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Early local recurrence and one-year mortality of rectal cancer after restricting the neoadjuvant therapy regime

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ABSTRACT

Introduction: To reduce the risk of local recurrence after rectal cancer surgery, neoadjuvant radiotherapy (RT) can be applied. However, as this causes morbidity and increases mortality, new Dutch guidelines withhold RT in low-risk patients. The aim of this study is to investigate if early local recurrence and one-year mortality in rectal cancer patients has changed since this more restricting indication for neoadjuvant RT was introduced in 2014.

Methods: This retrospective study included all consecutive patients treated with a mesorectal excision for primary rectal cancer in the Amphia Hospital, the Netherlands, between January 2011 and July 2016. Data were extracted from the electronic patient records. Survival data were collected from the Municipal Personal Records Database.

Results: Between 2011 and July 2016, 407 resections of primary rectal cancer without synchronic metastases were performed, 225 under the old guidelines and 182 under the new guidelines. Significantly fewer patients received neoadjuvant treatment under the new guidelines (89% vs 41%, $p < 0.001$). Both clinical tumour stage ($p = 0.001$) and clinical lymph node stage ($p < 0.001$) were lower in the new group, but no difference in pathologic TN-stage was found. There was no difference in one-year local recurrence (2.2% in both groups, $p = 0.987$), nor in one-year mortality (5.3% vs 3.8%, $p = 0.479$).

Conclusion: Introducing a new guideline and thereby restricting the indication for neoadjuvant RT in rectal cancer patients did not increase the early local recurrence rate or decreased one-year mortality in our hospital.

Introduction[1]

Rectal cancer resection has a high risk of local recurrence: 25 years ago more than 20% of the rectal cancer patients developed a local recurrence after surgery in the Netherlands [1]. Since then, the risk of local recurrence after rectal cancer surgery has been reduced due to several factors. First of all the quality of rectal cancer surgery has increased considerably by the introduction of the total mesorectal excision (TME) [2]. Furthermore, most patients in the Netherlands were treated with neoadjuvant short-course radiotherapy (SCRT, 5 × 5 Gray) or chemoradiotherapy (CRT) before 2014 as RT reduces the risk of local recurrence [3,4].

Although RT reduced rectal cancer-related mortality, it increased the mortality risk due to other causes by 4% in the first year. In patients aged 75 and older treated with RT, this resulted in an increased total mortality risk [3]. Furthermore, RT causes long-term disadvantages, such as a higher prevalence of sexual dysfunction [5,6] and faecal and urinary incontinence [6–8].

To reduce this morbidity and mortality associated with RT, the indications for neoadjuvant therapy were restricted in new Dutch guidelines that were implemented in April 2014 [9]. The decision to apply neoadjuvant treatment is based on clinical tumour and

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[1] cN-stage: clinical lymph node stage (based on MRI), cT-stage: clinical tumour stage (based on MRI), CRM: circumferential resection margin, CRT: chemoradiotherapy, EMVI: extramural venous invasion, pN-stage: pathologic lymph node stage, pT-stage: pathologic tumour stage, RT: radiotherapy, SCRT: short course radiotherapy, TME: total mesorectal excision.

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lymph node staging on preoperative MRI. No neoadjuvant treatment is indicated in patients without suspicious lymph nodes and less than 5 mm extramural invasion [9]. Furthermore, the criteria for suspicious lymph nodes have become stricter.

Although the MERCURY-study showed the ability to identify low-risk tumours on MRI, clinical lymph node status was not used as a criterion to apply neoadjuvant therapy in that study [10] in contrast to the Dutch guidelines [9]. As previous studies suggest that MRI may be insufficient to correctly assess clinical lymph node stage [11–13], this raises the question if the incidence of local recurrence has increased, since fewer patients receive neoadjuvant RT.

Therefore, the aim of this study was to determine if the implementation of the new Dutch guidelines for rectal cancer treatment resulted in an increase in local recurrence and difference in one-year mortality.

Methods

This study is a retrospective cohort study, including all consecutive patients treated with a mesorectal excision for primary rectal cancer in the Amphia Hospital, the Netherlands, between January 2011 and July 2016. Patients with an indication for intraoperative RT were excluded, as they were referred to another hospital. Patients with a local recurrence after previous treatment or synchronous metastases were also excluded. This study was conducted according to the STROBE-guidelines for Reporting Observational Studies.

The patients were identified throughout the Netherlands Comprehensive Cancer Organisation. Additional patient characteristics and data were obtained retrospectively from the electronic patient records. Survival data were collected from the Municipal Personal Records Database.

Until April 2014, all patients were treated according to the old guidelines, and after that, the new Dutch guidelines were applied. The treatment of all patients diagnosed with rectal cancer was discussed in a multidisciplinary meeting.

Clinical TNM-stage

The same MRI protocol was used during both guidelines. Existing MRI reports were studied to extract data on clinical tumour (cT) and lymph node (cN) stage, defined according to the fifth edition of the TNM-classification [14]. As we aimed to evaluate the value of the current MRI-based guideline in daily clinical practice, MRIs were not reassessed.

The clinical tumour and lymph node stage described in the report were used. If no differentiation between stage cN1 and cN2 could be made based on the MRI report, cN-stage was regarded cN+. If no information was described in the report, these data were considered missing.

The old guidelines defined suspicious lymph nodes as >5 mm in diameter [15]. The new guidelines defined suspicious lymph nodes as >9 mm, or 5–9 mm with two out of three malignant features (round form, irregular margins, and heterogeneous texture) or <5 mm with all three malignant features [9].

Distance of the tumour from the anorectal junction was obtained from the MRI reports and colonoscopy reports and defined according to distance of the distal end of the tumour from the anorectal junction. Proximal rectal tumours were more than 10 cm from the anorectal junction, mid-rectal tumours five to 10 cm and distal rectal tumours less than 5 cm.

Neoadjuvant and adjuvant therapy

The indications for neoadjuvant therapy in both the old and new guidelines are mentioned in the appendix. The most imported change is that patients with clinical tumour stage ≤ T3ab (<5 mm extramural invasion) without suspicious lymph nodes do no longer have an indication for SCRT [9].

Short course radiotherapy (SCRT) consisted of 5 × 5Gy RT followed by resection within five days after the last dose of RT. CRT consisted of a total dose of 45–50 Gray RT and oral Capecitabine followed by restaging with an MRI. Resection was performed 8–12 weeks after the last dose of RT. In case of contraindications for chemotherapy, RT was given without chemotherapy, followed by surgery after the same interval. Adjuvant chemotherapy was not advocated in both the old and new guidelines.

Operative treatment

Surgery was performed or supervised by six certified gastrointestinal/oncological surgeons. All robot-assisted operations were performed by three surgeons. Type of operation and type of resection were recorded prospectively.

Postoperative pathology results

Pathologic anatomical examination was performed according to the Dutch pathology guidelines, based on the fifth edition of the TNM-classification, using a standardized protocol [14,16]. If the CRM was microscopically >1 mm free of tumour cells, the resection was defined as tumour-negative (R0-resection). If tumour cells were infiltrating the resection margin or the tumour-free distance was <1 mm, this was considered as microscopically tumour positive resection margins (R1-resection).

Concordance between neoadjuvant treatment and pathology

If patients did not receive neoadjuvant treatment in the new guidelines based on MRI-staging and one to three pathological lymph nodes were found (pN1) after histopathologic examination, then SCRT should have been indicated. If four or more pathological lymph nodes were found (pN2) or if the tumour invaded other organs (pT4) or if the circumferential margin (CRM) was tumour positive (R1-resection), CRT should have been administered. If patients had undergone SCRT and pathologic examination showed a pN2-stage, pT4-stage or tumour-positive CRM, we considered these patients undertreated; they should have undergone CRT.

Follow-up and recurrence

Follow-up was performed according to a local protocol, based on the interpretation of the international and Dutch guidelines for the treatment of rectal cancer [9,15]. The follow-up schedule was the same before and after April 2014. Patients visited the outpatient clinic once every three to six months for five years postoperatively, and each time they completed a carcinoembryonic antigen (CEA)-test, an ultrasound examination of the liver and a thoracic X-ray. If deemed necessary, other diagnostic modalities were added, such as a computed tomography (CT) scan, MRI or a positron-emission tomography (PET) scan. One and five year after surgery, a routine colonoscopy was performed. In case of the presence of polyps and depending on the polyp characteristics, another colonoscopy was planned in line with the guidelines for follow-up after polypectomy [17].

If local recurrence occurred, the date of the first radiological or endoscopic confirmation of recurrent disease was registered as

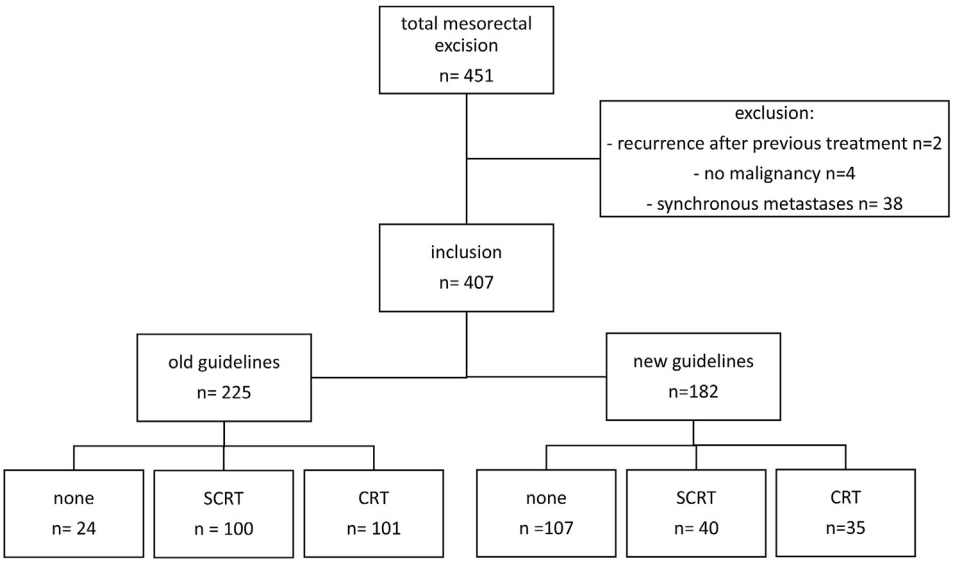


Fig. A. Flowchart of included patients.

Table A.1
Patient and clinical tumour characteristics for all included patients treated for primary rectal cancer from January 2011 until July 2016.

		Old guidelines	New guidelines	Difference
Number of patients n		225	182	
Male n (%)		142(63)	111 (61)	NS (p = 0.661)
Age (Mean ± SD)		68 ± 10	67 ± 10	NS (p = 0.880)
BMI (Mean ± SD)		26 ± 5	26 ± 4	NS (p = 0.712)
ASA-classification n (%)				NS (p = 0.062)
	ASA 1	25(11)	35(19)	
	ASA 2	143(64)	109(60)	
	ASA 3	56(25)	42(21)	
	ASA 4	1(0.5)	0(0)	
Neoadjuvant treatment n (%)				**p < 0.001**
	None	24 (11)	107 (59)	
	SCRT	100 (44)	40 (22)	
	CRT	81 (36)	24 (13)	
	RT + long waiting interval	20 (9)	11 (6)	
Clinical tumour stage n (%)				**p = 0.001**
	≤cT1	0 (0)	9 (5)	
	cT2	70 (31)	84 (46)	
	cT3	113 (50)	65 (36)	
	cT4	11 (5)	7 (4)	
	missing	31 (14)	17 (9)	
Clinical lymph node stage n (%)				**p < 0.001**
	cN0	52 (23)	100(55)	
	cN1	49 (22)	42 (23)	
	cN2	33 (15)	17 (9)	
	cN+	67 (30)	8 (4)	
	missing	24 (11)	15 (8)	
Clinical tumour- and lymph node stage n(%)				
	cT1-3N0	49 (22)	98 (54)	
	cT1-3N1	43 (19)	39 (21)	
	cT2-4N2	33 (15)	14 (8)	
	cT2-3N+	55 (24)	7 (4)	
	cT4N0-2	11 (5)	7 (4)	
	Missing	34 (15)	17	
Tumour location based on MRI				NS (p = 0.537)
	Proximal	19 (8)	22 (12)	
	Middle	67 (30)	66 (36)	
	Distal	73 (32)	59 (32)	
	Missing	66 (29)	35 (19)	
Tumour location based on colonoscopy				NS (P = 0.055)
	Proximal	63 (28)	71 (39)	
	Middle	87 (39)	56 (31)	
	Distal	75 (33)	55 (30)	

BMI: body mass index; ASA: American Society of Anesthesiologists; SCRT: short course radiotherapy; CRT: chemoradiation therapy; RT + long waiting: radiotherapy with 8–12 weeks waiting interval until resection.

Table A.2
Surgical and pathologic tumour characteristics for all included patients treated for primary rectal cancer from January 2011 until July 2016.

	Old guidelines	New guidelines	Difference
Number of patients n	225	182	
Type of surgery n (%)			**p < 0.001**
Robot assisted laparoscopic	57 (25)	150 (82)	
Open	45 (20)	6 (3)	
Laparoscopic	123 (55)	26 (14)	
Type of resection n (%)			NS (p = 0.628)
APR	68 (30)	51 (28)	
LAR/AR	157 (70)	131 (72)	
LAR	147 (65)	110 (60)	
AR	10 (4)	21 (12)	
Pathologic tumour stage n (%)			NS (p = 0.367)
(y)pT0	25 (11)	7 (4)	
(y)pTis	1 (0.5)	2 (1)	
(y)pT1	16 (7)	15 (8)	
(y)pT2	65 (29)	62 (34)	
(y)pT3	114 (51)	91 (50)	
(y)pT4	4 (2)	5 (3)	
Pathologic lymph node stage n (%)			NS (p = 0.988)
(y)pN0	158 (70)	128 (70)	
(y)pN1	48 (21)	38 (21)	
(y)pN2	19 (8)	16 (9)	
Tumour regression# n (%)			NS (p = 0.970)
No regression	5 (5)	2 (6)	
Partial regression	45 (45)	17 (49)	
Complete regression	25 (25)	8 (23)	
Missing	26 (26)	8 (23)	
Number of examined lymph nodes			**p < 0.001**
Mean ± SD	12 ± 6	17 ± 7	
Radical resection n (%)			NS (p = 0.608)
R0	214 (95)	171 (94)	
R1	11 (5)	11 (6)	

APR: abdominoperineal resection; LAR: low anterior resection; AR: anterior resection; R0: resection margins microscopically free of tumour cells; R1: resection margins microscopically involved # tumour regression in patients treated with chemoradiotherapy or radiotherapy with long waiting interval.

date of recurrence. Local recurrence was defined as clinical suspicion of recurrence based on diagnostic tests with or without pathology confirmation. Time to recurrence or mortality was measured from the date of surgical resection. In patients without recurrence the date of last oncological follow up was used for the analyses of recurrence and disease-free survival. Time since surgical resection was used for overall survival.

Primary and secondary outcomes

The primary outcome is development of local recurrence within the time of follow up. The secondary outcomes are overall survival and disease-free survival.

Statistical analysis

Statistical analysis was performed with SPSS version 19. Patient characteristics were compared using the Chi-Square test or Fisher's exact test if the number of expected values was lower than five. Survival and recurrence were visualised using a Kaplan-Meier curve. A p-value < 0.05 was considered as a significant difference.

Ethics approval

For ethical approval we consulted the Medical Research Ethics Committees United (MEC-U). Referring to this study (reference number W17.154) conformation was received that the Medical Research Involving Human Subject Act (WMO) does not apply and therefore an official approval of this study by the MEC-U is not required under the WMO.

Results

Between January 2011 and July 2016, 451 patients underwent a mesorectal excision for rectal cancer in our hospital. Of these patients, 44 were excluded for further analysis; two patients had recurrent disease from previous colorectal cancer; four were suspected to have rectal cancer but had no malignancy on pathological examination; 38 had synchronous metastases (20 patients under the old guidelines, 18 patients under the new guidelines) (Fig. A). The remaining 407 patients were included, 225 of whom had been treated according to the old guidelines and 182 according to the new Dutch guidelines.

Baseline patient characteristics did not differ between both

Table A.3
Accuracy of neoadjuvant treatment under the new guidelines.

Neoadjuvant treatment n (%)			
None	**107 (59)**		
Undertreatment		22 (21)	
pT1-4N1			18 (17)
pT2-4N2			4 (4)
Correct treatment (pT1-3N0)		85 (79)	
SCRT	**40 (22)**		
Overtreatment (pT2-3N0)		20 (50)	
Undertreatment (pT3N2)		5 (13)	
Correct treatment (pT1-3N1)		15 (38)	
CRT/RT + long waiting interval	**35 (19)**		
ypT1-4N0		23 (66)	
ypT2-3N1		5 (14)	
ypT3-4N2		7 (20)	

SCRT: short course radiotherapy; CRT: chemoradiation therapy; RT + long waiting: radiotherapy with 8–12 weeks waiting interval until resection.

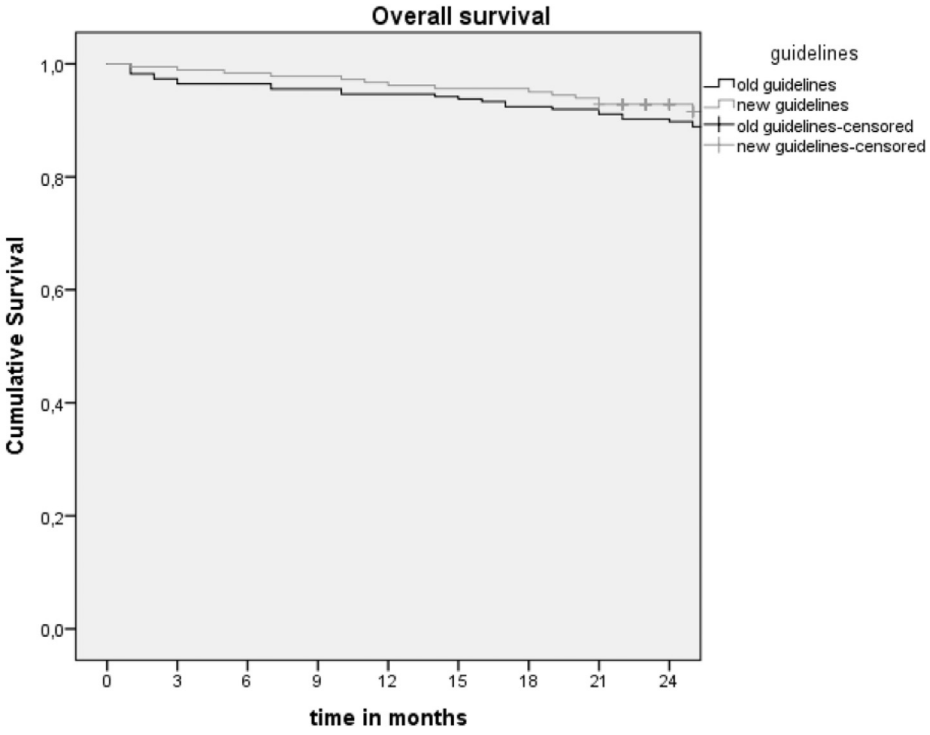
Table B
One-year recurrence rates and mortality rates of all patients with primary rectal cancer.

	Old guidelines	New guidelines	Difference
Total n	225	182	
Local recurrence n (%)			
<1 year	5 (2.2)	4 (2.2)	NS (p = 0.987)
<2 years	7 (3.1)	6 (3.3)	NS (p = 0.916)
Mortality n (%)			
<30 days	1 (0.4)	–	NS (p = 1.00)
<1 year	12 (5.3)	7 (3.8)	NS (p = 0.479)

groups (Table A.1). Patients treated according to the new guidelines had lower tumour and lymph node stages ($p = 0.001$ and $p < 0.001$). Tumour location did not differ between both groups. Neoadjuvant treatment was applied significantly less frequently in the new group (89% vs 41%, $p < 0.001$). Under the old guidelines, four acute resections (2%) were performed because of an ileus caused by an obstructive proximal rectal tumour, the remaining patients were elective cases. Only 2 of 24 patients (8%) treated without neoadjuvant therapy in the old guidelines did not have an indication for neoadjuvant therapy (small, proximal tumours without suspicious lymph nodes). The remaining patients had a contraindication for radiotherapy, no proven malignancy or the tumour was preoperatively considered to be located in the sigmoid. Of the 107 patients treated without radiotherapy in the new guidelines, only 3 patients (3%) had a contraindication for radiotherapy. Under the new guidelines no acute resections were performed.

After April 2014, more patients underwent a robot-assisted laparoscopic resection than before April 2014 (25% vs 82%, $p < 0.001$) and fewer patients received an open or laparoscopic resection (20% vs 3% and 55% vs 14%) (Table A.2). Type of resection (abdominoperineal resection (APR) or low anterior resection (LAR)) did not differ between both periods.

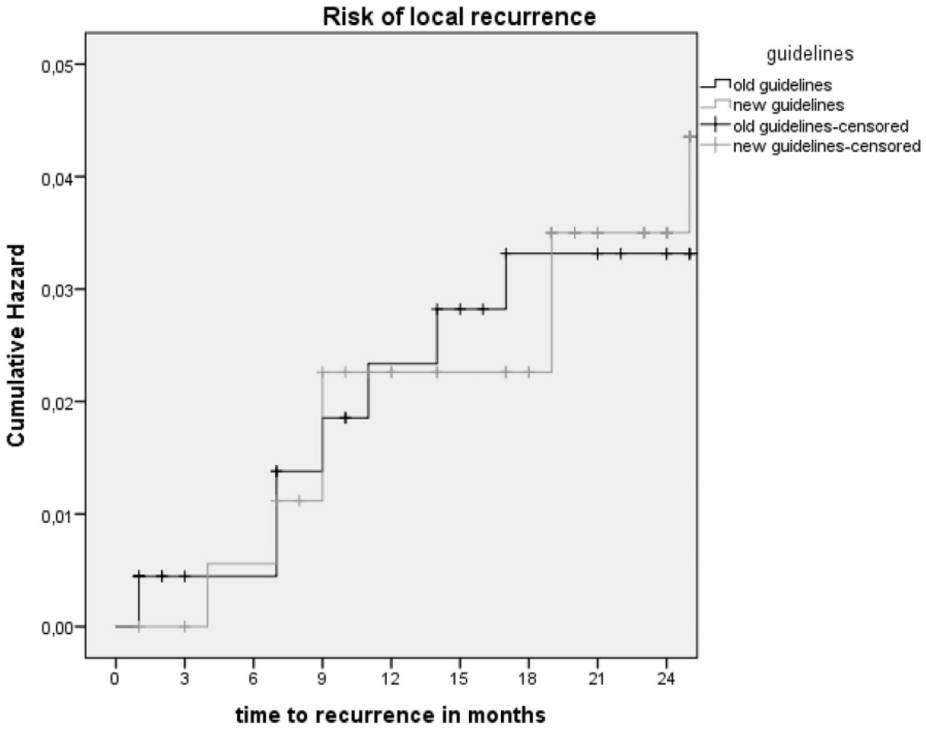
No difference was found in pathologic tumour staging, nor in



*no significant difference (p = 0.111)

	Time in months				
	0	6	12	18	24
Old guidelines					
Number of patients at risk	225	217	213	208	203
Death N	8	4	5	5	8
(proportion)	(0.04)	(0.02)	(0.02)	(0.02)	(0.04)
Cumulative proportion of survival	0.96	0.95	0.92	0.90	0.87
New guidelines					
Number of patients at risk	182	179	176	174	152
Death N	3	3	2	5	5
(proportion)	(0.02)	(0.02)	(0.01)	(0.03)	(0.04)
Cumulative proportion of survival	0.98	0.97	0.96	0.93	0.89

Fig. B1. Survival after resection of rectal cancer (time in months).



*no significant difference (p = 0.855)

	Time in months				
	0	6	12	18	24
Old guidelines					
Number of patients at risk	225	215	207	201	198
Recurrence N (proportion)	1 (0.0)	4 (0.02)	2 (0.01)	0 (0.0)	2 (0.01)
New guidelines					
Number of patients at risk	182	179	171	164	131
Recurrence N (proportion)	1 (0.01)	3 (0.02)	0 (0.00)	2 (0.02)	2 (0.02)

Fig. B2. Risk of local recurrence after resection of rectal cancer (time in months).

pathologic lymph node staging (Table A.2). In 43% of cT2-tumours and 67% of cT3-tumours tumour staging was correct in patients treated without neoadjuvant therapy or with SCRT. In 81% of cN0-tumours and 36% of cN1-tumours staging was correct and both overstaging and understaging occurred. Significantly more lymph nodes were examined after April 2014 (17 vs 12, $p < 0.001$). Retrospectively, 21% (22 patients) of the patients operated without neoadjuvant treatment in the new group were undertreated and should have been treated with SCRT or CRT (Table A.3). Of the patients treated with SCRT in the new group, 13% (5 patients) should have been treated with CRT (Table A.3). In the old group 7% (7 patients) treated with SCRT should have been treated with CRT. No significant difference in surgical outcomes was seen between both groups (Table A.2).

Local recurrence

After a median follow-up of 50 months (IQR 40–59), 12 of 225 patients (5.3%) in the old group developed local recurrence. Median time to recurrence was 16 months (IQR 8–32). Five patients (2.2%) had local recurrence within one year after surgery and seven patients (3.1%) within two years after surgery (Table B). One-year mortality was 5.3% (12 patients).

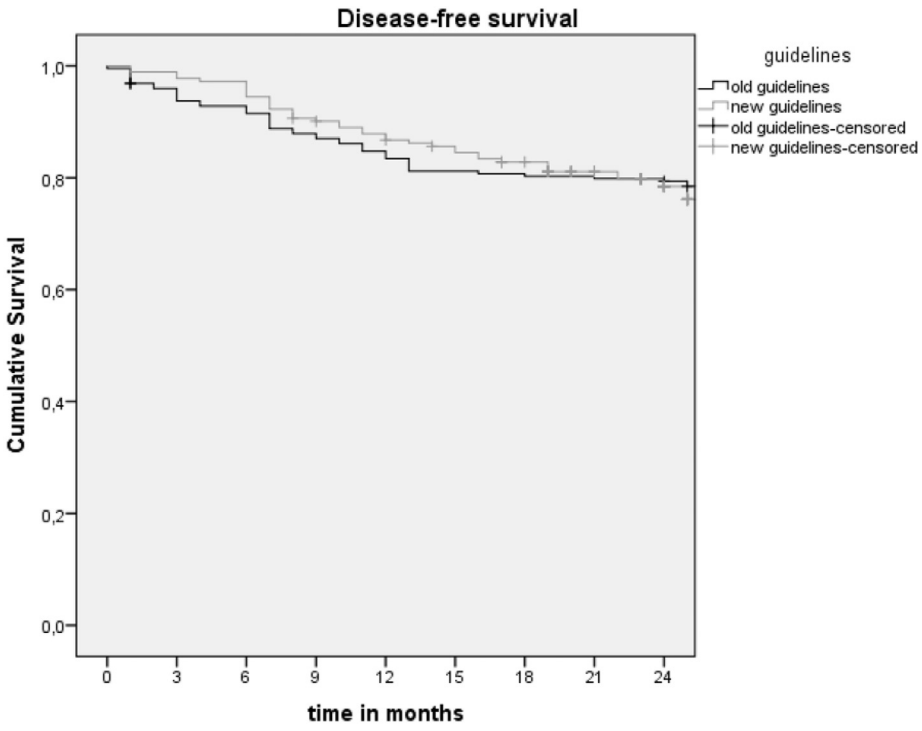
After a median follow-up of 29 months (IQR 23–36), 8 of 182 patients (4.4%) in the new group developed local recurrence. Ninety-eight percent of patients surviving one-year post-operatively had at least one-year follow-up. Median time to recurrence was 14 months (IQR 8–24). Four patients (2.2%) had local recurrence within one year after surgery and six patients (3.3%) within two years after surgery (Table B). One-year mortality was 3.8% (7 patients).

No difference in overall survival (Fig. B.1, $p = 0.111$), local recurrence (Fig. B.2, $p = 0.855$) or disease-free survival (Fig. B.3, $p = 0.869$) was found between both groups.

Table C shows the individual characteristics of each patient with local recurrence.

Discussion

Under the new Dutch guidelines, patients without suspicious



*no significant difference (p = 0.869)

	Time in months				
	0	6	12	18	24
Old guidelines					
Number of patients at risk	225	207	189	180	178
Recurrence or death N	16	18	9	2	11
(proportion)	(0.07)	(0.09)	(0.05)	(0.01)	(0.06)
Cumulative proportion of survival	0.93	0.85	0.81	0.80	0.75
New guidelines					
Number of patients at risk	182	177	158	144	116
Recurrence or death N	5	17	9	5	5
(proportion)	(0.03)	(0.10)	(0.06)	(0.04)	(0.05)
Cumulative proportion of survival	0.97	0.88	0.83	0.80	0.76

Fig. B3. Disease-free survival after resection of rectal cancer (time in months).

lymph nodes on preoperative MRI no longer received preoperative RT, even though previous studies suggested that MRI cannot accurately predict actual lymph node stage [11–13]. Also, in the new guideline the criteria for suspicious lymph nodes were modified. Therefore, the aim of this study was to determine whether local recurrence rate after rectal cancer surgery increased after the implementation of the new Dutch guidelines that restricted the indication for neoadjuvant therapy.

Our comparison of 225 patients treated according to the old guidelines and 182 patients treated according to the new guidelines showed that after the implementation of the new Dutch guidelines, more patients were considered to have clinical lymph node negative rectal cancer on MRI than under the old guidelines: 55% versus 23%. As expected, fewer patients have thus been treated with neoadjuvant therapy and more than half of the patients treated according to the new guideline did not receive any type of neoadjuvant therapy.

The difference in clinical lymph node stage was expected, as the criteria for suspicious lymph nodes on MRI have become stricter. In the old guidelines all lymph nodes > 5 mm were regarded as suspicious lymph nodes. In the new guidelines lymph nodes had to be > 9 mm or have malignant features to be considered suspicious. Therefore, a proportion of patients considered lymph node positive in the old guidelines would be considered lymph node negative in the new guidelines. In the group of patients treated with SCRT or without neoadjuvant treatment (and thus no regression of lymph node metastasis [18,19]), no difference in pathological lymph node staging is found between the old and new guidelines. Therefore, we believe the difference in clinical lymph node staging to be caused by the changes in criteria for suspicious lymph nodes.

Between both groups a significant difference in clinical tumour stage was found. In particular more cT3-tumours were diagnosed in the old group and more cT2-tumours in the new group. The introduction of a nationwide screening program for colorectal

Table C
Characteristics of all 20 patients with local recurrence.

sex	age	cTN-stage	Neoadjuvant treatment	Correct neoadjuvant treatment?	(y)pTN-stage	Radical resection	Time till recurrence (months)	Guidelines	Type of resection
F	68	cT3N2	CRT		ypT3N2	R1	1	Old	Lap APR
M	62	cT2N2	CRT		ypT3N2	R1	7	Old	RAL APR
M	57	–	–		pT3N2	R1	7	Old	LAR
M	61	–	–		pT3N0	R0	9	Old	Lap AR
F	64	–	–		pT4N2	R1	11	Old	AR
M	51	cT3N2	CRT		ypT3N0	R0	14	Old	Lap LAR
M	80	cT3N1	RT + long interval		ypT2N0	R0	17	Old	Lap APR
F	74	cT3N1	CRT		ypT4N0	R0	26	Old	Lap LAR
F	66	cT4N+	CRT		ypT3N0	R0	27	Old	APR
F	70	cT3N+	SCRT		pT3N0	R0	34	Old	Lap LAR
M	55	cT3N+	CRT		ypT0N0	R0	42	Old	Lap LAR
M	68	cT3N2	CRT		ypT3N1	R0	53	Old	RAL LAR
M	70	cT3N1	RT + long interval	Yes	ypT3N2	R0	4	New	RAL APR
F	71	–	–	No	pT3N1	R1	7	New	RAL APR
M	46	cT3N2	CRT	Yes	ypT2N1	R0	9	New	RAL LAR
F	68	cT2N0	–	Yes	pT3N0	R0	9	New	Lap LAR
M	62	cT3N2	CRT	Yes	ypT3N0	R0	19	New	RAL LAR
F	62	cT3N2	CRT	Yes	ypT2N0	R1	19	New	RAL APR
M	74	cT2N0	–	Yes	pT2N0	R0	25	New	RAL APR
M	80	cT1N0	–	No	pT3N1	R0	29	New	Lap APR

cTN-stage: clinical tumour and lymph node stage; CRT: chemoradiation therapy; SCRT: short course radiotherapy; RT + long interval: radiotherapy with 8–12 weeks waiting interval until resection; pTN: pathologic tumour and lymph node stage; ypTN: pathologic tumour and lymph node stage after CRT or RT + long interval; lap: laparoscopic, RAL: robot assisted laparoscopic; APR: abdominoperineal resection; LAR: low anterior resection; AR: anterior resection.

cancer in 2014 might have contributed to an increase of smaller tumours. Furthermore, only 43% of patients with cT2-tumours and 67% of cT3-tumours were staged correctly. Previous analyses of a more extensive cohort in our hospital (including this cohort) showed correct staging in 44% of patients with cT2-tumours and 72% of cT3-tumours [11]. Moreover, subanalysis of patients treated without neoadjuvant radiotherapy or with SCRT directly followed by surgery (thus no or minimal downstaging [18,19]) showed no difference in pathological tumour staging between the old and new group. Therefore, it is questionable if the two groups indeed differed in clinical tumour stage. Besides, both cT2-tumours and cT3ab-tumours are regarded low-risk tumours, so even if a difference in cT2-tumours and cT3-tumours would exist, this might not cause a difference in local recurrence.

While the proportion of patients treated with CRT or RT with long interval until surgery was halved after April 2014, the pathologic tumour stage and pathologic lymph node stage did not differ between both groups. This might indicate that there was no increase in undertreatment after the implementation of the new guidelines, since in case of undertreatment a shift towards higher pathology stage might have been expected.

More robot-assisted laparoscopic resections were performed in the new group. This is not expected to cause a difference in recurrence rates, as previous research has shown no difference in early local recurrence rates after robotic or laparoscopic TME resection [20,21].

Although clinical staging on preoperative MRI is more important in the new guidelines and MRI can be sufficient to identify good prognosis tumours [10], a previous meta-analysis showed that, MRI is insufficient to determine clinical lymph node stage [12]. This was confirmed in unpublished research from our study group [11] After changing the MRI criteria for lymph node staging, understaging of lymph nodes occurred more frequently in our hospital [11]. Due to understaging, we found that 15% of patients treated for rectal cancer in the new group did not receive adequate neoadjuvant treatment. Therefore, one might expect to find a higher risk of early local recurrence. However, no significant difference in early local rectal cancer recurrence was found between the two groups. We also did not demonstrate a significant difference in 1-year-mortality. Due to the short follow up time, this study evaluated early local recurrence and therefore a possible difference in local recurrence after more than two years cannot be ruled out. However, a large randomised controlled trial showed after twelve year follow-up that the majority of local recurrences occur within two years of surgery [4,22,23].

To our knowledge, this is the first study that compared the risk of early local recurrence after the indications for preoperative RT were restricted. The TME-trial described a local recurrence rate of 5.3% in the first two years after surgery, which is higher than in our study [4]. However, patients in that trial were randomised between TME-surgery alone and preoperative SCRT followed by TME-surgery. Patients treated with CRT were not included and no risk stratification was used to determine the indication for RT. A previous study that compared a more restricted radiotherapy regime in Norway and a regime comparable with the current Dutch guidelines in Sweden showed two-year local recurrence rates of 4% in both countries after 2007 [24].

Limitations

With twenty patients with early local recurrence, the numbers in our study are relatively small. Therefore, it is difficult to demonstrate a difference in local recurrence rate and to determine whether recurrence rates were affected by not treating patients with the correct neoadjuvant treatment in a multivariate analysis. Larger, multi-centre studies are of utmost importance. Furthermore, we calculated only one-year and two-year recurrence rates due to the lack of longer follow-up, as the guidelines have been implemented in 2014. Unfortunately, the national database of cancer patients in the Netherlands contains no specific data on local recurrence and therefore this cannot be studied on a national basis. Besides, we do not have data regarding cause of mortality as the Municipal Personal Records Database does not contain cause of death, so it is not possible to identify mortality caused by complications from radiotherapy. However, previous research showed that increased mortality after radiotherapy is mostly attributable to cardiovascular and infectious causes [3]. Therefore it is not possible to identify all mortality attributable to radiotherapy, even if cause of death is known.

Conclusion

In this single-centre study, restricting the indications for preoperative radiotherapy in rectal cancer did not lead to an increase of early local rectal cancer recurrence or decrease in one-year-mortality. Until new research becomes available, there seems to be no reason to change the 2014 guidelines.

Conflict of interest statement

We have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2018.12.006.

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