Mucinous adenocarcinoma (MAC) is a histological subtype of colorectal cancer. Population-based studies have indicated that MACs accounts for 3.9% to 19% of colorectal cancer worldwide. According to the World Health Organization, MAC is “an adenocarcinoma in which a substantial amount of mucin (>50% of the tumor) is retained within the tumor.”

The oncologic behavior of MAC differs from nonmucinous adenocarcinoma (non-MAC). In particular, MAC has a worse prognosis than the non-MAC form. Several studies have reported the characteristics of MAC, but these reports have limitations. Because MAC is relatively rare among adenocarcinomas, few large-scale studies on it have been performed. Even for a large-scale study, the period of data collection would need to be as long as 30 years to compare the results with hereditary nonpolyposis colorectal cancer (HNPCC) and sporadic cancer. Limited information is provided in retrospective studies.

Postoperative survival for patients with MAC by stage is unclear and factors related to the survival of patients with MAC have not been well studied. Therefore, our aim in this study was to characterize patients with colorectal MAC through evaluation of a large, institution-based cohort with long-term follow-up.
perineural invasion, microsatellite instability (MSI) status), and adjuvant therapy were collected and analyzed. MAC was defined as a tumor containing more than half mucin by volume on histologic examination with pools of extracellular mucin containing malignant epithelium as acinar structure, strips of cells, or single cells. Colorectal cancer was staged according to the seventh American Joint Committee on Cancer tumor node metastasis staging system. All pathologic slides were examined by 2 experienced colorectal pathologists. High-frequency MSI (MSI-H) was defined as ≥2 of the 5 markers exhibiting instability, and low-frequency MSI (MSI-L) was defined as when only 1 of the 5 markers was unstable. Tumors with MSI-L belong to the category of microsatellite stability (MSS) tumors because they have a common molecular background. Tumors that exhibited MSI-H were classified as MSI and other tumors were classified as having MSS. All colorectal resection was performed with curative intent. This study was approved by the Institutional Review Board of Samsung Medical Center, Seoul, Korea.

Postoperative adjuvant treatment depended on the patient’s general condition and compliance and physician preference. Postoperative 5-fluorouracil-based chemotherapy was considered for all patients with T3, T4, or node-positive disease. Local recurrence, distant metastasis, 5-year disease-free
survival (DFS), and 5-year overall survival (OS) were assessed. Patients were followed at 3-month intervals for 2 years, at 6-month intervals for the next 3 years, and annually thereafter. On a semiannual basis or on suspicion of recurrence, follow-up examinations, including clinical history, physical examination, serum CEA assay, chest x-ray, abdominal pelvic computed tomography (CT) or magnetic resonance imaging, colonoscopy, or positron emission tomography (PET) scanning, were performed. Recurrence was determined by clinical and radiologic examination or histologic confirmation. The main pattern of recurrence was recorded as the first site of detectable failure during the follow-up period.

Statistical analyses were carried out using the Statistical Package for the Social Sciences for Windows, version 18.0 (SPSS Inc, Chicago, IL). The significance of differences between the groups was evaluated using a $\chi^2$ test or analysis of variance, as appropriate. Survival rates were calculated using the Kaplan–Meier method and prognostic factors and survival curves were compared using log-rank test factors. Factors that were significant ($P < 0.05$) on univariate analysis were entered into multivariate analysis using the Cox model. Variables potentially related to the risk of DFS or OS with $P < 0.05$ were included in multivariate analysis. A $P$ value of $0.05$ was considered statistically significant.

**RESULTS**

The demographic features of patients with MAC and non-MAC are in Table 1. The 2 groups showed no differences in sex, pathologic N category, bowel obstruction, bowel perforation, and lymphovascular or perineural invasion. Patients with MAC were younger than those with nonmucinous carcinoma ($P = 0.012$) and had larger tumor sizes ($P < 0.001$), higher preoperative CEA ($P < 0.001$) and higher pathologic T stage ($P < 0.001$). MAC was mainly located in the right colon (49.3% MAC vs 21.2% non-MAC, $P = 0.001$). Patients with MSI-H were more often in the mucinous group (Table 1). Adjuvant therapy such as concurrent chemoradiotherapy, chemotherapy, or radiotherapy was administered to 215 patients (78.5%) in the mucinous group and 3860 (62.2%) in the nonmucinous group. The median follow-up period was 48.0 months (range: 0–165 months).

We analyzed 5-year DFS and 5-year OS between the 2 groups and found that 5-year DFS was 76.5% in the mucinous group and 83.2% in the nonmucinous group ($P = 0.008$). The 5-year OS results were significantly different at 81.3% for the mucinous group versus 87.4% for the nonmucinous group ($P = 0.005$) (Figure 1). In subgroup analysis for stage 3 colorectal cancer, there was difference in the 5-year DFS, 75.7% in the mucinous group and 68.0% in the nonmucinous group ($P = 0.018$). Five-year OS of stage 3 was also different (88.5% vs 71.0%, respectively) ($P < 0.001$). But, 5-year DFS and OS in stages 0, 1, and 2 revealed that there were no significant differences between the 2 groups.

Univariate analyses demonstrated that age ($P < 0.001$), tumor size ($P < 0.001$), cancer location ($P < 0.001$), preoperative CEA (>5 ng/mL) ($P < 0.001$), pathologic T category ($P < 0.001$), pathologic N category ($P < 0.001$), bowel obstruction ($P < 0.001$), lymphovascular invasion ($P < 0.001$), perineural invasion ($P < 0.001$), and mucinous histology ($P = 0.001$) were associated with DFS. Multivariate analysis confirmed that age ($P < 0.001$), location of cancer ($P < 0.001$), preoperative CEA (>5 ng/mL) ($P < 0.001$), pathologic T category ($P < 0.001$), pathologic N category ($P < 0.001$), bowel obstruction ($P = 0.030$), and perineural invasion ($P < 0.001$) were independent prognostic factors for DFS. However, mucinous histology (MAC or non-MAC) was not an independent factor for DFS ($P = 0.071$) (Table 2).

The results of univariate analyses of the relationships between tested factors and OS were not different from the results for DFS. Multivariate analysis confirmed that age ($P < 0.001$), cancer location ($P < 0.001$), preoperative CEA (>5 ng/mL) ($P < 0.001$), pathologic T category ($P < 0.001$), pathologic N category ($P < 0.001$), bowel obstruction ($P = 0.009$), and perineural invasion ($P < 0.001$) were independent prognostic factors for OS (Table 3).

Multivariate subgroup analysis for colon location without rectal cancer revealed that age ($P < 0.001$), preoperative CEA (>5 ng/mL) ($P < 0.001$), pathologic T category ($P = 0.013$), pathologic N category ($P = 0.001$), perineural invasion ($P = 0.020$), and mucinous histology ($P = 0.026$) were independent factors for DFS (Table 4). However, in multivariate analysis, mucinous histology for rectal location was not an independent prognostic factor ($P = 0.854$). In addition, we performed subgroup analysis according to cancer stage. Multivariate analysis for stage III colorectal cancer revealed that mucinous histology had no significance for DFS ($P = 0.057$).

Recurrence occurred in 58 of 274 patients (21.2%) in the MAC group and in 919 of 6201 (14.8%) in the non-MAC group ($P = 0.004$). Locoregional recurrence was 17.2% (10/58) in the
TABLE 2. Predictive Factors for Disease-Free Survival by Univariate and Multivariate Analyses of the Cohort (n = 6475)

|                          | Univariate Analysis |          |          |          | Multivariate Analysis |          |          |          |
|--------------------------|---------------------|----------|----------|----------|-----------------------|----------|----------|----------|
|                          | HR                  | 95% CI   | P        | HR                  | 95% CI   | P        |          |
| Age, y                   | >60/≤60             | 1.72     | 1.49–1.98| <0.001   | 1.83                  | 1.43–2.34| <0.001   |
| Sex                      | Male/female         | 1.03     | 0.89–1.19| 0.676    | 1.22                  | 0.94–1.58| 0.127    |
| Size, cm                 | >4.5/≤4.5           | 1.87     | 1.62–2.16| <0.001   | 2.03                  | 1.59–2.60| <0.001   |
| Location of cancer       | Rectum/colon        | 1.67     | 1.45–1.92| <0.001   | 2.03                  | 1.59–2.60| <0.001   |
| Preoperative CEA         | >5/≤5               | 2.56     | 2.19–2.99| <0.001   | 1.87                  | 1.45–2.40| <0.001   |
| T category               | 3, 4/Tis, 1, 2      | 3.77     | 3.00–4.75| <0.001   | 3.05                  | 1.91–4.86| <0.001   |
| N category               | +/−                  | 2.88     | 2.49–3.32| <0.001   | 2.13                  | 1.63–2.80| <0.001   |
| Bowel obstruction        | +/−                  | 1.49     | 1.23–1.81| <0.001   | 1.42                  | 1.03–1.94| 0.030    |
| Bowel perforation        | +/−                  | 1.26     | 0.66–2.44| 0.485    | 1.17                  | 0.89–1.54| 0.275    |
| Lymphovascular invasion  | +/−                  | 2.59     | 2.14–3.12| <0.001   | 2.59                  | 2.14–3.12| <0.001   |
| Perineural invasion      | +/−                  | 3.37     | 2.63–4.33| <0.001   | 3.37                  | 2.63–4.33| <0.001   |
| MSI status               | MSI-H/MSI-L, MSS     | 0.78     | 0.46–1.30| 0.336    | 0.78                  | 0.46–1.30| 0.336    |
| Adjuvant therapy         | +/−                  | 1.12     | 0.96–1.30| 0.145    | 1.12                  | 0.96–1.30| 0.145    |
| Mucinous histology       | MAC/non-MAC          | 1.59     | 1.21–2.10| 0.001    | 1.59                  | 0.96–2.58| 0.071    |

CEA = carcinoembryonic antigen, CI = confidence interval, HR = hazard ratio, MAC = mucinous adenocarcinoma, MSI-H = high-frequency microsatellite instability, MSI-L = low-frequency microsatellite instability, MSS = microsatellite stability, Tis = carcinoma in situ.

TABLE 3. Predictive Factors for Overall Survival by Univariate and Multivariate Analyses of the Cohort (n = 6475)

|                          | Univariate Analysis |          |          |          | Multivariate Analysis |          |          |          |
|--------------------------|---------------------|----------|----------|----------|-----------------------|----------|----------|----------|
|                          | HR                  | 95% CI   | P        | HR                  | 95% CI   | P        |          |
| Age, y                   | >60/≤60             | 1.83     | 1.59–2.10| <0.001   | 2.01                  | 1.57–2.57| <0.001   |
| Sex                      | Male/female         | 1.03     | 0.89–1.18| 0.722    | 1.22                  | 0.94–1.58| 0.133    |
| Size, cm                 | >4.5/≤4.5           | 1.75     | 1.52–2.02| <0.001   | 1.90                  | 1.48–2.44| <0.001   |
| Location of cancer       | Rectum/colon        | 1.59     | 1.39–1.83| <0.001   | 1.82                  | 1.42–2.34| <0.001   |
| Preoperative CEA         | >5/≤5               | 2.40     | 2.05–2.80| <0.001   | 2.92                  | 1.83–4.66| <0.001   |
| T category               | 3, 4/Tis, 1, 2      | 3.48     | 2.76–4.38| <0.001   | 3.48                  | 2.76–4.38| <0.001   |
| N category               | +/−                  | 2.81     | 2.43–3.24| <0.001   | 2.81                  | 2.43–3.24| <0.001   |
| Bowel obstruction        | +/−                  | 1.53     | 1.26–1.86| <0.001   | 1.53                  | 1.26–1.86| <0.001   |
| Bowel perforation        | +/−                  | 1.24     | 0.64–2.39| 0.524    | 1.24                  | 0.64–2.39| 0.524    |
| Lymphovascular invasion  | +/−                  | 2.59     | 2.15–3.13| <0.001   | 2.59                  | 2.15–3.13| <0.001   |
| Perineural invasion      | +/−                  | 3.15     | 2.46–4.05| <0.001   | 3.15                  | 2.46–4.05| <0.001   |
| MSI status               | MSI-H/MSI-L, MSS     | 0.75     | 0.45–1.26| 0.276    | 0.75                  | 0.45–1.26| 0.276    |
| Adjuvant therapy         | +/−                  | 1.02     | 0.88–1.19| 0.796    | 1.02                  | 0.88–1.19| 0.796    |
| Mucinous histology       | MAC/non-MAC          | 1.49     | 1.13–1.96| 0.005    | 1.49                  | 1.13–1.96| 0.005    |

CEA = carcinoembryonic antigen, CI = confidence interval, HR = hazard ratio, MAC = mucinous adenocarcinoma, MSI-H = high-frequency microsatellite instability, MSI-L = low-frequency microsatellite instability, MSS = microsatellite stability, Tis = carcinoma in situ.

MAC group and 13.7% (126/919) in the non-MAC group (P = 0.451). Distant recurrence was 75.9% (44/58) and 81.1% (745/919), respectively (P = 0.329). In distant recurrence, lung metastasis occurred more often in the nonmucinous group (20.5% vs 39.2%, P = 0.013) but peritoneal metastasis was found more often in the mucinous group (31.8% vs 5.8%, P < 0.001) (Table 5).

DISCUSSION

MAC is an uncommon and rare histopathological type of colorectal cancer. In this study, patients with MAC were younger, had larger tumor sizes, a majority of right-sided colon cancer, and more advanced status and MSI-H compared with patients with non-MAC. These results were in accordance with other several studies.1–5 The proportion of MAC was 4.2% in this study, in close agreement with other studies, which reported results of 3.9% to 19%.1–5 Although several similar studies have been reported, they had a small sample size; our report was a large-scale, long-term study.

Even though poorer DFS and OS were seen for the MAC group compared with the non-MAC group, MAC histology was not a significant prognostic factor for DFS or OS. These results were in agreement with the previous studies.3,5,11 In subgroup analysis according to primary cancer location, mucinous histology was not a prognostic risk factor in subgroup analysis of cancers of the rectum but was an independent prognostic factor for cancers of the colon. The reason might be that MAC
had marginal significance in the nonmucinous group. Several studies suggest that a high rate of peritoneal metastases (36%–48.2%) is observed in patients with MAC.13–15 The reason for the peritoneal metastasis is not clear, but 1 study hypothesized that the production of mucus under pressure allows cancers to separate tissue planes in the bowel wall and gain access to the peritoneal cavity. In addition, the fluid produced by these tumors is taken up by the lymphatic system, which helps to push the tumor into regional lymph nodes.16 Peritoneal metastases are associated with poor prognosis. Survival is even worse if metastases to other organs are present.17 Therefore, in patients with MAC, imaging techniques such as PET-CT should be employed carefully during follow-up for early detection of peritoneal metastases.

More MSI-H is found in MAC than non-MAC patients.12,18 MSI status was not a significant prognostic factor in our results, even in subgroup analysis according to stage (data not shown). This result was in close agreement with a previous study.12 CRC patients with MSI-H have a significantly better prognosis compared to patients with intact mismatch repair.19,20 Well-planned studies are required to resolve this issue.

The limitations of this study were that it was from a single institution and the retrospective study design might result in biases. The 2 groups had different clinicopathologic characteristics. However, our report did not intend to compare and analyze equivalent groups, but to determine the characteristics of MAC and non-MAC.

In conclusion, MAC was found at more advanced stage and was mainly located at the right side of the colon. MAC indicated a worse prognosis for colon cancer. Our data suggested that patients with MAC could benefit from closer follow-up because their high rates of peritoneal metastasis are a known factor for poor prognosis. The biological behavior of MAC differs from non-MAC, so patients with MAC require special awareness during follow-up.

REFERENCES
1. Stewart SL, Wike JM, Kato I, et al. A population-based study of colorectal cancer histology in the United States, 1998–2001. Cancer. 2006;107:1128–1141.

## TABLE 4. Predictive Factors for Disease-Free Survival by Univariate and Multivariate Analyses for Cancers of the Colon (n = 4097)

| Variable                  | Univariate Analysis | Multivariate Analysis |
|---------------------------|---------------------|-----------------------|
|                           | HR | 95% CI  | P   | HR | 95% CI  | P   |
| Age, y                    |    |         |     |    |         |     |
| >60/≤60                   | 2.09 | 1.71–2.56 | <0.001 | 2.52 | 1.73–3.69 | <0.001 |
| Sex                       |    |         |     |    |         |     |
| Male/female               | 1.09 | 0.89–1.32 | 0.420 |     |         |     |
| Size, cm                  |    |         |     |    |         |     |
| >4.5/≤4.5                 | 2.04 | 1.67–2.50 | <0.001 | 1.34 | 0.92–1.95 | 0.126 |
| Preoperative CEA          |    |         |     |    |         |     |
| >5/≤5                     | 2.71 | 2.18–3.37 | <0.001 | 1.83 | 1.27–2.64 | 0.001 |
| T category                |    |         |     |    |         |     |
| 3, 4/Tis, 1, 2            | 4.45 | 3.09–6.42 | <0.001 | 2.45 | 1.20–4.97 | 0.013 |
| N category                |    |         |     |    |         |     |
| –/–                       | 2.59 | 2.13–3.15 | <0.001 | 1.94 | 1.34–2.83 | 0.001 |
| Bowel obstruction         |    |         |     |    |         |     |
| +/-                       | 1.83 | 1.45–2.30 | <0.001 | 1.47 | 0.99–2.19 | 0.054 |
| Bowel perforation         |    |         |     |    |         |     |
| +/-                       | 1.44 | 0.64–3.23 | 0.373 |     |         |     |
| Lymphovascular invasion   |    |         |     |    |         |     |
| +/-                       | 2.28 | 1.76–2.95 | <0.001 | 1.24 | 0.83–1.86 | 0.294 |
| Perineural invasion       |    |         |     |    |         |     |
| +/-                       | 2.72 | 1.87–3.96 | <0.001 | 1.72 | 1.09–2.72 | 0.020 |
| MSI status                |    |         |     |    |         |     |
| MSI-H/MSI-L, MSS           | 0.77 | 0.43–1.39 | 0.391 |     |         |     |
| Adjuvant therapy          |    |         |     |    |         |     |
| +/-                       | 0.88 | 0.72–1.08 | 0.210 |     |         |     |
| Mucinous histology        |    |         |     |    |         |     |
| MAC/non-MAC               | 1.60 | 1.12–2.29 | 0.009 | 1.99 | 1.08–3.63 | 0.026 |

CEA = carcinoembryonic antigen, CI = confidence interval, HR = hazard ratio, MAC = mucinous adenocarcinoma, MSI-H = high-frequency microsatellite instability, MSI-L = low-frequency microsatellite instability, MSS = microsatellite stability, Tis = carcinoma in situ.

## TABLE 5. Recurrence Patterns

|          | Mucinous | Nonmucinous | P  | Value |
|----------|----------|-------------|----|-------|
| Total    | 58/274 (21.2%) | 919/6201 (14.8%) | 0.004 |
| Locoregional | 10 (17.2%) | 126 (13.7%) | 0.451 |
| Distant | 44 (75.9%) | 745 (81.1%) | 0.329 |
| Liver | 9 (20.5%) | 255 (34.2%) | 0.060 |
| Lung | 9 (20.5%) | 292 (39.2%) | 0.013 |
| Liver and lung | 0 (0.0%) | 33 (4.4%) | 0.250 |
| Peritoneum | 14 (31.8%) | 43 (5.8%) | <0.001 |
| Distant lymph | 6 (13.6%) | 75 (10.1%) | 0.441 |
| node | | | |
| Other site | 6 (13.6%) | 47 (6.3%) | 0.110 |
| Both | 4 (6.9%) | 48 (5.2%) | 0.543 |
2. Du W, Mah JT, Lee J, et al. Incidence and survival of mucinous adenocarcinoma of the colorectum: a population-based study from an Asian country. Dis Colon Rectum. 2004;47:78–85.

3. Chew MH, Yeo SA, Ng ZP, et al. Critical analysis of mucin and signet ring cell as prognostic factors in an Asian population of 2,764 sporadic colorectal cancers. Int J Colorectal Dis. 2010;25:1221–1229.

4. Lee WS, Chun HK, Lee WY, et al. Treatment outcomes in patients with signet ring cell carcinoma of the colorectum. Am J Surg. 2007;194:294–298.

5. Kang H, O’Connell JB, Maggard MA, et al. A 10-year outcomes evaluation of mucinous and signet-ring cell carcinoma of the colon and rectum. Dis Colon Rectum. 2005;48:1161–1168.

6. Bosman FT. WHO Classification of Tumors of the Digestive System. 4th ed. Lyon: IARC; 2010.

7. Verhulst J, Ferdinande L, Demetter P, et al. Mucinous subtype as prognostic factor in colorectal cancer: a systematic review and meta-analysis. J Clin Pathol. 2012;65:381–388.

8. You JF, Hsieh LL, Changchien CR, et al. Inverse effects of mucin on survival of matched hereditary nonpolyposis colorectal cancer and sporadic colorectal cancer patients. Clin Cancer Res. 2006;12:4244–4250.

9. Laiho P, Launonen V, Lahermo P, et al. Low-level microsatellite instability in most colorectal carcinomas. Cancer Res. 2002;62:1166–1170.

10. Sung CO, Seo JW, Kim KM, et al. Clinical significance of signet-ring cells in colorectal mucinous adenocarcinoma. Mod Pathol. 2008;21:1533–1541.

11. Nitsche U, Zimmermann A, Spath C, et al. Mucinous and signet-ring cell colorectal cancers differ from classical adenocarcinomas in tumor biology and prognosis. Ann Surg. 2013;258:775–782.

12. Kim SH, Shin SJ, Lee KY, 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;20:3407–3413.

13. Hugen N, van de Velde CJ, de Wilt JH, et al. Metastatic pattern in colorectal cancer is strongly influenced by histological subtype. Ann Oncol. 2014;25:651–657.

14. Catalano V, Loupakis F, Graziano F, 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;100:881–887.

15. Negri FV, Wouterspoon A, Cunningham D, et al. Mucinous histology predicts for reduced fluorouracil responsiveness and survival in advanced colorectal cancer. Ann Oncol. 2005;16:1305–1310.

16. Sugarbaker PH. Mucinous colorectal carcinoma. J Surg Oncol. 2001;77:282–283.

17. Lemmens VE, Kloaler YL, Verwaal VJ, et al. Predictors and survival of synchronous peritoneal carcinomatosis of colorectal origin: a population-based study. Int J Cancer. 2011;128:2717–2725.

18. Ward R, Meagher A, Tomlinson I, et al. Microsatellite instability and the clinicopathological features of sporadic colorectal cancer. Gut. 2001;48:821–829.

19. Popat S, Huhner R, Houlston RS. Systematic review of microsatellite instability and colorectal cancer prognosis. J Clin Oncol. 2005;23:669–618.

20. Merok MA, Ahlquist T, Ruuvik EC, et al. Microsatellite instability has a positive prognostic impact on stage II colorectal cancer after complete resection: results from a large, consecutive Norwegian series. Ann Oncol. 2013;24:1274–1282.