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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Association between epidermal growth factor receptor mutation status, clinicopathological characteristics and TTF-1 expression in lung adenocarcinoma – a single center study

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SUMMARY

Introduction/Objective The presence of epidermal growth factor receptor (EGFR) mutations is the best predictor of response for therapy with tyrosine kinase inhibitors. In this study, we investigate association between EGFR mutations and clinicopathological characteristics and thyroid transcription factor (TTF-1) expression in lung adenocarcinomas (AD).

Methods We analyzed 142 surgical samples from patients with histologically confirmed lung AD from January 2010 to December 2015. All tumor tissues were reclassified according to the World Health Organization criteria and EGFR mutations detected by real-time polymerase chain reaction. TTF-1 expression was detected by immunohistochemistry in 83 out of 142 cases. The association between EGFR and TTF-1 expression was analyzed using the χ^2 test or Fisher's exact test with SPSS software version 20.0.

Results This study included 78 male and 64 women with a median age of 61.6 (range, 42–82) years. Acinar (ACN) and solid (SOL) were the most common histological types (47.9% and 38.7%, respectively). TTF-1 expression was present in 69 of 83 (83%) ADs. The EGFR mutation was found in 7%, more frequently in women, and patients with smoking history, and acinar type of AD, whereas it had no association with age and pathological stage and TTF-1 expression.

Conclusion In conclusion, the results of this study demonstrate that the presence of EGFR mutations is associated with some clinical characteristics and histologic type of ADs, but not with TTF-1 expression.

Keywords: adenocarcinoma; EGFR mutation; clinicopathological characteristics; TTF-1 expression

INTRODUCTION

Epidermal growth factor receptor (EGFR) consists of 486 amino acids and 170 kDa in size. It is part of the ErbB family of structurally related receptor tyrosine kinases: EGFR (HER1, ErbB1), HER2 (Neu, ErbB2), HER3 (ErbB3) and HER4 (ErbB4), which are involved in signal transduction pathways and play a key role in the regulation of cellular proliferation and apoptosis. Molecular analysis of the mutation status for EGFR is critical for treatment of tyrosine kinase inhibitors (TKIs), which show improved progression-free survival (PFS) and overall survival in inpatients with adenocarcinomas (AD), which is second most frequent histological type of lung cancer found in surgically treated lung cancer patients in Serbia [1, 2, 3]. According to international guidelines, conventional identification of EGFR genotype requires tissue/cytologic samples (Ti/Cy), but in the last five years, EGFR testing can be performed by analyzing circulating-free tumor DNA (cfDNA) in peripheral blood samples. EGFR mutations are more frequent in tumors with ADs histology, in never-smokers or light smokers, in female, and in patients with East Asian ethnicities. The most frequent EGFR mutations are in-frame deletions of exon 19 and the exon 21 L858R mutation [4, 5]. Previous investigations have demonstrated that EGFR gene mutation is mainly detected in patients with lepidic (LP), papillary (PAP), micropapillary (MPP), and acinar (ACN) types, whereas the mutation rate is extremely low in patients with the solid (SOL) histological type [6–9].

Thyroid transcription factor 1 (TTF-1), is a homeodomain nuclear protein that belongs to the NK2 family of transcription factor. TTF1 is recommended as one of a panel of lineage-specific immunohistochemical markers for AD differentiation and may modulate lung cancer biology. Clinicopathologic features such as age, sex, smoking status, histological type, and pathological stage were similar between TTF-1-positive and TTF-1-negative tumors. TTF-1-positive tumors have more commonly EGFR mutations, as well as better response to EGFR TKIs comparing to TTF-1-negative tumors, but TTF-1 negativity should not be the exclusion criteria for EGFR testing [10, 11, 12].

In the present study, we investigated the association between EGFR mutation status, clinicopathological characteristics, and TTF-1 expression in lung AD.

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METHODS

Surgical samples of 142 patients with lung AD admitted to the Institute for Lung Diseases of Vojvodina (Sremska Kamenica, Serbia) between January 2010 and December 2015 were retrospectively analyzed.

Clinicopathological parameters including age, sex, smoking history, pathological stage, and histological type were recorded. The histological classification was done based on 2015 WHO classification system and all samples were divided into five groups (ACN, PAP, MPP, LP, or SOL).

One hundred forty-two surgical samples were fixed in 10% formalin, embedded in paraffin, cut on four-micron-thick sections and stained with routine H&E staining. Eighty-three of them were deparaffinized and incubated in a citrate buffer (10 mM sodium-citrate monohydrate, pH 6.5) at 120°C for 20 minutes in an autoclave. The sections were reacted for one hour with antibody of TTF-1 (monoclonal antibody, Denmark DAKO products) and then incubated with a commercially available detection kit (DAKO EnVision Plus-HRP, Dako, Glostrup, Denmark) following the manufacturer's instructions. Positive and negative controls were used as appropriate. TTF-1 expression was rendered semiquantitatively on a score 0–2. Tumors were scored according to TTF-1 expression into following scores: 0 (lack of expression), score 1 (< 50%) and score 2 (≥ 50%) based on the percentage of positively stained tumor cells of any intensity.

The EGFR mutations (in exons 18, 19, 20, and 21) was done with the Cobas EGFR Mutation Test (Roche, Basel, Switzerland) "Real time PCR." The Cobas Sample Preparation Kit (Roche) was used for the sample preparation and DNA extraction. Automatic amplification and detection were done on the Cobas z 480 Analyzer (Roche).

Statistical analysis

Pearson's χ^2 test and Fisher's exact test were used to compare frequencies of clinicopathological variables; p-values < 0.05 were considered statistically significant. All analyses were performed using IBM SPSS Statistics, Version 21.0 (IBM Corp., Armonk, NY, USA).

The study was done in accord with standards of the institutional committee on ethics.

RESULTS

One hundred forty-two patients diagnosed with infiltrative AD (Figure 1) which had been surgically resected were included in this study. The median age of all patients was 61.6 years (ranging 42–82). The majority of patients were males (78; 54.9%), and 13 of 142 (9.2%) had no-smoking history (Table 1).

Most common histological types were ACN (68; 47.9%) and SOL (55; 38.7%), with most frequent pathological stage IIA according to the 7th TNM classification system (Table 2).

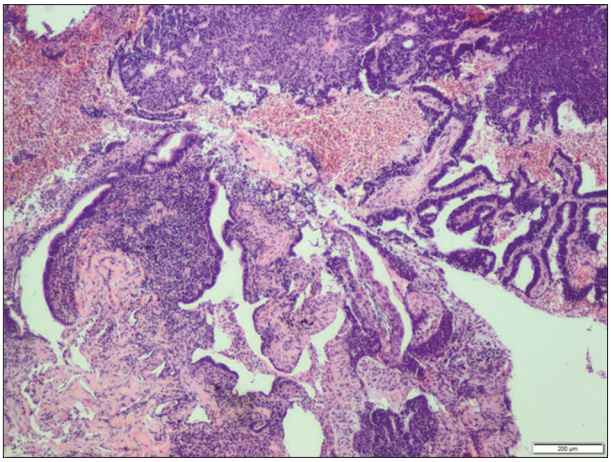

Figure 1. Acinic type adenocarcinoma (H&E, 10×)

Table 1. Patient characteristics and epidermal growth factor receptor (EFGR) mutation status

Clinical characteristics	Frequency	EGFR status, n (%)		p
		positive	negative	
Total	142	10 (7)	132 (93)	
Age, years Median Range	 61.6 42–82	 65.5 46–82	 61.3 42–82	
Sex Male Female	 78 (54.9) 64 (45.1)	 3 (2.1) 7 (4.9)	 75 (52.8) 57 (40.1)	0.114
Smoking history Never Former/current	 13 (9.2) 129 (90.8)	 3 (2.1) 7 (4.9)	 10 (7) 122 (85.9)	0.05

Table 2. Histopathological characteristics of adenocarcinomas and epidermal growth factor receptor (EFGR) mutation status

Histopathological characteristics	Frequency	EGFR status, n (%)		p
		positive	negative	
Histological type				
LP	6 (4.2)	0 (0)	6 (4.2)	0.32
ACN	68 (47.9)	8 (5.6)	60 (42.3)	
PAP	9 (6.3)	0 (0)	9 (6.3)	
SOL	55 (38.7)	2 (1.4)	53 (37.3)	
MPP	4 (2.8)	0.(0)	4 (2.8)	
Stage				
IA	32 (22.5)	3 (2.1)	29 (20.4)	0.46
IB	24 (16.9)	1 (0.7)	23 (16.2)	
IIA	35 (24.6)	2 (1.4)	33 (23.2)	
IIB	28 (19.7)	4 (2.8)	24 (16.9)	
IIIA	21 (14.8)	0 (0)	21 (14.8)	
IV	2 (1.4)	0 (0)	2 (1.4)	
Total	142 (100)	10 (7)	132 (93)	

LP – lepidic; PAP – papillary; MPP – micropapillary; SOL – solid; ACN – acinar

Table 3. Association between TTF-1 expression and epidermal growth factor receptor (EFGR) mutations

TTF-1 expression	Frequency	EGFR status, n (%)	
		positive	negative
Score 0	14 (16.9)	2 (2.4)	12 (14.5)
Score 1	3 (7.2)	0 (0)	6 (7.2)
Score 2	63 (75.9)	3 (3.6)	60 (72.3)
Total	83 (100)	5 (6)	78 (94)

Sixty-three (75.9%) of the 83 cases of lung AD showed TTF-1 expression levels corresponding to score 2 (Figure

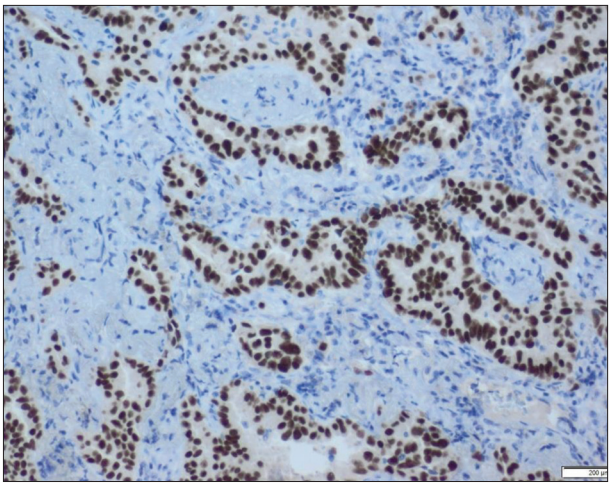

Figure 2. TTF-1-positive expression in adenocarcinoma cells (IHC, 10×)

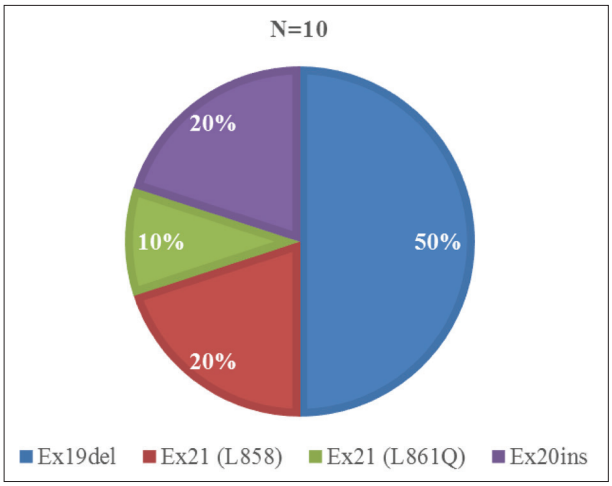

Figure 3. The proportion of epidermal growth factor receptor mutations

2), 3 (7.2%) to score 1, and 14 (16.9%) cases lack of TTF-1 expression (Table 3).

EGFR mutations in exons 18, 19, 20, or 21 were examined in 142 cases of lung AD. The overall frequency of EGFR mutation was 7% (10 of 142). Five cases had an in-frame deletion in exon 19, three cases had exon 21 substitutions (L858R, L861Q), and two cases exon 20 insertions. Multiple mutations (≥ 2) and other EGFR mutations were not observed (Figure 3).

Three male and seven female patients harbored EGFR mutation ($p = 0.114$). Three patients with EGFR gene mutation were non-smokers. ($p = 0.05$) (Table 1). The EGFR mutations were found in eight ADs with ACN histological type and in two with SOL histological type ($p = 0.32$). Other histological types were without EGFR mutations. Pathological stage with EGFR mutations were: IIB, IIA, and IB (4, 3, and 1; $p = 0.46$) (Table 2). Association between TTF-1 protein expression and EGFR mutation status is shown in Table 3. Three cases with TTF-1 expression (score 2) had EGFR mutations. Also, EGFR mutations were present in two cases lack of TTF-1 expression (score 0) (Table 3).

DISCUSSION

In recent years, significant progression has been obtained in the molecular biological research of lung ADs with EGFR mutation. EGFR mutation is a protein on cell surface with intracellular tyrosine kinase (TK) activity due to targetable activating mutations. These tumors are susceptible to TKIs such as gefitinib, erlotinib, or afatinib [9].

Ti/Cy samples are mostly obtained by sampling of the primary tumor or a metastatic lymph node. The median EGFR test turnaround time for Ti/Cy samples was 11 days for Europe and eight days for Japan. When tumor samples are unavailable, cfDNA is a feasible sample for EGFR mutation analysis because the overall concordance of EGFR mutation status between matched Ti/Cy and plasma samples was 89%. It is important to conduct mutation testing in specialized laboratories, using sensitive mutation testing methods to ensure accuracy of the results. In Europe, 43 laboratories perform the Ti/Cy testing, while in five laboratories both analysis of Ti/Cy and cfDNA in peripheral blood samples are performed [11, 13, 14]. At our institution, both methods of EGFR mutation testing have been implemented in clinical practice three years ago.

Since computed tomography (CT) is routinely used in lung cancer diagnosis, as CT imaging is more readily available than biopsies, many researchers proposed analysis CT imaging for predicting EGFR mutations [15]. The presence of emphysema or airway abnormality predicts a wild type status of EGFR, while the presence of any ground glass component indicates EGFR mutations [16]. Recently, the deep learning model provides a non-invasive and easy to use method for predicting the EGFR mutation status. Wang et al. [17] retrospectively collected data from 844 lung AD patients with pre-operative CT images, EGFR mutation, and clinical information from two hospitals. The deep learning score demonstrated significant differences in EGFR-mutant and EGFR-wild type tumors ($p < 0.001$).

ADs are the most common histological subtypes of lung carcinoma, and it has been shown that this is associated with activating mutations in the EGFR gene in 15% of European and 47% of Japanese patients [18]. The most common EGFR mutations include exon 19 deletion. Other recurrent mutations, in exon 18-point mutations in position G719, in exon 21 L861Q mutation, and in-frame exon 19 insertions are rare (3%; 2%, and < 1%) [19–22]. In our study, EGFR mutations were detected in 10 of 142 (7%) cases of AD, five of 10 were deletion in exon 19, similar to results in other studies.

The association between EGFR mutations with patients' age, sex, and smoking status has been demonstrated in numerous studies with a variety of cases [23–26]. In this investigation, EGFR gene mutation was mainly observed in patients aged > 60 years, which is consistent with previous findings.

Mutations were found more frequently in women (69.7%), in patients who had never smoked (66.6%), and

in those with adenocarcinomas (80.9%) ($p < 0.001$) [22, 26]. Contrary to these results, in our study, EGFR mutations were more frequently detected in smokers (seven of 10 cases). These differences are probably due to different lifestyles.

Many authors have studied the association between EGFR mutations and histologic type of AD and TTF-1 expression, as well as pathologic stage of the disease [27–30]. Villa et al. [31] reported that the most common histologic type seen in the EGFR-mutant-positive ADs was LP (44%). Contrary to these results, Zhang et al. [22] reported that ACN type most frequently correlated with EGFR mutation, which is consistent with our results. In our study, ACN (7/10) and SOL (3/10) type were independent predictors of EGFR mutation. EGFR-mutated ADs may develop through a distinct carcinogenetic pathway, in which the MPP element may play an important role in promoting progression and has prognostic value [32]. In our results, MPP histologic type was detected in four of 142 (2.8%) cases with wild type EGFR ADs. Pi et al. [27] showed that EGFR mutation was significantly higher in stage IA than in stage IIB ($p = 0.002$). In our study, there was no difference in EGFR mutations between stage IA and stage IIB, probably because it was a single center study with a small number of cases.

TTF-1 is expressed in the distal bronchial epithelium, including type II alveolar epithelial cells and terminal respiratory epithelial cells, as well as in lung carcinoma: frequently in small cell carcinoma and in ADs [10]. Sixty-six of 83 cases (79.5%) of lung ADs included in this study showed score 2 (75.9%) of TTF-1 expression, while three (7.2%) showed score 1. These results suggest that lung ADs expressed TTF-1. In recent years, many studies have mentioned the association between TTF-1 expression and EGFR mutations [10, 12, 32, 33]. The TTF-1 positivity staining was strongly correlated with the presence of EGFR mutations ($p < 0.001$) and TTF-1 negativity was said to be a good predictor of EGFR wild type mutations [32]. The results of the Svaton et al. [29] study suggested that patients with EGRF wild type lung ADs and a lack of TTF-1 expression may have significantly lower PFS and overall survival, and TTF-1 expression may be a useful predictor of TKIs efficacy in patients with EGFR wild type lung ADs. The patients, TTF-1-positive or -negative ADs, could benefit from the first-line chemotherapy [30]. Therefore, a lack of TTF-1 expression should not exclude patients from EGFR testing.

To our knowledge, this is the first study that investigates the association between EGFR mutation and TTF-1 expression in Serbia. Among tumors in which immunohistochemical analysis to TTF-1 antibody was performed ($n = 83$), EGFR mutations were detected in five cases: in three tumors with score 2 of TTF-1 expression and in two tumors a lack of TTF-1 expression (Table 3).

CONCLUSION

The results of this study demonstrate that the presence of EGFR mutations is associated with some clinical characteristics and histologic type of AD, but not with TTF-1 expression.

Conflict of interest: None declared.

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Удруженост мутационог статуса рецептора епидермалног фактора раста са клиничкопатолошким карактеристикама и експресијом ТТФ-1 у аденокарциному плућа – студија једног центра

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САЖЕТАК

Увод/Циљ Присуство мутација рецептора епидермалног фактора раста (РЕФР) најбољи је предиктор одговора на терапију инхибиторима тирозинске киназе. У овој студији смо истраживали удруженост мутација РЕФР-а са клиничкопатолошким карактеристикама и експресијом тироидног транскрипционог фактора 1 (ТТФ-1) у аденокарциномима плућа.

Методе Анализирана су 142 хируршка узорка болесника са хистолошки потврђеним аденокарциномом плућа у периоду од јануара 2010. до децембра 2015. године. Сви туморски узорци су рекласификовани према критеријумима СЗО и код свих су мутације РЕФР-а детектоване методом ланчане реакције полимеразе у реалном времену. Експресија ТТФ-1 је одређена имунохистохемијски у 83 од 142 случаја. Асоцијација мутација РЕФР-а и експресије ТТФ-1 је анализирана употребом χ^2 теста или Фишеровог теста.

Резултати У студију је било укључено 78 мушкараца и 64 жене просечне старости 61,6 (од 42 до 82) година. Ацинарни и солидни типови су били најчешћи хистолошки типови (47,9% и 38,7%). Експресија ТТФ-1 била је присутна у 69 од 83 (83%) аденокарцинома. Мутације РЕФР-а су детектоване у 7% случајева, чешће код жена, бивших и активних пушача, са ацинарним хистолошким типом и нису биле повезане са годинама, патолошким стадијумом болести и експресијом ТТФ-1.

Закључак Резултати ове студије показују да је присуство мутација РЕФР-а удружено са неким клиничким карактеристикама и хистолошким типом аденокарцинома, али не и са експресијом ТТФ-1.

Кључне речи: аденокарцином; мутације рецептора епидермалног фактора раста; клиничкопатолошке карактеристике; експресија ТТФ-1