

论著·临床研究

¹⁸F-MD-PSMA PET/CT 显像在中高危前列腺癌初始分期中的应用价值

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[摘要] **目的**·评估¹⁸F-MD-PSMA PET/CT在中高风险前列腺癌(prostate cancer, PCa)患者初始分期中的应用价值。**方法**·对2017年9月至2022年6月在上海交通大学医学院附属新华医院就诊的67例中高危PCa患者采用¹⁸F-MD-PSMA PET/CT进行初步分期;患者在¹⁸F-MD-PSMA PET/CT检查前2周内接受常规成像(conventional imaging, CI),包括多参数磁共振成像(multi-parameter magnetic resonance imaging, mp-MRI)和全身骨显像(bone scintigraphy, BS),其中25例患者同期进行了¹⁸F-FDG PET/CT检查。评估¹⁸F-MD-PSMA PET/CT对初始分期的灵敏度(sensitivity, SEN)、特异度(specificity, SPEC)、阳性预测值(positive predictive value, PPV)、阴性预测值(negative predictive value, NPV)及准确率(accuracy, ACU),并将结果与¹⁸F-FDG PET/CT、mp-MRI和BS的结果进行对比。以术后病理的T、N分期结果及临床随访的骨转移结果为参考标准进行Kappa一致性检验,分析¹⁸F-MD-PSMA PET/CT及CI在诊断原发灶累及范围、区域淋巴结转移、骨转移方面与参考标准的一致性,计算Kappa系数,并进行比较。**结果**·在67例PCa患者中,38例接受了根治性前列腺切除术并且有完整的病理学诊断资料,其中分别有27例和1例患者同时接受了区域淋巴结清扫术和扩大盆腔淋巴结清扫术,以病理结果作为诊断金标准。mp-MRI和¹⁸F-MD-PSMA PET/CT诊断包膜内病灶的检出率均为100%,诊断双侧腺叶内病灶的SEN分别为26.3%和63.2%,SPEC均为75.0%。与病理结果进行Kappa一致性检验,结果显示¹⁸F-MD-PSMA PET/CT诊断包膜外侵犯(extraprostatic extension, EPE)、精囊腺侵犯(seminal vesicle invasion, SVI)、膀胱颈侵犯(bladder neck invasion, BNI)的一致性均高于mp-MRI。Fisher确切概率法显示,2种检查方法诊断EPE、SVI的SEN($P=0.226$, $P=0.491$)和SPEC($P=1.000$, $P=0.342$),以及诊断BNI的SEN(均 $P=1.000$)比较,差异均无统计学意义。在诊断淋巴结转移方面,基于淋巴结数量分析,¹⁸F-MD-PSMA PET/CT与病理结果的一致性高于mp-MRI(Kappa系数分别为0.555和0.137);Fisher确切概率法提示2种检查方法的SEN和SPEC差异均无统计学意义($P=0.562$, $P=0.829$)。基于患者分析,¹⁸F-MD-PSMA PET/CT与病理结果一致性高于mp-MRI(Kappa系数分别为0.850和0.313);两者SEN比较,差异无统计学意义($P=1.000$)。在诊断骨转移方面,基于骨病灶数量分析,¹⁸F-MD-PSMA PET/CT与随访结果的一致性高于BS(Kappa系数分别为0.500和0.299);Fisher确切概率法提示2种检查方法的SEN比较,差异无统计学意义($P=0.219$)。基于患者分析,¹⁸F-MD-PSMA PET/CT与随访结果的一致性高于BS(Kappa系数分别为0.953和0.766);两者的SEN比较,差异无统计学意义($P=1.000$)。¹⁸F-MD-PSMA PET/CT检测后,21例(31.3%)患者的风险分层上升,1例(1.5%)风险分层下降;32例(47.8%)患者的初始分期改变,其中27例(40.3%)上调,5例(7.5%)下调。**结论**·¹⁸F-MD-PSMA PET/CT在诊断中高风险PCa患者的双侧腺叶内病灶、EPE、SVI、区域淋巴结转移及骨转移方面,相比CI具有一定的优势,并在此基础上改变了部分患者临床分期及转移状态的诊断。

[关键词] 前列腺癌; 初始分期; ¹⁸F-MD-PSMA PET/CT; 多参数磁共振成像; 全身骨显像**[DOI]** 10.3969/j.issn.1674-8115.2023.07.009 **[中图分类号]** R445.6; R737.25 **[文献标志码]** A

Role of ¹⁸F-MD-PSMA PET/CT in initial stage of intermediate and high risk prostate cancer

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[Abstract] **Objective**·To evaluate the role of ¹⁸F-MD-PSMA PET/CT in the initial stage of patients with moderate and high risk prostate cancer (PCa). **Methods**·A total of 67 patients with moderate and high risk PCa who were treated in Xinhua Hospital,**[基金项目]** 国家自然科学基金青年基金(82001856)。**[作者简介]** 严叶青(1997—),女,硕士生;电子邮箱:yanyeqing97@163.com。**[通信作者]** 傅宏亮,电子邮箱:fuhongliang@hotmail.com。**[Funding Information]** National Natural Science Foundation of China(82001856)。**[Corresponding Author]** FU Hongliang, E-mail: fuhongliang@hotmail.com。

Shanghai Jiao Tong University School of Medicine from September 2017 to June 2022 were initially staged by ^{18}F -MD-PSMA PET/CT. Conventional imaging (CI), including multi-parameter magnetic resonance imaging (mp-MRI) and bone scintigraphy (BS), were performed within two weeks before ^{18}F -MD-PSMA PET/CT. Twenty-five patients underwent ^{18}F -FDG PET/CT at the same time. The sensitivity (SEN), specificity (SPEC), positive predictive value (PPV), negative predictive value (NPV) and accuracy (ACU) of ^{18}F -MD-PSMA PET/CT in the initial stage were evaluated, and the results were compared with those of ^{18}F -FDG PET/CT, mp-MRI and BS. The consistency of ^{18}F -MD-PSMA PET/CT and CI in terms of primary lesion, regional lymph node metastasis and bone metastasis was evaluated by Kappa consistency test referring to the postoperative pathological T and N staging results and bone metastasis results of clinical follow-up. Kappa coefficient was calculated and compared. **Results** Of the 67 patients with PCa, 38 patients underwent radical prostatectomy and had completed pathological data, with 27 patients undergoing regional lymphadenectomy and 1 patient undergoing expanded pelvic lymphadenectomy at the same time. The pathological results were obtained as gold standard. The detection rates of mp-MRI and ^{18}F -MD-PSMA PET/CT in diagnosing intrathecal lesions were both 100%. The SENs in diagnosing bilateral intralobular lesions were 26.3% and 63.2%, respectively; the SPECs were both 75.0%. The Kappa consistency test showed that the consistency of ^{18}F -MD-PSMA PET/CT in diagnosis of extracapsular extension (EPE), seminal vesicle invasion (SVI), and bladder neck invasion (BNI) was higher than that of mp-MRI. Fisher's exact test showed that there were no statistically significant differences in SEN ($P=0.226$, $P=0.491$) and SPEC ($P=1.000$, $P=0.342$) between the two methods for diagnosing EPE and SVI, as well as SEN ($P=1.000$) for diagnosing BNI. In terms of diagnosis of lymph node metastasis, based on the analysis of lymph node numbers, the consistency between ^{18}F -MD-PSMA PET/CT and pathological results was higher than that of mp-MRI (Kappa coefficients of 0.555 and 0.137, respectively). Fisher's exact test showed that there were no statistically significant differences in SEN and SPEC between the two examination methods ($P=0.562$, $P=0.829$). Based on the patients, the consistency between ^{18}F -MD-PSMA PET/CT and pathological results was higher than that of mp-MRI (Kappa coefficients of 0.850 and 0.313, respectively). There was no statistically significant difference in SEN between the two methods ($P=1.000$). In terms of diagnosis of bone metastasis, based on the analysis of bone lesion numbers, the consistency between ^{18}F -MD-PSMA PET/CT and clinical follow-up results was higher than that of BS (Kappa coefficients of 0.500 and 0.299, respectively). Fisher's exact test showed that there was no statistically significant difference in SEN between the two methods ($P=0.219$). Based on the patients, the consistency between ^{18}F -MD-PSMA PET/CT and clinical follow-up results was higher than that of BS (Kappa coefficients of 0.953 and 0.766, respectively). There was no statistically significant difference in SEN between the two methods ($P=1.000$). The risks of 21 patients (31.3%) were increased after ^{18}F -MD-PSMA PET/CT detection, with 1 patient (1.5%) decreasing. The initial stage of 32 cases (47.8%) were changed after ^{18}F -MD-PSMA PET/CT detection, with 27 cases (40.3%) upstaged and 5 cases (7.5%) downstaged. **Conclusion** ^{18}F -MD-PSMA PET/CT is superior to CI in the diagnosis of bilateral intralobular lesions, EPE, SVI, regional lymph node metastasis and bone metastasis in intermediate and high risk PCa, and on this basis, the diagnosis of clinical stage and metastatic status of some patients has been changed.

[Key words] prostate cancer; initial stage; ^{18}F -MD-PSMA PET/CT; multi-parameter magnetic resonance imaging; bone scintigraphy

据统计, 前列腺癌 (prostate cancer, PCa) 已成为全球男性第二大常见恶性肿瘤^[1]。近年来, PCa 在中国的发病率迅速上升^[2]。PCa 的诊断和初始分期是确定治疗计划的关键。因此, 病灶累及范围的精确划界, 对于诊断该病至关重要。

虽然目前的临床指南仍建议使用常规成像 (conventional imaging, CI) 方法, 包括多参数磁共振成像 (multiparametric magnetic resonance imaging, mp-MRI) 和全身骨显像 (bone scintigraphy, BS) 对中高危 PCa 患者进行初始分期, 但这些方法在评估 PCa 病情方面存在局限性。在过去 10 余年中, 前列腺特异性膜抗原 (prostate-specific membrane antigen, PSMA) 作为 PCa 成像的优良靶点, 已引起越来越多的关注。利用 PSMA 的正电子发射断层扫描 (positron emission tomography, PET) 成为了一种有价值的 PCa 诊断和分期方法。

PSMA 是一种几乎完全由前列腺组织和肿瘤相关的新生血管产生的非分泌型 II 型跨膜蛋白^[3]。与正

常组织相比, 其在原发性和转移性 PCa 细胞中过度表达^[4]。经过多年临床前研究, ^{68}Ga -PSMA 于 2012 年作为 PET 示踪剂被引入^[5], 实现了基于 PSMA 成像的临床突破。与 ^{68}Ga 相比, ^{18}F 因更佳的物理特性逐渐取而代之^[6]。现有的 ^{18}F 标记的配体包括 DCFBC、DCFPyL 和 PSMA-1007。其中, 第二代低相对分子质量探针 ^{18}F -DCFPyL, 较第一代的 DCFBC 具有更高的亲和力和更高的靶本比, 已获得了美国食品药品监督管理局批准^[7]。本研究引入了一种在 DCFPyL 基础上修饰的新型 PSMA 特异性小分子抑制剂 ^{18}F -MD-PSMA, 旨在评估 ^{18}F -MD-PSMA PET/CT 在中高风险 PCa 患者的初始分期中的诊断效能。

1 对象与方法

1.1 研究对象及临床资料收集

纳入 2017 年 9 月—2022 年 6 月在上海交通大学医学院附属新华医院核医学科就诊并接受 ^{18}F -MD-

PSMA PET/CT 初始分期的中高危 PCa 病例。中高危 PCa 的诊断根据为美国国家综合癌症网络 (National Comprehensive Cancer Network, NCCN) 指南 (2018 版)^[8]。患者在¹⁸F-MD-PSMA PET/CT 检查前 2 周内接受 CI 检查,包括 mp-MRI 和 BS;其中 25 例患者同期进行了¹⁸F-FDG PET/CT 检查。

纳入标准:① 经穿刺后组织病理学证实的 PCa。② 组织病理学 Gleason 评分 ≥ 7 或前列腺特异性抗原 (prostate-specific antigen, PSA) ≥ 10 ng/mL。③ 在¹⁸F-MD-PSMA PET/CT 检查前 2 周内完成 mp-MRI 和 BS 检查。排除标准:① 已接受 PCa 相关治疗。② 存在已知的其他恶性肿瘤。

收集患者的临床资料,包括年龄、血清 PSA 水平等,以及完成 PSMA PET/CT 检查后患者后续接受的治疗方案、血清 PSA 水平变化、术后病理结果 (包括 Gleason 评分)、影像学检查随访资料 (包括盆腔 MRI 及 BS)、是否死亡及死亡原因等。

1.2 ¹⁸F-MD-PSMA 显像方法

¹⁸F 离子在新华医院回旋加速器单元生产。使用商业合成模块 FastLab™ (GE Healthcare, Waukesha, 美国) 合成¹⁸F-MD-PSMA。检查前无需禁食。静脉注射约 3.7 MBq/kg ¹⁸F-MD-PSMA,从注射结束到开始扫描的摄取时间均为 1~2 h。使用 Siemens Biograph-64mCT PET/CT (Siemens Healthcare, 美国) 在 3D 断层扫描仪上采集图像,每个床位 2 min,视野包括头骨到股骨中部。低剂量 CT 扫描用于衰减校正和解剖标测,使用 OSEM-3D 算法对数据进行迭代重建 (3 次迭代,24 个子集及 3 mm 3D 高斯滤波器)。西门子工作站用于图像读取并显示各种切面 (轴向、矢状和冠状) 的 PET、CT 和 PET/CT 融合图像。

1.3 影像学及病理学解读

PET/CT 显像结果由 2 位核医学科医师双盲阅片。PET/CT 阳性的标准为存在不包括生理性摄取区域在内的可见的示踪剂摄取显著增加的病灶区域。通过手动勾画感兴趣区得到最大标准化摄取值 (SUV_{max})。无论 CT 是否发现任何潜在病变,半定量标准化摄取值 (SUV) 比率 (病变的 SUV_{max}/周围背景中的 SUV 均值) 用于辅助视觉分析。发现轻度局灶性摄取,则认为比率 ≥ 1.5 为显著。BS 结果由 2 位核医学科医师双盲阅片。在结合病史或其他检查排除骨良性病变所致的假阳性后,存在放射性计数明显高于或者低

于健侧、邻近骨骼放射性计数的病灶,判定为骨转移阳性。在阅片出现分歧时,通过讨论达成共识。mp-MRI 由一位放射科医师单独阅片。病理结果由一名病理科医师对完整的组织切片进行解读。所有阅片者对其他检验或检查结果等信息均不知情。

1.4 统计学分析

采用 SPSS 27.0 软件进行统计分析。正态分布的定量资料以 $\bar{x} \pm s$ 表示,采用 *t* 检验进行比较;非正态分布的定量资料以 $M (Q1, Q3)$ 表示,采用秩和检验进行比较;定性资料以频数和百分比表示。计算¹⁸F-MD-PSMA PET/CT、¹⁸F-FDG PET/CT、mp-MRI、BS 的灵敏度 (sensitivity, SEN)、特异度 (specificity, SPEC)、阳性预测值 (positive predictive value, PPV)、阴性预测值 (negative predictive value, NPV) 及准确率 (accuracy, ACU),并通过 Fisher 确切概率法比较 2 种方法诊断效能。以术后病理的 T 分期、N 分期结果及临床随访的骨转移结果为参考标准进行 Kappa 一致性检验,分析¹⁸F-MD-PSMA PET/CT、CI 在原发灶累及范围、区域淋巴结转移、骨转移方面与参考标准的一致性,计算 Kappa 系数,并进行比较。 $P < 0.05$ 表示差异具有统计学意义。

2 结果

2.1 患者临床特征

对 67 例中高危 PCa 患者进行了初始分期,5 例 (7.5%) 处于中等风险,27 例 (40.3%) 处于高风险、35 例 (52.2%) 处于极高风险。

患者完成¹⁸F-MD-PSMA PET/CT 检查后的随访时间最短为 3 个月,最长为 64 个月,中位随访时间为 49.5 个月。在完成¹⁸F-MD-PSMA PET/CT 检查后的半年内,44 例 (65.7%) 患者接受了根治性前列腺切除术 (radical prostatectomy, Rp),经随访后获得了 38 例患者完整的病理学诊断资料。分别有 27 例和 1 例患者在接受了 Rp 的同时接受了区域淋巴结清扫术 (regional lymph node dissection, RLND) 和扩大盆腔淋巴结清扫术 (extended pelvic lymph node dissection, ePLND),5 例 (7.5%) 患者接受了根治性外放射治疗 (external beam radiotherapy, EBRT),13 例 (19.4%) 患者接受了雄激素剥夺治疗 (androgen deprivation therapy, ADT),3 例 (4.5%)

患者接受了化学治疗。2例患者在完成¹⁸F-MD-PSMA PET/CT检查后失访。

2.2 CI与¹⁸F-MD-PSMA PET/CT在初始分期中的诊断性能比较

2.2.1 T分期 在¹⁸F-MD-PSMA PET/CT后半年内接受了Rp并获得了病理结果的38例PCa患者中, pT2、pT3a、pT3b、pT4分别在10、13、8、7例患者中经病理诊断证实。包膜外侵犯(extraprostatic extension, EPE)、精囊腺侵犯(seminal vesicle invasion, SVI)、

膀胱颈侵犯(bladder neck invasion, BNI)分别在28、11、7例患者中经病理诊断证实。

mp-MRI、¹⁸F-FDG PET/CT、¹⁸F-MD-PSMA PET/CT对包膜内病灶的检出率分别为100.0%、57.1%、100.0%。mp-MRI和¹⁸F-MD-PSMA PET/CT诊断双侧腺叶内病灶的SEN分别为26.3%和63.2%, SPEC均为75.0%。mp-MRI、¹⁸F-MD-PSMA PET/CT诊断EPE、SVI和BNI的SEN、SPEC、PPV、NPV和ACU见表1。

表1 CI与¹⁸F-MD-PSMA PET/CT在PCa初始分期中的诊断效能比较

Tab 1 Comparison of diagnostic performance between CI and ¹⁸F-MD-PSMA PET/CT in initial staging of PCa

Organ/region examined	TP/n	FP/n	TN/n	FN/n	SEN/%	SPEC/%	PPV/%	NPV/%	ACU/%
EPE									
mp-MRI	13	1	9	15	46.4	90.0	92.9	37.5	57.9
¹⁸ F-MD-PSMA PET/CT	25	6	4	3	89.3	40.0	80.6	57.1	76.3
SVI									
mp-MRI	3	2	25	8	27.3	92.6	60.0	75.8	73.7
¹⁸ F-MD-PSMA PET/CT	8	5	22	3	72.7	81.4	61.5	88.0	78.9
BNI									
mp-MRI	3	1	30	4	42.9	96.8	75.0	88.2	86.8
¹⁸ F-MD-PSMA PET/CT	3	0	31	4	42.9	100.0	100.0	88.6	86.8
Regional lymph nodes (N1)									
Per-lesion									
mp-MRI	5	6	387	42	10.6	98.5	45.5	90.2	89.1
¹⁸ F-MD-PSMA PET/CT	25	11	381	22	53.2	96.9	70.3	94.5	92.5
¹⁸ F-FDG PET/CT	12	6	213	32	29.2	99.5	66.7	86.7	87.6
Per-patient									
mp-MRI	3	0	17	8	27.3	100.0	100.0	68.0	71.4
¹⁸ F-MD-PSMA PET/CT	10	1	16	1	90.9	94.1	90.9	94.1	92.9
¹⁸ F-FDG PET/CT	5	3	6	0	62.5	96.3	66.7	100.0	78.6
Skeleton (M1b)									
Per-patient									
BS	13	2	32	3	81.3	94.1	86.7	91.4	90.0
¹⁸ F-MD-PSMA PET/CT	15	0	34	1	93.8	100.0	100.0	97.1	98.0
Per-lesion									
BS	11	8	366	34	25.0	97.9	57.9	91.5	90.0
¹⁸ F-MD-PSMA PET/CT (per lesion)	24	18	356	21	54.5	95.2	57.1	94.4	90.7

Note: TP—true positive; FP—false positive; TN—true negative; FN—false negative.

与病理结果进行Kappa一致性检验(表2)。mp-MRI和¹⁸F-MD-PSMA PET/CT诊断EPE的P值均为0.040, Kappa系数分别为0.251和0.324; 诊断SVI的P值分别为0.100和0.001, Kappa值分别为0.237和0.514; 诊断BNI的P值分别为0.002和0.000, Kappa系数分别为0.475和0.550。¹⁸F-MD-PSMA PET/CT的一致性均高于mp-MRI。Fisher确切概率法提示, 2种

检查方法诊断EPE、SVI的SEN ($P=0.226$, $P=0.491$)和SPEC ($P=1.000$, $P=0.342$), 以及诊断BNI的SEN (均 $P=1.000$)比较, 差异均无统计学意义。

2.2.2 N分期 27例接受RLND和1例接受ePLND的患者, 共切除440枚区域淋巴结和10枚非区域淋巴结, 其中47枚区域淋巴结和10枚非区域淋巴结经病理诊断证实为转移灶。

表2 mp-MRI 与 ¹⁸F-MD-PSMA PET/CT 诊断 EPE、SVI、BNI 与病理结果的一致性(n)

Tab 2 Consistency of mpMRI and ¹⁸F-MD-PSMA PET/CT in diagnosis of EPE, SVI and BNI with pathological results (n)

Imaging method	Pathologic diagnosis of EPE		Pathologic diagnosis of SVI		Pathologic diagnosis of BNI	
	+	-	+	-	+	-
mp-MRI						
+	13	1	3	2	3	1
-	15	9	8	25	4	30
¹⁸ F-MD-PSMA PET/CT						
+	25	6	8	5	3	0
-	3	4	3	22	4	31

¹⁸F-MD-PSMA PET/CT 较 mp-MRI 发现了更多转移性淋巴结 (图1)。mp-MRI、¹⁸F-MD-PSMA PET/

CT、¹⁸F-FDG PET/CT 诊断区域淋巴结转移的 SEN、SPEC、PPV、NPV 和 ACU 见表1。

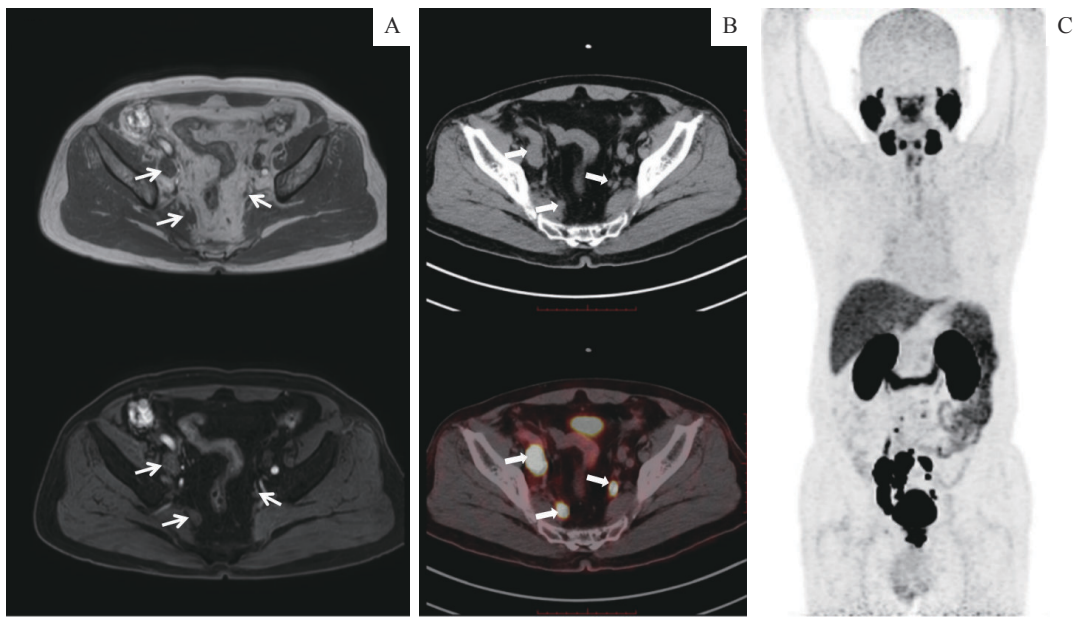


Figure 1 Note: A. Pelvic mp-MRI showed enlargement of the right iliac lymph nodes with abnormal signal which supported the diagnosis of metastasis lymph nodes and a small left iliac lymph node (white thin arrows). B. ¹⁸F-MD-PSMA PET/CT demonstrated abnormal ¹⁸F-MD-PSMA uptake not only at the right iliac lymph nodes, but also at the left iliac lymph node which was less than 1 cm in diameter (white thick arrows). C. Maximum intensity projection (MIP) image demonstrated more abnormal ¹⁸F-MD-PSMA uptake of metastatic lymph nodes in pelvic region.

图1 一例患者 mp-MRI 与 ¹⁸F-MD-PSMA PET/CT 对盆腔淋巴结的评估结果比较

Fig 1 Comparison of evaluation results of pelvic lymph nodes between mp-MRI and ¹⁸F-MD-PSMA PET/CT in a patient

将 mp-MRI、¹⁸F-MD-PSMA PET/CT 的诊断结果与病理结果进行 Kappa 一致性检验 (表3)。基于淋巴结数量分析的 P 值均为 0.000, ¹⁸F-MD-PSMA PET/CT 与病理结果的一致性高于 mp-MRI (Kappa 系数分别为 0.555 和 0.137); Fisher 确切概率法提示 2 种检查方法的 SEN 和 SPEC 比较, 差异均无统计学意义 (P=0.562, P=0.829)。基于患者分析的 P 值分别为 0.023 和 0.000, ¹⁸F-MD-PSMA PET/CT 与病理结果一致性高于 mp-MRI (Kappa 系数分别为 0.850 和 0.313); Fisher 确切概率法提示两者的 SEN 比较, 差异无统计学意义 (P=1.000)。

2.2.3 M 分期 在 50 例具有完整全身骨扫描资料的

PCa 患者中, 16 例患者共 419 处骨病灶经临床诊断及随访综合判断为转移灶。BS、¹⁸F-MD-PSMA PET/CT 诊断骨转移的 SEN、SPEC、PPV、NPV 和 ACU 见表 1。其中, 2 例 BS 假阳性均为退变所致。将 BS、¹⁸F-MD-PSMA PET/CT 的诊断结果与临床随访结果进行 Kappa 一致性检验 (表4)。基于骨病灶数量分析的 P 值均为 0.000, ¹⁸F-MD-PSMA PET/CT 与随访结果的一致性高于 BS (Kappa 系数分别为 0.500 和 0.299); Fisher 确切概率法提示 2 种检查方法的 SEN 比较, 差异无统计学意义 (P=0.219)。基于患者分析的 P 值均为 0.000, ¹⁸F-MD-PSMA PET/CT 与随访结果的一致性高于 BS (Kappa 系数分别为 0.953 和 0.766);

表3 mp-MRI与¹⁸F-MD-PSMA PET/CT在诊断区域淋巴结转移方面与病理结果的一致性(*n*)

Tab 3 Consistency of mp-MRI and ¹⁸F-MD-PSMA PET/CT in diagnosis of regional lymph node metastasis with pathological results (*n*)

Imaging method	Pathologic diagnosis of lymph node metastasis	
	+	-
Per-patient		
mp-MRI		
+	3	0
-	8	17
¹⁸ F-MD-PSMA PET/CT		
+	10	1
-	1	16
Per-lesion		
mp-MRI		
+	5	6
-	42	387
¹⁸ F-MD-PSMA PET/CT		
+	25	12
-	22	381

Fisher确切概率法提示2种检查方法的SEN差异无统计学意义($P=1.000$)。

2.3 ¹⁸F-MD-PSMA PET/CT在评估病情中的价值

2.3.1 ¹⁸F-MD-PSMA PET/CT对风险分层的评估 67例中高危患者,经¹⁸F-MD-PSMA PET/CT检查,21例(31.3%)患者的风险分层上升,其中有9例(13.4%)和12例(17.9%)患者分别从中危升级为高危、从高危升级为极高危;另有1例(1.5%)患者的风险分层

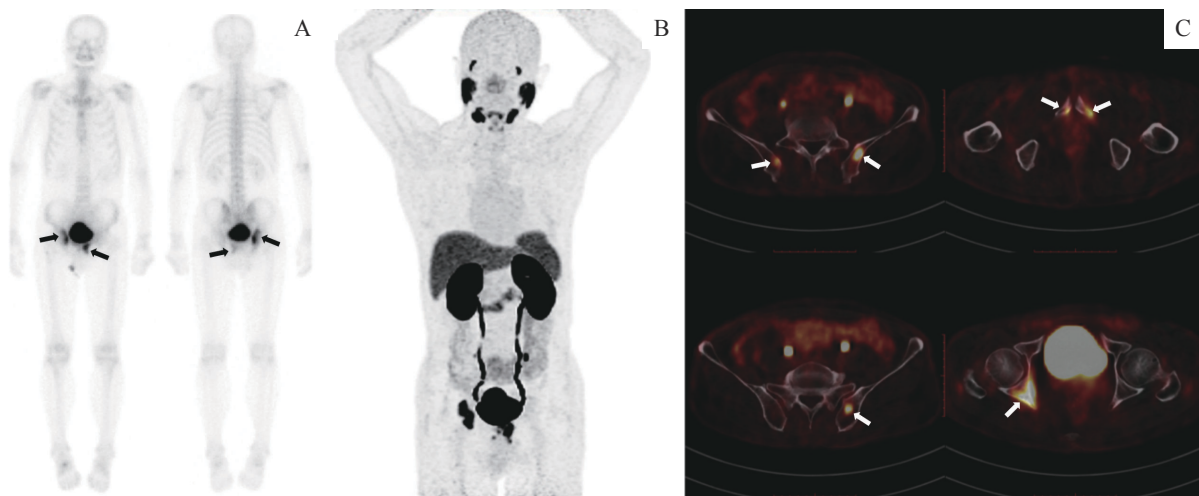
表4 BS与¹⁸F-MD-PSMA PET/CT在诊断骨转移方面与临床随访结果的一致性(*n*)

Tab 4 Consistency of BS and ¹⁸F-MD-PSMA PET/CT in diagnosis of bone metastasis with clinical follow-up results (*n*)

Imaging method	Clinical diagnosis of bone metastasis	
	+	-
BS		
+	11	8
-	34	366
¹⁸ F-MD-PSMA PET/CT		
+	24	18
-	21	356

下降(MRI误诊了SVI)。

2.3.2 ¹⁸F-MD-PSMA PET/CT对初始分期的评估 67例中高危患者,经¹⁸F-MD-PSMA PET/CT检查,38例(56.7%)患者T期上调,15例(22.4%)患者N期上调,13例(19.4%)患者M期上调。32例患者(47.8%)患者的初始分期发生了改变,其中27例(40.3%)上调,5例(7.5%)下调。分期下调是因为经临床判断,3例患者的MRI或BS对骨转移的判断结果呈假阳性,2例患者¹⁸F-MD-PSMA PET/CT对骨转移的结果判断呈假阴性。其余35例(52.2%)患者的初始分期没有发生改变。9例(13.4%)患者新发现了区域淋巴结转移,4例(6.0%)新发现了非区域淋巴结转移,9例(13.4%)新发现了骨转移,13例(19.4%)骨转移的患者发现其他骨转移灶(其中5例由寡转移变为多发骨转移,见图2),1例(1.5%)新发现了肺转移。



Note: A. BS image demonstrated oligometastasis status with 2 lesions in right hip joint and left pubic bone (black arrows). B. MIP image of ¹⁸F-MD-PSMA PET/CT demonstrated 6 lesions with high ¹⁸F-MD-PSMA uptake. C. Fusion images of PET and CT showed abnormal high uptake of ¹⁸F-MD-PSMA at bilateral ilium, right acetabulum and bilateral pubis (white arrows).

图2 一例患者BS与¹⁸F-MD-PSMA PET/CT评估结果比较

Fig 2 Comparison of evaluation results of BS and ¹⁸F-MD-PSMA PET/CT in a patient

对67例患者在完成¹⁸F-MD-PSMA PET/CT初始分期后进行了预后随访,其中4例(6.0%)发生了生化复发,6例(9.0%)发生了影像学进展,5例(7.5%)因PCa并发症死亡。在27例初始分期上调的患者中,仅1例(3.7%)患者在随访过程中发生了生化复发、影像学进展及死亡事件。

3 讨论

PCa的术前分期对病情的评估、治疗方案的选择具有重要的参考价值。目前,mp-MRI和BS作为术前分期的常规成像方法在临床应用中仍具有局限性,各研究变异性较大,SEN及ACU也普遍偏低。

METSER等^[9]从病变水平对55例怀疑PCa的男性患者进行分析,发现mp-MRI对于原发灶检测的SEN为67%。SONNI等^[10]的研究对425个PCa病灶节段进行分析,发现mp-MRI对包膜内病灶的检出率仅为35%。DONATO等^[11]对58例男性的回顾性队列研究发现,mp-MRI在诊断前列腺内病灶的ACU为69%,检测单灶病变的SEN为90%,而诊断双侧和多灶性病变的SEN仅为21%和19%。在检测EPE方面,mp-MRI的SEN为35.0%~66.2%,SPEC为89.0%~92.0%^[12-13]。而另一项对50例PCa患者的前瞻性研究^[14]显示,mp-MRI检测EPE的SEN、SPEC、PPV、NPV及ACU分别为76.5%~94.1%、45.5%~84.9%、43.8%~76.2%、83.3%~96.6%和58.0%~88.0%,在检测SVI方面分别为57.1%~85.7%、86.1%~97.7%、40.0%~85.7%、92.5%~97.7%和82.0%~96.0%。

近年来,PSMA PET/CT在PCa中的应用越来越受到重视。本研究报道了在中高危PCa中使用¹⁸F-MD-PSMA PET/CT进行初始分期的单中心初步经验。精确的T分期有助于为PCa患者选择合适的治疗方案。本研究结果显示,¹⁸F-MD-PSMA PET/CT对双侧疾病的诊断较mp-MRI具有更高的SEN(分别为63.2%和26.3%),该结果与较多相关研究结果基本吻合^[9,11,15]。然而,在诊断EPE、SVI方面,多项研究^[10,15-16]提示mp-MRI较PSMA PET/CT具有更大的优势,与本研究的结果相反。可能的原因包括:①研究人群的风险分层存在差异。本研究中高危人群高达92.5%,而部分报道中的研究对象以低中危为主^[15,17]。②与更高物理空间分辨率的¹⁸F及更高亲和

力和靶本比的新型小分子抑制剂¹⁸F-MD-PSMA的使用有关。③本研究中,为显示更大的盆腔范围,部分患者以普通盆腔MRI代替前列腺mp-MRI,这也是本研究的缺陷之一。在诊断BNI方面,mp-MRI及¹⁸F-MD-PSMA PET/CT在本研究中的表现相近,与其他研究的结论相符^[15,18]。

术前准确检测淋巴结转移,有助于N1期患者清除转移性淋巴结而减少肿瘤负荷,同时也可以减少不必要的ePLND,降低因侵入性操作带来的并发症风险。据研究,PSMA PET/CT诊断区域淋巴结转移的SEN为33.3%~84.0%,SPEC为82.0%~100.0%,ACU为88.5%~95.2%,MRI分别为27.3%~43.9%、85.4%~97.1%和72.3%~87.6%^[19-23]。总体上,2种方法检测区域淋巴结转移时都表现出较低的SEN及较高的SPEC,但PSMA PET/CT更具优势^[15,21]。本研究得出了相似的结果,¹⁸F-FDG PET/CT则介于两者之间。这可能是由于传统的影像学检查具有一定的局限性,通常以淋巴结的大小作为评估转移的标准。当病理性淋巴结表现出异常的解剖特征,如形态呈非椭圆形或短轴直径超过1 cm时,MRI通常可以识别。对于直径小于1 cm的淋巴结,MRI较难作出有效诊断。尽管大小及形态未见异常,PSMA PET/CT示踪剂对转移性淋巴结的特异性亲和力使之可视化。这种特点使¹⁸F-MD-PSMA PET/CT检测转移性淋巴结的SEN显著高于MRI,但其假阳性率也更高。这可能是由示踪剂经肾脏排泄,在输尿管走行区的浓聚造成的。另外,本研究中有部分患者经¹⁸F-MD-PSMA PET/CT检查发现非区域淋巴结转移,并经ePLND得到病理学证实,而¹⁸F-FDG PET/CT表现为阴性。¹⁸F-MD-PSMA PET/CT使这类患者获得了进一步减少肿瘤负荷的机会。

远处转移状态对PCa患者治疗方案的确立至关重要。对于骨病灶来说,较难通过活检明确,因此检查准确率的提高有助于临床对可疑骨病灶的诊断。本研究结果显示,¹⁸F-MD-PSMA PET/CT在诊断骨转移方面,较传统成像方法具有明显的优势,其SEN、SPEC、PPV、NPV和ACU均高于BS,这一结果与大部分研究结果相吻合^[24-26]。在我国,由于PSA筛查尚未全面普及,初诊即诊断为局部晚期或存在转移性病变的比例较高,预后也普遍较差。传统上,包括Rp和根治性放疗在内的局部治疗仅用于治疗局限性PCa;而对于有转移证据的患者,即使是单个盆腔淋

巴结阳性,也意味着失去了积极治疗机会,大多接受ADT联合化学治疗进行系统性、姑息性的治疗。然而,近年来的研究提出了寡转移PCa (oligometastatic prostate cancer, OPC)的概念。骨或淋巴结转移灶数量 ≤ 5 个(即寡转移)的患者,通过对其原发灶及转移灶进行局部治疗,能使寡转移状态在较长时间内维持稳定^[27-29]。本研究中的2例BS呈假阳性后,经随访证实均由退变造成。另外,还有5例由CI评估为寡转移的患者,经PSMA PET/CT评估为多发骨转移。本研究认为,¹⁸F-MD-PSMA PET/CT的应用有利于寡转移患者得到局部治疗的机会,也避免了无意义的手术或局部治疗给多发转移的患者带来的损伤。

¹⁸F-MD-PSMA PET/CT的局限性表现在以下几个方面。第一,阳性PSMA成像是基于转移灶中PSMA的表达,但事实上并不是所有的转移灶都有PSMA表达,因此存在假阴性的可能性。第二,如果转移灶过小,尽管有PSMA摄取,但分辨率的限制使病变不可见。第三,由于尿液放射性的影响,PSMA PET/CT成像较难清晰地判断膀胱颈、输尿管或其他邻近组织的累及,而在软组织分辨率方面又不及MRI。

本研究还存在以下潜在缺陷。由于实际和伦理问题,某些淋巴结及骨转移灶的病理学证实不可行,骨转移只能通过每个病灶的纵向随访而得到证实,无法将病理证实的转移性淋巴结与影像结果一一对应;研究中未能严格执行予患者前列腺mp-MRI检查,而是予以盆腔MRI检查;未能分析除骨转移(M1b)以外的其他远处转移等。

利益冲突声明/Conflict of Interests

所有作者声明不存在利益冲突。

All authors disclose no relevant conflict of interests.

伦理批准和知情同意/Ethics Approval and Patient Consent

本研究涉及的所有项目均已通过上海交通大学医学院附属新华医院医学伦理委员会的审核批准(审批号XHEC-C-2017-055)。受试对象或其亲属已经签署知情同意书(1.0/2017.1.20)。临床试验在美国临床试验注册库(ClinicalTrials.gov)注册(NCT03507595)。

All experimental protocols in this study were reviewed and approved by the Medical Ethics Committee of Xinhua Hospital, Shanghai Jiao Tong University School of Medicine (Approval Letter XHEC-C-2017-055). Consent letters have been signed by the research participants or their relatives (1.0/2017.1.20). Clinical trials were registered (NCT03507595, ClinicalTrials.gov).

作者贡献/Authors' Contributions

严叶青、傅宏亮参与研究设计、数据收集及整理;严叶青负责统计分析、论文撰写;梁胜、马玉飞、蔡利生参与了¹⁸F-MD-PSMA的制备;杨斌、傅宏亮、王辉参与患者招募;邹仁健负责图像采集及处理。所有作者均阅读并同意了最终稿件的提交。

YAN Yeqing and FU Hongliang contributed to the design of the study, collection and organization of the data. YAN Yeqing contributed to statistical analysis and manuscript writing. LIANG Sheng, MA Yufei and CAI Lisheng contributed to the production of ¹⁸F-MD-PSMA. YANG Bin, FU Hongliang and WANG Hui were responsible for recruiting patients. Images were collected and processed by ZOU Renjian. All authors have read the last version of paper and consented for submission.

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参·考·文·献

- [1] BRAY F, FERLAY J, SOERJOMATARAM I, et al. Global cancer statistics 2018: globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries[J]. *CA Cancer J Clin*, 2018, 68(6): 394-424.
- [2] 顾秀瑛, 郑荣寿, 张思维, 等. 2000—2014年中国肿瘤登记地区前列腺癌发病趋势及年龄变化分析[J]. *中华预防医学杂志*, 2018, 52(6): 586-592.
GU X Y, ZHENG R S, ZHANG S W, et al. Analysis on the trend of prostate cancer incidence and age change in cancer registration areas of China, 2000 to 2014[J]. *Chinese Journal of Preventive Medicine*, 2018, 52(6): 586-592.
- [3] TROYER J K, BECKETT M L, WRIGHT G L. Detection and characterization of the prostate-specific membrane antigen (PSMA) in tissue extracts and body fluids[J]. *Int J Cancer*, 1995, 62(5): 552-558.
- [4] WRIGHT G L, HALEY C, BECKETT M L, et al. Expression of prostate-specific membrane antigen in normal, benign, and malignant prostate tissues[J]. *Urol Oncol*, 1995, 1(1): 18-28.
- [5] AFSHAR-OROMIEH A, MALCHER A, EDER M, et al. Reply to Reske et al.: pet imaging with a [⁶⁸Ga]gallium-labelled PSMA ligand for the diagnosis of prostate cancer: biodistribution in humans and first evaluation of tumour lesions[J]. *Eur J Nucl Med Mol Imaging*, 2013, 40(6): 971-972.
- [6] WERNER R A, DERLIN T, LAPA C, et al. ¹⁸F-labeled, PSMA-targeted radiotracers: leveraging the advantages of radiofluorination for prostate cancer molecular imaging[J]. *Theranostics*, 2020, 10(1): 1-16.
- [7] FDA approves ¹⁸F-DCFPyL PET agent in prostate cancer[J]. *J Nucl Med*, 2021, 62(8): 11N.
- [8] KOH W J, ABU-RUSTUM N R, BEAN S, et al. Uterine neoplasms, version 1. 2018, NCCN clinical practice guidelines in oncology[J]. *J Natl Compr Canc Netw*, 2018, 16(2): 170-199.



- [9] METSER U, ORTEGA C, PERLIS N, et al. Detection of clinically significant prostate cancer with ¹⁸F-DCFPyL PET/multiparametric MR [J]. *Eur J Nucl Med Mol Imaging*, 2021, 48(11): 3702-3711.
- [10] SONNI I, FELKER E R, LENIS A T, et al. Head-to-head comparison of ⁶⁸Ga-PSMA-11 PET/CT and mpMRI with a histopathology gold standard in the detection, intraprostatic localization, and determination of local extension of primary prostate cancer: results from a prospective single-center imaging trial[J]. *J Nucl Med*, 2022, 63(6): 847-854.
- [11] DONATO P, ROBERTS M J, MORTON A, et al. Improved specificity with ⁶⁸Ga PSMA PET/CT to detect clinically significant lesions “invisible” on multiparametric MRI of the prostate: a single institution comparative analysis with radical prostatectomy histology[J]. *Eur J Nucl Med Mol Imaging*, 2019, 46(1): 20-30.
- [12] CAGLIC I, SUSHENTSEV N, SHAH N, et al. Comparison of biparametric *versus* multiparametric prostate MRI for the detection of extracapsular extension and seminal vesicle invasion in biopsy naïve patients[J]. *Eur J Radiol*, 2021, 141: 109804.
- [13] BOESEN L, CHABANOVA E, LØGAGER V, et al. Prostate cancer staging with extracapsular extension risk scoring using multiparametric MRI: a correlation with histopathology[J]. *Eur Radiol*, 2015, 25(6): 1776-1785.
- [14] POPIȚA C, POPIȚA A R, ANDREI A, et al. Local staging of prostate cancer with multiparametric-MRI: accuracy and inter-reader agreement [J]. *Med Pharm Rep*, 2020, 93(2): 150-161.
- [15] YILMAZ B, TURKAY R, COLAKOGLU Y, et al. Comparison of preoperative locoregional Ga-68 PSMA-11 PET-CT and mp-MRI results with postoperative histopathology of prostate cancer[J]. *Prostate*, 2019, 79(9): 1007-1017.
- [16] KOSEOGLU E, KORDAN Y, KILIC M, et al. Diagnostic ability of Ga-68 PSMA PET to detect dominant and non-dominant tumors, upgrading and adverse pathology in patients with PIRADS 4-5 index lesions undergoing radical prostatectomy[J]. *Prostate Cancer Prostatic Dis*, 2021, 24(1): 202-209.
- [17] UCAR T, GUNDUZ N, DEMIRCI E, et al. Comparison of ⁶⁸Ga-PSMA PET/CT and mp-MRI in regard to local staging for prostate cancer with histopathological results: a retrospective study [J]. *Prostate*, 2022, 82(15): 1462-1468.
- [18] ÇELEN S, GÜLTEKİN A, ÖZLÜLERDEN Y, et al. Comparison of ⁶⁸Ga-PSMA-I/T PET-CT and multiparametric MRI for locoregional staging of prostate cancer patients: a pilot study[J]. *Urol Int*, 2020, 104(9/10): 684-691.
- [19] ARSLAN A, KARAAARSLAN E, LEVENT GÜNER A, et al. Comparing the diagnostic performance of multiparametric prostate MRI *versus* ⁶⁸Ga-PSMA PET-CT in the evaluation lymph node involvement and extraprostatic extension[J]. *Acad Radiol*, 2022, 29(5): 698-704.
- [20] HOPE T A, EIBER M, ARMSTRONG W R, et al. Diagnostic accuracy of ⁶⁸Ga-PSMA-11 PET for pelvic nodal metastasis detection prior to radical prostatectomy and pelvic lymph node dissection: a multicenter prospective phase 3 imaging trial[J]. *JAMA Oncol*, 2021, 7(11): 1635-1642.
- [21] MAURER T, GSCHWEND J E, RAUSCHER I, et al. Diagnostic efficacy of ⁶⁸gallium-PSMA positron emission tomography compared to conventional imaging for lymph node staging of 130 consecutive patients with intermediate to high risk prostate cancer[J]. *J Urol*, 2016, 195(5): 1436-1443.
- [22] WOO S, SUH C H, KIM S Y, et al. The diagnostic performance of MRI for detection of lymph node metastasis in bladder and prostate cancer: an updated systematic review and diagnostic meta-analysis [J]. *AJR Am J Roentgenol*, 2018, 210(3): W95-w109.
- [23] BUDÁUS L, LEYH-BANNURAH S R, SALOMON G, et al. Initial experience of ⁶⁸Ga-PSMA PET/CT imaging in high-risk prostate cancer patients prior to radical prostatectomy [J]. *Eur Urol*, 2016, 69(3): 393-396.
- [24] YUMINAGA Y, ROTHE C, KAM J, et al. ⁶⁸Ga-PSMA PET/CT *versus* CT and bone scan for investigation of PSA failure post radical prostatectomy[J]. *Asian J Urol*, 2021, 8(2): 170-175.
- [25] PYKA T, OKAMOTO S, DAHLBENDER M, et al. Comparison of bone scintigraphy and ⁶⁸Ga-PSMA PET for skeletal staging in prostate cancer[J]. *Eur J Nucl Med Mol Imaging*, 2016, 43(12): 2114-2121.
- [26] ACAR E, BEKIŞ R, POLACK B. Comparison of bone uptake in bone scan and Ga-68 PSMA PET/CT images in patients with prostate cancer[J]. *Curr Med Imaging Rev*, 2019, 15(6): 589-594.
- [27] RUSTHOVEN C G, JONES B L, FLAIG T W, et al. Improved survival with prostate radiation in addition to androgen deprivation therapy for men with newly diagnosed metastatic prostate cancer [J]. *J Clin Oncol*, 2016, 34(24): 2835-2842.
- [28] SATKUNASIVAM R, KIM A E, DESAI M, et al. Radical prostatectomy or external beam radiation therapy *vs* no local therapy for survival benefit in metastatic prostate cancer: a SEER-medicare analysis[J]. *J Urol*, 2015, 194(2): 378-385.
- [29] OST P, REYNDERS D, DECAESTECKER K, et al. Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: a prospective, randomized, multicenter phase II trial [J]. *J Clin Oncol*, 2018, 36(5): 446-453.

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