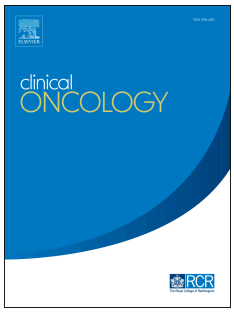

Trends and Variation in the Use of Radiotherapy in Non-metastatic Rectal Cancer: a 14-year Nationwide Overview from the Netherlands

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Trends and variation in the use of radiotherapy in non-metastatic rectal cancer: a 14-year nationwide overview from the Netherlands

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Ethics Statement: According to the Central Committee on Research involving Human Subjects (CCMO), this type of observational study does not require approval from an ethics committee in the Netherlands. In a privacy-review by assigned employees of the Netherlands Comprehensive Cancer organisation (which maintains the Netherlands Cancer Registry), the anonymous presentation of the data in this study was approved.

Original Article

Trends and Variation in the Use of Radiotherapy in Non-metastatic Rectal Cancer: a 14-year Nationwide Overview from the Netherlands

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Abstract

Aims: This study describes nationwide primary radiotherapy utilisation trends for non-metastasised rectal cancer in the Netherlands between 2008 and 2021. In 2014, both colorectal cancer screening and a new guideline specifying prognostic risk groups for neoadjuvant treatment were implemented.
Materials and methods: Patients with non-metastasised rectal cancer in 2008–2021 (*n* = 37 510) were selected from the Netherlands Cancer Registry and classified into prognostic risk groups. Treatment was studied over time and age. Multilevel logistic regression analyses were carried out to identify factors associated with (i) radiotherapy versus chemoradiotherapy use for intermediate rectal cancer and (ii) chemoradiotherapy without versus with surgery for locally advanced rectal cancer.
Results: For early rectal cancer, the use of neoadjuvant radiotherapy decreased (15% to 5% between 2008 and 2021), whereas the use of endoscopic resections increased (8% in 2015, 17% in 2021). In intermediate-risk rectal cancer, neoadjuvant chemoradiotherapy (43% until 2011, 25% in 2015) shifted to radiotherapy (42% in 2008, 50% in 2015), the latter being most

often applied in older patients. In locally advanced rectal cancer, the use of chemoradiotherapy without surgery increased (2–4% in 2008–2013, 17% in 2019–2021). Both neoadjuvant treatment in intermediate disease and omission of surgery following chemoradiotherapy in locally advanced disease varied with increasing age (odds ratio$_{>75vs<50}$: 2.17, 95% confidence interval 1.54–3.06) and treatment region (Southwest and Northwest odds ratio 0.63, 95% confidence interval 0.42–0.93 and odds ratio 0.65, 95% confidence interval 0.44–0.95, respectively, compared with the North).
Conclusion: Treatment patterns in non-metastasised rectal cancer significantly changed over time. Effects of both the national screening programme and the new treatment guideline were apparent, as well as a paradigm shift towards organ preservation (watch-and-wait). Observed regional variations may indicate adoption differences regarding new treatment strategies.

Key words: Dutch overview; national cancer registry; radiotherapy; rectal cancer; treatment trends

Introduction (A head)

Colorectal cancer is the third most common cancer type globally, and the second leading cause of cancer mortality. About one third of colorectal cancer cases regard rectal cancer. Surgery is the standard treatment for rectal cancer, with a decreased risk of locoregional recurrence when the mesorectal fat including the mesorectal fascia (MRF) is resected together with the tumour [1–3] (total mesorectal excision; TME). Preoperative (chemo)radiotherapy may further decrease the locoregional recurrence risk [3–5], and a waiting period of several weeks between the completion of (chemo)radiotherapy and surgery enables downstaging of the tumour and lymph node status [5,6]. For patients with tumours reaching towards the MRF or other organs, downstaging could be essential to reduce the risk of an irradical resection. Several international guidelines exist for the (neoadjuvant) treatment of rectal cancer, but global differences in treatment are apparent due to a lack of evidence or equipoise. From 2008 onwards in the Netherlands, the indications for neoadjuvant (chemo)radiotherapy have become specified. Neoadjuvant radiotherapy was advised for cT2-4N0-1/XM0 rectal cancer and neoadjuvant chemoradiotherapy in case of an involved MRF (≤1 mm margin between the tumour and the MRF) or four or more clinically positive lymph nodes. A new Dutch guideline was released in 2014, in which neoadjuvant treatment in early rectal cancer (cT1-3bN0-XM0) was no longer advised. Furthermore, specifications were given for the use of neoadjuvant radiotherapy (intermediate disease: cT1-3N1/cT3c-d; uninvolved MRF) and chemoradiotherapy (locally advanced disease: cT4, or cT3 with involved MRF, and/or cN2/extramesorectal pathological lymph nodes). Table 1 summarises the Dutch guidelines regarding (chemo)radiotherapy for rectal cancer, largely based on magnetic resonance imaging (MRI) staging.

Table 1 here

Over the years, MRI has become a crucial tool in adequate staging as well as response evaluation and surveillance for rectal cancer. Furthermore, MRI allows for the selection of patients who may benefit from neoadjuvant treatment and those who may not.

In a selection of patients who received neoadjuvant (chemo)radiotherapy, a pathological complete response is seen at the time of surgery [5,7]. This led to the introduction of the organ-sparing 'watch-and-wait' concept, in which surgery is delayed and sometimes even omitted in the case of a clinical complete response [8]. Interest in this strategy has grown over the years and the strategy is monitored in the national watch-and-wait programme as well as the International W&W Database. Also, treatment intensification strategies have been introduced to increase the probability of a clinical complete response, including offering localised dose escalation or the addition of systemic treatment before or after (chemo)radiotherapy.

The changing treatment guidelines and growing interest in organ-sparing treatment changed the treatment patterns for rectal cancer in the Netherlands. Furthermore, a nationwide screening programme for colorectal cancer was gradually implemented in the period 2014–2019 for people aged 55–75 years. This led to the detection/removal of premalignant lesions and/or asymptomatic tumours and changed the stage distribution of rectal cancer. Together with a decreased incidence of rectal cancer, it further changed the radiotherapy treatment patterns in rectal cancer over the years. Some publications have provided an overview of radiotherapy use in rectal cancer treatment in the Netherlands, but

a nationwide comprehensive overview focused on the trends and variation in radiotherapy use in non-metastasised rectal cancer treatment including data up to 2021 is lacking [9–12]. Therefore, the aims of this nationwide study were to investigate the trends and variation in the use of radiotherapy in the broader context of non-metastasised rectal cancer treatment in the Netherlands between 2008 and 2021, with stratification for early, intermediate-risk and locally advanced disease.

Materials and Methods (A head)

Study Population (B head)

Patients diagnosed with cT1-4N0/XM0 and cTXN1-2M0 rectal cancer in 2008–2021 were selected from the Netherlands Cancer Registry (NCR). The NCR includes information on patient, disease and primary treatment of all cancer diagnoses in the Netherlands. The data from the NCR are extracted by trained registrars from patients' medical records in all Dutch hospitals.

Definitions (B head)

The clinical T-, N- and M-stages were coded according to TNM6 (2008–2009), TNM7 (2010–2016) and TNM8 (2017–2021). Clinically involved MRF data were registered from 2015 and the subclassification of cT3 stage (related to the extent of extramural invasion) was available from 2018. The resulting missing information in earlier years called for an alternative prognostic risk group classification: early rectal cancer was defined as cT1-2N0/XM0 and intermediate rectal cancer as cT1-3/XN1M0. Patients with cT3N0/XM0 were randomly assigned to the early or intermediate-risk group, keeping the actual proportion of cT3N0 (with known extramural invasion) in both groups intact: 81.5% in the early group, 18.5% in the intermediate group. Locally advanced rectal cancer was defined as cT4 and/or cN2 in the alternative classification. Supplementary Table S1 defines and numericises this alternative classification. Patients who could not be stratified into a risk group because of incomplete TNM information (cTXNX or cTXN0) were excluded from this study (*n* = 5877).

Patients' comorbidities at the time of diagnosis were available for the South region only until 2015 and thereafter for a limited number of patients. Comorbidities were classified based on the Charlson Comorbidity Index (CCI) categories (see Supplementary Table S2). World Health Organization (WHO) Performance Status was available from 2015.

Treatment modalities analysed included short-course radiotherapy, chemoradiotherapy, other radiotherapy, chemotherapy, surgery and endoscopic resection. Minimal travel time for radiotherapy was stratified (<15, 15–30 and >30 min). The hospital in which the patient was diagnosed was classified (i) according to type, (ii) whether a radiotherapy department constituted a part and (iii) into three equal groups according to its annual number of non-metastasised rectal cancer diagnoses: low (≤22), intermediate (23–41) or high volume (≥42 patients). Regional variation was investigated by dividing the Netherlands into five regions according to patients' residence: North, East, South, Southwest and Northwest (see Supplementary Figure S1).

Analyses

Patient, disease and hospital characteristics were presented and stratified into the various risk groups. Treatment trends for early, intermediate and locally advanced rectal cancer were described over time and by age groups with 5-year intervals, except for 70–75 years (to prevent separation of screening ages into different groups). Age groups with <50 patients were not presented. For the stratification into the risk groups the alternative classification was used. To validate this classification, trends in treatment in 2015–2021 were also described for early, intermediate and locally advanced rectal cancer using the original classification (see Supplementary Figures S2–S4).

In the supplementary material, the evolution of stage distribution, use of endoscopic resection, chemoradiation without surgery and radiotherapy versus chemoradiotherapy are shown, the latter both overall and stratified for each region. In addition, the treatment of locally advanced rectal tumours is displayed stratified for the regions.

Multilevel logistic regression analyses were carried out to identify factors associated with (i) application of radiotherapy versus chemoradiotherapy for intermediate rectal cancer, stratified for diagnoses before and since 2014 to distinguish older from more recent years and (ii) application of chemoradiotherapy not followed by surgery versus chemoradiotherapy followed by surgery for locally advanced rectal cancer diagnosed since 2014. Diagnoses before 2014 were excluded, given the then limited use of chemoradiotherapy without surgery. The analyses on chemoradiotherapy with/without surgery were repeated in a sensitivity analysis including only a subset of patients younger than 70 years (reported in the supplementary material), to exclude older patients who may have been omitted from surgical treatment due to frailty.

Multilevel analyses correct for nesting of patients within hospitals. For each association investigated in the analyses, distinct models were created. A model included a random effect and random intercept for the hospital level if the corrected Akaike Information Criterion (AIC), a mathematical method for evaluating how well a model fits the data), improved compared with the model with only a random intercept. For each investigated association, a set of variables for adjustment was selected. When univariable inclusion resulted in at least a 5% change in the odds ratio of interest compared with the unadjusted multilevel odds ratio, a variable was included in the adjustment set. Ninety-five per cent confidence intervals were calculated and reflect probable odds ratio estimates. Analyses were carried out in SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results (A head)

In total, 37 510 patients were diagnosed with early (44%), intermediate (30%) and locally advanced (25%) rectal cancer from 2008 to 2021. The proportion of early disease increased since 2014 (see Supplementary Figure S5). Disease, patient and hospital characteristics were comparably distributed for the various risk groups (Table 2). About 70% of patients diagnosed with early, intermediate and locally advanced rectal cancer fell into the 50–75 years age group. Of all patients, 63% were male. For all prognostic risk groups, but mainly for intermediate and locally advanced rectal cancer, the absolute incidence decreased after 2015.

Table 2 here

Supplementary Figures S6A–F show the overall use of radiotherapy versus chemoradiotherapy over time, overall as well as separately per region.

In early rectal cancer, the use of neoadjuvant radiotherapy followed by surgery decreased from 61% to 7% in the years between 2008 and 2021, and neoadjuvant chemoradiotherapy followed by surgery decreased from 15% to 5% in this period (Figure 1A) The application of surgery without neoadjuvant treatment increased from 14% to 71% between 2008 and 2015. After 2015, this number decreased to 59%, coinciding with the increase in endoscopic resections (8% in 2015, 17% in 2021). For all ages ≤85 years, surgery without neoadjuvant (chemo)radiotherapy was the most frequently applied treatment (Figure 1B). In the age groups eligible for screening, the proportion of patients receiving endoscopic resections (10%) or surgery without neoadjuvant (chemo)radiotherapy (50%) was highest, while neoadjuvant radiotherapy was used the least (39%).

Figure 1 here

In intermediate rectal cancer, there seemed to be a shift in 2008–2015 from neoadjuvant chemoradiotherapy followed by surgery (43% until 2011, 25% in 2015) to neoadjuvant radiotherapy followed by surgery (42% in 2008, 50% in 2015) (Figure 2A). Chemoradiotherapy without surgery was increasingly applied between 2015 and 2018 (2–10%), as well as short-course radiotherapy without surgery. With increasing age, (chemo)radiotherapy use decreased and patients more often underwent surgery without neoadjuvant treatment (6–10% for ages 35–49 years, 17% for ages 81–90 years) (Figure 2B). Younger patients more often received neoadjuvant chemoradiotherapy followed by surgery, whereas older patients more often received neoadjuvant radiotherapy followed by surgery.

Figure 2 here

A marked expansion of the ‘other treatment’ category is evident for the more advanced age groups in all risk groups, predominantly accounted for by an increase in less-invasive treatment (predominantly short-course radiotherapy without surgery) in this population.

Variations in the application of radiotherapy versus chemoradiotherapy for intermediate rectal cancer are shown in Table 3, stratified according to period. Patients at older ages were more likely to receive neoadjuvant radiotherapy instead of chemoradiation,

as the odds ratios for ages >75 years compared with <50 years demonstrate (in 2008–2013: odds ratio7.02, 95% confidence interval 5.22–9.45; in 2014–2021: odds ratio 3.54; 95% confidence interval 2.72–4.61). In 2008–2013, the use of radiotherapy versus chemoradiation was higher for more recent years and for the Northwest compared with the North region (odds ratio 1.44; 95% confidence interval 1.01–2.06). Patients with comorbidity in ≥2 versus 0 categories and those with a performance status of 2–4 versus 0 had a higher probability of receiving radiotherapy compared with chemoradiotherapy.

Table 3 here

In locally advanced rectal cancer, overall radiotherapy use (including chemoradiotherapy) remained stable over time (91%) (Figure 3A). The use of neoadjuvant chemoradiotherapy followed by surgery decreased from 61% until 2016 to 40% in 2021, whereas chemoradiotherapy without surgery was increasingly applied (2–4% until 2013, 17% in 2019–2021). The use of neoadjuvant chemotherapy followed by chemoradiotherapy and surgery has increased slightly since 2016, whereas short-course radiotherapy use followed by chemotherapy with/without surgery increased greatly from 1% in 2019 to 13% in 2021. Chemoradiotherapy was less often applied with increasing age (Figure 3B). Older patients more often received surgery with neoadjuvant radiotherapy than younger patients (7% for ages 40–44 years, 29% for ages 81–85 years), whereas younger patients more often received neoadjuvant chemoradiotherapy than older patients (74% versus 20%, respectively).

Figure 3 here

Supplementary Figure S7A–E shows the trends in therapies for patients with locally advanced rectal cancer separated per region.

Table 4 shows variation in application of neoadjuvant chemoradiotherapy without versus with surgery for locally advanced rectal cancer after 2014. Increased application of chemoradiotherapy without surgery is demonstrated by the odds ratio of 1.21 (95% confidence interval 1.17–1.26) for each more recent year. Compared with patients aged <50 years, older patients were more likely to receive chemoradiotherapy without surgery (odds ratio 50–75 years: 1.40, 95% confidence interval 1.05–1.87; odds ratio >75 years: 2.17, 95% confidence interval 1.54–3.06). Patients living in the Southwest and Northwest, compared with the North, were less likely to have surgery omitted following chemoradiotherapy.

Table 4 here

Discussion (A head)

This nationwide study investigated radiotherapy use in primary non-metastasised rectal cancer treatment from 2008 to 2021. For early rectal cancer, less neoadjuvant treatment was given and more endoscopic resections occurred. For intermediate rectal cancer, neoadjuvant chemoradiotherapy shifted to neoadjuvant radiotherapy. For patients with locally advanced rectal cancer, an increase was seen in the application of chemoradiotherapy without surgery.
These observed trends reflect both the new treatment guideline and the introduction of the national screening programme for colorectal cancer in 2014. The latter led to a reduced incidence of rectal cancer, changed prognostic risk group distribution and the increased application of endoscopic resections by the gastroenterologist for early rectal cancer, which coincided with relative declining use of surgical treatment.

Changing Neoadjuvant Treatment (B head)

In the years preceding the scope of this study, radiotherapy for rectal cancer was given either preoperatively or postoperatively. During 1997–2008, radiotherapy use increased in the Netherlands, predominantly the preoperative use, as the Dutch TME-trial proved preoperative radiotherapy to be effective in reducing the local recurrence risk [13]. The national guideline published in 2008 subsequently advised preoperative radiotherapy for cT2-4N0-1 disease [14]. The new national guideline, published in 2014, no longer advised neoadjuvant radiotherapy for cT1-3b tumours, which resulted in a clear decrease in neoadjuvant radiotherapy use for early rectal cancer, as shown in our study.

We observed a decline in the use of neoadjuvant chemoradiotherapy and an increase in neoadjuvant radiotherapy in 2008–2014 for intermediate rectal cancer, which may result from the general belief that de-escalation of neoadjuvant treatment for this group (in line with the existing guideline) was warranted. Also, the definition of involved MRF became more strict over time, resulting in fewer patients considered to have MRF-involved disease and, therefore, being indicated for receiving neoadjuvant chemoradiotherapy. As our intermediate group could include MRF-involved disease, this may also have contributed to the shift towards neoadjuvant radiotherapy instead of chemoradiotherapy.

In intermediate disease, we found older and more frail patients to be more likely to receive the less intensive neoadjuvant radiotherapy than neoadjuvant chemoradiation. The regional difference found only in 2008–2013 may indicate early adoption of neoadjuvant radiotherapy instead of neoadjuvant chemoradiation.

Organ Preservation (B head)

Several studies have reported a pathological complete response rate of 10–20% after neoadjuvant chemoradiotherapy for patients with locally advanced rectal cancer [5,7]. For these patients, a watch-and-wait policy can be introduced in an attempt to prevent, or at least delay, surgical treatment [15]. This non-surgical management has received growing interest of patients who want to avoid the risks of surgery and preserve their rectum. This paradigm shift towards organ preservation is also illustrated in the current study. The use of chemoradiotherapy not followed by surgery increased for locally advanced rectal cancer and

the use of chemoradiotherapy for younger patients with intermediate rectal cancer increased, illustrating the pursuit for organ preservation.

For locally advanced rectal cancer diagnosed since 2014, we found that older and frailer patients (having a worse performance status) were more likely to have surgery omitted following chemoradiation. The regional variation found for chemoradiotherapy without versus with surgery possibly indicates differences in adoption or belief of organ-preserving treatment. In the sensitivity analysis (see Supplementary Table S3), excluding patients aged ≥70 years with the aim of excluding those who may have been omitted from surgical treatment due to frailty, chemoradiation without surgery was also less likely in the South compared with the North, as well as in non-university compared with university hospitals. The latter possibly reflects university hospitals being the first to adopt innovative treatment choices – at least for younger patients. In the Netherlands, ongoing studies such as the TESAR and international STAR-TREC phase II–III trials [16,17] aim to provide more insight into appropriate patient selection for organ preservation.

Several strategies are being explored to potentially improve the chance of a complete response, including increasing the total radiotherapy dose [18]. Providing dose escalation through external beam radiotherapy increases the risk of complications, however [19–21]. The findings of, among others, the OPERA trial, have led to the justification in international guidelines of endoluminal contact brachytherapy as a feasible option for organ preservation in early rectal tumours [22,23]. The challenge in the upcoming years will remain performing adequate patient selection for a potential organ-sparing pathway. Unfortunately, dose escalation has not yet been specified as a registered item in the NCR for our study period and could therefore not be evaluated. The addition of systemic treatment before or after (chemo)radiotherapy is another strategy that may improve the complete response chance. Adding chemotherapy may have a more significant role in the prevention of systemic disease for patients with rectal cancer [24–28]. Short-course radiotherapy followed by chemotherapy (CAPOX or FOLFOX) before TME in locally advanced rectal cancer increased pathological response, compared with chemoradiotherapy (RAPIDO study) [29]. In the current study, a surge in the application of the 'RAPIDO' treatment scheme for patients with locally advanced rectal cancer was apparent since 2019, corresponding to the time when the trial results became widespread. However, concerns regarding toxicity of the RAPIDO regimen not outweighing the potential benefits may limit the use of this scheme in future years.

For future research, it would be insightful to study the consequences of the observed shift in treatment trends on oncological outcomes.

In the current study, de-escalation of treatment was seen in those aged >80 years. This is not surprising, considering the potential risks of surgical, radiotherapeutic and systemic treatment for this (often) frail population. The elderly frail population with rectal cancer entail a heterogeneous group for which no standardised treatment protocol is suitable, rendering decision-making challenging. Nevertheless, refraining from treatment ultimately leads to tumour progression and often debilitating symptoms. Multidisciplinary evaluation, including geriatric assessment, may prove useful in defining the best suitable treatment. Short-course therapy followed by a waiting period may allow for an eventual R0 resection [6,30]. For patients who are inoperable or refuse surgery, palliative radiotherapy may alleviate symptoms [31]. We, likewise, observed short-course (palliative) radiotherapy without surgery most often at older ages.

Strengths and Limitations (B head)

This paper shows novel and recent data concerning nationwide treatment trends for patients with rectal cancer. It provides a comprehensive overview stratified for risk groups, enabling the evaluation of compliance with changing guidelines for these specific groups.

Limitations include the necessity of using an alternative risk group classification. However, the alternative classification showed comparable treatment trends in 2015–2021 to the original classification (see Supplementary Figures S2–S4), suggesting that it was a relatively accurate method of classification for investigating treatment patterns. In addition, it was impossible to adjust all analyses for comorbidities and performance status given their limited availability. Information on dosage and fractionation schemes were also unavailable, hampering the evaluation of potentially changing radiotherapy schemes.

Conclusions (A head)

This paper illustrates the changing landscape regarding radiotherapeutic treatment in the context of multimodal treatment for rectal cancer between 2008 and 2021 in the Netherlands, characterised in particular by the introduction of the national screening programme for colorectal cancer and the new national guideline for neoadjuvant treatment published in 2014. In addition, the beginning paradigm shift towards organ preservation is revealed, which is expected to expand within the coming years.

Ethics statement

According to the Central Committee on Research involving Human Subjects (CCMO), this type of observational study does not require approval from an ethics committee in the Netherlands. In a privacy review by assigned employees of the Netherlands Comprehensive Cancer Organisation (which maintains the Netherlands Cancer Registry), the anonymous presentation of the data in this study was approved.

Conflicts of interest

J. Evers reports that financial support was provided by Nederlandse Vereniging voor Radiotherapie en Oncologie. S. Siesling reports that financial support was provided by University of Nicosia, external evaluation committee for public health. M. Berbee has patent Maastro HDR rectal applicator issued to Varian Medical Systems.

Author contributions

A-SEV was responsible for conceptualisation, validation and writing the original draft of the manuscript. JE was responsible for conceptualisation, methodology, software, formal analysis, reviewing and editing the manuscript and visualisation. SS was responsible for conceptualisation and reviewing and editing the manuscript. MJA and ME were responsible for conceptualisation, formal analysis, validation, reviewing and editing the manuscript and supervision. HS, MCWMB, JB, VL and PB were responsible for conceptualisation and reviewing and editing the manuscript. MB was responsible for conceptualisation, formal analysis, reviewing and editing the manuscript and supervision.

Appendix A. Supplementary data

[AQ1]Supplementary data to this article can be found online at

[Typesetter: please change 'Figure 1' to 'Figure S1' etc for all figures in the supplementary material file. Tables have been changed as they were Word docs]

References

[1] Heald RJ, Ryall RDH. Recurrence and survival after total mesorectal excision for rectal cancer. Lancet 1986;327:1479–82. https://doi.org/10.1016/S0140-6736(86)91510-2.
[2] Arbman G, Nilsson E, Hallböök O, Sjödahl R. Local recurrence following total mesorectal excision for rectal cancer. Br J Surgery 2005;83:375–9. https://doi.org/10.1002/bjs.1800830326.
[3] Kapiteijn E, Putter H, van de Velde CJH. Impact of the introduction and training of total mesorectal excision on recurrence and survival in rectal cancer in The Netherlands. Br J Surgery 2002;89:1142–9. https://doi.org/10.1046/j.1365-2168.2002.02196.x.
[4] van Gijn W, Marijnen CAM, Nagtegaal ID, Kranenbarg EM-K, Putter H, Wiggers T et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. Lancet Oncol 2011;12:575–82. https://doi.org/10.1016/S1470-2045(11)70097-3.
[5] Sauer R, Becker H, Hohenberger W, Rodel C, Wittekind C, Fietkau R et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351:1731–40. https://doi.org/10.1056/NEJMoa040694.
[6] Erlandsson J, Lörinc E, Ahlberg M, Pettersson D, Holm T, Glimelius B et al. Tumour regression after radiotherapy for rectal cancer – results from the randomised Stockholm III trial. Radiother Oncol 2019;135:178–86. https://doi.org/10.1016/j.radonc.2019.03.016.
[7] Maas M, Nelemans PJ, Valentini V, Das P, Rodel C, Kuo L-J et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. Lancet Oncol 2010;11:835–44. https://doi.org/10.1016/S1470-2045(10)70172-8.
[8] Habr-Gama A, Perez RO, Nadalin W, Sabbaga J, Ribeiro U, Silva e Sousa AH et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg 2004;240:711–8. https://doi.org/10.1097/01.sla.0000141194.27992.32.
[9] Brouwer NPM, Bos ACRK, Lemmens VEPP, Tanis PJ, Hugen N, Nagtegaal ID et al. An overview of 25 years of incidence, treatment and outcome of colorectal cancer patients: results from the Netherlands Cancer Registry. Int J Cancer 2018;143:2758–66. https://doi.org/10.1002/ijc.31785.
[10] Detering R, De Neree Tot Babberich MPM, Bos ACRK, Dekker JWT, Wouters MWJM, Bemelman WA et al. Nationwide analysis of hospital variation in preoperative radiotherapy use for rectal cancer following guideline revision. Eur J Surg Oncol 2020;46:486–94. https://doi.org/10.1016/j.ejso.2019.12.016.
[11] Koëter T, Elferink MA, Verhoeven RHA, Zimmerman DDE, Wasowicz DK, Verheij M et al. Hospital variance in neoadjuvant rectal cancer treatment and the influence of a national guideline update: results of a nationwide population-based study. Radiother Oncol 2020;145:162–71. https://doi.org/10.1016/j.radonc.2019.12.020.
[12] Gietelink L, Wouters MWJM, Marijnen CAM, Van Groningen J, Van Leersum N, Beets-Tan RGH et al. Changes in nationwide use of preoperative radiotherapy for rectal

cancer after revision of the national colorectal cancer guideline. Eur J Surgical Oncol 2017;43:1297–303. https://doi.org/10.1016/j.ejso.2016.12.019.

[13] Kapiteijn E, Marijnen CAM, Nagtegaal ID, Putter H, Steup WH, Wiggers T et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. New Engl J Med 2001;345:638–46. https://doi.org/10.1056/NEJMoa010580.

[14] Jobsen JJ, Aarts MJ, Siesling S, Klaase J, Louwman WJ, Poortmans PMP et al. Use of primary radiotherapy for rectal cancer in the Netherlands between 1997 and 2008: a population-based study. Clin Oncol 2012;24:e1–8. https://doi.org/10.1016/j.clon.2011.09.009.

[15] Dattani M, Heald RJ, Goussous G, Broadhurst J, São Julião GP, Habr-Gama A et al. Oncological and survival outcomes in watch and wait patients with a clinical complete response after neoadjuvant chemoradiotherapy for rectal cancer: a systematic review and pooled analysis. Ann Surg 2018;268:955–67. https://doi.org/10.1097/SLA.0000000000002761.

[16] Borstlap WAA, Tanis PJ, Koedam TWA, Marijnen CAM, Cunningham C, Dekker E et al. A multi-centred randomised trial of radical surgery versus adjuvant chemoradiotherapy after local excision for early rectal cancer. BMC Cancer 2016;16:513. https://doi.org/10.1186/s12885-016-2557-x.

[17] Rombouts AJM, Al-Najami I, Abbott NL, Appelt A, Baatrup G, Bach S et al. Can we *S*ave the rectum by watchful waiting or *T*rans *A*nal microsurgery following (chemo) *R*adiotherapy versus *T*otal mesorectal excision for early *RE*ctal *C*ancer (STAR-TREC study)?: protocol for a multicentre, randomised feasibility study. BMJ Open 2017;7:e019474. https://doi.org/10.1136/bmjopen-2017-019474.

[18] Appelt AL, Ploen J, Vogelius IR, Bentzen SM, Jakobsen A. Radiation dose-response model for locally advanced rectal cancer after preoperative chemoradiation therapy. Int J Radiat Oncol Biol Phys 2013;85:74–80. https://doi.org/10.1016/j.ijrobp.2012.05.017.

[19] Gunderson LL, Calvo FA, Willett CG, Harrison LB. Rationale and historical perspective of intraoperative irradiation. In: Gunderson LL, Willett CG, Calvo FA, Harrison LB, editors. Intraoperative irradiation, Totowa, NJ: Humana Press; 2011, p. 3–26. https://doi.org/10.1007/978-1-61779-015-7_1.

[20] Okunieff P, Sundararaman S, Metcalfe S, Chen Y. Biology of large dose per fraction irradiation. Intraoperative irradiation: techniques and results. 2nd ed. Totowa, NJ: Humana Press; 2011, p. 27–47.

[21] Allee PE, Tepper JE, Gunderson LL, Munzenrider JE. Postoperative radiation therapy for incompletely resected colorectal carcinoma. Int J Radiat Oncol Biol Phys 1989;17:1171–6. https://doi.org/10.1016/0360-3016(89)90522-1.

[22] Gerard J-P, Barbet N, Schiappa R, Magné N, Martel I, Mineur L et al. Neoadjuvant chemoradiotherapy with radiation dose escalation with contact X-ray brachytherapy boost or external beam radiotherapy boost for organ preservation in early cT2–cT3 rectal adenocarcinoma (OPERA): a phase 3, randomised controlled trial. Lancet Gastroenterol Hepatol 2023;8:356–67. https://doi.org/10.1016/S2468-1253(22)00392-2.

[23] Stewart AJ, Van Limbergen EJ, Gerard J-P, Appelt AL, Verhaegen F, Berbee M et al. GEC ESTRO ACROP consensus recommendations for contact brachytherapy for rectal cancer. Clin Transl Radiat Oncol 2022;33:15–22. https://doi.org/10.1016/j.ctro.2021.12.004.

[24] Calvo FA, Serrano FJ, Diaz-González JA, Gomez-Espi M, Lozano E, Garcia R et al. Improved incidence of pT0 downstaged surgical specimens in locally advanced rectal cancer (LARC) treated with induction oxaliplatin plus 5-fluorouracil and preoperative chemoradiation. Ann Oncol 2006;17:1103–10. https://doi.org/10.1093/annonc/mdl085.

[25] Fernandez-Martos C, Garcia-Albeniz X, Pericay C, Maurel J, Aparicio J, Montagut C et al. Chemoradiation, surgery and adjuvant chemotherapy versus induction chemotherapy followed by chemoradiation and surgery: long-term results of the Spanish GCR-3 phase II randomized trial. Ann Oncol 2015;26:1722–8. https://doi.org/10.1093/annonc/mdv223.

[26] Cercek A, Roxburgh CSD, Strombom P, Smith JJ, Temple LKF, Nash GM et al. Adoption of total neoadjuvant therapy for locally advanced rectal cancer. JAMA Oncol 2018;4:e180071. https://doi.org/10.1001/jamaoncol.2018.0071.

[27] Golo D, But-Hadzic J, Anderluh F, Brecelj E, Edhemovic I, Jeromen A et al. Induction chemotherapy, chemoradiotherapy and consolidation chemotherapy in preoperative treatment of rectal cancer – long-term results of phase II OIGIT-01 Trial. Radiol Oncol 2018;52:267–74. https://doi.org/10.2478/raon-2018-0028.

[28] Markovina S, Youssef F, Roy A, Aggarwal S, Khwaja S, DeWees T et al. Improved metastasis- and disease-free survival with preoperative sequential short-course radiation therapy and FOLFOX chemotherapy for rectal cancer compared with neoadjuvant long-course chemoradiotherapy: results of a matched pair analysis. Int J Radiat Oncol Biol Phys 2017;99:417–26. https://doi.org/10.1016/j.ijrobp.2017.05.048.

[29] Bahadoer RR, Dijkstra EA, Van Etten B, Marijnen CAM, Putter H, Kranenbarg EM-K et al. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial. Lancet Oncol 2021;22:29–42. https://doi.org/10.1016/S1470-2045(20)30555-6.

[30] François E, De Bari B, Ronchin P, Nouhaud E, Martel-Lafay I, Artru P et al. Comparison of short course radiotherapy with chemoradiotherapy for locally advanced rectal cancers in the elderly: a multicentre, randomised, non-blinded, phase 3 trial. Eur J Cancer 2023;180:62–70. https://doi.org/10.1016/j.ejca.2022.11.020.

[31] Cameron MG, Kersten C, Vistad I, Fosså S, Guren MG. Palliative pelvic radiotherapy of symptomatic incurable rectal cancer – a systematic review. Acta Oncol 2014;53:164–73. https://doi.org/10.3109/0284186X.2013.837582.

Table 1

Dutch guidelines for neoadjuvant (chemo)radiotherapy for patients with non-metastasised rectal cancer

Date	TNM classification*	Neoadjuvant treatment
2008–2014	cT1N0	None
	cT2-4 N0/N1, and distance to MRF >1 mm	5 × 5 Gy preoperative radiotherapy
	Distance to MRF ≤1 mm or cN2	Preoperative chemoradiotherapy
2014 onwards	cT1-2N0 or cT3a-bN0; distance to MRF >1 mm	None
	cT1-3N1 or cT3c-d; distance to MRF >1 mm	5 × 5 Gy preoperative radiotherapy
	cT4 or cT3 with distance to MRF ≤1 mm and/or cN2/extramesorectal pathological lymph nodes	Preoperative chemoradiotherapy

*As staged on magnetic resonance imaging/endorectal ultrasound for 2008–2014 and magnetic resonance imaging for 2014 onwards.
MRF, mesorectal fascia.

Table 2
Disease, patient and hospital characteristics, for patients diagnosed with non-metastatic rectal cancer in the Netherlands, stratified for early, intermediate and locally advanced disease (*n* = 37 510)

	Early *n* = 16 669		Intermediate *n* = 11 291		Locally advanced *n* = 9550	
	n	(%)	*n*	(%)	*n*	(%)
Clinical T-stage						
TX	n/a		514	(4.6)	112	(1.2)
T1	3432	(20.6)	176	(1.6)	19	(0.2)
T2	6875	(41.2)	1854	(16.4)	462	(4.8)
T3	6362	(38.2)	8747	(77.5)	5136	(53.8)
T4	n/a		n/a		3821	(40.0)
Clinical N-stage						
NX	1801	(10.8)	170	(1.5)	272	(2.8)
N0	14 868	(89.2)	1284	(11.4)	1000	(10.5)
N1	n/a		9837	(87.1)	1190	(12.5)
N2	n/a		n/a		7088	(74.2)
Year of diagnosis						
2008–2012	4948	(29.7)	3603	(31.9)	2821	(29.5)
2013–2017	6642	(39.8)	4813	(42.6)	4349	(45.5)
2018–2021	5079	(30.5)	2875	(25.5)	2380	(24.9)
Sex						
Men	10 547	(63.3)	7274	(64.4)	5637	(59.0)
Women	6122	(36.7)	4017	(35.6)	3913	(41.0)
Age at time of diagnosis						
<50 years	645	(3.9)	663	(5.9)	890	(9.3)
50–75 years	11 724	(70.3)	7896	(69.9)	6620	(69.3)
>75 years	4300	(25.8)	2732	(24.2)	2040	(21.4)
Region of residence						
North	2292	(13.8)	1495	(13.2)	1346	(14.1)
East	2688	(16.1)	1953	(17.3)	1964	(20.6)
South	4208	(25.2)	2677	(23.7)	2481	(26.0)
Southwest	3602	(21.6)	2438	(21.6)	1673	(17.5)
Northwest	3879	(23.3)	2728	(24.2)	2086	(21.8)
Comorbidities assessed *	5689	(34.1)	3625	(32.1)	3394	(35.5)
No comorbidity in any CCI category	2988	(52.5)	2005	(55.3)	2007	(59.1)
Comorbidities in 1 CCI category	1650	(29.0)	985	(27.2)	912	(26.9)
Comorbidities in ≥2 CCI categories	1051	(18.5)	635	(17.5)	475	(14.0)
Most frequent comorbidities						
Diabetes mellitus	827	(14.5)	566	(15.6)	479	(14.1)
Chronic pulmonary disease	622	(10.9)	397	(11.0)	328	(9.7)
Other malignancy	649	(11.4)	366	(10.1)	287	(8.5)
WHO performance status available †	4461	(26.8)	3624	(32.1)	3739	(39.2)
Performance status 0	2997	(67.2)	2288	(63.1)	2112	(56.5)
Performance status 1	1130	(25.3)	1057	(29.2)	1287	(34.4)

Performance status 2–4	334	(7.5)	279	(7.7)	340	(9.1)
Minimal travel time for radiotherapy						
<15 min	5892	(35.3)	3892	(34.5)	3318	(34.7)
15–30 min	9108	(54.6)	6259	(55.4)	5310	(55.6)
>30 min	1669	(10.0)	1140	(10.1)	922	(9.7)
Diagnosed in a university hospital ‡§	975	(5.9)	570	(5.1)	631	(6.6)
Radiotherapy as part of the diagnosing hospital ‡	2918	(17.5)	1967	(17.4)	1844	(19.3)
Volume in the hospital of diagnosis ‡‖						
Low volume of diagnoses	2316	(13.9)	1637	(14.5)	1346	(14.1)
Intermediate volume of diagnoses	4880	(29.3)	3272	(29.0)	2839	(29.7)
High volume of diagnoses	9457	(56.8)	6369	(56.5)	5360	(56.2)

CCI, Charlson Comorbidity Index; n/a, not applicable; WHO, World Health Organization

* Before 2015, comorbidities were only assessed for patients diagnosed in the South region.

† Available only since 2015.

‡ Hospital of diagnosis is missing for 34 patients.

§ Including the single cancer-specific hospital in the Netherlands.

‖ The one third of hospitals with the lowest number of M0 rectal cancer diagnoses (average ≤22/year) were classified as low volume, the one third of hospitals with the highest number of M0 rectal cancer diagnoses (average ≥42/year) were classified as high volume, the other one third of hospitals were classified as intermediate volume.

Table 3

Adjusted odds ratios of receiving radiotherapy versus chemoradiation (with or without induction/consolidation radiotherapy), stratified for patients diagnosed with intermediate rectal cancer before 2014 (*n* = 4058) and since 2014 (*n* = 5581) in the Netherlands

	Diagnosed before 2014		Diagnosed since 2014	
	Radiotherapy, *n* = 2106 Chemoradiotherapy, *n* = 1952		Radiotherapy, *n* = 3604 Chemoradiotherapy, *n* = 1977	
	Odds ratio *	(95%CI)	Odds ratio †	(95%CI)
Year of diagnosis (continuously)	**1.12**	**(1.08–1.16)**	1.03	(1.00–1.05)
Sex				
Men	Reference		Reference	
Women	1.14	(0.99–1.31)	1.04	(0.93–1.17)
Age at time of diagnosis				
<50 years	Reference		Reference	
50–75 years	**1.75**	**(1.35–2.26)**	**1.56**	**(1.24–1.98)**
>75 years	**7.02**	**(5.22–9.45)**	**3.54**	**(2.72–4.61)**
Region of residence				
North	Reference		Reference	
East	1.30	(0.90–1.86)	1.08	(0.79–1.48)
South	0.96	(0.66–1.38)	0.99	(0.72–1.36)
Southwest	0.71	(0.49–1.02)	0.97	(0.71–1.33)
Northwest	**1.44**	**(1.01–2.06)**	1.34	(0.99–1.83)
Comorbidities ‡				
No comorbidity in any CCI category	n/a		Reference	
Comorbidity in 1 CCI category	n/a		1.24	(0.97–1.59)
Comorbidity in ≥2 CCI categories	n/a		**1.48**	**(1.11–1.98)**

WHO performance status [§]				
Performance status 0	n/a		Reference	
Performance status 1	n/a		1.04	(0.88–1.23)
Performance status 2–4	n/a		**3.17**	**(2.15–4.66)**
Hospital of surgery				
Non-university	Reference		Reference	
University [‖]	1.17	(0.74–1.84)	1.43	(0.99–2.08)
Volume in the hospital of surgery [¶]				
Low volume of diagnoses	Reference		Reference	
Intermediate volume of diagnoses	1.07	(0.75–1.53)	0.91	(0.69–1.19)
High volume of diagnoses	1.18	(0.83–1.66)	1.03	(0.78–1.35)

95%CI, 95% confidence interval; CCI, Charlson Comorbidity Index; WHO, World Health Organization.
Values in bold are statistically significant

[*] Multilevel logistic regression models with only a random effect were applied for all factors. The analyses on year of diagnosis, age, region and volume of diagnosis were not adjusted, as none of the variables fulfilled the criteria for inclusion in the adjustment sets. The analysis on sex was adjusted for age. The analysis on type of hospital was adjusted for region and volume of diagnosis.

[†] A multilevel logistic regression model with both a random intercept and a random effect was applied for number of comorbidities. The analyses on year of diagnosis, sex and age were not adjusted, as none of the variables fulfilled the criteria for inclusion in the adjustment sets. The analyses on region, number of comorbidities, performance status and type of hospital were adjusted for age. The analysis on volume of diagnosis was adjusted for type of hospital. NB: the number of comorbidities and performance status were not included in adjustment sets, considering their limited availability.

[‡] Comorbidities were assessed for 2395 (43%) of the patients diagnosed since 2014.

[§] WHO performance status was available for 3138 (56%) of the patients diagnosed since 2014.

[‖] Including the single cancer-specific hospital in the Netherlands.

[¶] The one third of hospitals with the lowest number of M0 rectal cancer diagnoses (average ≤22/year) were classified as low volume, the one third of hospitals with the highest number of M0 rectal cancer diagnoses (average ≥42/year) were classified as high volume, the other one third of hospitals were classified as intermediate volume.

Table 4

Adjusted odds ratios of receiving chemoradiation without surgery versus chemoradiation with surgery, for patients diagnosed with locally advanced rectal cancer since 2014 in the Netherlands (*n* = 4019)

	Diagnosed since 2014	
	Chemoradiation without surgery, *n* = 730 Chemoradiation, *n* = 3289	
	Odds ratio [*]	(95%CI)
Year of diagnosis (continuously)	**1.21**	**(1.17–1.26)**
Sex		
Men	Reference	
Women	0.89	(0.76–1.06)
Age at time of diagnosis		
<50 years	Reference	
50–75 years	**1.40**	**(1.05–1.87)**
>75 years	**2.17**	**(1.54–3.06)**
Region of residence		
North	Reference	
East	0.84	(0.59–1.21)
South	0.74	(0.50–1.09)

Southwest	**0.63**	**(0.42–0.93)**
Northwest	**0.65**	**(0.44–0.95)**
Comorbidities †		
No comorbidity in any CCI category	Reference	
Comorbidity in 1 CCI category	0.99	(0.68–1.43)
Comorbidity in ≥2 CCI categories	1.56	(1.00–2.44)
WHO performance status ‡		
Performance status 0	Reference	
Performance status 1	0.88	(0.71–1.08)
Performance status 2–4	**1.55**	**(1.02–2.36)**
Hospital of diagnosis		
Non-university	Reference	
University §	1.46	(0.92–2.33)
Volume in the hospital of diagnosis ‖		
Low volume of diagnoses	Reference	
Intermediate volume of diagnoses	1.42	(0.97–2.08)
High volume of diagnoses	1.42	(0.97–2.08)

95%CI, 95% confidence interval; CCI, Charlson Comorbidity Index; WHO, World Health Organization.
Values in bold are statistically significant.

* A multilevel logistic regression model with both a random intercept and a random effect was applied for number of comorbidities. The analyses on year of diagnosis, sex and region were not adjusted, as none of the variables fulfilled the criteria for inclusion in the adjustment sets. The analysis on age was adjusted for year of diagnosis. The analyses on number of comorbidities and performance status were adjusted for age. The analysis on type of hospital was adjusted for year of diagnosis, region and volume of diagnosis. The analysis on volume of diagnosis was adjusted for type of hospital. NB: the number of comorbidities and performance status were not included in adjustment sets, considering their limited availability.

† Comorbidities were assessed for 1835 (46%) of the patients diagnosed since 2014.

‡ WHO performance status was available for 2718 (68%) of the patients diagnosed since 2014.

§ Including the single cancer-specific hospital in the Netherlands.

‖ The one third of hospitals with the lowest number of M0 rectal cancer diagnoses (average ≤22/year) were classified as low volume, the one third of hospitals with the highest number of M0 rectal cancer diagnoses (average ≥42/year) were classified as high volume, the other one third of hospitals were classified as intermediate volume.

Fig 1. Treatments for early rectal cancer. (A) Treatment trends over time. (B) Treatment trends per age group. CT, chemotherapy; RT, radiotherapy; CRT, chemoradiotherapy.

Fig 2. Treatment trends for intermediate rectal cancer. (A) Treatment trends over time. (B) Treatment trends per age group. CT, chemotherapy; RT, radiotherapy; CRT, chemoradiotherapy.

Fig 3. Treatment trends for locally advanced rectal cancer. (A) Treatment trends over time. (B) Treatment trends per age group. CT, chemotherapy; RT, radiotherapy; CRT, chemoradiotherapy.

Author query

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Table 1

Dutch guidelines for neoadjuvant (chemo)radiotherapy for patients with non-metastasized rectal cancer.

*as staged on MRI/endorectal ultrasound for 2008-2014 and MRI for 2014 onwards.

Date national guideline	TNM classification*	Neoadjuvant treatment
2008-2014	cT1N0	None
	cT2-4 N0/N1, and distance to MRF >1 mm	5 x 5 Gy preoperative radiotherapy
	Distance to MRF ≤1mm or cN2	Preoperative chemoradiotherapy
2014- onwards	cT1-2N0 or cT3a-bN0; distance to MRF >1mm	None
	cT1-3N1 or cT3c-d; distance to MRF >1mm	5 x 5 Gy preoperative radiotherapy
	cT4 or cT3 with distance to MRF ≤1mm and/or cN2/extramesorectal pathological lymph nodes	Preoperative chemoradiotherapy

MRF = mesorectal fascia

Table 2. Disease, patient and hospital characteristics, for patients diagnosed with non-metastatic rectal cancer in the Netherlands, stratified for early, intermediate and locally advanced disease (N=37,510)

	Early N = 16,669		Intermediate N = 11,291		Locally advanced N = 9,550	
	n	(%)	n	(%)	n	(%)
Clinical T-stage						
TX	n/a		514	(4.6)	112	(1.2)
T1	3,432	(20.6)	176	(1.6)	19	(0.2)
T2	6,875	(41.2)	1,854	(16.4)	462	(4.8)
T3	6,362	(38.2)	8,747	(77.5)	5,136	(53.8)
T4	n/a		n/a		3,821	(40.0)
Clinical N-stage						
NX	1,801	(10.8)	170	(1.5)	272	(2.8)
N0	14,868	(89.2)	1,284	(11.4)	1,000	(10.5)
N1	n/a		9,837	(87.1)	1,190	(12.5)
N2	n/a		n/a		7,088	(74.2)
Year of diagnosis						
2008-2012	4,948	(29.7)	3,603	(31.9)	2,821	(29.5)
2013-2017	6,642	(39.8)	4,813	(42.6)	4,349	(45.5)
2018-2021	5,079	(30.5)	2,875	(25.5)	2,380	(24.9)
Sex						
Men	10,547	(63.3)	7,274	(64.4)	5,637	(59.0)
Women	6,122	(36.7)	4,017	(35.6)	3,913	(41.0)
Age at time of diagnosis						
<50 years	645	(3.9)	663	(5.9)	890	(9.3)
50-75 years	11,724	(70.3)	7,896	(69.9)	6,620	(69.3)
>75 years	4,300	(25.8)	2,732	(24.2)	2,040	(21.4)
Region of residence						
North	2,292	(13.8)	1,495	(13.2)	1,346	(14.1)
East	2,688	(16.1)	1,953	(17.3)	1,964	(20.6)
South	4,208	(25.2)	2,677	(23.7)	2,481	(26.0)
Southwest	3,602	(21.6)	2,438	(21.6)	1,673	(17.5)
Northwest	3,879	(23.3)	2,728	(24.2)	2,086	(21.8)
Comorbidities assessed [A]	5,689	(34.1)	3,625	(32.1)	3,394	(35.5)
No comorbidity in any CCI category	2,988	(52.5)	2,005	(55.3)	2,007	(59.1)
Comorbidities in 1 CCI category	1,650	(29.0)	985	(27.2)	912	(26.9)
Comorbidities in ≥2 CCI categories	1,051	(18.5)	635	(17.5)	475	(14.0)
Most frequent comorbidities						

Diabetes Mellitus	827	(14.5)	566	(15.6)	479	(14.1)
Chronic Pulmonary Disease	622	(10.9)	397	(11.0)	328	(9.7)
Other malignancy	649	(11.4)	366	(10.1)	287	(8.5)
WHO performance status available [B]	4,461	(26.8)	3,624	(32.1)	3,739	(39.2)
Performance status 0	2,997	(67.2)	2,288	(63.1)	2,112	(56.5)
Performance status 1	1,130	(25.3)	1,057	(29.2)	1,287	(34.4)
Performance status 2-4	334	(7.5)	279	(7.7)	340	(9.1)
Minimal travel time for radiotherapy						
<15 minutes	5,892	(35.3)	3,892	(34.5)	3,318	(34.7)
15-30 minutes	9,108	(54.6)	6,259	(55.4)	5,310	(55.6)
>30 minutes	1,669	(10.0)	1,140	(10.1)	922	(9.7)
Diagnosed in a university hospital [C D]	975	(5.9)	570	(5.1)	631	(6.6)
Radiotherapy as part of the diagnosing hospital [C]	2,918	(17.5)	1,967	(17.4)	1,844	(19.3)
Volume in the hospital of diagnosis [C E]						
Low volume of diagnoses	2,316	(13.9)	1,637	(14.5)	1,346	(14.1)
Intermediate volume of diagnoses	4,880	(29.3)	3,272	(29.0)	2,839	(29.7)
High volume of diagnoses	9,457	(56.8)	6,369	(56.5)	5,360	(56.2)

CCI: Charlson Comorbidity Index; n/a: not applicable

[A] Before 2015, comorbidities were only assessed for patients diagnosed in the South region.

[B] Available only since 2015.

[C] Hospital of diagnosis is missing for 34 patients.

[D] Including the single cancer-specific hospital in the Netherlands.

[E] The one third of hospitals with the lowest number of M0 rectal cancer diagnoses (average ≤22 p/year) were classified as low volume, the one third of hospitals with the highest number of M0 rectal cancer diagnoses (average ≥42 p/year) were classified as high volume, the other one third of hospitals were classified as intermediate volume.

Table 3. Adjusted odds ratios (OR) of receiving radiotherapy (RT) versus chemoradiation (CRT) (with or without induction/consolidation RT), stratified for patients diagnosed with intermediate rectal cancer before 2014 (N=4,058) and since 2014 (N=5,581) in the Netherlands

	Diagnosed before 2014		Diagnosed since 2014	
	RT, N = 2,106 CRT, N = 1,952		RT, N = 3,604 CRT, N = 1,977	
	OR [A]	(95%CI)	OR [B]	(95%CI)
Year of diagnosis (continuously)	**1.12**	**(1.08-1.16)**	1.03	(1.00-1.05)
Sex				
Men	Reference		Reference	
Women	1.14	(0.99-1.31)	1.04	(0.93-1.17)
Age at time of diagnosis				
< 50 years	Reference		Reference	
50-75 years	**1.75**	**(1.35-2.26)**	**1.56**	**(1.24-1.98)**
> 75 years	**7.02**	**(5.22-9.45)**	**3.54**	**(2.72-4.61)**
Region of residence				
North	Reference		Reference	
East	1.30	(0.90-1.86)	1.08	(0.79-1.48)
South	0.96	(0.66-1.38)	0.99	(0.72-1.36)
Southwest	0.71	(0.49-1.02)	0.97	(0.71-1.33)
Northwest	**1.44**	**(1.01-2.06)**	1.34	(0.99-1.83)
Comorbidities [C]				
No comorbidity in any CCI category	n/a		Reference	
Comorbidity in 1 CCI category	n/a		1.24	(0.97-1.59)
Comorbidity in ≥2 CCI categories	n/a		**1.48**	**(1.11-1.98)**
WHO performance status [D]				
Performance status 0	n/a		Reference	
Performance status 1	n/a		1.04	(0.88-1.23)
Performance status 2-4	n/a		**3.17**	**(2.15-4.66)**
Hospital of surgery				
Non-university	Reference		Reference	
University [E]	1.17	(0.74-1.84)	1.43	(0.99-2.08)
Volume in the hospital of surgery [F]				
Low volume of diagnoses	Reference		Reference	
Intermediate volume of diagnoses	1.07	(0.75-1.53)	0.91	(0.69-1.19)
High volume of diagnoses	1.18	(0.83-1.66)	1.03	(0.78-1.35)

OR: odds ratio, RT: radiotherapy, CRT: chemoradiation, 95%CI: 95%% confidence interval, CCI: Charlson Comorbidity Index; values in bold are statistically significant

[A] Multilevel logistic regression models with only a random effect were applied for all factors. The analyses on year of diagnosis, age, region and volume of diagnosis were not adjusted, as none of the variables fulfilled the criterium for inclusion in the adjustment sets. The analysis on sex was adjusted for age. The analysis on type of hospital was adjusted for region and volume of diagnosis.

[B] A multilevel logistic regression model with both a random intercept and random effect was applied for number of comorbidities. The analyses on year of diagnosis, sex and age were not adjusted, as none of the variables fulfilled the criterium for inclusion in the adjustment sets. The analyses on region, number of comorbidities, performance status and type of hospital were adjusted for age. The analysis on volume of diagnosis was adjusted for type of hospital. NB. number of comorbidities and performance status were not included in adjustment sets, considering their limited availability.

[C] Comorbidities were assessed for 2,395 (43%) of the patients diagnosed since 2014.

[D] WHO performance status was available for 3,138 (56%) of the patients diagnosed since 2014.

[E] Including the single cancer specific hospital in the Netherlands.

[F] The one third of hospitals with the lowest number of M0 rectal cancer diagnoses (average ≤22 p/year) were classified as low volume, the one third of hospitals with the highest number of M0 rectal cancer diagnoses (average ≥42 p/year) were classified as high volume, the other one third of hospitals were classified as intermediate volume.

Table 4. Adjusted odds ratios (OR) of receiving chemoradiation (CRT) without surgery versus CRT with surgery, for patients diagnosed with locally advanced rectal cancer since 2014 in the Netherlands (N=4,019)

	Diagnosed since 2014	
	CRT without surgery, N = 730 CRT, N = 3,289	
	OR [A]	(95%CI)
Year of diagnosis (continuously)	**1.21**	**(1.17-1.26)**
Sex		
Men	Reference	
Women	0.89	(0.76-1.06)
Age at time of diagnosis		
< 50 years	Reference	
50-75 years	**1.40**	**(1.05-1.87)**
> 75 years	**2.17**	**(1.54-3.06)**
Region of residence		
North	Reference	
East	0.84	(0.59-1.21)
South	0.74	(0.50-1.09)
Southwest	**0.63**	**(0.42-0.93)**
Northwest	**0.65**	**(0.44-0.95)**
Comorbidities [B]		
No comorbidity in any CCI category	Reference	
Comorbidity in 1 CCI category	0.99	(0.68-1.43)
Comorbidity in ≥2 CCI categories	1.56	(1.00-2.44)
WHO performance status [C]		
Performance status 0	Reference	
Performance status 1	0.88	(0.71-1.08)
Performance status 2-4	**1.55**	**(1.02-2.36)**
Hospital of diagnosis		
Non-university	Reference	
University [D]	1.46	(0.92-2.33)
Volume in the hospital of diagnosis [E]		
Low volume of diagnoses	Reference	
Intermediate volume of diagnoses	1.42	(0.97-2.08)
High volume of diagnoses	1.42	(0.97-2.08)

OR: odds ratio, CRT: chemoradiation, 95%CI: 95%% confidence interval, CCI: Charlson Comorbidity Index; values in bold are statistically significant

[A] A multilevel logistic regression models with both a random intercept and random effect was applied for number of comorbidities. The analyses on year of diagnosis, sex and region were not adjusted, as none of the variables fulfilled the criterium for inclusion in the adjustment sets. The analysis on age was adjusted for year of diagnosis. The analyses on number of comorbidities and performance status were adjusted for age. The analysis on type of hospital was adjusted for year of diagnosis, region and volume of diagnosis. The analysis on volume of diagnosis was adjusted for type of hospital. NB. number of comorbidities and performance status were not included in adjustment sets, considering their limited availability.

[B] Comorbidities were assessed for 1,835 (46%) of the patients diagnosed since 2014.

[C] WHO performance status was available for 2,718 (68%) of the patients diagnosed since 2014.

[D] Including the single cancer specific hospital in the Netherlands.

[E] The one third of hospitals with the lowest number of M0 rectal cancer diagnoses (average ≤22 p/year) were classified as low volume, the one third of hospitals with the highest number of M0 rectal cancer diagnoses (average ≥42 p/year) were classified as high volume, the other one third of hospitals were classified as intermediate volume.

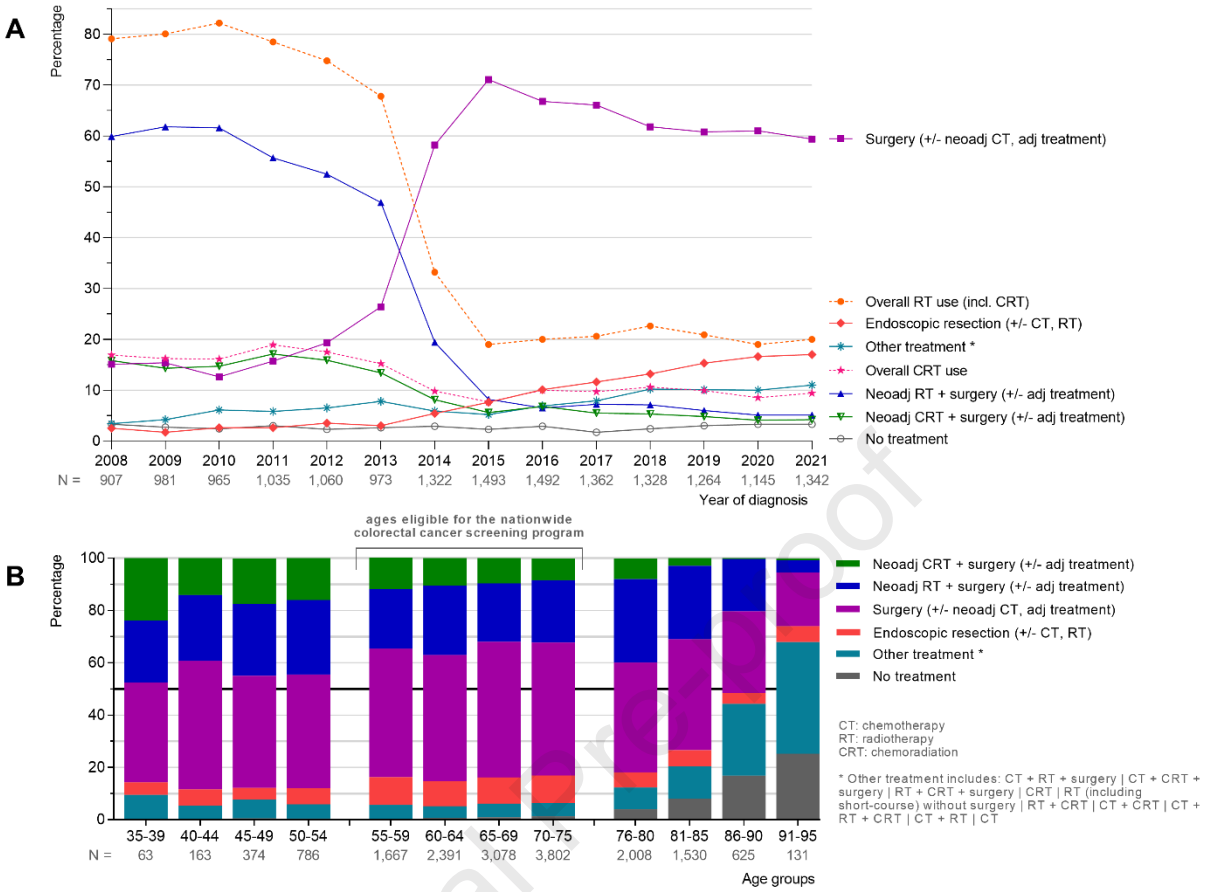

Figure 1. Treatments for early rectal cancer. A) Treatment trends over time. B) Treatment trends per age group.

CT = chemotherapy
RT = radiotherapy
CRT = chemoradiotherapy

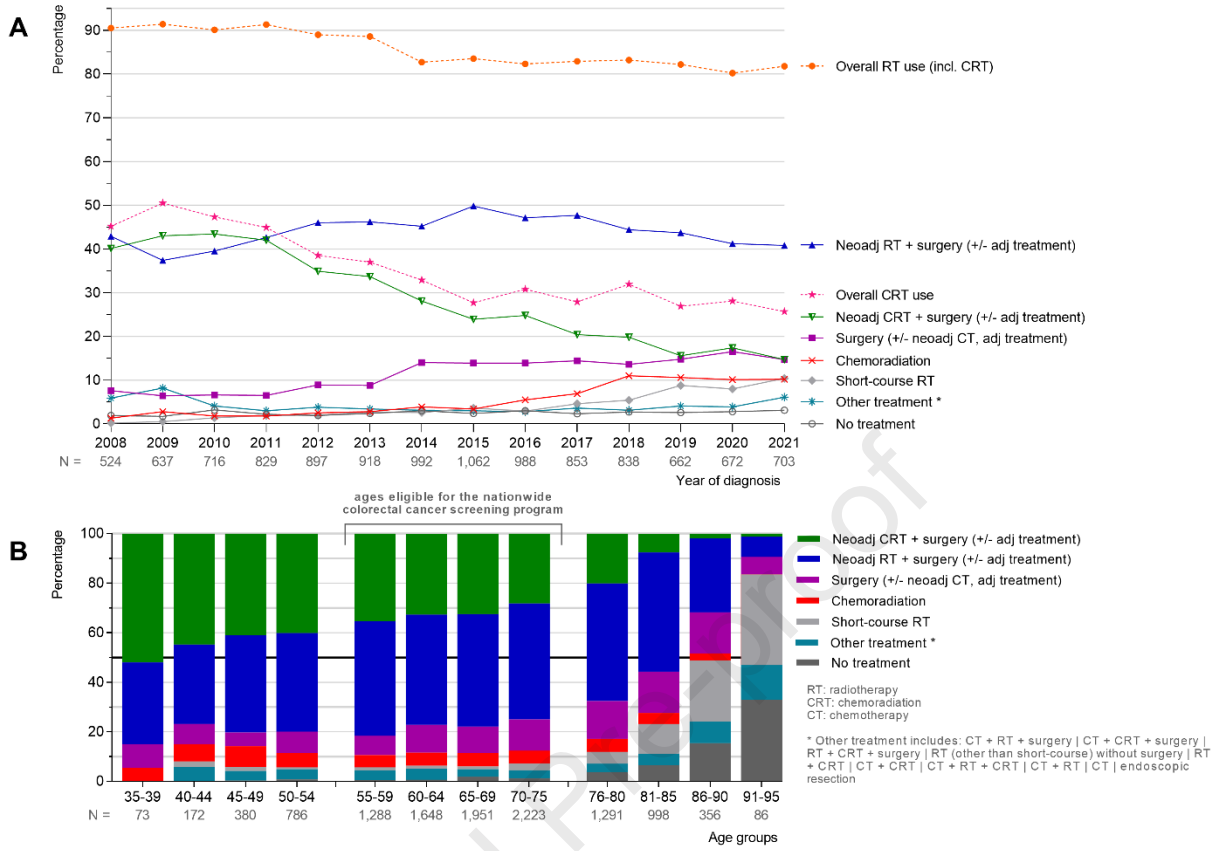

Figure 2. Treatment trends for intermediate rectal cancer. A) Treatment trends over time. B) Treatment trends per age group.

CT = chemotherapy
RT = radiotherapy
CRT = chemoradiotherapy

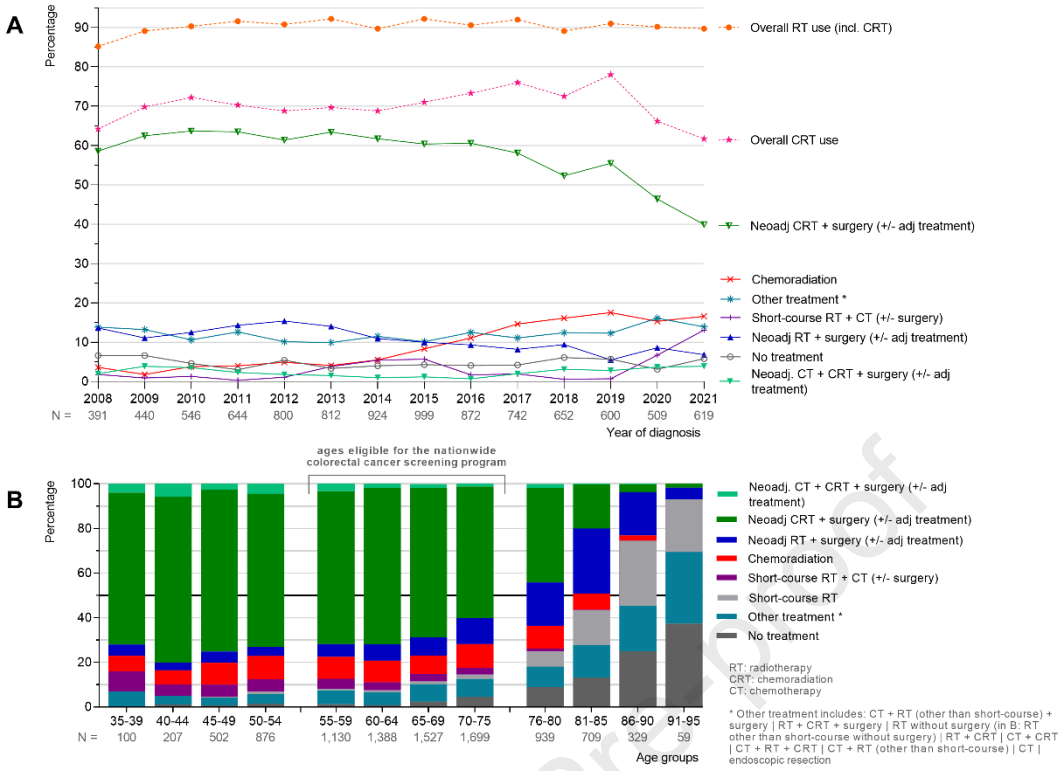

Figure 3. Treatment trends for locally advanced rectal cancer. A) Treatment trends over time. B) Treatment trends per age group.

CT = chemotherapy
RT = radiotherapy
CRT = chemoradiotherapy

Highlights

- The implementation of the national colorectal cancer screening programme saw a surge of new early rectal cancer diagnoses, corresponding with more endoscopic resections in this time.
- The implementation of a new national guideline in 2014 resulted in a decrease in neoadjuvant treatment for early rectal cancer.
- For intermediate rectal cancer, a shift was seen from neoadjuvant chemoradiotherapy to radiotherapy.
- The paradigm shift towards organ preservation was apparent, particularly for locally advanced rectal cancer.

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Jelle Evers reports financial support was provided by Nederlandse Vereniging voor Radiotherapie en Oncologie. Sabine Siesling reports financial support was provided by University of Nicosia, external evaluation committee for public health. Maaike Berbee has patent Maastro HDR rectal applicator issued to Varian Medical Systems.

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