ARAŞTIRMA/ORIGINAL ARTICLE

Gülhane Tıp Derg 2015;57: 31 - 35
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doi: 10.5455/gulhane. 173337

Factors affecting the number of dissected lymph nodes in rectum tumor resections

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ÖZET

Rektum tümör rezksiyonlarında diseke edilen toplam lenf nodu sayısını etkileyen faktörler

Kolorektal rezeksiyonlarda metastatik lenf nodu sayısının tümör evrelemesinde güvenilir bir kriter olarak kullanılabilmesi için diseke edilen toplam lenf nodu sayısının belirli bir eşiğin üzerinde olması gerekmektedir. Ancak neoadjuvan tedavi almış rektum rezeksiyonlarında asgari lenf nodu sayısına ulaşmakta zorlanılabilmektedir. Bu çalışmada, neoadjuvan tedavi almış rektum rezeksiyonlarında, diseke edilen toplam lenf nodu sayısındaki değişime etkili olabilecek faktörler araştırılmıştır. Rektum rezeksiyonu yapılmış 102 olgu yeniden incelenmiştir. Toplam lenf nodu sayısının hasta ve tümör ile ilişkili çeşitli faktörlerle ilişkisi değerlendirilmiştir. Yüksek dereceli, musinöz komponentli, ekstramural derinliğe ulaşan, perinöral invazyon gösteren, yetersiz histolojik regresyon izlenen, radiyal cerrahi sınırı pozitif saptanan, tanı anında lenf nodu metastazı bulunan, rezeksiyonu son yıllarda yapılan ve genç yaştaki olgularda daha fazla sayıda lenf nodu diseke edildiği saptanmıştır. Diseksiyondaki en büyük lenf nodu çapı arttıkça diseke edilen toplam lenf nodu sayısının da artığı belirlenmiştir. Kriterler içinden; hasta yaşı, tümör derinliği ve en büyük lenf nodu çapının diseke edilen toplam lenf nodu sayısını istatistiksel olarak anlamlı derecede etkilediği bulunmuştur. Kolorektal tümör rezeksiyonlarında diseke edilen toplam lenf nodu sayısını çeşitli faktörlerin etkiledigi genel kabul görmüştür. Burada, neoadjuvan tedavi almış tümörlü rektum rezeksiyonu gibi spesifik bir grupta hangi faktörlerin öne çıkabileceği istatistiksel olarak değerlendirilmiş ve tartışılmıştır.

Anahtar Kelimeler: Rektum tümörü, lenf nodu diseksiyonu.

SUMMARY

In colorectal resections, to use the number of metastatic lymph nodes as a reliable tumor staging criterion, the total number of dissected lymph nodes must be above a certain threshold. However, it is difficult to reach required number after neoadjuvant treatment. In this study, we especially evaluated the factors which may affect the number of dissected lymph nodes from rectum resections received neoadjuvant therapy. One hundred two rectum resections were reviewed. The relation with the number of dissected lymph nodes and some criteria of patient and tumor were evaluated. The number of dissected lymph nodes was greater in high grade tumors from younger patients showing mucinous component, perineural invasion, positive radial surgical margin, and with metastatic lymph node. Inadequate tumor regression, extramural tumor depth, and being resected in recent years were also correlated with increased number of dissected lymph nodes. We noticed that the diameter of the largest lymph node has an impact on the total number of lymph nodes. Among these criteria, the patient's age, tumor depth and the diameter of the largest dissected lymph node were most statistically significant. We evaluated the rectum resections after neoadjuvant therapy as a unique model and discussed the factors should be considered while dissecting the lymph nodes.

Key words: *Rectum tumor, lymph node dissection.*

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Makalenin Geliş Tarihi: Nov 21, 2014 • **Kabul Tarihi:** Jan 07, 2015 • **Çevrim İçi Basım Tarihi:** 15 Şubat 2015

Introduction

Surgical resection is one of the most effective treatment methods for colorectal tumors. Results of pathological evaluation obtained from the surgically resected samples are the most valuable data for the prediction of patients' prognosis. TNM staging, namely anatomical progression of tumor is accepted as a significant prognostic factor obtained through the pathological evaluation (1,2)

The number of lymph node metastases (N) is one of the main criteria for TNM staging of tumors. (1,2) Previous studies demonstrated that total number of dissected lymph node has been found to be associated with the number of lymph node metastases (3-6). The total number of dissected lymph node should be above a certain threshold in order to the fact that the number of metastatic lymph node can be used as a reliable criterion.

The threshold value for the number of dissected lymph node is recommended between 10-14 (1), or above 12 (2) in colorectal carcinomas. The number of dissected lymph node has a prognostic importance as well. (1,2,7-10). Therefore, applying surgical and pathological technics in order to increase total number of lymph node has an importance. In literature, the factors that lead to low number of dissected lymph node from colon tumors has been discussed. Factors associated with patients such as obesity (11), age (2), factors associated with the features of tumors, surgical processes (12-15) and pathological evaluation (3,16) and the related factors have been revealed to effect on total number of dissected lymph nodes.

The number of dissected lymph nodes from rectum tumors has been found to decrease after neoadjuvant therapy in previous studies. (17,18). Sometimes in daily practice, it is also difficult to obtain sufficient amount of lymph node from rectum resections after neoadjuvant therapy.

In the current study, the factors other than neoadjuvan therapy related factors that may affect the number of lymph node in rectum dissections were evaluated. For this purpose, rectum resections following neoadjuvant therapy were investigated as a subgroup instead of investigating all colorectal tumors.

Material and Methods

The pathological reports and slides of 102 cases which underwent rectum resection following neoadjuvant therapy due to rectum carcinoma between 2004-2011 years were reviewed again in our hospital.

During neoadjuvant therapy, radiotherapy was administered in a way that a daily dose of 1.8-2 Gy with 23-25 fractions, so totally 45-50 Gy dose was administered. 5-FU with a dose 400 mg/m2/day and Ca Leucovorin with a dose 20 mg/m2/day

Table II: Distribution of the cases for different variables

Variable	Subgroup of the variable	Number of Cases (n)	Percentage of Cases (%)
Age	< 40 (early onset)	12	11,8
	≥ 40 (non-early onset)	90	88,2
Gender	Male	66	64,7
	Female	36	35,3
Tumor histologic type	"unusual"	12	12,5
	"usual"	84	87,5
Tumor grade	High (grade 3-4)	14	14,6
	Low (grade 1-2)	82	85,4
Tumor depth (T)	Extramural (T3-T4)	79	77,5
	Intramural (T1-T2)	23	22,5
Perineural invasion	Positive	17	17,7
	Negative	79	82,3
Radial surgical margin	Positive	19	18,6
	Negative	83	81,4
Histologic regression grade	High (poor (grade 3) or minimal (grade 2) response)	85	83,3
	Low (complete (grade 0) or moderate (grade1) response)	17	16,7
Metastatic lymph node status	Positive (N1-N2)	55	53,9
	Negative (N0)	47	46,1
Resection year	≥ 2009	33	32,4
	≤ 2008	69	67,6

were administered at the first and third day of radiotherapy. Surgery was performed by low anterior resection or abdominoperineal resection in accordance with mesorectal excision procedure. Pathological evaluations were carried out according to protocols endorsed by AJCC, CAP (1,2). The evaluations between 2004-2008 years were performed by general pathologists, whereas between 2009-2011 years evaluations were done by specialized pathologists who has specialized knowledge about gastrointestinal system.

The age, gender of patients and histologic type, depth, grade of tumor, the distance of tumors to radial surgical border, histologic regression of tumor depending on the neoadjuvant therapy, the presence of metastatic lymph node, maximum size of dissected lymph node and resection year are included in the current study which may be in association with the changes in the total number of dissected lymph nodes from rectum resections.

The dissociation of cases according to criteria was determined by frequency analysis. As the first part of the study, the association between total number of dissected lymph nodes and other variables were analyzed by T-test and Pearson correlation analysis. In the second part, the variables which have an impact on the change of the total number of dissected lymph nodes were analyzed by linear regression analysis (SPSS15.0, SPSS Inc, Chicago, USA).

Results

Totally minimum 4 - maximum 32 lymph nodes were dissected from resection samples. The average of lymph node totally dissected was found to be 13.7. The maximum size of dissected lymph node ranged from 0.2 cm to 1.6 cm and average size was found to be 0.63 cm. (Table I). Depending on the neoadjuvant therapy, six subjects (5.9%) were seen complete response. The distribution of subjects according to variables divided into groups was performed by frequency analysis test (Table II).

Table I: Frequency analysis results for "dissected total lymph node number" and "largest lymph node diameter".

	Dissected total lymph node number (n)	Largest lymph node diameter (cm)
Mean ± SD	13,7 ± 7,4	0,63 ± 0,30
Median (min-max)	13 (4-32)	0,50 (0,20-1,60)

SD: standard deviation

The number of dissected lymph node was found to be much

Table III: Association between "dissected lymph node number" and the included variables.

Variable	Subgroup of the variable	Mean of dissected total lymph node number ± SD*	p †
Age	< 40 (early onset)	18 ± 6,8	0,033†
	≥ 40 (non-early onset)	13,1 ± 6,8	
Gender	Male	13,6 ± 6,4	0,224
	Female	13,9 ± 9,2	
Tumor histologic type	"unusual"	16,9 ± 10,4	0,102
	"usual"	13,3 ± 6,8	
Tumor grade	High (grade 3-4)	16,4 ± 10,5	0,173
	Low (grade 1-2)	13,4 ± 6,9	
Tumor depth (T)	Extramural (T3-T4)	14,9 ± 7,4	0,002†
	Intramural (T1-T2)	9,4 ± 6,1	
Perineural invasion	Positive	13,9 ± 7,5	0,212
	Negative	13,5 ± 6,3	
Radial surgical margin	Positive	16,2 ± 9,6	0,105
	Negative	13,1 ± 6,8	
Histologic regression grade	High (poor (grade 3) or minimal (grade 2) response)	14,0 ± 7,8	0,420
	Low (complete (grade 0) or moderate (grade1) response)	12,4 ± 5,9	
Metastatic lymph node status	Positive (N1-N2)	14,5 ± 8,3	0,227
	Negative (N0)	12,7 ± 6,2	
Resection year	≥ 2009	14,8 ± 7,9	0,324
	≤ 2008	12,2 ± 6,3	

*SD: standard deviation

†: Variables have a statistically significant association with "dissected lymph node number" ($p<0.05$).

more in rectum resections with mucinous component, high stage (stage III-IV), high grade (grade 3- 4), perineural invasion and extramural invasion (T3-T4) than opposite situations. In subjects with young age, lymph node metastasis at the time of diagnosis, positive radial surgical border and recently resected, it was detected that dissected lymph node number was much more.

Of all these criteria, early onset (<40 years old) tumors were found to be dissected much more lymph node (average 18) statistically significant than non-early onset (≥ 40 years old) tumors (average13.6), ($p=0.033$). Additionally, the number of lymph node was found to be higher significantly in extramural (T3-T4) tumors compared to intramural (T1-T2) tumors ($p=0.002$) (Table III). There was a statistically significant correlation and association in this study between total number of lymph node and the maximum size of dissected lymph node. The max size of dissected lymph node was found to be in association with total number of lymph node in a positive way ($r= +0.351$) significantly ($p<0.001$).

Moreover, we investigated the potential effects of tumor characteristics on dissected total lymph node number through calculation of values utilizing linear regression analysis. Due to results, the age of patients, depth of tumor, and maximum size of dissected lymph node were found to effect on total number of dissected lymph node statistically significant (Table IV)

Discussion

In order to lymph node metastasis is used as a reliable criterion in colorectal tumors, total number of dissected lymph node is to be above a certain threshold (1,2). Previously, the number of metastatic lymph node was demonstrated to be associated with total number of dissected lymph nodes (3-6). The total number of dissected lymph node has a prognostic importance (1,2,7-10). Survival was found to be increased as the number of lymph node increased in patients with stage 2 (N0) (9,19,20). It was revealed that the dissection of lymph node above the recommended threshold was found to be in association with the increase of survival both in stage 2 (N0) and stage 3 (N1-N2) patients (8,10)

Mean number of dissected lymph nodes from colorectal tumor resections should be considered as a quality control for the institutions on colon cancer care (21). Due to the significance of dissected lymph nodes, the factors which may effect on the changes of total number of dissected lymph nodes were investigated in colorectal tumor resections in literature.

Table IV: The criteria affecting the total lymph node number significantly.

Factors	β*	p†
Age (< 40:early onset vs. ≥40:non-early onset)	5.8	0 .006
Tumor depth (intramural:T1-T2 vs. extramural:T3-T4)	4.3	0.018
Diameter of the largest lymph node (cm)	7.3	0.002

***: β effect value in linear regression analysis**

†: Variables have a statistically significant effect to "dissected lymph node number" (p<0.05).

According to literature up to date, mostly general evaluations were performed colorectal tumors regardless of specific localization either colon or rectum (22). Factors effecting on the number of lymph node can be evaluated under four different categories; patient related factors, tumor related factors, pathological evaluation and surgery related factors.

In colorectal tumor resections, fewer number of lymph node dissections were demonstrated in old patients (8,23). Our study confirmed previous studies as well, total number of lymph node was found to be associated with the patient's age statistically significant in a negative way. We also proved this correlation in a different way by dividing the patients into two subgroups as early onset (< 40 years old) and non-early onset (≥ 40 years old) tumors. Early onset tumors have been defined with special characteristics (24) and with this report one more added on those. Moreover, there is no association found in our study between patient gender and yielded lymph node which is consistent with the literature (23). Previously, in colorectal resections from obese patients with high BMI, a patient related factor, fewer lymph nodes was demonstrated to be dissected (13). The length of resection material was revealed to be positively correlated with total number of lymph node in colorectal resections (25). The association between the localization of tumor and dissected lymph node is controversial. The number of dissected lymph node in right colon tumors has been found to be higher in majority (8). However, some studies revealed that much more lymph node was dissected in left colon compared to right colon (25). Some studies found no association regarding localization of tumors (23).

The size, depth and overall stage of tumor have been indicated in literature the most associated tumor characteristics with yielded lymph node number. It was stated that dissected lymph node number was much more from tumors with late stage and higher depth into the intestine wall (8,23). Consistent with the previous studies, our findings showed that depth of tumor and lymph node metastasis (late stage) was found to be positively correlated with total number of dissected lymph node.

This is the first study showing positive correlation between total number of lymph node and histological regression grade which is an indicator of the vital tumor volume after neoadjuvant therapy. In other words, it was shown that the number of dissected lymph node from ones which responded neoadjuvant therapy completely or moderately (low regression grade) was fewer than ones that responded poor or minimal (high regression grade) to neoadjuvant therapy.

In primer colorectal tumor resections, much more lymph node was stated to be dissected than recurrent tumor resections (26). Total number of lymph node was found to be high in K-RAS mutated tumors compared to K-RAS wild type tumors (25).

In literature, it is the common opinion regarding surgery and pathological evaluation that as the experience and specialization increase, yielded lymph node number increases. Gastrointestinal surgery fellowship-trained surgeons dissected more lymph nodes than nonfellowship-trained surgeons did (12,13). Surgical technics (14) and special procedures (15) were also defined as effective factors for dissected lymph node number. Dissections performed by specialized pathologist's assistants had been yielded more lymph nodes than pathology residents (3). The number of dissected lymph nodes was found to be different among pathologists (26,5). The type of hospital was found to be associated with yielded lymph node number. Total number of yielded lymph node in cancer center or academic university hospitals was found to be higher than total number of yielded lymph node in community hospitals (21,27). Usage of specific solutions simplifying the dissection of lymph node and longer fixations has been determined to increase the number of yielded lymph node (16).

In this study, an association was found between the year of evaluation and total number of lymph node which is parallel to literature (23,26). This result probably depends on interest on the topic and specialized pathologist and surgeons. In our study, the mean of total number of dissected lymph node was increased after 2009, specialized gastrointestinal pathologist started to study in pathology department.

In literature, it was revealed that fewer lymph nodes dissected from rectum resections compared to colon resections (26). Neoadjuvant therapy is denoted as a prominent factor to the cause of this circumstance (17,18,26). There are a few number studies which evaluated rectum tumor resections taken neoadjuvant therapy among each other. In those studies, resections obtained from obese patients (11), tumors with low stage (T) (28), fewer lymph nodes were dissected. Dissected lymph node from rectum resections taken neoadjuvant therapy has been declared to have effect on prognosis (29).

In cases of rectum resections without lymph node metastasis which took neoadjuvant treatment, the decrease of recommended threshold for dissected total number of lymph node has been declared to have no effect on prognosis. (28)

In colorectal tumor resections, dissected total number of lymph node has been acknowledged to be effected by various factors. In this study, rectum tumors treated with neoadjuvant therapy were handled as a specific group. The factors that may have association with or effect on total number of lymph node were statistically evaluated. In conclusion, besides taking neoadjuvant treatment, factors related with patient, tumor and pathological evaluations are shown to effect for rectum resections. In the low number lymph node situations, it is re-

commended to pathologists try to recover “as many as possible lymph node” (16,30).

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