Original Article

The Significance of Preoperative Radiologic Lymph Node Enlargement in Early Colorectal Cancer

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Key Words
Colorectal cancer;
Lymph node enlargement;
Benign;
Outcome;
Prognosis

Purpose. Preoperative radiologic lymph node enlargement is common but its prognostic value remains unclear. We tried to investigate the significance of benign lymph node enlargement in early colon cancer.
Methods. We performed a retrospective chart review to assess the results of colorectal cancer patients who underwent curative surgery at the National Cheng Kung University Hospital from January 2012 to December 2016.
Results. A total of 382 patients with CRC who underwent curative surgery were analysed. Benign lymph node enlargement and TMN stage both had prognostic value in outcome. Stage II colorectal cancer patients in benign lymph node enlargement group had better overall survival significantly. The overall survival of patients with right-sided colon cancer and patients with rectal cancer in the BLNE group both had the trend to have relatively better overall survival.
Conclusions. Benign lymph node enlargement could be a significant prognosis factor in predicting survival in early colorectal cancer.
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Colorectal cancer (CRC) is a very common malignant tumor worldwide. Lymph node metastasis in CRC usually indicates a poor prognosis and is an important factor in deciding on additional adjuvant treatment.[1-3] Patients with node-negative and node-positive diseases have a 5-year survival rate of 70%-90% and 20%-80%, respectively. Survival was improved in the node-positive group by adjuvant chemotherapy.[4] In general, the lymphatic system participates in the immune response by providing structural and functional support for the delivery of antigens and antigen-presenting cells to draining lymph nodes. Additionally, inflammation will influence lymphocyte proliferation and differentiation.[5-7] The lymphocytic reaction may indicate the host's immune response to tumor cells. Previous literature has revealed the association between the presence of high tumor-infiltrating lymphocyte levels (e.g., CD57+, CD8+, CD45RO+, or FOXP3+ cells) and a favorable outcome in CRC.[8-13] Preoperative lymph node enlargement on radiological

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imaging with histologically proven node-negative is commonly observed in clinical practice. However, the prognostic value remains unclear in patients and CRC with benign lymph node enlargement (BLNE). Radiological lymph node enlargement seemed to have a poor outcome in clinical stage IIB cervical cancer.[14] However, one multicenter study demonstrated a better outcome in patients with CRC treated with BLNE.[15]

This study aimed to retrospectively review the role of BLNE in the outcomes of patients with early-stage CRC.

Materials and Methods

Patients

A retrospective chart review was performed from a prospectively maintained database for patients with CRC who underwent curative surgery at the National Cheng Kung University Hospital (NCKUH) from January 2012 to December 2016. The inclusion criteria are (1) > 18 years of age; (2) histologically node-negative disease; (3) no distant metastasis; and (4) pathological stages I, or II by the tumor, node, and metastasis (TNM) staging system. The pathological stage was according to the American Joint Committee on Cancer, 7th edition.[16] The exclusion criteria were (1) familial adenomatous polyposis syndrome, hereditary nonpolyposis CRC, and other hereditary CRC; (2) emergent surgery; (3) < 12 surgically salvaged lymph nodes; (4) cancer history or concurrent cancer; (5) receiving concurrent neoadjuvant chemo-radiotherapy; and (6) histological Tis stage. In total, 382 patients were enrolled in this study (Fig. 1). The patients were divided into two groups. Patients with and without enlarged lymph nodes were enrolled in the BLNE and non-BLNE groups, respectively.

Assessment of enlarged lymph node

Lymph node metastasis in CRC has different imaging criteria.[17-26] Previous reports revealed a 5-mm cut-off value as the most frequently used size criteria for nodal status in rectal cancer.[27,28] One study demonstrated that node metastases occurred in 36.5% of nodes measuring > 5 mm, compared with 13.3% of nodes measuring ≤ 5 mm.[29] Additionally, one study revealed that a 4-mm threshold for mesorectal nodes could be proposed as a normal node size.[30] Our study identified enlarged lymph nodes as ≥ 5 mm in the longest axis on radiologic images.

Follow-up methods

All patients received regular follow-up protocols at clinics. The follow-up protocol included a serum tumor marker (carcinoembryonic antigen [CEA]), abdomen contrast CT every 3-6 months, and annual colonoscopy examination in the first 5 years and then as needed.

Tumor location

The cecum, ascending colon, hepatic flexure, and

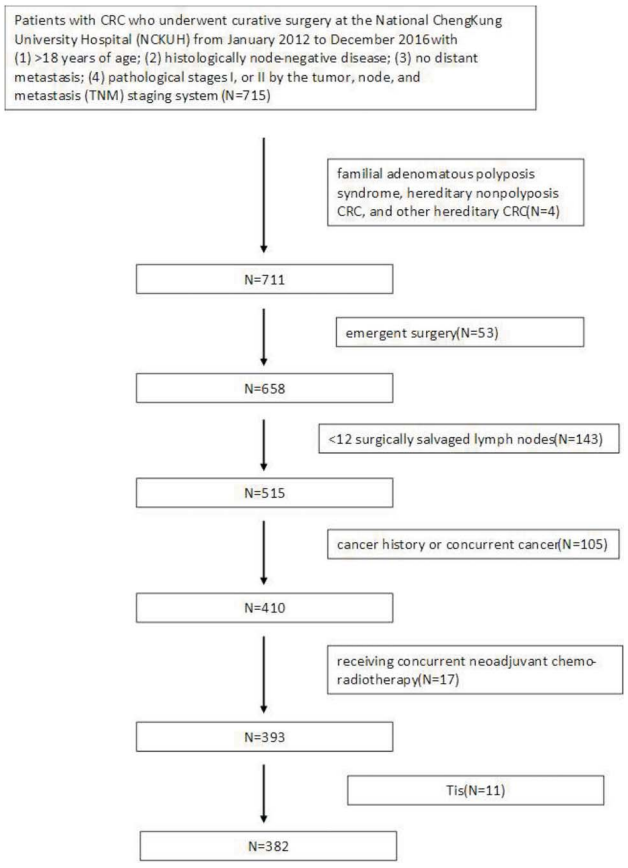

Fig. 1. 382 patients were enrolled in our study.

proximal two-thirds of the transverse colon originated from the midgut during embryologic development. The distal one-third of the transverse colon, splenic flexure, sigmoid colon, descending colon, and rectum have originated from the hindgut. The tumors arising from the cecum to the proximal two-thirds of the transverse colon were considered right-sided tumors, and those arising from the distal one-third of the transverse colon to the sigmoid colon were considered left-sided tumors.[31,32]

Statistical analysis

Disease-free survival (DFS) was defined as the time from curative surgery to the date of documented recurrence or the last clinical follow-up. Overall survival (OS) was defined as the time from curative surgery to the date of death or last clinical follow-up. The Kaplan-Meier estimate was used for survival analysis. Fisher's exact test was used for categorical variables and an independent t-test for continuous variables. All the statistical analyses were performed using MedCalc® Statistical Software version 20.218 (MedCalc Software Ltd., Ostend, Belgium).

Results

This study analysed 382 patients with CRC who underwent curative surgery from January 2012 to December 2016 at the NCKUH. Patient demographics and clinical data are summarized in Table 1. The me-

Table 1. Demographics and clinical data

Variable	Total (n = 382)	BLNE group (n = 178)	Non-BLNE group (n = 204)	*p* value
Age, years (IQR)	65 (57-74)	64.5 (57-76)	65.5 (58-73)	0.627
Gender				0.356
Male	191	94 (53%)	97 (48%)	
Female	191	84 (47%)	107 (52%)	
Diabetes mellitus	67	37 (21%)	30 (15%)	0.1382
Preoperative bowel obstruction	33	24 (13%)	9 (3%)	0.0018
CEA				0.0498
≤ 5	260	110 (62%)	150 (74%)	
> 5	107	58 (33%)	49 (24%)	
Missing data	15	10 (6%)	5 (2%)	
Tumor location				0.0987
Right-sided colon	140	67 (38%)	73 (36%)	
Left-sided colon	158	81 (46%)	77 (38%)	
Rectum	84	31 (17%)	53 (26%)	
T stage (TNM)				< 0.0001
T1	66	11 (6%)	55 (27%)	
T2	85	27 (15%)	58 (28%)	
T3	211	126 (71%)	85 (42%)	
T4a	7	6 (3%)	1 (0.5%)	
T4b	13	8 (4%)	5 (2%)	
Lymph node harvest, mean (SD)		24.29 (10.63)	20.17 (8.05)	< 0.0001
Adenocarcinoma subtype				0.0178
Well or moderately differentiated adenocarcinoma	366	165 (93%)	201 (99%)	
Poorly differentiated adenocarcinoma	15	12 (7%)	3 (1%)	
TNM stage				< 0.0001
Stage I	151	37 (21%)	114 (56%)	
Stage II	231	141 (79%)	90 (44%)	
Post-operative adjuvant chemotherapy	191	114 (64%)	77 (38%)	< 0.0001

BLNE = benign lymph node enlargement; CEA = carcinoembryonic antigen.

dian follow-up time was 83 months (range: 0-127 months). Of the 382 patients, 191 were male and 191 were female. The median age of patients in the BLNE and non-BLNE groups was 64.5 and 65.5 years, respectively. Additionally, 140 (36.65%) tumors are located in the right-sided colon, 158 (41.36%) in the left-sided colon, and 84 (21.99%) in the rectum. Most patients (211, 55.23%) were in the T3 stage, 66 (17.28%) were in the T1 stage, 85 (22.25%) were in the T2 stage, 7 (1.83%) were in the T4a stage, and 13 (3.40%) were in the T4b stage. TNM staging revealed 151 (39.53%) patients in stage I, and 231 (60.47%) in stage II. All the patients' basic demographic characteristics are summarized in Table 1.

We analysed the possible risk factors for disease free survival and overall survival. The gender, tumor location, and pre-operactive CEA level had no significant difference. Old age (greater than 60 year-old) only had poor overall survival with hazard ratio 2.3339. We noted BLNE and stage had significant progstic outcomes bothly. All the variants analysis were summarized at Table 2.

Additionally, 28 patients in BLNE group had recurrence, and 7 patients (3.9%) had local recurrence while 21 patients (11.8%) had distant metastasis. Of these 28 patients, 14 patients received surgery for tumor relapse and 14 patients did not. In non-BLNE group, 22 patients had recurrence, and 3 patients (1.5%) had local recurrence while 19 patients (9.3%) had distant metastasis. Of these 22 patients, 6 patients received surgery for recurrence and 16 patients did not (Table 3). Because there were too many factors might affect outcome, such as multiple metastasis, multiple

Table 3. Tumor recurrence

	BLNE group (n = 178)	Non-BLNE group (n = 204)
Local recurrence	7 (3.9%)	3 (1.5%)
Distant metastasis	21 (11.8%)	19 (9.3%)
Liver	12	9
Lung	10	8
Peritoneum	1	4
Bone	0	1
Small bowel	2	0
Ovary	1	0
Abdominal wall	0	1
Management		
Surgical treatment	14	6
Non-surgical treatment	14	16

Table 2. Prognostic factors for DFS and OS

Variable	DFS			OS		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age (> 60 y)	0.5267	0.1915-1.4490	0.2144	2.3339	1.3294-4.0976	0.0032*
Gender (male)	1.4158	0.5470-3.6643	0.4605	1.2552	0.7390-2.1319	0.4004
Preoperative bowel obstruction	1.5380	0.2780-8.5085	0.6219	1.4621	0.5536-3.8620	0.4433
CEA (> 5)	1.7097	0.4357-6.7087	0.4419	3.6074	1.7596-7.3955	0.0005*
Tumor location			0.2566			0.7255
Right-sided	REF	REF		REF	REF	
Left-sided	2.6420	0.9024-7.7350		1.2710	0.7004-2.3065	
Rectum	2.8751	0.7890-10.4766		1.2319	0.5939-2.5553	
Histology			0.5670			0.4378
Well or moderately differentiated	REF	REF		REF	REF	
Poor differentiated	2.1591	0.1548-30.1062		0.5785	0.1452-2.3053	
TNM stage			0.0127*			0.0016*
Stage I	REF	REF		REF	REF	
Stage II	3.4129	1.2999-8.9604		2.3977	1.3935-4.1255	
BLNE	2.8146	1.0822-7.3200	0.0338*	0.7352	0.4321-1.2510	0.2567
Post-operative adjuvant chemotherapy	1.0811	0.4176-2.7985	0.8724	0.6658	0.3915-1.1324	0.1333

DFS = disease-free survival; OS = overall survival; CEA = carcinoembryonic antigen; REF = reference; BLNE = benign lymph node enlargement.

* Significant difference with $p < 0.05$.

treatment, R0 resection or not, we did not make detailed discussion here.

The comparison of patients in stages I and II revealed better OS and DFS in the earlier stage group; stage I had better outcome than stage II ($p = 0.016$ and 0.0127, respectively) (Fig. 2). Thus, we compared the OS and DFS according to the TNM stage in the BLNE and non-BLNE groups. No statistical significance was found in patients in stage I between BLNE and non-BLNE groups ($p = 0.6243$). While patients in stage II in the BLNE group had better OS ($p = 0.0171$) (Fig. 3). The DFS found no statistical significance between the BLNE and non-BLNE groups in patients in stages I and II.

The BLNE group had better OS than the non-BLNE group, but with no statistical significance ($p = 0.2567$). In subgroups, the OS of patients with right-sided colon cancer and patients with rectal cancer in the BLNE group had the same trend ($p = 0.0433$ and 0.1284, respectively) (Fig. 4).

The non-BLNE group had better DFS than the BLNE group ($p = 0.0444$). DFS of patients with left-sided colon cancer in the non-BLNE group was better

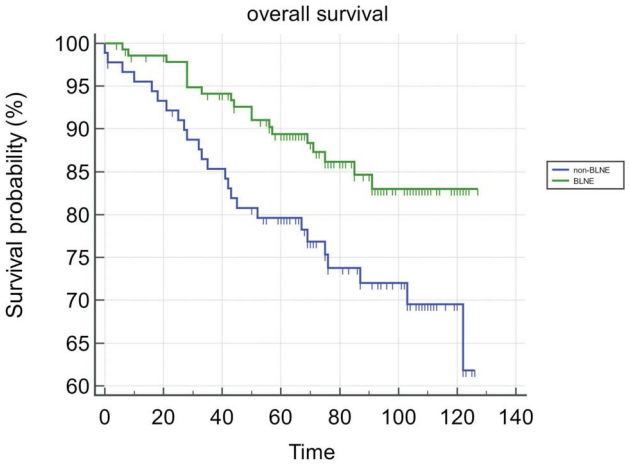

Fig. 3. Kaplan-Meier survival curve showed the BLNE group had better overall survival in stage II cases.

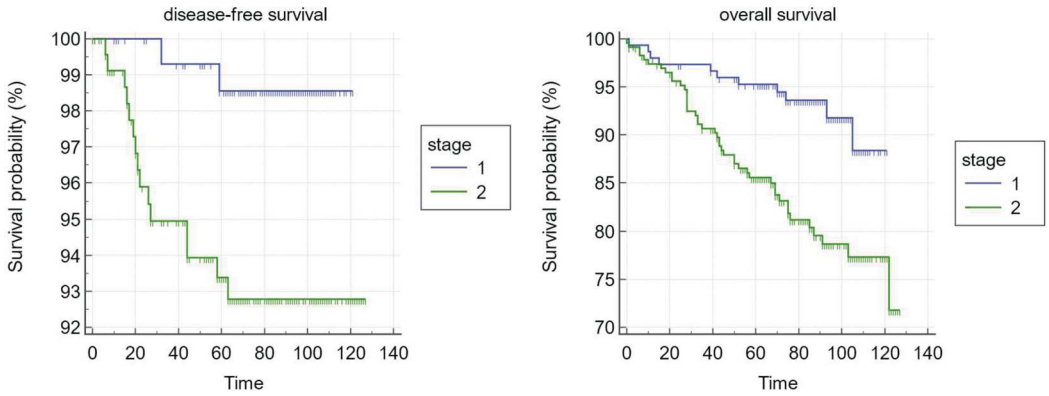

Fig. 2. Kaplan-Meier survival curve showed that stage I has better overall survival.

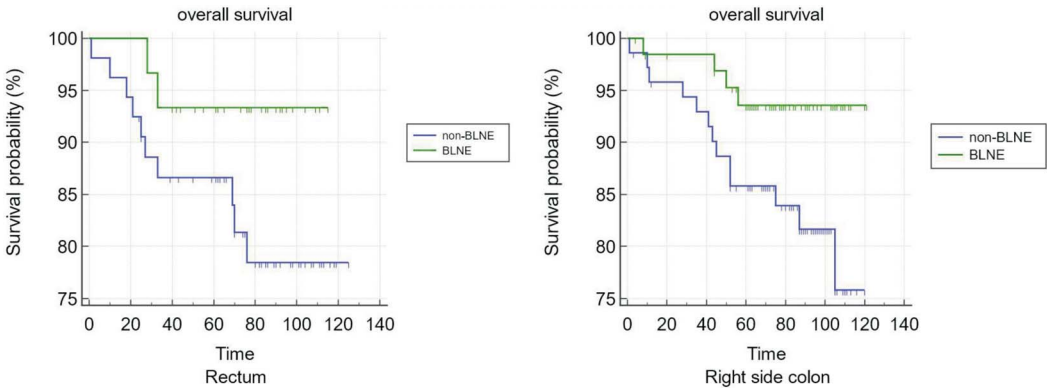

Fig. 4. In subgroup analysis, Kaplan-Meier survival curve showed the BLNE group had better overall survival in right side colon and rectum.

than the BLNE group in subgroups ($p = 0.0154$).

Discussion

Our study revealed that patients and early CRC with BLNE had better OS than those without. It is compatible with the previous multi-institutional cohort study, which was the first to assess the prognostic significance of BLNE in patients with CRC.[15] However, the OS of all patients between the BLNE and non-BLNE groups had no statistical significance. We found that stage I and stage II had different survival curve. In subgroups, patients with stage II CRC with BLNE had significantly better OS than those without. However, DFS in patients with CRC without BLNE was significantly longer than in those with BLNE.

Lymph node status is an important element of the TNM staging system, and lymph node metastasis is an important factor in predicting OS and DFS in patients with CRC. Additionally, lymph node metastasis is an important factor in determining the use of adjuvant chemotherapy.[33-35] Ogino et al.[36] demonstrated that lymphocytic reactions to the tumor were associated with improved prognosis among patients with CRC, independent of the lymph node count and other clinical, pathologic, and molecular characteristics. Moreover, the immune response may cause lymph node enlargement and reflect specific tumoral molecular alterations associated with indolent tumor behavior. Their study suggested a possible role for the host immune response as an independent prognostic factor in patients with CRC. Many studies revealed that tumor-infiltrating inflammation and immune response could be favorable prognostic factors for CRC.[37-40] High levels of specific subsets of infiltrating lymphocytes (e.g., CD57+, CD8+, CD45RO+, or FOXP3+ cells) are associated with favorable outcomes in CRC.[8-13] Huang et al.[15] hypothesized that an enlarged benign lymph node would reflect tumor antigen-specific T-cell accumulation in a tumor-draining area and reveal an immune response to tumor antigens. We have assented to their point of view. Lymph node enlargement might be induced by an immune reaction. The immune response could bring tumor-infiltrating lymphocytes, thereby leading to improved survival. We hypothesized there may be the presence of micrometastasis in the resected lymph nodes, which was not detected by the pathologist. And in our study, there were more stage II patients (79%) in BLNE group. These two reasons may cause shorter DFS in the BLNE group, but the OS remained favorable.

Our study had several limitations. First, this is a retrospective cohort study of a single institution with a relatively small number of patients. Additionally, the clinical outcome might be influenced by the institution's experience and standard practice. Second, the immunohistochemical features of the enlarged lymph nodes were not investigated. Histopathologic evaluations should be performed to confirm the correlation between clinical and immunological findings. Third, some patients received adjuvant chemotherapy after curative surgery, and it might influence their survival. Finally, a precise histopathologic protocol should be established to obtain accurate data.

Conclusion

BLNE could be a significant prognosis factor in predicting survival in early CRC, although more analysis of the molecular mechanisms and tumor-lymphocyte reactions should be investigated.

Conflicts of Interest

None.

Funding Supports

None.

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原　著

術前影像學淋巴結腫大於早期大腸癌之顯著性

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目的　術前影像學上之淋巴結腫大十分常見，但其預後價值仍不清楚，因此我們嘗試研究術前影像學淋巴結腫大之顯著性。

方法　我們以回溯性研究分析於 2012 年 1 月至 2016 年 12 月間於國立成功大學附設醫院接受根治性手術之大腸直腸癌病人之成效。

結果　共有 382 位接受根治性手術之大腸直腸癌病人進入分析，良性淋巴結腫大及 TMN 分期系統皆有預後價值，具有良性淋巴結腫大之第二期大腸直腸癌病患有顯著性較好之整體存活率，而具有良性淋巴結腫大之右側大腸癌及直腸癌之病患則有相對較好整體存活率之傾向。

結論　良性淋巴結腫大能成為顯著預後因子去預測早期大腸直腸癌之存活率。

關鍵詞　大腸直腸癌、淋巴結腫大、良性、成效、預後。