

RESEARCH ARTICLE



Factors associated with short recurrence-free survival in completely resected colon cancer

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ABSTRACT

Background: Several factors could affect disease recurrence in surgically resected colon cancer. While the role of certain factors such as cancer stage and grade is well established, the role of other factors (e.g., histological subtypes) is yet to be determined.

Objective: Therefore, we conducted a study to evaluate the impact of several factors in recurrence-free survival (RFS) in patients who were disease free following surgical resection of the colon cancer.

Design/Methods: Data were collected for patients with Stage I–III colon cancer who underwent complete surgical resection of the tumor between January 2010 and December 2015 in our institution. A total of 90 subjects met the inclusion criteria and were included in the study. The following factors were collected at the time of surgical resection of the colonic tumor: patient's age, gender, colon cancer stage, grade and histological subtype, body mass index, hemoglobin A1c, and smoking history.

Results: A total of 28 patients (31%) developed recurrence and had a mean follow-up time of 19.8 months (range: 2–54.4 months). Median RFS was 54.4 months with a 5-year RFS of 49%. Advanced colonic cancer stage and mucinous histological subtype were associated with shorter RFS with an HR of 2.37, 95% CI = 1.38–4.06, and 95% CI = 1.02–5.90, respectively. Current smokers or those who quit less than 15 years earlier tended to have worse RFS with an HR of 2.47, 95% CI = 0.98–6.27.

Conclusion: Advanced colon cancer stage and mucinous histological subtype are independent risk factors for cancer recurrence and shorter RFS in completely resected colonic tumor.

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1. Introduction

Colon cancer is the third most common cause of cancer-related death in the USA [1]. Although the total incidence of colon cancer continues to decline, its incidence in individuals younger than the age of 50 has steadily increased at around 2% per year from 1993 to 2013 [1]. According to the American Joint Committee on Cancer 2010, colon cancer is classified into four stages based on the degree of colonic wall infiltration, lymph node involvement, and distant metastasis [2]. The standard of care for node-positive colon cancer without distant metastasis (Stage III) is surgery followed by 12 cycles of adjuvant oxaliplatin with fluorouracil (5FU) and folinic acid (FOLFOX chemotherapy). On the other hand, there is no role of adjuvant chemotherapy in Stage I colon cancer after surgical resection. Studies did not confirm the benefit of adjuvant chemotherapy in patients with Stage II disease. However, adjuvant chemotherapy is included as an option for several high-risk Stage II patients, such as those with suboptimal lymph nodes dissection [3].

When patients have a similar number of lymph node resections, a higher number of lymph nodes involved is associated with inferior survival and worse outcomes [4,5]. Furthermore, Aldecoa et al. showed that higher molecular lymph node tumor burden in grossly negative lymph node cancer (Stage I–II) is associated with inferior prognosis [6].

Histologically, most cases of colorectal cancer (CRC) fall under the adenocarcinoma category. The College of American Pathologists and American Joint Committee on Cancer (CAP/AJCC) recommended the use of gland formation with defined cutoffs as a grading system. Gland formation in less than 50% of the lesion is labeled as Grade III (poorly differentiated), 50–90% gland formation is labeled as Grade II (moderately differentiated), and >90% gland formation is labeled as Grade I (well differentiated) [7]. In contrast to surgical stage, histological grade has no established role in selecting candidates for adjuvant chemotherapy, with the exception of poorly differentiated Stage II CRC patients, among other risk factors, who are considered high risk and could be offered adjuvant chemotherapy [8].

Most colonic adenocarcinomas are histologically classified as adenocarcinoma not otherwise specified (NOS). Mucinous adenocarcinoma (MA) comprises about 10% of colonic cancer histology while signet ring comprises about 1%. The World Health Organization (WHO) defines adenocarcinoma as a mucinous type when mucin glycoprotein constitutes 50% or more of the pathological specimen. While signet ring histology is usually associated with poorer prognosis, the effect of mucinous subtype on survival and recurrence in CRC patients is yet to be determined [9,10].

High microsatellite instability (MSI-H) in CRC has been linked to higher disease-free periods and overall survival (OS); therefore, adjuvant chemotherapy is not recommended for Stage II colonic adenocarcinoma with MSI-H [11]. Furthermore, conflicting data exist regarding the effect of body mass index (BMI) and smoking status on recurrence-free survival (RFS) in CRC patients [12,13].

Owing to the controversy in the literature about the impact of potential factors that could influence disease recurrence, we conducted a study, which examines the effect of demographics as well as clinically relevant variables on colon cancer recurrence. We examined the effect of cancer stage, grade, histological subtypes, smoking history, BMI, and hemoglobin A1c at the time of surgical resection of the colonic mass on RFS following complete surgical resection of colon cancer. A better understanding of these factors will potentially allow us to risk stratify surgically resected CRC patients into groups with significant differences in recurrence outcomes. Such a risk stratification may provide guidance in selecting optimal candidates for adjuvant chemotherapy, especially among elderly patients who are more prone to chemotherapy-related toxicities.

2. Methods

2.1. Patients

Consecutive patients who had been diagnosed with Stage I–III colonic adenocarcinoma between January 2010 and December 2015 at Hurley Medical Center (Flint, Michigan, USA) were included in this study. Patients were required to have complete curative surgical resection. Patients who had rectal cancer, had gross post-operative residual disease, died within 30 days of surgery, received preoperative chemotherapy, or received pre- or post-operative radiotherapy were excluded. In total, 90 subjects met the inclusion criteria and were included in this study. Data collection commenced following acquisition of institutional review board approval.

All the patients who received adjuvant chemotherapy completed the pre-planned 12 cycles of FOLFOX chemotherapy. FOLFOX adjuvant protocol consisted of leucovorin 200 mg/m² intravenous (IV) on Day 1,

followed by 5-fluorouracil (5-FU) 400 mg/m² IV once then 2400 mg/m² IV over 46 h, and oxaliplatin 85 mg/m² IV on Day 1 every 2 weeks.

The pathological slides were interpreted by the same group of pathologists, who are well experienced in CRC pathology. Tumors with a mucinous component that constitutes more than 50% of the lesion were labeled as mucinous adenocarcinoma (MA) as per the WHO definition. The WHO grading system was used to categorize the cancer grade, while surgical staging was classified according to AJCC 2010.

In addition to the patient's age and gender, the following factors, which could potentially affect tumor recurrence, were collected at the time of surgical resection of the colon cancer mass: stage, grade, lymphocytic infiltration of the tumor, serum preoperative carcinoembryonic antigen level, histological subtype (MA, non-mucinous cancer (NMA)), BMI, hemoglobin A1c, and smoking history. Smoking status was defined as current smoker (any patient who continued smoking up to the date of the surgery or quit less than 15 years prior to the date of surgery) or non-smoker (any patient who never smoked or quit more than 15 years prior to the date of colon cancer surgery).

The clinical data were collected through electronic medical records.

2.2. Statistical analysis

Data were presented descriptively as proportions, means, or medians as appropriate. The statistical analysis was performed using chi-square test for categorical variables and *t*-test for continuous variables. The primary end points were RFS defined as the time from surgery to the date of first documented recurrence, last follow-up, or death. Survival was estimated by the Kaplan–Meier method and comparisons were made by the log-rank test. All factors with *p*-values <0.05 were entered into multivariate analysis using the backward stepwise Cox regression method. All statistical analyses were performed utilizing the SPSS version 19 (SPSS Inc., Chicago, IL).

3. Results

3.1. Patient characteristics

We identified a total of 90 patients with Stage I–III colon cancer who underwent complete surgical resection, with a median follow-up of 25.4 months from the date of surgery. Mean age was 64.2. A total of 52% of patients were males. A total of 19 cases (21%) were Stage I, 26 (29%) were Stage II, and 45 (50%) were Stage III disease. A total of 35 patients (78%) with Stage III and 4 (15%) with Stage II received adjuvant chemotherapy.

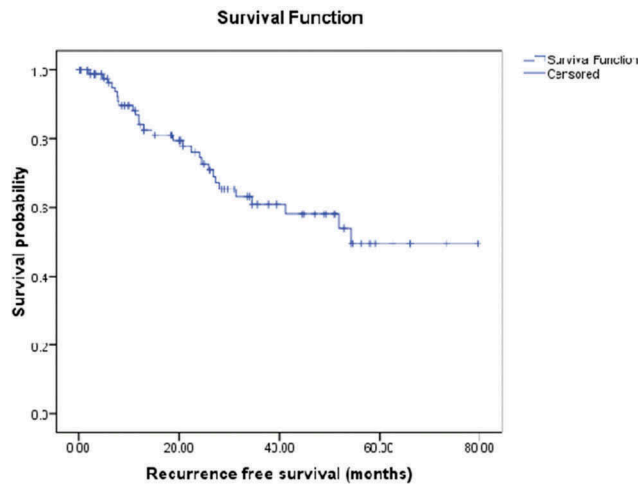


Figure 1. Recurrence-free survival in patients with surgically treated colon cancer.

3.2. RFS outcomes

At a mean follow-up time of 19.8 months (range: 2.0–54.4 months), 28 patients (31%) developed recurrence; 24 patients had Stage III, while 4 patients had Stage II disease. Median RFS was 54.4 months with a 5-year RFS of 49% (Figure 1). There was no

Table 1. Patients’ characteristics and results of univariate analysis for factors affecting recurrence-free survival.

| Clinical variable | n (%) | Median RFS (months) | 5-year RFS | p-Value |
|---------------------------|------------|---------------------|------------|---------|
| Gender: | | | | |
| Male | 47 (52%) | 42.3 | 41% | 0.42 |
| Female | 43 (48%) | Unreached | 57% | |
| Age: | | | | |
| <60 | 38 (42%) | 31.3 | 50% | 0.25 |
| ≥60 | 52 (58%) | 54.4 | 49% | |
| Grade: | | | | |
| Grade I or II | 82 (91%) | 54.4 | 49% | 0.16 |
| Grade III | 8 (9%) | 11.3 | 43% | |
| TNM stage: | | | | |
| Stage I or II | 45 (50%) | Unreached | 86% | <0.001 |
| Stage III | 45 (50%) | 27.2 | 22% | |
| Histology: | | | | |
| Mucinous | 10 (11%) | 14.6 | 18% | 0.003 |
| Others | 79 (87%) | Unreached | 54% | |
| Unknown | 1 | | | |
| Lymphocytic infiltration: | | | | |
| Yes | 23 (26%) | Unreached | 72% | 0.13 |
| No | 66 (73%) | 52.0 | 43% | |
| Unknown | 1 (1%) | | | |
| CEA level: | | | | |
| <5 | 54 (60%) | Unreached | 56% | 0.11 |
| ≥5 | 11 (12%) | 18.7 | 33% | |
| Unknown | 25 (28%) | | | |
| HbA1c: | | | | |
| <6 | 59 (66.5%) | Unreached | 57% | 0.55 |
| ≥6 | 28 (31%) | 52.0 | 35% | |
| Unknown | 3 (0.5%) | | | |
| BMI: | | | | |
| <25 | 29 (32%) | Unreached | 52% | 0.41 |
| ≥25 | 59 (65%) | 54.4 | 48% | |
| Unknown | 2 (3%) | | | |
| Smoking status: | | | | |
| Current smoker | 10 (11%) | 7.6 | 25% | 0.01 |
| Never or quit smoking | 78 (87%) | Unreached | 53% | |
| Unknown | 2 (2%) | | | |

RFS: recurrence-free survival; CEA: carcinoembryonic antigen; BMI: body mass index.

significant difference in the median follow-up between patients who had recurrence and those who did not (24.7 months vs. 26.4 months, respectively). Table 1 illustrates the patients’ characteristics and results of univariate analysis.

Patient age, sex, tumor grade, lymphocytic infiltration of the tumor, pre-operative carcinoembryonic antigen (CEA) level, peri-operative hemoglobin A1c, BMI, and adjuvant chemotherapy were not associated with a statistically significant difference in RFS. However, Stage III disease, mucinous histology, and smoking were identified as significant predictors of RFS in univariate analysis (Figure 2, Figure 3, and Figure 4, respectively).

3.3. Results of multivariate analysis

In the multivariate analysis, Stage III disease and mucinous histology were the only statistically significant independent factors that predicted inferior RFS (Table 2).

4. Discussion

Cancer stage is the most significant predictor of OS in colon cancer. The survival rates for Stage I, Stage II, and Stage III were 74%, 54%, and 49%, respectively, according to the data from Surveillance, Epidemiology and End Results [14]. Due to the lack of long-term follow-up, and since RFS correlates with OS in colon cancer patients who received adjuvant chemotherapy [15], we decided to measure RFS as a primary outcome. Consistent with data from other studies, our study confirmed that patients with Stage III colon cancer have statistically significant inferior RFS rates compared to Stage I and II disease.

Mucin is a glycoprotein that can be secreted by different kinds of cancer cells, which would indicate cellular dedifferentiation and expression of originally silent genes. Different cutoffs are being used to

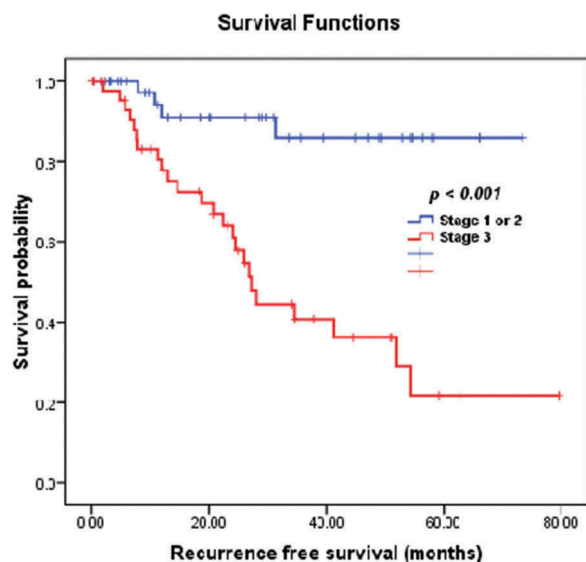


Figure 2. Kaplan–Meier recurrence-free survival estimation according to stage.

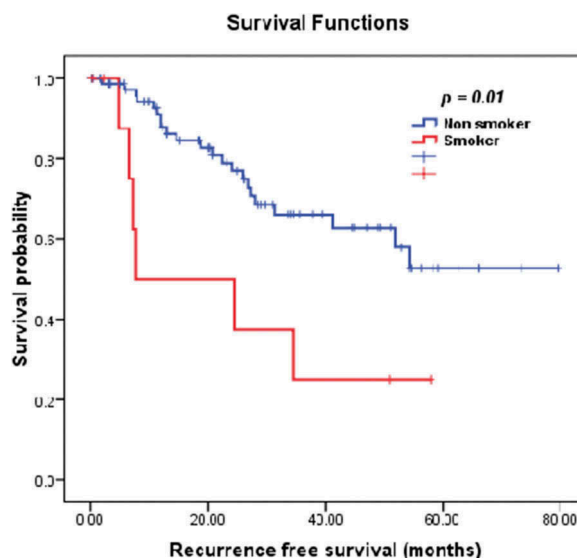


Figure 4. Kaplan–Meier recurrence-free survival estimation by smoking status.

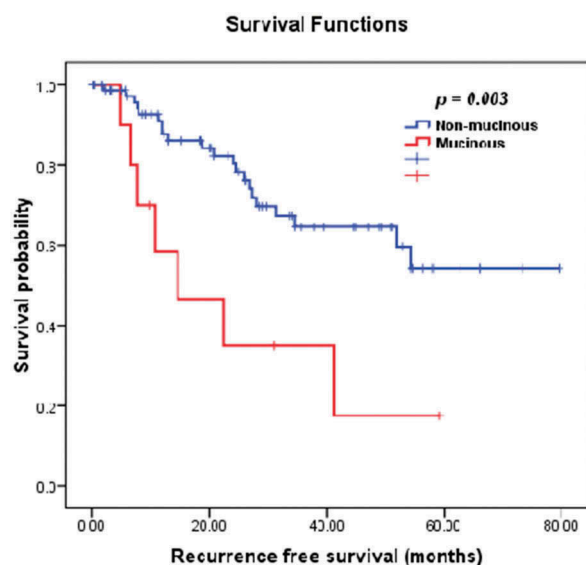


Figure 3. Kaplan–Meier recurrence-free survival estimation by histologic subtype (non-mucinous vs. mucinous).

classify colonic adenocarcinoma as mucinous. According to Simonds et al. and Umpleby et al., mucin should constitute at least 60% of the colonic cancer specimen to be labeled as MA [16,17], while a cutoff level of 50% is being used in WHO classification [18]. This difference in cutoff value may explain the higher incidence of MA in the western countries compared to those in Asia [16,19]. Many studies showed that patients with MA of the rectum had worse prognosis in terms of RFS and OS compared to non-mucinous adenocarcinoma (NMA) [9,19,20]. On the other hand, the prognostic significance of MA of the colon is yet to be determined. A study of 135 patients who were diagnosed with colonic adenocarcinoma and received adjuvant 5-Fluorouracil showed worse OS and poor response to adjuvant chemotherapy in MA compared to NMA [21]. In another study

Table 2. The results of multivariate analysis.

| Factor | HR (95% CI) | p-Value |
|-------------------------|------------------|---------|
| Mucinous adenocarcinoma | 2.46 (1.02–5.90) | 0.045 |
| Other histology | 1 | |
| Stage III | 2.37 (1.38–4.06) | 0.002 |
| Stage I or II | 1 | |
| Current smoker | 2.47 (0.98–6.27) | 0.056 |
| Non-smoker | 1 | |

conducted by Kanemistu et al. [22], MA patients with either complete or incomplete surgical resection had worse outcomes compared to non-mucinous types. Moreover, MA was associated with a 2–8% increase in risk of death in Verhulst et al.'s meta-analysis [23].

On the other hand, other studies did not confirm the worse prognosis in patients with MA compared to NMA of the colon [19,24]. An analysis from the National Cancer Database showed inferior OS in MA of the rectum but not of the colon [9]. Interestingly, Hogan et al. reported an improved survival in patients with MA [25].

Of note, patients with colonic MA tend to be younger, tend to present with advanced stage, and more likely to have right-sided tumors, peritoneal metastasis, and incomplete resection of the colonic tumor [22,23,26,27]. Microsatellite instability (MSI) of more than 40% frequently occurs in right-sided colonic cancer and carries better prognostic outcomes compared to microsatellite stable (MSS) tumors [11,26]. MA of the colon might have MSI, which would affect cancer recurrence and survival [26]. The presence of MSI in MA might be a major factor that accounts for the observed discrepancy in outcomes among different studies. Moreover, heterogeneity of the studied population, including both MA of the colon and rectum, and lack of assessment of RFS were also major limitations, which probably contributed to the discrepancies in the observed outcomes in

the previous studies. A retrospective analysis of 394 patients who had curative resection of Stage III colon cancer, in which 5.1% of them had mucinous component, 5.3% had MA, and 6.6% had MSI-H, revealed worse RFS in MA compared to non-MA types [10] with no difference in recurrence between MSI-MA and MSS-MA; however, RFS was significantly inferior in MSS-MA but not in MSI-MA when compared to NMA. The lack of a statistically significant difference in the former is likely a result of the small number of MSI-MA subjects, which is considered a limiting factor in that study [10].

A significantly worse RFS in MA compared to non-mucinous histology was found in our study. These data are consistent with data from the above-mentioned studies formulating a worse prognosis in MA.

MA tends to have MSI, BRAF mutation, and aberrant hyper-methylation, particularly CPG island phenotype (CIMP). CIMP may confer resistance to adjuvant 5-fluorouracil, which might provide an explanation for the observed inferior survival in mucinous histology [28,29].

Despite being a risk factor for colon cancer, few studies evaluated the effect of cigarette smoking on RFS. A study from the North Central Cancer Treatment Group that included 1968 participants showed a significant inferior RFS of people who had ever smoked compared to those who had not [14]. Data from a Cancer and Leukemia Group B study (CALGB 89803) showed statistically significant inferior disease-free survival in participants who smoked 12 packs/year or more at age 30 or younger [30]. In multivariate analysis, our study showed closely significant inferior RFS in participants who were smokers at the time of surgery compared to those who were not or had quit smoking.

The effect of BMI on RFS was examined among participants in the Adjuvant Colon Cancer Endpoints database. Obesity and low BMI were significant predictors of shorter time to recurrence [12]. On the other hand, data from CALGB 89803 did not show any influence of BMI on RFS or OS [31]. Our data did not show any effect of BMI or hemoglobin A1c at the time of surgical resection on RFS with different cutoff levels.

We acknowledge some limitations in our study; the small sample size and number of relapses render the study underpowered to detect the role of certain variables on RFS. For example, lymphocytic infiltration of the colon cancer is associated with an improvement in the OS and RFS in many studies irrespective of the presence of DNA mismatch repair defects [32–34]. Our data showed higher 5-year RFS in the lymphocytic infiltration group (72% vs. 43%). However, the difference did not reach statistical significance. Furthermore, a smaller number of Grade 3

tumors amongst our patients (8%) limits the assessment of high-grade histology on RFS.

The retrospective design of the study, the group of patients in Stage III colon cancer who did not receive adjuvant chemotherapy (22.2%), and the selection bias that probably occurred in the group of patients who received adjuvant chemotherapy, who might have had worse disease on presentation, are considered major factors that may explain the lack of a statistically significant effect of chemotherapy on RFS. To our knowledge, this is the first study that evaluated the role of various demographic and disease-related factors on RFS of colon cancer patients in the Flint population. Furthermore, it provides valuable information about disease demographics at our institution over the last 5 years.

5. Conclusion

Advanced cancer stage and mucinous histology predict inferior RFS following complete surgical resection of colon cancer. Large prospective studies with additional information about MSI, BRAF, and K-RAS mutations of the colonic mass would provide more conclusive data about the effect of mucinous histology and smoking on disease-free survival in colon cancer.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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