非小细胞肺癌患者葡萄糖代谢显像半定量指标与肿瘤增殖指数相关性

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摘　要:[目的]评价最大标准化摄取值(SUVmax)与 Ki-67 相关性,以期对接受氟[^{18}F]-氟代脱氧葡萄糖(^{18}F-fluorodeoxyglucose)正电子发射断层显像/计算机体层摄影(^{18}F-FDG PET/CT)检查的非小细胞肺癌(NSCLC)患者的肿瘤增殖活性预估判断。[方法]回顾性分析我院经手术病理证实的 111 例初发 NSCLC 的临床病理资料和 ^{18}F-FDG PET/CT 显像结果。采用多因素线性回归和亚组分析对原发灶 SUVmax 和 Ki-67 进行相关分析。以不同的界值将 SUVmax 转变为二分类变量,分别与 Ki-67 以及其他临床参数进行用多因素 Logistic 回归,寻找 SUVmax 与 Ki-67 相关的最佳界值。[结果]多因素线性回归显示病理亚型、TNM 分期、原发灶最大径,Ki-67 与 SUVmax 中度相关(r=0.66)。亚组相关分析提示:当原发灶为腺泡为主型时、以及不论有无淋巴结转移,SUVmax 均与 Ki-67 相关。多因素 Logistic 回归显示分类变量 SUVmax(界值 2.5)与 Ki-67 相关(P=0.01)。[结论]NSCLC 的原发病灶葡萄糖代谢显像半定量参数 SUVmax 与肿瘤增殖活性指标 Ki-67 中度相关,SUVmax≥2.5 提示肿瘤增殖活跃,初步判断患者预后不良。

主题词:非小细胞肺癌;^{18}F-FDG PET/CT;最大标准化摄取值;Ki-67
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Relationship Between SUVmax in ^{18}F-FDG PET/CT and Expression of Ki-67 in Patients with Non-small Cell Lung Cancer

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Abstract: [Objective] To investigate the association between the preoperative maximum standardized uptake value(SUVmax) of primary lesions measured on ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) and expression of Ki-67 labeling index (Ki-67) in patients with non-small cell lung cancer (NSCLC). [Methods] One hundred and eleven patients with NSCLC received surgical treatment and the ^{18}F-FDG PET/CT examination was performed preoperatively. The SUVmax values of ^{18}F-FDG PET/CT were estimated, and the expression of Ki-67 in cancer tissue was detected with histoimmunochemistry SP method. The association between SUVmax and Ki-67 expression, and the association of dichotomized SUVmax (2.5), mean SUVmax and median SUVmax with Ki-67 was analyzed with multivariate Logistic regression, respectively. [Results] Multiple linear regression showed regardless of pathological subtypes, TNM stage and maximum diameter of primary lesion, Ki-67 and SUVmax displayed a moderate correlation (r=0.66). In acinar predominant adenocarcinoma, N_0 or N_{1-3}, SUVmax was significantly correlated with Ki-67. Dichotomous SUVmax (cutoff point: 2.5) was significantly associated with Ki-67(P=0.01). [Conclusion] A moderate relationship exists between the SUVmax values and Ki-67 expression. SUVmax ≥2.5 of primary lesion may suggest active tumor proliferation and poor prognosis of patients with NSCLC.

Subject words: non-small cell lung cancer; ^{18}F-FDG PET/CT; maximum standardized uptake value; Ki-67

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非小细胞肺癌(non-small cell lung cancer,NSCLC)是一组起源相似而生物学行为及预后不同的异质性肿瘤。影响NSCLC预后的因素众多,有文献报道的相关预后因素多达150种以上[1]。肿瘤细胞增殖活性[2-4]及葡萄糖代谢活性[5-6]都被认为是具有重要临床价值的NSCLC预后因素。增殖活性指标增殖细胞核抗原指数(Ki-67 labeling index,Ki-67)从细胞增殖角度反映肿瘤细胞的生物学特性,氟[^{18}F]-氟代脱氧葡萄糖(^{18}F-fluorodeoxyglucose)正电子发射断层显像/计算机体层摄影(positron emission tomography/computed tomography,^{18}F-FDG PET/CT)检查的半定量指标标准化摄取值(standardized uptake value,SUV),从肿瘤代谢活性角度反映肿瘤细胞的生物学特性,肿瘤增殖依赖于糖代谢。因此,理论上SUV应与Ki-67有着一定的内在联系。现有多项研究肯定了SUV与Ki-67呈正相关[2,7-15],但这些文献多用单因素分析,未考虑病理亚型[7],或未考虑TNM分期差异[7-10],或两者均未考虑[11-14],而NSCLC是一组具有较高异质性的肿瘤,病理亚型和TNM分期不同其肿瘤代谢活性和增殖活性都有差异。

本研究将最大标准化摄取值(maximum standardized uptake value,SUVmax)与Ki-67以及年龄、性别、病理亚型、分化程度、TNM分期、N分期、M分期和原发灶最大径进行相关性分析,运用多因素线性回归寻找SUVmax与NSCLC临床病理特征,尤其是SUVmax与Ki-67之间潜在联系;并探索以SUVmax评估Ki-67的界值,以期对^{18}F-FDG PET/CT的NSCLC患者的肿瘤增殖活性的预估判断。

1 资料与方法

1.1 临床资料

回顾性收集我院2010年7月至2014年9月经手术病理证实的111例初发NSCLC的临床病理资料(包括性别、年龄、病理亚型、分化程度、TNM分期、Ki-67)和术前^{18}F-FDG PET/CT原发灶的SUVmax值(Table 1)。所有病例的病理结果均经手术病理获得,手术病理检查与^{18}F-FDG PET/CT检查的时间差不超过4周。TNM分期参照国际肺癌研究联合会(international

Table 1 Baseline of the clincal parameters[a]

Clinic parameters	N	Frequency (%)
Age[a] [Mean±SD (Range)]	111	63.5±10.0(38~84)
Gender		
Male	77	69.4
Female	34	30.6
Pathological subtype		
Adenocarcinoma	71	64.0
Acinar predominant	29	26.1
Papillary predominant	6	5.4
Solid predominant	10	9.0
Other[b]	26	23.4
Squamous cell carcinoma	37	33.3
Highly differentiated predominant	3	2.7
Moderately differentiated predominant	20	18.0
Poorly differentiated predominant	13	11.7
Other[c]	1	0.9
Other subtype[d]	3	2.7
TNM Stage		
Ⅰ	37	33.3
Ⅱ	22	19.8
Ⅲ	32	28.8
Ⅳ	20	18.0
N Stage		
N_0	53	47.7
N_{1-3}	58	52.3
N_1	21	18.9
N_2	23	20.7
N_3	14	12.6
M Stage		
M_0	90	81.1
M_1	18.9	18.9
	Median	Q1[e] Q3[f]
SUVmax[a]	7.70	4.0 11.2
Maximum diameter of primary lesion[a] (mm)	30	20 50
Ki-67[a]	0.30	0.10 0.50

a:Test of normality demonstrated age was normal distribution,but SUVmax,maximum diameter of primary lesion and Ki-67 were skewed distribution.
b:1 case of adenocarcinoma in situ,1 case of minimally invasive adenocarcinoma,2 cases of lepidic predominant invasive adenocarcinoma,1 case of micropapillary predominant invasive adenocarcinoma,18 cases of non-single predominant invasive adenocarcinoma and 3 cases of variant invasive adenocarcinoma (1 case of invasive mucinous adenocarcinoma,1 case of intestinal adenocarcinoma and 1 case of colloid carcinoma).
c:2 cases can't be identified which degree of differentiation was predominant.
d:1 case of adenosquamous carcinoma,1 case of large cell carcinoma,1 case of bronchial sarcomatoid carcinoma.
e:lower quartile.
f:upper quartile.

association for the study of lung cancer,IASLC）第 7 版肺癌 TNM 分期标准。

1.2 检查方法

显像仪器为 Gemini GXL PET/CT(Philips Medical Systems,Cleveland,OH)。每例患者在 PET/CT 显像当日均要求空腹 6h 以上,并禁止剧烈运动。患者注射 ^{18}F-FDG(0.10mCi/kg,3.7 MBq/kg)后安静休息 60~80min,排尿后进行 PET/CT 显像。首先进行 CT 全身平扫,扫描范围从颅底至股骨中段;扫描参数为层厚 2mm,螺距 0.81,管电压 120kV,电流 100mA,矩阵 512×512。随之行 PET 图像采集,扫描参数为矩阵 144×144,18cm(1.5min)/床位,共 8~9 个床位。然后每位患者接受了屏气状态下的胸部 CT 平扫,管电压 120kV,管电流 100mA。图像重建后由 EBW V3.5.2.2264、PET/CT Application Suite V1.5.1A 进行图像融合。根据横断面、矢状面、冠状面 3 个不同层面确定病灶位置，在其放射性摄取最高层面上勾画感兴趣区(region of interest,ROI),由计算机根据受检者体重、显像剂注射剂量、注射时间以及 ROI 放射性计数自动计算出病灶的标准化摄取值(standardized uptake value,SUV)。本研究取 SUV 最大值(maximum standardized uptake value,SUVmax）作为分析指标。

1.3 Ki-67 免疫组化测定及判定标准

按常规 SP 法操作,具体步骤参照试剂盒说明。Ki-67 阳性细胞在细胞核着棕黄色,随机选取 10 个高倍镜视野(×400)计数阳性细胞数,求平均数。

1.4 统计学处理

应用 SAS 9.2 统计软件进行数据分析。计数资料采用构成比描述，计量资料采用［均数±标准差或中位数(Q1,Q3)］描述。本研究中 SUVmax、Ki67、最大径为偏态分布，因此两组间对比采用 Wilcoxon Rank-Sum 检验或 Mann-Whitney *U* 检验，偏态分布数据相关性分析采用秩相关。对因变量进行对数转换,对无序多分类变量进行哑变量设置,采用逐步多元线性回归进行多因素分析。检验水准 α=0.05。

2 结 果

2.1 SUVmax 与临床病理特征相关性

对年龄、性别、TNM 分期、N 分期、M 分期、病理分型、原发灶最大径、Ki-67 与 SUVmax 进行多因素线性回归分析。首先,采用残差正态性检验,发现残差不符合正态性,因此,对因变量 SUVmax 进行对数转换,然后进行共线性诊断,发现 TNM 分期和 M 分期共线性问题严重,采用逐步回归法筛选变量,同时对病理分型进行哑变量设置,肺腺癌(简称腺癌)为对照组,X1 为肺鳞状细胞癌,X2 为其他类型，最终参数检验结果可知病理亚型、TNM 分期（TNM)、原发灶最大径(D)和 Ki-67(Ki-67)(Figure 1)与 SUVmax 相关,回归方程为:

SUVmax=0.62+0.38X1-0.59X2+0.16TNM stage+0.013D+0.66Ki-67

基于分化程度、N 分期(淋巴结转移与否)、M 分期进行分层,腺癌的腺泡为主型(P=0.009)、N_0 期(无淋巴结转移)(P<0.001)、$N_{1\text{-}3}$ 期(淋巴结转移)(P=0.01)的各组内 SUVmax 与 Ki-67 显著性相关(Table 2)。

2.2 SUVmax 界值选择

选取 SUVmax 2.5、SUVmax 均值 7.85、SUVmax 中位数 7.70 作为界值，将 SUVmax 转变为二分类变量,分别与 Ki-67 以及其他临床因素(年龄、性别、

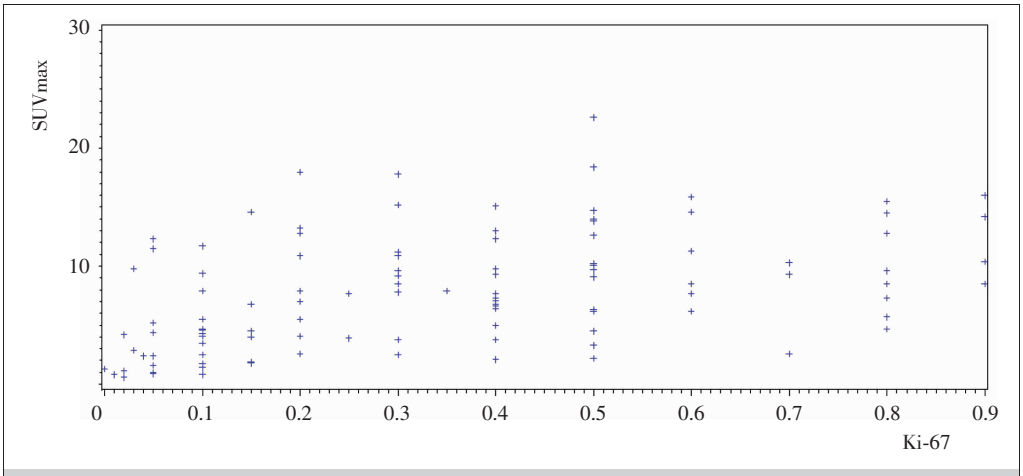

Figure 1 Scatter plot of correlation between Ki-67 and SUVmax in 111 patients

Table 2 The correlation analysis between SUVmax and Ki-67

Clinic parameters	N	Correlation coefficient	*P*
Pathological subtype			
Adenocarcinoma	71	0.42[a]	<0.001
Acinar predominant	29	0.48[a]	0.009
Papillary predominant	6	0.56[a]	0.250
Solid predominant	10	–0.01[b]	0.980
Squamous cell carcinoma	37	–0.08[a]	0.650
Moderately differentiated predominant	20	0.16[a]	0.500
Poorly differentiated predominant	13	–0.34[b]	0.260
N stage			
N_0	53	0.65[a]	<0.001
N_{1-3}	58	0.33[a]	0.010
M stage			
M_0	90	0.49[a]	<0.001
M_1	21	0.32[a]	0.150

a:Spearman correlation analysis.b:Pearson correlation analysis.

Table 3 Multivariate Logistic regression[a] between dichotomous SUVmax with deferent cutoff point and clinic parameters

Cutoff point of SUVmax	Parameters	B	OR (95%CI)	Wald	*P*
SUVmax=2.5	Ki-67	7.660	2122.623(6.30~715128.267)	6.656	0.010
	Diameter	0.186	1.204(1.052~1.379)	7.270	0.007
	N stage				
	N_0	–2.715	0.066(0.006~0.681)	5.213	0.022
	N_{1-3}		1.000		
SUVmax=7.85[b]	Ki-67	0.806	2.240(0.202~24.803)	0.432	0.511
	Diameter	0.060	1.062(1.031~1.093)	15.709	<0.001
SUVmax=7.70[c]	Ki-67	0.895	2.448(0.220~27.239)	0.530	0.467
	Diameter	0.064	1.067(1.034~1.101)	16.231	<0.001

a:There were age,TNN stage,N stage,pathologic subtype,maximal diameter of primary lesion and Ki-67 which had been chosen in multivariate Logistic regression. Besides Ki-67,the parameters with P<0.05 was demonstrated in table 3. b:7.85 was mean of SUVmax. c:7.70 was median of SUVmax.

TNM 分期、N 分期、M 分期、病理分型、原发灶最大径)进行多元 Logistic 回归分析,寻找与 Ki-67 相关最高的 SUVmax 界值,结果显示 SUVmax=2.5 作为界值时,SUVmax 与 Ki-67 显著性相关(Table 3)。

3 讨 论

^{18}F-FDG PET/CT 检查所得最大标准化摄取值(maximum standardized uptake value,SUVmax)是衡量肿瘤葡萄糖代谢程度的半定量指标,可在分子水平对肿瘤进行显像,通过 SUVmax 对局部葡萄糖代谢情况进行量化分析,从代谢活性角度反映肿瘤细胞的生物学特性。细胞增殖是能量代谢增加的基础,异常分裂和增殖是肿瘤细胞的特点,需要大量的能量代谢支持。增殖细胞核抗原(Ki-67)属于免疫球蛋白,系鼠单克隆抗体,抗霍奇金淋巴瘤细胞株的部分细胞核抗体,细胞增殖的各期(G1,S,G2 和 M)中均有表达,但在细胞静止期 G0 期则几乎不表达。Ki-67 指数是反映细胞增殖的重要指标。围绕 Ki-67 展开了大量恶性肿瘤方面的研究,肯定了其预后价值[2,15–17]。^{18}F-脱氧胸腺嘧啶核苷(^{18}F-FLT)是胸苷嘧啶类似物,一般认为是反映肿瘤细胞增殖能力的正电子显像剂。相比 ^{18}F-FDG,理论上 ^{18}F-FLT 与 Ki-67 关联程度更直接,这些结论也得到临床研究证实[11,18–19]。但有研究表明影响 ^{18}F-FLT 摄取因素并不仅仅是细胞增殖水平,可能也存在其他机制[20],相较 ^{18}F-FDG,^{18}F-FLT 与 Ki-67 相关性并不优于 ^{18}F-FDG[21]。而 ^{18}F-FDG 在临床中已经得到广泛地应用,肿瘤细胞增殖主要依赖于糖酵解供能,其细胞恶变的多种信号转导通路都接受糖代谢调控[22]。

本研究针对 NSCLC 原发病灶,对 ^{18}F-FDG PET/CT SUVmax 和 Ki-67 关联分析,多因素线性回归和亚组分析显示 Ki-67 与 SUVmax 中度正相关,这与之前的临床研究[8,14–15,21,23]和荟萃分析[2,19]结果基本一致。本研究将 SUVmax=2.5 以及 111 个原发病灶 SUVmax 中位数和均数分别与 Ki-67 行多因素 Logistic 回归分析,以确定 SUVmax 预估 Ki-67 界值,结果显示 SUVmax=2.5,这个在肿瘤定性中得到广泛认识的界值,是预测肿瘤增殖特性的最优界值,有助于简化临床应用。当然,本研究亚组分析样本量较小,部分亚组呈小样本;预估 Ki-67 的 SUVmax=2.5 还需要得到前瞻性、大样本研究的进一步验证。

总之,葡萄糖代谢显像半定量指标 SUVmax 与 Ki-67 有着较强的关联,对于接受 ^{18}F-FDG PET/CT 的 NSCLC 患者,SUVmax≥2.5 提示肿瘤增殖活跃,从而初步判断患者预后不良。

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