Recurrence risk factors in elderly patients with stage II colorectal cancer

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Abstract

Background: We investigated the risk factors for recurrence in high risk stage II colorectal cancer patients over 75 years old.
Methods: This study included 79 patients who underwent primary colorectal surgery at Minami Kyousai Hospital from January 2015 to June 2019. The inclusion criteria were as follows: (1) age over 75 years old, (2) histologically confirmed stage II colorectal adenocarcinoma after curative surgery, and (3) no other active malignancy. A Cox proportional hazards model was used to identify the risk factors for recurrence.
Results: The recurrence free survival rates at 1, 2, and 3 years after surgery were 92.6%, 78.8%, and 61.9%. The risk factors for recurrence were tumor location and lymph-node dissection.
Conclusion: This study revealed that left-sided colorectal cancer and under D2 dissection are risk factors for recurrence of stage II colorectal cancer in the elderly. Patients with these risk factors should be considered for adjuvant chemotherapy.

Keywords: Stage II colorectal cancer, risk factors of recurrence, elderly patients

Introduction

Colorectal cancer is a disease with a high frequency of morbidity and mortality. Over 1.8 million new colorectal cancer cases and 881,000 deaths are estimated to occur in 2018, accounting for about 1 in 10 cancer cases and deaths in the world. Colorectal cancer ranks third in terms of incidence but second in terms of mortality. In addition, colorectal cancer incidence has shown an increasing trend year by year. Complete resection is essential for curing colorectal cancer, but adjuvant chemotherapy is also considered in cases of advanced colorectal cancer. Adjuvant chemotherapy is recommended for patients with stage III and high-risk stage II colorectal cancer. Given positive findings from three large phase III trials, six months of adjuvant chemotherapy with fluoropyrimidines and oxaliplatin is the current worldwide standard of care for patients with stage III colon cancer. However, while the benefits of adjuvant chemotherapy have been clearly established for stage III colon cancer, the benefits in stage II colon cancer remain controversial.

Two phase III trials failed to demonstrate a survival benefit with adjuvant chemotherapy in stage II colon cancer11,12). However, several studies have shown that the benefits of adjuvant chemotherapy among patients with stage II colon cancer are limited to patients with high-risk features13-15). The risk factors for high-risk stage II colon cancer are defined in ASCO 2004 as <12 lymph nodes sampled, pT4 stage, perforation, poorly differentiated adenocarcinoma, mucinous carcinoma, and signet-ring cell carcinoma16); in the ESMO guidelines, the risk factors are <12 lymph nodes sampled, poorly differentiated tumor, vascular or lymphatic or perine-ural invasion, pT4 stage and clinical presentation with intestinal occlusion or perforation17). High-risk stage II colorectal cancer patients are treated with the same adjuvant chemotherapy as stage III patients.

Recently, the number of elderly patients with colorectal cancer has shown a marked increase compared with previous years. According to the Surveillance, Epidemiology, and End Results (SEER) database, approximately 70% of all colorectal cancer cases develop in patients over 65 years old, and about 40% of patients are over 75 years old. People ≥60 years old make up 12.3% of the global population, and by 2050, that number will...
rise to almost 22%\(^{(8)}\). However, a great deal of evidence is based on data obtained in non-elderly people <80 years old\(^{(9)}\). Therefore, the risk factors for recurrence in the elderly are not always the same as those indicated in the guidelines.

The present study clarified the risk factors for recurrence in elderly patients in order to reduce the unnecessary administration of adjuvant chemotherapy in elderly patients who are likely to experience chemotherapy-related adverse events.

**Patients and methods**

**Patients**

The study subjects were selected from the medical records of consecutive patients who underwent primary colorectal surgery at the Minami Kyousai Hospital from January 2015 to June 2019. The inclusion criteria were as follows: (1) age over 75 years old, (2) histologically confirmed stage II colorectal adenocarcinoma after curative surgery, and (3) no other active malignancy.

Tumors located in the cecum to the transverse colon were defined as right-sided cancers, and those located in the left colonic flexure to the rectum were defined as left-sided cancers.

**Surgical procedure and follow-up**

It was decided at the conference whether to perform open surgery or laparoscopic surgery. Complete mesocolic excision (CME) was performed in colon cancer procedures and total mesorectal excision (TME) was performed for rectal cancer procedures. Adequate resection margins were determined following JSSCR guidelines. D2 or D3 lymphadenectomies were performed in almost cases. Patients were followed up at the Minami Kyousai Hospital. The CEA and CA19-9 tumor marker levels were checked at least every three months for five years. Patients underwent a computed tomography (CT) every six months until five years after surgery.

**Evaluations and statistical analyses**

A Cox proportional hazards model was performed to identify the risk factors for recurrence. The recurrence-free survival (RFS) was defined as the period between colorectal surgery and recurrence or death, whichever came first. The data of the patients who did not experience an event were censored on the date of the final observation. RFS curves were calculated using the Kaplan-Meier method. P values of <0.05 were considered to indicate statistical significance. The survival data were obtained from hospital records. The R software program (v3.5.2) was used for all of the statistical analyses.

This study was approved by the Institutional Review Board (IRB) of the Minami Kyousai Hospital (approval number: epidemiological study 29-10-3).

**Results**

**General characteristics**

Seventy-nine patients were evaluated in the present study. The patient characteristics are described in Table 1. The median age was 81 (range: 75–90) years old. Forty-two patients were male, and 37 were female. Sixty-four patients had a primary colon tumor, and 15 had a primary rectal lesion.

Forty-five patients had right-sided cancer, and 34 had left-sided lesions. Sixty-nine patients were T3, seven were T4a, and three were T4b. Adjuvant chemotherapy was performed in nine patients.

**Surgical and pathological findings**

The operative details and pathological findings are summarized in Table 2. Tumors were located in the cecum in 6, in the ascending colon in 26, in the transverse colon in 13, in the descending colon in 5, in the sigmoid colon in 14, in the RS in 6, in the Ra in 6, and in the Rb in 3. Laparoscopic surgery was performed in 32 patients and open surgery in 47. Eight patients underwent ileocecal resection, 27 right hemicolectomy, 10 transverse colectomy, 6 descending colectomy, 12 sigmoidectomy, 7 high anterior resection, 3 low anterior resection, 4 Hartmann’s procedure, and 2 abdominoperitoneal resection. D3 lymph node dissection was performed in 67 patients. D1 or D2 dissection was performed in 12 patients. Five patients had fewer than 12 lymph nodes sampled, and 74 had at least 12 lymph nodes samples. Histologically, 71 patients were tub, while 8 were others. Lymphatic invasion was absent in 59 patients and present in 20. Vascular invasion was absent in 30 patients and present in 49.

**Table 1  General patient characteristics**

| Number of patients | Percentage (%) |
|--------------------|----------------|
| **Gender**         |                |
| Male               | 42             | 53.2           |
| Female             | 37             | 46.8           |
| **Location**       |                |
| Colon              | 64             | 81.0           |
| Rectum             | 15             | 19.0           |
| **Sideness**       |                |
| Right              | 45             | 57.0           |
| Left               | 34             | 43.0           |
| **T stage**        |                |
| T3                 | 69             | 87.3           |
| T4a                | 7              | 8.9            |
| T4b                | 3              | 3.8            |
| **N stage**        |                |
| N0                 | 79             | 100.0          |
| **Adjuvant chemotherapy** |            |
| Absent             | 70             | 88.6           |
| Present            | 9              | 11.4           |
The RFS and recurrence risk factors

RFS survival curves are shown in Fig. 1. After a median follow-up of 22 (range: 1.0–57.3) months, the 1-, 2-, and 3-year RFS rates were 92.6%, 78.8%, and 61.9%. The risk factors for recurrence are summarized in Table 3. A univariate analysis revealed that the tumor location, lymph-node dissection, and Neutrophil-to-Lymphocyte Ratio (NLR) were related to outcomes. On a multivariate Cox proportional-hazards regression analysis, the tumor location and lymph-node dissection were significant risk factors for recurrence.

Regarding the relationship between the location and recurrence risk factors, it has been reported that patients with left-sided colon cancer have a better prognosis than those with right-sided cancer. However, the results of this study showed that left-sided colorectal cancer was itself a risk factor for recurrence. In comparing the clinicopathological background characteristics, the rate of venous invasion in cases of left-sided colorectal cancer was higher than that in cases of right-sided cancer (right-sided 51.1% vs. left-sided 76.5%). There were no marked differences in other clinicopathological background characteristics between right and left-sided cancers.

Of note, there have been some reports that venous invasion is a risk factor for recurrence. Eeghen et al. examined whether or not extramural venous invasion in 184 patients with stage I and II colon cancer was a risk factor for recurrence using a caldesmon staining technique. They found that venous invasion was indeed a predictor of recurrence in stage I and II colon cancer. Horn et al. investigated the clinical data of 128 patients with rectal cancer. Neural invasion had the strongest association with local recurrences, whereas venous invasion was found to be the third-strongest independent predictor of metastasis, after the lymph node status and extent of local tumor infiltration. They concluded that checking for the presence of venous and neural invasion was a reliable way of predicting recurrences after radical resection of rectal cancer. The high rate of venous invasion in left-sided colorectal cancer patients may be a risk factor for recurrence. There were 10 instances of recurrences in the

### Table 2  Type of surgery and pathological findings

| Location       | Number of patients | Percentage (%) |
|----------------|--------------------|----------------|
| Cecum          | 6                  | 7.6            |
| Ascending      | 26                 | 32.9           |
| Transverse     | 13                 | 16.5           |
| Descending     | 5                  | 6.3            |
| Sigmoid        | 14                 | 17.7           |
| RS             | 6                  | 7.6            |
| Ra             | 6                  | 7.6            |
| Rb             | 3                  | 3.8            |

| Approach       | Number of patients | Percentage (%) |
|----------------|--------------------|----------------|
| Open           | 47                 | 59.5           |
| Laparoscopic   | 32                 | 40.5           |

| Procedure       | Number of patients | Percentage (%) |
|-----------------|--------------------|----------------|
| Ileocecal resection | 8                 | 10.1           |
| Right hemicolectomy  | 27                | 34.2           |
| Transverse colectomy   | 10               | 12.7           |
| Descending colectomy    | 6                 | 7.6            |
| Sigmoidectomy          | 12                | 15.2           |
| High anterior resection | 7                | 8.9            |
| Low anterior resection  | 3                 | 3.8            |
| Hartmann procedure     | 4                 | 5.1            |
| Abdominoperitoneal resection | 2 | 2.5 |

| Lymph node dissection | Number of patients | Percentage (%) |
|-----------------------|--------------------|----------------|
| ≤D2                   | 12                 | 15.0           |
| D3                    | 67                 | 85.0           |
| The number of lymph nodes sampling | | |
| <12                   | 5                  | 6.3            |
| ≥12                   | 74                 | 93.7           |

| Histological type    | Percentage (%) |
|----------------------|----------------|
| Tub                  | 71             |
| Others               | 8              |

| Lymphatic invasion   | Percentage (%) |
|----------------------|----------------|
| Absent               | 59             |
| Present              | 20             |

| Vascular invasion    | Percentage (%) |
|----------------------|----------------|
| Absent               | 30             |
| Present              | 49             |

Discussion

The present study clarified the risk factors for recurrence of stage II colorectal cancer in elderly patients. We found that left-sided colorectal cancer and under D2 dissection were risk factors for recurrence of stage II colorectal cancer in the elderly. The RFS rate was examined by the Kaplan-Meier method, and risk factors were subjected to univariate and multivariate analyses using the Cox hazard model. In the univariate analysis, the tumor location, lymph-node dissection and NLR were recurrence risk factors. In the multivariate analysis, the tumor location and lymph-node dissection were risk factors for recurrence.
present study. Of those 10 cases, 4 were in right-sided patients and 6 were in left-sided patients. Of the 4 cases of right-sided recurrence, 1 (25%) was under D2 dissection, whereas 2 of the 6 cases (33%) of left-sided recurrence were under D2 dissection. Poor dissection may increase the risk of recurrence in left-sided cancer, resulting in left-sided cancer being a risk factor for recurrence.

Regarding the relationship between lymph node dissection and recurrence risk factors, it has been reported that D3 dissection should be performed even in elderly colorectal cancer patients. Numata et al. investigated 378 patients with pathological stage II and III colon cancer who underwent primary resection with either D2 or D3 lymph node dissection using the propensity matching method. They reported that D3 lymph node dissection provided a better RFS than D2 lymph node dissection after primary resection for elderly patients with pathological stage II or III colon cancer. Takahashi et al. examined a surgical database of 2065 patients ≥80 years old who underwent surgery for colorectal cancer at 41 hospitals in Japan between 2003 and 2007. The patients were divided into groups according to the number of lymph nodes harvested. They reported that harvesting ≥12 lymph nodes provided a survival benefit in patients ≥80 years old with stage II or III colon cancer. Our results are consistent with these previous reports.

In the present study, while the NLR was included as a risk factor for recurrence in the univariate analysis, the multivariate analysis did not show it to be a risk factor for recurrence. Ding et al. evaluated whether or not the NLR predicted the risk of recurrence in patients with stage IIA colon cancer undergoing curative resection without adjuvant chemotherapy. A Cox’s regression analysis showed that an elevated NLR (>4) (hazard ratio, 4.88; P < 0.01)

### Table 3 Uni- and multivariate Cox proportional hazards analyses of the clinic-pathological factors for the recurrence-free survival

| Factors                          | No | Univariate analysis | Multivariate analysis |
|----------------------------------|----|---------------------|-----------------------|
|                                  |    | OR  | 95%CI       | P value | OR  | 95%CI       | P value |
| Gender                           |    |     |             |         |     |             |         |
| Female                           | 37 | 1.000 |           | 0.550          |     |             |         |
| Male                             | 42 | 1.336 | 0.517-3.457 |         |     |             |         |
| Location                         |    |     |             |         |     |             |         |
| Colon                            | 64 | 1.000 |           | 0.074          |     |             |         |
| Rectum                           | 15 | 2.394 | 0.918-6.246 |         |     |             |         |
| Location                         |    |     |             |         |     |             |         |
| Right side                       | 45 | 1.000 |           | 1.000          |     |             | 0.042  |
| Left side                        | 34 | 2.806 | 1.052-7.485 | 1.000 | 2.797 | 1.038-7.540 |         |
| Surgical approach                |    |     |             |         |     |             |         |
| Open                             | 47 | 1.000 |           | 0.891          |     |             |         |
| Laparoscopic                     | 32 | 1.069 | 0.414-2.762 |         |     |             |         |
| Lymph node dissection            |    |     |             |         |     |             |         |
| D3                               | 67 | 1.000 |           | 0.004          |     | 1.000 | 0.028          |
| ≤D2                              | 12 | 4.047 | 1.562-10.481| 1.000 | 3.102 | 1.038-8.503 |         |
| Number of lymph nodes sampling   |    |     |             |         |     |             |         |
| ≤12                              | 74 | 1.000 |           | 0.372          |     | 1.000 | 0.950          |
| <12                              | 5  | 1.960 | 0.448-8.576 |         |     |             |         |
| UICC T status                    |    |     |             |         |     |             |         |
| T4                               | 10 | 1.000 |           | 0.927          |     |             |         |
| T1-T3                            | 69 | 1.072 | 0.243-4.726 |         |     |             |         |
| Histological type                |    |     |             |         |     |             |         |
| Others                           | 8  | 1.000 |           | 0.998          |     |             |         |
| Tub                              | 71 | 78125000 | 0-inf     |         |     |             |         |
| Lymphatic invasion               |    |     |             |         |     |             |         |
| Absent                           | 59 | 1.000 |           | 0.060          |     |             |         |
| Present                          | 20 | 2.499 | 0.963-6.486 |         |     |             |         |
| Vascular invasion                |    |     |             |         |     |             |         |
| Present                          | 49 | 1.000 |           | 0.810          |     |             |         |
| Absent                           | 30 | 1.123 | 0.434-2.904 |         |     |             |         |
| Adjuvant Chemotherapy            |    |     |             |         |     |             |         |
| Present                          | 9  | 1.000 |           | 0.998          |     |             |         |
| Absent                           | 70 | 81967213 | 0-inf     |         |     |             |         |
| CEA level                        |    |     |             |         |     |             |         |
| ≤5.0 ng/mL                       | 45 | 1.000 |           | 0.169          |     |             |         |
| >5.0 ng/mL                       | 33 | 1.958 | 0.752-5.100 |         |     |             |         |
| CA19-9 level                     |    |     |             |         |     |             |         |
| >37.0 U/mL                       | 4  | 1.000 |           | 0.865          |     |             |         |
| ≤37.0 U/mL                       | 74 | 1.199 | 0.158-9.101 |         |     |             |         |
| NLR                              |    |     |             |         |     |             |         |
| ≤median                          | 34 | 1.000 |           | 0.037          |     | 1.000 | 0.137          |
| >median                          | 44 | 3.393 | 1.076-10.70 | 1.000 | 2.487 | 0.747-8.271 |         |

UICC: Union for International Cancer Control
NLR: Neutrophil Lymphocyte Rate
and fewer lymph nodes sampled (<15 lymph nodes; hazard ratio, 3.80; P < 0.05) were adverse prognostic factors for the RFS. Hongcai et al. performed a systematic literature search using PubMed, EMBASE, and the Cochrane Library databases to evaluate the prognostic value of the NLR in patients with colorectal cancer. They reported that a preoperative NLR might be an effective predictive biomarker of the prognosis in patients with colorectal cancer. If our study had included more subjects, the NLR might also have been found to be a risk factor for recurrence.

This study is limited by its retrospective observation of a small number of single-center cases. We would like to increase the number of cases and conduct further investigations in the future.

In conclusion, this study revealed that left-sided colorectal cancer and under D2 dissection were risk factors for recurrence of stage II colorectal cancer in the elderly. Patients with these risk factors should be considered for adjuvant chemotherapy.

ACKNOWLEDGMENTS:
Not applicable.

CONFLICT OF INTEREST STATEMENT:
None declared.

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