Original Article

The Utility of Preoperative CT Scans for the Differentiation of Mucinous versus Non-mucinous Colorectal Adenocarcinoma

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Abstract

Introduction: To assess the utility of preoperative computed tomography (CT) scans for the differentiation of mucinous versus non-mucinous colorectal adenocarcinoma.

Methods: A retrospective study was conducted for a blind comparative assessment of preoperative abdominal CT scans in 143 participants, with either mucinous or non-mucinous colorectal adenocarcinoma (47 vs 96 participants) as determined from surgical specimens, by two experienced abdominal radiologists.

Results: The mean tumor size was significantly greater in mucinous group (p-value <0.001). The presence of a heterogeneous enhancement and an area of hypoattenuation greater than two-thirds of tumor volume were more frequently visualized in mucinous group (p-value = 0.001 and p-value <0.001, respectively). The combination of a heterogeneous enhancement plus an area of hypoattenuation more than two-thirds of tumor volume had diagnostic utility for mucinous adenocarcinoma with a sensitivity, specificity, and accuracy of 66.0%, 95.8%, and 86.0%, respectively.

Conclusions: Preoperative CT scans have potential for the differentiation of mucinous versus non-mucinous colorectal adenocarcinoma.

Keywords: Colorectal CA, Computed tomography (CT), Mucinous adenocarcinoma, Non-mucinous adenocarcinoma, Preoperative evaluation

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Introduction

Mucinous adenocarcinoma is a subtype of colorectal adenocarcinoma, characterized by a large amount of extracellular mucin content, at least 50.0% of the tumor volume as World Health Organization criteria.[1] The mucinous subtype has a reported 5.0-15.0% prevalence of colorectal adenocarcinoma and is associated with early metastases, rapid tumor recurrence after surgery, and poor prognosis. Patients with this tumor subtype require more aggressive surgery and closer postoperative follow up than patients with non-mucinous colorectal adenocarcinoma.[2-4]

Preoperative biopsy is the standard practice for evaluation of the tumor subtype, yet misclassification can occur because the mucin content is located predominantly in the submucosal layer. Preoperative imaging studies may help for the accurate prediction of the mucinous subtype. Tumors with a high signal intensity on T2-weighted magnetic resonance imaging (MRI) have been reported for mucinous tumors, attributed to the high mucin content.[5,6] Prior reports involving computed tomography (CT) studies have characterized the mucinous adenocarcinoma features such as a large tumor size, eccentric growth, heterogeneous enhancement, large hypoattenuation area, and intratumor calcification.[7]

To assess the utility of preoperative computed tomography (CT) scans for the differentiation of mucinous versus non-mucinous colorectal adenocarcinoma, a retrospective blinded review of the preoperative CT scans in both groups was conducted at our hospital in Bangkok, Thailand.

Methods

Study Participants

A single-center, retrospective study was conducted at a 2,200-bed university hospital in central Thailand. The study was approved by the hospital institutional review board, with a waiver of the need for written informed consent due to the study's retrospective design. The study cohort was comprised of patients who had preoperative abdominal CT scans within two months of surgery and a postsurgical diagnosis of either mucinous or non-mucinous colorectal adenocarcinoma from January 2005 through July 2017. Each participant's pathology specimen was a whole surgical specimen (not a core biopsy). The study exclusion criteria were patients who had undergone preoperative radiation or chemotherapy, the identification of two primary malignancies, and synchronous colonic lesions.

By a retrospective review of the archived surgical pathology and radiology records at our hospital, 143 patients were identified as the final study cohort. The study cohort included 68 female (47.6%) and 75 male (52.4%) patients and the overall mean age (standard deviation or S.D.) was 65.0 (11.8) years old. There were 47 participants (32.9%) with mucinous adenocarcinoma and 96 participants (67.1%) with non-mucinous adenocarcinoma. There were similar proportions of women in the mucinous (22, 46.8%) and the non-mucinous (46, 47.9%) groups (*P*-value = 1.000). The mean age (S.D.) was similar for the mucinous group (62.6 (11.4) years) and the non-mucinous group (66.1 (11.9) years) (*P*-value = .930). Data collection included the basic demographic data, clinical data (carcinoembryonic antigen or CEA level, treatments, and the treatment outcomes), and surgical pathology data (tumor size, location, degree of differentiation, histology subtype as mucinous vs. non-mucinous, tumor margin, adjacent organ invasion, and lymphatic spreading).

CT Techniques

Over a 12-year, 6-month study period, CT scans were performed using a variety of CT scanners, including three 64-slice CT scanners (***LightSpeed VCT*** and ***Discovery CT750 HD***, General Electric (GE) Healthcare, United States; and ***SOMATOM Definition Flash,*** Siemens, Germany) and a 256-slice CT scanner (***Revolution CT,*** GE Healthcare, and United States). Images were obtained from patients in the supine position with a breath hold during the entire scan covering the whole abdomen. The slice collimations were 1.25 millimeters (mm, reconstructed at 7.0 mm) and 1.5 mm (reconstructed at 7.0 mm) for the GE and Siemens scanners, respectively. Both thin and thick sliced images were available in Picture Archiving and Communication System (PACS) for routine clinical practice and retrospective review. All the participants underwent pre- and postcontrast studies, before and after a bolus intravenous injection of 80-100 milliliters (mL) of nonionic iodinated contrast

agent, followed by 20 mL of water via a power injector at a rate of 3 mL/second. Each participant had a portovenous phase with an 80-second delay for the postcontrast study. An additional arterial phase at a 35-second delay or a delayed bladder phase were available in some participants. Oral and rectal contrast administration was obtained as patients' tolerance, but varied over the study observation period, either using water or diluted water-soluble contrast.

CT Analysis

Two abdominal radiologists (with 22 and 13 respective years of experience in abdominal CT evaluation) separately reviewed the CT scans for each group in a random fashion. Each radiologist knew that the participants were diagnosed with colorectal adenocarcinoma, but were blinded to the clinical data and surgical pathology. The details from the CT analysis included:

1. Tumor location: Each tumor location was described by anatomical segments (rectum, rectosigmoid, sigmoid, descending colon, transverse colon, ascending colon, and cecum). Some large tumors occupying more than one anatomical segment were also documented.

2. Tumor size: Each tumor size was described by its maximal diameter and length (centimeter, cm). The ***maximal diameter*** was measured by the combination of two walls in circumferential lesions (not including the colonic lumen), or a single wall lesion in eccentric lesions. The ***length*** was roughly estimated by the summation of each short, angulated segment, not using the straight line.

3. Tumor morphology: The morphology of each tumor was classified as a ***circumferentia****l* vs. ***eccentric*** pattern; and ***infiltrative*** vs. ***mass-forming*** pattern.

4. Enhancement pattern: The enhancement pattern of each tumor was defined as a ***homogenous*** vs. ***heterogeneous*** enhancement.

5. Area of hypoattenuation: The area of hypoattenuation within each tumor on the portovenous phase was identified by eye estimation and categorized into three groups: less than 1/3 of the tumor volume, 1/3-2/3 of the tumor volume, and more than 2/3 of the tumor volume.

6. Internal calcification: The ***presence*** or ***absence*** of the internal calcification of each tumor was evaluated by a precontrast CT study.

7. Extracolonic spreading: The ***presence*** or ***absence*** of extracolonic spreading of each tumor was identified by the adjacent pericolonic fat stranding or gross extracolonic mass.

8. Adjacent organ invasion: The ***presence*** or ***absence*** of adjacent organ invasion of each tumor was assessed and described in detail.

9. Colonic obstruction: The ***presence*** or ***absence*** of colonic obstruction caused by each tumor was evaluated.

10. Complications: The complications caused by each tumor **(*fistula*** or ***perforation*)** were identified and recorded in detail.

11. Lymphadenopathy: The ***presence*** or ***absence*** of adjacent and remote lymphadenopathy was assessed in each participant. Lymphadenopathy was recognized if it had a short diameter of greater than 10 mm, a central necrotic portion, or the presence of a group of smaller lymph nodes.

12. Distant metastases: The ***presence*** or ***absence*** of metastatic lesions from colorectal adenocarcinoma were evaluated in each participant and recorded in details (liver, lung, bone, peritoneum, etc.). In participants with liver metastases, the presence or absence of internal calcification within liver masses were assessed by a precontrast CT study. Lung metastases were limitedly identified only if their locations were at lung bases included in the abdominal CT scans.

Any discrepancies between the two radiologists were solved by a consensus review.

Statistical Analysis

The demographic data was presented as the number (%) and mean ± S.D. The chi-square test and Fisher's exact test were used to compare the CT appearances between the two groups. A 2-sample t-test was performed to compare the quantitative variable between the two groups. All the statistical data analyses were performed by using PASW 18.0 (SPSS Inc.). A 2-sided p-value of less than or equal to 0.05 was considered as statistically significant.

Results

Study Participants

From the study cohort of 143 participants, there were 47 participants with mucinous adenocarcinoma and 96 participants with non-mucinous adenocarcinoma. Elevated CEA levels (> 3.4 ng/mL) were observed in 34 (72.3%) participants in

the mucinous group and in 63 (65.6%) participants in the non-mucinous group (*P*-value = .419). Positive tumor margins were identified in 12 (25.5%) mucinous adenocarcinomas and 4 (4.2%) non-mucinous adenocarcinomas (*P*-value < .001).

CT Analysis (Table 1)

1. Tumor location: Most tumors in each group were predominantly located in the rectum, rectosigmoid, and sigmoid colon: 35/47 (74.5%) of mucinous tumors and 70/96 (72.9%) of non-mucinous tumors. Right-sided colonic tumors in the cecum and ascending colon were seen in 8/47 (17.0%) mucinous tumors and 8/96 (8.3%) non-mucinous tumors. Overall, there was no significant difference in tumor location between the two groups (*P*-value = .368).

2. Tumor size: Mucinous tumors were significantly larger in the size measured as the maximal diameter (*P*-value < .001) and length (*P*-value < .001).

3. Tumor morphology (Figure 1, 2): Both groups showed a circumferential pattern slightly more than an eccentric pattern (*P*-value = .482); and an infiltrative pattern more than a mass-forming pattern (*P*-value = .516).

4. Enhancement pattern (Figure 1, 2): All the tumors in the mucinous group showed a heterogeneous enhancement versus 81.3% of tumors in the non-mucinous group (*P*-value = .001).

5. Area of hypoattenuation (Figure 1, 2): Most tumors (66.0%) in the mucinous group showed an area of hypoattenuation more than 2/3 of the tumor volume compared to 4.2% of tumors in the non-mucinous group (*P*-value < .001).

6. Internal calcification (Figure 3): The mucinous group had a tendency to show internal calcification (27.7%) more frequently than the non-mucinous group (14.6%), but the difference did not reach the statistical significance (*P*-value = .061).

7. Extracolonic spreading: There was no statistical difference in extracolonic spreading between the two tumor groups (*P*-value = .144).

8. Adjacent organ invasion: Six cases (12.8%) in the mucinous group showed adjacent organ invasions, including 2 cases of small bowel invasion, 2 cases of bladder invasion, 1 case of hepatic invasion, and 1 case of vaginal invasion. Four cases (4.2%) in the non-mucinous group showed adjacent organ invasions, including 3 cases of uterine invasion and 1 case of bladder invasion. However, there was no statistical significance between the two groups for this imaging feature (*P*-value = .081).

9. Colonic obstruction: Tumors in the mucinous group were less likely associated with colonic obstruction compared to in the non-mucinous group (25.5% vs. 34.4%). However, this difference did not reach the statistical significance (*P*-value = .285).

10. Complications: Tumors in the mucinous group tended to have fistulas and perforations more frequently than in the non-mucinous group (4.3% vs. 0.0%, and 2.1% vs. 0.0%, respectively). However, these complications were quite rare and the difference did not reach statistical significance (*P*-value = .106 and *P*-value = .329 for fistulas and perforations, respectively).

11. Lymphadenopathy: There was no statistical difference in lymphadenopathy between the two groups (*P*-value = .426).

12. Distant metastases: Overall, there was no significant difference in distant metastases between the two tumor types (*P*-value = .272). Internal calcification within liver metastases was identified in one-third (4 of 12) of the non-mucinous tumors **(Figure 4)** versus none of the mucinous tumors (*P*-value = .028).

Diagnostic test parameters: Together, the mucinous adenocarcinoma imaging characteristics of a heterogeneous enhancement and a large area of hypoattenuation more than two-thirds of the tumor volume were associated with a sensitivity, specificity, and accuracy of 66.0%, 95.8%, and 86.0%, respectively **(Table 2**).

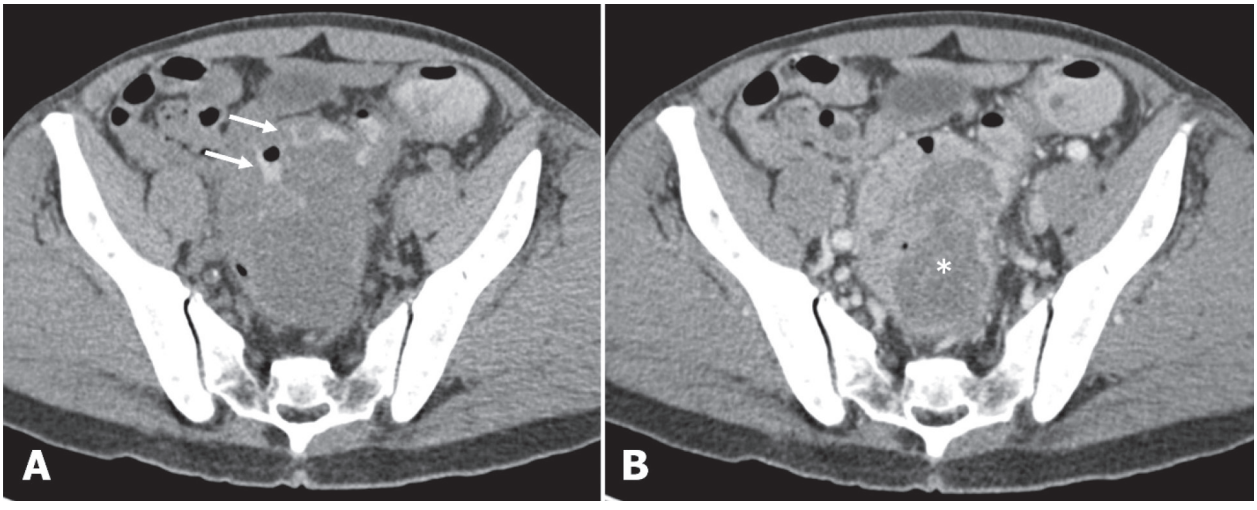

Figure 1 CT appearances of mucinous rectosigmoid CA.

a. Axial precontrast CT of a 62-year-old man demonstrates a large eccentric, infiltrative mass at the rectosigmoid colon. White arrows outline the contrast in the colonic lumen, emphasizing the eccentric nature of this mass.
b. Axial postcontrast CT of the same patient demonstrates heterogeneous enhancement of this colonic mass. The area of hypoattenuation (*) is more than 2/3 of the tumor volume.

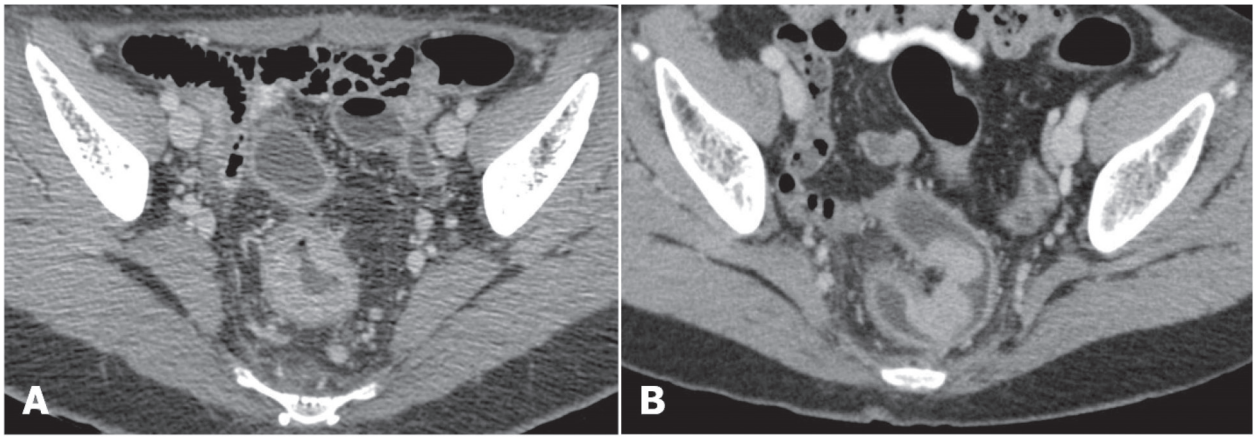

Figure 2 Various CT appearances of non-mucinous CA.

a. Axial postcontrast CT of a 43-year-old woman demonstrates a circumferential, infiltrative lesion at the rectum. It shows heterogeneous enhancement with an area of hypoattenuation < 1/3 of the tumor volume.
b. Axial postcontrast CT of a 67-year-old woman demonstrates a small eccentric, mass-forming lesion, originanting from the right lateral wall of the rectum. It shows homogeneous enhancement with an area of hypoattenuation < 1/3 of the tumor volume.

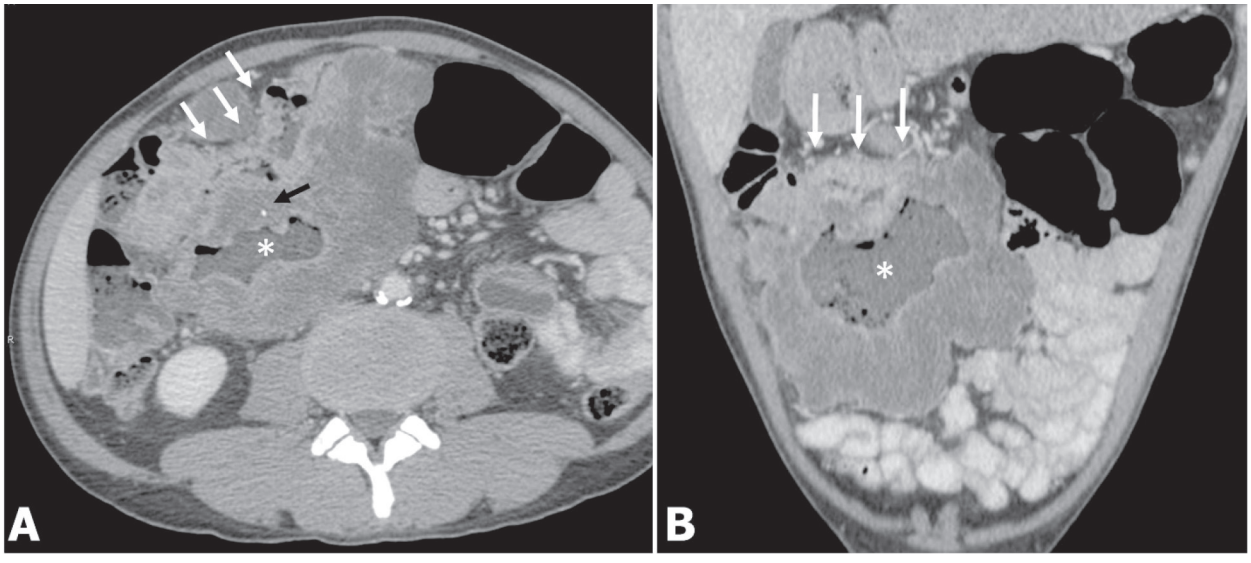

Figure 3 Mucinous CA with internal calcification.

a. and b. Axial and coronal postcontrast CT of a 47-year-old man demonstrate a large eccentric, exophytic, mass-forming lesion with internal cavitation (*), originating from the posteroinferior wall of the right transverse colon. The white arrows outline the anterosuperior wall of the right transverse colon. This large colonic mass shows heterogeneous enhancement with an area of hypoattenuation > 2/3 of the tumor volume. The black arrow in a. indicates a small internal calcification within the mass.

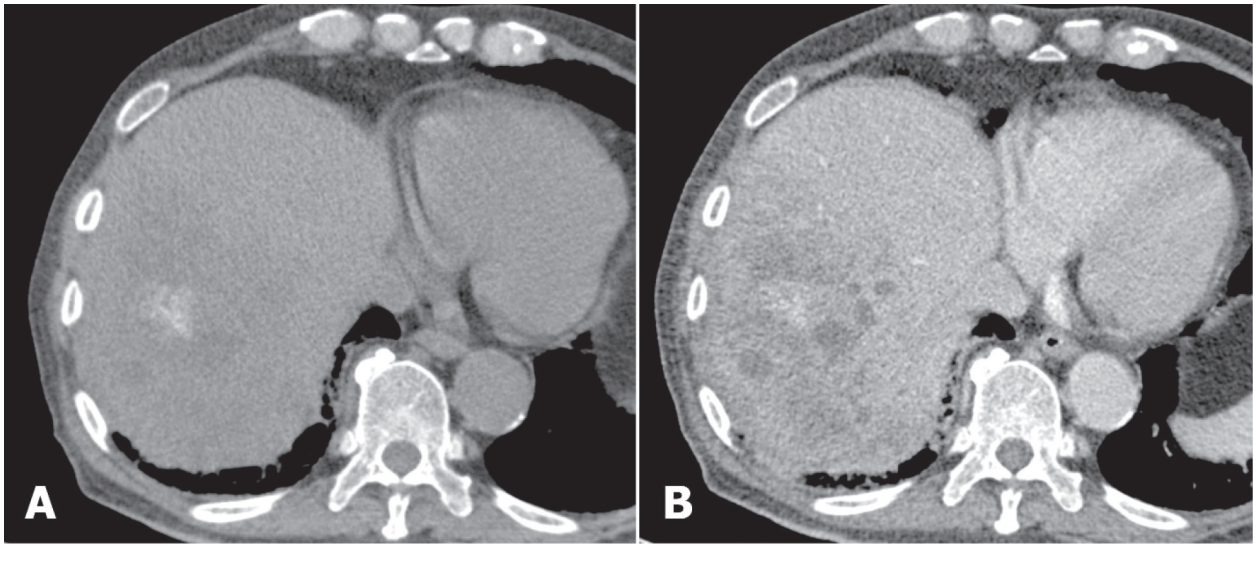

Figure 4 Non-mucinous CA with calcified liver metastasis.

a. and b. Axial precontrast and postcontrast CT of an 88-year-old man demonstrate a large heterogeneous hypodense liver metastasis in the right hepatic lobe. It shows internal calcification in the central area. His colonic mass at the transverse colon also shows internal calcification (not shown). His colonic mass pathology reveals mucin component of 5.0%.

Table 1 Comparison of computed tomography (CT) appearances in the 143 patients with mucinous versus non-mucinous colorectal adenocarcinoma

CT Appearances	Number (%)		*P*-value
	Mucinous Group (N = 47)	**Non-mucinous Group** (N = 96)	
Tumor location			.368
Rectum	13 (27.7)	24 (25.0)	
Rectum / Rectosigmoid	4 (8.5)	3 (3.1)	
Rectosigmoid	9 (19.1)	15 (15.6)	
Rectosigmoid / Sigmoid	0 (0.0)	1 (1.0)	
Sigmoid	9 (19.1)	26 (27.1)	
Sigmoid / Descending	0 (0.0)	1 (1.0)	
Descending	2 (4.3)	10 (10.4)	
Transverse	2 (4.3)	8 (8.3)	
Transverse / Ascending	2 (4.3)	1 (1.0)	
Ascending	2 (4.3)	5 (5.2)	
Ascending / Cecum	4 (8.5)	2 (2.1)	
Tumor size (cm): Mean ± S.D.			
Maximal diameter	4.7 ± 2.1	3.1 ± 1.4	< .001
Length	7.7 ± 3.9	5.4 ± 2.2	< .001
Tumor morphology			
Circumferential pattern	25 (53.2)	57 (59.4)	.482
Eccentric pattern	22 (46.8)	39 (40.6)	
Infiltrative pattern	36 (76.6)	78 (81.3)	.516
Mass-forming pattern	11 (23.4)	18 (18.8)	
Enhancement pattern			.001
Homogeneous	0 (0.0)	18 (18.8)	
Heterogeneous	47 (100.0)	78 (81.3)	
Area of hypoattenuation			< .001
1/3 of tumor	7 (14.9)	76 (79.2)	
1/3 - 2/3 of tumor	9 (19.1)	16 (16.7)	
>2/3 of tumor	31 (66.0)	4 (4.2)	
Internal calcification	13 (27.7)	14 (14.6)	.061
Extracolonic spreading	45 (95.7)	84 (87.5)	.144
Adjacent organ invasion	6 (12.8)	4 (4.2)	.081
Colonic obstruction	12 (25.5)	33 (34.4)	.285
Complications			
Fistula	2 (4.3)	0 (0.0)	.106
Perforation	1 (2.1)	0 (0.0)	.329
Lymphadenopathy	46 (97.9)	90 (93.8)	.426
Distant metastases*	18 (38.3)	28 (29.2)	.272
Liver	11 (23.4)	12 (12.5)	.028
Calcified liver masses†	0 (0.0)	4 (33.3)	
Lung	1 (2.1)	8 (8.3)	.272
Bone	0 (0.0)	0 (0.0)	-
Peritoneum	12 (25.5)	13 (13.5)	.076

Remarks: * Some participants had more than one organ metastases.
† The percentages of calcified liver masses used the no. of participants with liver metastases in each group as denominators.

Table 2 Significant CT appearances for differentiation of the 47 mucinous and 96 non-mucinous colorectal adenocarcinomas

Enhancement	Area of Hypoattenuation	Number (%)	
		Mucinous Group (N = 47)	Non-Mucinous Group (N = 96)
Homogeneous	<1/3 of tumor	0 (0.0)	17 (17.7)
	1/3 - 2/3 of tumor	0 (0.0)	1 (1.0)
	>2/3 of tumor	0 (0.0)	0 (0.0)
Heterogeneous	<1/3 of tumor	7 (14.9)	59 (61.5)
	1/3 - 2/3 of tumor	9 (19.1)	15 (15.6)
	>2/3 of tumor	31 (66.0)	4 (4.2)

Discussion

The major finding of this comparative study of preoperative CT scans in patients with colorectal adenocarcinoma was that the mucinous tumor subtype involved a larger tumor size, heterogeneous tumor enhancement, and a larger area of hypoattenuation when compared to in the non-mucinous group.

In our study, there were no significant differences in age, gender, or CEA level for the two patient groups. These results contrast with several prior studies that reported mucinous adenocarcinoma, relative to non-mucinous tumors, were associated with a younger age, female predominance, and high CEA levels. These were partly explained by the differences in the nationality of the participants in our study and prior studies, and partly by the small sample size of our study. Nevertheless, the mucinous group in our study showed a significantly higher incidence of a positive tumor margin, large tumor size, heterogeneous enhancement, and a large area of hypoattenuation, compared to in the non-mucinous group, thus agreeing with the findings in prior studies.[2-7] These appearances may be attributed to the large amount of extracellular mucin content seen in mucinous tumors, causing an increase of the tumor volume, heterogeneous enhancement and a large area of hypoattenuation seen on the CT scans. Although a mucin lake can be detected as an area of hypoattenuation on precontrast phase, it is well distinguished from enhanced mucosal wall on portovenous phase. This was the reason why we designed to evaluate the area of hypoattenuation within the tumor on portovenous phase. Additionally, intratumor calcification within the colonic mass was visualized in 13 (27.7%) mucinous adenocarcinomas compared to in 14 (14.6%) non-mucinous adenocarcinomas (*P*-value = .061). Calcified liver metastasis was not visualized in any of the mucinous adenocarcinoma cases, yet were visualized in 4 cases from the non-mucinous group, two of which showed internal calcification in the colonic masses. While calcified liver metastases on a CT scan should raise the index of suspicion for primary mucin producing adenocarcinoma, our study findings did not support this association. Nevertheless, we did not have pathological proof of these liver masses. Further studies with more participants or with pathological proof of these liver masses. Further studies with more participants or with pathological proof of liver metastases would be able to clarify this issue.

In applying two significant CT findings from our study (heterogeneous enhancement and an area of hypoattenuation more than two-thirds of the tumor volume) as the imaging criteria for the diagnosis of mucinous adenocarcinoma, the test utility had 66.0% sensitivity, 95.8% specificity, and 86.0% accuracy. We were not able to calculate predictive values of these criteria because the prevalence of mucinous and non-mucinous tumors in our study did not reflect the true prevalence estimates. To get enough participants in the mucinous group, we expanded the study time to a period of 12 years and 6 months. In the same period, we could have gotten many more participants in the non-mucinous group, but we selected only 96 consecutive non-mucinous patients backwards from July 2017 to be studied. With our criteria for the diagnosis of mucinous tumors, there were 4 false positive cases from the non-mucinous group. The histopathology

review of these 4 cases showed a variable mucin content of 5.0% to 20.0%. These 4 cases showed areas of extensive fibrinopurulent inflammation, necrosis, or both **(Figure 5)**, causing a heterogeneous enhancement and a large area of hypoattenuation on the CT images. This issue was suggested in a prior study[7] and emphasized by our study.

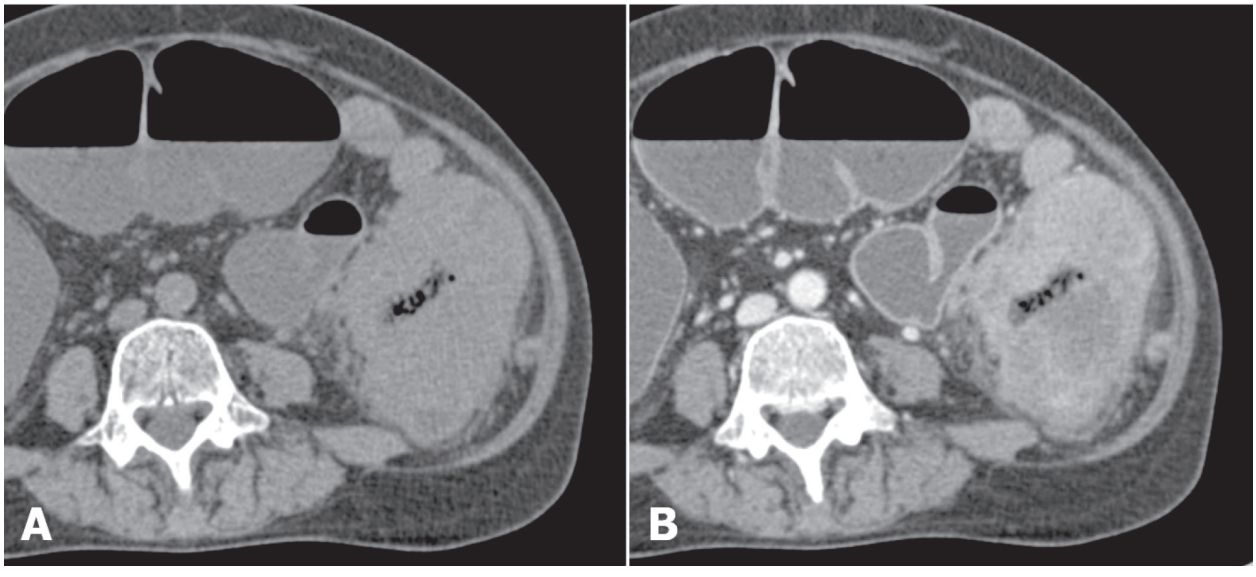

Figure 5 Non-mucinous CA with a large area of hypoattenuation.

a. Axial precontrast CT of a 67-year-old woman demonstrates a large infiltrative lesion at the descending colon.
b. Axial postcontrast CT of the same patient demonstrates heterogeneous enhancement of this colonic mass with a large area of hypoattenuation, more than 2/3 of the tumor volume. Her pathology reveals mucin content of 10.0% with areas of extensive fibrinopurulent inflammation and necrosis.

Liu et al.[8] reported the use of radiomics parameters from dual-energy CT images for differentiation between metastatic lymph nodes and nonmetastatic lymph nodes in patients with mucinous colorectal adenocarcinoma. Radiomics is a novel field of medical imaging that aims to extract a large number of quantitative features from medical images using data characterization algorithms. It has the potential to show disease characteristics that are difficult to be appreciated by human eye alone. Further studies using radiomics for prediction of mucinous colorectal adenocarcinoma should be performed.

This study had notable limitations inherent in the retrospective design conducted at a single institution. Second, the prevalence of mucinous and non-mucinous tumors in the present study did not reflect the true prevalence estimates as described earlier. Third, the area of hypoattenuation within the tumor was estimated roughly by the radiologists' opinion as routinely performed in clinical practice. It was not accurately measured either in density or volume. Forth, with the retrospective design and the relatively rare prevalence of mucinous adenocarcinoma, we could not control the participants in both groups to be in the same staging, this would affect the result of tumor size described in this study. Lastly, although the findings were from a limited sample size, the patients were consecutively identified over a 12-year, 6-month period and the methods of analysis accounted for the variations in the CT scanners, the details in the CT techniques used, the surgical pathology reports, and involved the re-assessment of some of the specimens.

In conclusion, the findings from this study support that a preoperative CT scan can potentially identify mucinous adenocarcinoma relative to non-mucinous adenocarcinoma. A colonic mass with heterogeneous enhancement and an area of hypoattenuation more than two-thirds of the tumor volume should increase the preoperative index of suspicion for mucinous adenocarcinoma.

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Compliance with Ethics Requirements Yes
Conflict of interest There are no potential conflicts of interest to declare.

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