



肺癌气道播散的影像学研究进展

许 驰, 沈雨雯, 石逸秋, 李 明, 刘可夫

Research Progress on Radiology in Spread Through Air Space in Lung Cancer

XU Chi, SHEN Yuwen, SHI Yiqiu, LI Ming, and LIU Kefu

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肺癌气道播散的影像学研究进展

许驰^a, 沈雨雯^a, 石逸秋^a, 李明^b, 刘可夫^a

南京医科大学附属苏州医院 a) 放射科; b) 病理科, 江苏 苏州 215008

摘要: 肺癌气道播散 (STAS) 是指肿瘤细胞以微乳头状细胞团、实性细胞巢或单个细胞等形式存在于主瘤体之外的气道中。随着肺癌研究的不断深入, 预测肺癌 STAS 在诊治和预后中有重要的价值, 因此在 2015 年世界卫生组织将其确定为肺腺癌的一种新的侵袭方式。近年来, 利用影像学方法预测 STAS 的有无已经成为研究的热点。目前相关研究的结果已证实了影像学预测 STAS 的可行性, 进一步深入的研究对发现更加可靠和准确的影像学预测方法十分必要。本文就 STAS 的病理学、临床意义及影像学方面的研究进展予以综述。

关键词: 影像学; 肺癌; 气道播散

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据全球癌症数据统计显示, 2020 年估计有 1930 万新发癌症病例和近 1000 万癌症死亡病例, 其中, 肺癌是癌症死亡的主要原因, 据估计死亡人数约 180 万^[1]。肺癌气道播散 (spread through air space, STAS) 是指肿瘤细胞以微乳头状细胞团、实性细胞巢或单个细胞等形式存在于主瘤体之外的气道中^[2], 这一概念是 1980 年 Kodama 等^[3]在对 1 例在主病灶外的气道中发现同源癌细胞的肺癌病例的报道中首次提出。目前关于 STAS 的中文表述有气道播散^[4]、气腔播散^[5]、肺泡间转移^[6]、肺泡间隙转移^[7]等, 目前尚未有统一的中文术语。

随着近年来对肺癌研究的不断深入, 研究者们发现 STAS 对肺癌预后有着不可忽视的影响, 2015 年世界卫生组织将其确定为肺腺癌的一种新的侵袭方式。本文就 STAS 的病理学、相关临床意义及影像学方面的研究进展予以综述。

1 STAS 相关病理研究

STAS 是否与取材过程中导致的肿瘤细胞移位有关。Metovic 等^[8]对 51 例肺癌手术标本进行取材, 每次取材均包括肿瘤前后组织, 为避免刀片的影响, 每切一次均更换洁净刀片, 结果发现肿瘤前后组织的 STAS 发生率无明显差别。Lu 等^[9]发现, 即使在手术过程中刀片没有经过瘤体而仅进行了肺的楔形切除, 在瘤体周围的肺组织中也发现 STAS 的存在, 说明 STAS 是客观存在的。但也有研究报道 93% 的瘤体外肺泡腔内的组织碎片是由于手术或者病理标本处理过程引起的机械性位移所致^[10], Villalba 等^[11]也发现人为导致的肿瘤细胞的移位现象。总的来说, STAS 是客观存在的, 人为的因素可能会夸大 STAS 发生率, 因此需要严格规范标本取材的过程。

术中冰冻切片诊断 STAS 的可行性。Waltz 等^[12]发现冰冻切片检测 STAS 的特异性高 (100%), 但灵敏度 (50%) 和阴性预测值 (8%) 都很低, 与石蜡包埋切片相比, 冰冻切片诊断 STAS 的总体准确率为 74%^[13]。因此用冰冻切片诊断 STAS 是不可靠的, 这可能与大部分冰冻切片中没有足够的癌周

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组织而影响 STAS 的诊断有关^[11]。

术前支气管肺泡灌洗液诊断 STAS 的可行性。有研究^[14]显示术前支气管肺泡灌洗液诊断 STAS 的敏感性、特异性、阳性预测值和阴性预测值分别为 45%、71%、86% 和 26%，利用术前支气管肺泡灌洗液诊断 STAS 的可靠性尚需要进一步研究。但另有学者^[15]发现肺腺癌标本的灌洗液诊断 STAS 的敏感性、特异性和阳性预测值分别为 80%、100% 和 100%，且灌洗液和石蜡切片中 STAS 细胞的形态极其相似，提示术后标本支气管肺泡灌洗液可用于诊断 STAS。

STAS 与肺癌组织类型之间的关系。STAS 更常见于微乳头状、乳头状和实体瘤等更具侵袭性的肺癌类型中^[16-20]，STAS 阳性在中低分化肺癌中比例高于高分化肺癌^[21]，浸润性腺癌中比例高于原位癌^[22]。

STAS 会导致更广泛的淋巴结转移、更多的胸膜及神经血管侵犯^[4, 18, 23-24]，纵隔淋巴结肿大被认为是 STAS 阳性的独立预测因子^[25]。

2 STAS 的临床相关研究

关于 STAS 与肺癌患者的年龄、性别及吸烟情况等的关系，目前不同的研究，结果并不一致。有研究认为年龄是最佳预测因子之一，且 STAS 阳性肺癌患者更年轻^[26-27]；男性肺癌患者出现 STAS 的概率更高^[24, 27]；吸烟是 STAS 的相关因素^[27-28]。但另一些研究却认为 STAS 的存在与患者年龄、性别及是否吸烟无关^[4, 16-17, 22-23, 28]。

STAS 与肺癌外科术式的相关研究。原发性肺腺癌患者接受亚肺叶切除术后，STAS 阳性者的无复发生存期及总生存期显著低于 STAS 阴性者^[29]，但在肺叶切除组中复发率没有明显差异^[30]。但另一项关于直径 ≤ 2 cm 的非小细胞肺癌患者的研究结果显示，虽然 STAS 阳性患者的累积复发率比阴性患者高，但采用肺叶切除和亚肺叶切除并不影响 STAS 阳性患者的总体生存率^[31]。目前更倾向于将肺叶切除术作为合并 STAS 的早期肺腺癌（直径 ≤ 3 cm）患者的标准术式^[32]。

STAS 是肺癌复发的重要因素。临床分期为 T1N0M0 的肺腺癌患者中，STAS 阳性者更易复发，且 STAS 阳性是 T1b 和 T1c 期肺腺癌复发的危险因素^[5]。

3 STAS 的影像学特征

3.1 常规 CT 特征的价值

STAS 与瘤体实变比例 (consolidation tumor ratio, CTR) 的相关性研究。CTR 是 STAS 的独立危险因素^[17, 27, 33]。在 ≤ 3 cm 的肺腺癌中，CTR 能较好的对 STAS 进行预测，但是特异性较差^[32]。与使用结节长径的模型相比，使用 CTR 的模型对 STAS 具有更好的预测性能^[16]。纯实性结节、部分实性结节及实性成分占比 $> 50\%$ 是 STAS 的重要预测因子^[34]，实性结节出现 STAS 的概率是部分实性结节的 3 倍^[19]。虽然纯磨玻璃结节中也能发现 STAS，但发生率较低，有文献报道纯磨玻璃结节中 STAS 出现的概率为 2.42%^[32]。

STAS 与肿瘤直径及结节实变部分直径的关系。Zhuo 等^[25]和 Zhang 等^[32]的结果显示结节最大直径、实性成分最大直径与 STAS 显著相关。实性成分最大直径预测 STAS 的敏感性和特异性分别为 73.9% 和 69.1%，临界值为 1.18 cm^[18]。也有部分研究报道 STAS 阳性与阴性组间肿瘤最大直径不存在差异^[17, 19]。总的来说，可认为瘤体直径及实变部分直径越大，STAS 出现的概率越高，但是其对 STAS 的诊断能力仍不如 CTR。

其他常规 CT 征象与 STAS 的关系，一些研究认为 STAS 与分叶征^[4, 6, 21, 25, 33]及毛刺征^[6, 18, 21, 25]、肿瘤周围卫星灶、瘤体边界模糊^[4, 17]相关，分叶与毛刺说明了肿瘤的膨胀性及浸润性生长，瘤体边缘模糊与卫星灶可能与肿瘤肺内播散及堵塞小支气管相关。另外，支气管充气征^[7, 19, 32, 35]、胸膜牵拉^[4, 7, 35]、血管集束征^[32]、肺气肿^[6]等 CT 征象也被认为与 STAS 相关。有研究^[4]还认为 STAS 阳性者瘤体多位于中下叶 (51.16%)、阴性者瘤体多位于上叶 (67.07%)，而左右侧肺 STAS 发生率无明显差异。

3.2 能谱 CT 的价值

尹柯等^[36]基于双能量CT回顾性分析了52例实性肺腺癌结节定量参数在STAS阳性与阴性组间的差异,发现动脉期碘浓度、动脉期标准化碘浓度及静脉期碘浓度间的差异存在统计学意义。其预测STAS的曲线下面积(area under the curve, AUC)分别为0.82、0.83及0.73,其中动脉期碘浓度和动脉期标准化碘浓度均为实性肺腺癌STAS的独立预测因子,两者联合诊断的AUC为0.89,作者认为双能量CT能有效帮助预测实性肺腺癌STAS的发生。

目前这方面的研究刚刚起步,需要更多的研究对上述结果进行验证。

3.3 影像组学的价值

Chen等^[20]基于机器学习建立的模型在内部验证和外部验证的AUC分别为0.63和0.69。Liu等^[37]的模型对STAS的误判率仅为7.69%。有研究^[38]利用5个不同制造商、11个不同机构和22个不同型号CT的图像建立了STAS的预测模型,并进行了前瞻性的外部验证设计,最后该模型内外部验证的精度分别为0.66和0.78。上述结果说明影像组学在临床上诊断STAS具有一定的可行性。

研究发现基于瘤周组学特征的模型相比于基于瘤体组学特征的模型可对STAS进行更加精准的预测,将瘤体及瘤周组学特征结合后能得到更高的诊断性能。Zhuo等^[25]基于瘤体影像组学特征建立的列线图及提取结节周围0.5、1.0和1.5cm内的影像组学特征建立的诺莫图对STAS都有着良好的预测性能。另有研究^[39]发现,相对于瘤体本身的影像组学特征,瘤周1.5cm的组学特征对STAS具有更好的预测性能,且将瘤体特征与瘤周特征结合后预测效果更佳。Qi等^[17]对瘤周0.2、0.4、0.6、0.8、1.0和2.0cm的组学特征进行提取分析,也认为将肿瘤内部和周围的组学特征进行结合后才能更好地预测STAS(其建立的模型在训练和验证集中的AUC和诊断准确度分别为0.907、0.897、0.909和0.849),且瘤体周围特征对STAS的预测至关重要(占总的有效特征的75%)。

总的来说,人工智能的应用将进一步帮助影像学在临床实践中更好地预测STAS。

3.4 PET/CT 的价值

研究提示STAS与肿瘤的高代谢相关。研究发现肿瘤代谢体积(metabolic tumor volume, MTV)与肿瘤CT体积(CT volume, CTV)的比值 >1 能用于预测STAS的发生^[40]。STAS阳性的瘤体标准化摄取值(standardized uptake value, SUV)明显高于阴性者^[24],用最大SUV值预测STAS的AUC为0.74,当诊断界值取2.48时,其敏感性为89.5%,特异性为52.8%^[41]。

当肿瘤与肝脏的SUV比值(SUV T/L)小于0.65时,排除STAS的敏感性和特异性分别为84.1%、55.9%;将CT上磨玻璃成分体积百分比 $\geq 75\%$ 、SUV T/L比值 ≤ 0.65 和贴壁生长型肺癌结合后建立的分层流程图预测STAS阳性的敏感性、特异性分别为79.3%和68.5%^[42]。

4 小结

综上所述,STAS在诊治和预后中有重要的价值,利用影像学方法预测STAS成为近年来的研究热点。常规CT的一些特征(如CTR、分叶及毛刺征)可用于STAS的预测;相比于常规CT特征,影像组学显示了更好地预测STAS的能力,但其临床实用性有待提高;PET/CT及能谱CT在预测STAS中也表现出很高的价值。

目前研究证实了影像学预测STAS的可行性,但由于目前研究数量相对较少,研究样本也较小,研究的结果尚存在差异性,因此需要进一步深入研究来发现更加可靠和准确的影像学预测方法。

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Research Progress on Radiology in Spread Through Air Space in Lung Cancer

XU Chi^a, SHEN Yuwen^a, SHI Yiqiu^a, LI Ming^b, LIU Kefu^{a✉}

a). Department of Radiology; b). Department of Pathology, The Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou 215008, China

Abstract: The spread through air space (STAS) in lung cancer refers to the presence of tumor cells in the airway outside the main tumor body in the form of micropapillary cell clusters, solid cell nests, or individual cells. The researches of lung cancer in recent years discover the significant value of STAS for diagnosis, treatment, and prognosis, therefore the World Health Organization designated it as a new invasive pattern of lung adenocarcinoma in 2015. Predicting the presence of STAS by medicine imaging has been the research highlight in recent years. Though the feasibility of predicting STAS by medicine imaging has been confirmed, more in-depth researches are necessary for establishing more reliable and accurate prediction method in medicine imaging. This article reviews the research progresses of pathology, clinical significance and medicine imaging on STAS.

Keywords: radiology; lung cancer; spread through air space



作者简介: 许驰, 女, 南京医科大学放射影像学在读硕士研究生, 目前主要从事胸部疾病影像评估的研究, E-mail: 2478875596@qq.com; 刘可夫[✉], 男, 南京医科大学附属苏州医院放射科主任医师、博士研究生导师, 主要从事影像新技术临床应用研究, E-mail: lkf77@126.com。