·综 述·

PET显像新技术在子宫恶性肿瘤中的进展

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[摘 要] 子宫恶性肿瘤主要有宫颈癌与子宫内膜癌,分别位列中国女性恶性肿瘤发病率的第2、3位,其死亡率逐年递增,发病人群也趋于年轻化。为实现个体化精准治疗需对子宫病灶进行准确分期和疗效评估。子宫恶性肿瘤正电子发射断层扫描(positron emission tomography,PET)显像(包括葡萄糖代谢、细胞增殖、雌激素受体、生长抑素受体、肿瘤乏氧和成纤维细胞激活蛋白抑制剂显像等)在肿瘤分期、监测靶向治疗反应及早期识别放化疗耐药等方面具有显著优势,已成为宫颈癌及子宫内膜癌诊疗研究的热点方向。

[关键词] 宫颈癌;子宫内膜癌;PET显像

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Progress of new PET imaging techniques in uterine malignancies

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[**Abstract**] Uterine malignant tumors mainly include cervical cancer and endometrial cancer, which are the second and third most common female malignant tumors in China, respectively. The mortality of uterine malignant tumors is increasing by years, and the patients tend to be younger. In order to achieve individualized and accurate treatment, accurate staging of uterine lesions and high-quality therapeutic evaluation are needed. Positron emission tomography (PET) imaging of uterine malignant tumors, including glucose metabolism, cell proliferation, estrogen receptor, somatostatin receptor, hypoxia imaging and fibroblast activation protein inhibitor imaging, has significant advantages in tumor staging, monitoring response to targeted therapy, and early identification of chemoradiotherapy resistance. It has become a hot research topic in diagnosis and treatment of cervical and endometrial cancer.

[**Key words**] cervical cancer; endometrial cancer; PET imaging

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近年来,中国女性宫颈癌(cervical cancer,CC)与子宫内膜癌(endometrial cancer,EC)的发病率与死亡率逐年递增,发病人群也趋于年轻化[1]。CC与EC患者常伴有阴道流血、排液等病史,可通过诊刮、阴道镜、宫腔镜等有创检查确诊。常规影像学检查包括阴道超声、CT和磁共振(magnetic resonance,MR),但它们对全身多发转移的检出率不高,且其参数变化无法及时反映治疗效果。正电子发射断层扫描(positron emission tomography,PET)显像可以在一次检查中整合代谢、解剖信息,是一种全身无创性的检查手段,其中以^{18}F-脱氧葡萄糖(^{18}F-fluoro-2-deoxyglucose,^{18}F-FDG)应用最为成熟。但^{18}F-FDG显像剂具有许多局限,如子宫炎性及生理性摄取导致的假阳性改变,或是由于肿瘤糖代谢不显著而致的假阴性表现[2-4],因此众多新型PET显像剂及新设备正在研发。本文将针对新型PET显像剂及新设备在CC及EC诊疗中的应用作一综述。

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1　CC新型显像剂

CC与高危人乳头瘤病毒持续感染密切相关，早期患者可无明显症状，随着病情进展会出现接触性阴道出血、异常排液等。CC的病理分型包括宫颈鳞癌、腺癌、腺鳞癌及神经内分泌肿瘤等。新型核素显像通过整合肿瘤的表型特征和解剖学细节，实现对CC的高质量评估，目前已成为诊疗研究中的热点。

1.1　新型广谱肿瘤显像剂

成纤维细胞活化蛋白（fibroblast activation protein，FAP）是肿瘤相关成纤维细胞特异性表达的一种表面抗原[5]，选择性表达于90%以上的上皮类肿瘤细胞[6]。成纤维细胞激活蛋白抑制剂（FAP inhibitor，FAPI）是FAP的特异性酶抑制剂，可被放射性核素^{68}Ga标记用于肿瘤显像。Dendl等[7]对CC患者行^{68}Ga-FAPI PET检查发现，原发和继发性病灶均具有较好的吸收率和对比度；并且患者脑实质背景对^{68}Ga-FAPI的摄取显著低于^{18}F-FDG，这有利于精确勾画转移灶及后续制定放疗计划。Zhang等[8]研究发现，^{68}Ga-FAPI PET较^{18}F-FDG PET可检出更多CC患者的淋巴结转移灶，这可能与^{68}Ga-FAPI成像的靶本比更高有关。此外，FAPI还可被治疗性核素^{177}Lu、^{90}Y等标记用于治疗，从而实现诊疗一体化[9-10]。然而在子宫体部恶性肿瘤中，由于月经周期、子宫术后瘢痕或子宫肌瘤都有可能造成子宫局部^{68}Ga-FAPI高摄取，因此仍需更大规模的前瞻性研究来证实^{68}Ga-FAPI在子宫疾病，尤其是EC中的临床价值[11-12]。

1.2　细胞乏氧显像剂

放射治疗是恶性肿瘤的主要治疗方式之一，研究表明，肿瘤灶微环境的乏氧状态影响肿瘤侵袭性和放化疗耐药性[13]，放疗前通过量化病灶的乏氧程度能提供更精准的肿瘤覆盖靶点，予以更高放疗剂量照射乏氧区域的同时也减少放射性直肠炎、膀胱炎的发生[14]。现有的乏氧显像剂分两类：氟标硝基咪唑类和铜标N4-甲基硫代半脲类。

氟标硝基咪唑类乏氧显像剂包括^{18}F-FMISO、^{18}F-FETNIM及^{18}F-FAZA等。^{18}F-FMISO是缺氧成像最广泛的硝基咪唑化合物，但在乏氧组织中摄取及常氧组织中清除均较缓慢，在注射后2~4 h才可采集图像，因此检查耗时长且病灶背景对比差[15]。新一代硝基咪唑化合物^{18}F-FETNIM可突破^{18}F-FMISO的部分局限性[16]，但由于在^{18}F-FETNIM PET图像中CC病灶较难与相邻正常软组织区分开来，限制了它在测量肿瘤缺氧体积中的使用[14]。^{18}F-FAZA较^{18}F-FMISO具有更好的血液和非靶组织清除率，且在肠道摄取偏低，因此腹部图像质量优于^{18}F-FMISO[17]，但它经泌尿系统排泄，容易干扰邻近病变的检出。

铜标的N4-甲基硫代半脲类显像剂以^{60}Cu-ATSM表现最佳，^{60}Cu-ATSM具有更快的药代动力学，注射后30 min即可成像，并且ATSM具有亲脂性，泌尿系统排泄不明显，图像质量更好，是评估盆腔病变的理想显像剂[18]。Dehdashti等[19]研究证实，治疗前^{60}Cu-ATSM乏氧显像可预测疗效，肿瘤-肌肉摄取（T/M）比值>3.5可区分缺氧肿瘤、常氧肿瘤以及有复发可能的肿瘤，同时^{60}Cu-ATSM摄取与无进展生存期和总生存期呈负相关。有学者认为，CC的^{60}Cu-ATSM显像与肿瘤进展及血管生成相关分子标志物——血管内皮生长因子（vascular endothelial growth factor，VEGF）、表皮生长因子（epidermal growth factor receptor，EGFR）、环氧化酶-2（cyclooxygenase-2，COX-2）、糖类抗原-9（carbohydrate antigen-9，CA-9）的过度表达和预后不良相关[20]。然而，CC放射治疗引起的靶区血管损伤可能会使血流减少，从而干扰^{60}Cu-ATSM的摄取；同时，放射治疗直接引起的肿瘤细胞坏死也会减少^{60}Cu-ATSM的摄取[21]。

1.3　细胞增殖显像剂

研究表明，同步放化疗在有效抑制CC细胞增殖的同时可导致病灶区域的炎性反应，因此治疗后病灶区持续存在轻到中度^{18}F-FDG摄取，这无法反映真实的肿瘤活性残留[19]。^{18}F-氟代胸苷（^{18}F-fluorothymidine，^{18}F-FLT）是^{18}F标记的胸腺嘧啶核苷，在胸腺激酶的作用下被磷酸化进而局限在细胞内，是应用最广泛的细胞增殖显像剂[22]。^{18}F-FLT不被放化疗后的宫颈炎性灶所摄取，因此较^{18}F-FDG更适用于治疗反应的监测及化疗耐药的早期识别[23]。Paulina等[24]通过联合分析39例CC患者的^{18}F-FDG及^{18}F-FLT PET图像发现，原发肿瘤的糖酵解总量/增殖总量和^{18}F-FDG代谢体积越高，患者预后越差；且不同分化程度的CC摄取^{18}F-FLT的SUVmax差异有统计学意义。另外，放疗会导致骨髓严重损伤，增加患者贫血及感染风险，因此减少对造血功能活跃的红骨髓区照射是减轻并发症的有效方法[25-26]。相比^{18}F-FDG PET，^{18}F-FLT PET有助于鉴别黄骨髓与红骨髓，从而使^{18}F-FLT增殖显像更适合CC患者调强放疗方案的规划[27]。

1.4　生长抑素受体（somatostatin receptor，SSTR）显像剂

宫颈神经内分泌癌（neuroendocrine cervix carci-

noma，NECC)是一种以SSTR过度表达为特征的罕见肿瘤，最主要的病理类型是小细胞癌[28-29]。NECC有极高的淋巴转移和血行播散倾向，甚至早期确诊的患者病死率也较高，大部分患者因确诊时已存在远处转移而失去接受根治性手术的机会，因此在疾病局限期确诊至关重要[30]。SSTR配体可被^{68}Ga标记用于成像，常见的神经内分泌肿瘤显像剂包括：^{68}Ga-DOTA-TOC、^{68}Ga-DOTA-TATE和^{68}Ga-DOTA-NOC。2017年Andres等[31]报告了1例小细胞型NECC患者，该患者先前行全身增强CT检查未发现转移灶，然而行^{68}Ga-DOTA-TATE PET显示出高摄取的原发灶和孤立性骨盆骨转移灶，且均被活检证实。众多研究认为，^{68}Ga-DOTA-TATE PET检测初发或复发的神经内分泌肿瘤非常准确[32]，^{68}Ga-DOTA-TATE PET对SSTR阳性表达的NECC的敏感性为96%，特异性为100%[33]。但原发于宫颈的NECC比较罕见，因此，现阶段关于SSTR PET在NECC中的研究较少。

2 EC新型显像剂——雌激素受体(estrogen receptor，ER)显像剂

EC是发生在子宫内膜的上皮性恶性肿瘤，多发生于围绝经期及绝经后妇女。根据EC发病机制和生物学行为将其分为雌激素依赖型和非雌激素依赖型。大部分EC属于雌激素依赖型，它的发生与无孕激素拮抗的雌激素持续刺激直接相关。当雌激素与ER结合后，可促进癌细胞的存活和增殖，因此ER可作为EC成像的靶点。ER有两种异构体：ERα和ERβ，针对这两种靶点的代表性显像剂分别为16α-^{18}F-17β-雌二醇(16α-^{18}F-fluoroestradiol，^{18}F-FES)、2-^{18}F-氟-6-(6-羟基萘-2-基)吡啶-3-醇[2-^{18}F-fluro-6-(6-hydroxynaphthalen-2-yl)pyridin-3-ol，^{18}F-FHNP]。

研究认为，ERα阳性患者行内分泌治疗后的临床缓解率较ERα阴性的患者更高且生存时间更长，治疗前及治疗中监测ERα受体变化可优化患者治疗方案，因此ERα有望作为EC患者预后的潜在分子标志物[34-35]。^{18}F-FES是一种雌激素类似物，已成功用于乳腺癌和其他妇科癌症患者的ER成像[36-37]。一项包含67例患者的研究表明[38]，EC原发灶的^{18}F-FES SUVmean是影响患者无进展生存期的独立预后因素，并与肿瘤分期、组织学、淋巴血管间隙受累和淋巴结转移显著相关。另一项研究认为，高级别EC会通过加速葡萄糖代谢而降低雌激素依赖性，因此^{18}F-FDG与^{18}F-FES的SUVmean比值(^{18}F-FDG/^{18}F-FES)与EC的国际妇产科联盟(Federation of International of Gynecologists and Obstericians，FIGO)分期和和侵袭性相关；^{18}F-FDG/^{18}F-FES=2.0鉴别良恶性病灶的准确度为86%，优于^{18}F-FDG(68%)及MR(77%)[39]。因此^{18}F-FES PET在EC精准诊断及辅助制定治疗决策上具有优势。

ERβ和ERα具有相反的生物学功能，有发挥抗增殖和促肿瘤细胞凋亡的作用，其表达水平随肿瘤进展而下调[40]。基于此，研究人员开发出一种ERβ受体选择性显像剂——^{18}F-FHNP，其标记产率和比活度高，对ERβ具有优先亲和力。Antunes等[41-42]研究发现，^{18}F-FHNP代谢率Ki(^{18}F-FHNP的血浆时间-活性曲线斜率值)及SUV值可评估ERβ的表达。另有研究表明，ERβ阳性但ERα阴性的乳腺癌患者可因行他莫昔芬内分泌治疗而获益[43]，因此评估肿瘤ERβ的表达状态是必要的。这些临床前结果表明^{18}F-FHNP具有很好的前景，但^{18}F-FHNP PET目前仅应用于乳腺癌，仍需大量临床前和临床研究探索EC患者行^{18}F-FHNP PET成像的临床价值。

3 PET/MR技术

近年来，PET/MR迅速兴起，目前的PET/MR一体机成像是将PET成像的分子信息和MR高软组织分辨率的解剖信息结合的多模态成像新技术，在某些方面优于PET/CT，有望成为妇科癌症患者成像评估的支柱[44]。一项纳入46例CC患者的研究也指出：PET对淋巴结转移和FIGO分期的诊断价值高于单独的MR成像，而MR成像对病理分化程度的诊断价值高于PET。因此，PET/MR联合成像的临床价值更大[45]。Schwartz等[46]认为^{18}F-FDG PET/CT和PET/MR均能明确CC及EC的诊断，它们对区域淋巴结和腹部转移灶的检出率相似，然而PET/MR能更清晰地显示病灶及其肿瘤对宫旁组织和膀胱的侵犯，从而优化疾病分期或治疗方法。对于妊娠早期CC患者，须避免使用对比增强成像以免伤害胎儿，研究发现给予^{18}F-FDG后，胎儿受辐射剂量低于有确定性影响的阈值[47]，且^{18}F-FDG PET/MR对恶性肿瘤的敏感性高于常规的增强成像[48]，因此更鼓励在妊娠期间使用^{18}F-FDG PET/MR检查[49]。也有研究认为虽然全身^{18}F-FDG PET/MR并不能获得比^{18}F-FDG PET/CT更高的分期准确性，然而在复发的妇科肿瘤患者中，^{18}F-FDG PET/MR显著提升了肿瘤复发灶的检出率以及复发灶分期的准确性[50-51]。虽然PET/MR成本相对较高，其有关临床研究相对较少，但相

信MR技术和新型显像剂的不断发展势必赋予PET/MR更加光明的未来。

4　总结与展望

现阶段，针对CC及EC的新型核素显像剂层出不穷，各类相关临床试验也陆续开展（表1）。与传统检查手段相比，新型核素显像剂及新设备能更加细致地探索肿瘤微环境，不仅对肿瘤转移灶具有独特的诊断价值，且能够测量体内肿瘤行为、表征整体肿瘤负荷并捕获肿瘤表型异质性，因此在优化疾病诊断、治疗方面都有着巨大的潜能。相信随着核医学和分子生物学等学科的融合发展，肿瘤核素显像在核医学分子影像领域的应用也愈发广阔，也期待核素放药及检查设备能够不断探索精进、推陈出新，早日在临床诊疗中发挥更显著的优势。

表1　核医学显像剂在子宫恶性肿瘤应用中的基本情况

Table 1　Basic information of nuclear medicine imaging agents in uterine malignant tumors

探针类型	显像机制	代表探针	临床意义
葡萄糖代谢类	肿瘤细胞葡萄糖代谢变化	^{18}F-FDG	应用最广泛的广谱肿瘤显像剂，可用于肿瘤分期、治疗疗效评估
细胞蛋白类	肿瘤特异性表达成纤维细胞活化蛋白	^{68}Ga-FAPI ^{177}Lu-FAPI	广谱肿瘤显像剂，辐射剂量低，CC成像靶本比高，用于核素治疗
细胞缺氧显像	肿瘤增殖造成乏氧状态	^{18}F-FETNIM ^{18}F-FAZA ^{60}Cu-ATSM	指导CC放疗方案，预测CC预后
细胞增殖显像	肿瘤细胞核酸代谢变化	^{18}F-FLT	评估CC、EC放化疗疗效，指导治疗方案选择
细胞受体类			
ERα	特异性结合表达ERα的EC细胞	^{18}-F-FES	指导EC内分泌治疗
ERβ	结合表达ERβ的EC细胞	^{18}F-FHNP	显示表达ERβ的EC
SSTR	特异性结合表达SSTR的NECC	^{68}Ga-DOTA-TATE	NECC诊断及分期

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