Araştırma Makalesi *Research Article*

Pamukkale Tıp Dergisi
Pamukkale Medical Journal

doi:https://dx.doi.org/10.31362/patd.567575

The effects of primary tumour location on patients with all stages of colorectal cancer

Kolorektal kanserde evrelerine göre primer tümör lokasyonunun etkileri

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Gönderilme tarihi:19.05.2019 Kabul tarihi: 30.07.2019

Abstract

Purpose: The aim of this study was to examine the effects of tumor localization in early and advanced stage colon cancer patients.

Materials and Methods: This retrospective study enrolled 249 primary colorectal cancer (CRC) patients at medical oncology department of Adnan Menderes University between 2013-2017.

Results: In early stage, left sided tumors were significantly more common in males (p=0.027). In right sided tumours recurrence developed earlier in female patients (p=0.043) and female sex young age were unfavorable prognostic factors for the relapse time. Positive and unknown RAS mutation status were found to be unfavorable prognostic factors for both side. In metastatic stage, patients with RAS mutant left sided tumors lived longer than RAS negative patients (49.0 vs 25.5 months respectively, p<0.001). In right sided tumors anti-EGFR agents provided longer OS and PFS than anti VEGF agents;11 and 1.8 months respectively. In left sided tumors, there was no difference, only PFS was longer with anti-VEGFR agents (13 months vs 6.3 months). In RAS positive patients, OS and PFS were longer with anti-VEGFR treatment in the left side tumors (OS 49.0 months vs 30.6 months PFS, 13.2 months vs 7.2 months, p=0.784).

Conclusions: In our study, the efficacy results of the treatment which was given according to the primary tumor location were not compatible with the literature. Primer tumor location is a transition period for understanding of molecular subtypes for the colon cancer. The on-going studies of genomic differences between right and left sided tumors will be able to better clarify the biologic explanation of the observed difference.

Key Words: Colorectal cancer, primary tumour location, stage.

Oktay E, Degirmencioglu S. The effects of primary tumour location on patients with all stages of colorectal cancer. Pam Med J 2019;12:433-443.

Özet

Amaç: Bu çalışmanın amacı erken ve ileri evre kolon kanseri hastalarında tümör lokalizasyonunun etkilerini incelemektir.

Gereç ve Yöntem: 2013-2017 arasında Adnan Menderes Üniversitesi'nin Tıbbi Onkoloji Bölümü'ne başvuran primer kolorektal kanser tanılı hasta retrospektif olarak tarandı ve 249 hasta çalışmaya dahil edildi.

Bulgular: Erken evrede, sol taraftaki kolorektal kanserler erkeklerde anlamlı olarak daha yaygındı (p=0,027). Sağ taraftaki tümörlerde nüks kadın hastalarda daha erken gelişti (p=0,043). Kadın cinsiyet, genç yaş nüks süresi için bağımsız prognostik faktörlerdi. RAS mutasyonun olmasının veya mutasyon durumunun bilinmemesinin her iki taraftaki tümörler için olumsuz prognostik faktörler olduğu bulundu.

Metastatik evrede, sol taraftaki tümörlerde RAS mutant olan hastaların yaşam süresi daha uzundu. (sırasıyla 49,0'a 25.5 ay, p<0,001). Sağ kolon yerleşimli kanserlerde birinci basamak tedavide anti-EGFR ajanları kullanan hastalarda anti-VEGFR ajanları alanlara göre ortalama yaşam süresi (OS) 11 ay, progresyona kadar geçen süre (PFS) 1.8 ay daha uzundu. Sol kolon tümörlerinde, ilk basamak tedavide fark yoktu. Ancak anti-VEGFR ajanlarıyla PFS daha uzundu (13 ay vs 6.3 ay). PANRAS pozitif antiVEGFR tedavisi alan hastalar içinde sol kolon yerleşimli tümörlerde OS ve PFS daha uzundu (OS 49.0 ay-30.6 ay; PFS, 13.2 ay ve 7.2 ay, p=0,784).

Sonuç: Çalışmamızda primer tümör lokasyonuna göre verilen tedavinin etkinlik sonuçları literatürle uyumlu değildi. Primer tümörün yeri, kolon kanserinde moleküler alt tiplerin anlaşılması için bir geçiş dönemidir. Sağ ve sol taraftaki tümörler arasında genomik farklılıkları araştıran çalışmalar, gözlenen farkın biyolojik açıklamasının daha iyi anlaşılmasını mümkün kılacaktır.

Anahtar Kelimeler: Kolorektal kanser, primer tümör lokalizasyonu, evre.

Oktay E, Degirmencioglu S. Kolorektal kanserde evrelerine göre primer tümör lokasyonunun etkileri. Pam Tıp Derg 2019;12:433-443.

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Introduction

Colorectal cancer (CRC) is the second leading cause of cancer-related deaths in many countries [1]. Therefore, this malignancy has always been intensely investigated and widely discussed. Recent studies focused on the differences between right and left colon cancer. These studies showed that tumours from different locations of the colon behave molecularly and clinically different. These differences were attributed to the genetic factors, environmental factors, the differentiation of embryogenic origins of the right and left colon as well as the bacterial flora [2, 3]. Studies investigating the differences between the right and left colon tumours revealed that right colon tumours were more common in women with higher grades and advance stage at diagnosis than the left colon tumours. Mucinous histology was found to be higher in the right colon tumours. Microsatellite instability, CpG island methylator phenotype (CIMP)-high, mutagenic metabolites of cytochrome p450, MAPK signalling, RAS, BRAF and PIK3CA mutations were more commonly detected in right colon tumours. Chromosomal instability, activation of the epithelial growth factor receptor (EGFR) pathway, KRAS, DCC and P53 mutations, HER1 and HER2 gene amplification and aneuploidy were observed more frequently in left colon tumours [3-6].

Based on these findings many studies were performed regarding the evaluation of treatment options. Current phase 3 studies and meta analysis showed that, overall survival (OS) of the patients with the right colon tumours was shorter than the patients with the left colon tumours. In addition, when the efficacy of the treatments and progression free survival (PFS) were analysed tumour location was found to be important for the treatment choice in colon cancer. Studies showed that patients with RAS wild-type left-sided colon cancer had a significantly greater survival benefit from the addition of anti- anti-EGFR treatment compared with anti-vascular endothelial growth factor (VEGF) treatment to standard chemotherapy [1, 3, 7]. In addition, anti-VEGF treatments were found to be more effective in right colon tumours. These new findings changed the colon cancer treatment algorithms all over the world.

The aim of this study was to examine the characteristics of patients with right and left colon tumors, effects of tumor localization in early and advanced stage colon cancer patients, as well as the efficacy of treatment on overall survival (OS), the progression free survival (PFS) and the disease free survival (DFS) to update our treatment options.

Materials and methods

Patient selection

This retrospective study enrolled with histologically confirmed primary colorectal cancer (CRC) patients who underwent CRC treatment at medical oncology department of Adnan Menderes University between 2013-2017. Clinical information on each patient was obtained from the database of hospital medical records. All of the patient files which were accessible were included in the study. Only 249 CRC patients' data were able to be reached. The study was approved by the medical ethics committee of Adnan Menderes University. Since the study was retrospective, no approval form was obtained from the patients.

The following clinicopathological characteristics were collected: sex (male vs. female), age (<65 years vs. ≥65 years), stage, date of diagnosis, date of death, tumor location, presence or absence of adjuvant therapy, recurrence date, chemotherapy treatments at metastatic stage, progression date and mutation status.

Statistical Analysis

All analyses were conducted by www.e-picos.com, New York, NY. Continuous variables were presented by means and standard deviation values and categorical variables were expressed by frequencies and percentages. The relationship among the categorical variables was analyzed with the chi-square test Univariate survival analysis was performed using the Kaplan-Meier method with the log-rank test. A cox-regression analysis was run to understand multivariate interaction of prognostic factors. A p-value less than 0.05 was considered as statistically significant.

Results

Patient Characteristics and Treatment Properties

In total, 146 (59.6%) male and 99

(40.4%) female patients were included. The characteristics of the 245 patients are summarized in Table 1. There were 27 (11%) stage I, 69 (28.2%) stage II, 94 (54.4%) stage III and 55 (22.4%) stage IV diseases. Sixty-six (26.9%) of the patients had right sided colon tumor and 81 (33.1%) of them were left sided colon and 98 (40%) rectum tumor. At the time of diagnosis, 51 (77.2%) and 139 (77.7%) patients were diagnosed as early stage, 15 (32.8%) and 40 (22.3%) patients were diagnosed as metastatic stage in right side and left side tumors respectively (p=0.949).

Table 1. Patient and disease characteristics.

Age (Mean, SD)	62.4	12.8
Sex (n, %)		
Male	146	59.6
Female	99	40.4
Stage (n, %)		
1	27	11
2	69	28.2
3A	11	4.5
3B	70	28.6
3C	13	5.3
4	55	22.4
Primary location (n,%)		
Right-sided	66	26.9
Left-sided	179	73.1
Colon	81	33.1
Rectum	98	40.0
Family History (n,%)		
Absent	61	24.0
Present	22	9.0
Unknown	162	66.1
Histological Type (n, %)		
Adenocancer	217	88.6
Mucinous	28	11.4
Comorbidity (n, %)		
Absent	125	51
Present	120	49
Operation (n, %)		
Absent	26	10.6
Present	219	89.4
RAS Mutation (n, %)		
Absent	33	13.5
Present	47	19.2
Unknown	165	67.5
Status (n, %)		
Alive	157	64.1
Ex	88	35.9

n: number of patients SD: Standard deviation

Relation Between The Clinical Outcome and The Tumor localization in Early Stage CRC Patients

Primary tumor location and patient characteristics in early stage CRC patients were shown in Table 2. Left side tumors were significantly more common in males (p=0.027). There were no statistically significant differences between the right and left side tumors in other clinicopathological parameters. The relationship between relapse time and clinical parameters were examined between right and left colon in Table 3. Recurrence developed earlier in female patients when compared to the male patients in right colon tumors (p=0.043). Cox-regression analyses showed that stage and positive and unknown RAS mutation status were independent unfavorable prognostic factors for relapse time in early stage CRC (Table 4). Cox analysis was performed separately for the right and the left colon (Table 5). Female sex, young age were independent unfavorable prognostic factors for the relapse time in early stage right colon cancer patients. Positive and unknown RAS mutation status were found to be unfavorable prognostic factors for both right and left side tumors.

Relation Between The Clinical Outcome and The Tumor Localization in Metastatic Stage CRC Patients

Primary tumor location and patient characteristics in metastatic stage CRC patients were shown in Table 6. Data also included patients who developed recurrence after adjuvant therapy. Liver metastasis was found to be more common in the left side tumors. However, other parameters were not statistically significant. OS and PFS were analyzed between right and left side tumors and compared the parameters in metastatic stage CRC (Table 7, 8). Male patients had a longer OS than female patients in right sided tumors (49.1 vs 15.9 months respectively, p<0.036). Patients with RAS mutant left sided tumors lived longer than RAS negative patients (49.0 vs 25.5 months respectively, p<0.001). OS was 11 months and PFS was 1.8 months longer with anti-EGFR agents in first-line treatment in right sided tumors, however it was not statistically significant. In left sided tumors, there was no difference in OS, but PFS was longer with anti-VEGFR agents in first-line treatment but it was not significant (13 months vs 6.3 months). In RAS positive patients, antiEGFR treatment can not be applied. Therefore, it is the only kind of data pertaining to this patient group. With antiVEGFR treatment, OS and PFS were longer in the left side tumors compared to the right side tumors. However, in RAS positive group, it was not statistically significant (OS 49.0 months vs 30.6 months PFS 13.2 months vs 7.2 months, p=0.784). In multivariate analysis young age and negative RAS mutation were found to be negative prognostic factors on OS. There were not able to determine any statistically significiant prognostic factor on PFS. Cox analysis was performed separately for right and left colon like early stage CRC patients. However, in cox regression analysis, we could not show effective prognostic factor for OS or PFS.

Discussion

In this study, the influence of primary tumor location in CRC was analyzed. Although there were no significant differences in the survival times and the PFS between antiEGFR and antiVEGFR front-line targeted therapies for metastatic CRCs, left sided tumors were superior to right sided tumors in terms of the survival times and the PFS. When subgroup analyses were conducted, liver metastasis were found to be more common in the left sided tumors. In addition, male patients had a longer lifespan than female patients with the right sided tumors. Also, patients with RAS mutant left sided tumors lived longer than patients with RAS negative tumors. However, there was no difference in RAS mutation status and survival among the right-sided tumors. Studies showed that patients with RAS wild-type right-sided colon cancer had a significantly greater survival benefit from the addition of VEGF treatment to the standard chemotherapy [1, 3, 7]. On the other hand, in this study, although statistically not significant front-line anti-EGFR treatments were found to be more effective in right colon tumours on OS and PFS. Survival benefit between these treatments in the left sided tumors (25.3 vs 25.6 months) were not detected in the analyses. However antiVEGFR front-line targeted therapies provided better PFS in left side tumors (13 vs 6.3 months, not statistically significant, p=0.268). On the contrary, current phase 3 studies and meta analysis showed that patients with RAS wild-type left-sided

Table 2. Relationship between primary tumor location and patient characteristics in early stage.

	Right Side		Left Side		*p*
Age (Mean, SD)	62.3	13.7	61.7	12.8	0.777
Sex (n, %)					
Male	24	47	90	64.7	0.027
Female	27	53	49	35.3	
Stage (n, %)					
1	4	7.8	23	16.5	
2	20	39.2	49	35.3	
3A	5	9.8	6	4.3	0.232
3B	18	35.2	52	37.4	
3C	4	8.0	9	6.5	
Histological Type (n, %)					
Adenocancer	42	82.4	124	89.2	0.207
Mucinous	9	17.6	15	10.8	
RAS Mutation (n, %)					
Absent	4	7.9	11	7.9	
Present	3	5.9	16	11.5	0.514
Unknown	44	86.2	112	80.6	
Family History (n, %)					
Absent	15	26.2	39	25.2	
Present	8	73.8	11	73.3	0.249
Unknown	28		89		
Recurrens (n, %)					
Absent	39	89.2	103	90.4	0.739
Present	12	10.8	36	9.6	
Status (n, %)					
Alive	38	74.5	109	78.4	0.568
Ex	13	25.5	30	21.6	
DFS(Median, Std.Error)	46.62	7.37	38.52	2.88	0.324
OS After Relaps(Median, Std.Error)	44.10	5.43	74.9	10.40	0.607
OS(Median, Std.Error)	50.75	7.66	44.29	3.35	0.452

n: number of patients,SD: Standard deviation, DFS: Disease Free Survival, OS: Overall Survival

Table 3. Relapse time analyses between tumor location and other parameters.

	Median (months)	95% C.I.		*p*	Median (months)	95% C.I.		*p*
		Lower	Upper			Lower	Upper	
Sex								
Male	39.2	18.0	65.5	*p* <0.043	41.6	25.3	57.8	0.647
Female	9.1	1.6	16.6		30.3	23.7	36.9	
Stage								
1	.	.	.		13.4	068	26.1	
2	15	12.6	17.4		61.1	34.1	88.2	
3A	38	17.2	58.7	0.270	19.8	7.1	32.4	0.225
3B	59.8	0.11	119.6		32.6	24.6	40.6	
3C	10.4	0.0	22.1		16.8	27.2	21.8	
Histological Type								
Adenocancer	33.7	13.8	53.5	0.552	32.3	26.3	38.3	0.927
Mucinous	15.3	3.2	27.3		38.5	5.9	71.2	
Family History								
Absent	25.9	3.5	48.3		66.3	33.0	99.6	
Present	51.5	0.0	119.6	0.505	38.6	17.9	59.2	0.261
Unknown	24.9	7.7	42.1		29.9	23.3	36.6	
Adjuvan Treatment								
Absent	16.4	15.8	17.0	0.389	25.9	15.8	36.0	0.645
Present	36.8	14.1	59.6		39.6	27.6	51.7	
RAS Mutation								
Absent	22.3	1.74	42.7		26.5	15.7	37.2	
Present	30.2	11.5	48.9	0.475	32.8	20.2	45.5	0.700

Table 4. Cox regression - multivariate recurrens time analyses in early stage crc.

	OVERALL SURVIVAL				
	B	*p*	HR	95.0% CI	
				Lower	Upper
Age	0.011	0.420	1,694	0.733	3.912
Sex	0.344	0.318	1.411	0.718	2.774
Stage	**-2.596**	**0.004**	**13.411**	**2.275**	**79.043**
RAS	**-2.395**	**0.000**	**0.091**	**0.041**	**0.202**
Tumor Location	0.527	0.217	1.694	0.733	3.912
Histologic Type	0.587	0.192	1.799	0.744	4.347
Family History	0.455	0.406	1.576	0.464	5.353

Table 5. Cox regression - multivariate relapse time analyses between tumor location.

	Right Colon					Left Colon				
	B	*p*	HR	95.0% CI		B	*p*	HR	95.0% CI	
				Lower	Upper				Lower	Upper
Sex	**-1.788**	**0.075**	**0.167**	**0.023**	**1.198**	0.124	0.772	1.133	0.489	2.624
Age	**0.155**	**0.018**	**1.167**	**1.027**	**1.326**	-0.001	0.936	0.999	0.964	1.034
RAS	**-7.216**	**0.003**	**0.001**	**0.000**	**0.084**	**-2.229**	**0.000**	**0.108**	**0.043**	**0.268**
Histologic Type	1.800	0.150	6.048	0.523	70.00	-0.036	0.949	0.964	0.318	2.928

Table 6. Relationship between primary tumor location and patient characteristics in metastatic stage.*

	Right Side		Left Side		*p*
Age*(Mean, SD)*	64.4	14.9	61.08	12.1	0.24
Sex (n, %)					
Male	17	63	45	60	0.732
Female	10	37	31	40	
Metastasis Location (n, %)					
Liver	4	7.8	31	16.5	0.006
Lung	3	39.2	7	35.3	
Local Recurrens	3	9.8	9	4.3	
Periton	9	35.2	5	37.4	
>1 Location	8	8.0	24	6.5	
Histological Type (n, %)					
Adenocancer	22	81.5	68	89.4	0.283
Mucinous	5	18.5	8	10.6	
RAS Mutation (n, %)					
Absent	10	37	20	26.4	0.368
Present	9	33	37	48.6	
Unknown	8	30	19	25.0	
Family History (n, %)					
Absent	5	18.5	13	17.1	0.559
Present	3	11.1	4	5.2	
Unknown	19	70.4	59	77.7	
Treatment (n, %)					
CT	9	10.8	25	9.6	0.836
CT+antiEGFR	3	89.2	6	90.4	
CT+antiVEGFR	12		38		
PFS (Median, SD)	16.4	2.10	26.4	3.0	0.328
Status (n, %)					
Alive	5	18.5	19	25	0.494
Ex	22	81.5	57	75	
OAS (Median, SD)	69.4	12.3	76.4	8.8	0.883

* recurrent patients were included in this group. n: number of patients,SD: Standard deviation, PFS: Progression Free Survival

Table 7. Survival analyses between tumor location and other parameters in metastatic stage crc.

	Right Colon				Left Colon			
	Median (months)	95% C.I.		*p*	Median (months)	95% C.I.		*p*
		Lower	Upper			Lower	Upper	
Sex								
Male	49.1	19.9	60.3	<0.036	47.0	36.7	57.3	0.789
Female	15.9	9.4	22.5		54.5	37.2	71.7	
Histological Type								
Adenocancer	33.5	16.8	50.2	0.657	33.8	27.5	40.0	0.113
Mucinous	21.6	17.5	45.1		66.3	16.5	116.1	
Family History								
Absent	32.4	0	65.6	0.136	50.8	30.8	85.8	0.116
Present	66.7	10.5	123.0		58.3	37.7	63.9	
Unknown	23.4	10.7	36.0		33.1	25.1	41.0	
RAS Mutation								
Absent	35.5	14.0	9.1	0.793	25.5	18.7	26.9	<0.001
Present	30.7	12.8	5.6		49.0	35.2	46.9	
1. Line Treatment Tyoe								
RAS(-)*								
antiEGFR	46.6	0	122.0	0.802*	25.3	10.6	40.1	0.65*
antiVEGFR	35.6	6.9	64.9		25.6	17.6	33.7	
RAS(+)								
antiEGFR	0	0	0		0	0	0	
antiVEGFR	30.6	0.0	65.9		49.0	35.2	62.8	

* Only RAS negative patients were compared. EGFR: Epidermal Growth Factor Receptor, VEGFR: Vascular Endothelial Growth Factor Receptor

Table 8. Progression free survival analysis in metastatic stage crc patients.

	Right Colon				Left Colon			
	Median (months)	95% C.I.		*p*	Median (months)	95% C.I.		*p*
		Lower	Upper			Lower	Upper	
Sex								
Male	9.1	5.2	13.0	0.933	12.8	9.6	16	0.926
Female	8.5	4.4	12.5		13.5	7.1	19.8	
Histological Type								
Adenocancer	9.0	5.5	12.6	0.693	13.3	9.8	16.8	0.660
Mucinous	10.7	4.9	16.6		9.6	8.5	10.7	
Family History								
Absent	8.3	5.8	10.7	0.706	14.6	9.4	17.6	0.352
Present	11.4	0.5	23.0		15.1	3.8	7.0	
Unknown	8.4	5.3	11.4		11.8	8.4	9.0	
RAS Mutation								
Absent	10.5	6.4	14.5	0.323	11.8	6.4	17.2	0.552
Present	7.0	3.9	10.1		13.2	9.9	16.9	
1. Line Treatment Tyoe*								
RAS(-)								
antiEGFR	12.5	5.9	0.9	0.689*	6.3	0.1	12.6	0.268*
antiVEGFR	10.7	1.6	7.5		13.0	6.7	33.7	
RAS(+)								
antiEGFR	0	0	0		0	0	0	
antiVEGFR	7.2	3.2	11.2		13.2	9.8	16.3	

* Only RAS negative patients were compared. EGFR: Epidermal Growth Factor Receptor, VEGFR: Vascular Endothelial Growth Factor Receptor

Table 9. Cox regression - multivariate analyses in metastatic stage crc.

	OVERALL SURVIVAL					DISEASEFREE SURVIVAL				
	B	*p*	HR	95.0% CI		B	*p*	HR	95.0% CI	
				Lower	Upper				Lower	Upper
Sex	0.315	0.306	1.370	0.750	2.502	0.113	0.705	1.120	0.623	2.015
Age	**0.066**	**0.000**	**1.068**	**1.032**	**1.105**	0.016	0.323	1.016	0.945	1.048
RAS	**-1.341**	**0.000**	**0.262**	**0.125**	**0.546**	0.037	0.919	0.964	0.473	1.964
Tumor Location	-0.168	0.650	0.845	0.408	1.750	-0.474	0.195	0.622	0.304	1.275
Histologic Type	0.227	0.633	1.255	0.495	3.181	0.273	0.578	1.314	0.502	3.435
Family History	-1.221	0.126	0.295	0.061	1.462	-0.791	0.279	0.454	0.109	1.895
1. Line Treatment Tyoe*	0.109	0.887	1.115	0.246	5.048	0.616	0.470	1.852	0.348	9.854

colon cancer had a significantly greater survival benefit from the addition of antiEGFR treatment when compared with the antiVEGF treatments. We analysed the PFS and OS time of the left and right sided RAS mutant tumors' which were all treated with antiVEGFR agent. OS and PFS were longer in the left side tumors compared to the right side tumors, however it was not statistically significant (OS: 49.0 vs 30.6 months, PFS: 13.2 vs 7.2 months, *p*=0.784). In contrast, in alliance study, left sided tumors with KRAS mutant were associated with poorer OS compared with right sided tumors with KRAS mutant [3, 8]. Currently, data on RAS mutant left side tumors versus right side tumors are limited; therefore, the prognostic and predictive value of the primary tumour site within the RAS mutant population still requires evaluation. In multivariate analysis, young age and the negative RAS mutation status were found to be negative prognostic factors on OS, however the statistical effect of prognostic factors could not be determined on PFS.

It has been shown that patients with right side tumors are older and more often female, and the disease is associated with advanced tumor stages, increased tumor size, poorly differentiated tumors, and the tumors with different molecular patterns. Many studies have demonstrated poorer OS and PFS in patients with right sided tumors [9, 10]. In this study, we examined the differences in clinicopathologic parameters between the right and the left sided colon cancers not only in metastatic disease but also in early stage CRC. In this study, we showed that the left side tumors were significantly more common in males (*p*=0.027). We analysed clinical parameters affecting the relapse time in the right and left side tumors. In this current study, DFS was found shorter in female with right side tumors (*p*=0.043). The other parameters did not provide statistically significant differences between the right and left side tumors. COX Regression analyses showed that advance stage (stage III) and the positive and the unknown RAS mutation status were independent unfavorable prognostic factors for DFS in early stage CRC. This multivariate analysis was performed separately for the right and the left colon. Female sex, young age were independent unfavorable prognostic factors for relapse time in early stage right colon cancer patients. Positive and unknown RAS mutation status was found to be unfavorable prognostic factor for both right and left side tumors. The survival time after relapse was also examined. In the right side tumors, the survival time after recurrence was 44.5 months, while it was 74.9 months in the left side tumors.

This study has several limitations. Firstly, as a retrospective study from a single institution with a small number of patients, the statistical power is obviously limited. Secondly, the regimens of the adjuvant chemotherapy and the front-line chemotherapy for the metastatic stage were different.

In conclusion; in our study, the efficacy results of the treatment which was given according to the primary tumor location were not compatible with the literature. We believe that primer tumor location is a transition period for understanding of molecular subtypes at the colon cancer. The on-going studies of genomic differences between right and left sided tumors will able to better clarifying of the biologic explanation of the observed difference. Until more definitive studies available all patients with RAS wild type tumors can be considered for anti-EGFR treatments. Therefore much largely scaled prospective studies are needed and also the further studies should be focused on clinicopathological and genetic factors and their effects on OS, PFS and DFS separately on the right and the left colon.

Conflict of Interest: Authors declare there is no conflict of interest.

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