

病理亚型在 I 期肺腺癌手术方式选择中作用的研究进展

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摘要: 诊断技术的进步使越来越多的 I 期肺腺癌被早期发现。手术切除是 I 期肺腺癌的首选治疗方式。2011 年,新的肺腺癌病理亚型分类标准由国际肺癌研究会/美国胸科学会/欧洲呼吸学会提出。2015 年,气道内播散这一新的病理学特征被引入最新版的 WHO 分型。近年来的研究显示病理亚型在影响 I 期肺腺癌患者预后的同时对手术方式选择也有重要的指导作用。既往回顾性研究提示术中冰冻病理在诊断肺腺癌病理亚型方面有着较好的准确性,未来可以用于指导 I 期肺腺癌手术方式的选择。

关键词: 肺腺癌;手术方式;病理学

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Guidance of Pathological Subtypes for Choice of Surgical Approaches in Lung Adenocarcinoma Stage I

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Abstract: More stage I lung adenocarcinomas are detected early due to the advances in diagnostic techniques. Surgical resection is the first choice of treatment for stage I lung adenocarcinoma. In 2011, a new adenocarcinoma classification was proposed by International Association for the Study of Lung Cancer(IASLC)/American Thoracic Society(ATS)/European Respiratory Society(ERS). And in 2015, spread through air spaces (STAS) as a new pathological feature was introduced in the latest WHO classification. Recent studies have shown that pathological subtypes have an effect on both the prognosis and the choice of surgical approaches in patients with stage I lung adenocarcinoma. Retrospective studies indicated that intraoperative frozen section had a relatively good accuracy for diagnosing the pathological subtypes of lung adenocarcinoma and it may be used to guide the surgical approaches for stage I lung adenocarcinoma in the future.

Key words: lung adenocarcinoma; surgical approach; pathology

近年来,随着低剂量薄层 CT 在肺癌筛查中的应用, I 期非小细胞肺癌的占比越来越高^[1]。其中腺癌是最主要的病理类型。手术切除是 I 期肺腺癌最有效的治疗方式^[2]。随着对肺腺癌理解的深入,国际肺癌研究会/美国胸科学会/欧洲呼吸学会(IASLC/ATS/ERS)于 2011 年提出了肺腺癌的新分类标准^[3]。

而在 2015 年,一种新的病理学特征——气道内播散(spread through air spaces, STAS)被提出,并被引入最新版的 WHO 肺癌病理分型^[4]。研究显示病理亚型是 I 期肺腺癌手术方式选择的重要指征,而术中冰冻病理在鉴别肺腺癌病理亚型上有着较好的准确性^[5]。本文对近年来关于病理亚型影响 I 期肺腺癌手术方式及术中冰冻应用于鉴别肺腺癌病理亚型的相关研究进行简要综述。

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1 IASLC/ATS/ERS 肺腺癌分型及 STAS

最新版的分类标准根据肿瘤的浸润程度将肺腺癌分为非典型腺瘤样增生(atypical adenomatous hyperplasia, AAH)、原位腺癌(adenocarcinoma in situ, AIS)、微浸润腺癌(minimally invasive adenocarcinoma, MIA)和浸润型腺癌(invasive adenocarcinoma, IAC)。浸润型腺癌依据其主要的组织学成分,可以进一步分为贴壁状、腺泡状、乳头状、微乳头状和实体状腺癌^[3-4]。大量研究显示该新分类标准与 I 期肺腺癌患者的预后密切相关。其中,非典型腺瘤样增生、原位腺癌和微浸润腺癌的预后最好,术后 5 年无复发生存率和总生存率可以达到 100%^[6-8]。而浸润型肺腺癌的预后较差,术后易出现复发和转移。在浸润型肺腺癌的各个亚型中,贴壁状、腺泡状、乳头状腺癌的预后相对较好,5 年生存率在 83%~90%之间,但微乳头状和实性腺癌的预后较差,5 年生存率仅为 67%~76%^[9]。另外,研究显示在贴壁状的腺癌中,贴壁成分占比越高,患者的预后越好^[10]。

气道内播散(STAS)是新近才被发现的一种病理学特征,它是指肿瘤细胞以单个细胞、实体癌巢或是微乳头结构这三种形式存在于肿瘤外缘肺实质的气腔内^[4,11]。STAS 存在于约 38%的 I 期肺腺癌,尤其多见于微乳头状和实性腺癌^[11-12]。尽管有少数研究认为 STAS 可能是由于人为原因造成的,但多数研究均支持 STAS 是一种新的肿瘤侵袭模式。Kadota 等^[11]则提出了鉴别 STAS 与切割造成的播散的方法:在组织内随机分布的肿瘤细胞或癌巢支持 STAS 的诊断,而形成锯齿状边缘的肿瘤细胞或是从肺泡壁延伸出的条带状的肿瘤细胞则多是由于手术切割造成。多项研究显示 STAS 与 I 期肺腺癌术后复发及预后密切相关,STAS 的出现预示着更高的复发风险和不良预后^[11-13]。有学者指出 STAS 或许可以作为分期系统中的一个因素来更准确地预测预后^[14]。

2 病理亚型对切除方式的影响

目前 I 期肺腺癌切除方式包括肺叶切除和亚肺叶切除(肺段切除和楔形切除)。相对于肺叶切除,亚肺叶切除能更好地保留肺组织及肺功能,降低围手术期并发症的发生率^[15]。尽管基于 1995 年开展的一

项随机对照试验的结果,肺叶切除仍是 I 期肺腺癌的标准切除方式^[16],但随着大量肺小结节的早期发现,亚肺叶切除被越来越多地应用于 I 期肺腺癌的治疗^[17]。众多回顾性研究显示,在 I 期肺癌中亚肺叶切除能取得与肺叶切除相似的疗效,尤其是对于 $\leq 2\text{cm}$ 的肿瘤^[18-19]。然而这些研究均是仅基于肿瘤大小来分析对比两种切除方式的预后,其所观察到的等效性可能由在 $\leq 2\text{cm}$ 的肿瘤中占有较大比例的 AAH、AIS、MIA 这三种病理亚型的良好预后驱使所致^[20]。

病理亚型除是影响预后的重要因素外,在 I 期肺腺癌切除方式选择上也是除肿瘤大小之外的一个重要的指征^[5]。研究显示对于 AAH/AIS/MIA,亚肺叶切除可取得与肺叶切除相似的预后,同时又能保留更多正常的有功能的肺组织^[7-8]。因此,对于这部分患者,亚肺叶切除可能是更好的选择。而对于浸润型肺腺癌,目前研究结论不一。Dembitzer 等^[21]开展的一项回顾性队列研究显示在早期浸润型肺腺癌中,肺叶切除并不能取得较亚肺叶切除更好的预后。但该研究由于样本量太少,因此结论论证强度不大。而后发表的两项基于美国 SEER 数据库的研究表明,对于 $\leq 2\text{cm}$ 的浸润型肺腺癌,肺段切除能取得与肺叶切除相同的预后,但楔形切除的预后较差^[20,22]。而另一项基于 SEER 数据库对比在 $\leq 3\text{cm}$ 的浸润型肺腺癌中两种亚肺叶切除方式(肺段 vs 楔形)预后的研究显示,楔形切除组和肺段切除组的预后无明显差异^[23]。尽管上述几项基于大型数据库的研究样本量充足,但由于纳入了未行淋巴结检查的患者,因此结论存在较大争议。此外上述研究均未对 I 期浸润型肺腺癌的各个亚型进行单独分析。Cox 等^[24]利用 NCDB 数据库对比了在 I 期附壁型肺腺癌中肺叶与亚肺叶切除在预后上的差异。研究者发现当纳入未行淋巴结检查的患者时,亚肺叶切除组的预后较肺叶切除组差,但当排除这部分患者后,亚肺叶切除组预后与肺叶切除组无明显差异。Nitadori 等^[25]分析了 734 例在 1995~2009 年期间于 Memorial Sloan-Kettering 癌症中心行肺叶和亚肺叶切除的 I 期浸润型肺腺癌($\leq 2\text{cm}$)患者术后复发的情况,他们发现在有微乳头成分($\geq 5\%$)的患者中,亚肺叶切除组的 5 年复发率为 34.2%,明显高于肺叶切除组的复发率(19.1%),而大部分患者为局部复发。进一步的分析

发现当切缘 $\geq 1\text{cm}$ 时,微乳头成分出现($\geq 5\%$)所造成的亚肺叶切除组患者术后复发增加的现象就会消失。对于 I 期浸润型肺腺癌的其他病理亚型,目前暂无两种切除方式对比的研究报道。

而对于 STAS,近来发表的几项研究均表明其是 I 期肺腺癌亚肺叶切除术后复发及不良预后重要的危险因素。Masai 等^[12]对 508 例行亚肺叶切除术的患者进行研究后发现 STAS 与患者的术后局部复发密切相关,但进一步分析发现当切缘 $\geq 2\text{cm}$ 时,患者的局部复发率为零。而在一项对 1500 例 I 期肺腺癌进行倾向性评分匹配分析的回顾性研究中,研究者发现在有 STAS 的患者中,亚肺叶切除组的复发率和肺癌相关死亡率是肺叶切除组的 3 倍^[13],且尽管目前认为切缘大于 2cm 或大于肿瘤直径能降低亚肺叶切除术后的复发率^[26-27],但在该研究中,取得大于肿瘤直径的手术切缘并不能降低亚肺叶切除组患者的术后局部复发率。

3 病理亚型对淋巴结清扫方式的影响

淋巴结清扫是肺癌手术的一个重要环节。尽管研究显示系统性淋巴结采样和选择性淋巴结清扫能取得与系统性淋巴结清扫相似的效果^[28-32],但系统性纵隔淋巴结清扫仍是目前 I 期肺腺癌淋巴结清扫的标准模式^[33]。然而,对于没有淋巴结转移的患者,预防性淋巴结清扫对患者的预后无益^[28,32]。且纵隔淋巴结清扫会导致术后并发症如喉返神经损伤、乳糜瘘、心房颤动、支气管残端缺血、肺组织漏气等的发生率的增加,进而导致术后死亡率的上升^[34-36]。因此在提倡减少手术创伤的今天,寻找能准确预测纵隔淋巴结状态的指标是 I 期肺腺癌淋巴结清扫方式选择的关键。

既往研究显示肺癌淋巴结转移率随着肿瘤的增大而逐渐增高,而在 $<1\text{cm}$ 的肿瘤中没有纵隔淋巴结的转移,因此认为对于 $<1\text{cm}$ 的肺癌,可以不行系统性纵隔淋巴结清扫^[37-38]。而后续的研究发现即使是在 $<1\text{cm}$ 的肺癌甚至是在 $<0.5\text{cm}$ 的肺癌中,仍有纵隔淋巴结转移的可能性^[6,39]。Cheng 等^[6]的研究显示在纵隔淋巴结阳性和阴性的 I 期肺癌中,肿瘤的平均大小仅差 4mm。因此,单独依靠肿瘤大小无法准确预测 I 期肺腺癌纵隔淋巴结的状态。

近来发表的研究显示病理亚型在预测纵隔淋巴结转移与否上的准确性优于肿瘤大小^[6,39-40]。Zhang 等^[40]分析了 243 例外周肺小结节患者的病理结果后发现在鳞癌、原位腺癌、微浸润腺癌和附壁为主的浸润型腺癌中没有纵隔淋巴结的转移。Yu 等^[39]对 2268 例 $\leq 3\text{cm}$ 的临床 I 期肺腺癌患者分析后也同样发现原位腺癌、微浸润腺癌和附壁为主的浸润型腺癌没有纵隔淋巴结转移。且在 Liu 等和 Cheng 等后续开展的两项研究中,研究者发现对于病理亚型为原位腺癌、微浸润腺癌和附壁为主的浸润型腺癌患者,不进行纵隔淋巴结清扫或仅进行局限性淋巴结清扫能取得与系统性纵隔淋巴结清扫相似的预后^[6,7]。因此,对于病理亚型为原位腺癌、微浸润腺癌和附壁为主的浸润型腺癌患者,不进行系统性纵隔淋巴结清扫是可行的。而对于其他肺腺癌病理亚型,众多研究显示微乳头成分与实性成分的出现与纵隔淋巴结转移密切相关,在有这两种成分的 I 期肺腺癌患者中,近一半的患者有淋巴结转移,且淋巴结转移率随着这两种病理成分的增加和附壁成分的减少而升高^[39,41-42]。因此对于有微乳头成分与实性成分的 I 期肺腺癌,系统性纵隔淋巴结清扫在改善肿瘤预后上是必不可少的。

4 术中冰冻病理鉴别肺腺癌病理亚型

鉴于病理亚型对 I 期肺腺癌手术方式选择有重要的指导作用,如能在术前或术中准确诊断肺腺癌的病理亚型,则能根据病理亚型决定相应的切除方式及淋巴结清扫方式。目前肺腺癌病理亚型的术前或术中诊断主要有 3 种方式:CT 检查、术前穿刺病理、术中冰冻病理。然而术前 CT 检查诊断肺腺癌病理亚型的准确性依赖于设备参数的设定及界值的选择,这造成其准确性很不稳定,敏感性波动于 42%~100%之间,特异性波动于 45%~100%之间^[43-44]。而对于术前穿刺病理,研究显示其与术后石蜡病理结果对比的吻合率仅有 58.6%^[45]。另外,目前 STAS 只能在手术切除标本上进行鉴别和诊断^[46]。因此,目前看来,术中冰冻病理是较为理想的选择。研究显示术中冰冻病理在鉴别浸润型肺腺癌(IAC)与非浸润型肺腺癌(AAH/AIS/MIA)方面有着较高的准确性,敏感性在 93%~97%之间,特异性在 92%~100%

之间^[6-7,47-48]。在一项依据术中冰冻病理(AAH/AIS/MIA vs IAC)指导术式选择的大型回顾性研究中,仅有0.9%的患者(7/803)因术中冰冻病理诊断失误而造成手术切除范围不够^[7]。但术中冰冻在诊断浸润型肺腺癌各个亚型(微乳头型、实体型等)及STAS上,目前国内外研究较少。现有研究表明术中冰冻病理诊断STAS有着较高的特异性(92%~100%),但敏感性较差(50%~71%);同样,术中冰冻病理在诊断微乳头等浸润型腺癌亚型上有着较高的特异性,但敏感性较差^[13,49-51]。

尽管术中冰冻病理在诊断肺腺癌病理亚型方面显示出较好的准确性,但目前国内外尚无依据术中冰冻病理诊断来指导I期肺腺癌术式选择的前瞻性研究,且此项技术目前仍有较大的改善及提升空间。既往研究显示术中冰冻病理的错误诊断主要来源于取材不足所致的诊断失误,特别是对于体积较小的肿瘤,如果仅对一张冰冻病理切片进行分析,就可能造成某些病理成分的遗漏,最终导致诊断错误^[49-50,52]。因此,术中行多张冰冻病理切片(至少2张)的取材和分析能降低漏诊率和误诊率,但相应的花费和收益需要进一步的研究来评估^[7,50]。目前我国多数医院的病理科能满足术中行2张及以上冰冻切片取材的要求^[7,47-48]。另外,有研究指出对标本行磷酸盐缓冲液膨胀处理,以及进行弹性纤维染色能显著提高冰冻病理诊断的准确性^[7,50,53],然而目前我国这两种方法并未常规使用,但考虑到未来术中冰冻应用于指导I期肺腺癌术式选择的前景,利用其提高诊断的准确性还是有必要的。此外,冰冻病理诊断准确性的提高还有赖于术中病理医生和术者及时充分的沟通和交流^[54]。

综上所述,病理亚型在I期肺腺癌手术方式选择上有着重要的作用。基于目前的研究结果,在肿瘤切除方式上,对于病理亚型为非典型腺瘤样增生、原位腺癌和微浸润腺癌的I期肺腺癌,亚肺叶切除是一种可行的选择;而对于I期浸润型肺腺癌,肺叶切除仍是较为合理的选择;在淋巴结清扫方式上,除非典型腺瘤样增生、原位腺癌、微浸润腺癌和附壁为主的浸润型腺癌外,其余病理亚型均需行系统性纵隔淋巴结清扫。术中冰冻病理能准确地鉴别浸润型肺腺癌与非浸润型肺腺癌,其应用于术中指导I期肺腺癌手术方式选择上有着较好的前景。未来需要

更多的研究来明确在I期肺腺癌各个病理亚型中不同手术方式的预后,并探讨术中冰冻病理应用于指导临床I期肺腺癌手术方式选择的可行性,从而为患者制定有效、微创、合理的治疗方案。

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