Does Location of the Tumor Affect Prognosis, Survival, and Relapse in Patients With Stage 3 Colorectal Cancers?

Evre 3 Kolorektal Karsinom Tanılı Hastalarda Tümör Yerleşim Yerinin Nüks, Prognoz ve Sağ Kalım Üzerine Etkisi

Yusuf ILHAN, Sema SEZGIN GOKSU, Ali Murat TATLI, Gökhan KARAKAYA, Mustafa Serkan ALEMDAR, Fatma YALCIN MUSRI, Hasan Senol COSKUN

Akdeniz University Faculty of Medicine, Department of Medical Oncology, Antalya, Turkey

Correspondence Address
Yazışma Adresi

Yusuf ILHAN
Akdeniz University Faculty of Medicine, Department of Medical Oncology, Antalya, Turkey

E-mail: dryusufilhan@gmail.com

Received \ Geliş tarihi : 11.03.2020
Accepted \ Kabul tarihi : 07.04.2020
Online published : 04.03.2021
Elektronik yayın tarihi

Cite this article as:
Bu makaleye yapılacak atıf:
Ilhan Y, Sezgın Goksu S, Tatlı AM, Karakaya G, Alemdar MS, Yalcın Musrı F, Coskun HS. Does location of the tumor affect prognosis, survival, and relapse in patients with stage 3 colorectal cancers? Akd Med J 2021; 7(1):71-6.

Yusuf ILHAN
ORCID ID: 0000-0002-2875-6876
Sema SEZGIN GOKSU
ORCID ID: 0000-0002-8026-764X
Ali Murat TATLI
ORCID ID: 0000-0001-9696-1102
Gökhan KARAKAYA
ORCID ID: 0000-0002-7970-307X
Mustafa Serkan ALEMDAR
ORCID ID: 0000-0002-7663-6182
Fatma YALCIN MUSRI
ORCID ID: 0000-0003-2502-3797
Hasan Senol COSKUN
ORCID ID: 0000-0003-2969-7561

DOI: 10.17954/amj.2021.2672

ABSTRACT

Objective: There are many factors that affect prognosis in colorectal cancers. Recent studies have shown the effect of tumor location on the prognosis. The purpose of our study is to evaluate the relationship between tumor location and the overall survival and recurrence rate in patients with stage 3 colon cancer.

Material and Methods: Patients diagnosed with stage 3 colorectal cancer and followed up at the Akdeniz University Medical Faculty were included in the study. 231 patients' information was accessed retrospectively using the hospital database. Patients were grouped into right and left colon cancers similar to those in the literature according to tumor location, and all data were analyzed.

Results: 171 (74%) patients had left colon cancer whereas right colon cancer was present in 60 (26%). There was no significant relationship between the tumor location and recurrence rates of the patients (p=0.82). The mean overall survival for left colon cancers was 97.5±6.6 (95% CI, 84.6-110.5) months; for right colon cancers it was 74.3±5.7 (95% CI, 63.0-85.5) months. Although the mean duration of overall survival was higher in left colon cancers, there was no statistically significant difference between the groups (p=0.38)

Conclusion: We think that there may be a relationship between tumor location and prognosis in colon cancer. In our study, the prognosis was worse in right colon cancer but no statistically significant difference was found between the groups. The relationship between tumor location and survival in stage 3 disease could not be shown clearly. Future studies on this subject may be useful in clinical practice.

Keywords: Prognosis, Stage 3 colon cancer, Tumor location

ÖZ

Amaç: Kolorektal kanserlerde prognozu etkileyen birçok faktör vardır. Son yıllarda tümör yerleşim yerinin de prognoz üzerine etkisini gösteren çalışmalar mevcuttur. Çalışmamızın amacı; Evre 3 kolon kanser tanılı hastalarda genel sağ kalım ve nüks oranının, tümör lokalizasyonu ile ilişkisini değerlendirmektir.

Gereç ve Yöntemler: Çalışmaya evre 3 kolorektal kanser tanılı, Akdeniz Üniversitesi Tıp Fakültesi'nde takip edilen hastalar dahil edildi. 231 hastanın bilgilerine retrospektif olarak hastane veritabanı kullanılarak ulaşıldı. Hastalar tümör lokalizasyonuna göre, literatürdeki çalışmalara benzer olarak sağ ve sol kolon kanseri olarak gruplandırıldı ve verileri analiz edildi.

Bulgular: Hastaların 171'in de (%74) sol kolon tümörü; 60'ın da (%26) sağ kolon tümörü tespit edildi. Hastaların tümör yerleşim yeri ile nüks oranları arasında anlamlı bir fark saptanmadı (p=0,82). Sol kolon kanserleri için ortalama GSK 97,5±6,6 (%95 CI, 84,6-110,5) ay, sağ kolon kanserleri için 74,3±5,7 (%95 CI, 63,0-85,5) ay olarak saptandı. Sol kolon kanserlerinde ortalama GSK süresi daha yüksek olmakla birlikte gruplar arası istatistiksel anlamlı bir fark saptanmadı (p=0,38).

Sonuç: Kolon kanserinde tümör lokalizasyonu ile prognoz arasında ilişki olabileceği düşünülmektedir. Bizim çalışmamızda evre 3 hastalıkta sağ kolon kanserlerinin prognozu daha kötü görülmekle birlikte gruplar arasında istatistiksel anlamlılık gösterilemedi. Bu konuda ileride yapılacak çalışmaların klinik uygulamada yararlı olabileceği görüşündeyiz.

Anahtar Sözcükler: Prognoz, Evre 3 kolon kanseri, Tümör lokalizasyonu

INTRODUCTION

Colorectal cancer is the most common cancer of the gastrointestinal tract and is an important cause of morbidity and mortality among cancers worldwide (1). The colon is anatomically defined from the caecum to the splenic flexure as the right colon and from the splenic flexure to the anal canal as the left colon.

There are embryological, pathological, cytogenetic and clinical differences between the right and left colon, as shown in previous studies in the literature. The right side of the colon (caecum, proximal 2/3 of the transverse colon, and the ascending colon) embryologically originates from the midgut and is supplied by the superior mesenteric artery. The left side of the colon embryologically originates from the hindgut and is supplied by the inferior mesenteric artery (2,3).

It is also known that there are some genetic differences in tumor development between the right and left colon. Defects in DNA repair genes (microsatellite instability) and BRAF mutations are more prominent as regards the pathogenesis of right colon cancers (RSCC) while chromosomal instability and aneuploidy are more common in left colon cancers (LSCC) (4,5). Histologically, right colon cancers originate from polypoid lesions that grow more towards the colon lumen; left colon cancers are often infiltrative tumors that tend to envelop the lumen and are often diagnosed by findings of obstruction (6,7).

Recently, many studies have emphasized that tumor location in colon cancer is an important prognostic factor. Many studies have shown that right colon cancers have lower survival rates than left colon cancers (4,7,8). However, there is conflicting evidence for the relationship between tumor location and prognosis for non-metastatic early-stage cancers (9,10).

Since the literature lacks sufficient clear data on non-metastatic early-stage colon cancers, our study aims to evaluate the relationship between tumor location and recurrence, prognosis, and survival in patients with stage 3 colon cancer who were treated with adjuvant chemotherapy.

MATERIALS and METHODS

A total of 231 patients who were followed up at the Department of Medical Oncology of Akdeniz University Medical Faculty between 2004 and 2017 and whose data could be accessed were analyzed retrospectively. All patients included in the study were diagnosed with stage 3 colon cancer. This study was approved by the Akdeniz University Faculty of Medicine Clinical Research Ethics Committee and was conducted in accordance with the declaration of Helsinki. (Approval Date/ Number: 11.01.2017/14).

All of the 231 patients included in the study underwent adjuvant chemotherapy after the operation. As adjuvant chemotherapy, 5-fluorouracil, oxaliplatin, leucovorin (FOLFOX), oxaliplatin and oral capecitabine (CAPEOX) or single agent capecitabine was preferred and the chemotherapy regimen of each patient was recorded.

All information about the patients was obtained using the hospital database and the archive. Patients whose last follow-up visit was more than 6 months ago or who did not have regular follow-up visits were not included in the study. The pathology report dates were recorded as the patient diagnosis dates.

Patients were grouped as in previous studies in the literature; the right colon group consisted of cancers occurring in the caecum, the ascending colon, hepatic flexure, and the transverse colon; while the left colon group included primary tumors from the splenic flexure to the anal canal (2, 4). The tumor location was determined based on the operation records and colonoscopy findings.

The demographic characteristics, pathologic features, recurrence status, overall survival (OS), and disease-free survival (DFS) were recorded.

Descriptive statistics were used to analyze the clinical parameters and the tumor characteristics according to the location of the colon cancer. Descriptive statistics are presented with frequency, percent, mean, standard deviation. Categorical variables were compared using the chi-square test. The Shapiro Wilk test and independent-sample t-test were used for the assumption of normality in analyzing differences between the numerical values of the groups. OS and DFS analyzes were performed using the Kaplan-Meier method. In all statistical analyses, a p-value of less than 0.05 was considered as statistically significant. Statistical analyses were performed using the 'SPSS 23.0' package program.

RESULTS

Patient baseline characteristics

There were 231 patients consisting of144 (62.3%) men and 87 (37.7%) women. The median age of the population was 58 years. 171 (74%) patients had left colon and 60 (26%) patients had right colon cancer. FOLFOX was used as adjuvant chemotherapy in 155 patients (67.1 %), CAPEOX in 69 patients (29.9%), and oral capecitabine in 7 patients (3.0%).

Clinicopathologic features of patients with RSCC and LSCC

The basic demographic characteristics of the patients are given in detail in Table I for the right and left colon tumors. The mean age for the left and right colon tumors was 58.2 and 58.0 years, respectively, and there was no statistically significant difference between the groups. Gender distributions of the right and left colon cancers were similar.

Patients were grouped according to the grade of tumor invasion (T stage) and the number of lymph nodes (N stage) by pathologic evaluation. Similar rates were observed between the tumor invasion grade, lymph node involvement, and lymphovascular invasion rates in the right and left colon cancer groups and no statistically significant difference was found. Although the rate of lymphovascular invasion was higher in right colon cancer, there was no statistically significant difference between the groups.

Systemic diseases such as diabetes mellitus, hypertension, and coronary artery disease were also questioned. The presence of accompanying chronic diseases in the right and left colon cancer groups was seen at similar rates.

The mean follow-up time of the patients was 44.07±1.80 months (95% CI, 40.5-47.6) (minimum: 2, maximum: 142 months). Disease recurrence rate was similar for right and left colon cancers (right colon: 36.7%, left colon: 35.1%). There were 45 (26.3%) deaths in the left colon group and 16 (26.7%) in the right colon group.

Survival Analysis

The mean follow-up time of the patients was 44.07±1.80 months (95% CI, 40.5-47.6) (minimum: 2, maximum: 142 months). There were 61 deaths in the follow-up period. The mean OS time for all patients was 96.7±5.71 months (95% CI, 85.5-107.9). According to the Kaplan-Meier analyses, the 3-year overall survival rate for all patients with stage 3 colorectal cancer was 73%, and the 5-year overall survival rate was calculated as 64%. The mean OS for left colon cancers was 97.5±6.6 (95% CI, 84.6-110.5) months. The mean OS for right colon cancers was 74.3±5.7 (95% CI, 63.0-85.5). Although the mean OS time was worse in right colon cancers, no statistically significant difference was

Table I: Baseline characteristics according to the location of colon cancer.

Characteristics	Right Colon (n= 60)	Left Colon (n= 171)	P-value
Age (mean ± SD)	58.2 ± 13.00	58.00 ± 11.37	0.92
Sex			0.09
Female	28 (46.7%)	59 (34.5%)	
Male	32 (53.3%)	112 (65.5%)	
T stage (TNM)			0.18
T1-T2	1 (1.7%)	13 (7.6%)	
T3	37 (61.7%)	97 (56.7%)	
T4	14 (23.3%)	30 (17.5%)	
Unknown	8 (13.3%)	31 (18.1%)	
N stage (TNM)			0.94
1-3 lymph node (N1)	25 (41.7%)	65 (38.0%)	
4-6 lymph node (N2a)	17 (28.3%)	45 (26.3%)	
≥ 7 lymph node (N2b)	10 (16.7%)	30 (17.5%)	
Unknown	8 (13.3%)	31 (18.1%)	
LVI			0.32
Yes	20 (33.3%)	39 (22.8%)	
No	9 (15.0%)	28 (16.3%)	
Unknown	31(51.7%)	104 (60.8%)	
Adjuvant treatment			0.04
FOLFOX	34 (56.7%)	121 (70.8%)	
CAPEOX/Capecitabine	26 (43.3%)	50 (29.2%)	
Adjuvant RT			0.00
Yes	2 (3.3%)	105 (61.4%)	
No	58 (96.7%)	66 (38.6%)	

SD: Standard deviation, **TNM:** Tumor-Node-Metastasis, **LVI:** Lymphovascular invasion, **FOLFOX:** 5-fluorouracil, oxaliplatin, leucovorin., **CAPEOX:** capecitabine, oxaliplatin., **RT:** Radiation therapy.

observed between the groups. For left colon cancers, 3- and 5-year OS ratios were 75% and 66%, respectively. For right colon cancers, these rates were calculated as 68% and 58%, respectively. There was no statistically significant difference between the groups (p=0.38). The overall survival analysis of patients according to tumor location is given in Figure 1.

82 of 231 patients suffered a recurrence during follow-up (35.4%). The mean duration of DFS for all patients was calculated as 89.7±4.49 months (95% CI, 80.9-98.5). The 3-year disease-free survival rate was 58%; the 5-year disease-free survival rate was calculated as 57%. The mean DFS time was 90.8±5.1 months (95% CI, 80.7-100.9) for left colon tumors and 65.0±6.2 months (95% CI, 52.8-77.2) for right colon tumors. The 3-year and 5-year disease-free survival rates for left colon cancers were estimated at 57%. The 3-year and 5-year DFS rates for right colon cancers were calculated as 58% and 55%, respectively. There was no statistically significant difference between the groups (p=0.38). Disease-free survival time between the two groups is given in Figure 2.

Patients were also grouped according to T and N stages, and survival analysis was evaluated. There was no statistically significant relationship between tumor T stage and overall survival time. If the number of pathologic lymph nodes increased, the OS and DFS times in stage 3 disease were worse. In the subgroup analyzes, there was a statistically significant relationship between lymph node involvement and OS durations in the left colon cancers; this relationship was not shown in the right colon cancers (left colon p=0.015, right colon p=0.63). There was also no statistically significant relationship between lymphovascular invasion and OS durations.

Patients were also evaluated according to the adjuvant chemotherapy agents. There was no statistically significant difference in overall survival between the fluorouracil-based treatment group and the capecitabine-based treatment group. (left colon p=0.71, right colon p=0.29). The survival analyzes for the adjuvant chemotherapy agent for left and right colon cancers are detailed in Figure 3. (Left colon Figure 3A/Right colon Figure 3B)

DISCUSSION

Although the relationship between tumor location and the prognosis and treatment response is better known in metastatic colorectal cancers, there are only an insufficient number of studies on stage 3 disease. However, a lot of data is present in the literature about the relationship between tumor location and prognosis in colorectal cancers. Although many studies have shown that left colon cancers have a better prognosis, no significant difference was found in some studies on metastatic colorectal cancers (4,11-13).

Our study was performed only in a stage 3 colorectal cancer group. The mean OS for left colon cancers was 97.5±6.6 (95% CI, 84.6-110.5) months. The mean OS for right colon cancers was 74.3±5.7 (95% CI, 63.0-85.5) months. The overall 5-year survival rates were 66% and 58%, respectively. Although the mean overall survival of right colon cancers was lower, no statistically significant difference was found between the groups (p=0.38). A recent study by Jung et al. conducted on patients with non-meta-

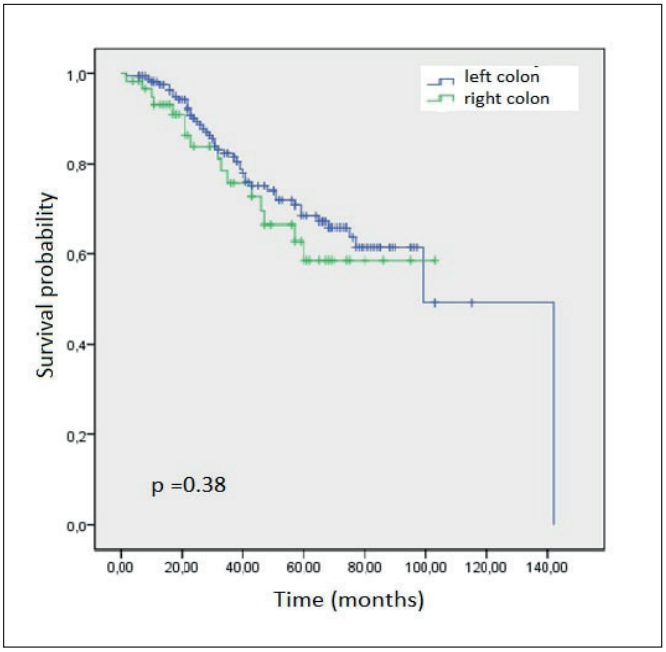

Figure 1: Overall survival according to the location of the colon cancer.

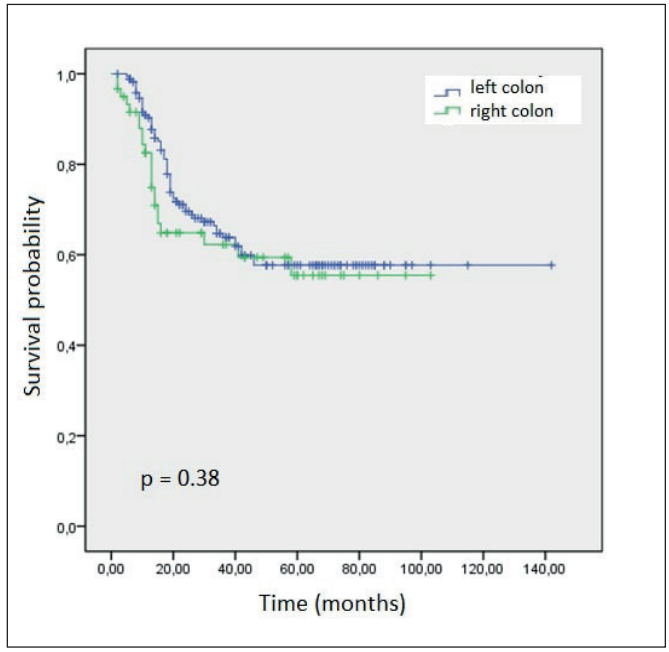

Figure 2: Disease-free survival according to the location of the colon cancer.

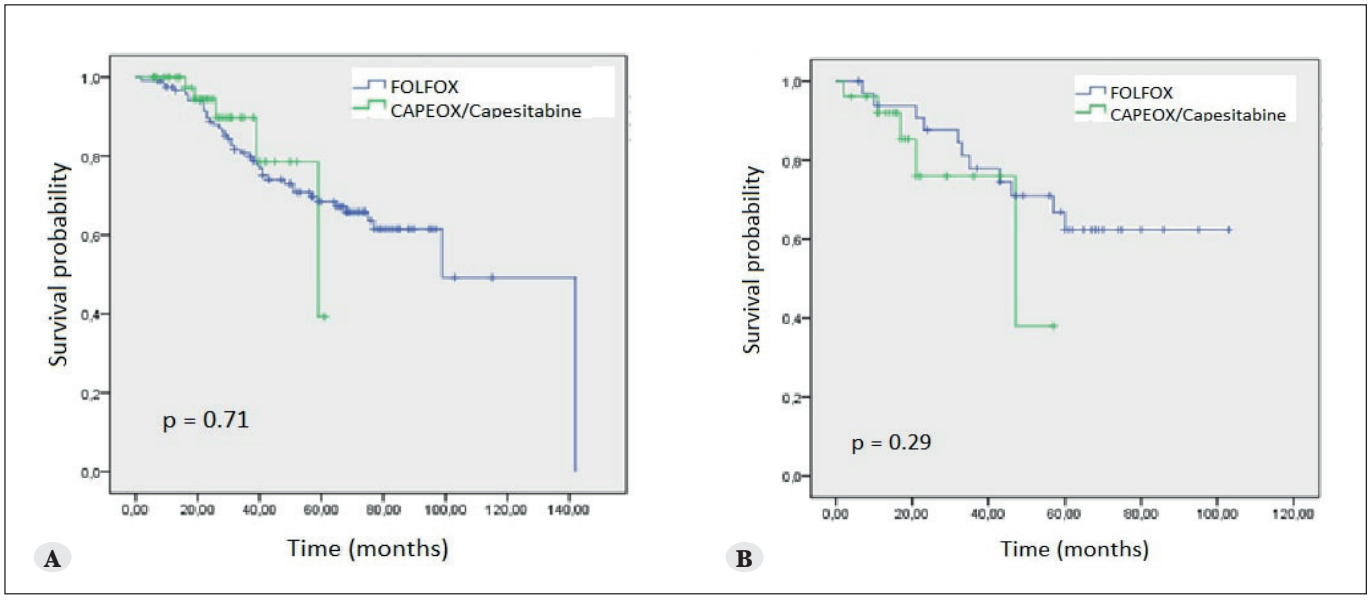

Figure 3: Overall survival according to the adjuvant chemotherapy agents for the left and right colon.

static colorectal cancer has shown that right colon cancer is worse as regards stage 3 disease; however, this difference has not been demonstrated in stage 1 and 2 disease (10). Another study by Qiu et al, has been shown that right colon cancers in stage 2 disease have a better prognosis but there was no difference in stage 3 disease, in contrast to other studies in the literature (14). As mentioned earlier, there are embryological, anatomical and genetic differences between right and left colon cancers. The right side of the colon embryologically originates from the midgut and is supplied by the superior mesenteric artery. The left side of the colon embryologically originates from the hindgut and is supplied by the inferior mesenteric artery. Chromosomal instability (adenomatous carcinoma sequence, KRAS and p53 mutations) are predominant in the development of left colon tumors, while microsatellite instability is more prominent in the pathogenesis of right colon cancers (2,3,7,15). In addition, between 2.5% and 20% of BRAF mutations occur in colorectal cancers. These mutations are closely related to right colon cancers and are thought to be associated with apoor prognosis (4,7,10,16).

The recurrence rate was 35.1% and 36.7% respectively, in the left colon group and right colon group in this study. The recurrence rates were similar among the groups and no statistically significant difference was observed (p=0.82). In a study by Liu et al., recurrence and metastases were more frequent in right colon tumors than in left colon tumors in all stages (12). Our study does not support this finding in terms of recurrence.

Anti-EGFR (anti-epidermal growth factor receptor) treatments are frequently used in colorectal cancer cases. Recently, the response to anti-EGFR treatment has been reported to be better in patients with metastatic left colon cancers. In addition, these studies have shown that primary tumor location is a strong predictive factor for the response rate to EGFR inhibitors (4,8,17,18). As a result of these studies, the 2017 National Comprehensive Cancer Network (NCCN) guideline has recommended the use of monoclonal antibodies developed against EGFR as a first-line treatment in stage 4 colorectal cancers in only left colon tumors (8,19). For this reason, different treatment approaches can be applied for left and right colon tumors in metastatic diseases. We also thought that there might be different approaches to adjuvant treatment in stage 3 disease. In our study, there was no statistically significant difference between overall survival and adjuvant chemotherapy agent use. The current data are inadequate to change the treatment approach for right and left colon tumors in stage 3 disease and further investigations are needed.

Factors such as retrospective planning of our study, the single-center planning, and the relatively low number of patients may be considered as limitations. Moreover, the presence of accompanying diseases of the patients and the experience of the surgeons performing the operations may have affected survival. The information on the pathological and genetic conditions of the patients was also inadequate due to the deficiencies in the database.

CONCLUSION

Our study evaluated the relationship between tumor location and the prognosis and survival in stage 3 colorectal cancer cases. Similar to many studies in the literature, right colon cancers had a worse prognosis than left colon cancers, but no statistically significant difference was found between the groups. We believe that future prospective randomized controlled trials of the subject may be more beneficial in clinical practice.

Ethics Committee Approval: This research complies with all the relevant national regulations, institutional policies and is in accordance the tenets of the Helsinki Decleration, and has been approved by the Akdeniz University Medical Faculty Clinical Research Ethics Committee (Approval Date/ Number: 11.01.2017/14).

Conflict of Interest: None Declared.

Financial Disclosure: The authors declared that this study has received no financial support.

Authors roles: **SSG:** Designing the study and writing the article, **AMT:** Designing the study, writing the article, **GK:** Collecting data, working with statistics, **FYM:** Collecting data, reviewing the article, **MSA:** Collecting data, reviewing the article, **HŞC:** Designing the study, reviewing the article, mentor.

REFERENCES

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2013. CA Cancer J Clin 2013; 63:11-30.
2. Mik M, Berut M, Dziki L, Trzcinski R, Dziki A. Right- and left sided colon cancer - clinical and pathological differences of the disease entity in one organ. Arch Med Sci 2017; 13(1):157-62.
3. Arıncı K, Elhan A. Anatomi Cilt I. 4. Baskı. Ankara, Güneş Kitabevi 2006; 251-61.
4. Tejpar S, Stintzing S, Ciardiello F, Tabernero J, Van Cutsem E, Beier F, Esser R, Lenz HJ, Heinemann V. Prognostic and predictive relevance of primary tumor location in patients with RAS wild-type metastatic colorectal cancer: Retrospective analyses of the CRYSTAL and FIRE-3 trials. JAMA Oncol 2017; 3(2):194-201.
5. Kumar V, Cotran RS, Robbins SL. Temel patoloji. Çevikbaş U (Ed). 7. Baskı. İstanbul, Nobel Tıp Kitabevleri 2003; 580-5.
6. Papadakis MA, Mcphee SJ. Current medical diagnosis and treatment. Rabow MW (ed). 55. Baskı. New York, McGraw-Hill Education 2016;1615-22.
7. Huang CW, Tsai HL, Huang MY, Huang CM, Yen YS, Ma CJ, Wang JY. Different clinicopathologic features and favorable outcomes of patients with stage III left-sided colon cancer. World J Surg Oncol 2015; 13:257.
8. Venook AP, Niedzwiecki D, Innocenti F, Fruth B, Greene C, O'Neil BH, Shaw J, Atkins J, Horvath LE, Polite B, Meyerhardt JA, O'Reilly EM, Goldberg R, Hochster HS, Blanke CD, Schilsky R, Mayer RJ, Bertagnolli M, Lenz HJ. Impact of primary tumor location on overall survival (OS) and progression-free survival (PFS) in patients (pts) with metastatic colorectal cancer (mCRC): Analysis of CALGB/SWOG 80405 (Alliance) [abstract]. In: 2016 ASCO Annual Meeting; Chicago (IL), USA. Alexandria (VA): American Society of Clinical Oncology, 2016.
9. Warschkow R, Sulz MC, Marti L, Tarantino I, Schmied BM, Cerny T, Güller U. Better survival in right-sided versus left-sided stage I - III colon cancer patients. BMC Cancer 2016; 16:554.
10. Jung MK, Shin US, Ki YJ, Kim YB, Moon SM, Sung SJ. Is the location of the tumor another prognostic factor for patients with colon cancer?. Ann Coloproctol 2017; 33(6):210-8.
11. Holch JW, Ricard I, Stintzing S, Modest DP, Heinemann V. The relevance of primary tumor location in patients with metastatic colorectal cancer: A meta-analysis of first-line clinical trials. Eur J Cancer 2017; 70:87-98.
12. Liu F, Li C, Jia H, Yang L, Wu Y, Zhao J, Cai S, Zhu J, Xu Y. Is there a prognostic value of tumor location among Chinese patients with colorectal cancer?. Oncotarget 2017; 8(24):38682-92.
13. Moritani K, Hasegawa H, Okabayashi K, Ishii Y, Endo T, Kitagawa Y. Difference in the recurrence rate between right- and left-sided colon cancer: A 17-year experience at a single institution. Surg Today 2014; 44(9):1685-91.
14. Qiu MZ, Pan WT, Lin JZ, Wang ZX, Pan ZZ, Wang FH, Yang DJ, Xu RH. Comparison of survival between right-sided and left-sided colon cancer in different situations. Cancer Medicine 2018; 7(4):1141-50.
15. Gervaz P, Bucher P, Morel P. Two colons-two cancers: Paradigm shift and clinical implications. J Surg Oncol 2004; 88:261-6.
16. Yamauchi M, Lochhead P, Morikawa T, Huttenhower C, Chan AT, Giovannucci E, Fuchs C, Ogino S. Colorectal cancer: A tale of two sides or a continuum? Gut 2012; 61: 794-7.
17. Schrag D, Weng S, Brooks G, Meyerhardt JA, Venook AP. The relationship between primary tumor sidedness and prognosis in colorectal cancer [abstract]. In: 2016 ASCO Annual Meeting; 2016 Jun 3-7; Chicago (IL), USA. Alexandria (VA): American Society of Clinical Oncology; 2016.
18. Arnold D, Lueza B, Douillard JY, Peeters M, Lenz HJ, Venook A, Heinemann V, Van Cutsem E, Pignon JP, Tabernero J, Cervantes A, Ciardiello F. Prognostic and predictive value of primary tumor side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials. Ann Oncol 2017; 28:1713-29.
19. Benson AB, Venook AP, et al. NCCN guidelines version 2.2017 colon cancer. Mart 2017. Available online: https://www.nccn.org.