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Quantitative MRI assessment of mucinous rectal adenocarcinoma to predict tumour response after neoadjuvant therapy

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AIM: To evaluate the association between volume ratio of the mucus pool and tumour response to neoadjuvant therapy in patients with mucinous rectal adenocarcinoma (MC).

MATERIALS AND METHODS: The volume of the mucus pool and whole tumour on pre-therapeutic T2-weighted magnetic resonance imaging (MRI) of 79 patients was measured using semi-automated software. Mucus pool volume, whole tumour volume, and volume ratio of the mucus pool were compared to tumour response and tumour and lymph node down-staging after neoadjuvant therapy using receiver operating characteristic curve (ROC) and multivariate logistic regression analysis.

RESULTS: After preoperative neoadjuvant therapy of rectal MC, the rate of pathological complete response, tumour downstaging, tumour response, and lymph node downstaging were 9%, 48%, 39% and 58%, respectively. Tumour downstaging more frequently occurred in patients with a mucus pool volume ratio of at least 68.3% (area under the ROC curve [AUC], 0.793 with 95% confidence interval [CI]: 0.693–0.893), and at least 62.1% for identifying those with a higher tumour response with an AUC of 0.739 (95% CI: 0.630–0.847).

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CONCLUSION: A higher volume ratio of mucus pool in patients with MC may be related to more tumour downstaging and therapy response, and therefore, could serve as an independent imaging biomarker for predicting tumour response to neoadjuvant therapy.
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Introduction

Mucinous rectal adenocarcinoma (MC) is a histological subtype of rectal carcinoma, which represents approximately 10% of rectal cancers, characterised by an abundant extracellular mucus pool that constitutes >50% of the whole tumour volume.[1,2] Patients with MC tend to have a higher pathological stage at the time of diagnosis, a greater tendency to metastasise and exhibit local recurrence, and an unfavourable overall prognosis compared to patients with non-mucinous rectal cancer.[3–6] The neoadjuvant therapy efficiency for MC is less than that for non-mucinous adenocarcinoma[6]; however, adjuvant therapy is an independent factor for improvement of overall MC patient survival.[7] MC patients have benefited from preoperative neoadjuvant therapy, which should be recommended for the treatment of patients with the MC subtype.[8–10]

Rectal magnetic resonance imaging (MRI) allows detection of the mucus pool, which distinguishes MC from non-mucinous rectal cancer.[11,12] The mucus pool has bright high signal intensity on T2-weighted imaging.[13] Diagnosis of MC by pre-therapeutic MRI has been shown to be diagnostically superior to preoperative initial biopsy, and MRI identification for the mucus pool can be used to predict the efficacy of neoadjuvant therapy[6]; however, there have been no previously published reports on whether the proportion of the mucus pool within the whole MC tumour, as visualised by pre-therapeutic MRI, is associated with the responsive of the tumour to preoperative neoadjuvant therapy. Because of differences in the efficacy of neoadjuvant therapy between MC and non-mucinous rectal adenocarcinoma, it was hypothesised that the variation in the proportion of the mucus pool as measured by pre-therapeutic MRI could be representative of the differences in biological characteristics between these tumours, and, whether the proportion of mucus pool is related to the response to neoadjuvant therapy.

The purpose of this study was to evaluate the association between the volume ratio of the mucus pool and the response of the tumour to neoadjuvant therapy in patients with rectal MC.

Materials and methods

The study was approved by the institutional review board, and the informed consent requirement for this retrospective study was waived.

Study population

The pathology databases of consecutive patients with histopathologically confirmed rectal MC (n=127) were selected retrospectively from the electronic medical records system from January 2012 to May 2017. Inclusion criteria were patients who had undergone a rectal MRI examination for the initial diagnosis; who had high signal intensity on pre-therapeutic MRI T2-weighted images of the whole tumour[11,14] and a mucus pool with a volume percentage of >50% of the tumour according to the measurement data obtained as described below; and who had undergone neoadjuvant therapy, and surgical resection. Patients (n=48) that did not meet the inclusion criteria were excluded. Seventy-nine consecutive patients (mean age, 52 years; range, 20–78 years; 53 men with a mean age of 52 years [range, 20–75 years] and 26 women with a mean age of 52 years [range, 27–78 years]) were identified and enrolled in this retrospective study. Patients enrolled in this study underwent neoadjuvant therapy (5-fluorouracil, leucovorin, and oxaliplatin treatment group [n=42]; 5-fluorouracil and a total dose of 46–50.4 Gy of radiation group [n=37]), followed by radical surgical resection.

Image acquisition

MRI images were obtained using a 1.5-T system (Optix-360, GE Healthcare, USA) with an eight-element body-array coil. Patients received an antispasmodic (10 mg anisodamine hydrochloride injection, Hangzhou Minsheng Pharmaceutical, China) to minimise bowel peristalsis-related artefacts. Sagittal, axial, and coronal T2-weighted fast spin-echo MRI sequences of the rectum were obtained along with axial T1-weighted fast spin-echo imaging and diffusion-weighted imaging sequences. Routine T2-weighted imaging sequences were performed with the following parameters: 4320 ms repetition time (TR)/120 ms echo time (TE); 224×320 matrix; 28 cm field of view; 19 echo train length (ETL); 4 mm section thickness; 1 mm section gap; and scanning time from 4 to 11 minutes. This study focused on the T2-weighted imaging sequence.

Evaluation of the mucus pool

The findings from the first diagnostic rectal MRI examination prior to neoadjuvant treatment were considered the natural state of the mucus pool within the whole tumour. T2-weighted imaging on pre-therapeutic MRI examination was used to identify and measure the volume of the mucus

pool.[11,14] The volume of the mucus pool and whole tumour were measured independently by a radiologist (reader 1: *., with 4 years of experience in reporting pelvic and rectal MRI data) by manually tracing the outer edge of the lesion on the axial, coronal, and sagittal T2 weighted MRI images. Areas of the mucus pool were defined as regions with a bright-high-signal-intensity confined to the rectal wall and/or infiltrated to the perirectal space. The boundaries of the whole tumour and mucus pool were outlined manually as mentioned above. Fig 1 shows that the whole tumour and mucus pool volumes were displayed automatically in a three-dimensional format and were calculated by summing each cross-sectional volume at a workstation (Advantage Workstation 4.1; GE Medical Systems). The proportion of the mucus pool was calculated as follows: (mucus pool volume/whole tumour volume) × 100.

Evaluation of tumour staging using baseline MRI

Two gastrointestinal radiologists (*. and*, with 5 and 20 years of experience in rectal MRI) independently reviewed the T2-weighted images retrospectively from the first rectal MRI examination and determined the radiological T and N categories (Fig 2). T categories were defined as follows: T1, tumour lesion was confined to the submucosal layer; T2, tumour signal intensity extending to the muscularis propria with irregularity and/or thickening of the muscle layer; T3, tumour invasion through the muscularis propria into the subserosa or into non-peritonealised perirectal tissues; T4, tumour penetrating to the surface of the visceral peritoneum or invading directly into other organs or structures.[15,16] Lymph node staging was performed according to the number of lymph nodes suspected of being malignant,

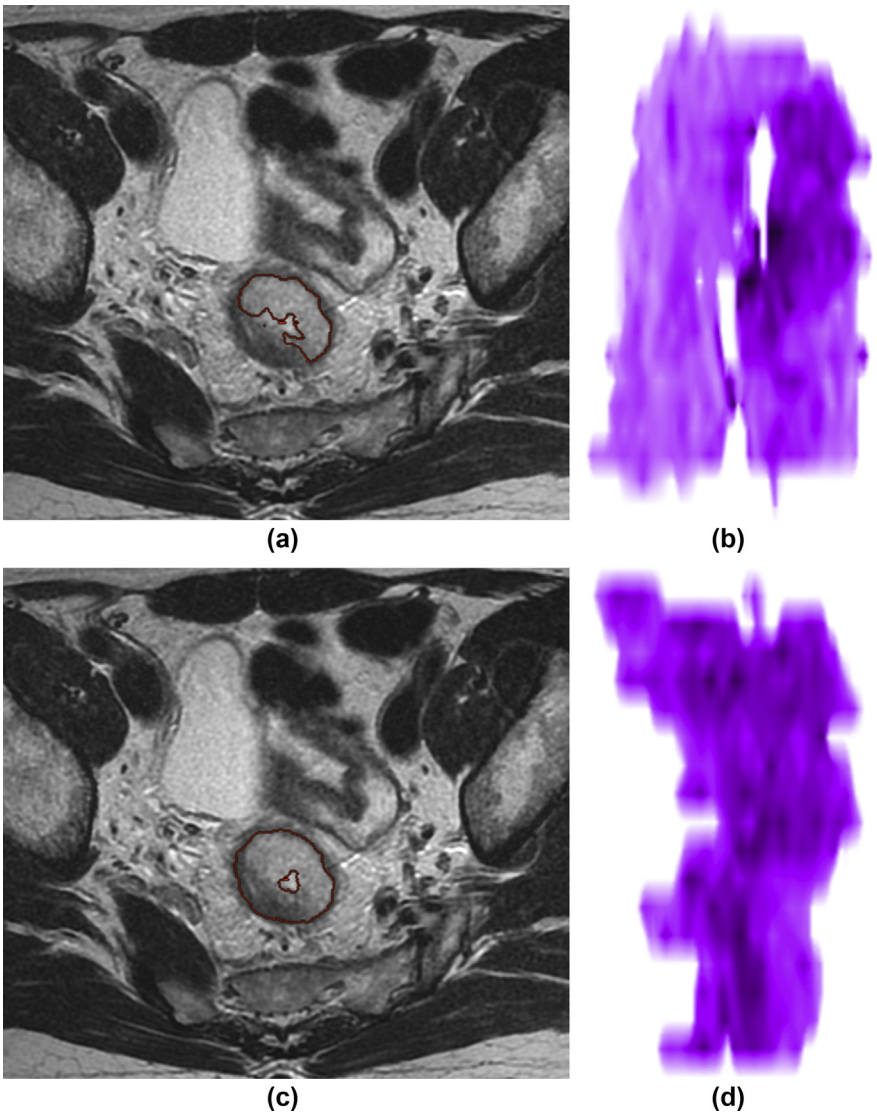

Figure 1 (a) T2-weighted fast spin-echo axial MRI volumetric image and (b) volume-rendered image of the mucus pool obtained in a 48-year-old man prior to neoadjuvant therapy. The volume of the mucus pool was 21.3 ml. (c) T2-weighted fast spin-echo axial oblique MRI volumetric image and (d) volume-rendered image of whole tumour in the same patient, which had a volume of 35.2 ml. The volume ratio of the mucus pool was 60.5%.

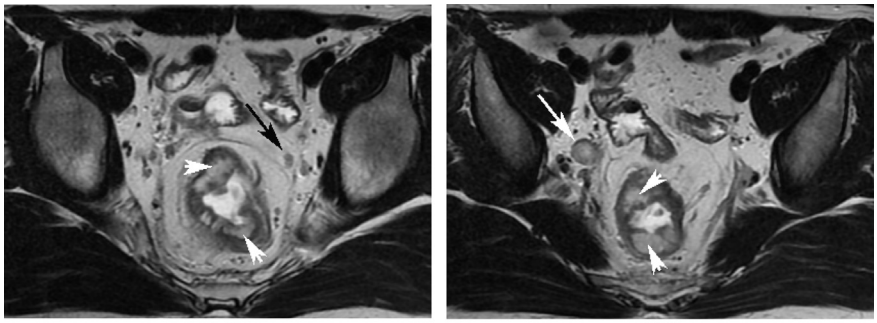

Figure 2 (a) T2 weighted MRI image of a patient with T3 disease showing the tumour contained a notable mucus pool (white arrows) that infiltrated the full extent of the rectal wall. There is a lymph node (N1 stage) with an ill-defined border, irregular margin on the front left side of the rectal mesorectal fascia (black arrow). (b) The mucus pool (white arrows) has a bright-high-signal intensity and appears in another image of the same patient. Also shown is a mucus node (white arrow) on the right side of the iliac blood vessels.

which was determined based on an ill-defined border, irregular margin, or mixed intranodal signal intensity, and with a short diameter of >5 mm. N categories were defined as follows: N0, absence of suspected malignant lymph node; N1, presence of 1–3 regional lymph nodes suspected of being malignant; N2, presence of four or more regional lymph nodes suspected of being malignant.[17] Perirectal mucus nodes, which had a bright high signal intensity on T2-weighted MRI, were included in addition to the lymph node staging as the presence of high-signal-intensity mucus nodes, or the absence of mucus nodes (Fig 2). Discrepant results were reassessed in consensus.

Histopathological examination and evaluation of the tumour pathological responsiveness

Histopathological tumour assessment and nodal staging were performed according to the TNM system by a pathologist (*, with >20 years of experience). To assess the pathological responsiveness of the tumours and lymph nodes to neoadjuvant therapy, the patients were divided into downstaging and non-downstaging groups (Table 1). Tumour downstaging was defined whenever a patient staged as T4, T3 or T1–2 on the pre-therapeutic MRI examination was later staged as T3, T2, or T0, respectively, or lower upon histopathological examination after the neoadjuvant therapy and surgery. Lymph node downstaging was defined as when patients staged as N1–2 on the pre-therapeutic MRI examination were later staged as N0 upon the histopathological examination following surgery. Patients that did not meet the above criteria were defined as non-downstaging. As to the histopathological examination, according to the 7th AJCC staging and Ryan *et al.*,[18] all patients were categorised into those whose tumours responded to therapy (responsive group, no viable cancer cells, or single cancer cells) and those whose tumours did not respond to therapy (non-responsive group, residual cancer outgrown by fibrosis, significant fibrosis outgrown by cancer, or no fibrosis with extensive residual cancer) based on the tumour regression grade (TRG).

Statistical analysis

Statistical analysis was performed using SPSS (version 19.0). Associations between mucus pool volume, whole tumour volume, mucus pool volume ratio, clinical characteristics, tumour and lymph node downstaging, and tumour pathological responsiveness were studied univariately. The chi-squared test was used for categorical variables and Fisher's exact test was used for categorical variables with small cell counts, and the unpaired independent samples

Table 1
Pre- and post-neoadjuvant therapy (NT) tumour (T) and lymph node (N) staging and pathological tumour regression grading (TRG) in 79 patients.

Tumour and lymph node staging		TRG[c]			Total
Pre-T stage[a]	Post-T stage[b]	TGR 1	TGR 2	TGR 3	
T1-2	T1-2	0	1	2	3
T3	T0	8	0	0	8
T3	T1-2	6	2	0	8
T3	T3	9	13	14	36
T4	T0	2	0	0	2
T4	T1-2	2	1	0	3
T4	T3	4	12	1	17
T4	T4	0	0	2	2
Pre-N stage[a]	Post-N stage[b]	TGR 1	TGR 2	TGR 3	
N0	N0	10	2	2	14
N0	N1	1	2	1	4
N0	N2	1	0	0	1
N1	N0	4	6	3	13
N1	N1	3	3	1	7
N1	N2	0	0	1	1
N2	N0	7	8	5	20
N2	N1	5	3	3	11
N2	N2	0	5	3	8

Data are numbers of patients; TRG 1: no viable cancer cellsor single cells or small groups of cancer cells; TRG 2: residual cancer outgrown by fibrosis; TRG 3: significant fibrosis outgrown by cancer.

[a] Tumour and lymph node stages based on pre-therapeutic MRI examination.

[b] Pathological tumour and lymph node stages based on surgical specimens after neoadjuvant therapy.

[c] The three-point TRG systems based on surgical specimens after neoadjuvant therapy.

t-test or Mann–Whitney *U*-test was used for continuous variables with normal or skewed distributions, respectively. The Kruskal–Wallis test was used to evaluate the relationship between tumour and lymph node staging on pre-therapeutic MRI with neoadjuvant therapy response.

The diagnostic performances of mucus pool volume, whole tumour volume and volume ratio of mucus pool for predicting tumour downstaging and pathological responsiveness were calculated with receiver operating characteristic (ROC) curve analysis. The optimal cut-off values with the optimised combination of sensitivity and specificity were also calculated from each ROC curve. The area under the ROC curve (AUC) and 95% confidence intervals (CIs) were calculated.[19] Multivariate logistic regression analysis was performed to identify factors that were associated with tumour downstaging and pathological responsiveness after neoadjuvant therapy. The backward elimination of the least significant variables based on the log likelihood ratio was used to confirm that the excluded covariates did not change the model fit significantly. Odds ratios (ORs) with 95% confidence intervals were estimated. A p-value of <0.05 was considered indicative of a significant difference.

In addition, a randomly sampled subgroup ($n=20$) was also evaluated, according to the above method, by reader 1 (*) and another reader (reader 2: *, with 5 years of experience evaluating and reporting pelvic MRI data) 1 month later, respectively. Intra-observer correlation coefficients (ICCs) for continuous variables were used for inter–and intra-observer agreement between the volumetry by reader 1 and reader 2, as well as between the twice-generated volumetry by reader 1. Referring to the Fleiss criterion, an ICC >0.75 was considered to indicate evaluations in good agreement.

Results

Twenty patients with mean age of 49.1 ±16.4 years were selected randomly from 79 patients to assess whether observer agreement was representative of the entire cohort. The ICC between the two study radiologists was 0.795 (95% CI: 0.490–0.919) for mucus pool volumetry and 0.818 (95% CI:0.550–0.927) for whole tumour volumetry. The ICC between two measurements made by reader 1 was 0.897 (95% CI: 0.745–0.959) and 0.877 (95% CI: 0.693–0.951) for mucus pool and whole tumour volumetry, respectively. For the volume ratio of the mucus pool, the ICC was 0.875 (95%CI: 0.681–0.951) between the two radiologists and 0.904 (95% CI: 0.761–0.962) between the twice-generated volumetry by reader 1.

Tumour downstaging

The mucus pool and whole tumour volumes and volume percentages of the mucus pool were significantly different between the groups with and without tumour downstaging (Table 2, Fig 3). There was a significant difference in the rate of tumour downstaging among patients with different T stages on pre-therapeutic MRI. Meanwhile, the rate of tumour downstaging in patients with T4 staging at pre-therapeutic MRI was significantly higher than for other stages. The AUC of predicting tumour downstaging based on the volume ratio of the mucus pool was 0.793 and tumour downstaging was more common in patients with a volume ratio of th emucus pool of at least 68.3% (accuracy, 76%; sensitivity, 74%; specificity, 78%; positive predictive value [PPV], 76%; negative predictive value [NPV], 76%; Fig 4, Table 4). Multivariate logistic regression analysis indicated that the volume ratio of the mucus pool was the only significant factor associated with tumour downstaging (Table 3).

Tumour pathological responsiveness

There was a significant difference between the volume percentage of the mucus pool in responsive tumours and in non-responsive tumours. There was a significant difference in the tumour pathological responsiveness rate among patients with different N stages upon pre-therapeutic MRI examination imaging. Of note, tumour pathological responsiveness rate in patients with mucus nodes on pre-therapeutic MRI was higher than those without any mucus node. The AUC for predicting tumour response based on the volume ratio of the mucus pool was 0.739 and the accuracy, sensitivity, specificity, PPV, and NPV at the most optimal cut-off point were 65%, 87%, 50%, 53%, and 86%, respectively (Table 4). Logistic regression analysis indicated that the volume ratio of the mucus pool and presence of a mucus node on pre-therapeutic MRI were significant factors associated with tumour responsiveness (Table 3). Six (8%) of the 79 patients had a pathological complete response (pCR). The volume ratio of the mucus pool in patients with a pCR was higher than that in those without a pCR, which had a statistically significant difference (81.8±12% versus 68.4±13.9%, $p=0.007$).

Lymph node downstaging

There was a significant difference in the rate of lymph node downstaging between different pre-therapeutic N stages. Unfortunately, the AUCs of the performance for the prediction of lymph node downstaging based on the mucus pool and whole tumour volumes, and volume ratio of the mucus pool failed (Fig 4, Table 4).

Discussion

The present results indicate that patients with a high proportion of mucus pool may have higher tumour downstaging and responsiveness after neoadjuvant therapy. In the present study, the incidence of advanced tumour stages (T3–4) was 96%, demonstrating that the MC mucus pool was more likely to spread outside the rectum and infiltrate adjacent organs or the peritoneum. Patients exhibited tumour downstaging at a rate of 48%, which was higher than the rate of 30% reported by Shin *et al.*[20] and slightly lower than the 52% reported by Grillo-Ruggieri *et al.*[21] Upon further analysis, it was found the rate of tumour downstaging (92%)

Table 2
Sex, age, stages, mucus pool volume and ratio characteristics in patients.

Characteristic	Tumour downstaging (n=38)	Tumour non-downstaging (n=41)	p-Value	Responsive tumour (n=31)	Unresponsive tumour (n=48)	p-Value	Lymph node downstaging (n=37)	Lymph node non-downstaging (n=27)	p-Value
Sex			0.808			0.368			0.495
Male	26 (49)	27 (51)	…	22 (42)	31 (58)	…	23 (55)	19 (45)	…
Female	12 (46)	14 (54)	…	9 (35)	17 (65)	…	14 (64)	8 (36)	…
Mean age (years)[a]	490.8±14.4	54.6±14.3	0.017	49.2±14.8	54.3±14	0.121	53.1±13.7	50.3±15.5	0.467
Preoperative Treatment			0.927			0.108			0.777
Chemotherapy	20 (48)	22 (52)	…	13 (31)	29 (69)	…	22 (56)	17 (44)	…
Chemoradiotherapy	18 (49)	19 (51)	…	18 (49)	19 (51)	…	15 (60)	10 (40)	…
Removable distant metastasis			0.358			0.31			0.332
M0	34 (48)	37 (52)	…	27 (38)	44 (62)	…	33 (59)	23 (41)	…
M1	4 (50)	4 (50)	…	4 (50)	4 (50)	…	4 (50)	4 (50)	…
Mucus pool volume (ml)[b]	23.5 (15.3–48.2)	14.9 (9.4–24.8)	0.003	19.7 (11.7–36.7)	16.5 (10.8–27.7)	0.609	18.6 (10.4–33.3)	26.6 (12.6–28.7)	0.573
Whole tumour volume (ml)[b]	29.8 (20.7–68.3)	22.12 (14.7–37.4)	0.045	28 (14.9–43.1)	27.8 (18.5–43.2)	0.651	30.1 (19.0–49.6)	26.6 (15.8–40.9)	0.366
Volume ratio of mucus pool (%)[a]	77.08±12.45	63.56±12.80	<0.001	76.86±13.37	65.67±13.19	<0.001	66.33±13.19	69.20±14.07	0.411
MRI tumour staging			<0.001			0.247			0.589
T2	0 (0)	3 (100)	…	0 (0)	3 (100)	…	1 (33)	2 (67)	…
T3	16 (31)	36 (69)	…	23 (44)	29 (56)	…	22 (56)	17 (44)	…
T4a–4b	22 (92)	2 (8)	…	8 (33)	16 (67)	…	14 (66)	8 (34)	…
MRI lymph node staging			0.453			0.026			0.025
N0	11 (61)	7 (39)	…	12 (67)	6 (33)	…	0 (0)	5 (100)	…
N1	9 (43)	12 (57)	…	7 (33)	14 (67)	…	12 (60)	8 (20)	…
N2	18 (45)	22 (55)	…	12 (30)	28 (70)	…	25 (64)	14 (36)	…
MRI mucus node			0.289			0.015			0.543
Presence	8 (62)	5 (38)	…	9 (69)	4 (31)	…	6 (50)	6 (50)	…
Absence	30 (45)	36 (55)	…	22 (33)	44 (67)	…	31 (60)	21 (40)	…

Categorical variables are expressed as numbers of patients (%).
Quantitative variables are expressed as the means ± standard deviation.
[a] Values are means ± standard deviation.
[b] Values are medians, with the interquartile ranges in parentheses.

in patients with T4 staging disease on pre-therapeutic MRI was higher than in patients with T2 and T3 disease, which is consistent with the literature on the rate of tumour downstaging (87%) in T4 stage patients.[21] This suggests that the mucus pool in pre-therapeutic T4 stage patients involving adjacent organs or peritoneal structures may be changed after neoadjuvant therapy and not included in the tumour infiltration range in pathological analysis and thus those patients with T4 stage were restaged to a pathological T3 or less stage after neoadjuvant therapy.[22]

The tumour pathological responsiveness rate in this study was 39%, which is similar to a previously reported rate of 38%.[23] It was found that patients with MRI N0 staging had a significantly higher rate of tumour pathological responsiveness than those with N1–2 staging, suggesting patients without regional lymph node metastases may be more sensitive to neoadjuvant therapy. In this study, 8% of patients with MC achieved pCR, which is a rate similar to that of 6% in another report.[23] After preoperative therapy, rectal adenocarcinoma can be

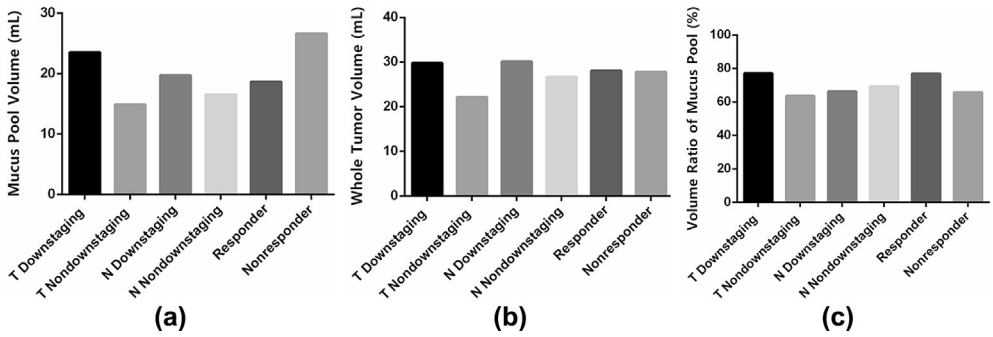

Figure 3 The three column charts express the medians of the mucus pool volume (a), the medians of the whole tumour volume (b), and the means of the volume ratio of mucus pool (c) in different groups of patients with or without tumour downstaging, lymph node downstaging and tumour responder, respectively.

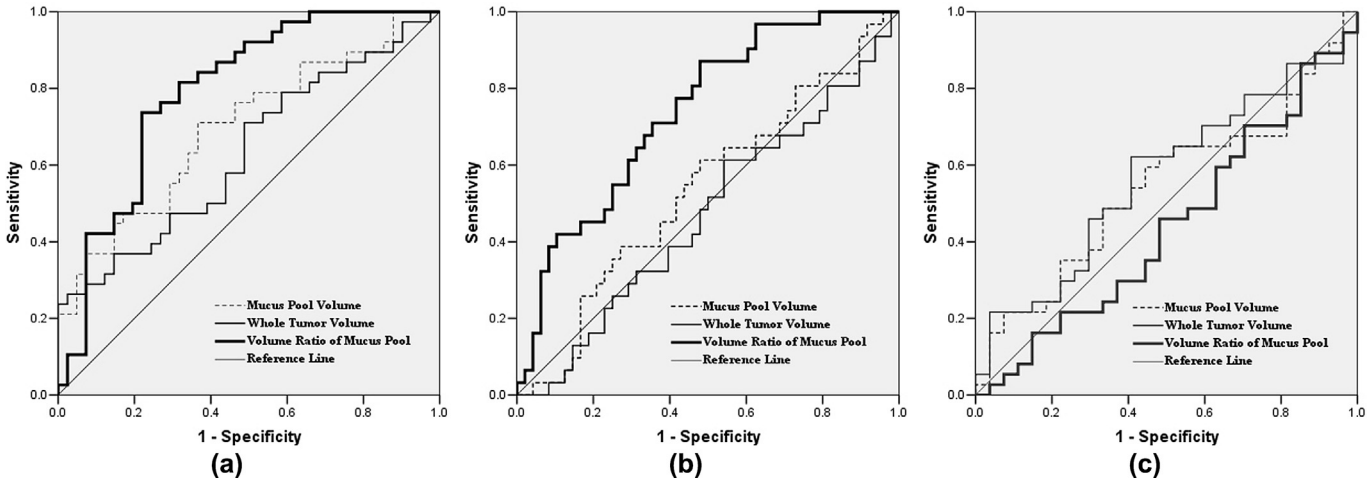

Figure 4 ROC curves evaluating the diagnostic value of assessing tumour downstaging (a), tumour responder (b) and lymph node downstaging (c) based on measuring the mucus pool volume, whole tumour volume, volume ratio of the mucus pool, respectively.

converted into acellular mucin without any tumour cells,[24] from which it can be inferred that patients with MC can theoretically develop a pCR after neoadjuvant therapy. In the present study, the volume proportion of the mucus pool was a significant factor associated with tumour pathological responsiveness after neoadjuvant therapy. It is speculated that there may be a difference in the composition of mucin tissue and non-mucin tissue in MC patients before neoadjuvant therapy, such as fewer tumour cells in mucin tissue than in non-mucin tissue. There are very few tumour cells in the mucus pool before neoadjuvant therapy, which may be the main reason that patients with a high volume ratio of the mucus pool exhibit tumour downstaging more frequently and a better tumour pathological responsiveness to neoadjuvant therapy. If the whole tumour had a higher proportion of mucus pool, then there would be fewer remaining solid tumour components with viable tumour cells. Another speculation

Table 3
Results of multivariate logistic regression analysis with stepwise backward elimination.

Parameter	Tumour downstaging OR	*p*-Value	Responsive tumour OR	*p*-Value	Lymph node downstaging OR	*p*-Value
Age	Not in final model	…	Not in final model	…	Not in final model	…
Mucus pool volume	Not in final model	…	Not in final model	…	Not in final model	…
Whole tumour volume	1.016 (.998, 1.034)	0.089	Not in final model	…	Not in final model	…
Volume ratio of mucus pool	1.075 (1.031, 1.121)	0.001[a]	1.065 (1.022, 1.110)	0.003[a]	Not in final model	…
Presence of mucus node	Not in final model	…	8.605 (1.909, 38.784)	0.005[a]	Not in final model	…
MRI lymph node staging	Not in final model	…	Not in final model	…	Not in final model	…

As an example, an odds ratio (OR) of 1.075 shows that an increased volume ratio of mucus pool leads to a 7.5% increase rate of tumour downstaging. Data in parentheses are 95% CI.

[a] Marked parameters are each independently associated with downstaging or a responsive tumour.

Table 4
The diagnostic performances of the cut-off values for the different variables in predicting tumour downstaging, tumour responder and lymph node downstaging.

	Variable	AUC (95%CI)	Cut-off	Accuracy	Sensitivity	Specificity	PPV	NPV
T downstaging								
	Mucus pool volume (ml)	0.679 (0.581, 0.813)	25.6	63%	47%	78%	67%	62%
	Whole tumour volume (ml)	0.631 (0.507, 0.754)	66.1	62%	26%	95%	83%	58%
	Volume ratio of mucus pool (%)	0.793 (0.693, 0.893)	68.3	76%	74%	78%	76%	76%
Responder								
	Mucus pool volume (ml)	0.534 (0.403, 0.665)	17.2	56 %	61%	52%	45%	70%
	Whole tumour volume (ml)	0.470 (0.339, 0.601)	23.9	51 %	61%	44%	41%	64%
	Volume ratio of mucus pool (%)	0.739 (0.630, 0.847)	62.1	65%	87%	50%	53%	86%
N downstaging								
	Mucus pool volume (ml)	0.542 (0.399, 0.684)	19.8	56%	49%	67%	67%	49%
	Whole tumour volume (ml)	0.567 (0.425, 0.708)	27.1	61%	62%	59%	68%	53%
	Volume ratio of mucus pool (%)	0.439 (0.296, 0.583)	53.5	56%	86%	15%	58%	44%

AUC, area under the receiver operating characteristic curve; PPV, positive predictive value; NPV, negative predictive value.

could be that tumours with a large mucus ratio are less dedifferentiated than tumours with less mucus. This finding suggests that patients with a large mucus pool upon pre-therapeutic MRI may be more suitable for preoperative neoadjuvant therapy as they are more likely to have better pathological responsiveness.

In terms of N downstaging, patients with N1–2 staging on pre-therapeutic MRI displayed a high rate of lymph node downstaging (63%), which was completely different to tumour responsiveness. It can be hypothesised that overevaluation of lymph node staging on MRI may be one of the reasons for the high rate of lymph node downstaging seen in other studies.[25,26] In addition, mucus nodes were specifically noted in the present study, which are significantly different to normal lymph nodes and present as bright-high-signal-intensity on pre-therapeutic MRI T2-weighted imaging. As to normal lymph nodes, in the present study, patients without positive lymph node metastasis on pre-therapeutic MRI T2-weighted imaging had a higher tumour response rate after neoadjuvant therapy. In contrast, patients with mucus nodes had slightly higher tumour pathological responsiveness than those lacking mucus nodes after neoadjuvant therapy. This suggests that the biological characteristics between lymph nodes and mucus nodes may be different; however, the pathology of mucus nodes was not studied further. Mucus nodes on pre-therapeutic MRI may be part of the mucus pool, with no viable tumour cells or very few tumour cells. Thus mucus nodes should be noted in the clinic, as their appearance on initial MRI may be a factor predicting better tumour pathological responsiveness to neoadjuvant therapy.

Certain limitations of the present study should be mentioned. First, the study was a retrospective study, and thus, there may have been a selection bias. To the authors' knowledge, the overall efficiency of neoadjuvant therapy for MC was less than that for non-mucus adenocarcinoma; however, non-mucus adenocarcinoma cases were not included as controls. In the present study, some MC patients with a high proportion of mucus pool were shown to have higher tumour downstaging and responsiveness after neoadjuvant therapy, but the cause and mechanism of this result need to be elucidated in future studies. Second, difficulties were encountered delineating the ROI of the mucus pool using subjective judgment, despite defining a bright-high-signal intensity on T2-weighted imaging as a mucus pool, according to previously published literature.[14,27] In addition, other clinical factors, such as disease-free survival (DFS) and cancer-specific survival (CSS), were not analysed, and differences in these factors have been reported between MC and non-MC.[4,7,21,28,29] Therefore, further studies are required to determine whether the proportion of the mucus pool is related to DFS and CSS. Moreover, T1-weighted and diffusion-weighted imaging sequences were obtained, but were not analysed in this retrospective study. As the apparent diffusion coefficient (ADC) has been used to predict the efficacy of neoadjuvant therapy in patients with non-MC,[30] it should be used to assess patients with MC in future studies. Finally, there are more parameters that are worth studying, such as the distance from the lower edge of the tumour to the anal margin, tumour size, the relationship to the perianal complex, circumferential resection margin, and extramural venous invasion (EMVI); these should also be included in further studies of patients with MC.[31]

In conclusion, the present findings indicate that the mucus pool volume ratio of MC as visualised by pre-therapeutic MRI is associated with the tumour pathological responsiveness to preoperative neoadjuvant therapy.

Conflict of interest

The authors declare no conflict of interest.

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