*Original Article*

# Predictive Factors and Prognosis of Stage I-III Colon Cancer Patients According to Early Recurrence Time after Curative Resection

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***Key Words***
Colorectal cancer;
Curative resection;
Early recurrence;
Recurrence factors

***Purpose.*** Colorectal cancer poses a significant public health issue, with increasing incidence rates globally in recent decades. Surgical resection remains the primary treatment for stage I-III colon cancer, but a portion of these patients experience recurrence postoperatively. This study aimed to investigate factors predicting recurrence postcurative surgery to determine high-risk patients who could benefit from more intensive follow-up.
***Methods.*** This retrospective study included patients who underwent curative resection for stage I-III colon cancer from January 2017 to December 2019. Data on patient demographics, surgical details, pathological findings, and molecular markers were collected from two hospital databases. The study reviewed the timing and location of recurrences, assessing patients at 6 months, 1 year, and 2 years postoperatively.
***Results.*** A total of 132 patients were analyzed, predominantly male (61.36%), with an average age of 64.31 years. The follow-up averaged 48.38 months. Within two years postoperatively, 76.5%, 45.4%, and 15.9% of patients experienced a recurrence within 2 years, 1 year, and 6 months, respectively. Factors, such as high postoperative carcinoembryonic antigen levels and poor tumor differentiation, were significantly associated with higher recurrence rates and shorter overall survival, with a median of 51.65 months.
***Conclusion.*** The results indicate that patients with elevated carcinoembryonic antigen levels and poorly differentiated tumors postoperatively are particularly susceptible to early recurrence and demonstrate poorer long-term survival. Therefore, these patients should be considered for intensified surveillance post-resection to enable timely recurrence detection and potentially improve survival outcomes.

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Colorectal cancer (CRC) is the third most prevalent tumor in both sexes, making it one of the most prevalent malignancies.[1] According to CRC treatment guidelines, resection surgery, neoadjuvant or adjuvant chemotherapy, and radiotherapy are the most current recommended approaches for managing CRC. The cancer stage and patient-specific considerations primarily influenced the selection of management st-

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rategy. However, resection surgery is typically indicated across nearly all disease stages.[2]

Curative surgery remains the mainstay of treatment for patients diagnosed with stage I-III colon cancer, but a subset of these patients experience recurrence during postoperative follow-up.[3] A randomized trial comparing various follow-up intensities detected CRC recurrence in 16.6% of patients with stage I-III CRC, with a mean time to recurrence of 4.4 years.[4] Another study reported that 30% of patients with stage I-III CRC experienced recurrence postoperatively intended to be curative.[5] Over recent decades, several prognostic factors have been determined that adversely affect disease outcomes. These include male sex, advanced cancer stage, high tumor grade, mucinous histology, lymphovascular invasion (LVI), perineural invasion (PNI), and elevated serum carcinoembryonic antigen (CEA) levels.[6,7]

This study described the recurrence rates of colon cancer after curative resection and determined predictive factors associated with recurrence in this patient cohort. CRC recurrence, whether local or as distant metastasis, was considered to indicate curative treatment failure. This study aimed to delineate high-risk individuals who may benefit from intensified surveillance strategies.

## Materials and Methods

This study extracted data from a prospectively maintained CRC database at two tertiary hospitals. This comprehensive database encompasses four primary components: (1) demographic details, such as age, sex, American Society of Anesthesiology (ASA) score, and pre- and post-treatment tumor markers (CEA and CA 199); (2) surgical information, including primary tumor location; (3) pathological data regarding the tumor, such as tumor, node, metastases stage, histological type, gross morphology, size, differentiation grade, presence or absence of LVI and PNI, lateral margins, and the status of microsatellite instability (MSI) and BRAF mutation; (4) follow-up data that records intervals of recurrence, recurrence sites, and the patient's condition at the last follow-up.

This study enrolled 1565 patients with stage I-III CRC at Taipei Veterans General Hospital and Chi Mei Hospital from January 2017 to December 2019 (Fig. 1). Of them, 519 with appendix, rectal, and anal tumors were excluded. Colon tumors that were not of adenocarcinoma, mucinous, or medullary type were also be excluded. Additionally, patients who underwent palliative resection, with missing data, and those lost to follow-up were excluded. Of 990 patients with stage I-III CRC receiving curative resection, 132 (13.3%) experienced recurrence during follow-up. Among these 132 patients, 101 (76.5%), 60 (45.4%), and 21 (15.9%) experienced recurrence within 2 years, 1 year, and 6 months after curative resection. We classified the patients into early and late recurrence groups based on these three time points for statistical analysis.

A comprehensive surveillance program was implemented for all patients, consisting of follow-up appointments every 3 months for the first 2 years after curative resection, biannually for the subsequent 3 years, and annually thereafter. These follow-ups included physical examinations, CEA/CA199 measurements, chest X-rays, abdominal sonography, and/or abdominal computed tomography (CT). Additional diagnostic procedures were conducted, such as chest CT, whole-body bone scans, or whole-body positron emission tomography to locate the recurrence, in cases where tumor recurrence was suspected. Recurrence was the detection of a recurrent lesion confirmed by pathological analysis or by a progressively increasing size on imaging studies, such as CT or colonoscopy. Post-recurrence survival was identified by the period from the date of tumor recurrence to the date of the last follow-up. The last follow-up date for the surviving patients was October 2023. The medians of follow-up interval, overall survival (OS), and disease-free survival were 51.65 months, 51.25 months, and 14.1 months, respectively.

Statistical Package for the Social Sciences version 26 (IBM, Chicago, US) was used for statistical analyses. Categorical data were compared using Pearson's chi-square tests as indicated, continuous data were used as independent *t*-tests. The Kaplan-Meier method was used for survival analysis, and the difference was evaluated using the log-rank test. Univariate and

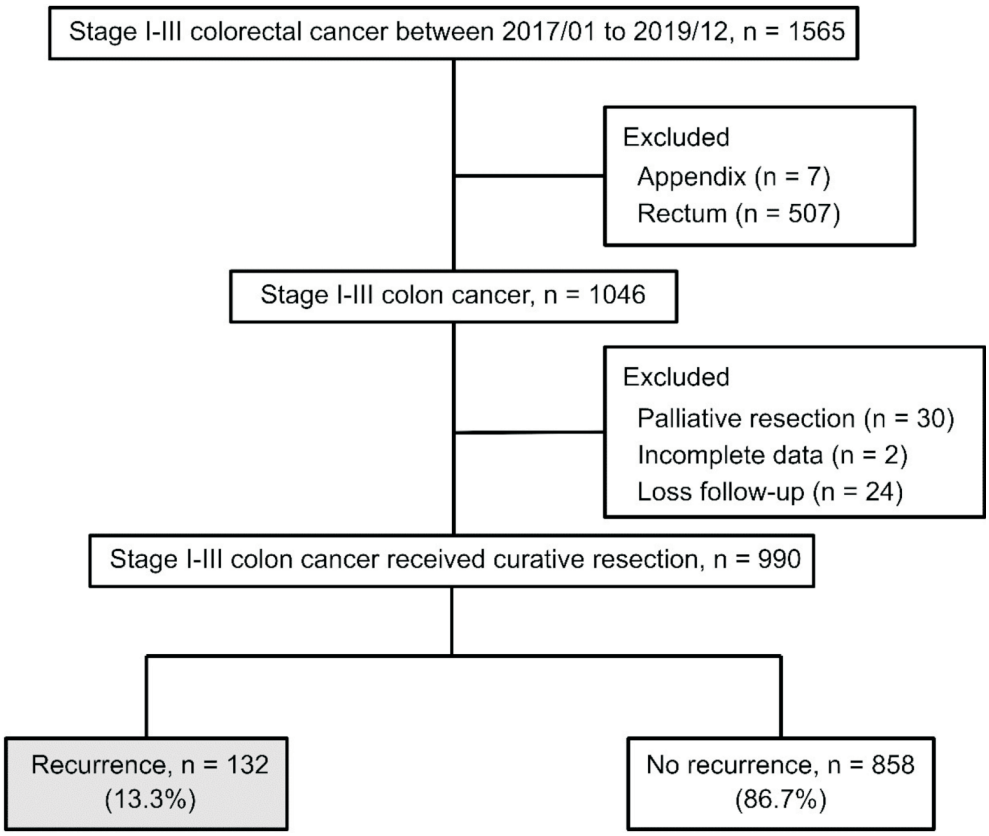


**Fig. 1.** Selection of patient charts for study inclusion.

multivariate logistic regression models were conducted for risk factors analysis. All results were considered clinically significant at a $p$-value of $< 0.05$.

# Results

This survey included 990 patients with stage I-III CRC who underwent curative resection at our center, 132 (13.3%) of whom experienced tumor recurrence during follow-up. The mean age of the patients with recurrence was 64.3 years (±standard deviation [SD]: 14.4), and 82 (62.1%) patients were men. Patients were followed for a median period of 51.65 months. At the endpoint of the cohort, 45 (34%) patients had passed away.

Most patients experienced recurrence, including 101 (76.5%), 60 (45.4%), and 21 (15.9%) patients within 2 years, 1 year, and 6 months within post-curative surgery, respectively. We classified the patients into early and late recurrence groups based on these three time points. We compared the differences between these groups and analyzed potential risk factors associated with early recurrence.

## Patients' characteristics

First, we used a two-year cut-off point to distinguish between early and late recurrence and revealed no statistically significant differences between the two groups in terms of age, sex, ASA score, tumor location, tumor size, preoperative and postoperative tumor markers (CEA and CA199) (mean of the first post-op follow-up interval ± SD [months] = 3.98 ± 1.27), and pathological features, including T stage, N stage, histology, differentiation grade, LVI, PNI, as well as molecular status (MSS and MSI-H), and BRAF mutation (Table 1-A). A subsequent analysis using one year as the cut-off for grouping indicates that the early recurrence group was statistically significantly older during diagnosis compared to the late recurrence group (mean [years] ± SD) (67.4 ± 13.9 vs.

**Table 1-A.** Patients' characteristics of the overall population and in those with recurrence (Cut-off: 2 years)

| | With recurrence (n = 132) | Early recurrence (n = 101) | Late recurrence (n = 31) | *p*-value |
|---|---|---|---|---|
| Age at diagnosis (mean years ± SD) | 64.3 ± 14.4 | 63.8 ± 13.7 | 65.9 ± 16.6 | 0.468 |
| Gender | | | | 0.595 |
| Male | 82 (62.1%) | 64 (63.4%) | 13 (41.9%) | |
| Female | 50 (37.9%) | 37 (36.6%) | 18 (58.1%) | |
| ASA | | | | 0.781 |
| 1-2 | 71 (53.8%) | 55 (54.5%) | 16 (51.6%) | |
| 3-4 | 61 (46.2%) | 46 (45.5%) | 15 (48.4%) | |
| Location of the primary tumor | | | | 0.289 |
| Right side colon | 49 (37.1%) | 35 (34.7%) | 14 (45.2%) | |
| Left side colon | 83 (62.9%) | 66 (65.3%) | 17 (54.8%) | |
| Size of the tumor (mean cm ± SD) | 4.88 ± 2.62 | 5.1 ± 2.78 | 4.19 ± 1.89 | 0.09 |
| Preoperative CEA (ng/ml) | | | | 0.261 |
| < 5 | 65 (49.2%) | 47 (46.5%) | 18 (58.1%) | |
| ≥ 5 | 67 (51.8%) | 54 (53.5%) | 13 (41.9%) | |
| Postoperative CEA (ng/ml) | | | | 0.257 |
| < 5 | 109 (82.6%) | 82 (81.2%) | 28 (90.3%) | |
| ≥ 5 | 23 (17.4%) | 19 (18.8%) | 3 (9.7%) | |
| Preoperative CA199 (U/mL) | | | | 0.316 |
| < 36 | 102 (77.3%) | 76 (75.2%) | 26 (83.9%) | |
| ≥ 36 | 30 (22.7%) | 25 (24.8%) | 5 (16.1%) | |
| Postoperative CA199 (U/mL) | | | | 0.138 |
| < 36 | 117 (88.6%) | 88 (87.1%) | 30 (96.8%) | |
| ≥ 36 | 15 (11.4%) | 13 (12.9%) | 1 (3.2%) | |
| pT stage | | | | 0.468 |
| T1-T2 | 13 (9.8%) | 11 (10.9%) | 2 (6.5%) | |
| T3-T4 | 119 (90.2%) | 90 (89.1%) | 29 (93.5%) | |
| pN stage | | | | 0.244 |
| N0 | 48 (36.4%) | 34 (33.7%) | 14 (45.2%) | |
| N+ | 84 (63.6%) | 67 (66.3%) | 17 (54.8%) | |
| Lateral margin | | | | 0.364 |
| Free | 123 (93.2%) | 30 (96.8%) | 93 (92.1%) | |
| Involved | 9 (6.8%) | 1 (3.2%) | 8 (7.9%) | |
| Histology | | | | |
| Adenocarcinoma | 120 (90.9%) | 94 (93.1%) | 26 (83.9%) | 0.097 |
| Mucinous | 11 (8.3%) | 6 (6%) | 5 (16.1%) | 0.023* |
| Medullary | 1 (0.8%) | 1 (0.9%) | 0 (0%) | |
| Differentiation grade | | | | 0.470 |
| Well/moderate | 123 (93.2%) | 95 (94.1%) | 28 (90.3%) | |
| Poor | 9 (6.8%) | 6 (5.9%) | 3 (9.7%) | |
| LVI | | | | 0.332 |
| Absent | 84 (63.6%) | 62 (61.4%) | 22 (71%) | |
| Present | 48 (36.4%) | 39 (38.6%) | 9 (29%) | |
| PNI | | | | 0.570 |
| Absent | 97 (73.5%) | 73 (72.3%) | 24 (77.4%) | |
| Present | 35 (26.5%) | 28 (27.7%) | 7 (22.6%) | |
| Molecular status | | | | 0.335 |
| MSS | 124 (93.9%) | 96 (95%) | 28 (90.3%) | |
| MSI-H | 8 (6.1%) | 5 (5%) | 3 (9.7%) | |
| BRAF | | | | 0.335 |
| Wild type | 124 (93.9%) | 96 (95%) | 28 (90.3%) | |
| Mutation | 8 (6.1%) | 5 (5%) | 3 (9.7%) | |

**Table 1-B.** Patients' characteristics of the overall population and in those with recurrence (Cut-off: 1 year)

| | With recurrence (n = 132) | Early recurrence (n = 60) | Late recurrence (n = 72) | *p*-value |
|---|---|---|---|---|
| Age at diagnosis (mean years ± SD) | 64.3 ± 14.4 | 67.4 ± 13.9 | 61.8 ± 14.4 | 0.027* |
| Gender | | | | 0.646 |
| Male | 82 (62.1%) | 36 (60%) | 46 (63.9%) | |
| Female | 50 (37.9%) | 24 (40%) | 26 (36.1%) | |
| ASA | | | | 0.799 |
| 1-2 | 71 (53.8%) | 33 (55%) | 38 (52.8%) | |
| 3-4 | 61 (46.2%) | 27 (45%) | 34 (47.2%) | |
| Location of the primary tumor | | | | 0.921 |
| Right side colon | 49 (37.1%) | 22 (36.7%) | 27 (37.5%) | |
| Left side colon | 83 (62.9%) | 38 (63.3%) | 45 (62.5%) | |
| Size of the tumor (mean cm ± SD) | 4.88 ± 2.62 | 5.40 ± 3.17 | 4.46 ± 1.99 | 0.027* |
| Preoperative CEA (ng/ml) | | | | 0.589 |
| < 5 | 65 (49.2%) | 28 (46.7%) | 37 (51.4%) | |
| ≥ 5 | 67 (51.8%) | 32 (53.3%) | 35 (48.6%) | |
| Postoperative CEA (ng/ml) | | | | 0.021* |
| < 5 | 109 (82.6%) | 45 (75%) | 64 (90.1%) | |
| ≥ 5 | 23 (17.4%) | 15 (25%) | 7 (9.9%) | |
| Pre-op CA199 (U/mL) | | | | 0.161 |
| < 36 | 102 (77.3%) | 43 (71.7%) | 59 (81.9%) | |
| ≥ 36 | 30 (22.7%) | 17 (28.3%) | 13 (18.1%) | |
| Postoperative CA199 (U/mL) | | | | 0.042* |
| < 36 | 117 (88.6%) | 50 (83.3%) | 67 (94.4%) | |
| ≥ 36 | 15 (11.4%) | 10 (16.7%) | 4 (5.6%) | |
| pT stage | | | | 0.22 |
| T1-T2 | 13 (9.8%) | 8 (13.3%) | 5 (6.9%) | |
| T3-T4 | 119 (90.2%) | 52 (86.7%) | 67 (93.1%) | |
| pN stage | | | | 0.51 |
| N0 | 48 (36.4%) | 20 (33.3%) | 28 (38.9%) | |
| N+ | 84 (63.6%) | 40 (66.7%) | 44 (61.1%) | |
| Lateral margin | | | | 0.95 |
| Free | 123 (93.2%) | 56 (45.5%) | 67 (54.5%) | |
| Involved | 9 (6.8%) | 4 (6.7%) | 5 (6.9%) | |
| Histology | | | | |
| Adenocarcinoma | 120 (90.9%) | 54 (90%) | 60 (83.3%) | 0.27 |
| Mucinous | 11 (8.3%) | 3 (5%) | 9 (12.5%) | 0.14 |
| Medullary | 1 (0.8%) | (%) | (%) | |
| Differentiation grade | | | | 0.53 |
| Well/moderate | 123 (93.2%) | 55 (91.7%) | 68 (94.4%) | |
| Poor | 9 (6.8%) | 5 (8.3%) | 4 (5.6%) | |
| LVI | | | | 0.95 |
| Absent | 84 (63.6%) | 38 (63.3%) | 46 (63.9%) | |
| Present | 48 (36.4%) | 22 (36.7%) | 26 (36.1%) | |
| PNI | | | | 0.22 |
| Absent | 97 (73.5%) | 41 (68.3%) | 56 (77.8%) | |
| Present | 35 (26.5%) | 19 (31.7%) | 16 (22.2%) | |
| Molecular status | | | | 0.79 |
| MSS | 124 (93.9%) | 56 (93.3%) | 68 (94.4%) | |
| MSI-H | 8 (6.1%) | 4 (6.7%) | 4 (5.6%) | |
| BRAF | | | | 0.64 |
| Wild type | 124 (93.9%) | 57 (95%) | 67 (93.1%) | |
| Mutation | 8 (6.1%) | 3 (5%) | 5 (6.9%) | |

**Table 1-C.** Patients' characteristics of the overall population and in those with recurrence (Cut-off: 6 months)

| | With recurrence (n = 132) | Early recurrence (n = 20) | Late recurrence (n = 112) | *p* value |
|---|---|---|---|---|
| Age at diagnosis (mean years ± SD) | 64.3 ± 14.4 | 68.9 ± 15.4 | 63.5 ± 14.1 | 0.119 |
| Gender | | | | 0.476 |
| Male | 82 (62.1%) | 11 (55%) | 71 (63.4%) | |
| Female | 50 (37.9%) | 9 (45%) | 41 (36.6%) | |
| ASA | | | | 0.114 |
| 1-2 | 71 (53.8%) | 14 (70%) | 57 (50.9%) | |
| 3-4 | 61 (46.2%) | 6 (30%) | 55 (49.1%) | |
| Location of the primary tumor | | | | 0.831 |
| Right side colon | 49 (37.1%) | 7 (35%) | 42 (37.5%) | |
| Left side colon | 83 (62.9%) | 13 (65%) | 70 (62.5%) | |
| Size of the tumor (mean cm ± SD) | 4.88 ± 2.62 | 6.54 ± 4.00 | 4.59 ± 2.18 | 0.002* |
| Preoperative CEA (ng/ml) | | | | 0.576 |
| < 5 | 65 (49.2%) | 11 (55%) | 54 (48.2%) | |
| ≥ 5 | 67 (51.8%) | 9 (45%) | 58 (51.8%) | |
| Postoperative CEA (ng/ml) | | | | 0.018* |
| < 5 | 109 (82.6%) | 13 (65%) | 96 (86.5%) | |
| ≥ 5 | 23 (17.4%) | 7 (35%) | 15 (13.5%) | |
| Preoperative CA199 (U/mL) | | | | 0.399 |
| < 36 | 102 (77.3%) | 14 (70%) | 88 (78.6%) | |
| ≥ 36 | 30 (22.7%) | 6 (30%) | 24 (21.4%) | |
| Postoperative CA199 (U/mL) | | | | 0.143 |
| < 36 | 117 (88.6%) | 16 (80%) | 101 (91%) | |
| ≥ 36 | 15 (11.4%) | 4 (20%) | 10 (9%) | |
| pT stage | | | | 0.980 |
| T1-T2 | 13 (9.8%) | 2 (10%) | 11 (9.8%) | |
| T3-T4 | 119 (90.2%) | 18 (90%) | 101 (90.2%) | |
| pN stage | | | | 0.521 |
| N0 | 48 (36.4%) | 6 (30%) | 42 (37.5%) | |
| N+ | 84 (63.6%) | 14 (70%) | 70 (62.5%) | |
| Lateral margin | | | | 0.726 |
| Free | 123 (93.2%) | 19 (95%) | 104 (92.9%) | |
| Involved | 9 (6.8%) | 1 (5%) | 8 (7.1%) | |
| Histology | | | | |
| Adenocarcinoma | 120 (90.9%) | 18 (90%) | 96 (85.7%) | 0.125 |
| Mucinous | 11 (8.3%) | 0 (0%) | 12 (10.7%) | |
| Medullary | 1 (0.8%) | (%) | (%) | |
| Differentiation grade | | | | 0.011* |
| Well/moderate | 123 (93.2%) | 16 (80%) | 107 (95.5%) | |
| Poor | 9 (6.8%) | 4 (20%) | 5 (4.5%) | |
| LVI | | | | 0.06 |
| Absent | 84 (63.6%) | 9 (45%) | 75 (67%) | |
| Present | 48 (36.4%) | 11 (55%) | 37 (33%) | |
| PNI | | | | 0.474 |
| Absent | 97 (73.5%) | 16 (80%) | 81 (72.3%) | |
| Present | 35 (26.5%) | 4 (20%) | 31 (27.7%) | |
| Molecular status | | | | 0.423 |
| MSS | 124 (93.9%) | 18 (90%) | 106 (94.6%) | |
| MSI-H | 8 (6.1%) | 2 (10%) | 6 (5.4%) | |
| BRAF | | | | 0.829 |
| Wild type | 124 (93.9%) | 19 (95%) | 105 (93.8%) | |
| Mutation | 8 (6.1%) | 1 (5%) | 7 (6.3%) | |

61.8 ± 14.4, $p = 0.027$). Furthermore, the tumor size at diagnosis in the early group was significantly larger than in the late group (mean[cm] ± SD, 5.40 ± 3.17 vs. 4.46 ± 1.99, $p = 0.027$). Additionally, a significantly higher proportion of the early group demonstrated abnormal postoperative tumor markers, including both CEA (25% vs. 9.9%, $p = 0.021$) and CA199 (16.7% vs. 5.6%, $p = 0.042$), compared to the late group (Table 1-B). Finally, the analysis reveals that the tumor size at diagnosis in the early recurrence group was larger compared to the late recurrence group (mean [cm] ± SD) (6.54 ± 4.00 vs. 4.59 ± 2.18, $p = 0.002$), and the proportion of patients with abnormal CEA levels postoperatively was significantly higher in the early group, taking six months as the cut-off. Additionally, a higher proportion of tumors in the early group exhibited poor differentiation compared to the late group, a difference that reached statistical significance (20% vs. 4.5%, $p = 0.011$) (Table 1-C).

## Clinical outcomes of patients with recurrence

The groups demonstrated no significant differences in overall and post-treatment survival when categorized by 1-year and 2-year cut-offs. However, the early group exhibited marginally lower OS and post-treatment survival rates than the late group (Tables 2A and 2B). In contrast, patients who experienced recurrence within 6 months postoperatively demonstrated significantly lower OS compared to those in the other group when categorized based on a 6-month cut-off (mean [months] ± SD) (34.7 ± 20.7 vs. 51.8 ± 17.0, $p = 0.009$). However, no significant difference in post-treatment survival was found between these groups (Table 2C). The Kaplan-Meier method was used for survival outcome analysis to estimate survival functions, and the log-rank test was used to assess differences between groups to identify statistical significance in survival rates across different categories. This method enables a robust comparison of survival probabilities over time among distinct groups within the study. Fig. 2 presented Kaplan-Meier survival curves grouped by the three cut-offs of 6 months, 1 year, and 2 years. The analysis indicated that the early recurrence group demonstrated significantly lower OS than the late recurrence group

**Table 2-A.** Clinical outcomes of patients with recurrence (cut-off: 2 years)

| | Early recurrence (n = 101) | Late recurrence (n = 31) | *p*-value |
|---|---|---|---|
| Overall survival, Median (mean ± SD) | 48.3 (46.8 ± 19.7) | 55.3 (57.1 ± 11.3) | 0.137 |
| Post-recurrence survival, Median (mean ± SD) | 36.4 (34.2 ± 19.1) | 37.2 (37.42 ± 12.7) | 0.984 |
| Condition | | | 0.266 |
| Alive | 64 (63.4%) | 23 (74.2%) | |
| Dead | 37 (36.6%) | 8 (25.8%) | |

**Table 2-B.** Clinical outcomes of patients with recurrence (cut-off: 1 year)

| | Early recurrence (n = 60) | Late recurrence (n = 72) | *p*-value |
|---|---|---|---|
| Overall survival, Median (mean ± SD) | 46.0 (42.4 ± 21.2) | 56.8 (53.5 ± 16.0) | 0.049* |
| Post-recurrence survival, Median (mean ± SD) | 35.8 (34.6 ± 20.9) | 37.4 (35.4 ± 16.4) | 0.383 |
| Condition | | | 0.191 |
| Alive | 36 (60%) | 51 (70.8%) | |
| Dead | 24 (40%) | 21 (29.2%) | |

**Table 2-C.** Clinical outcomes of patients with recurrence (cut-off: 6 months)

| | Early recurrence (n = 20) | Late recurrence (n = 112) | *p*-value |
|---|---|---|---|
| Overall survival, Median (mean ± SD) | 36.0 (34.7 ± 20.7) | 52.1 (51.8 ± 17.0) | 0.009* |
| Post-recurrence survival, Median (mean ± SD) | 30.9 (30.6 ± 21.1) | 32.5 (30.7 ± 18.6) | 0.137 |
| Condition | | | 0.103 |
| Alive | 10 (50%) | 77 (68.8%) | |
| Dead | 10 (50%) | 35 (31.3%) | |

when grouped by 1 year ($p = 0.049$) and 6 months ($p = 0.009$), emphasizing the effect of recurrence timing on long-term patient outcomes. Fig. 3 shows Kaplan-Meier survival curves for post-recurrence survival, categorized by the three cut-offs of 6 months, 1 year, and 2 years. The analysis revealed no significant difference in survival rates between the groups defined by these intervals.

### Risk factors of early recurrence

We conducted univariate and multivariate analyses to determine risk factors associated with early recurrence. Table 3A shows that postoperative CEA, pT stage, pN stage, differentiation grade, LVI, and PNI, along with other factors, including age, gender, ASA score, tumor size, tumor location, margins, MSI, and BRAF mutation, did not reach statistical significance. Switching to a 1-year cut-off, elevated postoperative CEA levels were determined as an independent predictor of early recurrence (Table 3B). Both elevated postoperative CEA levels and poor tumor differentiation were identified as independent risk factors for early recurrence using a 6-month cut-off (Table 3C).

## Discussion

### Incidence of recurrence

Resection surgery is the only curative treatment for non-metastatic diseases, particularly crucial for patients with early-stage CRC. This surgical approach is pivotal in effectively managing and potentially treating these patients. The primary objective of postoperative follow-up in patients with cancer is to detect tumor recurrence early, thereby enabling prompt intervention and potentially improving survival outcomes. Unfortunately, robust data on recurrence in CRC are scarce, and an evidence-based definition for what constitutes early recurrence following resection

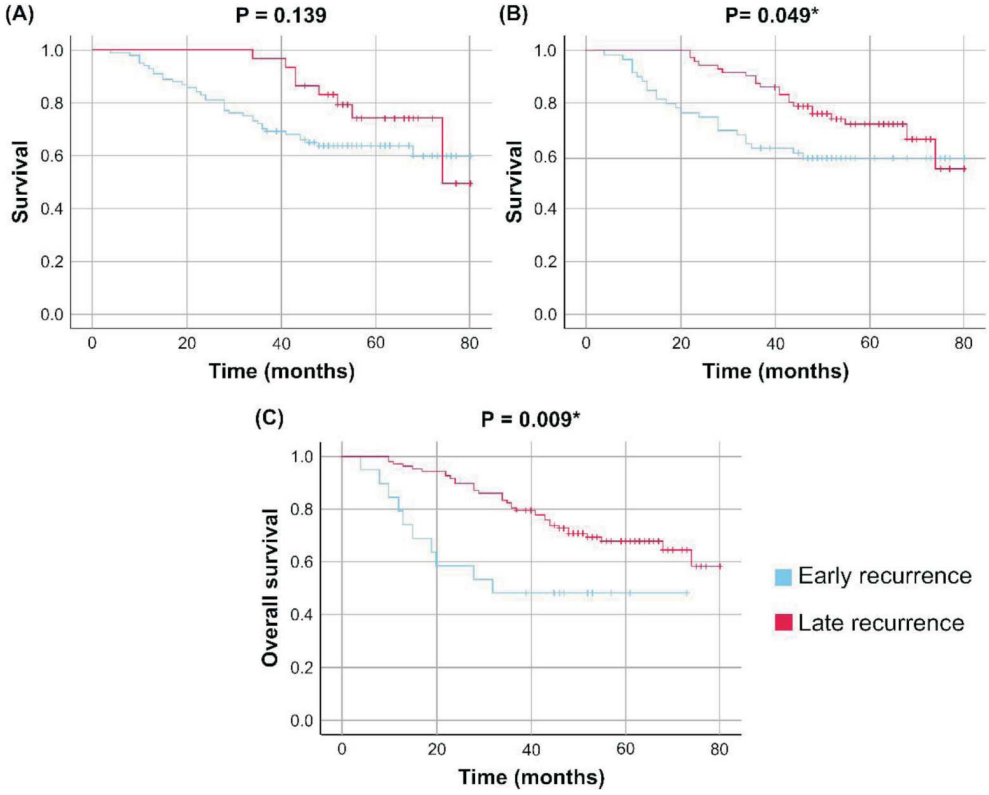


**Fig. 2.** Kaplan-Meier curves of early and late recurrences for overall survival (OS). (A) Cut-off of 2 years; (B) cut-off of 1 year; (C) cut-off of 6 months.

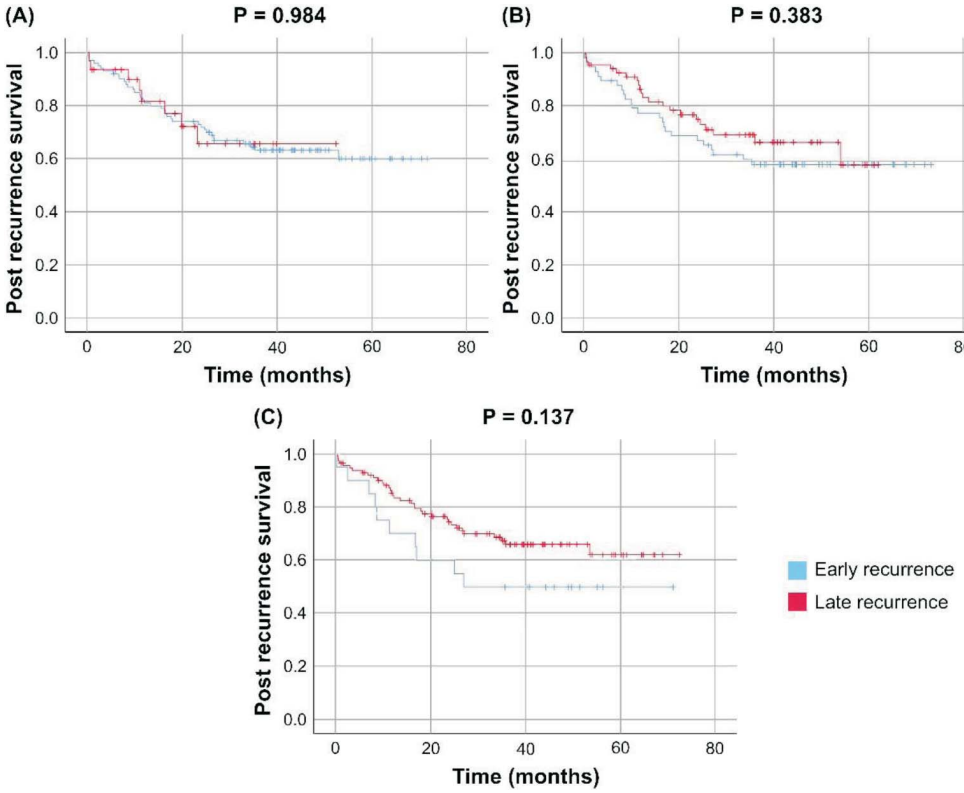


**Fig. 3.** Kaplan-Meier curves of early and late recurrences for post-recurrence survival. (A) Cut-off of 2 years; (B) cut-off of 1 year; (C) cut-off of 6 months.

**Table 3-A.** Logistic regression on risks of early recurrence (cut-off: 2 year)

| Variables | Univariate analysis | | | |
|---|---|---|---|---|
| | n | Odds ratio | 95% CI | *p*-value |
| Postoperative CEA (ng/ml) | | | | 0.265 |
| < 5 | 109 | 1 (ref) | | |
| ≥ 5 | 23 | 2.09 | 0.57-7.60 | |
| pT stage | | | | 0.473 |
| T1-T2 | 13 | 1 (ref) | | |
| T3-T4 | 119 | 0.564 | 0.12-2.70 | |
| pN stage | | | | 0.247 |
| N0 | 48 | 1 (ref) | | |
| N+ | 84 | 1.62 | 0.72-3.68 | |
| Differentiation grade | | | | 0.475 |
| Well/moderate | 123 | 1 (ref) | | |
| Poor | 9 | 0.589 | 0.14-2.51 | |
| LVI | | | | 0.334 |
| No | 84 | 1 (ref) | | |
| Yes | 48 | 1.54 | 0.64-3.68 | |
| PNI | | | | 0.571 |
| No | 97 | 1 (ref) | | |
| Yes | 35 | 1.32 | 0.51-3.40 | |

is currently unavailable. This gap emphasizes the need for further research to improve follow-up protocols in colon cancer treatment.

This comprehensive study presented accurate and recent population-based recurrence data after primary surgical treatment for stage I-III CRC. A total of 132 patients with CRC experienced disease recurrence after a median follow-up of 51.65 months. The overall recurrence rate in this cohort was 13.3%, which was consistent with the literature. A previous study on 763 Japanese patients with stage I-III CRC revealed a recurrence rate of 15.2% at 36.4 months postoperatively.[8] Torre LA, et al. observed a recurrence rate of 18.7% in the American population.[9] Our study reported the proportions of recurrence by cancer stage of 2.8%, 10.7%, and 25.1% for stages I, II, and III, respectively. Additionally, the majority of recurrences occurred within two years (n = 101, 76.5%). Nearly half (60 [45.4%]) of the patients experienced recurrence within 1 year and 21 (15.9%) patients within just 6 months.

**Table 3-B.** Logistic regression on risks of early recurrence (cut-off: 1 year)

| Variables | n | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|---|
| | | Odds ratio | 95% CI | *p*-value | Odds ratio | 95% CI | *p*-value |
| Post-op CEA (ng/ml) | | | | 0.025* | | | 0.021* |
| < 5 | 109 | 1 (ref) | | | 1 (ref) | | |
| ≥ 5 | 23 | 3.05 | 1.12-8.08 | | 3.24 | 1.01-7.36 | |
| pT stage | | | | 0.23 | | | |
| T1-T2 | 13 | 1 (ref) | | | | | |
| T3-T4 | 119 | 0.49 | 0.15-1.57 | | | | |
| pN stage | | | | 0.51 | | | |
| N0 | 48 | 1 (ref) | | | | | |
| N+ | 84 | 1.27 | 0.62-2.60 | | | | |
| Differentiation grade | | | | 0.53 | | | |
| Well/moderate | 123 | 1 (ref) | | | | | |
| Poor | 9 | 1.55 | 0.39-6.03 | | | | |
| LVI | | | | 0.94 | | | |
| No | 84 | 1 (ref) | | | | | |
| Yes | 48 | 1.02 | 0.50-2.09 | | | | |
| PNI | | | | 0.22 | | | |
| No | 97 | 1 (ref) | | | | | |
| Yes | 35 | 1.62 | 0.74-3.53 | | | | |

**Table 3-C.** Logistic regression on risks of early recurrence (cut-off 6 months)

| Variables | n | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|---|
| | | Odds ratio | 95% CI | *p*-value | Odds ratio | 95% CI | *p*-value |
| Post-op CEA (ng/ml) | | | | 0.023* | | | 0.027* |
| < 5 | 109 | 1 (ref) | | | 1 (ref) | | |
| ≥ 5 | 23 | 3.45 | 1.19-10.02 | | 3.47 | 1.15-10.46 | |
| pT stage | | | | 0.98 | | | |
| T1-T2 | 13 | 1 (ref) | | | | | |
| T3-T4 | 119 | 0.98 | 0.20-4.80 | | | | |
| pN stage | | | | 0.52 | | | |
| N0 | 48 | 1 (ref) | | | | | |
| N+ | 84 | 1.4 | 0.50-3.92 | | | | |
| Differentiation grade | | | | 0.02* | | | 0.024* |
| Well/moderate | 123 | 1 (ref) | | | 1 (ref) | | |
| Poor | 9 | 5.35 | 1.29-22.04 | | 5.36 | 1.24-23.21 | |
| LVI | | | | 0.065 | | | |
| No | 84 | 1 (ref) | | | | | |
| Yes | 48 | 2.47 | 0.94-6.50 | | | | |
| PNI | | | | 0.476 | | | |
| No | 97 | 1 (ref) | | | | | |
| Yes | 35 | 0.653 | 0.20-2.10 | | | | |

## Risk factors of recurrence

### Post-operative CEA

Risk factors for a recurrence time of 2 years were not significant. However, elevated postoperative CEA level was identified as an independent risk factor for relapse within 1 year, and even 6 months. Patients with elevated CEA were 3.24 times to more likely develop early recurrence in 1 year and 3.47 times in 6 months. This indicates that higher CEA level postop-

eratively is particularly indicative of early recurrence risks within the first year. Patients with elevated post-operative CEA had a 5.97 times higher risk for recurrence in 2 years, considered the most compelling risk factor, within the published literature.[10]

**Post-operative CA 199**

No significant factors were observed in this study in terms of postoperative CA 199. Some studies revealed that patients with elevated post-operative CA 199 were 3.03-3.77 times more likely to develop early recurrence than patients with normal value post-operative CA 199.[6,10-12] Accordingly, laboratory values, such as CEA and CA 199, play crucial roles as the prognostic factors of recurrence and may act as biomarkers to detect or predict recurrence incidence in patients with surgically treated CRC.[13]

**Depth of invasion (pT stage)**

This study did not identify the depth of invasion as an independent factor for early recurrence. However, contrasting results have been reported in the literature. Osterman et al. revealed that patients with pT4 stage CRC were 2.27 times more likely to develop early recurrence within 2 years compared to patients with less advanced stages.[14] Additionally, Tsai, et al. revealed that patients with the pT4 stage were 3.16 times more likely to experience early recurrence within 1 year.[12] These results indicate the increased risk of advanced local tumor invasion in predicting early recurrence.

**Pathologic N stage (pN stage)**

This study did not identify the pathological N stage as an independent risk factor for early recurrence. Other literature indicated a notable trend that patients with positive nodal status were reported to be 2.56 times more likely to experience a relapse within 2 years compared to those without nodal involvement.

**Grade of differentiation**

This study reported poor differentiation grade as an independent risk factor for early recurrence within 1 year. Patients with poorly differentiated tumors were 5.36 times more likely to experience early recurrence within this timeframe. This finding is congruent with existing literature, which consistently emphasizes the critical role of tumor differentiation in forecasting the likelihood of early recurrence.[11,12,15,16] Tumors that were poorly differentiated appeared to demonstrate more aggressive behavior and a higher tendency to spread, a factor that contributed to their propensity for earlier relapse.

**Overall survival**

Survival in cases of early recurrence has remained persistently poor. We observed that OS curves with early recurrences exhibited a worse prognosis (Figs. 2, 3), and the survival after recurrence in 1 year was significantly lower in patients with an early CRC recurrence than in those with late recurrence. Early post-operative recurrence was associated with poor survival outcomes following the current literature.[11,15-17]

## Limitation

The limitations of this study are related to its retrospective nature. Our results cannot be generalized to the whole population because this is a single-center study with a small sample size. Additionally, the trend between pre- and postoperative tumor markers is lacking, and we are unable to analyze the prognostic effect of primary resection. These factors must be considered when planning future research.

# Conclusion

This study revealed elevated postoperative CEA as an independent risk factor of early recurrence, with minimal residual disease and occult metastasis as the reason. More attention to these individuals during follow-up is warranted.

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**原　著**

# 第 I-III 期結腸癌患者接受根治性切除後早期復發的預測因素與預後

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林宏鑫 [1,3]　林春吉 [1,3]　藍苑慈 [1,3]　王煥昇 [1,3]　姜正愷 [1,3]　楊純豪 [1,3,4]
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**目的**　結腸直腸癌是一個重大的公共衛生議題，幾十年來全球的發病率不斷上升。對於第一至第三期結腸癌患者而言，手術切除仍是主要的治療方法，但有部分患者在手術後會出現復發。本研究旨在探討預測手術治癒後早期復發的因素，識別出高風險患者。

**材料與方法**　本回顧性研究納入在 2017 年 1 月至 2019 年 12 月期間，進行根治性切除手術的第一至第三期結腸癌患者。從臺北榮民總醫院及奇美醫院數據庫中收集患者的資料、手術相關細節、病理發現和分子標記等數據、復發的時間與預後，並將患者以不同復發時間作為切點 (手術後 6 個月、1 年和 2 年) 分為早期復發與晚期復發兩組進行分析。

**結果**　本研究有 132 名患者發生復發，其中男性佔 61.36%，平均年齡為 64.31 歲。追蹤時間平均為 48.38 個月。手術後兩年內有 76.5% 的患者出現復發，一年內為 45.4%，六個月內為 15.9%。術後 CEA 數值異常和腫瘤分化不良與早期復發的獨立風險因子，和較短的存活期有顯著的相關性。

**結論**　研究發現，術後 CEA 數值異常和腫瘤分化差的患者特別容易早期復發，且長期生存率較低。因此，這些患者應該在根治性手術後進行密切追蹤，以便及時發現復發並改善預後。

**關鍵詞**　大腸癌、根治性切除、早期復發、復發因素。