Benchmarking recent national practice in rectal cancer treatment with landmark randomized controlled trials

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Abstract

Aim A Snapshot study design eliminates changes in treatment and outcome over time. This population based Snapshot study aimed to determine current practice and outcome of rectal cancer treatment with published landmark randomized controlled trials as a benchmark.

Method In this collaborative research project, the dataset of the Dutch Surgical Colorectal Audit was extended with additional treatment and long-term outcome data. All registered patients who underwent resection for rectal cancer in 2011 were eligible. Baseline characteristics and outcome were evaluated against the results of the Dutch TME trial and the COLOR II trial from which the original datasets were obtained.

Results A total of 71 hospitals participated, and data were completed for 2102 out of the potential 2633 patients (79.8%). Median follow-up was 41 (interquartile range 25–47) months. Overall circumferential resection margin (CRM) involvement was 9.3% in the Snapshot cohort and 18.5% in the Dutch TME trial. CRM positivity after laparoscopic resection was 7.8% in the Snapshot and 9.5% in the COLOR II trial. Three-year overall local recurrence rate in the Snapshot was 5.9%, with a disease-free survival of 67.1% and overall survival of 79.5%. Benchmarking with the randomized controlled trials revealed an overall favourable long-term outcome of the Snapshot cohort.

Conclusion This study showed that current rectal cancer care in a large unselected Dutch population is of high quality, with less positive CRM since the TME trial and oncologically safe implementation of minimally invasive surgery after the COLOR II trial.

Keywords Rectal cancer, snapshot study, oncologic outcomes

What does this paper add to the literature?
This is the first study to benchmark long-term outcomes of a population based cohort against the results of landmark randomized controlled trials. We were able to demonstrate that rectal cancer care in the Netherlands has improved considerably over the years but that there is still scope for improvement in current clinical care.

Introduction

Rectal cancer treatment has become a multimodality approach, although surgical resection is still the cornerstone. The introduction of pelvic MRI has significantly changed rectal cancer management and multidisciplinary team discussion is mandatory and essential for a patient tailored approach. Rectal surgery has significantly changed over the last few decades with quality controlled resections according to predefined anatomical planes, minimally invasive techniques and enhanced recovery protocols.

Decisions on treatment approaches in current daily practice are mainly based on (sub-)analyses of multicentre randomized controlled trials (RCTs) [1–5]. Despite the high level of evidence, there are also disadvantages related to RCTs [6]. The study population is often subject to strict inclusion and exclusion criteria. Therefore, RCTs might not reflect the real-life patient population [7]. In addition, inclusion in RCTs is often from expert centres. Besides the issue of external validity, these trials often have a long accrual period, require sufficient length of follow-up and are published at a time when some of the included interventions have already evolved. This is a well-known drawback of longitudinal studies.

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[1]Dutch Snapshot Research Group members are listed in Appendix.

A cross-sectional Snapshot study design rapidly provides insight into current clinical practice. Using the principles of collaborative research as first described by Pinkney and colleagues, a large amount of data can be acquired in a short period of time by involving a large group of physicians [8,9].

This Snapshot study aimed to determine long-term outcomes of rectal cancer resections performed in 2011 in the Netherlands. Previous publications from the Dutch Surgical Colorectal Audit already provided insight into treatment strategies of the Dutch hospitals at that time, revealing for example an almost routine use of preoperative radiotherapy and a high proportion of low Hartmann's procedure (low anterior resection with end colostomy) [10–13]. This illustrates the value of population based studies and raises questions on the impact of such specific strategies on overall long-term outcome. To address the issue of the external validity of RCTs, also from a historical perspective, data of the Snapshot cohort were benchmarked using the original datasets from two earlier conducted landmark RCTs, the Dutch TME trial and the COLOR II trial [3,14].

Method

This multicentred, resident led, retrospective, cross-sectional Snapshot study was conducted according to a predefined protocol and executed as collaborative research under the name of the Dutch Snapshot Research Group, in close collaboration with the Dutch Surgical Colorectal Audit [15,16]. The Dutch Surgical Colorectal Audit is a nationwide prospective registry of all patients undergoing surgery for a primary colorectal cancer. Participation in this registry is mandatory by the inspectorate of healthcare. The Dutch Surgical Colorectal Audit was initiated in 2009 and provides baseline characteristics and postoperative outcomes until 30 days following the surgical resection.

All registered rectal cancer resections in 2011 were identified from the Dutch Surgical Colorectal Audit. Data until 30 days postoperatively from the Dutch Surgical Colorectal Audit were extended through a Snapshot study design with additional data on diagnostic and treatment modalities, as well as long-term surgical and oncological outcomes. The year 2011 was chosen based on a weighted balance between representativeness for current practice on one hand and adequate follow-up on the other. Contrary to the Dutch Surgical Colorectal Audit, participation in this long-term Snapshot study was voluntary. All hospitals ($n = 94$) registering in the Dutch Surgical Colorectal Audit were invited for this research project, and eventually 71 hospitals agreed to participate in the Snapshot study. As

not every centre in the Netherlands participated in this Snapshot study on long-term outcomes, baseline data of included patients in the Snapshot study were compared with Dutch Surgical Colorectal Audit data of the patients who were registered in the Dutch Surgical Colorectal Audit but not included in the Snapshot study. The design of the study and the preparation of the paper were performed according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [17].

Data collection

For data collection, a web-based tool was developed and controlled on privacy regulations by Medical Research Data Management (MRDM, Deventer, The Netherlands). MRDM has extensive experience in anonymous patient registries. In every participating hospital, one or two surgical residents, supervised by one surgical consultant, was responsible for the data collection. Patient details from the year 2011 were only accessible in the primary centre of treatment in compliance with the Declaration of Helsinki [18]. Each participating hospital had a period of 5 months (May–October 2015) to collect the additional data. Subsequently, the data were analysed for discrepancies and missing values. These were communicated back to the local investigators, who got an extra period of 1 month for data correction. Final data extraction was carried out on 15 January 2016. The combined set of short-term data retrieved from the Dutch Surgical Colorectal Audit and long-term data retrieved through a Snapshot study design was made anonymous by MRDM and was sent to the central research coordinator.

Benchmarking with landmark RCTs

The most recent, large, mainly European trial on laparoscopic *vs* open rectal resection was selected for benchmarking the Snapshot cohort, namely the COLOR II trial (recruitment 2004–2010) [19]. To place these data into historical perspective, the Dutch TME trial was selected (recruitment 1996–1999). This landmark RCT was published in 2001 [20]. The original datasets from the COLOR II and Dutch TME trial were provided by the principal investigators in order to analyse the data for the three main surgical procedures separately: low anterior resection (LAR), abdominoperineal resection (APR) and low Hartmann's procedure. Only the eligible Dutch patients out of the Dutch TME trial were included for the present analysis, because these data are the most up to date as the dataset is updated every few years. For the purpose of

benchmarking, patient and treatment characteristics as well as 3-year oncological outcome parameters were analysed. The definition of circumferential resection margin (CRM) positivity varied: the definition in Snapshot and the Dutch TME cohort was ≤ 1 mm; the definition in the COLOR II was < 2 mm. The definitions of the other oncological parameters, surgical procedures, as well as the study objectives and inclusion and exclusion criteria of the selected trials are summarized in Table S1).

Statistical analysis

Patient, treatment and outcome data were determined separately for the three main surgical procedures (LAR, APR, Hartmann), as these would be performed in different patient subgroups which would influence short- and long-term outcome measures. Categorical or dichotomous outcomes were presented as absolute numbers and percentages. The chi-squared test was used for intergroup analyses. Continuous outcomes were reported as median with interquartile range (IQR) or mean with standard deviation (SD), in accordance with their distribution. The Kaplan–Meier method was used to determine the actuarial 3-year local recurrence, distant recurrence, disease-free survival and overall survival rates from the date of surgery. Comparison of subgroups regarding recurrence and survival were performed using the log-rank test. All analyses were performed with IBM SPSS statistics, version 23.00 (IBM Corp., Armonk, New York, USA).

Ethics

The Medical Ethical Committee of the Academic Medical Center in Amsterdam, The Netherlands, reviewed and approved the observational study design and decided that informed consent did not need to be obtained because there was no additional burden for the patient due to the design of the study.

Results

Demographics and baseline characteristics Snapshot cohort

Additional data were collected for a total of 2102 patients out of the potential 2633 (79.8%) patients who were originally registered in 2011. A total of seven cases were excluded after the data verification period. Four patients had recurrent rectal cancer, one patient was referred with missing data, and two patients appeared not to have rectal cancer. Median completeness of data

at hospital level was 100% (IQR 96.7–100). Mean age was 67 years (SD 11.2) and 62.9% were men. Median follow-up was 41 (IQR 25–47) months. LAR was performed in 998 (47.6%) patients, APR in 639 (30.5%) and low Hartmann's procedure in 402 (19.2%) patients. Local excision followed by completion total mesorectal excision (TME) was performed in 34 (1.6%) patients and 22 (1.1%) patients underwent a proctocolectomy. Comparing Dutch Surgical Colorectal Audit data of included patients with the remaining 531 patients from non-participating centres revealed no significant differences in patient characteristics, apart from a significantly lower M-stage in the non-participating centres (5.2% vs 9.3%, P < 0.05). More resections were performed laparoscopically (46.8% vs 33.3%, P < 0.001) and 30-day mortality was lower (2.7% vs 5.2%, P = 0.005) in the Snapshot population compared to the remaining cohort of non-participating centres (Table S2).

Benchmarking baseline characteristics with RCTs

Table 1 displays the baseline characteristics for the Snapshot cohort, the COLOR II and the Dutch TME trial, with subdivision into LAR, APR and low Hartmann's procedure within the study populations. The original Dutch TME paper reported on 1861 patients, of whom 1530 were included in the Netherlands. Of these, 50 patients were found to be ineligible pre-randomization and 37 patients did not undergo a rectal resection. For the present analysis we included 1443 patients from the Dutch TME trial. The proportions of APR in the Snapshot cohort, COLOR II and Dutch TME were 30.5%, 26.5% and 30.6%, respectively. The Snapshot cohort had a higher proportion of low Hartmann's procedure compared to the COLOR II and Dutch TME (19.2% vs 4.5% and 5.4%). The majority of patients in the COLOR II were above 70 years of age, compared with the majority being under 70 years in the Snapshot and Dutch TME. There were more American Society of Anesthesiologists (ASA) III patients in the COLOR II compared to the Snapshot, with highest proportions in the low Hartmann's subgroups (42.6% and 25.8%, respectively).

Within the APR subgroups, the proportion of distal tumours within 3 cm from the anal verge was the highest in the Snapshot, compared to the COLOR II and Dutch TME (70.0% vs 50.0% and 60.9%). The proportion of pT3 tumours was the highest in the Dutch TME trial [57.2% vs 50.3% (COLOR II) and 46.1% (Snapshot)], with a slightly higher proportion of pT4 tumours in the Snapshot [5.1% vs 2.9% (COLOR II) and 3.5% (Dutch TME)]. The proportion of patients with Stage III disease was similar among the three

Table 1 Baseline characteristics of the Snapshot, COLOR II and Dutch TME trial.

	Snapshot cohort, 2011				COLOR II, 2004–2010				Dutch TME, 1996–1999*				P value†
	Total cohort (n = 2095)‡	LAR (n = 998)	APR (n = 639)	Low Hartmann (n = 402)	Total cohort (n = 1044)§	LAR (n = 609)	APR (n = 277)	Low Hartmann (n = 47)	Total cohort (n = 1443)	LAR (n = 924)	APR (n = 441)	Low Hartmann (n = 78)	
Gender (male)	1317/2095 (62.9%)	631/997 (63.3%)	418/639 (65.5%)	232/402 (57.7%)	659/1044 (63.1%)	378/609 (62.0%)	183/277 (66.1%)	31/47 (66.0%)	924/1443 (64.0%)	570/924 (61.7%)	304/441 (68.9%)	50/78 (64.1%)	0.78
Age													
≤ 60	565/2095 (27%)	342/998 (34.3%)	176/639 (27.5%)	39/402 (9.7%)	98/1044 (9.4%)	66/609 (10.8%)	24/277 (8.7%)	1/47 (2.1%)	506/1443 (35.1%)	339/924 (36.7%)	146/441 (33.1%)	21/77 (26.9%)	< 0.01
61–70	687/2095 (32.8%)	344/998 (34.5%)	229/639 (35.8%)	93/402 (23.1%)	252/1044 (24.1%)	154/609 (25.3%)	63/277 (22.7%)	4/47 (8.5%)	497/1443 (34.4%)	317/924 (34.3%)	165/441 (37.4%)	15/77 (19.2%)	
> 70–80	642/2095 (30.6%)	271/998 (27.2%)	177/639 (27.7%)	172/402 (42.8%)	371/1044 (35.5%)	223/609 (36.6%)	92/277 (33.2%)	13/47 (27.7%)	363/1443 (25.2%)	230/924 (24.9%)	104/441 (23.6%)	29/77 (37.2%)	
> 80	201/2095 (9.6%)	41/998 (4.1%)	57/639 (8.9%)	98/402 (24.4%)	323/1044 (30.9%)	166/609 (27.3%)	98/277 (35.4%)	29/47 (61.7%)	77/1443 (5.3%)	38/924 (4.1%)	26/441 (5.9%)	13/77 (16.7%)	0.03
ASA I	544/2046 (26.6%)	317/973 (32.6%)	158/627 (25.2%)	60/392 (15.3%)	224/1023 (21.9%)	140/597 (23.5%)	54/270 (20%)	5/47 (10.6%)	Not reported	Not reported	Not reported	Not reported	
ASA II	1159/2046 (56.6%)	532/973 (54.7%)	373/627 (59.5%)	225/392 (57.4%)	601/1023 (58.7%)	362/597 (60.6%)	161/270 (59.6%)	21/47 (44.7%)	Not reported	Not reported	Not reported	Not reported	
ASA III	331/2046 (16.2%)	123/973 (12.6%)	93/627 (14.8%)	101/392 (25.8%)	192/1023 (18.8%)	92/597 (15.4%)	54/270 (20%)	20/47 (42.6%)	Not reported	Not reported	Not reported	Not reported	
ASA IV	12/2046 (0.6%)	1/973 (0.1%)	3/627 (0.5%)	6/392 (1.5%)	6/1023 (0.6%)	3/597 (0.5%)	1/270 (0.4%)	1/47 (2.1%)	Not reported	Not reported	Not reported	Not reported	
BMI mean (SD)	26.0 (4.1)	26.0 (3.8)	26.1 (4.3)	25.8 (4.6)	26.2 (4.4)	26.1 (4.5)	26.3 (4.5)	26.4 (4.0)	25.5 (3.8)	25.4 (3.8)	25.9 (3.7)	25.3 (4.0)	0.02¶
Distance anal verge													
≤ 3 cm	484/1612 (30.0%)	58/777 (7.5%)	360/514 (70.0%)	54/288 (18.8%)	124/791 (15.7%)	19/456 (4.2%)	105/210 (50.0%)	0	272/1380 (19.7%)	27/911 (3%)	238/391 (60.9%)	7/78 (9%)	< 0.01
3.1–7.0 cm	560/1612 (34.7%)	284/777 (36.6%)	136/514 (26.5%)	129/288 (44.8%)	231/791 (29.2%)	123/456 (27.0%)	93/210 (44.3%)	13/35 (37.1%)	487/1380 (35.3%)	306/911 (33.6%)	142/391 (36.3%)	39/78 (50%)	
> 7 cm	568/1612 (35.2%)	435/777 (56.0%)	18/514 (3.5%)	105/288 (36.5%)	436/791 (55.1%)	314/456 (68.9%)	12/210 (5.7%)	22/35 (62.9%)	621/1380 (45.0%)	578/911 (63.4%)	11/391 (2.8%)	32/78 (41%)	
pT stage													
pT0–pTis	178/2034 (8.8%)	72/969 (7.4%)	66/623 (10.6%)	33/390 (8.5%)	31/1002 (3.1%)	35/595 (5.9%)	10/270 (3.7%)	1/47 (2.1%)	31/1443 (2.1%)	23/924 (2.5%)	7/441 (1.6%)	1/78 (1.3%)	< 0.01
pT1	156/2034 (7.7%)	79/969 (8.2%)	45/623 (7.2%)	20/390 (5.1%)	78/1002 (7.8%)	56/595 (9.4%)	16/270 (5.9%)	1/47 (2.1%)	74/1443 (5.1%)	58/924 (6.3%)	15/441 (3.4%)	1/78 (1.3%)	
pT2	658/2034 (32.4%)	329/969 (34.0%)	218/623 (35.0%)	100/390 (25.6%)	335/1002 (33.4%)	184/595 (30.9%)	113/270 (41.9%)	11/47 (23.4%)	462/1443 (32.0%)	287/924 (31.1%)	155/441 (35.1%)	20/78 (25.6%)	
pT3	938/2034 (46.1%)	462/969 (47.7%)	254/623 (40.8%)	201/390 (51.5%)	527/1002 (52.6%)	306/595 (51.4%)	127/270 (47.0%)	26/47 (55.3%)	825/1443 (57.2%)	528/924 (57.1%)	246/441 (55.8%)	51/78 (65.4%)	
pT4	104/2034 (5.1%)	27/969 (2.8%)	39/623 (6.3%)	36/390 (9.2%)	31/1002 (3.1%)	14/595 (2.4%)	4/270 (1.5%)	8/47 (17%)	51/1443 (3.5%)	28/924 (3.0%)	18/441 (4.1%)	5/78 (6.4%)	
pN0	1279/2000 (63.9%)	612/961 (63.7%)	408/608 (67.1%)	224/380 (58.9%)	657/1016 (64.7%)	378/593 (63.7%)	180/269 (66.9%)	25/47 (53.2%)	855/1443 (59.3%)	543/924 (58.8%)	270/441 (61.2%)	42/78 (53.8%)	< 0.01
pN+	721/2000 (36.1%)	349/961 (36.3%)	200/608 (32.9%)	156/380 (41.1%)	359/1016 (35.3%)	215/593 (36.3%)	89/269 (33.1%)	22/47 (46.8%)	588/1443 (40.7%)	318/924 (41.2%)	171/441 (38.8%)	36/78 (46.2%)	< 0.01

Table I (Continued).

	Snapshot cohort, 2011				COLOR II, 2004–2010				Dutch TME, 1996–1999*				P value†
	Total cohort (n = 2095)‡	LAR (n = 998)	APR (n = 639)	Low Hartmann (n = 402)	Total cohort (n = 1044)§	LAR (n = 609)	APR (n = 277)	Low Hartmann (n = 47)	Total cohort (n = 1443)	LAR (n = 924)	APR (n = 441)	Low Hartmann (n = 78)	
M0	1844/2032 (90.7%)	906/968 (93.6%)	555/623 (89.1%)	335/389 (86.1%)	1040/1044 (99.6%)	571/573 (99.7%)	256/257 (99.7%)	46/47 (97.9%)	1356/1443 (94.0%)	880/924 (95.2%)	414/441 (93.9%)	62/78 (79.5%)	< 0.01
M1	188/2032 (9.3%)	62/968 (6.4%)	68/623 (10.9%)	54/389 (13.9%)	4/1044 (0.4%)	2/573 (0.3%)	1/257 (0.4%)	1/47 (2.1%)	87/1443 (6.0%)	44/924 (4.8%)	27/441 (6.1%)	16/78 (20.5%)	
Intra-operative characteristics													
Laparoscopic approach	958/2044 (46.9%)	510/973 (52.4%)	273/627 (43.5%)	154/392 (39.3%)	699/1044 (67.0%)	395/609 (64.9%)	196/277 (70.8%)	31/47 (66.0%)	Not applicable	Not applicable	Not applicable	Not applicable	< 0.01
Elective	2008/2046 (98.1%)	958/973 (98.5%)	624/627 (99.5%)	375/392 (95.7%)	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	

LAR, low anterior resection; APR, abdominoperineal resection; ASA, American Society of Anesthesiologists; BMI, body mass index.

*Only the 'eligible' Dutch patients were included in the presented analysis of the Dutch TME.

†P values were calculated for the total cohorts per study group.

‡Also includes patients with proctocolectomy (n = 22) and patients who underwent local excision followed by completion total mesorectal excision (n = 34).

§In the COLOR II, 111 patients underwent a partial mesorectal excision.

¶Tested with one-way ANOVA.

studies: 36.1% (Snapshot), 35.9% (COLOR II) and 36.4% (Dutch TME). The low Hartmann's subgroups in all studies had the highest proportions of pT4 tumours, pN1–2 stage and synchronous metastasis. The Snapshot cohort includes 9.3% M1 disease, and was an unexpected intra-operative finding in 0.5% in the COLOR II and in 6.0% in the Dutch TME trial.

A laparoscopic approach was applied in the Snapshot cohort in 46.9% of the patients, with a conversion rate of 134/930 (14.4%). As a result of 2:1 randomization, 66.7% of patients underwent a laparoscopic procedure in the COLOR II, with a conversion rate of 121/695 (17.4%). Laparoscopic TME surgery was not performed at the time of the Dutch TME trial in the Netherlands [3].

In the Snapshot cohort and COLOR II, 89.5% and 61.9% respectively of the patients received some form of preoperative therapy (Table 2). Because of the randomized intervention, preoperative short-course radiotherapy was applied in 50.4% in the Dutch TME. Postoperative radiotherapy was applied in 0.1%, 2.1% and 5.7% in the Snapshot, COLOR II and Dutch TME respectively. Adjuvant chemotherapy was administered in 7.0%, 26.7% and 4.1%, respectively.

Oncological outcomes

The oncological outcomes of the Snapshot, COLOR II and Dutch TME are presented in Table 3. The overall proportion of CRM involvement in patients with a reported CRM was 9.3%, 9.5% and 18.9% ($P < 0.01$), respectively. CRM positivity was higher after APR compared to LAR in all three study groups. Within the APR subgroups, the proportion of positive CRM was almost threefold higher in the Dutch TME trial compared to the Snapshot and COLOR II. The overall CRM positivity of laparoscopic and open resections was 7.8% and 10.6% ($P = 0.06$) in the Snapshot and 9.5% and 10.0% ($P = 0.26$) in the COLOR II trial, respectively.

The overall actuarial 3-year local recurrence rate of the Snapshot cohort was 5.9%. For LAR, APR and low Hartmann's procedure, the local recurrence rate was 3.4%, 6.7% and 11.5% ($P < 0.01$) respectively. Corresponding rates in the COLOR II were 5.0% for the total population and 4.7%, 6.8% and 5.8% ($P = 0.60$) per surgical procedure, respectively. In the Dutch TME, the 3-year local recurrence rates were 7.1% for the total population and 5.6%, 10.1% and 7.9% ($P = 0.02$) per surgical procedure, respectively. Local recurrence rates for the surgery alone and preoperative short-course radiotherapy groups of the Dutch TME trial were 9.2% and 2.0% ($P < 0.01$) for LAR, 12.9% and 7.2% ($P = 0.05$) for APR and 14.6% and 2.9% ($P = 0.08$) for

Table 2 Perioperative treatment.

	Snapshot cohort, 2011				COLOR II, 2004–2010				Dutch TME, 1996–1999				P value*
	Total cohort (n = 2095)	LAR (n = 998)	APR (n = 639)	Low Hartmann (n = 402)	Total cohort (n = 1044)	LAR (n = 609)	APR (n = 277)	Low Hartmann (n = 47)	Total cohort (n = 1443)	LAR (n = 924)	APR (n = 441)	Low Hartmann (n = 78)	
Preoperative treatment													
None	219/2095 (10.5%)	112/998 (11.2%)	27/639 (4.2%)	66/402 (16.4%)	425/1005 (42.3%)	263/583 (45.1%)	50/266 (18.8%)	28/47 (59.6%)	719/1443 (49.8%)	465/924 (50.3%)	220/441 (49.9%)	34/78 (43.6%)	< 0.01
5 × 5 Gy	916/2095 (43.7%)	481/998 (48.2%)	229/639 (35.8%)	182/402 (45.3%)	260/1005 (25.9%)	133/583 (22.8%)	109/266 (41.0%)	9/47 (19.1%)	724/1443 (50.2%)	459/924 (49.7%)	221/441 (50.1%)	44/78 (56.4%)	< 0.01
CRT	684/2095 (32.6%)	273/998 (27.4%)	288/639 (45.1%)	113/402 (28.1%)	266/1005 (26.5%)	154/583 (26.4%)	93/266 (35%)	7/47 (14.9%)	–	–	–	–	
Other RT schedule	66/2095 (3.2%)	22/998 (2.2%)	30/639 (4.7%)	13/402 (3.2%)	0	31/583 (5.3%)	11/266 (4.1%)	2/47 (4.3%)	–	–	–	–	
Only chemotherapy	8/2095 (0.4%)	7/998 (0.7%)	0/639	1/402 (0.2%)	5/1005 (0.5%)	2/583 (0.3%)	1/266 (0.4%)	1/47 (2.1%)	–	–	–	–	
Neoadjuvant treatment regimen unknown	202/2095 (9.6%)	103/998 (10.3%)	65/639 (10.2%)	27/402 (6.7%)	2/1005 (0.2%)	0	2/266 (0.7%)	0	–	–	–	–	
Postoperative treatment													
Long-course RT	2/2095 (0.1%)				4/1044 (0.4%)				73/1443 (5.1%)				< 0.01
CRT	1/2095 (0.05%)				18/1044 (1.7%)				10/1443 (0.7%)				
Chemotherapy	145/2095 (7.0%)				279/1044 (26.7)				57/1395 (4.0%)				

LAR, low anterior resection; APR, abdominoperineal resection; CRT, chemoradiotherapy; RT, radiotherapy.

* *P* values were calculated for the total cohorts per study group.

Table 3 Oncological outcomes of the Snapshot cohort and RCTs.

	Snapshot cohort, 2011				COLOR II, 2004–2010				Dutch TME, 1996–1999				
	Total cohort (n = 2095)	LAR (n = 998)	APR (n = 639)	Low Hartmann (n = 402)	Total cohort (n = 1044)	LAR (n = 609)	APR (n = 277)	Low Hartmann (n = 47)	Total cohort (n = 1443)	LAR (n = 924)	APR (n = 441)	Low Hartmann (n = 78)	P value*
CRM involvement	143/1538 (9.3%)†‡	51/739 (6.9%)	59/487 (12.1%)	32/282 (11.3%)	84/881 (9.5%)‡§	39/508 (7.7%)	32/235 (13.6%)	7/40 (17.5%)	267/1410 (18.9%)‡	120/900 (13.3%)	128/433 (29.6%)	19/77 (24.6%)	< 0.01
3-year local recurrence rate	5.9%	3.4%	6.7%	11.5%	5.0%	4.7%	6.8%	5.8%	7.1%	5.6%	10.1%	7.9%	< 0.01¶
3-year distant recurrence rate	21.2%	17.9%	23.6%	26.1%	17.7%	18.1%	20.7%	29.7%	20.8%	18.0%	26.0%	24.1%	0.145¶
3-year DFS survival	67.1%	73.7%	64.3 %	55.6%	74.5 %	75.2 %	71.1 %	51.0 %	67.2%	70.5%	63.8%	47.4%	< 0.01
3-year overall survival	79.5%	87%	76.4%	66.9%	85.5%	86.6%	82.5 %	61.9 %	76.1	79%	73.7%	55.1%	< 0.01

LAR, low anterior resection; APR, abdominoperineal resection; CRM, circumferential resection margin; DFS, disease-free survival.

* P values were calculated for the total cohorts per study group.

†CRM was considered to be involved when the free margin was 1 mm or less.

‡The CRM was only calculated for patients with a proven pT1–pT4 carcinoma.

§In the COLOR II the CRM was considered positive when the margin was less than 2 mm.

¶The log-rank test was used to calculate the P value.

low Hartmann, respectively. Overall local recurrence rates for laparoscopic and open resections were 5.0% and 6.6% ($P = 0.42$) in the Snapshot and 5.0% and 5.0% ($P = 1$) in the COLOR II, respectively.

The actuarial metachronous distant recurrence rate of the total Snapshot cohort was 21.1%. This was 18.0% and 20.8% ($P = 0.145$) in the COLOR II and Dutch TME, respectively. Three-year disease-free survival was 67.1%, 74.5% and 67.2% ($P < 0.01$), respectively.

The 3-year overall survival of the Snapshot cohort was 79.5%, which was 87%, 76.4% and 66.9% ($P < 0.01$) for LAR, APR and low Hartmann, respectively. Corresponding 3-year overall survival rates in the COLOR II were 86.6%, 82.7% and 62.8% ($P < 0.01$), and in the Dutch TME 79%, 73.7% and 55.1% ($P < 0.01$), respectively. Figure 1 shows the Kaplan–Meier curves for local recurrence after LAR and APR for each of the studies. The overall survival curves are displayed in Fig. 2.

Discussion

Collaborative research made it possible to retrieve long-term data for 75% of all rectal cancer resections in 2011 in the Netherlands, from both expert and non-expert centres. Remarkable differences as well as similarities with the COLOR II and Dutch TME trial were observed. Historical comparison with the Dutch TME trial (accrual period 1996–1999) revealed substantially lower CRM positivity rates in the Snapshot, especially in the APR subgroup. Three-year overall survival was the lowest in the Dutch TME trial for all types of surgical procedures. This most probably illustrates the significant impact of historical changes in patient management over time. Fixed tumours were excluded from the TME trial based on digital rectal examination. MRI and downstaging regimens were not used. Multidisciplinary team approaches with optimized clinical staging, multimodality treatment and improved perioperative care have become essential components of rectal cancer care in recent years, and were standard during the COLOR II and Snapshot inclusion periods (2004–2011). Similar proportions of positive CRM and 3-year oncological outcomes were found for patients who underwent LAR and APR in the Snapshot study and COLOR II trial, both overall and among those who had laparoscopic surgery. This shows the oncologically safe implementation of minimally invasive rectal cancer surgery in the Netherlands. Even though rectal cancer populations of COLOR II and Snapshot were treated in more or less the same time period (2004–2011), some of the obvious differences in patient characteristics and management did not seem to influence oncological outcome. For example, neoadjuvant therapy and young patients (< 60 years) were relatively overrepresented in the Snapshot cohort, while adjuvant chemotherapy was more often applied in the COLOR II.

The COLOR II included older patients and patients with a higher ASA classification compared to the Snapshot cohort. This showed that not only the 'favourable patients' were included in the COLOR II trial, which is a common prejudice when discussing the results of RCTs [21].

Regarding the main surgical procedures, low Hartmann's procedure is significantly underrepresented in the RCTs, underlining the additional value of population based studies. This specific patient group constitutes mainly elderly frail patients with more often locally advanced and metastasized tumours. A relatively high local recurrence rate was observed, compared to LAR and APR. In the Snapshot, the 11.3% CRM positivity translated into an 11.5% 3-year local recurrence rate. In the low Hartmann's subgroup of the COLOR II trial, a 17.5% CRM positivity was found to result in only 5.8% local recurrence after 3 years. This may partly be related to a small difference in definition of CRM positivity (≤ 1 mm *vs* < 2 mm, respectively). However, a similar low ratio as in the COLOR II was found in the Dutch TME trial (24.6% CRM+ with only 7.9% 3-year local recurrence). One of the explanations for the higher local recurrence after low Hartmann's might be more residual mesorectum after this procedure in the Snapshot cohort, not resulting in CRM positivity but possibly leading to nodal recurrences in retained mesorectum [22].

The Dutch TME trial showed almost a threefold higher CRM positivity after APR in comparison with the Snapshot and COLOR II, which translated into similar differences in local recurrence rates. However, overall survival was almost identical between the APR subgroups of the Snapshot and Dutch TME, with better survival in the COLOR II. There is no clear explanation for this observation, but clearly the quality of the APR procedure has improved over time [23]. A better understanding of surgical anatomy with preoperative MRI as a road map and optimized surgical technique have substantially improved outcome after APR. The Snapshot cohort serves as an indicator that such improvements can be accomplished outside a trial setting.

In 2011, the use of neoadjuvant radiotherapy in the Netherlands was remarkably high compared to other European countries [12]. This was related to the former National Guideline, which recommended neoadjuvant radiotherapy for almost every rectal carcinoma except for cT1N0 and proximal cT2N0 tumours. The
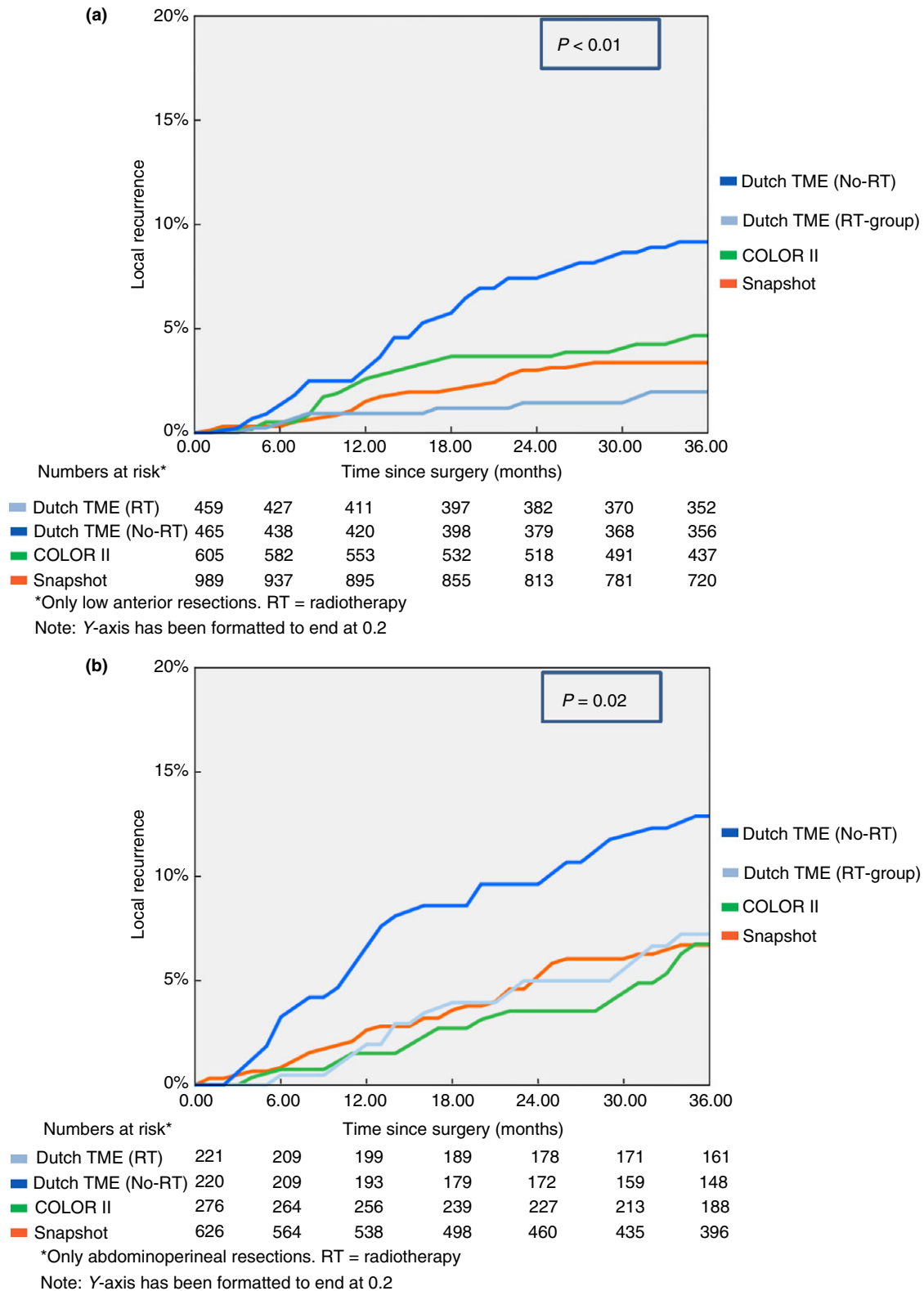
(a)

Numbers at risk*

Dutch TME (RT)	459	427	411	397	382	370	352
Dutch TME (No-RT)	465	438	420	398	379	368	356
COLOR II	605	582	553	532	518	491	437
Snapshot	989	937	895	855	813	781	720

*Only low anterior resections. RT = radiotherapy

Note: Y-axis has been formatted to end at 0.2

(b)

Numbers at risk*

Dutch TME (RT)	221	209	199	189	178	171	161
Dutch TME (No-RT)	220	209	193	179	172	159	148
COLOR II	276	264	256	239	227	213	188
Snapshot	626	564	538	498	460	435	396

*Only abdominoperineal resections. RT = radiotherapy

Note: Y-axis has been formatted to end at 0.2

Figure 1 (a) Kaplan–Meier plot of local recurrence following LAR in Snapshot, COLOR II and the Dutch TME trial. (b) Kaplan–Meier plot of local recurrence following APR in Snapshot, COLOR II and the Dutch TME trial.
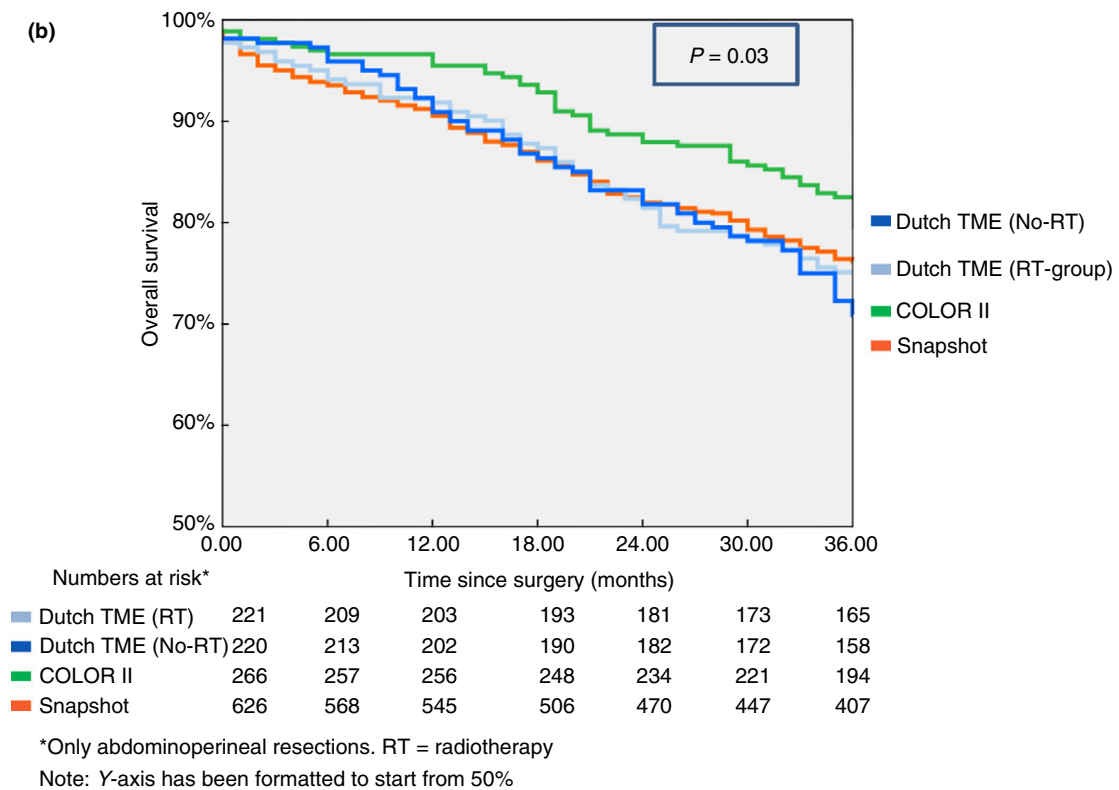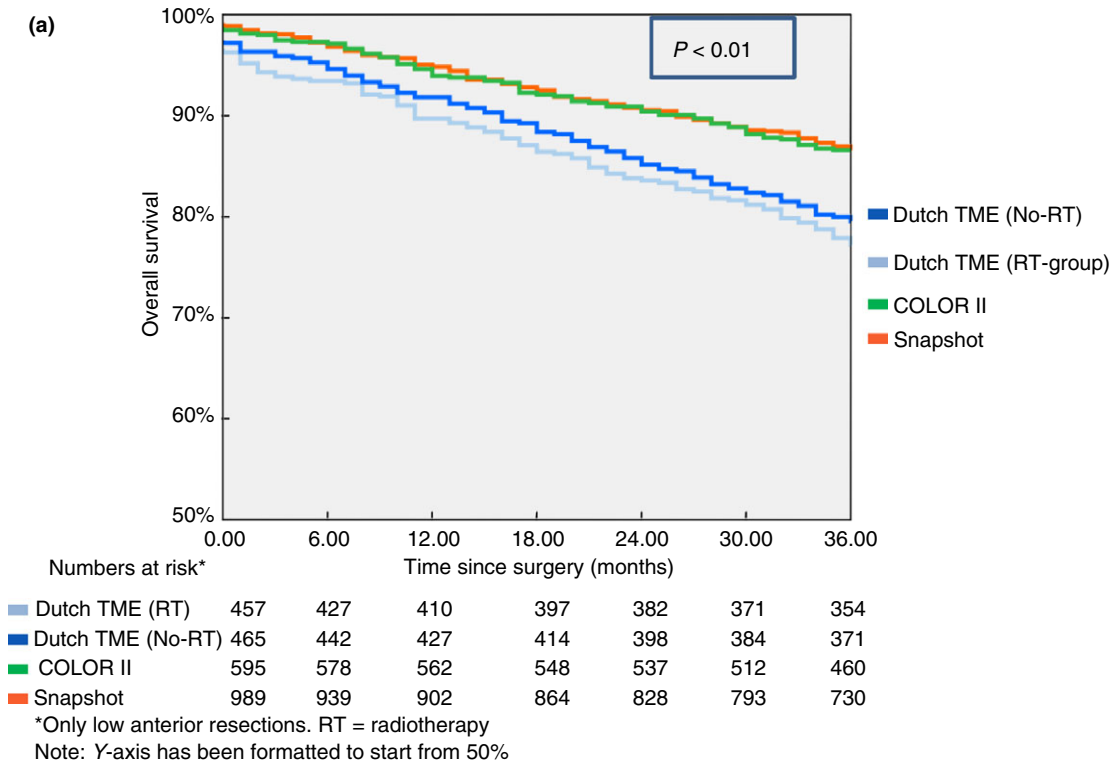
(a)

Numbers at risk*							
	0.00	6.00	12.00	18.00	24.00	30.00	36.00
Dutch TME (RT)	457	427	410	397	382	371	354
Dutch TME (No-RT)	465	442	427	414	398	384	371
COLOR II	595	578	562	548	537	512	460
Snapshot	989	939	902	864	828	793	730

*Only low anterior resections. RT = radiotherapy
Note: Y-axis has been formatted to start from 50%

(b)

Numbers at risk*							
	0.00	6.00	12.00	18.00	24.00	30.00	36.00
Dutch TME (RT)	221	209	203	193	181	173	165
Dutch TME (No-RT)	220	213	202	190	182	172	158
COLOR II	266	257	256	248	234	221	194
Snapshot	626	568	545	506	470	447	407

*Only abdominoperineal resections. RT = radiotherapy
Note: Y-axis has been formatted to start from 50%

Figure 2 (a) Kaplan–Meier plot of overall survival following LAR in Snapshot, COLOR II and the Dutch TME trial. (b) Kaplan–Meier plot of overall survival following APR in Snapshot, COLOR II and the Dutch TME trial.

associated toxicity, worse long-term functional outcomes, lower absolute benefits with improved TME surgery and the development of more accurate imaging modalities for clinical staging led to a decrease in radiotherapy use after changing the recommendations in the revised Dutch National Guideline of 2014 [12,24].

Adjuvant chemotherapy in rectal cancer has never been recommended in the Dutch guideline, and a recently published RCT supports this [25,26]. However, there is still controversy on the additional value of adjuvant chemotherapy in rectal cancer, which explains the differences between the Snapshot and Dutch TME trial, on one hand, and the COLOR II including the majority of patients outside the Netherlands on the other.

As participation was voluntary, it was not possible to present the long-term outcomes in patients from non-participating centres, which is one of the limitations of this study. There was a lower degree of laparoscopic surgery and higher 30-day mortality rate in the non-participating centres, despite similar patient characteristics. An earlier Dutch Surgical Colorectal Audit analysis showed that teaching and university centres had lower mortality rates than non-teaching centres [27]. Mainly small non-teaching hospitals did not participate in this Snapshot study, as no residents or specialist nurses were available. Other limitations are the retrospective data collection from patient files and not being aware of the whole rectal cancer population from which the study cohorts were included.

By benchmarking the results of this population based study against the results of landmark RCTs, we were able to demonstrate that rectal cancer care in the Netherlands has considerably improved over the years. Low Hartmann's procedure, being underrepresented in RCTs, turned out to be a commonly applied procedure in the elective setting for medically unfit patients with advanced disease. Although worse outcome of this subgroup is probably related to patient related factors, there might be a potential for improvement. Collecting large datasets in a short time period using collaborative research enables timely evaluation of daily practice and helps to identify fields for further research and quality improvement.

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References

1 den Dulk M, Smit M, Peeters KC et al. A multivariate analysis of limiting factors for stoma reversal in patients with rectal cancer entered into the total mesorectal excision (TME) trial: a retrospective study. *Lancet Oncol* 2007; **8:** 297–303.

2 Peeters KC, Tollenaar RA, Marijnen CA et al. Risk factors for anastomotic failure after total mesorectal excision of rectal cancer. *Br J Surg* 2005; **92:** 211–6.

3 Bonjer HJ, Deijen CL, Haglind E, Group CIS. A randomized trial of laparoscopic versus open surgery for rectal cancer. *New Engl J Med* 2015; **373:** 194.

4 Snijders HS, Bakker IS, Dekker JW et al. High 1-year complication rate after anterior resection for rectal cancer. *J Gastrointest Surg* 2014; **18:** 831–8.

5 Junginger T, Gonner U, Trinh TT, Lollert A, Oberholzer K, Berres M. Permanent stoma after low anterior resection for rectal cancer. *Dis Colon Rectum* 2010; **53:** 1632–9.

6 Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *New Engl J Med* 2000; **342:** 1887–92.

7 Mol L, Koopman M, van Gils CW, Ottevanger PB, Punt CJ. Comparison of treatment outcome in metastatic colorectal cancer patients included in a clinical trial versus daily practice in The Netherlands. *Acta Oncol* 2013; **52:** 950–5.

8 Bhangu A, Kolias AG, Pinkney T, Hall NJ, Fitzgerald JE. Surgical research collaboratives in the UK. *Lancet* 2013; **382:** 1091–2.

9 Dowswell G, Bartlett DC, Futaba K, Whisker L, Pinkney TD, Wmrc. How to set up and manage a trainee-led research collaborative. *BMC Med Educ* 2014; **14:** 94.

10 Jonker FH, Tanis PJ, Coene PP, van der Harst E, Dutch Surgical Colorectal Audit Group. Impact of neoadjuvant radiotherapy on complications after Hartmann procedure for rectal cancer. *Dis Colon Rectum* 2015; **58:** 931–7.

11 Jonker FH, Tanis PJ, Coene PL, Gietelink L, van der Harst E, Dutch Surgical Colorectal Audit Group. A comparison of low Hartmann's procedure with low colorectal anastomosis with and without defunctioning ileostomy after radiotherapy for rectal cancer: results from a national registry. *Colorectal Dis* 2016; **18**: 785–92.

12 van Leersum NJ, Snijders HS, Wouters MW *et al*. Evaluating national practice of preoperative radiotherapy for rectal cancer based on clinical auditing. *Eur J Surg Oncol* 2013; **39**: 1000–6.

13 Ortiz H, Wibe A, Ciga MA *et al*. Multicenter study of outcome in relation to the type of resection in rectal cancer. *Dis Colon Rectum* 2014; **57**: 811–22.

14 Kapiteijn E, Marijnen CA, Nagtegaal ID *et al*. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001; **345**: 638–46.

15 Van Leersum NJ, Snijders HS, Henneman D *et al*. The Dutch Surgical Colorectal Audit. *Eur J Surg Oncol* 2013; **39**: 1063–70.

16 Gietelink L, Wouters MW, Tanis PJ *et al*. Reduced circumferential resection margin involvement in rectal cancer surgery: results of the Dutch Surgical Colorectal Audit. *J Natl Compr Canc Netw* 2015; **13**: 1111–9.

17 von Elm E, Altman DG, Egger M *et al*. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; **370**: 1453–7.

18 General Assembly of the World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *J Am Coll Dent* 2014; **81**: 14–8.

19 Bonjer HJ, Deijen CL, Abis GA *et al*. A randomized trial of laparoscopic versus open surgery for rectal cancer. *N Engl J Med* 2015; **372**: 1324–32.

20 den Dulk M, Putter H, Collette L *et al*. The abdominoperineal resection itself is associated with an adverse outcome: the European experience based on a pooled analysis of five European randomised clinical trials on rectal cancer. *Eur J Cancer* 2009; **45**: 1175–83.

21 Braunholtz DA, Edwards SJ, Lilford RJ. Are randomized clinical trials good for us (in the short term)? Evidence for a 'trial effect'. *J Clin Epidemiol* 2001; **54**: 217–24.

22 Bondeven P, Hagemann-Madsen RH, Laurberg S, Pedersen BG. Extent and completeness of mesorectal excision evaluated by postoperative magnetic resonance imaging. *Br J Surg* 2013; **100**: 1357–67.

23 van Leersum N, Martijnse I, den Dulk M *et al*. Differences in circumferential resection margin involvement after abdominoperineal excision and low anterior resection no longer significant. *Ann Surg* 2014; **259**: 1150–5.

24 http://www.oncoline.nl/Colorectaalcarcinoom (accessed September 2015).

25 Breugom AJ, Swets M, Bosset JF *et al*. Adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with rectal cancer: a systematic review and meta-analysis of individual patient data. *Lancet Oncol* 2015; **16**: 200–7.

26 Breugom AJ, van Gijn W, Muller EW *et al*. Adjuvant chemotherapy for rectal cancer patients treated with preoperative (chemo)radiotherapy and total mesorectal excision: a Dutch Colorectal Cancer Group (DCCG) randomized phase III trial. *Ann Oncol* 2015; **26**: 696–701.

27 Kolfschoten NE, Marang van de Mheen PJ, Gooiker GA *et al*. Variation in case-mix between hospitals treating colorectal cancer patients in the Netherlands. *Eur J Surg Oncol* 2011; **37**: 956–63.

Appendix

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Definitions.

Table S1. Study objectives, in- and exclusion criteria of landmark RCT's.

Table S2. Characteristics of patients of participating and non-participating centres in the Snapshot study.