· 论著 ·

肺腺癌新分类与表皮生长因子受体基因突变之间的关系

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[摘 要] **目的**:探讨肺腺癌新分类与表皮生长因子受体(epidermal growth factor receptor,*EGFR*)基因突变之间的关系。**方法**:共纳入中日友好医院2010年3月至2014年12月经手术肺切除术后且病理证实为浸润性肺腺癌患者94例,对其进行*EGFR*基因突变检测;入组患者均按照2011年国际肺癌研究学会(Intemational Association for the Study of Lung Cancer,IASLC)、美国胸科学会(American Thoracic Society,ATS)和欧洲呼吸学会(European Respiratory Society,ERS)分类方法进行肺腺癌亚型分类,分析肺腺癌新分类与*EGFR*基因突变之间的关系;采用SPSS 20.0统计软件卡方检验分析,$P<0.05$为差异有统计学意义。**结果**:入组的94例肺腺癌患者,男、女患者均为47例;年龄24~79岁,中位年龄61岁,60岁及以上48例,60岁以下46例;既往或现在吸烟者34例,不吸烟者60例。根据病理分期,Ⅰ期患者34例,Ⅱ期患者17例,Ⅲ期24例,Ⅳ期19例。*EGFR*基因外显子19突变例数22,外显子20突变例数2,外显子21突变例数26,外显子10和21同时突变例数1,入组患者*EGFR*基因总突变率为54.3%(51/94),其中腺泡状为主型肺腺癌*EGFR*突变例数24例,伏壁状为主型肺腺癌14例,乳头状为主型肺腺癌与实体状为主型肺腺癌均为5例,微乳头状为主型肺腺癌3例,黏液腺癌为0;腺泡状为主型肺腺癌较非腺泡状为主型肺腺癌*EGFR*突变率高,但差异无统计学意义(66.7% *vs.* 46.6%, $P=0.057$);实体状为主型肺腺癌较非实体状为主型肺腺癌*EGFR*突变率低,差异有统计学意义(26.3% *vs.* 61.3%, $P=0.005$);黏液腺癌较非黏液腺癌*EGFR*基因突变率低,差异有统计学意义(0 *vs.* 57.3%, $P=0.018$)。**结论**:不同的病理亚型肺腺癌*EGFR*突变率存在差异,其中腺泡状为主型肺腺癌较非腺泡状为主型肺腺癌的*EGFR*基因突变发生率高,实性为主型肺腺癌较非实性为主肺腺癌*EGFR*突变发生率低,黏液腺癌较非黏液腺癌*EGFR*基因突变率低。

[关键词] 肺腺癌;表皮生长因子受体;基因突变
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Correlation between the new lung adenocarcinoma classification and epidermal growth factor receptor mutation

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ABSTRACT **Objective**: To evaluate the association of the histological subtype of lung adenocarcinoma with epidermal growth factor receptor (*EGFR*) mutation. **Methods**: A total of 94 patients with resected lung adenocarcinoma in the Department of Thoracic Surgery of China-Japan Friendship Hospital from January 2010 to December 2014 were enrolled in the study. All specimens were tested for *EGFR* mutation by a company. In the 94 patients, histological subtypes were classified according to the 2011 International Association for the Study of Lung Cancer and American Thoracic Society and European Respiratory Society classification. We compared the association with the histological subtype of lung adenocarcinoma with *EGFR* mutation frequency by the χ^2 test, with SPSS 20.0. **Results**: The 94 patients of surgically resected lung adenocarcinomas were included in this analysis, of whom, 47 were male and 47 female (male : female = 1 : 1). The median age was 61 (range: 24 – 79) years, and 48 of the 94 patients were 60 years and above. Regarding the pathological staging, 34 patients were diagnosed as Stage Ⅰ of the disease, 17 as Stage Ⅱ, 24 as Stage Ⅲ, and 19 as Stage Ⅳ. Among the 51 patients with *EGFR* mutation, exon 19 mutation was 22, exon 20 mutation was 2, exon 21 mutation was 26, exon 20 and 21 mutation were 1, and the total *EGFR* mutation rate was 54.3% (51/94). The cases of *EGFR* gene mutation of acinar predominant lung adenocarcinoma, lepidic predominant lung adenocarcinoma, papillary predominant lung adenocarcinoma, solid predominant lung adenocarcinoma, micropapillary predominant lung adenocarcinoma and mucious adenocarcinoma were 24, 14, 5, 5, 3, and 0, respectively. The rate of *EGFR* gene

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mutation of acinar predominant lung adenocarcinoma was higher than that of non-acinar predominant lung adenocarcinom, but there was not statistically significant (66.7% *vs.* 46.6%, $P=0.057$). The rate of *EGFR* gene mutation of solid predominant lung adenocarcinoma was lower than that of non-solid predominant lung adenocarcinom (26.3% *vs.* 61.3%, $P=0.005$). The rate of *EGFR* gene mutation of mucious adenocarcinoma was lower than that of non-mucious adenocarcinom (0 *vs.* 57.3%, $P=0.018$). **Conclusion**: There is heterogeneity of *EGFR* mutation in lung adenocarcinoma. The presence of lung adenocarcinoma with acinar indicates a higher *EGFR* mutation rate, while the solid and mucinous component indicates a lower *EGFR* mutation rate.

KEY WORDS Epidermal growth factor receptor; Lung adenocarcinoma; Mutation

肺癌是当今世界最常见的恶性肿瘤，男性肺癌的发病率最高，女性肺癌发病率仅次于乳腺癌[1]。根据组织学特征和治疗方法的不同，可以把肺癌分成两大类：非小细胞肺癌（non-small cell lung cancer，NSCLC）和小细胞肺癌（small cell lung cancer，SCLC）。NSCLC 占肺癌总病例数的 75%～85%，其中腺癌又是主要的类型。2011 年国际肺癌研究学会（Intemational Association for the Study of Lung Cancer，IASLC）、美国胸科学会（American Thoracic Society，ATS）和欧洲呼吸学会（European Respiratory Society，ERS）联合多学科共同发起了关于肺腺癌的国际多学科分类方法[2]。该肺腺癌新分类方法提供了统一的专业术语及诊断标准，取消了细支气管肺泡癌这一分类，新增了 4 个命名：原位腺癌、微浸润性腺癌、浸润性腺癌和浸润性黏液型腺癌，其中浸润性腺癌包括伏壁状为主、腺泡状为主、乳头状为主、微乳头状为主、实体状为主、黏液腺癌、胎儿型腺癌、胶样癌和肠型腺癌。

据统计，肺腺癌患者的总手术切除率仅有 25%，5 年生存率低于 20%[1]，靶向药物的临床应用一定程度上改善了这一现状。表皮生长因子受体（epidermal growth factor receptor，*EGFR*）是一种蛋白酪氨酸激酶受体（receptor tyrosine kinase，RTK）[3]。研究证实，具有 *EGFR* 基因突变的肺腺癌患者接受 *EGFR* 酪氨酸激酶抑制剂（tyrosine kinase inhibitors，TKIs）的治疗能够明显改善生存期[4-5]。相对于化疗，*EGFR* 基因突变的肺腺癌患者接受 *EGFR*-TKIs 治疗的总生存率（overall survival，OS）和无进展生存率（progress free survival，PFS）明显改善[6-7]。大量数据已表明，*EGFR*-TKIs 已经成为肺腺癌患者的标准治疗。美国病理学协会、IASLC 最近出版了肺癌 *EGFR* 突变的分子检测建议，指出患有晚期肺腺癌的所有患者，无论性别、种族、是否有吸烟史或其他临床危险因素，都应该进行 *EGFR* 基因检测[8]。

尽管近年来已经发表了一些关于 *EGFR* 突变的腺癌亚型的报道，但是新的肺腺癌病理亚型分类与 *EGFR* 突变的关系仍尚未明确，因此，本研究通过检测 94 例肺腺癌患者 *EGFR* 的突变情况，探讨新的肺腺癌分类中不同病理亚型与 *EGFR* 突变之间的关系。

1　资料与方法

1.1　研究对象

共纳入中日友好医院 2010 年 3 月至 2014 年 12 月经手术肺切除术后病理证实为浸润性肺腺癌患者 94 例。组织学类型根据世界卫生组织（World Health Organization，WHO）（2015 年）肺肿瘤组织学分类方法确诊为肺腺癌。病理分期是根据美国癌症联合委员会（American Joint Committee on Cancer，AJCC）提出的癌症分期方法。

1.2　研究方法

所有入组肺腺癌患者均按照 2011 年 IASLC/ATS/ERS 提出的分类方法进行肺腺癌亚型分类。

EGFR 基因突变情况由益善生物技术股份有限公司测定，检测患者 *EGFR* 主要突变基因 18、19、20 及 21 外显子。

1.3　统计学分析

采用 SPSS 20.0 软件，统计分析方法采用卡方检验及 Fisher 精确概率法分析分类变量，$P<0.05$ 认为差异有统计学意义。

2　结果

纳入的 94 例肺腺癌患者中，男、女均为 47 例；年龄 24～79 岁，中位年龄 61 岁，60 岁及以上 48 例，60 岁以下 46 例。根据吸烟史统计，既往或现在吸烟者 34 例，不吸烟者 60 例。根据病理分期，Ⅰ期患者 34 例，Ⅱ期患者 17 例，Ⅲ期 24 例，Ⅳ期 19 例。*EGFR* 基因外显子 19 突变例数 22，外显子 20 突变例数 2，外显子 21 突变例数 26，外显子 10 和 21 突变例数 1，具体见表 1。

入组 94 例肺腺癌患者 *EGFR* 基因总突变率为 54.3%（51/94），其中，腺泡状为主型肺腺癌 *EGFR* 突变例数 24 例，伏壁状为主型肺腺癌 14 例，乳头状为主型肺腺癌与实体状为主型肺腺癌均为 5 例，微

乳头状为主型肺腺癌3例,黏液腺癌为0;腺泡状为主型肺腺癌较非腺泡状为主型肺腺癌 *EGFR* 突变率高,但差异无统计学意义(66.7% *vs.* 46.6%,P = 0.057);伏壁状为主型肺腺癌与非伏壁状为主型肺腺癌 *EGFR* 突变率差异无统计学意义(66.7% *vs.* 50.7%,P = 0.195);乳头状为主型肺腺癌与非乳头状为主型肺腺癌 *EGFR* 突变率差异无统计学意义(55.6% *vs.* 54.1%,P = 1.000);实体状为主型肺腺癌较非实体状为主型肺腺癌 *EGFR* 突变率低(26.3% *vs.* 61.3%,P = 0.005);微乳头状为主型肺腺癌与非微乳头状为主型肺腺癌 *EGFR* 突变率差异无统计学意义(75.0% *vs.* 53.3%,P = 0.735);黏液腺癌较非黏液腺癌 *EGFR* 基因突变率低(0 *vs.* 57.3%, P = 0.018)。不同的病理亚型肺腺癌*EGFR*突变率存在差异,其中腺泡状为主型肺腺癌*EGFR*基因突变率较高,实体状为主型肺腺癌与黏液腺癌 *EGFR* 基因突变率较低,具体见表2。

3 讨论

在检测到特定基因突变之前,肺癌靶向药物已经应用于临床,研究显示厄洛替尼、吉非替尼等能够明显改善患者病情[9-10]。厄洛替尼与吉非替尼在临床的应用引起了人们对肺癌 *EGFR* 分子特点的探索,研究发现,一些基因突变使肺腺癌对吉非替尼的敏感性提高[11],对这部分吉非替尼治疗敏感的患者进行 *EGFR* 基因的突变分析发现腺苷三磷酸依赖性TK区域发生突变[11-12]。当前,*EGFR* TKIs 已经作为肺腺癌的标准治疗出现在临床。

EGFR 基因比较常见的突变区域是外显子19和外显子21突变[13]。据 Eberhard 等[13] 及 Paez 等[14]的研究,最常见的 *EGFR* 基因突变是外显子21点突变(L858R)和外显子19的缺失(del746-750)。Sakurada 等[15]报道,外显子19和外显子21突变占非小细胞肺癌的 *EGFR* 总突变的86%。本研究中,在 *EGFR* 基因突变的外显子中,外显子19和21的突变率最高,分别为43.1%(22/51)和52.9%(27/51)。

Sun 等[16]表示 *EGFR* 突变除与实体状为主腺癌有关外,还与乳头状、伏壁状为主型和黏液腺癌有关,而与微乳头状腺癌无关,其他的研究[17-19]结果也不完全一致。研究[20-21]表明,*EGFR* 突变主要在微乳头状腺癌中比较常见,其次是乳头状、腺泡状和伏壁状为主的腺癌,*EGFR* 突变少见于实体状为主型腺癌。本研究显示,94例入组肺腺癌患者 *EGFR* 基因突变率54.3%(51/94),腺泡状为主型肺腺癌 *EGFR* 突变例数24例,伏壁状为主型肺腺癌14例,乳头状为主型肺腺癌与实体状为主型肺腺癌均为5例,微乳头状为主型肺腺癌3例,黏液腺癌为0;*EGFR*基因突变常见于腺泡状为主、伏壁状为主型肺腺癌,少见于乳头状为主、实体状为主、微乳头状为主及黏液腺癌,与之前文献报道结果并不完全一致[16-21]。

表1 94例肺腺癌患者临床病理特征

Table 1 Clinicopathological features of 94 cases of lung adenocarcinomas

Clinicopathological features	*n*
Total	94
EGFR	
Mutation	51
Wild	43
Age/years	
≥60	48
<60	46
Gender	
Male	47
Female	47
Smoking history	
Yes	34
No	60
Pathological staging	
Ⅰ	34
Ⅱ	17
Ⅲ	24
Ⅳ	19
Histological subtypes	
Lepidic	21
Papillary	9
Solid	19
Micropapillary	4
Acinar	36
Mucinous	5
Exon	
Exon 19	22
Exon 20	2
Exon 21	26
Exon 18 and 21	1

EGFR, epidermal growth factor receptor.

Lee 等[22]对138例肺切除标本研究分析发现,微小浸润性肺腺癌、乳头状为主肺腺癌和原位腺癌 *EGFR* 基因突变率较高。Kim 等[23]通过对小组织活

检肺腺癌标本研究发现,*EGFR* 基因突变率最高的是乳头状为主腺癌,达 81.3%,其次为伏壁状为主(70.4%)、腺泡状为主(58.1%)。Nakamura 等[24]的研究发现腺泡状为主肺腺癌 *EGFR* 基因突变率高。本研究显示,腺泡状为主型肺腺癌较非腺泡状为主型肺腺癌 *EGFR* 突变率高,但差异无统计学意义(66.7% *vs.* 46.6%,$P=0.057$);实体状为主型肺腺癌较非实体状为主型肺腺癌 *EGFR* 突变率低(26.3% *vs.* 61.3%,$P=0.005$);黏液腺癌较非黏液腺癌 *EGFR* 基因突变率低(0 *vs.* 57.3%,$P=0.018$)。伏壁状为主型、乳头状为主型、微乳头状为主型肺腺癌 *EGFR* 突变率差异无统计学意义($P>0.05$)。本研究结果与其他研究结果[22-24]不完全一致,原因可能是本研究样本量较小,纳入的对象均为浸润性肺腺癌患者,不包括微小浸润性肺腺癌、原位腺癌的患者。

表 2　94 例肺腺癌患者组织学亚型与 *EGFR* 基因突变的关系

Table 2　Relationship between *EGFR* gene mutation and histologic subtypes with and without certain components of 94 lung adenocarcinoma cases

Histologic subtype	*EGFR* mutation, n(%)	*EGFR* wild, n(%)	P
Acinar			0.057
Yes	24(66.7)	12(33.3)	
No	27(46.6)	31(53.4)	
Lepidic			0.195
Yes	14(66.7)	7(33.3)	
No	37(50.7)	36(50.7)	
Papillary			1.000
Yes	5(55.6)	4(44.4)	
No	46(54.1)	39(45.9)	
Solid			0.005
Yes	5(26.3)	14(73.7)	
No	46(61.3)	29(38.7)	
Micropapillary			0.735
Yes	3(75.0)	1(25.0)	
No	48(53.3)	42(46.7)	
Mucinous			0.018
Yes	0(0)	5(100.0)	
No	51(57.3)	38(42.7)	

EGFR, epidermal growth factor receptor.

浸润性肺腺癌是肺腺癌新分类中的主要类型,腺泡状为主肺腺癌 *EGFR* 突变率更高,而实体状为主型、黏液腺癌等却较低。目前不管哪种肺腺癌的组织学亚型,都不能完全预测 *EGFR* 的突变状态,肺腺癌组织学亚型与 *EGFR* 基因突变是否具有确定关系仍需要我们进一步探索。

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