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THE EFFECT OF PRIMARY LOCALIZATION OF COLORECTAL CANCER ON KRAS STATUS AND ITS PROGNOSTIC VALUE

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ABSTRACT

Relevance: *Colorectal cancer (CRC), arising from the right-sided or left-sided colon, is a separate clinical and pathological unit. The status of KRAS and its predictive value in CRC remain controversial.*

The study aimed to *explore the effect of primary tumor localization on KRAS gene status in CRC.*

Methods: *The study included 60 patients with colon and rectal cancer. The KRAS mutation test was performed on paraffin-coated tumor samples using PCR methods. Colon cancer was divided into right-sided colon cancer (RSCC) and left-sided colon cancer (LSCC).*

Results: *KRAS mutation was found much more often in rectal cancer (RC) and sigmoid colon (SC) (p=0.413) than in tumors in other parts of the colon. A combined analysis of our data and previously published data showed that KRAS mutation was more common in PSTC, especially in the area of the hepatic bend of the colon than in LSTC (p=0.120). The association of the KRAS mutation with the patient's age (p<0.012) and the duration of hospitalization (p<0.001) was established.*

Conclusion: *Our study revealed no significant difference in the KRAS status between colon cancer and rectal cancer. However, KRAS mutation was much more common in RSCC compared to LSCC. Patients with RSCC with mutated KRAS also had a worse prognosis and required longer hospitalization compared to wild-type KRAS. However, patients with LSCC did not demonstrate a similar effect.*

Keywords: *colon cancer, rectal cancer, sigmoid cancer, KRAS mutation.*

Introduction: Colorectal cancer (CRC) is the third most common malignancy worldwide. It accounts for approximately 9.6% of all new cancer cases and has a mortality rate of 6% [1]. The 5-year survival rate for CRC is 65.0% according to the National Institute of Oncology (Bethesda, USA) [2]. CRC can be divided into colon cancer, sigmoid colon cancer, and rectal cancer by the location of the primary tumor. Colon cancer can be further classified into right-sided colon cancer (RSCC) and left-sided colon cancer (LSCC), cancer of the splenic and hepatic bend of the colon, and cancer of the rectosigmoid junction. In recent years, there is increasing evidence that there are significant differences between RSCC and LSCC with respect to clinical findings, pathology, genetic mutations, and survival time [3]. Thus, tumor location is an important factor that affects the prognosis of CRC.

The RAS gene family is one of the most studied and best characterized of the known cancer-related genes. Of the three human RAS isoforms, KRAS is the most frequently altered gene, with mutations occurring in 17-25% of all cancers. KRAS mutations are among the most dominant mutations and account for 7% to 80% in CRC, 25% to 87% in pancreatic cancer, and 25% to 48% in lung cancer [4]. KRAS encodes a GTPase binding protein and plays an important role in activation of the epidermal growth factor receptor (EGFR).

CRC represents an excellent system and a suitable model for investigating both the carcinogenesis process and the molecular mechanisms underlying tumor development. It results from the accumulation of alterations in genes that regulate the processes of epithelial development and cell differentiation. A study using this model allows the collection of basic information from the formation of one or more adenomas to their possible transformation into metastatic cancer [5]. Therefore, *KRAS* status is used as an important biological marker to select suitable patients. To date, many studies have reported the clinicopathological features of CRC, and some studies have also analyzed the *KRAS* status in RSCC and LSCC. However, the results of the *KRAS* status in RSCC and LSCC remain controversial [6-8]. This article reports the authors' findings of clinicopathological findings and *KRAS* status in patients with CRC after surgical treatment, and compares *KRAS* status in RSCC and LSCC.

The study aimed to explore the effect of primary tumor localization on KRAS gene status in CRC.

Materials and Methods:

Patients

This retrospective study included patients with confirmed diagnosis of CRC, who received surgical treatment in the Municipal State Enterprise on the Right of Economic Management 'Multidisciplinary Medical Center' of Astana city from May 2022 to December 2022. Inclusion criteria were as follows: CRC confirmed by histological examination of postoperative material. Patients with unknown *KRAS* status or who received anti-EGFR agents in the preoperative period were excluded.

Detailed information on the patients' age, sex, histological differentiation, primary tumor location, tumor infiltration, nodal status, distant metastases, primary tumor stage according to the American Joint Committee on Can-

cer (AJCC) classification, length of hospitalization, and survival was collected. The location of the primary tumor was determined on the basis of pathological, endoscopic, and operative findings.

This study was approved by the Local Ethical Committee of the "Astana Medical University" NCJSC, Decision of the Local Bioethics Commission of NJSC AMU No. 2 dated 23.02.2022. Each patient was familiarized with the purpose and objectives of the study and signed a written informed consent to participate in the study.

KRAS Mutational Analysis and Sequencing

Mutations in *KRAS* 12 and 13 codons in exon 2 were detected using amplification resistant mutation system (ARMS) PCR techniques. Blood samples, resected tissue samples frozen in liquid nitrogen, and formalin-fixed and paraffin-embedded (FFPE) samples of the removed tumor were collected from each patient. The study was carried out at the "National Laboratory Astana" Private Institution following the protocol of Nazarbayev University JSC, IREC No. 03-2021 dated 21.04.2021.

Statistical analysis

Demographic and clinicopathological characteristics of the patients were stratified according to the location of the primary tumor and the status of the *KRAS* mutation. Continuous variables were presented as mean ± standard deviation and compared using the Student's t test. Summary statistics for patients were presented as sums of categorical variables. The differences between wild-type *KRAS* (*KRAS WT*) and mutant *KRAS* (*KRAS MT*) in each group were evaluated using the χ2 test. Analyses were performed using the Jamovi software ver. 2.3.

Results:

Clinical and Epidemiological Characteristics of Patients with CRC

This study included 60 patients with CRC, of them 32 females and 28 males. The mean age of the patients was 68±11 years. The mean duration of hospitalization was 14 days. The details of the included CRR patients are summarized in Tables 1 and 2.

Table 1 – Descriptive Characterization of Quantitative Measurements of Patients with CRC

Parameters	M	95% CI/Q_1-Q_3	n	min	max
Age, M±SD	68±11	65-71	60	44	85
Duration of hospitalization, months	14	9-22	60	4	33
Recurrence-free survival (days), months	254	177-773	60	10	917
Life expectancy, months	298	204-790	60	10	1117

Table 2 – Descriptive statistics of categorical indicators of CRC patients

Parameters	Categories	Abs.	%	95% CI
Sex	F	32	53.3	40.0-66.3
	M	28	46.7	33.7-60.0
Localization	C-r of hepatic bend of the colon	10	16.7	8.3-28.5
	C-r of rectum	18	30.0	18.8-43.2
	C-r splenic angle of the large intestine	3	5.0	1.0-13.9
	C-r of the sigmoid colon	17	28.3	17.5-41.4
	C-r of the ascending colon	11	18.3	9.5-30.4
	C-r of rectosigmoid junction	1	1.7	0.0-8.9
Stage	I	6	10.0	3.8-20.5
	II	24	40.0	27.6-53.5
	III	20	33.3	21.7-46.7
	IV	10	16.7	8.3-28.5
Localization of metastases	0	50	83.3	71.5-91.7
	Lung	2	3.3	0.4-11.5
	Liver	8	13.3	5.9-24.6
Surgery	Abdominoperineal resection	4	6.7	1.8-16.2
	Laparoscopic right-sided hemicolectomy	1	1.7	0.0-8.9
	Laparoscopic resection	5	8.3	2.8-18.4
	Left hemicolectomy	2	3.3	0.4-11.5
	Hartmann operation	6	10.0	3.8-20.5
	Anterior resection	15	25.0	14.7-37.9
	Right hemicolectomy	23	38.3	26.1-51.8
	Transanal endorectal descending procto-plasty	2	3.3	0.4-11.5
	Transvers ostomy	2	3.3	0.4-11.5
Postoperative complications	Abscess of the anterior abdominal wall	2	3.3	0.4-11.5
	Respiratory failure	2	3.3	0.4-11.5
	Ileotransverse anastomosis failure, perito-nitis	2	3.3	0.4-11.5
	Anastomosis failure	2	3.3	0.4-11.5
	none	46	76.7	64.0-86.6

End of Table 2

	Peritonitis	2	3.3	0.4-11.5
	Scarry stricture of the anastomosis	2	3.3	0.4-11.5
	Small intestinal fistula	2	3.3	0.4-11.5
Histological differentiation	Highly differentiated adenocarcinoma	6	10.0	3.8-20.5
	Low differentiated adenocarcinoma	6	10.0	3.8-20.5
	Low-differentiated neuroendocrine carcinoma	2	3.3	0.4-11.5
	Moderately differentiated adenocarcinoma	46	76.7	64.0-86.6
WT	*KRAS WT,* no mutation detected	51	85.0	73.4-92.9
	KRAS WT, mutation detected	9	15.0	7.1-26.6
Regime	0	28	46.7	33.7-60.0
	FOLFIRI	2	3.3	0.4-11.5
	FOLFOX	10	16.7	8.3-28.5
	FOLFOX+FOLFIRI	4	6.7	1.8-16.2
	FOLFOXIRI	16	26.7	16.1-39.7

Clinicopathological characteristics of CRC with different KRAS statuses

51/60 patients with colon cancer had mutated *KRAS,* and the remaining 9 had wild-type *KRAS genes* (*KRAS WT).* Separation of study participants according to *KRAS* status did not show clear differences in primary tumor location (p=0.413). However, a significant difference was found between RSCC and LSCC with respect to sex (p=0.014). Therefore, in women, the tumor was more often located in the rectum and ascending colon, while in men it was located in the sigmoid colon and the hepatic bend of the colon. In terms of *KRAS* status, the tumor was most commonly localized in the hepatic flexure of the colon (30.6%), ascending colon (25%), and sigmoid colon (19.4%) (Figure 1). Therefore, patients with tumors in the hepatic bend of the colon had a median age of 60 years (Q_1-Q_3, 57-63) and patients with tumors in the ascending colon had a median age of 74 years (Q_1-Q_3, 70-77) (Table 3).

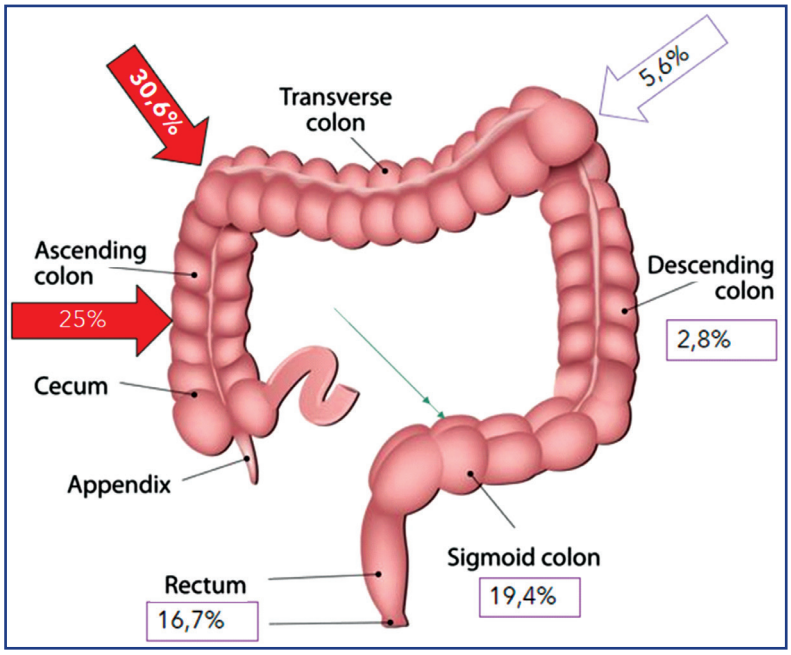

Figure 1 - Localization of tumors with *KRAS* mutation in the colon and rectum

Table 3 – Association between age and tumor localization indices in CRC

Localization	Возраст			*p*
	Me	Q_1-Q_3	n	
C-r of hepatic bend of the colon	60	57-63	10	0,014* $p_{\text{C-r of the ascending colon-C-r of hepatic bend of the colon}} = 0,021$
C-r of rectum	68	62-76	18	
C-r splenic angle of the large intestine	49	49-62	3	
C-r of the sigmoid co-lon	74	67-76	17	
C-r of the ascending colon	74	70-77	11	
C-r of rectosigmoid junction	63	63-63	1	

*Note: * differences in parameters were statistically significant (p < 0.05)*

Discussion: In this study that analyzed the clinicopathological characteristics of 60 cases of colorectal, sigmoid colon, and rectal cancer, the authors found no significant difference in relation to *the status of KRAS*. However, associative relationships were found between KRAS status and the clinicopathological characteristics of CRC. Therefore, the KRAS mutation in exon 2, codons 12 and 13 appeared to be more characteristic of men (66.7%, p<0.001). In women, wild-type KRAS was detected more frequently (33.3%). Furthermore, the presence of the KRAS mutation was associated with age. Thus, it was characterized by a mean age of 72 years, compared to 62 years for the wild type (p=0.005). The positive status of KRAS was also more frequent in patients with stage II and III cancer (p=0.012).

By dividing CRC cases according to the KRAS status, we found that RSCC was more associated with KRAS mutations than LSCC, 55.6%, compared to 27.8% of sigmoid colon cancers and 16.7% of rectal cancers. We see that the KRAS mutation is characteristic of RSCC by comparing data from our study with 18 studies found in scientific databases. Furthermore, we found an obvious difference in overall survival (OS) and hospitalization duration in RSCC and LSCC with respect to KRAS status by combining the data from the studies. That is, patients with RSCC with the KRAS mutation have a shorter OS and a longer hospitalization time (22 months) than those with wild-type KRAS, whereas patients with LSCC with the KRAS mutation do not have significant differences in OS compared to those with wild-type KRAS. These results indicated that both tumor location and KRAS status play an important role in the prognosis of the course of CRC.

Studies have shown that the right and left colons have different embryological origins, so tumors that arise from different parts of the colon have different molecular carcinogenic properties, including KRAS mutations, BRAF mutations, and microsatellite instability [9-11]. KRAS has been confirmed to be a proto-oncogene that induces oncogenesis in some cancers. In CRC, the status of the KRAS mutation and the location of the tumor are associated with the efficacy of targeted therapy. In this study, the KRAS status did not have an obvious difference in colon cancer or rectal cancer, but showed a significant difference in RSCC and LSCC, which was consistent with the findings of Natsume et al. [8] and Tong et al. [12], but differed from the data of Cushman-Vokoun et al. [7].

Since the anti-EGFR therapy effect on CRC is related to the KRAS status, many studies evaluating the prognostic value of the KRAS status in patients with CRC observed the association between the KRAS mutation and a poor prognosis for CRC [6, 7, 13, 14]. The differences in genetic mutations between RSCC and LSCC allow to assume the prognostic value of tumor location and KRAS status in CRC.

Conclusion: Our study demonstrated that there were no significant differences in KRAS status between colon cancer and rectal cancer. However, the KRAS mutation was much more common in RSCC compared to LSCC. Furthermore, patients with RSCC with mutated KRAS had a worse prognosis compared to wild-type KRAS, but no similar effect was observed in LSCC.

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АҢДАТПА

КОЛОРЕКТАЛЬДЫ ҚАТЕРЛІ ІСІКТІҢ БАСТАПҚЫ ЛОКАЛИЗАЦИЯСЫНЫҢ KRAS МӘРТЕБЕСІНЕ ЖӘНЕ ОНЫҢ БОЛЖАМДЫҚ МӘНІНЕ ӘСЕРІ

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Өзектілігі: *Асқазанның Өзектілігі: Тоқ ішектің оң және сол жақ бөлімдерінде дамитын қатерлі ісік жеке клиникалық-патологиялық бірлік болып саналады. Kras мәртебесі және оның колоректалды қатерлі ісік кезіндегі болжамдық маңызы түбегейлі анықталмаған болып отыр.*

Зерттеудің мақсаты: *ісіктің бастапқы орналасуының CRR-дегі KRAS генінің күйіне әсерін зерттеу.*
Әдістері: *Зерттеуге тоқ ішек және тік ішек қатерлі ісігімен ауыратын 60 науқас қатысты. KRAS мутация сынағы ПТР әдістерін қолдана отырып, парафинге құйылған ісік үлгілерінде жүргізілді. Тоқ ішек қатерлі ісігі тоқ ішектің оң жақ қатерлі ісігі және сол жақ ішек қатерлі ісігі болып бөлінді.*
Нәтижелері: *KRAS мәртебесіне қатысты тоқ ішек қатерлі ісігі мен тік ішек қатерлі ісігінің арасында айтарлықтай айырмашылық жоқ. KRAS мутациясы тік ішектің және сигма тәрізді ішектің қатерлі ісігінде жиі кездесетіні анықталды (p=0,413). Біздің деректеріміздің және алдыңғы жарияланған деректердің біріктірілген нәтижелері KRAS мутациясы сол жақ тоқ ішек қатерлі ісігіне қарағанда оң жақ тоқ ішек қатерлі ісігінде, әсіресе бауыр иілімі аймағында орналасуы бойынша жиі кездесетінін көрсетті (p=0,120). KRAS мутациясы науқастың жасына (p<0,012) және ауруханаға жатқызу ұзақтығына (p<0,001) байланысы анықталды.*
Қорытынды: *Біздің зерттеуіміз тоқ ішек және тік ішек қатерлі ісігі арасындағы KRAS мәртебесінде айтарлықтай айырмашылықтың жоқтығын көрсетті. Алайда, KRAS мутациясы қатерлі ісіктің оң жақпен салыстырғанда сол жақ тоқ ішекте әлдеқайда жиі кездеседі. Бұл жағдайда KRAS мутациясы бар оң жақ тоқ ішек қатерлі ісігі кезінде науқастардың өмір сүру ұзақтығы және ауруханада болу ұзақтығы жағынан жабайы типтегі KRAS-пен салыстырғанда нашар болжамға ие болды, бірақ сол жақ тоқ ішектің қатерлі ісігі кезінде мұндай әсер байқалмады.*
Түйінді сөздер: *Тоқ ішек қатерлі ісігі, тік ішек қатерлі ісігі, сигма тәрізді ішектің қатерлі ісігі, KRAS мутация.*

АННОТАЦИЯ

ВЛИЯНИЕ ПЕРВИЧНОЙ ЛОКАЛИЗАЦИИ КОЛОРЕКТАЛЬНОГО РАКА НА СТАТУС *KRAS* И ЕГО ПРОГНОСТИЧЕСКОЕ ЗНАЧЕНИЕ

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Актуальность: *Колоректальный рак (КРР), возникающий из правосторонней или левосторонней ободочной кишки, представляет собой отдельную клинико-патологическую единицу. Статус KRAS и его прогностическая ценность при КРР остаются спорными.*
Цель исследования *– изучение влияния первичной локализации опухоли на статус гена KRAS при КРР.*
Методы: *В исследование были включены 60 больных раком толстой кишки и прямой кишки. Тест на мутацию KRAS проводился на образцах опухолей, залитых в парафин, с использованием методов ПЦР. Рак толстой кишки делили на рак правой стороны толстой кишки (ПСТК) и рак левосторонней толстой кишки (ЛСТК). Проведен анализ исследований, в которых сообщалось о связи мутации KRAS с клиническими особенностями и прогнозом КРР.*
Результаты: *Мутация KRAS встречалась гораздо чаще при раке прямой кишки (РПК) и сигмовидной кишки (РСК) (p=0,413), чем при опухолях в других отделах ободочной кишки. Объединенный анализ наших данных и предыдущих опубликованных данных показал, что мутация KRAS чаще встречалась при ПСТК, в особенности в области печеночного изгиба толстой кишки, чем при ЛСТК (p=0,120). Установлена связь наличия мутации KRAS с возрастом пациента (p<0,012) и длительностью госпитализации (p<0,001).*
Заключение: *Наше исследование продемонстрировало отсутствие существенной разницы в статусе KRAS между раком толстой кишки и раком прямой кишки. Однако мутация KRAS встречалась гораздо чаще при ПСТК по сравнению с ЛСТК. При этом пациенты ПСТК с мутацией KRAS имели плохой прогноз общей выживаемости и увеличение длительности госпитализации по сравнению с KRAS дикого типа, но у пациентов с ЛСТК не наблюдалось аналогичного эффекта.*
Ключевые слова: *рак толстой кишки, рак прямой кишки, рак сигмовидной кишки, KRAS мутация.*

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