微乳头为主型肺腺癌研究进展

赵琪[1,2] 杨瑞娜[2] 王甄[3] 王海瑞[4] 姜志怡[5] 常保萍[2]
[1]河南科技大学临床医学院,河南洛阳 471000
[2]河南科技大学第一附属医院肿瘤内科,河南洛阳 471000
[3]洛阳市第三人民医院呼吸内科,河南洛阳 471000
[4]河南科技大学第二附属医院呼吸内科,河南洛阳 471000
[5]汝阳县人民医院肿瘤科,河南洛阳 471200

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微乳头为主型腺癌(micropapillary predominant adenocarcinoma,MPA)是肺腺癌中具有高度侵袭性的一种亚型[1],相比于其他亚型具有相对独特的病理特征及肿瘤免疫微环境。1997 年,Silver 和 Askin 首次在肺癌中描述了微乳头结构(micropapillary pattern,MPP)[2],MPP 以中央缺少纤维血管的乳头状肿瘤细胞簇为病理特征[3],有助于与其他肺腺癌亚型相鉴别。2011 年国际肺癌研究协会/美国胸科学会/欧洲呼吸学会(International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society,IASLC/ATS/ERS)统一将手术切除样本中 MPP > 5% 增量的肺腺癌称为 MPA,并将 MPA 作为一种新的组织学类型加入肺腺癌病理分类中[4],其他亚型还包括:实体为主型(solid predominant adenocarcinoma,SPA)、乳头状为主型(papillary predominant adenocarcinoma,PPA)、腺泡为主型(acinar predominant adenocarcinoma,APA)、贴壁为主型(lepidic predominant adenocarcinoma,LPA)。与其他亚型相比,MPA 恶性程度高、复发率高、易远处转移、预后差。本文将从病理特征、影像学检查、治疗及预后等方面探讨 MPA 的研究进展。

一、病理特征

病理学诊断对 MPA 患者的临床管理至关重要。MPP 常见于肿瘤的周边区域[5],典型的病理特征为肺泡间隙或结缔组织间隙内乳头状或花状的肿瘤细胞簇,这些细胞簇中央缺少纤维血管[3],见图 1。最近,有研究报道了一种新的 MPP 被称为丝状结构,表现为纤细、丝状、中央缺乏纤维血管的结构,在肺泡壁基底层至少有 3 个瘤细胞堆积[6]。MPP 肿瘤细胞通常体积小且呈立方体,细胞核异质性很小[7],E-钙黏蛋白和 β-连环蛋白的存在使得肿瘤细胞紧密连接,而层粘连蛋白及基底膜的丢失导致肿瘤细胞与基质分离,并且肿瘤细胞的极性消失,这些特征可能参与了 MPA 的转移过程[8]。

多项研究表明,MPP 与肺腺癌的不良预后因素相关。Sumiyoshi 和 Koga 等[8,9]观察到,MPP 与高淋巴管侵袭率相关,MPA 患者具有更高的 N 分期,66.7% 的患者处于 N1 和 N2 期[10]。肺腺癌组织中微乳头成分的比例与胸膜侵犯程度、血管内肿瘤血栓形成和通过气腔扩散程度呈正相关[11~13]。

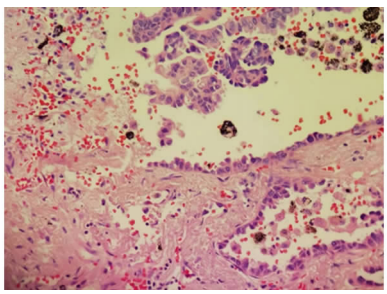

图 1 微乳头结构[HE 染色(×200),中央缺少纤维血管的乳头状肿瘤细胞簇]

二、影像学检查

影像学检查在肺癌患者的诊断中有重要作用,MPA 病情进展快,更需要影像学检查早期识别。CT 检查是肺腺癌患者最常规的影像学检查,CT 扫描中 MPA 常表现为部分实性和分叶状结节[14],多发于双肺上叶,边界较清楚。分叶征、毛刺征常见,少见空气支气管征及空泡征。刘子珊等[15]分析了 61 例 MPA/SPA 患者的临床资料和 CT 表现,发现 55.7% 的患者病灶最大直径≥2 cm,病灶直径与 MPA/SPA 的恶性程度相关。18F-FDG PET/CT 检查已逐渐成为评价肺癌分期的常规方法[16]。PET/CT 的最大标准化摄取值(SUVmax)是描述器质性病变葡萄糖摄取的半定量指标,Nakamura等[17]提出,浸润性肺腺癌中 MPA 的 SUVmax 最高,在按组织学分类(低、中、高级别)划分的亚组中,SUVmax 越高,复发风险越大。而 Sun 等[18]认为,T 分期相同时,SPA 患者 SUVmax 最高[18]。Cha 等[19]表明 SUVmax ≥ 7 是微乳头或实体成分存在的独立预测因素。总体来说,SUVmax 值高预示更差的病理分型和预后[20]。

三、治疗

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通信作者:常保萍,E-mail:changbaoping2020@126.com,河南省洛阳市洛龙区关林路 636 号

(一)手术

目前临床上早期肺癌患者的手术治疗更倾向于肺叶切除及系统性淋巴结清扫,对于早期 MPA 患者,手术标本中 MPP 的存在导致患者术后复发风险升高、复发时间提前,术后 1 年左右复发风险最高[21,22]。Nitadori 等[23]报道 MPA 患者接受肺段切除或楔形切除术后局部复发率增加,5 年累计复发率为 34.2%。当手术切缘距病灶 <1 cm 时,微乳头成分≥5% 与局部复发风险显著相关,手术切缘距病灶≥1 cm 时复发概率降低。表明对于 MPA 患者,肺段切除或楔形切除不是最佳的术式。Xu 等[24]报道病灶 <2 cm 的 MPA 患者接受肺叶切除 + 系统性淋巴结清扫术比亚肺叶切除术 + 局限淋巴结清扫术拥有更好的长期生存率;而对于微乳头成分 <5% 的患者,扩大手术范围并不能显著改善患者的预后。

(二)化疗

对于 IA 期患者,美国国立综合癌症网络指南不建议行术后辅助治疗[25],Wang 等[26]探讨"卡铂 + 培美曲塞"辅助化疗对 IA 期 MPA 患者总生存期(overall survival,OS)/无进展生存期(progress free survival,PFS)的影响,多因素分析显示辅助化疗是 MPA 患者 OS(无化疗 *vs.* 化疗 *HR*:2.054,95% *CI*:1.085 ~ 3.886,*P* = 0.027)及 PFS(无化疗 *vs.* 化疗 *HR*:2.205,95% *CI* 1.118 ~ 4.349,*P* = 0.022)的预测因素。Qian 等[27]将 IB 期肺腺癌患者分为不含实体/微乳头成分组、实体/微乳头成分 <5% 组和 SPA/MPA 组,比较 3 组患者辅助化疗的获益情况。4 个周期基于铂类的辅助化疗显著改善了 SPA/MPA 组的疾病特异性生存期(disease specific survival,DSS)(*HR*:0.46,95% *CI*:0.22 ~ 0.93,*P* = 0.031)和无复发生存期(recurrence-free survival,RFS)(*HR*:0.48,95% *CI*:0.26 ~ 0.88,*P* = 0.017)。以上结果表明辅助化疗可使 IA、IB 期 MPA 患者生存获益,未来还需要更多的研究探讨其他分期患者的化疗获益情况,探索对 MPA 患者疗效更优的化疗方案。

(三)靶向治疗

1. 表皮生长因子受体:表皮生长因子受体(epidermal growth factor receptor,EGFR)基因突变是肺腺癌最常见的驱动基因突变,中国肺腺癌患者 EGFR 突变频率约为 50.2%[28]。EGFR 酪氨酸激酶抑制剂(tyrosine kinase inhibitor,TKI)是具有 EGFR 突变的肺癌患者的一线治疗方法,血清癌胚抗原(carcinoembryonic antigen,CEA)联合神经元烯醇化酶(neuron-specific enolase,NSE)可预测晚期肺腺癌患者 EGFR-TKI 治疗的疗效[29]。一代/二代 EGFR-TKI 可使患者的中位无进展生存期提升至 9.2 ~ 14.7 个月[30],但易出现耐药和疾病进展,其中最常见的耐药基因突变为 EGFR T790M 突变[31],第三代 EGFR-TKI 能很好地抑制这一耐药基因突变,并且相比于一代药物显著延长中位无进展生存期、有较高的中枢神经系统反应率并带来 OS 获益[32-34],使其成为晚期 EGFR 突变非小细胞肺癌(non-small-cell lung carcinoma,NSCLC)患者的标准一线治疗。

MPA 患者 EGFR 基因突变频率高于其他亚型[35~37],MPA 可作为 EGFR 突变的预测因子[5]。然而,由于种族差异、纳入样本量不同和其他因素,一些研究对 EGFR 突变状态和主要组织亚型之间的关系存在争议[38~40]。一项纳入 9 022例患者的回顾性分析表明,在所有病理亚型中,LPA 患者 EGFR 突变率更高,且亚洲人群与其他人种的 EGFR 突变状态与病理亚型的关系是一致的[41]。Wang 等[42]对 162 例微乳头成分不占优势的肺癌标本进行 EGFR 基因检测,发现最常见的突变类型为 19Del(27.1%),其次为 21 L858R(26.0%),18 G719X(4.3%),20 外显子插入突变(20ins)(1.9%)。Cai 等[43]报道在含 MPP 的肺腺癌患者中,EGFR 总突变率为 91.4%,19Del 或 21 L858R 发生率为 79.4%,耐药突变 20ins 和 T790M 的发生率为 8.6%,该研究未将每一突变类型的频率单独罗列,也未具体阐明纳入研究的患者微乳头成分的比例是否相同。EGFR 不同突变类型发生的频率是否与微乳头成分的比例有关?发生耐药突变患者所含微乳头成分是否与经典突变患者不同?这些问题还需要进行更深一步的研究。若能得到有意义的结果,将指导这些患者靶向治疗药物的选择。一项研究表明,在具有 EGFR 突变的含有 MPP 的肺腺癌患者中接受 EGFR-TKI 治疗与未接受 TKI 治疗相比,复发后生存率显著提高[44]。目前,国内外在研究不同 EGFR-TKI 治疗 MPA 患者的疗效方面尚处空白。

2. 间变性淋巴瘤激酶:在间变性淋巴瘤激酶(anaplastic lymphoma kinase,ALK)突变与肺腺癌亚型关系的研究中,不同学者的结论不尽相同。Yu 等[45]对 2 299 例手术切除的肺腺癌患者 ALK 突变率与病理亚型的关系进行了探索,发现所有亚型中 MPA 患者 ALK 重排发生率为 7.6%,位居第二。一项回顾性研究的多因素回归分析证实 MPP 为 ALK 基因突变的独立预测因素[40],但该研究为单中心的回顾性研究,结果可能存在选择偏倚。另外有研究显示 ALK 重排更易发生在 SPA 患者中[46]。目前还没有报道评估 ALK-TKI 对 MPA 患者的疗效。

3. 间充质-上皮细胞转化:间充质-上皮细胞转化(mesenchymal-epithelial transition,MET)基因最常见的突变类型为基因扩增(1% ~5%)和 14 外显子跳跃突变(2% ~4%)[47],Li 等[48]报道 MPA 患者 MET 基因突变率为 12.5%,然而该研究存在很大的局限性,只纳入了 16 例 MPA 患者。Koga 等[9]发现 T1 期肺腺癌中 MPP 阳性(MPP > 10%)的患者磷酸化 c-Met 的表达明显高于 MPP 阴性组,且 MPP 的比例升高与淋巴转移相关。因此,c-Met 的磷酸化可能参与了 MPP 的侵袭性生物学行为。MET 抑制剂为 MPA 患者的治疗提供了另一种选择。

此外,ROS1、RET、BRAF、HER-2 等其他肺腺癌中观察到的驱动基因突变因其发生率低,缺少大样本与病理亚型关系的研究。期待未来探索靶向药物疗效的研究能深入到不同病理亚型层面,为肺腺癌患者提供个性化治疗方案。

(四)免疫治疗

近年来,免疫治疗在 NSCLC 中显示出良好的效果,肿瘤微环境是影响免疫治疗效果的关键因素[49]。肿瘤程序性死

亡配体 1(programmed death-ligand 1,PD-L1)高表达和 T 细胞浸润程度高的患者对免疫检查点抑制剂有良好的反应[50,51]。Zhang 等[52]发现微乳头成分含量高的肿瘤组织周围区域有更多的 CD4 + 和 CD8 + T 细胞浸润,并且 PD-L1 的表达增加,表明微乳头肿瘤细胞可能通过形成免疫抑制微环境来促进天然免疫逃逸,免疫治疗可能因此使 MPA 患者获益。根据中华医学会肺癌临床诊疗指南(2022 版)[53],对于非鳞癌驱动基因阴性患者一线免疫治疗的建议:PD-L1 表达阳性(≥1%)的患者可单药使用帕博利珠单抗,但 PD-L1 高表达(≥50%)的患者从中获益更明显。因此,免疫治疗是 MPA 患者比较重要的一个治疗方案。

(五)放疗

辅助放疗是局部晚期肺腺癌根治术后的重要辅助治疗手段之一。目前关于不同病理亚型肺腺癌患者辅助放疗疗效的研究较少。石祥宇[54]评估了不同病理亚型肺腺癌根治性切除及系统性淋巴结清扫术后辅助放疗对预后的影响发现,对于 MPA/SPA 组,放疗与未放疗中位 OS 为 28.3 *vs.* 27.4 个月($\chi^2 = 0.076$, $P = 0.783$),中位无病生存期(median disease-free survival,mDFS)为 25.3 *vs.* 24 个月($\chi^2 = 0.117$, $P = 0.7$)。术后放疗并不能显著改善 MPA/SPA 患者的预后。Warth 等[55]发现辅助放疗只能提高 SPA 患者的 DFS,不能改善非 SPA 患者的预后。该研究存在一定局限性,因其没有严格按照 IASLC/ATS/ERS 病理分类方法进行分组,只分为 SPA 组和非 SPA 组,因此,并不能明确辅助放疗对 MPA 患者的疗效。

四、预后

Yanagawa 等[56]发现,MPP 与预后不良相关,即使肿瘤组织中微乳头成分不占主导优势,患者的 RFS 与 OS 也低于无 MPP 的患者。Li 等[57]发现,Ⅰ ~ Ⅲ期含 MPP 的 EGFR 突变的肺腺癌患者术后 DFS(13 月 *vs.* 22 个月;$P < 0.001$)和 OS(56 月 *vs.* 74 月;$P < 0.001$)更短,MPP 是脑转移发生率增加和术后脑转移发生时间缩短的独立预后不良因素。最近,一项荟萃分析研究了 MPP 对 IA 期肺腺癌患者预后的影响,共纳入 10 项回顾性研究中的 5 257 例 IA 期患者,伴和不伴 MPP 的复发率分别为 32%(95% *CI*:20% ~ 44%)和 7%(95% *CI*:4% ~ 10%),提示 MPP 与较差的 OS 显著相关[58]。

微乳头为主型肺腺癌是浸润性肺腺癌中恶性程度最高的亚型。早期 MPA 患者术后局部复发风险高,手术切除范围及淋巴结清扫范围对 MPA 患者的预后有影响,故术前或术中应尽快明确患者病理类型以确定手术方式。影像学检查中 PET/CT 的 SUVmax 值对 MPA 有一定的预测作用,且 SUVmax 值越大预示着预后更差。对于晚期不可手术的肺腺癌患者,MPA 的诊断存在挑战,目前尚无特异的分子生物标志物将 MPA 与其他亚型相鉴别。基于小样本的研究表明辅助化疗可使 IA、IB 期 MPA 患者生存获益,对晚期 MPA 患者的疗效还需进一步探讨。MPA 患者 EGFR、ALK 基因突变频率相对较高,PD-L1 表达水平、T 细胞浸润程度高,意味着相应的靶向治疗和免疫治疗可能使患者获益,建议今后靶向及免疫药物临床研究将病理亚型纳入分层研究,推动深化肺癌精准化、个体化治疗进而改善患者预后。

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