Factors associated with poor lymph node harvest after colorectal cancer surgery in Menoufia University Hospitals

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Received: 04 April 2022
Revised: 28 April 2022
Accepted: 08 May 2022
Published: 04 January 2023

The Egyptian Journal of Surgery 2023, 41:714–718

Objectives

Adequate lymph node harvest (LNH) is an important factor for the correct staging and subsequent proper adjuvant therapy for patients with colon cancer. Dissection of more than or equal to 12 lymph nodes (LNs) is recommended by American Joint Committee on Cancer to be adequate, and below this number is considered insufficient, which will affect adjuvant therapy. So, we aimed in this study to analyze the clinicopathological and surgical factors associated with poor LNH.

Patients and methods

We have retrospectively analyzed the data of 75 patients who underwent curative resection for stages I–III colon cancer in Menoufia University Hospital, Egypt, between January 2020 and March 2022. Variables like age, sex, primary site, type of surgery, specimen length, tumor size, and stage were evaluated for their effect on the LNH.

Results

Of 75 patients, 11 (14.67%) patients had poor LNH (≤12). On univariate analysis, inadequate LNH (≤12) was associated with male patients, left colon+cancer, pT3-T4 diseases, short distal margin, resected specimen length, and after neoadjuvant therapy. On multivariate analysis, length of specimen, surgical margin, and after neoadjuvant therapy were found to significantly affect LNH.

Conclusion

Elderly, male patients with left colon cancer, shorter specimen length, advanced tumor stage, and after neoadjuvant therapy were at increased risk of a poor LNH.

Keywords:
colon cancer, lymph node harvest, neoadjuvant

Egyptian J Surgery 2023, 41:714–718

1110-1121

Introduction

Colorectal cancer (CRC) is a significant cause of cancer-related deaths worldwide [1]. In Egypt, the estimated rate of colon neoplasms is 6.5% of all malignant tumors, and data released by the National Cancer Institute registry at Cairo University show that CRC morbidity and mortality rank sixth among all malignancies and that they are increasing year after year, along with changes in lifestyle [2]. Complete tumor resection plus lymph node harvest (LNH) plays a key role in the treatment of operable localized colon neoplasms [3]. Examination of an adequate number of lymph nodes (LN) is an important factor for the correct staging and subsequent therapy for patients with CRC. The presence of metastatic LNs represents a step toward systemic tumor spread, and it is also considered a strong indicator of adverse prognosis, and node metastasis is the major determinant of adjuvant therapy for patients with colon cancer [4]. Tumor node metastasis staging system, developed and maintained by the Union for International Cancer Control and American Joint Committee on Cancer, recommended that examination of at least 12 LN is required for adequate colon neoplasm staging [5]. LNH is affected by numerous factors related to the patient, the tumor, and surgical and histopathological practice [6]. The aim of this current study was to determine the clinicopathological and surgical factors associated with poor LNH.

Patients and methods

In this retrospective study, 75 patients who had locoregional primary invasive colonic adenocarcinoma were included, and they were treated at General Surgery Department, Menoufia University Hospitals, between January 2020 and March 2022. Patients with colonic adenocarcinoma stages I–III and who underwent curative resection, and patients with and without neoadjuvant therapy were included in this study. Exclusion criteria included patients presented with pathologies other than adenocarcinoma, metastatic disease in the colon, synchronous colon cancer, and palliative surgery patients. This study was approved by the local ethics committee of the Faculty of Medicine, Menoufia University (Approval No.4/2022SURG), and written patient consent was not obtained because of the retrospective nature of this study.

Before surgery, all patients were subjected to full clinical assessment, laboratory investigations, and imaging studies such as chest and pelvi-abdominal computed tomography. According to the standard for colon cancer surgery (done by the same surgical team), central vascular ligation was emphasized to enable adequate LNH. The mean number of total LN examined was initially calculated. Gross and microscopic pathological examinations were done by the same pathological team in our university hospitals according to the 8th edition of the American Joint Committee on Cancer tumor node metastasis classification [7]. LNs were identified by hematoxylin and eosin staining. Subsequently, the number of patients who had adequate LNH (≥12) and the number of patients who had inadequate LNH (<12) in their pathologic report were determined. All potential tumor (anatomical site, tumor size, grade, and the total number of involved LNs), demographic data, and treatment (type of surgery and neoadjuvant treatment) characteristics were evaluated for their effect on the number of LNH. Tumors located in the region from the ileocecal valve to the distal part of the transverse colon were known as right colon cancer, and tumors located in the region from splenic flexure to anorectal junction were known as left colon cancer.

Statistical analysis

The data analysis was performed using SPSS (Statistical Package for the Social Sciences Inc., Chicago, Illinois, USA) program, version 20 for Windows. Descriptive statistics were used to summarize the demographic characteristics of patients in which qualitative data were presented in the form numbers and percentages and quantitative data were presented in the form of SD, mean, and range. Univariate and multivariate logistic regression models were applied to assess the influence of primary tumor characteristics on the number of LNH. In addition, 95% confidence intervals (CIs) were determined for the odds ratio (OR) values obtained by logistic regression models. Statistical significance was demonstrated for results (P<0.05).

Results

A total of 75 patients were included in this study, of which 44 (58.67%) were males and 31 (41.33%) were females, and 23 (30.67%) patients were less than or equal to 65 years. The mean number of evaluated nodes was 22.13 ± 10.92 in surgically treated patients with colon cancer. Adequate LNH (≥12 LN) was performed in 64 (85.3%) patients and inadequate (<12 LN) was done in 11 (14.7%) patients (Table 1).

Table 1 Clinicopathological data of 75 surgically treated patients with colon cancer (stages I–III)

Factors	*n* (%)	Mean±SD
Sex		
Male	44 (58.67)	
Female	31 (41.33)	
Age		61.34 ± 12.87
≤65 years	23 (30.67)	
>65 years	52 (69.33)	–
BMI (kg/m^2)		26.98 ± 5.31
<25	26 (34.67)	
≥25	49 (65.33)	
Elective/emergency		
Elective	58 (77.33)	
Emergency	17 (22.67)	
Open/laparoscopic		
Open	51 (68.00)	
Laparoscopic	24 (32.00)	
Primary site		
Right colon	21 (28.00)	
Left colon	54 (72.00)	
Primary tumor stage		
T0	2 (2.67)	
T1	5 (6.67)	
T2	7 (9.33)	
T3	53 (70.67)	
T4	8 (10.67)	
Tumor size (cm)		4.73 ± 2.91
<5	48 (64.00)	
≥5	27 (36.00)	
Tumor differentiation		
Well	17 (22.67)	
Moderate	46 (61.33)	
Poor	7 (9.33)	
Undefined	5 (6.67)	
LN harvest		22.13 ± 10.92
<12	11 (14.67)	
≥12	64 (85.33)	
Specimen length		17.32 ± 2.45
<20 cm	52 (69.33)	
≥ 20 cm	23 (30.67)	
TNM stage		
Stage I	16 (21.33)	
Stage II	32 (42.67)	
Stage III	27 (36.00)	
Extranodal involvement		
Yes	6 (8.00)	
No	69 (92.00)	
Lymphovascular invasion		
Yes	9 (12.00)	
No	66 (88.00)	
Free tumor nodule		
Yes	6 (8.00)	
No	69 (92.00)	
Perineural invasion		
Yes	8 (10.67)	
No	67 (89.33)	
Neoadjuvant therapy		
Yes	26 (34.67)	
No	49 (65.33)	

BMI, basal metabolic index; LN, lymph node; TNM, tumor node metastasis.

Based on univariate analysis, inadequate LNH was found to be higher in male patients, but this was not significant (*P*=0.718). Moreover, inadequate LNH was higher in old patients more than 65 years, patients with BMI more than or equal to 25, tumors of the left colon, pT3-4, open surgery, small tumor size, surgical margin less than 5 cm (*P*=0.29), and shorter specimen length (*P*=0.016). Using a multivariate logistic regression analysis, inadequate LNH was significantly associated with shorter resected specimen (*P*=0.03, OR=4.698, 95% CI=1.163–18.985) and surgical margin less than 5 cm (*P*=0.05, OR=3.956, CI=0.977–16.021). Of 75 patients, 26 (34.67%) patients received neoadjuvant therapy followed by curative-intent surgery with at least 4–6-week interval. Of them, seven (26.92%) patients had inadequate LNH, and this was significant according to univariate and multivariate analyses (*P*=0.038 and 0.037, respectively) (Table 2).

Discussion

The presence of neoplastic cells in LN is the most important prognostic factor in CRC after tumor resection. The number of sampled and histologically analyzed LNs is also considered as a marker for adequate staging, quality of surgery, pathologic analysis, and survival rate [8]. Therefore, inadequate LN examination is a common pitfall in the pathologic staging of CRC cancer. This staging defect causes a great clinical challenge for predicting the prognosis and determining adjuvant treatments [9]. There are many factors that can influence LNH such as sex and age of the patient, BMI, location of the tumor, neoadjuvant therapy, surgical technique, and pathologist's handling of the specimen. Deodhar *et al*. [5] stated that distal colonic location, small tumor volume, early stage, neoadjuvant therapy, and preoperative radiotherapy were factors adversely affecting the LN yield.

In the present study, the total number of patients with inadequate LNH were 11 (14.7%) patients, which was similar to the literature. The female sex had a relatively higher LNH, and this result was similar to the previous studies but this relation is still unclear [10,11]. In contrast, Morcos *et al*. [12] stated that female sex adversely affected the LNH. In a retrospective study, Shen *et al*. [13] reported that inadequate LNH was associated with old age, and this finding was similar to our results. Moreover, Tekkis *et al*. [14] and Tsai *et al*. [15] reported that fewer LN are removed in elderly patients, which may be associated with the decrease in immunological and inflammatory reactions to cancer tissues in elderly patients, so that LNs might not be visible to the surgeon and the pathologist.

Although some studies have reported inadequate numbers of LN being removed in patients with a high BMI, the effect of BMI on the number of dissected LNs is still unclear [16]. In this current study, there was no significant difference between the number of LN removed in low-weight and normal-weight patients (BMI <25 kg/m^2) and overweight and obese patients (BMI >25 kg/m^2). Moreover, our study has demonstrated that laparoscopic surgery was associated with higher LNH even if it did not reach statistical significance, and this was in agreement with many studies [17,18].

Inadequate LNH was associated with patients with left colon tumors in our current study, and this finding was similar to previous studies [11,19]. This may be explained by variant lymphatic anatomy (i.e. a natural decline in LN numbers with more distal progression within the colonic mesentery, and there is a disproportionate number of LNs exist along the ileocolic artery) and other variations in tumor biology, such as microsatellite instability [20]. Moreover, differences in embryonic development or a greater length of the mesenteric root have been discussed as possible causes [21].

Tekkis *et al*. [14] demonstrated that tumor differentiation was associated with the number of removed LN, so that poorly differentiated tumors had more LNH compared with well or moderately differentiated neoplasms, and these findings are consistent with our study. In contrast, Mekenkamp *et al*. [22] stated that poor differentiation grade of the tumor was associated with decreased number of LN harvest.

Ong and Schofield [6] and Moro-Valdezate *et al*. [23] demonstrated that the number of LN obtained in resection specimen for colon cancer was associated with the length of the resected segment and the tumor size, and regarding our data, inadequate LNH was associated with shorter specimen length less than 20 cm in both univariate and multivariate analyses. Tumor size is an established predictor of LNH [24], which was confirmed by our study. Larger tumors may be more visible on pathologic examination owing to increased cancer antigen and inflammation response. It has been proposed that larger tumors elicit an intense antigenic immune response within the regional LNs basin, making them more visible to pathologic examination and possibly leading to increasing LNH [19]. In the study by Orsenigo *et al*. [10], higher LN counts were associated with pT3-T4 diseases, and this finding is similar to our study.

Table 2 Univariate and multivariate logistic regression analyses of clinicopathological factors affecting lymph node harvest

Variables	LNH ≥ 12 [*n* (%)]	LNH < 12 [*n* (%)]	Univariate		Multivariate	
			OR (95% CI)	*P* value	OR (95% CI)	*P* value
Sex						
Male	37 (84.09)	7 (15.91)	0.783 (0.208–2.946)	0.718		
Female	27 (87.10)	4 (12.90)				
Age						
≤65 years	19 (82.61)	4 (17.39)	0.739 (0.193–2.823)	0.658		
>65 years	45 (86.54)	7 (13.46)				
BMI (kg/m^2)						
<25	23 (88.46)	3 (11.54)	1.496 (0.361–6.200)	0.579		
≥25	41 (83.67)	8 (16.33)				
Elective/emergency						
Elective	52 (89.66)	6 (10.34)	3.611 (0.943–13.827)	0.061	1.084 (0.085–13.877)	0.951
Emergency	12 (70.59)	5 (29.41)				
Open/laparoscopic						
Open	43 (84.31)	8 (15.69)	0.768 (0.185–3.195)	0.717		
Laparoscopic	21 (87.50)	3 (12.50)				
Primary site						
Right colon	17 (80.95)	4 (19.05)	0.633 (0.164–2.437)	0.506		
Left colon	47 (87.04)	7 (12.96)				
Primary tumor stage						
T3 + 4	54 (88.52)	7 (11.48)	3.086 (0.760–12.533)	0.115	5.273 (0.219–126.900)	0.306
T0 + 1+2	10 (71.43)	4 (28.57)				
Tumor size (cm)						
<5	42 (87.50)	6 (12.50)	1.591 (0.436–5.803)	0.482		
≥5	22 (81.48)	5 (18.52)				
Tumor differentiation						
Poor+undefined	10 (83.33)	2 (16.67)	0.833 (0.156–4.445)	0.831		
Well+Moderate	54 (85.71)	9 (14.29)				
Specimen length						
≥20 cm	48 (92.31)	4 (7.69)	5.250 (1.358–20.303)	0.016*	4.698 (1.163–18.985)	0.03*
<20 cm	16 (69.57)	7 (30.43)				
Surgical margin						
≥5 cm	46 (92.00)	4 (8.00)	4.472 (1.166–17.147)	0.029*	3.956 (0.977–16.021)	0.05*
<5 cm	18 (72.00)	7 (28.00)				
Extranodal involvement						
Yes	4 (66.67)	2 (33.33)	0.300 (0.048–1.882)	0.199		
No	60 (86.96)	9 (13.04)				
Lymphovascular invasion						
Yes	6 (66.67)	3 (33.33)	0.276 (0.057–1.327)	0.108		
No	58 (87.88)	8 (12.12)				
Free tumor nodule						
Yes	4 (66.67)	2 (33.33)	0.300 (0.048–1.882)	0.199		
No	60 (86.96)	9 (13.04)				
15.Perineural invasion						
Yes	5 (62.50)	3 (37.50)	0.226(0.045–1.131)	0.070		
No	59 (88.06)	8 (11.94)				
16. Neoadjuvant therapy						
Yes	19 (73.08)	7 (26.92)	0.241 (0.063–0.922)	0.038*	0.069 (0.006–0.852)	0.037*
No	45 (91.84)	4 (8.16)				

BMI, basal metabolic index; CI, confidence interval; LNH, lymph node harvest; OR, odds ratio.
*Significant as *P* value < 0.05.

Our results showed that there was a statistically significant difference in univariate and multivariate analyses regarding surgical margin, and poor LNH was associated with surgical margin less than 5 cm. This finding was in agreement with the study done by Morikawa *et al*. [25], who stated that close surgical margin was associated with low numbers of LN being removed.

Extranodal involvement, free tumor nodule, lymphovascular, and perineural invasion are indicators of tumor aggression. Their relationship with the number of dissected LN could not be demonstrated by previous studies. Gelos *et al*. [26] showed that the presence of lymphovascular invasion did not correlate with LNH, and this was in agreement with our findings. Moreover, in our study, neoadjuvant treatment had a significant effect on the number of LNH in both univariate and multivariate models. Inadequate LNH was associated with patients who had taken neoadjuvant therapy, and these findings are in agreement with previous studies [12,27]. However, Gurawalia *et al*. [28] concluded that removal of fewer than 12 LN in patients with neoadjuvant radiotherapy with or without chemotherapy should be considered as a good indicator of tumor response with better local disease control and a good prognostic factor, rather than as a pointer of poor diligence of the surgical and pathological assessment.

The limitations of our study included unicentric study and lower number of cases.

Conclusion

The LNH is affected by various factors. LN may be more difficult to identify in specimens from patient who are elderly, male patients, smaller tumor size and stage, shorter specimen length, and after neoadjuvant therapy. LNH can be increased by investment of time and good technical skill of LN dissection, thereby accurately staging patients and making them receive appropriate treatment.

Acknowledgements

Authorship contributions: surgical practices: M.H., M.M.A., and M.A.E. Concept: M.H. and M.A.E. Design: M.M.A. and M.H., Data collection or processing: M.M.A. and M.A.E.. Analysis or interpretation: M.M.A., Writing and revision: M.H. and M.M.A.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA J Clin 2018; 68:394–424.

2 Ibrahim AS, Khaled HM, Mikhail NN, Baraka H, Kamel H. Cancer incidence in Egypt: results of the national population-based cancer registry program. J Cancer Epidemiol 2014; 2014:43771.

3 Rentsch M, Schiergens T, Khandoga A, Werner J. Surgery for colorectal cancer – trends, developments, and future perspectives. Visc Med 2016; 32:184–191.

4 Chang GJ, Rodriguez-Bigas MA, Skibber JM, Moyer VA. Lymph node evaluation and survival after curative resection of colon cancer: systematic review. J Natl Cancer Inst 2007; 99:433–441.

5 Deodhar KK, Budukh A, Ramadwar M, Bal MM, Shrikhande SV. Are we achieving the benchmark of retrieving 12 lymph nodes in colorectal carcinoma specimens? Experience from a tertiary referral center in India and review of literature. Indian J Pathol Microbiol 2012; 55:38–42.

6 Ong MLH, Schofield JB. Assessment of lymph node involvement in colorectal cancer. World J Gastrointest Surg 2016; 8:179–192.

7 Jessup JM, Goldberg RM, Asare EA, Benson AB, Brierly JD, Chang A. *AJCC cancer staging manual*. 8th ed. New York: Springer-Verlag; 2017. 251–274.

8 Destri GL, Carlo ID, Scilletta R, Scilletta B, Puleo S. Colorectal cancer and lymph nodes: the obsession with the number 12. World J Gastroenterol 2014; 20:1951–1960.

9 National Comprehensive Cancer Network [NCCN]. NCCN clinical practice guidelines in oncology. Principles of pathologic review for colon and rectal cancer. NCCN clinical practice guidelines, version 2.2016. Available at: https://www2.trikobe.org/nccn/guideline/archive/colorectal2016/english/rectal.pdf. [Accessed June 04, 2016].

10 Orsenigo E, Gasparini G, Carlucci M. Clinicopathological factors influencing Lymph node yield in colorectal cancer: a retrospective study. Gastroenterol Res Pract 2019; 2019:5197914.

11 Bostancı MT, Yılmaz I, Saydam M, Seki A, Demir P, İmamoğlu GI, Gökçe A. Factors associated with poor lymph node dissection of colon neoplasm. Turk J Colorect Dis 2021; 31:322–329.

12 Morcos B, Baker B, Al Masri M, Haddad H, Hashem S. Lymph node yield in rectal cancer surgery: effect of preoperative chemoradiotherapy. Eur J Surg Oncol 2010; 36:345–349.

13 Shen SS, Haupt BX, Ro JY, Zhu J, Bailey HR, Schwartz MR. Number of lymph nodes examined and associated clinicopathologic factors in colorectal carcinoma. Arch Pathol Lab Med 2009; 133:781–786.

14 Tekkis PP, Smith JJ, Heriot AG, Darzi AW, Thompson MR, Stamatakis JD. Association of Coloproctology of Great Britain and Ireland. A national study on lymph node retrieval in resectional surgery for colorectal cancer. Dis Colon Rectum 2006; 49:1673–1683.

15 Tsai HL, Huang CW, Yeh YS, Ma CJ, Chen CW, Lu CY, *et al*. Factors affecting the number of lymph nodes harvested and the impact of examining a minimum of 12 lymph nodes in stage I-III colorectal cancer patients: a retrospective single-institution cohort study of 1167 consecutive patients. BMC Surg 2016;16:17.

16 Kuo YH, Lee KF, Chin CC, Huang WS, Yeh CH, Wang JY. Does body mass index impact the number of LNs harvested and influence long-term survival rate in patients with stage III colon cancer? Int J Colorectal Dis 2012; 27:1625–1635.

17 Wu Z, Zhang S, Aung LHH, Ouyang J, Wei L. Lymph node harvested in laparoscopic versus open colorectal cancer approaches. Surg Laparosc Endosc Percutan Tech 2012; 22:5–11.

18 Vennix S, Pelzers L, Bouvy N, Beets GR, Pierie JP, Wiggers T, Breukink S. Laparoscopic versus open total mesorectal excision for rectal cancer. Cochrane Database Syst Rev 2014; 4:CD005200.

19 Chou JF, Row D, Gonen M, Liu Y-H, Schrag D, Weiser MR. Clinical and pathologic factors that predict Lymph node yield from surgical specimens in colorectal cancer: a population-based study: a population-based study. Cancer 2010; 116:2560–2570.

20 Kim YW, Jan KM, Jung DH, Cho MY, Kim NK. Histological inflammatory cell infiltration is associated with the number of lymph nodes retrieved in colorectal cancer. Anticancer Res 2013; 33:5143–5150.

21 Betge J, Harbaum L, Pollheimer MJ, Lindtner RA, Kornprat P, Ebert MP, langner C. Lymph node retrieval in colorectal cancer: determining factors and prognostic significance. Int J Colorectal Dis 2017; 32:991–998.

22 Mekenkamp LJM, van Krieken JHJM, Marijnen CAM, van de Velde CJH, Nagtegaal ID. Pathology Review Committee and the Co-operative Clinical Investigators. Lymph node retrieval in rectal cancer is dependent on many factors—the role of the tumor, the patient, the surgeon, the radiotherapist, and the pathologist. Am J Surg Pathol 2009; 33:1547–1553.

23 Moro-Valdezate D, Pla-Marti V, Martin-Arevalo J, Belenguer-Rodrigo J, Arago-Chofre P, Ruiz-Carmona MD, Checa-Ayet F. Factors related to lymph node harvest: does a recovery of more than 12 improve the outcome of colorectal cancer?. Colorect Dis 2013; 15:1257–1266.

24 Onitilo AA, Stankowski RV, Engel JM, SAR D. Adequate lymph node recovery improves survival in colorectal cancer patients. J Surg Oncol 2013; 107:828–834.

25 Morikawa T, Tanaka N, Kuchiba A, Nosho K, Yamauchi M, Hornick JL, *et al*. Predictors of lymph node count in colorectal cancer resections: data from US nationwide prospective cohort studies. Arch Surg 2012; 147:715–723.

26 Gelos M, Gelhaus J, Mehnert P, Bonhag G, Sand M, Philippou S, Mann B. Factors influencing lymph node harvest in colorectal surgery. Int J Colorectal Dis 2008; 23:53–59.

27 Rullier A, Laurent C, Capdepont M, Vendrely V, Belleannée G, Bioulac-Sage P, Rullier E. Lymph nodes after preoperative chemoradiotherapy for rectal carcinoma: number, status, and impact on survival. Am J Surg Pathol 2008; 32:45–50.

28 Gurawalia J, Dev K, Nayak SP, Kurpad V, Pandey A. Less than 12 Lymph nodes in the surgical specimen after neoadjuvant chemo-radiotherapy: an indicator of tumor regression in locally advanced rectal cancer? J Gastrointest Oncol 2016; 7:946–957.