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REVIEW ARTICLE

Clinical impact of the new IASLC/ATS/ERS lung adenocarcinoma classification for chest surgeons

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Abstract In 2011, a new pathological classification of lung adenocarcinoma was proposed by the International Association for the Study of Lung Cancer, the American Thoracic Society and the European Respiratory Society. The new criteria classify adenocarcinomas into eight subtypes according to their histological features. The criteria introduce a new concept of early stage lung cancer, consisting of adenocarcinoma in situ and minimally invasive adenocarcinoma, and categorize invasive adenocarcinomas by the predominant histological pattern. In addition to morphological differences among subtypes, the classification also considers the tumor behavior based on the genetic background within each subtype. We herein review the clinical impact of this new classification for chest surgeons based on the data from several recent validation studies from various institutions.

Keywords Lung cancer · Adenocarcinoma · Subtype · Chest surgery · Prognosis

Introduction

Adenocarcinoma is the most prevalent histological type of lung cancer, accounting for 50–70 % of resected lung cancers [1], and its prevalence is still increasing worldwide [2]. Strategies to diagnose and treat this histological type are, therefore, critically important. A new pathological classification for lung adenocarcinoma was proposed by the International Association for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS) and the European Respiratory Society (ERS) in 2011 [3]. The main revisions from the previous 1999/2004 World Health Organization (WHO) classification [4] were the omission of the term bronchioloalveolar carcinoma (BAC) [5] and abolishment of the category of mixed subtype adenocarcinoma. The term BAC was abolished to avoid confusion between non-mucinous BAC and mucinous BAC, owing to the substantial differences in the biological and clinical features of these subtypes, and due to the need to clearly distinguish them terminologically. In particular, non-mucinous BAC, including the non-invasive early adenocarcinomas, such as type A and type B in Noguchi's classification [6], shows a remarkably good prognosis, whereas most mucinous BACs are invasive and have a worse prognosis than non-mucinous BAC.

Among other alterations, the mixed subtype adenocarcinoma category was abolished, because it accounted for as many as 80 % of adenocarcinomas. The new classification more precisely categorizes these formerly mixed type adenocarcinomas in accordance with the predominant histological pattern, as determined by the percentages of constituent histological components. Following the revision, preinvasive adenocarcinomas such as Noguchi's type A and type B have been classified as adenocarcinoma in situ (AIS), while most type C cases are classified as minimally invasive adenocarcinoma (MIA) or lepidic-type invasive adenocarcinoma. Invasive adenocarcinomas are defined by the predominant histological subtype; namely lepidic predominant invasive adenocarcinoma (LPA), acinar

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Table 1 The new classification of lung adenocarcinoma in resected specimens, 2011 (IASLC/ATS/ERS)

New classification	Abbreviation in this review
Preinvasive lesions	
Atypical adenomatous hyperplasia (AAH)	
Adenocarcinoma in situ (≤3 cm pure lepidic growth without invasion)	AIS
Nonmucinous	
Mucinous	
Mixed nonmucinous/mucinous	
Adenocarcinoma	
Minimally invasive adenocarcinoma (≤3 cm lepidic predominant tumor with ≤5 mm invasion)	MIA
Nonmucinous	
Mucinous	
Mixed nonmucinous/mucinous	
Invasive adenocarcinoma	
Lepidic predominant (formerly nonmucinous BAC pattern, with >5 mm invasion)	LPA
Acinar predominant	APA
Papillary predominant	PPA
Micropapillary predominant	MPA
Solid predominant	SPA
Variants of invasive adenocarcinoma	
Invasive mucinous adenocarcinoma (formerly mucinous BAC)	IMA
Colloid	CA
Fetal (low and high grade)	FA
Enteric	EA

BAC bronchioloalveolar carcinoma

predominant invasive adenocarcinoma (APA), papillary predominant invasive adenocarcinoma (PPA), micropapillary predominant invasive adenocarcinoma (MPA), solid predominant invasive adenocarcinoma (SPA) and other variants of invasive adenocarcinoma, including invasive mucinous adenocarcinoma (IMA; formerly termed mucinous BAC, colloid (CA), fetal (FA) and enteric (EA) adenocarcinoma) (Table 1) [7].

Although this reclassification is theoretically reasonable, its clinical impact on the diagnostic, therapeutic, and prognostic considerations requires further validation. Suitable improvements in future revisions warrant broad discussion among researchers, including oncologists, pulmonologists, pathologists, radiologists, molecular biologists and chest surgeons. To date, however, no substantial and comprehensive evaluation of the impact of this classification on chest surgeons has yet appeared.

Here, we broadly review the impact of the new IASLC/ATS/ERS pathological classification of lung adenocarcinoma, with particular regard to chest surgery.

The proportion of adenocarcinoma subtypes among institutions

The proportions of individual adenocarcinoma subtypes obtained using the new classification system are interesting. Reports from different institutions or countries are shown in Table 2 [8–17].

The percentages of each subtype differ among countries and ethnicities in several ways. First, countries differ in the proportion of AIS + MIA; the proportions are high in Japanese and Korean patients, ranging from 11.3 to 13.8 %, but are relatively low in China, the US, Australia and European countries, ranging from 0 to 5.1 % of the cases. A similar trend was seen for LPA, with 8.1–28.3 % of cases in Japan and Korea being LPA vs. 2.7–10.6 % of cases in other regions. It is unclear whether the low proportions of lepidic-type adenocarcinomas (AIS + MIA + LPA) [18] in areas other than Japan and Korea are due to racial and ethnic causes, or whether some other reason exists. One plausible reason is the prevalence of chest computed tomography (CT) in these regions. This is because chest radiography (CR) alone is generally unable to image these lesions, which show up as focal ground-glass opacities, which are generally detectable only on chest CT. In Japan, chest CT plays an important role in detecting lepidic-type early adenocarcinomas. Increased proportions of AIS, MIA and LPA in resected lung cancers improve the postoperative survival in this patient group. In fact, the postsurgical survival in patients with stage IA non-small cell lung cancer (NSCLC) is significantly better in Japan than in the US [19], although the reason for this has not been identified.

Second, the most frequent subtype appears to differ by race, with APA being the most prevalent in Caucasians, ranging from 40 to 46.9 %, whereas PPA is the most prevalent in Asians, ranging from 30.7 to 40.7 %, although exceptions exist. As with the frequency of lepidic-type adenocarcinoma, it is unclear whether the differences in the most prevalent subtype do in fact reflect differences among countries or ethnicities. Another plausible reason is the variation in the interpretation of pathological diagnoses between countries or institutions, because APA and PPA co-exist in many adenocarcinoma cases. Further, variations might be present in the criteria used to interpret APA and PPA among pathologists in different regions or institutions, potentially biasing the subtyping toward the predominant histological type. However, since most studies have found no major survival difference between APA and PPA [8, 9, 12], an inconsistent classification between these two subtypes might not affect the postoperative survival.

Third, the percentage of SPA varied widely among reports, from 6.5 to 37.6 %. It has been noted that large

Table 2 The proportion (%) of adenocarcinoma subtypes (IASLC/ATS/ERS) by race

References (year, country)	Ethnicity	No. of patients	AIS + MIA	LPA	APA	PPA	MPA	SPA	IMA	CA + FA + EA + NA
Russell [8] (2011, Australia)	Caucasian	210	8 (3.8)	10 (4.8)	**84 (40.0)**	26 (12.4)	14 (6.7)	49 (23.3)	10 (4.8)	9 (4.3)
Yoshizawa [9] (2011, US)	Caucasian[a]	514	9 (1.8)	29 (5.6)	**232 (45.1)**	143 (27.8)	12 (2.3)	67 (13)	13 (2.5)	9 (1.8)
Warth [10] (2012, Germany)	Caucasian	487	0	41 (8.4)	**207 (42.5)**	23 (4.7)	33 (6.8)	183 (37.6)	0	0
Mansuet-Lupo [11] (2014, France)	Caucasian	407	1 (0.3)	11 (2.7)	**191 (46.9)**	73 (17.9)	4 (1.0)	109 (26.8)	16 (3.9)	2 (0.5)
Gu [12] (2013, China)	Asian	292	15 (5.1)	31 (10.6)	**112 (38.4)**	36 (12.3)	30 (10.3)	52 (17.8)	10 (3.4)	6 (2.1)
Song [13] (2013, China)	Asian	261	6 (2.3)	19 (7.3)	76 (29.1)	**80 (30.7)**	42 (16.1)	34 (13.0)	0	4 (1.5)
Hung [14] (2013, Taiwan)	Asian	283	0	31 (11)	88 (31.1)	**98 (34.6)**	43 (15.2)	23 (8.1)	0	0
Lee [15] (2013, Korea)	Asian	138	19 (13.8)	39 (28.3)	**57 (41.3)**	8 (5.8)	2 (1.4)	9 (6.5)	4 (2.9)	0
Yoshizawa [16] (2013, Japan)	Asian	440	53 (12.0)	36 (8.1)	61 (13.8)	**179 (40.7)**	19 (4.3)	78 (17.7)	10 (2.2)	4 (0.9)
Tsuta [17] (2013, Japan)	Asian	904	102 (11.3)	136 (15.1)	98 (10.8)	**338 (37.4)**	61 (6.7)	124 (13.7)	45 (5.0)	0
SMU[b] (2014, Japan)	Asian	320	41 (12.9)	42 (13.1)	94 (29.4)	**112 (35.0)**	5 (1.6)	23 (7.2)	3 (1.0)	0

Bold text indicates the most common subtype in each study

AIS adenocarcinoma in situ, *MIA* minimally invasive adenocarcinoma, *LPA* lepidic predominant invasive adenocarcinoma, *APA* acinar predominant invasive adenocarcinoma, *PAP* papillary predominant invasive adenocarcinoma, *MPA* micropapillary predominant invasive adenocarcinoma, *SPA* solid predominant invasive adenocarcinoma, *IMA* invasive mucinous adenocarcinoma, *CA* colloid, *FA* fetal, *EA* enteric, *NA* not applicable

[a] Caucasian = 91 %

[b] St Marianna University School of Medicine, unpublished data

cell carcinoma lacking squamous differentiation is clinicopathologically indistinguishable from SPA [20]. Additionally, large cell carcinoma and SPA are similar with regard to the *KRAS* mutation rates, at 43 and 38 %, respectively ($p = 0.62$). Pathologists should, therefore, carefully distinguish large cell carcinoma or other undifferentiated carcinomas from SPA.

Finally, the percentage of MPA also varied widely, ranging from 1.0 to 16.1 %. Given the poor prognosis of this subtype [21, 22], different proportions of MPA in patient groups would be expected to markedly affect the postoperative survival rates. Solving these problems in the pathological diagnosis of subtypes requires the establishment of a common consensus for objective criteria [23]. Achieving such a consensus would be aided by international or multi-institutional workshops for pathologists to standardize the pathological diagnosis of lung adenocarcinoma.

Radiographic findings of individual subtypes

It is well recognized that atypical adenomatous hyperplasia (AAH) and lepidic-type adenocarcinomas, including AIS, MIA and LPA, usually show up as focal ground-glass opacities (GGOs) on chest CT. However, only a few studies [15, 24] have evaluated the features of chest CT findings for the differential diagnoses of other adenocarcinoma subtypes under the new classification. In a retrospective study [24] of 300 resected small lung adenocarcinoma lesions less than 20 mm in diameter, 114 of the 142 air-containing lesions were AIS and 28 were MIA. In contrast, 30 of the 158 solid-density lesions were AIS, 24 were MIA and 104 were invasive adenocarcinoma. Invasive adenocarcinomas commonly showed notches and pleural tags. Thus, the study did not show complete correspondence between the radiographic findings and histological subtype. In a second study [15], adenocarcinoma subtypes shared similar frequencies of CT features, such as bubble-like lucency, cavities, notching and a lobulated border. The frequencies differed only for an air bronchogram and round shape; an air bronchogram was found in 100 % of IMA and a round shape was found in 62.5 % of AIS cases. These two studies indicate that it is difficult to distinguish individual subtypes based on the radiological findings, particularly for tumors forming sub-solid or solid lung nodules such as APA, PPA, SPA and MPA.

An elevated maximum standardized uptake value (SUVmax) in fluorodeoxy glucose-positron emission tomography combined with CT (FDG-PET/CT) was found to be closely associated with SPA or MPA, and patients with these adenocarcinoma subtypes had a higher risk of recurrence than patients with APA or PPA in an intermediate-risk group [25]. This study indicates the usefulness of FDG-PET/CT combined with subtyping for predicting the prognoses of patients with adenocarcinomas.

Postoperative survival of patients with the different subtypes

The postoperative survival of the patients with each subtype in different institutions is shown in Table 3. Although there were differences in the stage of disease, common characteristics of each subtype can be recognized.

Adenocarcinoma in situ and minimally invasive adenocarcinoma

Adenocarcinoma in situ and MIA are generally detected as small round-shaped GGO lesions with a relatively clear margin on high-resolution chest CT [26]. When a solid component cannot be seen in the shadow, these lesions are sometimes called pure GGOs, most of which are AIS. Multiple studies [27–29] have reported that AIS and MIA are lepidic-type early adenocarcinomas which show no recurrence after complete resection, and the postoperative 5-year disease-free survival (DFS) for these subtypes has been 100 % [8, 9, 12, 16, 17].

Lepidic predominant invasive adenocarcinoma

Non-invasive and invasive lepidic-type adenocarcinomas consist of three subtypes: AIS, MIA and LPA [18]. In the probable carcinogenesis sequence from AAH to invasive adenocarcinoma [30], LPA is postulated to be the stage following MIA. The postoperative 5-year DFS in patients with LPA has ranged from 71.9 to 93.8 %, and the 5-year overall survival (OS) ranged from 86 to 100 % (Table 3) [8, 9, 12, 16, 17]. In an analysis [18] of resected specimens from 139 patients with lepidic-type adenocarcinoma (two with AIS, 34 MIA and 103 with LPA), no recurrence was found in patients with AIS and MIA. In contrast, patients with LPA experienced a recurrence rate of 8 %, which appears to be lower than the 19 % reported for non-lepidic-type adenocarcinomas ($p = 0.003$).

Acinar predominant invasive adenocarcinoma

The 5-year DFS rates after the resection of APA have ranged from 54 to 84 %, and the 5-year OS rates ranged from 67 to 81.2 %. These rates, therefore, appear worse than those for LPA (Table 3). Of note, the prognosis in patients this subtype was worse in those who had tumors with a cribriform component [31]. This specific type was a distinct subtype with a high risk of recurrence, and the

Table 3 The postoperative survival according to the lung adenocarcinoma subtype

Studies	AIS	MIA	LPA	APA	PPA	MPA	SPA	IMA	CA + FA + EA + NA	Stage	*p*
Yoshizawa (2011) [9]											
Number of patients	1	8	29	232	143	12	67	13	9	IA + IB	
5-year DFS (%)	100	100	90	84	83	67	70	76	71		<0.001[c]
Russesll (2011) [8]											
Number of patients	1	7	10	84	26	14	49	10	9	IA-III	
5-year OS (%)	100	100	86	68	71	38	39	51	51		<0.001[d]
Gu (2013) [12]											
Number of patients	1	14	31	112	36	30	52	16[a]		IA-IV	
5-year DFS (%)	100	100	71.9	54.0	56.1	25.7	45.7	62.5[a]			ND
5-year OS (%)	100	100	91.4	72.2	71.2	46.6	57.9	73.1[a]			ND
Yoshizawa (2013) [16]											
Number of patients	20	33	36	61	179	19	78	10	4	IA-IIIA	
5-year DFS (%)	100	100	93.8	69.7	66.7	0	43.3	88.8	ND		ND
5-year OS (%)	100	100	100	81.2	74.7	NR	39.1	88.8	ND		ND
Tsuta (2013) [17]											
Number of patients	69	33	136	98	338	61	124	45	0	IA-IV	
5-year OS (%)	98[b]		93	67	74	62	58	76	NA		ND

AIS adenocarcinoma in situ, *MIA* minimally invasive adenocarcinoma, *LPA* lepidic predominant invasive adenocarcinoma, *APA* acinar predominant invasive adenocarcinoma, *PAP* papillary predominant invasive adenocarcinoma, *MPA* micropapillary predominant invasive adenocarcinoma, *SPA* solid predominant invasive adenocarcinoma, *IMA* invasive mucinous adenocarcinoma, *CA* colloid, *FA* fetal, *EA* enteric, *DFS* disease-free survival, *OS* overall survivbal, *NA* not applicable, *ND* not described, *NR* not reached

[a] Data from from IMA + CA + EA + FA

[b] Data from AIS + MIA

[c] Gray's test

[d] Cox regression model

presence of a cribriform pattern is an independent predictor of recurrence which identifies a poor prognostic subset among APA. In fact, the 5-year DFS rate for patients with a <10 % cribriform pattern was 84 %, whereas that for patients with a ≥10 % cribriform pattern was 73 % ($p < 0.001$). The new classification does not refer to a cribriform component in APA, but this type might warrant independent classification in a further revision.

Papillary predominant invasive adenocarcinoma

The 5-year DFS rates after the resection of PPA have ranged from 56.1 to 83 %, and the 5-year OS rates ranged from 71 to 74.7 %. These survival rates were similar to those of APA, but were apparently worse than those of LPA (Table 3). This subtype is the most common subtype described in most reports from Asian countries to date.

Micropapillary predominant invasive adenocarcinoma

The 5-year DFS rates after the resection of MPA have ranged from 0 to 67 %, and the 5-year OS rates ranged from 38 to 62 %. These survival rates are worse than those for APA or PPA (Table 3). Other studies have supported these findings. For instance, patients with micropapillary and solid predominant tumors had a significantly worse DFS than those with other subtypes ($p < 0.001$) [13]. The mean OS times were shown to differ significantly among LPA (78.5 months), APA (67.3 months), SPA (58.1 months), PPA (48.9 months) and MPA (44.9 months) ($p = 0.007$) [10]. This latter study is unique, because it found that the OS was worse for PPA than for SPA.

Solid predominant invasive adenocarcinoma

The 5-year DFS rates after the resection of SPA have ranged from 43.3 to 70 %, and the 5-year OS rates ranged from 39 to 58 %. These rates are worse than those of APA and PPA, and were similar to those of MPA (Table 3).

Variants of invasive adenocarcinoma

This group includes rare subtypes, although IMA is the most common. In patients with IMA, the 5-year DFS rates

Table 4 Postoperative survival in the aggregated lung adenocarcinoma subtype groups

	No. of patients	Stage	Low-risk group	Intermediate-risk group	High-risk group	*p* (DFS)	*p* (OS)
Yoshizawa (2011) [9]	514	IA + IB	AIS + MIA	LPA + APA + PPA	SPA + MPA + IMA + CA	<0.001[a]	0.06[a]
Warth (2012) [10]	487	IA–IV	LPA	APA	PPA + SPA + MPA + Others	0.001[b]	0.001[b]
Gu (2013) [12]	292	IA–IV	AIS + MIA	LPA + APA + PPA + others	SPA + MPA	<0.001[c]	0.002[c]
Tsuta (2013) [17]	904	IA–IV	AIS + MIA	LPA + APA +PPA	SPA + MPA + others	ND	0.01[d]
Song (2013) [13]	261	IA–IIIA	MIA + LPA	APA + PPA + IMA	SPA + MPA + others	<0.001[e]	ND
SMU[g] (2014)	320	IA–IV	AIS + MIA + LPA	APA + PPA + IMA	SPA + MPA	<0.0001[f]	0.0014[f]

AIS adenocarcinoma in situ, *MIA* minimally invasive adenocarcinoma, *LPA* lepidic predominant invasive adenocarcinoma, *APA* acinar predominant invasive adenocarcinoma, *PPA* papillary predominant invasive adenocarcinoma, *MPA* micropapillary predominant invasive adenocarcinoma, *SPA* solid predominant invasive adenocarcinoma, *IMA* invasive mucinous adenocarcinoma, *DFS* disease-free survival, *OS* overall survival, *ND* not described

[a] Gray's test

[b] Logrank test

[c] Logrank test

[d] Cox regression

[e] Logrank test

[f] Logrank test

[g] St. Marianna University School of Medicine, unpublished data

have ranged from 76 to 88.8 %, and the 5-year OS rates have ranged from 51 to 88.8 %. These rates are superior or at least comparable to those of APA and PPA (Table 3). The other variants, namely CA, FA and EA, are rarely seen, and survival information is not available.

Subgroups of aggregated subtypes

Although the results of several studies [32] did not reach statistical significance in either univariate or multivariate analyses, probably due to the small number of patients with these individual subtypes, most studies [9, 10, 12, 13, 17] demonstrated the predictive value of the new adenocarcinoma classification. When the patients with these subtypes were grouped into low-, intermediate- and high-risk groups, postoperative survival differences among the aggregated groups could be clearly detected (Table 4).

Associations of driver mutations with subtypes

Various driver mutations in lung adenocarcinomas have been reported. The genes that have received the most study to date include the epidermal growth factor receptor (*EGFR*) gene, the Kirsten rat sarcoma viral oncogene homolog (*KRAS*) gene and the echinoderm microtubule-associated protein-like 4-anaplastic lymphoma receptor tyrosine kinase (*EML4-ALK*) fusion gene [33–37]. Other aberrant genes rarely found in lung adenocarcinomas are V-raf murine sarcoma viral oncogene homolog B1 (*BRAF*), phosphatidylinositol-4,5-biphosphate 3-kinase, catalytic subunit α (*PIK3CA*), human epidermal growth factor receptor type 2 (*HER2*), mesenchymal–epithelial transition factor tyrosine kinase (*MET*) and mitogen-activated protein kinase kinase 1 (*MEK1*) [38–41]. Small molecule inhibitors of tyrosine kinases involved in the signal transduction for cell proliferation have been developed for clinical use, including gefitinib, erlotinib and afatinib for *EGFR*, and crizotinib and ceritinib for *EML4-ALK* [33, 34, 42–46].

Several studies [11, 15–17, 47–51] have analyzed the relationships between adenocarcinoma subtypes and the well-documented genetic mutations in *KRAS*, *EGFR*, and *ALK-EML4* (Table 5). *KRAS*-mutated adenocarcinomas and *EGFR*-mutated adenocarcinomas differ in several clinical features. A meta-analysis [52] suggested that *KRAS* mutations are associated with a worse OS in patients with NSCLC, particularly in patients with adenocarcinoma in the early stages. In contrast, several other studies [53] showed that patients with completely resected NSCLC carrying the *EGFR* mutation have a significant survival advantage over patients with tumors harboring wild-type *EGFR*. A Japanese study [54] comparing the postoperative survival in 32 adenocarcinoma patients with the *KRAS* mutation and 148 patients with the *EGFR* mutation showed a better OS in the *EGFR*-mutated group ($p = 0.0271$).

In terms of the survival after tumor recurrence, the *EGFR*-mutated group had a better median survival time (46.7 months) than the *KRAS*-mutated group (26.0 months). In a US study [55] which analyzed an adenocarcinoma group, 25 % of whom had a *KRAS* mutation and 20 %

Table 5 Percentages of driver mutations in the lung adenocarcinoma subtypes

Authors (country, year) mutated gene	AIS	MIA	LPA	APA	PPA	MPA	SPA	IMA	Others
Yoshizawa (Japan, 2013) [16]									
EGFR	85.7	83.3	71.4	38.4	68.5	40.1	14.3	0	ND
KRAS	0	8.3	0	23.1	4.5	0	25.0	100	ND
Tsuta (Japan, 2013) [17]									
EGFR	39.0[b]		44.6	32.3	56.0	39.7	15.8	0	ND
KRAS	4.0[b]		9.2	3.7	15.6	16.2	5.3	74.4	ND
ALK	0[b]		0	14.4	2.4	15.0	6.5	2.2	ND
Lee (Korea, 2013) [15]									
EGFR	50.0	81.8	74.4	52.6	50.0	50.0	11.1	0	ND
Kim (Korea, 2013) [47]									
EGFR	NA	NA	37.5	40.4	36.1	23.1	8.1	20.0	ND
KRAS	NA	NA	25.0	7.7	4.9	0	8.1	0	ND
ALK	NA	NA	0	17.6	27.9	15.4	56.4	30.0	ND
Li (China, 2013)[a] [48]									
EGFR	57.1[b]		88.9	44.6	57.9	84.6	22.6	0	ND
KRAS	28.6[b]		11.1	14.1	13.2	0	21.0	44.4	ND
Song (China, 2013) [49]									
EGFR	0	16.7	72.2	42.1	40.5	73.9	16.7	NA	0
Yanagawa (Japan, 2014) [50]									
EGFR	62	60	77	49	50	43	28	0	NA
Russell (Australia, 2013) [51]									
EGFR	NA	NA	NA	44.0	0	38.0	5.0	NA	0
KRAS	NA	NA	NA	12.0	0	7.7	42.9	NA	0
Mansuet-Lupo (France, 2014) [11]									
EGFR	NA	NA	18.2	11.0	13.7	50.0	2.8	0	0
KRAS	NA	NA	27.3	31.4	32.9	25.0	33.0	75.0	0

AIS adenocarcinoma in situ, *MIA* minimally invasive adenocarcinoma, *LPA* lepidic predominant invasive adenocarcinoma, *APA* acinar predominant invasive adenocarcinoma, *PAP* papillary predominant invasive adenocarcinoma, *MPA* micropapillary predominant invasive adenocarcinoma, *SPA* solid predominant invasive adenocarcinoma, *IMA* invasive mucinous adenocarcinoma, *NA* not applicable due to no cases, *ND* not described

[a] Data from smokers

[b] Data from AIS + MIA

had an *EGFR* mutation, the patients with *EGFR*-mutated lung cancers were at lower risk of death than those without *EGFR* mutations ($p < 0.001$). When smokers and non-smokers were compared in Asian lung cancer patients, the *EGFR* mutation rate was found to have decreased, while the *KRAS* mutation rate increased with an increased cumulative smoking dose, measured in pack years (no. of packs/day × years of smoking) [48]: the respective mutation rates for <10, 11–20, 21–30, 31–40, 41–50 and >50 pack years were 74.2, 61.5, 39.7, 39.1, 30.4 and 15.1 % for *EGFR*, but 9.7, 7.6, 15.5, 19.6, 21.7 and 27.3 % for *KRAS*. Based on these findings, an *EGFR* mutation is considered to be a tobacco-unrelated good prognostic factor frequently seen in Asians, a *KRAS* mutation is considered to be a tobacco-related worse prognostic factor frequently seen in Caucasians.

The studies listed in Table 5 illustrate the following important points. First, the somatic mutations in lung adenocarcinoma differ by race or ethnicity. The frequency of *KRAS* mutations is high in Caucasians, whereas the frequency of *EGFR* mutations is high in Asians, regardless of the adenocarcinoma subtype. Concerning *EGFR* mutations and adenocarcinoma subtypes, the trends in mutation rates in PPA differed between Caucasians and Asians, being relatively high (36.1–68.5 %) in Asians and low (0–13.7 %) in Caucasians. In contrast, a *KRAS* mutation was commonly found at a high frequency in IMA cases in both Caucasians and Asians. The *EGFR* mutation rates in SPA were low (2.8–15.8 %) in both Caucasians and Asians [49]. Moreover, one study [56] reported an overall response rate for EGFR-TKI in *EGFR*-mutated SPA which was significantly worse than in other subtypes (61 vs. 88 %, $p = 0.03$), and the median progression-free survival and OS after EGFR-TKI treatment were significantly shorter for patients with SPA than for those with other subtypes of lung adenocarcinoma, suggesting that EGFR-TKI is less effective for SPA harboring an *EGFR* mutation. Patients undergoing EGFR-TKI therapy should, therefore, be treated after considering the adenocarcinoma subtype.

With regard to the histological features of lung cancer harboring the *ALK-EML4* fusion gene, *ALK*-rearranged tumors were associated with a younger age, frequent nodal metastasis and a higher stage of disease at diagnosis [47]. In addition, these *ALK*-rearranged tumors were more likely to be found in SPA (56.4 %), followed by IMA (30.0 %) and PPA (27.9 %), and were not observed in LPA (Table 5).

In a multivariate analysis, the most significant morphological features that distinguished *ALK*-rearranged tumors from *ALK*-negative tumors were cribriform formation, the presence of mucin-containing cells, a close relationship to adjacent bronchioles, the presence of psammoma bodies and the SPA subtype [47]. However, another study [17] showed the conflicting result that *ALK*-positive tumors were more frequently found in MPA (15.0 %) and APA (14.4 %) cases than SPA (6.5 %) cases. The mutation rates among adenocarcinomas in 349 female Chinese never-smokers were 76.2 % in *EGFR*, 4.3 % in *EML4-ALK* fusions, 4.6 % in *HER2*, 2.0 % in *KRAS* and 0.6 % in *BRAF* [57].

Future issues related to surgical treatments and adenocarcinoma subtypes

Subtypes with a better prognosis

Pure GGO lesions only detectable on chest CT, most of which belong to type A and type B in the Noguchi classification [6], can be cured by sublobar resection, such as wedge resection or segmentectomy [27, 28]. Since the new criteria have recategorized localized non- and slightly invasive small BACs as AIS and MIA, these two subtypes can be resected completely by limited resection without systematic nodal dissection, as described in a review article on the new adenocarcinoma subtypes [3]. A preoperative definite diagnosis of these subtypes by transbronchial biopsy or percutaneous needle biopsy is difficult, and a pathological diagnosis is usually obtained using the resected specimen after surgery. Thus, the most important preoperative information for the diagnosis of AIS and MIA is image analysis by high-resolution chest CT. AIS usually grows slowly, but the speed differs on a case-by-case basis, and a consensus on the optimum timing of the resection for AIS showing pure GGO has yet to be obtained.

Recently, cases showing multifocal AIS or MIA have been reported [58]. For lesions located in the periphery of the lung, multiple wedge resection for early lung cancers is a reasonable means of preserving the lung function. However, if multiple lesions are located near the hilum in different lobes, organ-sparing surgery is often difficult. In such cases, the timing of surgery and selection of surgical procedure should be done following a thorough evaluation of the clinical factors, including the patient age, speed of tumor growth and estimated postoperative residual lung function.

Lepidic predominant invasive adenocarcinoma is more often found in females, and lymph node metastasis is less common for LPA than for other non-lepidic subtypes [59]. In one study [60] which analyzed adenocarcinomas less than 20 mm in diameter, the 5-year DFS rate in 21 patients with LPA was 100 %, compared with 74 % in 43 patients with non-lepidic invasive adenocarcinomas ($p = 0.035$). Since the 5-year DFS and OS after the resection of LPA were around 90 % in most reports, limited resection and selected nodal dissection might be applicable for this subtype. A recent randomized trial which compared lymph node sampling with systematic nodal dissection for stage T1-2N0 nonhilar N1 NSCLC showed that systematic nodal dissection identified occult node-positive disease in 3.8 % of patients, but was not associated with a benefit in terms of the overall survival [61]. These results may support the omission of, or selective use of, mediastinal nodal dissection [62] for this less-invasive adenocarcinoma subtype, LPA. However, the presence of a residual tumor at the surgical margin should be carefully confirmed during surgery to prevent local recurrence, particularly when the tumor is large [18]. Even in small tumors showing GGO less than 2 cm in size, adenocarcinoma developed as cut-end recurrence in four of 26 patients who underwent limited resection more than 5 years after initial surgery [63]. The authors of that study concluded that limited resection should still be performed only in a trial setting, even for GGO lesions. Ongoing randomized trial comparing segmentectomy vs. lobectomy for small-sized peripheral NSCLC will provide useful information about the efficacy of limited resection [64].

Subtypes with a worse prognosis

The percentage of the micropapillary component was reported to be associated with local recurrence after limited lung resection: lung adenocarcinoma with a micropapillary component of 5 % or greater was associated with a greater risk of recurrence than that with a micropapillary component of less than 5 % (5-year cumulative incidence of recurrence, 34.2 vs. 12.4 %, $p < 0.001$) [21]. This report directly indicated that there is a histological characteristic of adenocarcinoma which rendered affected tumors unsuitable for limited resection. Since most adenocarcinoma subtypes can be pathologically diagnosed only by the resected specimen after surgery, the problem is, therefore, how to diagnose the adenocarcinoma subtypes preoperatively to enable selection of the proper surgical option. We emphasize the importance of a multidisciplinary tissue management strategy to obtain a preoperative diagnosis for tumor subtyping from small biopsy samples [65].

As the postoperative survival of MPA and SPA is significantly worse than that of other subtypes [10, 13, 66], combined therapy with surgery requires further discussion. MPA and SPA are common in tumors greater than stage I, and a size $\geq$2.5 cm, pure solid type and a SUVmax $\geq$ 7 are all predictors of a poor DFS [22].

A patient group with advanced-stage MPA + PPA + SPA showed a better response rate, progression-free survival and

OS to platinum-based chemotherapy than an LPA + APA group (36.9 vs. 25.4 %, $p = 0.034$; 6.4 vs. 5.5 months, $p = 0.009$, and 25 vs. 16.8 months, $p = 0.023$; respectively) [67]. This study concluded that patients with high-risk adenocarcinoma in advanced stages have a longer OS than patients with intermediate-risk adenocarcinoma, unlike the case in early stages, probably due to a better response to chemotherapy. If this is true, the ability of radical surgery with systematic lymph node dissection combined with induction or adjuvant chemotherapy to improve the survival of SPA or MPA should be confirmed in future. Although their prognosis is generally worse than that of other subtypes, MPA and SPA show differences in genetic aberrations: the *EGFR* mutation rate is higher in MPA than SPA, whereas *KRAS* mutations are more common in SPA. Therapeutic strategies, including the use of EGFR-TKI, should therefore be differentially considered for MPA and SPA.

Future directions

The strategies used to treat lung adenocarcinoma should be planned after considering the new IASLC/ATS/ERS classification for adenocarcinoma subtypes. Particularly for chest surgeons, the important considerations in surgery for lung adenocarcinoma include the extent of lung resection, omission of nodal dissection and appropriateness of combined therapy [68–70]. After the new classification has been validated, additional knowledge will allow the subtyping to be further improved and refined, and for a consensus to be reached regarding the optimum treatment of each subtype.

References

1. Asamura H, Goya T, Koshiishi Y, Sohara Y, Eguchi K, Mori M, et al. A Japanese Lung Cancer Registry study: prognosis of 13,010 resected lung cancers. J Thorac Oncol. 2008;3:46–52.
2. Nakamura H, Saji H. A worldwide trend of increasing primary adenocarcinoma of the lung. Surg Today. 2014;44:1004–12.
3. Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger KR, Yatabe Y, 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. 2011;6:244–85.
4. Colby TV, Noguchi M, Henschke C, Vazquez MF, Geisinger K, Yokose T, et al. Adenocarcinoma. In: Travis WD, Brambilla E, Muller-Hermelink KH, Harris CC, editors. Pathology and genetics of tumors of the lung, pleura, thymus and heart. Lyon: IARC-Press; 2004. p. 35–44.
5. Zell JA, Ou SH, Ziogas A, Anton-Culver H. Epidemiology of bronchioloalveolar carcinoma: improvement in survival after release of the 1999 WHO classification of lung tumors. J Clin Oncol. 2005;23:8396–405.
6. Noguchi M, Morikawa A, Kawasaki M, Matsuno Y, Yamada T, Hirohashi S, et al. Small adenocarcinoma of the lung. Histologic characteristics and prognosis. Cancer. 1995;75:2844–52.
7. Travis WD, Brambilla E, Riely GJ. New pathologic classification of lung cancer: relevance for clinical practice and clinical trials. J Clin Oncol. 2013;31:992–1001.
8. Russell PA, Wainer Z, Wright GM, Daniels M, Conron M, Williams RA. Does lung adenocarcinoma subtype predict patient survival? A clinicopathologic study based on the new International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary lung adenocarcinoma classification. J Thorac Oncol. 2011;6:1496–504.
9. Yoshizawa A, Motoi N, Riely GJ, Sima CS, Gerald WL, Kris MG, et al. Impact of proposed IASLC/ATS/ERS classification of lung adenocarcinoma: prognostic subgroups and implications for further revision of staging based on analysis of 514 stage I cases. Mod Pathol. 2011;24:653–64.
10. Warth A, Muley T, Meister M, Stenzinger A, Thomas M, Schirmacher P, et al. The novel histologic International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification system of lung adenocarcinoma is a stage-independent predictor of survival. J Clin Oncol. 2012;30:1438–46.
11. Mansuet-Lupo A, Bobbio A, Blons H, Becht E, Ouakrim H, Didelot A, 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;146:633–43.
12. Gu J, Lu C, Guo J, Chen L, Chu Y, Ji Y, et al. Prognostic significance of the IASLC/ATS/ERS classification in Chinese patients-A single institution retrospective study of 292 lung adenocarcinoma. J Surg Oncol. 2013;107:474–80.
13. Song Z, Zhu H, Guo Z, Wu W, Sun W, Zhang Y. Prognostic value of the IASLC/ATS/ERS classification in stage I lung adenocarcinoma patients–based on a hospital study in China. Eur J Surg Oncol. 2013;39:1262–8.
14. Hung JJ, Jeng WJ, Chou TY, Hsu WH, Wu KJ, Huang BS, et al. Prognostic value of the new International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society lung adenocarcinoma classification on death and recurrence in completely resected stage I lung adenocarcinoma. Ann Surg. 2013;258:1079–86.
15. Lee HJ, Kim YT, Kang CH, Zhao B, Tan Y, Schwartz LH, et al. Epidermal growth factor receptor mutation in lung adenocarcinomas: relationship with CT characteristics and histologic subtypes. Radiology. 2013;268:254–64.
16. Yoshizawa A, Sumiyoshi S, Sonobe M, Kobayashi M, Fujimoto M, Kawakami F, et al. Validation of the IASLC/ATS/ERS lung adenocarcinoma classification for prognosis and association with EGFR and KRAS gene mutations: analysis of 440 Japanese patients. J Thorac Oncol. 2013;8:52–61.
17. Tsuta K, Kawago M, Inoue E, Yoshida A, Takahashi F, Sakurai H, et al. The utility of the proposed IASLC/ATS/ERS lung adenocarcinoma subtypes for disease prognosis and correlation of driver gene alterations. Lung Cancer. 2013;81:371–6.
18. Kadota K, Villena-Vargas J, Yoshizawa A, Motoi N, Sima CS, Riely GJ, et al. Prognostic significance of adenocarcinoma in situ, minimally invasive adenocarcinoma, and nonmucinous lepidic predominant invasive adenocarcinoma of the lung in patients with stage I disease. Am J Surg Pathol. 2014;38:448–60.
19. Kawaguchi T, Matsumura A, Fukai S, Tamura A, Saito R, Zell JA, et al. Japanese ethnicity compared with Caucasian ethnicity and never-smoking status are independent favorable prognostic factors for overall survival in non-small cell lung cancer: a collaborative epidemiologic study of the National Hospital Organization Study Group for Lung Cancer (NHSGLC) in Japan and a Southern California Regional Cancer Registry databases. J Thorac Oncol. 2010;5:1001–10.

20. Hwang DH, Szeto DP, Perry AS, Bruce JL, Sholl LM. Pulmonary Large Cell Carcinoma Lacking Squamous Differentiation Is Clinicopathologically Indistinguishable From Solid-Subtype Adenocarcinoma. Arch Pathol Lab Med. 2013;138:626–35.
21. Nitadori J, Bograd AJ, Kadota K, Sima CS, Rizk NP, Morales EA, et al. Impact of micropapillary histologic subtype in selecting limited resection vs lobectomy for lung adenocarcinoma of 2 cm or smaller. J Natl Cancer. 2013;1(105):1212–20.
22. Cha MJ, Lee HY, Lee KS, Jeong JY, Han J, Shim YM, et al. Micropapillary and solid subtypes of invasive lung adenocarcinoma: clinical predictors of histopathology and outcome. J Thorac Cardiovasc Surg. 2014;147:921–8.
23. Warth A, Cortis J, Fink L, Fisseler-Eckhoff A, Geddert H, Hager T, et al. Training increases concordance in classifying pulmonary adenocarcinomas according to the novel IASLC/ATS/ERS classification. Virchows Arch. 2012;461:185–93.
24. Honda T, Kondo T, Murakami S, Saito H, Oshita F, Ito H, et al. Radiographic and pathological analysis of small lung adenocarcinoma using the new IASLC classification. Clin Radiol. 2012;2013(68):e21–6. doi:10.1016/j.crad.2012.09.002.
25. Kadota K, Colovos C, Suzuki K, Rizk NP, Dunphy MP, Zabor EC, et al. FDG-PET SUVmax combined with IASLC/ATS/ERS histologic classification improves the prognostic stratification of patients with stage I lung adenocarcinoma. Ann Surg Oncol. 2012;19:3598–605.
26. Godoy MC, Naidich DP. Overview and strategic management of subsolid pulmonary nodules. J Thorac Imaging. 2012;27:240–8.
27. Nakamura H, Saji H, Ogata A, Saijo T, Okada S, Kato H. Lung cancer patients showing pure ground-glass opacity on computed tomography are good candidates for wedge resection. Lung Cancer. 2004;44:61–8.
28. Nakata M, Sawada S, Yamashita M, Saeki H, Kurita A, Takashima S, et al. Objective radiologic analysis of ground-glass opacity aimed at curative limited resection for small peripheral non-small cell lung cancer. J Thorac Cardiovasc Surg. 2005;129:1226–31.
29. Yoshida J, Nagai K, Yokose T, Nishimura M, Kakinuma R, Ohmatsu H, et al. Limited resection trial for pulmonary ground-glass opacity nodules: fifty-case experience. J Thorac Cardiovasc Surg. 2005;129:991–6.
30. Nakamura H, Hirata T, Taguchi M, Kitamura H. Ground-glass opacities showing an adenoma-to-carcinoma sequence in the lung. Gen Thorac Cardiovasc Surg. 2008;56:421–3.
31. Kadota K, Yeh YC, Sima CS, Rusch VW, Moreira AL, Adusumilli PS, et al. The cribriform pattern identifies a subset of acinar predominant tumors with poor prognosis in patients with stage I lung adenocarcinoma: a conceptual proposal to classify cribriform predominant tumors as a distinct histologic subtype. Mod Pathol. 2014;27:690–700.
32. Westaway DD, Toon CW, Farzin M, Sioson L, Watson N, Brady PW, et al. The International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society grading system has limited prognostic significance in advanced resected pulmonary adenocarcinoma. Pathology. 2013;45:553–8.
33. Lynch T, Bell D, Sordella R, Gurubhagavatula S, Okimoto R, Brannigan B, 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;350:2129–39.
34. Paez J, Janne P, Lee J, Tracy S, Greulich H, Gabriel S, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science. 2004;304:1497–500.
35. Rodenhuis S, Slebos RJ, Boot AJ, Evers SG, Mooi WJ, Wagenaar SS, et al. Incidence and possible clinical significance of K-ras oncogene activation in adenocarcinoma of the human lung. Cancer Res. 1988;48:5738–41.
36. Slebos RJ, Kibbelaar RE, Dalesio O, Kooistra A, Stam J, Meijer CJ, et al. K-ras oncogene activation as a prognostic marker in adenocarcinoma of the lung. N Engl J Med. 1990;323:561–5.
37. Soda M, Choi YL, Enomoto M, Takada S, Yamashita Y, Ishikawa S, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature. 2007;448:561–6.
38. Oxnard GR, Binder A, Janne PA. New targetable oncogenes in non-small-cell lung cancer. J Clin Oncol. 2013;31:1097–104.
39. Serizawa M, Koh Y, Kenmotsu H, Isaka M, Murakami H, Akamatsu H, et al. Assessment of mutational profile of Japanese lung adenocarcinoma patients by multitarget assays: a prospective, single-institute study. Cancer. 2014;120:1471–81.
40. Wang R, Pan Y, Li C, Zhang H, Garfield D, Li Y, et al. Analysis of Major Known Driver Mutations and Prognosis in Resected Adenosquamous Lung Carcinomas. J Thorac Oncol. 2014;9:760–8.
41. Shames DS, Wistuba II. The evolving genomic classification of lung cancer. J Pathol. 2014;232:121–33.
42. Goss GD, O'Callaghan C, Lorimer I, Tsao MS, Masters GA, Jett J, et al. Gefitinib versus placebo in completely resected non-small-cell lung cancer: results of the NCIC CTG BR19 study. J Clin Oncol. 2013;31:3320–6.
43. Inoue A, Kobayashi K, Maemondo M, Sugawara S, Oizumi S, Isobe H, et al. Updated overall survival results from a randomized phase III trial comparing gefitinib with carboplatin-paclitaxel for chemo-naive non-small cell lung cancer with sensitive EGFR gene mutations (NEJ002). Ann Oncol. 2013;24:54–9.
44. Kwak EL, Bang YJ, Camidge DR, Shaw AT, Solomon B, Maki RG, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med. 2010;363:1693–703.
45. Camidge DR, Bang YJ, Kwak EL, Iafrate AJ, Varella-Garcia M, Fox SB, et al. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. Lancet Oncol. 2012;13:1011–9.
46. Shaw AT, Kim DW, Mehra R, Tan DS, Felip E, Chow LQ, et al. Ceritinib in ALK-rearranged non-small-cell lung cancer. N Engl J Med. 2014;370:1189–97.
47. Kim H, Jang SJ, Chung DH, Yoo SB, Sun P, Jin Y, et al. A comprehensive comparative analysis of the histomorphological features of ALK-rearranged lung adenocarcinoma based on driver oncogene mutations: frequent expression of epithelial-mesenchymal transition markers than other genotype. PloS One. 2013;8:e76999. doi:10.1371/journal.pone.0076999.
48. Li H, Pan Y, Li Y, Li C, Wang R, Hu H, et al. Frequency of well-identified oncogenic driver mutations in lung adenocarcinoma of smokers varies with histological subtypes and graduated smoking dose. Lung Cancer. 2013;79:8–13.
49. 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;30:645. doi:10.1007/s12032-013-0645-1.
50. 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;98:453–8.
51. Russell PA, Barnett SA, Walkiewicz M, Wainer Z, Conron M, Wright GM, 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. 2013;8:461–8.
52. Meng D, Yuan M, Li X, Chen L, Yang J, Zhao X, et al. Prognostic value of K-RAS mutations in patients with non-small cell lung cancer: a systematic review with meta-analysis. Lung Cancer. 2013;81:1–10.

53. Izar B, Sequist L, Lee M, Muzikansky A, Heist R, Iafrate J, et al. The impact of EGFR mutation status on outcomes in patients with resected stage I non-small cell lung cancers. Ann Thorac Surg. 2013;96:962–8.
54. Sonobe M, Kobayashi M, Ishikawa M, Kikuchi R, Nakayama E, Takahashi T, et al. Impact of KRAS and EGFR gene mutations on recurrence and survival in patients with surgically resected lung adenocarcinomas. Ann Surg Oncol. 2012;19(Suppl 3):S347–54.
55. D'Angelo SP, Janjigian YY, Ahye N, Riely GJ, Chaft JE, Sima CS, et al. Distinct clinical course of EGFR-mutant resected lung cancers: results of testing of 1118 surgical specimens and effects of adjuvant gefitinib and erlotinib. J Thorac Oncol. 2012;7:1815–22.
56. Yoshida T, Ishii G, Goto K, Yoh K, Niho S, Umemura S, et al. Solid predominant histology predicts EGFR tyrosine kinase inhibitor response in patients with EGFR mutation-positive lung adenocarcinoma. J Cancer Res Clin. 2013;139:1691–700.
57. Zhang Y, Sun Y, Pan Y, Li C, Shen L, Li 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. 2012;18:1947–53.
58. Sim HJ, Choi SH, Chae EJ, Kim HR, Kim YH, Kim DK, et al. Surgical management of pulmonary adenocarcinoma presenting as a pure ground-glass nodule. Eur J Cardiothorac Surg 2014 Feb 23 [Epub ahead of print].
59. Hu HD, Wan MY, Xu CH, Zhan P, Zou J, Zhang QQ, et al. Histological subtypes of solitary pulmonary nodules of adenocarcinoma and their clinical relevance. J Thorac Dis. 2013;5:841–6.
60. Araki K, Kidokoro Y, Hosoya K, Wakahara M, Matsuoka Y, Takagi Y, et al. Excellent prognosis of lepidic-predominant lung adenocarcinoma: low incidence of lymphatic vessel invasion as a key factor. Anticancer Res. 2014;34:3153–6.
61. Darling GE, Allen MS, Decker PA, Ballman K, Malthaner RA, Inculet RI, et al. Randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in the patient with N0 or N1 (less than hilar) non-small cell carcinoma: results of the American College of Surgery Oncology Group Z0030 Trial. J Thorac Cardiov Surg. 2011;141:662–70.
62. Shapiro M, Kadakia S, Lim J, Breglio A, Wisnivesky JP, Kaufman A, et al. Lobe-specific mediastinal nodal dissection is sufficient during lobectomy by video-assisted thoracic surgery or thoracotomy for early-stage lung cancer. Chest. 2013;144:1615–21.
63. Nakao M, Yoshida J, Goto K, Ishii G, Kawase A, Aokage K, et al. Long-term outcomes of 50 cases of limited-resection trial for pulmonary ground-glass opacity nodules. J Thorac Oncol. 2012;7:1563–6.
64. Nakamura K, Saji H, Nakajima R, Okada M, Asamura H, Shibata T, et al. A phase III randomized trial of lobectomy versus limited resection for small-sized peripheral non-small cell lung cancer (JCOG0802/WJOG4607L). Jpn J Clin Oncol. 2010;40:271–4.
65. Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger K, Yatabe Y, et al. Diagnosis of lung cancer in small biopsies and cytology: implications of the 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification. Arch Pathol Lab Med. 2013;137:668–84.
66. Woo T, Okudela K, Mitsui H, Tajiri M, Yamamoto T, Rino Y, et al. Prognostic value of the IASLC/ATS/ERS classification of lung adenocarcinoma in stage I disease of Japanese cases. Pathol Int. 2012;62:785–91.
67. Campos-Parra AD, Aviles A, Contreras-Reyes S, Rojas-Marin CE, Sanchez-Reyes R, Borbolla-Escoboza RJ, et al. Relevance of the novel IASLC/ATS/ERS classification of lung adenocarcinoma in advanced disease. Eur Respir J. 2014;43:1439–47.
68. Yoshino I. Substantial risk affects the stage-dependent outcomes of cisplatin-based adjuvant chemotherapy for completely resected non-small cell lung cancer. Surg Today. 2014;44:302–6.
69. Yasuda M, Nagashima A, Haro A, Saitoh G. Treatment of the postoperative recurrence of lung cancer in octogenarians. Surg Today. 2014;44:1626–32.
70. Uramoto H, Shimokawa H, Hanagiri T, Ichiki Y, Tanaka F. Factors predicting the surgical outcome in patients with T3/4 lung cancer. Surg Today. 2014. doi:10.1007/s00595-014-0861-0.