

# Re-Examining Distal Resection in Colon Cancer

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**ABSTRACT:** **Background:** In colon cancer, data regarding proximal and distal metastasis to lymph nodes remains scarce.

**Objectives:** To evaluate lymph node distribution along the longitudinal axis of the colon as related to a tumor to re-examine the common practice of 5 cm proximal and 2 cm distal resection margins.

**Methods:** We studied 106 patients (53 males and 53 females, mean age  $67.9 \pm 10$  years) who had undergone left hemicolectomy or sigmoidectomy. Colonic cancer specimens were divided into five zones proximally and distally to the tumor. For each zone, overall lymph node evaluation and ratio was performed.

**Results:** The mean number of retrieved lymph nodes per patient was  $24.3 \pm 12$ , with 54.9% of the nodes concentrated in zone I, 22.1% in zone II, 9.5% in zone III, 10.3% in zone IV, and 3% in zone V. While most positive nodes were found in zone I, significant numbers were also detected in both directions proximally and distally to the tumor.

**Conclusions:** It seems that longer colonic segments proximally, and especially distally, should be considered for resection to significantly reduce the chances of finding involved lymph node.

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**KEY WORDS:** colon cancer, resection, margins, lymph node, colectomy

Colorectal cancer is the third most common cancer in both men and women, following breast cancer in women and prostate cancer in men [1]. It is estimated that there are approximately 100,000 cases of colorectal cancer diagnosed in the United States annually, and worldwide over one million cases [2].

The increase in cancer screening leading to early detection and multimodality therapy has contributed to a marked decline in colorectal cancer mortality rates in the past two decades [3,4]. However, colorectal cancer remains the second most common cause of cancer death with more than 600,000 deaths reported worldwide each year [5].

Although approximately 75% of cases of colorectal cancers are potentially curable, currently the only curative treatment for colon cancer is radical surgery followed by adjuvant treatment when indicated [5]. The success of this oncologic procedure is judged by two parameters: the achievement of free margins and

the number of harvested lymph nodes. Dukes was among the first to recognize the significance of lymph node involvement in colorectal cancer in the 1930s, and began staging patients according to the presence of positive nodes and depth of invasion into the intestinal wall [6]. At present, the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) TNM classifies the progressions of cancer staging according to the extension of the primary tumor and the presence of lymph node metastasis [7,8].

However, the minimum number of harvested lymph nodes recommended for accurate staging remains controversial. The *AJCC 7th Ed Cancer Staging Manual* states that at least 10 lymph nodes should be harvested to ensure accurate staging [9], while the National Cancer Institute recommends that at least 12 should be harvested in order to define a case as lymph node negative [10].

Despite these national guidelines, a population-based analysis showed that only 37% of patients receive adequate lymph node lymphadenectomy and pathological evaluation [11]. Based on the common knowledge that venous and lymphatic drainage is the basic principle of surgical oncology, left hemicolectomy is defined as the resection of the transverse colon left of the middle colic vessels to the level of the upper rectum. Although a vast quantity of data exist on lymphadenectomy and its influence on the staging of colon cancer, the extent or length of the colon segment that should be resected proximally and distally to the tumor based on lymph node drainage is less clear.

Thus, the aim of our study was to evaluate lymph node distribution along the longitudinal axis of the colon as related to the tumor in order to re-examine the common practice of 5 cm proximal resection margins and 2 cm distal resection margins.

## PATIENTS AND METHODS

This prospective study was performed with the authorization of the institutional review committee of our medical center (No. 4/14). Inclusion criteria were patients who underwent left hemicolectomy or sigmoidectomy for malignancy. Patients who underwent emergency surgery were excluded. Colectomies were performed by five colorectal surgeons using an open technique according to a standard approach. The dissection status with regard to the main blood vessel supply as a reference point in left hemicolectomy includes

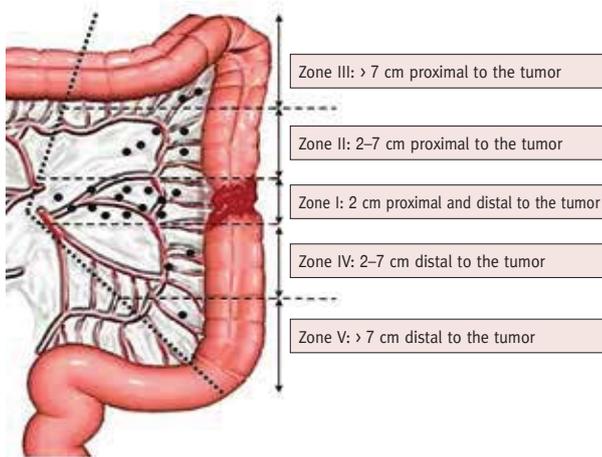
resection of lymph nodes along the left branch of the middle colic, left colic, and the first branch of the first sigmoidal pedicle. The anatomic level for distal resection in sigmoidectomy was at the peritoneal reflections. All resections were conducted according to the oncological recommendations to the base of the meso.

Ex vivo colonic specimens following left hemicolectomy or sigmoidectomy for cancer were freshly marked by metal clips at a distance of 2 cm and 7 cm proximally and distally to the tumor macroscopic edges, as judged by the senior surgeon present during the operation. The specimens were divided into five zones: zone I (central zone) includes the tumor and up to 2 cm proximal and distal from macroscopic tumor edges, zone II includes 2 to 7 cm proximal to the tumor, zone III includes 7 cm or more proximal to the tumor, zone IV includes 2 to 7 cm distal to the tumor, and zone V includes 7 cm and more distal to the tumor [Figure 1].

Specimens were further assessed at the Institute of Pathology for tumor grade, T stage, margin status, overall number of retrieved nodes, lymphatic/vascular invasion, and the ratio of lymph nodes harvested to the number of positive nodes in each zone. Lymph node retrieval was performed by using acetone as a fat-clearing solution. Specimens were hematoxylin- and eosin-stained, and evaluated by two dedicated pathologists.

Lymph node count was performed based on the zones bordered by metal clips. Lymph node ratio was calculated for the overall number of harvested nodes and for each zone. Statistical analyses were performed at the Department of Statistics at the Tel Aviv University. The association between two categorical variables was assessed using either chi-square or Fisher's exact tests. To compare quantitative (continuous) variables between two independent groups, a two sample *t*-test was applied as well as a non-parametric Mann-Whitney test. All statistical tests applied were two-tailed, and a *P* value of  $\leq 0.05$  was considered statistically significant.

Figure 1. Schematic presentation of colonic zones



RESULTS

There were 106 patients in the study: 53 males and 53 females, mean age  $67.9 \pm 10$  years. Patient data are summarized in Table 1. Of the evaluated specimens, 2575 lymph nodes were harvested with a mean of 24.3 lymph nodes per patient. As expected, most lymph nodes (1414) were detected in zone I (54.9%); 571 were harvested in zone II (22.1%), 245 in zone III (9.5%), 267 in zone IV (10.3%), and 78 in Zone V (3%) [Figure 1 and Figure 2]. Overall, 35% of the patients were found to have involved lymph nodes. All resected margins were tumor free.

Figure 3 shows the number of patients with positive lymph nodes in the various zones that were studied. One patient had one-quarter of lymph nodes positive in zone II with no involvement of any of the other 19 lymph nodes (7 in zone I, 4 in zone III, 6 in zone IV, and 2 in zone V).

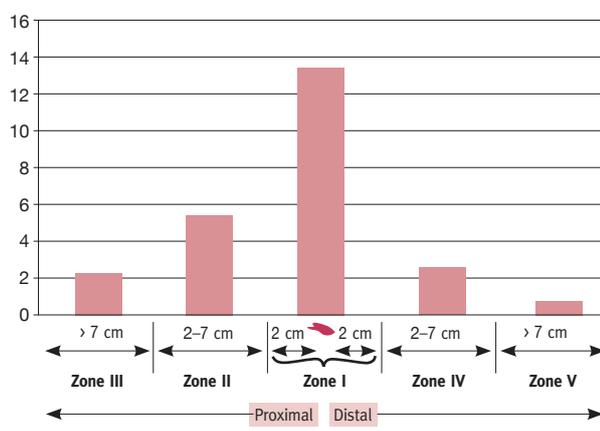
DISCUSSION

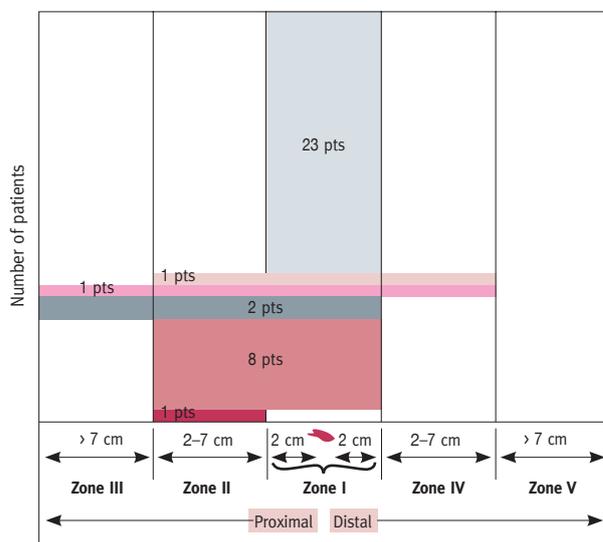
Different variables are involved and relevant to the overall number of harvested lymph nodes: patient age [8] and body mass index [12]; tumor location [13], size [14], and post-chemoradiation treatment; surgical technique including extent of resection, extent of colon, and lymph node resection; and

Table 1. Patient characteristic

Overall number of patients	106	
Gender: male / female	53 / 53	
Mean age (years)	$67.9 \pm 10$	
Mean lymph nodes per patient	$24.3 \pm 12$	
T stage	0	7.5%
	1	9.4%
	2	24.5%
	3	58.4%

Figure 2. Average number of harvested lymph nodes per zone



**Figure 3.** Number of patients with positive lymph nodes per zone

pathologic technique of node retrieval [15], technique of staining, and specimen sectioning [16].

Lymphatic colonic drainage is based on five stations: epicolic, paracolic, intermediate, principal, and retroperitoneal nodes. Although the well-accepted theory of “ordinary” lymphatic flow based on the perpendicular arterial and venous architecture is logical, some diversions from this rule have been reported [5]. About half the patients with lymphatic involvement have peritumoral lymph node metastasis and one-third show additional central lymphatic spread along the main colonic arterial trunk with 10–12% central node involvement [17].

Nelson and a National Cancer Institute expert panel [9] reported in consensus guidelines that 5–10 cm of normal bowel on either side of the primary tumor appears to be the shortest recommended length to remove epicolic and paracolic (along the marginal vessel) lymph nodes and to minimize anastomotic recurrences. They also concluded that the length of ileum resected does not appear to affect local recurrence in tumors of the ascending colon. Morikawa and colleagues [18] reviewed 311 colon cancer specimens and concluded that in the longitudinal spread most lymph node metastasis was seen within 10 cm.

Furthermore, Devereux and Deckers [19] investigated the contributions of the pathological margins and Dukes’ stage to local recurrence in patients with colorectal carcinoma. They concluded that it appears that margins are not as important in preventing local recurrences of Dukes’ A lesions as they are for both Dukes’ B and C lesions. They showed that if the resected margins (proximal and distal) were less than 5 cm, the incidence of local recurrences increased from 9% to 43%, or almost fivefold.

The extent of the mesenteric resection, measured by the number of vascular pedicles, is a significant predictor of lymph

node harvest independent of the length of bowel resected [20]. Scarce data exist regarding the distribution of lymph node involvement along the longitudinal axis of the colon on the “lateral wings” proximally and distally to the tumor. Thus, it was our aim in this study to help fill this knowledge gap.

We collected prospective data based on 106 colonic cancer specimens (left hemicolectomy and sigmoidectomy) and divided it into the five zones previously described. We found the average number of retrieved lymph nodes to be 24.3 nodes per specimen, with most concentrated in zone I and, as expected, most positive nodes were also concentrated in this zone; hence, the ratio of overall to positive lymph nodes was most significant in zone I. Knowing the proximal route of metastatic spread, we were not surprised to find a high rate of involved nodes even more than 7 cm proximally to the tumor. As a result, we question whether this finding should challenge the well-accepted 5 cm proximal resection theory [21].

Another interesting point was finding significant lymph node involvement distal to the tumor in zone IV. Could this be one of the factors explaining local recurrences in patients with shortened resection specimen distal to the tumor? Interestingly, distally to 7 cm, no involved nodes were detected in any of our patients. Thus, we believe that the practice of 2 cm distal resection margins might also be re-examined.

Moreover, in zone II, one patient showed positive nodes (1/4), while the other 19/23 nodes were negative. The tumor was a T3/N1 penetration, which might explain lymphatic channel obstruction and this finding as skip lymph node.

It should be noted that this model is not applicable in rectal cancer, as the limit of the distal resection line is dictated by tumor distance from the anal verge. In addition, a similar study was performed on formalin-preserved specimens. However, because formalin causes shrinkage of the tissue, freshly studied specimens will yield more accurate data.

To the best of our knowledge, this is the only study dealing with lymph node distribution along the longitudinal axis of resected specimens at fixed distances. Our results partially confirm the conclusion of the expert panel. The length of the resected specimen should be at least 5 cm proximally and probably more than 2 cm distally, as we found positive lymph nodes at a distance of up to 7 cm. Our findings also may explain the event of local recurrence in those patients in which shorter segments of the colon were resected.

## CONCLUSIONS

Most lymph nodes are concentrated within 2 cm proximally and distally to colon tumors. However, involved lymph nodes can be found proximally to 7 cm and distally up to 7 cm. While proximally the resected segment is usually long enough, a resection of longer colonic segment distally to the tumor should be considered. Further studies are needed to confirm our results to a point of certainty to justify a change in technique.

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**Capsule**

**Progress for pulmonary arterial hypertension (PAH)**

In pulmonary arterial hypertension (PAH), pulmonary arteries are thickened and occluded, and mitochondrial respiration is suppressed. Michelakis and colleagues treated lungs from PAH patients with dichloroacetate, a drug that inhibits the mitochondrial enzyme pyruvate dehydrogenase kinase. Dichloroacetate increased mitochondrial function, but the response was variable. This variable response was mirrored in a phase

1 trial, with some patients showing improved hemodynamics and functional capacity. Interestingly, patients with inactivating mutations in two genes encoding mitochondrial proteins were less responsive to dichloroacetate.

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**Capsule**

**Elucidating a bacterial sense of touch**

Bacteria can adhere to surfaces within the host. This leads to tissue colonization, induction of virulence, and eventually the formation of biofilms, which are multicellular bacterial communities that resist antibiotics and clearance by the immune system. Hug and co-authors showed that bacteria have a sense of touch that allows them to change their behavior rapidly when encountering surfaces. This tactile sensing makes use of the inner components of the flagellum,

a rotary motor powered by proton motif force that facilitates swimming toward surfaces. Thus, the multifunctional flagellar motor is a mechanosensitive device that promotes surface adaptation. In complementary work, Ellison and co-authors elucidated to the role of bacterial pili in a similar surface-sensing role.

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