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Original Research

Trends in incidence, treatment, and relative survival of colorectal cancer in the Netherlands between 2000 and 2021

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ABSTRACT

Background: The epidemiology of colorectal cancer (CRC) has changed rapidly over the years. The aim of this study was to assess the trends in incidence, treatment, and relative survival (RS) of patients diagnosed with CRC in the Netherlands between 2000 and 2021.

Patients and methods: 2 75667 patients diagnosed with CRC between 2000 and 2021 were included from the Netherlands Cancer Registry. Analyses were stratified for disease extent (localised: T1-3N0M0; regional: T4N0M0/T1-4N1-2M0; distant: T1-4N0-2M1) and localisation (colon; rectum). Trends were assessed with joinpoint regression.

Results: CRC incidence increased until the mid-2010s but decreased strongly thereafter to rates comparable with the early 2000s. Amongst other trend changes, local excision rates increased for patients with localised colon (2021: 13.6 %) and rectal cancer (2021: 34.9 %). Moreover, primary tumour resection became less common in patients with distant colon (2000–2021: 60.9–12.5 %) or rectal cancer (2000–2021: 47.8–6.9 %), while local treatment of metastases rates increased. Five-year RS improved continuously for localised and regional colon (97.7 % and 72.0 % in 2017, respectively) and rectal cancer (95.2 % and 76.3 % in 2017, respectively). The rate of anti-cancer treatments decreased in distant colon (2010–2021: 80.3 % to 67.2 %; $p < 0.001$) and rectal cancer (2011–2021: 86.0 % to 77.0 %; $p < 0.001$). The improvement of five-year RS stagnated for distant colon (2010–2017: 11.2 % to 11.9 %; average percentage of change [APC]: 2.1, 95 % confidence interval [CI]: −7.6, 4.7) and rectal cancer (2009–2017: 12.7 % to 15.6 %; APC: 1.4, 95 % CI: −19.1, 5.5).

Conclusions: Major changes in the incidence and treatment of CRC between 2000 and 2021 were identified and quantified. Five-year RS increased continuously for patients with localised and regional CRC, but stagnated for patients with distant CRC, likely caused by decreased rates of anti-cancer treatment in this group.

1. Introduction

Colorectal cancer (CRC) is the third most common cancer in males and females worldwide [1]. An increasing incidence of CRC has been noted in the population below the age of 50 years in Western countries [2–4], and the introduction of population screening for CRC in various countries has initiated major changes in overall incidence and stage-specific incidence within the population targeted for screening [5–7]. Population screening leads to the diagnosis of relatively more localised CRCs, while the relative incidence of regional and distant

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tumours decreases [5].

Recent advancements in diagnostics and treatment - both surgical and non-surgical - have proven effectiveness regarding oncological and survival outcomes. Several studies have shown an increase in relative and overall survival for both colon and rectal cancer patients over the last decades [8–10]. Moreover, CRC mortality has decreased in Europe and the USA [5,11].

The Netherlands Cancer Registry (NCR) is a high-quality nationwide cancer registry, and has been maintained since 1989 [12]. Data from the NCR can be used to visualise and quantify the rapidly changing trends in CRC over the last two decades. The aim of this study was to investigate the trends in incidence, treatment, and relative survival (RS) of CRC in the Netherlands between 2000 and 2021.

2. Methods

2.1. Data collection

Patient and clinical data were selected from the NCR, which registers all newly diagnosed malignancies since 1989, and is hosted by the Netherlands Comprehensive Cancer Organisation (IKNL). Data about patient characteristics, tumour characteristics and treatment are obtained from medical records by data managers of the NCR. Topography and morphology are coded using the International Classification of Diseases for Oncology [13]. TNM classification is used for tumour staging, according to the edition valid at time of diagnosis [14]. Vital status follow-up was completed until January 31, 2023 through linkage with the Municipal Personal Records Database. Patients ≥ 18 years diagnosed with CRC in the period 2000–2021 were included in this study. The privacy board of the NCR and the Dutch Colorectal Cancer Group (DCCG) have approved the conduct of the present study.

2.2. Statistical analysis

Patients were stratified by tumour localisation (colon: C18; rectum: C19, C20) and disease extent (localised: T1–3N0M0; regional: T4N0M0/T1–4N1–2M0; distant: T1–4N0–2M1). In principle, pathological TNM was used, but in patients who underwent neoadjuvant treatment or with an unknown pathological stage, clinical TNM was used. In case of multiple resections, the most extensive resection was reported. Transanal endoscopic microsurgery and transanal minimally invasive surgery were regarded as surgical resections; all other endoscopic resections were regarded local excisions.

Patients with unknown TNM stage were excluded (colon cancer: N = 7626, 4.0 %; rectal cancer: N = 3129, 3.6 %) from all analyses, except for the patient and tumour characteristics. The incidence analyses were conducted following the rules of the International Association of Cancer Registries [15].

Median values were presented with interquartile ranges (IQRs) and compared with the Kruskall-Wallis test.

Annual incidence was estimated per 100,000 person-years and standardised to the revised European Standard Population, resulting in Revised European Standardised Rates (RESR). Treatments were categorised, and the percentage of total treatments per year was presented. RS was estimated using the Pohar-Perme method [16], which weighs a patient's contribution to the net survival based on the expected survival for a counterpart based on sex, age and calendar year [17]. One-year, three-year and five-year RS outcomes were estimated for patients diagnosed until December 31st of 2021, 2019 and 2017, respectively.

Joinpoint regression analyses were used to test for trend changes [18], which allowed to fit multiple regression models which are connected via joinpoints. The joinpoint itself marks a trend change, and a period between two joinpoints represents a trend. A statistically significant trend is increasing or decreasing. The statistically best fitting model (0 versus one joinpoints based on the weighted Bayesian information criterion) was presented. Log-linear joinpoint models were used for incidence and RS data, resulting in average percentages of change (APC) with 95 % confidence intervals (CI) over a time period, while linear joinpoint models were used for the treatment trends.

P values < 0.05 were considered statistically significant. Statistical analyses were performed using SAS software, version 9.4 (SAS institute, Cary, NC) except for the RS analyses (Stata Statistical Software, Release 16. College Station, TX: StataCorp LLC) and trend analyses (Joinpoint Regression Program, Version 5.0, April 2023; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute). Plots were created using R version 5.0.0 with the "ggplot2″ package.

3. Results

3.1. Patient and tumour characteristics

Patient and tumour characteristics of the 275,667 included patients are provided in Table 1. Notably, a shift in distribution from localised rectal cancer to regional rectal cancer appeared between the 2000–2007

Table 1
Patient and tumour characteristics of included patients (N = 275,667).

	2000-2007 N (%)	2008-2014 N (%)	2015-2021 N (%)
Localisation			
Colon	55,325 (66)	64,613 (69)	68,479 (70)
Rectum	28,783 (34)	29,221 (31)	29,246 (30)
Colon cancer			
Disease extent			
Localised	23,998 (43)	27,353 (42)	32,325 (47)
Regional	16,635 (30)	19,519 (30)	19,895 (29)
Distant	11,634 (21)	14,887 (23)	14,545 (21)
Other[a]	3058 (6)	2854 (5)	1714 (3)
Age at diagnosis			
18–54 years	5349 (10)	5346 (8)	5561 (8)
55–74 years	27,094 (49)	32,229 (50)	36,933 (54)
≥ 75 years	22,882 (41)	27,038 (42)	25,985 (38)
Sex			
Female	27,859 (50)	30,915 (48)	32,692 (48)
Male	27,466 (50)	33,698 (52)	35,787 (52)
Morphology			
Non-mucinous adenocarcinoma	44,360 (80)	53,596 (83)	58,435 (85)
Mucinous adenocarcinoma	8419 (15)	7804 (12)	5806 (8)
Signet cell carcinoma	665 (1)	931 (1)	869 (1)
Other	1881 (3)	2282 (4)	3369 (5)
Rectal cancer			
Disease extent			
Localised	12,473 (43)	10,142 (35)	11,136 (38)
Regional	9462 (33)	12,271 (42)	12,399 (42)
Distant	5284 (18)	5799 (20)	5155 (18)
Other[a]	1564 (5)	1009 (3)	556 (2)
Age at diagnosis			
18–54 years	3853 (13)	3684 (13)	3612 (12)
55–74 years	15,898 (55)	16,432 (56)	17,331 (59)
≥ 75 years	9032 (31)	9105 (31)	8303 (28)
Sex			
Female	11,979 (42)	11,332 (39)	10,976 (38)
Male	16,804 (58)	17,889 (61)	18,270 (62)
Morphology			
Non-mucinous adenocarcinoma	25,527 (89)	26,735 (91)	27,325 (93)
Mucinous adenocarcinoma	2462 (9)	1803 (6)	1130 (4)
Signet cell carcinoma	190 (1)	199 (1)	175 (1)
Other	604 (2)	484 (2)	616 (2)

Localised; T1-3N0M0. Regional; T4N0M0 or T1-4N1-2M0. Distant; T1-4N0-2M1.

[a] The category "other" included patients with TX tumors or T0 tumors without prior neoadjuvant treatment. The proportional differences between the three time-period were statistically significant (P < 0.05) for all variables included in the table.

and 2008–2014 time-periods.

3.2. Incidence

The incidence of localised, regional, and distant colon cancer increased between 2000–2016, 2000–2014 and 2000–2012, respectively (Fig. 1, Table 2). Thereafter, the incidence of these three groups decreased. The incidence of regional and distant rectal cancer increased between 2000 and 2016 and 2000–2014, respectively, and decreased thereafter. The incidence of localised rectal cancer showed no statistically significant trend change between 2000 and 2018 but decreased between 2018 and 2021.

3.3. Anti-cancer treatment

The rates of anti-cancer treatment (i.e., curative or palliative treatment, treatment of recurrences excluded) for localised and regional colon and rectal cancer patients changed slightly but remained high during the study period (colon cancer: ≥93 %; rectal cancer: ≥95 %, Fig. 2, Appendix 1 [Table]). The rate of anti-cancer treatment was stable for distant colon cancer patients between 2000 and 2010 (77.7–80.3 %, $p = 0.057$), but decreased thereafter (2010–2021: 80.3–67.2 %, $p < 0.001$). In distant rectal cancer patients, the rate of anti-cancer treatment increased between 2000 and 2011 (76.0–86.0 %, $p < 0.001$), but decreased thereafter (2011–2021: 86.0–77.0 %, $p < 0.001$).

3.4. Resection

In localised colon cancer patients, the local excision rate increased between 2009 and 2021 (5.6 % to 13.6 %, $p < 0.001$), while the surgical resection rate decreased during the same period (94.0 % to 80.8 %, $p < 0.001$, Fig. 3, Appendix 2 [Table]). The proportion of distant colon cancer patients treated with a surgical resection combined with local treatment of metastases (LTM) increased between 2000 and 2016 (4.4–20.2 %, $p < 0.001$). Within this group, the rate of no resection increased as well (2000–2015: 34.6–54.6 %, $p < 0.001$; 2015–2021: 54.6–67.9 %, $p < 0.001$).

The local excision rate in patients with localised rectal cancer increased between 2007 and 2021 (10.6–34.9 %, $p < 0.001$), while the rate of no resection increased (2000–2017: 1.9–7.6 %, $p < 0.001$; 2017–2021: 7.6–14.4 %, $p = 0.003$) and the surgical resection rate

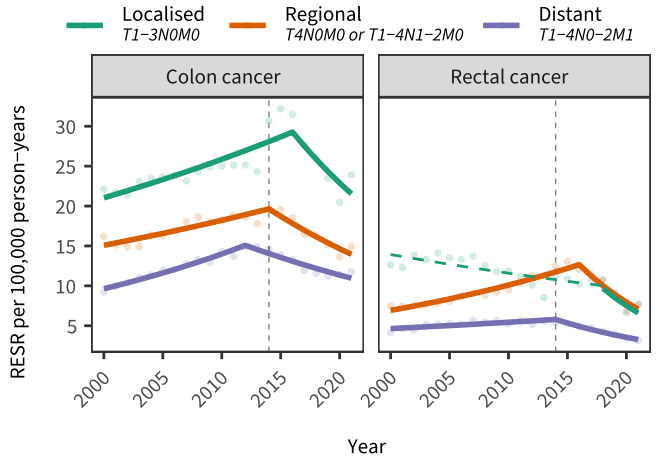

Fig. 1. Trends in colorectal cancer incidence in the Netherlands between 2000 and 2021, stratified for localisation and disease extent. *Dots represent the actual percentages per year. Solid lines represent the modelled trend changes which were statistically significant ($p < 0.05$). Dashed lines represented modelled trend changes which were statistically insignificant ($p \geq 0.05$). RESR; Revised European Standardised Rate.*

Table 2
Trends In Colorectal Cancer Incidence in The Netherlands Between 2000 and 2021, Stratified for Localisation and Disease Extent.

	Time period	RESR per 100,000 person-years in first and last year of time period	APC (95 % CI) over time period
Colon cancer			
Localised	2000-2016	22.10 to 31.49	2.1[b] (1.4, 3.1)
	2016-2021	31.49 to 23.94	-6.0[b] (−12.2, −2.5)
Regional	2000-2014	16.19 to 19.71	1.9[b] (1.3, 2.7)
	2014-2021	19.71 to 14.93	-4.8[b] (−6.9, −3.2)
Distant	2000-2012	9.22 to 14.91	3.8[b] (3.2, 4.5)
	2012-2021	14.91 to 11.75	-3.5[b] (−4.5, −2.6)
Rectal cancer			
Localised	2000-2018	12.63 to 10.71	-1.8 (−2.6, 4.6)
	2018-2021	10.71 to 7.64	-11.6[b] (−24.5, −3.1)
Regional	2000-2016	7.51 to 12.06	3.8[b] (3.1, 4.7)
	2016-2021	12.06 to 7.73	-11.0[b] (−15.6, −7.5)
Distant	2000-2014	4.13 to 5.37	1.6[b] (0.8, 2.5)
	2014-2021	5.37 to 3.16	-7.8[b] (−10.4, −5.9)

RESR; Revised European Standard Rate. APC; average percentage of change (per year). CI; confidence interval. Localised; T1-3N0M0. Regional; T4N0M0 or T1-4N1-2M0. Distant; T1-4N0-2M1. Statistically significant trend changes were denoted with an asterisk.

[b] Time periods were defined by the joinpoint regression analysis.

decreased (2000–2007: 91.0–86.7 %, $p < 0.002$; 2007–2021: 86.7–50.7 %, $p < 0.001$). In patients with regional rectal cancer, an increased rate of no resection (2013–2021: 9.5–27.2 %, $p < 0.001$) was accompanied with a decreased rate of surgical resection (2013–2021: 90.0–71.1 %, $p < 0.001$). The rate of no resection increased among distant rectal cancer patients (2000–2009: 45.2–68.6 %, $p < 0.001$; 2009–2021: 68.6–78.2 %, $p < 0.001$). The rate of surgical resection and LTM increased between 2000 and 2015 (6.4–21.6 %, $p < 0.001$) and decreased slightly thereafter (2015–2021: 21.6–14.2 %, $p = 0.036$).

3.5. Neoadjuvant treatment

In localised rectal cancer patients, the rate of TME without neoadjuvant (chemo)radiation decreased (2000–2009: 65.7–21.4 %, $p = 0.003$, Appendix 3 [Figure], Appendix 4 [Table]) and thereafter increased (2009–2021: 21.4–42.2 %, $p = 0.001$). The rate of neoadjuvant radiotherapy with TME decreased strongly between 2007 and 2021 (47.7–4.4 %, $p < 0.001$). After the rate of neoadjuvant chemoradiation with TME increased between 2000 and 2010 (0.3–11.7 %, $p < 0.001$), it decreased as well (11.7–4.1 %, $p < 0.001$). The watch-and-wait approach (i.e., omission of surgical resection in case of a clinical complete response after neoadjuvant treatment) was effectuated increasingly (2000–2016: 1.0–6.4 %, $p < 0.001$; 2016–2021: 6.4–11.5 %, $p < 0.001$), and the rate of local excision only increased between 2008 and 2021 (11.7–32.1 %, $p < 0.001$).

The rate of neoadjuvant radiotherapy with TME increased sharply between 2000 and 2002 for patients with regional rectal cancer (26.8–54.8 %, $p = 0.018$), but decreased thereafter (2002–2021: 54.8–28.0 %, $p < 0.001$). The rate of neoadjuvant chemoradiation with TME increased between 2000 and 2011 (2.1–44.3 %, $p < 0.001$), but decreased thereafter as well (2011–2021: 44.3–26.1 %, $p < 0.001$). The

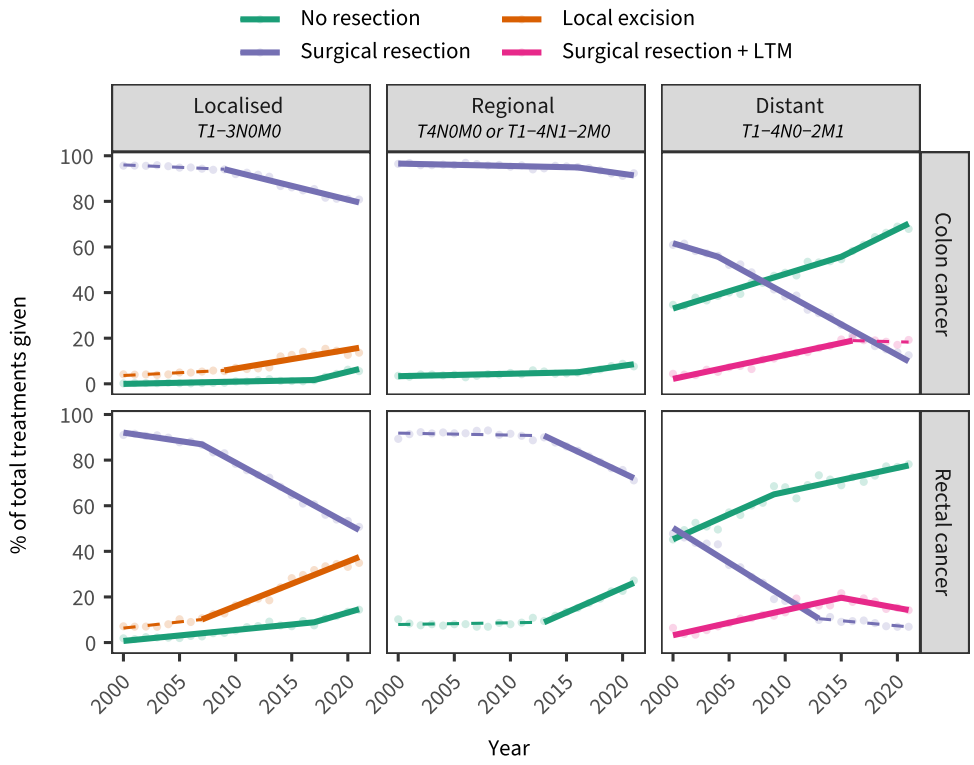

Fig. 2. Trends in anti-cancer treatment (i.e., curative or palliative treatment, not including treatment of possible recurrences) for colorectal cancer in the Netherlands between 2000 and 2021, stratified for localisation and disease extent. *Dots represent the actual percentages per year. Solid lines represent the modelled trend changes which were statistically significant ($p < 0.05$). Dashed lines represented modelled trend changes which were statistically insignificant ($p \geq 0.05$).*

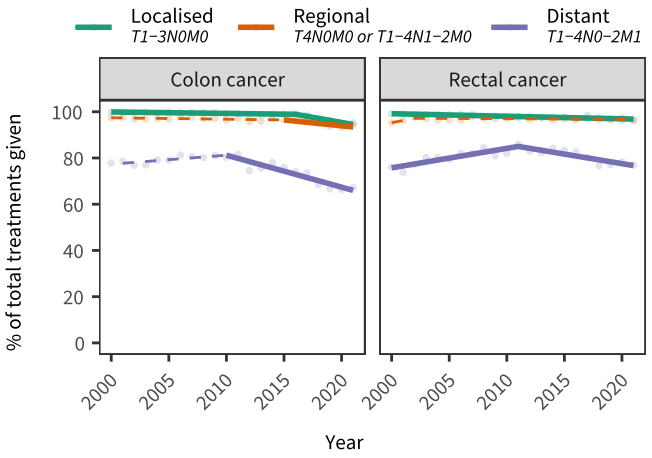

Fig. 3. Trends in type of resection for colorectal cancer in the Netherlands between 2000 and 2021, stratified for localisation and disease extent. *Dots represent the actual percentages per year. Solid lines represent the modelled trend changes which were statistically significant ($p < 0.05$). Dashed lines represented modelled trend changes which were statistically insignificant ($p \geq 0.05$). LTM; local treatment of metastases (includes metastasectomy and ablation).*

watch-and-wait approach became more common (2000–2013: 5.3–7.0 %, p = 0.026; 2013–2021: 7.0–23.5 %, p < 0.001). The rate of TME without neoadjuvant (chemo)radiation decreased between 2000 and 2011 (47.3–10.8 %, p < 0.001), but increased thereafter (2011–2021: 10.8–16.9 %, p = 0.004).

Administration of neoadjuvant chemotherapy increased between 2019 and 2021 for surgically treated patients with regional colon cancer (2.3–5.2 %, p < 0.001, Appendix 5 [Figure] and Appendix 6 [Table]. A similar trend was identified in patients with regional rectal cancer, while not statistically significant (2019–2021: 0.6–7.3 %, p = 0.073).

3.6. Adjuvant treatment

Treatment with adjuvant chemotherapy became more common in patients with surgically resected regional colon cancer between 2000 and 2015 (44.0–61.8 %, p < 0.001, Appendix 7 [Figure] and Appendix 8 [Table]), but administration rates decreased slightly thereafter (2015–2021: 61.8–55.8 %, p = 0.035). The median age of patients differed significantly between patients with regional disease who were and were not treated with adjuvant chemotherapy (median: 65 years, IQR: 58–72 versus median: 78 years, IQR: 71–83, respectively; p < 0.001). After a stable rate between 2000 and 2006 (p = 0.933), administration of adjuvant chemotherapy for patients with surgically resected regional rectal cancer became uncommon (2006–2021: 27.5–2.6 %, p < 0.001).

3.7. Systemic treatment for unresected distant tumours

Treatment with targeted therapy (administered with or without chemotherapy) was introduced between 2004 and 2008 (0.3–27.6 %, p = 0.010) for patients with unresected distant colon cancer, and its use stabilised thereafter (p = 0.127, Appendix 9 [Figure], Appendix 10 [Table]). The rate of treatment with chemotherapy only decreased between 2004 and 2021 (43.5–16.1 %, p < 0.001) for this group. The median age of patients with unresected distant colon cancer who were treated with chemotherapy (68 years, IQR: 60–75), targeted therapy (65 years, IQR: 57–72) or who received no systemic treatment (77 years, IQR: 70–83) differed significantly (p < 0.001). Among patients with unresected distant rectal cancer, the administration of targeted therapy surged between 2005 and 2008 (2.0–38.8 %, p = 0.004) and stabilised thereafter (p = 0.370). It became less common to give chemotherapy only (2003–2021: 47.0–20.3 %, p < 0.001) in this group. Again, the median age of patients with unresected distant rectal cancer differed between the respective treatments (p < 0.001): 65 years (IQR: 57–73) for chemotherapy, 63 years (IQR: 55–70) for targeted therapy, and 75

years (IQR: 67–82) for no systemic treatment.

3.8. Relative survival

Since 2010, five-year RS has increased for localised and regional colon and rectal cancer, while the increasing trends in five-year relative survival for distant colon and rectal cancer patients have stagnated in 2010 and 2009, respectively (Fig. 4, Table 3).

4. Discussion

This study investigated the trends in incidence, treatment and RS of patients diagnosed with localised, regional, and distant colon and rectal cancer in the Netherlands between 2000 and 2021. The incidence of CRC in 2021 is comparable with the incidence rates in the early 2000 s, after peaking around the introduction of nationwide population screening in 2014. Moreover, the present study showed notable changes in the treatment of colon and rectal cancer since 2000. RS rates predominantly increased, especially in the first studied decennium. During the second decennium however, RS rates did not increase anymore for patients with distant disease.

Nationwide population screening for CRC has been implemented in the Netherlands during the 2014–2019 period for the population aged 55–75 years, [6,19] which caused a clear pattern: incidences increased until the years in which the screening was implemented, and decreased thereafter. The incidence of localised rectal cancer behaved differently, however. No statistically significant trend change was found between 2000 and 2018 (APC: −1.8; 95 % CI: −2.6, 4.6). Between 2018 and 2021, the incidence of localised rectal cancer decreased strongly, corresponding to the trends of other subgroups. An explanation for the diverging trend between 2000 and 2018 could lie in the implementation of routine preoperative magnetic resonance imaging (MRI) in the early 2000s [20] The proportion of clinically positive lymph nodes increased due to preoperative imaging with MRI, and consequentially clinical localised rectal cancer cases migrated to clinical regional rectal cancer cases [21]. Localised rectal cancer aside, the incidence rates in 2021 largely corresponded to those in 2000.

An increasing trend in local excision rates for stage I rectal cancer in the Netherlands has been described between 2013 and 2018 [22]. The present study showed that the increasing trend in local excision rate for localised rectal cancer was initiated in 2007 and has accelerated ever since to 34.9 % in 2021. The local excision rate for localised colon cancer has increased evidently since 2009 as well (5.6 % in 2009 to 13.6 % in 2021), but not as strongly as for localised rectal cancer. Nonetheless, technical advancements in the local treatment of T1 colon cancer (e.g., endoscopic full thickness resection and laparoscopic wedge resection) could boost local excision rates in the future. [23,24].

For localised rectal cancer, neoadjuvant radiotherapy followed by TME swiftly became uncommon after publication of the Dutch TME-trial in 2007 (2007–2021, 47.2–4.4 %) [25]. An increase in local excisions was also noted, accelerated by the implementation of the population screening between 2014 and 2019. Screening leads to a higher proportion of T1 rectal cancers, which are more suitable for local excision [6, 22]. A more subtle, but interesting increased use of the watch-and-wait approach for localised rectal cancer was identified since 2000. Since then, several randomised studies have shown organ preservation rates between 60 and 90 % for localised rectal cancers [26–28]. The acceleration of the trend between 2016 and 2021 (6.4–11.5 %) closely corresponds to the initiation of the STAR-TREC study in 2017 [29].

Treatment with neoadjuvant chemoradiation or short-course radiotherapy followed by TME became the standard treatment for regional rectal cancer between 2000 and 2010 [25,30]. Moreover, these neoadjuvant treatments can lead to complete responses which are suitable for a watch-and-wait approach [31]. The present results indicate that this approach has been adapted swiftly in clinical practice for regional rectal cancer patients (2013–2021, 7.0–23.5 %). Neoadjuvant chemotherapy is currently not administered frequently to regional rectal cancer patients (2021: 7.3 %).

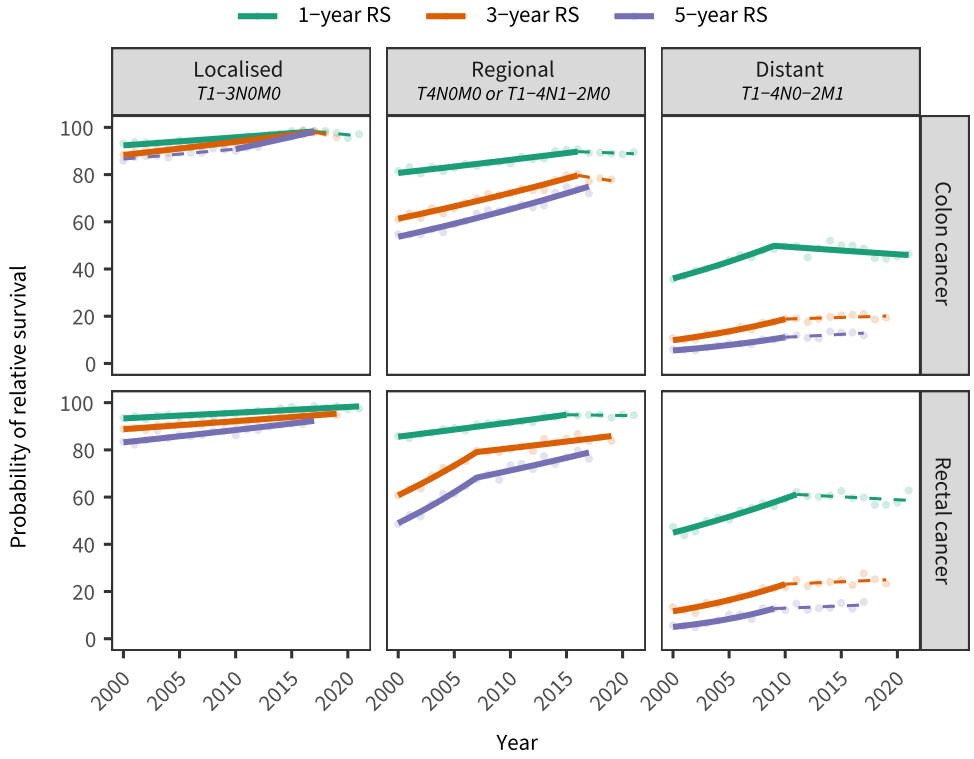

Fig. 4. Trends in one-, three- and five-year relative survival after diagnosis of colorectal cancer in the Netherlands between 2000 and 2021, stratified for localisation and disease extent. Dots represent the actual percentages per year. Solid lines represent the modelled trend changes which were statistically significant ($p < 0.05$). Dashed lines represented modelled trend changes which were statistically insignificant ($p \geq 0.05$). RS; relative survival.

Table 3
Trends in one-, three- and five-year relative survival after diagnosis of colorectal cancer in the Netherlands between 2000 and 2021, stratified for localisation and disease extent.

	Time period	RS estimate in % in first and last year of time period	APC (95 % CI)over time period
Colon cancer			
Localised			
1-year RS	2000-2017	93.2 to 98.4	0.4[c] (0.3, 0.7)
	2017-2021	98.4 to 97.1	-0.5 (−1.9, 0.2)
3-year RS	2000-2017	88.5 to 98.5	0.6[c] (0.5, 1.2)
	2017-2019	98.5 to 95.8	-1.0 (−2.2, 0.5)
5-year RS	2000-2010	85.9 to 90.0	0.5 (−0.2, 0.7)
	2010-2017	90.0 to 97.7	1.1[c] (0.8, 2.1)
Regional			
1-year RS	2000-2016	81.6 to 90.7	0.7[c] (0.5, 3.6)
	2016-2021	90.7 to 89.5	-0.2 (−2.9, 0.6)
3-year RS	2000-2016	61.0 to 80.3	1.6[c] (1.5, 2.1)
	2016-2019	80.3 to 77.9	-0.9 (−4.5, 1.1)
5-year RS	2000-2017	54.7 to 72.0	2.0[c] (1.7, 2.3)
Distant			
1-year RS	2000-2009	35.5 to 48.5	3.7[c] (2.8, 5.0)
	2009-2021	48.5 to 46.4	-0.7[c] (−1.4, −0.1)
3-year RS	2000-2010	10.7 to 18.9	6.7[c] (5.3, 9.2)
	2010-2019	18.9 to 19.4	0.7 (−2.1, 2.4)
5-year RS	2000-2010	6.0 to 11.2	7.3[c] (5.7, 14.4)
	2010-2017	11.2 to 11.9	2.1 (−7.6, 4.7)
Rectal cancer			
Localised			
1-year RS	2000-2021	93.5 to 97.5	0.3[c] (0.2, 0.3)
3-year RS	2000-2019	88.9 to 94.6	0.4[c] (0.3, 0.5)
5-year RS	2000-2017	83.4 to 95.2	0.6[c] (0.5, 0.8)
Regional			
1-year RS	2000-2015	85.8 to 95.1	0.7[c] (0.6, 0.8)
	2015-2021	95.1 to 94.7	-0.1 (−0.7, 0.3)
3-year RS	2000-2007	60.6 to 79.6	3.8[c] (3.1, 4.8)
	2007-2019	79.6 to 83.8	0.7[c] (0.3, 1.0)
5-year RS	2000-2007	48.6 to 67.6	4.9[c] (3.7, 7.3)
	2007-2017	67.6 to 76.3	1.5[c] (0.1, 2.2)
Distant			
1-year RS	2000-2011	47.4 to 62.1	2.8[c] (2.2, 3.9)
	2011-2021	62.1 to 62.8	-0.4 (−1.6, 0.4)
3-year RS	2000-2010	13.3 to 21.7	7.1[c] (5.3, 10.8)
	2010-2019	21.7 to 23.3	0.9 (−3.6, 2.9)
5-year RS	2000-2009	5.6 to 12.7	11.0[c] (7.5, 31.5)
	2009-2017	12.7 to 15.6	1.4 (−19.1, 5.5)

RS; relative survival. APC; average percentage of change (per year). CI; confidence interval. Localised; T1-3N0M0. Regional; T4N0M0 or T1-4N1-2M0. Distant; T1-4N0-2M1. Statistically significant trend changes were denoted with an asterisk.

[c] Time periods were defined by the joinpoint regression analysis.

For regional colon cancer patients, the administration of neoadjuvant chemotherapy has doubled between 2019 and 2021 (2.3–5.2 %) following a recommendation in the same year to consider neoadjuvant chemotherapy for cT4N0–2M0 colon cancer patients based on the FOxTROT study results from 2019 [32,33]. While the neoadjuvant approach is relatively novel, adjuvant chemotherapy has been recommended for regional colon cancer patients since the 1990s [34–36]. The present study has shown that a considerable proportion of patients with regional colon cancer were not treated with adjuvant chemotherapy, while this would have been recommended by the treatment guidelines. Regional disease was defined as pT4N0 of pT1–4N1–2 in the present study. Previous studies have shown that a high age is a strong predictor of non-administration of adjuvant chemotherapy in the Netherlands, [37,38] and these results were confirmed by the evident difference in median age between patients who were and were not treated with adjuvant chemotherapy. Notably, a slightly decreasing trend in the administration of adjuvant chemotherapy was identified between 2015 and 2021, and this rate could possibly decrease further in the foreseeable future due to promising results of circulating tumour DNA (ctDNA) guided administration of adjuvant chemotherapy [39,40].

In contrast to colon cancer, great international variation exists on the recommendations for adjuvant chemotherapy for regional rectal cancer, [41,42] but the guideline in the Netherlands does not recommend adjuvant chemotherapy nonetheless based on the results of two large trials [33]. The Dutch-Swedish PROCTOR-SCRIPT showed that there was no benefit of adjuvant fluoropyrimidine chemotherapy to neoadjuvant (chemo)radiation [43]. The British CHRONICLE trial was not able to show an advantage of the adjuvant CAPOX regimen (i.e. capecitabine and oxaliplatin chemotherapy). While these studies were still ongoing, the administration of adjuvant chemotherapy for regional rectal cancer in the Netherlands fell from 27.5 % in 2006 to 2.6 % in 2021.

The long-awaited results from the CAIRO4 study presented at ASCO 2023 showed that upfront primary tumour resection did not provide a benefit in patients with distant disease in comparison with immediate initiation of systemic chemotherapy [44]. In 2021, 67.9 % and 78.2 % of distant colon and rectal cancer patients were treated without a surgical resection, respectively. The increased effectiveness of systemic therapies has likely contributed to the downfall of primary tumour resection. The present study showed that the use of targeted therapies as first-line treatment (e.g., bevacizumab) rapidly increased since their introduction, before stabilising in 2008.

The five-year RS estimates of distant colon and rectal cancer patients increased until 2010 and 2009, whereas the five-year RS of localised and regional colon and rectal cancer patients increased until the end of the study period. The timelines of previous population-based studies in the Netherlands did not reach far enough to identify the abovementioned stagnation for distant colon and rectal cancer [9,45]. The explanation for this stagnation probably lies in the decreasing trends of anti-cancer treatment for distant patients (colon: 2010–2021: 80.3–67.2 %, $p < 0.001$; rectum: 2011–2021: 86.0–77.0 %, $p < 0.001$). While there are continuous improvements in treatment of patients with distant disease, the present study showed that less than before patients with distant disease have been treated with anti-cancer treatment. Only

approximately one in two patients with unresected distant disease was treated with systemic therapy in 2021 (colon cancer: 49.0 %; rectal cancer: 56.4 %). On a population level therefore, the added RS benefit for patients who were treated with novel anti-cancer treatments, is likely cancelled out by the increased proportion of patients who have not been treated with anti-cancer treatment, and consequentially have detrimental RS. The five-year RS rates for distant patients in 2017 were 11.9 % (colon) and 15.6 % (rectum), which can be considered moderate compared to the 8.0–17.3 % (colon) and 8.9–22.9 % (rectum) ranges of five-year net survival rates found in the SURVMARK-2 project in seven high-income countries between 2010 and 2014 [46]. Age at diagnosis might play an important role – whether or not as a proxy for other factors – in administration of anti-cancer treatment, as the median age of patients with unresected distant disease who were treated with systemic treatment was approximately ten years younger than in patients who were not treated with systemic treatment. Future studies should aim to unravel the exact trends of the treatment of patients with distant disease in the Netherlands, because the extent of the results of the present study did not allow for an in-detail assessment.

The present study is unique in its stratification of disease extent to localised (T1–3N0M0), regional (T4N0M0/T1–4N1–2M0) and distant (T1–4N0–2M0), enhancing the interpretation of the current trends in neoadjuvant and adjuvant treatment of colon and rectal cancer. The high-quality registration of the NCR enabled this stratification due to its limited missingness in staging and treatment variables. However, the chosen stratification could also be seen as a limitation of this study, as it restricts the comparability with other population-based studies which used different stratifications (e.g., stage I, II, III colon cancer or early-stage, intermediate, locally advanced rectal cancer). Another limitation could be the limited amount of detail in the results. For example, no differentiation was made between different surgical techniques or types of radiation and systemic treatments. The extent of the results did not allow for such detail. Nonetheless, these data are registered in the NCR, and could therefore be subject to future studies. Lastly, it should be considered that several factors which are known to have an important impact on the treatment for CRC (e.g., comorbidities, performance status, patient preference) were not registered in detail, and therefore could not be presented or adjusted for.

In conclusion, there were major changes in the incidence and treatment of CRC in the Netherlands between 2000 and 2021, which were accompanied by a continuous improvement in five-year relative survival for patients with localised and regional colon and rectal cancer. Since approximately 2010, the previously increasing five-year relative survival rates for distant colon and rectal cancer patients have stagnated.

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CRediT authorship contribution statement

Pauline A.J. Vissers: Conceptualization, Methodology, Validation, Writing – review & editing. **Johannes H.W. de Wilt:** Conceptualization, Methodology, Project administration, Supervision, Validation, Writing – review & editing. **Felice N. van Erning:** Conceptualization, Methodology, Validation, Writing – review & editing. **Leon M.G. Moons:** Validation, Writing – review & editing. **Henk M.W. Verheul:** Validation, Writing – review & editing. **Maaike Berbee:** Validation, Writing – review & editing. **Femke P.C. Sijtsma:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Writing – review & editing. **Marloes A.G. Elferink:** Conceptualization, Methodology, Validation, Writing – review & editing. **Hidde Swartjes:** Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

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.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.114104.

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