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MCM6、MCM7、KIAA1522 蛋白联合检测对非小细胞肺癌诊断及预后预测的临床价值研究 *

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摘要 目的:筛选肺癌蛋白分子标志物,寻找可诊断及预测肺癌预后的蛋白标志物。**方法:**选择2014年8月~2019年7月于西安市第四医院确诊并进行肺部切除手术的非小细胞肺癌(non-small-cell lung Cancer, NSCLC)患者80例,采用免疫组织化学(immunohistochemistry, IHC)检测 NSCLC 患者肺癌组织标本和癌旁 MCM2(Minichromosome maintenance protein2, 微小染色体维持蛋白2)、MCM5(Minichromosome maintenance protein5, 微小染色体维持蛋白5)、MCM6(Minichromosome maintenance protein6, 微小染色体维持蛋白6)、MCM7(Minichromosome maintenance protein7, 微小染色体维持蛋白7)、KIAA1522 和 KIAA0317 蛋白表达阳性率,探讨多蛋白联合检测对 NSCLC 诊断及预后预测的临床应用价值。**结果:**肺癌组织中 MCM2、MCM5、MCM6、MCM7、KIAA1522 和 KIAA0317 的阳性表达率均显著高于癌旁正常肺组织($P<0.05$),其中 MCM6、MCM7 和 KIAA1522 在 50%以上;以 MCM6、MCM7、KIAA1522 蛋白联合检测肺癌组织,不同性别、不同年龄、类型和分期的 NSCLC 患者的联合蛋白阳性率无统计学差异($P>0.05$),且蛋白阳性率均大于 80%;MCM7 高表达较之低表达或不表达的病例,显著增加患者的死亡风险($P=0.000$)。男性($P=0.031$)、III~IV 期患者($P<0.001$)、以及低分化程度($P=0.012$)也是患者的不良预后因素,多因素回归分析显示, MCM7 是一个独立的预测指标 ($P=0.000$),与患者生存具有显著相关性,对预后有一定的预测作用。**结论:**NSCLC 患者肺癌组织中 MCM6、MCM7 和 KIAA1522 呈高表达,三者联合检测对 NSCLC 的检测具有较高的准确性、敏感性和特异性,高水平的 MCM7 表达提示肺癌患者的不良预后。

关键词:非小细胞肺癌;蛋白标志物;临床诊断;预后指示

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A Study on the Diagnostic and Prognostic Prediction Value of Combined Detection of MCM6, MCM7, and KIAA1522 for Non-Small Cell Lung Cancer*

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ABSTRACT Objective: Screening for molecular markers of lung cancer proteins to find protein markers that can diagnose and predict the prognosis of lung cancer. **Methods:** Eighty patients with NSCLC diagnosed in the Fourth Hospital of Xi'an from August 2014 to July 2019 and undergoing lung resection were selected, IHC was used to detect the positive rate of MCM2, MCM5, MCM6, MCM7, KIAA1522 and KIAA0317, to explore the clinical value of combined detection of multiple proteins in the diagnosis and prognosis prediction of NSCLC. **Results:** The positive rates of MCM2, MCM5, MCM6, MCM7, KIAA1522 and KIAA0317 in lung cancer tissues were significantly higher than normal tissues adjacent to cancer ($P<0.05$), of which MCM6, MCM7 and KIAA1522 were more than 50%. In the joint detection of lung cancer tissues, there was no statistically significant difference in the combined protein positive rate of NSCLC patients of different genders, different ages, types and stages ($P>0.05$), and the protein positive rate was more than 80%; MCM7 high expression was lower than low expression or not The expressed cases significantly increased the patient's risk of death ($P=0.000$). Males ($P=0.031$), patients with stage III to IV ($P<0.001$), and poor differentiation ($P=0.012$) are also the poor prognostic factors of patients. Multivariate regression analysis shows that MCM7 is an independent predictor ($P=0.000$), which has a significant correlation with the survival of patients and has a certain predictive effect on prognosis. **Conclusion:** MCM6, MCM7 and KIAA1522 are highly expressed in lung cancer tissues of NSCLC patients. The combined detection of the three has high accuracy, sensitivity and specificity for the detection of NSCLC. The high level of MCM7 expression indicates poor prognosis of lung cancer patients.

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前言

非小细胞肺癌约占肺癌的 80%，全球肺癌发病率正逐年上升，且其五年生存率极低，一个非常重要的原因是多数患者就诊时已是晚期，或者因为较早转移而失去手术机会。因此，早期诊断可以为治疗提供机会，并有助于改善患者预后。目前，肺癌常见的诊断方式包括胸部 X 射线照射、支气管镜下刷片或取活检、低剂量螺旋 CT、痰液和支气管肺泡灌洗液的细胞学检查^[1-5]等，但均存在适用度、敏感性、特异性等局限性。此外，临床上也常用血清肿瘤标志物如细胞角 21-1 蛋白片段(CYFRA21-1)、癌胚抗原(CEA)、神经元特异性烯醇化酶(NSE)、糖类抗原 125(CA125)和组织多肽抗原(TPA)^[6-9]等单独或联合检测，但良性肿瘤、炎症等良性病变也存在上述指标水平的增高，容易导致误诊。

细胞学检查在支气管刷检标本、灌洗标本、痰液胸腔积液等的检测中有重要作用^[10-12]。将蛋白分子水平异常检测作为肺癌肿瘤标志物能更适当的反映肺癌的生物学行为的异质性，为肺癌的预警和诊断提供重要指导^[13]。因此，本研究采用免疫组织化学法检测非小细胞肺癌患者肺癌组织标本，筛选肺癌蛋白分子标志物，探讨多蛋白联合检测对诊断不同临床特征肺癌患者的价值，以期对肺癌患者的诊断和预后预测提供辅助依据。

1 材料与方法

1.1 研究对象

选择 2014 年 8 月~2019 年 7 月于本院确诊并进行肺部切除手术的非小细胞肺癌(NSCLC)患者 80 例。本研究中所用的组织标本均为临床诊断后的剩余标本，于术中或支气管镜检查时切除肺癌组织和癌旁正常组织，标本均为无坏死的新鲜组织，-80℃冰箱保存备用。其中，男性 58 例，女性 22 例，年龄范围为 36~84 岁，中位年龄 61 岁，鳞癌 41 例，腺癌 39 例。根据 UICC 第八版 TNM 标准^[14]，I 期 17 例，II 期 26 例，III 期 33 例，

IV 期 4 例。

1.2 纳入与排除标准

纳入标准：依据我国 2015 版肺癌诊疗指南^[15]诊断，经过病理组织学确诊；为初诊、原发性肺癌；行肺癌根治术患者，术前未接受过放化疗，患者知情同意，医院伦理委员会批准。排除标准：经过放/化疗患者，心、肝、肾等器官功能不全者，患有其他肿瘤类型或既往患其他肿瘤患者。

1.3 研究方法

1.3.1 主要试剂与仪器 MCM6 抗体 (Proteintech), MCM7 抗体(Santa Crus Biotechnology), KIAA1522(Sigma), SP 法免疫组化试剂盒(中杉金桥), DAB Kit(中杉金桥, ZLI-9018), 苏木素染料(中杉金桥, ZLI-9040), 30%过氧化氢(Alfa Aesar); 组织芯片制备仪(北京博医康实验仪器有限公司), 低温高速离心机(Thermo Scientific), 涡旋振荡器(IKA), 医用微波炉(Galanz)等。

1.3.2 免疫组织化学方法(IHC)步骤 将肺组织切片进行二甲苯脱蜡、梯度乙醇水化后用 PBS 浸洗 3 次，每次 5 min，经 3%过氧化氢中封闭 15 min 消除内源性酶，经抗原修复后 PBS 缓冲液洗 3 次，每次 5 min，加一抗，次日去掉多余一抗后 PBS 洗 3 次，每次 3 min，加二步法免疫组化检测试剂盒 II，37℃避光孵育 30 min，PBS 洗 3 次，每次 3 min，DAB 显色 10~60 s，水洗终止显色，苏木素复染 5~20 s，1%氨水充分返蓝，经梯度乙醇脱水、风干后封片，镜下观察无重叠的肿瘤细胞，阳性细胞背景清晰，呈棕黄色颗粒，对阳性细胞比例和染色强度进行半定量测定。

1.3.3 染色评分标准 参照免疫组化结果评分系统^[16]制定细胞核抗原半定量评价。镜下观察细胞核着色明显为阳性，记录该组织芯的标记指数(LI)：阳性细胞在全部肿瘤细胞中的占比，取 3 个组织芯的均值为该病例的最终评分(0%~100%)。

综合细胞染色强度和阳性细胞占比进行胞浆或胞膜抗原半定量评价，见表 1。记录每个组织芯的百分比评分×显色强度，取 3 个组织芯的判决书为最终评分。阴性：0~3 分，弱 - 中等阳性：3~9 分，强阳性：9~12 分。

表 1 胞浆或胞膜抗原半定量评价标准

Table 1 Semi-quantitative evaluation criteria of cytoplasmic or membrane antigen

Score	Evaluation of protein expression	Color Type Description
Percentage	0	Tumor cell color<10 %
	1	Tumor cell color 10 %~20 %
	2	Tumor cell color 20 %~50 %
	3	Tumor cell color 50 %~80 %
	4	Tumor cell color>80 %
Color strength	0	No Color
	1	Weak color
	2	Medium color
	3	Strong color

1.4 统计学分析

采用 SPSS 19.0 分析数据,通过单因素分析及 χ^2 检验对数据进行分析,生存分析采用 Cox 回归分析, $P<0.05$ 为差异有统计学意义。

2 结果

2.1 NSCLC 组织标本中 MCM2、MCM5、MCM6、MCM7、KIAA1522 和 KIAA0317 的表达

本研究对 NSCLC 患者肺癌组织和配对癌旁正常组织进行

检测,筛选出 6 个在肺癌组织中高表达,在癌旁正常组织中低表达或不表达的蛋白。根据参考文献^[17],制定 MCM2、MCM5、MCM6、MCM7 的 cut-off 值为 15 %,KIAA1522、KIAA0317 cut-off 值为 6 分。按照 cut-off 值,各蛋白阳性表达率见表 2。这六种蛋白在肺癌组织中的阳性率均显著高于癌旁正常组织($P<0.05$)。其中,MCM6、MCM7 和 KIAA1522 在肺癌组织中阳性率均在 50 %以上,分别为 61.2 %、67.5 %和 56.3 %,且在正常组织中的阳性率仅为 2.5 %、1.3 %和 0 %。

表 2 蛋白标志物在肺癌及癌旁正常组织中的表达阳性率(例,%)

Table 2 Positive rate of the protein expression in lung cancer tissues and normal tissue adjacent to cancer (n,%)

Protein	Lung cancer tissue	Normal tissue adjacent to cancer
MCM2	34(42.5)*	4(5)
MCM5	36(45.0)*	3(3.8)
MCM6	49(61.2)*	2(2.5)
MCM7	54(67.5)*	1(1.3)
KIAA1522	45(56.3)*	0(0)
KIAA0317	39(48.8)*	4(5)

Note: compare with the normal tissue adjacent to cancer, * $P<0.05$.

2.2 MCM6、MCM7、KIAA1522 蛋白表达与 NSCLC 临床特征的相关性分析

为提高对 NSCLC 组织检测的准确性,选 MCM6、MCM7、

KIAA1522 蛋白联合检测肺癌组织,结果显示不同性别、不同年龄、类型和分期的 NSCLC 患者的联合蛋白阳性率无统计学差异($P>0.05$),且蛋白阳性率均大于 80 %,见表 3。

表 3 MCM6、MCM7、KIAA1522 联合检测与 NSCLC 临床特征的关系(例,%)

Table 3 The relationship between MCM6, MCM7, KIAA1522 combined detection and different clinical features of NSCLC (n,%)

Clinical features		n	Multi-protein detection
Sex	Male	58	49 (84.48)
	Female	22	18 (81.82)
Age	≤ 60	63	53 (84.13)
	>60	17	14 (82.35)
Tumor type	SCC	41	36 (87.70)
	ADC	39	32 (82.05)
Stage I-II		43	35 (81.40)
III-IV		37	31 (83.78)

2.3 MCM7 蛋白的表达与 NSCLC 患者预后的关系

在所研究组织病例中,有 74 例随访资料,随访时间为 94 ~1945 d,对上述蛋白的表达情况与患者总生存和临床病理参数进行相关性分析,见表 4。单因素回归分析显示,MCM7 高表达显著增加患者的死亡风险 ($P=0.000$)。男性($P=0.031$)、III-IV 期患者($P<0.001$)、以及低分化程度($P=0.012$)也是患者的不良预后因素。多因素回归分析显示 MCM7 是一个独立的预测指标($P=0.000$),与患者生存具有显著相关性,对预后有一定的预测作用。

3 讨论

肺癌是一种复杂的多基因参与疾病,从分子水平对肺癌进

行诊断已经成为目前重要的方向,适当的肿瘤标志物在诊断中有非常重要的意义,但迄今为止,肺癌的发生和发展机制尚未完全阐明。微小染色体维持蛋白(Minichromosome maintenance, MCM)复合物是 DNA 复制和延伸的关键蛋白,由 MCM 家族 6 个具有类似结构的亚单位组成,分别为 MCM2~MCM7,MCM 被认为是 DNA 的解链酶,并且在复制叉的延伸中起关键作用^[18,19]。在组织中,MCM 的表达水平与细胞增殖程度呈正比,推测 MCM 蛋白可作为一种特异标志标识增殖细胞^[20]。肿瘤细胞具有强增殖能力,针对 MCM 的这种特性,大量研究表明 MCM 与多种肿瘤密切相关,如乳腺癌、宫颈癌、肺癌^[21-24]等。其中,MCM7 是该家族中重要成员,也是一种与细胞增殖相关的因子,研究显示 MCM7 在肝癌、前列腺癌、结肠癌^[25-27]等多种肿

表 4 NSCLC 组织标本单因素和多因素回归分析
Table 4 Univariate and multivariate analysis of survival in NSCLC tissue samples

Variable	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	P	HR	95% CI	P
MCM 7						
High vs. low	1.973	1.387-2.793	0.000	1.916	1.364-2.658	0.000
Age						
>60 vs. ≤ 60	1.254	0.835-1.823	0.063			
Sex						
Male vs. female	1.537	1.025-2.083	0.031	1.772	1.188-2.482	0.004
Tumor type						
SCC vs. ADC	1.353	0.884-1.634	0.083			
Stage						
I~II vs. III~IV	2.546	1.712-3.669	0.000	1.682	0.932-2.503	0.018
Tumor differentiation						
Well vs. Moderate vs. poorly	1.284	1.004-1.733	0.012	1.094	0.834-1.476	0.430
Smoking history						
Non vs. current or former smoker	1.244	0.890-1.727	0.075			

Note: HR=Hazard Ratio.

瘤中高表达,且与预后有关。KIAA 蛋白是一种粘附连接蛋白,但目前对其研究较少,与恶性肿瘤发生发展的关系尚不明确,但在食管癌、乳腺癌和肺腺癌中呈现高表达状态^[28-31]。

本研究结果为:与癌旁正常肺组织相比,肺癌组织中 MCM2、MCM5、MCM6、MCM7、KIAA1522 和 KIAA0317 的阳性表达率明显较高,表明肺癌组织中以上蛋白呈现高表达,而在癌旁正常组织中低表达或者不表达。进一步分析中,不同性别、不同年龄、类型和分期的 NSCLC 患者的联合蛋白阳性率无统计学差异($P>0.05$),且蛋白阳性率均大于 80%,表明上述蛋白联合检测在不同性别,不同年龄,类型和分期的患者中均可获得较好的检测效果。此外分析患者 MCM7 的阳性表达与患者总生存和临床病理参数,显示 MCM7 的高表达和肺癌患者的不良预后显著相关,且较之年龄、性别、临床分期等病理参数,MCM7 依旧是一个独立的预测指标,表明 MCM7 可为患者的预后提供一定的预测作用。以往临床研究中,对 MCM 家族和 KIAA 家族联合检测在 NSCLC 中的表达情况中的相关研究较少,而本研究将以上两种蛋白家族联合检测,从而能够更好的对 NSCLC 患者的机体情况和病情进行了解,也为后续治疗及预后预测提供了更可靠的参考价值。

综上所述,NSCLC 患者肺癌组织中 MCM6、MCM7 和 KIAA1522 呈高表达,三者联合检测对 NSCLC 的检测具有较高的准确性、敏感性和特异性,高水平的 MCM7 表达提示肺癌患者的不良预后。

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