

# Prognostic factors affecting survival in stage 3 colorectal cancers

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## Abstract

**Aim:** Colorectal cancer has become a significant problem in Turkey. In this study, we consider the clinical and pathologic factors that affect survival in stage 3 colorectal cancer.

**Material and Methods:** We analyzed patients who underwent radical surgery for stage 3 colorectal cancer between January 2012 and March 2018 at the Ortadogu Hospital, Adana, Turkey. The age and gender of the patients, the length of the colectomy specimen, the location and size of the tumors, TNM stage and the number of retrieved lymph nodes were evaluated. The lymphovascular and perineural invasion was examined.

**Results:** In the group, 73 were men and 52 were women, ranging in age from 22 to 88 years (mean age, 58 years). There were 29 cases of right colon cancer, 30 cases of left colon cancer and 66 cases of rectal cancer. Lymphovascular and perineural invasion were present in 78 patients (62.4%) and 30 patients (24.0%) respectively. Twenty-one patients received preoperative adjuvant therapy. No significant difference was found between tumor size and invasion and mortality. However, we found a statistically significant difference between age, metastatic lymph node, total lymph node number, and mortality. According to the Log-Rank test, we found that lymphovascular and perineural invasion were significant for survival.

**Conclusions:** The number of metastatic lymph nodes had a poor prognosis on the survival, we found that the high total number of retrieved lymph nodes affected prognosis in a good way. We conducted that perineural and lymphovascular invasion is a factor affecting the survival adversely in stage 3 colorectal cancers.

**Keywords:** Retrieval of Pericorectal Lymph Nodes; Stage 3 Colorectal Carcinoma; T-Classification; N-Classification, Neoadjuvant Therapy; Understaging.

## INTRODUCTION

Colorectal cancer stays an important reason of morbidity and mortality through the world. When gender is combined, colorectal cancer ranks fourth in cancer mortality (1). There have been many successes in managing colorectal cancer in the last few decades.

These include the availability of the useful screening tool, progression in the surgical technique, progress in treatment modalities, and more (2-4). In conclusion, patients may have a better prognosis and a better quality of life after colorectal cancer is diagnosed. Therefore, cancer survival analysis is a key indicator of effective early diagnosis and improvement in cancer treatment.

To estimate overall survival in an individual patient, the prognostic power of the stage can be further strengthened

by a number of clinical, disease and patient characteristics (5,6). Prognostic factors include intestinal wall depth of tumor invasion and presence of nodal metastases (5), performance status, comorbid conditions such as diabetes, the presence of venous or lymphatic invasion, and tumor (7,8).

The American Joint Cancer Committee and the International Union against Cancer (AJCC kol UICC) TNM systems are the most widely used staging system for colorectal cancer.

The TNM stage identified the clinical population that most prognostication tools address. Need to correct the prognosis for individual patients in the TNM stages is still ongoing. In each stage grouping, a large number of tools have been identified, which are based on a number

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of additional prognostic information to personalize estimates (6). Colorectal cancer has become a major problem in Turkey. In this study, we discuss the clinical and pathological factors affecting survival in stage 3 colorectal cancers.

## MATERIAL and METHODS

Between January 2012 and March 2018, 125 patients with stage 3 colorectal cancer underwent radical surgery in our clinic. Written approval was obtained from Cukurova University Faculty of Medicine Clinical Ethical Board.

Open surgery was performed by a surgeon for all patients and standard colon resection was performed with lymph node dissection depending on the location of the tumor. Neoadjuvant chemoradiotherapy was performed in 21 patients in primary rectal cancer.

Age and gender of the patients, length of the sample, location and size of tumors, depth of invasion, and the number of retrieved and metastatic lymph nodes were evaluated postoperatively. The lymphovascular and perineural invasion was examined. The depth of invasion and the number of metastatic lymph nodes assisted the disease using the 7th edition of the AJCC / UICC TNM classification (9). The location of the tumors was classified in the right colon (distal transverse colon from the cecum), in the left colon (splenic flexor to sigmoid colon) and rectum.

### Statistical analysis

Statistical analysis was performed using the statistical package SPSS software (Version 17.0, SPSS Inc., Chicago, IL, USA). For each continuous variable, normality was checked by Kolmogorov Smirnov and Shapiro-Wilk tests and by histograms. All numerical data are expressed as median values (Minimum-Maximum) or as proportions.

Comparisons between groups were applied using Student T-test or One Way ANOVA for normally distributed data and Mann Whitney U test for the data not normally distributed.

Overall survival time was defined as the years elapsed between the date of after operation and death as a result of disease (and the last follow-up date). Overall survival was analyzed using the Wald test, and the log-rank test was used to examine their relationship when different parameters were applied. The survival curve was plotted using the standard Kaplan-Meier methodology. Values of  $p < 0.05$  were considered statistically.

## RESULTS

In the group, 73 were men and 52 were women, ranging in age from 22 to 88 years (mean age, 58 years). Mean tumor size was  $5.5 \pm 2.2$  (1-15), metastatic lymph node number was  $2.9 \pm 5.4$  (0-32), total lymph node number was  $36.1 \pm 21.6$  (3-127) (table 1).

There were 29 cases of right colon cancer, 30 cases of left colon cancer and 66 cases of rectal cancer. Among the 125 patients in this study, the clinical tumor classification was as follows: T2 (tumor invading the muscularis propria) in 1

patient (0.8%), T3 (tumor invading through the muscularis into pericolorectal) in 119 patients (95.2%). The clinically lymph node classification was N0 (no regional lymph node metastasis) in 57 patients (45.6%), N1 (metastasis in 1-3 regional lymph nodes) in 37 patients (29.6%), N2 (metastasis in  $\geq 4$  regional lymph nodes) in 31 patients (24.8%). The pathologic tumor classification was as follows: well-differentiated adenocarcinoma in 21 patients (16.8%), moderately differentiated adenocarcinoma in 88 patients (70.4%), poorly differentiated adenocarcinoma in 7 patients (5.6%), and mucinous carcinoma in 9 patients (7.2%). Lymphovascular and perineural invasion were present in 78 patients (62.4%) and 30 patients (24.0%) respectively. Twenty-two patients received preoperative adjuvant therapy. 102 patients were alive, 23 patients ex and 6 patients were not informed (table 2).

**Table 1. Demographic and clinical parameters 1**

|                       | Mean $\pm$ SD   | Range |
|-----------------------|-----------------|-------|
| Age                   | 58.3 $\pm$ 14.1 | 22-88 |
| Tumor size            | 5.5 $\pm$ 2.2   | 1-15  |
| Metastatic lymph node | 2.9 $\pm$ 5.4   | 0-32  |
| Total lymph node      | 36.1 $\pm$ 21.6 | 3-127 |

**Table 2. Demographic and clinical parameters 2**

|                                | n   | Life |       |
|--------------------------------|-----|------|-------|
|                                |     |      | %     |
| <b>Age</b>                     |     |      |       |
| <60                            | 65  |      | 52.0  |
| $\geq 60$                      | 60  |      | 48.0  |
| <b>Sex</b>                     |     |      |       |
| Male                           | 73  |      | 58.4  |
| Female                         | 52  |      | 41.6  |
| <b>Localization</b>            |     |      |       |
| Right colon cancer             | 29  |      | 23.2  |
| Left colon cancer              | 30  |      | 24.0  |
| Rectum                         | 66  |      | 52.8  |
| <b>Grade</b>                   |     |      |       |
| 1                              | 21  |      | 18.1  |
| 2                              | 88  |      | 75.9  |
| 3                              | 7   |      | 6.0   |
| <b>Tumor Size</b>              |     |      |       |
| <5                             | 42  |      | 33.6  |
| $\geq 5$                       | 83  |      | 66.4  |
| <b>Invasion</b>                |     |      |       |
| <1                             | 60  |      | 48.0  |
| $\geq 1$                       | 65  |      | 52.0  |
| <b>Stage</b>                   |     |      |       |
| 3                              | 125 |      | 100.0 |
| <b>Lymphovascular invasion</b> |     |      |       |
| No                             | 47  |      | 37.6  |
| Yes                            | 78  |      | 62.4  |
| <b>Perineural invasion</b>     |     |      |       |
| No                             | 95  |      | 76.0  |
| Yes                            | 30  |      | 24.0  |
| <b>Life</b>                    |     |      |       |
| Life                           | 102 |      | 77.8  |
| Ex                             | 23  |      | 16.7  |
| Unknown                        | 6   |      | 4.5   |

A total of 125 patients were enrolled in the study, however, because of the lack of information from 6 patients, the survival analysis was performed on 119 patients.

When we compared survival analysis by Chi-square test regarding the age, gender, location, grade, tumor size, invasion, nodal status, T status, stage, preoperative adjuvant therapy findings, no significant difference could be obtained ( $p > 0.05$ ). However, we found a statistically significant relationship between perineural and lymphovascular invasion and mortality (table 3).

|                                | Life |      | Ex |      | Total |      | P            |
|--------------------------------|------|------|----|------|-------|------|--------------|
|                                | n    | %    | n  | %    | n     | %    |              |
| <b>Age</b>                     |      |      |    |      |       |      |              |
| <60                            | 57   | 55.9 | 8  | 34.8 | 65    | 52.0 | 0.105        |
| ≥60                            | 45   | 44.1 | 15 | 65.2 | 60    | 48.0 |              |
| <b>Sex</b>                     |      |      |    |      |       |      |              |
| Male                           | 59   | 57.8 | 14 | 60.9 | 73    | 58.4 | 0.820        |
| Female                         | 43   | 42.2 | 9  | 39.1 | 52    | 41.6 |              |
| <b>Localization</b>            |      |      |    |      |       |      |              |
| Right colon cancer             | 24   | 23.5 | 5  | 21.7 | 29    | 23.2 | 0.923        |
| Left colon cancer              | 25   | 24.5 | 5  | 21.7 | 30    | 24.0 |              |
| Rectum                         | 53   | 52.0 | 13 | 56.6 | 66    | 52.8 |              |
| <b>Grade</b>                   |      |      |    |      |       |      |              |
| 1                              | 18   | 18.6 | 3  | 15.8 | 21    | 18.1 | 0.148        |
| 2                              | 75   | 77.3 | 13 | 68.4 | 88    | 75.9 |              |
| 3                              | 4    | 4.1  | 3  | 15.8 | 7     | 6.0  |              |
| <b>Tumor Size</b>              |      |      |    |      |       |      |              |
| <5                             | 31   | 30.4 | 11 | 47.8 | 42    | 33.6 | 0.143        |
| ≥5                             | 71   | 69.6 | 12 | 52.2 | 83    | 66.4 |              |
| <b>Invasion</b>                |      |      |    |      |       |      |              |
| <1                             | 50   | 49.0 | 10 | 43.5 | 60    | 48.0 | 0.652        |
| ≥1                             | 52   | 51.0 | 13 | 56.5 | 65    | 52.0 |              |
| <b>Lymphovascular invasion</b> |      |      |    |      |       |      |              |
| No                             | 44   | 43.1 | 3  | 13.0 | 47    | 37.6 | <b>0.008</b> |
| Yes                            | 58   | 56.9 | 20 | 87.0 | 78    | 62.4 |              |
| <b>Perineural invasion</b>     |      |      |    |      |       |      |              |
| No                             | 83   | 81.4 | 12 | 52.2 | 95    | 76.0 | <b>0.006</b> |
| Yes                            | 19   | 18.6 | 11 | 47.8 | 30    | 24.0 |              |

When we performed a survival analysis with the Mann-Whitney test, no significant difference was found between tumor size and invasion and mortality. However, we found a statistically significant difference between age, metastatic lymph node, total lymph node number and mortality (table 4).

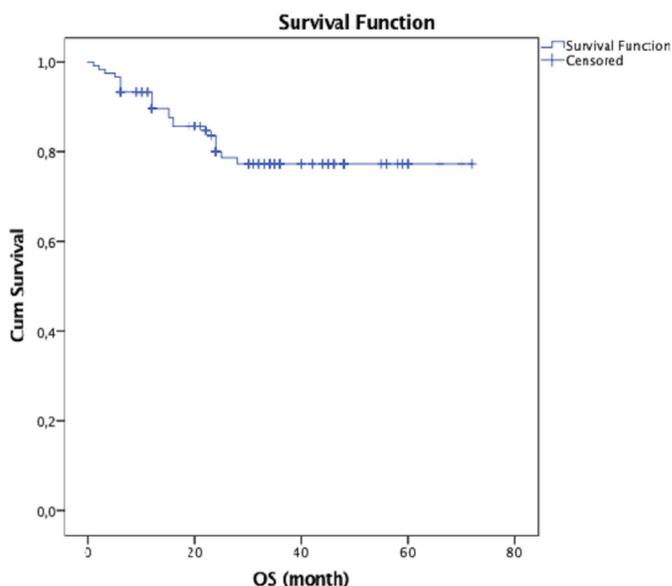
|                              | Life       | Ex        | P     |
|------------------------------|------------|-----------|-------|
| <b>Age</b>                   | 56.9±13.9  | 64.8±13.0 | 0.014 |
| <b>Tumor size</b>            | 5 (1-15)   | 5 (2-10)  | 0.423 |
| <b>Invasion</b>              | 2 (0-6)    | 2 (1-3)   | 0.820 |
| <b>Metastatic lymph node</b> | 1 (0-20)   | 2 (0-32)  | 0.009 |
| <b>Total lymph node</b>      | 31 (7-127) | 24 (3-99) | 0.075 |

**p: Mann-Whitney Test**

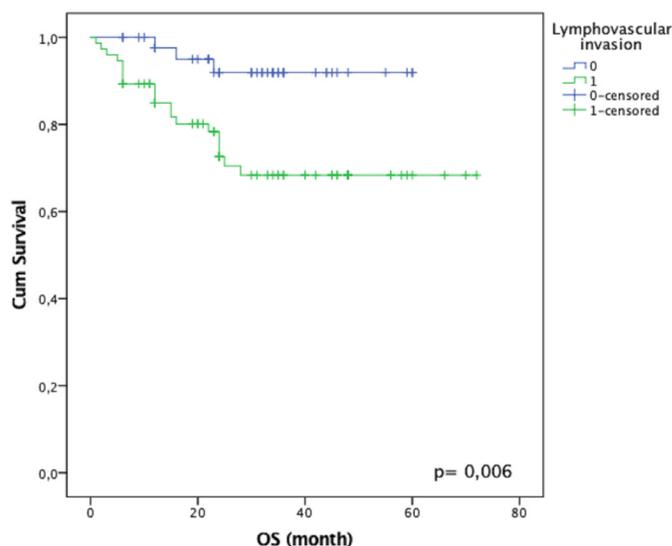
According to the Log-Rank test, we found that lymphovascular and perineural invasion were significant for the survival (table 5). The 5-year survival of the Kaplan-Meier Curve is shown in graphs 1, 2 and 3 of the survival functions of lymphovascular and perineural invasion.

|                                | Predictic Survival (month) mean±SE | 95% CI mean | 1 year % | 2 year % | 5 year % | p     |
|--------------------------------|------------------------------------|-------------|----------|----------|----------|-------|
| <b>Overall survival</b>        | 59.1±2.4                           | 54.4-63.8   | 89.8     | 80.0     | 80.0     | -     |
| <b>Lymphovascular invasion</b> |                                    |             |          |          |          |       |
| No                             | 56.5±1.9                           | 52.9-60.3   | 97.6     | 91.8     | 91.8     | 0.006 |
| Yes                            | 53.8±3.4                           | 47.1-60.6   | 84.9     | 72.6     | 68.3     |       |
| <b>Perineural invasion</b>     |                                    |             |          |          |          |       |
| No                             | 61.5±2,3                           | 57.1-65.9   | 93.4     | 86.2     | 84.5     | 0.001 |
| Yes                            | 45.4±6.0                           | 33.5-57.2   | 78.0     | 69.3     | 53.3     |       |

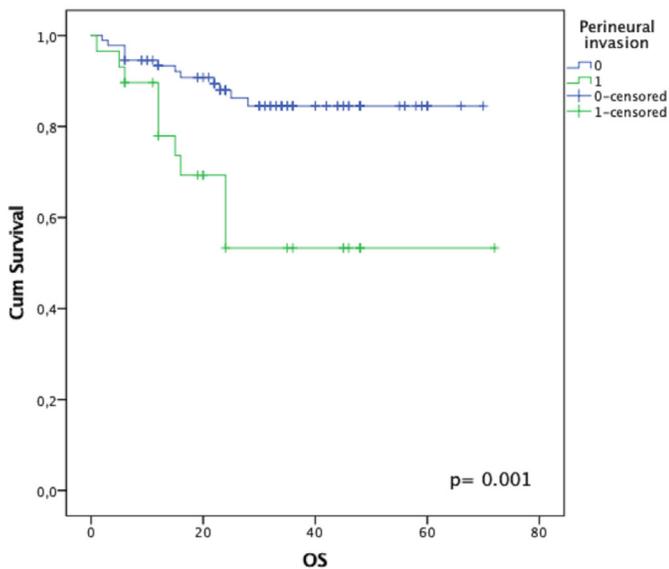
**p: Log-Rank test**



**Graphic 1.** The 5-year Kaplan-Meier overall survival function



**Graphic 2.** The 5-year Kaplan-Meier survival function of the lymphovascular invasion



**Graphic 3.** The 5-year Kaplan-Meier survival function of the perineural invasion

## DISCUSSION

Colon cancer is an important cause of morbidity and mortality through the world and is now the significant cause of gastrointestinal cancer incidence (10). This study summarizes the available information on the 125 prognostication tool for stage 3 colorectal cancer from a single center.

The morbidity and mortality of CRC have shown a marked increase in both urban and rural areas over the last 30 years. Because of the improvement in surgical technique and treatment, 5-year overall survival of CRC increased by around 76%.

In the evaluation of socio-demographic factors (age group, gender), none of them were found to have a significant relationship to predict survival independently. Regarding age group (60 years and under 60 years) prognosis was found to be worse in advanced age patients despite the lack of statistical significance. This finding consists of other studies reporting poor prognostic factors for an older age (11-13).

There is no significant difference in the survival between males and females in the univariate analysis which is conflicting with Al-Ahwal MS and Oberoi DV studies reporting male predominance(14,15).

For the CRC in the literature, different clinical and pathological prognostic factors have been proposed, such as tumor differentiation, tumor stage (17), tumor stage (17). However, in our study, we could not find a significant difference between tumor localization, tumor size, grade, and stage. We found that the number of metastatic and total lymph nodes in the univariate analysis was the factor affecting the survival. This study did not find a relationship between grade and survival as in Hassan MR and et al. studies but found a relationship between metastatic lymph node and survival (18).

Our 5-year survival was 77%. It was higher than a few Asian countries like Singapore, Malaysia, and Iran (19-21). The 5-year survival rates in developed countries in Canada, America, and Europe were very close to the survival rates in our study (22,23). In our study, we determined that perineural and lymphovascular invasion is the most important factor affecting survival. We found that the rate of survival was statistically worse in patients with lymphovascular or perineural invasion.

## CONCLUSION

In conclusion, the overall survival rate for stage 3 colorectal cancer patients in our clinic is generally between European countries and higher Asian countries. Although the number of metastatic lymph nodes had a poor prognosis on the survival, we found that the high total number of retrieved lymph nodes affected prognosis in a good way.

This shows that the number of lymph nodes removed during the operation is very important.

We concluded that perineural and lymphovascular invasion is a factor affecting the survival in a bad sense and that it should be examined and analyzed in this aspect of the operation specimen.

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