Kocaeli Med J 2019; 8; 1:153-160

Tıkayıcı Kolorektal Kanserlerde Cerrahi Strateji ve Lenf Nodu Oranının Sonuçlar ve Prognoz Üzerine Etkisi

Surgical Strategies and Prognostic Significance of Lymph Node Ratio in Obstructive Colorectal Cancers

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ÖZ

GİRİŞ ve AMAÇ: *Tıkayıcı kolorektal kanserlerde kısa ve uzun dönem sonuçların değerlendirmesi ve lenf nodu oranının prognostik öneminin ortaya konması amaçlanmıştır.*

YÖNTEM ve GEREÇLER: *Ocak 2001-Eylül 2007 tarihleri arasında tıkayıcı kolorektal kanser nedeniyle acil şartlarda ameliyat edilen hastalar geriye dönük olarak derlenmiştir. Cerrahi sonuçlar ve sağkalım değerlendirilmiş olup ortanca lenf nodu oranına göre gruplar arasında genel ve hastalıksız sağkalım karşılaştırmaları yapılmıştır*

BULGULAR: *Toplam 64 hasta [erkek (n=33, %51,6), ortanca yaş: 68,5] hasta derlendi. Ortanca lenf nodu oranı 0.09 idi. Proksimal ve distal tümörlerde perioperatif morbidite, mortalite ve küratif rezeksiyon oranları farklı değildi. Beş yıllık genel sağkalım %34,4, ortanca sağkalım süresi 19 ay olarak bulundu. Proksimal ve dital tümörler ile erken ve ilere evre tümörlerde genel sağkalım ve hastalıksız sağkalım istatistiksel olarak farklı değildi (p>0.05). Ortanca lenf nodu oranına göre gruplar arasında genel sağkalım ve hastalıksız sağkalım açısından istatistiksel anlamlı farklılık yoktu (p>0.05).*

TARTIŞMA ve SONUÇ: *Tıkayıcı distal kolorektal kanserlerde cerrahi stratejiye karar verirken daha objektir kriterler kullanılmalıdır. Tıkayıcı kolorektal kanseri olan hastalarda prognoz kötü olmasına rağmen, küratif rezeksiyon yapılan ve perioperatif komplikasyonları atlatan hastalar daha iyi uzun dönem sonuçlara sahiptir. Ortanca lenf nodu oranı tıkayıcı kolorektal kanserlerde prognostik anlam göstermemiştir.*

Anahtar Kelimeler: *tıkayıcı kolorektal kanser, lenf nodu oranı, sağkalım, sonuçlar*

ABSTRACT

INTRODUCTION: *To investigate the effect of preoperative obstruction in patients with colorectal cancer (CRC) on short and long-term outcomes and to find out the prognostic significance of lymph node ratio (LNR).*

METHODS: *This retrospective study included patients operated for obstructive CRC under emergency conditions. Surgical outcomes and survival analysis were evaluated in all cohorts. Overall survival (OS) and disease free survival (DFS) rates were compared between patient groups according to median LNR value.*

RESULTS: *A total of 64 patients [male (n=33, 51.6%), median age: 68.5 years] were retrieved. Median LNR was calculated as 0.09. Perioperative morbidity and mortality and curative resection rates were not different between patients with proximal and distal tumors. 5-year OS rate and median survival for all patients were 34.4% and 19 months, respectively. OS and DFS did not significantly differ between patients in early and advanced stage disease and with proximal and distal tumors (p>0.05). OS and DFS did not show significant difference in patient groups according to median cut-off LNR value (p>0.05).*

DISCUSSION and CONCLUSION: *More objective criteria should be used while deciding on surgical strategy for obstructive distal CRCs. Although obstruction is associated with poor overall prognosis, patients who have curative resection and survive from perioperative complications have favorable long-term results. Median LNR did not show any prognostic significance for obstructive CRCs.*

Keywords: *obstructive colorectal cancer, lymph node ratio, survival, outcomes*

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Başvuru Tarihi: 19.05.2018
Kabul Tarihi: 03.01.2019

INTRODUCTION

Between 7% and 47% of the patients with colorectal cancer (CRC) present with obstruction (1). Lack of consensus regarding the management and prognostic factors of obstructive CRCs still remains as an important issue for general surgeons. It is reported that the patients who underwent emergent CRC operation have poorer prognosis than elective cases (2,3). Increased per-operative risks, decreased curative resection rates, advanced age; impaired general medical condition, distal location and advanced stage are some factors associated with poor prognosis (3).

Most surgeons agree on performing resection and primary anastomosis (RPA) for proximally located obstructive tumors. There are reports depicting that RPA can also be performed safely for distally located obstructive tumors (4). However, there is still a controversy regarding short and long term outcomes of proximal and distal obstructive tumors. Some reports reveal poor prognosis with proximal tumors while some suggest vice versa.

Although at least 12 lymph nodes are required for adequate pathologic evaluation, that number can be reached in only 37% of all patients (5). However some investigators have reported that there is a certain heterogeneity among the patients with stage III disease in terms of prognosis (6). It is also indicated that frequency of patients with lymph node metastasis does not increase with the evaluation of more lymph nodes (7).

Better staging systems are required to select patients who will benefit most from novel approaches (8). With emphasis to the limitations of AJCC/UICC staging system, lymph node ratio (LNR - positive lymph nodes/ total number of lymph nodes examined) is suggested as a surrogate marker of a better prognostic stratification in spite of the presence of lymph node metastasis (9). Integration of LNR to the conventional staging systems may potentially alter the management of patients with CRC. However there is not a well-established cut-off value for LNR to properly stratify patients (7).

In the present study, we aimed to investigate how preoperative obstruction affects the surgical decision, short and long-term outcomes and the prognostic significance of LNR in patients with obstructive CRC.

METHODS

This retrospective study was designed to analyze the results of patients operated in an emergency setting and subsequently diagnosed with obstructive CRC at XXXXX University Hospital between January 2001 and September 2007. XXXXXX University School of Medicine, Institutional Review Board approved the study protocol.

As our aim was to determine at least five-year survival, patients who lack five-year follow-up data were not included in the study. Demographics and pathological data and surgical characteristics were obtained from medical charts.

Intestinal obstruction was defined as having no gas and feces discharge at least for the last 24 hours accompanied with the clinical findings of obstruction as abdominal distention, colicky abdominal pain and nausea. In addition to these clinical findings, imaging methods were also used to corroborate colorectal obstruction. All patients were operated within 24 hours after their admission and usually at night duty hours. Other obstruction causes were excluded from the study. Total colectomy cases were also excluded in order to properly compare the effects of Hartmann procedure (HP) and RPA on survival outcomes and perioperative complications. All patients were followed-up by our team and medical oncologists according to standard oncologic criteria after being discharged.

Patients who were healthy or with mild systemic diseases were categorized as American Society of Anesthesiologists (ASA) score I-II. Patients with severe systemic diseases whether it threatens the life or not were categorized as ASA III-IV. Obstructive tumors were classified according to tumor localization. Tumors located in cecum, ascending colon, hepatic flexure and transverse colon were classified as proximal tumors, and the other segments of colon and rectum were classified as distal tumors. Pathological TNM (tumor-node-metastasis) staging was based on AJCC/UICC system. Stage I and II tumors were identified as early stage whereas stage III and IV were identified as advanced stage. LNR cut-off level was assigned as median value of ratio of malignant lymph node involvement to total lymph nodes harvested.

Morbidity was defined as any complications occurring within 30 days after index operation. Mortality was defined as death within the same

period. In situations when resection of the primary tumor could not be achieved, palliative operations like by-pass procedure or loop stoma opening were performed. Margin negative resections (R0) without residual distant metastasis were defined as curative resections and microscopically or macroscopically positive resections (R1/2) or resections with residual distant metastasis were defined as palliative resections. Overall survival (OS) was defined from the date of surgery to the date of death or last follow-up. Disease free survival (DFS) analysis was implemented on patients who have curative resection and did not develop postoperative mortality. The interval from curative operation to the first recurrence was expressed as DFS. Recurrence whether loco-regional or distant was confirmed histologically, clinically and/or radiologically. In order to determine the effects of LNR on outcomes, patients who had curative resection (n=33) instead of palliative operation were included in the comparative survival analysis.

Variable distributions were assessed by Kolmogorov Smirnov or Shapiro Wilk normality tests. Normally distributed variables were expressed as mean ± standard deviation (SD), and non-normally distributed variables were expressed as median (range). Categorical variables were compared with Chi-square or Fisher's exact tests. Continuous variables were compared with independent samples T test or Mann-Whitney U tests. Kaplan-Meier method was used to estimate overall and disease-free survival. Log-rank test was used to compare Kaplan-Meier survival estimates between two groups. A p value <0.05 was accepted as statistically significant. Statistical analysis was performed using SPSS for Windows, Version 15.0. Chicago, SPSS Inc.

RESULTS

During the study period, 64 patients underwent emergent operations for obstructive CRC. Demographic and clinical data of the patients included in the study were summarized in **Table 1.** As tumor resection could not be performed in six patients with un-resectable disease, they had palliative operations instead of a curative approach.

Table 1.Demographic and clinical characteristics

Characteristic	Total (64)
Median Age, y (range)	68.5 (31-95)
Male/Female, n (%)	33/31 (51.6/48.4)
ASA Score, n (%)	
ASA I – II	34 (53.1)
ASA III – IV	30 (46.9)
Localization, n (%)	
Proximal	13 (20.3)
Distal	51 (79.7)
Stage, n (%)	
I	3 (4.7)
II	20 (31.3)
III	16 (25)
IV	25 (39)

ASA: American Society of Anesthesiology

Four of them had by-pass procedure and two were managed with loop colostomy. Of the 58 patients who had primary tumor resection, 18 had palliative resections generally due to distant metastasis. Only one patient with stage IV disease had a concomitant resection for solitary small liver metastasis and was included in the curative group. Postoperative mortality occurred in 12 (18.8%) patients. Seven of them were in curative resection group. Thus recurrence and DFS analyses were carried out on remaining 33 patients. Recurrence was identified in 9 (27.3%) patients, 8 were with only liver metastasis and one with only loco-regional recurrence. Postoperative morbidity was determined in 23 (35.9%) patients. The main reasons for postoperative morbidity and mortality were cardiovascular and septic complications. Ten (15.6%) patients required re-operation. These operative and postoperative characteristics were depicted in **Table 2.**

Table 2. Operative and postoperative period characteristics

Characteristic	Total (64)
Type of operation, n(%)	
Curative resection	40 (62.5)
Palliative resection	18 (28.1)
Palliative operation	6 (9.4)
Post-operative morbidity, n(%)	23 (35.9)
Re-operation rate, n(%)	10 (15.6)
Post-operative mortality, n(%)	12 (18.8)
Lymph nodes retrieved, median (range)	15.5 (1-67)
Lymph node ratio, median (range)	0.09 (0-1)
Colostomy closure rate after HP (n=24), (%)	9 (37.5)
Recurrence rate (n=33), (%)	9 (27.3)

**HP: Hartmann Procedure*

Surgical treatment results were evaluated according to tumor localization. Morbidity, mortality and curative resection rates were not significantly different between patients with proximal or distal tumors (p>0.05, Table 3). HP was performed for 24 (51%) of 47 patients who were operated for distal tumor. Of these patients, 26 and 21 patients were ASA I-II and ASA III-IV, respectively. Thirteen (50%) patients in the ASA I-II group and 11 (52.4%) patients in the ASA III-IV group underwent HP (p=0.87). Eleven (45.8%) of 24 patients who underwent HP and 10 (43.5%) of 23 patients who underwent RPA developed morbidity (p=0.44). Seven (29.2%) patients who had HP and 3 (13%) patients who had RPA died in the postoperative period (p=0.14). Colostomy closure was achieved in 9 of 24 patients (37.5%) who underwent HP.

Table 3. Comparisons according to the localization

	Proximal (n=13) (n, %)	Distal (n=51) (n, %)	p
Type of operation[a]			
RPA	11 (84.6)	23 (45.0)	0.002
HP	0	24 (47.2)	
PO	2 (15.4)	4 (7.8)	
Curative resection	8 (61.5)	32 (62.7)	0.93
Morbidity	2 (15.4)	21 (41.1)	0.076
Mortality	2 (15.4)	10 (19.6)	0.73

[a]RPA:Resection and primary anastomosis, HP:Hartmann procedure, PO:Palliative operation.

While 5-year OS rate for all patients was 34.4%, in patients who had curative resection it was 52.5%. (Figure 1, Figure 2) The median survival of all patients and curative resection group were 19 and 75 months, respectively. In patients who had curative resection and survived in postoperative follow-up period, 5-year OS and DFS rates were 63.6% and 68.8%, respectively. (Figure 3). Median survival was not achieved. Mean OS and DFS were calculated as 87.6 (69.9-105.4) and 97.1 (78.4-155.6) months, respectively for these patients.

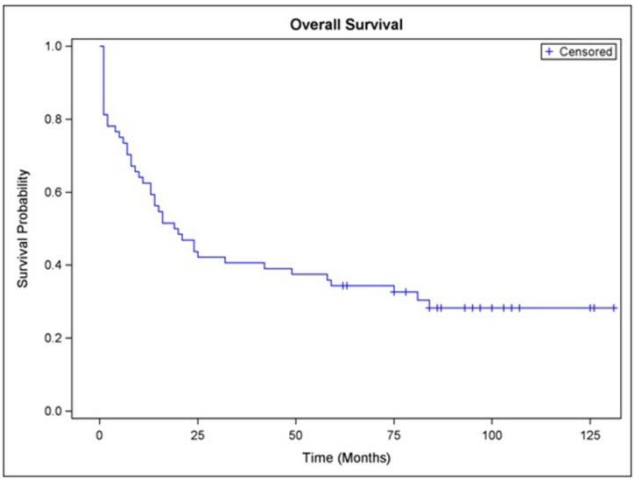


Figure 1. Overall survival rates

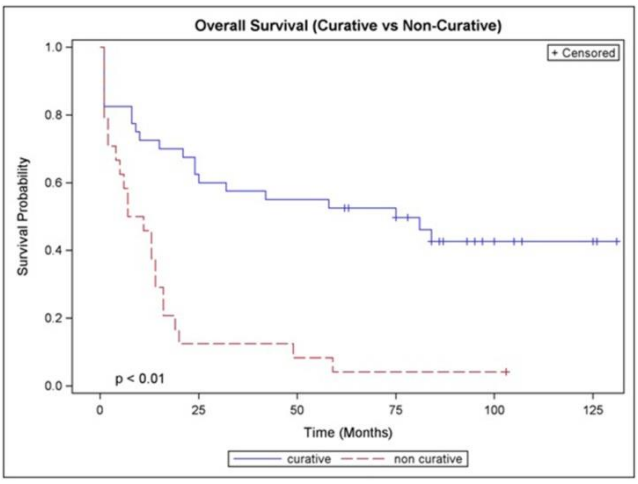


Figure 2. Disease free survival rates

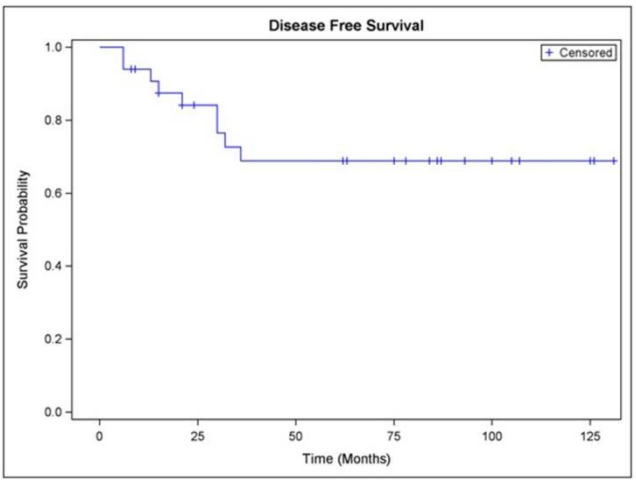


Figure 3. Overall survival (Curative–Non-curative) rates

No statistically significant differences were found between proximally and distally localized tumor groups regarding the OS and DFS rates (p=0.69 and p=0.88). Similarly, when the data were analyzed for early and advanced staged groups, OS and DFS rates showed no difference between two groups (p=0.24 and p=0.09). No significant effect of median LNR value was

observed on either OS or DFS (p=0.28 and p=0.38) (Figure 4).

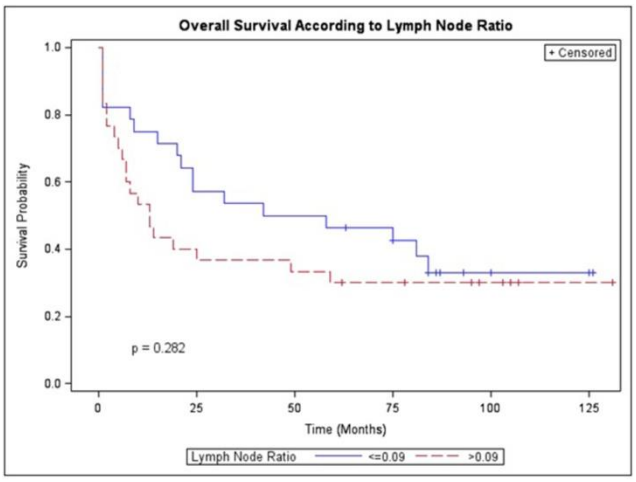


Figure 4. Overall survival rates according to the lymph node ratio

DISCUSSION

Today's literature related to the tumor prognosis has focused on understanding the molecular carcinogenesis and developing molecular markers to predict the outcome. However, clinical factors having an influence on tumor prognosis should not be underestimated (10). Obstruction remains a common clinical situation for colorectal carcinomas (CRCs). Approximately 15-20% of all colonic neoplasms, which are usually slow-growing tumors, are still diagnosed with obstruction under emergent conditions despite cancer screening programs (2,10). Obstruction in CRCs is accompanied by lower survival rate and poor prognosis (11,12). Nevertheless, it is seen that survival rate increases when factors impairing the patient prognosis are known and a change in surgical strategy is achieved pertinent to this condition.

Obstructive CRCs most commonly affect elderly patients having comorbidities (3,12). Tas F et al. calculated the median age of diagnosis for all patients with CRC in Turkey as 58 in their study (13). The distribution of male and female patients was similar and the median age was calculated as 68.5 (31-95 years) in our study. As it is seen, we can also state that obstructive CRCs are diagnosed in advanced ages, as in previous literature. However number of patients appeared similar when the patients were separated into two groups as ASA I-II and ASA III-IV which is inconsistent with the previous studies in terms of comorbidities.

Overall and curative resection rates are usually lower in obstructive CRCs than elective tumors due to the fact that obstructive CRCs mostly occur in advanced stages and these rates change between 46% and82% (14,15). Thus, use of endoscopic self-expansion metallic stents (SEMS) as a bridge to surgery or for palliation became an issue. But it had high rates of re-intervention and complications (16). We had no experience on endoscopic stenting at our clinic anyway. Clearly, surgical treatment should be performed in patients who can tolerate surgery since short and long-term results of surgery are better (2,15). Our overall resection and curative resection rates exceeded 90% and 60%, respectively.

A significant discussion regarding emergent CRCs in literature is about the type of surgical treatment according to tumor localization and their short-term results. RPA is a generally safe and recommended method for proximal colonic tumors (2,4,15). In distal colonic obstruction, treatment options are broader, and continue to be a source of controversy. One-step surgery for obstructive distal colonic tumors should not be considered as carrying a higher risk than proximal tumors any more (15). It was also pointed out that surgical morbidity and mortality rates were increased with HP compared to primary anastomosis (17). Furthermore, colostomy closure after HP is not an easy procedure and many patients are left with permanent stoma. At the highest rate, only 45% of stoma is closed (16). In this study, HP was performed for approximately half of the patients with distal obstructive tumors. We noticed that ASA scores which may be thought as a reason for this high rate, were not valuable [ASAIII-IV: 10 patients (43.5%) in RPA vs. 11 patients (45.9%) in HP group; p>0.05] in performing HP. No difference could be found regarding morbidity and mortality between primary anastomosis and HP methods for distal tumors, either.The general opinion that, in case of emergency HP is the choice of operation, should be changed.

Different views are expressed regarding short and long term results of obstructive proximal and

distal colonic tumors. There are studies declaring that tumor localization has no effect in prognosis after curative surgery (3,10,15) as well as studies reporting that the prognosis of the obstructive right colonic tumors are worse (11,18,19). Obtaining these different results may be expected since the patient characteristics and treatment types were heterogenic. No difference was found in this study, too, regarding the prognosis of proximal or distal obstructive CRCs.

Reported mortality and morbidity rates for patients with obstructive CRCs were 15-20% and 40-50%, respectively (16,20,21). On the other hand, it is advocated that mortality must remain under 20% (22). Probably the most important morbidity in patients who underwent RPA is anastomosis leakage regarding its detrimental effects. The acceptable anastomosis leakage rate in literature is between 2% and 16% (4,10,21). Only 2 (8.7%) patients developed anastomosis leakage in our series. This low rate may demonstrate that; some of the patients left with stoma could perhaps be ended with primary anastomosis at index operation.

There is a controversy in patients with CRCs regarding how obstruction affects the survival. Some authors proposed that the negative effect of emergency surgery was confined to only early postoperative period and patients who survived from perioperative complications had similar outcomes to elective cases in the long term (23). On the other hand, others reported that the long-term survival of patients with obstructive CRC was lower than the elective cases even though the potential curative surgery had been performed (12,20). Nearly half of the patients who underwent curative surgery for obstructive CRCs reached a 5-year survival (12,14,20). That rate was 52.5% in the present study. In patients who had curative resection and survived in early postoperative period, 5-year OS and DFS rates were 63.6% and 68.8%, respectively. These rates seemed similar with elective cases but 5-year OS for all patients was quite low, 34.4%.

Researchers put forward the concept of lymph node ratio to eliminate the defects in AJCC/UICC staging system for reasons such as the problem of staging in patients with lower number of harvested lymph nodes than required (5,24,25), worseness of the prognosis of some patients in stage II than the ones in stage III (24) and an apparent heterogeneity in the prognosis of the patients in stage III (6,8,26). That LNR, the importance of which was first identified by Berger et al. (9) for OS, DFS and cancer-specific survival in colon cancer, is superior to classic p(N) staging in estimating the prognosis and should be included in AJCC/UICC staging system (27, 28). Patients who underwent a curative resection were separated into two groups according to AJCC/UICC system as early stage (stage I-II) and metastatic advanced stage (stage III-IV) in this study, too, and no significant difference was found in the survival analysis. This result might indicate the deficiency of current staging system.

However, it is not clear in literature that which cut-off value of LNR is the actual prognostic value and patients above which LNR value will benefit from adjuvant treatment (25). Some researchers divided LNRs into quarters to find the cut-off value and accepted the ratio in which 5-year DFS dropped sharply (8,9,29). Others suggested the median LNR as the cut-off value (27,30). We, also accepted the median LNR value which was 0.09 in our study as the cut-off value and no difference was found in the survival analysis carried out between groups according to this value. This may be due to the limited number of patients or the necessity of taking another cut-off value into consideration. On the other hand, it can be said that LNR and cut-off values of LNR accepted for elective cancers in literature cannot be adapted to emergencies yet. Our study appears to be the first in literature regarding the LNR and cut-off values of LNR in emergent CRCs.

As in many retrospective studies, this study also has some limitations. Especially, relatively limited number of patients in the study may lead to some factors which may affect the postoperative outcomes be overlooked. Some of the series we made a comparison with did not include the rectal cancer or other emergencies with colorectal obstruction.

CONCLUSIONS

Discussions are continuing over the management of obstructive distal CRC cases and more objective criteria should be used while deciding on surgical strategy which still remains as an important problem in the practice of general surgery. Although obstruction is associated with poor overall prognosis, patients who have curative resection and survive from perioperative complications have favorable long-term results. In our study, median LNR did not show any prognostic significance for obstructive CRCs. Future prospective/comparative studies should be performed to better define the impact of lymph node ratio on prognosis of obstructive colorectal cancer cases.

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