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• 专题报道 •

肺部小结节的外科临床诊治进展

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[摘要] 肺部小结节是肺部常见疾病,也是肺癌进展的初始阶段。本文阐述了肺部小结节的定义、肺部小结节良恶性的区分,概述了常用的肺部小结节诊断方法,并对国内外常用指南的肺部小结节随访策略进行了比较,最后解释了肺部小结节手术外科治疗原则中的微创手术原则、精准治疗原则和加速康复原则,旨在为肺部小结节的临床诊断及治疗提供发展方向。

[关键词] 肺部小结节; 肺肿瘤; 早期诊断; 外科手术

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Progress in surgical diagnosis and treatment of pulmonary small nodules

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[Abstract] Pulmonary small nodules are common diseases of the lung, and are the initial stage of lung cancer progression. This review describes the definition of pulmonary small nodules, the identification methods of benign and malignant pulmonary small nodules, and the common diagnostic methods for pulmonary small nodules. In addition, we compared the follow-up strategies of pulmonary small nodules in common guidelines at home and abroad. We also explained the principles of minimally invasive surgery, precise treatment and accelerated rehabilitation of pulmonary small nodules, providing directions for the clinical diagnosis and treatment of pulmonary small nodules.

[Key words] pulmonary small nodules; lung neoplasms; early diagnosis; operative surgical procedures

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肺癌目前已成为世界范围内发病率和死亡率最高的恶性肿瘤之一^[1]。近年我国肺癌的发病率和死亡率均呈持续上升趋势,其发病率在男性恶性肿瘤患者中居首位、在女性患者中居第2位,尽管现今肺癌的治疗手段已取得了很大进展,但其死亡率无论在男性还是女性中仍位列所有恶性肿瘤的首位^[2]。绝大多数肺癌在确诊时已为晚期,已失去手术根治机会,因此预后较差,我国肺癌的5年生存率仅为16.1%^[3]。2011年,美国国家肺癌筛查试验(National Lung Screening Trial, NLST)首次报道低剂量计算机断层扫描(computed tomography,

CT)筛查在高危人群中可降低肺癌的死亡率^[4]。因此,肺癌最有效的控制手段仍然在于早期筛查、早期诊断和早期治疗。肺部小结节可能是肺部疾病进展的初始阶段,肺部磨玻璃样变可能是肺癌的早期病变。正确诊断肺部小结节,判断其良恶性,对开展相应的临床治疗具有重要意义。但肺部小结节的过度诊断、过度治疗会增加社会医疗费用和患者的心理负担,为此,迫切需要制定合理、便捷的诊疗规范。本文就肺部小结节的定义、良恶性区分、诊断方法、随访策略以及治疗方法等作一综述,以期肺癌的临床诊断及治疗提供参考。

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1 肺部小结节定义及分类

肺部小结节是肺癌筛查中最常发现的局灶性、类圆形、影像学表现密度增高的阴影、一般认为直径小于 20 mm 的结节为小结节,直径小于 5 mm 的为微小结节;可单发或多发,不伴肺不张、肺门肿大或胸腔积液^[5]。不同密度的肺部小结节,其恶性概率不同,依据小结节密度将其分为 3 类:磨玻璃样结节(ground-glass nodule, GGN)、部分实性结节和实性结节。GGN 以纯磨玻璃影(ground-glass opacity, GGO)为主要特点,磨玻璃成分为均匀的磨砂状阴影,在病理上往往对应原位腺癌或不典型腺瘤样增生,进展慢;部分实性结节可伴有空泡征、支气管充气征或微小实性成分,直径小于 5 mm 的实性成分以微浸润性腺癌多见;实质结节为致密均匀的小结节,伴有分叶、刷状毛刺、胸膜牵拉征时恶性的可能性大,病理类型多为浸润性腺癌,以腺泡状、乳头状和实性亚型为主^[6-7]。

2 肺部小结节良恶性区分

鉴别肺部小结节良恶性的目的在于早期发现恶性病变,避免良性肺部小结节患者的过度治疗。患者的临床危险因素评估、CT 检查的结节特征常作为肺部小结节良恶性评估的重要指征。

在对患者的临床危险因素评估中,年龄是恶性肺部小结节最重要的危险因素之一。恶性肺部小结节在 30 岁以下人群中少见,在 70 岁以上人群中的比例接近 88%,即年龄越大肺部结节恶性的可能性越大^[8]。恶性肿瘤病史或肺癌家族史、患者的临床症状如咯血、消瘦等均是恶性孤立性肺结节(solitary pulmonary nodule, SPN)的危险因素^[9-10]。慢性阻塞性肺疾病、弥漫性肺纤维化和肺结核病史也是临床高危因素,其中弥漫性肺纤维化患者发生肺癌的风险增加 8.25 倍^[11]。

根据 CT 检查中显现的肺部结节的大小、边缘、密度等影像特点,结合临床经验,参照有效模型,可以预测结节的良恶性及恶性程度。结节的大小与其恶性概率有关,直径小于 5 mm 肺结节的恶性概率低于 1%,11~20 mm 肺结节的恶性概率为 33%~64%,大于 20 mm 肺结节的恶性概率达到 64%~82%^[12]。当肺部结节大于 8 mm 时,需着重考虑结节恶性病变的可能性^[5,13];毛刺状或分

叶状边界通常较光滑边界的恶性病变的可能性高,磨玻璃样或半实质样肺部结节的恶性概率高^[14-16]。

3 肺部小结节的诊断方法

肺部小结节的诊断极为重要,诊断方法有多种,但定性诊断较为困难。目前肺部小结节诊断的常用方法包括:影像学检查、经皮穿刺活组织检查、虚拟支气管镜导航系统(virtual bronchoscopic navigation, VBN)下的活组织检查及胸腔镜手术病理组织检查。

影像学检查因其无创性而普遍使用,其主要观察肺部小结节的大小、体积、体积倍增时间及形态特征。常用的影像学检查方法主要有胸部 CT、正电子发射型计算机断层显像(positron emission tomography-computed tomography, PET-CT)等。肺部结节检查显示病灶形态的最具诊断价值的征象是分叶征象,较小肺癌的内部结构不均匀,常表现为结节征、空泡征、支气管充气征,有时表现为混杂的磨玻璃样密度,增强扫描后绝大多数有强化^[16-17]。此外,针对肺部小结节还可采取一些特殊 CT 检查手段提高其诊断率,朱慧媛等^[18]发现对于常规 CT 检查难以确诊或诊断信心不足的结节、对直径小于 8 mm 的肺结节采用超高分辨率 CT 靶扫描可较常规 CT 检查提供更高的图像质量,可提高肺部小结节的诊断率。苏雷等^[19]对手术治疗的肺部小结节病例进行了回顾性分析,患者行术前胸部 CT 扫描,后施行胸腔镜治疗孤立性肺小结节,结果发现肺部小结节的静态影像学特征对其诊断有重大意义。

当 PET 诊断的灵敏度不佳或显现出假阳性指征时,可选用 CT 引导下的经皮肺穿刺活组织检查,诊断准确率约为 90%^[20]。但 X 线、CT 或超声引导下经皮肺穿刺活组织检查较易导致出血、气胸、猝死等严重并发症^[21-22]。近年开展的 VBN 是一种基于 CT 的三维成像术,其通过图像识别建立虚拟支气管路径,引导支气管镜到达目标病灶进行活组织检查,从而达到提高肺小结节活组织检查阳性率的目的^[23]。VBN 技术突破了传统支气管镜仅能进入段支气管镜的技术瓶颈,显著提高了支气管镜检查深入肺末端的程度,为肺部小结节的诊断提供了前所未有的微创诊断解决方案,是早期肺癌发现和诊断的重大突破,并且为术前提提供了精确的病理参考和手术标记,大大提

高了肺部手术的安全性和准确性。Herth 等^[24]利用 VBN 技术进行了一项经支气管镜下肺外周结节取样术的前瞻性、单臂干预性研究, 结果显示在 83% 的患者中取得成功, 病理学活组织检查结果与手术切除的病理结果完全一致。当临床高度怀疑恶性病变且尚未定性诊断时, 可行电视胸腔镜手术切除后再进行病理检查。

4 肺部小结节病变的随访策略

目前针对肺部小结节的处理指南层出不穷, 国际上比较常用的指南有美国国家综合癌症网络 (National Comprehensive Cancer Network, NCCN) 指南、Fleischner 学会指南、美国胸科医

师协会 (American College of Chest Physicians, ACCP) 指南和亚洲共识^[25]。各大指南建议的肺部小结节评估筛查目标人群非常相似, 但对于阳性结果的 CT 随访策略却有所不同, 且在筛查风险方面仍有争议, 未达成统一共识。上述指南中应用较多的是 NCCN 指南和 Fleischner 学会指南。

2018 年 NCCN 指南中针对胸部 CT 上的单发或多发实性结节, 分别按照危险因素高低、结节大小 (表 1) 和结节类型 (表 2)^[26], 提出不同的随访时间建议。该指南提出对肺小结节进行评估时, 需要胸外科、放射科、呼吸科等多学科共同合作, 以给出最优的诊断及制定后续的治疗措施^[26]。

表 1 肺部实性小结节随访建议 (基于危险因素、结节大小)^[26]

| Size d/mm | Low-risk factor | High-risk factor |
|-----------|---|---|
| ≤4 | No follow-up | CT scan at 12 months, if stable, does not require further follow-up |
| 4-6 | CT scan at 12 months, if stable, does not require further follow-up | CT scan at 6-12 months, if stable, repeat CT scan at 18-24 months |
| 6-8 | CT scan at 6-12 months, if stable, repeat CT scan at 18-24 months | CT scan at 3-6 months, if stable, repeat CT scan at 9-12 months and 24 months |
| >8 | For CT scans at 3, 9, and 24 months, consider PET-CT or biopsy | For CT scans at 3, 9, and 24 months, consider PET-CT or biopsy |

CT: Computed tomography; PET-CT: Positron emission tomography-computed tomography

表 2 肺部实性小结节随访建议 (基于结节类型)^[26]

| Type of nodule | Size of nodule | Follow-up visit |
|----------------------------------|---|--|
| Isolated ground-glass nodules | <5 mm | No follow-up |
| | ≥5 mm | CT scan at 3 months. CT once a year for at least 3 years |
| Isolated partially solid nodules | The real component is always <5 mm | CT scan at 3 months. CT once a year for at least 3 years |
| | The real component is always ≥5 mm | Biopsy or surgical resection |
| Multiple subsolid nodules | Ground-glass nodules ≤5 mm | CT scan at 2 years and 4 years |
| | Ground-glass nodules >5 mm, no preponderant lesions | CT scan at 3 months. CT once a year for at least 3 years |
| | Partially or solid components dominated by nodules | CT scan at 3 months, biopsy or surgical excision if persistent (especially if solid component >5 mm) |

CT: Computed tomography

现在广泛应用于临床的肺实性小结节处理指南是 Fleischner 学会指南。该学会于 2013 年和 2017 年分别发布了针对亚实性小结节的指南及重新修订了肺小结节评估指南。在 2017 年版指南中, 随访间期被确定为一个时间区间而不是确切的时间点。该指

南整合简化了实性结节和亚实性结节的推荐指南, 并对多发结节提出专门的指导意见。对于成年人偶发性肺部小结节的推荐处理意见为: (1) 所有胸部 CT 检查均应采取薄层连续的方式 (层厚 ≤1.5 mm, 最好 1.0 mm), 应进行 CT 重建; (2) 推荐常规保存冠状

面、矢状面的重建信息(证据级别为 IA,属于强烈推荐的高级别临床证据);(3)胸部 CT 检查应该采用低剂量(证据级别为 IA,属于强烈推荐的高级别临床证据)。具体内容见表 3^[27]。

表 3 2017 年版 Fleischner 学会关于成年人群偶发性肺部小结节的推荐处理意见^[27]

Tab 3 Recommended treatment of incidental pulmonary small nodules in adults by the Fleischner Society in 2017^[27]

| Type of nodule | Size of nodule | | | Note |
|---------------------------|---|---|--|--|
| | <6 mm (<100 mm ³) | 6-8 mm (100-250 mm ³) | >8 mm (>250 mm ³) | |
| Solid nodule | | | | |
| Solitary nodule | | | | |
| Low-risk factor | No routine follow-up | First CT scan in 6-12 months, secondary CT scan in 18-24 months | Three months CT reexamination, PET-CT or tissue biopsy can be selected | Low-risk populations with nodules <6 mm do not require follow-up |
| High-risk factor | Select CT follow-up after 12 months | First CT scan in 6-12 months, secondary CT scan in 18-24 months | Three months CT reexamination, PET-CT or tissue biopsy can be selected | Some high-risk patients with suspicious nodular shape and upper leaf can choose to review CT after 1 year |
| Multiple nodule | | | | |
| Low-risk factor | No routine follow-up | First CT scan in 3-6 months, secondary CT scan in 18-24 months | First CT scan in 3-6 months, secondary CT scan in 18-24 months | Most suspicious nodules can be processed according to the guidelines. The follow-up interval can be adjusted according to size and risk |
| High-risk factor | Select CT follow-up after 12 months | First CT scan in 3-6 months, secondary CT scan in 18-24 months | First CT scan in 3-6 months, secondary CT scan in 18-24 months | Most suspicious nodules can be processed according to the guidelines. The follow-up interval can be adjusted according to size and risk |
| Type of nodule | Size of nodule | | Note | |
| | <6 mm (<100 mm ³) | 6-8 mm (100-250 mm ³) | | |
| Substantial nodule | | | | |
| Solitary nodule | | | | |
| Ground-glass lesion | No routine follow-up | First CT scan is performed after 6-12 months to determine stability and then CT is reviewed every 2 years until 5 years | | If part of the suspected nodule is <6 mm follow up for 2 or 4 years. If the solid component increases or the nodule increases, consider resection |
| Partially solid nodule | No routine follow-up | Initial CT examination was performed 6-12 months later to determine stability. If there is no change or solid component <6 mm, CT will be reviewed every year up to 5 years | | In practice, only nodules ≥6 mm can be diagnosed as partially solid nodules, and those <6 mm should not be followed up. Persistent subsolid nodules with a solid component >6 mm are more likely to be malignant |
| Multiple nodule | CT reexamination was performed 3-6 months later, and if there was no stability or change, CT reexamination could be performed in the second quarter of the year | CT was reexamined 3-6 months later, and further treatment could be conducted according to the principle of isolated nodules | | Multiple, <6 mm of ground glass nodules are mostly benign, but in some high-risk patients, follow-up at the second or fourth year can be selected for review |

The above recommendations are not applicable to lung cancer screening, immunodeficiency patients and malignant tumor patients. The size of the nodule is measured by the average length and diameter, rounded to the millimeters. The risk factors were as follows: age, gender, family history of lung cancer, family history of emphysema, nodular nature (solid/partially solid/pure glass), location of nodules (upper/lower middle lobe), number of nodules, and burrs. CT: Computed tomography; PET-CT: Positron emission tomography-computed tomography

尽管上述最新的肺部小结节处理指南的循证医学数据充分,但是在具体实施过程中,仍然面对是否适用于中国人群的问题。Fleischner 学会指南是根据患者有无吸烟及其他危险因素将肺

部小结节分为低风险与高风险,但实际临床上发现新发患者中无吸烟史的女性患者居多。因此 Fleischner 学会指南也有一定的局限性,同时其操作过程相对烦琐。

我国近年也制定了肺部小结节防治专家共识及处理建议, 比如中华医学会呼吸病学分会肺癌学组和中国肺癌防治联盟专家组制定的《肺部结节诊治中国专家共识》^[7]、中国抗癌协会肺癌专业委员会提出的《孤立性肺结节的处理》^[28]、中华医学会放射学分会心胸学组制定的《肺亚实性结节影像处理专家共识》^[29], 但其间的争议仍然较多。同济大学附属上海市肺科医院在肺部小结节方面

积累了大宗病例及丰富的手术经验^[30], 该院蒋雷教授根据临床实践亦提出了一个方便可行的肺部小结节诊治规范^[31] (表4), 该规范遵循的原则是: 肺部小结节越小生长越缓慢, 其危险性越小, 反之亦然; 规范应容易理解, 便于临床操作, 适用于普通人群; 暂不考虑患者的风险因素和小结节倍增时间; 对无法确定性质的小结节, 强调胸部CT平扫终身随访; 规范应与时俱进。

表4 同济大学附属上海市肺科医院蒋雷教授提出的肺部小结节诊治规范^[31]

Tab 4 Diagnosis and treatment of pulmonary small nodules by Professor Jiang Lei of Shanghai Pulmonary Hospital, Tongji University^[31]

| Type of nodule | Size of nodule <i>d</i> /mm | | |
|---|--|--|--|
| | ≤5 | >5, ≤8 | >8 |
| Suspected malignant small nodules in the lung | The initial follow-up was in 12 months, followed by plain chest CT scan every 12-24 months without surgery | The initial follow-up was in 6 months, and surgery was not recommended. After that, surgery was performed every 12 months, and plain chest CT scan was performed | The initial follow-up was within 3 months, and the operation of MIA and IA was suspected. After that, the operation was performed every 6-12 months, as appropriate, and plain chest CT scan was performed. The solid part >8 mm can be conducted for PET-CT or biopsy |

CT: Computed tomography; MIA: Minimally invasive adenocarcinoma; IA: Invasive adenocarcinoma; PET-CT: Positron emission tomography-computed tomography

5 肺部小结节的外科治疗原则

对于肺部小结节手术方式的选择, 国外的大型非随机对照临床研究显示早期肺癌患者解剖性肺段切除的术后复发率和5年生存率与肺叶切除远期效果接近^[32]。近年对于肿瘤直径小于20 mm的非小细胞肺癌(non-small cell lung cancer, NSCLC)施行肺段切除的系列报道结果显示, 其无复发生存率和总生存率并不低于肺叶切除术^[33-35]。病理类型为原位腺癌、微浸润腺癌的纯磨玻璃样病变的手术方式已推荐为亚肺叶切除(肺段或楔形切除)而非肺叶切除^[36]。在肿瘤的病理学分期早期, 外科医师对疾病的理解尚不透彻, 因此对原位腺癌手术方式的选择过于保守, 多为肺叶切除。随着对原位腺癌的深入认识, 选择术式应尽量避免肺叶切除, 尽量保留正常肺组织。

肺部小结节应遵循的手术原则为微创手术原则、精准治疗原则、加速康复原则。微创手术原则: 肺部小结节手术方式以楔形切除术和肺段或亚肺段切除术为主, 避免肺叶切除术, 不做全肺切除术; 对于多发性肺部小结节, 排除转移后, 应当分别对待, 着重处理危险最大的小结节, 附带处理同

侧的肺周边结节; 手术方式宜选择肋间单孔或剑突下单孔胸腔镜手术。Gonzalez-Rivas等^[37]于2012年报道了单孔胸腔镜肺段切除术, Jiang等^[38]也较早报道了单孔胸腔镜下的基底段切除技巧。研究显示, 对于双侧病变同期手术, 选择剑突下肺段或亚肺叶切除在技术上也是可行的, 同时可以避免肋间神经损伤、消除术后长期慢性疼痛等^[39-40]。

精准治疗原则包括两层含义: 一是术前、术中的精准病变定位; 二是亚肺叶、肺段或亚肺段切除术, 应最大程度地保留患者肺功能。术前肺部小结节常见的定位方法主要有术前CT三维重建定位、CT引导下在紧邻病变处注射亚甲蓝定位、CT引导下置入弹簧圈或注入化学胶定位, 术前置入导引钢丝(Hookwire)定位, 术中超声定位等, 各种定位方法均有其优缺点。Hookwire定位技术可于术前精准定位病灶, 操作方便, 这也是能够广泛开展精准治疗的主要原因之一^[41]。近年三维肺支气管血管重建(three dimensional-computed tomography bronchography and angiography, 3D-CTBA)的应用为精准的肺段切除术提供了有力的技术支持^[42]。

加速康复外科(enhanced recovery after surgery, ERAS)最早由丹麦哥本哈根大学Henrik Kehlet

教授提出并倡导,是指在围手术期综合应用快速通道麻醉、微创技术、合理管理疼痛、早期恢复饮食和早期运动等一系列优化措施,减少手术患者的生理及心理创伤应激,促进患者术后康复^[43]。在胸外科,ERAS也已逐渐渗入临床各个环节。同济大学附属上海市肺科医院ERAS的经验主要包括:

(1)术前做好宣教、嘱患者戒烟、有效的肺功能锻炼及科学的肠道准备。目前并不提倡术前禁食时间过长,一般采取麻醉前6h禁食固体食物,麻醉前2h仍可进食清流质。(2)术中应用胸腔镜微创技术尤其是单孔胸腔镜或剑突下单孔技术,优化麻醉方案(ERAS要求术中麻醉效果稳定,术后应激反应轻,麻醉后恢复快)。在手术操作不困难的前提下可以适当采取无插管技术,即以胸段硬膜外麻醉+静脉镇痛镇静+迷走神经阻滞的麻醉方式代替传统全身麻醉应用于非气管插管胸腔镜手术中。(3)术后加强管道管理,并倡导有效镇痛和多模式镇痛^[44]。

6 小结

肺部小结节的发病率越来越高,现有的诊断与治疗技术尚存在不足,制定合理、便捷并适合我国人群的肺部小结节诊疗规范已成为首要任务。同济大学附属上海肺科医院结合临床经验制定的肺部小结节诊疗规范方便可行,易于理解,对于普通人群的适用性较好,为临床诊断和治疗提供了发展方向。

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