

Mucinous rectal cancers: clinical features and prognosis in a population-based cohort

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Abstract

Purpose: Mucinous rectal cancers are generally associated with poor prognosis. This study aimed to clinically characterize mucinous rectal cancers in a defined region of Sweden.

Methods: All patients with rectal cancer in Uppsala and Dalarna, Sweden, between 2010 and 2018, were identified using the Swedish Colorectal Cancer Registry. Data were verified and updated by way of medical, radiology, and histopathology reports. Patients were selected if magnetic resonance imaging, biopsy, and/or surgical specimen were mucinous. Primary outcomes were overall survival (OS), time to recurrence (TTR), pattern of metastatization, and downstaging. Risk factors for recurrence were analysed with univariable and multivariable analyses.

Results: Of 1220 patients with rectal cancer, 263 (22 per cent) had a mucinous specimen, median (interquartile range; i.q.r.) age was 71 (63–77) years, and 152 (58 per cent) were men. Most were localized in the low–middle rectum (76 per cent) and were stage III (53 per cent), or stage IV (28 per cent). The 5-year OS was 55 per cent (95 per cent c.i. 49 to 62); after total mesorectal excision ($n = 164$), 5-year OS was 75 per cent (95 per cent c.i. 68 to 83), and 5-year TTR was 68 per cent (95 per cent c.i. 60 to 77). In those with complete response (pCR), pStage I, pStage II, and pStage III, 5-year TTR was 93 per cent, 85 per cent, 74 per cent, and 44 per cent respectively. Synchronous metastasis was most common in the liver (64 per cent) and metachronous in the lungs (58 per cent). pCR was achieved in 14 patients, (13 per cent); whereas T and N category downstaging was achieved in 31 (28 per cent) and 67 patients (61 per cent) respectively. Perineural invasion had the strongest association with recurrence (hazard ratio 6.34, 95 per cent c.i. 2.50 to 16.10).

Conclusion: Mucinous rectal cancers have high recurrence rates, but pCR rate is more than 10 per cent. Perineural invasion is the main feature associated with recurrence.

Introduction

Mucinous rectal cancers are often diagnosed at an advanced stage and are clinically associated with an aggressive course; a pathological complete response (pCR) and tumour (T) and nodal (N) downstaging are uncommon after standard preoperative treatments^{1–8}.

The reported prevalence of mucinous rectal cancer varies depending on whether histopathological examination of the biopsy/surgical specimen or if the staging MRI is the chosen method for identification of mucin. It is estimated that 5–20 per cent^{2,9,10} of all rectal cancers contain mucin at greater than 50 per cent of the tumour mass. Today, MRI is considered the best preoperative diagnostic method for mucin identification as it accurately identifies the mucin in 97 per cent^{2,11} of cases, whereas biopsies often fail to capture it². Although histopathological examination of the surgical specimen is the final confirmation of mucin, the specimen is often affected by preoperative treatments¹², and not always available in cases of disseminated disease or watch-and-wait (W&W) strategies.

Mucinous colorectal cancers are associated with peritoneal metastases^{13,14} and are often studied as a single entity;

however, they are associated with poor prognosis when localized in the rectum^{10,15}. Despite repeated evidence of a more aggressive disease, treatment strategies do not differ between mucinous and non-mucinous rectal cancer¹⁶. This study aimed to review and analyse all consecutively diagnosed mucinous rectal cancers in a population-based cohort of a representative region of Sweden, and to clinically characterize this subgroup, with respect to long-term survival, pattern of metastatization, and downstaging after preoperative treatment.

Method

Study population

All patients diagnosed with a primary rectal cancer between 2010 and 2018 in two regions of Sweden (Uppsala and Dalarna) were identified via the Swedish Colorectal Cancer Registry (SCRCR)¹⁷, a national quality registry for colorectal cancer, and U-CAN, a biobank with prospective inclusion since 2010¹⁸. The SCRCR has 98–99 per cent coverage¹⁷, and by using U-CAN as a complement, nearly all rectal cancers are identified. Data retrieval from the registry was made on 30 April 2019. In 2018,

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the population of region Uppsala was 380 000 and the population of region Dalarna was 290 000. All included rectal cancers were located 0–15 cm from the anal verge, measured by rigid rectoscopy, and categorized as located in the high (15–11 cm), middle (10–6 cm), or low (5–0 cm) rectum.

All patients underwent an initial review of registry data and any indication of presence of mucin (or missing information) was noted. All patients with potentially mucinous adenocarcinoma underwent a thorough review of medical, radiology, and histopathology reports to fill in missing information and to verify registered data for final inclusion in the mucinous rectal cancer cohort. The regional ethics committee approved the study.

Management of rectal cancer

All patients were managed according to the national guidelines, including preoperative staging with high-resolution MRI of the pelvis, computed tomography of abdomen and thorax, and a mandatory discussion at a multidisciplinary team conference. Staging, surgical treatment, and chemotherapy (CT) were performed in either Uppsala University Hospital, or in the regional hospitals of Dalarna (Falun or Mora), whereas radiotherapy (RT) and chemoradiotherapy (CRT) were performed in Uppsala. Treatment of stage I–III rectal cancer with curative intent included local excision, primary surgery, short-course RT (5 × 5 Gy in 1 week; scRT) followed by immediate surgery, scRT, and delayed surgery, CRT (2 × 25 Gy with concomitant capecitabine), scRT followed by CT (scRT + CT), scRT + CT + W&W, and scRT + W&W. During the study interval, the randomized multicentre Stockholm III trial¹⁹

comparing scRT with immediate or delayed surgery, or long-course RT alone to 50 Gy in 5 weeks for resectable rectal cancers, and the phase-III multicentre randomized trial RAPIDO^{20,21}, comparing standard therapy for locally advanced rectal cancer, CRT, with scRT + CT, a total neoadjuvant therapy concept, were ongoing, and patient entry was closed in January 2013 and June 2016 respectively. After that, a Swedish phase-II multicentre study, LARCT-US²², further evaluated scRT + CT for patients with high-risk rectal cancer. In addition, a national multicentre cohort study of W&W started in 2017²³. Routine follow-up was conducted after 1 and 3 years after surgery with computed tomography of the liver, abdomen and lungs, and carcinoembryonic antigen (CEA), and after 5 years with colonoscopy. Patients with stage IV rectal cancer treated with curative intent and radical surgery were followed every sixth month after metastatic surgery. Medical treatment of metastatic disease followed the European Society for Medical Oncology guidelines²⁴.

Clinical and histopathological data

The SCRCR contains information about baseline characteristics, preoperative staging, surgical treatment, histopathological classification, oncological treatments, and follow-up information. Registry data were verified by way of medical, radiology, and histopathology reports. Missing data were filled in and follow-up information was updated. The TNM stage was reported according to the Seventh Edition of the International Union Against Cancer TNM Classification on Malignant tumours²⁵. The high-resolution MRI examinations followed the MERCURY protocol²⁶. The proportion of mucin was not routinely

Mucinous MRI	Mucinous biopsy	Mucinous surgery	Number of patients n = 263	
Blue	Blue	Blue	28	MRI + any histology
Blue	Orange	Blue	57	
Blue	Orange	Orange	3*	
Blue	Blue	Red	15†	MRI only
Blue	Orange	Orange	57‡	
Blue	Red	Red	49§	
Blue	Red	Red	1¶	Two histology
Orange	Blue	Blue	7	
Red	Blue	Blue	3	
Orange	Orange	Blue	29#	One histology
Red	Orange	Blue	8	
Red	Blue	Orange	1**	
Orange	Blue	Red	3††	
Red	Red	Blue	1	
Orange	Blue	Orange	1‡‡	

Fig. 1 Identification of mucinous rectal cancer via preoperative MRI reports, and/or preoperative biopsy, and/or surgical specimen.

Blue, mucin; orange, no mucin; red, missing info (not done or missing information). *All had received preoperative treatment. †Never underwent surgery. ‡All had received preoperative treatment. §Never underwent surgery except one with missing histopathology report. ¶Never underwent biopsy/surgery. Only best supportive care. #Nineteen had received preoperative treatment. **Had received preoperative treatment. ††Two had received preoperative treatment. One had no visible tumour after local excision. ‡‡Had received preoperative treatment

specified by the radiologists in the reports, but the tumours were described as variations of 'mucinous', or 'containing mucin' in free text. To validate the MRI reports as a basis for inclusion, a radiologist specialized in rectal cancer MRI performed a blinded re-examination for a randomized proportion of the MRI reports with descriptions interpreted as mucinous and non-mucinous rectal cancer, or when information on mucin was missing. All patients underwent a preoperative rigid rectoscopy and the distance from the anal verge to the tumour was noted. Information on inflammatory bowel disease (IBD) and heredity was retrieved from the medical records. Patients are routinely asked for cancer prevalence in the family and confirmed and suspected cases were noted. Histopathology was reported according to the WHO classification of tumours of the digestive system²⁷, where a mucinous adenocarcinoma is defined as being greater than or equal to 50 per cent of extracellular mucin.

Outcomes of interest

The primary outcomes of interest were overall survival (OS) and time to recurrence (TTR), calculated from date of diagnosis to death from any cause and recurrence respectively. The neoadjuvant rectal (NAR) score, an endpoint surrogate for OS after preoperative treatments, was also calculated with the formula $(5 \text{ ypN} - 3 (\text{cT} - \text{ypT}) + 12)^2 / 9.61$, resulting in 24 possible scores between 0 and 100. Patients were grouped into NAR-low (less than 8), NAR-intermediate (8–16) and NAR-high (above 16), with NAR-high having the poorest prognosis²⁸. Updated follow-up data were retrieved from the medical records and the last follow-up date was 19 May 2020. In addition, the pattern of synchronous and metachronous metastasis was characterized, and finally, histopathological T-downstaging was defined as lowering cT3/cT4 to ypT0–2 or cT2 to ypT1–T0, and N-downstaging was defined as lowering cN2–N1 to ypN0 after scRT + delayed surgery, scRT + CT, or CRT.

Statistical analysis

Continuous data are presented as median with inter quartile range (i.q.r.). A chi-squared test and Fisher's exact test were used for group comparisons with categorical data and a Mann-Whitney *U* test was used to compare continuous data. OS and TTR were calculated with Kaplan–Meier analysis and presented as proportion surviving and proportion recurrence-free respectively, after 5 years from diagnosis with 95 per cent confidence intervals (c.i.). In TTR analysis, both distant and local recurrence were events, and patients were censored at death or at last follow-up. Differences in survival were analysed with a log rank test. Risk factors for recurrence were analysed with univariable and multivariable Cox proportional hazard regression analyses and presented as hazard ratios (HR) with 95 per cent confidence intervals. All variables in the univariable analyses were included in the multivariable analysis. As MRI reports were the only modality of inclusion for some patients, a blinded, and randomized re-examination of MRI scans was performed. The agreement between the original MRI reports and the re-examination of MRI was calculated with Cohen's kappa ([supplementary material](#)). A *P* value lower than 0.05 was considered statistically significant. R version 4.0.3 (R foundation for Statistical Computing, Vienna, Austria) was used for statistical analyses.

Table 1 Clinical and pathological features of patients with mucinous rectal cancer between 2010 and 2018

Clinical characteristics	Total n = 263 (100%)	Clinical stage I–III n = 190 (72%)	Clinical stage IV n = 73 (28%)
Sex			
Male	152 (58)	105 (55)	47 (64)
Female	111 (42)	85 (45)	26 (36)
Age (years), median (i.q.r.)	71 (63–77)	71 (63–78)	69 (62–76)
Region			
Uppsala	149 (57)	101 (53)	48 (66)
Dalarna	114 (43)	89 (47)	27 (34)
Localization at rectoscopy			
High 11–15 cm	63 (24)	50 (26)	13 (18)
Middle 6–10 cm	104 (40)	73 (38)	31 (42)
Low 0–5 cm	96 (37)	67 (35)	29 (40)
cTumour category			
cT1	3 (1)	3 (2)	0 (0)
cT2	30 (11)	29 (15)	1 (1)
cT3a	20 (8)	17 (9)	3 (4)
cT3b	44 (17)	39 (21)	5 (7)
cT3c	41 (16)	33 (17)	8 (11)
cT3d	21 (8)	12 (6)	9 (12)
cT4a	33 (13)	21 (11)	12 (16)
cT4b	69 (26)	35 (18)	34 (47)
Missing info	2 (1)	1 (1)	1 (1)
cNode category			
cN0	53 (20)	50 (26)	3 (4)
cN1a	17 (6)	13 (7)	4 (5)
cN1b	51 (19)	41 (22)	10 (14)
cN1c	3 (1)	1 (1)	2 (2)
cN1x	19 (7)	17 (9)	2 (2)
cN2a	62 (24)	45 (24)	17 (23)
cN2b	36 (14)	14 (7)	22 (30)
cN2x	19 (7)	8 (4)	11 (15)
cMissing info	3 (1)	1 (1)	2 (2)
cMetastasis category			
cM0	190 (72)	190 (100)	0 (0)
cM1a	43 (15)	0 (0)	43 (55)
cM1b	30 (13)	0 (0)	30 (45)
cStage			
Stage I	25 (10)	25 (13)	0 (0)
Stage II	25 (10)	25 (13)	0 (0)
Stage III	139 (53)	139 (73)	0 (0)
Stage IV	73 (28)	0 (0)	73 (100)
Missing info	1 (0.04)	1 (1)	0 (0)
MRI MRF			
Positive	133 (51)	72 (39)	57 (78)
Negative	128 (49)	112 (59)	16 (22)
Not done	2 (1)	2 (1)	0 (0)
Missing info	1 (0.04)	1 (1)	0 (0)
MRI EMVI			
Positive	115 (44)	66 (35)	49 (67)
Negative	137 (52)	120 (63)	17 (23)
Not done	2 (1)	2 (1)	0 (0)
Missing info	9 (3)	2 (1)	7 (10)
MRI largest diameter mm			
Median (i.q.r.)	55 (40–70)	50 (39–65)	68 (49–85)
Not done	2 (1)	2 (1)	0 (0)
Missing info	5 (2)	0 (0)	5 (7)
CEA			
Median (i.q.r.)	6 (3–14)	5 (2–10)	11 (4–32)
Missing info	29 (11)	17 (9)	12 (16)
Heredity			
Yes	6 (2)	3 (2)	3 (4)
Suspected	6 (2)	4 (2)	2 (2)
No	201 (76)	147 (77)	54 (74)
Not investigated	50 (19)	36 (19)	14 (19)
IBD			
Crohn's disease	3 (1)	3 (2)	0 (0)
Ulcerous colitis	3 (1)	2 (1)	1 (1)
No	257 (98)	185 (97)	72 (99)

i.q.r., interquartile range; MRF, mesorectal fascia; EMVI, extramural vascular invasion; IBD, inflammatory bowel disease; CEA, carcinoembryonic antigen. Numbers are n (%) unless otherwise stated.

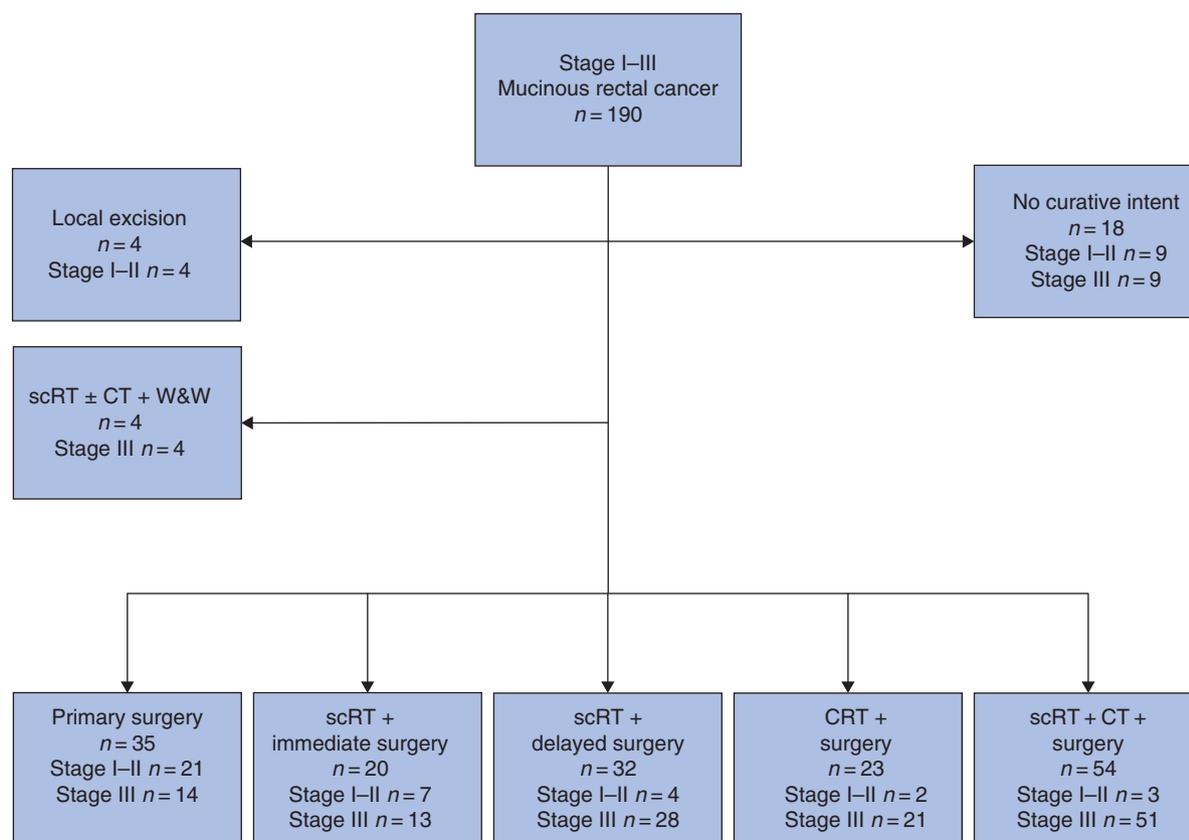


Fig. 2 Flow chart of treatment strategies for patients with clinical stage I-III mucinous rectal cancer between 2010 and 2018. scRT; short-course radiotherapy, CT, chemotherapy; CRT, chemoradiotherapy; W&W, watch and wait.

Results

Study population

Between 2010 and 2018, 1220 patients were diagnosed with rectal cancer (region Uppsala $n = 584$, region Dalarna $n = 636$). Of these, 291 patients had a mucinous-appearing tumour at MRI, and/or preoperative biopsy, and/or surgical specimen. Patients undergoing primary surgery without preoperative treatment who had radiological suspicion of mucin but no mucin at histopathological examination of the biopsy or the primary tumour ($n = 21$) were excluded. In addition, seven patients without preoperative treatment and less than 50 per cent of mucin in the surgical specimen were also excluded, leaving 263 (22.0 per cent) patients for further analysis (Fig. 1). MRI reports were the only modality of diagnosis and inclusion criteria in 107 patients. The random blinded re-examination of MRI conducted in 52 patients (26 mucinous, 21 non-mucinous, and five with missing MRI-information) resulted in a Cohen's kappa value of 0.74 (95 per cent c.i. 0.554 to 0.935) for the MRI reports (not including the five with missing MRI-information; [supplementary material](#)).

Clinical and pathological features

The mucinous rectal cancer cohort included 263 patients; 152 (58 per cent) were male and overall, the median age was 71 (i.q.r.) (63–77) years at the time of diagnosis. Most tumours were localized in the low to middle part of the rectum. The tumours had advanced clinical T categories with cT4b being most common ($n = 69$, 26 per cent), and a majority had lymph node-positive disease with 90 (34 per cent) patients having cN1 category and 117 (44 per cent) patients with a cN2 category.

Synchronous distant metastases were found in 73 (28 per cent) patients. Preoperative MRI revealed positive mesorectal fascia (MRF) in 133 (51 per cent), extramural vascular invasion (EMVI) in 115 (44 per cent), and a median (i.q.r.) tumour length of 55 (40–70) mm. CEA had a median value of 6 (3–14), and the prevalence of hereditary colorectal cancer and IBD was less than 5 per cent and 2 per cent respectively (Table 1).

Clinical features of patients with clinical stage I-III mucinous rectal cancer ($n = 190$, 72 per cent) are shown in Table 1. Treatment with non-curative intent was chosen in 18 patients due to high age, and/or co-morbidity, and/or personal request, and comprised palliative RT or CT, contact RT (Papillon technique), or best supportive care. Local excision was conducted in four cases of cT1–2 tumour category, of whom two experienced local recurrence, and one had non-radical local excision, and received contact RT. Four patients had clinical complete response (cCR) after preoperative treatment and were followed according to the W&W program²³. Two of these had local regrowth and one underwent surgery. The remaining 164 patients underwent total mesorectal excision (TME) surgery with or without preoperative treatment. The most common therapy regimen was scRT + CT (Fig. 2). The TME resections performed were anterior resection ($n = 76$), abdominoperineal rectal resection ($n = 76$), Hartmann's operation ($n = 11$), and proctocolectomy ($n = 1$), and the result of histopathological examination are shown in Table 2. pT3b and pT3c were the most common pT categories and pN0 was the most common pN category. Most tumours had moderate-to-high differentiation grade and lymphovascular invasion, EMVI, and/or tumour deposits, were present in just higher than 10 per cent, and

Table 2 Histopathological results after total mesorectal excision in patients with stage I–III mucinous rectal cancer between 2010 and 2018

Histopathology	Total n = 164 (100%)	
	Overall n (%)	After neo-adjuvant treatment* n
pTumour stage		
pT0	14 (9)	14
pT1	4 (2)	4
pT2	36 (22)	26
pT3a	12 (7)	9
pT3b	33 (20)	27
pT3c	30 (18)	22
pT3d	6 (4)	5
pT4a	18 (11)	14
pT4b	11 (7)	8
pNodal stage		
pN0	105 (64)	87
pN1a	13 (8)	12
pN1b	17 (10)	11
pN1c	2 (1)	1
pN2a	12 (7)	8
pN2b	14 (9)	9
Missing info	1 (1)	
Differentiation grade		
Moderate-high	90 (55)	
Low	51 (31)	
Complete response	14 (9)	
Missing info	9 (5)	
Lymphovascular invasion		
Yes	18 (11)	
No	124 (76)	
Complete response	14 (9)	
Missing info	8 (5)	
EMVI		
Yes	20 (12)	
No	122 (74)	
Complete response	14 (9)	
Missing info	9 (5)	
Perineural invasion		
Yes	31 (19)	
No	110 (67)	
Complete response	14 (9)	
Missing info	9 (5)	
Tumour deposits		
Yes	20 (12)	
Suspected	128 (78)	
No	16 (10)	
Radical resection margin		
R1	4 (2)	
R0	156 (95)	
RX	3 (2)	
Missing info	1 (1)	

* Number of patients included in the overall population, with ypT and ypN after preoperative treatment.

EMVI, extramural vascular invasion; R1, not tumour-free microscopic resection margin; R0, tumour-free macroscopic resection margin; RX, resection margin not assessable.

perineural invasion in 19 per cent. None of the patients had presence of signet ring cells, and 95 per cent had microscopic radical surgery.

Clinical features of patients with synchronous metastatic mucinous rectal cancer ($n=73$, 28 per cent) are shown in [Table 1](#). These patients had more advanced cT and cN categories, more often positive MRF and presence of EMVI on MRI, larger tumours, and higher CEA compared with non-metastatic patients. There was an initial curative intent or conversion situation in 30 patients with distant metastases, of

whom 21 underwent resection of metastases (liver surgery $n=18$, lung surgery $n=2$, and para-aortal lymph node resection $n=1$). Sixteen patients were considered tumour-free after both metastasis and TME surgery. Six patients with lateral lymph node metastases underwent preoperative treatment and TME surgery with curative intent, and five were considered tumour-free after completed treatment.

Survival

The 5-year OS for all included patients was 55 per cent (95 per cent c.i. 49 to 62). For patients staged I–III undergoing TME surgery, 5-year OS was 75 per cent (95 per cent c.i. 68 to 83), and 68 per cent (95 per cent c.i. 60 to 77) were recurrence-free after 5 years. OS for pathological stages and pCR are shown in [Fig. 3](#): in patients with pCR, 5-year OS was 93 per cent (95 per cent c.i. 80 to 100), and in stage I 79 per cent (95 per cent c.i. 64 to 96), in stage II 79 per cent (95 per cent c.i. 69 to 91), and in stage III 64 per cent (95 per cent c.i. 51 to 80). Ninety-three per cent (95 per cent c.i. 80 to 100) were recurrence-free after 5 years after pCR. In pathological stage I, 85 per cent (95 per cent c.i. 73 to 100) were recurrence-free, in stage II 74 per cent (95 per cent c.i. 62 to 89), and in stage III 44 per cent (95 per cent c.i. 29 to 66) ([Fig. 3](#)). Of the 16 stage IV patients who were tumour-free after distant metastasis and TME surgery, 36 per cent (95 per cent c.i. 17 to 75) were recurrence-free after 5 years. One of five patients with lateral metastases had recurrence after curative treatment.

The NAR score was calculated for patients treated before surgery with delayed surgery, and 21 (19 per cent) were NAR-low (15 scRT+CT, 5 CRT, 1 scRT), 50 (46 per cent) were NAR-intermediate, and 37 (34 per cent) were NAR-high. In addition, NAR score correlated well with OS with NAR-low having the best OS and NAR-high the worst ([Fig. 4](#)).

Perineural invasion was the strongest independent risk factor for recurrence in a multivariable Cox proportional regression analysis model (HR 6.35, 95 per cent c.i. 2.50 to 16.10). Positive lymph nodes and tumour deposits were also associated with recurrence ([Table 3](#)).

To analyse the potential effect of using different inclusion criteria for mucinous rectal cancer, OS was analysed based on which combinations of MRI, preoperative biopsy, and surgical specimen were positive for mucin. OS was worse for patients with only positive MRI, and patients with both mucinous preoperative biopsy and surgical specimen, but no mucin on MRI (or missing MRI), had better prognosis. When excluding stage IV patients from the OS analysis, only patients with concordant endoscopic biopsy and surgical specimen with mucin and no MRI with mucin had worse OS ($n=5$) ([supplementary material](#)).

Pattern of metastatization

The pattern of synchronous distant metastatization is shown in [Fig. 5](#). The liver was the most common site (64 per cent), followed by lung (33 per cent), lateral lymph nodes (30 per cent), central lymph nodes (23 per cent), and peritoneum (8 per cent). The remaining sites were uncommon and present in patients with multiple sites of metastasis. Most patients with lateral lymph node metastases also had other distant metastases (15 of 22, 68 per cent).

Metachronous distant metastasis or local recurrence occurred in 43 (26 per cent) patients with stage I–III who underwent TME surgery. The pattern of recurrence is also shown in [Fig. 5](#). The lung was the most common site of distant metachronous disease (58 per cent), followed by liver (23 per cent), and peritoneum (17 per cent). Of 164 patients undergoing TME surgery, 6 (4 per cent) had a local recurrence.

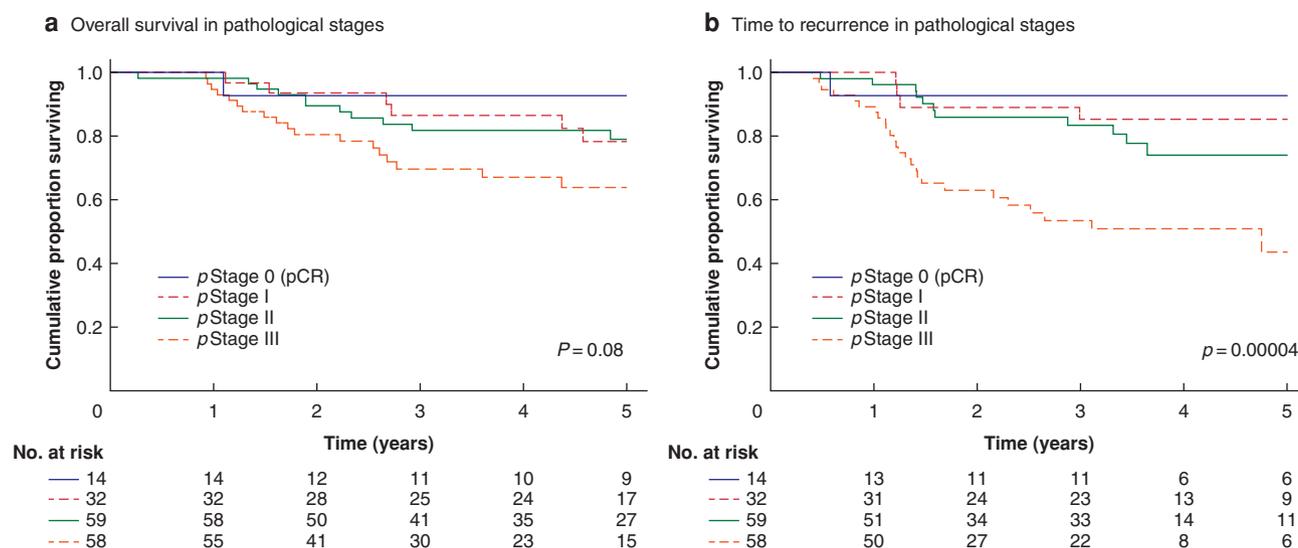


Fig. 3 Overall survival and time to recurrence in pathological stage 0–III for patients with mucinous rectal cancer undergoing total mesorectal excision surgery between 2010 and 2018 ($n = 164$).

a Overall survival. b Time to recurrence. One patient was excluded due to incomplete staging. pCR, pathological complete response.

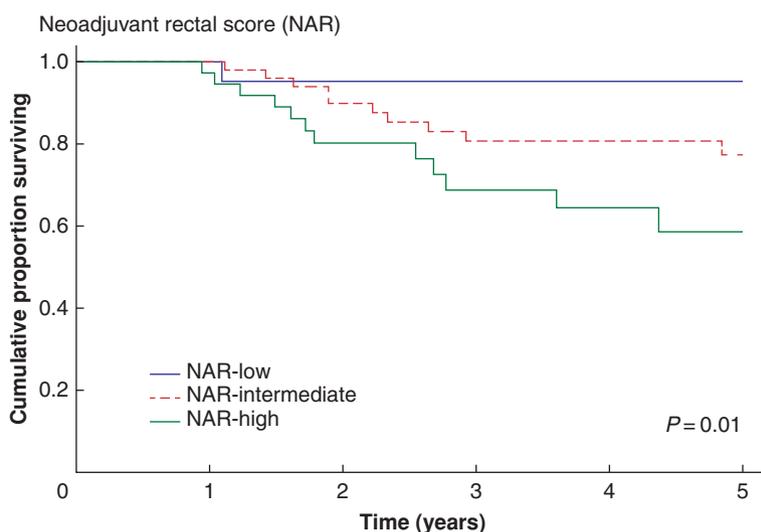


Fig. 4 Overall survival for patients with clinical stage I–III mucinous rectal cancer who underwent total mesorectal excision surgery after preoperative treatment with delayed surgery, separated by neoadjuvant rectal (NAR) scores ($n = 109$).

Tumour and nodal downstaging

Treatment strategies scRT + CT ($n = 54$), scRT + delayed surgery ($n = 32$), and CRT ($n = 23$) resulted in pCR in 14 (13 per cent) patients (12 scRT + CT, 0 scRT, 2 CRT) with a pCR rate of 22 per cent for scRT + CT, 0 per cent for scRT and 9 per cent for CRT. T-category downstaging was achieved in 31 (28 per cent) patients (18 scRT + CT, 5 scRT, 8 CRT) with a downstaging rate of 33 per cent for scRT + CT, 16 per cent for scRT, and 35 per cent for CRT. N-category downstaging was achieved in 67 (61 per cent) patients (37 scRT + CT, 16 scRT, 14 CRT) with a downstaging rate of 69 per cent for scRT + CT, 50 per cent for scRT, and 61 per cent for CRT.

Discussion

In this study, preoperative MRI, preoperative biopsies, and surgical specimens identified a large population-based cohort of stage I–IV

mucinous rectal cancers, which was clinically characterized. Although the proportion without recurrence was lower than expected for rectal cancer in general, pCRs were not uncommon, especially after scRT + CT. In addition, different patterns of metastases were found for synchronous and metachronous distant metastases, with the liver being the most common site in synchronous disease and lung in metachronous disease.

Mucinous colorectal cancer is often studied as a single entity, but there are differences between mucinous rectal cancer and colonic cancer. Mucinous colonic cancer is more prevalent in women but here, mucinous rectal cancer was more common in men, as previously reported¹⁰. Mucinous tumours constitute a decreasing proportion from the right colon to rectum¹⁰, but in the rectum, the mucinous tumours were more often localized in the middle and lower parts. The aetiology of mucinous colorectal cancer is unknown, but patients with IBD and Lynch syndrome have increased proportions of mucinous tumours²⁹. Here, the prevalence of IBD and heredity was, however, low.

Table 3 Univariable and multivariable Cox proportional regression hazard analysis for risk of recurrence in patients with mucinous rectal cancer undergoing total mesorectal excision surgery (n = 164)

Clinical and histopathological characteristics	Univariable HR (95% c.i.)	Multivariable HR (95% c.i.)	Multivariable P
Sex			
Female	1.00	1.00	
Male	1.01 (0.56–1.84)	1.43 (0.65–3.17)	
Age (per year)	1.002 (0.97–1.03)	0.98 (0.95–1.02)	
Localization at rectoscopy			
High 11–15 cm	1.00	1.00	
Middle 6–10 cm	0.65 (0.31–1.37)	1.40 (0.49–3.98)	
Low 0–5 cm	0.89 (0.43–1.85)	1.80 (0.65–4.93)	
pTumour category			
ypT0	0.29 (0.04–2.28)	0.70 (0.07–6.44)	
pT1	0 (0)	0 (0)	
pT2	1.00	1.00	
pT3	1.33 (0.59–3.01)	1.18 (0.42–3.32)	
pT4	2.93 (1.21–7.09)	1.14 (0.28–4.65)	
pNode category			
pN0	1.00	1.00	
pN1	3.29 (1.57–6.85)	2.76 (1.05–7.21)	0.039
pN2	4.96 (2.41–10.19)	4.91 (1.66–14.50)	0.004
Differentiation grade			
Moderate-high	1.00	1.00	
Low	1.89 (1.02–3.48)	1.90 (0.80–4.55)	
Complete response	0.26 (0.03–1.90)	-	
Lymphovascular invasion			
Yes	1.74 (0.77–3.94)	0.19 (0.05–0.75)	0.018
No	1.00	1.00	
Complete response	0.21 (0.03–1.54)	-	
EMVI			
Yes	2.20 (1.01–4.79)	2.73 (0.82–9.09)	
No	1.00	1.00	
Complete response	0.22 (0.03–1.59)	-	
Perineural invasion			
Yes	5.16 (2.74–9.70)	6.35 (2.50–16.10)	<0.0001
No	1.00	1.00	
Complete response	0.31 (0.04–2.33)	-	
Missing info	-	-	
Tumour deposits			
Yes	4.57 (2.31–9.07)	2.70 (1.04–6.99)	0.040
No	1.00	1.00	
Radical resection margin			
No	4.69 (1.13–19.52)	1.44 (0.15–14.14)	
Yes	1.00	1.00	
Not assessable	4.16 (1.001–17.30)	1.68 (0.22–12.98)	

HR, hazard ratio; EMVI, extramural vascular invasion.

Mucinous rectal cancer is diagnosed at a more advanced stage. In this study, only 19 per cent were diagnosed in clinical stage I–II, 53 per cent at stage III, and 28 per cent at stage IV. Data from the SCRCR between 2010 and 2018, show that 42 per cent of patients with rectal cancer in Sweden were at clinical stage III and 22 per cent at stage IV at the time of diagnosis³⁰. Mucinous differentiation has been reported as an independent unfavourable prognostic factor in rectal cancer^{10,15} but in a large register-based population study from the Netherlands, this negative prognostic impact was only seen in the beginning of the study interval. The authors suggested that improved treatment strategies with preoperative CRT and TME surgery could be one explanation³¹. In the present study, the 5-year OS at all stages was 55 per cent, which is in line with others^{10,15,31}. Five years after TME surgery, 68 per cent of the patients were recurrence-free. In a recently published review article on recurrence after radical colorectal cancer surgery during the same interval in Sweden, the corresponding number was 79 per cent³². Perineural invasion showed the strongest association with recurrence, followed by positive lymph nodes. Perineural

invasion is a known factor associated with advanced disease, poor response after preoperative treatments, and recurrence^{33,34}.

As a complement, the NAR score was calculated and correlated with OS²⁸, and 19 per cent had NAR-low associated with the best prognosis (the majority seen after scRT + CT). These results are similar to the entire population of rectal cancers in Sweden³⁵.

Sixteen patients with synchronous metastases (the majority had liver metastases) underwent curative and radical treatment, and 36 per cent were recurrence-free after 5 years, which was slightly less than reported for all patients with rectal cancer undergoing liver surgery in Sweden, but numbers are small³⁶.

Mucinous colorectal cancer is associated with peritoneal metastases, but the majority originates from colon cancers, and in mucinous rectal cancers, other sites are more common^{13,14}. This was confirmed in the present study, where synchronous peritoneal metastases were more uncommon than liver, lung, and central and lateral lymph nodes, in that order. Interestingly, the pattern of metastasis differed between synchronous and metachronous disease as metachronous metastases were most common in the lungs. In addition, there was a tendency towards

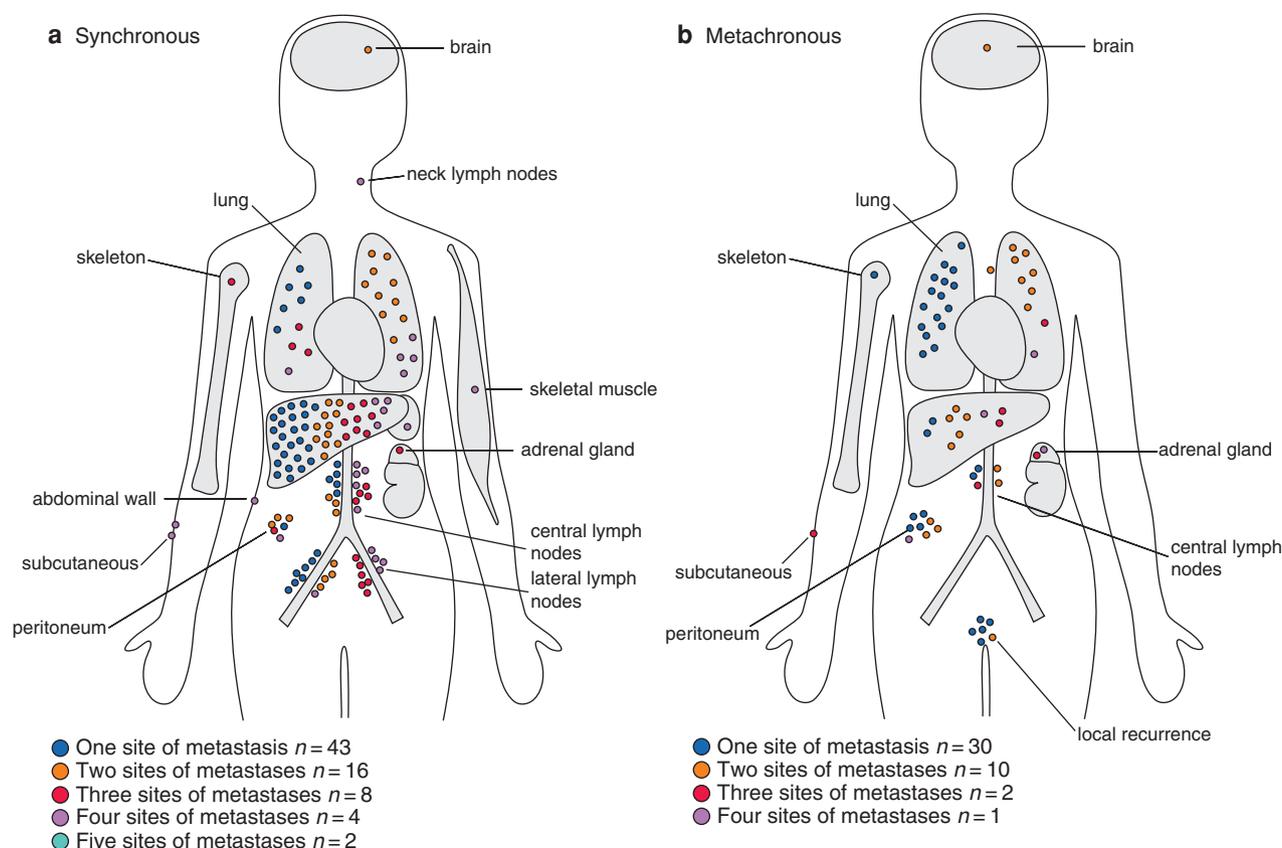


Fig. 5 a Pattern of synchronous metastatization in stage IV mucinous rectal cancer. b Pattern of metachronous disease in patients with previous stage I-III mucinous rectal cancer who underwent total mesorectal excision surgery.

peritoneal metastases being more common with metachronous disease and a possible explanation could be iatrogenic seeding during surgery. Mucinous rectal cancer has also been reported as a risk factor for local recurrence³⁷, but in a meta-analysis published in 2016¹, no increased risk of local recurrence for mucinous locally advanced rectal cancer treated with preoperative CRT was found. Accordingly, local recurrence rate of 4 per cent was seen here, which is the same as in the SCRCR for all rectal cancers in Sweden between 2010 and 2016³⁰.

Thirteen per cent had pCR after preoperative treatment with delayed surgery and T-category downstaging was seen in 28 per cent, and N- category downstaging in 61 per cent. Reported downstaging results for mucinous adenocarcinoma vary^{3,6-8,38}, and some caution should be made when comparing differences in reported downstaging as treatment regimens differ and the cN category is notoriously difficult to assess on MRI³⁹. However, pCR of 13 per cent is in the upper interval with those who report pCR rates of mucinous rectal cancer. Here, scRT + CT was given in most cases, reflecting the inclusion in the RAPIDO and LARCT-US studies^{19,20,22}. In fact, 12 (22 per cent) patients who received scRT + CT had a pCR, which is similar to the results of the RAPIDO study where a pCR rate of 28 per cent and 14 per cent was seen in the scRT + CT and CRT groups respectively. Here, for CRT, the pCR rate was 9 per cent and for scRT with delayed surgery, the pCR rate was 0.

This study has several limitations. First, all patients did not meet the same inclusion criteria of 'mucinous rectal cancer'. The reason for this was that patients with disseminated disease, older inoperable patients, or tumours affected by preoperative treatments were not excluded systematically *a priori*. MRI is

considered the safest preoperative method for identifying mucin^{2,11} but the proportion of mucin was seldom described in the MRI reports, which can explain the relative high prevalence of mucinous rectal cancer^{2,9,10}. When a subgroup of the MRI reports was randomly re-examined, the cases of disagreement indicated that some of the included patients could be non-mucinous. On the other hand, re-examination also judged some patients with non-mucinous histopathology as MRI mucinous. In addition, induction of mucin pools is sometimes seen after preoperative treatment¹² but does not impair survival⁴⁰ and would have improved the survival rates if included in the present cohort; however, patients with only mucinous histopathology had the same OS as patients that were positive for mucin on both MRI and histopathology. Besides the limitations of MRI, the mucinous rectal cancer cohort was not compared with a corresponding population of non-mucinous rectal cancer and comparisons with other studies are notoriously difficult; however, as population-based characteristics of rectal cancer are well established, distinct characteristics of mucinous rectal cancer should have been identified. Finally, the retrospective nature of the study increases the risk of missing or misinterpreted data; however, by combining population-based data from the prospectively updated SCRCR with retrospective review, a large consecutive cohort with detailed information was analysed.

According to the present analysis, mucinous rectal cancer has advanced T category and positive N category at the time of diagnosis. Although the proportion without recurrence is lower than expected for rectal cancer in general, complete response after preoperative treatment with delayed surgery, especially

not after scRT+CT, is not uncommon. Perineural invasion had the strongest association with recurrence, which occurred mostly in the lungs, whereas synchronous metastases were most common in the liver.

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Supplementary material

[Supplementary material](#) is available at *BJS Open* online.

Data availability

Data will be made available upon personal request and according to the ethical permits. As they contains traceable and personal information they are not suitable for uploading to a public site.

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