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晚期肺腺癌患者一线使用 EGFR–TKI 获得性耐药后 T790M 与预后的相关性

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[摘　要]　**目的：**探讨循环肿瘤DNA(circulating tumor DNA，ctDNA)鉴定的EGFR基因20位外显子T790M突变状态与晚期肺腺癌(lung adenocarcinoma，LUAD)患者一线使用EGFR-TKI获得性耐药和预后的相关性。**方法：**回顾性分析2012年1月至2016年1月南京总医院一线使用EGFR-TKI获得性耐药的晚期LUAD患者93例，按照QIAamp循环核酸试剂盒说明提取外周血ctDNA，采用二代测序(next generation sequencing，NGS)的方法对ctDNA中T790M突变进行鉴定，分析其与临床特征和预后的相关性。**结果：**在93例一线使用EGFR-TKI获得性耐药的晚期LUAD患者，T790M阳性突变率为52.7%(49/93)，T790M突变与晚期LUAD患者的年龄、临床分期、组织学亚型、ECOG评分、初始EGFR突变类型、EGFR-TKI种类差异均无统计学意义(P>0.05)；但与性别、吸烟史、EGFR-TKI耐药后进展类型、EGFR-TKI耐药后血CEA水平、EGFR-TKI耐药后治疗方案比较差异有统计学意义(P<0.05)，EGFR-TKI耐药后血CEA预测T790M阳性的cut-off值为90.1 μg/L，其中敏感度44.9%、特异度90.9%，曲线下面积0.639(95%CI 0.526~0.752)；T790M阳性突变患者的中位无进展生存期(progression-free survival，PFS)和总生存期(overall survival，OS)分别为12.4，29.5个月，均较T790M突变阴性的6.2，18.1个月显著延长(P<0.001)；Cox单因素和多因素回归分析均提示T790M突变阳性是PFS(RR=0.302，95%CI 0.162~0.560；P<0.001)和OS(RR=0.422，95%CI 0.250~0.715；P=0.001)的独立影响因素。**结论：**T790M突变与晚期LUAD患者的性别、吸烟史、EGFR-TKI耐药后进展类型、EGFR-TKI耐药后血CEA水平、EGFR-TKI耐药后治疗方案有关，同时是PFS和OS的独立影响因素。

[关键词]　肺腺癌；二代测序；T790M；表皮生长因子受体酪氨酸激酶抑制剂；循环肿瘤DNA；预后

Correlation with EGFR-TKI in the first-line treatment of advanced lung adenocarcinoma acquired T790M and prognosis

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Abstract **Objective:** T790M mutation is the main resistance mechanism of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI). Serum circulating tumor DNA (ctDNA) is an ideal method to detect T790M mutations. This study aimed to explore the relationship between ctDNA identified EGFR T790M mutation status and EGFR-TKI acquired resistance and prognosis in patients with advanced lung adenocarcinoma (LUAD). **Methods:** Ninety-three patients with advanced LUAD who acquired resistance with EGFR-TKI in the first-line of Nanjing general hospital from January 2012 to January 2016 were analyzed retrospectively. The ctDNA was extracted from peripheral blood according to the instructions of circulating nucleic acid kit QIAamp and mutational status of T790M in ctDNA was tested using next generation sequencing (NGS), which clinical features and prognosis were further to analyzed. **Results:** In 93 cases of advanced LUAD patients who were treated with EGFR-TKI in the first-line, T790M mutation was 52.7% (49/93). There was no statistically significant difference between T790M mutation and age, clinical stage, histological subtype, ECOG score, initial EGFR mutant type, EGFR-TKI types of drugs (all $P>0.05$). However, it was related to sex, smoking history, type of progression after EGFR-TKI resistance, level of serum CEA after EGFR-TKI resistance and therapeutic regimen after EGFR-TKI resistance (all $P<0.05$). The cut-off value of serum CEA after EGFR-TKI resistance predicting T790M positive was 90.1 μg/L, with a sensitivity and a specificity was 44.9% and 90.9%, respectively. The area under curve was 0.639 (95% CI 0.526–0.752). T790M mutation positive patients had prolonged PFS and OS compared with T790M negative patients (PFS, 12.4 months vs 6.2 months, $P<0.001$; OS, 29.5 months vs 18.1months, $P<0.001$). Cox univariate and multivariate regression analysis indicated that T790M mutation positive was PFS (RR =0.302; 95% CI 0.162–0.560; $P<0.001$) and OS (RR =0.422; 95% CI 0.250–0.715; $P=0.001$) independent influencing factors. **Conclusion:** T790M mutation was related to sex, smoking history, the level of serum CEA after EGFR-TKI resistance, type of progression after EGFR-TKI resistance, which was an independent influencing factors of PFS and OS.

Keywords lung adenocarcinoma; next generation sequence; T790M; epidermal growth factor receptor-tyrosine kinase inhibitor; circulating tumor DNA; prognosis

表皮生长因子受体酪氨酸激酶抑制剂(epidermal growth factor receptor-tyrosine kinase inhibitor，EGFR-TKIs)作为治疗携带EGFR基因敏感突变的晚期非小细胞肺癌(non-small cell lung cancer，NSCLC)患者的高效临床药物，其客观缓解率(objective response rate，ORR)高达70%[1-2]，无进展生存期(progression-free survival，PFS)为8~13个月[3]。然而，经过一段治疗时间，几乎不可避免地发生耐药。与获得性耐药发生最常见的突变通常是位于EGFR基因第20外显子上的一个次级点突变(EGFR T790M突变)，约占所有获得性耐药机制的半数以上[4]，其他耐药机制包括MET扩增、HER2扩增、BRAF突变、ALK融合以及转化为小细胞肺癌等[5-6]。目前，大量临床试验[5,7]显示携带T790M敏感突变的晚期肺腺癌(lung adenocarcinoma，LUAD)患者通常可以从第三代EGFR-TKIs(奥希替尼、艾维替尼)显著获益，同时基于液体活检技术作为一种新兴、非侵入性且具有高敏感性逐渐被应用于临床之中。本研究以对EGFR-TKI耐药的晚期LUAD患者为研究对象，收集耐药后患者的外周血，使用NGS的方法检测EGFR T790M突变状态，并分析其与临床特征和预后的相关性，为晚期LUAD患者后续治疗方案提供临床参考依据。

1 对象与方法

1.1 对象

收集2012年1月至2016年1月在南京总医院一线接受EGFR-TKI(吉非替尼、厄洛替尼、埃克替尼)治疗的93例晚期肺腺癌患者，所有患者经病理证实为晚期肺腺癌且伴有EGFR基因敏感突变(19-del，21-L858R)，所有患者在耐药后以外周血为液体活检标本进行NGS检测。在首次出现疾病进展或T790M突变前，不允许交叉使用化疗和其他EGFR-TKI，同时根据相关指南、方针，允许EGFR-TKI在剂量方面的增减。按照实体瘤疗效评

价(RECIST 1.1)标准，每隔6~8周进行CT影像学评估。本研究经南京总医院伦理委员会批准，同时每位患者均签署知情同意书。PFS定义为患者从口服EGFR-TKI第1天开始到第1次出现疾病进展、死亡和最后一次随访的时间(以月为单位)，OS定义为从EGFR-TKI 治疗的第1天开始至死亡或最后一次随访的时间(以月为单位)。

1.2 纳入患者的特征

其中男性占比为40.9%(38/93)，女性59.1%(55/93)；年龄29~86(中位59)岁；吸烟者占比为25.8%(24/93)，不吸烟者74.2%(69/93)；IIIB期、IV期(国际抗癌联盟第七版肺癌TNM分期)分别占比为7.5%(7/93)和92.5%(86/93)；全部患者均经病理证实为浸润性腺癌，其中贴壁为主型、腺泡为主型、乳头为主型、微乳头为主型、实体为主型(2011年IASLC/ATS/ERS公布的国际多学科新分类方案)[8]分别占比为15.1%(14/93)，55.9%(52/93)，17.2%(16/93)，6.5%(6/93)，5.4%(5/93)；所有患者ECOG评分为0~3分，其中0~1分、2~3分别占比为58.1%(54/93)和41.9%(39/93)；所有患者在EGFR-TKI治疗前均伴有EGFR基因敏感突变且均无T790M阳性突变，其中19-del和21-L858R分别占比为48.4%(45/93)和51.6%(48/93)；第一代EGFR-TKI耐药后接受第三代EGFR-TKI(奥希替尼)治疗和含铂双药化疗的患者分别占比为57.0%(53/93)和43.0%(40/93)(表1)。

表1 晚期LUAD患者T790M突变状态的临床特征

Table 1 Clinical characteristics of T790M mutation status in advanced LUAD

临床特征	*n*	T790M(−)	T790M(+)	χ^2	*P*
性别				8.801	0.003
男	38	25	13		
女	55	19	36		
年龄/岁				1.705	0.216
<60	51	21	30		
⩾60	42	23	19		
吸烟史				4.861	0.034
无	69	28	41		
有	24	16	8		
临床分期				1.766	0.249
IIIB期	7	5	2		
IV期	86	39	47		
组织学亚型				7.142	0.129
贴壁为主型浸润性腺癌	14	10	4		
腺泡为主型浸润性腺癌	52	20	32		
乳头为主型浸润性腺癌	16	7	9		
微乳头为主型浸润性腺癌	6	3	3		
实体为主型浸润性腺癌	5	4	1		
ECOG评分				0.053	0.836
0~1	54	25	29		
2~3	39	19	20		

续表1

临床特征	*n*	T790M(−)	T790M(+)	χ^2	*P*
EGFR突变类型				1.870	0.214
19-del	45	18	27		
21-L858R	48	26	22		
EGFR-TKI种类				0.482	0.786
吉非替尼	63	30	33		
厄洛替尼	13	7	6		
埃克替尼	17	7	10		
EGFR-TKI耐药后进展类型				7.894	0.007
局部进展	46	15	31		
远处转移	47	29	18		
EGFR-TKI耐药后血CEA水平/(μg·L^{-1})				14.758	<0.001
<90.1	67	40	27		
≥90.1	26	4	27		
EGFR-TKI耐药后治疗方案				64.033	<0.001
奥希替尼	53	6	47		
含铂双药化疗	40	38	2		

1.3 标本的收集和T790M突变的检测

所有患者均经影像学评估进展后采取外周静脉血10~15mL于DNA保护真空管(厦门AmoyDx公司)中，并将所有血液样本均在36 h内于2 500 r/min，4 ℃条件下离心10 min，上清转移至新的离心管于15 800 r/min、4 ℃条件下继续离心15 min，最终得到的上清液于−80 ℃超低温冰箱保存，按照QIAamp(德国Qiagen公司)循环核酸试剂盒说明提取外周血循环肿瘤DNA(circulating tumor DNA，ctDNA)，并采用二代测序(NGS)的方法对ctDNA中T790M突变进行鉴定。

1.4 随访

通过电话的方式进行随访，全部患者均得到随访，无失访。所有患者的随访时间为2~78个月，截止到2018年6月1日，全部93例患者中存活19例，死亡74例，中位PFS为9.5个月，中位OS为24.2个月。

1.5 统计学处理

数据均采用SPSS 22.0软件进行统计分析。计数资料采用(%)表示，行χ^2检验；血CEA水平预测T790M阳性突变的最佳临界点采用受试者工作特征曲线(receiver operation curve，ROC)曲线计算获得；采用Kaplan-Meier法进行生存预后分析并行Log-Rank检验；Cox比例风险模型分析影响PFS和OS的因素，P<0.05为差异有统计学意义。

2 结果

2.1 EGFR-TKI耐药后患者的临床特征与T790M突变状态分析

所有获得性耐药的晚期LUAD患者中，T790M阳性突变率为52.7%(49/93)。T790M阳性突变与年龄、临床分期、组织学亚型、ECOG评分、初始EGFR突变类型、EGFR-TKI种类均无统计学意义(P均>0.05)；但与性别(χ^2=8.801，P=0.003)、吸烟史(χ^2=4.861，P=0.034)、EGFR-TKI耐药后进展类型(χ^2=7.894，P=0.007)、EGFR-TKI耐药后血CEA水平(χ^2=14.758，P<0.001)、EGFR-TKI耐药后治疗方案(χ^2=64.033，P<0.001)比较差异有统计学意义(表1)。

2.2 EGFR-TKI 耐药后血 CEA 预测 T790M 阳性最佳分界点

EGFR-TKI耐药后血CEA预测T790M阳性的敏感度为44.9%，特异度为90.9%，临界值(cut-off)为90.1 μg/L，曲线下面积(AUC)为0.639(95%CI 0.526~0.752，*P*=0.021；图1)。

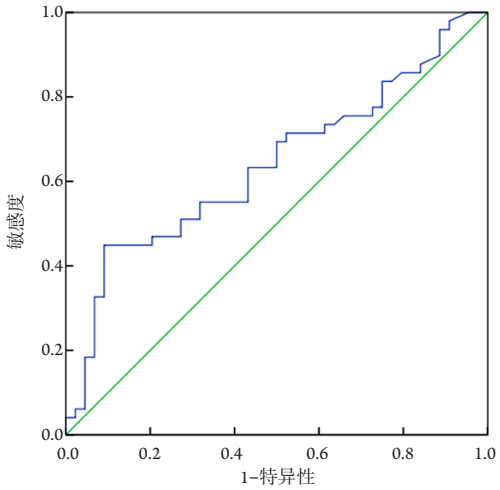

图1 EGFR-TKI耐药后血CEA预测T790M阳性ROC曲线

Figure 1 Level of serum CEA after EGFR-TKI resistance predicting T790M positive by ROC curve

2.3 T790M 突变状态与晚期 LUAD 预后的相关性

分别采用Kaplan-Meier法对可能影响患者PFS和OS的因素进行生存分析。T790M阳性突变患者的中位PFS和中位OS分别为12.4，29.5个月，均较T790M突变阴性的6.2，18.1个月显著延长(Log Rank *P*<0.001；图2，图3)；Cox单因素和多因素回归分析均提示T790M突变阳性是PFS(RR=0.302，95%CI 0.162~0.560；*P*<0.001)和OS(RR=0.422，95%CI 0.250~0.715；*P*=0.001)的独立影响因素，Cox单因素回归分析提示临床分期是PFS(RR =0.277，95%CI 0.123~0.621；*P*=0.002)的影响因素，而性别、年龄、吸烟史、分化程度、EGFR-TKI耐药后进展类型、EGFR-TKI耐药后血CEA水平对PFS和OS影响均无统计学意义(*P*均>0.05；表2，3)。

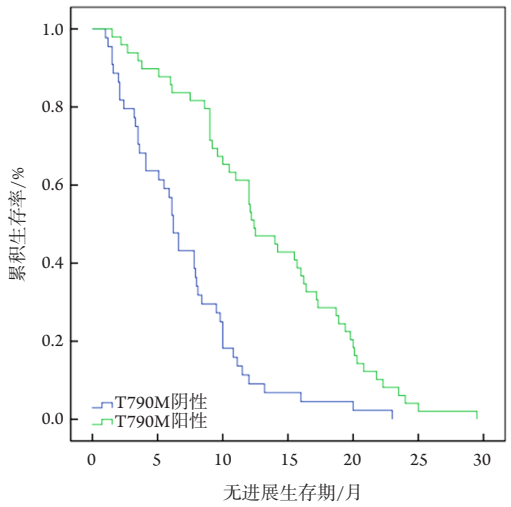

图2 T790M突变状态对PFS影响结果比较

Figure 2 Comparison of the effect of T790M mutation status on PFS

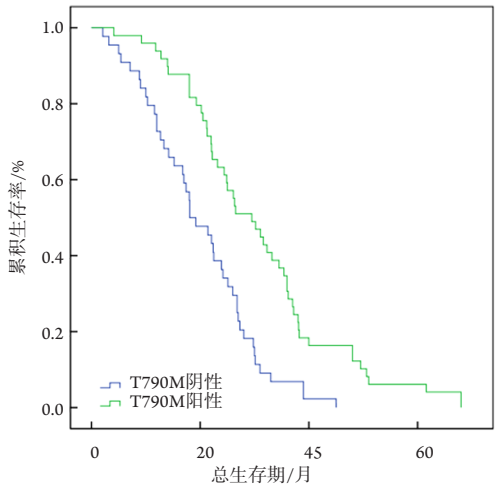

图3 T790M突变状态对OS影响结果比较

Figure 3 Comparison of the effect of T790M mutation status on OS

表2 影响晚期LUAD患者PFS相关因素的单因素和多因素Cox回归分析

Table 2 Analysis of PFS related factors in patients with advanced LUAD by univariate and multivariate Cox regression

参数	单因素Cox回归分析		多因素Cox回归分析	
	RR(95% CI)	*P*	RR(95% CI)	*P*
性别	0.839 (0.546~1.287)	0.421	1.315 (0.672~2.574)	0.424
年龄	1.295 (0.852~1.967)	0.226	1.172 (0.750~1.833)	0.485
吸烟史	1.188 (0.738~1.913)	0.479	1.243 (0.617~2.504)	0.543
临床分期	0.277 (0.123~0.621)	0.002	0.446 (0.190~1.043)	0.063
组织学亚型	1.143 (0.893~1.463)	0.290	1.166 (0.920~1.477)	0.205
EGFR-TKI耐药后进展类型	1.375 (0.904~2.091)	0.137	0.847 (0.513~1.401)	0.519
EGFR-TKI耐药后血CEA水平	0.720 (0.456~1.137)	0.159	1.068 (0.628~1.815)	0.809
T790M突变	0.345 (0.223~0.534)	<0.001	0.302 (0.162~0.560)	<0.001

表3 影响晚期LUAD患者OS相关因素的单因素和多因素Cox回归分析

Table 3 Analysis of OS related factors in patients with advanced LUAD by univariate and multivariate Cox regression

参数	单因素Cox回归分析		多因素Cox回归分析	
	RR (95% CI)	*P*	RR (95% CI)	*P*
性别	0.977 (0.643~1.482)	0.912	1.534 (0.810~2.906)	0.189
年龄	1.236 (0.815~1.874)	0.319	1.265 (0.789~2.028)	0.329
吸烟史	1.239 (0.776~1.981)	0.370	1.547 (0.762~3.142)	0.227
临床分期	0.462 (0.211~1.011)	0.053	0.619 (0.272~1.409)	0.253
组织学亚型	1.113 (0.865~1.433)	0.405	1.071 (0.838~1.367)	0.584
EGFR-TKI耐药后进展类型	1.409 (0.924~2.148)	0.111	1.100 (0.699~1.730)	0.681
EGFR-TKI耐药后血CEA水平	0.762 (0.481~1.207)	0.247	0.989 (0.578~1.691)	0.967
T790M突变	0.422 (0.271~0.653)	<0.001	0.422 (0.250~0.715)	0.001

3 讨论

第一代EGFR-TKIs目前已被批准为EGFR基因敏感突变的晚期NSCLC患者的首选治疗方法[9-10]。然而，几乎所有患者在10~12个月后会不可避免地产生获得性耐药[11]。液体活检作为一种新兴的肿瘤基因突变检测技术，相较于传统组织活检具有操作简单、非侵入性、能更有效识别肿瘤异质性等优点。研究[7,12]表明液体活检检出T790M阳性突变率和组织的一致性约为80%。本研究在所有一线使用EGFR-TKI治疗后耐药的晚期LUAD患者中T790M阳性检出率为52.7%，这与在高加索人群[13]和东亚人群[14]中研究结果一致。然而，魏媛等[15]利用扩增阻滞突变系统(Amplification Refractory Mutation System，ARMS)在49例继发耐药的NSCLC中检测出T790M突变率为30.6%，Sun等[16]研究结果表明T790M突变阳性率在东亚人群的突变率偏低。因此种族因素、检测方法以及肿瘤异质性等原因可能影响外周血T790M突变的检出率[17]。本研究采用二代测序技术(next generation sequence，NGS)对所有患者外周血进行检测，该方法可以获得完整的基因序列，同时能检测出多种基因异常，因此敏感性较一代测序技术高。

本研究结果显示T790M突变与晚期LUAD患者的年龄、临床分期、组织学亚型、ECOG评分、EGFR-TKI种类均无关，与既往研究[18-19]结果一致，但与性别、吸烟史有关。有研究[20-22]表明约2/3的T790M突变阳性常见于不吸烟的女性患者，但一

项纳入49例耐药晚期NSCLC的研究[15]指出T790M阳性突变率与性别、吸烟史均无关，这可能与研究入组的人群以及T790M的检测方法有关，因此关于性别、吸烟史与T790M获得性突变的关系有待后期进一步研究。本研究发现T790M突变与EGFR-TKI耐药后进展类型密切相关，但与初始EGFR突变类型比较差异无统计学意义。有报道[23-24]指出T790M突变状态与晚期NSCLC患者软脑膜和骨转移密切相关，说明T790M阳性突变与晚期LUAD患者的远处转移密切相关，同时Matsuo等[25]研究发现EGFR 19del比其他类型的突变有着较高的T790M阳性突变率。由于本研究样本例数较少，尚未得出此结论，有待于后续增加样本量进一步研究。

CEA一直被认为是NSCLC(尤其是腺癌)的肿瘤标志物，血CEA水平随着疾病的进展以及治疗干预波动[26]。Qin等[27]研究发现吉非替尼治疗的晚期NSCLC患者，高CEA组的PFS显著优于低CEA组；Cui等[28]研究指出与正常血CEA水平相比，血CEA水平升高的晚期NSCLC患者有着更长的PFS；也有研究[29]表明高CEA水平与更久OS显著相关。本研究结果显示EGFR-TKI耐药后T790M突变阳性患者血CEA水平显著高于阴性患者，耐药后血CEA水平预测T790M阳性突变的cut-off值为90.1 μg/L，可能的原因是EGFR-TKI耐药后高的血CEA水平与T790M获得性突变有关，但诊断效能偏低，后续仍需更大型研究加以验证。

最后在预后方面，T790M突变阳性的晚期LUAD患者的PFS和OS均较阴性患者显著延长，Cox单因素和多因素回归分析均提示T790M突变阳性是PFS和OS的独立影响因素，这与Ma等[30]和Oxnard等[19]研究结果一致。在一项纳入33例EGFR-TKI耐药的晚期NSCLC研究[31]显示：T790M突变阳性患者的PFS较突变阴性显著延长，但Sakai等[32]检测了75例晚期NSCLC患者血浆T790M突变，结果显示获得性T790M突变阳性组与阴性组比较差异无统计学意义。Uramoto等[33]指出EGFR-TKI耐药的患者中伴有T790M阳性突变组5年生存率也远高于阴性组。因此，在EGFR-TKI治疗后耐药的患者中，T790M阳性突变可能提示肿瘤惰性生长且具有相对较好的预后。可能的原因首先是由于肿瘤的异质性[34]；其次除了T790M突变引起耐药外，其他机制(c-met基因扩增、KRAS基因激活等)[19,35]可能与肿瘤细胞的早期侵袭和转移有关，最终导致T790M阴性患者呈现出不良预后；而且有相当一部分T790M阳性突变的耐药患者可能对后续的化疗药物更敏感[19,36]。

综上所述，NGS方法测序、分析肿瘤外周血有利于发现一些潜在的耐药机制，T790M获得性突变是EGFR-TKIs耐药的晚期LUAD患者预后良好的因素，这种获得性突变产生的机制错综复杂，未来仍需进一步探索。

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