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Molecular-Genetic Status of Colorectal Cancer

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Abstract This study was conducted on the basis of the Department of Coloproctology of the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology in Tashkent. The study included 78 patients with colorectal cancer (CRC) of stage II-IV of the disease who underwent surgical treatment in the department of Coloproctology of the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology. Performing cytoreductive surgery on patients with colorectal cancer with liver metastases may help improve the quality of life of these patients in the long term.

Keywords Colorectal cancer, Metastases, Cytoreductive surgery, Polychemotherapy

1. Introduction

In the Republic of Uzbekistan, according to official statistics, 1,818 patients with colorectal cancer were identified in 2022, of which 290 patients (16.0%) were diagnosed with stage IV of the disease. 936 patients died from colorectal cancer in the country. The ratio of deaths to patients remains high, reflecting the effectiveness of ongoing anti-cancer measures, including diagnostic and treatment measures, at 51.5% in 2022 [3,7].

Surgical treatment, as an independent method, is effective for colon cancer in stages I-II. In colon cancer of the I stage of the disease, the effectiveness of surgical intervention as an independent treatment method has been proven, in other cases - a preoperative course of radiation therapy is necessary. Approximately 25-40% of patients who received CRP treatment according to the radical program (stages I-II) develop disease recurrence or develop distant metastases [2]. Distant metastases, among patients with stage III of the disease, appear in almost 35% of cases after potentially radical treatment. In this case, the progression of the disease is due to the activation of tumor cells that migrated from the primary tumor site before surgery. To address this issue, adjuvant chemotherapy is prescribed worldwide [4,5,6].

Thus, the increase in CRP morbidity worldwide, including in the Republic of Uzbekistan, and the high frequency of disease progression after treatment determine the relevance of this issue for the oncological service. Studying and identifying prognostic factors that influence long-term treatment outcomes will allow for individualized treatment of patients.

Purpose of the research. Improvement of a multidisciplinary approach to the timely diagnosis of metastatic colorectal cancer.

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2. Material and Methods

This study was conducted on the basis of the coloproctology department of the Republican Specialized Medical Scientific and Practical Center of Oncology and Radiology in Tashkent.

The retrospective group included data on 360 patients with stage II-IV colorectal cancer who received surgical treatment in the coloproctology department of the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology (RSMPMCOR). The study did not include patients with primary multiple synchronous/metachronous malignant neoplasms, patients receiving surgical treatment for colorectal malformation in other medical institutions of the Republic of Uzbekistan.

The diagnosis was made based on complaints, medical history, physical examination, morphological examination of tumor material, and data from instrumental and laboratory examination methods. Patients received adjuvant/non-adjuvant treatment in accordance with the current algorithms for the diagnosis and treatment of colorectal cancer patients, approved by the Ministry of Health of the Republic of Uzbekistan. The study material was: patients' peripheral blood, paraffin blocks of tumor tissue, fresh frozen tumor and normal colon tissue, isolated circulating tumor cells.

The prospective group included data from 78 patients with metastatic colorectal cancer II-IV.

The material for the study was fixed with 10% neutral formalin for 24 hours, poured into paraffin, and 3-4 μm thick sections were prepared on an Accu-Cut SRM 200 rotary microtome from the Sakura (Japan) company. The cuts were applied to highly adhesive glass and dried vertically in a thermostat at a temperature of 55-56 ℃ for 10 hours.

Extraction of total RNA preparations. Fragments of the colon tissue removed during the surgical intervention were crushed with a disposable sterile scalpel and placed in test tubes containing a lysing solution containing guanidine isothiocyanate, sodium citrate, sarcosil, and DTT.

Analysis of multiple parallel microRNA sequencing data. Determining the expression level of microRNA using NGS technology involves comparing the nucleotide sequence of sequencing cDNA molecules in each sample with known microRNA nucleotide sequences presented in miRBase/ mirGeneDB databases.

When processing the initial research materials, IBM SPSS Statistics 23 (Stat Soft, USA) and MedCalc 19.3.0 (MedCalc Software bv, USA) programs were used.

3. Results

The prospective study group included 78 patients (27 men and 51 women) diagnosed with metastatic colorectal cancer (stage IV of the disease), who underwent molecular genetic studies.

The study included patients aged 26 to 74 years, with an average age of 59.2 years and a median age of 60.0 years. The average age of the men included in the study was 60.4 years, the median was 62.0 years, and the women were 58.6 and 60.0 years, respectively (p=0.352).

In the vast majority of cases, colon cancer was diagnosed in 57 patients (73.1%), and rectosigmoid joint cancer in 21 patients (26.9%). The degree of tumor differentiation corresponded to 2-3 in 66 patients: 2 - 45 patients (57.7%), 3 - 21 (26.9%). Lymphovascular invasion was detected in 74 patients (94.9%), perineural invasion - in 71 (91.0%).

The size of the primary focus (according to TNM classification category T) in 34 patients corresponded to T3 (43.6%), T4 - in 41 (52.6%) (Figure 1). Only in 11 patients were regional lymph nodes not affected, in 31 (39.7%) patients - regional lesion corresponded to the N1 category, in 36 (46.2%) - N3.

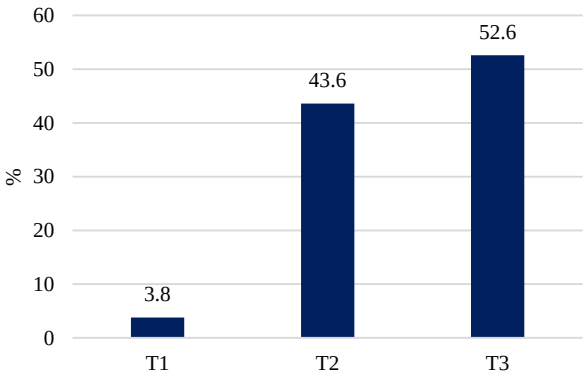

Figure 1. Distribution of patients with metastatic colorectal cancer depending on the size of the primary focus

Table 1. Distribution of patients with identified KRAS, NRAS mutations and MSI

Parameters	Number of patients with mutations, abs.p., %:		
	KRAS	NRAS	MSI
All patients (n=78)	36 (46,2%)	3 (3,8%)	26 (33,3%)
Men (n=27)	13 (48,1%)	2 (7,4%)	10 (37,0%)
Women (n=51)	23 (45,1%)	1 (2,0%)	16 (31,4%)

KRAS mutation was detected in 36 patients (46.2%), NRAS - in 3 (3.8%), microsatellite instability (MSI) was determined in 26 (33.3%). No significant differences were found in the frequency of mutation detection among men and women (p>0.05) (Table 1).

The total one-year survival in the group of patients without KRAS mutations was 76.2±6.6%, two-year - 56.4±7.8%, three-year - 43.2±9.6%, median - 33.0 months (95% CI 17.3-48.7 months), in the group of patients with KRAS mutations - 97.2±2.7%, 52.8±8.3%, 23.3±7.3% and 25.0 months (95% CI 20.6-29.4 months), respectively. The risk of death in patients with metastatic colorectal cancer with KRAS mutations is 1.1 times higher than among patients without mutations (differences are insignificant).

For the NRAS gene, the assessment of distant outcomes (total survival) was not carried out due to the small number of patients with mutations in the NRAS gene (3 patients).

The survival rate of patients with HightMSI and Stable MSI in this patient sample does not differ.

In addition to the mutations described above, the following molecular genetic changes were identified in the KRAS, NRAS, and MSI genes, which are presented in Table 2. Most of the identified molecular genetic changes were in combination with mutations in several genes. As can be seen from the presented data, 41 patients (52.6%) had mutations in the TR53 gene, 29 (37.2%) had mutations in the APC gene, 14 (17.9%) had mutations in the SMAD4 gene, 12 (15.4) had mutations in the RNF43 gene, and 10 (12.8%) had mutations in the ARID1A gene.

Table 2. Results of molecular genetic testing of patients with metastatic colorectal cancer

Mutations	Number of patients with molecular genetic changes (n=78)	
	Absolute number (%)	%, 95% CI
BRAF (G466A)	**3 (3,8)**	1,6-8,0
BRCA1 (E181, E286)	2 (2,6)	0,8-6,1
BRACA2	**5 (6,4%)**	3,6-11,8
BRCA2 (Y352)	2 (2,6)	0,8-6,1
BRCA2 (T2125fs*12)	3 (3,8)	1,6-8,0
MET (amp)	**5 (6,4%)**	3,6-11,8
NF1 (E106)	**3 (3,8)**	1,6-8,0
APC (все)	**29 (37,2)**	26,5-48,0
APC (A1283fs*5)	3 (3,8)	1,6-8,0
APC (E1544, R2237, S2464Y, S2307L, R1114)	2 (2,6)	0,8-6,1
APC (K1370)	4 (5,1)	2,6-10,0
APC (L1488fs*20, R876)	5 (6,4%)	3,6-11,8
APC (N1300fs5)	3(3,8)	1,6-8,0
APC (R213,E1353)	5 (6,4%)	3,6-11,8
APC (R232)	1 (1,3)	0,1-3,8
APC (R564, T1556fs)	1 (1,3)	0,1-3,8
APC (splice site 1312+2T>C)	2 (2,6)	0,8-6,1
APC (splice site 835-8A>G)	1 (1,3)	0,1-3,8

APC (T1135, T1556)	2 (2,6)	0,8-6,1
APC (T1445fc*28)	1 (1,3)	0,1-3,8
APC (T1445fs*, R564)	2 (2,6)	0,8-6,1
ARID1A (всего)	**10 (12,8)**	5,4-20,2
ARID1A (Q152)	3 (3,8)	1,6-8,0
ARID1A (Q766)	2 (2,6)	0,8-6,1
ARID1A (R1276)	4 (5,1)	2,6-10,0
ARID1A (W2048)	1 (1,3)	0,1-3,8
ATM	**5 (6,4%)**	3,6-11,8
ATM (R2598Q, R337C)	2 (2,6)	0,8-6,1
ATM (S1993fs*7)	3 (3,8)	1,6-8,0
CDK6 (amp)	**3** (3,8)	1,6-8,0
CDK12 (P526fs)	2 (2,6)	0,8-6,1
CTNNB1	**9 (11,5)**	4,4-18,6
CTNNB1(K335T)	3(3,8)	1,6-8,0
CTNNB1 (T41A)	6 (7,7)	1,8-13,6
ERBB3 (K329E)	**3** (3,8)	1,6-8,0
FBW7	**9 (11,5)**	4,4-18,6
FBW7 (E79)	3 (3,8)	1,6-8,0
FBW7 (R465c)	5 (6,4%)	3,6-11,8
FBW7 (loss)	1 (1,3)	0,1-3,8
HGF (amp)	2 (2,6)	0,8-6,1
PIK3CA	**8 (10,2)**	4,8-16,9
PIK3CA (R357Q)	4 (5,1)	2,6-10,0
PIK3CA (E542K)	2 (2,6)	0,8-6,1
PIK3R1 (Q579, S147, K567E)	2 (2,6)	0,8-6,1
PTCH1	**9 (11,5)**	4,4-18,6
PTCH1 (E47)	2 (2,6)	0,8-6,1
PTCH1 (Y31fs)	4 (5,1)	2,6-10,0
PTCH1 (S1203fs*52)	3 (3,8)	1,6-8,0
PTEN	**9 (11,5)**	4,4-18,6
PTEN (E7)	1 (1,3)	0,1-3,8
PTEN (K267fs)	5 (6,4%)	3,6-11,8
PTEN (loss)	3 (3,8)	1,6-8,0
RNF43	**12 (15,4)**	7,4-23,4
RNF43 (R337)	5 (6,4%)	3,6-11,8
RNF43 (S41)	2 (2,6)	0,8-6,1
RNF43 (N179fs*6)	3 (3,8)	1,6-8,0
RNF43 (G659fs)	2 (2,6)	0,8-6,1
SMAD4	**14 (17,9)**	9,4-26,4
SMAD4 (A361H)	2 (2,6)	0,8-6,1
SMAD4 (D537Y)	2 (2,6)	0,8-6,1
SMAD4 (loss)	3 (3,8)	1,6-8,0
SMAD4 (Loss exons 11-12)	3 (3,8)	1,6-8,0
SMAD4 (M503fs*4)	4 (5,1)	2,6-10,0
TP53	**41 (52,6)**	41,5-63,7
TP53 (A282T)	3 (3,8)	1,6-8,0
PTP53 (250L)	2 (2,6)	0,8-6,1
TP53 (P301fs*5)	3 (3,8)	1,6-8,0
TP53 (R248Q)	3 (3,8)	1,6-8,0
TP53 (R273C)	3 (3,8)	1,6-8,0
TP53 (R342)	3 (3,8)	1,6-8,0
TP53 (RS42)	3 (3,8)	1,6-8,0
TP53 (spice site 919+1G>T)	3 (3,8)	1,6-8,0
TP53 (splice site 559+1G>A)	6 (7,7)	1,8-13,6
TP53 (V172P)	3 (3,8)	1,6-8,0
TP53(V272M)	3 (3,8)	1,6-8,0
TP53 (V73Wfs*50, P152Rfs*18)	3 (3,8)	1,6-8,0
TP53 (Y163C)	3 (3,8)	1,6-8,0
SETD2 (splice site 7238+1G, E2021fs*126)	2 (2,6)	0,8-6,1
MEK1 (D67N)	**3** (3,8)	1,6-8,0
RET	6 (7,7)	1,8-13,6
RET (E511K)	**3** (3,8)	1,6-8,0
RET (T930M)	**3** (3,8)	1,6-8,0
ASXL1 (G645fs*58)	**3** (3,8)	1,6-8,0
ATR (I774fs*5)	**3** (3,8)	1,6-8,0
CASP8 (F296fs*11)	**3** (3,8)	1,6-8,0
CIC (P1597fs*23)	**3** (3,8)	1,6-8,0
CTCF (T204fs*26)	**3** (3,8)	1,6-8,0
FANCG (S387fs*16)	**3** (3,8)	1,6-8,0
MLL2 (P647fs*283, V3089fs*30)	**3** (3,8)	1,6-8,0
MSH2 (Q4)	**3** (3,8)	1,6-8,0
MSH3	6 (7,7)	1,8-13,6
MSH3 (K383fs*32)	3 (3,8)	1,6-8,0
MSH3 (L383)	3 (3,8)	1,6-8,0
MSH6 (F1088fs*2, F1088fs*3)	**3** (3,8)	1,6-8,0
NOTCH3 (P695fs*165)	**3** (3,8)	1,6-8,0
PIK3C2B (R287fs*92)	**3** (3,8)	1,6-8,0
QKI (K134fs*14)	**3** (3,8)	1,6-8,0
RB1 (R7fs*24)	**3** (3,8)	1,6-8,0
ATRX (G960fs*10)	**3** (3,8)	1,6-8,0
SPEN (R2010H)	2 (2,6)	0,8-6,1
RICTOR (amplification)	**3** (3,8)	1,6-8,0
SOX9	6 (7,7)	1,8-13,6
SOX9 (E261)	3 (3,8)	1,6-8,0
SOX9 (T460fs*118)	3 (3,8)	1,6-8,0
SMAD2 (S464)	3 (3,8)	1,6-8,0
FBXW7	6 (7,7)	1,8-13,6
FBXW7 (A564H)	3 (3,8)	1,6-8,0
FBXW7 (R465C)	3 (3,8)	1,6-8,0
FGFR2 (A550L)	**3** (3,8)	1,6-8,0
RAD21 (amplification)	**3** (3,8)	1,6-8,0
CRKL (amplification)	**3** (3,8)	1,6-8,0
MYC (amplification)	**3** (3,8)	1,6-8,0
EGFR (amplification)	**3** (3,8)	1,6-8,0
MTAP	6 (7,7)	1,8-13,6

MTAP (amplification)	3 (3,8)	1,6-8,0
MTAP (loss)	3 (3,8)	1,6-8,0
CDKN2 (loss)	3 (3,8)	1,6-8,0
GABRA6 (K173T)	**3** (3,8)	1,6-8,0
POLE (A2159H)	**3** (3,8)	1,6-8,0
NOTCH1 (A1134T)	**3** (3,8)	1,6-8,0
FANCL (A213A)	**3** (3,8)	1,6-8,0
FANCD2 (A748H)	**3** (3,8)	1,6-8,0
BTK (G411A)	**3** (3,8)	1,6-8,0

The overall survival rate of patients without APC mutations was: one-year - 88.6±5.4%, two-year - 51.4±8.4%, three-year - 26.7±7.8%, median - 24.0 months (95% CI 17.1-30.9 months); with mutations: 76.7±6.4%, 57.0±7.7%, 35.6±9.7% and 28.0 months (16.8-39.2 months), respectively.

The overall survival rate among colorectal cancer patients was assessed based on the presence/absence of RNF43 mutations. Thus, one-year survival was 86.4±4.2% in the group without mutations and 83.3±10.8% among patients with RNF43 mutations, two-year survival was 52.3±6.2% and 66.7±13.6%, three-year survival was 32.2±6.7% and 25.4±14.3%, and the median survival was 25.0 months both among patients without mutations and among patients with RNF43 mutations.

In the group of patients without mutations in SMAD4, the overall survival rate is somewhat higher than among patients with mutations. Thus, the one-year overall survival rate was 87.5±4.1% in the group of patients without mutations and 78.6±11.0% in the group of patients with mutations, the two-year survival rate was 56.9±6.3% and 34.3±13.1%, the three-year survival rate was 32.6±6.8% and 25.7±12.3%, respectively. The median survival rate was also higher in the group of patients without mutations (27.0 months (95% CI 20.8-33.2 months) compared to the group without mutations (14.0 months (95% CI 8.5-19.5 months).

Also, in the group of patients without TP53 mutations, the overall survival rate is somewhat higher than among patients with mutations. Thus, the one-year overall survival rate was 86.5±5.6% in the group of patients without mutations and 85.4±5.5% in the group of patients with mutations, the two-year survival rate was 61.5±8.1% and 48.1±7.9%, and the three-year survival rate was 37.8±9.5% and 25.6±7.6%, respectively. The median survival rate was also higher in the group of patients without mutations (29.0 months (95% CI 21.4-36.6 months) than in the group without mutations (22.0 months (95% CI 14.8-29.2 months).

For treatment of this category, patients received the following types of treatment: targeted therapy was administered to 45 (57.7%) patients, palliative/symptomatic treatment - 33 (42.3%). Patients receiving targeted therapy or symptomatic/ pallative treatment were comparable in the main comparison parameters, except for the most frequent registrations of SMAD4 and TR53 changes among those receiving symptomatic treatment (Table 3).

Table 3. Comparison parameters of patients receiving targeted therapy and symptomatic/pallative treatment

Parameters	Treatment scheme (abs. number, %)		p
	target therapy	symptomatic/ pallative treatment	
Localization Colon Rectum	 32 (77,1%) 13 (28,9%)	 25 (75,8%) 8 (24,2%)	0,648
Degree of differentiation 1 2 3	 7 (15,6%) 25 (55,6%) 13 (28,9%)	 5 (15,2%) 20 (60,6%) 8 (24,2%)	0,888
Category T T2 T3 T4	 2 (4,4%) 21 (46,7%) 22 (48,9%)	 1 (3,0%) 13 (39,4%) 19 (57,6%)	0,740
Category N N0 N1 N2	 6 (13,3%) 18 (40,0%) 21 (46,7%)	 5 (15,2%) 13 (39,4%) 15 (45,5%)	0,975
KRAS (have/no)	22 (45,5%)/23 (51,1%)	14 (42,6%)/19 (57,6%)	0,572
NRAS (have/no)	3 (6,7%)/42 (93,3%)	0/33 (100,0%)	0,131
MSI Hight (have/no)	14 (31,1%)/31 (68,9%)	11 (33,3%)/20 (66,7%)	0,691
APC (have/no)	22 (48,9%)/23 (51,1%)	21 (63,6%)/12 (63,6%)	0,196
RNF43 (have/no)	6 (13,3%)/39 (86,7%)	6 (18,2%)/27 (81,8%)	0,558
SMAD4 (have/no)	1 (2,2%)/44 (97,8%)	13 (39,4%)/20 (60,6%)	**<0,001**
TP53 (have/no)	17 (37,8%)/28 (62,2%)	24 (72,7%)/9 (27,3%)	**0,003**

In the targeted therapy group, the one-year survival rate was 88.9±4.7%, 2-year survival 61.2±7.4%, 3-year survival 38.7±8.5%, 4-year survival 31.0±9.7%, and the median survival rate was 32.0 months (95% CI 25.0-39.0 months). After palliative/symptomatic treatment, one-year total survival was 81.8±6.7%, 2-year - 45.3±8.7%, 3-year - 20.1±8.1%, 4-year - not achieved, median - 16.0 months (95% CI 5.2-26.8 months). The risk of death in patients with metastatic colorectal cancer without targeted drug treatment is 1.3 times higher than among patients receiving targeted therapy.

Based on the obtained results of the dissertation research, assessment of long-term treatment outcomes, and analysis of literature data, we developed a treatment algorithm for patients with metastatic colorectal cancer.

4. Conclusions

Conducting a molecular genetic study among patients with metastatic colorectal cancer in the Republic of

Uzbekistan made it possible to determine the frequency of a wide spectrum of genetic changes (available on the NGFR panel), as well as to assess the frequency of KRAS, NRAS mutations, and microsatellite instability (the most characteristic genetic changes in metastatic colorectal cancer) among patients in the Republic of Uzbekistan. Thus, KRAS mutations were detected in 36 patients (46.2%), NRAS - in 3 (3.8%), microsatellite instability (MSI) was determined in 26 (33.3%), mutations in the TR53 gene were detected in 41 patients (52.6%), in 29 (37.2%) - APC, in 14 (17.9%) - SMAD4, in 12 (15.4) - RNF43, in 10 (12.8%) - ARID1A. BRAF mutation was detected in only 3 patients, and BRCA (BRCA1 and BRCA2) - in 7 patients. Most of the identified molecular genetic changes were in combination with mutations in several genes.

Molecular genetic testing for metastatic colorectal cancer is primarily conducted to determine the possibility of using targeted drugs for the treatment of the pathology. Correct administration of expensive targeted drugs allowed for an increase in overall 3-year survival from 20.1±8.1% (in the group of patients receiving symptomatic/paliative treatment) to 38.7±8.5% (in the group of patients receiving targeted therapy prescribed based on molecular genetic testing results) and the median overall survival from 16.0 months (95% CI 5.2-26.8 months) to 32.0 months (95% CI 25.0-39.0 months).

The conducted research allowed us to develop an algorithm for treating patients with metastatic colorectal cancer, the application of which allows for an increase in the proportion of resectable foci, thereby increasing the life expectancy of patients with metastatic colorectal cancer.

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