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$^{99}Tc^{m}$-depreotide 显像对肺部病灶的鉴别诊断价值

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【摘要】Depreotide 是一种人工合成的十肽生长抑素类似物，含生长抑素受体结合序列和 $^{99}Tc^{m}$ 配位序列。通过荟萃分析肺部病灶的 $^{99}Tc^{m}$-depreotide 显像资料显示，$^{99}Tc^{m}$-depreotide 鉴别肺部病灶良恶性的灵敏度为 94.2%(95%可信区间：90.5%，97.9%)，特异度为 61.2%(95%可信区间：50.7%，71.7%)，诊断准确率为 81.6%，阳性预测值为 81.1%，阴性预测值为 83.2%；对于 1.5 cm 以下的孤立性肺结节(SPN)，$^{99}Tc^{m}$-depreotide 显像特异性极高，显像阳性是手术治疗的适应证；对于 1.5 cm 以上的 SPN，因其灵敏度高，$^{99}Tc^{m}$-depreotide 显像阴性者可进行系列 CT 扫描随访观察。

【关键词】肺肿瘤；硬币病变，肺；淋巴结；肿瘤转移；$^{99}Tc^{m}$-depreotide

The clinical value of $^{99}Tc^{m}$-depreotide scintigraphy in differentiating malignant from benign lesions in the lung

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【**Abstract**】Depreotide is a synthetic 10-aminoacid peptide which is comprised of a somatostain receptor binding sequence and a technetium coordinating sequence. A meta-analysis is performed to estimate the diagnostic efficiency of $^{99}Tc^{m}$-depreotide scintigraphy. The sensitivity, specificity, accuracy, positive predictive value and negative predictive value of $^{99}Tc^{m}$-depreotide SPECT in distinguishing pulmonary lesions were, respectively, 94.2% (95% confidence interval (CI): 90.5%, 97.9%), 61.2% (95% CI: 50.7%, 71.7%), 81.6%, 81.1% and 83.2%. In patients with a small solitary pulmonary nodule (<1.5 cm) and positive $^{99}Tc^{m}$-depreotide SPECT, the risk of malignancy is high. On the other hand, patients with a large solitary pulmonary nodule (>1.5 cm) and a negative scan may be recommended for serial CT follow-up, since the sensitivity in those subjects was high.

【**Key words**】Lung neoplasms; Coin lesion, pulmonary; Lymph nodes; Neoplasm metastasis; $^{99}Tc^{m}$-depreotide

肺癌是最常见的恶性肿瘤之一，大多数肺癌初诊时已处于不可切除的晚期，而肺癌分期与生存率关系密切，ⅠA 期(≤3 cm 的局限性肺部肿物)患者的 5 年生存率可达 73%，而ⅢB 期患者不足 10%[1]。常规诊断方法如 X 线胸片、CT 和痰液脱落细胞学检查等存在较高的不确定诊断率，早期诊断价值往往不能令人满意。近年来，应用 $^{99}Tc^{m}$-

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depreotide 进行生长抑素受体显像在孤立性肺结节(solitary pulmonary nodule, SPN)良恶性鉴别、肺部肿物良恶性鉴别和区域淋巴结及骨转移等方面显示出良好的发展前景。

1 $^{99}Tc^m$-depreotide 的结构及特性

Depreotide 是一种人工合成的分子质量为1356.7 u 的十肽生长抑素类似物，由一个环状六肽和一个线状四肽组成，环状六肽是生长抑素受体(somatostain receptor, SSTR)的结合序列，含 N_3S 的线状四肽与 $^{99}Tc^m$ 配位结合[2]。由 Diatide 公司开发生产的 depreotide 放射性配套药盒配置简便，将 $^{99}Tc^m$ 与 depreotide 充分混匀后，沸水中孵育 10 min 即可形成高放射化学纯度的 $^{99}Tc^m$-depreotide。$^{99}Tc^m$-depreotide 具有两种异构形式：顺式和反式，反式与顺式之比为 10:90。两种异构体都能与 SSTR 结合，而顺式异构体的亲和力更高，体内 SSTR 阳性的肿瘤组织对顺式异构体的摄取是反式异构体的 2 倍。有趣的是，尽管受体结合序列并不出现构象改变，但 depreotide 与 $^{99}Tc^m$ 配位结合后显示出比游离 depreotide 更高的 SSTR 亲和力[2]。与奥曲肽不同的是，奥曲肽主要与 SSTR2 结合，而 $^{99}Tc^m$-depreotide 结合的 SSTR 亚型更广，包括 SSTR2、SSTR3 和 SSTR5[2]，因此诊断的癌谱范围更广，在包括肺癌、神经内分泌肿瘤、淋巴瘤、乳腺癌、甲状腺癌等诊断方面显示出良好的应用前景。1999 年 8 月 3 日，FDA 批准 $^{99}Tc^m$-depreotide 作为一种 SSTR 显像剂应用于 CT 和(或) X 线胸片发现的肺部病灶良、恶性鉴别。

2 $^{99}Tc^m$-depreotide 的药代动力学和生物学分布

注射后 5 min，11%~21%的 $^{99}Tc^m$-depreotide 与血浆蛋白结合，肝、肾和胃肠道可生理性摄取，且以肝、肾摄取较多；注射后 90 min 进行 SPECT 延迟显像可获得较佳的影像质量。正常肺组织摄取甚微，而肺癌则高度摄取 $^{99}Tc^m$-depreotide。Shih 等[3]研究进一步显示：不同病理类型肺癌的肿瘤/正常肺摄取比值(T/N)存在差异，鳞癌最高(3.5)，腺癌(1.89)和大细胞肺癌(1.2)较低，T/N 超过 3.5 很可能是鳞癌，因此测定 T/N 也许对肺癌进行分型诊断有帮助。鳞癌对 $^{99}Tc^m$-depreotide 的高摄取率表明，肿瘤和肿瘤周围新生血管大量表达 SSTR，这不仅对肺癌分型诊断而且对受体介导靶向治疗均有指导意义。同时，他们对 $^{99}Tc^m$-depreotide 的生物学分布进行了总结：① 正常肺组织微量摄取，而肺癌组织高度摄取，使 $^{99}Tc^m$-depreotide 特别适合于探测肺癌；② 肺内高强度的放射活性可为肺内病灶的分类提供有用的信息；③胸骨和胸椎微弱摄取可用作影像定位的解剖标志。他们的研究进一步表明，$^{99}Tc^m$-depreotide 显像类似于骨扫描，只是骨与骨髓放射性比值相对较低；$^{99}Tc^m$-depreotide 主要通过肾脏清除，大部分清除发生在注射后 4 h 内。

3 $^{99}Tc^m$-depreotide 显像与 SPN 良恶性鉴别

3.1 SPN

10%~20%的肺癌患者初始表现为 SPN[4]。SPN 是完全被肺实质包绕的直径 3 cm 以内的单发圆形或卵圆形不透亮病灶，无淋巴结肿大和肺不张[5]。SPN 的恶性率在 10%~70%之间[6]，肿瘤、炎症、血管病变、损伤、先天性畸形、类风湿性结节、肉芽肿和结节病都可表现有 SPN。准确鉴别 SPN 的良恶性相当重要，因为发现并治疗恶性肿瘤越早则预后越好，同时可以避免良性病变进行胸部手术带来相关的并发症和病死率。X 线胸片、CT 影像表现为中心性、弥散性、爆米花样钙化及结节大小两年保持稳定者提示为良性，出现放射冠、斑点状钙化或离心性钙化者提示为恶性[7]；而 MRI 鉴别 SPN 良恶性价值极其有限。但是，传统影像学往往不能对 SPN 的良恶性提供决定性结论，因为许多结节并不出现钙化，且多数患者并无既往 X 线胸片和 CT 影像对照。因此，对于局限于肺组织内的 SPN，寻找一种能早期进行良恶性鉴别的新技术有很高的临床价值。

3.2 SPN 的良恶性鉴别

由于 SPECT 仪自身分辨率的原因，对于小于 1 cm 的恶性肿瘤可能难以发现，从而可能出现假阴性结果。然而，≤10 mm 的肺结节 95%为良性[8]，动态 CT 结果也显示，直径在 6 mm 以下的肺部结节而无恶性肿瘤病史者恶性率不超过 1%[9]。

3.2.1 $^{99}Tc^m$-depreotide 与 ^{18}F-氟脱氧葡萄糖(^{18}F-fluoro deoxygluwse, ^{18}F-FDG)鉴别 SPN 的异同

应用 ^{18}F-FDG PET 早期鉴别 SPN 良恶性已得到

医学界认可[10-11]，然而过高的医疗成本和显像剂^{18}F-FDG供应问题限制了其在低收入患者中的应用。荟萃分析资料显示，^{99}Tc^{m}-depreotide SPECT对SPN良恶性鉴别的灵敏度、特异度、阳性预测值和阴性预测值分别为95%、82%、90%和91%，而^{18}F-FDG PET对SPN良恶性鉴别分别为95%、82%、91%和90%，结果表明，^{18}F-FDG PET对SPN的良恶性鉴别的效能并不明显优于^{99}Tc^{m}-depreotide显像[12]。Halley等[13]对^{18}F-FDG PET和^{99}Tc^{m}-depreotide SPECT诊断恶性SPN进行对比性研究发现，两者灵敏度分别为94.4%和88.9%，^{18}F-FDG PET灵敏度较高，但差异无统计学意义；对类癌瘤而言，^{99}Tc^{m}-depreotide SPECT的敏感性还高于^{18}F-FDG PET；根据SPN大小的分组研究显示：1.5 cm以下的SPN，^{18}F-FDG PET的准确性和敏感性较高，两者特异性相同，而1.5 cm以上的SPN，^{99}Tc^{m}-depreotide显像的准确性和特异性较高，两者敏感性相同。欧洲一项多中心的研究结果显示：^{99}Tc^{m}-depreotide显像对SPN良恶性鉴别灵敏度、特异度和准确率分别为89%、67%和81%，对1.5 cm以上的SPN上述指标分别为93%、33%和77%，对1.5 cm以下的SPN上述指标分别为75%、96%和88%，结果提示：对于1.5 cm以下的SPN，^{99}Tc^{m}-depreotide显像的真阴性率极高，若显像阳性则提示恶性的可能极大，除非手术禁忌，否则就应手术治疗；对于1.5 cm以上的SPN，因其灵敏度高达93%，^{99}Tc^{m}-depreotide显像阴性者可进行系列CT扫描随访观察[14]。

3.2.2 ^{99}Tc^{m}-depreotide与^{99}Tc^{m}-奥曲肽鉴别SPN的异同

^{99}Tc^{m}-奥曲肽也是一种SSTR的显像剂，Płachcińska等[15]研究显示，^{99}Tc^{m}-奥曲肽对SPN良恶性鉴别的灵敏度为90%(27/31)，特异度为79%(15/19)，结果表明^{99}Tc^{m}-奥曲肽显像也是鉴别SPN良恶性的有效手段。一项对比研究显示：^{99}Tc^{m}-奥曲肽显像和^{99}Tc^{m}-depreotide显像在鉴别SPN良恶性方面诊断效能相似，但^{99}Tc^{m}-depreotide在肺部肿瘤中放射性浓聚更高，其肿瘤/血池放射性比值明显高于^{99}Tc^{m}-奥曲肽，而^{99}Tc^{m}-奥曲肽在肺部本底区域显示较高的非均匀性[16]。因此，^{99}Tc^{m}-depreotide影像更有利于阅片分析，其肺部单发病灶轮廓更便于勾画，也许在肿瘤放疗确定精确靶区时更有实用价值。

4 ^{99}Tc^{m}-depreotide对肺肿瘤的诊断价值

荟萃分析近5年Medline上9篇有病理结果的前瞻性连续性研究资料(包括583个肺部病灶)结果显示：^{99}Tc^{m}-depreotide鉴别肺部病灶良恶性的灵敏度达94.2%(95%可信区间：90.5%，97.9%)，而特异度较低，仅为61.2%(95%可信区间：50.7%，71.7%)，诊断准确率为81.6%(476/583)，阳性预测值为81.1%(352/434)，阴性预测值为83.2%(124/149)。除特异性较低外，敏感性、准确性、阳性预测值和阴性预测值均显示较高的水平(表1)。

表1 ^{99}Tc^{m}-depreotide对肺部病灶良恶性鉴别的灵敏度和特异度

作者	研究对象	肺部病灶(恶性/良性)	灵敏度(%)	特异度(%)
Axelsson[17]	可疑肺癌	99 (66/33)	94	52
Boundas[18]	可疑恶性肺病灶	57 (23/34)	100	65
Płachcińska[16]	孤立性肺结节	18 (6/12)	100	50
Ferran[19]	肺部病灶性质不明	29(20/9)	85	89
Naalsund[14]	孤立性肺结节	118(73/45)	89	67
Chciałowski[20]	外周孤立性肺结节	27(18/9)	94	44
Bååth[21]	可疑肺癌	28(18/10)	94	70
Martins[22]	肺部病灶性质不明	40(31/9)	97	63
Kahn[23]	可疑肺癌	157(122/35)	94	51

Axelsson等[17]在对可疑肺癌的研究中发现，肺炎病灶对^{99}Tc^{m}-depreotide的诊断特异性影响较大，包括肺炎病灶时特异度仅为52%，而排除肺炎病灶特异度明显提高达77%。肺炎可能是导致^{99}Tc^{m}-depreotide特异性降低的重要因素，对临床或其他影像学表现有肺炎可能的^{99m}Tc-depreotide阳性患者进行短时间治疗性诊断也许会使一部分患者受益。Ferran等[19]对29例肺部病灶性质不明的患者进行了^{99}Tc^{m}-depreotide SPECT和^{18}F-FDG PET-CT对比性研究，20例患者的恶性病灶^{18}F-FDG均为阳性，而^{99}Tc^{m}-depreotide探测出17例，9例良性病灶用两种方法均有8例显示为阴性；以^{18}F-FDG标准化摄取值3.5和^{99}Tc^{m}-depreotide靶/本底比值1.3为阈值，^{18}F-FDG鉴别肺部病灶的灵敏度和特异度为95%和89%，^{99}Tc^{m}-depreotide为84%和88%，两者差异并无统计学意义。

5 ^{99}Tc^{m}-depreotide诊断肺肿瘤区域淋巴结和骨转移

不同阶段的肺肿瘤患者生存率不同。肿瘤最大

径≤3 cm、周围包绕肺组织及脏层胸膜、支气管镜见肿瘤侵及肺叶支气管而未侵及主支气管、无淋巴结和远处转移的患者5年生存率为73%，而出现淋巴结转移的患者5年生存率低于46%[1]。因此，肿瘤有无转移是决定肿瘤预后的重要因素，是选择治疗方案的关键要素。应用解剖学影像技术如螺旋CT判断淋巴结的状态完全基于淋巴结的大小，而对淋巴结的大小与肿瘤是否累及淋巴结的相关性并不令人满意，故功能影像技术引起了人们的关注，Danielsson等[24]研究显示：$^{99}Tc^{m}$-depreotide对于区域淋巴结转移的灵敏度可达99%，更有意义的是，其阴性预测值可达98%，虽然CT阳性预测值较$^{99}Tc^{m}$-depreotide显像更高，但也仅为70.2%，因此，即使CT发现淋巴结肿大的患者，如果$^{99}Tc^{m}$-depreotide显像阴性，可以排除淋巴结转移。

不少肺癌患者前期症状和体征表现很少，发现时已属晚期。晚期肺癌容易出现骨转移，患者预后变差、禁忌手术且生存时间缩短。目前对于骨转移疑似患者首选评价指标仍是全身骨扫描，而全身骨扫描虽然灵敏度高但特异性较差。其他影像学方法：X线平片、CT等灵敏度较低且结论易受同时并存的疾病如外伤、骨关节炎等影响；MRI反映骨髓的能力较强，但缺乏特异性，诊断结论常模棱两可。与传统骨扫描反映骨转移瘤的皮质骨反应不同的是，$^{99}Tc^{m}$-depreotide显像反映的是肿瘤原发灶和转移灶SSTR表达情况，是纯粹意义的分子影像。Mena等[25]研究显示：对于表达SSTR的小细胞肺癌和非小细胞肺癌，$^{99}Tc^{m}$-depreotide显像除能显示骨骼转移灶外，还能显示其他病灶包括原发灶、骨外转移灶（如脑实质）。因此，$^{99}Tc^{m}$-depreotide显像更有助于临床全面了解患者的病情，制定更合适的治疗方案。

综上所述，$^{99}Tc^{m}$-depreotide对肺部结节或肺部肿物良恶性鉴别具有良好的性能，可作为不能进行^{18}F-FDG PET的地区和患者的有价值替代方法。肺癌（包括小细胞肺癌和非小细胞肺癌）及其转移灶常过度表达SSTR，$^{99}Tc^{m}$-depreotide显像除了显示肺部原发灶外，还能显示淋巴转移灶、骨转移灶及其他组织转移灶，对于肺癌诊断、临床分期具有较高的临床价值。

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