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ORIGINAL ARTICLE

Which is the worse prognostic factor in patients with stage III colorectal cancer: tumor 4 or node 2?

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Summary

Purpose: *In the tumor (T), node (N), metastasis (M) American Joint Committee on Cancer (AJCC), and Union for International Cancer Control (UICC) (8th edition) staging system, N stage is more prominent than T stage. Our study aimed to compare the lymph node status of T4 tumors in stage III colorectal cancer (CRC).*

Methods: *A total of 475 patients (209; 44% female and 266; 56% male) were included in the study. The median follow-up period was 49 (4-176) months. The patients were separated into four groups according to their stage during diagnosis: group 1 (T4N2), group 2 (T4N1), group 3 (T1-3N2), and group 4 (T1-3N1). The disease-free survival (DFS) and overall survival (OS) of all the groups were calculated.*

Results: *The median OS was 40.5 months in group 1, 67 months in group 2, 87 months in group 3, and 138.5 months in group 4 (p<0.001). The N2 patients were separated into two groups according to their T stage: group 1 and group 3. Group 1 patients were associated with a worse OS than group 3 patients (p=0.017). The T4 patients were separated into two groups according to their N stage: group 1 and group 2. There was no statistically significant difference between group 1 and group 2 (p=0.243).*

Conclusions: *Our study showed that patients with T4 stage have worse survival rates when compared with N2 patients in stage III CRC. These results support the TNM staging system to be T-dominant rather than N-dominant.*

Key words: *AJCC staging system, colorectal carcinoma, lymph node metastasis, prognostic prediction, T4 stage*

Introduction

Long life is associated with an increased incidence of colon cancer. The risk of developing colorectal cancer (CRC) in the population over 80 years old is 5-fold higher than the population under 50 years [1]. In 2018, 1.84 million new cases of CRC and 881,000 disease-related deaths were registered [2]. This information shows that the incidence of CRC in the aging of the world's population will increase further [3,4]. Despite curative operations, the survival results of stage III CRC disease are not good enough. Therefore, it is essential to determine which patients will benefit from adjuvant therapies.

Pathologic stage is the most important indicator of survival following resection of CRC [5,6]. The tumor, node, metastasis (TNM) staging system of the American Joint Committee on Cancer (AJCC) and Union Internationale Contre Le Cancer (UICC) is considered the international standard for CRC staging [5,7]. Currently, the 8th edition of the TNM staging system is used in the United States and some other countries, whereas some European countries continue to use the 7th edition. All of the TNM staging systems use similar anatomical elements and the same principles that were in-

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herited from the Dukes staging system that was developed in 1932 [8]. Stage III disease was separated into three groups according to the 8th edition of the TNM classification: IIIA (T1-2N1/1cM0; T1N2aM0), IIIB (T3-4aN1/1cM0; T2-3N2aM0; T1-2N2bM0), and IIIC (T3-T4aN2bM0; T4aN2aM0; T4bN1/2M0) [5].

In the AJCC TNM staging system, the N stage is more prominent than the T stage, and except for patients with distant metastasis, all patients with lymph node involvement are defined as stage III. However, the Surveillance, Epidemiology, and End Results (SEER) database has shown that stage IIIA patients (T1-2N1 and T1N2a) and stage I (T1/2N0) patients have similar 5-year overall survival (OS) [9]. On the other hand, stage IIC patients (T4bN0) have a poor prognosis, similar to that of stage IIIB patients (T3-4aN1, T2-3N2a, and T1-2N2b) [10].

This study aimed to compare the prognostic value of lymph node status and T4 tumors in patients with stage III CRC.

Table 1. Demographic features and tumor characteristics of the patients stratified by subgroups

Demographics	*Group1 (T4N2) n (%)*	*Group2 (T4N1) n (%)*	*Group3 (T1-3N2) n (%)*	*Group4 (T1-3N1) n (%)*	*p value*
Gender					0.888
Female	17/38 (44.7)	17/44 (38.6)	47/103 (45.6)	128/290(44.1)	
Male	21/38 (55.3)	27/44 (61.4)	56/103 (54.4)	162/290(55.9)	
Age, years					0.288
18-49	8/38 (21.1)	5/44 (11.4)	27/103 (26.2)	68/290(23.4)	
50-64	15/38 (39.5)	24/44 (54.5)	50/103 (48.5)	120/290(41.4)	
65+	15/38 (39.5)	15/44 (34.1)	26/103 (25.2)	102/290(35.2)	
Tumor localization					<0.001
Right colon	22/38 (57.9)	11/44 (25)	23/103 (22.3)	73/290(25.1)	
Left colon	7/38 (18.4)	23/44 (52.3)	31/103 (30.1)	93/290 (32.1)	
Rectum	9/38 (23.7)	10/44 (22.7)	49/103 (47.6)	124/290 (42.8)	
Lymphatic invasion					0.005
Present	28/38 (73.7)	32/44 (72.7)	71/103 (68.9)	158/290 (54.5)	
Absent	10/38 (26.3)	12/44 (27.3)	32/103 (31.1)	132/290 (45.5)	
Vascular invasion					<0.001
Present	24/38 (63.2)	25/44 (56.8)	60/103 (58.3)	111/290 (38.3)	
Absent	14/38 (36.8)	19/44 (43.2)	43/103 (41.7)	179/290 (61.7)	
Perineural invasion					0.002
Present	19/38 (50)	17/44 (38.6)	42/103 (40.8)	76/290 (26.2)	
Absent	19/38 (50)	27/44 (61.4)	61/103 (59.2)	214/290 (73.8)	
Grade					<0.001
1	1/38 (2.6)	1/44 (2.3)	6/103 (5.8)	23/290 (7.9)	
2	16/38 (42.1)	26/44 (59.1)	65/103 (63.1)	217/290 (74.8)	
3	18/38 (47.4)	14/44 (31.8)	27/103 (26.2)	47/290 (16.2)	
Undifferentiated	3/38 (7.9)	3/44 (6.8)	5/103 (4.9)	3/290 (1)	
Mucinous component					0.001
Present	17/38 (44.7)	18/44 (40.9)	28/103 (27.2)	58/290 (20)	
Absent	21/38 (55.3)	26/44 (59.1)	75/103 (72.8)	232/290 (80)	
Obstruction					0.166
Present	5/38 (13.2)	9/44 (20.5)	8/103 (7.8)	32/290 (11)	
Absent	33/38 (86.8)	35/44 (79.5)	95/103 (92.2)	258/290 (89)	
Perforation					0.001
Present	3/38 (7.9)	3/44 (6.8)	1/103 (1)	2/290 (0.7)	
Absent	35/38 (92.1)	41/44 (93.2)	102/103 (99)	288/290 (99.3)	
Tumor size (cm)					0.026
≥5cm	27/36 (75)	20/38 (52.6)	46/94 (48.9)	120/249 (48.2)	
<5cm	9/36 (25)	18/38 (47.4)	48/94 (51.1)	129/249 (51.8)	

Methods

In this cross-sectional, retrospective study, archive records between January 2000 and July 2014 of all patients with stage III CRC who were treated at Marmara University Medical Faculty Hospital were used. Patients without follow-up, whose pathology report could not be obtained, and who did not undergo adequate surgery were excluded. Patients with initial surgery, whose pathology reports could be accessed, and who had pT1/2/3/4 or pN1/2/3 without metastasis were included. We used the 2017 AJCC staging system (8th edition) for pathological TNM staging. We separated the patients into four groups according to their stages during diagnosis: group 1 (T4N2M0), group 2 (T4N1M0), group 3 (T1–3N2M0), and group 4 (T1–3/N1M0). The characteristics affecting the prognosis, such as tumor localization (right colon, left colon and/or rectum), the presence of a mucinous component, obstruction, perforation, and lymphatic, vascular or perineural invasion, were determined. Then, the patients were stratified. Data from 691 patients were examined. Sixty-one patients were lost to follow-up, and the 60 patient's pathology report could not be obtained. In total, 570 patients with CRC met the criteria for inclusion and were evaluated. We excluded 95 patients who did not undergo adequate surgery. A total of 475 patients were included in the study for statistical analysis.

Ethics

This study was approved by the institutional review board of the hospital and was performed in compliance with all principles of the Declaration of Helsinki. As the data were retrospective in nature and analyzed anonymously, informed consent was not obtained from the patients.

Statistics

All statistical analyses were carried out using IBM SPSS vers. 20 (SPSS Inc., Chicago, IL, USA). The normality test was performed using the Kolmogorov-Smirnov test. The Kruskal-Wallis test was performed comparing continuous variables between groups. The chi-square test was performed for categorical variables. Survival rates were calculated using the Kaplan-Meier method, and the log-rank test assessed the differences between the groups. Univariate hazard ratios and independent predictors of disease-specific survival and OS were identified by Cox proportional hazard analysis. The stepwise procedure was set to a threshold of 0.05. Statistical significance was defined as $p<0.05$.

Results

Demographic data from four subgroups are shown in Table 1. The median age of the patients was 60 years (range 33–86) in group 1, 60 years (range 31–82) in group 2, 58 years (range 22–80) in group 3, and 59 years (range 25–84) in group 4. Of the patients, 38 were in group 1 (T4N2), 44 were in group 2 (T4N1), 103 were in group 3 (T1-3N2), and 290 were in group 4 (T1-3N1). No statistically significant difference was observed in terms of age ($p=0.288$) and gender ($p=0.888$) distribution. Group1 tumors were mostly located in the right colon, while the tumors in the other groups were left or rectal ($p=0.001$). The ratio of the lymphatic, vascular, and perineural invasion was correlated with a high T and N stage. Group 1 patients were found to have high lymphatic ($p=0.005$), vascular ($p<0.001$), and perineural invasion ($p=0.002$) when compared with the other subgroups. Similarly, group 1 patients had the highest level in terms of grade 3 (47.4%) and mucinous carcinoma rates (7.9%), while group 4 had the lowest (16.2% and 1%, respectively). The rate of detecting the obstruc-

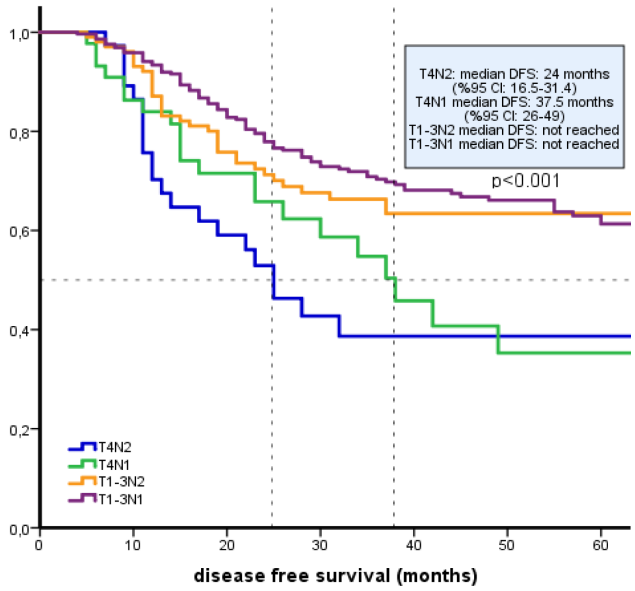

Figure 1. Disease-free survival (DFS) analysis for subgroups.

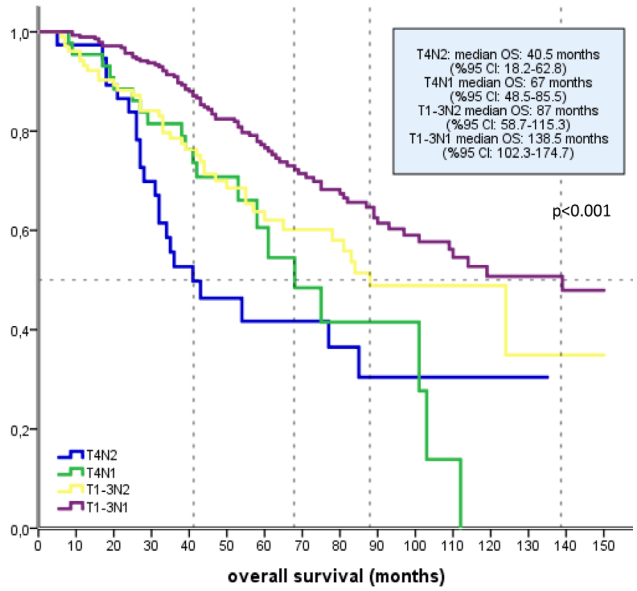

Figure 2. Overall survival (OS) analysis for subgroups.

tion at diagnosis was similar in all groups. But the rate of perforation at diagnosis was significantly higher in groups 1 and 2 when compared with the other groups (p=0.001).

Disease-free survival (DFS)

Figure 1 shows the Kaplan–Meier estimates for DFS by the patient group. The median follow-up was 49 months (4-176). A total of 148 patients were divided into T4N2 (n=21,55.3%), T4N1 (n=21,47.7%), T1-3N2 (n=34,33%), and T1-3N1 (n=92,31.7%) patient groups-who were not metastatic during diagnosis-and were evaluated. Disease-free median survival times were 24 months (16.5–31.4, 95% CI), 37.5 months (26–49, 95% CI), and not reached in the T4N2, T4N1, T1-3N2, and

Table 2. Prognostic factors of overall mortality

Factors	*Univariate analysis*		*Multivariate analysis*	
	HR (%95 CI)	*p value*	*HR (%95 CI)*	*p value*
Genders				
Female	Reference	0.863		
Male	0.97 (0.72-1.33)			
Age, years				
<50	Reference		Reference	
50-65	1.44 (0.92-2.23)	0.023	1.47 (0.94-2.30)	0.094
65+	1.94 (1.24-3.05)	0.004	1.91 (1.20-3.03)	0.006
Localization				
Right colon	Reference			
Left colon	1.25 (0.87-1.80)	0.225		
Tumor diameter, cm				
≤5	Reference			
>5	1.05 (0.76-1.47)	0.758		
Obstruction				
Absent	Reference			
Present	1.56 (1.02-2.38)	0.042		
Perforation				
Absent	Reference			
Present	1.84 (0.76-4.49)	0.179		
Lymphatic invasion				
Absent	Reference			
Present	1.06 (0.77-1.45)	0.742		
Vascular invasion				
Absent	Reference			
Present	1.27 (0.93-1.73)	0.129		
Perineural invasion				
Absent	Reference		Reference	
Present	1.73 (1.26-2.37)	0.001	1.65 (1.19-2.28)	0.002
Grade				
1& 2	Reference			
3	1.49 (1.08-2.06)	0.017		
Mucinous component				
Absent	Reference			
Present	1.26 (0.89-1.79)	0.189		
TN stage				
T1-3N1	Reference		Reference	
T1-3N2	1.58 (1.08-2.32)	0.018	1.58 (1.08-2.32)	0.019
T4N1	2.22 (1.35-3.64)	0.002	2.07 (1.26-3.40)	0.004
T4N2	3.07 (1.91-4.94)	<0.001	2.48 (1.52-4.02)	<0.001

T1-3N1 patient groups, respectively (p<0.001). The 3-year DFS scores were 39%, 50.6%, 63%, and 69.9% in the T4N2, T4N1, T1-3N2, and T1-3N1 patient groups, respectively (p<0.001). The 5-year DFS scores were 39%, 35%, 63%, and 61% in the T4N2, T4N1, T1-3N2, and T1-3N1 patient groups, respectively (p<0.001). The relapse rate was higher in patients with T4 tumors than in patients without T4 tumors. In contrast, when T4N2 and T4N1 patient groups were compared and when T1-3N2 and T1-3N1 patient groups were compared, they had similar relapse rates.

Overall survival (OS)

Figure 2 shows the Kaplan–Meier estimates for OS by the patient group. In patients with T4N2, T4N1, T1-3N2 and T1-3N1, median OS was 40.5 months (18.2–62.8), 67 months (48.5–85.5), 87 months (58.7–115.3), and 138.5 months (102.3–174.7) respectively (p<0.001). Two N2 groups were separated with or without T4. T4N2 patients had the shortest survival period of 40.5 months, and median survival in the T1-3N2 patient group was determined to be 87 months. There was a statistically significant difference between the two N2 groups (HR:0.49; p=0.017). Also, the two T4 groups separated with N1 or N2. For T4N1 and T4N2 patients, the survival difference between the groups did not reach statistical significance [67 vs. 40.5 months; HR: 0.67 (0.34–1.32); p=0.243]. The 3-year OS rates were 53%, 79%, 77%, and 90% in the T4N2, T4N1, T1-3N2, and T1-3N1 patient groups, respectively (p=0.001). The 5-year OS rates were 42%, 55%, 62%, and 76% in the T4N2, T4N1, T1-3N2, and T1-3N1 patient groups, respectively (p=0.033).

Relapse pattern analysis

A relapse pattern analysis was performed in all patients. The relapse time of T4N2, T4N1, T1-3N2, and T1-3N1 patient groups was 11 months (8.7–13.2), 14.5 months (10.5–18.4), 12 months (8.1–15.8), and 19.5 months (16.7–22.2), respectively. In Cox regression analysis, accepting the T1-3N1 group as reference, the risk of relapse was significantly higher in the T4N2 (HR:3.07; p<0.001), T4N1 (HR: 2.22; p=0.002), and T1-3N2 (HR:1.58; p=0.018) patient groups. The recurrence sites of the disease were divided into four groups: the peritoneum, liver, lung, and local recurrence. The ratio of local recurrence in the T4N2 (23.7%) and T4N1 (18.2%) patient groups was significantly higher than in the T1-3N2 (8.7%) and T1-3N1 (10.3%) patient groups (p=0.038). The ratio of peritoneal carcinomatosis was significantly higher in the T4N2 (15.8%) and T4N1 (9.1%) patient groups as compared to the T1-3N2 (2.9%) and T1-3N1 (4.6%) patient groups (p=0.002). The ratio of liver and lung metastases were found to be similar in all groups.

Cox regression analysis for OS

We performed univariate and multivariate analyses to assess the predictive value for OS in all patients (Table 2).

Univariate Cox regression analysis

Univariate analysis identified several variables significantly associated with OS, including age >65 (HR:1.94 [1.24–3.05]; p=0.004), presence of obstruction at diagnosis (HR: 1.56 [1.02–2.38]; p=0.042), presence of perineural invasion (HR:1.73 [1.26–2.37]; p=0.001), high grade T and N status (HR:1.49 [1.08–2.06]; p=0.017), T1-3N2 group (HR:1.58 [1.08–2.32]; p=0.018), T4N1 group (HR:2.22 [1.35–3.64]; p=0.002), and T4N2 group (HR:3.07 [1.91-4.94]; p<0.001). However, sex (HR:0.97 [0.72–1.33]; p=0.863, tumor location (HR:1.25 [0.87–1.80]; p=0.225), primary tumor diameter (HR: 1.05 [0.76-1.47]; p=0.758), presence of lymphatic invasion (HR:1.06 [0.77–1.45]; p=0.742), presence of vascular invasion (HR:1.27 [0.93-1.73]; p=0.129), presence of mucinous component (HR:1.26 [0.89-1.79]; p=0.189), and presence of perforation at diagnosis (HR:1.84 [0.76–4.49]; p=0.179) were not associated with OS.

Multivariate Cox regression analysis

In multivariate Cox regression analysis, age >65 (HR:1.91 [1.20–3.03]; p=0.006); T and N status: T1-3N2 (HR:1.58 [1.08–2.32]; p=0.019), T4N1 (HR: 2.07 [1.26–3.40]; p=0.004), and T4N2 (HR:2.48 [1.52–4.02]; p<0.001); and presence of perineural invasion (HR:1.65 [1.19–2.28]; p=0.002) were associated with an increased risk of death.

Discussion

Our study showed that the presence of T4 in patients with stage III CRC is the most critical parameter that increases the risk of relapses. N1 and N2 stages had no significant effect on the risk of relapse in the absence of T4. So, patients with T4 stage have worse survival rates when compared with N1/2 in patients with stage III CRC.

From the Dukes staging system to the 8th edition AJCC staging system, the N staging system was always more dominant than the T staging system [5,8]. In the presence of nodal involvement, patients were defined as stage III regardless of T stage, whereas T4N0 locally advanced tumors were defined as stage II. However, it has been shown in

several studies that the presence of pathological T4 is associated with poor prognosis in patients with curatively resected stages II and III CRC. Mori et al showed that the T4N0 (stage IIc) patient group had worse survival than the stage IIIA patient group [11]. In another article, stage I–III patients in the SEER database were divided into five groups according to T and N subgroups (T1, T2, T3, T4a, and T4b and N0, N1a, N1b, N2a, and N2b). Twenty-five groups with different T and N weights were created, and the effect of T and N stages on survival was calculated according to 5-year OS. Considering all patients with CRC, the relative prognostic importance of the T stage was 58%, the relative prognostic significance of the N stage was 42%, the relative prognostic weight of the T stage was 61%, and the relative prognostic weight of the N stage was calculated as 39% in patients with rectal localization [12]. Also, in a study conducted by Snaebjornsson et al, patients in all stages were evaluated and the presence of T4 was found the worst prognostic indicator as compared to the reference categories (T4, HR:5.05; M1, HR:4.93;and N2, HR:3.01) [13].

However, the importance of T4 has not been adequately investigated in patients with stage III CRC. Kim et al have shown that the presence of T4 was the most negative prognostic parameter as compared to the other 25 histopathological and immunohistochemical factors, independent of the adjuvant chemotherapy regimen in stages II and III MSI-H patients (T4, HR:4.91; R: T1-3; N2, HR:2;and R: N0-1) [14]. The data obtained from the SEER database published by Gunderson et al showed that the T4aN1 and T4N2 patient groups had a similar prognosis, and the T4N0 patient group, classified as stage II, had a worse prognosis than the T1-2N1-2 patient groups classified as stage III [9]. In our study, the relapse rates in the T4 patient groups were higher than those of the T1-3N1 and T1-3N2 patient groups, independent of the N stage (N1 or N2). There was no significant difference in relapse rates between the T4N2 and T4N1 patient groups. Similarly, there was no significant difference between the T1-3N2 and T1-3N1 patient groups. In the evaluation of relapse risk, regarding the T1-3N1 patient group, the risk of relapse was increased by 2.63 times in the T4N2 patient group and 2.08 times in the T4N1 patient group, but in the T1-3N2 patient group, the risk of relapse was similar. The T4N2 patient group had the highest relapse risk (as expected), and similar relapse rates were observed in the T4N1 patient group. Our study suggests that the N stage had no significant effect on the risk of relapse in patients with stage III CRC with T4 disease. Similarly, the rate of relapse in patients with T1–3 stage groups was significantly lower as compared to the T4 stage group, whereas the N1 or N2 stage did not change the risk of relapse in this group. Based on these data, it was stated that T stage should be more weighted in the TNM staging system [12,15].

Despite aggressive surgical resection and adjuvant chemotherapy, approximately 30–35% of patients diagnosed with stage III CRC relapse within 5 years from diagnosis [16–19]. Relapses generally occur as a local recurrence, peritoneal carcinomatosis (PC), and liver and lung metastases. PC, due to relapse of CRC, has a rather poor prognosis. Even with the use of standard chemotherapy with targeted therapy agents, the median survival is below 24 months. In some series with complete cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy, median survival of up to 41 months and a 5-year survival rate of 42–49% were reported [20], although in some series, median survival rates of 20–30 months have been reported [21,22]. However, patients with prolonged survival in this series usually had a low peritoneal cancer burden and could undergo complete resection [23]. In the literature, there are few studies with a high level of evidence about predictive factors that are effective with regard to the development of PC after curative surgery. A few studies show that the presence of T4 was considered to be a risk factor for the development of PC, while the presence of N2 could not be shown to be associated with an increased risk of PC development [24,25]. In our study, similarly, the risk of local recurrence was higher in T4 than in T1–3, regardless of nodal involvement as N1 or N2.

Limitations in this study were its retrospective design and the T4 patient groups who were not separated, such as T4a and T4b. Multi-institutional and prospective randomized controlled trials are required to confirm our preliminary findings.

Conclusions

In contrast to the commonly used staging systems, we have shown that T is a more important prognostic factor than N in stage III CRC. We also showed that a higher T value was associated with a higher relapse rate than the N value. In the future TNM staging systems, we believe that the regulation of a T-dominated system will provide more appropriate stage-prognosis information.

Conflict of interests

The authors declare no conflict of interests.

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