

EGFR 突变的 IV B 期肺腺癌临床特征、 组织病理生长模式与预后分析

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摘要 目的 探讨人类表皮生长因子受体(EGFR)突变的胸腔外多发转移性(IV B 期)肺腺癌临床病理特征、组织病理生长方式以及患者预后的相关性。方法 收集安徽医科大学第一附属医院和中国科学技术大学附属第一医院 EGFR 突变 IV B 期肺腺癌患者 488 例。收集临床病理资料、EGFR 基因突变亚型、转移部位、组织病理生长方式及生存信息, 并使用 χ^2 检验、fisher 确切概率法探究转移情况与各临床特征之间的关系; 使用 Kaplan-Meier 法对各临床特征下的中位无进展生存期(PFS)进行生存分析; 采用单因素、多因素 Cox 回归分析各临床特征对预后影响。结果 EGFR 突变的 IV B 期肺腺癌的转移方式与组织病理生长方式相关($P < 0.05$), 单器官多处转移组微乳头型占比较多器官转移组高(51.1% vs 41.1%), 而多器官转移组实体型占比较多单器官多处转移组高(23.8% vs 14.2%); 多发脑或多发骨转移与组织病理生长方式及肿瘤分化程度相关; 相比于多发骨转移组, 多发脑转移组腺泡型占比降低, 而微乳头型占比升高, 且低分化占比明显升高($P < 0.05$)。实体型生长方式为主的患者的中位无进展生存期(PFS)较其他生长方式患者更短(12.7 月 vs 17.8 月, $P < 0.05$), 低分化组患者 PFS 低于中分化组(15.6 月 vs 17.8 月, $P < 0.05$)。EGFR 常见敏感突变和罕见突变患者的 PFS 差异显著(17.3 月 vs 10.2 月, $P < 0.005$)。Cox 比例风险回归模型提示实体生长方式、低分化、罕见单基因突变是预后的不良因素。结论 EGFR 突变的 IV B 期肺腺癌患者转移方式、转移部位均与肿瘤的组织病理生长方式相关, 且患者的 EGFR 突变亚型、肿瘤的组织病理生长方式及分化程度能够影响患者的预后。

关键词 EGFR 突变; IV B 期肺腺癌; 转移部位; 单器官多处转移; 多器官转移; 生长方式; 预后

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肺腺癌是肺癌最主要的组织学亚型^[1], 80% 以上患者确诊时处于晚期, 肿瘤发生不同程度的侵袭和转移^[1], 患者预后较差, 其中 25% ~ 30% 患者生存期不超过 3 个月^[2]。特别是胸腔外多发转移性(IV B 期)肺腺癌患者因发生胸膜外多发转移, 预后更差^[2], 已成为肺腺癌治疗的重点和难点。

在中国, 45% ~ 55% 的晚期非小细胞肺癌患者有 EGFR 基因突变驱动发生^[3], 针对 EGFR 突变的靶向治疗已成为此类患者的首选治疗方案, 患者生活质量和生存期得到显著获益^[4]。然而, IV B 期肺腺癌 EGFR 突变的类型分布及 EGFR 基因内共突变特征报道较少, 其与临床及预后的相关性尚不清楚。

同时, 在早期肺腺癌中, 研究^[5]已证明高级别的组织病理生长方式—微乳头和实体型生长方式与患者的不良预后显著相关, 但在晚期肿瘤中, 尤其是 IV B 期患者中, 其相关性尚不明确。因此, 对 EGFR 突变的 IV B 期肺腺癌患者的临床病理特征、组织病理生长方式和 EGFR 突变亚型进行研究, 探究它们之间的相关性以及对预后的影响, 以期为此类患者治疗方案的制定和预后预测提供新的思路。

1 材料与方法

1.1 研究对象 分别收集 2019 年 5 月至 2022 年 8 月于安徽医科大学第一附属医院(19 例)、2019 年 11 月至 2023 年 9 月于中国科学技术大学附属第一医院(469 例)初治的含 EGFR 突变的 IV B 期肺腺癌患者共 488 例, 随访截止时间为 2024 年 9 月。患者入组条件如下: ① 年龄 ≥ 18 岁, 临床、病理资料完整, 患者同意接受随访; ② 符合 2023 肿瘤 TNM 分期的初诊 IV B 期原发性肺癌, 即发生胸腔外单器官的多发转移(M1c1)或胸腔外多器官的转移

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(M1c2)^[6];③ 活检(支气管镜下活检、经皮肺穿刺活检、淋巴结穿刺活检)组织病理确诊为肺腺癌;④ 肿瘤组织基因检测结果明确为 *EGFR* 突变,包括 *EGFR* 19 号外显子缺失(19del)和 L858R 常见突变^[7] 以及 18 号外显子(G719X)、20 号外显子(20ins)、S768I、T790M)和 21 号外显子(L861Q)罕见突变^[8]。排除标准:① 临床、病理、基因变异或随访资料不完整;② 心、肝、肾等重要器官严重功能障碍;③ 合并其他系统重大疾病。本研究经安徽医科大学第一附属医院及中国科学技术大学附属第一医院伦理委员会批准(伦理批件号:20200893、2024KY 伦审第 297 号)。

1.2 研究方法 收集所有患者的性别、年龄、家族史、吸烟史、确诊日期等基本情况。记录 *EGFR* 单位点突变包括常见突变(19del、L858R)、罕见突变(G719X、20ins、S768I、T790M、L861Q 等)及两个或以上位点基因内共突变类型。依据第九版肺癌 TNM 分期标准^[6]、影像学资料(胸腹部 CT、头颅 MRI、PET-CT、骨扫描)等,对转移情况进行统计与分类,分为单器官多处转移组和多器官转移组;按照转移具体部位及出现概率分为骨、脑、其他,即除骨、脑以外的远处器官(肝、肾、肾上腺、胸壁、除区域淋巴结以外的远处淋巴结等)转移;单器官多处转移组分为(骨、脑)两个亚组,多器官转移组分为(骨+脑、骨+其他、脑+其他、骨+脑+其他、其他+其他)五个亚组。调取患者的组织学切片,按照第五版世界卫生组织(World Health Organization, WHO)肺腺癌组织学亚型分类标准^[9],对苏木精伊红(hematoxylin eosin, HE)染色切片进行组织病理学分型,每张切片均由 3 位病理科医师共同阅片,最终得到患者的 4 种组织病理生长方式(腺泡型、乳头型、微乳头型、实体型)(图 1);同时依据第五版 WHO 肺腺癌组织学亚型分类标准^[9]对组织病理学亚型进行预后分组,以腺泡型及乳头型为主属于中分化组,以微乳头及实体型为主属于低分化组^[5, 9]。

1.3 随访与资料收集 通过医院系统及电话收集患者胸腹部 CT、头颅 MRI、骨扫描结果和肿瘤指标,依据 WHO 实体瘤疗效评价标准(response evaluation criteria in solid tumors, RECIST)对所有的患者评估,随访截止日期为 2024 年 9 月 15 日。临床随访结局采用疾病无进展生存期(progression-free survival, PFS)这一指标,其具体定义为:从术后获得病理诊断的日期开始,一直持续到出现疾病进展、患者死亡或者进行末次随访的时间间隔。

1.4 统计学处理 运用 SPSS 26.0 软件进行数据分析,定性资料用 $n(\%)$ 表示,并使用 χ^2 检验、fisher 确切概率法进行组间比较;使用 Kaplan-Meier 进行生存分析,生存曲线的差异比较运用 Log-rank 检验,使用 Cox 比例风险回归模型对预后及各临床特征进行单因素和多因素分析, $P < 0.05$ 为有统计学意义。

2 结果

2.1 患者一般资料 488 例 *EGFR* 突变的 IVB 期肺腺癌患者基本临床资料包括性别、年龄、吸烟史、肿瘤家族史、转移情况、组织学生长方式,见表 1。单器官多处转移和多器官转移分别占 56.1% 和 43.9%。单器官多处转移组仅有骨(77.4%)和脑转移(22.6%),多器官转移组中含骨转移比例高于脑转移(98.1% vs 83.6%),其他转移部位少见。生长方式占比从高到低依次为微乳头型(46.7%),腺泡型(32.4%),实体型(18.4%)和乳头型(2.5%),以上 4 种生长方式见图 1。

表 1 患者基本临床特征

Tab. 1 Clinical characteristics of the patients

Characteristics	Number of patients $n(\%)$
Age	
< 65 years	219 (44.9)
> = 65 years	269 (55.1)
Gender	
Male	222 (45.5)
Female	266 (54.5)
Smoking history	
Yes	98 (20.1)
No	390 (79.9)
Family history	
Yes	19 (3.9)
No	469 (96.1)
Metastasis status	
Single-organ	274 (56.1)
Multiple brain	212 (77.4)
Multiple bone	62 (22.6)
Multi-organ	214 (43.9)
Bone + brain	156 (72.9)
Bone + other	33 (15.4)
Brain + other	2 (0.9)
Bone + brain + other	21 (9.8)
Other + other	2 (0.9)
Histopathological growth pattern	
Acinar	158 (32.4)
Papillary	12 (2.5)
Micropapillary	228 (46.7)
Solid	90 (18.4)

Other denotes distant organs other than bone and brain (liver, kidney, adrenal gland, chest wall, distant lymph nodes other than regional lymph nodes, etc).

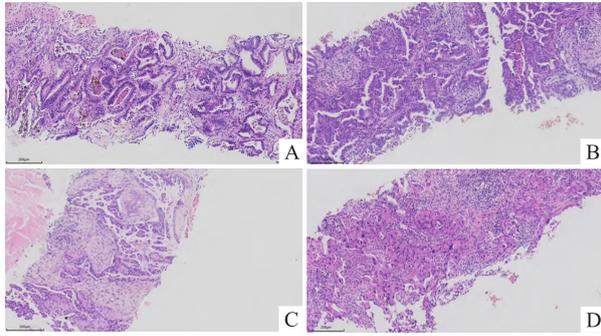


图1 肺腺癌主要组织病理生长方式

Fig.1 Main histopathological growth patterns of pulmonary adenocarcinoma

A: acinar; B: papillary; C: micropapillary; D: solid.

2.2 EGFR 基因分布情况 依据 EGFR 基因突变亚型,488 例患者中 19del 突变占 46.9%, L858R 突变占 40.8%, 罕见单突变占 7.8% (38 例), 基因内共突变占 4.5% (22 例) (图 2A)。38 例罕见单突变中 20ins、G719X、L861Q 和 S768I 分别占 47.3%、23.7%、23.7% 和 5.3% (图 2B)。22 例 EGFR 基因内共突变中最常见的为 G719X + S768I (22.7%) 和 L858R + T790M (22.7%), 其次为 L858R + S768I (18.2%) 和 19del + L858R (13.6%)。(图 2C)。

2.3 转移部位与临床基本特征、基因特征、组织病理生长方式、分化情况的关系 χ^2 及 Fisher 精确概率法结果如表 2、表 3 所示,单器官多处转移组与多器官转移组病理生长方式不同 ($\chi^2 = 8.60, P = 0.04$),主要表现为单器官多处转移组微乳头型占比较多器官转移组高 (51.1% vs 41.1%),而多器官转移组实体型占比较多器官多处转移组高 (23.8%

vs 14.2%);多发脑转移组病理生长方式与多发骨转移组存在明显差异 ($\chi^2 = 12.39, P = 0.006$),多发脑转移组微乳头型占比高,而多发骨转移组腺泡型占比高;多发脑转移组分化程度与多发骨转移组存在明显差异 ($\chi^2 = 8.30, P = 0.004$),相比于多发骨转移,多发脑转移组低分化占比明显升高 (表 2)。单器官多处转移与多器官转移组在性别、年龄、吸烟史、家族史及基因特征上均无显著性差异 (均 $P > 0.05$),同样多发骨转移与多发脑转移在性别、年龄、吸烟史、家族史及基因特征上无显著性差异 (均 $P > 0.05$) (表 2)。如表 3 示,多器官转移患者不同转移情况在性别、年龄、吸烟史、家族史、生长方式、分化情况和基因特征上均无显著性差异 (均 $P > 0.05$)。

2.4 影响 IVB 期肺腺癌患者的 PFS 因素 分析发现,年龄、性别、吸烟史和家族史、转移情况对 PFS 无显著影响 ($P > 0.05$) (见表 4)。实体型生长方式为主患者的中位无进展生存期 (median progression-free survival, mPFS) 最短,低分化组比中分化组具有更短的 PFS (15.6 月 vs 17.8 月, $P = 0.04$) (见表 4、图 3A);具有常见单突变的患者较罕见单突变患者表现出较长的 mPFS (17.3 月 vs 10.2 月, $P < 0.01$) (见表 4、图 3B)。

如表 5 所示,单因素 Cox 回归分析显示,生长方式影响患者预后,相对于腺泡型,实体型的风险比 (hazards ratio, HR) 为 1.622 (95% CI: 1.211 ~ 2.280, $P < 0.01$),提示实体型预后较其他类型差;肿瘤低分化为 IVB 期肺腺癌患者 PFS 的危险因素 ($HR = 1.284, 95\% CI: 1.015 \sim 1.626$);EGFR 罕见

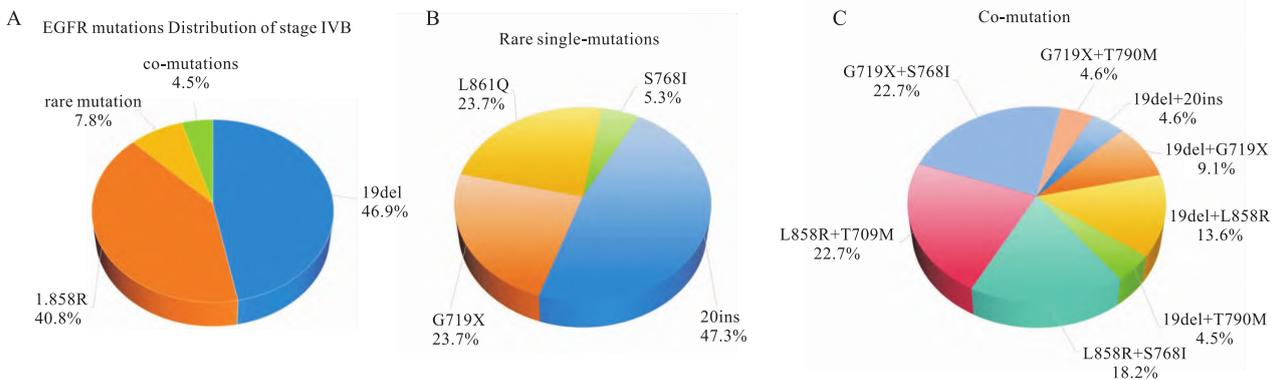


图2 EGFR 突变分布情况

Fig.2 Distribution of EGFR mutations

A: The distribution of EGFR mutations in 488 patients; B: Gene distribution of 38 patients with EGFR rare single mutations; C: Gene distribution of 22 patients with EGFR intra-gene co-mutations; Co-mutation: mutations at two or more sites within the EGFR gene.

表 2 IVB 期肺腺癌患者转移情况与临床特征、基因特征及生长方式的关系
Tab.2 Correlation of metastasis situation and clinical features, genetic characteristics and growth pattern with pulmonary adenocarcinoma of stage IVB patients

Characteristics	Patients of stage IVB (n = 488)				Single-organ multiple metastases (n = 274)			
	Single-organ multiple metastases (n = 274)	Multi-organ metastatic (n = 214)	χ^2 value	P value	Bone (n = 212)	Brain (n = 62)	χ^2 value	P value
Age			0.30	0.59			0.69	0.41
< 65 years	120 (43.8%)	99 (46.3%)			90 (42.5%)	30 (48.4%)		
> = 65 years	154 (56.2%)	115 (53.7%)			122 (57.5%)	32 (51.6%)		
Gender			< 0.01	0.95			3.32	0.07
Male	125 (45.6%)	97 (45.3%)			103 (48.6%)	22 (35.5%)		
Female	149 (54.4%)	117 (54.7%)			109 (51.4%)	40 (64.5%)		
Smoking history			0.47	0.49			1.04	0.31
Yes	52 (19.0%)	46 (21.5%)			43 (20.3%)	9 (14.5%)		
No	222 (81.0%)	168 (78.5%)			169 (79.7%)	53 (85.5%)		
Family history			0.62	0.43				0.43 *
Yes	9 (3.3%)	10 (4.7%)			6 (2.8%)	3 (4.8%)		
No	265 (96.7%)	204 (95.3%)			206 (97.2%)	59 (95.2%)		
EGFR mutation			0.90	0.64			1.35	0.58
Common mutations	237 (86.5%)	191 (89.3%)			181 (85.4%)	56 (90.3%)		
Rare mutations	23 (8.4%)	15 (7.0%)			20 (9.5%)	3 (4.8%)		
Co-mutations	14 (5.1%)	8 (3.7%)			11 (5.2%)	3 (4.8%)		
Growth pattern			8.60	0.04			12.39	< 0.01
Acinar	88 (32.1%)	70 (32.7%)			79 (37.3%)	9 (14.5%)		
Papillary	7 (2.6%)	5 (2.3%)			4 (1.9%)	3 (4.8%)		
Micropapillary	140 (51.1%)	88 (41.1%)			100 (47.2%)	40 (64.5%)		
Solid	39 (14.2%)	51 (23.8%)			29 (13.7%)	10 (16.1%)		
Differentiation status			0.01	0.93			8.30	< 0.01
Moderately differentiated	95 (34.7%)	75 (35.0%)			83 (39.2%)	12 (19.4%)		
Poorly differentiated	179 (65.3%)	139 (65.0%)			129 (60.8%)	50 (80.6%)		

* P value calculated by Fisher's exact probability method.

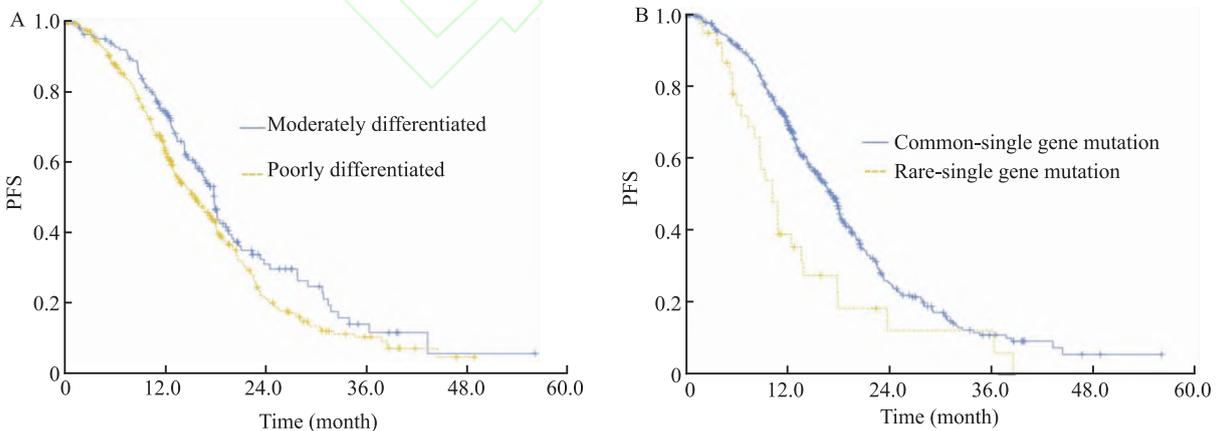


图 3 不同分化程度及不同类型基因突变患者的生存曲线

Fig.3 Survival curves for patients with varying differentiation grades and different types of gene mutations

A: Survival curve in moderately and poorly differentiated patients; B: Survival curve of Common single gene mutation and rare mutation.

单突变是预后危险因素 ($HR = 1.919, 95\% CI: 1.307 \sim 2.818$)。多因素 Cox 回归分析显示,低分化是预后危险因素 ($HR = 1.315, 95\% CI: 1.038 \sim 1.667$); 罕见单突变是预后危险因素

($HR = 2.130, 95\% CI: 1.439 \sim 3.153$); 男性是预后的危险因素 ($HR = 1.371, 95\% CI: 1.054 \sim 1.782$); 而吸烟史是预后的保护因素 ($HR = 0.686, 95\% CI: 0.491 \sim 0.959$)。

表3 多器官转移患者转移情况与临床特征、基因特征及生长方式相关性

Tab.3 Correlation of metastasis situation, clinical features, genetic characteristics and growth pattern of patients with multi-organ metastasis

Characteristics	Bone + brain	Bone + other	Brain + other	Bone + brain + other	Other + other	P value
	(n = 156)	(n = 33)	(n = 2)	(n = 21)	(n = 2)	
Age						0.23
< 65 years	75 (48.1%)	11 (33.3%)	1 (50.0%)	12 (57.1%)	0	
> = 65 years	81 (51.9%)	22 (66.7%)	1 (50.0%)	9 (42.9%)	2 (100%)	
Gender						0.13
Male	64 (41.0%)	21 (63.6%)	1 (50.0%)	10 (47.6%)	1 (50.0%)	
Female	92 (59.0%)	12 (36.4%)	1 (50.0%)	11 (53.4%)	1 (50.0%)	
Smoking history						0.28
Yes	29 (18.6%)	10 (30.3%)	0	7 (33.3%)	0	
No	127 (81.4%)	23 (69.7%)	2 (100%)	14 (66.7%)	2 (100%)	
Family history						0.62
Yes	7 (4.5%)	1 (3.0%)	0	2 (9.5%)	0	
No	149 (95.5%)	32 (97.0%)	2 (100%)	19 (90.5%)	2 (100%)	
EGFR mutation						0.86
Common mutations	137 (87.8%)	30 (91.0%)	2 (100%)	20 (95.2%)	2 (100%)	
Rare mutations	13 (8.3%)	2 (6.1%)	0	0	0	
Co-mutations	6 (3.8%)	1 (3.0%)	0	1 (4.8%)	0	
Growth pattern						0.60
Acinar	53 (34.0%)	7 (21.2%)	1 (50.0%)	9 (42.9%)	0	
Papillary	5 (3.2%)	0	0	0	0	
Micropapillary	61 (39.1%)	16 (48.5%)	0	9 (42.9%)	1 (50.0%)	
Solid	37 (23.7%)	10 (30.3%)	1 (50.0%)	3 (14.3%)	1 (50.0%)	
Differentiation status						0.25
Moderately differentiated	58 (37.2%)	7 (21.2%)	1 (50.0%)	9 (42.9%)	0	
Poorly differentiated	98 (62.8%)	26 (78.8%)	1 (50.0%)	12 (57.1%)	2 (100%)	

表4 不同临床病理特征IVB期肺腺癌患者的PFS差异分析

Tab.4 Analysis of the differences in PFS among patients with stage IVB lung adenocarcinoma with different clinicopathological characteristics

Characteristics	PFS		χ^2 value	P value
	Median time(month)	95% CI		
Age			0.12	0.73
< 65 years	16.5	14.6 – 18.5		
> = 65 years	16.7	14.5 – 18.8		
Gender			1.48	0.23
Male	15.1	13.0 – 17.2		
Female	17.8	16.4 – 19.3		
Smoking history			0.90	0.34
Yes	16.5	12.4 – 20.5		
No	16.7	15.1 – 18.2		
Family history			<0.01	1.00
Yes	19.6	16.4 – 22.7		
No	16.5	15.0 – 18.0		
Gene mutation			11.97	<0.01
Common mutations	17.3	16.0 – 18.5		
Rare mutations	10.2	7.5 – 13.0		
Co-mutations	16.0	11.4 – 20.5		
Single gene mutation			11.43	<0.01
Common-single gene mutation	17.3	16.0 – 18.5		
Rare -single gene mutation	10.2	7.5 – 13.0		
Histopathological growth pattern			10.16	0.02
Acinar	17.8	16.5 – 19.1		
Papillary	18.0	11.4 – 24.5		
Micropapillary	17.4	15.4 – 19.4		

表 4 续

Characteristics	PFS		χ^2 value	P value
	Median time(month)	95% CI		
Solid	12.7	10.8 – 14.5		
Differentiation status			4.35	0.04
Moderately differentiated	17.8	16.7 – 19.0		
Poorly differentiated	15.6	13.5 – 17.7		
Metastasis status			1.35	0.25
Single-organ	16.6	14.8 – 18.5		
Multi-organ	16.9	14.7 – 19.0		
Single-organ			2.63	0.11
Bone	17.2	15.3 – 19.1		
Brain	15.5	10.7 – 20.4		

表 5 单因素和多因素 Cox 回归分析临床病理、基因、生长方式与 PFS 关系

Tab.5 Univariate and multivariate Cox regression analysis of the relationship between clinicopathological, genetic, growth pattern and PFS

Characteristics	Univariate Cox regression analysis		Multivariate Cox regression analysis	
	HR(95% CI)	P value	HR(95% CI)	P value
Age				
< 65years	1		1	
> = 65 years	1.039 (0.834 – 1.296)	0.73	1.084 (0.867 – 1.356)	0.48
Gender				
Female	1		1	
Male	1.146 (0.919 – 1.429)	0.23	1.371 (1.054 – 1.782)	0.02
Smoking history				
No	1		1	
Yes	0.875 (0.664 – 1.154)	0.34	0.686 (0.491 – 0.959)	0.03
Family history				
No	1		1	
Yes	0.999 (0.594 – 1.680)	1.00	1.112 (0.653 – 1.895)	0.70
Histopathological growth pattern		0.02		
Acinar	1		-	-
Papillary	1.289 (0.705 – 2.359)	0.41	-	-
Micropapillary	1.208 (0.930 – 1.570)	0.16	-	-
Solid	1.662 (1.211 – 2.280)	<0.01	-	-
Differentiation status				
Moderately differentiated	1		1	
Poorly differentiated	1.284 (1.015 – 1.626)	0.04	1.315 (1.038 – 1.667)	0.02
Gene mutations		<0.01		<0.01
Common-single mutation	1		1	
Rare-single mutation	1.919 (1.307 – 2.818)	<0.01	2.130 (1.439 – 3.153)	<0.01
Co-mutations	0.876 (0.512 – 1.499)	0.63	0.947 (0.551 – 1.629)	0.85
Metastasis status				
Single-organ	1		1	
Multi-organ	1.140 (0.913 – 1.423)	0.247	1.150 (0.920 – 1.438)	0.22

3 讨论

通过对 488 例 EGFR 突变的 IVB 期肺腺癌患者进行研究,深入探究了临床病理特征、组织病理生长方式及基因特征与患者 PFS 的相关性,为该领域的临床实践和研究提供有价值的参考依据。

在基因特征方面,本研究发现 EGFR 常见突变在 IVB 期肺腺癌患者中占比高达 87.7%,这一比例

与先前相关研究报道的 80% ~ 90% 区间高度吻合,再次凸显了常见突变在该疾病进程中的关键地位^[7]。对于罕见单突变,20ins、G719X、L861Q 和 S768I 等突变的占比情况也与部分已有研究结果相近^[8]。对于基因内共突变,约 78% 的共突变由常见突变与罕见突变组合而成,其中 T790M 合并 L858R 突变的情况最为普遍,与先前的研究^[10]结果相似。常见突变的高频率出现或许在肿瘤的启动和演进中

扮演核心驱动角色,而复杂的共突变模式则可能通过影响下游信号通路、基因表达调控网络等机制,从而影响细胞间信号传导,造成肿瘤微环境改变^[11],进而对患者的预后产生潜在且深远的影响。

组织病理生长方式上,既往组织学亚型研究只针对于手术标本,目前尚未有共识对活检小标本进行组织学亚型分类,但基于 Yu et al 研究^[10]提示局部组织能代替同一肿瘤内不同区域之间的差异性,因此本研究对 IV B 期肺腺癌患者组织进行亚分类,并发现 IV B 期患者主要呈腺泡、乳头、微乳头和实体型,未发现贴壁型。不同于早期肺腺癌 *EGFR* 突变多见于贴壁型^[12-13],这可能是肿瘤进展至晚期转移阶段,微环境改变、基因表达谱变化及细胞间相互作用重塑等因素所致^[11]。

转移部位方面,肺癌最常见的转移部位是骨和脑^[14],本研究对 IV B 期肺腺癌患者转移情况进行分析发现单器官多处转移组中多发骨转移比例较多发脑转移更高,多器官转移组中含有骨转移比率最高,其次是含脑转移,其他转移比例少。有研究^[15]发现 30%~50% 的晚期肺腺癌患者在肺癌诊断时有初始骨转移,可能是因为骨组织微环境更有利于肿瘤细胞生存、定植和扩散,此外,骨转移引发的病理生理改变会加剧患者病情恶化,研究^[16]显示与非骨转移相比,肺癌诊断时骨转移与较差的预后密切相关,并可能与复杂的多器官转移共存。对于脑转移,血脑屏障为肺癌细胞转移和生长提供了有利的微环境,同样肿瘤细胞定植后也可能改变血脑屏障^[17],增加了脑转移患者的治疗难度,万畅等^[18]发现相比于野生型,*EGFR* 突变患者在脑转移灶中免疫相关通路上调明显,但原发灶中未发现,由于脑转移灶和原发病灶生物学及微环境的差异导致治疗效果的不同,由此可见,针对原发灶治疗的同时需密切观察脑转移灶情况。本研究显示,单器官多处转移病理生长方式对比多器官转移有差异,单一器官多发骨、脑转移的生长方式及分化程度不同,提示肿瘤细胞转移潜能和模式受生长方式调控,不同转移部位肿瘤细胞具有独特生物学特性,但本研究未发现多器官转移与生长方式、基因特征及分化情况的相关性,可能存在其他关键因素有待进一步研究。

本研究生存分析显示,基因突变情况、组织病理生长方式和分化程度与患者 PFS 有关。其中共突变患者的 mPFS 与常见单突变相近,这可能与共突变中大多包含一个常见突变位点有关。在组织学方面,实体型增长方式 mPFS 最低,而其他类型相对较

高。低分化患者 mPFS 低于中分化患者。Cox 回归结果显示,罕见突变、低分化是影响患者 PFS 的危险因素。这些结果支持了既往关于分化程度影响预后的研究^[9,19]。然而本研究未发现转移部位与预后的相关性,与既往研究^[20]有所不同,可能反映了现代靶向治疗和免疫治疗在改善预后方面取得的效果。本研究 Cox 多因素分析发现男性是预后的危险因素;而吸烟是保护因素,这可能与吸烟患者可能因为吸烟相关的不适症状而更早期地去就医检查,从而使得疾病在相对早期就被发现,进而获得了更好的治疗机会。

本研究作为一项真实世界研究,仍存在一些局限性:首先,PFS 评估依赖临床医师的主观判断,可能存在一定偏倚;其次,研究仅在本地区两家医院开展,存在地域局限性。这些局限性提示未来有必要开展更大规模的多中心前瞻性研究,以进一步验证本研究的发现。

综上所述,本研究发现 IV B 期肺腺癌患者以微乳头型和腺泡型为主要生长方式,骨转移较脑转移更为常见,且多器官转移与肿瘤生长方式密切相关;*EGFR* 突变类型、组织分化程度是影响患者预后的关键因素。本研究为理解晚期肺腺癌的生物行为提供了重要依据。

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Analysis of clinical features, histopathological growth patterns and prognosis in stage IV B pulmonary adenocarcinoma with *EGFR* mutations

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Abstract Objective To investigate the correlations among clinicopathological features, histopathological growth

patterns and prognosis of extrapulmonary multiple metastatic (stage IVB) pulmonary adenocarcinoma with epidermal growth factor receptor (*EGFR*) mutations. **Methods** A total of 488 eligible patients with adenocarcinoma of stage IVB from the First Affiliated Hospital of Anhui Medical University and the First Affiliated Hospital of University of Science and Technology of China were collected. Clinicopathological data, *EGFR* gene mutation subtypes, metastatic sites, histopathological growth patterns and survival information were collected. The chi-square test (χ^2 test) and Fisher's exact probability method were used to detect the correlation between the metastasis status and various clinical characteristics; the Kaplan-Meier method was used to conduct survival analysis on the median Progression-Free Survival (PFS) under different clinical characteristics. Cox univariate and multivariate regression analyses were conducted to evaluate the impact of various clinical characteristics on prognosis. **Results** The metastatic patterns of stage IVB pulmonary adenocarcinoma with *EGFR* mutations was correlated with histopathological growth patterns ($P < 0.05$). In the group with multiple metastases in a single organ, the proportion of micropapillary type in the group with multiple metastases in a single organ was higher than that in the group with multiple-organ metastases (51.1% vs 41.1%), while the proportion of solid type in the group with multiple-organ metastases was higher than that in the group with multiple metastases in a single organ (23.8% vs 14.2%). Multiple brain or multiple bone metastases were correlated with histopathological growth patterns and tumor differentiation degree. Compared with the multiple bone metastases group, the proportion of acinar type decreases in the multiple brain metastasis group, while the proportion of micropapillary type increased. Moreover, the proportion of poorly differentiated tumors increased significantly ($P < 0.05$). Compared with multiple bone metastases, the proportion of poorly differentiated tumors significantly increases in the group with multiple brain metastases. The median progression-free survival (PFS) of patients with a predominant solid growth pattern was shorter than that of patients with other growth patterns (12.7 months vs 17.8 months, $P < 0.05$). The PFS of patients in the poorly differentiated group was worse than that in the moderately differentiated group (15.6 months vs 17.8 months, $P < 0.05$). There were significant differences in PFS among patients with common sensitive mutations and rare mutations *EGFR* (17.3 months vs 10.2 months, $P < 0.005$). Cox proportional hazards regression model suggested that solid growth pattern, poor differentiation and rare single gene mutation were adverse prognostic factors. **Conclusion** In stage IVB pulmonary adenocarcinoma patients with *EGFR* mutations, both the metastatic patterns and metastatic sites are significantly correlated with the histopathological growth patterns of tumors. Moreover, the *EGFR* mutation subtypes as well as the histopathological growth patterns and differentiation degree of tumors significantly affect the prognosis of patients.

Key words *EGFR* mutation; pulmonary adenocarcinoma of stage IVB; metastatic sites; single-organ multiple metastases; multi-organ metastases; growth patterns; prognosis

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