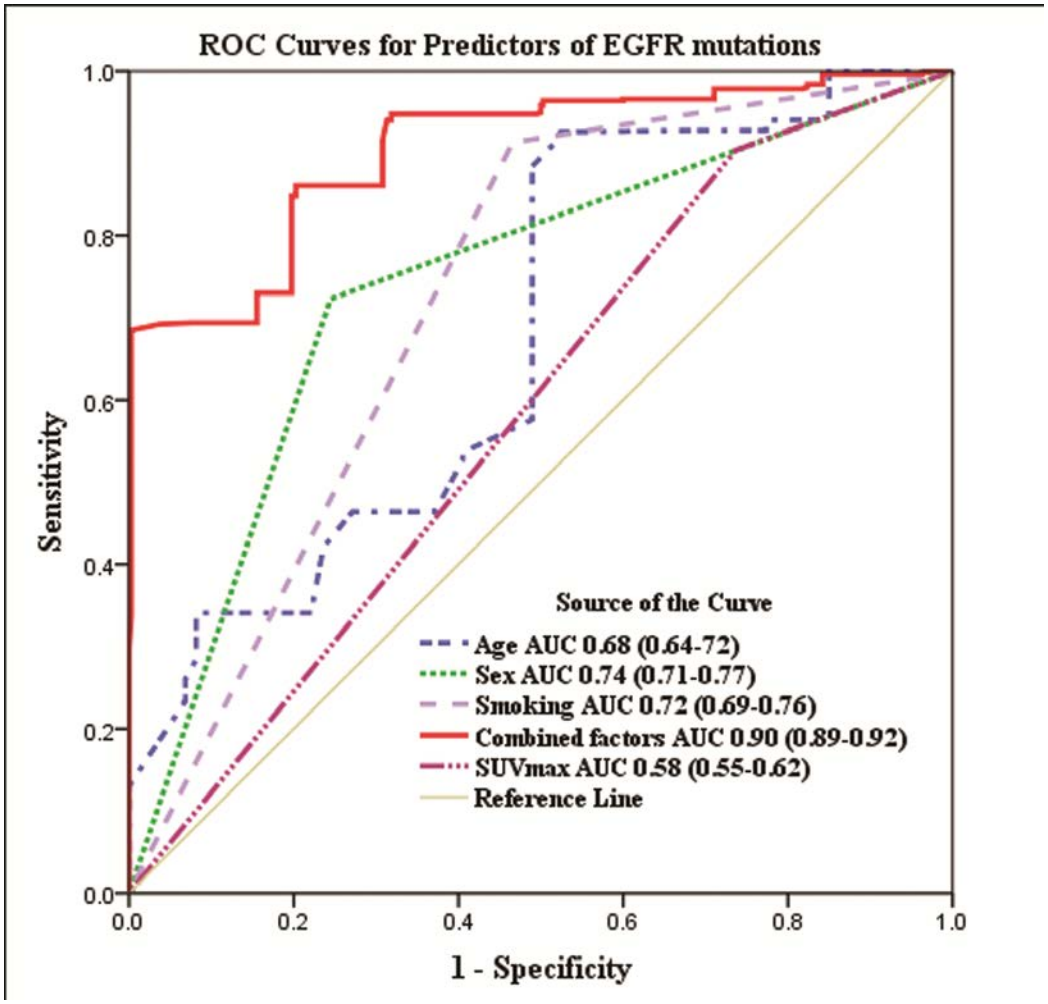


Figure 5


ROC Curves for Predictors of EGFR mutations
Sensitivity
1 - Specificity
0.0
0.2
0.4
0.6
0.8
1.0
Source of the Curve
Age AUC 0.68 (0.64-72)
Sex AUC 0.74 (0.71-0.77)
Smoking AUC 0.72 (0.69-0.76)
Combined factors AUC 0.90 (0.89-0.92)
SUVmax AUC 0.58 (0.55-0.62)
Reference Line