The Impact of Metastatic Lymph Node Size on Long-Term Outcomes Following Curative Colectomy for Pathological Stage III Colon Cancer

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Abstract

Background: In node-positive colon cancer, the impact of MLN size on prognosis is controversial. The aim of this study was to clarify the impact of metastatic lymph node (MLN) size on long-term outcomes in patients undergoing curative resection for pStage III colon cancer.

Methods: This study enrolled patients who underwent curative colectomy for pStage III colon cancer between January 2013 and December 2015. All eligible patients were divided into four groups based on the short-axis diameter of the largest MLN: Group A, < 5 mm; Group B, ≥ 5 mm and < 10 mm; Group C, ≥ 10 mm and < 15 mm; and Group D, ≥ 15 mm. We performed univariate and multivariate analysis using Cox proportional hazard regression models to identify clinicopathological factors affecting recurrence-free survival (RFS).

Results: A total of 209 patients were analyzed. We evaluated 7305 LNs, of which 644 were metastatic. The 5-year RFS rates of Groups A, B, C, and D were 82.3%, 74.6%, 74.5%, and 60.7%, respectively. In univariate analysis, age older than 70 years, Group D (largest MLN ≥ 15 mm), and the absence of adjuvant chemotherapy were significantly associated with RFS. In multivariate analysis, Group D (hazard ratio [HR], 3.95; 95% confidence interval [CI], 1.34–11.65; p=0.01) and the absence of adjuvant chemotherapy (HR, 2.44; 95% CI, 1.26-4.72; p<0.01) were independently associated with worse RFS.

Conclusion: A maximum MLN ≥ 15 mm was significantly associated with worse RFS in stage III colon cancer. Bulky MLNs might be a poor prognostic factor in node-positive colon cancer.

Introduction

Lymph node (LN) metastasis is one of the most important prognostic factors in patients undergoing curative resection for colon cancer [1]. To assess the degree of LN metastasis, it is essential to determine the number of metastatic LNs (MLNs); this number was incorporated into the TNM staging system both in the Union for International Cancer Control and in the American Joint Committee on Cancer [2, 3]. Furthermore, multiple studies demonstrated that the number of LNs examined was associated with long-term outcomes in colon cancer because stage migration was avoided by harvesting a large number of LNs [4–6]. Little is known about how LN size influences prognosis. In node-negative colon cancer, large non-MLNs were reported to be associated with better prognosis due to a strong immune response [7–10]. In node-positive colon cancer, the impact of MLN size on prognosis is controversial because few studies have examined this question, and their results differed in terms of whether MLN size affected long-term outcomes [11, 12]. This study was conducted to clarify the impact of MLN size on long-term outcomes in patients undergoing curative resection for pathological stage III colon cancer.

Materials And Methods

Patient selection
Patients who underwent curative colectomy for primary pathological stage III colon cancer at Shizuoka Cancer Center in Japan between January 2013 and December 2015 were included. The exclusion criteria were synchronous or metachronous colorectal cancer and concomitant surgical procedures for other cancers. Patient characteristics and pathological and surgical findings were recorded in a prospective database. Data collection and analysis were approved by the institutional review board of Shizuoka Cancer Center Hospital (institutional code: J2019-135). The cecum, ascending colon, and transverse colon were classified as the right-sided colon, and the descending colon and sigmoid colon were classified as the left-sided colon. Pathological T or N stage was classified according to the tumor node metastasis (TNM) classification system [2].

Measurement of lymph node size

After removal of fresh specimens, colorectal surgeons manually identified all LNs. The short-axis diameter of each dissected LN was measured, and the LN was fixed in 10% buffered formalin for 24 hours; the pathological diagnosis was recorded for each dissected LN, as previously reported [13–15]. All eligible patients were divided into four groups based on the short-axis diameter of the largest MLN: Group A, < 5 mm; Group B, ≥ 5 mm and < 10 mm; Group C, ≥ 10 mm and < 15 mm; and Group D, ≥ 15 mm. Clinicopathological characteristics and long-term outcomes were compared between groups.

Treatment

In accordance with the Japanese Society for Cancer of the Colon and Rectum Guideline for the Treatment of Colorectal Cancer [16], D2 LN dissection was performed for clinical T1 tumors, and D3 LN dissection was performed for tumors of clinical stage T2 or higher. In patients without LN metastasis who were older than 75 years or who had a high risk of preoperative complications from comorbidities, D2 LN dissection was performed for tumors of clinical stage T2 or higher. In D2 LN dissection, pericolic and intermediate LNs were removed. In D3 LN dissection, pericolic, intermediate, and main LNs were removed and tumor-supplying arteries were divided at their origins. Laparoscopic surgery was the first choice; open surgery was performed only when laparoscopic surgery was judged unsuitable for ensuring oncological safety or when patients refused laparoscopic surgery. In principle, 5-fluorouracil–based adjuvant chemotherapy was administered to patients younger than 75 years who did not have any severe comorbidity.

Surveillance protocol

Surveillance was performed for 5 years after surgery. The surveillance protocol at our institution was as follows: an interview, physical examination, and blood tests, including carcinoembryonic antigen and cancer antigen 19–9, were performed every 3 months for the first 3 years after surgery and then every 6 months thereafter. Chest, abdominal, and pelvic CTs were performed every 6 months. Colonoscopy was performed 1, 3, and 5 years after surgery. Recurrence was confirmed by pathological assessment or by progressively increasing tumor size in imaging studies.

Statistical analysis

Categorical variables are presented as numbers (percentages). Continuous variables are presented as medians (range). Categorical variables were compared using the chi-squared test and continuous
variables were compared using the Mann-Whitney U test. Overall survival (OS) and recurrence-free
survival (RFS) were calculated using the Kaplan-Meier method and compared using the log-rank test. We
performed univariate and multivariate analyses using the Cox proportional hazards regression model to
identify clinicopathological factors affecting RFS. All statistical analyses were performed with the
statistical program R version 1.40 (http://www.r-project.org/). A p value less than 0.05 was considered
statistically significant.

Results

Patient characteristics

A total of 216 patients underwent curative colectomy for primary pathological stage III colon cancer
between January 2013 and December 2015. Patients who had synchronous or metachronous colorectal
cancer (n = 5) and who underwent concomitant surgical procedures for other cancers (n = 2) were
excluded. The remaining 209 patients were analyzed. We evaluated a total of 7305 LNs, of which 644
were metastatic. The median short-axis diameter of MLNs was 5 mm (range 1–40 mm) and the median
short-axis diameter of the largest MLN in each patient was 8 mm (range, 1–40 mm). Among the eligible
patients, 40 (19%), 79 (38%), 51 (24%), and 39 (19%) were categorized into Groups A, B, C, and D,
respectively. The patient characteristics are presented in Table 1. There were no significant differences
between Group A and the other Groups in terms of age, sex, operative approach, histology, or number of
dissected LNs. The proportion of patients with right-sided colon cancer was higher in Group D than in
Group A, the median tumor size was significantly larger in Groups C and D than in Group A, the proportion
of patients undergoing D3 dissection was higher in Groups B, C, and D than in Group A, and the
proportion of patients with T3 cancers was higher in Group D than in Group A. The proportion of patients
with N2 cancers and the number of MLNs were significantly higher in Groups B, C, and D than in Group A.
The proportion of patients who underwent adjuvant chemotherapy was higher in Group C than in Group
A.
Table 1  
Clinicopathological characteristics of the study patients

| Characteristic                     | Group A                  | Group B                  | p*         | Group C                  | p**         | Group D                  | p***        |
|-----------------------------------|--------------------------|--------------------------|------------|--------------------------|------------|--------------------------|------------|
| MLN < 5mm                         | n = 40                   | 5mm ≤ MLN < 10mm         |            | 10mm ≤ MLN < 15mm        |            | 15mm ≤ MLN               |            |
| Age, years [median (range)]       | 69.5 (37–86)             | 69.0 (39–86)             | 0.61       | 65.0 (39–86)             | 0.12       | 70.0 (39–86)             | 0.74       |
| Sex                               |                          |                          |            |                          |            |                          |            |
| Male                              | 25 (62.5)                | 39 (49.4)                |            | 23 (45.1)                |            | 21 (53.8)                |            |
| Female                            | 15 (37.5)                | 40 (50.6)                |            | 28 (54.9)                |            | 18 (46.2)                |            |
| Tumor location                    |                          |                          |            |                          |            |                          |            |
| Right-sided colon                 | 19 (47.5)                | 47 (59.5)                |            | 32 (62.7)                |            | 29 (74.4)                |            |
| Left-sided colon                  | 21 (52.5)                | 32 (40.5)                |            | 19 (37.3)                |            | 10 (25.6)                |            |
| Tumor size, cm [median (range)]   | 3.3 (0.5–8.0)            | 3.5 (1.0–10.0)           | 0.84       | 4.5 (1.5–11.0)           | 0.03       | 5.0 (1.0–11.0)           | 0.02       |
| Operative approach                |                          |                          |            |                          |            |                          |            |
| Laparoscopic surgery              | 39 (97.5)                | 79 (100)                 |            | 49 (96.1)                |            | 38 (97.4)                |            |
| Open surgery                      | 1 (2.5)                  | 0 (0)                    |            | 2 (3.9)                  |            | 1 (2.6)                  |            |
| LN dissection                     |                          |                          |            |                          |            |                          |            |

Values in parentheses represent percentages unless otherwise noted.

LN, lymph node; MLN, metastatic lymph node; well, well differentiated adenocarcinoma; mod, moderately differentiated adenocarcinoma; por, poorly differentiated adenocarcinoma; muc, mucinous adenocarcinoma

*Comparing the Group A to the Group B

**Comparing the Group A to the Group C

***Comparing the Group A to the Group D
| Characteristic | Group A MLN < 5mm | Group B 5mm ≤ MLN < 10mm | Group C 10mm ≤ MLN < 15mm | Group D 15mm ≤ MLN | p* | p** | p*** |
|---------------|------------------|---------------------------|---------------------------|-------------------|----|-----|-----|
| n = 40        | n = 79           | n = 51                    | n = 39                    |                   |    |     |     |
| D3            | 17 (42.5)        | 50 (63.3)                 | 41 (80.4)                 | 28 (71.8)         |    |     |     |
| D2            | 23 (57.5)        | 29 (36.7)                 | 10 (19.6)                 | 11 (28.2)         |    |     |     |
| Histology     |                 |                           |                           |                   | 0.27 | 0.63 | 0.62 |
| Well or mode  | 39 (97.5)        | 72 (91.1)                 | 48 (94.1)                 | 37 (94.9)         |    |     |     |
| Por or muc    | 1 (2.5)          | 7 (8.9)                   | 3 (5.9)                   | 2 (5.1)           |    |     |     |
| Pathological T stage |         |                           |                           |                   | 0.54 | 0.10 | 0.02 |
| T1            | 8 (20.0)         | 9 (11.4)                  | 3 (5.9)                   | 1 (2.5)           |    |     |     |
| T2            | 6 (15.0)         | 15 (19.0)                 | 5 (9.8)                   | 6 (15.4)          |    |     |     |
| T3            | 10 (25.0)        | 26 (32.9)                 | 22 (43.1)                 | 20 (51.3)         |    |     |     |
| T4            | 16 (40.0)        | 29 (36.7)                 | 21 (41.2)                 | 12 (30.8)         |    |     |     |
| Pathological N stage | < 0.01  | < 0.01                  | < 0.01                    |                   |    |     |     |
| N1            | 39 (97.5)        | 56 (70.9)                 | 37 (72.5)                 | 22 (56.4)         |    |     |     |
| N2            | 1 (2.5)          | 23 (29.1)                 | 14 (27.5)                 | 17 (43.6)         |    |     |     |

Values in parentheses represent percentages unless otherwise noted.

LN, lymph node; MLN, metastatic lymph node; well, well differentiated adenocarcinoma; mod, moderately differentiated adenocarcinoma; por, poorly differentiated adenocarcinoma; muc, mucinous adenocarcinoma

*Comparing the Group A to the Group B

**Comparing the Group A to the Group C

***Comparing the Group A to the Group D
| Characteristic | Group A | Group B | p*  | Group C | p** | Group D | p*** |
|---------------|---------|---------|------|---------|------|---------|------|
| Number of dissected LNs [median (range)] | 31 (18–93) | 33 (16–70) | 0.65 | 34 (14–42) | 0.32 | 34 (14–74) | 0.39 |
| Number of MLNs [median (range)] | 1 (1–6) | 2 (1–24) | < 0.01 | 2 (1–19) | < 0.01 | 3 (1–18) | < 0.01 |
| Adjuvant chemotherapy | 19 (47.5) | 52 (65.8) | 0.07 | 38 (74.5) | < 0.01 | 23 (59.0) | 0.37 |

Values in parentheses represent percentages unless otherwise noted.

LN, lymph node; MLN, metastatic lymph node; well, well differentiated adenocarcinoma; mod, moderately differentiated adenocarcinoma; por, poorly differentiated adenocarcinoma; muc, mucinous adenocarcinoma

*Comparing the Group A to the Group B

**Comparing the Group A to the Group C

***Comparing the Group A to the Group D

**Long-term outcomes**

The median follow-up time was 54 months. Figures 1 and 2 show the OS and RFS curves of each Group, respectively. Table 2 shows the 5-year OS and RFS rates of each Group. There were no significant differences in OS rates between Groups. The RFS rate in Group D was significantly lower than that in Group A. The RFS rates in Groups B and C were also lower than that in Group A, although the differences were not significant. A larger maximum MLN diameter was associated with a lower RFS.
Table 2
Comparison of long-term outcomes by size of the largest metastatic lymph node

| Group | MLN Condition | n | 5-year overall survival rate (%) | 5-year recurrence-free survival rate (%) | p* | p** | p*** |
|-------|---------------|---|----------------------------------|----------------------------------------|----|-----|------|
| A     | MLN < 5mm     | 40| 94.9                             | 82.3                                   |    |     |      |
| B     | 5mm ≤ MLN < 10mm | 79| 91.2                             | 74.6                                   | 0.92|     |      |
| C     | 10mm ≤ MLN < 15mm | 51| 93.9                             | 74.5                                   | 0.69|     | 0.08 |
| D     | 15mm ≤ MLN    | 39| 77.9                             | 60.7                                   | 0.02|     |      |

MLN, metastatic lymph node

*Comparing the Group A to the Group B
**Comparing the Group A to the Group C
***Comparing the Group A to the Group D

Prognostic factors

To identify clinicopathological factors affecting RFS, univariate and multivariate analyses were performed using Cox proportional hazards regression models, and the results are shown in Table 3. Univariate analysis indicated that age above 70 years, Group D (largest MLN ≥ 15 mm), and the absence of adjuvant chemotherapy were all significantly associated with worse RFS. Multivariate analysis revealed that Group D (hazard ratio [HR], 3.95; 95% confidence interval [CI], 1.34–11.65; \( p = 0.01 \)) and the absence of adjuvant chemotherapy (HR, 2.44; 95% CI, 1.26–4.72; \( p < 0.01 \)) remained significantly associated with worse RFS.
Table 3
Univariate and multivariate analyses by the Cox proportional-hazard regression model

| Variables         | Overall 5-year RFS rate (%) | Univariate analysis | Multivariate analysis |
|-------------------|----------------------------|---------------------|-----------------------|
|                   | HR | 95% CI | p  | HR | 95% CI | p  |
| **Univariate analysis** |     |       |    |     |       |    |
| **Age**           |     |       |    |     |       |    |
| < 70 years        | 110 (52.6) | 79.7 | 1 | 1 | 1 | 1 |
| ≥ 70 years        | 99 (47.4) | 66.8 | 1.89 | 1.89–3.28 | 0.03 | 1.36 | 0.72–2.56 | 0.34 |
| **Sex**           |     |       |    |     |       |    |
| Male              | 108 (51.7) | 75.4 | 1 | 1 | 1 | 1 |
| Female            | 101 (48.3) | 72.1 | 1.06 | 0.62–1.83 | 0.82 | 1.01 | 0.56–1.82 | 0.98 |
| **Tumor location** |     |       |    |     |       |    |
| Right-sided colon | 127 (60.8) | 72.0 | 1 | 1 | 1 | 1 |
| Left-sided colon  | 82 (39.2) | 76.7 | 0.78 | 0.44–1.38 | 0.40 | 1.25 | 0.67–2.36 | 0.48 |
| **Tumor size**    |     |       |    |     |       |    |
| < 5.0cm           | 130 (62.2) | 79.1 | 1 | 1 | 1 | 1 |
| ≥ 5.0cm           | 79 (37.8) | 63.0 | 1.55 | 0.90–2.68 | 0.11 | 0.82 | 0.45–1.53 | 0.55 |
| **Lymph node dissection** |     |       |    |     |       |    |
| D3                | 136 (65.1) | 73.2 | 1 | 1 | 1 | 1 |
| D2                | 73 (34.9) | 74.6 | 0.93 | 0.52–1.68 | 0.81 | 0.96 | 0.46–2.00 | 0.94 |
| **pT**            |     |       |    |     |       |    |
| T1                | 21 (10.1) | 80.4 | 1 | 1 | 1 | 1 |

Values in parentheses represent percentages unless otherwise noted.

well, well differentiated adenocarcinoma; mod, moderately differentiated adenocarcinoma; por, poorly differentiated adenocarcinoma; muc, mucinous adenocarcinoma; MLN, metastatic lymph node; RFS, recurrence-free survival; HR, hazard ratio; CI, confidence interval
| Variables                  | Overall | 5-year RFS rate (%) | Univariate analysis | Multivariate analysis |
|----------------------------|---------|---------------------|---------------------|-----------------------|
|                            |         |                     | HR                  |                       |
|                            |         |                     | 95% CI              | p                     |
|                            |         |                     | HR                  | 95% CI               | p          |
| T2                         | 32 (15.3) | 87.5               | 0.86               | 0.19–3.84            | 0.84       |
|                            |         |                     | 0.68               | 0.1–3.25             | 0.63       |
| T3                         | 78 (37.3) | 80.5               | 1.41               | 0.41–4.86            | 0.59       |
|                            |         |                     | 1.03               | 0.27–3.90            | 0.97       |
| T4                         | 78 (37.3) | 59.6               | 3.20               | 0.98–10.50           | 0.05       |
|                            |         |                     | 2.77               | 0.75–10.27           | 0.13       |
| pN                         |         |                     |                     |                       |            |
| N1                         | 154 (73.7) | 76.3              | 1                   |                       | 1          |
| N2                         | 55 (26.3)  | 67.1              | 1.53               | 0.87–2.72            | 0.14       |
|                            |         |                     | 1.15               | 0.57–2.33            | 0.70       |
| Histology                  |         |                     |                     |                       |            |
| Well or mod                | 196 (93.8) | 74.6              | 1                   |                       | 1          |
| Por or muc                 | 13 (6.2)   | 61.5              | 1.88               | 0.74–4.73            | 0.18       |
|                            |         |                     | 1.31               | 0.46–3.72            | 0.61       |
| Group based on size of the largest MLN |         |                     |                     |                       |            |
| A: MLN < 5mm               | 40 (19.1)  | 82.3              | 1                   |                       | 1          |
| B: 5mm ≤ MLN < 10mm       | 79 (37.8)  | 74.6              | 1.56               | 0.62–3.94            | 0.34       |
|                            |         |                     | 1.83               | 0.70–4.78            | 0.22       |
| C: 10mm ≤ MLN < 15mm      | 51 (24.4)  | 74.5              | 1.71               | 0.65–4.51            | 0.28       |
|                            |         |                     | 2.26               | 0.79–6.46            | 0.13       |
| D: 15mm ≤ MLN             | 39 (18.7)  | 60.7              | 3.00               | 1.16–7.73            | 0.02       |
|                            |         |                     | 3.95               | 1.34–11.65           | 0.01       |
| Adjuvant chemotherapy     |         |                     |                     |                       |            |
| Present                   | 132 (63.2) | 79.3             | 1                   |                       | 1          |
| Absent                    | 77 (36.8)   | 63.3             | 2.10               | 1.22–3.62            | < 0.01     |
|                            |         |                     | 2.44               | 1.26–4.72            | < 0.01     |

Values in parentheses represent percentages unless otherwise noted.

well, well differentiated adenocarcinoma; mod, moderately differentiated adenocarcinoma; por, poorly differentiated adenocarcinoma: muc, mucinous adenocarcinoma; MLN, metastatic lymph node; RFS, recurrence-free survival; HR, hazard ration; CI, confidence interval
Discussion

In this study, we evaluated the impact of MLN diameter on long-term outcomes following curative colectomy for pathological stage III colon cancer by classifying 209 patients into four groups according to the largest MLN diameter. Compared to the RFS in Group A (MLN < 5 mm), that in Group D (MLN ≥ 15 mm) was significantly lower, and it was also lower in Groups C and D, but the differences were not significant. The multivariate analysis of RFS demonstrated that a maximum MLN diameter ≥ 15 mm was significantly associated with worse RFS, and the HR increased with MLN diameter. These results suggest that MLN diameter affected recurrence, and the presence of bulky MLNs was a poor prognostic factor in pathological stage III colon cancer. Two previous studies evaluated the impact of MLN size on prognosis in stage III colorectal cancer [11, 12]. One, which used a cutoff value of 5 mm to define a large MLN, reported that there were no significant differences in OS or disease-free survival (DFS) between patients with large and small MLNs [11]. The other, which used a cutoff value of 10 mm, demonstrated that patients with large MLNs had worse OS and DFS than those with small MLNs, and large MLN diameter was identified as an independent poor prognostic factor in a multivariate analysis of DFS [12]. Based on these results, patients in our study were classified into four groups to more precisely evaluate the relationship between MLN diameter and prognosis. Schrembs et al. analyzed the association between OS and the LN metastasis to LN size ratio (MSR) and demonstrated that smaller MSR values correlated with longer OS [17]; that is, a high proportion of tumor components in MLNs was associated with worse prognosis. In our study, a maximum MLN diameter ≥ 15 mm was significantly associated with worse prognosis; therefore, most of the normal lymphatic tissue might be replaced by tumor cells in bulky MLNs. Furthermore, in gastric cancer and esophageal cancer, MLN size was also reported to be a poor prognostic factor [18–20]. MLN size might reflect malignant potential in gastrointestinal cancers.

The absence of adjuvant chemotherapy was also associated with worse RFS in the multivariate analysis in this study. In pathological stage III colon cancer, adjuvant chemotherapy for 6 months is recommended by the Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines [16]. Recent large studies reported that adjuvant chemotherapy for 3 months was noninferior to 6 months in terms of disease-free survival in low-risk stage III colon cancer, including T1, T2, T3, and N1 disease [21, 22]. However, even for this type of cancer, adjuvant chemotherapy for 6 months might be optimal if MLNs are bulky.

There are several limitations to this study. First, this was a retrospective study that was conducted at a single institution and that enrolled a relatively small number of patients. That might be why there were no significant differences in RFS between Group A (MLN < 5 mm) and Group B (MLN ≥ 5 mm and < 10 mm) or Group C (MLN ≥ 5 mm and < 10 mm). Second, in both univariate and multivariate analyses of RFS, there were no significant differences in N stage, which has been considered to be the most powerful independent prognostic factor in stage III colon cancer [23–25]. The reason for this discrepancy is unclear. The proportion of N2 cancers was significantly higher in Group D (MLN ≥ 15 mm) than in Group A (MLN < 5 mm), which might have resulted in the difference in RFS between the two groups. Therefore, multivariate analysis that included both the N stage and MLN size was performed to minimize this bias.
In conclusion, our findings indicate that a maximum MLN $\geq 15$ mm was significantly associated with worse RFS in stage III colon cancer. Bulky MLNs might be a poor prognostic factor in node-positive colon cancer.

**Declarations**

**Ethics approval** This study was approved by the institutional review board of Shizuoka Cancer Center hospital (Institutional code, J2019-135).

**Consent to participate** Informed consent was obtained from all individual participants included in the study.

**Consent for publication** Not applicable.

**Availability of data and material** All relevant data are available on request due to privacy/ethical restrictions.

**Competing interests** The authors declare that they have no competing interest.

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**Authors’ Contributions** CM and YY drafted the paper. YY designed this study. CM, AS, HK, HH, SM, SK, MH and AN obtained and analyzed data.

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**References**

1. Weiser MR, Gönen M, Chou JF, Kattan MW, Schrag D. Predicting survival after curative colectomy for cancer: individualizing colon cancer staging. J Clin Oncol. 2011 Dec 20;29(36):4796–802.

2. Brierley JD, Gospodarowicz MK, Wittekind C. TNM classification of malignant tumours, Eighth edition. Oxford: Wiley-Blackwell; 2017.

3. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, Meyer L, Gress DM, Byrd DR, Winchester DP. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin. 2017 Mar;67(2):93–9.

4. Hashiguchi Y, Hase K, Ueno H, Mochizuki H, Kajiwara Y, Ichikura T, Yamamoto. Prognostic significance of the number of lymph nodes examined in colon cancer surgery: clinical application beyond simple measurement. Ann Surg. 2010 May;251(5):872–81.

5. Swanson RS, Compton CC, Stewart AK, Bland KI. The prognosis of T3N0 colon cancer is dependent on the number of lymph nodes examined. Ann Surg Oncol. 2003 Jan-Feb;10(1):65–71.
6. Le Voyer TE, Sigurdson ER, Hanlon AL, Mayer RJ, Macdonald JS, Catalano PJ, Haller DG. Colon cancer survival is associated with increasing number of lymph nodes analyzed: a secondary survey of intergroup trial INT-0089. J Clin Oncol. 2003 Aug 1;21(15):2912-9.

7. Mayr P, Aumann G, Schaller T, Schenkirsch G, Anthuber M, Märkl B. Lymph node hypoplasia is associated with adverse outcomes in node-negative colon cancer using advanced lymph node dissection methods. Langenbecks Arch Surg. 2016 Mar;401(2):181–8.

8. Märkl B, Schaller T, Kokot Y, Endhardt K, Kretsinger H, Hirschbühl K, Aumann G, Schenkirsch G. Lymph node size as a simple prognostic factor in node negative colon cancer and an alternative thesis to stage migration. Am J Surg. 2016 Oct;212(4):775–780.

9. Märkl B, Rößle J, Arnholdt HM, Schaller T, Krammer I, Cacchi C, Jähnig H, Schenkirsch G, Spatz H, Anthuber M. The clinical significance of lymph node size in colon cancer. Mod Pathol. 2012 Oct;25(10):1413–22.

10. Okada K, Sadahiro S, Suzuki T, Tanaka A, Saito G, Masuda S, Haruki Y. The size of retrieved lymph nodes correlates with the number of retrieved lymph nodes and is an independent prognostic factor in patients with stage II colon cancer. Int J Colorectal Dis. 2015 Dec;30(12):1685–93.

11. Rodriguez-Bigas MA, Maamoun S, Weber TK, Penetrante RB, Blumenson LE, Petrelli NJ. Clinical significance of colorectal cancer: metastases in lymph nodes < 5 mm in size. Ann Surg Oncol. 1996 Mar;3(2):124–30.

12. Dhar DK, Yoshimura H, Kinukawa N, Maruyama R, Tachibana M, Kohno H, Kubota H, Nagasue N. Metastatic lymph node size and colorectal cancer prognosis. J Am Coll Surg. 2005 Jan;200(1):20–8.

13. Yamaoka Y, Kinugasa Y, Shiomi A, Yamaguchi T, Kagawa H, Yamakawa Y, Furutani A, Numata M. Is it important to palpate lymph nodes in open surgery for colorectal cancer? Asian J Endosc Surg. 2017 May;10(2):143–7.

14. Yamaoka Y, Kinugasa Y, Shiomi A, Yamaguchi T, Kagawa H, Yamakawa Y, Numata M, Furutani A. Preoperative chemoradiotherapy changes the size criterion for predicting lateral lymph node metastasis in lower rectal cancer. Int J Colorectal Dis. 2017 Nov;32(11):1631–7.

15. Yamaoka Y, Kinugasa Y, Shiomi A, Yamaguchi T, Kagawa H, Yamakawa Y, Furutani A, Manabe S. The distribution of lymph node metastases and their size in colon cancer. Langenbecks Arch Surg. 2017 Dec;402(8):1213–21.

16. Hashiguchi Y, Muro K, Saito Y, Ito Y, Ajioka Y, Hamaguchi T, Hasegawa K, Hotta K, Ishida H, Ishiguro M, Ishihara S, Kanemitsu Y, Kinugasa Y, Murofushi K, Nakajima TE, Oka S, Tanaka T, Taniguchi H, Tsuji A, Uehara K, Ueno H, Yamanaka T, Yamazaki K, Yoshida M, Yoshino T, Itabashi M, Sakamaki K, Sano K, Shimada Y, Tanaka S, Uetake H, Yamaguchi S, Yamaguchi N, Kobayashi H, Matsuda K, Kotake K, Sugihiara K. Japanese Society for Cancer of the Colon and Rectum. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2019 for the treatment of colorectal cancer. Int J Clin Oncol. 2020 Jan;25(1):1–42.

17. Schrembs P, Martin B, Anthuber M, Schenkirsch G, Märkl B. The prognostic significance of lymph node size in node-positive colon cancer. PLoS One. 2018 Aug 10;13(8).
18. Cheong O, Oh ST, Kim BS, Yook JH, Kim JH, Im JT, Park GC. Large metastatic lymph node size, especially more than 2 cm: independent predictor of poor prognosis in node-positive gastric carcinoma. World J Surg. 2008 Feb;32(2):262–6.

19. Dhar DK, Kubota H, Kinukawa N, Maruyama R, Kyriazanos ID, Ohno S, Nagasue N. Prognostic significance of metastatic lymph node size in patients with gastric cancer. Br J Surg. 2003 Dec;90(12):1522–30.

20. Dhar DK, Tachibana M, Kinukawa N, Riruke M, Kohno H, Little AG, Nagasue N. The prognostic significance of lymph node size in patients with squamous esophageal cancer. Ann Surg Oncol. 2002 Dec;9(10):1010–6.

21. Yoshino T, Yamanaka T, Oki E, Kotaka M, Manaka D, Eto T, Hasegawa J, Takagane A, Nakamura M, Kato T, Munemoto Y, Takeuchi S, Bando H, Taniguchi H, Gamoh M, Shiozawa M, Mizushima T, Saji S, Maehara Y, Ohtsu A, Mori M. Efficacy and long-term peripheral sensory neuropathy of 3 vs 6 months of oxaliplatin-based adjuvant chemotherapy for colon cancer: The ACHIEVE phase 3 randomized clinical trial. JAMA Oncol. 2019;5:1574–81.

22. Grothey A, Sobrero AF, Shields AF, Yoshino T, Paul J, Taieb J, Souglakos J, Shi Q, Kerr R, Labianca R, Meyerhardt JA, Vernerey D, Yamanaka T, Boukovich I, Meyers JP, Renfro LA, Niedzwiecki D, Watanabe T, Torri V, Saunders M, Sargent DJ, Andre T, Iveson T. Duration of Adjuvant Chemotherapy for Stage III Colon Cancer. N Engl J Med. 2018 Mar;29(13):1177–88. 378(.

23. Greene FL, Stewart AK, Norton HJ. A new TNM staging strategy for node- positive (stage III) colon cancer: an analysis of 50,042 patients. Ann Surg. 2002 Oct;236(4):416–21.

24. Compton CC, Fielding LP, Burgart LJ, Conley B, Cooper HS, Hamilton SR, Hammond ME, Henson DE, Hutter RV, Nagle RB, Nielsen ML, Sargent DJ, Taylor CR, Welton M, Willett C. Prognostic factors in colorectal cancer. College of American Pathologists Consensus Statement 1999. Arch Pathol Lab Med. 2000 Jul;124(7):979–94.

25. Merkel S, Mansmann U, Papadopoulos T, Wittekind C, Hohenberger W, Hermanek P. The prognostic inhomogeneity of colorectal carcinomas Stage III: a proposal for subdivision of Stage III. Cancer. 2001 Dec 1;92(11):2754-9.

Figures
Figure 1. Overall survival

![Graph showing overall survival MLN, metastatic lymph node](image)

**Figure 1**

Overall survival MLN, metastatic lymph node
Figure 2. Recurrence-free survival

Recurrence-free survival MLN, metastatic lymph node