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Can horizontal diameter of colorectal tumor help predict prognosis?

Kolorektal kanserde horizontal çap prognozu tahminde yardım eder mi?

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ABSTRACT

Objective: We aimed to investigate the relationship between the horizontal tumor diameter and prognosis.

Material and Methods: Patients' records were analyzed retrospectively. Patient data, including age, gender, vertical penetration, anatomic location, differentiation of the tumor, tumor node metastasis (TNM) stage, survival rate, and disease-free survival, were analyzed to find out if there was any correlation with horizontal tumor diameter.

Results: A total of 439 colorectal cancer patients were enrolled. Patients were stratified into two groups according to the horizontal tumor diameter (≤4.5 cm vs. >4.5 cm). Poorly differentiated tumors were significantly larger than other differentiation groups (p=0.003). The horizontal diameter increased with increase in T-stage (p<0.001). Similarly, the number of positive lymph nodes increased significantly as the size of the horizontal tumor diameter increased (p<0.001). The relationship between TNM staging and the horizontal diameter of tumors in both groups was examined, and it was found that the progression of tumor stage was accompanied by increased horizontal diameter (p<0.001). It was also found that the horizontal tumor diameter was not correlated with local recurrence (p=0.063). However, distant metastasis was higher in patients with a tumor larger than 4.5 cm (p=0.02). Although the disease-free survival was shorter in patients with a horizontal tumor diameter more than 4.5 cm, the difference was not statistically significant.

Conclusion: There is a significant relation between horizontal diameter of the tumor and depth of the tumor, lymph node involvement, overall survival, and distant metastasis. Horizontal diameter of the tumor can possibly be used as a prognostic factor in colorectal cancer patients.

Key Words: Colon, rectum, tumor, horizontal diameter, prognosis

ÖZET

Amaç: Bu çalışmada horizontal tümör çapı ile prognoz arasındak ilişkiyi araştırmayı amaçladık.

Gereç ve Yöntemler: Hastalara ait kayıtlar geriye dönük olarak incelendi. Yaş, cinsiyet, vertikal penetrasyon, anatomik lokalizasyon, tümör diferansiyasyonu, tümör nod metastaz (TNM) evresi, yaşam süreleri ve hastalıksız sağkalım sürelerini içeren hasta bilgileri ile horizontal çap arasında olası ilişki araştırıldı.

Bulgular: Çalışmaya 439 kolorektal kanser hastası dahil edildi. Hastalar tümör çapına göre iki gruba ayrıldı (≤4,5 cm'e karşı >4,5 cm). Kötü diferansiye tümörler diğerlerine göre daha büyük çapa sahipti (p=0,003). Tümörün T evresi arttığında horizontal çap artmaktaydı (p<0,001). Benzer şekilde horizontal çap arttıkça pozitif lenf nodu sayısı da belirgin şekilde artmaktaydı (p<0,001). Her iki grupta TNM evreleri ve horizontal çap arasındaki ilişki incelendi ve TNM evresi artışının horizontal çapın artışına eşlik ettiği saptandı (p<0,001). Horizontal çap ile lokal nüks arasında ilişki olmadığı bulundu (p=0,063). Ancak 4,5 cm'den büyük tümörlerde uzak metastaz daha fazlaydı (p=0,02). Hastalıksız sağ kalım oranları 4,5 cm'den büyük tümörlerde daha kısa olmasına rağmen bu farklılık istatistiksel olarak anlamlı değidi.

Sonuç: Horizontal çap ile tümörün derinliği, lenf nodu tutulumu, genel sağkalım ve uzak metastaz arasında anlamlı bir ilişki olduğunu ve bu ilişkinin prognostik bir faktör olarak kullanılabileceğini düşünmekteyiz.

Anahtar Kelimeler: Kolon, rektum, tümör, horizontal çap, prognoz

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer among men and women in developed countries (1, 2). The preferred management of non-metastatic colon cancer is removal of the tumor and surrounding lymph nodes. Post-surgical treatment is closely related to the tumor node metastasis (TNM) staging system (3, 4).

Depth of tumor penetration (T), regional lymph node involvement (N), and distant metastasis (M) are major parameters predicting the prognosis in CRC patients. The literature data show that tumor staging may be more accurate and the prognosis may be more favorable as the number of harvested lymph nodes increases (5-7).

Several studies show that vertical penetration of the tumor on the bowel wall is related to the number of positive lymph nodes and a poorer prognosis. The relationship between horizontal tumor diameter and prognosis is still controversial (8-10). Few studies in gastric and colon cancer indicate that the horizontal

extension of the tumor could be an important prognostic factor (2, 11, 12).

In this study, we aimed to investigate the relationship between horizontal tumor diameter and prognosis, as well as other well-known prognostic factors of CRC.

MATERIAL AND METHODS

A total of 486 colorectal cancer patients who were treated in our surgical clinic between 1991 and 2012 were enrolled. Data were obtained from a CRC database and the medical records of the patients. Clinical information and follow-up data were obtained from hospital charts and electronic records. Patients who received neo-adjuvant therapy or underwent palliative resection, had a pathological diagnosis other than adenocarcinoma, and patients with inflammatory bowel disease were excluded (n=47). The remaining 439 patients were included in our retrospective analysis.

Adjuvant chemotherapy was given according to the lymph node involvement. Patients with node-negative tumors did not receive chemotherapy. Patients showing poor prognostic indicators, such as vascular invasion, perineural invasion, and preoperative high levels of CEA, received 5-fluorouracil-based chemotherapy, regardless of their nodal status.

Patient data, including age, gender, vertical penetration, anatomic location, and differentiation of the tumor; TNM stage, survival rate, and disease-free survival were analyzed to find out if there was any correlation with the horizontal tumor diameter. Tumors located from the cecum to the splenic flexure were defined as right-sided cancers, and tumors located from the splenic flexure to the sigmoid colon were defined as left-sided cancers. Tumors originating from the recto-sigmoid junction or rectum were defined as rectal cancers. Patients were staged using the 7th edition of the American Joint Committee on Cancer (AJCC) TNM staging system. Horizontal tumor diameters were determined from formalin-fixed cancer specimens based on the archived pathology report. We used receiver-operating characteristic (ROC) curves for the determination of the appropriate cut-off value of the tumor size, which affects long-term survival in all stages. Different cut-off levels were examined according to the ROC curve analysis to find out the best cut-off level to correlate the survival, disease-free survival, and the other prognostic parameters mentioned above.

Statistical Analysis

All statistical analyses were performed using Statistical Package for the Social Sciences 16.0 (SPSS Inc., Chicago, IL, USA). Student's t-test and chi-square test were used in order to determine the distribution of demographic characteristics of patients and to make probability charts. The Kaplan-Meier method was used in order to calculate cumulative survival rates according to the horizontal tumor diameter, lymph node metastasis (N stage), and TNM staging. The difference in survival rates between groups was calculated by using the log-rank test. Cox regression analysis was performed in order to determine the prognostic factors that affected the survival time ($p<0.05$).

RESULTS

Demographic characteristics of the patients, histological characteristics of the tumors, and overall survival are summarized in Table 1.

Table 1. Clinical and pathological characteristics of the patients

	n	%
Gender		
Female	188	42.8
Male	251	57.2
Age		
Mean±S.E.M	66.6±13.3	
Female	67.5±13.2	
Male	66±13.5	
Tumor location		
Right colon	117	26.7
Left colon	187	42.6
Rectum	135	30.8
Tumor differentiation		
High	74	16.9
Middle	333	75.9
Low	28	6.4
Undifferentiated	4	0.9
pT stage		
1	16	3.0
2	73	16.6
3	304	69.2
4	46	10.5
pN stage		
Median (range)	10 (1-67)	
Mean±S.E.M	12±0.4	
<12	257	58.5
≥12	182	41.5
0	257	58.5
1	135	30.8
2	47	10.7
TNM stage		
I	78	17.8
II	161	36.7
III	136	31
IV	64	14.6
Follow-up		
Alive	210	56
Dead	165	44
Overall survival (month)		
Median (range)	30.2 (0.1-237.1)	
Mean±S.E.M	42.3 ± 2.2	
Disease-free survival (month)		
Median (range)	22.6 (0-237.1)	
Mean±S.E.M	38±2.2	

S.E.M: standard error of the mean; pT: pathologic T stage; pN: pathologic N stage; LN: lymph node; TNM: tumor, node, metastasis

By using ROC curve analysis, we determined a cut-off value of 4.5 cm for the horizontal diameter to best discriminate between patients' survival in the whole group. Based on the ROC curve analysis, patients were stratified into two groups according to the horizontal tumor diameter (≤4.5 cm vs. >4.5 cm). The relationship between prognostic pathological features and the horizontal tumor diameter was examined (Table 2). The horizontal tumor diameter was significantly lower in left-sided tumors of the colon compared to the right-sided tumors (p=0.004). Poorly differentiated tumors were significantly larger than others when we used a cut-off value of 4.5 cm (p=0.003).

The depth of vertical tumor penetration was also analyzed, and it was found that the horizontal diameter increased with increase in T-stage (p<0.001). Similarly, the number of positive lymph nodes increased significantly as the size of the horizontal tumor diameter increased (p<0.001). The relationship between TNM staging and the horizontal diameter of tumors in both groups was examined, and it was found that the progression of tumor stage was accompanied by increased horizontal diameter (p<0.001). Cox regression analysis showed that TNM staging and horizontal diameter had a significant effect on survival (p<0.001, p=0.012, respectively).

It was also found that horizontal tumor diameter was not correlated with local recurrence (p=0.063). However, distant metastasis was higher in patients with a tumor larger than 4.5 cm (p=0.02). Patients with a horizontal tumor diameter less than 4.5 cm showed favorable survival (p=0.014) (Table 2). Although the disease-free survival was shorter in patients with a horizontal tumor diameter more than 4.5 cm, the difference was not statistically significant (p=0.06). Kaplan-Meier curves representing overall survival and disease-free survival for horizontal diameter of the tumor are shown in Figure 1 and Figure 2, respectively. The survival of patients whose tumors were >4.5 cm was significantly worse than patients whose tumors were ≤4.5 cm. According to these data, the survival rate decreased as tumor size increased.

Table 2. Patient demographics, tumor characteristics, and survival between two groups according to horizontal diameter

	≤4.5 cm (n=208)	>4.5 cm (n=231)	p
Gender			
Female	92	96	0.32
Male	116	135	
Age groups			
Median (range)	69 (21-92)	68 (22-93)	0.133
Mean±S.E.M	67.6±0.8	65.7±1	
Tumor location			
Right colon	40	77	0.004
Left colon	98	89	
Rectum	70	65	
Tumor Differentiation			
High	43	31	0.003
Middle	157	176	
Low	7	21	
Undifferentiated	1	3	
pT Stage			
1	13	3	<0.001
2	46	27	
3	137	167	
4	12	34	
pN Stage			
0	139	118	<0.001
1	53	80	
2	16	33	
TNM Stage			
I	53	25	0.001
II	74	87	
III	54	82	
IV	27	37	
Local recurrence			
Yes	16	28	0.063
No	166	167	
Distant metastasis			
Yes	44	66	0.02
No	122	110	
Unknown	42	55	
Follow-up			
Alive	117	93	0.001
Dead	64	101	
Missed	27	27	
Overall survival (month)			
Median (range)	31 (0.1-187.3)	28.5 (0.1-237.1)	0.014
Mean±S.E.M	47.9±3.3	37.2±2.8	
Disease-free survival (month)			
Median (range)	25.8 (0.1-187.3)	19.5 (0.1-237.1)	0.06
Mean±S.E.M	42.3±3.3	33.9±3	

DISCUSSION

TNM staging is the best prognostic parameter for patients with CRC (13). The average survival rate according to the stage of the tumor is 93% for stage 1, 78% for stage 2, 69% for stage 3, and 8% for stage 4, respectively (14). There are several studies indicating that tumor size is associated with the depth of invasion, lymph node metastasis, and survival in patients with gastric carcinoma (12, 15-17). However, the studies about the relationship between horizontal diameter of the tumor and prognosis in patients with CRC are limited and the results are controversial (18, 19). Kornprat et al. (2) identified 4.5 cm as the optimal cut-off value in a group of patients using ROC curve analysis, as we did, and they concluded that tumor size is the most important prognostic parameter for patients with CRC. Patients were evaluated according to this cut-off value, and the authors demonstrated that there was a significant relationship between tumor size and anatomic location of the tumor, high T and N classification, International Union against Cancer (UICC) stage, and tumor grade.

Right-sided tumors mostly do not cause any signs or symptoms in the early stages, and they are generally diagnosed when they attain a large size. These tumors are diagnosed

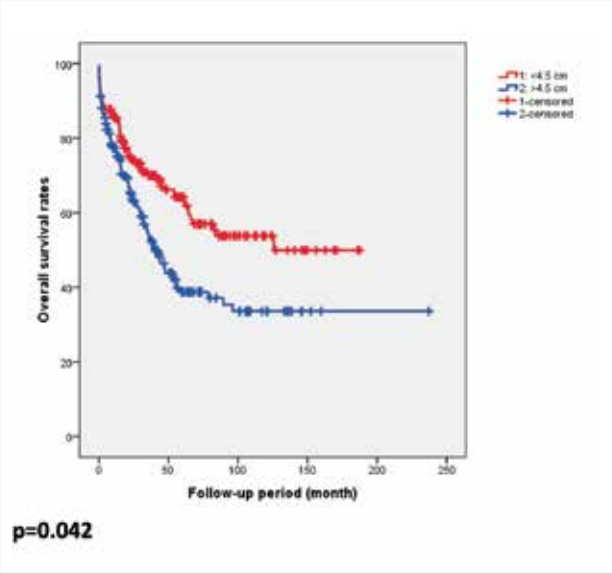


Figure 1. Kaplan-Meier curve of overall survival for horizontal diameter of colorectal tumors with a cut-off value of 4.5 cm

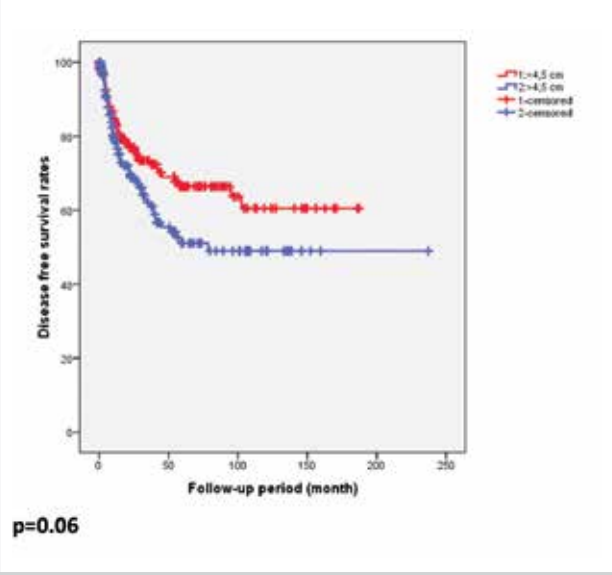


Figure 2. Kaplan-Meier curve of disease-free survival for horizontal diameter of colorectal tumors with a cut-off value of 4.5 cm

in the early stages with the technological improvement and common use of colonoscopy, but the problem is still going on. Several studies emphasized that larger tumors are more frequent in the right colon (2, 20, 21). We also found that proximal tumor cancers tended to have a larger diameter.

We investigated the relationship between tumor differentiation and horizontal diameter of the tumor, and we found that poor differentiation was associated with larger tumor size. Although Tekuchi et al. (22) and Kornprat et al. (2) also highlighted the same relationship, similar to our study; Matsuda et al. (23), Crozier et al. (18), and Bjerkest et al. (20) did not report such a relationship.

Wolmark et al. (19) compared tumor size with depth of penetration, and their results indicated that tumor size was smaller in Duke's stage C1 than stage C2. Such a relationship was shown in other studies that compared different-sized tumor groups by using TNM staging (18). Adachi et al. (12) and Saito et al. (17) showed a similar relationship in patients with gastric cancer. We also found that larger tumors penetrated deeper.

As the presence of lymph node involvement is used in order to determine adjuvant therapy in CRC patients, the relationship between horizontal diameter of the tumor and lymph node invasion could be important. According to our data, we found that there was a significant statistical relationship between the size of the horizontal diameter and lymph node invasion; large tumors were associated with more positive lymph nodes. Although some studies in the literature support our data (2, 19, 24), other studies concluded that the size of the horizontal diameter is not an important factor in determining lymph node involvement (18, 20, 25).

The significant relationship that was found in our study between horizontal diameter of the tumor and increases in both penetration depth and number of positive lymph nodes was also seen in TNM staging. Li et al. (26) found that the diameter of the tumor was smaller than 3 cm in patients with Duke's stage A or B, and it was greater than 3 cm in patients with Duke's stage C or D. Another study demonstrated that tumor size was significantly associated with UICC stage and concluded that increasing tumor diameter was not associated with either depth of invasion or lymph node involvement (2, 18). Poritz et al. (14) investigated the effect of tumor size on metastatic disease, and it was interesting that tumor volume was smaller in patients with metastatic disease compared to patients without metastatic disease. In our study, we found that local recurrence after surgery was not related with tumor size, but presence of distant metastasis was associated with tumor size.

In the literature, there are studies that have investigated the relationship between tumor size and survival rate (2, 27, 28). When overall survival rates and 5-year survival rates are examined, it is generally proposed that large tumors have a poor prognosis. In our study, we found no significant difference between groups regarding disease-free survival rates. However, the group with tumor size smaller than 4.5 cm had a better prognosis regarding overall survival rates.

The main limitation of our study was the retrospective nature. Another limitation was that medical records were not well completed at the beginning of the study, and patients were lost at follow-up. But, we thought that this study was important, as there are a limited number of publications related to this topic in the literature.

CONCLUSION

We have evaluated our groups by comparing them with TNM staging system, an approved prognostic scoring system, in order to determine the prognostic value of tumor size, and we concluded that horizontal diameter of CRC can possibly be used as a prognostic factor, as in gastric cancers.

Ethics Committee Approval: Ethical approval is not required because of the retrospective design of the study.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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