

肺癌中气腔播散的研究进展

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摘要: 2015年由世界卫生组织正式提出了气腔播散 (spread through air spaces) 这一种肺癌中独特的肿瘤侵袭模式, 气腔播散多见于肺腺癌。气腔播散是肺腺癌复发和预后不良的独立危险因素。本文将对于气腔播散的相关定义及分类、病理学及影像学特征、分子特征、手术方式选择及分级后对于肺癌预后影响等研究进展予以综述。

关键词: 肺腺癌; 气腔播散; 肺癌手术

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Research Progress of Spread through Air Spaces in Lung Cancer

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ABSTRACT: In 2015, the World Health Organization presented spread through air spaces (STAS), a unique tumor invasion mode in lung cancer, which is more common in lung adenocarcinoma. STAS is an independent risk factor for recurrence and poor prognosis of lung adenocarcinoma. This article will review the research progress on the definition and classification, pathological and imaging characteristics, molecular features, surgical method selection, and the impact of grading on the prognosis of lung cancer related to STAS.

KEY WORDS: lung adenocarcinoma; spread through air spaces; lung cancer surgery

1 STAS

据世界卫生组织国际癌症研究机构 (International Agency for Research on Cancer, IARC) 发布的2020年全球最新统计癌症数据, 肺癌估计有220万新发和180万死亡病例^[1]。其中, 非小细胞肺癌 (Non-small cell lung cancer, NSCLC) 约占肺癌总数85%^[2]。近年来随着低剂量 CT 对肺癌高危人群筛查的广泛开展和经胸腔镜肺微创手术的普及, 可以检出和治疗早期肺癌, 提高了病人的生存率和生活质量, 但早期肺癌手术切除后的 5 年复发率仍高达30%, 导致肺癌仍是癌症相关死亡的首位原因, 其5年生存率仅为 15%^[3-4]。肺癌的侵袭行为包括: (1) 非鳞屑样的组织生长模式; (2) 成纤维细胞增生伴结缔组织增

生; (3) 血管或胸膜侵犯。近年来, 随着病理学的进一步研究, 提出了气腔播散 (spread through air space, STAS) 这第四种肺癌侵袭模式。本文就STAS的临床病理特征相关性与对肺癌预后影响等研究进展作一综述。

1.1 STAS的定义和由来

最早于2013年, 由Onozato 等^[5]提出了“肿瘤岛”这一概念, 指出其是在主肿瘤灶边缘肺泡中可见孤立、悬浮的细胞簇, 多见于肺腺癌。在2015年, 世界卫生组织 (WHO) 正式提出了气腔播散, 并将其定义为: 肿瘤细胞以微乳头状簇、实性癌巢或单个肿瘤细胞的形式出现在主肿瘤周边的肺泡腔隙^[6]。在相关文献中, 肺腺癌中STAS的发生率为15%~73%^[7-13]。目前的研究, 将STAS分成以下3种组织学亚型: (1) 微乳头簇型, 肺泡腔中可见纤维血管轴心的乳头状结

构,较少在肺泡中形成环状结构;(2)肿瘤岛型,肺泡腔由实体肿瘤细胞填充成团巢样;(3)单个细胞型:由散在的、松散的单个肿瘤细胞组成。

1.2 STAS与影像学

影像学中 CT 是肺癌筛查最优的方法,其中是高分辨率薄层 CT 不仅能显示早期肺癌内部特征,如CTR等,而且能够观察肿瘤周边情况,如毛刺长短、支气管截断征、血管穿行等。对于肺腺癌术后合并STAS(+)的患者,影像学中肺结节含有磨玻璃成分具有特殊意义,对肺腺癌术后合并STAS(+)预后的判断需要考虑影像学是否含GGO成分及肿瘤的CTR。CTR越小者生存越好;反之,CTR越大者生存越差。Kim等^[14]分析了948名肺腺癌患者的术前CT和STAS的相关性,发现当肺结节的实性成分不足40%时,所有患者都没有STAS;而当实性成分超过40%,就出现STAS,且随着实行成分增高,STAS比例越高,纯实性结节的STAS比例接近70%。一项Meta分析^[15]指出肺结节实性成分百分比与STAS的关系,指出当肺结节实性成分百分比超50%时,出现STAS的风险会显著增高2.95倍。依据以上研究,可以进一步研究是否可在肺结节实性成分低于50%时,可选择亚肺叶切除,而当肺结节实性成分超过50%时,选择肺叶切除,进行亚组分析其预后有无明显差异。

1.3 STAS与不同手术方式的预后意义

最近的Meta分析显示,STAS是手术切除的肺腺癌患者的一个重要不良预后因素^[16-19]。此外,目前多项研究表明STAS与患者的生存及预后密切相关,STAS阳性者无复发生存期(recurrence-free survival, RFS)明显比阴性患者短^[20-22]。在肺腺癌中,根据肿瘤特征和患者的整体情况,有不同的手术方法,如肺楔形切除术、肺段切除术、肺叶切除术和全肺切除术^[32]。对于STAS患者,肺部分切除术是否会增加局部复发的风险,目前尚无共识。Kadota

等^[24]根据手术方式将STAS阳性的 I 期肺腺癌分为肺叶切除组和亚肺叶切除组,与肺叶切除组相比,亚肺叶切除组STAS阳性患者术后远处复发风险和局部复发率更高,但在肺叶切除组中,STAS的存在与5年累计复发率、远处复发率及局部复发率均无明显相关性,因此该研究认为STAS是 I 期肺腺癌肺段切除患者RFS的独立风险因素。一些研究表明,肺部分切除术与IA期患者和存在STAS患者的复发风险较高相关^[25-27]。然而,Kagimoto等^[28]研究人员36发现在STAS患者中,接受肺叶切除术的患者(5年RFS, 68.2%)和接受肺部分切除术的患者(5年RFS, 81.3%; $P=0.225$)之间的RFS差异无统计学意义。在伴有STAS的肺腺癌中,肺部分切除术与肺叶切除术相似,并没有增加局部复发。此外,关于辅助治疗,Chen等人^[29]发现辅助化疗改善了接受肺部分切除术的STAS(+)IA期患者及接受肺叶切除术的STAS(+)IB期患者的预后,但对于肺叶切除术的STAS(+)IA期患者,辅助治疗对于患者预后无明显改善。因此需要进一步的研究,去论证在IA期ADC中,肺部分切除术与肺叶切除术预后之间是否有显著差异,为进一步研究IA期STAS(+)接受亚肺叶切除的患者是否需要辅助治疗提供依据。

1.4 STAS的分级标准

目前已经有多次尝试根据距离肿瘤边缘的距离^[29-34]或肿瘤团簇的数量^[35-36]来对STAS进行分级。但是,无论是标准方法和STAS分级的意义尚未建立。关于STAS的形态学分级,Warth等人^[32]和Dai等人^[33]描述了有限和广泛的STAS,以三个肺泡的距离为界限,但没有获得两组之间的生存差异。最近,Han等人^[34]根据从肿瘤边缘到最远的STAS的距离对STAS的程度进行分级,根据STAS的存在是否接近或大于2.5 mm获得两组患者。他们回顾性分析了1869例切除的NSCLC的STAS程度与临床病理特征和预后意义之间的相关性。在765例(40.9%)中观察到STAS,其中456例STAS I

(24.4%)和309例STAS II (16.5%)。STAS在腺癌(ADC)(比鳞状细胞癌)、胸膜侵犯、淋巴血管侵犯和/或更高病理阶段的患者中更常见。在ADC中,根据STAS的程度,无复发生存率(RFS)、总生存率(OS)和肺癌特异性生存率(LCSS)差异有统计学意义。在IA期非粘液性ADC中,多变量分析显示STAS II与较短的RFS和LCSS显著相关(分别为 $P=0.001$ 和 $P=0.006$)。此外,STAS II是部分切除组和根治切除组复发的独立不良预后因素(分别为 $P=0.001$ 和 $P=0.023$)。总之,STAS II的存在是IA期非粘液性ADC的独立不良预后因素,无论切除程度如何。他们的研究结论是,根据STAS的程度,RFS和OS差异有统计学意义,特别是STAS大于2.5 mm的STAS患者生存期较短。此外,Uruga等^[36]将STAS分为低级别STAS(1-4个单细胞或簇)和高级别STAS(5或更多的单细胞或簇),发现高级别STAS患者的RFS和OS都比低级别STAS患者更短。因此,可以看出STAS定量分级评估更能精准预测患者的RFS和OS,但是目前STAS定量评估未形成共识,需进一步探索并形成STAS的分级标准。

1.5 STAS的分子特征

在近些年文献中,关于STAS(+)与基因突变及PD-1/PD-L1以往的研究结果是相互矛盾的。关于ALK突变,Tian等^[9]Lee等^[11],和Jia等^[25]也描述了STAS和ALK重排之间存在显著相关性。然而,关于EGFR的突变,Lee等人^[11]发现了STAS与野生型EGFR之间的关系。然而,Tian等人^[9]报道,STAS在EGFR阳性突变的患者中更为常见。对于STAS(+)与PD1/PDL1是否存在相关性,目前是存在争议的。Toyokawa等^[35]记录了STAS与PD-L1表达无显著相关性,然而,Wang等^[37]的研究表明,当基质细胞中PD-1表达超过10%的患者STAS阳性率明显增高,表达水平在5%~10%之间,PD-1与STAS较高的阳性率也存在相关性。由

此可见,STAS与分子改变如其他分子改变包括肿瘤蛋白p53、Kirsten大鼠肉瘤病毒致癌基因(KRAS)和ROS原癌基因1(ROS1)等及PD-1/PD-L1的关系有待进一步研究。由于样本差异及病理检测标准各不相同,导致各个研究结果有所较大差异,STAS与各分子因素之间的相关性仍要更多大样本、前瞻性的实验去进一步证实。

1.6 STAS是否是真实的体内现象存在争议

有人可能会认为,在VATS肺叶切除术等过程中,整个切除标本包括不同大小的肿瘤都被刚性胸壁的小口径孔挤压,这可能导致肿瘤周围的肿瘤细胞脱离。然而,Blaauwgeers等人^[38]之前的一项前瞻性研究。表明不同手术组(开胸手术与胸腔镜手术)中松散碎片的发生率差异无统计学意义。由于STAS与较高的ADC分期相关,其结果可能是由于ADC分期较高的患者可能会进行根治性手术和开胸手术。STAS是一种真实的体内现象还是一种体外的伪影是有争议的。在胸腔镜手术中,切除的含有肿瘤的肺标本通过微小的胸腔镜孔被挤压,这可能导致肿瘤细胞在肿瘤周围脱落,并移动到邻近的气腔^[39]。有趣的是,在目前的研究中,在ADC组中,开放入路组的STAS患病率高于VATS组。然而,根据病理分期分层后,根据手术入路的STAS频率没有差异。此外,大量研究表明^[29-36]STAS与ADC患者的不良预后独立相关。这些观点也支持了STAS是一种真实的、重要的生物现象,而不是虚假的人工伪影。

2 总结与展望

总的来说,STAS在肺癌中越来越常见,也有越来越多的研究表明,这一新的肺癌侵袭方式是早期肺癌复发转移和不良预后的独立影响因素。但是目前对于STAS分级标准上拥有较大争议,需要大量多中心研究及前瞻性研究确定标准。此外,由于术中冰冻对于STAS准确率并

不高,对于行亚肺叶手术的患者,是否行进一步肺叶切除,就需要更多STAS相关的影像组学研究来提高预测STAS的准确性来指导临床手术方案。在分子特征、人造伪像、术中诊断等方面,则需要更多与其相关的研究,在AI深度学习及多学科合作前提下,进一步提升STAS在肺癌临床应用上的价值。

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