Original Article

Risk Factors for Recurrence in Stage III Colon Cancer after Curative Resection and 12 Cycles of Adjuvant mFOLFOX6

Yu-Zu Lin[1]
Hou-Hsuan Cheng[1]
Sheng-Chieh Huang[1,2]
Hung-Hsin Lin[1,2]
Chun-Chi Lin[1,2]
Yuan-Tzu Lan[1,2]
Shih-Ching Chang[1,2]
Huann-Sheng Wang[1,2]
Shung-Haur Yang[1,2,3]
Wei-Shone Chen[1,2]
Tzu-Chen Lin[1,2]
Jen-Kou Lin[1,2]
Jeng-Kai Jiang[1,2]
[1]*Division of Colon & Rectal Surgery, Department of Surgery, Taipei Veterans General Hospital,*
[2]*School of Medicine, National Yang Ming Chiao Tung University,*
[3]*National Yang Ming Chiao Tung University Hospital, Taipei, Taiwan*

Key Words
Colon cancer;
Stage III;
mFOLFOX6;
Recurrence;
Risk

Purpose. After curative resection followed by adjuvant chemotherapy, patients with stage III colon cancer presented with a spectrum of risk for recurrence. We believe that identifying these risk factors will help to stratify the patients for optimal treatment.
Methods. Patients with stage III colorectal cancer who underwent curative resection and adjuvant chemotherapy were identified from a prospectively constructed database at Taipei Veterans General Hospital between January 2006 and March 2015. Disease-free survival (DFS) was determined from the date of surgery to the date of recurrence. Covariates that were potentially related to five-year DFS were identified and analyzed using the Cox proportional hazard model.
Results. A total of 197 patients were included in the study. The median follow-up time of the study was 6.1 years (range, 0.6-13). A total of 56 (28.4%) and 17 (8.6%) patients experienced recurrence and death, respectively. Recurrence and death were observed in 53 (26.9%) and 11 (5.6%) patients within 5 years of surgery, five-year DFS and overall survival (OS) were 73.1% and 94.4%. In the multivariable Cox regression model, the number of metastatic lymph nodes equal to or more than 15 ($p = 0.02$), obstruction at initial presentation ($p = 0.03$), and duration of mFOLFOX6 greater than 38 weeks ($p < 0.01$) were significantly associated with recurrence within five years following surgery.
Conclusions. For patients with stage III colon cancer receiving curative resection, the number of metastatic lymph nodes equal to or more than 15, obstruction at initial presentation, and duration of chemotherapy greater than 38 weeks were identified as independent risk factors for decreased five-year disease-free survival after 12 cycles of adjuvant mFOLFOX6. Strategies should be formulated to avoid postponing the schedule of chemotherapy. Modification of adjuvant treatment is warranted in patients with the non-modifiable risk factors.
[*J Soc Colon Rectal Surgeon* (*Taiwan*) *2021;32:139-149*]

Stage III colorectal cancer accounts for 22-38% of all cases, based on the 8th edition of the American Joint Committee on Cancer (AJCC) staging system,[1] with a five-year disease-specific survival rate of 66-78%.[2-4] Recurrence in stage III colon cancer after potentially curative resection is believed to be secondary to the presence of micrometastases at the time of surgery. The purpose of adjuvant chemotherapy is to era-

Received: April 30, 2021. Accepted: July 26, 2021.
Correspondence to: Dr. Jeng-Kai Jiang, Division of Colon & Rectal Surgery, Department of Surgery, Taipei Veterans General Hospital, No. 201, Sec. 2, Shipai Rd., Beitou District, Taipei 11217, Taiwan. Tel: 886-2-2875-7544 ext. 110; Fax: 886-2-2875-7639; E-mail: jkjiang@vghtpe.gov.tw

dicate micrometastases, thereby increasing the possibility of cure. Six months of mFOLFOX6 and CAPOX are both considered as standard adjuvant therapies for stage III colon cancer.[5]

Much effort has been made to identify stage II colorectal cancer patients with a greater risk of recurrence and to ensure that adjuvant chemotherapy is beneficial for them. The risk factors for recurrence that have been endorsed by the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) include T4 disease, poorly differentiated histologic features, bowel obstruction or perforation, lymphovascular invasion, perineural invasion, and inadequate lymph node sampling (< 12 lymph nodes).[5,6] However, there is no clear evidence suggesting that these high-risk factors for poor prognosis also play a role in predicting the effects of adjuvant treatment. As for stage III colon cancer, the NCCN guidelines consider T4 and N2 diseases as risk factors for recurrence.[5] The role of the widely established and used risk factors for stage II colon cancer remains controversial, while molecular biomarkers for prediction are still under investigation.

In stage III colorectal cancer patients, 50% are cured by surgery alone, 20% are cured by additional adjuvant chemotherapy with either mFOLFOX6 or CAPOX, and 30% experienced recurrence.[7] Therefore, there is a clear need to establish prognostic markers that can identify patients who are at an increased risk for recurrence to individualize adjuvant treatment for patients with high-risk stage III disease. Numerous studies have attempted to identify the risk factors for both stage II and III colon cancer, but few have focused exclusively on stage III disease. Moreover, most of these studies have discussed only a single factor. Our aim, therefore, was to investigate the risk factors for recurrence in patients with stage III colon cancer after surgical resection and adjuvant treatment with mFOLFOX6.

Materials and Methods

Patients

We reviewed the clinical and pathologic records of 1035 patients with stage III colorectal cancer, surgically resected between January 2006 and March 2015, at the Taipei Veterans General Hospital. The exclusion criteria were patients with appendiceal cancer, rectal cancer; synchronous or metachronous colon cancer; and other malignancies, such as lung cancer, lymphoma, and prostate cancer, and those with colon cancer other than adenocarcinoma. We also excluded patients who did not receive adjuvant chemotherapy, who received adjuvant chemotherapy at another institute, who received adjuvant chemotherapy other than mFOLFOX6, who received less than 12 cycles of mFOLFOX6, and who received oral chemotherapy after 12 cycles of mFOLFOX6. Finally, a total of 197 patients were eligible for this study (Fig. 1).

Clinical and pathologic features

We obtained data on sex, age at diagnosis, tumor location, tumor stage (based on AJCC TNM staging system[1]), total number of lymph nodes examined, tumor histology, tumor differentiation, lymphovascular and perineural invasion, isolated cancer nodule in the mesentery, lymphocytic reaction, tumor invasion pattern, preoperative carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9), and obstruction and perforation at diagnosis.

A two-tiered grading system was used for colon cancer based on the recommendations of the AJCC. Distal third of transverse colon was used as the distinction between right- and left-sided colon cancer.[8] Mucinous adenocarcinoma, by definition, is a subtype of colorectal cancer in which more than 50% of the tumor consists of extracellular mucinous components.[9] Lymphocytic reaction was interpreted by pathologists. It included peritumoral lymphocytic reaction, Crohn's-like reaction, and tumor-infiltrating lymphocytes. The normal range of CEA was defined as 0-4.9 ng/mL and that of CA 19-9 was defined as 0-37 U/mL.

Chemotherapy

All patients initially received mFOLFOX6 as the standard adjuvant chemotherapy, which consisted of oxaliplatin 85 mg/m^2 and leucovorin 400 mg/m^2 de-

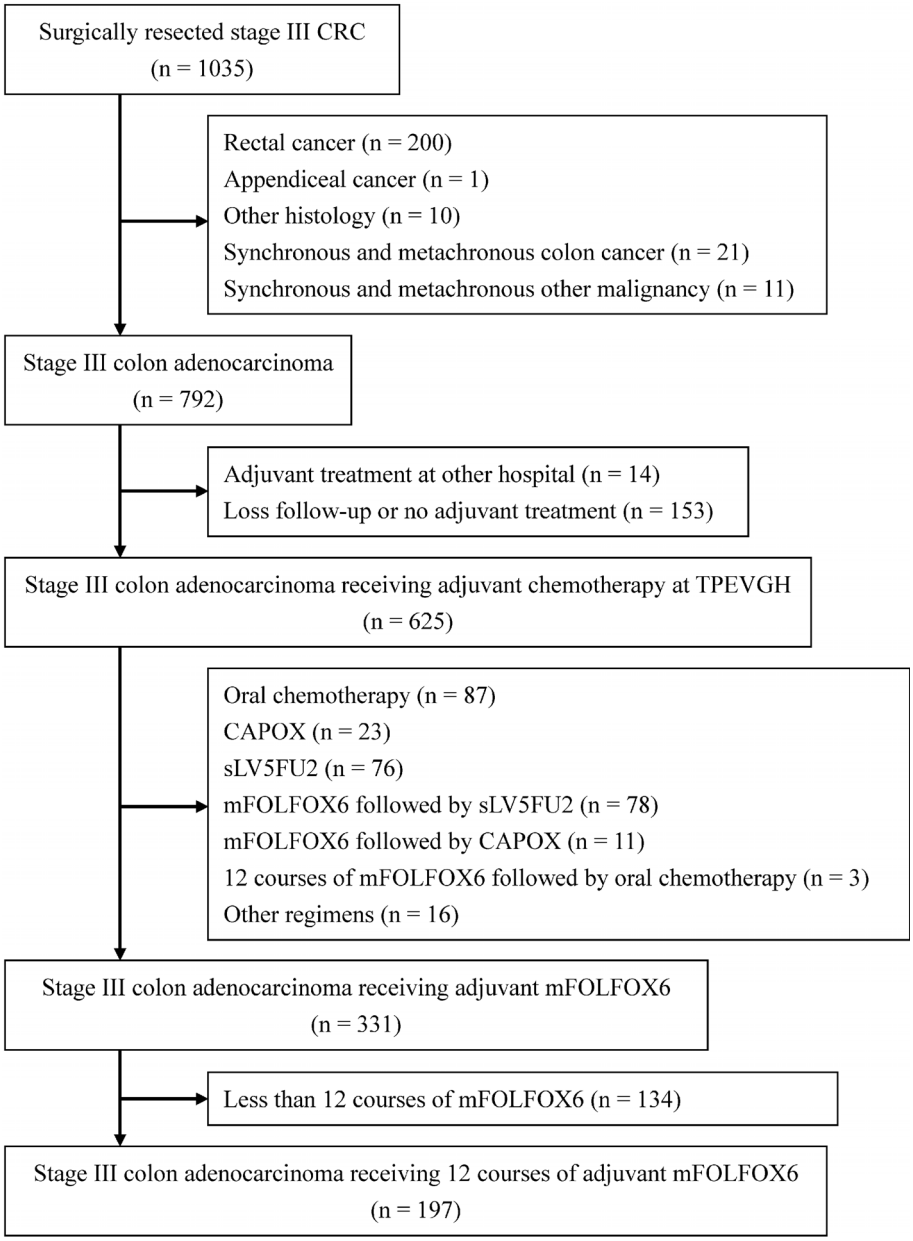

Fig. 1. Flow diagram of the study. Abbreviations: CRC, colorectal cancer; TPEVGH, Taipei Veterans General Hospital.

livered as a 2-hour intravenous infusion, followed by 5-fluorouracil 400 mg/m^2 as a bolus and 2400 mg/m^2 as a 46-hour intravenous infusion every two weeks for a total of 12 cycles. The treating physicians adjusted the dose and interval of 5-fluorouracil, leucovorin, and oxaliplatin as and if patients developed intolerance to the standard regimen. The type and degree of adverse events and the range of dosage modifications were determined by the treating physicians.

Follow-up

The patients were followed up until March 2020. The standard follow-up was scheduled once every three months for the first two years after surgery, followed by once every six months for three years, and then it was scheduled annually. The interval and methods of examination, including CEA, CA 19-9, colonoscopy, abdominal and chest computed tomography

(CT), abdominal ultrasound, and chest radiography, depended on the clinician's judgment and preference. All recurrences at both local (anastomotic and regional) and distant metastases were included. The primary outcome was disease-free survival (DFS), which was determined from the date of surgery to the date of recurrence. Deaths attributed to other causes, survival without recurrence, and loss of follow-up were treated by censoring. Overall survival (OS) was calculated and determined from the date of surgery to the date of death from any causes.

Statistics

Continuous variables were summarized as mean ± standard deviation (SD) or median (range). Categorical variables were summarized as numbers and percentages. We used univariable Cox proportional hazard model to identify covariates that were potentially related to five-year DFS. The covariates that displayed a p value of < 0.2 were entered into a multivariable Cox model. Statistical significance was set at $p < 0.05$. All analyses were performed using SPSS software (IBM SPSS Statistics, version 23).

Results

The median age of the patients was 61 years (range, 27-88). The median interval between surgery and the initiation of mFOLFOX6 was 3.9 weeks (range, 1.7-17.3). The median duration of the 12 cycles of mFOLFOX6 was 30 weeks (range, 24-58 weeks). The median follow-up time of the study was 6.1 years (range, 0.6-13). The median follow-up time for 141 patients without recurrence was 7 years (range, 0.8-13). During the last follow-up, 56 (28.4%) patients had experienced recurrence at a median time of 1.5 years (range, 0.6-6.9) after surgery. Three patients experienced recurrence after more than 5 years (6.1, 6.8, and 6.9 years) of surgery, with sites of recurrence involving the liver (n = 1), bone (n = 1), and distant lymph nodes (n = 2). Five-year DFS of the study population was 73.1%, with sites of recurrence including local recurrence (n = 4), liver (n = 18), lung (n = 8), distant lymph nodes (n = 10), peritoneum (n = 14), bone (n = 4), ovary (n = 6), and spleen (n = 1). Eleven patients had recurrence at more than one site. Five-year OS was 94.4%.

Patients with pT4, pN2, the number of metastatic lymph nodes equal or more than 15, perineural invasion, obstruction, or duration of mFOLFOX6 more than 38 weeks had a higher risk of recurrence within five years after surgery in the univariable analysis ($p < 0.05$) (Table 1). In addition to the aforementioned factors, isolated cancer nodules in the mesentery, lymphocytic reaction, and interval between surgery and mFOLFOX6 more than 7 weeks were identified as potential risk factors by univariable analysis ($p < 0.2$). Overall, eight factors were included in the multivariable Cox proportional hazards model (Table 2). Multivariable analysis identified the number of metastatic lymph nodes equal to or more than 15 (hazard ratio [HR], 4.23; 95% confidence interval [CI], 1.25-14.32; $p = 0.02$), obstruction at initial presentation (HR, 2.53; 95% CI, 1.10-5.83; $p = 0.03$), and duration of mFOLFOX6 more than 38 weeks (HR, 3.02, 95% CI, 1.45-6.31; $p < 0.01$) as independent risk factors (Fig. 2).

The hazard ratio of patients with each-metastatic lymph node increase was shown in Table 3. The median number of metastatic lymph nodes was 3 (range, 0-21). Two patients had N1c without positive lymph nodes. The median number of harvested lymph nodes was 21 (range, 6-121). The patient who had 121 lymph nodes in the specimen underwent total colectomy. The cut off number of metastatic lymph nodes was determined to be 15 because it was the only value that showed significant difference in hazard ratio ($p < 0.05$) after entering all the numbers of metastatic lymph nodes with $p < 0.2$ into multivariable Cox model.

Discussion

To the best of our knowledge, the present study is the first to examine the risk factors for recurrence in stage III colon cancer following surgical resection and administration of 12 cycles of adjuvant mFOLFOX6. The five-year DFS of the study population was 73.1%,

Table 1. Univariable Cox proportional hazard model for factors associated with recurrence

Variable	HR (95% CI)	*p* value
Age at surgery (10-year increase)	1.02 (0.99-1.04)	0.21
Gender		
Male	1.0 (reference)	
Female	1.10 (0.64-1.89)	0.73
Location		
Right	1.0 (reference)	
Left	0.73 (0.42-1.26)	0.26
pT		
pT1	1.0 (reference)	
pT2	1.65 (0.15-18.24)	0.68
pT3	2.25 (0.31-16.47)	0.42
pT4	4.61 (0.61-34.82)	0.14
pT		
pT1-3	1.0 (reference)	
pT4	2.16 (1.20-3.88)	0.01
pN		
pN1	1.0 (reference)	
pN2	2.04 (1.19-3.50)	0.01
Metastatic lymph nodes		
< 15	1.0 (reference)	
≥ 15	4.98 (1.55-16.0)	0.01
Sampled lymph nodes		
< 12	1.0 (reference)	
≥ 12	0.81 (0.38-1.72)	0.59
Histologic differentiation [a]		
Low grade	1.0 (reference)	
Hight grade	1.42 (0.76-2.65)	0.27
Mucinous carcinoma		
No	1.0 (reference)	
Yes	1.06 (0.33-3.38)	0.93
Lymphovascular invasion		
No	1.0 (reference)	
Yes	1.33 (0.79-2.28)	0.3
Perineural invasion		
No	1.0 (reference)	
Yes	2.54 (1.36-4.76)	< 0.01
Isolated cancer nodule in mesentery		
No	1.0 (reference)	
Yes	2.15 (0.77-5.97)	0.14
Lymphocytic reaction		
No	1.0 (reference)	
Yes	0.54 (0.25-1.14)	0.10
Infiltrative invasion pattern		
No	1.0 (reference)	
Yes	0.95 (0.38-2.38)	0.91
Pre-OP CEA [a]		
< 5	1.0 (reference)	
≥ 5	1.28 (0.69-2.37)	0.44
Pre-OP CA-199 [a]		
≤ 37	1.0 (reference)	
> 37	1.17 (0.58-2.39)	0.66
Obstruction		
No	1.0 (reference)	
Yes	2.42 (1.09-5.36)	0.03
Interval between surgery and mFOLFOX6 (week) [a]		
≤ 7	1.0 (reference)	
> 7	1.95 (0.7-5.41)	0.19
Adjuvant mFOLFOX6 duration (week) [a]		
≤ 38	1.0 (reference)	
> 38	3.19 (1.63-6.22)	< 0.01

DFS, disease free survival.
[a] Sample size for histologic differentiation (n = 194), pre-OP CEA (n = 180), pre-OP CA 19-9 (n = 176), interval between surgery and mFOLFOX6 (n = 196), and mFOLFOX6 duration (n = 195).

Table 2. Multivariable Cox proportional hazard model for factors associated with recurrence

Variable	HR (95% CI)	*p* value
pT		
pT1-3	1.0 (reference)	
pT4	1.54 (0.82-2.87)	0.18
Metastatic lymph nodes		
< 15	1.0 (reference)	
≥ 15	4.23 (1.25-14.32)	0.02
Perineural invasion		
No	1.0 (reference)	
Yes	1.69 (0.86-3.33)	0.13
Isolated cancer nodule in mesentery		
No	1.0 (reference)	
Yes	2.45 (0.83-7.23)	0.10
Lymphocytic reaction		
No	1.0 (reference)	
Yes	0.65 (0.30-1.39)	0.27
Obstruction		
No	1.0 (reference)	
Yes	2.53 (1.10-5.83)	0.03
Interval between surgery and mFOLFOX6 (week)		
≤ 7	1.0 (reference)	
> 7	1.59 (0.54-4.67)	0.40
Adjuvant mFOLFOX6 duration (week)		
≤ 38	1.0 (reference)	
> 38	3.02 (1.45-6.31)	< 0.01

HR, hazard ratio.
Sample size: 195 patients.

which is similar with the results of previous studies.[2,3] Most recurrences developed within the first two years after surgery. The multivariable Cox proportional hazard model showed that the number of metastatic lymph nodes equal to or greater than 15, obstruction at initial presentation, and duration of mFOLFOX6 more than 38 weeks were associated with a higher recurrence rate.

The number of metastatic lymph nodes is generally regarded as a high-risk factor in stage III colon cancer, and six months of adjuvant CAPOX or mFOLFOX6 is suggested for pN2 as a category 1 recommendation in the NCCN guideline.[5] The cut off value of metastatic lymph nodes between N1 and N2 is 4. Although variable numbers of metastatic lymph nodes showed increased recurrence risk in the univariable analysis in our study, only the number 15 and 16 were independent risk factors when constructing multivariable Cox model. It has been shown that higher number of metastatic lymph nodes was a stronger predictor for higher risk of recurrence in stage III patients after adjusting for chemotherapy. Each one-node increase in the number of positive lymph nodes was associated with 24% increased risk of 5-year DFS.[10] Our results suggest that greater number of metastatic lymph nodes increase the risk of recurrence even after chemotherapy, especially when metastatic lymph nodes are equal to or more than 15.

On the other hand, the number of harvested lymph nodes was not significantly associated with the risk of recurrence in the present study population. Many studies have found that the total number of lymph nodes in the specimen influences survival in both stage II and III diseases,[11-13] while several other studies have not demonstrated such an association.[14,15] The mechanism of potentially improved survival in patients with higher retrieved total lymph nodes remains to be fully elucidated. It has been postulated that improved sur-

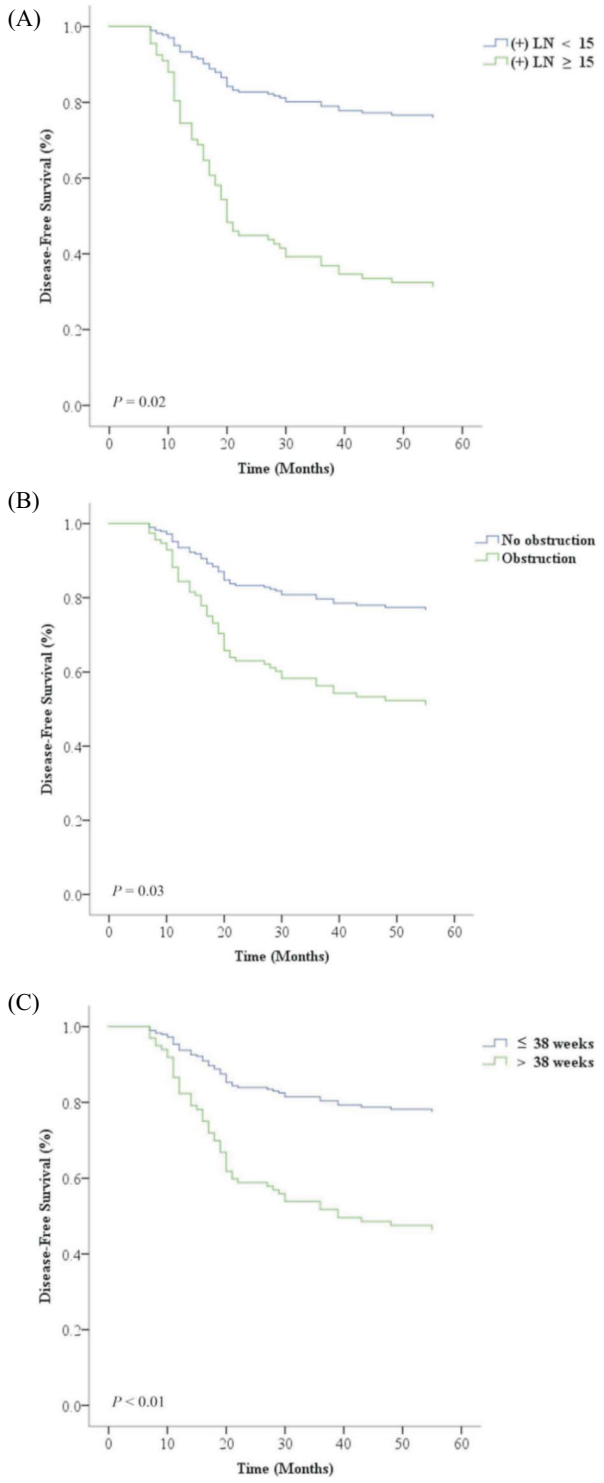

Fig. 2. Disease-free survival curve using multivariate Cox proportional hazard model. (A) Survival curve of patients with less and more than 15 metastatic lymph nodes. (B) Survival curve of patients with and without obstruction. (C) Survival curve of patients receiving 12 cycles of mFOLFOX6 with duration less and more than 38 weeks.

Table 3. Cumulative percentage of patients with different numbers of metastatic lymph nodes

No. of metastatic lymph nodes	n (%)	HR (95% CI)	*p*
0 [a]	2 (1.0)	NA	NA
1	53 (26.9)	0.17 (0.04-0.07)	0.01
2	37 (18.8)	1.06 (0.57-1.95)	0.86
3	28 (14.2)	1.77 (1.00-3.12)	0.04
4	21 (10.7)	1.99 (1.16-3.41)	0.01
5	11 (5.6)	2.10 (1.22-3.61)	0.01
6	15 (7.6)	2.01 (1.15-3.53)	0.01
7	8 (4.1)	2.46 (1.35-4.48)	< 0.01
8	3 (1.5)	2.35 (1.21-4.56)	0.01
9	6 (3.0)	2.79 (1.43-5.42)	< 0.01
10	3 (1.5)	2.04 (0.87-4.77)	0.10
11	2 (1.0)	2.18 (0.87-5.47)	0.10
13	1 (0.5)	2.25 (0.81-6.23)	0.12
14	3 (1.5)	2.73 (0.98-7.57)	0.05
15	2 (1.0)	4.98 (1.55-16.0)	0.01
16	1 (0.5)	40.49 (8.06-203.55)	< 0.01
21	1 (0.5)	NA	NA

NA, not applicable.
[a] Two patients had N1c without metastatic lymph nodes.

vival may be derived from stage migration, such that a more accurate pN stage could subsequently guide appropriate adjuvant treatment. However, extensive lymph node dissection is also correlated with improved survival in stage III patients.[11-13] This association may reflect that a higher number of harvested lymph nodes act as a marker of other factors, such as the quality of surgical resection, pathologic evaluation, patient comorbidities, and tumor biologic variability.[12,14] Such differences could contribute towards the lack of association between the total lymph node count and survival in our study.

Obstruction at initial presentation is also an independent risk factor for recurrence in stage III patients who have received 12 cycles of mFOLFOX6. The sites of recurrence within five years included the lungs (n = 2), distant lymph nodes (n = 2), peritoneum (n = 2), bone (n = 1), ovary (n = 1), and spleen (n = 1). Obstruction has been previously demonstrated to be a prognostic factor for stage II and III patients in multiple studies, while there were mixed results when discussing stage II and III populations individually.[16-18] Mixed data were obtained on the risk for recurrent sites, including local, peritoneal, and distant meta-

stases. The mechanism of recurrence of obstructive colon cancer remains unclear. It was postulated that these patients may have micrometastases at initial presentation and decreased quality of surgery due to emergent operation, thus leading to a higher risk of both local and distant metastases. The increased risk persisted even after 12 cycles of mFOLFOX6 in this study, and all patients presented with distant metastases when recurrence was identified. There was no pT4b disease in patients with obstruction who subsequently developed recurrence, which implied that all these colon tumors were resectable, contributing to the lack of local recurrence.

Duration of mFOLFOX6 was suggested to be 12 cycles in 24 weeks for stage III patients.[5] Our study revealed that delivering 12 cycles of mFOLFOX6 within a duration greater than 38 weeks was associated with decreased 5-year DFS. The reasons of the 19 patients (9.6%) who had prolonged duration of chemotherapy included neutropenia (n = 4), wedge resection of a lung nodule (n = 1), and unknown causes based on the medical records and laboratory tests (n = 14). Relative dose intensity (RDI), defined as the amount of a drug actually administered to the amount planned for a fixed time period, had been demonstrated to be associated with survival across different types and stages of solid organ cancers,[19,20] including stage III colon cancer.[21] Because the dose of each cycle of the chemotherapy drugs cannot be fully obtained in our study, the duration of a fixed number of chemotherapy cycles was used as an indicator for compliance. As a result, management for toxicities is important to improve the risk of recurrence. For dose-limiting neutropenia, early initiation of granulocyte colony-stimulating factor (G-CSF) may be an option. The rate of FOLFOX-related neutropenia, defined as < 1500 neutrophils/mcL, was reported to be 39-49% in the patients with stage III colon cancer.[22] Although there was no data for the impact of G-CSF on RDI or survival in stage III colon cancer, all-cause mortality is reduced in a meta-analysis of randomized controlled trials including solid organ cancers and lymphomas at all stages.[23] It is also important to explain the adjuvant mFOLFOX6 with the patients thoroughly to keep them adhered to chemotherapy as scheduled.

Beyond pN staging and obstruction, other prognostic features were known to influence the risk of recurrence for stage III patients in some studies, such as pT4, histologic differentiation, lymphovascular invasion, perineural invasion, lymphocytic reaction, preoperative CEA, and interval between surgery and chemotherapy.[24-33] Our study showed a trend for higher recurrence risk in patients with pT4 or perineural invasion in univariable analysis; however, these features were not independent factors in the multivariable model. Overall, our findings suggest that 12 cycles of mFOLFOX6 may be sufficient to diminish the effects of these risk factors.

Although the survival benefits of mFOLFOX6 have been well documented previously, the adverse effects of cumulative dose-dependent neurotoxicity could limit the cycles and prolong the duration of chemotherapy delivered to the patients. Among 625 patients with stage III colon cancer who received adjuvant chemotherapy at the Taipei Veterans General Hospital between January 2006 and March 2015, only 197 patients completed 12 cycles of mFOLFOX6. Several patients received CAPOX (n = 23), while some patients received oral tegafur/uracil or capecitabine alone (n = 87), owing to the patient's decision, old age, or comorbidities after thorough explanation. Others received sLV5FU2 (n = 76) because oxaliplatin was not covered by the National Health Insurance in Taiwan until February 2009. Some patients received regimens such as FOLFIRI, FOLFIRI combined with target therapy, mFOLFOX6 combined with target therapy, and 12 cycles of mFOLFOX6 followed by oral chemotherapy (n = 19) between 2006 and 2010. Of the remaining 420 patients who initially received mFOLFOX6, 78 patients had chemotherapy adjusted as sLV5FU2 due to patient intolerance, 134 patients did not complete the 12 cycles of mFOLFOX6 either due to patient's intolerance or based on the physician's judgment, and 11 patients had chemotherapy adjusted for CAPOX based on patient discomfort or consideration. These findings suggested that the toxicities associated with mFOLFOX6 could compromise compliance with adjuvant treatment, which is in accordance with previous observations.[34-36]

There are several limitations. Our study did not in-

clude molecular markers, such as microsatellite instability, BRAF, and KRAS. Although BRAF and KRAS mutations have been found to be associated with a poor prognosis in patients with preserved mismatch repair in previous studies,[37,38] these factors were not evaluated for every patient in our institute until 2014. In addition, the sample size in our study was small. The number of variables included in the multivariable Cox proportional hazard model was eight, which was greater than 10% of the events, i.e., recurrence within five years after surgery. It has been suggested that at least 10 events need to be observed per covariate to be included in the model.[39] Thus, the power of our multivariable analysis was limited.

Conclusion

For patients with stage III colon adenocarcinoma receiving curative resection, the number of metastatic lymph nodes equal to or more than 15, obstruction at initial presentation, and duration of chemotherapy more than 38 weeks, were identified as independent risk factors for decreased five-year DFS after 12 cycles of mFOLFOX6. Strategies should be formulated to avoid postponing the schedule of chemotherapy. Modification of adjuvant treatment is warranted in patients with the non-modifiable risk factors.

Acknowledgements

The study materials were retrieved from the database constructed by the Division of Colon and Rectal Surgery, Department of Surgery, Taipei Veterans General Hospital.

Source of Financial Support

None.

References

1. Jessup JM, et al. Colon and Rectum. In: M. B. Amin, Eds. AJCC Cancer Staging Manual. 8th. Chicago: Springer, 2017: 251.
2. Siegel RL, et al. Colorectal cancer statistics, 2020. *CA Cancer J Clin* 2020;70:145-64.
3. Brouwer NPM, et al. An overview of 25 years of incidence, treatment and outcome of colorectal cancer patients. *Int J Cancer* 2018;143:2758-66.
4. Metwally IH, et al. Epidemiology and survival of colon cancer among Egyptians: a retrospective study. *Journal of Coloproctology* 2018;38:24-9.
5. N. C. C. Network. Colon Cancer (Version 4. 2020) June 27, 2020; Available from: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf.
6. Labianca R, et al. Early colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013;24 Suppl 6:vi64-72.
7. Auclin E, et al. Subgroups and prognostication in stage III colon cancer: future perspectives for adjuvant therapy. *Ann Oncol* 2017;28:958-68.
8. Baran B, et al. Difference between left-sided and right-sided colorectal cancer: a focused review of literature. *Gastroenterology Res* 2018;11:264-73.
9. SR H, FT B, BP. Carcinoma of the colon and rectum. In: B. FT, C. F, H. RH, and T. ND, Eds. WHO classification of tumours of the digestive system. 4. Lyon: IARC, 2009:134-46.
10. Tsikitis VL, et al. Predictors of recurrence free survival for patients with stage II and III colon cancer. *BMC Cancer* 2014; 14:336.
11. Chen SL, Bilchik AJ. More extensive nodal dissection improves survival for stages I to III of colon cancer: a population-based study. *Ann Surg* 2006;244:602-10.
12. Chang GJ, et al. Lymph node evaluation and survival after curative resection of colon cancer: systematic review. *J Natl Cancer Inst* 2007;99:433-41.
13. Parsons HM, et al. Association between lymph node evaluation for colon cancer and node positivity over the past 20 years. *JAMA* 2011:1089-97.
14. Ren JQ, et al. Prognostic value of the lymph node ratio in stage III colorectal cancer. *Chinese Journal of Cancer* 2012; 31:241-7.
15. Wong SL, et al. Hospital lymph node examination rates and survival after resection for colon cancer. *JAMA* 2007:2149-54.
16. Katoh H, et al. Prognostic significance of preoperative bowel obstruction in stage III colorectal cancer. *Ann Surg Oncol* 2011;18:2432-41.
17. Cortet M, et al. Patterns of recurrence of obstructing colon cancers after surgery for cure: a population-based study. *Colorectal Dis* 2013;15:1100-6.
18. Dahdaleh FS, et al. Obstruction predicts worse long-term outcomes in stage III colon cancer: a secondary analysis of the N0147 trial. *Surgery* 2018;164:1223-9.
19. Lyman GH. Impact of chemotherapy dose intensity on cancer patient outcomes. *Journal of the National Comprehensive*

Cancer Network 2009;7:99-108.
20. Nielson CM, et al. Relative dose intensity of chemotherapy and survival in patients with advanced stage solid tumor cancer: a systematic review and meta-analysis. *Oncologist* 2021.
21. Aspinall SL, et al. Adjuvant chemotherapy for stage III colon cancer: relative dose intensity and survival among veterans. *BMC Cancer* 2015;15:62.
22. Gotfrit J, et al. Chemotherapy-induced neutropenia with FOLFOX in the adjuvant treatment of colorectal cancer. *Journal of Clinical Oncology* 2020;38:38.
23. Lyman GH, et al. The impact of the granulocyte colony-stimulating factor on chemotherapy dose intensity and cancer survival: a systematic review and meta-analysis of randomized controlled trials. *Ann Oncol* 2013;24:2475-84.
24. Snaebjornsson P, et al. pT4 stage II and III colon cancers carry the worst prognosis in a nationwide survival analysis. Shepherd's local peritoneal involvement revisited. *Int J Cancer* 2014;135:467-78.
25. Greene FL, Stewart Ak Fau - Norton HJ, Norton HJ. A new TNM staging strategy for node-positive (stage III) colon cancer: an analysis of 50,042 patients. *Ann Surg* 2002;236:416-21.
26. Betge J, et al. Intramural and extramural vascular invasion in colorectal cancer: prognostic significance and quality of pathology reporting. *Cancer* 2012;118:628-38.
27. Hogan J, et al. Lymphovascular invasion: a comprehensive appraisal in colon and rectal adenocarcinoma. *Dis Colon Rectum* 2015;58:547-55.
28. Liebig C, et al. Perineural invasion is an independent predictor of outcome in colorectal cancer. *J Clin Oncol* 2009;27:5131-7.
29. Huh JW, et al. Prognostic significance of lymphovascular or perineural invasion in patients with locally advanced colorectal cancer. *Am J Surg* 2013;206:758-63.
30. Prall F, et al. Prognostic role of CD8+ tumor-infiltrating lymphocytes in stage III colorectal cancer with and without microsatellite instability. *Hum Pathol* 2004;35:808-16.
31. Kim CG, et al. Preoperative serum carcinoembryonic antigen level as a prognostic factor for recurrence and survival after curative resection followed by adjuvant chemotherapy in stage III colon cancer. *Ann Surg Oncol* 2017;24:227-35.
32. Klein M, et al. Improved survival with early adjuvant chemotherapy after colonic resection for stage III colonic cancer: a nationwide study. *J Surg Oncol*. 2015;112:538-43.
33. Park D, et al. Analysis of reduced-dose administration of oxaliplatin as adjuvant FOLFOX chemotherapy for colorectal cancer. *Ann Surg Treat Res* 2018;94:196-202.
34. Grothey A, et al. Duration of adjuvant chemotherapy for stage III colon cancer. *N Engl J Med* 2018;378:1177-88.
35. Loree JM, et al. Survival impact of CAPOX versus FOLFOX in the adjuvant treatment of stage III colon cancer. *Clin Colorectal Cancer* 2018;17:156-63.
36. Argyriou AA. Updates on oxaliplatin-induced peripheral neurotoxicity (OXAIPN). *Toxics* 2015;3:187-97.
37. Taieb J, et al. Prognostic effect of BRAF and KRAS mutations in patients with stage III colon cancer treated with leucovorin, fluorouracil, and oxaliplatin with or without cetuximab: a post hoc analysis of the PETACC-8 trial. *JAMA Oncol* 2016;2:643-53.
38. Sinicrope FA, et al. Molecular markers identify subtypes of stage III colon cancer associated with patient outcomes. *Gastroenterology* 2015;148:88-99.
39. Peduzzi P, et al. Importance of events per independent variable in proportional hazards regression analysis II. Accuracy and precision of regression estimates. *Journal of Clinical Epidemiology* 1995;48:1503-10.

原　著

第三期大腸癌經腫瘤切除及輔助性化學治療後復發的危險因子

林育如[1]　鄭厚軒[1]　黃聖捷[1,2]　林宏鑫[1,2]　林春吉[1,2]　藍苑慈[1,2]　張世慶[1,2]
王煥昇[1,2]　楊純豪[1,2,3]　陳維熊[1,2]　林資琛[1,2]　林楨國[1,2]　姜正愷[1,2]

[1]臺北榮民總醫院　外科部　大腸直腸外科
[2]國立陽明交通大學　醫學系　外科學科
[3]國立陽明交通大學附設醫院

目的　第三期大腸癌經過手術切除及輔助性化學治療後，仍有部分的病人復發。辨識影響復發的危險因子可能協助病人得到相對應的治療。

方法　研究對象為第三期大腸癌的病人，自 2006 年一月至 2015 年三月，於臺北榮民總醫院接受大腸腫瘤切除手術及完整輔助性化學治療 (mFOLFOX6)。無病存活率定義為手術日至復發日。我們以 Cox proportional hazard model 找出可能會影響無病存活率的共變項，並進行多變數分析。

結果　合乎研究定義的病人共 197 位。病人追蹤的時間中位數為 6.1 年 (範圍：0.6~13)。總計 56 位 (28.4%) 病人發生復發，17 位 (8.6%) 病人死亡；其中五年內復發之病人共 53 位 (26.9%)，死亡之病人共 11 位 (5.6%)，五年無病存活率為 73.1%，五年整體存活率為 94.4%。經多變項 Cox model 分析後，與術後五年內復發有顯著相關的因子為淋巴結轉移數量大於或等於 15 個 ($p = 0.02$)、腫瘤合併阻塞 ($p = 0.03$)、接受 mFOLFOX6 的時間超過 38 周 ($p < 0.01$)。

結論　第三期大腸癌的病人經手術切除及 12 次輔助性 mFOLFOX6 後，淋巴結轉移數量大於或等於 15 個、腫瘤合併阻塞、接受 mFOLFOX6 的時間超過 38 周仍為降低五年無病存活率的獨立危險因子。以 mFOLFOX6 作為輔助性化學治療時，需對會造成延遲每一次化學治療的原因作出相對應的策略。而針對病人合併有無法被人為改變的危險因子，可能須調整輔助性化學治療的方式。

關鍵詞　大腸癌、第三期、輔助性化學治療、復發、風險。