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Impact of histopathological subtypes on invasive lung adenocarcinoma: from epidemiology to tumour microenvironment to therapeutic strategies

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Abstract

Lung adenocarcinoma is the most prevalent type of lung cancer, with invasive lung adenocarcinoma being the most common subtype. Screening and early treatment of high-risk individuals have improved survival; however, significant differences in prognosis still exist among patients at the same stage, especially in the early stages. Invasive lung adenocarcinoma has different histological morphologies and biological characteristics that can distinguish its prognosis. Notably, several studies have found that the pathological subtypes of invasive lung adenocarcinoma are closely associated with clinical treatment. This review summarised the distribution of various pathological subtypes of invasive lung adenocarcinoma in the population and their relationship with sex, smoking, imaging features, and other histological characteristics. We comprehensively analysed the genetic characteristics and biomarkers of the different pathological subtypes of invasive lung adenocarcinoma. Understanding the interaction between the pathological subtypes of invasive lung adenocarcinoma and the tumour microenvironment helps to reveal new therapeutic targets for lung adenocarcinoma. We also extensively reviewed the prognosis of various pathological subtypes and their effects on selecting surgical methods and adjuvant therapy and explored future treatment strategies.

Keywords Tumour microenvironment, Lung adenocarcinoma, Subtype, Histological, Pathology

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Introduction

Lung cancer is associated with most of the cancer-related deaths, and lung adenocarcinoma is the most prevalent histological type, accounting for >40% [1–3]. The pathological classification of lung tumours has been revised several times [4–8] (Fig. 1), and the five pathological subtypes of lung adenocarcinoma (lepidic, acinar, papillary, micropapillary, and solid), defined using predominant histopathological patterns, account for >90% of lung adenocarcinomas [9–12]. Pathological subtypes can distinguish prognosis, predict the efficacy of adjuvant therapy, guide the selection of surgical methods, reveal the law of clinical evolution to help accurately diagnose and treat tumours; however, controversies still exist [13–18]. Considering the differences in sample sizes, inclusion criteria, regions, and study results for the different pathological subtypes of invasive lung adenocarcinoma, here, we discuss these epidemiological features, biological characteristics, and impact on the clinical treatment to provide important insight and help to understand their distribution in the population, histological evolution, and clinical treatment decisions.

Epidemiological characteristics

Distribution in the population

Invasive lung adenocarcinomas are gradually becoming more aggressive and less differentiated distributions from lepidic to acinar/papillary to micropapillary/solid subtypes [6, 19]. Generally, the acinar subtype is the most prevalent; however, the papillary subtype has also been reported in some cases, which may be attributed to variability in the morphology of the acinar/papillary subtypes, leading to interobserver interpretation differences [20–26] (Table 1 and Supplementary Fig. 1). With the increase of invasive tumor size, lepidic patterns and subtypes decreased while solid patterns and subtypes increased [23, 27]. With an increase in the tumour stage, lepidic subtypes gradually decreased, and micropapillary/solid subtypes gradually increased [21].

Micropapillary/solid subtypes have poor prognosis; however, they account for a low proportion of invasive lung adenocarcinomas. The presence of micropapillary/solid patterns (>5% but not predominant), which are more frequent, also leads to poor prognosis. Therefore, these micropapillary/solid patterns must be clarified. A study including stage I-III lung adenocarcinomas

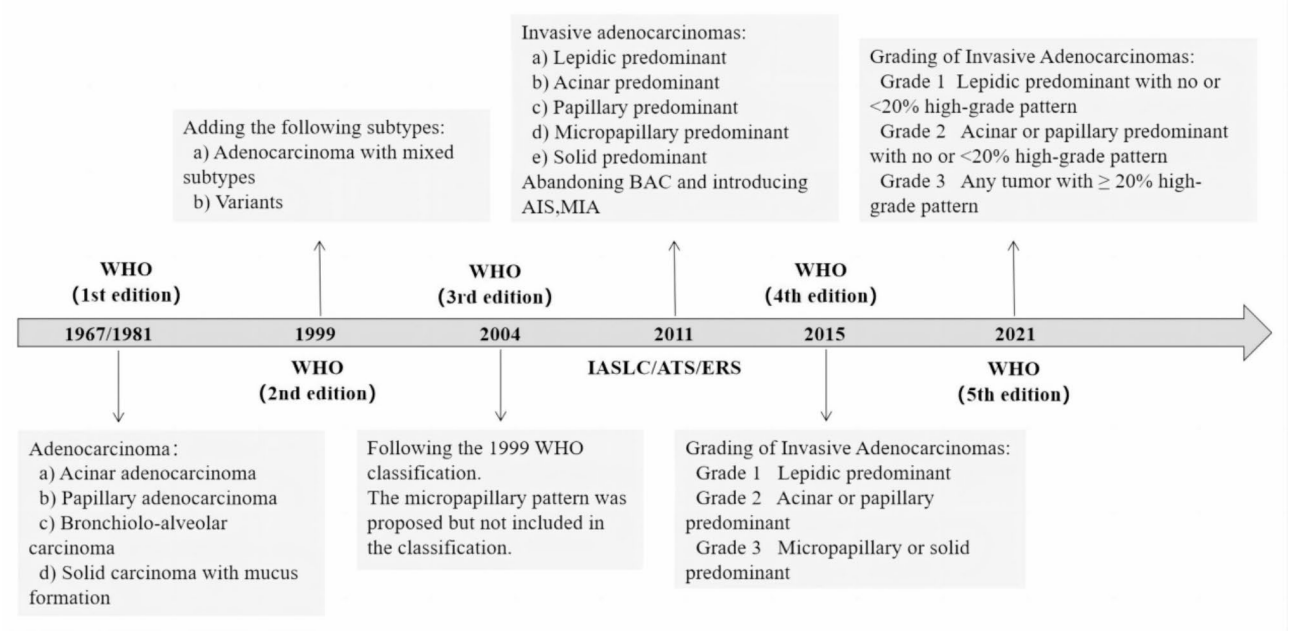

Fig. 1 The brief timeline of editions in pathological classification of lung adenocarcinoma[1]. *Abbreviations*: WHO, World Health Organization; IASLC/ATS/ERS, the International Association for the Study of Lung Cancer, American Thoracic Society and European Respiratory Society; BAC, bronchioloalveolar carcinoma; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma

[1] The original World Health Organization (WHO) version of lung tumours in 1967 and 1981 divided adenocarcinoma into four categories: acinar, papillary, bronchioloalveolar carcinoma (BAC), and solid cancer with mucous formation. The 3rd edition of 2004 continued the classification of mixed subtypes in 1999 and introduced micropapillary subtypes but did not include them in the classification. In 2011, the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society (IASLC/ATS/ERS) abandoned BAC, introduced adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), lepidic and micropapillary subtypes, and suggested that lung adenocarcinoma should be defined by major pathological subtypes. The 4th edition of the WHO classification in 2015 followed the new classification proposed by IASLC/ATS/ERS and proposed a grading system based on major pathological subtypes. The 5th edition of the 2021 classification emphasised the heterogeneity of lung adenocarcinoma and the influence of high-grade components, proposing a new grading system that combined major subtypes and high-grade components.

Table 1 The distribution of pathological subtypes of invasive lung adenocarcinoma

First author (year)	Number of patients	Stage	Pathological subtypes of lung adenocarcinoma (*n*)					
			Lepidic	Acinar	Papillary	Micro-papillary	Solid	Others*
Jeon (2021)	429	IA	195	184	34	2	14	—
Wang (2018)	1965	IA	177	878	743	8	61	98
Ito (2017)	324	IA	108	54	59	4	28	71
Hung (2014)	142	IA	16	55	49	14	8	—
Zhang (2013)	176	IA	14	40	72	10	12	28
Murakami (2015)	354	IA	109	61	70	6	30	78
Tsubokawa (2016)	347	IA	180	64	67	6	30	—
Zhao (2015)	201	IA	19	128	14	8	32	—
Luo (2016)	928	IB	6	473	361	12	76	—
Nitadori (2013)	734	IA1	125	308	135	43	94	29
Yoshiya (2016)	153	IA1	64	38	31	2	18	—
Kameda (2018)	1272	IA	171	613	251	69	168	—
Jeon (2022)	187	I	16	95	20	13	42	1
Ma (2021)	182	I	40	80	36	5	18	3
Moreira (2020)	496	I	87	206	79	34	61	29
Emoto (2019)	1468	I	159	676	258	144	231	—
Kadota (2019)	490	I	73	30	179	12	32	164
Kameda (2018)	1639	I	182	786	314	91	266	—
Chen (2018)	3308	I	319	1600	1239	17	133	—
Dai (2017)	235	I	83	99	41	2	10	—
Oskarsdottir (2016)	159	I	39	67	12	0	32	9
Ujiie (2015)	1120	I	137	453	244	68	146	72
Duhig (2015)	145	I	10	64	33	1	37	—
Hung (2014)	374	I	30	133	116	57	38	—
Kadota (2014)	1038	I	103	411	239	60	136	89
Song (2015)	261	I	19	76	80	42	34	10
Yoshizawa (2011)	514	I	29	232	143	12	67	31
Woo (2012)	179	I	43	59	16	1	12	48
Kameda (2018)	65	IIA	0	21	14	4	26	—
Hung (2014)	81	II	3	28	18	20	12	—
Oskarsdottir (2016)	82	II	11	38	5	1	26	1
Ito (2022)	2863	I-IIIA	521	537	1161	63	224	357
Rokutan-Kurata (2021)	1002	I-IIIA	133	98	539	36	154	42
Yoshizawa (2013)	440	I-IIIA	36	61	179	19	78	67
Oskarsdottir (2016)	285	I-IIIA	55	129	21	3	65	12
Westaway (2013)	152	I-IIIA	15	71	6	7	46	—
Moreira (2020)	300	I-IIIB	30	131	47	16	67	9
Sereno (2021)	620	I-III	73	249	89	14	169	26
Qiu (2022)	589	I-III	46	200	89	35	155	64
Bertoglio (2021)	431	I-III	69	203	67	9	83	—
Zhu (2021)	461	I-III	104	217	67	36	37	—
Yaldiz (2019)	491	I-III	75	150	80	5	158	23
Kim (2019)	301	I-III	23	152	41	29	56	—
Zhang (2019)	279	I-III	22	117	45	19	76	—
Qu (2019)	395	I-III	21	145	63	62	104	—
Kuang (2018)	356	I-III	36	172	47	61	40	—
Yanagawa (2016)	531	I-III	95	106	157	11	55	107
Lee (2015)	525	I-III	51	277	62	21	114	—
Tsao (2015)	575	I-III	23	148	99	39	266	—
Russell (2011)	210	I-III	10	84	26	14	49	27
Gu (2013)	292	I-III	31	112	36	30	52	31

Table 1 (continued)

First author (year)	Number of patients	Stage	Pathological subtypes of lung adenocarcinoma (*n*)					
			Lepidic	Acinar	Papillary	Micro-papillary	Solid	Others*
Hung (2014)	573	I-III	35	193	155	112	78	35
Yanagawa (2014)	486	I-III	89	99	136	11	51	100
Bian (2019)	276	I-IV	36	78	51	62	49	—
Kadota (2019)	735	I-IV	73	36	233	31	61	301
Guo (2017)	268	I-IV	66	126	31	10	35	25
Makinen (2017)	112	I-IV	3	59	8	7	25	10
Zhao (2016)	1244	I-IV	158	598	170	68	171	79
Warth (2016)	674	I-IV	35	264	95	54	226	—
Warth (2012)	487	I-IV	41	207	23	33	183	—
Mansuet-Lupo (2014)	407	I-IV	11	191	73	4	109	19
Watanabe (2015)	1852	I-IV	452	248	737	139	276	—
Tsuta (2013)	757	I-IV	136	98	338	61	124	147
Hu (2014)	981	I-IV	71	488	155	24	163	80
Da Cruz (2020)	253	IV	0	95	19	23	106	10

Others include AIS, MIA, invasive mucinous adenocarcinoma, colloid, cribriform, fetal and complex glands subtypes

showed that solid subtypes accounted for 10.4%, whereas micropapillary subtypes accounted for only 2.1%; however, the number of cases with solid and micropapillary patterns reached 18.3% and 9.4%, respectively [10]. In another study of stage I lung adenocarcinoma, solid and micropapillary subtypes were observed in only 4.3% and 0.9%, compared with 9.4% and 26.4% in cases with solid and micropapillary patterns, respectively [28]. Wang et al. [29] statistically analysed 6418 cases of lung adenocarcinoma ≤ 3 cm; they found 1.5% with micropapillary subtypes and 11.17% with micropapillary patterns. Another study also showed that micropapillary subtypes accounted for 3.1%, whereas the percentage with micropapillary patterns was as high as 38.4% [30].

Correlation with sex and smoking

A large retrospective study from Japan reported a higher proportion of males (64.4%) and smokers (74.0%) in micropapillary/solid subtypes, whereas a relatively lower proportion of males (44.3%) and smokers (43.2%) were found in lepidic subtypes [21]. Another Japanese study also found an increasing trend in the proportion of males and smokers from lepidic subtypes to micropapillary/solid subtypes, with the highest proportion in solid subtypes [31]. Two studies further found the highest proportion of males and smokers with solid subtypes, whereas micropapillary subtypes did not differ significantly from the other subtypes [26, 32]. Notably, studies from Asia have shown that lepidic subtypes are more common in females and non-smokers, whereas solid subtypes are more common in males and smokers [21, 31–34]. These data show that the pathological subtypes of invasive lung adenocarcinoma have a specific correlation with sex and smoking; however, due to differences in sample size and race, this association needs to be further confirmed using large-scale epidemiological investigations.

Correlation with other histological features

Malignant histological features of invasive lung adenocarcinomas, such as tumour spread through air spaces (STAS), pleural invasion, and lymphovascular invasion, are correlate with clinical features and pathological subtypes [35, 36]. A Korean study showed that STAS was most prevalent in micropapillary subtypes and rare in lepidic subtypes; this trend was observed in a Finnish study but was not statistically different [15, 34]. In lung adenocarcinomas with tumour diameter ≤ 3 cm, those with lepidic patterns < 50% presented more lymphovascular invasion and pleural invasion than those with lepidic patterns ≥ 50% [27]. Ito et al. [21] reported that lymphatic vessel, vascular, and pleural invasions tended to be more frequent in acinar/papillary and micropapillary/solid subtypes than in lepidic subtypes. Notably, several studies have reported similar results [26, 31, 34, 37]. In addition, micropapillary/solid subtypes have a higher mitotic count, indicating a poor prognosis [38]. These studies suggest that the aggressiveness of pathological subtypes is closely associated with histological features.

Correlation with imaging features

Invasive lung adenocarcinoma presents various imaging features, such as ground-glass opacity (GGO), mixed ground-glass opacity (mGGO), pure solid nodules, and air bronchogram, spiculation, lobulation, pleural retraction, vessel convergence sign, which are often associated with pathologic subtypes [39, 40].

Micropapillary/solid patterns were mainly present in the purely solid nodules and rarely in GGO. In a study

that included 1018 patients with GGO, no micropapillary or solid subtypes were found, and minimally invasive adenocarcinoma (MIA) was the most frequent in GGOs with nodules ≤ 20 mm and ≥ 50% ground glass appearance on CT imaging [40]. In this study, the incidence of micropapillary/solid patterns was 0.5% in GGO lung adenocarcinoma ≤ 2 cm, while the incidence of micropapillary/solid patterns was 9.5% in patients with lung adenocarcinoma ≤ 2 cm dominated by solid components. Another study found that 94 of 191 GGOs were invasive lung adenocarcinomas without micropapillary or solid subtypes, and 75% of pure GGOs were adenocarcinoma in situ (AIS) or MIA [41]. Similar results were obtained in several studies, whereas malignant features such as air bronchogram, spiculation, lobulation, pleural retraction, and signs of vessel convergence were more frequent in micropapillary/solid subtypes [39, 42–44].

On CT images, it is generally considered that GGO and solid components mainly reflect the non-invasive components of lepidic patterns and the invasive components represented by other histological patterns, respectively, but this is not absolute [45]. One study of 63 pure GGO lung adenocarcinomas found five were of acinar subtypes and three of papillary subtypes [46]. In a study of 146 cases of stage I invasive lung adenocarcinoma with pure GGO, 81 (55.5%) were of lepidic subtypes, 64 (43.8%) were of acinar/papillary subtypes, and 1 (0.7%) was a mucinous adenocarcinoma [47]. Ye et al. [48] found that among 501 cases of pure GGO, 31 had acinar/papillary patterns, and one each had mucinous adenocarcinoma and micropapillary/solid patterns. Ma et al. [49] found that the GGO ratio tended to be larger than the lepidic ratio, meaning that the clinical T stage based on the solid component's size on CT images tended to be lower than the pathological T stage, suggesting that the GGO component represented not only lepidic patterns but also other invasive histological patterns. In summary, while non-lepidic patterns can appear as GGO components on CT images, sometimes lepidic patterns can also appear as solid components on CT images.

The volume doubling time (VDT) and mass doubling time (MDT) of nodules on CT images can help determine the pathological type. The median VDT and MDT, respectively, were as follows: lepidic, 1140.6 and 970.1 days; acinar, 603.2 and 639.5 days; papillary, 599.0 and 624.3 days; solid/micropapillary, 232.7 and 221.8 days [43]. The tumour shadow disappearance rate (TDR) on CT images and the maximum standardised uptake value (SUVmax) on positron emission tomography (PET) were the lowest in lepidic subtypes and highest in micropapillary/solid subtypes [50]. The deep learning technology model based on CT image features of lung nodules shows superior efficiency in predicting pathological classification of lung adenocarcinoma [51, 52].

Biological characteristics

Genetic mutations

Epidermal growth factor receptor (EGFR)

Drugs that target driver alterations have improved the prognosis of lung adenocarcinoma, and some pathological patterns have been associated with specific gene mutations [53, 54]. EGFR mutations are the most typical driver gene mutations in Asian populations [55]. Notably, most studies have shown that the proportion of lepidic patterns positively correlates with EGFR mutations. However, the proportion of solid patterns negatively correlates with EGFR mutations, with the lowest EGFR mutation rate in solid subtypes and the highest in lepidic subtypes [56–59] (Table 2).

Kristen rat sarcoma viral oncogene (KRAS)

KRAS mutations, the most typical driver mutations in Western patients, are mutually exclusive to EGFR mutations and are found mostly in solid subtypes of invasive lung adenocarcinoma, but rarely in lepidic subtypes [60–63] (Supplementary Table 1). Rekhtman et al. [60] found that the incremental increase in the amount of solid patterns leaded to the enrichment of KRAS mutations, but they did not find a positive association between solid subtypes and KRAS mutations in another study of early-stage lung adenocarcinoma [64]. Considering that the differences in outcomes may be associated with populations, sample sizes, and inclusion and exclusion criteria, a meta-analysis of 27 studies showed that the mutation rate of KRAS in solid subtypes was significantly higher than that in lepidic subtypes, with a consistent correlation in Asian and non-Asian populations [56].

Anaplastic lymphoma kinase (ALK)

ALK rearrangement occurred in approximately 5% of lung adenocarcinomas [4, 65]. ALK rearrangement is more typical in solid subtypes and less common in lepidic subtypes [63, 66–68]. Cai et al. [68] analysed 629 lung adenocarcinomas and found no ALK mutation in lepidic subtypes. A study including 3224 lung adenocarcinomas found that the mutation rate of ALK was highest in solid (10.7%) and micropapillary (7.53%) subtypes and lowest in lepidic subtypes (1.00%) [63]. A Korean study showed that solid subtypes had the highest ALK mutation rate (6/50, 10.7%), and no ALK mutation was found in 23 lepidic subtypes [34]. Rodig et al. [66] also found that ALK mutations were more common in solid subtypes than in other subtypes.

Other genetic mutations

Similar to ALK, rare genetic mutations such as ROS1, RET, and MET are more typical in solid subtypes [65, 69–73]. BRAF V600E mutations are mainly found in micropapillary subtypes but rarely in lepidic and papillary

Table 2 Studies evaluating EGFR mutations in different pathological subtypes of invasive lung adenocarcinoma

First author (year)	Number of patients	Stage	Findings
Ito (2022)	2863	I-IIIA	The mutation rate of EGFR was highest in the lepidic subtype and lowest in the micropapillary/ solid subtype
Osawa (2021)	620	I	EGFR mutation correlated with the presence of lepidic or papillary component and the absence of acinar or solid component
Kim (2019)	301	I-III	The mutation rate of EGFR was highest in the lepidic subtype and lowest in the solid subtype
Zhao (2018)	1321	I-IV	The mutation rate of EGFR was higher in the acinar subtype
Dong (2016)	200	I-IV	EGFR mutation was positively associated with the acinar/papillary subtype and negatively associated with the solid subtype
Boukansa (2022)	150	I-IV	EGFR mutation was positively associated with the acinar/papillary subtype and negatively associated with the solid subtype
Wu (2016)	211	I-IV	EGFR mutation correlated with the presence of micropapillary /papillary component
Ding (2020)	215	I-IV	The mutation rate of EGFR was highest in the lepidic subtype and lowest in the solid subtype
Song (2013)	161	I-III	EGFR mutation was positively associated with the lepidic/ micropapillary subtype and negatively associated with the solid subtype
Yoshizawa (2013)	440	I-IIIA	EGFR mutation was positively associated with the lepidic/papillary subtype and negatively associated with the solid subtype
Hu (2014)	981	I-IV	The solid subtype was an independent predictor of a lower EGFR mutation rate
Tsuta (2013)	904	I-IV	EGFR mutation was positively associated with the papillary subtype and negatively associated with the solid subtype
Warth (2014)	425	I-IV	The mutation rate of EGFR was highest in the lepidic/micropapillary subtype and lowest in the solid subtype
Dong (2018)	610	I-IV	The mutation rate of EGFR was higher in the nonsolid subtype and lower in the solid subtype
Jiang (2019)	8824	I-IV	EGFR mutations was more common in the lepidic subtype and was rarely found in the solid subtype
Hong (2016)	250	I-IV	The mutation rate of EGFR was lowest in the solid subtype
Zhang (2014)	1302	I-III	The mutation rate of EGFR in lung adenocarcinoma with the presence of micropapillary component was 76.9%
Ito (2023)	877	I-II	EGFR mutation was more likely to be harbored in patients accompanied by > 5% lepidic component
Rekhtman(2013)	180	I-IV	EGFR mutation was positively associated with the proportion of lepidic component and negatively associated with the proportion of solid component

subtypes [63, 67, 74–76]. The mutation rates of these genes are relatively low and need to be verified using a large sample size. The TP53 mutation is the most prevalent tumour suppressor gene mutation in lung adenocarcinoma and is associated with cancer development and progression [77]. TP53 mutations occur in > 30% of lung adenocarcinomas, with mutation rates as high as > 60% in solid subtypes and approximately 10% in lepidic subtypes, consistent with the malignant progression of the pathological subtype [12, 34, 63].

Accurate prediction of gene expression based on pathological subtypes is still impossible, especially the correlation between rare gene mutations and pathological subtypes, which needs further confirmation; however, the gene mutation preference of pathological subtypes can be a guide for the clinical diagnosis and treatment selection of lung adenocarcinoma (Fig. 2).

Biomarkers

Protein expression and immunohistochemistry

Immunohistochemistry helps to identify the histological components of lung cancer, especially in poorly differentiated tumours [78, 79]. Thyroid transcription factor-1 (TTF-1) and Napsin A are markers of lung adenocarcinoma, whereas p63, p40, and CK5/6 are markers of lung squamous cell carcinoma [80]. When diagnosing poorly differentiated solid subtypes of lung adenocarcinoma, it is critical to establish that the tumour is a lung adenocarcinoma using TTF-1 and mucin staining [81]. Napsin A, a crucial marker of lung adenocarcinoma, rarely stains solid subtypes [82]. Tumours originating from club cells and TTF-1 expressing type II alveolar epithelial cells usually show GGO on CT, whereas those originating from the bronchial basal and mucous cells are TTF-1 negative and appear as solid nodules [6]. While TTF-1 expression was almost 100% in AIS, MIA and lepidic subtypes with GGO as the main image feature, it was slightly decreased in the acinar, papillary, micropapillary and solid subtypes [83, 84]. However, the slight difference in TTF-1 expression was not enough to distinguish the five major pathological subtypes, and Napsin A as an auxiliary indicator of TTF-1 also lacked specificity [6, 85].

A Japanese study found that the immunohistochemical expression of phosphorylated c-Met was positive in 22 of the 75 lung adenocarcinomas with ≥ 10% micropapillary patterns, whereas it was positive in only 5 of 50 lung

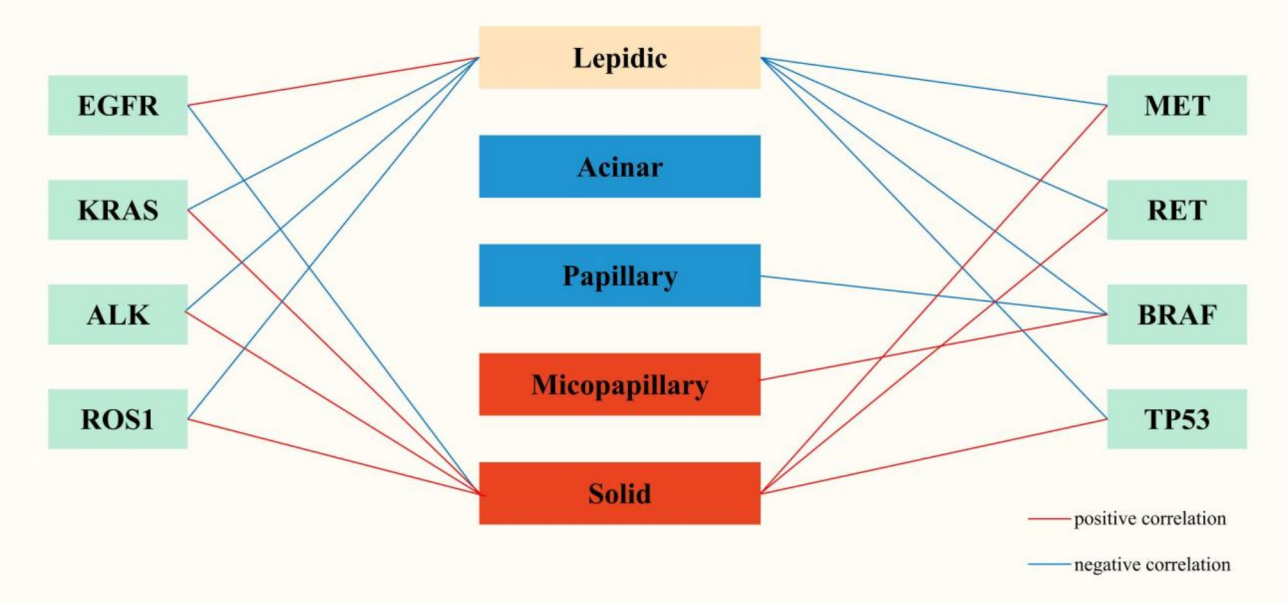

Fig. 2 Correlation between gene mutation and different pathological subtypes in invasive lung adenocarcinoma[1]

[1] Different pathological subtypes of invasive lung adenocarcinoma showed a correlation with gene mutation. The solid subtype showed opposite mutation characteristics of the lepidic subtype, the papillary subtype and the micropapillary subtype showed different BRAF mutation status. However, due to the strong histological heterogeneity of invasive lung adenocarcinoma, these possible mutational characteristics need to be further confirmed

adenocarcinomas with < 10% micropapillary patterns [86]. Another study found that cytoplasmic oestrogen receptors β (ERβ) expression was prevalent in micropapillary (61/94) and solid subtypes (56/72), but rare in lepidic subtypes (11/76), suggesting that cytoplasmic ERβ is associated with malignant progression and poor prognosis in lung adenocarcinoma [87]. Feng et al. [88] found that cyclin-dependent kinase subunit 2, a cell cycle-related protein associated with tumour progression and prognosis, had the highest expression in micropapillary subtypes and the lowest expression in lepidic subtypes. Another study found that C-X-C motif chemokine ligand 14 had a higher staining score in lung adenocarcinomas with micropapillary patterns than in those without [89]. However, the sensitivity and specificity of the above immunohistochemical indicators are insufficient to distinguish the five pathological subtypes of invasive lung adenocarcinoma.

Immunohistochemistry may be useful for the differential diagnosis of rare invasive mucinous, pulmonary colloid adenocarcinoma and pulmonary enteric adenocarcinomas [4, 85]. Invasive mucinous adenocarcinomas usually are CK7+, CK20+, HNF4α+, CDX2-, TTF-1-, and Napsin A- [4, 90, 91]. Colloid adenocarcinomas often co-express CDX2, TTF1, CK-7 and CK-20 [80, 92]. Primary pulmonary enteric adenocarcinomas express at least one intestinal differentiated immunohistochemical marker, such as CDX2, CK20, or MUC2, but more commonly CDX2+/CK7 + and TTF-1-/CK20-, and any combination is possible [93, 94].

Ki-67

Ki-67 has been widely used to evaluate tumour proliferation and is associated with poor prognosis [95, 96]. A study of stage I lung adenocarcinoma found that the median Ki-67 expression level was the highest (60%) in solid subtypes and the lowest (5%) in lepidic subtypes, all solid and micropapillary subtypes had Ki-67 expression levels ≥ 10%, 72.2% of solid subtypes had Ki-67 expression levels ≥ 50%, while none of the lepidic subtypes had Ki-67 expression levels ≥ 50% [96]. Another study found no statistical difference in disease-free survival (DFS) and overall survival (OS) of lepidic/acinar/papillary subtypes with Ki-67 expression ≥ 30% compared with micropapillary/solid subtypes [97].

Programmed cell death ligand 1 (PD-L1)

Overexpression of PD-L1 in tumour cells is a major mechanism of tumour immune escape; immune checkpoint inhibitors (ICIs) and targeting the PD-L1 pathway have shown significant clinical efficacy in treating lung cancer [98, 99]. PD-L1 expression, especially high expression, is more prevalent in solid subtypes but rarely appears in AIS, MIA, or lepidic subtypes [17, 58, 98]. A TCGA database study found that PD-L1 protein expression was significantly higher in solid subtypes than in other pathological subtypes by immunohistochemistry

[17]. Zhao et al. [58] reported PD-L1 positivity in only 1 of 23 lepidic subtypes, whereas solid subtypes had a higher PD-L1 positivity rate of 72.7%. Another study found that PD-L1 showed almost no expression in AIS and MIA, whereas 54.5% of solid subtypes had PD-L1 > 1% and 22.7% had PD-L1 ≥ 50%, only 7.8% of lepidic subtypes had PD-L1 > 1%, and no PD-L1 ≥ 50% was found [98].

Tumour mutational burden (TMB)

TMB is a new predictive biomarker for ICIs and is highest in solid subtypes [17, 100, 101]. Through next-generation sequencing of 604 lung adenocarcinomas with stage I to III, Caso et al. [102] found that median TMB increased with subtype invasiveness, and copy number amplifications of micropapillary/solid subtypes were significantly higher than that of lepidic subtypes ($p = 0.021$). Another study found that the proportion of high TMB in micropapillary/solid subtypes (12/23) was significantly higher than that in lepidic (8/95) and acinar/papillary subtypes (45/217) [103]. Dong et al. [17] found that the TMB of solid subtypes was much higher than that of other subtypes. Another Chinese study of stage I lung adenocarcinoma found the same results [77].

Tumour microenvironment

The tumour microenvironment (TME) is critical in regulating cancer progression and influencing therapeutic outcomes and varies among different pathological subtypes of lung adenocarcinomas [104] (Fig. 3).

Immune cells

Macrophages are the most abundant immune cell type in the TME, and tumour-associated macrophages (TAMs) promote tumour progression to malignancy [105]. TAMs was biased towards M2 type (alternatively activated), promoting tumour growth, invasion, and metastasis [106, 107]. Macrophages are enriched in solid and micropapillary morphology, while M2 macrophages play an important role in promoting histological progression [108]. Sorin et al. [105] found no significant differences in total lymphocyte counts among the five pathological subtypes, whereas the differences in myeloid cells were greater, especially the highest enrichment of CD163+ (a specific marker of M2 type) macrophages in solid subtypes. These results revealed macrophage phenotypic heterogeneity of lung adenocarcinoma histologic subtypes.

T cells are the core of mediating anti-tumor immunity, and their anti-tumor immune response depends on the interaction of CD4 + and CD8 + T cells with tumor

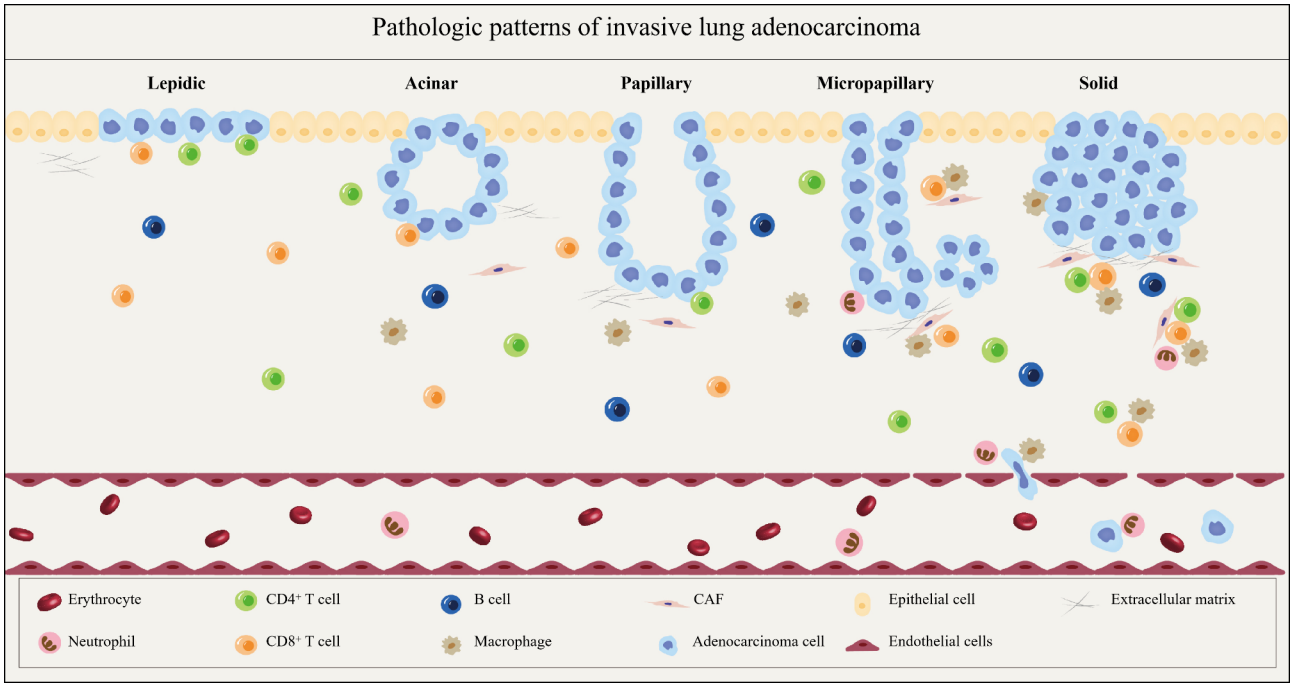

Fig. 3 Microenvironment regulation of the different pathologic patterns of invasive lung adenocarcinoma progression[1]. *Abbreviations*: CAF, cancer-associated fibroblast

[1] In the TMEs of different histopathological types, the number of lymphocytes was similar, but the interaction between lymphocytes was significantly different, and myeloid cells were more abundant in the solid subtype. CD8 + and CD4 + T cells interact more strongly with cancer cells in the lepidic subtype. In the high-grade subtype, the extracellular matrix (ECM) acts as a barrier to prevent immune cells from acting on cancer cells; however, neutrophils, endothelial cells, and macrophages interact more strongly with cancer cells, promoting tumour metastasis. Cancer-associated fibroblasts (CAFs) and M2 macrophages may play an important role in regulating histological progression.

antigens [109]. The amount of immune cells increased with the increase of malignancies, especially in solid subtypes, the immune cell infiltration of CD4 + T cells, CD8 + T cells, B cells (CD19+) and monocytes (CD11b+) was significantly higher than that of other subtypes [12]. Tavernari et al. [16] performed histopathology-guided multi-region sampling of 10 early primary lung adenocarcinomas and found that lymphoid and myeloid immune cells were enriched in solid patterns, which were highly associated with markers of T-cell exhaustion, suggesting that mechanisms of immune evasion occur in tumour samples with solid patterns. CD8 + T cells of the solid subtype have considerable cytotoxic activity; however, their annihilating ability is weakened by exhaustion and competitive hypoxia [110].

Cancer-associated fibroblasts (CAFs)

The histological progression of lung adenocarcinoma is spatially restricted and regulated by the TME but is not entirely a transition from low-grade to high-grade [11, 111]. Among all the stromal cells that populate the TME, CAFs are the most abundant and are critical in histological progression of lung adenocarcinomas [111, 112]. Sato et al. [111] injected A549 human lung adenocarcinoma cells into immunodeficient mices through four different routes and found that the tumours showed different histological subtypes of lung adenocarcinomas at various sites. They further found that solid subtype cells could form acinar subtype tumours after subcapsular injection, whereas solid subtype tumours could form after subcutaneous injection of acinar subtype cells. CAFs mediated paracrine TGF-β signalling induced this histological transformation process.

Spatial heterogeneity of TME

Single-cell technologies have revealed the complexity of the TME with unparalleled resolution, identifying differences between histological subtypes of lung adenocarcinoma [105, 110]. One single-cell sequencing study revealed that solid subtypes upregulate energy and substance metabolic activities, particularly folate-mediated one-carbon metabolism. The key gene methylenetetrahydrofolate dehydrogenase 2 (MTHFD2) could be a potential therapeutic target [110]. Signalling pathways associated with aggressiveness, metabolic activity, and immune response-related markers were also enriched in solid subtypes, suggesting that solid subtypes have a more powerful immune escape ability. But, invasive lung adenocarcinoma has extensive spatial heterogeneity [108].

The spatial relationship between cellular interactions has a greater prognostic value than cell frequency alone. Sorin et al. [105] found that the tendency of CD163 + macrophages and CD8 + T cells to interact was the strongest in high-grade subtypes, which was consistent with the role of CD163 + macrophages in suppressing CD8 + T cell function in the TME. The overall frequency of CD8 + and CD4 + T cells was not associated with disease progression; however, CD8 + and CD4 + T cells interacted more strongly with cancer cells in low-grade subtypes, and neutrophils and endothelial cells interacted more strongly with cancer cells in high-grade subtypes [105]. New single-cell resolution spatial transcriptomics will help further elucidate cellular interactions and cell state transitions in spatial architectures [108, 113, 114].

These findings demonstrate immune infiltration and alteration of the TME in histopathology from 'immune desert' at low-grade (lepidic) to 'immune activation' at mid-grade (acinar and papillary) to 'immune depletion' at high-grade (micropapillary, solid and complex glands). Proliferation and migration markers were enriched in solid subtypes, while development/morphogenesis markers were enriched in lepidic subtypes [16]. The intratumoural histological heterogeneity of invasive lung adenocarcinoma is consistent with the cancer cells' intrinsic characteristics and changes in the TME. The levels of hypoxia, acidification and glycolysis were higher in solid subtypes [110]. CAFs and hypoxic environments are critical in histological progression and immune infiltration of lung adenocarcinomas [110, 111, 115]. The lack of tumour-promoting stromal cells and reduced levels of specific expression of hypoxic markers are characteristic of lepidic subtypes, whereas the hypoxic environment and role of immunosuppressive macrophages may contribute to the immune depletion of solid subtypes [110, 116]. Neutrophil depletion can reduce tumour progression by attenuating macrophage recruitment and T-cell suppression while reducing lung squamous tumour growth and promoting the transformation to lung adenocarcinomas [117, 118]. However, involving neutrophils in the histological progression of invasive lung adenocarcinomas requires further investigation.

Clinical management

Prognosis

The TNM stage is the most typical grading system, and although it can better distinguish prognosis, it still gives a different prognosis for the same stage lung adenocarcinomas [25, 119]. Histopathological staging can help further differentiate the prognosis of lung adenocarcinoma. Lepidic subtypes had the best prognosis, similar to that of MIA; micropapillary/solid subtypes had the worst prognosis, and acinar/papillary subtypes were moderate. The results were inconsistent in individual studies due to different inclusion criteria and further potential differentiation of pathological subtypes, especially acinar/papillary subtypes (Supplementary Table 2).

Non-predominant histopathological patterns

Pathological subtypes named after the predominant histopathological patterns lead to the sometimes substantial neglect of the prognostic impact of other tumour histopathological patterns. The presence and proportion of lepidic patterns were positively correlated with prognosis, whereas the presence and proportion of micropapillary/solid patterns were negatively associated with prognosis [34, 120–122]. Moon et al. [123] found that the prognosis of stage I lung adenocarcinoma improved with the increase of lepidic patterns. A study including T1a-T1bN0M0 acinar/papillary subtypes found that the 5-year OS rate was 96.3% in the group with lepidic patterns as the second predominant component, 61.8% in the group with non-lepidic patterns as the second predominant component, while it was 96.8% in lepidic subtypes [124]. Another study also found that in acinar subtypes of stage IA, the group with ≥20% lepidic patterns had better OS and DFS than the one with <20% lepidic patterns [125]. A multicenter study found that pT1 lung adenocarcinomas with ≥5% micropapillary/solid patterns had poorer DFS and OS than those with <5% micropapillary/solid patterns and had a similar prognosis to pT2a [122]. A large-sample retrospective study found that the non-predominant solid group had worse DFS and OS than the solid absent group and similar to the solid predominant group in stage I lung adenocarcinoma [24]. Multiple studies have shown that non-predominant micropapillary/solid patterns, even ≥1%, can lead to a poor prognosis, suggesting that the focus should not be solely on micropapillary/solid subtypes [10, 126]. However, the cut-off values of micropapillary/solid patterns as prognostic factors and their spatial distribution in tumours need to be further investigated. A previous study also found that tumour marginal lepidic patterns were associated with a better prognosis, suggesting that inert tumour marginal patterns prevented tumour proliferation and invasion [127]. Whether high-grade patterns at the tumour margin or near the vasculature lead to more aggressive biological characteristics requires further investigation.

Protective effect of lepidic patterns

The prognosis of acinar/papillary subtypes with both lepidic and micropapillary/solid patterns is unclear. Hou et al. [128] divided acinar/papillary-predominant stage I lung adenocarcinomas into four groups based on lepidic and micropapillary/solid patterns: (a) lepidic + and micropapillary/solid -, (b) lepidic - and micropapillary/solid -, (c) lepidic + and micropapillary/solid +, and (d) lepidic - and micropapillary/solid + [128]. They found that the 5-year recurrence-free survival (RFS) rates in the four groups were 98.7%, 94.4%, 94.0%, and 81.9%, respectively, and the 5-year OS rates were 98.4%, 94.4%, 96.6% and 87.7%, respectively ($P < 0.001$). It could be seen that the prognosis was good when lepidic patterns and micropapillary/solid patterns were present simultaneously, and multivariate analysis showed that the lepidic - and micropapillary/solid + subtype was significantly associated with poorer RFS, indicating that lepidic patterns had a "protective role".

Other special histopathological patterns

However, some unique growth patterns associated with a poorer prognosis must be further distinguished, such as the cribriform, fused gland, and filigree patterns [129–131]. Cribriform growth patterns, first reported in lung cancer in 1978, are microscopically characterised as invasive back-to-back fused tumour glands with poorly formed glandular spaces lacking an intervening stroma or invasive tumour nests of tumour cells that produce glandular lumina without solid components [129, 132]. Cribriform subtypes have a higher rate of mitosis, necrosis, vascular, pleural, and lymphatic invasions and nuclear atypia than the traditional acinar subtypes and are more prone to lymph node metastasis [35, 132]. Cribriform growth patterns have been reported in 23.8–39.8% of invasive lung adenocarcinomas, and 6.8–60% of acinar subtypes can be categorised as cribriform subtypes, with cribriform subtypes accounting for 4.4–27.2% of lung adenocarcinomas, requiring high emphasis [25, 35, 132–135]. Fused glands were defined as glands with irregular borders, back-to-back glands without intervening stroma, or ribbon-like formations [130]. In the new international association for the study of lung cancer (IASLC) grading system, fused glands and cribriform patterns are categorised as high-grade patterns. However, the prognostic impact of fused glands remains controversial [130, 134, 136]. The filamentous pattern, defined as tumour cells growing in delicate, lace-like, narrow stacks of cells without fibrovascular cores, is a novel growth pattern identified recently with a prognosis similar to micropapillary subtypes [22, 131].

These histological growth patterns were highly correlated with prognosis and enriched the histopathological types of invasive lung adenocarcinomas, which helps to better guide clinical treatment [13]. It is also necessary to provide more precise guidance for determining histopathological morphology to reduce differences in pathological interpretations [22, 137]. The presence or proportion of high-grade subtypes may be conducive to prognostic differentiation and clinical applications [8, 13]. Cribriform growth patterns are associated with poor prognosis; however, further studies are required to determine whether a separate cribriform subtype is necessary [129, 132].

Effect on surgery

Lobectomy became the standard procedure for early-stage lung cancer based on the results of the clinical trial published in 1995; however, this trial had many shortcomings, including the absence of pathological differentiation and the lack of differentiation between segmentectomy and wedge resection in sublobectomy [138, 139]. With changes in the lung cancer spectrum, GGO lung cancer, which has biological characteristics different from those of pure solid lung cancer and has a better prognosis, has become the predominant type, requiring changes in surgical methods [140, 141]. MIA has been reported to have almost no lymph node metastasis, and the prognosis of sublobectomy is similar to that of lobectomy, with more lung function preserved [6, 142]. Different pathological subtypes of invasive lung adenocarcinoma have different lymph node metastasis and recurrence rates, which may benefit from different surgical methods.

Whether lobectomy can be avoided in lepidic subtypes?

Whether lobectomy can be avoided in lepidic subtypes with a prognosis similar to MIA requires further investigation. Wang et al. [143] found that 5-year RFS and OS in lepidic subtypes with tumour size ≤ 3 cm were not significantly different from those with lobotomy. In another study of 139 patients with stage I lepidic subtypes, none of whom had lymph node metastasis, patients who underwent limited mediastinal lymphadenectomy had a good prognosis comparable to those who underwent complete mediastinal lymphadenectomy [144]. In a large retrospective study of cT1-2N0M0 lepidic adenocarcinoma, 1544 (77.5%) patients underwent lobectomy, and 447 (22.5%) underwent sublobectomy [145]. No significant difference was seen in survival between patients who underwent sublobectomy with lymph node sampling and those who underwent lobectomy, suggesting the possibility of sublobectomy and limited mediastinal lymphadenectomy in lepidic subtypes [145]. Similarly, another postoperative analysis of pIA lung adenocarcinoma found no recurrence in lepidic subtypes after either lobectomy or sublobectomy at a median follow-up of 38.9 months [146]. Both these retrospective studies highlight the potential for sublobectomy and limited mediastinal lymphadenectomy for lepidic subtypes.

At present, most of the studies on the surgical methods for early lung cancer are based on tumour diameter and the consolidation-to-tumour ratio (CTR) on CT images. A multi-centre prospective clinical trial validated the specificity of mediastinal lymph node metastasis in cT1N0 invasive NSCLC, providing an important theoretical basis for the clinical application of limited mediastinal lymphadenectomy [147]. In this study, CTR ≤ 0.5, lepidic subtypes, and negative hilar nodes (stations 10–12) were used as predictors of negative mediastinal lymph nodes to accurately predict the status of all negative lymph nodes in the mediastinal region. Multiple previous studies have reported the effectiveness of sublobectomy in GGO lung cancer, which multiple prospective clinical trials have further confirmed that sublobectomy is safe and effective for lung cancer with tumour diameter ≤ 3 cm and CTR ≤ 0.5 [148–157] (Supplementary Table 3). GGO-dominated lung cancers were mostly of MIA and lepidic subtypes in these studies, suggesting the feasibility of sublobectomy and limited mediastinal lymphadenectomy for lepidic subtypes, but further verification was needed by high-quality prospective clinical trials [153].

Warning of micropapillary/solid patterns

The presence of micropapillary/solid patterns is associated with higher rates of lymph node and occult lymph node metastases, suggesting that lung adenocarcinomas containing micropapillary or solid patterns may benefit from lobectomy and complete mediastinal lymphadenectomy [9, 158–161]. Solid patterns are associated with extrathoracic recurrence, possibly reflecting an increased risk of blood transmission, whereas micropapillary patterns are associated with locoregional recurrence, suggesting that surgical margins are essential [9, 162]. An analysis of 734 patients with lung adenocarcinoma ≤ 2 cm showed no significant difference in cumulative incidence of relapse (CIR) during lobectomy between the micropapillary patterns ≥ 5% group and the micropapillary patterns < 5% group (19.1% vs. 12.9%, $P = 0.13$). When sublobectomy was performed, CIR in the ≥ 5% group was significantly higher than that in the < 5% group (34.2% vs. 12.4%, $P < 0.0001$). This suggests that sublobectomy may not be appropriate for lung adenocarcinoma with micropapillary patterns. Yao et al. [163] found that segmentectomy of lung adenocarcinoma ≤ 1 cm containing micropapillary patterns was similar to lobectomy, but that wedge resection had worse RFS and OS than segmentectomy and lobectomy, further suggesting that segmentectomy was still effective in smaller diameter lung adenocarcinoma with micropapillary patterns, but not suitable for wedge resection. Another study involving 1409 patients with invasive lung adenocarcinoma ≤ 1 cm also found that wedge resection yielded a significantly worse prognosis than anatomic resection in papillary and micropapillary/solid subtypes [164]. Xu et al. [165] found that the survival of the lobectomy group was better than that of the sublobectomy group and the survival of patients with systematic dissection was better than that of patients with limited lymph node dissection in lung adenocarcinomas ≤ 2 cm with micropapillary patterns > 5%. Therefore, more extensive resection may be

required for micropapillary/solid subtypes, even if the tumour diameter is ≤ 1 cm.

The effects of pathological patterns on the surgical methods used for early invasive lung adenocarcinoma need to be verified through more high-quality RCT studies. However, the representativeness and accuracy of preoperative biopsy and intraoperative frozen section (FS) diagnosis are critical factors affecting its research and application. FS diagnosis is superior to preoperative biopsy because it has more tissue for evaluation, which is an indispensable reference for tumour surgery, but misdiagnosis and misjudgment are inevitable [166]. The accuracy of FS diagnosis in differentiating invasive adenocarcinoma from AAH, AIS and MIA is as high as 93.7-95.9%, while that in differentiating major pathological subtypes is 68.0-94.0% [142, 147, 166–169]. A retrospective study found that FS diagnosis predicted major histological subtypes with an accuracy of 68% [166]. It showed poor sensitivity in identifying micropapillary patterns (37%), micropapillary subtypes (21%) and solid patterns (69%) and solid subtypes (79%), but encouraging specificity (94%, 99%; 96%, 94%). A study of 373 retrospective cases and 212 prospective multicenter cases found that the accuracy of FS in identifying the histological morphology of stage I lung adenocarcinoma was 79.1% and 89.6%, respectively [168]. Recently, a prospective study showed that FS was up to 94.0% accurate in diagnosing lepidic subtypes [147]. Multiple FSs can reduce the heterogeneity of lung adenocarcinoma and improve the diagnostic accuracy of pathological subtypes. An inflation method during cryosection could expand the alveolar space in FS and facilitate better identification of pathological subtypes [170, 171]. It is more feasible to identify the presence or absence of micropapillary/solid patterns than to quantify histological patterns and predict pathological subtypes [142, 172, 173]. Pathological subtyping of invasive lung adenocarcinomas has shown a specific role in guiding the selection of surgical methods; however, its effectiveness requires further research.

Adjuvant therapy

Adjuvant chemotherapy

Adjuvant chemotherapy is a vital lung cancer treatment; however, studies have shown that it only improves 5-year survival by 5% [174, 175]. The pathological subtypes of invasive lung adenocarcinoma correlate with the effect of adjuvant chemotherapy. By analysing the prognosis of 575 lung adenocarcinomas from four large clinical trials, Tsao et al. [176] found that adjuvant chemotherapy did not benefit the OS of all pathological subtypes; however, it only benefited the DFS of micropapillary/solid subtypes. In this study, OS among the different pathological subtypes in the observation group was the same, which was inconsistent with the results of most studies, and may the reason why micropapillary/solid subtypes had no benefit. Another study found that adjuvant chemotherapy improved OS in micropapillary/solid subtypes but not in acinar/papillary and lepidic subtypes, suggesting that micropapillary/solid subtypes can predict the efficacy of chemotherapy [177]. Adjuvant chemotherapy is not recommended for stage I lung adenocarcinomas. except for stage IB with high-risk factors. Studies have found that adjuvant chemotherapy may benefit stage IB micropapillary/solid subtypes [178–180]. Luo et al. [181] showed that adjuvant chemotherapy did not improve OS but significantly improved the DFS of stage IB micropapillary/solid subtypes based on the seventh edition of the TNM classification. This finding was confirmed in two other studies based on the eight editions of the TNM classification [179, 180]. Similarly, Wang et al. [182] found that the progression-free survival (PFS) and OS of stage IA micropapillary/solid subtypes could also benefit from adjuvant chemotherapy. However, whether micropapillary/solid subtypes can guide chemotherapy for early lung adenocarcinomas requires more evidence-based medical data.

Targeted therapies

Targeted drugs, such as EGFR tyrosine kinases inhibitors (EGFR-TKIs) and ALK-TKIs, have shown good effects in treating lung adenocarcinomas and improved patients' prognoses [183, 184]. However, different pathological subtypes of lung adenocarcinomas have shown different therapeutic responses. Lepidic subtypes are more prone to EGFR mutations, suggesting they may benefit more from EGFR-TKIs [56]. Yoshida et al. [185] found that the effect of EGFR-TKIs on EGFR mutation-positive solid subtypes was significantly worse than that on non-solid subtypes. But a study found that osimertinib combined with glycolytic inhibitors inhibited lung adenocarcinoma cells with high glycolytic levels more strongly in vitro than any monotherapy, suggesting that EGFR-TKIs combined with glycolytic inhibitors may be more effective against solid subtypes with high glycolytic levels; however, further animal validation is required [186].

Solid subtypes have a lower probability of EGFR mutations with a higher probability of KRAS and ALK mutations, suggesting that solid subtypes may benefit KRAS-TKIs and ALK-TKIs [56, 66, 187]. The completed Phase 3 clinical trial of KRAS-TKIs did not meet expectations, improving PFS by just 5 weeks compared to standard of care and failed to improve OS at all [188]. ALK-TKI has shown surprising efficacy in ALK-positive patients, especially alectinib, while immunotherapy is not recommended in ALK-positive patients due to low TMB and PD-1 expression levels and poor immunotherapy response [189–192]. ALK mutation and ALK-TKI further distinguish the heterogeneity of solid subtype lung

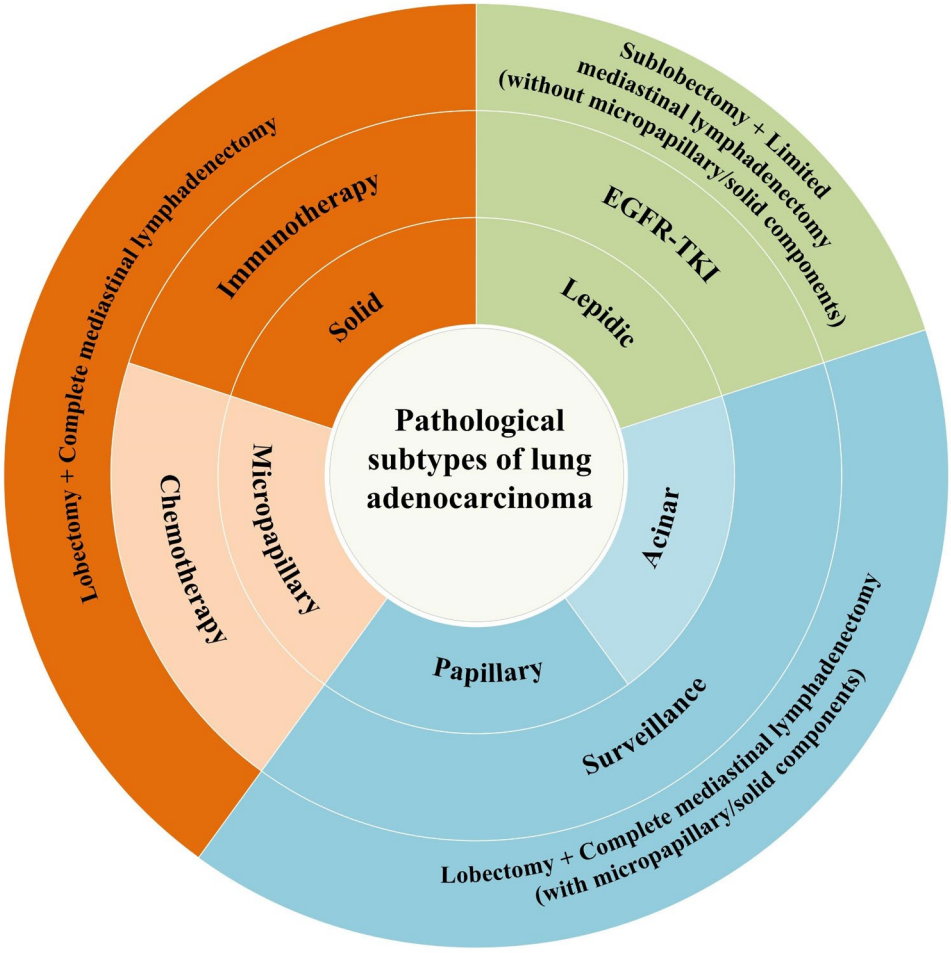

Fig. 4 Potential effect of pathological subtypes on treatment decision of stage IB lung adenocarcinoma[1]. *Abbreviations*: EGFR-TKIs, epidermal growth factor receptor tyrosine kinases inhibitors

[1] Lepidic subtypes are more prone to EGFR mutations and may benefit from EGFR-TKIs; however, their prognosis is better and adjuvant therapy may not be required. At the same time, only sublobectomy and limited mediastinal lymphadenectomy may be required for lepidic subtypes in the absence of micropapillary/solid components due to low metastasis characteristics. Micropapillary/solid subtypes require lobectomy, complete mediastinal lymphadenectomy, and postoperative adjuvant therapy due to high recurrence and metastasis, while solid subtypes with high PD-L1 expression rate may benefit more from immunotherapy. As the intermediate acinar/papillary subtype requires further differentiation, those containing high-grade components require more stringent treatment.

adenocarcinomas and provide an effective and precise treatment approach.

ICIs

Solid subtypes have higher TMB and exhibit increased PD-1 expression, leading to a better response to immunotherapy [17, 98, 193]. Studies have shown that EGFR-positive lung adenocarcinomas are almost always PD-L1 negative and rarely benefit from ICIs [194, 195]. In an open-label single-arm Phase II study (NCT02927301) [196], no tumour with EGFR-positive patients who received two doses of neoadjuvant atezolizumab monotherapy achieved radiographical response and MPR (primary pathological response). However, all tumours with the pathological complete response (PCR) were EGFR-negative and PD-L1 ≥ 50% [196]. Clinical trials on ICIs are highly anticipated if they can further reveal the relationship between the histological types of lung adenocarcinomas and immunotherapy responses [197].

Conclusion

Different pathological types of invasive lung adenocarcinoma show different epidemiological and biological characteristics, providing guidance for evaluating prognosis, selecting surgical methods, and adjuvant therapy (Fig. 4). Highly malignant pathological patterns need to be further distinguished. However, the cut-off value of high-grade patterns and how to guide the treatment of lung adenocarcinoma needs further investigation. Diagnosing pathological patterns requires more accurate

guidance to reduce subjective errors, and artificial intelligence-assisted diagnosis may help improve accuracy. The sensitivity of micropapillary/solid subtypes to chemotherapeutics remains unclear, and drug susceptibility tests of PDO and PDX models based on the pathological subtypes of invasive lung adenocarcinomas are necessary. Driver mutations are more like 'switches' that turn on the evolution of lung adenocarcinomas, whereas TME and transcriptional features are like 'machines' that determine the direction of the histological progression of invasive lung adenocarcinomas. The spatial interactions of TME cells and the molecular characteristics that promote malignant progression need to be further analysed. An in-depth study of the TME and histological progression of invasive lung adenocarcinomas can reveal the key pathways affecting the malignant progression of invasive lung adenocarcinomas. The development of novel drugs targeting the tumor microenvironment to block the histological deterioration or even reverse the histological transformation may be a new approach.

Abbreviations

TME	Tumour microenvironment
TLSs	Tertiary lymphoid structures
TIME	Tumour immune microenvironment
TNM	Tumour-node-metastasis
GGO	Ground-glass opacity
mGGO	Mixed ground-glass opacity)
VDT	Volume doubling time
MDT	Mass doubling time
TDR	Tumour shadow disappearance rate
SUV	Standardised uptake value
PET	Positron emission tomography
KRAS	Kristen rat sarcoma viral oncogene
IMA	Invasive mucinous adenocarcinoma
ALK	Anaplastic lymphoma kinase
TTF	Thyroid transcription factor
DFS	Disease-free survival
RFS	Recurrence-free survival
OS	Overall survival
DSS	Disease-specific survival
PD-L1	Programmed cell death ligand 1
FS	Frozen section
FP	Final pathology
PCR	Pathological complete response
STAS	Spread through air spaces
AAH	Atypical adenomatous hyperplasia
AIS	Adenocarcinoma in situ
MIA	Minimally invasive adenocarcinoma
CT	Computerised tomography
CTR	Consolidation-to-tumour ratio
EGFR	Epidermal growth factor receptor
CIR	Cumulative incidence of relapse
MTHFD2	Methylenetetrahydrofolate dehydrogenase 2
IASLC	International association for the study of lung cancer
ICIs	immune checkpoint inhibitors
CAF	Cancer-associated fibroblast
TAMs	Tumor-associated macrophages
PDO	Patient-derived organoids
PDX	Patient-derived xenograft

Supplementary Information

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Supplementary Material 1

Author contributions

SX, MW, YX and YH conceived the scoping review and participated in its design. SX, and HD developed and conducted the literature search strategy. SX, YT and ZW conducted the data screening and extraction. SX, SJ and FM carried out the data analyses. SX drafted the manuscript. SX, YT and MW prepared figures and tables. YX, YH, and MW revised the manuscript. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethical approval

Not applicable.

Competing interests

The authors declare no competing interests.

Conflict of interest

None declared.

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