Survival after Curative Resection for Stage I Colorectal Mucinous Adenocarcinoma

Liang Huang
Sun Yat-sen University Sixth Affiliated Hospital

Shuangling Luo
Sun Yat-sen University Sixth Affiliated Hospital

Sicong Lai
Sun Yat-sen University Sixth Affiliated Hospital

Yonghua Cai
Sun Yat-sen University Sixth Affiliated Hospital

Zhanzhen Liu
Sun Yat-sen University Sixth Affiliated Hospital

Huanxin Hu
Sun Yat-sen University Sixth Affiliated Hospital

Ziwei Zeng
Sun Yat-sen University Sixth Affiliated Hospital

Cory J Xian
University of South Australia

Jianghui Dong
University of South Australia

Liping Wang (liping.wang@mymail.unisa.edu.au)
University of South Australia  https://orcid.org/0000-0001-9355-1167

Liang Kang
Sun Yat-sen University Sixth Affiliated Hospital

Research

**Keywords:** mucinous adenocarcinoma; colorectal carcinoma; colorectal cancer, recurrence-free survival, overall survival rectal carcinoma; colorectal cancer, recurrence-free survival, overall survival

**DOI:** https://doi.org/10.21203/rs.3.rs-21102/v2

**License:** This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

Background: The prognostic value of the mucinous adenocarcinoma histotype on the early stages especially for stage I colorectal cancer (CRC) is still unclear. This study determined the clinicopathologic characteristics and long-term outcome of stage I colorectal mucinous adenocarcinomas (MAC).

Methods: Among the total of 503 patients with stage I CRC (56 having MAC and 447 having non-MAC) who underwent radical resection, the correlation between clinicopathological factors and MAC was analyzed. Multivariate analysis was performed to determine whether mucinous histotype itself was an independent prognostic impact in stage I patients.

Results: MACs were observed more frequently located in the colon than rectum ($p=0.046$), more frequently displayed the microsatellite instability (MSI) phenotype ($p=0.023$) and had a greater frequency of T2 stage ($p=0.001$). The rate of recurrence was 13.5% and the cancer-specific mortality was 4.3% among all stage I CRC patients. There was no difference in disease-free survival and overall survival between MACs and non-MACs. On multivariate analysis, older age ($p=0.030$; hazard ratio: 2.62), rectal cancer ($p=0.025$, hazard ratio: 5.42), lymphovascular invasion (LVI) ($p<0.001$, hazard ratio: 9.74), and microsatellite stability (MSS) phenotypes ($p=0.023$, hazard ratio: 4.21) were independently associated to poor survival of stage I CRC. A high carcinoembryonic antigen (CEA) level ($p=0.031$, hazard ratio: 1.95), rectal cancer ($p=0.045$, hazard ratio: 1.64), LVI ($p=0.002$, hazard ratio: 3.95) and MSS phenotypes ($p=0.012$, hazard ratio: 2.98) were independently related to short disease-free survival of stage I CRC.

Conclusions: Compared with non-MAC, MAC patients had more T2 patients and more MSI phenotypes in stage I CRC at presentation, but the mucinous histology is not a significant predictor of recurrence and prognosis in stage I CRC.

Background

Colorectal cancer (CRC) can be classified by histological evaluation of tumor specimens [1]. Colorectal mucinous adenocarcinomas (MAC) were defined when the tumor mass consisted 50% or more of mucinous ingredient, mostly extracellular; while the other tumors were defined as non-mucinous adenocarcinomas (non-MAC). Non-MAC is the most common type of CRC (>85%), while 10–15% of CRC patients are MAC [2]. MAC differs from non-MAC for its special clinicopathological characteristics, compared with non-MAC, MAC has long been associated with an inferior response to treatment, especially radiotherapy and chemotherapy [3]. The debate on the prognostic value of MAC in patients is ongoing, MAC is still considered to be a poor prognosis and refractory subtype of the disease. MAC presents a high microsatellite instability (MSI) status, young age and advanced stage at presentation [4, 5]. But the prognostic impact of MAC is controversial, some studies shown that mucinous histology was an independent negative prognostic factor [6, 7], but not in others [8, 9].

In general, MAC patients present a more advanced stage than non-MAC as shown in previous studies [10, 11]. It is well known that the inferior prognostic impact of MAC can be close related to the more
advanced progression at presentation [12]. However, most previous studies focused on its clinicopathological characteristics and prognosis of stage III and IV diseases. Moreover, the mucinous pathological subtype can also be a negative factor even for stage II CRC patients [13]. Few studies have focused the impact in survival between MAC and non-MAC of stage I CRC.

Thus, our study aimed to clarify the prognostic impact of MAC focusing on stage I CRC and correlate the mucinous histology with clinicopathological features of stage I CRC.

**Patients And Methods**

The study is a single center study, 5753 patients were analyzed retrospectively, all of them have undergone radical resections due to CRC by specialist surgeon in the Sixth Affiliated Hospital between January 2011 to May 2016. The following exclusion criteria were applied: patients with familial adenomatous polyposis (FAP), hereditary non-polyposis CRC (HNPCC); patients with synchronous or metachronous cancer; death due to non-cancer causes such as heart disease and cerebral infarction; patients underwent local excision or neoadjuvant therapy were also excluded. Among them, 542 patients (9.42%) were diagnosed as stage I CRC on histopathologic examination and met the criteria for enrollment. Of the 542 patients, 12 patients lost to follow-up, and 27 patients died from non-cancer causes. Therefore, 503 patients were analyzed in this study.

**Clinicopathologic evaluation**

Before surgery, patients underwent a baseline assessment of demographics and disease characteristics, blood carcinoembryonic antigen (CEA) tests, and tumor imaging. At least two pathologists, who are specialized in CRC, assessed the surgical specimens. Among the 503 patients, 56 were defined as MAC when the tumor mass consisted 50% or more of mucin ingredient, mostly extracellular; and the other tumors were defined as non-MAC. Hematoxylin and eosin staining was used to assess lymph nodes metastasis and lymphovascular invasion (LVI). Immunohistochemically (IHC) assessment of mismatch repair (MMR) genes in tissue samples were performed as described by Förster et al. [14]. The clinicopathological features of all 503 patients are shown in Table 1. All patients were staged by TNM classification criteria [15].

| Table 1. The relationship between clinicopathological characteristics and mucinous adenocarcinoma in stage I colorectal cancer |
### Table

| Variable       | MAC (n=56)  | non-MAC (n = 447) | p value |
|----------------|-------------|-------------------|---------|
| Sex            |             |                   |         |
| Male           | 33\±58.9%  | 243\±54.3%       | 0.518   |
| Female         | 23\±41.1%  | 204\±45.6%       |         |
| Age            |             |                   |         |
| ≤ 65           | 39\±69.6%  | 278\±62.2%       | 0.277   |
| > 65           | 17\±30.4%  | 169\±37.8%       |         |
| Preoperative CEA|            |                   |         |
| ≤5 ng/dL       | 51\±91.1%  | 390\±87.2%       | 0.413   |
| > 5 ng/dL      | 5\±8.9%    | 57\±12.8%        |         |
| T classification|            |                   |         |
| 1              | 7\±12.5%   | 157\±35.1%       | 0.001*  |
| 2              | 49\±87.5%  | 290\±64.9%       |         |
| Location       |             |                   |         |
| Colon          | 24\±42.9%  | 133\±29.7%       | 0.046*  |
| Rectal         | 32\±57.1%  | 314\±70.3%       |         |
| Size           |             |                   |         |
| <3cm           | 27\±48.2%  | 266\±59.5%       | 0.107   |
| ≥3cm           | 29\±51.8%  | 181\±40.5%       |         |
| LVI            |             |                   |         |
| (-)            | 52\±92.8%  | 435\±97.3%       | 0.073   |
| (+)            | 4\±7.2%    | 12\±2.7%         |         |
| Less than 12 lymph nodes |        |                   |         |
| Yes            | 9\±16.1%   | 82\±18.3%        | 0.678   |
| No             | 47\±83.9%  | 365\±81.7%       |         |
| MSI            |             |                   |         |
| Yes            | 5\±8.9%    | 13\±2.9%         | 0.023*  |
| No             | 51\±91.1%  | 433\±97.1%       |         |

MAC: mucinous adenocarcinomas
CEA: carcinoembryonic antigen
MSI: microsatellite instability

### Treatment

All patients underwent radical surgery. Colon cancer is completely removed by mesocolic excision with Lymph node (LN) dissection at R0-resection level. Resection of rectal cancer were performed by total mesorectal excision as described [16]. Recurrence occurred in 68 of 503 patients during follow-up and 25 patients underwent re-radical surgery. Laparoscopic surgery is performed for most patients.

### Data collection

The follow-up information of 503 patients was collect and analyzed. The median follow-up period of all cases was 59 months (2 to 103 months). According to the mucinous histology, patients were divided into two groups: the MAC group and the non-MAC group. Clinicopathologic factors (age, sex, preoperative CEA lever, tumor location, tumor size, T stage, histologic subtype, the number of obtained lymph nodes, LVI,
MSI status) were analyzed. We selected the 5-year disease-free survival (DFS) as the primary endpoint, which defined as the time from the date of radical resection to the diagnosis of cancer recurrence. The 5-year overall survival rate (OS) was selected as the second endpoint, defined as the time from the date of radical resection to death caused by cancer.

**Statistical analysis**

The associations between the discrete variables were analyzed by Spearman rank correlation test. p value <0.05 was regarded as statistically significant. Univariate analyses were performed by $\chi^2$ tests to evaluate the associations between clinical variables and the tumor histology. The survival probability was analyzed by Kaplan–Meier procedure, and the distribution differences were assessed by the log-rank test. Clinicopathologic factors such as age, sex, preoperative CEA lever, tumor location, tumor size, T stage, histologic subtype, the number of obtained lymph nodes, LVI, MSI status were analyzed. In multivariate analysis, cox proportional risk model (HR) was also used to evaluate the predictive value of various factors. The statistical analysis was carried out by using IBM SPSS ver. 20.0 (IBM, Armonk, NY, USA).

**Results**

Table 1 summarized the clinicopathologic characteristics, all the 503 stage I CRC patients were classified as the MAC group and non-MAC group. MAC was identified in 56 (11.1%) patients by pathology. MAC was found in 33 males (58.9%) and 23 females (41.1%); non-MAC was found in 243 males (54.4%) and 204 females (45.6%). The mean ages of patients with MAC and non-MAC were 54.7±13.2 years and 59.1±11.8 years, respectively (p=0.277). 49 (87.5%) of the 56 patients with MAC had tumors classified as T2 and only 7 (12.5%) as T1. In contrast, 290 (64.8 %) of the 447 non-MAC were classified as T2 (p=0.001). The MAC appeared to be found significantly more locate at colon than the non-MAC (p=0.046). MSI status was found in 5 (8.9%) patients with MAC and 13 (2.9%) with non-MAC (p=0.023). There were nearly significantly more LVI in MAC patients than non-MAC patients (7.1% vs. 2.6% percent; p= 0.073).

During the following period, 22 of all stage I patients (503) died of cancer. Relationships between clinicopathological factors and overall survival in all stage I CRC are shown in Table 2. On univariate and multivariate analysis, patients with rectal cancer, being older, LVI positive, MSS status were found to relate to poorer cancer specific overall survival significantly, however, mucinous histology itself had no significant prognostic effect on OS (Table 2, Figs. 1a, 2). Less than 12 lymph nodes is a risk factor, which may lead to low staging. We divided our patients into two groups, there was no difference in survival between LN<12 or LN≥12.

| Table 2. Univariate and multivariate analyses for overall survival in stage I colorectal cancer |
|-----------------------------------------------|
| MAC: mucinous adenocarcinomas |
| CEA : carcinoembryonic antigen |
| MSI : microsatellite instability |
### Table 3. Univariate and multivariate analyses for disease free survival in stage I colorectal cancer

| Variable                  | Univariate analysis | Multivariate analysis |
|---------------------------|---------------------|-----------------------|
|                           | Mean OS (95% CI)    | P-value               | HR (95% CI)          | P-value |
| **Gender**                |                     |                       |                      |         |
| Male                      | 94.7(92.1-97.3)     | 0.155                 |                      |         |
| Female                    | 99.7(96.7-102.7)    |                       |                      |         |
| **Age**                   |                     |                       |                      |         |
| ≤ 65                      | 99.9(97.3-102.4)    | **0.032**             | 2.620(1.100-6.238)   | **0.030**         |
| > 65                      | 94.0(90.3-97.8)     |                       |                      |         |
| **Preoperative CEA**      |                     |                       |                      |         |
| ≤5                        | 99.0(96.7-101.2)    | 0.082                 |                      |         |
| > 5                       | 95.5(89.4-101.6)    |                       |                      |         |
| **T classification**      |                     |                       |                      |         |
| T1                        | 90.1(86.1-95.1)     | 0.414                 |                      |         |
| T2                        | 98.6(95.8-100.7)    |                       |                      |         |
| **Lesion location**       |                     |                       |                      |         |
| Colon                     | 98.6(97.1-100.2)    | **0.042**             | 5.418(1.243-23.626)  | **0.025** |
| Rectal                    | 97.1(94.6-100.0)    |                       |                      |         |
| **Size**                  |                     |                       |                      |         |
| <3cm                      | 98.8(95.8-101.8)    | 0.691                 |                      |         |
| ≥3cm                      | 97.9(95.1-100.7)    |                       |                      |         |
| **Mucinous histology**    |                     |                       |                      |         |
| MAC                       | 93.8(89.5-98.2)     | 0.748                 |                      |         |
| non-MAC                   | 98.6(96.1-100.7)    |                       |                      |         |
| **LVI**                   |                     |                       |                      |         |
| (−)                       | 99.2(97.1-101.3)    | <0.001*               | 9.735(3.072-30.853)  | <0.001* |
| (+)                       | 76.2(57.5-95.0)     |                       |                      |         |
| **Less than 12 lymph nodes** |             |                       |                      |         |
| Yes                       | 95.1(91.3-98.7)     | 0.585                 |                      |         |
| No                        | 98.4(96.1-100.7)    |                       |                      |         |
| **MSI**                   |                     |                       |                      |         |
| Positive                  | 99.3(97.5-101.2)    | **0.018**             | 4.213(1.216-14.60)   | **0.023** |
| Negative                  | 82.9(71.2-94.6)     |                       |                      |         |

Discussion

It is difficult to determine the clinicopathologic characteristics and long-term outcome of stage I MAC. Even though the long-term survival of stage I CRC is thought to be much better, it is still unclear whether mucinous histology had significant prognostic effect on stage I CRC. Previous research shows poor survival for CRC patients with a higher mucinous content [17, 18], but there were also reports with opposite conclusions [19, 20]. Here, we analyzed the prognostic value of MAC focusing on stage I CRC and correlated the mucinous histology with clinical and pathological features of stage I CRC. Compared

68 (13.5%) of the 503 stage I patients experienced recurrence, including 20 (3.9%) with local recurrence and 48 (9.6%) with distant metastasis, the most recurrences occurred within 2 years after operation, as shown in Fig. 1b. On univariate and multivariate survival analysis, patients with rectal cancer, higher CEA level, LVI positive, MSS status were independently related to short DFS, while mucinous histology was also not a significantly predictor for recurrence (Table 3, Fig. 1b, Fig. 3).

MAC: mucinous adenocarcinomas
CEA : carcinoembryonic antigen
MSI : microsatellite instability
| Variable                  | Without recurrence (n=435) | With recurrence (n=68) | Univariate P-value | Multivariate HR (95% CI) | P-value |
|--------------------------|---------------------------|------------------------|-------------------|--------------------------|---------|
| Gender                   |                           |                        |                   |                          |         |
| Male                     | 233(53.6%)                | 43(63.2%)              | 0.100             |                          |         |
| female                   | 202(46.4%)                | 25(36.8%)              |                   |                          |         |
| Age                      |                           |                        |                   |                          |         |
| ≤ 65                     | 277(63.7%)                | 40(58.8%)              | 0.422             |                          |         |
| > 65                     | 158(36.3%)                | 28(41.2%)              |                   |                          |         |
| Preoperative CEA         |                           |                        |                   |                          |         |
| ≤5                       | 388(89.2%)                | 53(77.9%)              | **0.010**         | 1.947(1.065-3.562)       | **0.031** |
| > 5                      | 47(10.8%)                 | 15(22.1%)              |                   |                          |         |
| T classification         |                           |                        |                   |                          |         |
| T1                       | 146(33.6%)                | 18(26.5%)              | 0.298             |                          |         |
| T2                       | 289(66.4%)                | 50(73.5%)              |                   |                          |         |
| Lesion location          |                           |                        |                   |                          |         |
| Colon                    | 142(32.6%)                | 14(20.6%)              | **0.045**         | 1.646(0.919-2.949)       | **0.094** |
| Rectal                   | 293(67.4%)                | 54(79.4%)              |                   |                          |         |
| Size                     |                           |                        |                   |                          |         |
| <3cm                     | 255(58.6%)                | 38(55.9%)              | 0.790             |                          |         |
| ≥3cm                     | 180(41.4%)                | 30(44.1%)              |                   |                          |         |
| Mucinous histology       |                           |                        |                   |                          |         |
| MAC                      | 47(10.8%)                 | 9(13.2%)               | 0.618             |                          |         |
| non-MAC                  | 388(89.2%)                | 59(86.8%)              |                   |                          |         |
| LVI                      |                           |                        |                   |                          |         |
| (-)                      | 425(97.7%)                | 62(91.2%)              | **0.021**         | 3.950(1.670-9.343)       | **0.002** |
| (+)                      | 10(2.3%)                  | 6(8.8%)                |                   |                          |         |
| Less than 12 lymph nodes |                           |                        |                   |                          |         |
| Yes                      | 73(16.8%)                 | 18(26.5%)              | 0.081             |                          |         |
| No                       | 362(83.2%)                | 50(73.5%)              |                   |                          |         |
| MSI                      |                           |                        |                   |                          |         |
| Positive                 | 13(3.0%)                  | 6(8.8%)                | **0.020**         | 2.975(1.277-6.932)       | **0.012** |
| Negative                 | 422(97.0%)                | 62(91.2%)              |                   |                          |         |

patients, MAC had more T2 patients in stage I at presentation, more colon cancers and a higher MSI status. Many independent risk factors for recurrence and long-term survival were found in our study, including abnormal CEA level, LVI and MSS phenotypes. However, there was no correlation between mucinous histology and survival in stage I CRC.

In our study, univariate and multivariate analyses showed that that the histology pattern of MAC was not a prognostic factor for DFS or OS. Although the pathological T2-classification of MAC was higher in stage I patients than in non-MAC patients (87.5% vs 64.9%, \( p=0.001 \)), distinct clinical results were not observed. Du et al. [21] also reported that patients with MAC in stage III alone shown poorer DFS and OS compared with the non-MAC group, which means the worse survival of MAC patients might be due to regional lymph node metastasis.

Serum CEA is the most widely used tumor markers for diagnosis and recurrence monitoring of CRC. Several studies have investigated the ability of CEA to predict tumor recurrence and metastasis [22-24]. However, in stage I CRCs, there has been a paucity of evidence for it being a predictive factor for recurrence. Here, we found abnormal pretreatment CEA was an independent risk factor for recurrence.
even in stage I CRC. It suggests that if the serum CEA level is high preoperative in patients, the recurrence of CRC should be closely monitored, even in stage I CRC.

LVI is considered to be an early event in lymph node metastasis, and it has been proved to be an independent predictor of survival in CRC. The LVI group showed a higher risk of recurrence and a significantly lower overall survival rate in advanced CRC compared with the non-LVI group[25]. Meanwhile, LVI also has an independent predictor power for poor prognosis rectal cancer after neoadjuvant therapy and surgery [26]. However, the prognostic value of LVI in stage I CRC patient has not been well studied. Our study confirms that LVI is an important risk factor for stage I CRC recurrence. This suggests that LVI might be a sensitive marker for local recurrence and distant metastasis, even the patients without LN metastases.

The effect of MSI on the prognosis of CRC is controversial. MSI status influences the prognosis of CRC only in specific stages [27, 28]. Compared to MSS patients, MSI patients were found to possess worse survival in stage III colon cancer [29]. While opposite conclusion was found that MSI status was related to a better survival in stage II CRC [30,31]. Our study revealed that stage I CRC patients with MSI status showed a much better survival compared with the MSS group. MSI tumors were also found significantly associated with mucinous histology in stage I CRC patients, suggesting patients of MC are suitable for immunotherapy when recurrence and metastasis occur in the future.

**Abbreviations**

CEA: carcinoembryonic antigen; CRC: colorectal cancer; DFS: disease-free survival; FAP: familial adenomatous polyposis; HNPCC: hereditary non-polyposis CRC; IHC: Immunohistochemically; MAC: mucinous adenocarcinomas; MMR: assessment of mismatch repair; MSI: microsatellite instability; LN: Lymph node; LVI: lymphovascular invasion; non-MAC: non-mucinous adenocarcinomas; OS: overall survival.

**Declarations**

**Ethics approval and consent to participate:** The study protocol was reviewed and approved by the institutional review board of the Sixth Affiliated Hospital, Sun Yat-sen University, China [E2019052]. This study was carried out in accordance with the recommendations of the Declaration of Helsinki for biomedical research involving human subjects.

**Consent to publication:** Not applicable.

**Availability of data and materials:** Please contact the corresponding author for data on reasonable request.

**Competing interests:** The authors declare that they have no competing interests.
Funding: This study was supported by National Health and Medical Research Council (NHMRC) Grant (1158402), Natural Science Foundation of Guangdong Province (China) (2018A030313621), and National Natural Science Foundation of China (NSFC) (81671928).

Authors' contributions: Conceived and designed the study: LH, SLL, LPW, LK. Implemented the surgery: LH, SLL, SCL, YC, ZL. Patients follow-up: HH, ZZ. Analyzed and interpreted the data: LH. Wrote the manuscript: LH, JD, CX, LPW, LK. All authors read and approved the final manuscript.

Acknowledgements: Not applicable.

References

1. Weitz J, Koch M, Debus J, Hohler T, Galle PR, Buchler MW. Colorectal cancer. Lancet. 2005;365(9454):153-65; doi: 10.1016/S0140-6736(05)17706-X.

2. Hugen N, Brown G, Glynne-Jones R, de Wilt JH, Nagtegaal ID. Advances in the care of patients with mucinous colorectal cancer. Nat Rev Clin Oncol. 2016;13(6):361-9; doi: 10.1038/nrclinonc.2015.140.

3. Catalano V, Loupakis F, Graziano F, Torresi U, Bisonni R, Mari D, et al. Mucinous histology predicts for poor response rate and overall survival of patients with colorectal cancer and treated with first-line oxaliplatin- and/or irinotecan-based chemotherapy. Br J Cancer. 2009;100(6):881-7; doi: 10.1038/sj.bjc.6604955.

4. Luo C, Cen S, Ding G, Wu W. Mucinous colorectal adenocarcinoma: clinical pathology and treatment options. Cancer Commun (Lond). 2019;39(1):13; doi: 10.1186/s40880-019-0361-0.

5. Kim HJ. Mucinous Subtype in Patients With Colorectal Cancer. Ann Coloproctol. 2017;33(2):44-5; doi: 10.3393/ac.2017.33.2.44.

6. Soliman BG, Karagkounis G, Church JM, Plesec T, Kalady MF. Mucinous Histology Signifies Poor Oncologic Outcome in Young Patients With Colorectal Cancer. Dis Colon Rectum. 2018;61(5):547-53; doi: 10.1097/DCR.0000000000001060.

7. Kanemitsu Y, Kato T, Hirai T, Yasui K, Morimoto T, Shimizu Y, et al. Survival after curative resection for mucinous adenocarcinoma of the colorectum. Dis Colon Rectum. 2003;46(5):160-7; doi: 10.1007/s10350-004-6518-0.

8. Nitsche U, Friess H, Agha A, Angele M, Eckel R, Heitland W, et al. Prognosis of mucinous and signet-ring cell colorectal cancer in a population-based cohort. J Cancer Res Clin Oncol. 2016;142(11):2357-66; doi: 10.1007/s00432-016-2224-2.

9. Farhat MH, Barada KA, Tawil AN, Itani DM, Hatoum HA, Shamseddine AI. Effect of mucin production on survival in colorectal cancer: a case-control study. World J Gastroenterol. 2008;14(5):6981-5; doi: 10.3748/wjg.14.6981.

10. Kim SH, Shin SJ, Lee KY, Kim H, Kim TI, Kang DR, et al. Prognostic value of mucinous histology depends on microsatellite instability status in patients with stage III colon cancer treated with
adjuvant FOLFOX chemotherapy: a retrospective cohort study. Ann Surg Oncol. 2013;20(11):3407-13; doi: 10.1245/s10434-013-3169-1.

11. Park JS, Huh JW, Park YA, Cho YB, Yun SH, Kim HC, et al. Prognostic comparison between mucinous and nonmucinous adenocarcinoma in colorectal cancer. Medicine (Baltimore). 2015;94(15):e658; doi: 10.1097/MD.0000000000000658.

12. Mekenkamp LJ, Heesterbeek KJ, Koopman M, Tol J, Teerenstra S, Venderbosch S, et al. Mucinous adenocarcinomas: poor prognosis in metastatic colorectal cancer. Eur J Cancer. 2012;48(4):501-9; doi: 10.1016/j.ejca.2011.12.004.

13. Hu X, Li YQ, Li QG, Ma YL, Peng JJ, Cai S. Mucinous Adenocarcinomas Histotype Can Also be a High-Risk Factor for Stage II Colorectal Cancer Patients. Cell Physiol Biochem. 2018;47(2):630-40; doi: 10.1159/000490018.

14. Forster I, Brockmann M, Schildgen O, Schildgen V. Microsatellite instability testing in colorectal cancer using the QiaXcel advanced platform. BMC Cancer. 2018;18(1):484; doi: 10.1186/s12885-018-4400-z.

15. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin. 2017;67(2):93-9; doi: 10.3322/caac.21388.

16. Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery–the clue to pelvic recurrence? Br J Surg. 1982;69(10):613-6; doi: 10.1002/bjs.1800691019.

17. Verhulst J, Ferdinande L, Demetter P, Ceelen W. Mucinous subtype as prognostic factor in colorectal cancer: a systematic review and meta-analysis. J Clin Pathol. 2012;65(5):381-8; doi: 10.1136/jclinpath-2011-200340.

18. Nitsche U, Zimmermann A, Spath C, Muller T, Maak M, Schuster T, et al. Mucinous and signet-ring cell colorectal cancers differ from classical adenocarcinomas in tumor biology and prognosis. Ann Surg. 2013;258(5):775-82; discussion 82-3; doi: 10.1097/SLA.0b013e3182a69f7e.

19. Ahnen DJ, Wade SW, Jones WF, Sifri R, Mendoza Silveiras J, Greenamyer J, et al. The increasing incidence of young-onset colorectal cancer: a call to action. Mayo Clin Proc. 2014;89(2):216-24; doi: 10.1016/j.mayocp.2013.09.006.

20. Lupinacci RM, Mello ES, Coelho FF, Kruger JA, Perini MV, Pinheiro RS, et al. Prognostic implication of mucinous histology in resected colorectal cancer liver metastases. Surgery. 2014;155(6):1062-8; doi: 10.1016/j.surg.2014.01.011.

21. Du W, Mah JT, Lee J, Sankila R, Sankaranarayanan R, Chia KS. Incidence and survival of mucinous adenocarcinoma of the colorectum: a population-based study from an Asian country. Dis Colon Rectum. 2004;47(1):78-85; doi: 10.1007/s10350-003-0014-9.

22. Lee JL, Yu CS, Kim TW, Kim JH, Kim JC. Rate of pulmonary metastasis varies with location of rectal cancer in the patients undergoing curative resection. World J Surg. 2015;39(3):759-68; doi: 10.1007/s00268-014-2870-y.
23. Duffy MJ. Carcinoembryonic antigen as a marker for colorectal cancer: is it clinically useful? Clin Chem. 2001;47(4):624-30.

24. Lee JH, Lee JL, Kim JC. Identification of Recurrence-Predictive Indicators in Stage I Colorectal Cancer: Reply. World J Surg. 2017;41(6):1658-9; doi: 10.1007/s00268-017-3994-7.

25. Jiang HH, Zhang ZY, Wang XY, Tang X, Liu HL, Wang AL, et al. Prognostic significance of lymphovascular invasion in colorectal cancer and its association with genomic alterations. World J Gastroenterol. 2019;25(20):2489-502; doi: 10.3748/wjg.v25.i20.2489.

26. Sun Q, Liu T, Liu P, Luo J, Zhang N, Lu K, et al. Perineural and lymphovascular invasion predicts for poor prognosis in locally advanced rectal cancer after neoadjuvant chemoradiotherapy and surgery. J Cancer. 2019;10(10):2243-9; doi: 10.7150/jca.31473.

27. Lochhead P, Kuchiba A, Imamura Y, Liao X, Yamauchi M, Nishihara R, et al. Microsatellite instability and BRAF mutation testing in colorectal cancer prognostication. J Natl Cancer Inst. 2013;105(15):1151-6; doi: 10.1093/jnci/djt173.

28. Phipps AI, Limburg PJ, Baron JA, Burnett-Hartman AN, Weisenberger DJ, Laird PW, et al. Association between molecular subtypes of colorectal cancer and patient survival. Gastroenterology. 2015;148(1):77-87 e2; doi: 10.1053/j.gastro.2014.09.038.

29. Kohonen-Corish MR, Daniel JJ, Chan C, Lin BP, Kwun SY, Dent OF, et al. Low microsatellite instability is associated with poor prognosis in stage C colon cancer. J Clin Oncol. 2005;23(10):2318-24; doi: 10.1200/JCO.2005.00.109. 

30. Nazemalhosseini Mojarad E, Kashfi SM, Mirtalebi H, Taleghani MY, Azimzadeh P, Savabkar S, et al. Low Level of Microsatellite Instability Correlates with Poor Clinical Prognosis in Stage II Colorectal Cancer Patients. J Oncol. 2016;2016:2196703; doi: 10.1155/2016/2196703.

31. Gao P, Song YX, Xu YY, Zhe S, Sun JX, Xu HM, et al. Does the prognosis of colorectal mucinous carcinoma depend upon the primary tumour site? Results from two independent databases. Histopathology. 2013 Nov;63(5):603-15.

Figures
Kaplan-Meier survival curves show that patients with a higher carcinoembryonic antigen (CEA) level (a), rectal cancer (b), LVI positive (c), and microsatellite stability (MSS) status (d) are independently related to disease free survival.

Figure 1
Figure 2

Kaplan-Meier survival curves show that patients being older (a), with rectal cancer (b), lymphovascular invasion (LVI) positive (c), and microsatellite stability (MSS) status (d) are significantly related to a poorer overall survival.
Figure 3

Univariate and multivariate survival analyses, which showed no significant differences in patient survival between mucinous adenocarcinomas (MAC) and non-MAC colorectal cancer, overall survival (a) and disease free survival (b).