Histopathologic Characteristics of Pulmonary Adenocarcinomas with and without EGFR Mutation

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EGFR mutation played crucial role for responsiveness of non-small cell lung cancers to EGFR tyrosine kinase inhibitors. Almost the mutations were present in adenocarcinomas. Few had studied on histopathologic correlation with EGFR mutation in pulmonary adenocarcinomas. To obtain better view on pathobiology of pulmonary adenocarcinomas, we correlated exons 19 and 21 mutations with various histopathologic features by dissecting particular histological patterns from 60 surgically resected adenocarcinomas. Results: Gland-forming pattern, including bronchiloloalveolar carcinoma (BAC), well-formed acinar, and poorly-formed acinar patterns more frequently contains EGFR mutations than solid pattern (72.7% vs. 23.1%, p=0.002). EGFR mutations of each within the gland-forming pattern are not significantly different. Micropapillary pattern revealed less exon 19 mutations than the gland-forming pattern (12.5% vs. 66.7%, p=0.018), but tended to have more Exon 21 mutations than the others (33.3% vs. 11.9%, p=0.10). Tumors predominated by BAC pattern more commonly had exon 19 mutations than non-BAC predominated tumors (68.8% vs. 39.5%, p=0.046). EGFR-mutated tumors comprised less proportion of papillary pattern than tumors without mutation (mean=1.5% vs. 11.2%, p=0.049). Terminal respiratory unit (TRU) histology was associated with more EGFR mutations (72.4% vs. 42.1%, p= 0.036). Tumors smaller than 3.5 cm had more EGFR mutations than larger tumors (73.1% vs. 41.9%, p=0.018). Conclusion: High frequency of the mutation does not present only in BAC pattern, but also in well-formed and poorly-formed acinar patterns, suggesting them as usual spectrum of EGFR mutated adenocarcinomas. Other characteristics of EGFR-mutated adenocarcinomas include TRU-type histology, smaller size, and less solid phenotype.

Keywords: *Lung, Adenocarcinoma, Histopathology, EGFR mutation*

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In the recent years, a molecularly targeted therapy with small-molecule epidermal growth factor receptor tyrosine kinase (EGFR-TK) inhibitors had been studied in non-small cell lung cancers (NSCLC). The studies showed that there were occasional but dramatic responses in a small subset of patients [1,2]. Thereafter, attempts were made to specify clinical and biological markers that can predict the drug responsiveness as well as to understand the molecular mechanism that lied beneath [3,4]. Later studies showed that not the level of EGFR expression as defined by immunohistochemical study or EGFR gene amplification as defined by fluorescene in situ hybridization, but the activating mutation in exon 18 to 21 of the TK domain of EGFR that is strongly related with response to EGFR-TK inhibitors [3,5-9] and explain the pharmaco-molecular mechanism for the drug responsiveness [5]. This EGFR mutation was found to concentrate in a subgroup of NSCLC with formerly documented predictors, including non-smoker, female gender, Asian ethnic, adeno-

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carcinoma, and bronchioloalveolar carcinoma (BAC). The presence of EGFR mutation also has mutually inverse relationship with mutation of K-ras, one of down stream signal transduction pathways of EGFR that was found commonly in smokers [10-12]. Previous studies on NSCLC showed that almost all the EGFR mutations were present in adenocarcinomas and rarely in non-adenocarcinoma NSCLC, mostly squamous cell carcinomas [8,9,11-13]. The incidences of EGFR mutation in Asian adenocarcinomas reported from Taiwan, Korea, Japan, Chinese and Thailand (during submission by the second author) ranging from 24.5% to 55% were significantly higher than the incidences of 14 to 25% in other ethnics [9-12,14-16]. This difference suggested demographic and ethnic influences.

Because the mutation in EGFR-TK domain is almost exclusive for adenocarcinoma, our study would make a focus on adenocarcinoma rather than the entire NSCLC to gain better view on pathogenesis and biology of pulmonary adenocarcinoma. The objective of this study is to correlate EGFR mutation status with various histopathologic features, including histological subtypes. Apart from adenocarcinoma with BAC feature, few studies had correlated the molecular lesions with histopathologic features. Previous studies showed that adenocarcinomas originating from terminal respiratory unit (TRU), well to moderately differentiated adenocarcinomas and non-mucinous type of BAC had strong association with EGFR mutations [9-12,16]. However, since each adenocarcinoma usually contains mixture of histological patterns, and it is currently uncertain whether there is genotypic heterogeneity of EGFR mutation within each single tumor or not, therefore, the correlation might not be the most accurate to study from large tumor sections. Our study method is to correlate EGFR mutations with histological patterns using dissected tissue from surgically resected pulmonary adenocarcinomas.

Material and Method

The study specimens were archival paraffin-embedded tissue of unselected surgically resected pulmonary adenocarcinomas with available nodal status from department of pathology, faculty of medicine, chulalongkorn university, Thailand during 2000 to 2003. The study was reviewed and approved by King Chulalongkorn Memorial Hospital ethical committee. The study material used in this study is derived from the study formerly submitted by the second author and currently within the process. For histopathological interest, the patterns of adenocarcinoma were classified after the histological typing of lung neoplasm issued in 1999 by world health organization [17], which included BAC, acinar, papillary, and solid subtypes.

Acinar pattern was further separated into well-formed acinar and poorly-formed acinar. The latter is defined as glandular structure with multiple traversing bridges across the gland to a more solid sheet with cribiform lumens. Amount of micropapillary pattern in percent was also recorded, as it is recently recognized as quite a distinct histological pattern. The proportion of each histological pattern composing the tumor was estimated in percent, by examining all representative tumor tissue sections. The average number of slides examined per tumor was 3.9 (1.0 block/ 1 cm of tumor). The dominant histological pattern and various other pathologic features including tumor size, nodal metastasis, pleural invasion, nuclear grade, and TRU histology, were recorded.

Mutation analysis

Mapping with hematoxylin-eosin section, a 7-micron-thick paraffin-embedded tumor tissue section was marked for an area approximately 3 to 8 mm in greatest diameter that contained tumor cells of more than 70% and consisted of single pattern. The histological pattern in the dissected tissue was recorded before the marked areas were manually micro-dissected with needle, and subjected to DNA isolation as previously described [18]. Among exon 18 to 24 that had been shown to harbor mutation in pulmonary adenocarcinomas, exon 19 and 21 were selected for evaluation because they are far more common than the others, and together composed up to 90% of all mutations [6,8,11-13]. Isolated DNA samples were amplified by PCR for coding region of EGFR exon 19 and exon 21. Primers for exon 19 amplification are 5' tggatcccagaaggtgagaaag and 3' gcaaagcagaaactcacatcgag, and exon 21 are 5' taccgtggtgaaaacaccgc and 3' ccttactttgcctccttctgc. For exon 21, we used an additional 5' nested primer of which the sequence is tggtgaaaacaccgcagcatg to enhance the amplification efficiency. PCR products were then electrophoresed in polyacrylamide gel and visualized under UV transillumination. Positive PCR products were submitted to the bioservice unit, national institute of biotechnology, Bangkok, Thailand for direct sequencing of both exons. PCR and sequencing were repeated individually to confirm the presence of mutation.

The amount of pattern in the tumor, the pattern in dissected tissue, the predominant pattern, and various other pathologic features were correlated

with the EGFR mutation by using unpaired T-tests and chi-square tests as appropriated. For the latter, in case expected frequency is less than 5 in more than 20% of the data, Yates' correction is employed.

Results

The study comprises 60 adenocarcinomas. Molecular analyses for mutation in exon 19 and exon 21 are inconclusive in 1 and 8 cases, respectively. Exon 19 deletion mutation is present in 28 (47.5%) of 59 adenocarcinomas, while exon 21 point mutation is present in only 6 (11.5%) of 52 adenocarcinomas. There are 8 cases inconclusive for exon 21 mutation, 7 of them already have exon 19 mutation. When presence of mutation in exon 19 or exon 21 is regarded as positive and no mutation in both exons is regarded as negative, the overall mutation rate is 56.9% (33/58) with 2 inconclusive cases. The details on specific types of mutations within the exons together with non-pathologic information were reported in the article formerly submitted by the second author and will not be included here.

Mean ages of patients with and without EGFR mutation are 61.4 years (45-79 years, SD=10.2) and 61.3 years (31-86 years, SD=16.1), respectively. Adenocarcinomas with EGFR mutation are from 20 males and 13 females (1:0.65), while adenocarcinomas without the mutation are from 18 males and 7 females (1:0.38). There is no statistically significant difference in age and sex between tumors with and without EGFR mutation (p=0.98 and 0.37, respectively).

The relationship between EGFR mutation and amount of histological pattern is shown in Table 1. The tumors with EGFR mutation contain fewer amounts of papillary pattern than the tumors without mutation (mean=1.5% vs. 11.2%, p=0.049). EGFR-mutated adenocarcinomas contain larger amounts of BAC pattern (mean=33.2% vs. 18.2%) with borderline statistical significance (p= 0.087). The amounts of other patterns composing the tumors are not significantly different between tumors with and without EGFR mutation.

The correlation of EGFR mutation status with histological pattern in dissected tissue is displayed in Table 2. Overall, gland-forming pattern (including BAC, well formed acinar, and poorly formed acinar patterns) has EGFR mutation rate of 72.7%, which is significantly

Table 1. Relationship of EGFR mutation with proportion of histological pattern

Pattern	exon 19 or 21 mutation (n=33)	no exon 19 and 21mutation (n=25)	p value
Bronchioloalveolar	33.2% (21.9% to 45.5%)	18.2% (5.2% to 31.2%)	0.087
Well-formed acinar	26.2% (17.1% to 35.4%)	25.6% (15.1% to 36.1%)	0.93
Poorly-formed acinar	18.9% (10.0% to 27.9%)	13.6% (3.3% to 23.8%)	0.43
Solid	19.5% (8.2% to 30.9%)	30.6% (17.5% to 43.7%)	0.21
Papillary	1.5% (-4.8% to 7.9%)	11.2% (3.9% to 18.5%)	0.049*
Micropapillary **	19.4% (10.9% to 28.0%)	17.5% (6.6% to 28.4%)	0.78

The number represents mean with 95% confident interval in parenthesis
** exclude tumors containing solid and poorly-formed acinar pattern > 80% of tumor (with mutation, n=26; without mutation, n=16)
* Statistical significant difference ($p < 0.05$)

Table 2. Relationship of EGFR mutation with histological pattern in dissected tissue

Pattern	exon 19 mutation	exon 21 mutation	exon 19 or 21 mutation
Gland forming	22/33 (66.7%)*	2/28 (7.1%)	24/33 (72.7%) Ö
Bronchioloalveolar	6/9 (66.7%)	1/7 (14.3%)	7/9 (77.8%)
Well-formed acinar	5/6 (88.3%)	0/5 (0%)	5/6 (88.3%)
Poorly-formed acinar	11/18 (61.1%)	1/16 (6.3%)	12/18 (66.7%)
Solid	3/13 (23.1%)**	1/12 (8.3%)	3/13 (23.1%) ÖÖ
Micropapillary	1/8 (12.5%)***	3/9 (33.3%) §	4/8 (50%)
Papillary	0/2 (0%)	0/2 (0%)	0/2 (0%)

* vs. **, p = 0.008
* vs. ***, p = 0.018
§ exon 21, micropapillary vs. non-micropapillary, p = 0.100
Ö vs. ÖÖ, p = 0.002

different from solid pattern, which shows mutation in only 23.1% (p=0.002). Within the gland-forming pattern, the mutation rates for dissected BAC (77.8%), well formed acinar (88.3%), and poorly formed acinar patterns (66.7%) are not significantly different. Regarding exon 19, the gland-forming pattern shows significantly higher mutation rate (66.7%), compared to solid pattern (23.1%, p=0.008) and micropapillary pattern (12.5%, p=0.018). For exon 21, where only a total of 6 mutations are identified, they are found more commonly in micropapillary pattern (3/9, 33.3%) than the others, however, the statistical significance is borderline (p=0.10)

By correlating EGFR mutation with the predominant histological pattern (Table 3), the data show that tumors predominantly composed of BAC pattern more commonly have exon 19 mutation than tumors predominated by the other patterns (11/16, 68.8% vs. 17/43, 39.5%, p=0.046). However, when the 6 cases with exon 21 mutations were combined, the difference of overall mutation rates between BAC predominant and non-BAC predominant tumors is borderline significant (12/16, 75.0% vs. 21/42, 50%, p=0.086).

Correlation of various other pathologic features is present in Table 4. The authors found that the amount of BAC pattern and the presence of TRU type histology are significantly associated with EGFR mutation (p=0.020 and 0.036, respectively). Twenty-two of 31 (71.0%) adenocarcinomas containing 10 % or more of BAC pattern, and 21 of 29 (72.4%) adenocarcinomas with TRU-type histology have EGFR mutation. Tumors with more solid and papillary patterns tend to have no mutation (p=0.10 and 0.06, respectively). Of note, tumors smaller than 3.5 cm. more commonly have EGFR mutation than larger tumors (19/26, 73.1% vs. 13/31, 41.9%, p=0.018).

Table 3. Relationship of EGFR mutation with predominant histological pattern

Predominant pattern	Exon 19 mutation	Exon 21 mutation	exon 19 or 21 mutation
Bronchioloalveolar	11/16 (68.8%)*	1/12 (8.3%)	12/16 (75.0%)
Well formed acinar	6/15 (40.0%)	2/13 (15.4%)	8/14 (57.1%)
Poorly formed acinar	5/10 (50.0%)	2/11 (18.2%)	7/10 (70.0%)
Solid	6/14 (42.9%)	1/12 (8.3%)	6/14 (42.9%)
Micropapillary	-	-	-
Papillary	0/4 (0%)	0/4 (0%)	0/4 (0%)

* vs. others, p = 0.046

Table 4. Relationship of EGFR mutation with other histopathological parameters

Parameter	Exon 19 or 21mutation	no Exon 19 and 21 mutation	p value
Bronchioloalveolar ≥ 10% of tumor	22/31 (71.0%)	9/31 (29.0%)	0.020*
Bronchioloalveolar < 10% of tumor	11/27 (40.7%)	16/27 (59.3%)	
TRU histology	21/29 (72.4%)	8/29 (27.6%)	0.036*
non-TRU histology	8/19 (42.1%)	11/19 (57.9%)	
Solid ≥ 25% of tumor	9/21 (42.9%)	12/21 (57.1%)	0.10
Solid < 25% of tumor	24/37 (64.8%)	13/37 (35.1%)	
Papillary ≥ 50%	0/4 (0%)	4/4 (100%)	0.06
Papillary < 50%	33/54 (61.1%)	21/54 (38.9%)	
Micropapillary ≥ 25%	11/16 (68.8%)	5/16 (31.3%)	0.53
Micropapillary < 25%	16/27 (59.3%)	11/27 (40.7%)	
Tumor size ≥ 3.5 cm	13/31 (41.9%)	18/31 (58.1%)	0.018*
Tumor size < 3.5 cm	19/26 (73.1%)	7/26 (26.9%)	
Nuclear grade 3 predominance	11/18 (61.1%)	7/18 (38.9%)	0.61
Nuclear grade 1 or 2 predominance	22/40 (55.0%)	18/40 (45%)	
Nodal metastasis	15/28 (53.6%)	13/28 (46.4%)	0.70
No nodal metastasis	17/29 (58.6%)	12/29 (41.4%)	
Pleural invasion	19/33 (57.6%)	14/33 (42.4%)	0.97
No pleural invasion	11/19 (57.9%)	8/19 (42.1%)	

* significant difference

Discussion

The variation in EGFR mutation rate among NSCLC studies was resulted not only from the presence of different proportions of adenocarcinomas among the studies but also an obvious difference in frequency of the mutation between Asian and non-Asian adenocarcinomas, and whether the patients were pre-selected or unselected. Similarly, both Asian and western studies documented rarity of EGFR mutation in NSCLC other than adenocarcinoma [8,9,11-13]. Our study revealed overall EGFR mutation rate of 56.9%, which is comparable to those reported by other studies from Asian countries [9,10,12,14]. Similar to a study by Qin et al.[14], our exon 21 mutations are far less common than most other Asian studies, which documented comparable exon 19 and exon 21 mutation rates.

Although females are more common in adenocarcinomas with EGFR mutation than those without, the difference is not statistically significant (p=0.37), possibly because a small number of females (20 cases) in this study. Studies on NSCLC by Kosaka et al.[12] and Kim KS et al.[3] showed that non-smoker and adenocarcinoma were independent factors associated with EGFR mutation or response to EGFR-TK inhibitor, whereas female gender was not. Therefore, the relationship between female and EGFR mutation might be explained by the presence of more non-smokers among females.

In contrast to an observation made by Kim YH et al.[7] that papillary pattern predominance is strongly related to response to EGFR-TK inhibitor, our data show that there is less papillary pattern in the tumors with EGFR mutation. However, we have only 4 (7%) from 58 tumors that were predominated by papillary pattern and all of which have no mutation. In contrast, there were 17 (47%) papillary predominant tumors from 36 adenocarcinomas in Kim et al. series. A much higher incidence of papillary predominant adenocarcinomas might be due to different definition of papillary pattern. In our study, BAC with papillary feature was classified as BAC pattern, and to be defined as papillary pattern there has to be complex secondary and tertiary papillary structures.

Until now, there is no study specifically dissected single histological pattern to investigate the relationship with specific exon mutation of EGFR. Our data showed that the gland-forming pattern is significantly associated with overall EGFR mutation, compared to solid pattern (p=0.002). Among the gland-forming pattern, there was no significant difference between BAC, well-formed acinar and poorly-formed acinar patterns. Therefore, the high frequency of EGFR mutation does not present only in BAC component, but also in invasive acinar pattern (either well-formed or poorly-formed acinar pattern). The findings suggested that the usual spectrum of EGFR mutated adenocarcinomas encompasses pure BAC, to well-formed acinar, and to poorly-formed acinar pattern (well to moderately differentiated), while tumor with a lot of solid pattern (poorly differentiated tumor) is not characteristic for EGFR mutated adenocarcinomas. This is in keeping with the observations that EGFR mutations are more common in well to moderately differentiated adenocarcinomas, and BAC [9,12,16].

Overall mutation rate for the dissected micropapillary pattern is 50%. Of note, we found a significantly lower rate of exon 19 mutation in micropapillary pattern as compared to gland-forming pattern (12.5% vs. 66.7%, p= 0.018), but conversely, we found the highest rate of exon 21 mutation (33.3%) in micropapillary pattern, raising the question on whether there is any association between specific mutation and specific histological pattern. However, because there were only 9 dissected samples of micropapillary pattern, the exact relationship between exon 21 mutation and micropapillary pattern could not be concluded at this time.

When the predominant patterns are analyzed, a significant association between BAC predominance and exon 19 mutation is noted (p=0.046). The finding is in accordance with most previous studies making observation on BAC pattern. However, there is no uniformly specific definition on how much BAC pattern should compose a tumor to define a tumor as adenocarcinoma with BAC component. Therefore, we make an attempt to define a cut point where there is the highest statistical significance relationship with EGFR mutation, and found that BAC pattern composing 10% or more of tumor is the best cut point (p=0.020). Our study could not make an analysis based on mucinous and non-mucinous type of BAC because none of our BAC pattern satisfied mucinous type of BAC.

Terminal respiratory unit (TRU) type adenocarcinoma is an interesting concept that separates adenocarcinomas into two broad categories after the differentiations of tumor cells, and it was shown to strongly associate with EGFR mutation [10]. Using, merely histologic criteria of TRU type adenocarcinoma, we are able to classify 48 tumors. Ten tumors could not be classified due to the presence of too much area of solid and poorly formed acinar patterns within the tumor or there were mixed TRU and non-TRU histo-

logy. Interestingly, we found 29 TRU type adenocarcinomas, 21 (72.4%) of which have EGFR mutation, compared to 42.1% EGFR mutation in non-TRU tumors (p=0.036). Further analysis shows that TRU tumors have larger amounts of BAC pattern. TRU tumors have mean BAC component of 46.7% (95% CI, 35.9 to 57.5%), while non-TRU tumors have mean BAC component of only 8.4% (95% CI, -4.9 to 21.8%). The difference is statistically significant (p< 0.0001). Because, the recognition of "TRU-type" is recent and still not universally applied, one question still needed to be answered is that whether the lower EGFR mutation rate in non-Asian adenocarcinomas is caused by less TRU-type adenocarcinomas among non-Asians, or, with indifferent incidence of TRU-type tumor, a yet unknown mechanism causes more EGFR mutations in Asian TRU-type adenocarcinomas. Whether the former or latter answer is correct is not known, since there is no data on how common TRU-type adenocarcinomas in western is.

Our study shows that tumor size, in contrast to nodal metastasis status, has an association with EGFR mutation. Tumors smaller than 3.5 cm. more commonly have EGFR mutation (19/26, 73.1% vs. 13/31, 41.9%, p=0.018). Further analyses suggest that it could be explained by the fact that larger tumors contain more solid pattern, and a tendency that smaller tumors contain more BAC component and more frequently belong to TRU category. We found that tumors of 3 cm or larger in size contain more solid component than tumors smaller than 3 cm (mean = 30.8% vs. 9.7%, p=0.019). We noted that tumors smaller than 3.5 cm contain more BAC component than larger tumors (mean = 34.6% vs. 19.7%, p=0.084), and TRU type tumors are smaller than non-TRU tumors (mean = 3.4 cm vs. 4.4 cm, p=0.086), however the statistical difference is borderline. Because presence of EGFR mutation had been documented as early as in atypical adenomatous hyperplasia [10], and EGFR mutation has no association with nodal status, the mutation more likely contributes to tumorigenesis rather than metastatic progression.

We had found a remarkably low rate of EGFR mutation in dissected solid pattern. The lowest rate was noted in Huang et al study [9], where there was no mutation in all poorly differentiated adenocarcinomas. To explain the finding that most of solid patterns lack EGFR mutation, two hypotheses are considered. Firstly, adenocarcinomas lacking EGFR mutation have different oncogenesis. They have no EGFR mutation from the beginning. And by unknown mechanism, they have greater tendency to exhibit solid phenotype. Secondly, it is just because some adenocarcinomas that initially harbor EGFR mutation, later with tumor progression towards poorer differentiation, loss the mutant allele. An in-vitro study had reported a parent adenocarcinoma cell line containing EGFR mutation that lost the mutation in metastatic daughter cell line [19]. However, since the EGFR mutation have mutually exclusive relationship with K-ras mutation, which was found commonly in smokers [10-12], it is more logical to assume the first hypothesis that EGFR mutated and K-ras mutated adenocarcinomas are separated entities with different oncogeneses and biology. Since EGFR mutations in TK domain are very specific for adenocarcinomas of lung [5], a yet unknown airborne stimulus other than tobacco could play a crucial role.

In summary, data from our study and the currently available studies revealed that the characteristic features of adenocarcinomas with EGFR mutation include non-smoking, K-ras independent oncogenesis, terminal respiratory unit origin, non-mucinous cell type, smaller size, phenotypic spectrum from BAC to well-formed and poorly-formed acinar pattern (well to moderately differentiated), and less solid (poorly differentiated) phenotype. The association of micropapillary and papillary patterns to the mutation is still not clear. Although most histological features shown to be associated with EGFR mutation have high positive predictive values for EGFR mutation, they possess relatively lower level of negative prediction. Therefore, histological parameters could not be used to replace molecular tests in order to establish EGFR-targeted therapy. Nevertheless, the information on histopathologic correlation provides us better understanding on pathobiology and oncogenesis of the EGFR-mutated pulmonary adenocarcinomas.

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คุณลักษณะทางพยาธิวิทยาในมะเร็งปอดชนิดอะดีโนคาร์ซิโนมาที่มีและไม่มีความผิดปกติของจีนอีจีเอฟอาร์ (EGFR mutation)

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ความผิดปกติภายในจีน อีจีเอฟอาร์ (EGFR) มีบทบาทสำคัญ ต่อมะเร็งปอดชนิดเซลล์ไม่เล็กในการตอบสนองต่อยา ที่มีฤทธิ์ยับยั้งไทโรซีนไคเนส ของ อีจีเอฟอาร์ ความผิดปกติดังกล่าวเกือบทั้งหมดพบในมะเร็งปอดชนิดอะดีโนคาร์ซิโนมา พบว่ายังมีการศึกษาความสัมพันธ์ระหว่าง ความผิดปกติภายในจีน EGFR กับลักษณะทางพยาธิวิทยา จำนวนไม่มาก เพื่อเพิ่มความรู้ด้านพยาธิชีวภาพของมะเร็งปอดชนิดอะดีโนคาร์ซิโนมา คณะวิจัยทำการวิเคราะห์ความสัมพันธ์ระหว่าง เอกซอน 19 และ 21 กับลักษณะทางพยาธิวิทยาหลายชนิด โดยอาศัยการเลาะเนื้อเยื่อเพื่อให้ได้รูปแบบทางเนื้อเยื่อที่เจาะจง ในมะเร็งปอดชนิดอะดีโนคาร์ซิโนมาจำนวน 60 ราย พบว่า รูปแบบการสร้างต่อม ซึ่งประกอบไปด้วย รูปแบบ บรองคิโอโลอัลวีโอลา การสร้างต่อมแบบชัดเจน และการสร้างต่อมแบบไม่ชัดเจน มีความผิดปกติของจีน EGFR บ่อยกว่า รูปแบบทึบตัน (72.7% กับ 23.1%, p=0.002) โดยไม่พบความแตกต่างอย่างมีนัยสำคัญระหว่างสามรูปแบบ ภายในรูปแบบการสร้างต่อม รูปแบบไมโครปาปิลารี พบความผิดปกติที่เอกซอน 19 ได้น้อยกว่ารูปแบบการสร้างต่อม (12.5% กับ 66.7%, p=0.018) แต่มีแนวโน้มพบความผิดปกติที่เอกซอน 21 มากกว่า (33.3% กับ 11.9%, p=0.10) เนื้องอกที่ส่วนใหญ่ประกอบด้วยรูปแบบบรองคิโอโลอัลวีโอลา พบความผิดปกติที่เอกซอน 19 บ่อยกว่า (68.8% กับ 39.5%, p=0.046) เนื้องอกที่มีความผิดปกติของจีน EGFR มีรูปแบบปาปิลารีประกอบอยู่น้อยกว่า (เฉลี่ย =1.5% กับ 11.2%, p=0.049) เนื้องอกที่มีลักษณะทางเดินอากาศส่วนปลาย พบความผิดปกติของจีน EGFR ได้บ่อยกว่า (72.4% กับ 42.1%, p=0.036) เนื้องอกขนาดเล็กกว่า 3.5 ซ.ม. พบความผิดปกติของจีน EGFR ได้บ่อยกว่า (73.1% กับ 41.9%, p=0.018) โดยสรุป ความผิดปกติของจีน EGFR พบสูงไม่เฉพาะแต่ในรูปแบบ บรองคิโอโลอัลวีโอลา แต่รวมถึง รูปแบบการสร้างต่อมแบบชัดเจน และ การสร้างต่อมแบบไม่ชัดเจน ลักษณะทางพยาธิวิทยาอื่นที่สำคัญ ของมะเร็งปอดชนิดอะดีโนคาร์ซิโนมา ที่มีความผิดปกติของจีน EGFR ได้แก่ ลักษณะทางเดินอากาศส่วนปลาย ขนาดที่เล็กกว่า และรูปแบบทึบตันที่น้อยกว่า