

¹⁸F-FDG PET/CT肿瘤内代谢异质性指数预测胃腺癌隐匿性淋巴结转移的价值

Value of ¹⁸F-FDG PET/CT intra-tumor metabolic heterogeneity index for predicting occult lymph node metastasis in gastric adenocarcinoma

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·临床研究·

¹⁸F-FDG PET/CT 肿瘤内代谢异质性指数 预测胃腺癌隐匿性淋巴结转移的价值

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【摘要】目的 评估术前¹⁸F-氟脱氧葡萄糖(FDG) PET/CT 原发灶肿瘤内代谢异质性指数(HI)对胃腺癌隐匿性淋巴结转移(OLM)的预测价值。**方法** 回顾性分析2016年1月至2022年12月于郑州大学第一附属医院术前行¹⁸F-FDG PET/CT 检查的79例胃腺癌患者的临床资料，其中男性62例、女性17例，年龄(63.8 ± 9.0)岁。所有患者均于¹⁸F-FDG PET/CT 显像后1个月内行胃腺癌根治术，根据术后组织病理学检查结果分为 OLM 阳性组($n=39$)和 OLM 阴性组($n=40$)。采用卡方检验、两独立样本 t 检验(方差齐)和 Mann-Whitney U 检验对胃腺癌患者的临床特征、¹⁸F-FDG PET/CT 代谢参数进行组间比较。采用单因素及多因素 logistic 回归模型分析预测 OLM 的独立危险因素。采用受试者工作特征(ROC)曲线分析 HI 对 OLM 的诊断效能。**结果** OLM 阳性组与 OLM 阴性组间性别、分化程度及病理 T 分期差异均有统计学意义($\chi^2=3.903 \sim 6.361$ ，均 $P < 0.05$)。OLM 阳性组原发灶 HI-2 明显高于 OLM 阴性组 [4.98(2.68, 8.44) 对 2.61(1.84, 4.23)]，且差异有统计学意义($z=-3.178$ ， $P < 0.05$)；而 OLM 阴性组原发灶 SUV_{max}、SUV_{mean}、HI-1 [5.59(4.46, 7.51) 对 6.91(5.11, 10.64) = 3.33(3.06, 3.85) 对 3.65(3.25, 4.64) = 0.23±0.12 对 0.29±0.14] 均明显高于 OLM 阳性组，且差异均有统计学意义($z=-2.000$ 、-2.001， $t=2.096$ ；均 $P < 0.05$)。单因素 Logistic 回归模型分析结果显示，分化程度($OR=4.037$ ，95%CI: 1.295~12.585， $P < 0.05$)、病理 T 分期($OR=4.080$ ，95%CI: 1.310~12.709， $P < 0.05$)、HI-1($OR=0.025$ ，95%CI: 0.001~0.992， $P < 0.05$)和 HI-2($OR=7.368$ ，95%CI: 2.385~22.764， $P < 0.001$)是 OLM 的危险因素；多因素 logistic 回归模型分析结果显示，病理 T 分期($OR=4.780$ ，95%CI: 1.238~18.458， $P < 0.05$)和 HI-2($OR=6.893$ ，95%CI: 1.922~24.718， $P < 0.05$)是胃腺癌患者 OLM 的独立危险因素。ROC 曲线分析结果显示，HI-2 预测 OLM 的 ROC 曲线下面积(AUC)为 0.708(95%CI: 0.237~0.483， $P=0.001$)，当以其最佳临界值 4.962 进行预测时，其诊断 OLM 的灵敏度和特异度分别为 51.3%(20/39) 和 87.5%(35/40)。**结论** 胃腺癌术前¹⁸F-FDG PET/CT 原发灶肿瘤内代谢 HI 对胃腺癌 OLM 具有预测价值，且 HI-2 是 OLM 的独立危险因素。

【关键词】 胃肿瘤；淋巴结；肿瘤转移；正电子发射断层显像术；体层摄影术，X 线计算机；脱氧葡萄糖

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Value of ¹⁸F-FDG PET/CT intra-tumor metabolic heterogeneity index for predicting occult lymph node metastasis in gastric adenocarcinoma

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[Abstract] Objective To investigate the predictive value of ¹⁸F-fluorodeoxyglucose(FDG)

PET/CT primary lesions metabolic heterogeneity index for occult lymph node metastasis(OLM) in gastric cancer. **Methods** A retrospective analysis was performed on 79 patients [62 males, 17 females, age (63.8±9.0) years] with gastric cancer who underwent ¹⁸F-FDG PET/CT imaging and were diagnosed as clinical (c)N0 stage before surgery from January 2016 to December 2022 in the First Affiliated Hospital of Zhengzhou University. All patients underwent radical gastrectomy in our hospital within 1 month after imaging, and were divided into OLM-positive group and OLM-negative group according to postoperative pathology to determine whether there was lymph node metastasis. The following PET/CT parameters were measured: The maximum, mean and peak normalized uptake values (SUVmax, SUVmean, SUVpeak), tumor metabolic volume (MTV) and total focal glycolysis (TLG) of the primary lesions. And TLR (tumor - liver ratio), heterogeneity index -1 (HI-1) and heterogeneity index -2 (HI-2) were calculated. The t test and Mann-Whitney U test of two independent samples were used to compare the parameters between groups. The independent risk factors of OLM were analyzed by logistic regression. The diagnostic efficacy of heterogeneity index on OLM was analyzed by receiver operating characteristic (ROC) curve. **Results** A total of 39 (49.4%, 39/79) of the 79 patients were pathologically confirmed to have OLM. HI-2 in OLM positive group was higher than that in OLM negative group [4.98 (2.68, 8.44) vs 2.61 (1.84, 4.23), $z=-3.178$, $P < 0.05$], while SUVmax in OLM negative group was higher than that in OLM positive group [5.59 (4.46, 7.51) vs 6.91 (5.11, 10.64), $z=-2.000$, $P < 0.05$], SUVmean[3.33 (3.06, 3.85) vs 3.65 (3.25, 4.64), $z=-2.001$, $P < 0.05$], HI-1[0.23 ± 0.12 vs 0.29 ± 0.14 , $t=2.096$, $P < 0.05$] were significantly higher than those in OLM positive group. Multivariate logistic regression analysis showed that HI-2 was an independent risk factor for OLM [odds ratio (OR) =6.893, 95%CI: 1.922-24.718, $P < 0.05$]. The area under ROC curve (AUC) of HI-2 for OLM prediction was 0.708 (95%CI: 0.237-0.483, $P=0.001$), and the sensitivity and specificity for OLM diagnosis were 51.3% (20/39) and 87.5% (35/40), respectively, when the threshold was 4.962. **Conclusion** ¹⁸F-FDG PET/CT tumor metabolic heterogeneity index has predictive value for OLM in gastric cancer, and heterogeneity index -2 is an independent risk factor for OLM.

[Key words] Stomach neoplasms; Lymph nodes; Neoplasm metastasis; Positron-emission tomography; Tomography, X-ray computed; Deoxyglucose

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胃癌是最常见的恶性肿瘤之一。2020 年全球癌症统计数据显示，在 185 个国家或地区的 36 种癌症中，胃癌的发病率居第 5 位，病死率居第 4 位^[1]。我国胃癌患者总体 5 年生存率不足 50%，转移和术后复发是其预后差的主要原因，其中淋巴结转移是主要危险因素之一^[3]。评估淋巴结转移的重要指标之一是淋巴结大小，但胃癌患者中超过 60% 的转移淋巴结小于 8 mm^[4]，导致 CT 检出率较低。通过 ¹⁸F-FDG PET/CT 显像中葡萄糖代谢情况和淋巴结短径综合评估淋巴结转移，从而提高术前淋巴结分期的准确性^[5]。然而，在临幊上综合评估为 N0 期的胃癌患者中，仍可发现 11%~56% 的患者术后存在淋巴结转移^[6-7]，即隐匿性淋巴结转移(occult lymph node metastasis, OLM)。存在 OLM 的患者更易出现肿瘤复发，预后较差^[8]。因此，OLM

的早期确诊对临幊医师精准制定治疗方案及预后评估具有重要意义。¹⁸F-FDG PET/CT 有多个异质性指数(heterogeneity index, HI)，如变异系数^[9]、线性回归斜率^[10]等，有研究者发现 HI 对于多种恶性肿瘤的 OLM 具有预测价值^[11-12]。目前采用 HI 预测胃癌患者的 OLM 尚无有效依据。胃腺癌是胃癌最常见的类型，本研究旨在探讨胃腺癌患者术前 ¹⁸F-FDG PET/CT 显像中原发灶的肿瘤内代谢 HI 对胃癌 OLM 的预测价值。

1 资料与方法

1.1 研究对象

回顾性分析 2016 年 1 月至 2022 年 12 月于郑州大学第一附属医院术前行 ¹⁸F-FDG PET/CT 检查的 79 例胃腺癌患者的临床资料，其中男性 62 例、

女性17例，年龄(63.8±9.0)岁。所有患者均于显像后1个月内行胃腺癌根治术，根据术后组织病理学检查结果分为OLM阳性组($n=39$)和OLM阴性组($n=40$)。比较2组患者的年龄、性别、肿瘤原发灶部位、分化程度、Lauren分型、病理T分期、糖类抗原199(carbohydrate antigen199, CA199)、癌胚抗原(carcinoembryonic antigen, CEA)等。纳入标准：(1)组织病理学检查结果为胃腺癌；(2)¹⁸F-FDG PET/CT检查后1个月内行胃腺癌根治术。排除标准：(1)术前影像检查发现任何区域疑似转移的淋巴结(CT或MRI图像上淋巴结短径≥10 mm或¹⁸F-FDG PET/CT图像上SUV_{max}≥2.5)；(2)伴有远处转移；(3)行任何抗肿瘤治疗；(4)伴有其他活动性恶性肿瘤；(5)因胃充盈差导致病灶观察不清；(6)无组织病理学检查结果或临床资料不完整。因本研究为回顾性研究，豁免签署患者知情同意书。本研究符合《赫尔辛基宣言》的原则。

1.2 ¹⁸F-FDG PET/CT显像

使用德国Siemens公司的Biograph Truepoint 64型PET/CT仪进行扫描。¹⁸F-FDG由日本住友集团的HM-20医用回旋加速器生产自动化合成模块合成，放射化学纯度≥98%。所有患者行PET/CT检查前禁食6 h以上，空腹血糖水平≤11.1 mmol/L。按患者体质量静脉注射¹⁸F-FDG 3.70~5.55 MBq/kg，嘱患者于安静状态下休息60 min后行PET/CT扫描，扫描范围自颅顶至大腿中上段。头部CT扫描参数：管电压120 kV、管电流380 mA、层厚3 mm；体部CT扫描参数：管电压120 kV、管电流由设备根据患者的身高、体质量及扫描部位自动调整，0.8 s/周。随后于相同扫描范围行PET三维扫描，扫描参数：头部3 min/床位，体部2.5 min/床位，共采集4~6个床位。采用德国Siemens公司的Syngo True D软件对PET/CT图像进行融合重建，最终得到横断面PET/CT融合图像。

1.3 ¹⁸F-FDG PET/CT图像分析

由2名5年以上工作经验的核医学科主治医师独立阅片并对图像进行参数评估，意见不一致时与高年资主任医师讨论后决定。以原发灶SUV_{max}=2.5为阈值手动勾画ROI体积(volume of interest, VOI)。SUV主要包括SUV_{max}、SUV_{mean}和标准化摄取值峰值(peak of standard uptake value, SUV_{peak})。肿瘤/肝脏比值(TLR)为原发灶SUV_{max}与肝脏

SUV_{mean}的比值。体积参数包括肿瘤代谢体积(metabolic tumor volume, MTV)和糖酵解总量(total lesion glycolysis, TLG)。计算2个HI：(1)HI-1即CV，为SUV的标准差(standard deviation, SD)与SUV_{mean}的比值，即SD/SUV_{mean}如文献[9, 13]所述；(2)HI-2即根据不同的SUV临界值(40%SUV_{max}、60%SUV_{max}和80%SUV_{max})对MTV进行线性回归的斜率的绝对值，通过对既往文献提出的方法[10, 14]修改后得出。

1.4 统计学方法

应用IBM SPSS 27.0软件对数据进行统计学分析。符合正态分布的计量资料以 $\bar{x}\pm s$ 表示，组间比较采用两独立样本t检验(方差齐)；不符合正态分布的计量资料以 $M(Q_1, Q_3)$ 表示，组间比较采用Mann-Whitney U检验。计数资料采用频数(%)表示，组间比较采用 χ^2 检验。对于缺失数据采用直接删除法。采用Logistic回归模型对OLM的危险因素进行单因素和多因素分析，将单因素分析中 $P<0.05$ 的因素纳入后续多因素分析。绘制ROC曲线评估对单因素分析存在意义的HI的诊断效能。 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 患者临床特征

由表1可知，OLM阳性组与OLM阴性组间性别、分化程度及病理T分期差异均有统计学意义(均 $P<0.05$)，年龄、肿瘤原发灶部位、分化程度、Lauren分型、CA199水平升高和CEA水平升高组间差异均无统计学意义(均 $P>0.05$)。

2.2 ¹⁸F-FDG PET/CT原发灶不同代谢参数的比较

由表2可知，OLM阳性组原发灶HI-2明显高于OLM阴性组，且差异有统计学意义($P<0.05$)；而OLM阴性组原发灶SUV_{max}、SUV_{mean}、HI-1均明显高于OLM阳性组，且差异均有统计学意义(均 $P<0.05$)。

2.3 临床特征及代谢参数对OLM的预测价值

由表3单因素Logistic回归模型分析结果可知，分化程度、病理T分期、HI-1和HI-2是OLM的危险因素；由表3多因素Logistic回归模型分析结果可知，病理T分期和HI-2是胃腺癌患者OLM的独立危险因素。

ROC曲线分析结果显示，HI-1预测OLM的

表1 胃腺癌隐匿性淋巴结转移阳性组与阴性组患者的临床特征比较

Table 1 Comparison of clinical characteristics between the positive and negative groups in patients with occult lymph node metastasis of gastric adenocarcinoma

组别	年龄 (岁, $\bar{x} \pm s$)	性别(例, %)		肿瘤原发灶部位(例, %)			分化程度(例, %)		
		男	女	GEJ及胃底部	胃体及大小弯	胃窦及幽门区	中分化	中-低分化	低分化
OLM阳性组($n=39$)	62.82 ± 10.48	27(69.2)	12(30.8)	16(41.0)	11(28.2)	12(30.8)	8(20.5)	12(30.8)	19(48.7)
OLM阴性组($n=40$)	64.80 ± 7.22	35(87.5)	5(12.5)	21(52.5)	9(22.5)	10(25.0)	17(42.5)	13(32.5)	10(25.0)
检验值	$z=-0.196$	$x^2=3.903$			$x^2=1.045$			$x^2=6.061$	
P值	0.844	0.048			0.593			0.048	
组别	Lauren分型(例, %)			病理T分期(例, %)		CA199水平升高(例, %)		CEA水平升高(例, %)	
	肠型	弥漫型	混合型	T1~T2	T3~T4	CA199	CEA	CA199	CEA
OLM阳性组($n=39$)	16(41.0)	11(28.2)	12(30.8)	5(12.8)	34(87.2)	5(13.5)	4(10.8)	4(10.8)	4(10.8)
OLM阴性组($n=40$)	24(60.0)	9(22.5)	7(17.5)	15(37.5)	25(62.5)	7(18.9)	4(10.8)	4(10.8)	4(10.8)
检验值	$x^2=3.104$			$x^2=6.361$			$x^2=0.398$	0	
P值	0.212			0.012			0.528	1.00	

表2 胃腺癌隐匿性淋巴结转移阳性组与阴性组患者¹⁸F-FDG PET/CT代谢参数的比较 [$M(Q_1, Q_3)$ 或 $\bar{x} \pm s$]Table 2 Comparison of metabolic parameters of ¹⁸F-FDG PET/CT between positive and negative groups of patients with occult lymph node metastasis in patients with occult lymph node metastasis of gastric adenocarcinoma [$M(Q_1, Q_3)$ or $\bar{x} \pm s$]

组别	SUV _{max}	SUV _{peak}	SUV _{mean}	TLR	MTV(cm ³)	TLG(g)	HI-1	HI-2
OLM阳性组 ($n=39$)	5.59 (4.46, 7.51)	4.37 (3.23, 5.38)	3.33 (3.06, 3.85)	2.75 (2.20, 3.70)	11.94 (3.23, 30.90)	39.87 (9.48, 113.88)	0.23 ± 0.12	4.98 (2.68, 8.44)
OLM阴性组 ($n=40$)	6.91 (5.11, 10.64)	5.09 (3.90, 7.21)	3.65 (3.25, 4.64)	3.30 (2.42, 5.36)	12.32 (3.37, 20.86)	43.07 (11.69, 90.10)	0.29 ± 0.14	2.61 (1.84, 4.23)
检验值	$z=-2.000$	$z=-1.736$	$z=-2.001$	$z=-1.314$	$z=-0.074$	$z=-0.255$	$t=2.096$	$z=-3.178$
P值	0.045	0.083	0.045	0.189	0.941	0.799	0.039	0.001

AUC为0.360(95%CI: 0.237~0.483, $P=0.001$),因此HI-1不具有诊断价值。HI-2预测OLM的AUC为0.708(95%CI: 0.593~0.822, $P<0.05$)(图1),因此HI-2对OLM的诊断具有较好的准确率。当以最佳临界值4.962进行预测时,其诊断OLM的灵敏度和特异度分别为51.3%(20/39)和87.5%(35/40),典型患者图像见图2。

2.4 ROC曲线分析

3 讨论

手术切除是治疗胃癌的主要方法。然而,大部分胃癌患者在手术切除后仍会复发。OLM是胃癌患者术后复发的主要危险因素。近年来,¹⁸F-FDG PET/CT的肿瘤内代谢HI在肿瘤的临床分期和预后预测方面具有重要价值^[9,15-16]。Liu等^[9]发现肿瘤原发灶的HI在评估胃癌患者预后中具有重要价值。Kim等^[11]将HI用于食管癌区域淋巴结转移的

预测,显示了其较好的预测价值。在本研究中,单因素及多因素Logistic回归模型分析的结果表明HI-2是胃癌OLM的独立预测因子。HI-2由不同SUV临界值下的系列MTV的线性回归斜率计算得出,在工作站上易获取,且重复性较高。¹⁸F-FDG PET/CT诊断胃癌淋巴结转移的特异性虽高达73%~92%,但灵敏度仅为40%~54.7%^[17-19],在本研究中HI-2诊断OLM的灵敏度和特异度分别为51.3%和87.5%,因此肿瘤代谢HI对胃癌患者术前发现OLM具有重要的预测价值。

本研究发现肿瘤原发灶的SUV_{max}、SUV_{peak}、SUV_{mean}及TLR在预测胃癌OLM方面无明显价值,这与Na等^[20]的研究结果一致。但Yamada等^[21]分析113例晚期胃癌患者的临床资料发现,肿瘤原发灶SUV_{max}是淋巴结转移的有效预测指标。张在炬等^[22]发现SUV_{max}≥4.29作为胃癌淋巴结转移诊断标准时,其灵敏度和特异度分别为98.1%和45.7%。

表3 胃腺癌隐匿性淋巴结转移患者临床特征和¹⁸F-FDG PET/CT代谢参数的单因素及多因素Logistic回归模型分析

Table 3 Logistic univariate and multivariate regression analysis of clinical characteristics and ¹⁸F-FDG PET/CT metabolic parameters in patients with occult lymph node metastasis of gastric adenocarcinoma

临床特征和代谢参数	单因素分析		P值	多因素分析	
	OR(95%CI)			OR(95%CI)	P值
分化程度			0.054		0.174
中分化	1.000			1.000	
中-低分化	1.962(0.621~6.193)		0.251	1.667(0.432~6.435)	0.459
低分化	4.037(1.295~12.585)		0.016	3.467(0.918~13.096)	0.067
病理T分期					
T1-T2	1.000			1.000	
T3-T4	4.080(1.310~12.709)		0.015	4.780(1.238~18.458)	0.023
SUV _{max}	0.891(0.792~1.003)		0.055		
SUV _{peak}	0.877(0.758~1.014)		0.076		
SUV _{mean}	0.602(0.361~1.005)		0.052		
TLR	0.808(0.631~1.034)		0.090		
MTV(cm ³)	0.999(0.977~1.021)		0.901		
TLG(g)	0.998(0.994~1.003)		0.430		
HI-1	0.025(0.001~0.992)		0.045	0.537(0.007~39.527)	0.777
HI-2					
>4.962	7.368(2.385~22.764)		<0.001	6.893(1.922~24.718)	0.003
≤4.962	1.000			1.000	

注: FDG 为氟脱氧葡萄糖; PET 为正电子发射断层显像术; CT 为计算机体层摄影术; SUV_{max} 为最大标准化摄取值; SUV_{peak} 为标准化摄取值峰值; SUV_{mean} 为平均标准化摄取值; TLR 为原发灶 SUV_{max}/肝脏 SUV_{mean} 的比值; MTV 为肿瘤代谢体积; TLG 为糖酵解总量; HI 为异质性指数; CI 为置信区间

Oh^[23]等发现 SUV_{peak} 可能是胃癌患者淋巴结转移的独立危险因素。造成以上研究结果差异的原因可能与肿瘤异质性、部分容积效应和样本差异有关^[24]。本研究发现 OLM 阴性组 SUV_{max} 及 SUV_{mean} 高于 OLM 阳性组, 可能原因是阴性组中分化腺癌数目较多, 这与既往研究结果^[25-26] 相符。

MTV 和 TLG 是反映肿瘤负荷的代谢参数, 但目前关于 MTV 和 TLG 在预测胃癌淋巴结转移的价值方面具有一定的争议。周锦等^[27]发现 MTV 和 TLG 与肿瘤的 N 分期呈中度正相关。Xue 等^[28]发现 MTV 和 TLG 是胃癌淋巴结转移的独立预测因子。而王健林等^[29]发现 MTV 和 TLG 与胃癌的 N 分期无明显相关性。本研究也未发现 MTV 和 TLG 在预测胃癌 OLM 方面的价值。上述研究结果存在差异的原因可能为: (1)MTV 的获取方法尚未标准化, 不同的 SUV 截断值结果不同; (2)本研究只分析了 cN0 期胃癌患者, 与上述研究样本的范围不同; (3)胃部炎症及幽门螺杆菌感染等^[30] 均可导致对¹⁸F-FDG 的高摄取, 从而使代谢参数结果不

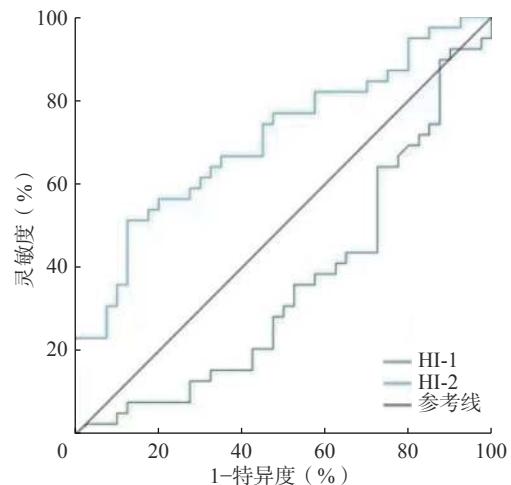


图1 异质性指数预测胃腺癌隐匿性淋巴结转移患者的受试者工作特征曲线 HI 为异质性指数

Figure 1 Heterogeneity index predicts receiver operator characteristic curves in patients with occult lymph node metastasis of gastric adenocarcinoma

可信。

我们的研究存在一定的局限性: (1)本研究是一项单中心、回顾性研究, 纳入的患者数量相对较

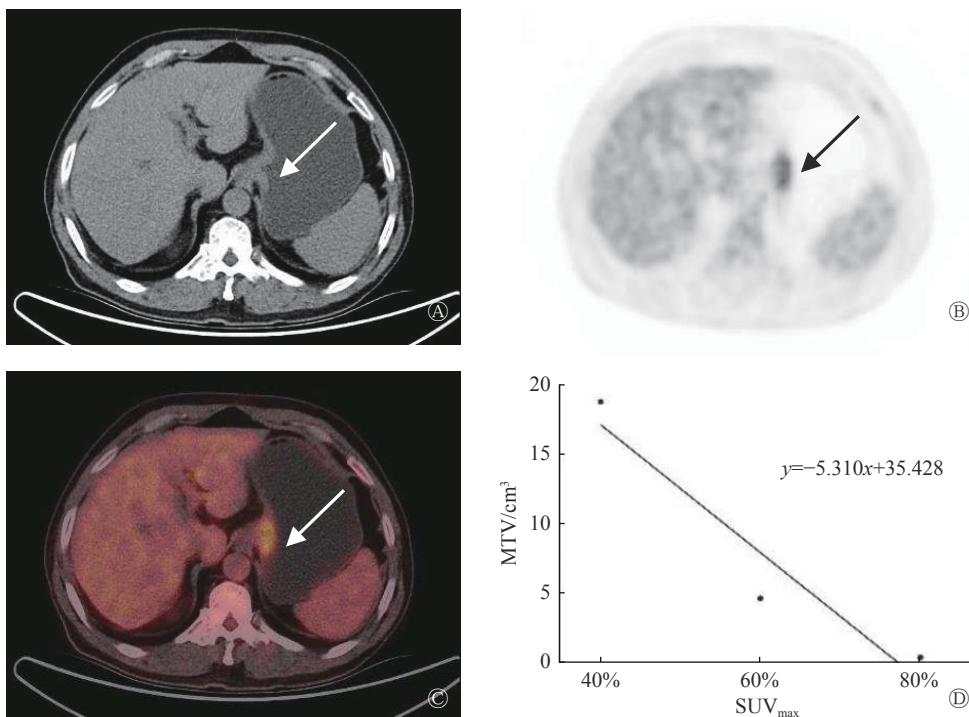


图2 胃腺癌隐匿性淋巴结转移患者(男性, 65岁)的¹⁸F-FDG PET/CT显像图和肿瘤内代谢异质性指数分析 A为病灶部位横断面软组织窗CT图, 示胃贲门部胃壁增厚(白色箭头所示); B为病灶部位横断面软组织窗PET图, 示胃贲门部代谢增高(黑色箭头所示); C为病灶部位横断面软组织窗PET/CT融合图, 示胃贲门部胃壁增厚(白色箭头所示), 代谢增高, SUV_{max}=8.62, MTV=32.55 cm³, TLG=126.41 g; D为MTV的线性回归方程图, 示肿瘤内代谢异质性高, HI-2为5.31。FDG为氟脱氧葡萄糖; PET为正电子发射断层显像术; CT为计算机体层摄影术; SUV_{max}为最大标准化摄取值; MTV为肿瘤代谢体积; TLG为糖酵解总量; HI为异质性指数。

Figure 2 Analysis of ¹⁸F-FDG PET/CT imaging and metabolic heterogeneity index in a patient (male, 65 years old) with occult lymph node metastasis of gastric adenocarcinoma

少; (2)MTV 和 HI 的测量尚无标准化方法; (3)正常胃壁的生理性摄取可能会产生部分容积效应从而对肿瘤¹⁸F-FDG PET/CT 的参数测量结果产生一定的影响, 延迟显像或许可以降低胃壁生理性摄取的干扰, 但需进一步的研究结果证实。

综上所述, 肿瘤原发灶 HI 对胃癌 OLM 具有一定的预测价值, 较高的 HI-2 是胃癌患者发生 OLM 的高危因素, 这些发现有助于临床精准制定个体化治疗方案。

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