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乳腺癌首发肺转移 38 例临床病理特征及预后因素

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[摘要] 目的: 比较乳腺癌原发灶与首发肺转移灶的临床病理特征, 探讨乳腺癌首发肺转移病例的临床病理特点与预后的关系。方法: 收集38例乳腺癌首发肺转移的病例临床资料及预后, 采用免疫组织化学检测雌激素受体(estrogen receptor, ER)、孕激素受体(progesterone receptor, PR)、人表皮生长因子受体2(human epidermal growth factor receptor 2, HER2), Ki-67, 甲状腺转录因子-1(thyroid transcription factor-1, TTF-1), GATA3在肺转移灶的表达。结果: 38例首发肺转移乳腺癌病理类型浸润性导管癌37例, 黏液癌1例。组织学分级I级4例, II级28例, III级6例; 分子分型luminal A型患者21例, luminal B型患者7例, HER-2过表达型3例, 三阴性乳腺癌(triple-negative breast cancer, TNBC)7例。TNM分期: I期10例, II期14例, III期13例, IV期1例。肺转移灶各组免疫组织化学指标阳性例数为ER 26, PR 22, HER-2 6, TTF-1 0, GATA3 37, 转移灶的组织学分级和Ki-67指数均高于原发灶($P<0.05$)。Kaplan-Meier生存曲线显示HER2过表达与TNBC3年和5年无病生存期低于luminal型($P<0.05$)。结论: 乳腺癌首发肺转移患者转移灶与原发灶病理类型相同, 但组织学分级和Ki-67指数高于原发灶, 分子分型可发生改变。与luminal型患者比较, HER2过表达与TNBC患者3年和5年无病生存期更短。联合检测GATA3, TTF-1, ER, PR, HER-2表达有助于乳腺癌肺转移的鉴别诊断。

[关键词] 乳腺癌; 肺转移; 预后; 分子分型

Clinicopathological features and prognostic factor analysis for 38 breast cancer patients with first-episode lung metastasis

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Abstract **Objective:** To compare the clinicopathological features of primary tumors and the lung metastatic tumors, and analyze the relationship between clinicopathological features and prognosis in patients with first-episode lung metastasis of breast cancer. **Methods:** Thirty-eight breast cancer patients with first-episode lung metastasis

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were identified. Immunohistochemical staining for estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), Ki-67, thyroid transcription factor-1 (TTF-1), GATA-3 were performed on the primary tumors and the lung metastatic tumors. **Results:** Thirty-seven of the 38 primary tumors were invasive ductal carcinoma, one was mucinous carcinoma. Carcinomas of nuclear Grade 3 were more frequent than those of Grade 1 or 2. Patients with Luminal A were more than those of Luminal B, HER2-overexpression and triple-negative breast cancer (TNBC). Twenty-six cases of ER, 22 PR, 6 HER2, 0 TTF-1, and 37 GATA-3 were found in the metastatic foci of lung. The histologic grade and Ki-67 index in metastatic tumor were higher than those in primary foci. In the patients with HER2 overexpression and TNBC, the disease-free survival (DFS) with lung metastasis was shorter than those with luminal subtypes. **Conclusion:** Metastatic tumors were similar to those of primary lesions in histological types, but their histological grade and Ki-67 index were higher than primary tumors. Compared with patients with luminal subtypes, HER2 overexpression and TNBC subtypes tend to associate with lung metastasis at the early stage. Detection of GATA-3 combined with TTF-1, ER, PR, and HER2 could be used in distinguishing the lung metastasis of breast cancer.

Keywords breast neoplasms; lung metastasis; prognosis; molecular subtype

乳腺癌是全世界女性最常见的恶性肿瘤之一，诊断后5年内的复发率较高，虽然早期发现和综合治疗使乳腺癌患者的预后改善显著，但仍有20%~30%的患者会发生远处转移，其中骨、肝、肺是乳腺癌最重要的转移部位^[1-2]，并且远处转移与患者的生存结果密切相关。本研究通过收集38例乳腺癌首发肺转移病例，比较原发灶与转移灶临床病理特征，探讨乳腺癌首发肺转移的临床病理特征与预后的关系。

1 对象与方法

1.1 对象

收集福建省肿瘤医院2014年1月至2018年5月38例乳腺癌首发肺转移患者，所有患者临床资料完整，经正电子发射计算机体层摄影(positron emission tomography, PET)-CT或CT证实肺为首发转移部位；并经穿刺活检或手术切除后病理证实为乳腺癌肺转移。本研究经福建省肿瘤医院医学伦理委员会批准，所有患者知情同意。

1.2 方法

1.2.1 免疫组织化学

标本经10%中性甲醛固定，石蜡包埋、4 μm厚切片。免疫组织化学采用罗氏全自动免疫组织化学仪(产地Roche Benchmark XT)检测，实验步骤参照说明书进行。一抗包括雌激素受体(estrogen receptor, ER)，孕激素受体(progesterone receptor, PR)，人表皮生长因子受体2(human epidermal growth

factor receptor 2, HER2)，Ki-67，甲状腺转录因子-1(thyroid transcription factor-1, TTF-1)，GATA3均购自福州迈新生物技术开发有限公司。用已知阳性组织作为阳性对照，用PBS代替一抗作为阴性对照。

1.2.2 结果判定

ER，PR及Ki-67阳性判断标准^[3]参照2015年《乳腺癌雌、孕激素受体免疫组织化学检测指南》进行评分，计算阳性细胞数百分率，以≥1%的肿瘤细胞核呈现不同程度的着色时判定为阳性，以<1%的肿瘤细胞核呈现不同程度的着色或完全无着色判定为阴性。根据2014年版乳腺癌HER2检测指南对HER2进行评分。乳腺癌组织学分级参照2012年版乳腺肿瘤WHO分类标准。乳腺癌分子分型^[4]标准如下：luminal A型，ER或PR(+)，HER2阴性；luminal B型，ER或PR(+)，HER2阳性；HER2过表达型，ER(-)，PR(-)，HER2阳性；三阴性乳腺癌(triple-negative breast cancer, TNBC)，ER(-)，PR(-)，HER2阴性。

1.2.3 随访

病例随访通过门诊复查及电话随访获取随访资料，无病生存时间(disease free survival, DFS)指从病理诊断乳腺癌起至首次确诊肺转移时间。总生存时间(overall survival, OS)指从病理诊断乳腺癌至死亡或随访结束时间，以月为单位。

1.3 统计学处理

采用SPSS 22.0软件进行数据分析。组间率的比较采用χ²检验；配对资料的比较采用配对t检验；生存曲线分析采用Kaplan-Meier法，单因素生存曲线比

较采用Log-rank检验。 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 临床资料

38例均为女性，年龄38~72(中位53)岁，转移灶标本穿刺活检标本28例，手术切除标本10例；原发性乳腺癌病理类型非特殊类型浸润性导管癌37例，黏液癌1例。组织学分级I级4例，II级28例，III级6例；分子分型luminal A型患者21例，luminal B型患者7例，HER2过表达型3例，TNBC7例。参照美国肿瘤联合委员会(American Joint Committee on Cancer, AJCC)第8版的TNM分期：I期10例，II期14例，III期13例，IV期1例，其中T1 14例、T2 18例、T3 1例、T4 5例；N0 18例、N1 13例、N2 4例、N3 3例；M0 38例。本组病例随访

时间1~86个月，中位随访时间47个月，3例失访，2例死亡。

2.2 原发灶与转移灶的临床病理特征比较

原发灶与转移灶在病理类型上无变化。在原发灶中ER阳性26例、PR阳性25例、HER2阳性9例；转移灶ER阳性26例、PR阳性22例、HER2阳性6例。在分子分型中发现3例发生分子分型转变。肺转移灶的Ki-67指数高于原发灶($P<0.05$)，转移灶组织学分级III级病例数较原发灶增多($P<0.05$ ；表1，图1)。

2.3 免疫组织化学结果

肺转移灶各组免疫组织化学指标阳性例为ER 26，PR 22，HER2 6，TTF-1 0，GATA3 37；无TTF-1阳性病例(图2，3)。

表 1 38例首发肺转移乳腺癌原发灶与转移灶临床病理特征比较(n=38)

Table 1 Comparison of clinicopathological features between primary and metastasis lesions in 38 breast cancer patients with first-episode lung metastasis (n=38)

组别	组织学分级			分子分型				
	I	II	III	I	II	III	IV	
原发性乳腺癌	4	28	6	21	7	2	8	
转移性肺乳腺癌	3	19	16	23	4	2	9	
<i>P</i>	0.041				0.809			
组别	ER		PR		HER2		Ki-67	
	+	-	+	-	+	-		
原发性乳腺癌	26	12	25	13	9	29	21.08 ± 16.26	
转移性肺乳腺癌	26	12	22	16	6	32	33.08 ± 20.64	
<i>P</i>	1.000		0.219		0.192		<0.001	

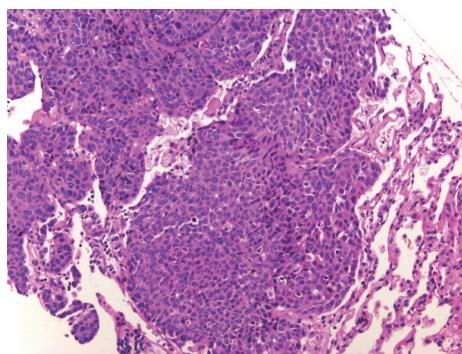


图1 肺转移性乳腺癌的肺组织中见乳腺癌细胞呈实质性片状、巢状分布，细胞异型性明显(HE, ×200)

Figure 1 Breast cancer cells are solid, flaky and nested in lung metastasis of breast carcinoma, with cellular pleomorphism (HE, ×200)

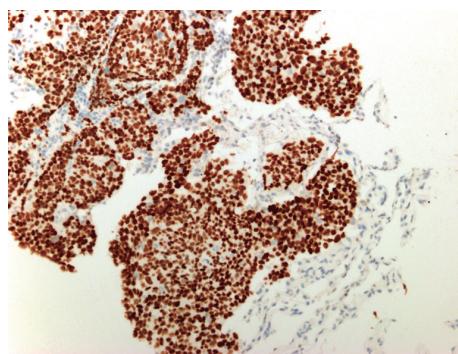


图2 肺转移性乳腺癌中肿瘤细胞核GATA-3呈弥漫强阳性表达(EnVision, ×200)

Figure 2 GATA-3 strongly positive expression in tumor cell nucleus of lung metastasis of breast carcinoma (EnVision, ×200)

2.4 乳腺癌分子分型与首发肺转移预后的关系

Kaplan-Meier生存曲线显示HER2过表达与TNBC 3年和5年DFS均低于luminal型($P<0.01$; 图4, 5)。

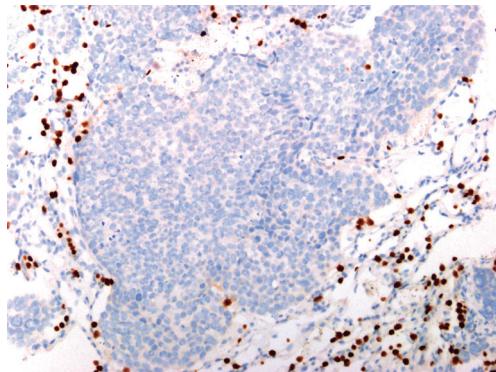


图3 肺转移性乳腺癌中正常肺泡上皮核TTF-1强阳性表达，癌细胞TTF-1阴性表达(×200)

Figure 3 TTF-1 strongly positive expression in alveolar epithelium, while negative expression in tumor cell in lung metastasis of breast carcinoma (×200)

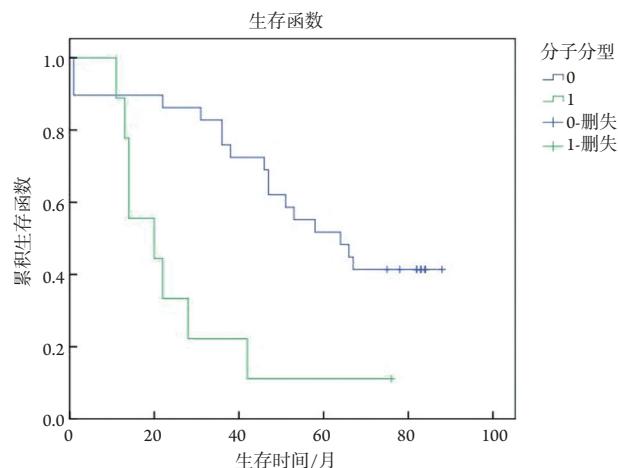


图5 Kaplan-Meier生存曲线显示HER2过表达与三阴性乳腺癌5年无病生存期低于luminal型乳腺癌($P=0.002$)

Figure 5 Kaplan-Meier survival curve showed HER2 overexpression and TNBC lower than luminal type breast carcinoma in 5-year DFS ($P=0.002$)

分子分型0: HER2过表达和三阴性乳腺癌；分子分型1: luminal型乳腺癌。

Molecular subtype 0 represents HER2 overexpression and TNBC;
Molecular subtype 1 represents luminal type.

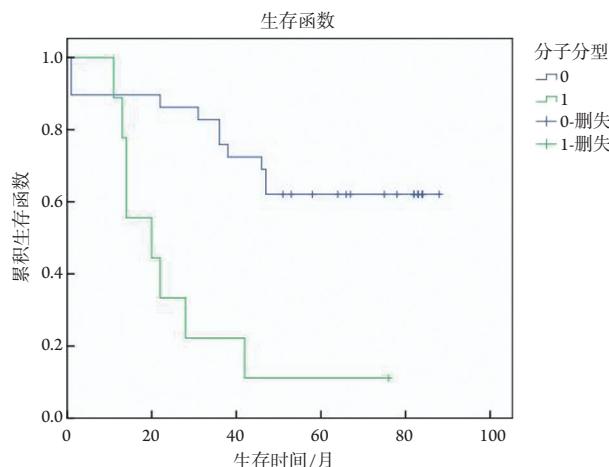


图4 Kaplan-Meier生存曲线显示HER2过表达与三阴性乳腺癌3年无病生存期低于luminal型乳腺癌($P<0.001$)

Figure 4 Kaplan-Meier survival curve showed HER2 overexpression and TNBC lower than luminal type breast carcinoma in 3-year DFS ($P<0.001$)

分子分型0: HER2过表达和三阴性乳腺癌；分子分型1: luminal型乳腺癌。

Molecular subtype 0 represents HER2 overexpression and TNBC;
Molecular subtype 1 represents luminal type.

3 讨论

绝大多数癌症患者的发病率和病死率与复发转移性有关。既往研究^[5-6]认为影响乳腺癌转移危险因素主要包括肿瘤大小、组织学分级、淋巴结受累、淋巴管侵犯和雌激素受体状态及HER2等。最近研究^[7]发现不同分子亚型的乳腺癌在预后和辅助化学药物治疗反应上差异有统计学意义。

乳腺癌的预后取决于几个因素，其中最明显的因素是激素受体情况。不同的乳腺癌亚型具有不同的器官转移特异性^[8-11]，HER2阳性的肿瘤具有较高的远处转移风险，通过多变量分析^[10]发现分子亚型与远处转移具有显著相关性。通过基因表达阵列和免疫组织化学研究^[9,11-12]都发现不同分子亚型的乳腺癌会转移到特定的实体器官。雌激素受体阳性和孕激素受体阳性的肿瘤患者更容易发生骨转移，HER2阳性或TNBC患者更容易有内脏转移倾向，如HER2⁺的患者比HER2⁻的患者更易发生肝转移，HR^{+/}/HER2⁻患者比TNBC和HR⁻/

HER2⁺更少发生肺转移。组织微阵列分析^[10]也证实luminal A亚型乳腺癌的肺转移率最低。在肿瘤复发的时间上, 分子亚型与远处转移出现的时间也具有显著差异, 所有在原发癌诊断5年内复发者几乎都是TNBC和HER2过表达型, 其发病率明显高于luminal亚型^[10]。本研究中38例首发肺转移乳腺癌病例中, 分子分型luminal A型21例, luminal B型7例, HER2过表达型2例, TNBC患者8例。生存分析显示TNBC和HER2过表达型乳腺癌的3年和5年DFS均明显短于luminal型, 与文献[10]报道一致。因本组病例数较少, 随访时间有限, 仅2例死亡, 无法行OS生存分析, 有待进一步扩大样本, 继续跟踪随访。

乳腺癌是一种异质性疾病, 不论是原发肿瘤的转移能力或转移时机上都有所不同, 研究^[13]证明高表达的孕激素受体情况与良好的预后相关。但在转移性乳腺癌中受体状态可能与原发肿瘤不同^[14]。本研究发现: 乳腺原发灶与肺转移灶临床病理类型相同, 但转移灶Ki-67指数均高于原发灶, 且组织学分级III级病例数增多。Ki-67指数虽然与是否转移无关, 但早期转移的肿瘤具有较高表达的指数。Tawfik等^[15]发现腋窝淋巴结的Ki-67高表达与患者的短生存期显著相关。目前仅少数的研究比较原发性和转移性乳腺癌组织分子分型, 研究^[16]发现在转移灶中ER, PR更可能为阴性表达, 而HER2经常是阳性。受体转换在非骨转移性乳腺癌中确实发生, 相对少见的是ER和HER2, 而PR更常见。HER2蛋白过表达水平和频率在原发性和转移性肿瘤之间较一致^[17]。本研究发现在分子分型方面, 转移灶ER表达改变2例, PR表达改变3例, HER2表达改变3例, 分子分型改变3例。其中ER和PR表达改变的病例均进行术后辅助化学药物治疗。HER2表达改变的3例均为原发灶阳性表达而转移灶阴性, 其中1例原发灶HER2阳性, 经赫赛汀靶向治疗后肺转移灶HER2转为阴性, 1例术后辅助化学药物治疗, 1例术后无治疗。本研究发现乳腺癌的分子分型存在一定的异质性表达, 提示有必要在乳腺癌转移灶重新检测分子分型, 能更好地为患者提供个体化精准治疗。

GATA3是一种锌结合转录因子, 调节许多人体组织类型的分化^[18], 包括乳腺腺上皮、T淋巴细胞、胸腺、肾等。在肺、胰腺、前列腺等组织中未发现GATA3的表达。在乳腺组织中GATA3有较高的特异性, 其特异性与敏感性均高于巨囊性病液体蛋白15(grosscystic disease fluid protein-15,

GCDFP-15)和乳腺珠蛋白(mammaglobin, MGB)。因此GATA3^[19]可以作为免疫组织化学标志物用来诊断乳腺癌, 文献[20]报道TTF-1在区分原发性肺腺癌和肺转移性腺癌上具有较高的敏感性和特异性。本研究认为联合检测GATA3, TTF-1, ER, PR, HER2表达可帮助乳腺癌肺转移的鉴别诊断。

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