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ORIGINAL ARTICLE

# Impact of the new rectal cancer definition on multimodality treatment and interhospital variability: Results from a nationwide cross-sectional study

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## Abstract

**Aim:** This study aimed to determine the consequences of the new definition of rectal cancer for decision-making in multidisciplinary team meetings (MDT). The new definition of rectal cancer, the lower border of the tumour is located below the sigmoid take-off (STO), was implemented in the Dutch guideline in 2019 after an international Delphi consensus meeting to reduce interhospital variations.

**Method:** All patients with rectal cancer according to the local MDT, who underwent resection in 2016 in the Netherlands were eligible for this nationwide collaborative cross-sectional study. MRI-images were rereviewed, and the tumours were classified as above or on/below the STO.

**Results:** This study registered 3107 of the eligible 3178 patients (98%), of which 2784 patients had an evaluable MRI. In 314 patients, the tumour was located above the STO (11%), with interhospital variation between 0% and 36%. Based on TN-stage, 175 reclassified patients with colon cancer (6%) would have received different treatment (e.g., omitting neoadjuvant radiotherapy, candidate for adjuvant chemotherapy). Tumour location

†Group information: Collaborators of the Dutch Snapshot Research Group are listed in the Appendix and wish to be indexed to the paper.

above the STO was independently associated with lower risk of 4-year locoregional recurrence (HR 0.529; $p=0.030$) and higher 4-year overall survival (HR 0.732; $p=0.037$) compared to location under the STO.

**Conclusion:** By using the STO, 11% of the prior MDT-based diagnosis of rectal cancer were redefined as sigmoid cancer, with potential implications for multimodality treatment and prognostic value. Given the substantial interhospital variation in proportion of redefined cancers, the use of the STO will contribute to standardisation and comparability of outcomes in both daily practice and trial settings.

**KEYWORDS**
rectal cancer, rectosigmoid, sigmoid cancer, sigmoid take-off, treatment

## INTRODUCTION

The distinction between a rectal and sigmoidal tumour has always been arbitrary and proximal rectal tumours and distal sigmoidal tumours have often been diagnosed as "rectosigmoid" tumours [1]. This distinction is essential because the multimodality treatment of rectal and sigmoid cancer differs. Patients with stage II–III sigmoid cancer benefit from adjuvant chemotherapy, while this is still not uniformly proven in rectal cancer, with remaining controversy [2–4]. On the other hand, the risk of locoregional recurrence (LR) can be significantly reduced with the use of neoadjuvant chemoradiotherapy in locally advanced rectal cancer [5, 6].

After two Delphi consensus rounds in 2019 with international colorectal experts among relevant disciplines, the sigmoid take-off (STO) was chosen as the preferred landmark for defining the rectum [7]. The STO is a radiological landmark that can be identified as the point where the sigmoid moves away from the sacrum horizontally in the sagittal plane and ventrally in the axial plane. This definition has been incorporated into the updated Dutch colorectal guidelines in 2019 to diagnose a rectal tumour as a tumour with its lower border located below, and a sigmoid tumour as one with its lower border above, the level of the STO [8]. With this new definition, the rectosigmoid term could be omitted which facilitates clinical decision-making during multidisciplinary team (MDT) meetings. This new definition is currently not included in the published international guidelines [9–12].

It is hypothesized that the rectal cancer definition based on the STO will result in a smaller population of patients still being diagnosed with rectal cancer on a nationwide scale [13], but to what extent is unknown. Furthermore, applying the STO as a more uniform definition to classify patients as either rectal or sigmoid will likely reduce interhospital variations. Reducing such variability is important for standardizing daily clinical practice, improving comparability between hospitals for the purpose of clinical auditing, and increasing homogeneity of included populations in future rectal cancer trials.

The aim of this national cross-sectional study was to retrospectively analyse the effects of implementing the STO as a uniform landmark, by determining the proportion of tumours previously diagnosed as rectal cancer which would now be classified as sigmoid cancer, the interhospital variability and assessing potential effects of the reclassification on treatment stratification. Furthermore, the long-term outcomes were analysed to evaluate differences in oncological behaviour.

**What does this paper add to the literature?**

The sigmoid take-off was recently chosen as the preferred landmark for defining the rectum and has been included in the Dutch National Guideline and is the first and only guideline which has incorporated this landmark. This study evaluates the potential effects of this new definition on clinical practice.

## METHOD

Since 2009, patients undergoing a surgical resection for colorectal cancer in the Netherlands are registered in the mandatory Dutch ColoRectal Audit (DCRA), which contains baseline characteristics and short-term outcomes until 30 days postoperatively [14]. All hospitals in the Netherlands performing rectal cancer surgery participate in the DCRA. This database was extended through a "Snapshot" design, a multicentre resident-led cross-sectional study [15]. A local collaborative team per hospital gathered additional information on diagnostics and treatment and long-term surgical and oncological outcomes from the original patient files. All 69 Dutch hospitals performing rectal cancer surgery in 2016 were invited to participate.

The study was performed according to Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement [16]. The Medical Ethical Committee of the Vrije Universiteit Medical Centre in Amsterdam, reviewed and approved the study protocol on 30th June 2020, and decided that the Dutch Medical Research Involving Human Subjects Act was not applicable. Each participating centre obtained approval for execution of the study from the local Institutional Review Board and decided whether their patients were asked to provide informed consent or the opportunity to opt-out.

## Patient selection and definition

All patients registered as having rectal cancer who underwent resection in 2016 were identified and these patients were provided to the collaborators of the participating hospitals. Patients were registered in the DCRA as having rectal cancer according to the local MDT. The applicable national guideline of 2016 lacked an explicit definition of the rectum, nor did the DCRA provide a specific definition at that time. In Dutch daily practice, a distance of the lower border of the tumour <15 cm from the anal verge measured by endoscopy was mostly used, besides imaging-based definitions using the promontory or peritoneal reflection as anatomical landmarks [17]. The applied definition for each of the local MDTs was not registered in the DCRA. Resections for regrowth after a watch and wait strategy or locoregional recurrence were excluded. For the current study, only patients with a visible tumour on MRI were included.

## Data collection

An online webtool for collecting the data was developed and processed by Medical Research Data Management (MRDM, Deventer, The Netherlands, NEN7510 and ISO27001 certified), who also processes the data from the DCRA. Surgeons and supervised surgical residents or physician assistants were responsible for the data collection from their hospital and only had access to the case report forms of the patients from their own centre. If a patient was referred for further treatment, letters from this hospital were used for information or the clinician from the hospital was contacted for follow-up information. The coordinating investigators received only anonymized data. Each participating hospital had a period of 3 months to collect the data and 1 month for data correction after data verification. The first hospitals started in October 2020 and the last hospital finished data collection in November 2021. Final extraction of the anonymized dataset combined with the DCRA dataset from 2016 was realized in December 2021.

## MRI evaluation

The local collaborators who were responsible for the data collection were asked to review the primary MRI scans of all included patients from their respective centre and classify the lower border of the tumour as "above", "on" or "below" the STO, and to measure the distance from the tumour to the anorectal junction (ARJ). A mandatory training was organized beforehand to promote unambiguous

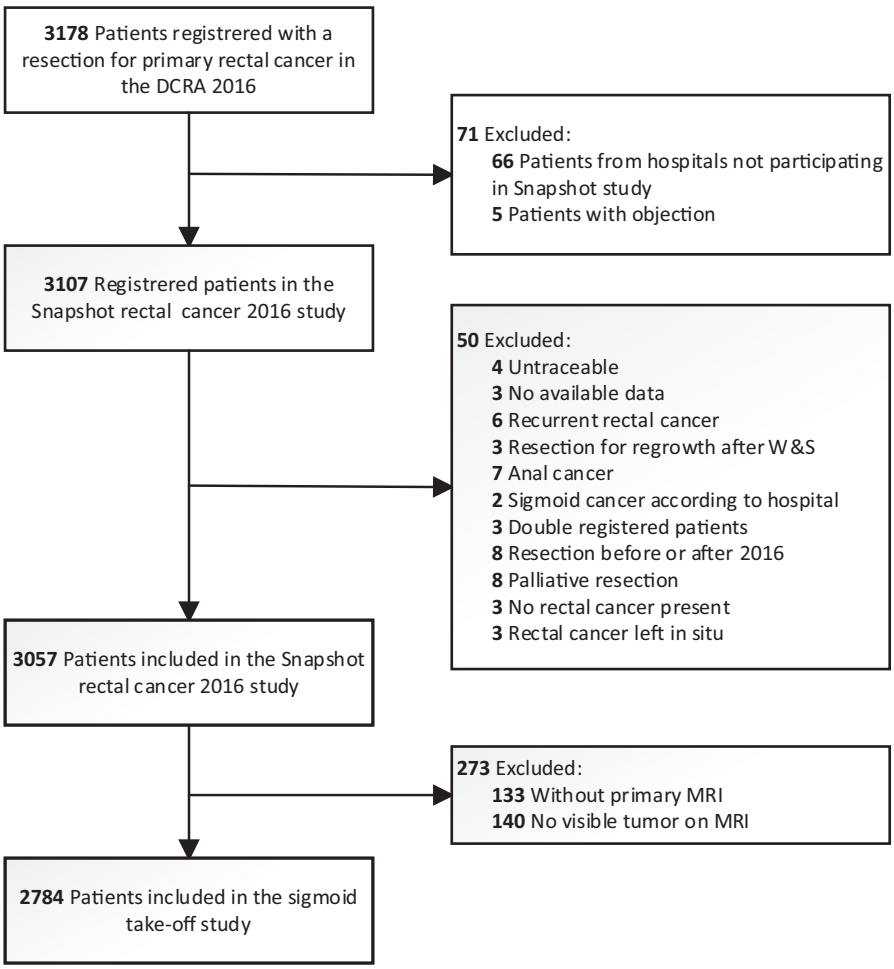



**FIGURE 1** Inclusion flowchart.

assessment [18]. The first five cases in each hospital were proctored by the coordinating researchers, who were trained by expert surgeons and radiologists who took part in the Delphi consensus project that resulted in the STO as the consensus landmark to define the rectum. Lastly, difficult cases could be consulted with the research team.

## End points

The end points were the proportion of tumours reclassified using the STO as sigmoid tumours, the interhospital variability, the potential change in neoadjuvant treatment strategy according to the 2019 published Dutch colorectal cancer guideline recommendations [19] and long-term oncological outcomes. Long-term outcomes included 4-year LR, distant recurrence (DR), disease-free survival (DFS) and overall survival (OS) rates. For the evaluation of potential change in treatment for tumours reclassified as sigmoid, patients with stage IV disease were excluded, because of possible different treatment intent.

## Dutch colorectal cancer guideline recommendations

According to the current Dutch colorectal cancer guidelines, neoadjuvant radiotherapy can be considered for intermediate risk rectal cancer (cT3c-dN0 or cT1-3N1 and >1 mm distance to the mesorectal fascia [MRF−]) and chemoradiotherapy is recommended for locally advanced rectal cancer (cT4 and/or MRF+ and/or N2 and/or enlarged lateral lymph nodes). The height of the tumour is not included in the indication for neoadjuvant radiotherapy. Adjuvant chemotherapy is not advised after curative resection of a rectal cancer, regardless of the pathological lymph node or margin status [3]. For colon cancer, neoadjuvant systemic chemotherapy can be considered in cases of locally advanced tumours requiring multivisceral resection (cT4bN0-2M0), and this can be replaced by chemoradiation for sigmoid tumours. This is, however, not standard treatment and should be discussed in the MDT meeting to determine the chance of a resection with clear margins. Adjuvant chemotherapy can be considered in patients with high-risk stage II (pT4N0M0) colon cancer and is recommended for stage III (pT1-4N1-2M0) [3].

## Statistical analysis

Analyses were performed with IBM SPSS statistics, version 27.00 (IBM Corp). Means with standard deviation (SD) are reported for normally distributed continuous variables and median with interquartile range (IQR) for non-normally distributed continuous variables. Continuous variables were compared with the *t*-test or Mann–Whitney U test. Categorical variables are presented as percentages and were compared using the $\chi^2$ test or Fisher's exact test. A two-sided *p*-value <0.05 was considered statistically significant. The Kaplan–Meier method was used to calculate the 4-year actuarial LR, DR, DFS and OS rates. Univariable Cox regression analyses were used to analyse the effect of covariates. A multivariable analysis with covariates with a *p*-value <0.10 in univariable analysis was performed to determine the independent association of tumour location in relation to the STO with LR and OS.

**TABLE 1** Baseline characteristics specified for tumours reclassified above versus at/below the sigmoid take-off for all tumour stages.

| Clinical values | Above STO (sigmoid) | At/below STO (rectal) | *p*-value |
|---|---|---|---|
| Total | 314 (11) | 2470 (89) | |
| Gender | | | |
| Male | 211 (67) | 1606 (65) | 0.445 |
| Female | 103 (33) | 864 (35) | |
| Age at resection, mean (SD) | 68 (9) | 67 (10) | 0.316 |
| BMI, mean (SD) | 26 (5) | 26 (5) | 0.520 |
| ASA classification | | | |
| ASA I/II | 247 (80) | 2026 (83) | 0.164 |
| ASA III/IV | 63 (20) | 419 (17) | |
| cT-stage | | | |
| cT1 | 8 (3) | 57 (2) | 0.633 |
| cT2 | 96 (31) | 713 (29) | |
| cT3 | 175 (56) | 1447 (59) | |
| cT4 | 31 (10) | 238 (10) | |
| cTx | 4 (1) | 15 (1) | |
| cN-stage | | | |
| cN0 | 156 (50) | 1068 (43) | 0.065 |
| cN1 | 94 (30) | 760 (31) | |
| cN2 | 64 (20) | 629 (26) | |
| cNx | 0 (0) | 13 (1) | |
| MRF | | | |
| MRF+ | 92 (29) | 773 (31) | 0.519 |
| MRF− | 205 (65) | 1593 (65) | |
| Unknown | 17 (5) | 104 (4) | |
| Synchronous metastases | | | |
| cM0 | 299 (95) | 2288 (93) | 0.101 |
| cM1 | 15 (5) | 180 (7) | |
| cMx | 0 (0) | 1 (0) | |
| Distance from anorectal junction on MRI, cm, mean (SD)[a] | 10 (2) | 4 (3) | <0.001 |
| Distance from the anus on endoscopy, cm, mean (SD)[b,c] | 13 (3) | 7 (4) | <0.001 |

*Note*: Presented tumour stage as based on the preoperative MRI.

Abbreviations: ASA, American Society of Anaesthesiologists; BMI, body mass index; MRF, mesorectal fascia; STO, sigmoid take-off.

[a]The distance from the anorectal junction on MRI was missing in two patients with a tumour at/below the sigmoid take-off.

[b]The exact measure point for determining the distance from the anus on endoscopy was not specified.

[c]The distance from the anus on endoscopy was missing in 12 patients with a tumour above the sigmoid take-off and in 73 patients with a tumour at/below the sigmoid take-off.

## RESULTS

### Baseline characteristics

Of the 69 hospitals performing rectal cancer resections in the Netherlands in 2016, 67 hospitals participated in the Snapshot study, of which eight hospitals were academic hospitals. Out of 3178 potentially eligible patients based on the DCRA registry, 3107 could be registered [98%], of whom 3057 patients fulfilled the inclusion criteria of the Snapshot study (Figure 1). Mean age was 67 years (SD 10) and 1985 patients were male (65%). For the current study, patients without an MRI ($n=133$) or without a visible tumour on MRI ($n=140$) were excluded, resulting in 2784 included patients. One hospital had no available MRI images ($n=24$), therefore patients from 66 hospitals were included in the current analyses.

### MRI review and reclassification of tumour location

Review of the original MRI images resulted in 314 patients (11%) that were reclassified as sigmoid cancer based on a lower border starting above the level of the STO. In the remaining 2470 patients (89%), the tumour was located on/below the STO, thereby still being defined as rectal cancer. Baseline characteristics of both groups are shown in Table 1. There were no significant differences in gender, age, cTNM-stage and MRF-status. Tumours above the STO had a mean distance of 10 cm from the ARJ, measured on MRI. The proportion of tumours above the STO is shown per hospital in Figure 2 and varied from 0% to 36%. This would result in a median proportion of tumours above the STO of 6% (IQR 1%–12%) for academic hospitals and 10% (IQR 7%–17%) for nonacademic hospitals.

### Received treatment and pathological results

Neoadjuvant chemoradiotherapy was given to 158 patients (50%) with a tumour above the STO and to 1516 patients (61%) with a tumour on/below the STO ($p<0.001$) (Table 2). A resection margin >1.0 mm was achieved in 307 patients (98%) with a tumour above the STO and in 2277 patients (93%) with a tumour on/below the STO ($p<0.001$). Adjuvant chemotherapy was administered in 14 patients (5%) with a tumour above the STO, of which two patients also received neoadjuvant radiotherapy, and in 53 patients (2%) with a tumour on/below the STO ($p=0.012$) of which 19 patients also received neoadjuvant radiotherapy.

### Potential change in neoadjuvant and adjuvant treatment strategy

Figure 3 shows the received treatment of the 299 patients with a stage I–III tumour above the STO and the potential change in treatment according to the current Dutch guideline recommendations for colon cancer, depending on pathological stages. A total of 171 out of 299 patients with a tumour above the STO (57%) would have been treated differently when following the current Dutch guidelines. This comprises 6% of the total study population. Main changes in treatment would be omitting neoadjuvant radiotherapy in 131 patients (5%) and 91 patients (3%) would have an indication for adjuvant chemotherapy. There was overlap of patients within these two groups.

### Long-term outcomes

The median follow-up was 49 months (IQR 35.0–55.0). The 4-year LR rate was 4% for tumours above the STO and 9% for tumours on/below the STO ($p=0.014$). The 4-year DR rate was 20% and 21% ($p=0.710$) and the 4-year DFS rate was 74% and 70%, respectively ($p=0.195$) for stage I–III tumours. The 4-year OS rate was 86% and 80%, respectively ($p=0.043$) (Figure 4A–D). In the multivariable analyses, location of the tumour above the STO remained significantly associated with a decreased risk of developing LR (hazard ratio [HR]: 0.529; 95% CI: 0.298–0.939; $p=0.030$) and a higher OS rate (HR: 0.732; 95% CI: 0.546–0.982; $p=0.037$) (Tables 3 and 4).

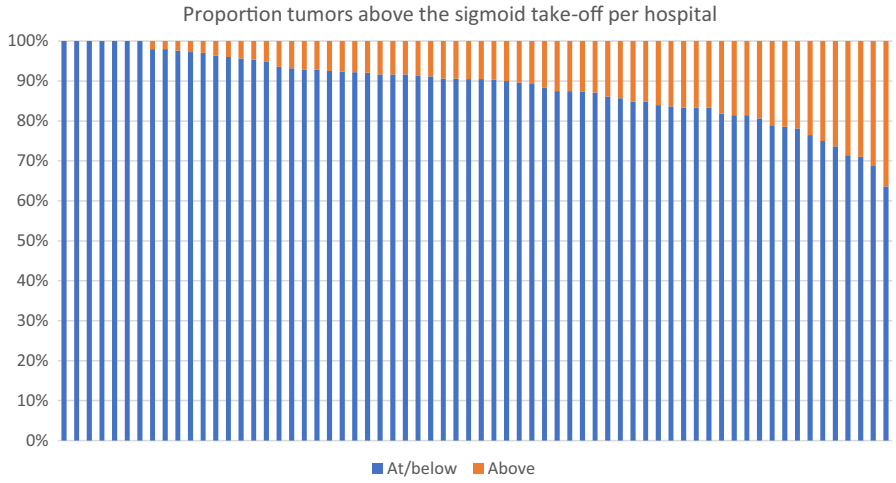



**FIGURE 2** The proportion of tumours above the sigmoid take-off per hospital.

**TABLE 2** Treatment and pathological results for all tumour stages.

| Clinical values | Above STO (sigmoid) | At/below STO (rectal) | *p*-value |
|---|---|---|---|
| Total | 314 (11) | 2470 (89) | |
| Neoadjuvant radiotherapy | | | |
| None | 156 (50) | 954 (39) | 0.002 |
| Yes, 5 x 5 Gy short interval | 52 (17) | 400 (16) | |
| Yes, 5 x 5 Gy long interval | 12 (4) | 177 (7) | |
| Yes, 5 x 5 Gy + systemic chemotherapy | 11 (4) | 87 (4) | |
| Yes, chemoradiotherapy | 81 (26) | 828 (34) | |
| Yes, other/type unknown | 2 (1) | 24 (1) | |
| Type of resection | | | |
| Local excision | 3 (1) | 127 (5) | <0.001 |
| Local excision + (L)AR | 0 (0) | 33 (1) | |
| Local excision + APR | 0 (0) | 18 (1) | |
| Sigmoid resection | 4 (1) | 2 (0) | |
| PME | 50 (16) | 99 (4) | |
| LAR | 254 (81) | 1524 (62) | |
| APR | 2 (1) | 653 (26) | |
| Proctocolectomy | 1 (0) | 12 (1) | |
| Unknown | 0 (0) | 2 (0) | |
| Multiple visceral resection | | | |
| Yes | 22 (7) | 186 (8) | 0.739 |
| Approach | | | |
| Laparotomy | 44 (14) | 426 (18) | 0.079 |
| Minimally invasive | 267 (86) | 1917 (82) | |
| Resection margin[a] | | | |
| R0 | 307 (98) | 2277 (93) | 0.001 |
| R+ | 7 (2) | 169 (7) | |
| (y)pT-stage | | | |
| (y)pT0 | 21 (7) | 194 (8) | <0.001 |
| (y)pT1 | 41 (13) | 328 (13) | |
| (y)pT2 | 74 (24) | 795 (32) | |
| (y)pT3 | 153 (49) | 1064 (43) | |
| (y)pT4 | 25 (8) | 87 (4) | |
| (y)pTx | 0 (0) | 2 (0) | |
| (y)pN-stage[b] | | | |
| (y)pN0 | 197 (63) | 1551 (66) | 0.293 |
| (y)pN1 | 76 (24) | 537 (23) | |
| (y)pN2 | 37 (12) | 254 (11) | |
| (y)pNx | 1 (0) | 1 (0) | |
| Adjuvant systemic chemotherapy | | | |
| No | 300 (95) | 2417 (98) | 0.012 |
| Yes | 14 (5) | 53 (2) | |

Abbreviations: APR, abdominoperineal resection; LAR, low anterior resection; PME, partial mesorectal excision; STO, sigmoid take-off.

Minimally invasive: laparoscopy, robot-assisted laparoscopy, transanal total mesorectal excision, single port approach.

[a]Resection margin was missing in 24 patients with a tumour at/below the sigmoid take-off.

[b](y)pN-stage was missing in 130 patients with a local excision.

## DISCUSSION

This nationwide cross-sectional study evaluated the proportion of tumours which were initially diagnosed as rectal cancer (using previously nonspecified clinical definitions), but would nowadays be diagnosed as sigmoid cancer according to the updated Dutch guidelines based on a lower tumour border starting above the STO. In this study, 11% of the previously diagnosed rectal cancer patients would be reclassified as having sigmoid cancer, leading to an overall potential change in treatment for 6% of the patients, not considering patients with metastasized disease. The proportion of reclassification as sigmoid cancer ranged between 0% and 36% among the 67 hospitals. Reducing this interhospital variability is important for benchmarking, especially considering that a tumour above the STO was independently associated with a lower LR- and higher OS risk compared to those on/below the STO.

This Snapshot study included 98% of the eligible patients who underwent a surgical resection for rectal cancer in 2016 in the Netherlands, allowing for a nearly complete overview of the national daily practice. Currently, patients with sigmoid cancer (located above the STO) will not qualify for neoadjuvant chemoradiotherapy, except when classified as cT4b, for which this can be considered according to the Dutch colorectal cancer guideline recommendations. Although the proportion of neoadjuvant chemoradiotherapy was lower in patients with tumours above the STO (50% vs. 61%), this would still mean a change in management in half of the reclassified patients. In cases of pathological lymph node metastases, adjuvant chemotherapy is nowadays indicated for these sigmoid tumours, but not for rectal cancer according to the Dutch guidelines, due to a lack of high quality evidence for a benefit in OS. However, whether this redefined patient group will benefit from adjuvant chemotherapy is unknown. In our cohort, this would have affected treatment management in 91 cases [3%]. This percentage could be higher, because a large portion of the patients received neoadjuvant treatment, which could have sterilized the initially pathological lymph nodes. As a critical note, this effect would have been less apparent in other countries worldwide in which adjuvant chemotherapy is standard of care in stage III rectal cancer [10, 12, 20, 21].

Although tumours above the STO received less neoadjuvant radiotherapy, the location of the tumour above the STO was independently associated with a lower LR rate. These results indicate that omitting neoadjuvant radiotherapy is expected to be safe for nonlocally advanced tumours above the STO. In a subgroup analysis of the Dutch TME trial, no advantage of neoadjuvant radiotherapy was found in patients with tumours located at a ≥10 cm distance from the anal verge, with a similarly low LR rate compared to the TME only group [5, 22]. An explanation for the higher LR rate, still significant after correcting for the R0 rate, in patients with a tumour at/below the STO might be that distal tumours are more likely to develop metastases in lateral lymph nodes, which are a major cause of LR [23, 24]. Unfortunately, the presence, size and location of LLNs were poorly described in the MRI reports in 2016 and were not re-evaluated for all patients.

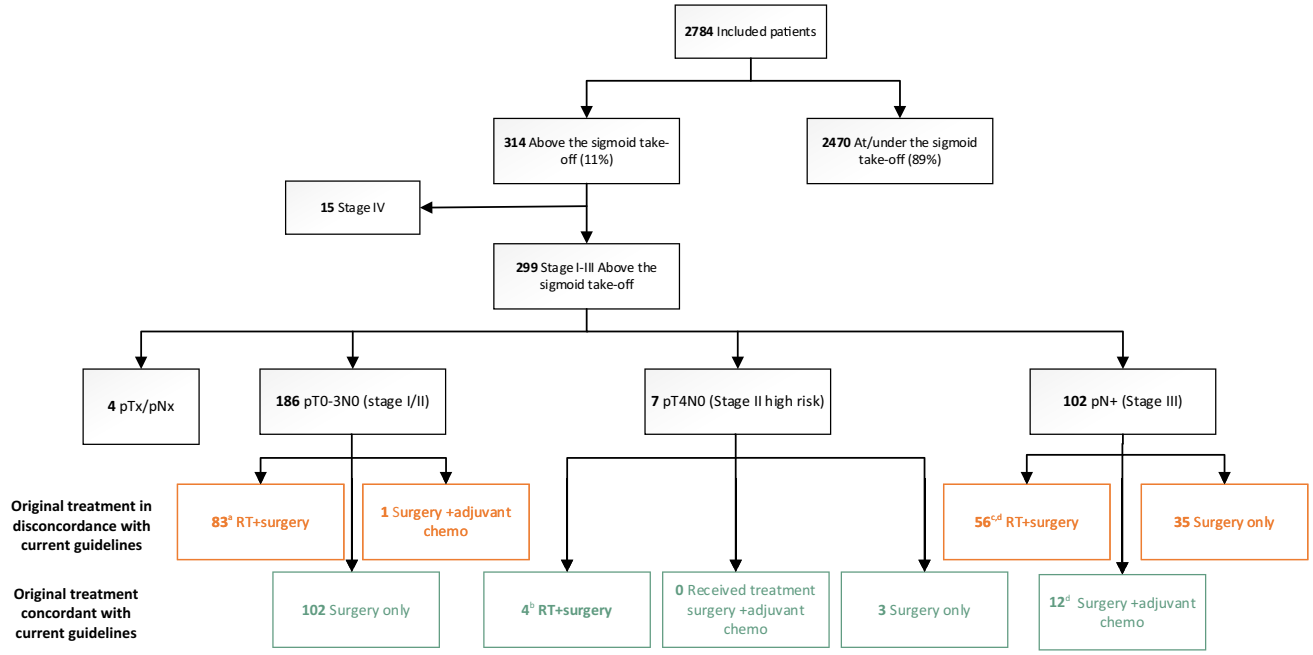



**FIGURE 3** Received treatment specified per (y)p-stage for stage I–III tumours. This flowchart shows the received treatment per (y)p-stage and whether this treatment was concordant with the current guidelines for colon cancer. For example, a patient with a pT2N1 tumour above the STO (stage III colon cancer) who only received surgery, would have had an indication for adjuvant chemotherapy. RT, radiotherapy. [a]Four patients had a cT4b tumour and were treated with CRT, according to the guidelines for (sigmoid) colon tumours. [b]Four patients had a cT4b tumour and were treated with CRT according to the guidelines for (sigmoid) colon tumours. [c]Eight patients had a cT4b tumour of which four patients received chemoradiation; however, no adjuvant chemotherapy was given in these patients. [d]Two patients received chemoradiation and adjuvant chemotherapy.

Omitting radiotherapy is not advised for cT4b (distal) sigmoid tumours, because these can still benefit from neoadjuvant chemoradiation to increase the chance of a clear resection margin. What the role of total neoadjuvant treatment, its use is still debatable in rectal cancer, will be for distal sigmoid tumours is still unknown. In a subanalyses of the RAPIDO trial, there was no significant difference in disease-related treatment failure between total neoadjuvant treatment and chemoradiation for tumours ≥10 cm from the anal verge [25]. Furthermore, the need for a clinical complete response in this patient group is not as high as for low rectal cancer, since the functional outcomes after a sigmoid resection are better than after low anterior resection.

Furthermore, patients with a tumour above the STO had a significantly higher OS, even when adjusted for positive resection margin and pelvic sepsis, which had a higher incidence for tumours on/below the STO. The DR rate also did not differ between both locations. This difference in OS might be explained by the higher incidence of LR for tumours at/below the STO, or by a distinct oncological behaviour of rectal cancers [26–28]. Several retrospective studies have evaluated the prognosis of rectosigmoid tumours compared to rectal and sigmoid tumours, but have shown contradictory results and used different definitions of the bowel segments, which could have biased the results [29–33].

The current study was a national cohort and is therefore able to provide a comprehensive overview of the impact of a change in definition of rectal cancer and potential impact on clinical practice. Furthermore, such a study can evaluate variation in clinical practice. The proportion of reclassified rectal cancer as sigmoid cancer varied between the hospitals (0%–36%). This may be explained by centralization of the more complex cases, which are often located in the distal rectum, but most likely using different definitions of the rectum by the local MDTs in 2016. Hospitals which previously used the promontory as a landmark, which is located more proximal than the sigmoid take-off (mean distance from the anal verge 19.3 cm), will have a high rate of reclassified sigmoid tumours. The hospitals which previously used the peritoneal reflection, which is located more distally than the sigmoid take-off, will have barely reclassified sigmoid tumours [13].

However, there will always remain a certain degree of variability in defining rectal cancer, even after implementing a consensus definition. This has been assessed by Bogveradze et al. [34] during which radiologists reached ≥80% consensus in 63% of the cases and colorectal surgeons in 58% of the cases. In the current study it was attempted to limit the impact of interobserver variability as much as possible by training all the reviewing clinicians and proctoring the first MRI evaluations [18]. Interobserver variability cannot be ruled out completely and is also present in other diagnostic assessments in clinical practice, such as clinical staging and assessment of other radiological landmarks such as mrEMVI [35, 36]. Nevertheless, this study indicates that implementing the STO as a landmark to define rectal cancer has the

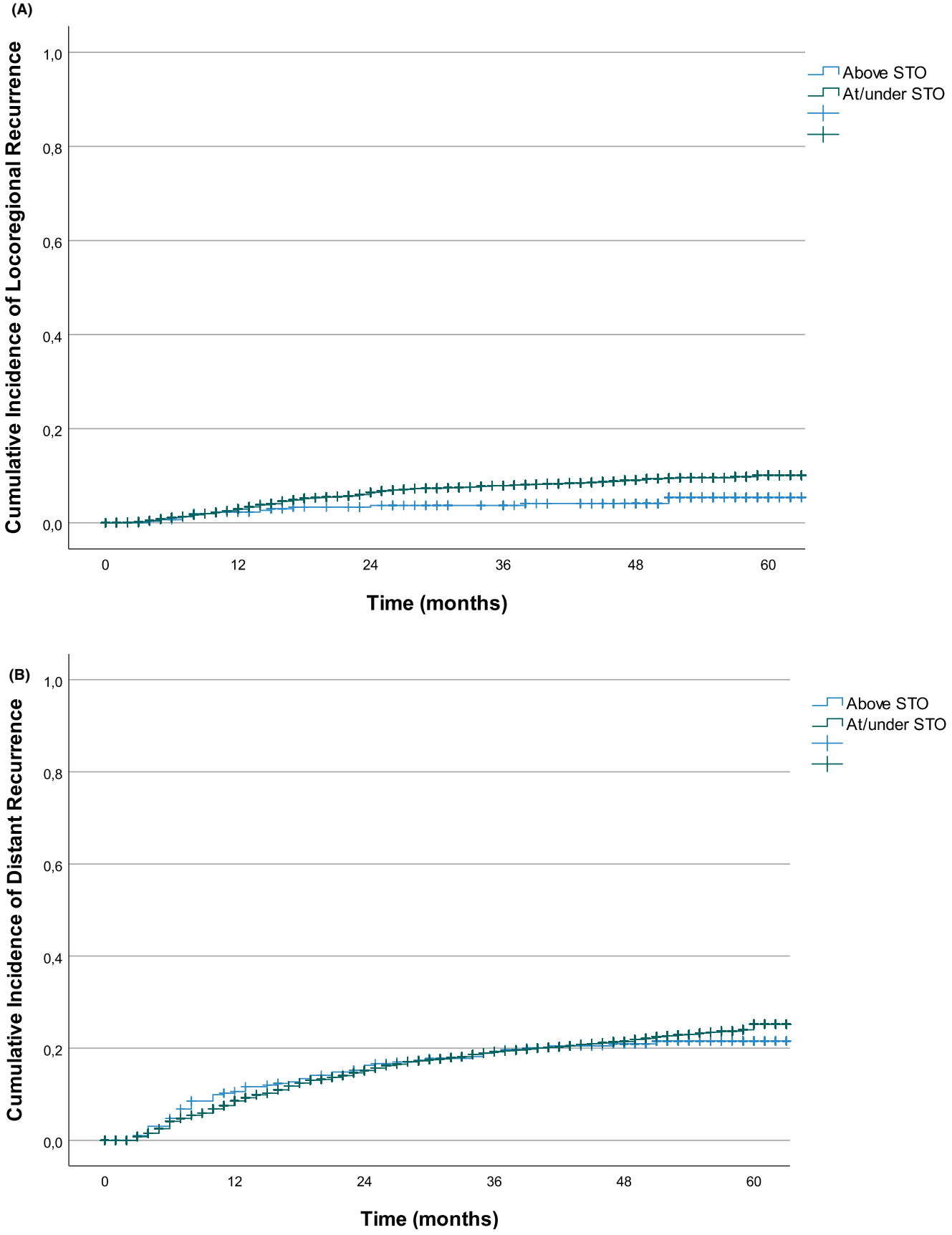
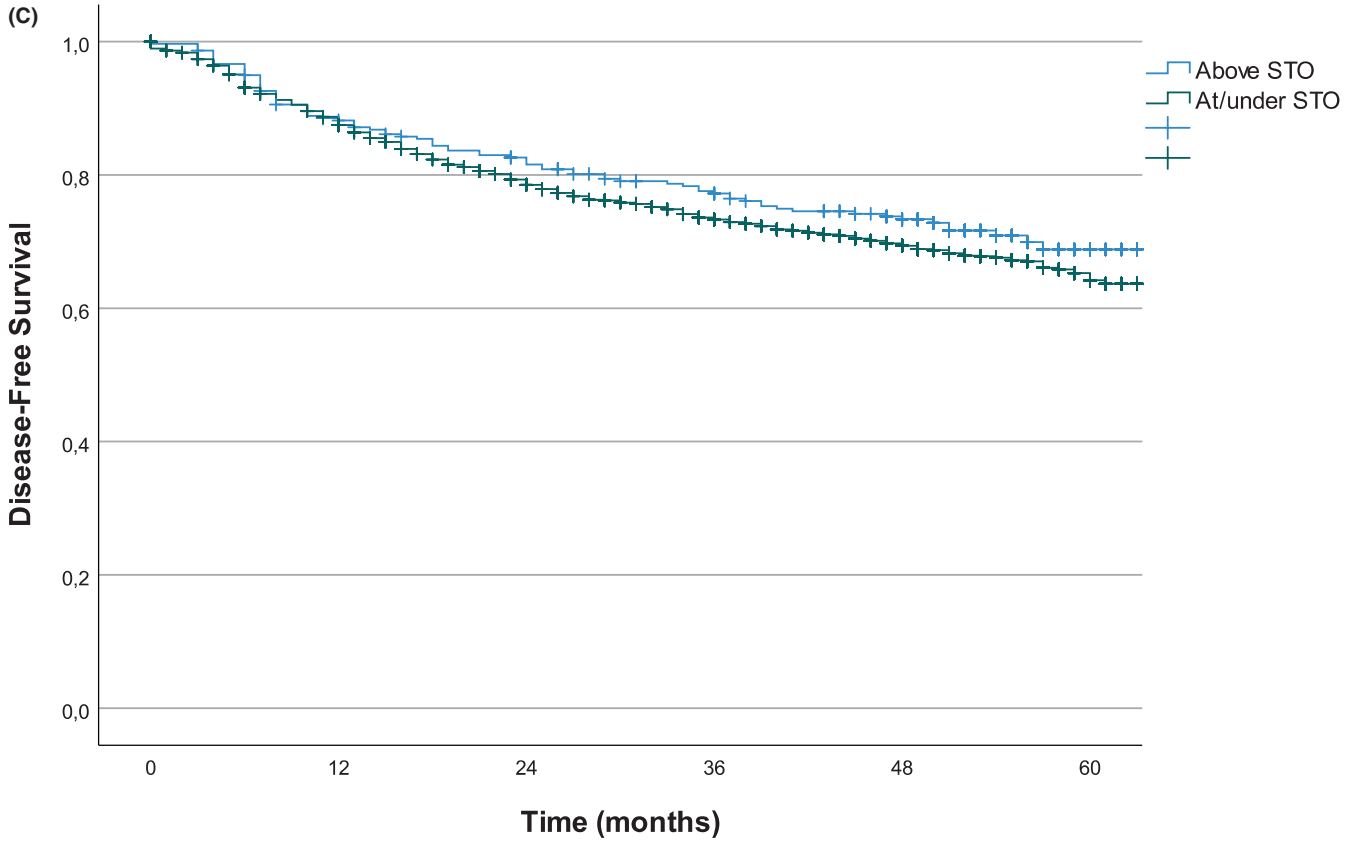



**FIGURE 4** (A) Locoregional recurrence rate, (B) distant recurrence rate, (C) disease-free survival and (D) overall survival according to location in relation to the sigmoid take-off landmark. [a]Only patients with stage I–III were included in the analyses for distant recurrence and disease-free survival.



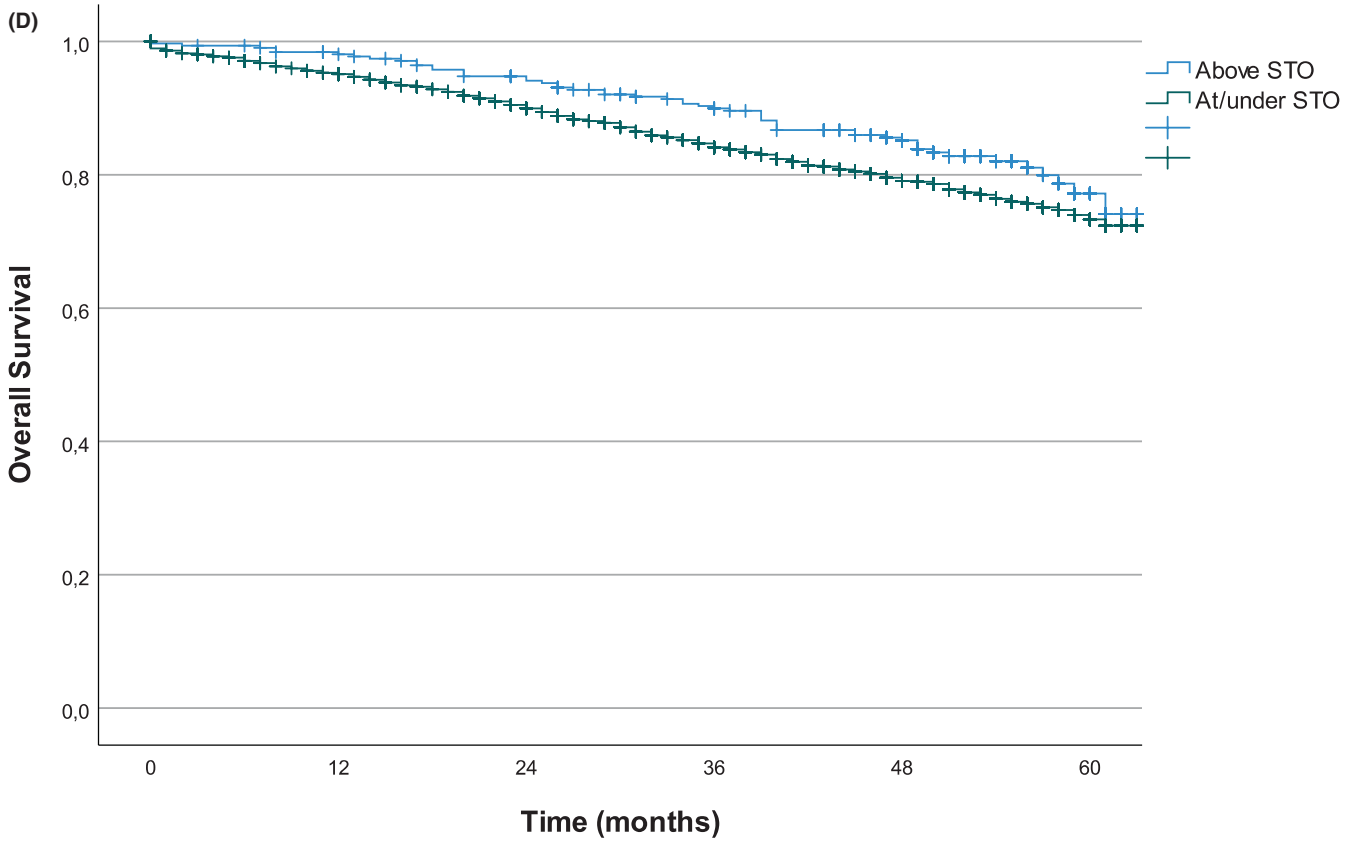




FIGURE 4 (Continued)

**TABLE 3** Univariable and multivariable analyses for locoregional recurrence.

| | | Univariable analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|---|
| **Variable** | **No** | **HR** | **95% CI** | ***p*-value** | **HR** | **95% CI** | ***p*-value** |
| STO | | | | | | | |
| At/under | 2470 | 1 | | 0.016 | 1 | | 0.030 |
| Above | 314 | 0.512 | 0.298–0.881 | | 0.529 | 0.298–0.939 | |
| Gender | | | | | | | |
| Male | 1817 | 1 | | 0.113 | | | |
| Female | 967 | 0.790 | 0.590–1.057 | | | | |
| Age | 2784 | 0.989 | 0.976–1.002 | 0.097 | 0.990 | 0.977–1.004 | 0.174 |
| ASA classification | | | | | | | |
| ASA I/II | 2273 | 1 | | 0.945 | | | |
| ASA III/IV | 482 | 1.013 | 0.702–1.462 | | | | |
| Neoadjuvant radiotherapy | | | | | | | |
| No | 1100 | 1 | | <0.001 | 1 | | <0.001 |
| Short interval | 453 | 0.296 | 0.153–0.571 | | 0.238 | 0.122–0.466 | |
| Long interval | 1221 | 1.539 | 1.162–2.039 | | 1.245 | 0.899–1.723 | |
| (y)pT-stage | | | | | | | |
| (y)pT0 | 215 | 1 | | <0.001 | 1 | | <0.001 |
| (y)pT1 | 369 | 4.593 | 1.375–15.347 | | 4.047 | 0.850–19.266 | |
| (y)pT2 | 869 | 3.364 | 1.042–10.862 | | 4.825 | 1.147–20.299 | |
| (y)pT3 | 1217 | 8.404 | 2.675–26.407 | | 99.930 | 2.419–40.761 | |
| (y)pT4 | 112 | 20.158 | 6.138–68.588 | | 17.585 | 4.039–76.562 | |
| (y)pN-stage | | | | | | | |
| (y)pN0 | 1748 | 1 | | <0.001 | 1 | | <0.001 |
| (y)pN1 | 613 | 2.410 | 1.750–3.320 | | 1.817 | 1.298–2.542 | |
| (y)pN2 | 291 | 3.782 | 2.620–5.461 | | 2.188 | 1.471–3.255 | |
| R-status | | | | | | | |
| R0 | 2584 | 1 | | <0.001 | 1 | | <0.001 |
| R+ | 176 | 5.980 | 4.329–8.259 | | 3.553 | 2.465–5.120 | |
| Synchronous metastases | | | | | | | |
| pM0 | 2587 | 1 | | 0.002 | 1 | | 0.569 |
| pM1 | 196 | 2.017 | 1.285–3.166 | | 0.864 | 0.523–1.427 | |
| Adjuvant chemotherapy | | | | | | | |
| No | 2717 | 1 | | 0.144 | | | |
| Yes | 67 | 0.354 | 0.088–1.426 | | | | |
| Pelvic sepsis | | | | | | | |
| No | 2248 | 1 | | 0.013 | 1 | | 0.041 |
| Yes | 390 | 1.554 | 1.097–2.201 | | 1.454 | 1.016–2.074 | |

Abbreviations: ASA, American Society of Anaesthesiologists; HR, hazard ratio; STO, sigmoid take-off.

potential to reduce interhospital variability, which will result in more standardized care with better comparability of outcomes between hospitals, for which accompanying training is essential.

The Delphi consensus paper on which this guideline change was based does not explain the motivation why the sigmoid take-off landmark was chosen as the preferred landmark and its benefit over other definitions, such as the anterior peritoneal reflection. In a previous publication of this study group, the authors mentioned that the mesorectum continues laterally and posteriorly above the peritoneal reflection, and they suggest that the peritoneal reflection landmark delineates the intraperitoneal and the extraperitoneal (upper) rectum [1]. Future research should evaluate the oncological outcomes of the reclassified group, to determine if the sigmoid take-off is a clinical reliable definition.

**TABLE 4** Univariable and multivariable analyses for overall survival.

| | | Univariable analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|---|
| **Variable** | **No** | **HR** | **95% CI** | ***p*-value** | **HR** | **95% CI** | ***p*-value** |
| STO | | | | | | | |
| At/under | 2470 | 1 | | 0.045 | 1 | | 0.037 |
| Above | 314 | 0.751 | 0.568–0.994 | | 0.732 | 0.546–0.982 | |
| Gender | | | | | | | |
| Male | 1817 | 1 | | 0.350 | | | |
| Female | 967 | 0.921 | 0.775–1.095 | | | | |
| Age | 2784 | 1.039 | 1.030–1.048 | <0.001 | 1.043 | 1.033–1.053 | <0.001 |
| ASA classification | | | | | | | |
| ASA I/II | 2273 | 1 | | <0.001 | 1 | | <0.001 |
| ASA III/IV | 482 | 2.009 | 1.672–2.414 | | 1.517 | 1.244–1.848 | |
| Neoadjuvant radiotherapy | | | | | | | |
| No | 1100 | 1 | | <0.001 | 1 | | <0.001 |
| Short interval | 453 | 0.970 | 0.734–1.281 | | 0.899 | 0.674–1.200 | |
| Long interval | 1221 | 1.931 | 1.606–2.323 | | 1.669 | 1.353–2.059 | |
| (y)pT-stage | | | | | | | |
| (y)pT0 | 215 | 1 | | <0.001 | 1 | | <0.001 |
| (y)pT1 | 369 | 0.914 | 0.575–1.455 | | 1.077 | 0.634–1.831 | |
| (y)pT2 | 869 | 0.875 | 0.584–1.311 | | 0.991 | 0.643–1.526 | |
| (y)pT3 | 1217 | 2.232 | 1.537–3.241 | | 1.648 | 1.098–2.474 | |
| (y)pT4 | 112 | 5.137 | 3.295–8.007 | | 3.075 | 1.901–4.973 | |
| (y)pN-stage | | | | | | | |
| (y)pN0 | 1748 | 1 | | <0.001 | 1 | | <0.001 |
| (y)pN1 | 613 | 1.773 | 1.458–2.155 | | 1.469 | 1.193–1.808 | |
| (y)pN2 | 291 | 3.558 | 2.883–4.391 | | 2.422 | 1.924–3.048 | |
| R-status | | | | | | | |
| R0 | 2584 | 1 | | <0.001 | 1 | | <0.001 |
| R+ | 176 | 3.625 | 2.893–4.541 | | 1.887 | 1.467–2.426 | |
| Synchronous metastases | | | | | | | |
| pM0 | 2587 | 1 | | <0.001 | 1 | | <0.001 |
| pM1 | 196 | 4.802 | 3.908–5.899 | | 3.143 | 2.510–3.935 | |
| Adjuvant chemotherapy | | | | | | | |
| No | 2717 | 1 | | 0.711 | | | |
| Yes | 67 | 0.901 | 0.520–1.562 | | | | |
| Pelvic sepsis | | | | | | | |
| No | 2248 | 1 | | 0.001 | 1 | | 0.001 |
| Yes | 390 | 1.413 | 1.143–1.746 | | 1.427 | 1.148–1.774 | |

Abbreviations: ASA, American Society of Anaesthesiologists; HR, hazard ratio; STO, sigmoid take-off.

## Limitations

The current study had limitations due to its retrospective nature. Patients without an MRI or no visible tumour on MRI (mostly due to a previously performed endoscopic resection) were excluded. A reason not to perform an MRI could be an initial diagnosis of a sigmoid tumour based on endoscopy which later changed to a rectal tumour based on intraoperative or pathological findings. Therefore, the proportion of tumours above the STO in the excluded patient group could be higher and consequently the proportion of sigmoid tumours in the whole cohort might be slightly higher than 11%. Furthermore, theoretically there might have

been patients with a previous diagnosis of sigmoid cancer that would now be diagnosed with rectal cancer according to the STO landmark, especially in large patients. The clinical consequences for this group could not be evaluated in this study. However, we expect that this group of patients was small because the mean distance from the lower border of the tumours above the STO to the anus on endoscopy was 13 cm, which is a few centimetres distal from the commonly used 15 cm distance from the anal verge to discriminate colon from rectal cancer.

## CONCLUSIONS

This nationwide cross-sectional study evaluated the proportion of patients initially diagnosed with rectal cancer according to the local MDT in 67 Dutch hospitals in 2016, but who would be diagnosed as sigmoid cancer according to the new STO landmark. This would result in a change of diagnosis from rectal to sigmoid cancer in 11% of the patients. Neoadjuvant radiotherapy would not be provided for half of those patients based on current guideline recommendations. The impact on adjuvant chemotherapy depends on local/national policies. Implementing the STO to standardize rectal cancer definition has the potential to reduce interhospital variability to a substantial degree.

### AUTHOR CONTRIBUTIONS

**Sanne-Marije J. A. Hazen**, **Tania C. Sluckin**, **Pieter J. Tanis** and **Miranda Kusters** made substantial contributions for the conception or design of this study. All authors and collaborators acquired the data, which were analysed by **Sanne-Marije J. A. Hazen** and **Tania C. Sluckin**. **Sanne-Marije J. A. Hazen**, **Tania C. Sluckin**, **Pieter J. Tanis**, and **Miranda Kusters** interpreted the results. **Sanne-Marije J. A. Hazen** drafted the initial manuscript with assistance from **Tania C. Sluckin**, **Pieter J. Tanis** and **Miranda Kusters**. **Karin Horsthuis**, **Doenja M. J. Lambregts**, **Regina G. H. Beets-Tan**, **Roel Hompes**, **Tineke E. Buffart**, **Corrie A. M. Marijnen** and all collaborators interpreted the results and revised and contributed to the intellectual content of the manuscript. All authors approved the final version of the manuscript to be submitted. All authors agreed to be accountable for all aspects of the work and ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved. **Sanne-Marije J. A. Hazen** had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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### CONFLICT OF INTEREST STATEMENT

None.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

### ETHICS STATEMENT

30 June 2020, by the Medical Ethical Committee of the Vrije Universiteit Medical Centre in Amsterdam.

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## APPENDIX A

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