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Research

Analysis of Molecular Differences in Metastatic Colorectal Cancers and Their Impact on Prognosis

Metastatik Kolorektal Kanserlerde Moleküler Farklılıkların Analizi ve Prognostik Sonuçları

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ABSTRACT

Objective: Colorectal malignancies are the third most common cancer types according to the World Health Organization and the second leading cause of cancer-related deaths. It is the most common type of cancer that results in mortality in lung and prostate cancer and after lung and breast cancer. Improvements in screening programs, an increase in their availability, and new developments in treatment strategies have resulted in better survival outcomes in the modern era. In terms of treatment; surgery, chemotherapy, targeted therapies, and immunotherapy can be used for colon cancer management. Combination regimens of fluoropyrimidine provide a survival advantage over the best supportive care in the treatment of metastatic colorectal cancer. In addition, adding targeted therapies to standard chemotherapy provided better survival than chemotherapy alone. As with many other malignancies, better survival outcomes are achieved in colorectal cancers with treatments tailored according to the molecular characteristics of the tumor. In this study, we aimed to analyze the effects of selected treatments on survival that are tailored according to molecular differences in metastatic colorectal cancers.

Methods: Patients aged 18 years or older, with pathologically confirmed metastatic colorectal cancer diagnosis, and who are suitable for intensive combination chemotherapy [Eastern Cooperative Oncology Group 0-2 (ECOG 0-2)], are enrolled in the study. Demographic findings (age, gender, ECOG performance status), clinical status (metastatic site, systemic treatments administered initially or in further steps, progression-free survival and overall survival), molecular findings [presence of Kirsten rat sarcoma viral oncogene homolog (KRAS), NRSAS, and BRAF mutations] and pathology-related data (histological type, differentiation, tumor location, microsatellite instability status, T and N stage, lymphovascular invasion, perineural invasion for early stage cancers at diagnosis which became metastatic later) were extracted from patients' files and evaluated retrospectively. The prognostic status was estimated using the Kaplan-Meier curve.

Results: The median survival time was 33.80±4.83 and the 5-year survival rate was 38%. The median survival time was observed as 29.32±5.33 in patients with KRAS mutant and 134.17±68.66 in patients with wild KRAS (p=0.005). While the median survival time in patients with neuroblastoma rat sarcoma (NRAS) mutant is 19.02±0.00, it is 33.80±4.83 in patients with Nras wild (p=0.62). While the median survival time was 26.28±12.14 in patients with BRAF mutant, it was 33.80±8.39 in patients with BRAF wild (p=0.055).

Conclusion: Survival without treatment is extremely low in patients with metastatic colorectal cancer, and new treatment strategies can be applied according to the molecular behavior of the tumor. Monoclonal antibodies are the most preferred targeted therapies. Examples of these antibodies are bevacizumab and aflibercept, which target vascular endothelial growth factor (VEGF), and cetuximab and panitumumab, which target epidermal growth factor receptor (EGFR). Among these treatments, anti-VEGF molecules are effective regardless of the presence of molecular biomarkers, whereas anti-EGFR treatments are only effective in the absence of mutations in the EGFR-RAS-RAF-MEK pathway.

Keywords: Colorectal cancer, metastasis, KRAS, NRSAS, BRAF, monoclonal antibodies, prognosis

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ÖZ

Amaç: Kolorektal kanserler Dünya Sağlık Örgütü verilerine göre en sık görülen 3. kanser türü olup kansere bağlı ölüm nedenlerinde ise tüm popülasyonda 2. sırada yer almaktadır. Erkeklerde akciğer ve prostat kanserinden, kadınlarda ise akciğer ve meme kanseriden sonra ölüme neden olan kanser tipidir. Bu noktada bakıldığında gerek tarama programlarının oluşturulması, gerekse tedavi stratejilerinde sağlanan gelişmeler günümüzde sağkalım üzerine olumlu gelişmelerin olduğunu göstermektedir. Tedavi stratejisi açısından bakıldığında kolon kanserinin yönetiminde cerrahi tedavi, kemoterapatikler, hedefe yönelik tedaviler ve immünoterapi uygulanabilmektedir. Metastatik kolorektal kanser tedavisinde fluoropirimidin kombinasyon rejimlerinin en iyi destek tedaviye kıyasla sağkalım avantajı sağladığı gösterilmiştir. Kemoterapiye eklenen hedefe yönelik tedaviler ile de sadece kemoterapiye kıyasla genel sağkalımda iyileşme sağlanmıştır. Monoklonal antikorlar en sık uygulanan hedefe yönelik tedavilerdir. Vasküler endotelyal büyüme faktörünü (VEGF) hedefleyen bevacizumab, aflibercept ve epidermal büyüme faktörü reseptörünü (EGFR) hedefleyen cetuximab, panitimumab bunlara örnektir. Bu tedaviler arasından anti-VEGF tedaviler, moleküler biyobelirteçden bağımsız olarak etkinlik gösterirken, anti-EGFR tedaviler EGFR-RAS-RAF-MEK yolağında mutasyon olmadığı durumlarda etki gösterirler. Pek çok kanser türünde olduğu gibi, kolorektal kanserlerde de tümörün moleküler özelliklerine göre seçilen tedaviler ile sağkalım sonuçları daha iyi elde edilmiştir. Bu çalışmada metastatik kolorektal kanserlerde moleküler farklılıkların analizi ve sonucuna göre seçilen tedavilerin sağkalım sonuçları araştırılacaktır.

Gereç ve Yöntem: Çalışmaya 18 yaş ve üzeri, metastatik kolorektal kanser tanısı patolojik olarak doğrulanmış, performans statüsü intensif kemoterapi kombinasyonuna uygun hastalar [(Doğu Kooperatif Onkoloji Grubu 0-2 (ECOG 0-2)] dahil edilecektir. Hastalara ait demografik (yaş, cinsiyet, ECOG performans statüsü), klinik (metastaz yeri, 1. basamak ve sonraki basmaklarda uygulanan sistemik tedaviler, progresyonsuz sağkalım ve genel sağkalım süreleri) moleküler [Kirsten sıçan sarkomu viral onkogen homologu (KRAS), NRSAS, BRAF mutasyon varlığı] ve patolojik datalar (tümör histolojik tip, diferansiasyon, tümör yerleşim yeri, mikrosatellit instabilite durumu, tanıda erken evre olup sonradan metastatik olanlar için T, N evresi, lenfovasküler invazyon, perinöral invazyon) retrospektif olarak hasta dosyalarından elde edilecektir. Prognostik durumu Kaplan-Meier ile hesaplanacaktır.

Bulgular: Median sağkalım süresi 33,80±4,83 ve 5 yıllık sağkalım oranı %38 olarak bulunmuştur. KRAS mutant olan hastalarda median sağkalım süresi 29,32±5,33 KRAS wild olan hastalarda 134,17±68,66 olarak gözlenmiştir (p=0,005). NRAS mutant olan hastalarda median sağkalım süresi 19,02±0,00 iken Nras wild olan hastalarda 33,80±4,83'tür (p=0,62). BRAF mutant olan hastalarda median sağkalım süresi 26,28±12,14 iken BRAF wild olan hastalarda 33,80±8,39 olarak bulunmuştur (p=0,055).

Sonuç: Metastatik kolorektal kanserlerde tedavisiz sağkalım son derece düşük olup, tümörün moleküler davranışına göre yeni tedavi stratejileri uygulanabilmektedir. Monoklonal antikorlar en sık uygulanan hedefe yönelik tedavilerdir. VEGF'yi hedefleyen bevacizumab, aflibercept ve EGFR'yi hedefleyen cetuximab, panitimumab bunlara örnektir. Bu tedaviler arasından anti-VEGF tedaviler, moleküler biyobelirteçden bağımsız olarak etkinlik gösterirken, anti-EGFR tedaviler EGFR-RAS-RAF-MEK yolağında mutasyon olmadığı durumlarda etki gösterirler.

Anahtar Kelimeler: Kolorektal kanser, metastaz, KRAS, NRSAS, BRAF, monoklonal antikorlar, prognoz

INTRODUCTION

Colon and rectum cancers are common malignancies with poor prognoses, especially in advanced stages (1). The prevalence of metastatic colorectal cancers (CRC) remains considerable despite significant advances in diagnostic methods and treatment, the implementation of screening programs, and the adoption of multidisciplinary approaches with particularly favorable benefits. New-generation chemotherapeutics and response-guided surgical strategies offer benefits to patients with metastatic CRC (2).

The therapeutic strategies for colon cancer include surgery, chemotherapy, targeted therapies, and immunotherapy. Fluoropyrimidine combination regimens provide a survival advantage in the treatment of metastatic CRC compared with the best supportive therapy (3). With the addition of targeted therapies to chemotherapy, overall survival (OS) has been improved compared with chemotherapy alone (4). Among targeted therapies, monoclonal antibodies are the most commonly used agents. Examples of such therapeutics include bevacizumab and aflibercept targeting vascular endothelial growth factor (VEGF), cetuximab, and panitumumab targeting epidermal growth factor receptor (EGFR). The efficacy of anti-VEGF treatment is independent of the molecular biomarker, but anti-EGFR treatment is effective only when there are no mutations in the EGFR-RAS-RAF-MEK pathway (5).

In this study, we aimed to evaluate the effects of the commonly used monoclonal antibodies VEGF- and EGFR-targeting therapeutics cetuximab and panitumumab on prognosis and survival in patients with metastatic CRC.

METHODS

We performed this study by using the data from a thesis study in the Hamidiye Institute of Health Sciences Molecular Oncology Ph.D. program. Upon University of Health Sciences Türkiye, Ümraniye Training and Research Hospital Clinical Research Ethics Committee (number: B.10.1.TKH.4.34.H.GP.0.01/157, date: 27.05.2021) approval, this study included patients, who were treated due to the diagnosis of metastatic CRC in the Medical Oncology Clinic of the University of Health Sciences Türkiye, Ümraniye Training and Research Hospital during the period between January 2016 and June 2021. Patients with missing data and severe comorbid diseases were excluded from the study. A total of 102 patients were included in the study. Patients' data were retrieved from the hospital's IT department.

Patients aged >18 years with a pathologically confirmed diagnosis of metastatic CRC and a suitable performance

status [Eastern Cooperative Oncology Group 0-2 (ECOG 0-2)] for intensive combination chemotherapy were included in the study.

Patients' demographic data (age, sex, and ECOG performance status), clinical features [metastatic site, first-line and second or higher lines of systemic treatment, progression-free survival (PS), and OS], molecular characteristics (KRAS, NRAS, and BRAF mutations), and pathologic diagnosis [histologic type, tumor differentiation, tumor location, microsatellite instability (MSI), T-N stages of metastatic patients with a diagnosis of early-stage disease, and lymphovascular and perineural invasion] were retrospectively retrieved from patients' files. Prognosis was estimated by the Kaplan-Meier analysis.

The primary aim of our study was to evaluate the outcomes of contemporary anti-VEGF and anti-EGF therapies in CRC and to analyze the molecular differences between right and left colon tumors along with their impact on prognosis using survival analyses on the data retrieved retrospectively. The secondary aims of the study were to evaluate the BRAF, KRAS, and NRAS mutation rates in patients with metastatic disease and to compare the age and sex of patients with lymphovascular and perineural invasion in surgical pathology specimens in light of the published information.

Statistical Analysis

Descriptive analysis (frequency distributions, percentage, mean, standard deviation (SD), 95% confidence intervals, median) were used as a statistical method to analyze the study data. We analyzed conformity to a normal distribution using graphical representations and the Kolmogorov-Smirnov test. For data without a normal distribution, the Kruskal-Wallis H test and Mann-Whitney U test were used to examine differences between groups. The chi-square test was used to examine discontinuous data. The results were examined using the 95% confidence interval at the $p<0.05$ significance level. The descriptive analysis in this study included frequency distributions, percentages, mean, SD (mean ± SD), 95% confidence intervals, and median.

The log-rank test was performed to examine the effects of chemotherapy regimens, molecular analysis findings, and disease stage on survival. Survival rates were calculated by the Kaplan-Meier survival analysis. The effects of chemotherapy regimens and genetic mutations on survival were also calculated in another log-rank analysis with correction for the stage at diagnosis. The SPSS and Microsoft Excel programs were used to analyze the data.

RESULTS

This study enrolled patients diagnosed with metastatic CRC in the Medical Oncology Clinic of the University of Health Sciences Türkiye, Ümraniye Training and Research Hospital between January 2016 and June 2021. A total of 102 patients were included in the study.

The mean age was 62.96±10.82 years (Figure 1). The mean ages of the male and female patients was 63.27±10.62 and 62.48±11.23 years, respectively (Table 1). There was not a statistically significant difference in age between the male and female patient groups (p=0.82). Among the subjects, 62 (60.8%) and 40 (39.2%) were male and female, respectively.

The genetic analyses of the patients revealed KRAS, NRAS, and BRAF mutations in 43 (42.2%), 3 (2.9%), and 8 patients (7.8%), respectively. Out of the 63 (61.8%) patients with MSI, 53 (52%) had MSI and 10 (9.8%) had MSI. The distribution of the TNM stages in accordance with the AJCC staging system was as follows: 2 (2.0%) patients in Stage 1, 14 (13.7%) patients in Stage 2, 24 (23.5%) patients in Stage 3, and 62 (60.8%) patients in Stage 4 (Figure 2).

Of the 40 patients who underwent surgery, lymphovascular invasion was negative in 15 patients (24.5%) had lymphovascular invasion and 25 (24.5%) had no lymphovascular invasion. The examination of the data for perineural invasion showed that it was negative in 21 (20.6%) but positive in 19 (18.6%) patients.

Of the 102 patients, peritoneal metastasis was detected in 19 patients (18.6%) and bone metastasis in 2 patients (2.0%). Figure 2 shows the distribution of metastatic patients. In the first-line treatment protocols, 3 patients (2.9%)

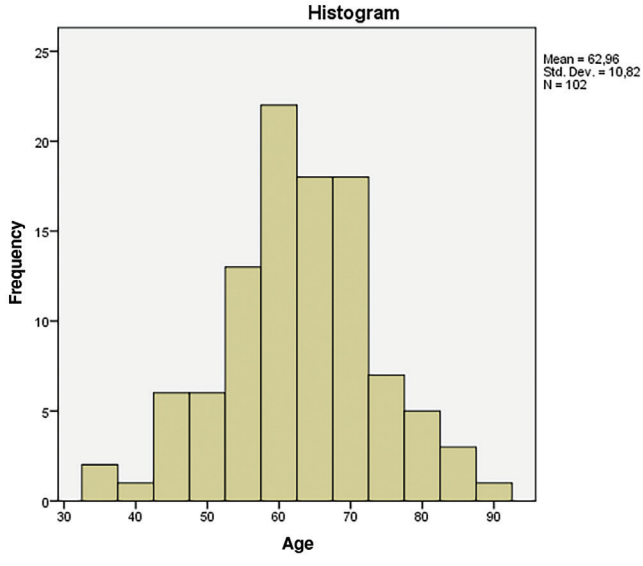

Figure 1. Graph of age distribution

received routine chemotherapy with FOLFOX [folinic acid (leucovorin), fluorouracil (5-FU), and oxaliplatin] or FOLFIRI [folinic acid (leucovorin), 5-FU, and irinotecan)], 57 patients (55.9%) received anti-VEGF therapy with bevacizumab, and 42 patients (41.3%) received anti-EGFR therapy with panitumumab or cetuximab, as third-generation chemotherapeutic agents in addition to the FOLFOX and FOLFIRI regimens. Of the 43 patients with progression, 6 received routine second-line chemotherapy protocols, and 28 and 9 started anti-VEGF and anti-EGFR therapy, respectively, as additional agents to second-line treatment. Seventeen of the 19 patients with progression for the third time started immunotherapy as indicated after molecular and genetic analysis (Table 2).

The median survival time of 33.80±4.83 months and a 5-year survival rate was 38%. The median survival times were as follows: 29.32±5.33 months in KRAS-mutant patients, 134.17±68.66 months in KRAS-wild patients (p=0.005); 19.02±0.00 months in NRAS-mutant patients and 33.80±4.83 months in NRAS-wild patients (p=0.62); and 26.28±12.14 in BRAF-mutant patients and 33.80±8.39 in BRAF-wild patients (p=0.055). Table 3 presents the 1- and 5-year survival rates and the comparison of survival with the results of KRAS, NRAS, and BRAF analyses. Figures 3-5 show Kaplan-Meier curves as a function of the genetic analysis results.

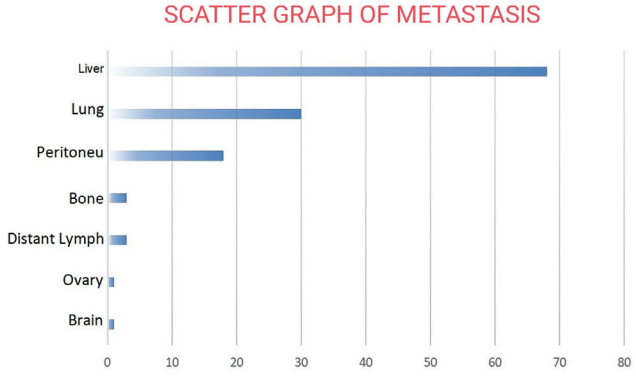

Figure 2. Metastasis distribution

Table 1. Age distribution by gender

		Gender	
		Male	**Female**
Mean		63.27	62.48
95% confidence interval	Lower limit	60.58	58.88
	Upper limit	65.97	66.07
Median		64	61
Standard deviation		10.62	11.23
Minimum		35	36
Maximum		84	91
Range		49	55
Interquartile range		13	15

DISCUSSION

Cancer remains a significant and preventable cause of death after heart disease. Several studies on the early diagnosis and prevention of cancer are available. Colon and rectum cancers are among the most common malignant tumors and the most important causes of cancer-related morbidity and mortality globally (6). The World Health Organization reports that, as of 2018, cancers of the colon and rectum were the third most common cancers worldwide (1.8 million cases) after those of the lung and breasts and the second most common cause of cancer-related mortality (862,000 deaths) after those of the lung (7).

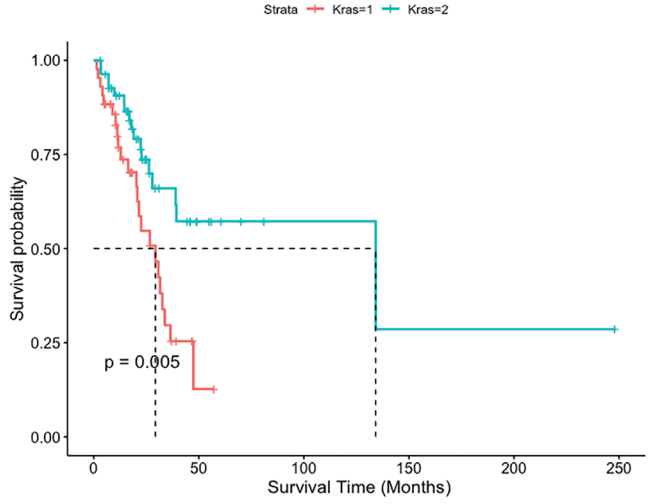

Figure 3. Survival curve obtained by KRAS analysis
KRAS: Kirsten rat sarcoma viral oncogene homolog

Table 2. Distribution of treatment protocols

	n (%)
First-line treatment	
Routine chemotherapy	3 (2.9%)
CT+anti-VEGF therapy	57 (55.9%)
CT+anti-EGF	42 (41.3%)
Second progression	
Routine chemotherapy	6 (14%)
CT+anti-VEGF therapy	28 (65.1%)
CT+anti-EGF	9 (20.9%)
Third progression	
Routine CT	1 (5.6%)
Immunotherapy	17 (94.4%)

VEGF: Endothelial growth factor, CT: Computed tomography, EGF: Epidermal growth factor receptor

The majority of colorectal tumors develop as a result of chromosomal instability and mutations in tumor suppressor genes and oncogenes (8). RAS oncogene mutations are found in approximately 50% of CRC cases. BRAF oncogene mutations are detected approximately in 5-10% of colorectal tumors. The *RAS* and *BRAF* genes encode intracellular proteins involved in the EGFR signaling pathway. Therefore, mutations in these genes can cause resistance to EGFR-targeting therapeutics. Therapeutic agents targeting VEGF, on the other hand, offer favorable survival benefits independent of any biomarker when combined with chemotherapy in metastatic colorectal cancer. The standard first-line systemic treatment for metastatic CRC is fluoropyrimidine-based chemotherapy with irinotecan or oxaliplatin, combined with targeted agents including anti-VEGF or anti-EGFR antibodies (9). In our study, 45% of the patients had RAS mutations and 7.8% had BRAF mutations, consistent with the published information. Besides molecular characteristics, the patients included in our study were clinically eligible candidates to receive an intensive chemotherapy. All patients received oxaliplatin or irinotecan combined with fluoropyrimidine as the first-line systemic treatment. All but 3 patients received targeted therapy with anti-EGFR (41.3%) and anti-VEGF (55.9%) agents in combination with this first-line chemotherapy regimen.

KRAS-mutant patients have a worse prognosis than wild-type patients (10). However, the absence of KRAS mutation predicts sensitivity to EGFR-targeting therapeutics (11). Similar to the reports by the majority of studies conducted to date, we found a significantly shorter OS in patients with RAS mutations than in patients with RAS-wild-type tumors. The median survival time was 29 months in KRAS-mutant patients and 134 months in KRAS-wild patients (p=0.005).

Recent studies have focused on conditions other than RAS mutations to identify patients who will benefit most from anti-EGFR-based therapies, which are first-line therapeutics in wild-type metastatic CRC. Subgroup analysis of data from randomized studies comparing "chemotherapy +anti-EGFR agents" vs. "chemotherapy +anti-VEGF agents" vs. "chemotherapy only" showed a correlation between anti-EGFR efficacy and the primary tumor site (6). Treatment with anti-EGFR agents confers a clinically significant survival benefit to RAS-wild tumors originating from the left colon. A pooled analysis of data from 5 randomized clinical trials (FIRE-3, CRYSTAL, PRIME, PEAK, and CALGB/SWOG 80405) revealed significant benefits in PS [hazard ratio (HR), 0.78; p=0.002] and OS (HR, 0.75; p<0.001) with cetuximab

Table 3. Comparison of genetic analysis and survival outcomes

		Survival% (year)			p-value
	Median Survival (months) (n±SD)	**1-year**	**3-year**	**5-year**	
Overall survival	33.80±4.83	85%	49%	38%	
Site					0.597
Right colon	32.65±3.01	79%	44%	29%	
Left colon	47.40±0.0	88%	55%	46%	
Rectum	33.80±7.31	82%	36%	36%	
KRAS					**0.005**
Mutant	29.37±5.33	76%	29%	12%	
Wild	134.17±68.66	90%	66%	57%	
NRAS					0.628
Mutant	19.02±0.0	NA	NA	NA	
Wild	33.80±4.83	84%	49%	39%	
BRAF					**0.055**
Mutant	26.28±12.14	72%	38%	NA	
Wild	33.80±8.39	86%	49%	43%	
MSI					**0.029**
Negative	26.71±4.48	78%	37%	24%	
Low	134.17±0.0	92%	74%	59%	
High	21.52±8.27	78%	31%	NA	high

MSI: Microsatellite instability BRAF: B-Raf proto-onkogen serin/threonin kinaz, NRAS: Neuroblastoma RAS viral oncogene homolog, KRAS: Kirsten rat sarcoma viral oncogene homolog, SD: Standard deviation

or panitumumab combined with chemotherapy only in tumors originating from the left colon (12). The FIRE-3 study (FOLFIRI plus Cetuximab Versus FOLFIRI plus Bevacizumab as First-Line Treatment for Patients with Metastatic Colorectal Cancer) showed OS benefit (38.3 vs. 28.0 months; HR, 0.63; p=0.002) with FOLFIRI/cetuximab compared with FOLFIRI/bevacizumab in tumors originating from the left colon. However, no significant differences were observed for tumors originating from the right colon (p=0.28). These results suggest that fluoropyrimidine-based chemotherapy combined with cetuximab or panitumumab has become the preferred first-line treatment option for patients with tumors originating from the left colon. On the contrary, anti-VEGF agents in combination with fluoropyrimidine-based chemotherapy have been recommended in the guidelines as the preferred first-line treatment regimen for patients with tumors originating from the right colon because of other molecular changes causing intrinsic resistance to anti-EGFR agents. In our study, the primary tumor site was another stratification factor.

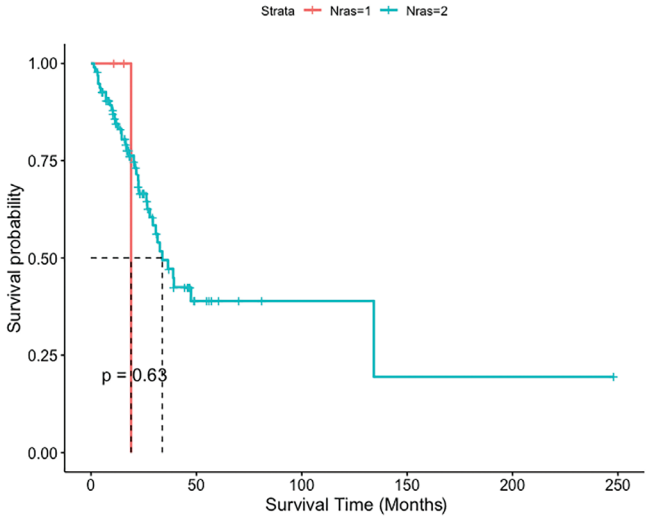

Figure 4. Survival curve obtained via NRAS analysis
NRAS: Neuroblastoma RAS viral oncogene homolog

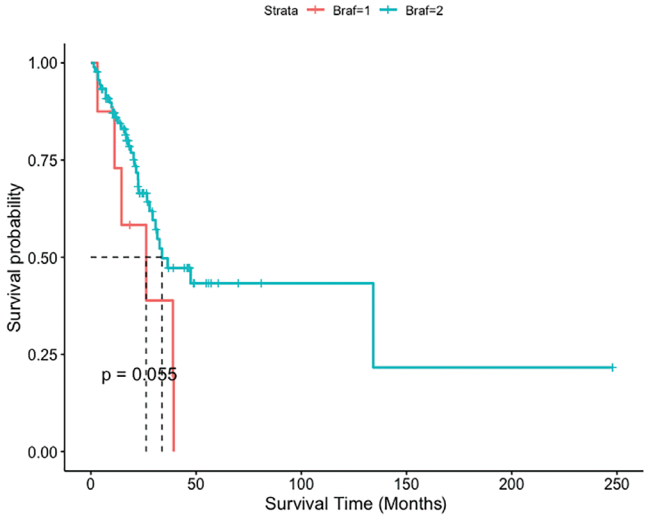

Figure 5. Survival curve determined by BRAF analysis
BRAF: B-Raf proto-onkogen serin/threonin kinaz

Tumors originating from the left colon were found in 52.9% of patients in our study. The survival analysis revealed a median OS of 33.80±4.83 months for all patients included in the study, consistent with the current literature. In our study, the median OS for patients with tumors originating from the left colon was longer but statistically insignificant compared with those originating from the right colon (32.65±3.01 months vs. 36.50±12.29 months, p=0.506). These figures are not consistent with the published information, and we believe that the small sample size of our study might have caused these results.

In the current era of personalized therapies, the discovery of novel prognostic and predictive biomarkers is extremely important for the management of CRC, as it is for the management of all solid tumors. One of these biomarkers is MSI. In most metastatic CRC cases, the MSI status is either MSI-stable (MSS) or mismatch repair-proficient (pMMR). The MSI-high (MSI-H)/mismatch repair-deficient (dMMR) feature occurs in 2-4% of all CRC. The benefit of this approach is limited, with a median OS of 13.6-21.5 months in patients with MSI-H/dMMR CRC treated using the standard first-line systemic therapy (13). Although MSS/pMMR tumors do not benefit from immunotherapy because of their immunosuppressive microenvironment, clinically significant benefits have been demonstrated with immunotherapy in MSI-H/dMMR tumors (14). A phase-III study reported fewer side effects with clinically and statistically significant survival benefits with the anti-PD1 monoclonal antibody pembrolizumab in MSI-H/dMMR tumors compared with standard fluoropyrimidine-based chemotherapy [median PS, respectively: Pembrolizumab vs. chemotherapy, 16.5 vs. 8.2 months; HR, 0.60 (95% CI, 0.45-0.80); p=0.0002] (14). MSI status could not be confirmed for all patients in our study. Of the patients with an established MSI status in our study, 15.9% had MSI-H tumors. This value was higher than that reported in the literature, suggesting that the small sample size of our study may have been the cause.

The most important limitation of this retrospective study is the selection bias resulting from the nature of the study. The MSI status was not established for all patients, and the expression of HER-2, another important biomarker, was not tested in this study, making it impossible for us to conduct further analyses. The small sample size is another limitation

of the study, as it might have affected reaching statistical significance. However, an important aspect of this study is testing for RAS and BRAF mutations and MSI in a single center to ensure homogeneity.

CONCLUSION

In this single-center retrospective study, we presented real-life data from clinical practice and analyzed molecular differences and associated prognostic outcomes in patients with metastatic colorectal cancer. The results of our study are consistent with those reported by previous randomized studies, from the aspect of the optimization of treatment efficacy, enabling the achievement of significant improvements in oncological endpoints through patient selection according to the primary tumor site and molecular characteristics.

ETHICS

Ethics Committee Approval: Approved by the Clinical Research Ethics Committee of University of Health Sciences Türkiye, Ümraniye Training and Research Hospital (number: B.10.1.TKH.4.34.H.GP.0.01/157, date: 27.05.2021).

Informed Consent: Retrospective study.

FOOTNOTES

Authorship Contributions

Surgical and Medical Practices: Ö.F.Ö., Concept: Ö.F.Ö., M.K.Y., Design: Ö.F.Ö., M.K.Y., M.Ö., S.K.T., Data Collection or Processing: Ö.F.Ö., H.Ş.Ü., M.Ö., S.K.T., Analysis or Interpretation: Ö.F.Ö., H.Ş.Ü., M.Ö., S.K.T., Literature Search: Ö.F.Ö., E.F.K., H.K.K., M.Ö., S.K.T., Writing: Ö.F.Ö., E.F.K., N.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Xi Y, Xu P. Global colorectal cancer burden in 2020 and projections to 2040. Transl Oncol. 2021;14:101174.
2. Das S, Ciombor KK, Haraldsdottir S, Goldberg RM. Promising new agents for colorectal cancer. Curr Treat Options Oncol. 2018;19:29.
3. Piedbois P, Buyse M, Rustum Y, Machover D, Erlichman C, Carlson RW, et al. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: Evidence in terms of response rate by the advanced colorectal cancer meta-analysis project. J Clin Oncol. 1992;10:896–903.
4. Piawah S, Venook AP. Targeted therapy for colorectal cancer metastases: A review of current methods of molecularly targeted therapy and the use of tumor biomarkers in the treatment of metastatic colorectal cancer. Cancer. 2019;125:4139-47.
5. Ohhara Y, Fukuda N, Takeuchi S, Honma R, Shimizu Y, Kinoshita I, Dosaka-Akita H. Role of targeted therapy in metastatic colorectal cancer. World J Gastrointest Oncol. 2016;8:642-55.
6. Van Cutsem E, Köhne CH, Láng I, Folprecht G, Nowacki MP, Cascinu S, et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. J Clin Oncol. 2011;29:2011-9.
7. De Roock W, Piessevaux H, De Schutter J, Janssens M, De Hertogh G, Personeni N, et al. KRAS wild-type state predicts survival and is associated to early radiological response in metastatic colorectal cancer treated with cetuximab. Ann Oncol. 2008;19:508-515.
8. Heinemann V, Kraemer N, Buchner H, Weikersthal LF, Decker T, Kiani A, et al. Somatic DNA mutations, tumor mutational burden (TMB), and MSI status: Association with efficacy in patients(pts) with metastatic colorectal cancer (mCRC) of FIRE-3 (AIO KRK-0306). J Clin Oncol. 2018;36:3591.
9. Bokemeyer C, Bondarenko I, Makhson A, Hartmann JT, Aparicio J, de Braud F, et al. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. J Clin Oncol. 2009;27:663-71.
10. Cerottini JP, Caplin S, Saraga E, Givel JC, Benhattar J. The type of K-ras mutation determines prognosis in colorectal cancer. Am J Surg. 1998;175:198-202.
11. Amado RG, Wolf M, Peeters M, Van Cutsem E, Siena S, Freeman DJ, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol. 2008;26:1626-34.
12. Holch JW, Ricard I, Stintzing S, Modest DP, Heinemann V. The relevance of primary tumour location in patients with metastatic colorectal cancer: A meta-analysis of first-line clinical trials. Eur J Cancer. 2017;70:87-98.
13. Tougeron D, Sueur B, Zaanan A, de la Fouchardiére C, Sefrioui D, Lecomte T, et al. Prognosis and chemosensitivity of deficient MMR phenotype in patients with metastatic colorectal cancer: An AGEO retrospective multicenter study. Int J Cancer. 2020;147:285-96.
14. André T, Shiu KK, Kim TW, Jensen BV, Jensen LH, Punt C, Smith D, et al. Pembrolizumab in microsatellite-instability-high advanced colorectal cancer. N Engl J Med. 2020;383:2207-18.