

• 专 论 Special comment •

I 期非小细胞肺癌患者肺穿刺活检是否增加胸膜复发和气腔播散的风险

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【摘要】 近年来,随着肺结节的比例升高,术前经皮肺穿刺活检或经支气管镜活检越来越受到重视。大量临床证据也证实,I 期非小细胞肺癌(non-small cell lung cancer, NSCLC)的肺穿刺活检是安全可行的。但是,由于肺磨玻璃结节的组织学特点,与实性结节相比穿刺时更容易发生出血或咳嗽,肿瘤细胞在血流或气流冲击下可能会沿着肺泡壁或针道种植,导致胸膜复发和气腔播散(spread through air spaces, STAS),尤其是胸膜下结节合并有脏层胸膜侵犯和淋巴细胞浸润时需要慎重选择。

【关键词】 肺癌;肺结节;肺活检;胸膜复发;肿瘤气腔播散

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Dose pulmonary puncture biopsy increase the risk of pleural recurrence and air space spread of tumor in patients with stage I non-small cell lung cancer? LIU Baodong. Department of Thoracic Surgery, Xuanwu Hospital, Capital Medical University, Beijing 100053, China

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【Abstract】 In recent years, with the increasing proportion of pulmonary nodules, preoperative percutaneous lung puncture biopsy and bronchoscopic biopsy have received more and more attention. A large amount of clinical evidences indicate that lung puncture biopsy of stage I non-small cell lung cancer (NSCLC) is safe and feasible. However, due to the histological characteristics of pulmonary ground-glass nodule (GGN), puncture biopsy of GGNs is more likely to cause bleeding and cough, and the tumor cells may be implanted along the alveolar wall or needle tract under the impact of blood flow or airflow, leading to the pleural recurrence and tumor spread through air spaces (STAS), when compared with puncture biopsy of solid nodules. Therefore, percutaneous lung puncture biopsy should be carefully adopted, especially for the patients who have subpleural nodules with visceral pleura invasion and lymphocyte infiltration. (J Intervent Radiol, 2024, 32: 7-11)

【Key words】 lung cancer; pulmonary nodule; lung puncture biopsy; pleural recurrence; tumor spread through air spaces

低剂量计算机断层扫描(low-dose computed tomography, LDCT)肺癌筛查的肺结节检出率约为20%^[1],而以磨玻璃影(ground-glass opacity, GGO)为特点的磨玻璃结节(ground-glass nodule, GGN)在接受LDCT肺癌筛查的美国人群中约占肺结节的9%^[2],而中国人群约占肺结节的23%^[3]。GGN根据实性成分的多少又分为纯磨玻璃结节(pure GGN, pGGN)和部分实性结节(part-solid nodule, PSN),而pGGN及PSN又称为亚实性结节(sub-solid nodule, SSN)^[4-6]。

与实性结节相比,GGN与肺腺癌的关系密切。2015年世界卫生组织(world health organization, WHO)第四版肺部肿瘤组织学方案中正式承认气腔播散(spread through air spaces, STAS)是肺腺癌播散的新方式,建议在病理报告中注明^[7]。

在临床实践中,如果术中诊断有困难或风险很高,术前活检是合适的;一般临床推荐对最大径>15 mm的pGGN,最大径>8 mm的实性结节或实性成分>5 mm的PSN活检。经支气管镜活检

(bronchoscopic biopsy, BB) 应该最好在计划好的外科手术中进行, 而不是一个单独的操作; 手术前单独的支气管镜检查对治疗决策来说可能是不需要的, 而且增加时间、成本和操作风险。有研究将 599 例接受完全切除的非小细胞肺癌(non-small cell lung cancer, NSCLC) 患者分为两组: 术前 BB 诊断组($n=367$), 术前 BB 未诊断组($n=232$); 结果术前 BB 未诊断组术后无复发率和预后明显好于诊断组, 即使两组数据经过倾向评分调整, 仍是如此^[8]。但是如果没有现场快速细胞学评估(rapid onsite cytologic evaluation, ROSE) 技术, 可能需要单独的操作。尽管研究报道经皮肺穿刺活检(percutaneous needle biopsy, PNB) 不影响 I 期 NSCLC 的预后^[9], 但是肺穿刺活检是否增加胸膜复发和 STAS 的风险尚不得而知, 本文对此加以论述。

1 肺穿刺

1.1 经皮肺穿刺活检

1976 年 Haaga 等首次报道 CT 引导下 PNB。根据穿刺针的外径将其分为不同的型号(gauge), PNB 一般用 16~22G。①细针抽吸活检(fine-needle aspiration, FNA), 21~22G 的穿刺针为细针, 通过获取高质量的细胞学标本用于疾病诊断。FNA 损伤较小, 并发症相对少; FNA 对良性疾病诊断准确性低, 对肿瘤精准分型也有其局限性。②切割针活检(core-needle biopsy, CNB), 16~18G 的穿刺针属于粗针, 通过切割病变获取组织学标本用于疾病诊断。CNB 损伤大, 并发症相对多; CNB 能提供更大体积的病变组织, 足以进行基因检测。

在 Meta 分析中, SSN 活检的敏感性为 92% (95%CI: 88%~95%), 特异性为 94% (95%CI: 84%~98%), 阴性似然比 0.1 (95%CI: 0.06~0.19), 阳性似然比 11.27 (95%CI: 4.2~30.6)^[10-11]。

一项回顾性研究报告 8 家医疗机构的多中心结果^[12], 9 384 初次 PNB (9 239 例患者), 有 27.6% (2 590/9 384) 无法确诊, 病灶大小、密度、活检针类型与此有关; 并发现结节 ≤ 1 cm 的 PNB 诊断率为 60.0%, SSN 的诊断率为 64.4%, 得出了 PNB 对 < 10 mm 的 SSN 可能不太有效的结论^[13]; 甚至 FNA 假阴性率达 51.8%^[14], CNB 假阴性率高达 41.6%~66.7%^[15-17]。

PNB 是一种相对安全的方法, 但并非没有风险^[18-21]。死亡率 0.01%~0.15%, 死因包括出血、心脏骤停、空气栓塞等, 严重并发症有气胸、肺内出血、咳

血、针道种植等。气胸最常见, 发生率 15%~51.8%, 1%~14.2% 需要放胸腔闭式引流。出血占第 2 位, 包括肺内出血、咯血和血胸等, 发生率为 1%~27%, 其中咯血发生率约 1.25%~23%, 有 17.8% (11.8%~23.8%) 的患者需要输血; 血胸为 0.20%~0.92%。针道种植非常罕见, 发生率 0.012%~0.061%。空气栓塞(范围为 0.02%~1.8%) 死亡率高, 致残率高; 2 mL 的气体进入脑循环即可致命, 0.5~1 mL 的气体栓塞冠脉即可引起心脏骤停。SSN 的穿刺较实性结节更容易发生出血, 肿瘤细胞在血流冲击下可能会沿着肺泡壁或针道种植, 导致胸膜复发和 STAS。

1.2 经气管镜活检

BB 作为 PNB 技术的补充, 越来越受到关注。但是它的操作需要在导航系统引导下进行, 另外它还需要 ROSE 技术, 并通过影像(透视、锥形束 CT 即 CBCT) 确认。2014 年 Gex 等^[22]荟萃分析了 15 个临床研究, 包括 1 033 个肺结节, 评价电磁导航支气管镜诊断肺结节的准确率和安全性, 发现电磁导航支气管镜诊断灵敏度为 64.9%, 准确率为 73.9%, 诊断肺癌的灵敏度为 71.1%, 气胸的发生率为 3.1%。迄今为止规模最大的前瞻性多中心电磁导航支气管镜研究—NAVIGATE 研究^[23]共纳入 29 家医院的 1 215 例患者, 49.1% 的患者病灶直径 < 20 mm。电磁导航支气管镜辅助获取的标本中 44% 为恶性, 诊断恶性肿瘤的敏感性、特异性、阳性预测值和阴性预测值分别为 69%、100%、100% 和 56%。1 年后确认的诊断准确率为 73%。尽管 BB 的并发症发生率较 PNB 低, 但是在局部麻醉下患者的剧烈咳嗽等气流冲击下, 可能会诱导肿瘤细胞的移动脱落而发生种植, 所以一般建议在计划好的外科手术中全身麻醉下进行。

2 胸膜转移

关于穿刺针道的胸膜种植转移早有报道^[24]。2017 年, Moon 等^[25]报道了一项关于 PNB 增加胸膜种植风险的研究。作者收集了 2009–2010 年期间接受手术治疗的 I 期 NSCLC 患者 392 例, 一组先接受 PNB 而后手术($n=243$), 一组未行 PNB 直接手术($n=149$)。结果 PNB 组和非 PNB 组的胸膜转移率分别为 9% 和 2% ($P=0.004$), 局部复发率分别为 19% 和 8% ($P=0.005$)。校正其他影响因素的前提下, PNB 将使胸膜复发的概率提高 5.27 倍, 但是可能与总无复发生存(recurrence free survival, RFS) 无关, 淋巴细

胞浸润可能是胸膜复发的危险因素。2019 年, Ahn 等^[26]报道了术前行 PNB 的 540 例 I 期 NSCLC 中, 42 例患者出现胸膜复发(5.1%); 34 例(6.3%)是 PNB 患者, 8 例(2.8%)非 PNB 患者; 26 例患者发生孤立性胸膜复发(3.1%); 20 例(3.7%)是 PNB 患者, 6 例(2.1%)是非 PNB 患者。在匹配后的多因素分析中, 只有脏层胸膜侵犯与胸膜复发 $HR=3.367(95\%CI\ 1.262\sim8.986, P=0.015)$ 和孤立性胸膜复发 $HR=3.216(95\%CI\ 1.037\sim9.978, P=0.043)$ 相关, 而 PNB 与胸膜复发均无相关性, 脏层胸膜侵犯和淋巴细胞浸润与胸膜复发显著相关。2022 年 Kim 等^[27]的研究也发现脏层胸膜侵犯和淋巴细胞浸润与胸膜复发显著相关。

一项 Meta 分析^[28]纳入 6 项研究 2 394 例 I 期 NSCLC 患者, 结果显示与其他诊断方法相比, PNB 活检与同侧胸膜复发风险相关 $HR=2.58(95\%CI\ 1.15\sim5.78)$, 伴有其他转移 $HR=1.99(95\%CI\ 1.14\sim3.48)$, 与小于 55 岁患者中生存率降低相关。在另一项 Meta 分析中^[29], 9 项研究 13 541 例 I 期 NSCLC 患者(PNB 组 $n=4\ 550$, 非 PNB 组 $n=8\ 991$), 分析 RFS 和总生存期(overall survival, OS)。非 PNB 组 OS 的 $HR=1.43(95\%CI\ 0.96\sim2.12, P=0.08)$ 和 RFS 的 $HR=1.59(95\%CI\ 1.25\sim2.01, P=0.0001)$ 均优于 PNB 组; 非 PNB 组胸膜复发率 $RR=2.40(95\%CI\ 1.42\sim4.07, P=0.001)$ 明显低于 PNB 组。而另 3 项 Meta 分析^[30-32]的结果显示, PNB 不会增加 I 期 NSCLC 患者的总复发和胸膜复发风险, 但 PNB 会增加胸膜下结节患者的胸膜复发风险。这些结果表明 PNB 不利于 I 期 NSCLC 患者的生存预后, 增加了胸膜复发的机会。

3 气腔播散

STAS 作为肺癌播散的新方式(其他包括间质、脉管及胸膜侵犯)是指在主肿瘤边界外的气腔内出现微乳头状细胞簇、实性细胞巢或单个肿瘤细胞^[8]。

关于 STAS 的研究, 最早可见于 1980 年。一位日本学者在一例肺腺癌患者的标本中, 用电子显微镜发现了在远离原发病灶的气腔中出现了分化差的肿瘤细胞, 并指出这是一种罕见的新型气道播散方式^[33]。2013 年, Onozato 等^[34]通过三维重建的方法在肺腺癌的标本中发现“孤立于肺泡腔内的肿瘤细胞”, 并首次将其定义为“肿瘤岛”。2015 年, Kadota 等^[35]针对 STAS 提出了组织学亚型分型: ①微乳头结构, 由没有纤维血管轴心的乳头结构组成, 偶尔在空气中形成环状结构; ②实体巢, 由实体肿瘤细胞组

成; ③单个细胞, 由散在的松散的单个细胞组成。

Uruga 等^[36]对 STAS 进行了半定量分析评估, 将其分为无 STAS、低 STAS(1~4 个单肿瘤细胞或 STAS 簇)和高 STAS(≥ 5 个单肿瘤细胞或 STAS 簇)。Toyokawa 等^[37]根据肿瘤细胞的数量也将 STAS 分为三类: “no STAS”(未见明确肿瘤细胞)、“low STAS”(1~4 个单个或簇状肿瘤细胞)及“high STAS”(5 个及 5 个以上单个或簇状肿瘤细胞)。Kadota 等^[35]发现距肿瘤边缘最远的 STAS 距离为 1.7 cm。Dai 等^[38]也指出 STAS 与肿瘤边缘的最大估计距离为 1.35 cm, 提示手术切缘至少大于 2 cm。Warth 等^[39]根据 STAS 距离主肿瘤的距离划分为“局限性”STAS(< 3 个肺泡距离)和“广泛性”STAS(> 3 个肺泡距离)。Han 等^[40]将 STAS 细胞簇与主肿瘤之间的距离小于 $2\ 500\ \mu m$ (一个 $\times 10$ 物镜的视野)定义为 STAS I 级, 大于 $2\ 500\ \mu m$ (一个 $\times 10$ 物镜的视野)定义为 STAS II 级。

STAS 的存在与年龄、吸烟史、实性结节、预后差、复发率高、辅助治疗、淋巴结转移、进展分期、脉管淋巴管浸润和胸膜侵犯、高度侵袭性的病理亚型、有丝分裂计数高和 Ki-67 指数高有关^[41-47]。最近的 3 项 Meta 分析均支持 STAS 是预后和复发的负性预测因子^[48-50]。

STAS 的 CT 影像学特征是小叶中心结节和分枝状阴影(树芽状结节), 边界不清, 磨砂玻璃衰减。STAS 还与毛刺、无支气管充气征、胸膜退缩和切迹的存在相关。

也有学者认为, STAS 是由于术中肿瘤组织受到人为挤压被破坏而造成的一种假象, 称为机械力(包括穿刺、挤压、反复膨胀、经小切口取出等); 也有可能是在肺标本取材切片过程中刀面上黏附少许肿瘤碎片或细胞簇, 称为通过刀表面播散, 从而导致肿瘤细胞脱落至肺泡腔内。

那么, 肺穿刺会不会因为出血或咳嗽引起的血流或气流等内力作用而增加 STAS 的发生率呢? Kameda 等^[51]将 808 例治愈性切除的 $\leq 2\ cm$ 肺腺癌患者分为穿刺组($n=465$; FNA=365, CNB=44, 两者=65)和非穿刺组($n=343$)。结果 STAS 发生率没有差异; 在 STAS(+)患者中, 肺叶切除术后复发率没有差异, 亚肺叶切除术后穿刺组局部复发率显著升高, 但是区域和远隔复发率没有差异; 在 STAS(-)患者中, 不管术式如何, 复发率没有差异。因此术前穿刺活检不增加 STAS 发生率。Lee 等^[52]对 2 169 例手术切除的 I 期 NSCLC 患者中 638 例 STAS(+)(29.4%), 结果表明, 术前活检(533 例)无论是 PNB 还是 BB, 均与

STAS 的发生无关。此外,在亚肺叶切除组,STAS(+)是复发和肺癌特异性死亡率重要危险因素。Hu 等^[53]将 322 例手术的 I 期 NSCLC 患者分为术中活检组($n=202$)、术前 PNB 组($n=66$)、术前 BB 组($n=54$),通过分层比较了 RFS。结果提示术前 PNB 和 BB 均不增加复发。Ding 等^[54]将 433 例手术切除的 I 期 NSCLC 患者分为穿刺组($n=88$;PNB 组 40 例,BB 组 48 例),非穿刺组($n=345$)。采用倾向评分匹配法进行匹配;PNB 组($n=38$)和 BB 组($n=28$)分别与非穿刺组比较。结果两组患者 STAS 发生率无显著性差异,PNB 组与非活检组(42.1% vs 34.2%, $P>0.05$),BB 组与非活检组(42.9% vs 46.4%, $P>0.05$);无论是 PNB 还是 BB 对根治术后 RFS 和 OS 无显著影响($P>0.05$)。以上结果提示,无论经皮或经支气管镜肺穿刺活检是否会增加 STAS 的发生,都不影响预后,因此 STAS 可能类似于循环肿瘤细胞的存在。

4 结论

I 期 NSCLC 的肺穿刺活检安全可行,但是穿刺可能会因为出血或咳嗽引起的血流或气流等内力作用而增加胸膜复发和 STAS 的风险,尤其是胸膜下结节存在脏层胸膜侵犯和淋巴细胞浸润时需要慎重选择。

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