Implications of the new MRI-based rectum definition according to the sigmoid take-off

The MIRECA Study Group; Burghgraef, Thijs A.; Hol, Jeroen C.; Rutgers, Marieke L.; Brown, Gina; Hompes, Roel; Sietses, Colin; Consten, Esther C.J.

Published in:
BJS open

DOI:
10.1093/bjsopen/zrad018

Publication date:
2023

OXFORD Collaborative Research

BJS Open, 2023, zrad018
https://doi.org/10.1093/bjsopen/zrad018
Original Article

Implications of the new MRI-based rectum definition according to the sigmoid take-off: multicentre cohort study

Thijs A. Burghgraef[1,2,*], Jeroen C. Hol[3,4], Marieke L. Rutgers[5], Gina Brown[6,7], Roel Hompes[5], Colin Sietses[3], Esther C. J. Consten[1,2] and the MIRECA Study Group

[1]Department of Surgery, Meander Medical Center, Amersfoort, The Netherlands
[2]Department of Surgery, University Medical Center Groningen, Groningen, The Netherlands
[3]Department of Surgery, Hospital Gelderse Vallei, Ede, The Netherlands
[4]Department of Surgery, Amsterdam UMC, location VUmc, Amsterdam, The Netherlands
[5]Department of Surgery, Amsterdam UMC, location AMC, Amsterdam, The Netherlands
[6]Department of Radiology, Royal Marsden, London, UK
[7]Department of Radiology, Imperial College London, London, UK

Correspondence to: Thijs A. Burghgraef, Department of Surgery, University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands; Department of Surgery, Meander Medical Center, Maatweg 3, 3813 TZ Amersfoort, The Netherlands (e-mail: ta.burghgraef@meandermc.nl)

Members of the MIRECA Study Group are co-authors of this study and are listed under the heading Collaborators.

Presented to the following meeting: Dutch Digestive Disease Days, 16 March 2022.

Abstract

Background: The introduction of the sigmoid take-off definition might lead to a shift from rectal cancers to sigmoid cancers. The aim of this retrospective cohort study was to determine the clinical impact of the new definition.

Methods: In this multicentre retrospective cohort study, patients were included if they underwent an elective, curative total mesorectal excision for non-metastasized rectal cancer between January 2015 and December 2017, were registered in the Dutch Colorectal Audit as having a rectal cancer according to the previous definition, and if MRI was available. All selected rectal cancer cases were reassessed using the sigmoid take-off definition. The primary outcome was the number of patients reassessed with a sigmoid cancer. Secondary outcomes included differences between the newly defined rectal and sigmoid cancer patients in treatment, perioperative results, and 3-year oncological outcomes (overall and disease-free survivals, and local and systemic recurrences).

Results: Out of 1742 eligible patients, 1302 rectal cancer patients were included. Of these, 170 (13.1 per cent) were reclassified as having sigmoid cancer. Among these, 93 patients (54.7 per cent) would have been offered another adjuvant or neoadjuvant treatment according to the Dutch guideline. Patients with a sigmoid tumour after reassessment had a lower 30-day postoperative complication rate (33.5 *versus* 48.3 per cent, $P < 0.001$), lower reintervention rate (8.8 *versus* 17.4 per cent, $P < 0.007$), and a shorter length of stay (a median of 5 days (i.q.r. 4–7) *versus* a median of 6 days (i.q.r. 5–9), $P < 0.001$). Three-year oncological outcomes were comparable.

Conclusion: Using the anatomical landmark of the sigmoid take-off, 13.1 per cent of the previously classified patients with rectal cancer had sigmoid cancer, and 54.7 per cent of these patients would have been treated differently with regard to neoadjuvant therapy or adjuvant therapy.

Introduction

Although colorectal cancer is often reported as a single entity, colon cancer and rectal cancer differ significantly regarding pathology, anatomy, treatment, and the risk for postoperative complications[1–3]. The standard treatment of rectal cancer consists of neoadjuvant therapy depending on tumour characteristics and total mesorectal excision (TME), followed by adjuvant therapy depending on national guidelines[4]. For colon cancer, neoadjuvant therapy is only considered in cT4bN0-2 tumours and further treatment consists of resection of the colonic segment with adequate lymphadenectomy, followed by adjuvant chemotherapy in patients with stage III disease[5].

Due to the difference in therapy between colon and rectal cancer, it is essential to accurately define what constitutes a distal sigmoid cancer and rectal cancer. However, until recently, no clear consensus existed regarding the definition of the rectum, with a subsequent variable classification of distal sigmoid cancer and proximal rectal cancer[6]. While the variation in definitions has its effect on the use of (neo)adjuvant therapy

Received: December 09, 2022. **Revised:** January 19, 2023. **Accepted:** January 25, 2023

for tumours in the watershed area of the recto-sigmoid, it also influences research outcomes, as different arbitrary cut-off points have been used in the literature[5,7–11]. To overcome these problems, a new definition has been proposed, defining the rectum as the anatomical portion of the colon below the sigmoid take-off (STO)[12]. This anatomical landmark can be assessed using MRI, and has been shown to be associated with moderate–good reliability[13–15].

Since its introduction, several studies and the Dutch clinical guideline have embraced the STO[5,16]. The implementation may lead to a decrease in the overall number of rectal cancer cases. In addition, as the Dutch colorectal cancer guideline does not recommend adjuvant chemotherapy in patients with rectal cancer with pathological positive lymph nodes, patients would be treated differently, if redefined as having sigmoid cancer according to the STO[5]. Therefore, the aim of this multicentre cohort was to describe the shift in rectal cancer diagnoses and its clinical implications, as an effect of using the STO definition, in a cohort of Dutch patients.

Methods

Study design

A retrospective multicentre cohort study was performed in 11 dedicated colorectal centres in the Netherlands. MRI of patients formerly diagnosed with rectal cancer was reassessed using the STO. Volume shifts of rectal cancer were registered, and clinical outcomes of STO-defined patients with rectal cancer were compared with STO-defined patients with sigmoid cancer. A protocol (regarding the design, methods, and statistical analysis) was composed before initiation of the study. The study was reported in accordance with the STROBE guidelines[17]. Informed consent was deemed unnecessary according to the Dutch Medical Treatment Agreement Act. The medical ethics committee and local ethics committees of all hospitals gave approval for the study (MEC-U, AW19.023 W18.100).

As this was not a prospective trial, it was not registered.

Aims

The primary aim was to describe the number of patients with sigmoid cancer after reassessment according to the STO, in patients registered in the Dutch Colorectal Audit (DCRA) as having rectal cancer. Secondary aims included comparison of intraoperative, postoperative, pathological, and oncological outcomes between STO-defined patients with rectal cancer and STO-defined sigmoid cancer patients after reassessment. As the Dutch guideline does not recommend adjuvant chemotherapy in node-positive rectal cancer patients, while this is offered in node-positive sigmoid cancer patients[5], another secondary aim was to register the number of patients that would have been treated differently with regard to neoadjuvant and adjuvant therapy due to use of the STO definition.

Patients

Patients were included if they: were older than 18 years; were registered as having rectal cancer in the DCRA database between 1 January 2015 and 31 December 2017; were treated with curative intent; and were treated using TME. Patients were excluded if they: were operated on in an emergency setting; had synchronous metastases; or if no preoperative MRI was available. Of note, patients were registered in the DCRA as having rectal carcinoma using several definitions, including, but not limited to: 15 cm from the anorectal junction (ARJ) using MRI; 15 cm from the anal verge using colonoscopy or the peritoneal fold using MRI[6].

Data and outcomes

Data were pseudonymized, and missing data were added in the electronic case report form using the local hospitals' electronic medical record. Baseline characteristics were provided from the DCRA database and included age, BMI, sex, ASA grade, distance in centimetres from the tumour to the ARJ using MRI and from the anal verge using colonoscopy, mesorectal fascia involvement using preoperative MRI, clinical TNM stage, and administration of (neo)adjuvant therapy. Registered outcomes were also provided from the DCRA database and included type of surgical approach, type of surgical procedure, type of stoma constructed, conversion, intraoperative complications, 30-day postoperative complications, 30-day major morbidity rate, 30-day mortality rate, anastomotic leakage, reintervention, readmission, length of stay, pathological TNM stage, quality of TME, positive circumferential margin, and radicality. Furthermore, 3-year overall survival (OS), disease-free survival (DFS), local recurrence (LR), systemic recurrence (SR), and permanent stoma rate were registered.

Specimen quality was defined according to Nagtegaal and Quirke[18], positive circumferential margin as less than or equal to 1 mm, and radicality as negative distal, proximal, and circumferential margins. Surgical complications were defined according to the DCRA database and included intra-abdominal abscess, ileus, wound infection, and anastomotic leakage. Morbidity rate was classified according to the Clavien–Dindo classification, with major morbidity rate being grade III or higher[19]. Anastomotic leakage was defined according to the definition of the International Study Group of Rectal Cancer, and was registered until the end of follow-up[20,21]. Three-year OS was defined as being alive after 3 years of follow-up. Three-year DFS was defined as being alive without recurrence after 3 years of follow-up. SR was defined as any distant metastasis, either pathologically proven or considered to be a lesion suspected for metastasis on imaging that showed growth on consecutive imaging. LR was defined as a tumour deposit located in the pelvic cavity, either pathologically proven or a lesion suspected for LR that showed growth on consecutive imaging if histopathological confirmation was absent. Finally, a permanent stoma was defined as having a stoma at the end of the follow-up interval.

Radiological reassessment

A tumour was defined as a rectal tumour if the lower border of the tumour was below the STO[12]. A low rectal tumour was defined according to the Low Rectal Cancer Development Programme (LOREC) definition: 'a tumour with its lower border at or below the origin of the musculus levator on the pelvic sidewall'[22]. Rectal tumours that were not defined as low rectal tumours were categorized as high rectal tumours. Six researchers reassessed MRI, four of them being medical doctors and two of them being senior medical students. They all received training from a senior researcher with extensive experience in assessing the STO. The training was given under supervision of a senior abdominal radiologist. Before being allowed to enter data in the electronic case report form, they would need to adequately assess ten MRIs. Researchers were retrained until ten consecutive MRIs were adequately reported.

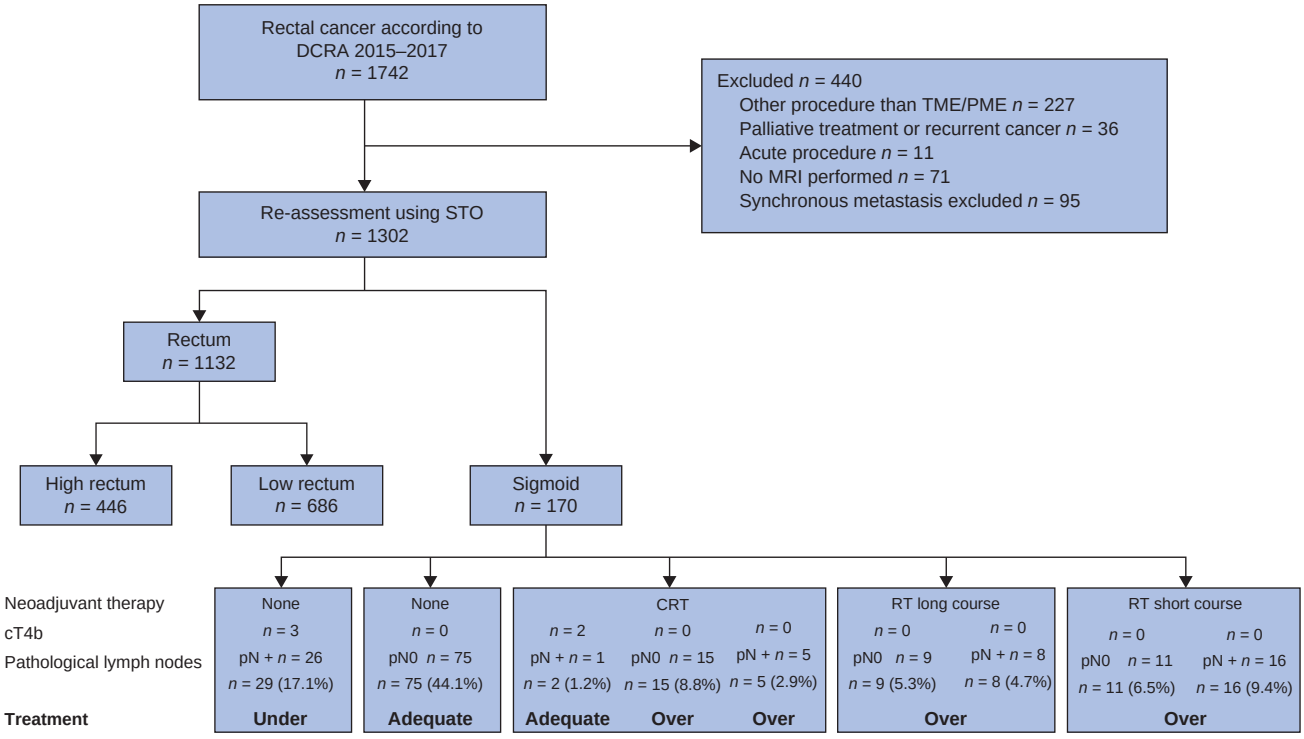

Fig. 1 Patient flow diagram

DCRA, Dutch Colorectal Audit; TME, total mesorectal excision; PME, partial mesorectal excision; STO, sigmoid take-off; High rectum, patients with an MRI-defined rectal tumour, but not a Low Rectal Cancer Development Programme (LOREC)-defined rectal tumour; Low rectum, patients with an LOREC-defined rectal tumour; CRT, chemoradiation; RT, radiotherapy.

Table 1 Baseline characteristics of all patients

	Total, *n* = 1302	Sigmoid, *n* = 170	Rectum, *n* = 1132	*P*
Age (years), mean(s.d.)	67(10.3)	68(10.5)	67(10.2)	0.371
BMI (kg/m^2), mean(s.d.)	26(4.3)	27(4.8)	26(4.2)	0.165
Sex ratio (M:F)	829 (63.7):473 (36.3)	109 (64.1):61 (35.9)	720 (63.6):412 (36.4)	0.965
ASA grade				
I	261 (20.0)	30 (17.7)	231 (20.4)	0.856
II	789 (60.6)	107 (62.9)	682 (60.3)	
III	243 (18.7)	32 (18.8)	211 (18.6)	
IV	9 (0.7)	1.1 (0.6)	8 (0.7)	
Distance to anal verge using colonoscopy (cm), median (i.q.r.)	8 (4–11)	13 (11–15)	7 (3–10)	<0.001
Distance to ARJ using MRI (cm), median (i.q.r.)	6 (3–9)	12 (10–14)	5 (2–8)	<0.001
LOREC	686 (52.7)	0 (0.0)	686 (60.6)	<0.001
MRF+	380 (29.2)	35 (20.6)	345 (30.5)	<0.001
Missing	22 (1.7)	17 (10.0)	5 (0.4)	
Clinical tumour class				
1	34 (2.6)	8 (4.7)	26 (2.3)	<0.001
2	392 (30.1)	54 (31.8)	338 (29.8)	
3	754 (57.9)	95 (55.9)	659 (58.2)	
4	113 (8.7)	6 (3.5)	107 (9.5)*	
Missing	9 (0.7)	7 (4.1)	2 (0.2)	
Clinical node class				
0	599 (46.0)	91 (53.5)	508 (44.9)*	0.070
1	416 (32.0)	45 (26.5)	371 (32.8)	
2	282 (21.6)	31 (18.2)	251 (22.2)	
Missing	5 (0.4)	3 (1.8)	2 (0.2)	
Neoadjuvant therapy				
None	537 (41.2)	103 (60.6)	434 (38.3)*	<0.001
Radiotherapy	386 (29.7)	44 (25.9)	342 (30.3)	
Chemoradiation	361 (27.7)	22 (12.9)	339 (29.9)*	
Missing	18 (1.4)	1 (0.6)	17 (1.5)	

Values are *n* (%) unless otherwise indicated. *Significant after post-hoc testing. s.d., standard deviation; i.q.r., interquartile range; ARJ, anorectal junction; LOREC, Low Rectal Cancer Development Programme; MRF+, mesorectal fascia involvement using preoperative MRI.

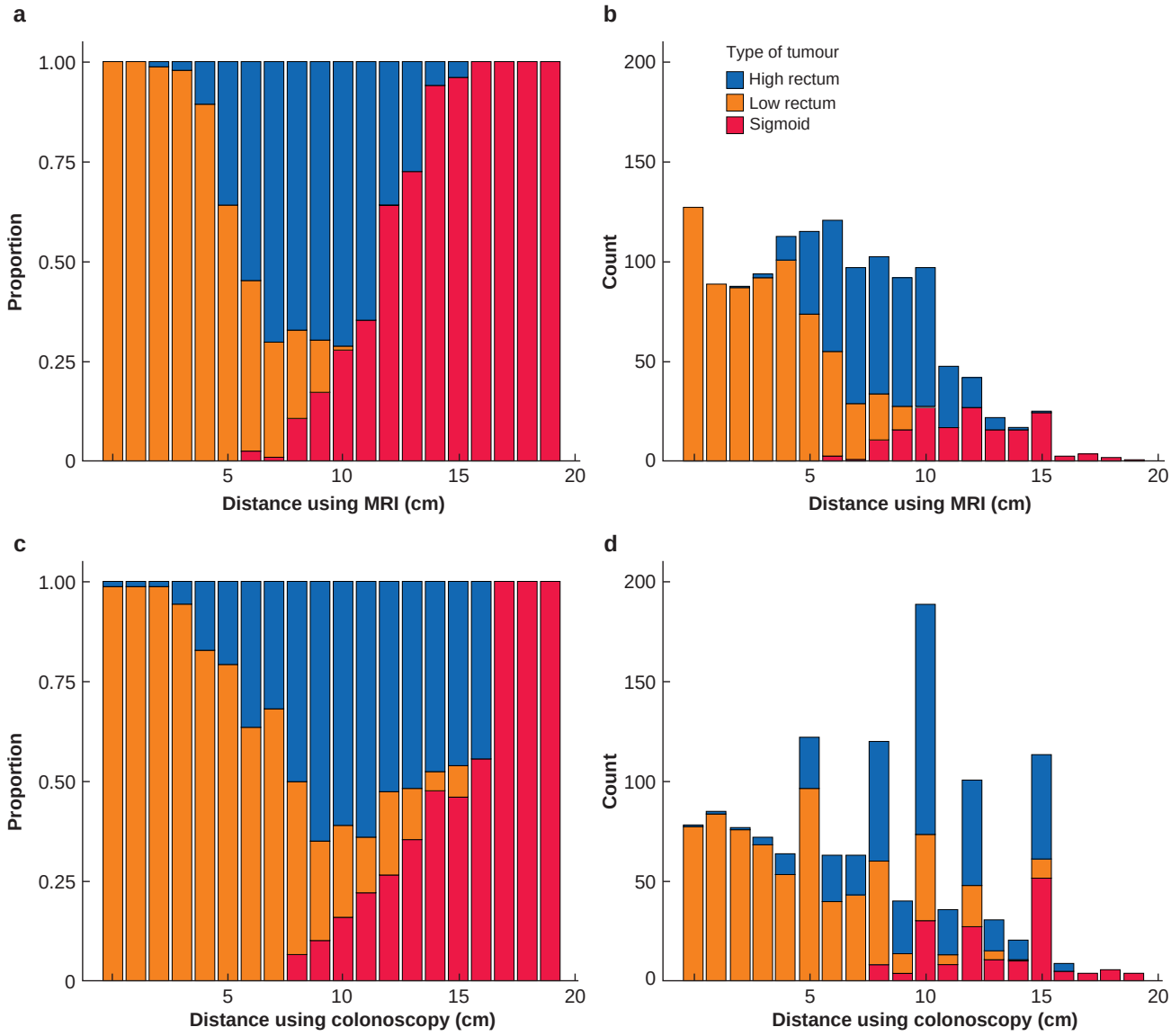

Fig. 2 Distribution of types of tumours relative to the distance to the anorectal junction

a Proportion of tumours relative to the distance using MRI. **b** Absolute number of tumours relative to the distance using MRI. **c** Proportion of tumours relative to the distance using colonoscopy. **d** Absolute number of tumours relative to the distance using colonoscopy. High rectum, rectal tumour according to sigmoidal take-off; Low rectum, rectal tumour according to the Low Rectal Cancer Development Programme criteria; Sigmoid, sigmoidal tumour according to sigmoidal take-off.

Statistical analysis

Descriptive statistics are given using a bar plot for the type of tumour relative to the distance from the ARJ using MRI and colonoscopy separately. Categorical data are presented as number and percentage. Continuous data are presented as mean and standard deviation (s.d.) or as median and interquartile range (i.q.r.) depending on the distribution. Univariable analysis was done using the chi-squared test for categorical data. The independent-sample *t* test or Wilcoxon's rank sum test was used for continuous data depending on the distribution. Differences in survival were tested using the log rank test. Post-hoc testing was performed using the Bonferroni test. $P < 0.05$ was considered significant. Analyses were conducted using R (version 3.6.1), with the packages 'Survival', 'Matching', 'Mice', and 'survminer'.

In the group of patients with a sigmoid tumour after reassessment using the STO, the number of patients that would have been treated differently according to the Dutch guideline was registered. Patients that would not have been treated differently were defined as 'adequately treated'. Patients that were not given adjuvant therapy, but should have been offered adjuvant therapy if the STO definition was used, were defined as 'undertreated'. Finally, patients that were treated with neoadjuvant therapy, but should not have been offered neoadjuvant therapy if the STO definition was used, were defined as 'overtreated'.

Results

In total, 1742 patients were identified as eligible, of which 440 were excluded, resulting in 1302 patients included in the analysis (*Fig. 1*). Of these patients, 170 (13.1 per cent) had a sigmoidal tumour, whereas 1132 patients had a rectal tumour according to the STO. The percentage of patients with a sigmoidal tumour according to the STO was 11.3, 1.3, 13.2, 17.1, 13.4, 12.1, 13.9, 14.8, 24.3, 10.9, and 10.2 per cent for the individual centres.

Table 2 Postoperative outcomes

	Total, $n = 1302$	Sigmoid, $n = 170$	Rectum, $n = 1132$	*P*
Technique				
Open	50 (3.8)	4 (2.4)	46 (4.1)	<0.001
Laparoscopic	642 (49.3)	102 (60.0)	540 (47.6)*	
Transanal TME	236 (18.1)	11 (6.5)	225 (19.9)*	
Robot-assisted TME	374 (28.8)	53 (31.1)	321 (28.4)	
Procedure				
APER	395 (30.3)	4 (2.4)	391 (34.5)*	<0.001
LAR + colostomy	173 (13.3)	22 (12.9)	151 (13.3)	
LAR + anastomosis	734 (56.4)	144 (84.7)	590 (52.2)*	
Stoma				
No stoma	377 (29.0)	107 (62.9)	270 (23.8)*	<0.001
Deviating ileostomy	355 (27.2)	36 (21.2)	319 (28.2)	
Ending ileostomy	8 (0.6)	1 (0.6)	7 (0.6)	
Deviating colostomy	33 (2.5)	4 (2.4)	29 (2.6)	
Ending colostomy	527 (40.5)	22 (12.9)	505 (44.6)*	
Unknown	2 (0.2)	0 (0.0)	2 (0.2)	
Conversion	54 (4.1)	5 (2.9)	49 (4.3)	0.522
Intraoperative complication	80 (6.1)	5 (2.9)	75 (6.6)	0.090
Postoperative complications	604 (46.4)	57 (33.5)	547 (48.3)	<0.001
Surgical complications	415 (31.9)	35 (20.6)	380 (33.6)	0.001
Abscess	82 (6.3)	6 (3.5)	76 (6.7)	0.154
Ileus	184 (14.1)	18 (10.6)	166 (14.7)	0.192
Wound infection	60 (4.6)	2 (1.2)	58 (5.1)	0.036
Anastomotic leakage	116 (15.8)	9 (6.2)	107 (18.1)	0.001
Major morbidity rate (Clavien–Dindo grade ≥III)	249 (19.1)	17 (10.0)	232 (20.5)	0.002
Mortality rate	14 (1.1)	3 (1.8)	11 (1.0)	0.584
Reintervention	212 (16.3)	15 (8.8)	197 (17.4)	0.007
Readmission	185 (14.2)	18 (10.6)	167 (14.8)	0.183
LOS (days), median (i.q.r.)	6 (5–9)	5 (4–7)	6 (5–9)	<0.001
(y)pT				
0	96 (7.4)	7 (4.1)	89 (7.9)	0.008
1	135 (10.4)	18 (10.6)	117 (10.3)	
2	454 (34.8)	46 (27.1)	408 (36.0)*	
3	573 (44.0)	89 (52.4)	484 (42.8)*	
4	39 (3.0)	10 (5.8)	29 (2.6)*	
Missing	5 (0.4)	0 (0.0)	5 (0.4)	
(y)pN				
0	886 (68.0)	113 (66.4)	773 (68.3)	0.534
1	288 (22.2)	36 (21.2)	252 (22.2)	
2	125 (9.6)	20 (11.8)	105 (9.3)	
Missing	3 (0.2)	1 (0.6)	2 (0.2)	
pM				
0	1257 (96.5)	166 (97.6)	1091 (96.3)	0.832
1	12 (0.9)	1 (0.6)	11 (1.0)	
Missing	33 (2.6)	3 (1.8)	30 (2.7)	
Incomplete TME	75 (5.8)	5 (2.9)	59 (5.2)	0.802
R1/R2	64 (4.9)	8 (4.7)	67 (5.9)	0.232
Follow-up time (months), median (i.q.r.)	36 (25–48)	36 (26–44)	36 (25–48)	0.992
Permanent stoma	659 (50.8)	32 (18.8)	627 (55.4)	<0.001
Three-year overall survival	1171 (89.9)	151 (88.8)	1020 (90.1)	0.703
Three-year DFS	1007 (77.3)	126 (74.7)	881 (77.8)	0.328
Three-year local recurrence	60 (4.6)	6 (3.5)	54 (4.8)	0.600
Multifocal	8 (0.6)	1 (0.6)	7 (0.6)	1.000
Three-year systemic recurrence	194 (14.9)	32 (18.8)	162 (14.3)	0.154

Values are *n* (%) unless otherwise indicated. *Significant after post-hoc testing. TME, total mesorectal excision; APER, abdominoperineal excision of the rectum; LAR, low anterior resection; LOS, length of stay; i.q.r., interquartile range; pT, pathological tumour stage; pN, pathological node stage; pM, pathological metastasis stage; TME, total mesorectal excision; R1/R2, microscopic or macroscopic irradical resection surgery; DFS, disease-free survival.

Baseline characteristics

Compared with STO-defined patients with rectal cancer, STO-defined patients with sigmoid cancer had fewer cT4 tumours, and more cN0 tumours, with a lower rate of patients receiving neoadjuvant therapy. Furthermore, tumours were more proximally located from the ARJ (*Table 1*). Significantly more patients did not receive a stoma during primary resection (23.8 *versus* 62.9 per cent, $P < 0.001$), more patients received an anastomosis (52.2 *versus* 84.7 per cent, $P < 0.001$), and fewer patients underwent an abdominoperineal excision of the rectum (APER) (34.5 *versus* 2.4 per cent, $P < 0.001$). Furthermore, 60.6 per cent of the rectal tumours were low rectal tumours according to the LOREC criteria, with the majority having a distance to the ARJ of 0–5 cm using MRI (*Fig. 2*).

Postoperative outcomes

The overall complication rate (33.5 *versus* 48.3 per cent, $P < 0.001$), surgical complication rate (20.6 *versus* 33.6 per cent, $P < 0.001$), and major morbidity rate (10.0 *versus* 20.5 per cent, $P < 0.001$) were significantly lower in the STO-defined sigmoid cancer group compared with the STO-defined rectal cancer group. Anastomotic leakage was significantly less present in the sigmoid group (6.2

versus 18.1 per cent, $P < 0.001$). The reintervention rate and length of stay were also significantly lower in the sigmoid group. Regarding pathological and oncological outcomes, more (y)pT3 (52.4 *versus* 42.8 per cent, $P = 0.02$), more (y)pT4 (5.9 *versus* 2.6 per cent, $P = 0.02$), and fewer (y)pT2 (27.1 *versus* 36.0 per cent, $P = 0.02$) tumours were seen in the sigmoid group. Radicality (4.7 *versus* 5.9 per cent, $P = 0.23$) did not differ significantly between the two groups. The median follow-up was comparable between the two groups (36 (i.q.r. 26–44) *versus* 36 (i.q.r. 25–48) months, $P = 0.992$). Three-year OS (88.8 *versus* 90.1 per cent, $P = 0.703$), 3-year DFS (74.7 *versus* 77.8 per cent, $P = 0.328$), and the 3-year LR rate (3.5 *versus* 4.8 per cent, $P = 0.601$) did not differ significantly. The permanent stoma rate at the end of follow-up was significantly lower in the sigmoid group (18.8 *versus* 55.4 per cent, $P < 0.001$) (*Table 2*).

Clinical implications

Of the 170 patients with a sigmoid tumour as defined by the STO, 93 patients (54.7 per cent) would have been treated differently if the STO definition had been used. Twenty-nine patients were undertreated, whereas 64 patients were overtreated. Twenty-nine patients did not receive neoadjuvant treatment, but would have received adjuvant treatment if correctly assessed and treated as having sigmoid cancer according to the Dutch guideline. These patients were categorized as undertreated. Of these, three patients with cT4b tumours should also have been treated with neoadjuvant treatment. Sixty-four patients received neoadjuvant therapy, but would not have been offered neoadjuvant therapy according to the Dutch guideline if they were treated as having sigmoid tumours and thus these patients were categorized as overtreated. Among these, 20 received chemoradiation, 17 received long-course radiotherapy, and 27 received short-course radiotherapy. On the other hand, 77 patients (45.3 per cent) would not be treated differently, as 75 patients would not receive neoadjuvant therapy if treated as having rectal cancer or adjuvant therapy if treated as having sigmoid cancer, and two patients would receive neoadjuvant treatment if treated as having sigmoid cancer as well as if they were treated as having rectal cancer, as they had a cT4b tumour (*Fig. 1*).

Discussion

This study aimed to evaluate the shift in rectal cancer diagnosis and its clinical implication, after retrospectively reassessing patients using the STO definition. In this study, 13.1 per cent of the patients classified as having a rectal tumour in the DCRA had a sigmoidal tumour according to the STO definition. Additionally, 54.7 per cent of the patients with an STO-defined sigmoid tumour would have been treated differently if they had been treated according to the Dutch guideline.

This study suggests a shift from patients with rectal cancer to patients with colon cancer as an effect of implementing the STO. The majority of STO-defined rectal tumours are a distance of between 0 and 10 cm from the ARJ using MRI, whereas the majority of STO-defined sigmoid tumours are situated between 10 and 15 cm. As tumours between 10 and 15 cm from the ARJ using MRI are most likely to be sigmoid tumours, these tumours will be excluded in new studies embracing the STO definition. Past studies used different definitions for rectal tumours. Mostly they were defined as rectal tumours based on a distance of 0–10 or 0–15 cm from the ARJ, using either colonoscopy or MRI[23–28]. The COLOR II, ALaCaRT, and ROLARR trials all defined rectal tumours as within 15 cm of the anal verge[24,26,27], and the ACOSOG trial used 12 cm from the anal verge as the cut-off. If the STO definition was used, a significant percentage of the included patients of these studies would now be classified as having colon cancer and therefore excluded[24,26,27]. This has several implications for interpreting previous scientific publications: first, the results of former studies are difficult to compare with the results of studies using the STO definition, as included patients differ; second, as patients with sigmoid tumours were associated with lower morbidity rates, fewer reinterventions, and shorter length of stay, whilst receiving less neoadjuvant therapy, the results of former studies might underestimate the morbidity rate and mortality rate of STO-defined patients with rectal cancer; and third, as the STO definition is increasingly used in clinical practice, the external validity of former studies decreases as well.

As expected, STO-defined sigmoid tumours are situated proximally, and patients with these tumours are less frequently offered neoadjuvant therapy compared with patients with rectal cancer. This partially explains the more favourable clinical outcome in this group. Additionally, more primary anastomoses were constructed in the sigmoid group, and more APERs were performed in the rectum group. Clearly, this is related to tumour height, as this is one of the key factors in the decision to construct an anastomosis. Furthermore, complication rates were significantly lower in the sigmoid group, with subsequently lower reintervention rates, and shorter lengths of hospital stay. Especially, anastomotic leakage was less prevalent in the sigmoid cancer group, which could explain the lower proportion of morbidity rate in this group. This is most likely also related to tumour height and neoadjuvant treatment. Indeed, patients with sigmoid cancer are not normally offered neoadjuvant therapy, which is an independent risk factor for anastomotic leakage as well[21,29]. The difference in morbidity rate between STO-defined sigmoid tumours that were formerly defined as rectal cancer, and STO-defined rectal tumours emphasizes the suggestion that sigmoid and rectal tumours differ significantly, and should therefore be treated differently.

Furthermore, the use of the STO definition has consequences for the clinical surgical practice of centres performing TME surgery as well, as the number of rectal cancer cases is likely to decrease by an estimated 13.1 per cent. This is in addition to the effects of increasingly used organ-preserving treatment options such as transanal endoscopic microsurgery (TEM), transanal minimally invasive surgery (TAMIS), and watch-and-wait programmes, using (total) neoadjuvant treatment[30–32]. Additionally, by using the more uniform STO definition, benchmarking between centres might be more accurate. The results of this study show that the proportion of sigmoid tumours that should have been excluded if the STO had been used differed between 1.1 and 24.3 per cent in the specific centres. The diluting effect on morbidity rates due to the inclusion of STO-defined sigmoid tumours differs between centres, impeding adequate benchmarking without using the STO.

In patients that were diagnosed with a sigmoid tumour according to the STO, more than half would have been treated differently if the Dutch clinical guideline had been applied. This number should, however, be interpreted with caution, as treatment guidelines will not be followed rigidly. According to the Dutch clinical guideline, adjuvant therapy is not offered in patients with rectal cancer that are diagnosed with positive lymph nodes as assessed by pathology examination, irrespective of previous neoadjuvant treatment[5]. As guidelines differ between countries regarding the recommendation of adjuvant chemotherapy in rectal cancer, the clinical consequences regarding change of treatment after implementing the STO differs as well[4]. This might be an explanation for the fact

that most papers about the STO arise from the Netherlands[13,15,33,34]. Nevertheless, the STO might better differentiate between rectal cancer and sigmoid cancer, and thereby promote appropriate neoadjuvant or adjuvant treatment.

Some limitations should be taken into account. First, this is a retrospective cohort of patients and thus bias might be apparent. Second, reassessment in this study was performed by researchers after extensive training, supervised by an abdominal radiologist. Previous research assessed the inter-observer agreement of the STO for radiologists or senior surgeons[13–15]. This might have affected the quality of radiological assessment. However, the researchers were trained under supervision of a radiologist, and were only allowed to participate after having assessed ten MRIs in a row adequately. Third, only patients formerly diagnosed with rectal cancer were reassessed, thereby neglecting former patients with sigmoid cancer that might have had STO-defined rectal cancer after reassessment. This could have resulted in an underestimation of patients with rectal cancer according to the STO. However, as former sigmoid cancer patients present with tumours more proximal in the colon, the number of patients initially diagnosed with sigmoid cancer that have a rectal cancer according to the STO is probably small.

Overall, 13.1 per cent of the patients formerly diagnosed with rectal cancer were diagnosed with sigmoid cancer according to the STO definition. These patients had a significantly lower risk of perioperative complications than patients with rectal cancer, with reduced risk of readmission, reintervention, and permanent stoma. Finally, 54.7 per cent of the patients with sigmoid cancer according to the STO would have received other neoadjuvant or adjuvant treatment, due to the change of the definition.

Collaborators

The MIRECA Study Group

R. M. P. H. Crolla, Department of Surgery, Amphia Hospital, Breda, The Netherlands; R. T. J. Geitenbeek, Department of Surgery, Meander Medical Center, Amersfoort, The Netherlands; A. A. W. van Geloven, Department of Surgery, Tergooi Hospital, Hilversum, The Netherlands; J. W. A. Leijtens, Department of Surgery, Laurentius Hospital, Roermond, The Netherlands; F. Polat, Department of Surgery, Canisius-Wilhelmina Hospital, Nijmegen, The Netherlands; A. Pronk, Department of Surgery, Diakonessenhuis, Utrecht, The Netherlands; A. B. Smits, Department of Surgery, St Antonius Hospital, Nieuwegein, The Netherlands; J. B. Tuynman, Department of Surgery, Amsterdam UMC, location VUmc, Amsterdam, The Netherlands; E. G. G. Verdaasdonk, Department of Surgery, Jeroen Bosch Hospital, 's Hertogenbosch, The Netherlands; P. M. Verheijen, Department of Surgery, Meander Medical Center, Amersfoort, The Netherlands.

Funding

The authors have no funding to declare.

Acknowledgements

The authors thank R. Knijff and D. M. Adams for collection of data.

Author contributions

Thijs A. Burghgraef (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing—original draft, Writing—review & editing), Jeroen C. Hol (Conceptualization, Data curation, Methodology, Writing—review & editing), Marieke L. Rutgers (Conceptualization, Data curation, Methodology, Writing—review & editing), Gina Brown (Conceptualization, Investigation, Methodology, Supervision, Writing—review & editing), Roel Hompes (Conceptualization, Investigation, Methodology, Supervision, Writing—review & editing), Colin Sietses (Conceptualization, Investigation, Methodology, Supervision, Writing—review & editing), and Esther C. J. Consten (Conceptualization, Investigation, Methodology, Supervision, Writing—review & editing)

Disclosure

R.H. receives fees from Applied Medical. E.C.J.C. receives fees from Intuitive Surgical. R.H. and E.C.J.C. declare no other conflict of interest. T.A.B., J.C.H., M.L.R., G.B., and C.S. declare no conflict of interest.

Data availability

Data are available upon request, this includes template data collection forms, raw data, and data or codes regarding the statistical analysis.

References

1. Van Der Sijp MPL, Bastiaannet E, Mesker WE, Van Der Geest LGM, Breugom AJ, Steup WH *et al.* Differences between colon and rectal cancer in complications, short-term survival and recurrences. *Int J Colorectal Dis* 2016;**31**:1683–1691
2. Tamas K, Walenkamp AME, de Vries EGE, van Vugt MATM, Beets-Tan RG, van Etten B *et al.* Rectal and colon cancer: not just a different anatomic site. *Cancer Treat Rev* 2015;**41**:671–679
3. Imperial R, Ahmed Z, Toor OM, Erdoğan C, Khaliq A, Case P *et al.* Comparative proteogenomic analysis of right-sided colon cancer, left-sided colon cancer and rectal cancer reveals distinct mutational profiles. *Mol Cancer* 2018;**17**:177
4. Poulsen LO, Qvortrup C, Pfeiffer P, Yilmaz M, Falkmer U, Sorbye H. Review on adjuvant chemotherapy for rectal cancer-why do treatment guidelines differ so much? *Acta Oncol (Madr)* 2015; **54**:437–446
5. Landelijke Werkgroep Gastro Intestinale Tumoren. *Richtlijn Colorectaal Carcinoom* 4.0. 2019. https://www.oncoline.nl/colorectaalcarcinoom (accessed 13 January 2020)
6. D'Souza N, de Neree Tot Babberich MPM, Lord A, Shaw A, Abulafi M, Tekkis P *et al.* The rectosigmoid problem. *Surg Oncol* 2018;**27**:521–525
7. Swedish Rectal Cancer Trial. Improved survival with preoperative radiotherapy in resectable rectal cancer. *N Engl J Med* 1997;**336**:980–987
8. Kapiteijn E, Marijnen CAAM, Nagtegaal ID, Putter HH, Steup WH, Wiggers T *et al.* Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001;**345**:638–646
9. Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R *et al.* Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004;**351**:1731–1740
10. Sebag-Montefiore D, Stephens RJ, Steele R, Monson J, Grieve R, Khanna S *et al.* Preoperative radiotherapy versus selective

postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. *Lancet* 2009;**373**:811–820
11. Fleshman J, Branda M, Sargent DJ, Boller AM, George V, Abbas M *et al.* Effect of laparoscopic-assisted resection vs open resection of stage II or III rectal cancer on pathologic outcomes: the ACOSOG Z6051 randomized clinical trial. *JAMA* 2015;**314**:1346–1355
12. D'Souza N, de Neree Tot Babberich MPM, d'Hoore A, Tiret E, Xynos E, Beets-Tan RGH *et al.* Definition of the rectum: an international, expert-based Delphi consensus. *Ann Surg* 2019;**270**:955–959
13. Hazen SMJA, Sluckin TC, Horsthuis K, Lambregts DMJ, Beets-Tan RGH, Tanis PJ *et al.* Evaluation of the implementation of the sigmoid take-off landmark in the Netherlands. *Colorectal Dis* 2022;**24**:292–307
14. Pedersen MRV, Otto PO, Vagn-hansen C, Sørensen T, Rafaelsen SR. Interobserver reliability and the sigmoid takeoff—an interobserver study. *Cancers (Basel)* 2022;**14**:2802
15. Bogveradze N, Lambregts DMJ, el Khababi N, Dresen RC, Maas M, Kusters M *et al.* The sigmoid take-off as a landmark to distinguish rectal from sigmoid tumours on MRI: reproducibility, pitfalls and potential impact on treatment stratification. *Eur J Surg Oncol* 2022;**48**:237–244
16. Hol JC, Dogan K, Blanken-Peeters CFJM, van Eekeren RRJP, de Roos MAJ, Sietses C *et al.* Implementation of robot-assisted total mesorectal excision by multiple surgeons in a large teaching hospital: morbidity, long-term oncological and functional outcome. *Int J Med Robot* 2021;**17**:e2227
17. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008;**61**:344–349
18. Nagtegaal ID, Quirke P. What is the role for the circumferential margin in the modern treatment of rectal cancer? *J Clin Oncol* 2008;**26**:303–312
19. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications. *Ann Surg* 2004;**240**:205–213
20. Rahbari NN, Weitz J, Hohenberger W, Heald RJ, Moran B, Ulrich A *et al.* Definition and grading of anastomotic leakage following anterior resection of the rectum : a proposal by the International Study Group of Rectal Cancer. *Surgery* 2010;**147**:339–351
21. Borstlap WAA, Westerduin E, Aukema TS, Bemelman WA, Tanis PJ. Anastomotic leakage and chronic presacral sinus formation after low anterior resection. *Ann Surg* 2017;**266**:870–877
22. Moran BJ, Holm T, Brannagan G, Chave H, Quirke P, West N *et al.* The English National Low Rectal Cancer Development Programme: key messages and future perspectives. *Colorectal Dis* 2014;**16**:173–178
23. Guillou PJ, Quirke P, Thorpe H, Walker J, Jayne DG, Smith AMH *et al.* Short-term endpoints of conventional versus laparoscopic- assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. *Lancet* 2005;**365**:1718–1726
24. van der Pas MHGM, Haglind E, Cuesta MA, Fürst A, Lacy AM, Hop WCJ *et al.* Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial. *Lancet Oncol* 2013;**14**:210–218
25. Jeong SY, Park JW, Nam BH, Kim S, Kang SB, Lim SB *et al.* Open versus laparoscopic surgery for mid-rectal or low-rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): survival outcomes of an open-label, non-inferiority, randomised controlled trial. *Lancet Oncol* 2014;**15**:767–774
26. Stevenson A, Solomon M, Lumley JWJ, Hewet P, Clouston ADA, Gebski VVJ *et al.* Effect of laparoscopic-assisted resection vs open resection on pathological outcomes in rectal cancer. The ALaCaRT randomized clinical trial. *JAMA* 2015;**314**:1356–1363
27. Jayne D, Pigazzi A, Marshall H, Croft J, Corrigan N, Copeland J *et al.* Effect of robotic-assisted vs conventional laparoscopic surgery on risk of conversion to open laparotomy among patients undergoing resection for rectal cancer. *JAMA* 2017;**318**:1569
28. Fleshman J, Branda ME, Sargent DJ, Boller AM, George VV, Abbas MA *et al.* Disease-free survival and local recurrence for laparoscopic resection compared with open resection of stage II to III rectal cancer: follow-up results of the ACOSOG Z6051 randomized controlled trial. *Ann Surg* 2019;**269**:589–595
29. McDermott FD, Heeney A, Kelly ME, Steele RJ, Carlson GL, Winter DC. Systematic review of preoperative, intraoperative and postoperative risk factors for colorectal anastomotic leaks. *Br J Surg* 2015;**102**:462–479
30. van der Valk MJM, Hilling DE, Bastiaannet E, Meershoek-Klein Kranenbarg E, Beets GL, Figueiredo NL *et al.* Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study. *Lancet* 2018;**391**:2537–2545
31. Bahadoer RR, Dijkstra EA, van Etten B, Marijnen CAM, Putter H, Kranenbarg EMK *et al.* Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2021;**22**:29–42
32. Conroy T, Bosset JF, Etienne PL, Rio E, François É, Mesgouez-Nebout N *et al.* Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol* 2021;**22**:702–715
33. Li F, Wang B, Lu S, Wang Y, Sun T, Wang H *et al.* Comparison of the sigmoid take-off with other definitions of the rectosigmoid junction: a retrospective comparative cohort analysis. *Int J Surg* 2020;**80**:168–174
34. D'Souza N, Lord A, Shaw A, Patel A, Balyasnikova S, Tudyka V *et al.* The sigmoid take-off: an anatomical imaging definition of the rectum validated on specimen analysis. *Eur J Surg Oncol* 2020;**46**:1668–1672