Incidence and Pattern of Nodal Metastasis in Colon and Rectal Cancer: a Study of 1012 Cases from Thailand

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ABSTRACT

Objective: Lymph node (LN) metastasis is a key to determine prognosis and adjuvant treatment for resectable colorectal cancer. This study aimed to determine and compare the incidence and pattern of LN metastasis between colon cancer and rectal cancer.

Methods: Medical and pathological reports of patients with stage I-III colorectal adenocarcinoma undergoing oncological resection between 2009 and 2013 at the Faculty of Medicine Siriraj Hospital were reviewed. The incidence and pattern of LN metastasis related to tumor staging between colon cancer and rectal cancer were analyzed.

Results: This study included 1012 cases (502 colon cancer and 510 rectal cancer). Compared with rectal specimens, colonic specimens had a larger tumor size (5.8 cm vs 5.0 cm; P<0.001), more T4 lesion (24% vs 6.3%; P<0.001) and more LNs harvested (24 vs 18; P<0.001). Nodal metastases were found in 552 specimens (54.5%). The rate of LN metastasis was 14.3% for T1 tumors, 25.6% for T2 tumors, 61.2% for T3 tumors, and 65.6% for T4 tumors. There was no significant difference in the overall rate of nodal metastasis between colon cancer and rectal cancer (52.6% vs 56.5%; P=0.22), but rectal cancer had more N2 staging (31% vs 22.5%; P=0.002). Rectal cancer yielded more median number of positive LN (4 vs 3; P=0.002) with a greater LN ratio (0.22 vs 0.12; P<0.001) than colon cancer. Based on the depth of tumor invasion, T3 rectal cancer had a significantly higher rate of LN metastasis (66.8% vs 55.7%; P=0.004) and a greater LN ratio (0.23 vs 0.10; P<0.001) than T3 colon cancer.

Conclusion: Although colon cancer had a larger tumor size and a higher percentage of deeper invasion, rectal cancer were associated with a higher number of positive LN, more N2 status and a greater LN ratio - especially T3 lesion.

Keywords: Colon cancer; rectal cancer; nodal metastasis; lymph node ratio; Thailand (Siriraj Med J 2020; 72: 386-390)

INTRODUCTION

The incidence of colorectal cancer (CRC) is rapidly increasing in Asia including Thailand. At present, CRC is the third common malignancy in Thai males and the fourth in Thai females, and accounts for 11% of cancer burden in Thailand.[1] Oncological resection remains a mainstay treatment of non-metastatic CRC. Meanwhile, the status of lymph node (LN) metastasis determines the prognosis of CRC and the need of adjuvant therapy. Negative resection margin and adequate LN harvested (more than 12 LNs) indicate the quality of surgical specimens. Therefore, many surgeons advocate extensive operations including complete mesocolic excision with central vascular ligation and D3 lymphadenectomy for

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colon cancer to achieve utmost removal of potentially cancer-harboring LN.[2] Apart from surgical extent, it was evident that the number of LN harvested was dependent on the length of surgical specimen, tumor size, depth of CRC invasion, and location of the tumor.[3]

Another interesting aspect of LN removal and nodal metastasis is that lymph nodes ratio (LNR), defined as the ratio of metastatic LN to the total number of LN harvested, is predictive of disease-free survival and overall survival in stage III CRC.[4] The LNR may provide an additional value to the N-stage of TMN classification for CRC. However, histopathology and nodal status of CRC could be various among tumor location and may be different among ethnics.[3,5] In Asian countries, most studies examining these subjects were based on the East Asia population.[6-10] It would be interesting to have this information form other regions of Asia including Southeast Asia. The objective of this study was to determine and compare the incidence and pattern of nodal metastasis between colon cancer and rectal cancer using a database from the largest hospital in Thailand.

MATERIALS AND METHODS

After obtaining ethics approval from the Institution's Ethics Committee (Si 122/2014), medical records and pathological reports of patients undergoing elective and emergency colectomy and/or proctectomy for stage I-III colorectal adenocarcinoma between 2009 and 2013in the Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, were reviewed. Our oncological principles of CRC resection included a resection margin at least 5 cm from colon cancer with the removal of node-baring mesentery and proximal ligation of the feeding vessels, and adequate or total mesorectal excision for rectal cancer.

The clinicopathological records were identified from the hospital's prospectively-collected database. Pathological reports were excluded from this review if patients had local excision or palliative resection, and those underwent an operation for recurrent CRC, carcinoma in situ, synchronous CRC, or familial adenomatous polyposis. Patients having neoadjuvant therapy were also excluded. Rectal cancer was defined as a tumor locating within 15 cm from the anal verge measured by an endoscopy. High-grade tumors were poorly differentiated adenocarcinoma, mucin-producing tumors, signet ring cells. Notably, pathologists would identify LNs by careful palpation a surgical specimen after proper formalin fixation. The seventh edition of UICC TNM staging system for colorectal cancer was used in this study. The primary outcomes measured were the incidence and pattern of nodal metastasis between colon cancer and rectal cancer. This study was performed in accordance with the Declaration of Helsinki.

All data were prepared and compiled using SPSS computer software (version 15.0 for Windows). Mean and standard deviation are presented for continuous data. The Kolmogorov-Smirnov test was used to test for the pattern of data distribution. Student unpaired *t*-tests were used to compare data between the two groups when they showed normal distribution. The Mann-Whitney *U* tests were used when data were not normally distributed. The Pearson χ 2 tests or Fisher's exact tests were used for categorical data. A P-value of less than 0.05 was considered statistically significant.

RESULTS

This study included 1012 cases (502 colon cancer and 510 rectal cancer). Patients with colon cancer was about 2-year older than those with rectal cancer (average age 64.7 years vs 62.6 years, P=0.011). Compared with rectal specimens, colonic specimens had a larger tumor size (5.8 cm vs 5.0 cm; P <0.001), more T4 lesion (24% vs 6.3%; P<0.001) and more harvested lymph nodes (24 vs 18; P<0.001) - but a comparable percentage of high-grade histology (5.4% vs 3.7%; P=0.21). Clinicopathological characteristics between colon cancer and rectal cancer are shown in Table 1.

Nodal metastases were found in 552 specimens (54.5%). The rate of nodal involvement was 14.3% for T1 tumors, 25.6% for T2 tumors, 61.2% for T3 tumors, and 65.6% for T4 tumors. There was no significant difference in the overall rate of nodal metastasis between colon cancer and rectal cancer (52.6% vs 56.5%; P=0.22), but rectal cancer had more N2 staging (31% vs 22.5%; P=0.002). Rectal cancer yielded more median number of positive LN (4 vs 3; P=0.002) with a greater LNR (0.22 vs 0.12; P<0.001) than colon cancer. Based on the depth of tumor invasion, T3 rectal cancer had a significantly higher rate of nodal metastasis (66.8% vs 55.7%; P=0.004) (Table 2) and a greater LNR (0.23 vs 0.10; P<0.001) than T3 colon cancer (Table 3).

DISCUSSION

This study examining 1012 surgical specimens of colorectal cancer in Thailand demonstrated that, although colon cancer had a larger tumor size and a higher percentage of deeper invasion, rectal cancer were associated with a higher number of LN metastasis, more N2 status and a greater lymph node ratio - especially T3 lesion. Rectal cancer appeared to be more aggressive than colon cancer.

TABLE 1. Clinicopathological characteristics between colon cancer and rectal cancer. Data are presented as mean ± standard deviation, median [interquartile range], or number (percentage).

Characteristics	Colon cancer (n=502)	Rectal cancer (n=510)	*P*-value
Age (years)	64.7 ± 13.3	62.6 ± 12.4	0.011
Male	265 (52.8)	278 (54.5)	0.58
Tumor size (cm)	5.8 ± 2.9	5.0 ± 1.8	<0.001*
High-grade tumor [a]	27 (5.4)	19 (3.7)	0.21
Tumor stage			<0.001*
T1	16 (3.2)	19 (3.7)	
T2	68 (13.5)	104 (20.4)	
T3	296 (59.0)	355 (69.6)	
T4	122 (24.3)	32 (6.3)	
Harvested lymph node	24 [17-36]	18 [13-25]	<0.001*
≥ 12 lymph node removal	453 (90.2)	424 (83.1)	0.001*
Node stage			0.008*
N0	238 (47.4)	222 (43.5)	
N1	151 (30.1)	130 (25.5)	
N2	113 (22.5)	158 (31.0)	
Of patients with nodal metastasis			
Positive lymph node	3 [1-6]	4 [2-7]	0.002*
Lymph node ratio (%)	0.12 [0.06-0.29]	0.22 [0.10-0.41]	<0.001*

*P-value <0.05

Note: [a] High-grade tumors were poorly differentiated adenocarcinoma, mucin-producing tumors, signet ring cells.

TABLE 2. Comparison between tumor stage and nodal stage in colon cancer and rectal cancer. Data are presented as number (percentage).

T stage	Proportion of nodal metastasis (%)			*P*-value
	Colorectal cancer (n=1012)	Colon cancer (n=502)	Rectal cancer (n=510)	
T1	5/35 (14.3)	4/16 (25.0)	1/19 (5.3)	0.16
T2	44/172 (25.6)	18/68 (26.5)	26/104 (25.0)	0.83
T3	402/651 (61.2)	165/296 (55.7)	237/355 (66.8)	0.004*
T4	101/154 (65.6)	77/122 (63.1)	24/32 (75.0)	0.21

*P-value <0.05

TABLE 3. Comparison between tumor stage and lymph node ratio (LNR) in colon cancer and rectal cancer. Data are presented as median [interquartile range].

T stage	Lymph node ratio		*P*-value
	Colon cancer (n=264)	Rectal cancer (n=288)	
T1	0.24 [0.08-0.84]	-	n/a
T2	0.10 [0.07-0.22]	0.17 [0.07-0.31]	0.54
T3	0.10 [0.05-0.25]	0.23 [0.10-0.44]	<0.001*
T4	0.16 [0.07-0.33]	0.20 [0.11-0.39]	0.19

*P-value <0.05

Abbreviation: n/a = not available

Surgical specimens of colon cancer in this study yielded more median number of LN harvested than those of rectal cancer (24 LNs vs 18 LNs). The number of colonic specimens containing adequate LN removal (at least 12 LNs) was also significantly higher than that of rectal specimens (90.2% vs 83.1%). These finding were consistent with those reported from Austria[3] and China[9] – where right-sided colon specimen had the highest number of LN harvested followed by left-sided colon and rectal specimens. Other factors influencing the number of LNs harvested included patient's age, tumor size, tumor staging, type of operation, and technique to identify LN in a surgical specimen.[11] The presence of at least 12 LNs in a CRC specimen is widely regarded as one of quality assurances for appropriate CRC operations. It is associated with proper staging, subsequent treatment, surveillance protocol and CRC prognosis.[8]

It is known that the possibility of nodal metastasis is related to the depth of tumor invasion. For example, using the Surveillance, Epidemiology, and End Results (SEER) cancer registry, the rate of nodal involvement for CRC was approximately 10% for T1 tumors, 20% for T2 tumors, 40% for T3 tumors, and 50% for T4 tumors. Moreover, nodal metastasis was more prominent in rectal cancer and poorly differentiated cancer.[12] Our findings confirmed this correlation and were in line with the results of this US population-based study as we found that the proportion of nodal metastasis increased by advanced T-staging and rectal cancer had more percentage of LN involvement than colon cancer – especially T3 lesions. In addition, rectal cancer also had more median number of positive LN, more N2 staging and a greater LNR than colon cancer.

A higher rate of nodal metastasis and greater LNR in rectal cancer shown in our study was supported by a review of population-based studies[11] and hospital-based cohorts.[10] For instance, a study of 2340 Chinese surgical patients with stage I-III CRC found that patients with rectal cancer had significantly more LNs involved and higher LNR than those with colon cancer.[10] There is no clear rationale why rectal cancer has more nodal involvement than colon cancer, but some possible explanation includes their differences in anatomical and oncological characteristics. Although LNR could be a significant prognostic factor for stage III CRC, its optimal cut-off point remains debatable for determining the regimen of adjuvant treatment and CRC survival.

It is interesting that the rates of nodal metastasis based on T-staging in our study appeared to be slightly higher than those reported in other studies[11,12] – ours ranged from 14.3% for T1 tumors to 65.6% for T4 tumors. One possible explanation for these findings is that the average size of the tumor was quite large (about 5-6 cm) in our study and a tumor with large diameter (especially more than 4.5 cm) could increase the risk of nodal involvement.[13] Also, some T1 tumors in our institute were treated by endoscopic removal or transanal excision thus resulting in those with large tumor or high-risk for nodal metastasis underwent oncological resection with LN-bearing area. Moreover, 50% of our cases were rectal cancer which was more prone to have LN metastasis.[10]

Our study benefited from a review of a prospectively-collected database of the largest hospitality in Thailand – which could be a good representative of real-world practice and overall clinicopathological characteristics of CRC in Thailand. However, there are some limitations of this observational study. First, the number of patient with T1 tumor was small - which represented a real picture of CRC in Thailand where the incidence of stage I CRC was less than 10% due to the lack of CRC screening and cancer awareness.[1] Therefore the incidence of LN metastasis in T1 lesion may be difficult to interpretate especially for T1 colon cancer. Specifically, there were 4 cases with LN metastasis out of 16 cases with T1 colon cancer (accounting for 25%). This should not be perceived as a true incidence of nodal involvement for T1 lesion because a majority of malignant colonic polyps were removed endoscopically in our institute thus leaving only high-risk T1 lesions for oncological resection. Second, the comparison of LNR in T1 tumors between colon cancer and rectal cancer cannot be performed because the rectal cancer group had only one case with LN metastasis. Hence, future studies with large sample size especially for early CRC are needed from Thailand. Third, the correlation between nodal status including LNR and oncological outcomes was beyond the scope of this study. However, several population-based prospective studies have shown a strong correlation between a high number of LNs harvested and better survival, and a prognostic indicator of LNR for stage III CRC.[11]

In summary, this single-center study demonstrated that the incidence of LN metastasis in CRC increased by the depth of tumor invasion. Although the overall rate of nodal metastasis between colon cancer and rectal cancer was comparable, rectal cancer had more median number of positive LN, more N2 staging and a greater LNR – especially T3 rectal cancer.

Conflict of Interests: The authors declare that we have no conflict of interest.

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