



## Original Article

# Higher cut-offs for the number of lymph nodes harvested do not predict better prognosis in patients with colon cancer



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### ABSTRACT

**Background:** Current threshold for minimum lymph node harvest may not be adequate for appropriate staging in colon cancer and newer surgical techniques may allow more lymph nodes to be harvested. The aim of this study was to examine the prognostic role of harvesting and examining lymph nodes higher in number than the recommended threshold ( $\geq 12$ ), in patients with colon cancer.

**Methods:** This retrospective study included 179 patients that underwent open colon resection for adenocarcinoma of the colon. A D3 resection with high vascular ligation was made so that large number of lymph nodes was removed in most patients. Differences in overall survival between below and above three cutoff points ( $\geq 18$ ,  $\geq 24$ ,  $\geq 40$ ) were estimated.

**Results:** During median 33 months of follow-up, 45 patients died and mean overall survival was  $108.7 \pm 5.6$  months (95% CI, 97.7–119.7). The mean number of lymph nodes harvested and examined was  $44.0 \pm 25.7$  (median 38; range, 7–150). No significant effect was found for three different cut-off values ( $\geq 18$ ,  $\geq 24$ , or  $\geq 40$  nodes) on mean overall survival ( $p > 0.05$  for all comparisons). The same was true for the whole study population as well as for N0 (N negative) and N1-2 (N positive) patient subgroups, when they are analyzed separately.

**Conclusions:** Our findings do not support the survival benefit of substantially higher number of lymph nodes harvested in colon cancer.

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## Pontos de corte mais altos para o número de linfonodos coletados não predizem melhor prognóstico em pacientes com câncer de cólon

### R E S U M O

#### Palavras-chave:

Câncer de colo  
Coleta de linfonodo  
Sobrevivência geral  
Prognóstico  
Número de linfonodos  
examinados

**Fundamento:** O limite atual para a coleta mínima de linfonodos pode não ser adequado para o estadiamento adequado no câncer de cólon e novas técnicas cirúrgicas podem permitir que um número maior de linfonodos seja coletado. O objetivo deste estudo foi examinar o papel prognóstico da coleta e exame de linfonodos em número maior do que o limite recomendado ( $\geq 12$ ), em pacientes com câncer de cólon.

**Método:** Este estudo retrospectivo incluiu 179 pacientes submetidos à ressecção aberta de cólon para adenocarcinoma de cólon. A ressecção D3 com ligadura vascular alta foi realizada para que um grande número de linfonodos fosse removido na maioria dos pacientes. As diferenças na sobrevida global entre abaixo e acima de três pontos de corte ( $\geq 18$ ,  $\geq 24$ ,  $\geq 40$ ) foram estimadas.

**Resultados:** Durante a mediana de 33 meses de seguimento, 45 pacientes morreram e a sobrevida global média foi de  $108,7 \pm 5,6$  meses (IC 95%: 97,7-119,7). O número médio de linfonodos coletados e examinados foi de  $44,0 \pm 25,7$  (mediana = 38; variação: 7-150). Nenhum efeito significativo foi encontrado para três valores de corte diferentes ( $\geq 18$ ,  $\geq 24$  ou  $\geq 40$  linfonodos) na sobrevida global média ( $p > 0,05$  para todas as comparações). O mesmo foi verdadeiro para toda a população do estudo, bem como para os subgrupos de pacientes N0 (N negativos) e N1-2 (N positivos), quando analisados separadamente.

**Conclusões:** Nossos achados não apoiam o benefício na sobrevida de um número substancialmente maior de linfonodos coletados no câncer de cólon.

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## Introduction

Detection of metastatic lymph nodes is critical for treatment planning and predicting survival in colon cancer. Lymph node involvement is associated with poor long term outcome,<sup>1</sup> and detection of lymph node involvement would allow identifying patients most likely to benefit from adjuvant treatment. Improving the accuracy of staging, thereby identifying more patients who will benefit from adjuvant treatment forms the rationale for harvesting increased number of lymph nodes.

The optimal number of lymph nodes to be harvested for accurate staging is still unclear, although most guidelines recommend harvesting at least 12 lymph nodes.<sup>1,2</sup> On the other hand, several studies found a relation between higher number of harvested lymph nodes and better survival outcomes in colorectal cancer.<sup>3</sup> Higher cutoff points such as 18, 24 or 36 lymph nodes have been testes in relatively small number of studies.<sup>3-5</sup> Thus, current threshold for minimum lymph node harvest may not be adequate.

Moreover, newer surgical techniques have the potential to allow far more lymph nodes to be harvested. For example, advanced resection techniques such as high vascular ligation may allow higher lymph node yield. Therefore, it seems critical to identify whether additional efforts to sample and examine higher numbers of lymph nodes would translate into better long-term clinical outcomes.

This study aimed to examine the prognostic role of harvesting and examining substantially high number of lymph nodes in patients with colon cancer.

## Patients and methods

### Patients

This retrospective study included patients who underwent open colon resection for adenocarcinoma of the colon localized between cecum and distal sigmoid colon. Patient data were retrieved from medical and follow-up records of the patients and most recent survival status was further confirmed by phone contact with patients or relatives. Following patients were excluded: patients that curative resection was not possible who received palliative decompression, patients with rectum cancer (localized within 15 cm from the anal verge), patients without available survival data, and patients that underwent laparoscopic resection. The study protocol was approved by the institutional local ethics committee (Acibadem Mehmet Ali Aydinlar University Medical Research Evaluation Committee, date, December 5, 2019; no. ATADEK-2019-19/13) and the study was performed in accordance with the ethical standards laid down in the Declaration of Helsinki. Due to the retrospective non-experimental nature of the study, informed consent was not required.

### Surgical technique

All patients were operated by experienced colorectal surgeons using open surgical technique. Dissections were done in conformity with embryological planes. A wide resection targeting macroscopically 10 cm of uninvolved surgical margins prox-

imal and distal to the tumor was done. A D3 resection with high vascular ligation was made with the aim of removing a large lymphovascular pedicle (e.g. 2 cm above the outlet of inferior mesenteric artery from aorta, at the site of ileocolic artery outlet from superior mesenteric artery). En bloc resection was done in patients with adjacent organ invasion. Extend of surgical resections were defined as follow: right hemicolectomy, from 10 cm proximal to ileocecal valve to the middle of transverse colon; extended right hemicolectomy, from 10 cm proximal to ileocecal valve to the splenic flexure; left hemicolectomy, from the middle of transverse colon to the proximal part of sigmoid colon; extended left hemicolectomy, from the middle of transverse colon to the distal part of sigmoid colon; total colectomy, from 10 cm proximal to ileocecal valve to the end of sigmoid colon; anterior resection, from the proximal part of descending colon to the end of sigmoid colon.

### Histopathological examination

Following fixation of urgical samples in 10% neutral buffered formalin (10% NBF) for a minimum of 36 h, only the tumor was stained with Indian ink, whereas the mesenteric region was not stained to allow better identification of lymph nodes. Standard sections were made from different parts of the tumor and sections necessary for the evaluation of the radial margin were obtained. Then, pericolic fat was stripped off the colon and cut in parallel 5-mm thin sections. The whole sample was carefully sectioned and dissected in an attempt to identify all lymph nodes using both inspection and palpation. All identified nodes were examined histologically. Lymph node sections are cut at 4  $\mu$ m and stained with hematoxylin–eosin (H-E) for routine histology. The total number of nodes identified and examined were reported.

### Follow-up

Patients were followed every three months during the first postoperative year, every six months during the second year, and annually thereafter. For the purpose of this study, patients or relatives were contacted to confirm survival status.

### Statistical analysis

For statistical analysis, (Statistical Package for Social Sciences) SPSS version 21 (IBM Corp.; Armonk, NY, USA) was used. Descriptive data were presented as mean  $\pm$  standard deviation or number (frequency), where appropriate. Mean overall survival (OS) was estimated using Kaplan-Meier test. OS was defined as the time period between surgery and death and patients alive at the last follow-up were censored. Log-rank test was used to compare patient subgroups of total number of retrieved lymph nodes in terms of overall survival. A p value of < 0.05 was considered an indication of statistical significance.

**Table 1 – Patient characteristics.**

Characteristic	n = 179
Age, y (mean $\pm$ SD)	65.2 $\pm$ 14.0
Male gender	108 (60.3%)
Stage	
0	3 (1.7%)
I	16 (8.9%)
II	49 (27.4%)
III	51 (28.5%)
IV	60 (33.5%)
Surgical treatment	
Right hemicolectomy	80 (44.7%)
Extended right hemicolectomy	11 (6.1%)
Left hemicolectomy	26 (14.5%)
Extended left hemicolectomy	3 (1.7%)
Total colectomy	4 (2.2%)
Anterior resection	55 (30.7%)
Chemotherapy	
No chemotherapy	55 (30.7%)
Neoadjuvant chemotherapy	14 (7.8%)
Adjuvant chemotherapy	110 (61.5%)

Unless otherwise stated data presented in n (%). SD, standard deviation.

**Table 2 – Histopathological findings.**

	n = 179
Grade	
1	20 (11.2%)
2	100 (55.9%)
3	59 (33.0%)
Differentiation	
Poor	49 (27.4%)
Moderate	109 (60.9%)
Well	21 (11.7%)
Perineural invasion	80 (44.7%)
Venous invasion	35 (19.6%)
Lymphatic invasion <sup>a</sup>	64 (36.0%)
Extranodal involvement <sup>a</sup>	64 (36.4%)

Unless otherwise stated data presented in n (%). <sup>a</sup>Not all patients have available data.

## Results

### Patients

A total of 179 patients were included. Most common symptoms on admission were as follows with decreasing frequency: abdominal pain, 24.6%; rectal bleeding, 18.4%; fatigue, 14%; anemia, 9.5%. Frequencies of comorbidities were as follows: hypertension, 39.1%; diabetes, 21.2%; coronary artery disease, 17.3%; and 8.4% of patients had another concomitant tumor. A family history of colorectal cancer was present in 8.9% of the patients. Table 1 shows other characteristics of the patients. Table 2 shows a summary of histopathological findings.

**Table 3 – Association between different cut-values for the number of lymph nodes harvested and survival outcomes for the whole study population and N subgroups.**

Cut-off values	Overall survival <sup>a</sup>	(95% CI)	P*
Whole study population (n = 179)			
<18 (n = 17)	106.4 ± 15.0	77.1–135.7	0.960
≥18 (n = 162)	108.2 ± 6.2	96.1–120.3	
<24 (n = 31)	109.9 ± 11.5	87.3–132.5	0.858
≥24 (n = 148)	100.5 ± 6.0	88.6–112.5	
<40 (n = 99)	107.5 ± 6.8	94.3–120.8	0.643
≥40 (n = 80)	82.0 ± 7.0	68.4–95.7	
Node negative patients (N0) (n = 76)			
<18 (n = 10)	121.1 ± 15.6	90.6–151.7	0.779
≥18 (n = 66)	130.5 ± 7.8	115.2–145.7	
<24 (n = 14)	124.0 ± 13.2	98.2–149.9	0.695
≥24 (n = 62)	123.3 ± 7.2	109.1–137.4	
<40 (n = 41)	133.9 ± 6.8	120.7–147.2	0.385
≥40 (n = 35)	87.9 ± 7.0	74.1–101.6	
Node positive patients (N1-2) (n = 103)			
<18 (n = 7)	70.3 ± 21.9	27.3–113.3	0.856
≥18 (n = 96)	86.7 ± 8.1	70.9–102.4	
<24 (n = 17)	95.6 ± 16.5	63.4–127.9	0.745
≥24 (n = 86)	74.5 ± 7.5	59.8–89.2	
<40 (n = 58)	83.5 ± 9.5	65.0–102.1	0.337
≥40 (n = 45)	72.2 ± 9.4	53.8–90.7	

<sup>a</sup> Overall survival in months ± standard error. \*Log-rank test p values for difference. CI, confidence interval.

### Effect of different cut-off values on overall survival

During median 33 months of follow-up, 45 patients died and mean overall survival was 108.7 ± 5.6 months (95% CI, 97.7–119.7). 1-year, 3-year and 5-year survival rates were 92%, 78%, and 70%, respectively. The mean number of lymph nodes harvested and examined was 44.0 ± 25.7 (median 38; range, 7–150). No significant effect was found for three different cut-off values (≥18, ≥24, or ≥40 nodes) on mean overall survival (Table 3). Fig. 1 shows Kaplan-Meier curves of overall survival for three different cut-off values. The same was true for the whole study population as well as for N0 (N negative) and N1-2 (N positive) patient subgroups, when they are analyzed separately. Moreover, when all patients with stage IV disease were excluded from the analysis, none of the cut-off values were associated with a difference in overall survival in all patients, node negative patients, and node positive patients.

### Discussion

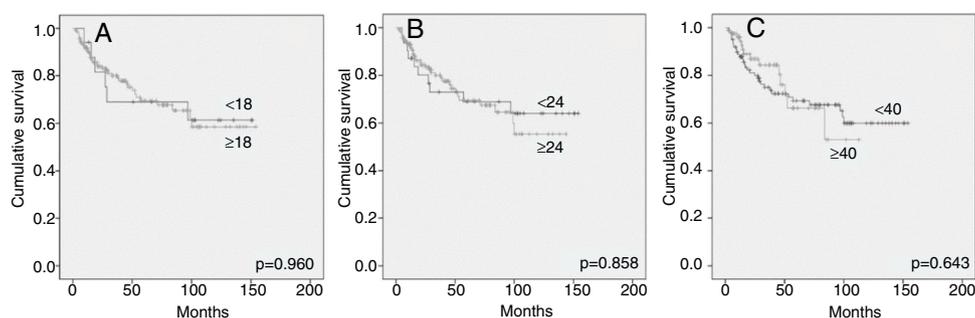
This study examined the value of harvesting, identifying and examining considerably high number of lymph nodes during surgical treatment in patients with colon cancer at different disease stages; however, could not find any survival benefit associated with high numbers of lymph nodes examined. To the best of our knowledge, this study is one of the few studies tested several relevant cutoff points for harvested lymph nodes for survival benefit, in the whole group of operated colon cancer patients as well as N subgroups (N positive and N negative patients).

Most of the previous studies have focused on the potential survival benefit of harvesting ≥12 lymph nodes,<sup>6–13</sup> mostly confirming the validity of widely recommended threshold. Although it is estimated that a minimum of 12 negative lymph nodes must be examined to rule out N positive disease with a >90% accuracy, the optimal number of lymph nodes to be harvested is still debated.<sup>14,15</sup> Harvesting ≥12 nodes can be considered a quality assurance tool.<sup>16</sup> On the other hand, a study found that increased number of lymph nodes examined after colectomy does not improve colon cancer staging but associated with a slight improvement in overall survival.<sup>13</sup>

To date, several studies examined the prognostic role of harvesting higher numbers of lymph node using different cutoff values. A very recent study examined the relationship between number of lymph nodes harvested and survival among patients that underwent colectomy for non-metastatic colon cancer.<sup>3</sup> That study used a large database and reported on the outcomes of more than quarter of a million patients. Patients with more than 24 harvested nodes had better survival than patients with 12–23 and <23 harvested nodes; and this relation was true across all N stages and across most other subgroup analyses. However, according to their findings, further increasing the number of node harvest does not seem to provide additional benefit, which is in line with our finding regarding the cutoff value of ≥40 nodes. Tsai et al. examined the prognostic significance of harvesting and examining at least 18 lymph nodes in patients with T2-4N0 non-metastatic colorectal cancer and found significant survival benefit when compared to the harvesting of <18 lymph nodes.<sup>4</sup> In the study by Chandrasinghe et al., harvesting ≥14 lymph nodes (slightly higher than the recommended threshold) was associated with better survival in stage II-III colorectal cancer patients and the survival benefit was evident for both colon cancer and rectal cancer.<sup>17</sup> In the study by Peeples et al. with 3534 colorectal cancer patients, harvesting ≥24 lymph nodes and harvesting up to 36 lymph nodes was associated with better survival for stage II and stage III disease, respectively.<sup>5</sup> Hashiguchi et al. identified number of lymph nodes examined as a prognostic factor with cut-off value of 20 for node-positive and 18 for node-negative cases, in their study with 859 operated non-metastatic colon cancers.<sup>18</sup>

Although not focusing on a specific cutoff value, a study from Sweden reported a positive association between total number of harvested lymph nodes and total number of positive nodes detected.<sup>19</sup> They detected 0.17 positive lymph node for every additional lymph node retrieved, suggesting that there may not be a minimum limit for lymph node retrieval. Higher number of lymph node harvested has been associated with several factors such as microsatellite instability, proximal tumor location, and low BMI.<sup>20,21</sup> Another factor may be the effort for the identification and examination of all retrieved lymph nodes by the pathologist. Specimen processing technique has been found to be important for the total number of harvested lymph nodes.<sup>22</sup> In this study, maximum effort has been made by the pathologist to identify and examine as much lymph nodes as possible from the surgical specimen.

Although our findings do not support the survival benefit of elevated cut-off values, we still admit that harvesting higher numbers of lymph nodes may have two potential benefits. Firstly, examining more lymph nodes will decrease the chance



**Fig. 1 – Kaplan-Meier curves of overall survival. a) < 18 versus  $\geq 18$  nodes harvested and examined, b) < 24 versus  $\geq 24$  nodes harvested and examined, c) < 40 versus  $\geq 40$  nodes harvested and examined. P values are obtained from log-rank test.**

of missing positive nodes, thereby reduce the chance of under staging. Appropriate staging would help better identify the patients who would most benefit adjuvant treatment, which may contribute to improved treatment outcomes. Secondly, higher number of lymph node harvest may have a treatment effect through removal of the metastatic lymph nodes, thus reducing tumor burden or enabling complete resection. Recent previous studies suggest that setting the  $\geq 12$  lymph node cutoff somewhat higher would result in improved survival outcomes in colorectal cancer. Cutoff values up to 36 nodes have been tested with encouraging results. On the other hand, our data do not support such benefit for any of the subgroups tested (N stage or M stage). Firstly, this may be due to the high number of lymph nodes sampled in this study, due to the efforts for harvesting high number of nodes during surgery as well as efforts for the identification and examination of as much nodes as possible during histopathological examination. Therefore, small number of lymph nodes was retrieved from only a minority of our patients. Only 2.8%, 9.5% and 17.3% our patients had less than 12, 18, and 24 nodes sampled, respectively. Such data distribution together with small sample size might have precluded finding survival difference between groups due to lack of contrast and inadequate power. Other possible explanations may be the inclusion of colon cancers but not rectum cancers.

Retrospective design and single institution setting are other important limitations of our study.

## Conclusions

Our findings do not support the survival benefit of substantially higher number of lymph nodes harvested in colon cancer.

## Conflicts of interest

The authors declare no conflicts of interest.

## Author's contributions

Both authors fully contributed to the study conception and design, material preparation, data collection and analysis, OSG drafted and developed the manuscript and LVT critically reviewed and revised it, finally both authors read and approved the final manuscript.

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