ARAŞTIRMA/ORIGINAL ARTICLE

Gülhane Tıp Derg 2013; 55: 7-13

doi:10.5455/gulhane.14264

Factors affecting the number of lymph nodes in specimens resected for colorectal cancer

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SUMMARY

Adequate lymph node evaluation is required for proper staging of colorectal cancer, and the number of lymph nodes examined is associated with survival. In this study, we aimed to evaluate the factors affecting the number of lymph nodes retrieved from specimens of patients operated for colorectal cancer. Medical records of 320 consecutive patients with colorectal cancer were evaluated retrospectively whom had curative resection between 2002 and 2007. Variables such as age, gender, tumor localization, depth of tumor invasion, number of lymph nodes retrieved, specimen length, stage and grade of disease, type of surgery, primary/recurrence disease' presence of preoperative chemo radiotherapy (CRT), surgeon, staff surgeon, pathologist, and staff pathologist were recorded and the results were evaluated statistically. Mean number of lymph nodes retrieved was 14.98 (0 to 129) and mean metastatic lymph node number was 2.37(0-25). Tumor localization, staging, primary/recurrence disease, length of specimen, type of operation, pathologist (resident pathologist), staff pathologist, staff surgeon, presence of CRT, affected statistically significiant in terms of lymph nodes harvested ($p \leq 0.05$). The hypothesis that disease recurrence occurred due to inaccurate staging. Maximal attention should be paid while doing oncologic surgery and should be paid to the total number of lymph nodes retrieved.

Key words: *Colon, rectum, pathology*

ÖZET

Kolorektal kanser için rezeke edilen spesmenlerde lenf nodu sayısını etkileyen faktörler

Kolorektal kanserlerin uygun evrelendirilmesi için yeterli lenf nodu değerlendirilmesi önemlidir ve elde edilen lenf nodu sayısı survival ile ilişkilidir. Bu çalışmada biz kolorektal kanser nedeniyle opere edilen hastaların patoloji örneklerinden elde edilen lenf nodu sayısını etkileyen faktörleri değerlendirmeyi amaçladık. 2002-2007 yılları arasında kolorektal kanser nedeniyle küratif rezeksiyon uygulanan 320 hastanın kayıtları retrospektif olarak değerlendirildi. Yaş, cinsiyet, tümör yeri, tümör derinliği, elde edilen lenf nodu sayısı, patoloji örneklerinin uzunluğu, evre, grade, cerrahi tipi, primer veya rekürrens durumu, preoperatif kemoradyoterapi varlığı, cerrah, uzman cerrah, patolog, uzman patolog kayıtları girildi ve sonuçlar istatistiksel olarak değerlendirildi. Ortalama 14,98(0-129) lenf nodu ve ortalama 2,37(0-25) metastatik lenf nodu elde edildi. Tümör yeri, evre, primer/rekürrens, patoloji örneklerinin uzunluğu, cerrahi tipi, patolog(makroskopist), uzman patolog, uzman cerrah, kemoradyoterapi varlığı istatistiksel olarak anlamlı şekilde çıkarılan lenf nodu sayısını etkiledi ($p \leq 0.05$).

Hastalığın rekürrensi doğru olmayan evreleme ile ilişkilidir. Onkolojik cerrahi yaparken maksimum dikkat harcamak ve yeterli lenf nodu sayısı elde etmek gereklidir.

Anahtar kelimeler: *Kolon, rektum, patoloji*

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Date submitted: 18.01.2012 • **Date accepted:** 27.04.2012 • **Online publication date:** 28.03.2013

Introduction

Colorectal cancer (CRC) is the fourth commonest form of cancer occurring worldwide and is the second leading cause of cancer deaths (1). Approximately 75 % of patients with CRC present with potentially curable disease that could be treated by surgical resection. Surgery should consist of resection of the diseased bowel with adequate surgical margin and en-bloc removal of lymph nodes and lymphatic channels draining the tumoral region (1, 2). The total number of nodes examined is central to correct staging and is important for both adjuvant treatment and the prediction of long-term survival in CRC patients. Thus, following surgical procedure, both sampling lymph nodes adequately and examining them painstakingly share a key role in guiding treatment (3, 4). Since patients with positive lymph nodes are more likely to develop a recurrent disease, they are currently referred to adjuvant therapy. Poor harvesting techniques used during surgery can result in inappropriate staging; these patients might lose the opportunity to benefit from adjuvant therapy (5, 6). On the other hand, inadequate lymph node sampling in CRC patients may increase the risk of local recurrence (7). According to the guidelines; in patients with negative lymph nodes, the minimum number of negative lymph nodes necessary for adequate staging should be 12. Overall, five-year survival of patients with no lymph node metastasis is up to 68%, compared with only 40% of those with lymph node involvement (1, 8-10). A large variation in the number of lymph nodes examined has been observed among patients treated in different pathology departments, hospitals, regions and countries. Several mechanisms influence staging and subsequent therapy, such as the thoroughness of the surgical lymphadenectomy, the extent and diligence of the pathologist's examina-

tion and the biological behaviour of the tumour and/or host. The present study was undertaken to evaluate factors affecting the number of lymph nodes retrieved from pathologic specimens resected from patients with colorectal cancer.

Material And Methods

Patients

Pathologic data from patients operated on for colorectal cancer at our university hospital between 2002 and 2007 were prospectively entered into a computerized database for storage, retrieval and analysis. During this period, a total of five hundred patients underwent surgical treatment, and complete data from 320 of them were available for statistical analysis. Records were reviewed for patient demographics, the number of lymph nodes harvested, length of specimens, disease stage, tumor grade, type of surgery, localization of tumor, primary/recurrent disease, presence of preoperative chemo radiotherapy (CRT), surgeon, supervising staff surgeon (if any), pathologist, and supervising staff pathologist (if any). Results were statistically evaluated. This study had been approved by the institutional research committee before the data entrance was initiated.

Procedural details

Preoperative evaluation included physical examination, computed tomography scan and routine blood measurements. Type of surgery was recorded as one of the follows: right colon resection, left colon resection, sigmoid resection, low anterior resection, abdominoperineal resection, total colectomy, and partial resection. Colon and lymph nodes draining the involved bowel part were resected by surgeons, followed by histological examination of the specimens by pathologist. The length of the bowel resected was measured. Localization of the tumor was categorized as being involved in the caecum, right colon, hepatic flexure, transverse colon, splenic flexure, left colon, sigmoid colon or rectum. Surgeons included in this study were numbered from 1 to 8 and pathologists included in this study were numbered from 1 to 10. Grade of tumors were recorded. Pathology reports included histological diagnosis, depth of invasion and the lymph node status.

Statistical Analysis

Results are expressed as the means±S.D., median (min-max), and percents. We used Kolmogorov-Smirnov and Levene tests to determine the distribution characteristics of variables and variance homogeneity. Differences between groups were tested for significance by t-test, Mann-Whitney U test, chi-square test, one-way ANOVA test and Kruskal Wallis test as appropriate. Bonferroni-adjusted Mann-Whitney U or Tukey tests were done for comparison of subgroups. The relationship between variables was analyzed by Pearson's correlation. Differences and correlations were considered significant at $P < 0.05$. Statistical analyses were performed by using SPSS 11.5 Statistical Package Program for Windows (SPSS Inc., Chicago, IL, USA).

Results

Three hundred and twenty patients (200 men, 120 women) were operated on for colorectal cancer. One patient requiring total colectomy was excluded from study as the high number of lymph nodes retrieved might have affected the statistical results (129 lymph nodes). Mean age of patients was 60.32, ranging between 21 to 92. Median amount of lymph nodes harvested in men was 14 and in women was 14 with a mean of 14.95 and 15.04, respectively. There was no statistically significant difference between gender and lymph node retrieval (p=0.925). In this study, age was divided into four groups (Table 1). The mean and median numbers of lymph nodes were found to be significantly higher (Kruskall-Wallis p=0.004) in under 50-year-old group when compared to older age groups (Table 1).

Tablo I. Age of patients

Age	*Frequency*	*Percent (%)*	*Mean*	*Median*	*p*
21-50 years	77	24.1	18.36	16.50	
51-60 years	70	21.9	15.09	14.00	
61-70 years	85	26.6	13.26	12.00	0.004
>70 years	88	27.5	13.66	12.50	
Total	**320**	**100**	14.98	14.00	

Overall, 153 patients (47.8%) had positive lymph nodes. Mean lymph node was 14.98. The median lymph node harvest in the negative lymph node group was 14 (range 0-44), while the median lymph node harvest in the positive lymph node group was 13 (range 1-46) with a mean of 15.07 and 14.89, respectively). There was no significant difference (p=0.513).

In the examination of specimens, it was found that samples having at least 12 lymph nodes were harvested in 198 patients (61.9%), and samples having 11 and less lymph nodes were retrieved in 122 patients (38.1%). Lymph node metastasis was found in 90 patients (45%) as at least 12 and above lymph node. Lymph node metastasis was found in 63 patients (51.6%) in the 11 and below lymph node group.

Table 2 shows the types of operations performed and studied by Anova, uni and multivariate analysis. The type of operation found to be a significant factor though Anova analysis for lymph node harvesting (p<0.001) and Tukey analysis showed that right and total colectomy remained significant variables for lymph node harvest (LNH).

There was a statistically significant association between length of specimen and LNH (R=0.347, p=0.001) with a mean length of 28.77 cm (min=9, max=150cm).

Table 3 represents tumor localizations and length of resection specimens. According to localization of tumors, number of lymph node retrieval in the right side was more than those in other sides, which was found to be statistically significant (p=0.022). The

Tablo II. Types of operation and lymph nodes harvested (APR: Abdominoperineal resection, *LAR: Low anterior resection, AR: Anterior resection, LN :Lymph node*).

Type of operation	Frequency	Mean LN harvested	95% CI for Mean	p
APR	33	11.27(0-39)	8.34-14.20	
LAR	76	15.34(0-43)	13.50-17.18	
AR	95	13.38(0-46)	11.89-14.87	
Left hemicolectomy	21	12.86(3-25)	10.17-15.55	<0.001
Right hemicolectomy	65	17.92(6-44)	15.85-20.00	
Total colectomy	15	21.40(5-44)	14.21-28.59	
Segmental resection	14	15.36(6-29)	10.67-15.91	
Total	**319**	**14.98**		

Tablo III. Localization of tumors and length of specimens

		Cases	Mean Length (cm)	
Length of specimens (cm) for localizations	Rectum	108	25.60(±8.491)	
	Left colon	127	26.67(±19.246)	
	Right colon	84	36.06(±22.083)	
	Total	319	28.77(±17.824)	
			LNH mean	**p**
The groups of specimen length (cm) and LNH	9-20	113	12.87(±7.372)	
	21-30	131	15.47(±7.421)	0.001
	31-150	75	17.32(±10.578)	
	Total	319	14.98(±8.407)	
Localization of tumors and LNH	Rectum	108	14.36(±8.325)	
	Left colon	127	13.26(±7.330)	0.022
	Right colon	84	18.39(±9.112)	
	Total	319	14.98(±8.407)	
Lymph node retrieval regardless of length of specimen	Rectum	108	14.59(±8.12)	
	Left colon	127	13.47(±8.11)	0.001
	Right colon	84	16.85(±7.34)	

length of specimens in the right colon, left colon, and rectum were compared with the number of lymph nodes retrieved. Although the length of the specimens increased respectively from rectum through right colon, lymph node retrieval in the rectum was higher than in the left colon. Nevertheless, the highest number of LNH was found in the right colon.

There was a statistically significant correlation between the localization of tumors and lymph node retrieval. However, we investigated whether a correlation existed between the length of specimens in different localizations and lymph node retrieval. As a result, there was a statistically significant result between localization of tumors and lymph node retrieval, regardless of the length of the specimen (P=0.001) (Table 3).

Lymph node retrieval in tumors with well-differentiated cancers was less than in tumors with poorly differentiated cancers. Although mucinous tumors had higher numbers of lymph nodes harvested than well and poorly differentiated cancers, this result was not statistically significant (p=0.94) (Table 4).

T staging was done in patients with CRC. There was a statistically significant difference between T staging and lymph node retrieval (p=0.026)(Table 4). The number of lymph nodes retrieved in patients with T3 and T4 was more than in patients with T1 and T2.

We compared lymph node harvest in the LN positive group (mean LNH:15.64) with that of a LN negative group (mean LNH:15.07), and we found no statistically significant difference between the two (p=0.682). However, there was a statistically significant result between N staging groups, according to the evaluation of lymph nodes N Staging (p=0.038)(Table 4).

There were no statistically significant difference between the groups that had tumors without metastasis and the group that had tumors with metastasis in terms of lymph node retrieval (p=0.700) (mean LNH: 14.91 and 15.42, respectively). Although the number of lymph nodes retrieved in the stage 1-2 group was higher than in the stage three group, the difference was not statistically significant (p=0.631).

When evaluating lymph node harvesting according to tumor staging, a statistically significant result was found by using Anova analysis (P=0.011)(Table 4).

The mean amount of lymph nodes were 15.27 in patients with a primary tumor, whereas there were 10.28 in patients with a recurrent tumor, which was found to be significant (p=0.002).

Lymph node retrieval in patients with rectum cancer (n=108 patients) that had been given radiotherapy prior to surgery (n=28 patients) was less than in patients without radiotherapy, which was found to be significant (mean LNH=11.4 and 15.4, respectively) (Anova p=0.030).

Eighty-four patients were operated on by surgeon residents. The mean amount of lymph nodes harvested was 14.02. Staff and faculty members operated on 235 patients. The mean amount of lymph nodes was 15.33, and this result was not statistically significant (p=0.223). Staff surgeons included in this study were numbered from 1 to 8 (Table 5). There was a difference in lymph node retrieval between individual staff surgeons, which was found to be significant (p=0.015).

One hundred and ninety-four specimens were examined by residents of the pathology department, while 125 specimens were examined by staff and faculty pathologist. There was a difference in lymph node retrieval between residents and staff patholo-

Tablo IV. Lymph node evaluating according to tumor staging and grading *(LNH: Lymph node harvesting)*

		Number of Cases	*LNH Mean*	*p*
T	1	10	12.30	0.026
	2	29	12.00	
	3	70	16.14	
	4	210	15.14	
N	0	172	14.91	0.038
	1	74	13.32	
	2	73	16.85	
M	0	271	14.91	0.7
	1	48	15.42	
Stage	1	31	11.45	0.011
	2a	39	16.49	
	2b	100	15.68	
	3a	5	19.20	
	3b	53	12.32	
	3c	43	16.85	
	4	48	15.42	
Grade	0	9	14.22	0.94
	1	10	10.50	
	2	244	15.18	
	3	32	16.50	
	mucinous	23	17.00	
	Clear cell	1	39	
Total		319	**14.98**	

gist-faculty members (16.11 for residents, 12.96 for staff and 15.75 for faculty) (p=0.006). In addition, staff pathologists were numbered from 1 to 10, and there was a statistically significant result between individual pathologists (p=0.016)(Table 5).

Discussion

Patients with positive lymph nodes need adjuvant chemotherapy following surgery, so both adequate lymph node retrieval and evaluation are important predictors of prognosis and valuable in planning treatment (11, 12). It is known that inadequate lymph node evaluation results in worse outcomes, such as tumor recurrence and lower patient survival, particularly in Stage I and II diseases (3, 13-16). One of the reasons for inadequate lymph node evaluation is the low number of lymph nodes retrieved (1, 11). The number of lymph nodes is a strong indicator of whether surgical operation and pathologic care is of good quality or not (14).

The first suggestion made by Fielding in 1991 was that a minimum of 12 lymph nodes was an adequate number for staging in patient with CRC (8). Many studies recommended that 12 lymph nodes were adequate for staging (1, 2, 4, 5, 15-17). In our study, though, the median number of lymph nodes retrieved was 14.00 (mean=14.98; range=0-46).

Tablo V. **Lymph node evaluating according to staff surgeon and staff pathologist** ***(LNH: Lymph node harvesting)***

		Number of Cases	*Mean LNH*	*p*
Surgeon	1	104	17.00	0.015
	2	37	13.81	
	3	26	11.27	
	4	24	17.58	
	5	22	15.32	
	6	18	12.56	
	7	17	14.29	
	8	71	13.80	
Pathologist	1	44	16.32	0.016
	2	42	16.62	
	3	36	12.92	
	4	35	15.14	
	5	32	13.66	
	6	28	16.64	
	7	28	10.11	
	8	19	18.42	
	9	30	15.93	
	10	25	14.20	
Total		**319**	**14.98**	

Not surprisingly, as the number of lymph nodes harvested increases, the possibility of detecting positive lymph nodes also increases. In addition, the possibility of retrieving more lymph nodes in Stage III patients is more than in Stage I and II patients because of the lymph nodes' diameter. As it is already known, if a lymph node is involved, the diameter of the lymph node is increased (6, 11, 18), so lymph nodes are easily detected by both surgeons and pathologists. Monig et al. showed that positive lymph nodes are larger than 5 mm in diameter (18). More lymph nodes were retrieved in patients with Stage IIIa than in patients with other stages. But only 5 patient have stage IIIa disease so that its reason is less patient in stage IIIa than the other groups.

Leibl et al. tried to explain whether there was a correlation between depth of wall penetration and lymph node retrieval (19), but they did not mention lymph node positivity. As it is expected, from T1 to T4, lymph node retrieval increases. We found a parallel result to previous studies. We found that mean lymph node retrieval in patients with T3 and T4 was more than mean lymph node retrieval in patients with T1 and T2. However, the reason for this is unclear (11). Thus, this issue calls for more investigation.

Localization of the tumor is a very important factor in harvesting more lymph nodes. Many studies confirmed that more lymph nodes were harvested in patients with right-sided localizations than in patients with other localizations (11, 14, 17, 20-22). Lymph node retrieval in both the right and the transverse colon were more common than in other localizations. Since both the right and transverse colon are longer than other parts of the colon, we thought that the length of the specimen might be one of the reasons why more lymph nodes were harvested in the right and transverse colon. So, there is a correlation between the length of the specimen and lymph node retrieval (21, 23); we found a significant association between specimen length and LNH.

In our study, we found that the age of the patient affected lymph node retrieval (p=0,004). In many studies it was proposed that there is a correlation between older age and low lymph node retrieval (11, 14, 23, 24). This difference may be related to the immune response of the patient; size and morphology

of lymph nodes which are modified by immune responses against neoplastic cell products. Older patients probably have a diminished immune response, which would explain the effect of age on the number of lymph nodes examined in this and other studies (11, 22, 23). In our study, though, median age was 61.50 years (mean age=60.67; range=21-92) and comparison of LNH in younger patients with older ones we found that there is a statistically significant difference between age and lymph node retrieval. According to many studies, lymph node retrieval was also affected by gender (11, 22, 25), but our results did not correlate with literature.

In one study, it was cited that residents found more lymph nodes in patients with CRC than staff (26). The greater amount of experience possessed by the surgeon and pathologist may play an important role in their retrieval of more lymph nodes (11). Pathology practice patterns may be more important than surgical practice patterns (25).Although there was no statistically significant difference between staff surgeons and residents, a difference in lymph node retrieval did exist between individual staff surgeons. Like the significant difference in lymph node evaluation between residents and staff pathologist-faculty members, we found statistically significant results between individual staff pathologists in lymph node evaluation.

However some studies have reported that lymph node ratio is a superior prognostic indicator and is defined as the quotient between positive LNs and total number of lymph nodes harvested (27, 28). In our study lymph node ratio of less harvesting group is higher than more harvesting group. It is an interesting result and may be effected by pathologists.

As a result; our results indicate that lymph node retrieval was not effected by gender, tumor differentiation, and M staging. The LNH was significantly effected by age, length of specimen, recurrent tumors, T and N staging, localization of tumor and presence of preoperative radiotherapy. There was also difference between residents and staff pathologist, and individual staff surgeon. All of these factors are likely to be more or less responsible for lymph node harvest.

Like other studies, our study has some limitations, but analysis of a single center may be advantage of this study to evaluate factors that impact lymph node retrieval. Although we may not adjust several factors in view of our knowledge, experience of surgeons and pathologist may be improved.

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