

The Association of Lymph Node Number with Prognosis/Prognostic Factors in Colorectal Cancer

Kolorektal Kanserde Prognoz / Prognostik Faktörler ile Lenf Nodu Sayısı İlişkisi

ERKAN ÖZKAN¹, MEHMET KAMİL YILDIZ¹, HACI MEHMET ODABAŞI¹, CENGİZ ERİŞ¹, HACI HASAN ABUOĞLU¹, EMRE GÜNAY¹, FÜGEN VARDAR AKER², ÜMİT TOPALOĞLU¹

¹Haydarpaşa Numune Eğitim Ve Araştırma Hastanesi, Genel Cerrahi Kliniği, İstanbul - Türkiye ²Haydarpaşa Numune Eğitim Ve Araştırma Hastanesi, Patoloji Kliniği, İstanbul - Türkiye

ÖZET

Amaç: Kolorektal kanser erkeklerde akciğer ve prostat, kadınlarda meme kanserini takiben kansere bağlı mortalitenin öncü nedenidir. Bu çalışmanın amacı kolorektal kanser cerrahisinde prognoz ve prognostik faktörler ile lenf nodu sayısı arasındaki ilişkiyi değerlendirmektir.

Yöntemler: Kolorektal kanser cerrahisi geçiren yüz yetmiş iki hasta yaş, cinsiyet, tümör çapı/yeri, tümörün invazyon derinliği, tümör evresi ve sağkalım açısından retrospektif olarak değerlendirilmiştir.

Bulgular: Çıkarılan lenf nodu ortalama (SS) sayısı 15.87 (7.62) (medyan, 14) idi. ≥ 65 yaş hastaların diğer yaş gruplarından anlamlı derecede daha düşük ortalama lenf nodu ve metastatik lenf nodu sayısı vardı ($p < 0.05$). Lenf nodu metastazı üzerine cinsiyet ilişkili anlamlı etki

ABSTRACT

Objective: Colorectal cancer is the leading cause of cancer-related mortality following lung and prostate cancer in men and breast cancer in women. The aim of the present study was to evaluate the relationship of lymph node number with prognosis and prognostic factors during colorectal cancer surgery.

Methods: One hundred seventy-two patients undergoing surgery for colorectal cancer were retrospectively evaluated in terms of age, gender, tumor diameter/location, tumor invasion depth, tumor stage, and survival.

Results: Mean (SD) number of excised lymph nodes was 15.87 (7.62) (median, 14). Patients ≥ 65 years of age had significantly lower mean number of lymph nodes and metastatic lymph nodes than other age groups

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Dr. Erkan Özkan

Bosna Bulvarı Taşlıbayır Sok. No: 28 B Blok

Kat: 3 D: 7 Üsküdar/ İstanbul-Türkiye

Tel: 0505.6478604

e-mail: dr.erkano@mynet.com

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tespit edilmemiştir ($p>0.05$). Sağ kolondan çıkarılan ortalama lenf nodu sayısı sol kolondan çıkarılanlardan fazlaydı ($p<0.05$). Ancak metastatik lenf nodu sayısı açısından tümör yerleşim yerleri arasında anlamlı fark yoktu ($p>0.05$). Lenf nodu metastazı bulunan hastaların olmayanlardan daha büyük bir tümör çapı vardı ($p<0.01$). Lenf nodlarının çoğu N0 olarak evrelendi (%44.2). Diğer gruplarla karşılaştırıldığında N2 grubunda mortalite daha yüksekti ($p<0.05$). Eksize edilen lenf nodu sayısı evre III-IV'te evre I-II'dekilerden daha fazlaydı ($p<0.01$). **Sonuç:** İleri yaş, tümör çapı/yeri, tümörün invazyon derinliği ve tümör evresi kolorektal kanserde lenf nodu tutulumuna ve çıkarılan lenf nodu sayısına etki etmektedir.

Anahtar Kelimeler: Kolorektal neoplazmlar, Lenf nodları, Lenfatik metastaz

($p<0.05$). No significant gender-related effect on lymph node metastasis was noted ($p>0.05$). The mean number of lymph nodes excised from the right colon was higher than the left colon ($p<0.05$). However, there was no significant difference between tumor locations in terms of the number of metastatic lymph nodes ($p>0.05$). Patients with lymph node metastasis had a greater tumor diameter than those without ($p<0.01$). Most of the lymph nodes were staged as N0 (44.2%). Mortality was higher in the N2 group compared to other groups ($p<0.05$). The number of excised lymph nodes was higher in stages III-IV than stages I-II ($p<0.01$).

Conclusion: Advanced age, tumor diameter/location, tumor invasion depth, and tumor stage affect lymph node involvement and excised lymph node number in colorectal cancer

Key words: Colorectal neoplasms, Lymph nodes, lymphatic metastasis

Introduction

Colorectal cancer is the leading cause of cancer-related mortality following lung and prostate cancer in men and breast cancer in women.¹ Since mortality is mainly associated with metastatic spread in patients with colorectal cancer, removal of the lymphoareolar tissue in which lymphatic drainage is present should also be performed according to vascular anatomy in addition to primary tumor resection. Lymph node metastasis is the most important prognostic factor for staging, morbidity and mortality in colorectal cancer.^{2,3} More extensive nodal resection reduces the cancer recurrence and allows for more accurate tumor staging.⁴ It is widely accepted that a minimum of 12 lymph nodes should be resected for accurate staging.^{5,6} Excision of a few lymph nodes suggests poor quality surgery or insufficient pathologic examination. The presence of positive lymph nodes requires administration of adjuvant chemotherapy in patients with colon cancer, and both adjuvant chemotherapy and radiotherapy in patients with rectal cancer.^{7,8} While the 5-year mean survival rate is >80% in patients without lymph node involvement, this rate is decreased to 40% in those with positive lymph node involvement.⁹ Therefore, adequate lymph node dissection

is of great importance. The aim of the present study was to evaluate the effect of the number of excised lymph nodes and positive lymph nodes during the colorectal cancer surgery on the prognosis and to investigate their relationship with other prognostic factors.

Material and Methods

One hundred seventy-two patients who underwent surgery for colorectal cancer in our hospital between December 2003 and November 2011 were included in the study. All patients were retrospectively reviewed in terms of age, gender, family medical history, baseline carcinoembryonic antigen, American Society of Anaesthesiologists (ASA) level, type of surgery (emergency or elective), tumor location, type of procedure, anastomosis technique, status of the excised lymph nodes (positive or negative), stage of the tumor, tumor diameter, survival, histopathology of the tumor, post-operative treatment, and follow-up. Patients receiving preoperative radiochemotherapy excluded from the study since it was thought to affect prognosis in colorectal cancers. In the present study, the surgical technique was almost based on oncologic

principles, such as total resection of the tumoral mass with clean proximal and distal surgical margins, high vascular ligation, and complete resection of the mesocolon. The target for adequate lymph node assessment was to excise at least 12 lymph nodes. Mechanical bowel cleaning was performed in all patients, except in cases of emergency surgery. A single dose of ceftriaxone sodium (1 g) and two doses of metronidazole (500 mg) were administered to all patients pre-operatively for prophylaxis. Reasons for emergency surgery included mechanical intestinal obstruction, rectal bleeding, and perforation. A circular stapler was used during the anastomosis procedure to maintain radical surgical margins, while sparing the sphincter mechanisms and reduce the time of surgery. The American Joint Committee on Cancer 2002 tumor, node, metastasis (TNM) staging system was used for tumor staging. Pathologic evaluation was performed by at least two pathologists.

Number Cruncher Statistical System 2007 & Primary Avionics Software System 2008 (Kaysville, UT, USA) was used for statistical analyses of the data. Following descriptive statistics (expressed as the mean and standard deviation), between-group comparisons of quantitative variables that were not normally distributed were performed by a Kruskal-Wallis test. A two-group comparison of variables that were normally distributed was performed by a Student's t-test, and a two-group comparison of variables that were not normally distributed was performed by a Mann-Whitney U test. A χ^2 test was used for the comparison of qualitative variables. The statistical significance level was considered as $p < 0.05$.

Results

Of 172 patients, 82 (47.7%) were female and 90 (52.3%) were male. The mean (SD) age was 62.43 (13.32) years (range, 28-87 years) and 93.03% of the patients were >40 years of age.

In the present study, 4 patients (2.32%) had a family history of colon cancer. The pre-operative carcinoembryonic antigen level was high in 66 patients (38.37%; mean, 23.6 ng/mL). The tumor was located in the left colon and rectum in 128 patients (74.41%). A circular stapler was used in 46 patients (26.74%) for anastomosis. Synchronous liver metastases were noted in 18 patients

(10.46%) in whom simultaneous metastasectomies were performed in addition to colon resections. Synchronous lung metastasis was also noted in two of these patients and a right upper lobectomy was performed by a thoracic surgeon. Fourteen of our patients with synchronous liver metastases are still alive (mean survival, 23.8 months), while four died at a mean of 13.5 months post-operatively. One of these patients received chemotherapy. On histopathologic examination, stage III (45.34%) was the most common stage and moderately differentiated adenocarcinoma (63.95%) was the most frequent diagnosis. The mean (SD) tumor diameter was 5.68 (2.76 cm) (range, 2-15 cm). The mean (SD) duration of follow-up was 19.22 (15.68) months. Metachronous liver metastases were noted in 12 patients (6.97%) at a mean time of 9.3 months (range, 6-16 months), and recurrence at the anastomosis line occurred in two patients (1.16%) at a mean time of 21 months.

The survival rate was 86.4% in stages I-II and 52.08% in stages III-IV. The general follow-up results revealed that 56 patients (32.6%) died at a mean of 12.7 months; 116 patients (67.4%) are still alive. Following the post-operative histopathologic evaluation, six cycles of chemotherapy, including 5-fluorouracil and folinic acid treatment, were administered at four weeks intervals to ninety-six patients who were diagnosed with stages III-IV. Radiotherapy was added to chemotherapy program in thirty-eight patients with stages III-IV tumors located in the rectum. Radiotherapy was initiated at a dose of 1.8 Gy/day on the 1st day of the 1st or 2nd chemotherapy cycle in these patients and a total dose of fifty Gy was administered. The mean number of excised lymph nodes was 15.7 (range, 6-51). The rate of removal of at least 12 lymph nodes was 70%. In the present study, the mean (SD) number of excised lymph nodes was 15.87 (7.62) (median, 14) and the rate of retrieving ≥ 12 lymph nodes was 70%; this rate was 61.1% in stage I-II patients. The maximum number of lymph node metastases was obtained in one piece was forty-five and the mean number of lymph node metastases was 4.4. According to lymph node staging, most of the patients were in the N0 group (44.2%) While there was no significant gender-related difference in terms of lymph node metastasis ($p > 0.05$), the mean tumor diameter was greater in patients with lymph node metastasis compared to those without lymph node metastasis ($p < 0.01$; Table 1).

Table 1. Relationship between lymph node metastasis, tumor diameter, and gender

	Lymph node metastasis				p
	Present (n=96)		Absent (n=76)		
^a Tumor diameter	Mean (SD)	Median	Mean (SD)	Median	0.003*
	6.60 (3.34)	5.5	4.62 (1.25)	4.5	
^b Gender, n(percent)					0.370
Female	48 (50)		34(44.7)		
Male	48 (50)		42(55.3)		
SD: standard deviation ^a Mann-Whitney U test; ^b X ² test; *p<0.01 Values are presented as mean (standard deviation) or number (percent)					

The mean (SD) tumor diameter was 6.60 (3.34) cm (median, 5.5 cm) in patients with lymph node metastasis, and 4.62 (1.25) cm (median, 4.5 cm) in those without lymph node metastasis. The difference between the tumor diameter in terms of presence of lymph node metastasis was statistically significant (p<0.01). The mean number of excised lymph nodes and metastatic lymph nodes in patients ≥65 years of age was lower compared to other age groups (p<0.05; Table 2). The mean number of excised lymph nodes in tumors located in the right colon was higher compared to the left colon (p<0.05); however, no significant differences were noted in tumor locations in terms of the mean number of metastatic lymph nodes (p>0.05; Table 3). No statistically significant difference was found between T stages in terms of the number of excised lymph nodes (p>0.05); however, the mean number of metastatic lymph

Table 2. Comparison of number of excised lymph nodes and metastatic lymph nodes according to age groups.

	Age (years)						p
	20-40		40-64		≥65		
	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median	
Excised lymph nodes	21.33 (11.97)	21.00	15.80 (8.02)	14.50	12.20 (3.23)	12.00	0.027*
Metastatic lymph nodes	3.83 (6.21)	1.50	4.77 (8.19)	1.50	1.00 (1.14)	0.50	0.048*
SD: standard deviation Kruskal-Wallis test; *p<0.05 Values are presented as mean (standard deviation)							

Table 3. Comparison of number of excised lymph nodes and metastatic lymph nodes according to tumor locations.

Tumor locations	Excised lymph nodes		Metastatic lymph nodes	
	Mean (SD)	Median	Mean (SD)	Median
Rectum	16.64 (9.40)	13	6.09 (8.89)	4.0
Rectosigmoid	15.46 (9.11)	12	0.92 (1.32)	0
Sigmoid	15.63 (3.32)	15	3.45 (5.95)	1.0
Transverse	20.00 (7.21)	18	1.67 (2.88)	0
Cecum	21.60 (1.17)	21	2.90 (3.92)	0
Ascending colon	21.33 (0.57)	21	0.33 (0.57)	0
Descending colon	16.00 (6.92)	14	2.80 (3.56)	2.0
Hepatic flexure	16.00 (8.87)	14	1.67 (1.50)	2.0
Splenic flexure	18.00 (5.47)	20	7.00 (9.34)	2.5
p	0.049*		0.317	
SD: standard deviation Kruskal-Wallis test; *p<0.05 Values are presented as mean (standard deviation)				

nodes was higher in patients with stage T4 compared to other stages (p<0.05; Table 4). While the mean (SD) number of excised lymph nodes was 13.92 (5.21) in patients with stage I-II, it was 20.26 (9.98) in patients with stage III-IV. The mean number of excised lymph nodes was higher in patients with stages III-IV compared to patients with stages I-II (p<0.01). An analysis of lymph node metastasis revealed that mortality was significantly higher in patients with N2 metastasis compared to other groups (p<0.05; Table 5).

Table 4. Comparison of number of excised lymph nodes and metastatic lymph nodes according to T staging.

Stage nodes	Excised lymph nodes		Metastatic lymph nodes	
	Mean (SD)	Median	Mean (SD)	Median
T1	11.67 (2.08)	11	0	0
T2	12.84 (5.80)	11	1.76 (3.72)	0
T3	15.09 (5.55)	14	2.38 (4.08)	1.0
T4	19.08 (10.01)	15	7.04 (9.77)	4.5
p	0.081		0.001*	
Kruskal-Wallis test; *p<0.01 Values are presented as mean (standard deviation)				

Table 5. Mortality assessment according to lymph node groups.

		Lymph node groups			P
		N0, n (percent)	N1, n (percent)	N2, n (percent)	
Mortality	Absent	66 (86.8)	24 (85.7)	26 (38.2)	0.001*
	Present	10 (13.2)	4 (14.3)	42 (61.8)	
X ² test; *p<0.01					
Values are presented as number (percent)					

Discussion

Colorectal cancer leads to significant morbidity and mortality worldwide. It is the second leading cause of cancer-related deaths in the United States.¹⁰⁻¹² According to Turkish Ministry of Health data in 2004,¹³ colorectal cancer ranks 7th among the ten most common cancers, with an incidence of 7.24/100,000. Moreover, approximately five thousand new cases are observed and three thousand two hundred deaths occur due to colorectal cancer annually. The goal of colorectal cancer surgery is tumor resection with clear proximal and distal surgical margins and en bloc removal of the lymphoareolar tissue in which lymphatic drainage is present according to vascular anatomy. Accurate lymph node staging is of great importance for the decision of adjuvant chemotherapy, which has a positive impact on patient survival. Positive lymph nodes denote the requirement for adjuvant chemotherapy in patients with colon cancer and adjuvant radiochemotherapy in patients with rectal cancer.

Inadequate lymph node evaluation is associated with negative outcomes in terms of tumor recurrence and patient survival in colorectal cancer. The basis of this association is unknown; however, it is most likely due to incorrect staging and thus not administering adjuvant therapy. Moreover, some authors have emphasized the requirement of adjuvant therapy in patients with negative lymph nodes due to low lymph node retrieval since these patients are at high risk for recurrence.^{14,15}

The International Union Against Cancer, the American Joint Committee on Cancer, and the National Cancer Institute have recommended that at least twelve lymph nodes should be removed for sufficient sampling.¹⁶⁻¹⁸ Along with the advances in standard pathologic evaluation methods, there have been developments in adequate

lymph node retrieval in recent years. In a population-based French study, it was reported that adequate lymph node evaluation could be performed in only 19% of lymph node-negative patients with colorectal cancer during the year 1990.¹⁹ In another population-based study in Canada, it was noted that assessment of a minimum number of twelve lymph nodes could be performed in only 27% of 1789 patients diagnosed with stage II disease between 1997 and 2000.²⁰ Despite the advances in lymph node retrieval, adequate lymph node evaluation could be performed in less than 50% of the patients in 2001. Surgical Oncology Program, Cancer Care Ontario has been developed as a multi-disciplinary surgery/pathology education program. Following this program, the target number of at least twelve lymph nodes was achieved in 60% of the patients in 2004, 69% in 2005, and 77% in 2006.¹¹ Steven *et al.*²¹ reported that in four hundred thirty-four patients diagnosed with colorectal cancer, the mean number of excised lymph nodes was 15.7 and the rate of retrieving at least twelve lymph nodes was 67.1%. In the present study, we also had similar results as Steven *et al.*

An increase in the prevalence of lymph node metastasis is expected as the tumor size increases in colorectal cancers due to increased tumor load. In the present study, we found that number of lymph node metastasis increased with tumor size.

There is no significant gender-related difference in the prevalence of colorectal cancer. Colorectal cancer occurs in both genders at similar rates.²² Mostafa *et al.*²³ reported the male-to-female ratio in a series of one thousand three hundred fifty-five patients with colorectal cancer to be 1.06, and Fazeli *et al.*²⁴ reported this ratio in another series of four hundred nineteen patients to be 1.1. In the present study, this ratio was also found to be 1.09. Nearly 60% of colorectal cancers are located in the left colon and rectum.²⁵ Gomez *et al.*²⁶ and Erkek *et al.*²⁷ reported this finding in 69% and 67% of their patients, respectively. In the present study, the tumors were located in the left colon and rectum in 74.4% of our patients. It has been demonstrated that tumor localization is significantly associated with the number of excised lymph nodes. Nancy *et al.*²⁸ reported in their large population-based study that the mean number of excised lymph nodes in patients with right colon cancer was approximately two times greater than those in patients

with left colon and rectum cancer. Prandi *et al.*¹⁵ also reported similar findings. Excision of more lymph nodes in right colon cancers compared to left colon and rectum cancers has been attributed to the fact that ileocaecal region has greater number of lymph nodes compared to the left colon and that the excised surgical piece is longer in right colon cancers.²¹ We also observed that the mean number of excised lymph nodes was higher in tumors located in the right colon. However, tumor location was not found to be associated with lymph node metastasis. It is more likely to identify positive lymph nodes when higher number of lymph nodes is retrieved. Therefore, it is not surprising that more lymph nodes were evaluated in patients with stage III disease compared to those with stage I and II disease.²⁹ In the present study, we had the same results.

The relationship between depth of wall penetration and the number of excised lymph nodes has not been established. Penetration of all layers of the intestinal wall might be attributable to the inflammation of the regional lymph nodes in patients with T3 or T4 tumors. Thus, the identification of lymph nodes that are not involved might have been easier. The presence of an aggressive-looking tumor requires a more extensive surgical or pathologic evaluation.³⁰ In the present study, the number of excised lymph nodes increased with the advance in tumor stage; however, this was not statistically significant ($p>0.05$). Nevertheless, the number of positive lymph nodes was significantly higher in T4 stage disease than other stages ($p<0.01$). Colorectal cancers often occur in the 6th decade of life, while 2%-8% of the patients are <40 years of age.³¹ Patients <40 years of age constituted 6.97% of our study population. A significant association between age and number of

excised lymph nodes has been reported in several studies. Steven *et al.*²¹ and Nancy *et al.*²⁸ noted that the number of excised lymph nodes and positive lymph nodes was lower in elderly patients compared to younger age groups. This has been attributed to the diminished immunologic and inflammatory response against cancer in elderly patients. We also found that the mean number of excised and metastatic lymph nodes in patients ≥ 65 years of age was significantly lower compared to other age groups. While the five-year mean survival rate is >80% in patients without lymph node metastasis, this rate is 40% in those with lymph node metastasis.⁹ The mean (SD) duration of follow-up was 19.22 (15.68) months (median, 15 months) in our study. Within this period, the survival rate was 86.84% in the N0 group and 47.91% in the lymph node metastasis group. The survival rate was decreased as the number of lymph node metastases increased. The survival rate was significantly lower in the N2 group compared to other groups.

In the present study, in patients with colorectal cancer, advanced age, tumor diameter and location, depth of tumor invasion, and stage of the tumor, but not gender, were found to affect lymph node involvement and the number of excised lymph nodes, thereby influence the prognosis of colorectal cancer.

It has been noted in previous studies on lymph node retrieval that the number of lymph nodes is crucial for accurate staging, diagnosis, and treatment planning and these are strongly associated with survival. Adherence to oncologic principles, such as high vascular ligation, complete resection of the mesocolon, and sufficient surgical margin resection is essential. The assessment of the resected samples by pathologists in addition to surgeons is important for adequate lymph node evaluation.

Kaynaklar

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