非 ^{18}F-氟脱氧葡萄糖的脑肿瘤 PET

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【摘要】 由于大脑皮质的葡萄糖摄取相对较高，常规 ^{18}F-氟脱氧葡萄糖（^{18}F-FDG）PET 对于脑肿瘤，特别是低度恶性脑肿瘤的显像有较大的局限性。近年来，各种特异性更高的放射性示踪剂如 ^{11}C-甲硫氨酸（^{11}C-MET），^{11}C-胆碱（^{11}C-choline），^{18}F-氟脱氧胸苷（^{18}F-FLT）等越来越多地应用于脑肿瘤显像。非 ^{18}F-FDG 的放射性示踪剂在脑肿瘤的显像中均具有脑本底摄取低、肿瘤影像对比度好、对低级别胶质瘤敏感性较高的优点，在脑肿瘤的诊断、鉴别诊断、放疗计划的制定及疗效监测等方面比 ^{18}F-FDG 有着明显的优势。

【关键词】 体层摄影术，发射型计算机；脑肿瘤；^{11}C-甲硫氨酸；^{11}C-胆碱；^{18}F-氟脱氧胸苷

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Non ^{18}F-fluorodeoxyglucose PET imaging of brain tumors

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【**Abstract**】 Due to the high uptake of the (^{18}F-fluoroleoxyjlucose, ^{18}F-FDG) in brain cortex, the conventional way of PET imaging for the brain tumors has been limited, especially when the tumor is of low WHO grade. Lately, some more specific PET imaging agents (^{11}C-methionine, ^{11}C-choline, ^{18}F-fluorothymidine, etc.) have been developed and are being applied to the PET imaging of brain tumors. The common advantages of these new agents are low background uptake, high contrast of tumor imaging and higher sensitivity for low-grade gliomas. These new agents are expected to make better application in diagnosis, differential diagnosis, planning of radiotherapy and treatment effectiveness monitering of brain tumors than ^{18}F-FDG. This article will make a brief introduction of the application of these non-^{18}F-FDG agents in aspects mentioned above.

【**Key words**】 Tomography, emission-computed; Brain tumor; ^{11}C-methionine; ^{11}C-choline; ^{18}F-fluorothymidine

脑肿瘤的早期发现、诊断及准确分级对于患者的治疗及预后有着至关重要的作用。PET 脑肿瘤显像最常用的放射性示踪剂为经典的 ^{18}F-氟脱氧葡萄糖（^{18}F-fluorodeoxyglucose, ^{18}F-FDG）。作为反映细胞组织葡萄糖代谢的示踪剂，^{18}F-FDG PET 已被广泛地用于脑肿瘤的检测、分级、疗效判断及预后评估。由于大脑皮质对于葡萄糖的相对高摄取，使得 ^{18}F-FDG PET 对于脑肿瘤显像的特异性及对低度恶性脑肿瘤显像的敏感性受到较大限制。目前，除代谢显像剂 ^{18}F-FDG 外，用于脑肿瘤 PET 的显像剂主要有氨基酸、胆碱及核酸类等代谢药物。

1 脑肿瘤的 PET 诊断

1.1 氨基酸代谢显像

目前，放射性核素标记的氨基酸代谢示踪剂有 ^{11}C-甲硫氨酸（^{11}C-methionine，^{11}C-MET），^{11}C-酪氨酸（^{11}C-tyrosine），^{18}F-氟酪氨酸（^{18}F-flouorotyrosine）及 ^{18}F-氟乙基酪氨酸（*O*-2-^{18}F-fluoroethyl-*L*- tyrosine, ^{18}F-FET）等，其共同优点是在正常脑组织中摄取量很低，因此对脑肿瘤检测准确率较高，对肿瘤边缘的描绘更清楚，尤其对于 ^{18}F-FDG 低摄取或等摄取的脑肿瘤诊断更有价值。

Chung 等[1] 研究显示，对于 ^{18}F-FDG 低摄取或等摄取的脑肿瘤，^{11}C-MET PET 的灵敏度和特异度可分别达到 89%和 100%，其中对胶质瘤的灵敏度为 92%。Langen 等[2]报道，80%的Ⅱ级胶质瘤对 ^{11}C-MET 的摄取高出正常脑组织 1.5 倍以上，而此时其葡萄糖的代谢通常都低于正常灰质。增高的 ^{11}C-MET 摄取并不直接代表肿瘤蛋白质合成的增加，其更直接地与 *L* 型氨基酸载体介导的氨基酸转运速率增加有关。研究证实，^{11}C-MET 的摄取与 Ki-

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67蛋白的表达、增殖细胞核抗原以及局部微血管的密度呈相关性，表明^{11}C-MET可作为肿瘤活性增殖的一个标志[1,3]。另有研究表明，^{11}C-MET的摄取与肿瘤的分级呈相关性，因此如与^{18}F-FDG PET联合诊断，^{11}C-MET PET对肿瘤分级十分有价值[4]。此外，肿瘤的组织学类型也影响到^{11}C-MET的摄取，相对于同等级的星形细胞瘤，少突胶质细胞瘤摄取^{11}C-MET的能力更高。^{11}C-MET也有其自身的局限性，Sunada等[5]报道，^{11}C-MET PET对于良性的脉络丛乳头状瘤可表现为高摄取的假阳性结果；脑内急性缺血灶及炎性病灶也可摄取^{11}C-MET，这对其在鉴别诊断中的作用应有一定的影响；作为^{11}C标记的放射性药物，过短的半衰期(20.4 min)限制其广泛的应用；而MET在体内分解代谢速度过快也使得对其进行体内动力学模型分析非常困难。

氨基酸代谢显像剂^{18}F-FET弥补了^{11}C-MET的不足，并以其较长的半衰期(109.6 min)使得不具备回旋加速器的PET中心也能够进行氨基酸代谢显像。已有动物实验结果显示，相对于^{18}F-FDG及^{11}C-MET，^{18}F-FET对于非肿瘤病变及炎性细胞表现为低摄取[6,7]。初步的临床研究显示，^{18}F-FET对于脑肿瘤的显像结果与^{11}C-MET相似[8]。Floeth等[9]的研究显示，^{18}F-FET PET对于胶质瘤显像的灵敏度比磁共振波谱稍差，分别为88%和100%，但特异度更高，分别为88%和81%，如两者联合应用，可显著提高诊断的准确性。Pauleit等[10]的研究显示，^{18}F-FET的摄取与肿瘤的组织类型有关，鳞状细胞癌多可表现为^{18}F-FET的高摄取，但腺癌及淋巴瘤则多表现为^{18}F-FET低摄取，因此^{18}F-FET用于脑转移性肿瘤的价值较有限。Floeth等[9]的研究显示，^{18}F-FET的摄取与胶质瘤的分级无明显相关性，这一特性与^{11}C-MET相似。

1.2 胆碱代谢显像

^{11}C-胆碱在血液中的清除较快，而其放射性活性在细胞组织中的分布于注射后5 min内即可达到稳定，因此注射^{11}C-胆碱后5 min即可显像，显著加快了患者的检查流程。由于正常脑组织对于胆碱也表现为低摄取，^{11}C-胆碱PET可以获得高对比度的脑肿瘤影像。有研究显示，高级别胶质瘤摄取^{11}C-胆碱的程度显著高于低级别胶质瘤[11]，并提示^{11}C-胆碱PET对于胶质瘤的分级有一定价值，但尚需进一步研究证实。Kwee等[12]报道，胆碱对于鉴别胶质瘤及类似肿瘤性的脱髓鞘病变比磁共振波谱更为有效。Tian等[13]和Ohtani等[11]的研究显示，^{11}C-胆碱的显著摄取常见于鳞状细胞癌、恶性淋巴瘤、增生的淋巴组织，中等摄取常见于多形性腺瘤及硬纤维瘤，星形细胞瘤及脂肪瘤则为低摄取；良性病变如炎性肉芽肿、纤维瘤、脑膜瘤、颅咽管瘤和低级别的毛细胞型星形细胞瘤也表现为显著的高摄取，因此，^{11}C-胆碱用于鉴别低级别胶质瘤及非肿瘤性病变还存在一定的困难。Zhang等[14]认为，上述假阳性结果可能是由于组织细胞或巨细胞的细胞膜对胆碱的高利用所致。

1.3 核酸代谢显像

^{18}F-氟脱氧胸苷(^{18}F-fluorothymidine, ^{18}F-FLT)能够直接评估细胞胸苷激酶的活性。^{18}F-FLT在体内被细胞胸苷激酶1(thymidine kinase-1, TK-1)磷酸化后滞留在细胞内，正常细胞的TK-1活性在DNA合成阶段升高10倍左右，而恶性肿瘤细胞TK-1活性的升高更为明显且表现为持续性[15]。Rasey等[16]用细胞培养实验显示，^{18}F-FLT的摄取与S期细胞的百分比及TK-1的活性相关性较好。Chen等[17]的研究显示，肿瘤对^{18}F-FLT的摄取较快，在注射后5~10 min即可达到峰值并可保持稳定达75 min，研究同时显示了^{18}F-FLT PET与Ki-67指数的相关性明显好于^{18}F-FDG PET，且高级别的胶质瘤对^{18}F-FLT的摄取明显高于低级别的胶质瘤及对照组，因此，^{18}F-FLT可作为反映胶质瘤增殖活性的指标。但是，Jacobs等[18]的研究显示，^{18}F-FLT对于胶质瘤的灵敏度略低于^{11}C-MET，分别为78.3%和91.3%，且^{18}F-FLT对鉴别低级别胶质瘤尤其是低级别的星形细胞瘤与非肿瘤病变的价值有限。

2 脑肿瘤治疗方案的制定

^{18}F-FDG PET有助于对脑肿瘤进行分级，但由于受到高本底摄取的限制，对于肿瘤浸润范围的判断能力有限，无法有效地区分低级别的肿瘤与周围正常脑组织。而示踪剂^{11}C-MET、^{18}F-FET、^{11}C-胆碱和^{18}F-FLT等都能够显示出对比度较好的脑肿瘤影像。肿瘤代谢最旺盛的部位往往处在肿瘤的边缘及浸润部位，活检结果显示在离MRI增强边缘3 cm处仍有肿瘤细胞存在，且80%的肿瘤复发位于距离原增强病灶边缘2 cm的范围内[9]。与增强的MRI图像结果相比，非^{18}F-FDG PET显示的病灶范围通常更大，因此对于肿瘤切除范围的制定及放疗靶区的勾划能够提供更完整的信息。

Pirotte等[19,20]的研究显示，在脑肿瘤的实质性区域和浸润区域都可同样表现为^{11}C-MET的摄取增

高，因此 ^{11}C-MET 用于 PET 引导下的定向穿刺活检较传统的 ^{18}F-FDG PET 有更好的效果。Grosu 等[21]已经成功地将 ^{11}C-MET PET 应用于立体定向放疗，其初步研究显示，相对于单纯的 CT 或 MRI 定位放疗，^{11}C-MET PET 定位后治疗的高级别胶质瘤复发患者中位生存期明显提高，分别为 5 个月和 9 个月。Ribom 等[22]报道，^{11}C-MET PET 还可用于判断低级别胶质瘤对放疗的敏感程度，对低级别胶质瘤的治疗方案的制定有重要价值。^{18}F-FET PET 对实质性胶质瘤的描绘亦优于 MRI，提示其用于胶质瘤的定向穿刺活检及三维适形放疗定位应比传统的 CT 及 MRI 应更有优势[19]。虽然 ^{18}F-FLT 的标准化摄取值(standardized uptake value, SUV)低于 ^{11}C-MET，但其肿瘤/本底比值高于 ^{11}C-MET，提示 ^{18}F-FLT PET 对脑肿瘤的描绘好于 ^{11}C-MET PET[18]。

3 脑肿瘤复发的鉴别、疗效监测及预后判断

^{18}F-FDG PET 对于脑肿瘤的疗效监测及预后判断已有较广泛的应用。在非 ^{18}F-FDG PET 中，^{11}C-MET PET 用于胶质瘤治疗后复发的判断及预后评估显示出比 ^{18}F-FDG PET 更大的优势。^{11}C-MET 的摄取可作为判断胶质瘤患者预后的独立因素[23]。Van Laere 等[24]对 30 例胶质瘤治疗后的患者分别进行 ^{11}C-MET PET 及 ^{18}F-FDG PET，并进行了 Kaplan-Meier 生存分析，结果显示，^{11}C-MET PET 可作为判断肿瘤复发及预测生存期的独立指标，而 ^{18}F-FDG PET 则无法做到上述两点。Rachinger 等[25]的研究则显示，^{18}F-FET PET 用于胶质瘤治疗后复发的诊断，其灵敏度和特异度分别达 100%和 92.9%。Chen 等[26] 发现，如果 SUV 分别以 0.82(灵敏度为 80%，特异度为 77.8%)和 3.36(灵敏度为 60%，特异度为 55.6%)作为阈值，^{18}F-FLT 相对于 ^{18}F-FDG，其摄取值对于预测脑肿瘤的进展及患者的生存期有更强的可靠性，即摄取低于阈值的患者其生存期显著长于摄取高于阈值的患者。

综上所述，由于目前尚无单一理想的影像学检查方法，因此多种影像学手段的结合是迄今最佳的非创伤性检查方法。非 ^{18}F-FDG PET 脑肿瘤显像作为常规影像学手段及 ^{18}F-FDG PET 的补充，其应用日益受到重视，并从多种途径反映出脑肿瘤的代谢异常，其共同的优势在于较低的脑本底摄取并因此提供了较好诊断特异性及对肿瘤形态更佳的影像。随着更多特异性更强的新示踪剂的研发，脑肿瘤的诊断及疗效必将会进一步提高。

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