2026, 51(5) DOI:10.11817/j.issn.1672-7347.2026.250253

结直肠癌*KRAS*基因突变位点与临床特征的关系

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[摘 要] 目的：结直肠癌是全球高发消化道恶性肿瘤，*KRAS*基因突变是其重要的分子特征，但不同突变位点的临床意义差异尚未明确。本研究探讨*KRAS*基因特定突变位点的分布特征，分析其与结直肠癌患者临床病理参数、生存预后的关联，为精准分层诊疗提供依据。**方法：**回顾性纳入2018年5月至2020年1月于郑州大学附属肿瘤医院接受手术治疗的550例结直肠癌患者，均留存肿瘤组织标本。采用聚合酶链反应(polymerase chain reaction，PCR)对所有标本进行*KRAS*基因突变筛查，计算总体突变率；采用Illumina Nova测序平台对其中的210例标本行高通量测序，明确*KRAS*基因第2号外显子第12、13位密码子的具体突变类型。收集患者年龄、性别、肿瘤分期、淋巴结转移状态、原发灶直径等临床病理资料，并通过门诊复查、电话随访获取生存数据，随访截止时间为2023年12月29日。采用单因素及多因素Cox比例风险回归模型，筛选影响患者预后的独立危险因素，变量纳入标准为单因素分析$P<0.10$及临床公认的关键变量(如肿瘤分期、淋巴结转移)。**结果：**550例标本中，232例检出*KRAS*基因突变，总体突变率为42.18%。210例行高通量测序的标本中，155例检出突变，突变率为73.81%；共检出7种突变类型，其中G12D为最常见位点(19.52%)，其次为G12V(12.86%)、G13D(12.86%)、G12S(10.95%)、G12A(8.57%)、G12C(8.10%)、双突变(G12D+G12V、G12V+G13D，各占0.48%)。临床特征关联分析显示：G12D突变型患者初诊时淋巴结转移比例为73.17%(30/41)，显著高于野生型的38.18%(21/55；$P<0.05$)，而原发灶直径≥4 cm的比例(36.59%)与野生型(25.45%)比较，差异无统计学意义($P>0.05$)；G12A、G12C、G12S、G13D突变型患者原发灶直径≥4 cm的比例分别为66.67%、76.47%、78.26%、66.67%，均显著高于野生型(均$P<0.05$)，但淋巴结转移比例与野生型差异无统计学意义($P>0.05$)。Cox比例风险回归分析结果显示：肿瘤分期III~IV期(*HR*=1.820，95% *CI* 1.194~2.774，$P=0.005$)、G12C突变(*HR*=2.014，95% *CI* 1.321~3.069，$P=0.001$)、G12D突变(*HR*=1.857，95% *CI* 1.218~2.930，$P=0.004$)、G12V突变(*HR*=1.751，95% *CI* 1.149~2.669，$P=0.009$)是结直肠癌患者死亡的独立危险因素。**结论：***KRAS*基因不同突变位点与结直肠癌临床特征存在特异性关联：G12D突变与淋巴结高转移风险相关，G12A、G12C、G12S、G13D突变与原发灶体积增大相关。G12C、G12D、G12V突变是患者预后的独立危险因素，可作为风险分层与个体化治疗的潜在分子标志物。

[关键词] 结直肠癌；*KRAS*基因；突变位点；临床特征；高通量测序；G12D突变；预后；淋巴结转移

Relationship between *KRAS* gene mutation sites and clinical characteristics in colorectal cancer

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收稿日期(Date of reception)：2025-05-19
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基金项目(Foundation item)：新疆维吾尔自治区卫生健康委员会“天山英才”高层次医药卫生项目(TSYC202301B044)；河南省科技厅科技攻关项目(232102311140)。This work was supported by the High-level Medical and Health Project of “Tianshan Talents” by the Health Commission of the Xinjiang Uygur Autonomous Region (TSYC202301B044) and the Science and Technology Research Project of the Science and Technology Department of Henan Province (232102311140), China.
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ABSTRACT

Objective: Colorectal cancer is a common gastrointestinal malignancy worldwide. *KRAS* gene mutation is an important molecular feature of colorectal cancer, but the clinical significance of different mutation sites remains unclear. This study aims to investigate the distribution characteristics of specific *KRAS* gene mutation sites and analyze their associations with clinicopathological parameters and survival outcomes in patients with colorectal cancer, thereby providing a basis for precise stratified diagnosis and treatment.

Methods: A total of 550 patients with colorectal cancer who underwent surgical treatment at the Affiliated Cancer Hospital of Zhengzhou University from May 2018 to January 2020 were retrospectively included, and tumor tissue specimens were retained from all patients. Polymerase chain reaction (PCR) was first used to screen all specimens for *KRAS* gene mutations, and the overall mutation rate was calculated. High-throughput sequencing was then performed on 210 of these specimens using the Illumina Nova sequencing platform to determine the specific mutation types at codons 12 and 13 of exon 2 of the *KRAS* gene. Clinicopathological data, including age, sex, tumor stage, lymph node metastasis status, and primary lesion diameter, were collected. Survival data were obtained through outpatient follow-up and telephone follow-up, with the follow-up cutoff date of December 29, 2023. Univariate and multivariate Cox proportional hazards regression models were used to identify independent risk factors affecting prognosis. Variables were included based on a univariate analysis threshold of $P<0.10$ and clinically recognized key variables, such as tumor stage and lymph node metastasis.

Results: Among the 550 specimens, *KRAS* gene mutations were detected in 232 cases, with an overall mutation rate of 42.18%. Among the 210 specimens subjected to high-throughput sequencing, mutations were detected in 155 cases, with a mutation rate of 73.81%. Seven mutation types were identified. G12D was the most common mutation site (19.52%), followed by G12V (12.86%), G13D (12.86%), G12S (10.95%), G12A (8.57%), G12C (8.10%), and double mutations, including G12D+G12V and G12V+G13D, each accounting for 0.48%. Analysis of associations with clinical features showed that the proportion of patients with lymph node metastasis at initial diagnosis was 73.17% (30/41) among patients with the G12D mutation, which was significantly higher than that in patients with wild-type *KRAS* [38.18% (21/55), $P<0.05$]. However, the proportion of patients with a primary lesion diameter ≥4 cm was 36.59% in the G12D mutation group, which did not differ significantly from that in the wild-type group (25.45%, $P>0.05$). The proportions of patients with a primary lesion diameter ≥4 cm were 66.67%, 76.47%, 78.26%, and 66.67% among patients with G12A, G12C, G12S, and G13D mutations, respectively, all of which were significantly higher than that in the wild-type group (all $P<0.05$). However, the proportions of lymph node metastasis in these mutation groups did not

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differ significantly from that in the wild-type group (*P*>0.05). Cox proportional hazards regression analysis demonstrated that tumor stage III－IV (*HR*=1.820, 95% *CI* 1.194 to 2.774, *P*=0.005), G12C mutation (*HR*=2.014, 95% *CI* 1.321 to 3.069, *P*=0.001), G12D mutation (*HR*=1.857, 95% *CI* 1.218 to 2.930, *P*=0.004), and G12V mutation (*HR*=1.751, 95% *CI* 1.149 to 2.669, *P*=0.009) were independent risk factors for death in patients with colorectal cancer.

Conclusion: Different *KRAS* gene mutation sites are specifically associated with clinical features of colorectal cancer. The G12D mutation is associated with a high risk of lymph node metastasis, whereas G12A, G12C, G12S, and G13D mutations are associated with increased primary tumor size. G12C, G12D, and G12V mutations are independent prognostic risk factors and may serve as potential molecular markers for risk stratification and individualized treatment.

KEY WORDS colorectal cancer; *KRAS* gene; mutation site; clinical feature; high-throughput sequencing; G12D mutation; prognosis; lymph node metastasis

结直肠癌是全球范围内常见的消化道恶性肿瘤，位居世界癌症发病率第三，癌症相关死亡率第二[1]，对医疗健康领域构成重大挑战[2]。结直肠癌的发生和发展与多种因素有关，其中遗传和环境因素尤为显著，而基因突变在疾病病程中起关键作用[3]。*KRAS*基因是人类癌症最常见的致癌基因之一，其编码的小GTP酶参与多个细胞信号转导通路，影响细胞增殖、分化、迁移和凋亡等生物学过程[4]。当*KRAS*基因突变时，所编码的蛋白质可能持续激活，从而干扰正常的生物学过程[5]。既往研究[6]表明，30%~40%的结直肠癌患者存在*KRAS*基因突变，该突变与结直肠癌的临床病理特征具有一定的相关性，并与发病机制、预后及治疗效果密切相关。虽然已有研究探讨了*KRAS*突变在结直肠癌患者中的临床特性和预后价值，但具体突变位点的分布比例及其与临床特征和预后之间的关系亟待深入研究。因此，本研究通过分析结直肠癌患者的测序结果，探讨基因突变位点与临床特征及预后的关系。

1 资料与方法

1.1 伦理声明

本研究已获得郑州大学附属肿瘤医院伦理委员会批准(审批号：2022-213-005)。所有参与者均签署了知情同意书。

1.2 一般资料

本研究回顾性分析2018年5月至2020年1月在郑州大学附属肿瘤医院接受手术治疗的550例结直肠癌患者的临床资料。其中男283例，女267例，年龄为46~75(58.91±7.16)岁。纳入标准：1)符合《中国结直肠癌肝转移诊断和综合治疗指南(2023版)》[7]诊断标准；2)所有肿瘤组织进行了*KRAS*基因检测；3)临床及随访资料完整。排除标准：1)合并其他恶性肿瘤；2)肠道炎性疾病；3)严重的脏器功能衰竭；4)处于哺乳或妊娠期的女性。

1.3 *KRAS*基因突变检测方法

1.3.1 *KRAS*基因提取

使用QIAamp®DNA微量核酸提取试剂盒和QIAamp DNA甲醛固定石蜡包埋组织试剂盒，从冷冻组织和甲醛固定石蜡包埋样本中提取DNA。然后通过NanoDrop 2000分光光度计和Qubit量子荧光计测定提取的DNA浓度。使用安捷伦2100生物分析仪和高灵敏度DNA试剂测量DNA的完整性。在质量控制步骤中，采用多重聚合酶链反应(polymerase chain reaction，PCR)评估甲醛固定石蜡包埋DNA的完整性。

1.3.2 *KRAS*靶向基因测序

使用*KRAS*基因检测试剂盒(北京雅康博生物科技有限公司，国械注准：20213401103)进行基因突变检测，该试剂盒可检测*KRAS*基因第2号外显子第12、13位密码子的常见突变类型，包括G12A、G12C、G12D、G12S、G12V、G13D等。实验过程严格遵循说明书进行。然而，由于PCR方法无法明确区分*KRAS*的具体突变位点，本研究选取210例样本进行二代测序(next-generation sequencing，NGS)分析。取5 μL DNA样品依次加入PCR反应条中，进行

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末端修复、加A拖尾和接头连接，然后使用xGen锁定探针池捕获NGS文库。通过12~13个PCR循环扩增捕获的DNA片段，循环参数设置为：预变性2 min，93 ℃；变性60 s，93 ℃；退火60 s，55 ℃；延伸60 s，72 ℃，并使用1×KAPA HiFi热启动Ready Mix试剂(美国赛默飞世尔科技公司产品)进行后续处理。扩增产物采用Rotor-Gene Q系统进行分析，根据荧光信号变化和扩增曲线确定产物中是否存在*KRAS*基因突变，将发生*KRAS*基因突变的产物录入文库。采用Illumina Nova测序仪以双端各测150 bp对文库产物进行测序。甲醛固定石蜡包埋样本采用超过3 000×的平均覆盖率测序，而配对样本则采用超过200×的平均覆盖率测序，详实记录数据。

1.4 随访

患者出院后通过门诊复查或电话访问的方式进行随访，以记录患者的生存结局。随访时间截至2023年12月29日，其间所有患者均未失访。

1.5 统计学处理

采用SPSS 25.0统计学软件进行数据分析。计量资料以均数±标准差($\bar{x}\pm s$)表示，比较采用t检验；计数资料以频数(构成比)表示，比较采用χ^2检验。通过Cox比例风险回归模型进行单因素与多因素分析，以探讨影响结直肠癌患者预后的危险因素。多因素分析模型的变量纳入标准为单因素分析中P<0.10的变量及临床公认的重要变量(如肿瘤分期、淋巴结转移等)。P<0.05为差异具有统计学意义。

2 结 果

2.1 结直肠癌患者*KRAS*基因突变位点分布

对550例结直肠癌样本进行PCR检测，发现232例存在*KRAS*基因突变，总体突变率为42.18%。由于PCR方法无法精确区分*KRAS*基因的具体突变位点，本研究从中选取了210例样本进行NGS，共发现155例存在*KRAS*基因突变，突变率为73.81%，具体突变位点分布如表1所示。其中，G12D位点突变的频率最高，占所有测序样本的19.52%(41/210)；其次为G12V(12.86%)、G13D(12.86%)、G12S(10.95%)、G12A(8.57%)、G12C(8.10%)、G12D+G12V双突变(0.48%)和G12V+G13D双突变(0.48%)。

表1 结直肠癌基因突变位点与临床特征的关系

Table 1 Relationship of *KRAS* gene mutation sites and clinical characteristics in colorectal cancer

临床特征	G12A/[例(%)] (n=18)	G12C/[例(%)] (n=17)	G12D/[例(%)] (n=41)	G12S/[例(%)] (n=23)	G12V/[例(%)] (n=27)	G13D/[例(%)] (n=27)	野生型/[例(%)] (n=55)	χ^2	P
年龄/岁								5.968	0.427
≥60	13(72.22)	7(41.18)	24(58.54)	12(52.17)	17(62.96)	16(57.14)	26(47.27)		
<60	5(27.78)	10(58.82)	17(41.46)	11(47.83)	10(37.04)	11(42.86)	29(52.73)		
性别								4.074	0.667
男	9(50.00)	9(52.94)	23(56.10)	15(65.22)	12(44.44)	14(53.57)	35(63.64)		
女	9(50.00)	8(47.06)	18(43.90)	8(34.78)	15(55.56)	13(46.43)	20(36.36)		
肿瘤分期								8.136	0.228
I+II	7(38.89)	7(41.18)	27(65.85)	13(56.52)	16(59.26)	11(40.74)	33(60.00)		
III+IV	11(61.11)	10(58.82)	14(34.15)	10(43.48)	11(40.74)	16(59.26)	22(40.00)		
病理类型								1.681	0.959
腺癌	15(83.33)	14(82.35)	36(87.80)	19(82.61)	21(77.78)	22(81.48)	44(80.00)		
鳞癌	3(16.67)	3(17.65)	5(12.20)	4(17.39)	6(22.22)	5(18.52)	11(20.00)		
淋巴结转移								18.717	0.005
是	8(44.44)	7(41.18)	30(73.17)	8(34.78)	15(55.56)	8(29.63)	21(38.18)		
否	10(55.56)	10(58.82)	11(26.83)	15(65.22)	12(44.44)	19(70.37)	34(61.82)		
肿瘤直径/cm								29.105	<0.001
≥4	12(66.67)	13(76.47)	15(36.59)	18(78.26)	10(37.04)	18(66.67)	14(25.45)		
<4	6(33.33)	4(23.53)	26(63.41)	5(21.74)	17(62.96)	9(33.33)	41(74.55)		

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2.2 结直肠癌基因突变位点与临床特征的关系

由于G12V+G12D、G13D+G12V双突变患者各仅有1例，因此在后续分析中将双突变患者排除在外。分析结果表明，G12D突变型患者淋巴结转移占比显著高于野生型(P<0.05)，而原发灶直径≥4 cm的比例与野生型比较，差异无统计学意义(P>0.05)；G12A、G12C、G12S、G13D突变型患者原发灶直径≥4 cm的比例，均显著高于野生型(均P<0.05，表1)。

2.3 结直肠癌患者预后的Cox比例风险回归分析

以患者预后生存情况(死亡=1，生存=0)为因变量，年龄、性别、肿瘤分期、病理类型、淋巴结转移、肿瘤直径、G12A突变、G12C突变、G12D突变、G12S突变、G12V突变、G13D突变为自变量进行单因素及多因素Cox比例风险回归分析。单因素分析结果表明，患者死亡风险与肿瘤分期、淋巴结转移、G12C突变、G12D突变、G12V突变、G13D突变均显著相关(均P<0.05)；多因素分析进一步揭示，肿瘤分期III~IV期(*HR*=1.820，95% *CI* 1.194~2.774，P=0.005)、G12C突变(*HR*=2.014，95% *CI* 1.321~3.069，P=0.001)、G12D突变(*HR*=1.857，95% *CI* 1.218~2.930，P=0.004)、G12V突变(*HR*=1.751，95% *CI* 1.149~2.669，P=0.009)均是结直肠癌患者死亡的危险因素(表2)。

表2　结直肠癌患者预后的Cox比例风险回归分析

Table 2　Cox proportional hazards regression analysis of prognosis in patients with colorectal cancer

变量	单因素分析			多因素分析		
	HR	95% *CI*	*P*	*HR*	95% *CI*	*P*
年龄	1.043	0.689~1.571	0.848			
性别	1.121	0.604~2.078	0.717			
肿瘤分期(I~II为参照)	1.502	1.117~2.019	0.007	1.820	1.194~2.774	0.005
病理类型	0.963	0.757~1.226	0.759			
淋巴结转移	1.216	1.003~1.474	0.046	1.105	0.780~1.527	0.545
肿瘤直径	1.351	0.894~2.043	0.154			
G12A突变	1.098	0.817~1.476	0.536			
G12C突变	1.539	1.236~1.887	<0.001	2.014	1.321~3.069	0.001
G12D突变	1.485	1.067~2.066	0.019	1.857	1.218~2.930	0.004
G12S突变	1.068	0.773~1.476	0.690			
G12V突变	1.476	1.164~1.871	0.001	1.751	1.149~2.669	0.009
G13D突变	1.275	1.028~1.582	0.027	1.006	0.886~1.143	0.927

3 讨　论

结直肠癌在全球范围内是第三常见的癌症，其中约40%的患者存在特定的基因突变[8]。近年来，随着精准医学的发展，靶向治疗已经成为结直肠癌个体化治疗和综合治疗方案的重要组成部分[9-10]。这些靶向药物针对肿瘤细胞中的特定基因突变，如*KRAS*或*BRAF*突变[11]，从而提升治疗的精确性，并为患者带来更高的治愈率和生存希望[12]。其中，*KRAS*基因在大鼠肉瘤病毒癌基因同源物(rat sarcoma virus oncogene homolog，RAS)家族中尤为突出[13]，是人类多种癌症中频繁出现的变异基因[14]。在癌症基因组图谱(The Cancer Genome Atlas，TCGA)结直肠癌队列中，*KRAS*基因的突变比例为35%~45%，其中G12D突变也是最常见的突变亚型，这与本研究报道的42.18%的总突变率及G12D为最常见位点(19.52%)的结果高度一致。*KRAS*基因负责编码一种小GTP酶，这种酶在细胞信号转导，尤其是在表皮生长因子受体信号转导途径中起关键作用[15]。当*KRAS*基因发生突变时，所编码的蛋白质可能持续处于激活状态，引发细胞不受控制的增殖，最终形成并促进肿瘤的发展[16]。在结直肠癌中，*KRAS*基因的突变不仅常见，而且已被证实对肿瘤的预后、治疗反应性及疾病进展均有显著的影响[17]。

本研究数据显示，G12D突变型患者的淋巴结转移比例高达73.17%(30/41)，显著高于野生型的38.18%(21/55)。这提示G12D突变可能与肿瘤更强的局部侵袭和淋巴结播散能力相关。其潜在机制为，

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G12D突变导致KRAS蛋白持续激活，可能通过异常增强丝裂原活化蛋白激酶(mitogen-activated protein kinase，MAPK)、磷脂酰肌醇3激酶/蛋白激酶B(phosphoinositide 3-kinase/protein kinase B，PI3K/Akt)等下游信号通路活性，促进上皮-间充质转化和细胞迁移，最终增加淋巴结转移的风险[18]。本研究发现G12A、G12C、G12S、G13D突变型患者中，肿瘤直径≥4 cm的比例均显著高于野生型患者。这表明这些位点的突变可能直接驱动了肿瘤细胞的增殖，导致原发灶在诊断时体积较大。其生物学基础可能是这些突变体对生长因子信号通路的反应性不同，或影响了细胞周期调控，从而表现为更快的肿瘤生长速率[19]。

本研究多因素Cox比例风险回归分析的结果提示，肿瘤分期及*KRAS*基因的G12C、G12D和G12V突变位点显著增加了结直肠癌患者的死亡风险($P<0.05$)，表明*KRAS*突变与肿瘤的侵袭性和治疗抗性密切相关。这些突变位点可能通过改变细胞信号转导途径来帮助癌细胞抵御细胞死亡和促进细胞增殖。因此，这些特定突变位点的存在显著提高了治疗失败的风险，从而恶化了疾病的预后[20]。Arena等[21]的研究也指出，携带*KRAS*基因突变位点的结直肠癌患者往往具有较差的预后。临床实践中，为携带高危G12C、G12D、G12V突变的患者制订个性化的治疗方案是十分必要的。

综上，结直肠癌的*KRAS*基因突变位点(G12D、G12A、G12C、G12S、G13D)与多种临床因素紧密相关，其中G12C、G12D、G12V突变显著提高了患者的死亡风险。然而，本研究也存在一定的局限性，如仅对550例患者中的210例进行了基因测序，可能存在选择偏倚。未来的研究需要扩大样本量，并对分子机制进行更深入的探讨。

作者贡献声明：马怡晨　研究设计，论文撰写与修改；赵九洲　数据采集；付强、马东阳　数据分析；艾克热木·玉苏甫、刘晓莉　研究设计，论文指导与审阅。所有作者阅读并同意最终的文本。

利益冲突声明：作者声称无任何利益冲突。

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