European Journal of Surgical Oncology 45 (2019) 870–876

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Association between the novel classification of lung adenocarcinoma subtypes and *EGFR/KRAS* mutation status: A systematic literature review and pooled-data analysis

Long Jiang [a, *], Mari Mino-Kenudson [b], Anja C. Roden [c], Rafael Rosell [d], Miguel Ángel Molina [e], Raja M. Flores [f], Lothar R. Pilz [g], Alessandro Brunelli [h], Federico Venuta [i], Jianxing He [a, **], Written on behalf of AME Lung Cancer Collaborative Group

[a] Department of Thoracic Surgery/Oncology, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou Institute of Respiratory Disease, China State Key Laboratory of Respiratory Disease, National Clinical Research Center for Respiratory Disease, Guangzhou, PR China
[b] Department of Pathology, Massachusetts General Hospital, Boston, USA
[c] Department of Laboratory Medicine and Pathology, Mayo Clinic Rochester, MN, USA
[d] Cancer Biology and Precision Medicine Program, Catalan Institute of Oncology, Hospital Germans Trias I Pujol, Ctra Canyet, Badalona, Barcelona, Spain
[e] Pangaea Biotech, S.L., Hospital Universitario Quirón Dexeus, Barcelona, Spain
[f] Department of Thoracic Surgery, Mount Sinai School of Medicine, New York, NY, USA
[g] Medical Faculty Mannheim, Heidelberg University, Theodor-Kutzer-Ufer 1, 68167, Mannheim, Germany
[h] Department of Thoracic Surgery, St. James's University Hospital, Leeds, UK
[i] Department of Surgery "Paride Stefanini"-Thoracic Surgery Unit, Policlinico Umberto I, University of Rome, Italy

ARTICLE INFO

Article history:
Received 1 October 2018
Received in revised form
6 January 2019
Accepted 5 February 2019
Available online 16 February 2019

Keywords:
EGFR
KRAS
Lung adenocarcinoma
IASLC/ATS/ERS classification

ABSTRACT

Objectives: This study aims to determine the association of *EGFR/KRAS* mutation status with histological subtypes of lung adenocarcinoma (LAC) based on the IASLC/ATS/ERS classification.
Methods: Pubmed and Cochrane databases were searched from January 2011 to June 2018 for studies that included patients with LAC who underwent surgical resection were classified according to the new IASLC/ATS/ERS classification. *EGFR/KRAS* status assessment was requireded. The primary outcome was determined by the odds ratio (OR) of the incidence of mutation status of certain of each histological subtype. The reference group consisted of *EGFR/KRAS* mutation negative patients.
Results: Twenty-seven eligible studies involving 9022 patients with mutation gene detection were included for analysis. Among them, 6717 (74.5%) patients were from the Asian region and, 2305 (25.5%) patients were from Non-Asian regions. The most prevalent subtype was acinar (34.7%), followed by papillary (22.9%), lepidic (18.9%), solid (13.6%), micropapillary (6.3%), and invasive mucinous adenocarcinoma (3.5%). *EGFR* mutations were more common in patients with resected lepidic predominant adenocarcinoma (OR,1.76; 95%CI, 1.38–2.24;$p < 0.01$) and were rarely found in solid predominant adenocarcinoma (OR,0.28; 95%CI, 0.23–0.34;$p < 0.01$) or IMA (OR,0.10; 95%CI, 0.06–0.14;$p < 0.01$). Conversely, *KRAS* mutations were characterized by IMA (OR,7.01; 95%CI, 5.11–9.62;$p < 0.01$), and were less frequently identified in lepidic (OR,0.58; 95%CI, 0.45–0.75;$p < 0.01$) and acinar (OR,0.65; 95%CI, 0.55–0.78;$p < 0.01$) predominant subtypes. Further analyses were performed in Asian and Non-Asian groups and the results were consistent.

Abbreviations: IASLC, International Association for the Study of Lung Cancer; ATS, American Thoracic Society; ERS, European Respiratory Society; EGFR, Epidermal Growth Factor Receptor; KRAS, Kristen rat sarcoma viral oncogene homolog; BAC, bronchioloalveolar carcinoma; LAC, lung adenocarcinoma; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma; IMA, invasive mucinous adenocarcinoma; TKIs, tyrosine kinase inhibitors.

* Corresponding author. Department of Thoracic Surgery/Oncology, the First Affiliated Hospital of Guangzhou Medical University, Guangzhou Institute of Respiratory Disease & China State Key Laboratory of Respiratory Disease, No. 151, Yanjiang Rd, Guangzhou, 510120, Guangdong Province, PR China.
** Corresponding author. Department of Thoracic Surgery/Oncology, the First Affiliated Hospital of Guangzhou Medical University, Guangzhou Institute of Respiratory Disease & China State Key Laboratory of Respiratory Disease, No. 151, Yanjiang Rd, Guangzhou, 510120, Guangdong Province, PR China.
E-mail addresses: drjiang_long@163.com (L. Jiang), drhe_jianxing@163.com (J. He).

https://doi.org/10.1016/j.ejso.2019.02.006

Conclusions: The current study confirms that the IASLC/ATS/ERS classification is associated with driver gene alterations in resected LAC.

Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide. Non–small cell lung cancer (NSCLC) accounts for approximately 80% of all cases of lung cancers, of which adenocarcinoma is now the most common subtype [1]. A new lung adenocarcinoma (LAC) classification system was proposed by the International Association for the Study of Lung Cancer, American Thoracic Society, and European.

Respiratory Society (IASLC/ATS/ERS) in 2011, based on the semiquantitative identification of the predominant histologic subtype [2]. The terms bronchioloalveolar carcinoma (BAC) and mixed subtype adenocarcinoma were eliminated. Instead, new concepts of early lung cancer such as adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA) were introduced. Other types of invasive adenocarcinoma were divided into lepidic-, acinar-, papillary-, micropapillary-, and solid-predominant adenocarcinoma, as well as invasive mucinous adenocarcinoma (IMA).

Epidermal growth factor receptor (*EGFR*) and *Kristen rat sarcoma viral oncogene homolog* (*KRAS*) mutations have been reported as the major driver genes in LAC [3–6]. Patients with *EGFR* mutations have been shown to receive a tremendous benefit from EGFR tyrosine kinase inhibitors (TKIs) in patients with advanced stage disease [7,8]. In contrast, patients with *KRAS* mutations are resistant to EGFR-targeted therapies [6]. Information about the prevalence of *EGFR/KRAS* mutations in the various subtypes defined by the new international histologic classification of lung adenocarcinoma is still limited. Therefore, we aim to perform a pooled-data analysis of available data to identify a possible association between the predominant histologic subtype and genetic alterations in resected LAC.

Methods

The search for studies that included patients with LAC who underwent surgical resection was performed as a systematic review, in accordance with the Meta-analysis of observational studies in epidemiology (MOOSE) guidelines for systematic reviews of observational studies. In addition, we also conducted our research in line with the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement for reporting systematic reviews and meta-analysis.

Search strategy and study selection

Two authors independently performed systematic literature search on Pubmed and Cochrane databases for relevant studies. As the new IASLC/ATS/ERS LAC classification was published in 2011, our search was restricted to the time period January 2011 to June 2018. No language restriction was applied. Studies were identified using a combination of the terms related to LAC (eg, "lung adenocarcinoma", "non-small cell lung cancer"), new classification (eg, "IASLC/ATS/ERS classification"), *EGFR* mutation (eg, "*EGFR*", "*epidermal growth factor receptor*") and *KRAS* mutation (eg, "*KRAS*", "*Kristen rat sarcoma viral oncogene homolog*"). The detailed search strategy is available in the supporting information. In addition, authors screened the reference lists of identified articles. Abstracts or conference proceedings were not included.

Study eligibility

Authors independently screened abstracts of the publications generated by our search. Studies had to meet the following criteria to be included: (1) all the included patients must undergo surgical resection; (2) patients had not undergone neo-adjuvant chemo-, radiation or EGFR-TKI therapy; (3) LAC was classified or re-confirmed according to the new IASLC/ATS/ERS classification on surgical samples. The processes of re-confirmation were performed by the authors in individual institutes in their studies; (4) patients must receive *EGFR* or *KRAS* mutation analysis and the detection methods should be recorded without limitation; (5) the authors must analyze the relationship between *EGFR* or *KRAS* status and the histological subtypes. (6) Reviews, case reports and editorials were excluded.

Data extraction quality assessment

Two authors independently reviewed and extracted the following data from each article: study region (Asia vs. non-Asia), study period, sample size, gender, mean age, tumor staging, detection method, number of predominant histologic subtypes, mutation detection and *EGFR/KRAS* mutations. Because the numbers of AIS/MIA were quite small in the included studies, we combined AIS/MIA with lepidic predominant LAC as lepidic predominant LAC for analysis. When there were studies involving the same cohort of patients, only the most comprehensive or recent publication was included. Any discrepancies were resolved by discussion and came to consensus with a third author. The methodological quality of the studies included was assessed using an 11-item checklist which was recommended by Agency for Healthcare Research and Quality (AHRQ). It is recommended for cross sectional studies. An item would be scored '0' if it was answered 'NO' or 'UNCLEAR'; if it was answered 'YES', then the item scored'1'. Article quality was assessed as follows: low quality = 0–3; moderate quality = 4–7; high quality = 8–11.

Data synthesis and analysis

The meta-analysis was conducted using RevMan 5.1.6 software (Cochrane Collaboration). The primary outcome was determined by the odds ratio (OR) of the incidence of mutation status of certain of each histological subtype. The incidence of *EGFR* mutation negative results in each certain histological subtype was regarded as the reference group. Standard X [2] test was used to evaluate the presence of statistically significant heterogeneity across the studies, and the inconsistency index (I [2]) was used to quantify the amount of heterogeneity [9]. We predefined heterogeneity as low (25%–49%), moderate (50%–74%), and high (75%–99%). Study level data were pooled using a random-effects model. Sensitivity analyses were performed according to the study region and mutation detection method. All statistical tests were performed 2-sided and the level of significance was set to $p = 0.05$.

Results

Study characteristics

The searches retrieved 311 records, all of them providing titles or abstracts in English language. After exclusion of studies based on study type and inadequate contents, finally 27 studies [10–36] involving a total of 9022 individuals from seven countries were included in the present study (Fig. 1). The quality score of each study was presented in Table 1. Thirteen studies were of high quality and fourteen studies were of moderate quality. There were no articles with low quality rating (Table 1). Among them, 20 studies [10,11,14,15,18–25,27,29–31,33–36] with a combined total of 6717 (74.5%) patients were from the Asian region (China, Japan, South Korea) and, 7 studies [12,13,16,17,26,28,32] with a combined total of 2305 (25.5%) patients were from Non-Asian regions (North America, Australia, France, Brazil). The included patients underwent surgical resection and received *EGFR* or *KRAS* mutation detections. According to the IASLC/ATS/ERS LAC classification, the most prevalent subtype was acinar (34.7%), followed by papillary (22.9%), lepidic (18.9%), solid (13.6%), micropapillary (6.3%), and invasive mucinous adenocarcinoma (3.5%)(Fig. 2). The detailed percentages of *EGFR* and *KRAS* mutations in each histological subtype were shown in Fig. 3.

The 7th TNM staging for NSCLC was used in the included studies. Ten studies [10,11,14,16,21,22,29,30,32,34] included patients from stage I to IV. Ten studies [12,13,15,19,23,24,28,31,33,35] included patients from stage I to III, and three studies [18,20,25] included stage I patients only. One study [17] consisted solely of stage III(N2) patients. In addition, one [22] of the studies only included smokers while another [21] included only never-smokers. Details of gender, staging, histologic subtype, method of mutation analysis and mutation status are shown in Table 1.

EGFR mutation status in LAC

A total of twenty-seven studies [10–16,18,19,21–24,26–29,31–36] were eligible for *EGFR* mutations analysis. The data are summarized

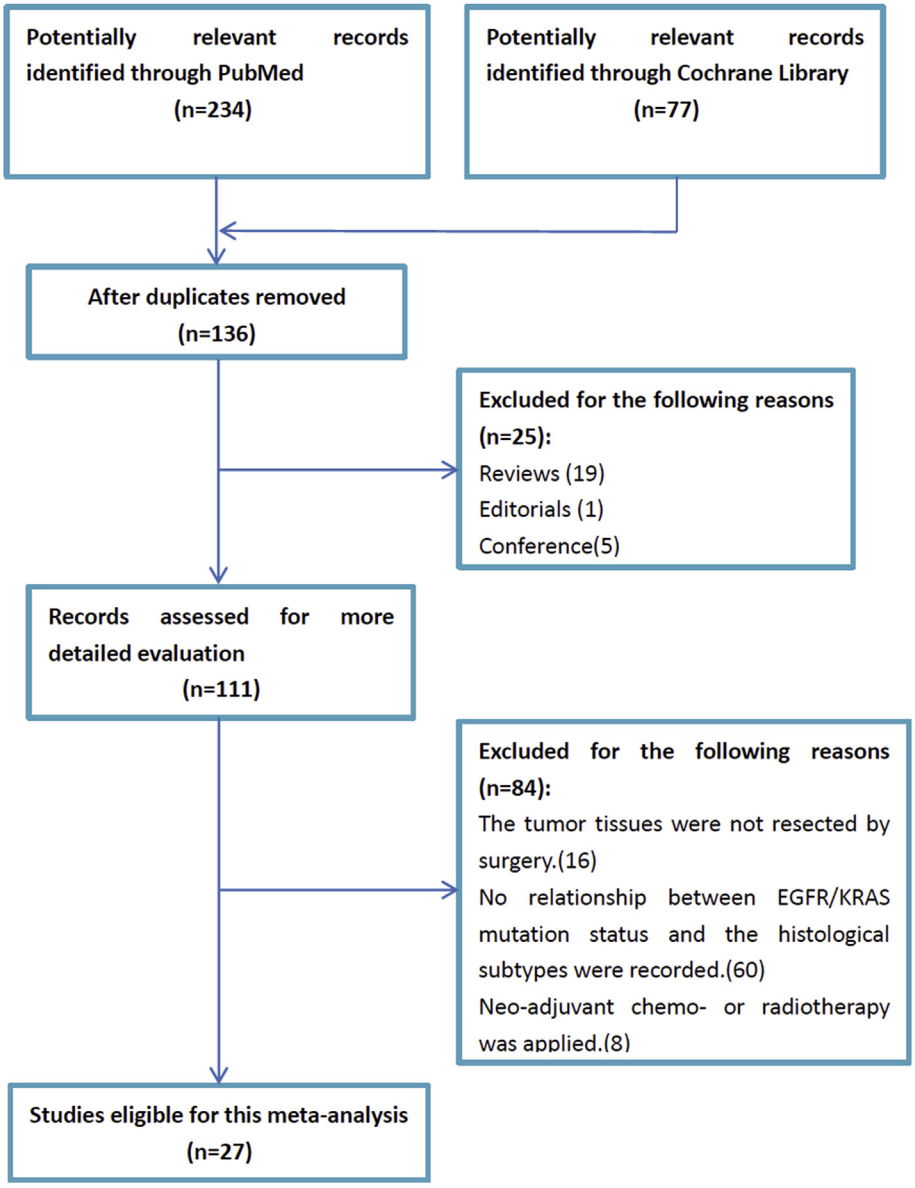

Fig. 1. Search process of the present meta-analysis.

Table 1
Characteristics of the included studies.

Study	Country	Period	No. of patients	Men (%)	Age, year	No. of Smokers (%)	TNM classification				IASLC/ATS/ERS classification							No. of mutation detection	EGFR+ (%)	KRAS+ (%)	Techniques of mutation analysis	Quality Score
							I	II	III	IV	AIS/MIA	Lep	Aci	Pap	Mpp	Solid	IMA					
Nakamura (2014)	Japan	2008.1–2013.12	320	69 (21.6)	Mean (SD): 68.7 (9.0)	176 (55)	291	20	6	3	41	42	94	112	5	23	3	320	130 (40.6)	–	PNA-LNA PCR	9
Dong (2016)	China	2005.3–2014.6	200	95 (47.5)	NR*	61 (30.5)	78	20	93	9	–	3	77	49	7	52	10	200	92 (46)	18 (9)	PCR and DS	8
Kadota (2014)	America	2002–2009	864	541 (62.6)	Median (range): 69 (23–96)	160 (18.5)	663	109	92	–	33	97	300	151	78	163	36	864	127 (15)	227 (26.3)	PCR and DS	8
Clay (2016)	Australia	2000.11–2011.12	178	85 (47.8)	Median (range): 68 (20–87)	138 (77.5)	110	32	36	–	8	10	76	26	17	33	3	178	53 (30)	50 (28)	HRMA	8
Chen (2014)	China	2006–2013	206	97 (47.1)	Mean (range): 61 (27–81)	62 (30.1)	64	49	60 (III and IV)		–	16	82	58	5	40	4	206	123 (59.7)	–	PCR and DS	7
Song (2013)	China	2010.1–2012.12	161	92 (57.1)	Median (range): 59 (34–76)	33 (20.5)	65	21	75	–	6	18	57	37	23	18	2	161	67 (41.6)	–	PCR and DS	7
Villa (2014)	America	2008–2011	200	59 (29.5)	NR	166 (83)	141	18	17	2	–	41	126	7	–	23	3	200	41 (20.5)	–	PCR and DS	8
Russell (2013)	Australia	1993–2011	69	31 (44.9)	Median (range): 65.3 (29–85.6)	50 (72.5)	NR				–	–	26	4	13	24	–	59	17 (29)	13 (22)	Sequenom's MassArray platform	6
Sun (2014)	China	2002.1–2011.12	136	79 (58.1)	Median (range): 57.6 (34–79)	33 (24.3)	NR				–	21	39	38	22	14	2	102	39 (38.2)	–	PCR-TaqMan	6
Lee (2013)	Korea	2007.10–2008.10	161	73 (45.3)	Mean (SD): 63 (10)	65 (40.4)	112	14	27	–	19	39	57	8	2	9	4	153	83 (54.2%)	–	PCR and DS	9
Nakagiri (2014)	Japan	1993.1–2002.12	147	87 (59.2)	Mean (SD): 62.9 (9.8)	NR	NR				38	104					5	147	70 (48)	10 (7)	PCR and DS	6
Zhang (2012)	China	2007.10–2011.7	349	0	Mean (SD): 57.9 (10.3)	0	206	33	99	11	10	34	183	54	6	46	14	349	266 (76.2)	7 (2)	PCR and DS	8
Li (2012)	China	2007.10–2011.7	230	223 (97)	Median (range): 59.5 (33–82)	All	72	54	99	5	7	9	92	38	13	62	9	230	100 (43.5)	38 (16.5)	PCR and DS	8
Liu(2014)	China	2008.1–2011.11	139	72 (51.8)	NR	53 (38.1)	57	43	39	–	–	25	55	12	5	4	11	139	65 (46.8)	–	PCR and DS	6
Shim (2011)	Korea	2005–2009	107	52 (48.6)	Mean (range): 61.3 (42–80)	87 (81.3)	42	21	44	–	–	8	34	32	12	21	–	107	54 (50.5)	–	PCR and DS	6
Wang (2015)	China	2011.1–2014.1	212	130 (61.3)	Median (range): 58 (36–76)	NR	212	–	–	–	106	106(IAC)						212	78 (36.8)	18 (8.5)	PCR and DS	5
Kadota (2016)	America	1995–2005	482	178 (36.9)	Median (range): 69 (33–89)	405 (84)	463	19	–	–	8	26	212	135	14	60	20	482	86 (18)	129 (27)	Sequenom's MassArray platform	6
Yu(2016)	China	2012.7–2014.12	668	NR	NR	NR	NR				63	43	230	192	52	66	22	668	263 (39.4)	–	ARMS	5
Andrenia (2015)	Brazil	2007–2012	125	49 (39.2)	Median (range): 71 (44–92)	79 (63.2)	67	22	36	–	–	24	67	23	–	11	–	125	27 (21.6)	33 (26.4)	PCR and DS	5
Hu(2014)	China	2007.2–2012.7	981	427 (43.5)	NR	310 (31.6)	515	140	284	42	33	71	488	155	24	163	44	981	635 (64.7)	69 (7)	PCR and DS	8
Liu(2014)	China	2007.5–2012.2	248	125 (50.4)	Median (range): 60 (24–81)	92 (37.1)	110	30	81	27	–	–	–	–	84	–	–	248	87 (35.1)	–	PCR and DS	6
Yanagawa (2014)	Japan	2002–2012	486	231 (47.5)	NR	220 (45.3)	376	71	39	–	86	89	99	136	11	51	14	241	131 (54.4)	–	PCR- invader method	8
Audrey (2014)	France	2001.6–2005.6	397	281 (70.8)	Median (range): 61 (19–84)	NR	185	101	104	7	–	11	191	73	4	109	16	397	38 (9.6)	136 (34)	PCR-TaqMan	7
Tsuta (2013)	Japan	1998.1–2002.12	904	459 (50.8)	Median (range): 63 (23–89)	458 (50.7)	579	149	141	–	102	136	98	338	61	124	45	879	356 (40.5)	96 (11.1)	HRMA	9
Cai (2015)	China	2004–2010	629	278 (44.2)	Median (range): 59 (27–82)	161 (25.6)	349	59	179	42	11	39	309	198	21	25	24	629	364 (57.9)	–	ARMS	8
Wang (2017)	China	2012.7–2015.7	376	161 (42.8)	Mean (SD): 58.8 (7.4)	166 (44.1)	180	94	102	–	37	38	150	67	19	56	9	376	153 (40.7)		PCR and DS	8
Yotsukura (2017)	Japan	2010.8–2014.12	369	192 (52)	Mean (SD): 66.2 (10.2)	192 (52)	324	45	–	–	85	62	11	153	0	13	17	369	160 (43.4)		PNA-LNA PCR	6

PNA-LNA PCR, peptide nucleic acid -locked nucleic acid polymerase chain reaction clamp method.
PCR and DS, polymerase chain reaction amplification and direct sequencing.
HRMA, high resolution melting analysis.
ARMS, amplification refractory mutation system.

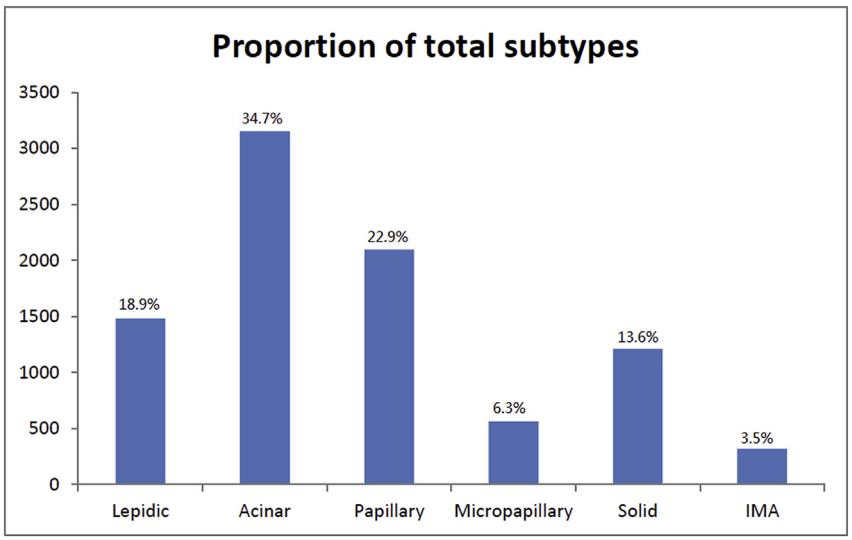

Fig. 2. The distribution of each lung adenocarcinoma subtype among all cases.

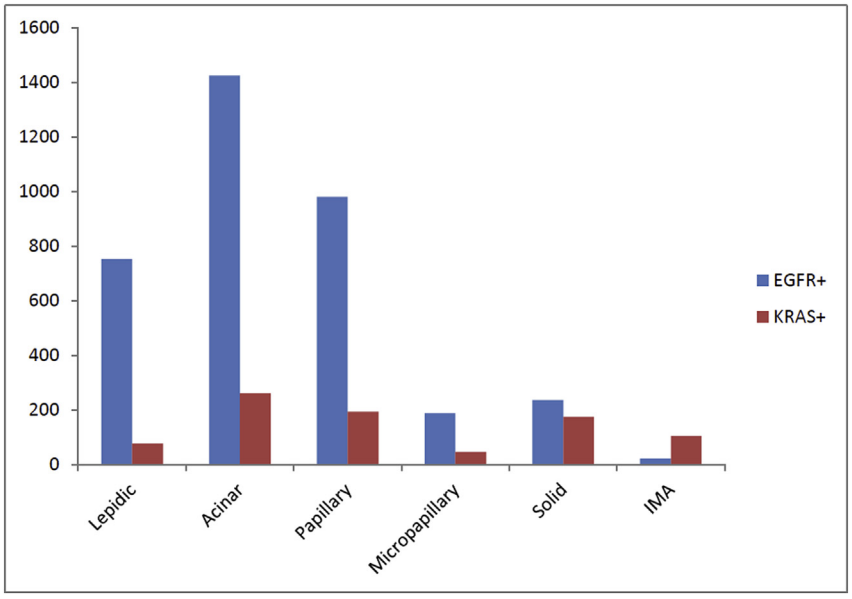

Fig. 3. The distribution of *EGFR* and *KRAS* mutation status of each lung adenocarcinoma subtype.

in Table 2. The distribution of *EGFR* mutation status in each subtype is shown in Fig. 3. From the pooled-data analysis we found that *EGFR* mutations were associated with the lepidic predominant subtype of LAC (OR,1.76; 95%CI, 1.38–2.24;$p < 0.01$) and, the heterogeneity was moderate with I [2] showing 66%. In contrast, solid predominant LAC (OR,0.28; 95%CI, 0.23–0.34; $p < 0.01$) and IMA (OR,0.10; 95%CI, 0.06–0.14; $p < 0.01$) were associated with lack of *EGFR* mutation. The heterogeneities were low for both types (Solid: I [2] = 16%; IMA: I [2] = 0%)(Table 2).

KRAS mutation status in LAC

Thirteen studies [11–13,21,22,25,26,28,29,32,33] were eligible for *KRAS* mutations analysis. The distribution of *KRAS* mutation status in each subtype is shown in Fig. 3. Data are summarized in Table 3. From the pooled-data analysis we found that *KRAS* mutations are associated with IMA (OR,7.01; 95%CI, 5.11–9.62; $p < 0.01$), the heterogeneity was moderate with I [2] showing 67%. In contrast, lepidic (OR,0.58; 95%CI, 0.45–0.75; $p < 0.01$) and acinar (OR,0.65; 95%CI, 0.55–0.78; $p < 0.01$) predominant LAC subtypes are associated with lack of *KRAS* mutations. The heterogeneities were low for both types (Lepidic: I [2] = 0%; Acinar: I [2] = 15%). (Table 3)

Subgroup analysis

Further exploration was performed according to the study region. In the Asian and the Non-Asian group, the results of *EGFR* mutation status indicated the same associations in the Asian and the Non-Asian group (Suppl. Table 1). The results were consistent except for the association between *KRAS* mutations and lepidic predominant subtype, which tended to be a negative trend of association in the non-Asian group (OR,0.74; 95%CI, 0.53–1.04; $p = 0.08$)(Suppl. Table 2).

Table 2
EGFR mutation status based on subtype of lung adenocarcinoma.

Variables	Total number of detection subjects	Total number of EGFR mutation (%)	EGFR + vs. EGFR- effect			Heterogeneity		
Histological Subtype			OR (95%CI)	Z	P	X^2	P	I^2
Lepidic	1482	752 (50.7)	1.76 (1.38–2.24)	4.55	P < 0.01	63.80	P < 0.01	66%
Acinar	3153	1425 (45.2)	1.19 (0.95–1.49)	1.54	P = 0.12	95.78	P < 0.01	76%
Papillary	2096	980 (46.8)	1.21 (0.97–1.50)	1.71	P = 0.09	70.32	P < 0.01	67%
Micropapillary	564	188 (33.3)	1.16 (0.71–1.90)	0.55	P = 0.50	85.45	P < 0.01	77%
Solid	1211	236 (19.5)	0.28 (0.23–0.34)	13.05	P < 0.01	27.53	P = 0.23	16%
IMA	318	21 (6.6)	0.10 (0.06–0.14)	11.10	P < 0.01	20.00	P = 0.52	0%

Table 3
KRAS mutation status based on subtype of lung adenocarcinoma.

Variables	Total number of detection subjects	Total number of KRAS mutation (%)	KRAS + vs. KRAS- effect			Heterogeneity		
Histological Subtype			OR (95%CI)	Z	P	X^2	P	I^2
Lepidic	728	76 (10.4)	0.58 (0.45–0.75)	4.07	P < 0.01	9.89	P = 0.45	0%
Acinar	1810	261 (14.4)	0.65 (0.55–0.78)	4.82	P < 0.01	11.75	P = 0.30	15%
Papillary	1046	193 (18.5)	1.09 (0.91–1.32)	0.93	P = 0.35	8.93	P = 0.54	0%
Micropapillary	237	46 (19.4)	1.03 (0.74–1.45)	0.20	P = 0.84	6.14	P = 0.74	0%
Solid	847	174 (20.5)	1.49 (0.97–2.29)	1.80	P = 0.07	36.86	P < 0.01	73%
IMA	197	104 (52.8)	7.01 (5.11–9.62)	12.06	P < 0.01	24.5	P < 0.01	67%

Discussion

To the best of our knowledge, the present study is the first pooled-data analysis clarifying the association between the novel IASLC/ATS/ERS LAC classification and *EGFR*/*KRAS* mutation status in resected tumors. We demonstrated that *EGFR* and *KRAS* mutations were significantly associated with specific histologic subtypes in resected LAC.

The investigation of oncogenic driver mutations in LAC has significantly facilitated personalized treatment and development of targeted drugs. Among the various mutations, *EGFR* mutation is the most common targetable driver mutation in advanced disease. Thus, following the publication of the IASLC/ATS/ERS classification of LAC, multiple groups have investigated the relationship between histological subtype and *EGFR* mutation status. A study by Shim et al. [24], found *EGFR* mutations in more than 50% of resected LAC with significant associations between *EGFR* mutations and micropapillary predominant tumors and the presence of any amount of lepidic pattern. In addition, *EGFR* mutations were also reported to be more frequent in lepidic [16,31], acinar [14,17,21,29], papillary [29,33] and micropapillary [15,18,22,24] predominant tumors. It is evident by literature that there is a difference in association between *EGFR* mutations and predominant histologic types between ethnicities, but in general there is no significant difference in terms of sample size. Instead, various patient selection and inclusion/exclusion criteria may have resulted in these different associations. The variability of proportions may be higher in small sample sizes but should be diminished when data are pooled. In the present study, the pooled-data analysis showed that *EGFR* mutations were more common in the lepidic predominant subtype, and were rarely identified in IMA and solid predominant subtypes, while, we did not find any significant association between *EGFR* mutations and acinar, papillary and micropapillary predominant subtypes. Furthermore, results were consistent both in Asian and Non-Asian population groups.

KRAS mutations have been identified as an adverse prognostic factor for patients with NSCLC and these tumors might predict resistance to *EGFR*-targeted therapy [6]. In one study of a homogenous cohort of patients with surgically resected early-stage lung adenocarcinomas, Kadota et al. [26] identified *KRAS* mutations to be an independent prognostic factor for OS with a HR of 1.87, after adjustment with important confounders such as vascular invasion and pathologic stage. These results imply that *KRAS* mutations may help identify patients with worse prognosis within this group.

Andreia et al. [28] found that *KRAS* mutations were significantly associated with the acinar predominant subtype. However, Kadota and his colleagues [12] identified IMA to be significantly associated with *KRAS* mutations and a complete absence of *EGFR* mutations. Moreover, *KRAS* mutations were more frequently detected in pure IMA than in mixed mucinous/nonmucinous tumors. Hence, the association noted between *KRAS* mutations and histological subtypes remains controversial. By performing a meta-analysis, however, we have shown that *KRAS*-mutated tumors are more common of IMA subtype, and less frequently exhibit lepidic or acinar predominant histology, although the negative trend of association of *KRAS* mutations with the lepidic predominant subtype was statistically non-significant in the non-Asian study region.

In addition, histologic features of LAC may play a role in predicting the outcome in patients with *EGFR* mutation who are treated with TKIs. Yoshida et al. [37] have shown that patients with *EGFR* mutations with solid predominant pattern of adenocarcinoma have significantly worse overall response to TKIs than those with other predominant patterns. Tsao et al. [38] reported that the benefits of adjuvant chemotherapy in the cohort following curative resection were limited to patients with solid and micropapillary predominant tumors while no benefit was seen in patients with acinar or papillary predominant adenocarcinoma. We hypothesize that there is some biology inherent to each predominant subtype that modulates response to systemic therapies. For patients with resected LAC, histological subtype of LAC in resected specimens can be used to help predict the likely *EGFR* mutation status, particularly in IMA and lepidic predominant adenocarcinoma.

Some limitations of our study need to be acknowledged. First, because of the nature of the included studies, the level of evidence of such kind of meta-analysis of observation studies might not be high enough because of the heterogeneity between studies. Differences in mutation detection methods could also have some impact on the comparison of LAC subtype with morphologic findings. Second, selection bias might have occurred because of incomplete reporting of the presence or absence of an association between mutation status and histologic subtype. Finally, the subjectivity and low interobserver concordance on histologic

subtyping among pathologists may have led to difference in proportions of predominant subtypes between the studies.

Conclusions

We found that *EGFR* mutations are more common in patients with resected lepidic predominant adenocarcinoma and are rarely found in solid predominant adenocarcinoma and IMA. In addition, *KRAS* mutations are more common in IMA, while they are less frequently identified in lepidic and acinar predominant subtypes. The histological subtype of LAC identified in resected specimens might be used to help predict the likely mutation status for diagnostic algorithm especially in patients with early NSCLC. The association between tumor morphology and drive gene mutation warrants further investigation.

Conflict of interest statement and source of funding

None

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.02.006.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA A Cancer J Clin 2015;65(1):5–29.
[2] Travis WD, Brambilla E, Noguchi M, et al. International association for the study of lung cancer/american thoracic society/european respiratory society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol: Off Pub Int Assoc Study Lung Cancer 2011;6(2):244–85.
[3] Rosell R, Moran T, Queralt C, et al. Screening for epidermal growth factor receptor mutations in lung cancer. N Engl J Med 2009;361(10):958–67.
[4] Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 2004;350(21):2129–39.
[5] Pao W, Miller VA. Epidermal growth factor receptor mutations, small-molecule kinase inhibitors, and non-small-cell lung cancer: current knowledge and future directions. J Clin Oncol Off J Am Soc Clin Oncol 2005;23(11):2556–68.
[6] Pao W, Wang TY, Riely GJ, et al. KRAS mutations and primary resistance of lung adenocarcinomas to gefitinib or erlotinib. PLoS Med 2005;2(1):e17.
[7] Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361(10):947–57.
[8] Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 2011;12(8):735–42.
[9] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21(11):1539–58.
[10] Nakamura H, Saji H, Shinmyo T, et al. Association of IASLC/ATS/ERS histologic subtypes of lung adenocarcinoma with epidermal growth factor receptor mutations in 320 resected cases. Clin Lung Cancer 2015;16(3):209–15.
[11] Dong YJ, Cai YR, Zhou LJ, et al. Association between the histological subtype of lung adenocarcinoma, EGFR/KRAS mutation status and the ALK rearrangement according to the novel IASLC/ATS/ERS classification. Oncol Lett 2016;11(4):2552–8.
[12] Kadota K, Yeh YC, D'Angelo SP, et al. Associations between mutations and histologic patterns of mucin in lung adenocarcinoma: invasive mucinous pattern and extracellular mucin are associated with KRAS mutation. Am J Surg Pathol 2014;38(8):1118–27.
[13] Clay TD, Russell PA, Do H, et al. Associations between the IASLC/ATS/ERS lung adenocarcinoma classification and EGFR and KRAS mutations. Pathology 2016;48(1):17–24.
[14] Chen Z, Liu X, Zhao J, Yang H, Teng X. Correlation of EGFR mutation and histological subtype according to the IASLC/ATS/ERS classification of lung adenocarcinoma. Int J Clin Exp Pathol 2014;7(11):8039–45.
[15] Song Z, Zhu H, Guo Z, Wu W, Sun W, Zhang Y. Correlation of EGFR mutation and predominant histologic subtype according to the new lung adenocarcinoma classification in Chinese patients. Med Oncol 2013;30(3):645.
[16] Villa C, Cagle PT, Johnson M, et al. Correlation of EGFR mutation status with predominant histologic subtype of adenocarcinoma according to the new lung adenocarcinoma classification of the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society. Arch Pathol Lab Med 2014;138(10):1353–7.
[17] Russell PA, Barnett SA, Walkiewicz M, et al. Correlation of mutation status and survival with predominant histologic subtype according to the new IASLC/ATS/ERS lung adenocarcinoma classification in stage III (N2) patients. J Thorac Oncol: off Pub Int Assoc Study Lung Cancer 2013;8(4):461–8.
[18] Sun Y, Yu X, Shi X, Hong W, Zhao J, Shi L. Correlation of survival and EGFR mutation with predominant histologic subtype according to the new lung adenocarcinoma classification in stage IB patients. World J Surg Oncol 2014;12:148.
[19] Lee HJ, Kim YT, Kang CH, et al. Epidermal growth factor receptor mutation in lung adenocarcinomas: relationship with CT characteristics and histologic subtypes. Radiology 2013;268(1):254–64.
[20] Nakagiri T, Sawabata N, Morii E, et al. Evaluation of the new IASLC/ATS/ERS proposed classification of adenocarcinoma based on lepidic pattern in patients with pathological stage IA pulmonary adenocarcinoma. Gen Thorac Cardiovasc Surg. 2014;62(11):671–7.
[21] Zhang Y, Sun Y, Pan Y, et al. Frequency of driver mutations in lung adenocarcinoma from female never-smokers varies with histologic subtypes and age at diagnosis. Clin Cancer Res Off J Am Assoc Canc Res 2012;18(7):1947–53.
[22] Li H, Pan Y, Li Y, et al. Frequency of well-identified oncogenic driver mutations in lung adenocarcinoma of smokers varies with histological subtypes and graduated smoking dose. Lung Canc 2013;79(1):8–13.
[23] Jie L, Li XY, Zhao YQ, et al. Genotype-phenotype correlation in Chinese patients with pulmonary mixed type adenocarcinoma: relationship between histologic subtypes, TITF-1/SP-A expressions and EGFR mutations. Pathol Res Pract 2014;210(3):176–81.
[24] Shim HS, Lee DH, Park EJ, Kim SH. Histopathologic characteristics of lung adenocarcinomas with epidermal growth factor receptor mutations in the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society lung adenocarcinoma classification. Arch Pathol Lab Med 2011;135(10):1329–34.
[25] Wang T, Zhang T, Han X, Liu XI, Zhou N, Liu Y. Impact of the international association for the study of lung cancer/American thoracic society/european respiratory society classification of stage IA adenocarcinoma of the lung: correlation between computed tomography images and EGFR and KRAS gene mutations. Exp Therapeutic Med 2015;9(6):2095–103.
[26] Kadota K, Sima CS, Arcila ME, et al. KRAS mutation is a significant prognostic factor in early-stage lung adenocarcinoma. Am J Surg Pathol 2016;40(12):1579–90.
[27] Yu Y, Jian H, Shen L, Zhu L, Lu S. Lymph node involvement influenced by lung adenocarcinoma subtypes in tumor size </=3 cm disease: a study of 2268 cases. Eur J Surg Oncol J Br Assoc Surg Oncol 2016;42(11):1714–9.
[28] de Melo AC, Karen de Sa V, Sternberg C, et al. Mutational profile and new IASLC/ATS/ERS classification provide additional prognostic information about lung adenocarcinoma: a study of 125 patients from Brazil. Oncology 2015;89(3):175–86.
[29] Hu H, Pan Y, Li Y, et al. Oncogenic mutations are associated with histological subtypes but do not have an independent prognostic value in lung adenocarcinoma. OncoTargets Ther 2014;7:1423–37.
[30] Chao L, Yi-Sheng H, Yu C, et al. Relevance of EGFR mutation with micropapillary pattern according to the novel IASLC/ATS/ERS lung adenocarcinoma classification and correlation with prognosis in Chinese patients. Lung Canc 2014;86(2):164–9.
[31] Yanagawa N, Shiono S, Abiko M, Ogata SY, Sato T, Tamura G. The correlation of the international association for the study of lung cancer (IASLC)/American thoracic society (ATS)/European respiratory society (ERS) classification with prognosis and EGFR mutation in lung adenocarcinoma. Ann Thorac Surg 2014;98(2):453–8.
[32] Mansuet-Lupo A, Bobbio A, Blons H, et al. The new histologic classification of lung primary adenocarcinoma subtypes is a reliable prognostic marker and identifies tumors with different mutation status: the experience of a French cohort. Chest 2014;146(3):633–43.
[33] Tsuta K, Kawago M, Inoue E, et al. The utility of the proposed IASLC/ATS/ERS lung adenocarcinoma subtypes for disease prognosis and correlation of driver gene alterations. Lung Canc 2013;81(3):371–6.
[34] Cai W, Lin D, Wu C, et al. Intratumoral heterogeneity of ALK-rearranged and ALK/EGFR coaltered lung adenocarcinoma. J Clin Oncol J Am Soc Clin Oncol 2015;33(32):3701–9.
[35] Wang T, Zhang Y, Liu B, Hu M, Zhou N, Zhi X. Associations between epidermal growth factor receptor mutations and histological subtypes of lung adenocarcinoma according to the IASLC/ATS/ERS classification in Chinese patients. Thoracic Canc 2017;8(6):600–5.
[36] Yotsukura M, Yasuda H, Shigenobu T, et al. Clinical and pathological characteristics of EGFR mutation in operable early-stage lung adenocarcinoma. Lung Canc 2017;109:45–51.
[37] Yoshida T, Ishii G, Goto K, et al. Solid predominant histology predicts EGFR tyrosine kinase inhibitor response in patients with EGFR mutation-positive lung adenocarcinoma. J Canc Res Clin Oncol 2013;139(10):1691–700.
[38] Tsao MS, Marguet S, Le Teuff G, et al. Subtype classification of lung adenocarcinoma predicts benefit from adjuvant chemotherapy in patients undergoing complete resection. J Clin Oncol J Am Soc Clin Oncol 2015;33(30):3439–46.