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Changes in rectal cancer treatment after the introduction of a national screening program; Increasing use of less invasive strategies within a national cohort

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ABSTRACT

Aim: Organ preserving treatment strategies and the introduction of a colorectal cancer-screening program have likely influenced the resection rates of rectal cancer. The aim of this study is to assess the influence of these developments on rectal cancer treatment and resection rates in the Netherlands.
Methods: Patients diagnosed with non-metastatic rectal cancer between 2013 and 2018, were selected from the Netherlands Cancer Registry. The distribution of surgical and neo-adjuvant treatment and resection rates were analyzed and compared over time.
Results: Between 2013 and 2018 22640 patients were diagnosed with non-metastatic rectal cancer**.** The incidence of early stage (cT1) disease increased from 141 (4%) in 2013 to 448 (12%) in 2018. The use of neoadjuvant radiotherapy and chemo-radiotherapy dropped from 39% to 21% and 34%–25%, respectively. A decrease in surgical resection rates (including TEM) was observed from 85% to 73%. The proportion of patients who underwent endoscopic resections increased from 3% to 10%. The decrease in surgical resection rates was larger in patients treated with neo-adjuvant chemo-radiotherapy.
Conclusion: An increase in stage I disease is noted after the introduction of the screening program. Surgical resection rates for rectal cancer have fallen over time. Endoscopic resections due to more early-stage disease probably accounts for a large part of this decline. Furthermore, a watch and wait approach after neo-adjuvant chemo-radiotherapy may play an important role as well.

1. Introduction

For the past 25 years, the incidence of colorectal cancer has increased [1]. For colon cancer, little has changed in the surgical and non-surgical treatment guidelines over the last decade. In contrast, treatment of rectal cancer has shifted towards less invasive and more organ preserving treatment strategies. While total mesorectal excision (TME surgery) remains the gold standard for rectal cancer, it is associated with significant morbidity. Furthermore a substantial impact on functionality and quality of life is observed after radical rectal resection [2]. Considering this, organ preserving surgery has emerged for early-stage rectal cancer and endoscopic resection options like endoscopic submucosal dissection (ESD) and endoscopic full thickness resection (EFTR) are increasing [3–6]. A colorectal cancer screening program was gradually launched in 2014 in the Netherlands [7]. This may probably result in more early stage rectal cancers as reported by previous studies from other countries.

The use of neoadjuvant radiotherapy for low-risk rectal cancer has greatly decreased, without changes in local recurrence rates [8]. In addition, watchful waiting protocols are gaining interest. Approximately 15–20% of patients with rectal cancer have complete pathological response after neoadjuvant therapy; in these patients, TME surgery can possibly be avoided with a proper selection strategy [9–11]. A watchful waiting strategy could be of

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special interest for elderly patients who are at greater risk of postoperative morbidity [12].

The aim of this study was to analyze the changes in rectal cancer treatment in the Netherlands on a population level after the introduction of a national screening program.

2. Methods

Data of patients diagnosed with non-metastatic rectal and rectosigmoid cancer between 2013 and 2018 were obtained from the Netherlands Cancer registry (NCR). This national registry uses the national pathology network (PALGA) and the national hospital discharge register as main sources. Data is collected by trained data clerks form medical records abiding by a data registration manual. The completeness of the cancer diagnoses is over 95%. Synchronous metastases were defined as metastases detected before the start of initial treatment or during surgical exploration. Tumor site and morphology were registered according to the ICD-O (C19.9 rectosigmoid and C20.9 rectum) [13] Tumor stages were recorded according to the Tumour, Node, and Metastasis (TNM) Classification of Malignant Tumors by the Union for International Cancer Control using the 7th edition for those diagnosed in 2013–2016, and the 8th edition for 2017–2018 [14,15]. The differences between the 7th and 8th edition for rectal cancer were considered negligible for this study. This study was approved by the Privacy Review Board of the Netherlands Cancer Registry and did not require approval from an ethics committee in the Netherlands.

2.1. Variables

Variables included age, gender, and treatment and socio-economic stage was defined based on the area code of patient residence using data from the Netherlands Institute for Social Research. The definition of surgical resection included both TME surgery as well as organ preserving surgical procedures like Transanal endoscopic microsurgery (TEM) and transanal minimally invasive surgery (TAMIS). Local resection included all types of endoscopic resection without subsequent surgical resection (e.g. ESD, EFTR). Organ preserving resection was defined as an endoscopic local resection without subsequent surgical resection or an organ sparing surgical resection (eg TEM or TAMIS). Completion TME was defined as an additional surgical resection after endoscopic local resection, due to the discretion of the treating physician.

2.2. Statistical analysis

All categorical variables were displayed as numbers with percentages and differences were tested using chi-square tests. Continuous variables were shown as medians with inter-quartile-range (IQR) and differences were tested using Kruskal-Wallis tests. All statistical analyses were performed using SPSS (version 26, IBM, Chicago, IL) and figures were generated using GraphPad Prism.

3. Results

3.1. Study cohort

In the study period, 22640 patients were diagnosed with rectal cancer. After 3199 rectal cancer diagnoses in 2013, the number of diagnoses increased up to 4055 rectal cancer diagnosis in 2015 and decreased to 3812 diagnoses in 2018.

The patient characteristics for each year are shown in Table 1. Median age was 69 in most years. The proportion of patients within the 55–75 year old age group increased from 59% (1897/3199) in 2013 to 66% (2496/3812) in 2018 ($P < 0.001$).

Over the study years, there was a change in the distribution of the tumor's clinical T-stage. The proportion of cT1 tumors increased from 4% (141/3199) in 2013 to 12% (N = 448/3812) in 2018 ($p < 0.001$). There was also a change in cN stages, with an increase in cN0 tumors. The proportion of cN0 tumors was 42% (1345/3199) in 2013, compared to 55% (2107/3812) in 2018 ($p < 0.001$).

The use of radiotherapy decreased during the study period from 39% (1256/3199) in 2013 to 21% (784/3812) in 2018 ($P < 0.001$) as shown in Fig. 1A. The use of chemo-radiotherapy decreased from 34% (1087/3199) in 2013 to 25% (970/3812) in 2018 ($P < 0.001$). While the proportion of patients who underwent surgical resection decreased from 85%% (2717/3199) in 2013 to 73% (2792/3812) in 2018 ($P < 0.001$) (Fig. 2B), the proportion of patients who underwent local resection increased from 3% (109/3199) in 2013 to 10% (398/3812) in 2018 ($P < 0.001$). When combined with surgical local excision, the overall rate of patients managed by local resection has doubled from 9% (276/3199) in 2013 to 18% (694/3812) in 2018 ($P < 0.001$). In patients 75 years and older the surgical resection rate dropped from 72% to 65% ($p < 0.001$).

3.1.1. Stage I disease

The number of patients with clinical stage I disease almost doubled during the study period from 580 in 2013 to 1052 in 2018 ($p < 0.001$). In these patients, the use of radiotherapy has decreased rapidly after 2013 as shown in Fig. 2A. In 2013, 47% of these patients underwent radiotherapy, in 2014 this proportion was 15%, and in each following year 4% of patients underwent radiotherapy ($p < 0.001$). Surgical resection of these tumors decreased from 86% (500/580) in 2013 to 73% (766/1052) in 2018 ($p < 0.001$). This coincided with an increase in local resections from 5% (31/580) in 2013 to 22% (227/1052) in 2018 ($p < 0.001$).

3.1.2. Stage II disease

The number of patients diagnosed with stage II rectal cancer was stable over the study period ($P = 0.084$). The use of chemo-radiation decreased from 28% (174/623) in 2013 to 22% (180/806) in 2018 ($p < 0.026$). Comparable to stage I disease, use of radiotherapy decreased in stage II disease from 53% (327/623) to 22% (173/806) in 2018 ($p < 0.001$). The number of patients who underwent local resection only was negligible, but the surgical resection rate declined from 86% (537/623) in 2013 to 80% (645/806) in 2018. The lower resection rates were most evident in the patient who underwent radiotherapy or chemo-radiotherapy, in whom the resection rate decreased from 89% (444/501) to 66% (232/353) ($p < 0.001$).

3.1.3. Stage III disease

The proportion of patients with stage III disease decreased from 50% in 2013 to 40% in 2018 ($p < 0.001$). In this patient group, the use of radiotherapy and chemo-radiation did not change over the years. The resection rate did change. Local resections were negligible, but the surgical resection rate decreased from 90% (1456/1613) in 2013 to 77% (1169/1518) ($p < 0.001$) in 2018. Resection rate in patients without (chemo-)radiotherapy did not change, but the resection rate in patients who underwent chemo-radiotherapy or radiotherapy decreased from 92% (1326/1444) to 78% (1013/1296) in 2018 ($p < 0.001$).

3.2. Trends in surgical resection

Out of all 17958 surgical resections 11769 (52%) were low anterior resections, the proportion of low anterior resections remained stable over time. The proportion of minimally invasive

Table 1
Patients and disease characteristics based on year of diagnosis.

	2013 (*n* = 3199)	2014 (*n* = 3863)	2015 (*n* = 4055)	2016 (*n* = 3829)	2017 (*n* = 3882)	2018 (*n* = 3812)	P value
Age, median (IQR)	69 (61–77)	69 (63–76)	67 (62–75)	68 (61–75)	69 (61–75)	69 (59–75)	<0.001
55–75 year old	1897 (59)	2444 (63)	5752 (68)	2652 (69)	2632 (68)	2496 (66)	<0.001
Male sex, n (%)	1977 (62)	2433 (63)	2593 (64)	2450 (64)	2436 (63)	2374 (63)	0.298
Socioeconomic state, (%)							
Low	950 (30)	1128 (29)	1216 (30)	1212 (32)	1222 (32)	1212 (32)	0.140
Middle	1324 (41)	1650 (43)	1709 (42)	1599 (42)	1621 (42)	1582 (42)	
High	925 (29)	1085 (28)	1130 (28)	1018 (27)	1039 (27)	1018 (27)	
cT category, n (%)							
1	141 (4)	258 (7)	363 (9)	409 (11)	435 (11)	448 (12)	<0.001
2	711 (22)	877 (23)	936 (23)	851 (22)	856 (22)	792 (21)	
3	1644 (51)	1857 (48)	1938 (48)	1840 (48)	1767 (46)	1802 (47)	
4	271 (9)	317 (8)	344 (9)	312 (8)	341 (9)	311 (8)	
X	412 (13)	519 (13)	455 (11)	406 (11)	472 (12)	446 (12)	
cN category, n (%)							
0	1345 (42)	1783 (46)	1921 (47)	1946 (51)	2077 (54)	2107 (55)	<0.001
1	952 (30)	997 (26)	1069 (26)	988 (26)	961 (25)	944 (25)	
2	661 (21)	775 (20)	826 (20)	714 (19)	641 (17)	574 (15)	
X	241 (8)	308 (8)	239 (6)	181 (5)	203 (5)	187 (5)	
Clinical stage, n (%)							
0	16 (1)	28 (1)	14 (0)	8 (0)	5 (0)	11 (0)	<0.001
I	580 (18)	867 (22)	1037 (26)	1026 (27)	1084 (28)	1052 (28)	
II	623 (20)	723 (19)	676 (17)	714 (19)	742 (19)	806 (21)	
III	1613 (50)	1772 (46)	1895 (47)	1702 (45)	1602 (41)	1518 (40)	
X	367 (12)	473 (12)	433 (11)	379 (10)	449 (12)	425 (11)	
Radiotherapy, n (%)	1256 (39)	1041 (27)	1004 (25)	835 (22)	811 (21)	784 (21)	<0.001
Chemoradiotherapy, n (%)	1087 (34)	1109 (29)	1134 (28)	1117 (29)	1014 (26)	970 (25)	<0.001
Surgical resection, n (%)	2717 (85)	3203 (83)	3267 (81)	3002 (78)	2977 (77)	2792 (73)	<0.001
Resection type							
TEM	167 (6)	259 (8)	293 (9)	309 (10)	326 (11)	296 (11)	<0.001
Low-anterior	1696 (62)	2035 (64)	2137 (65)	2007 (67)	2004 (67)	1890 (68)	
Abdominoperineal	810 (30)	862 (27)	809 (25)	660 (22)	622 (21)	579 (21)	
Other	44 (2)	47 (1)	28 (1)	26 (1)	25 (1)	27 (1)	
Completion TME	39 (1)	63 (2)	71 (2)	68 (2)	82 (2)	127 (3)	<0.001
Endoscopic local resection only, n (%)	109 (3)	231 (6)	291 (7)	298 (8)	356 (9)	398 (10)	<0.001
Endoscopic or surgical local resection only, n (%)	276 (9)	490 (13)	584 (14)	607 (16)	682 (18)	694 (18)	<0.001

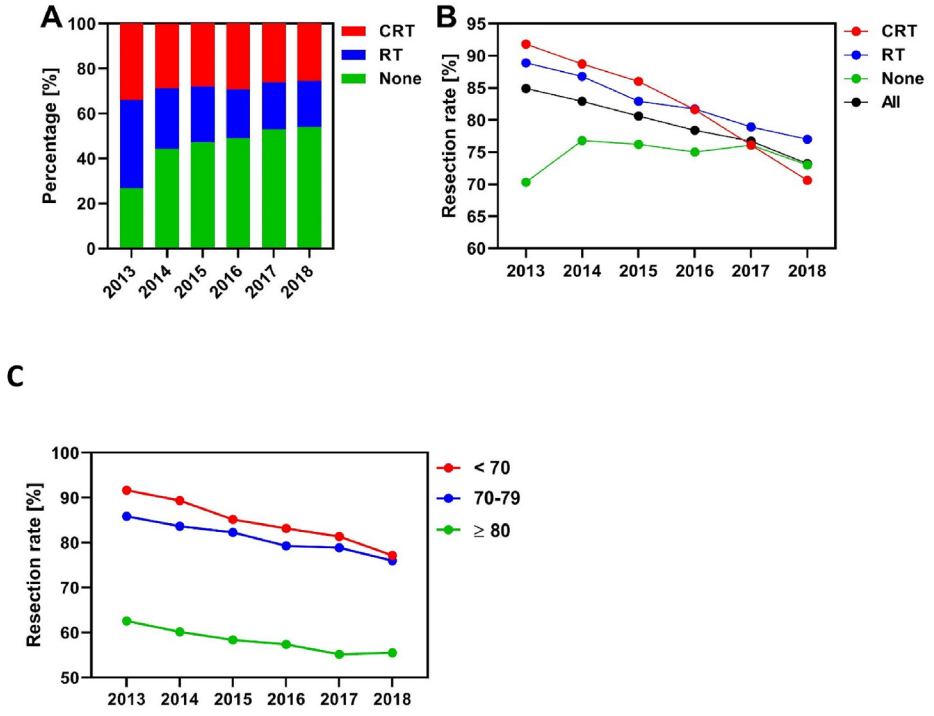

Fig. 1. (A) Proportion of patients treated with neoadjuvant therapy according to year of diagnosis (B) Trends in resection rates over the years, according to neoadjuvant treatment (C) Trends in resection rates over the years, according to age. Abbreviations: CRT: chemoradiotherapy, RT: short-course radiotherapy.

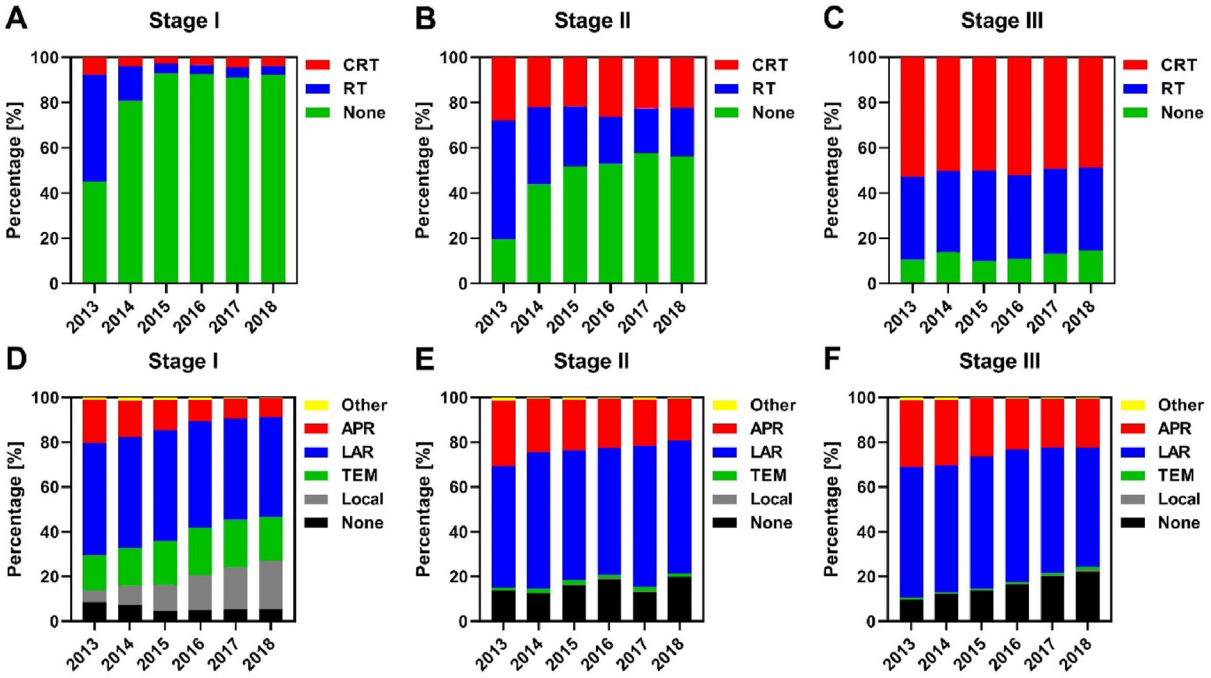

Fig. 2. (A) Distribution of patients treated with neoadjuvant therapy with stage 1 disease treated (B) Distribution of patients with stage 2 disease treated with neoadjant therapy. (C) Distribution of patients treated with neoadjuvant therapy with stage 3 disease (D) Distribution of resection type in patients with stage 1 disease (E) Distribution of resection type in patients with stage 2 disease (F) Distribution of resection type in patients with stage 3 disease. Abbreviations: CRT: chemoradiotherapy, RT: short-course radiotherapy, APR: abdominoperineal resection, LAR: Low-anterior resection, TEM: transanal endoscopic microsurgery, Local: endscopic local resection.

resections increased from 72% (1224/1696) in 2013 to 93% (1766/1890) in 2018 ($p < 0.001$), while the conversion rate decreased from 16% (192/1224) in 2013 to 7% (125/1766) in 2018 ($p < 0.001$). Over time less abdominoperineal resections were performed, from 810 in 2013 to 579 in 2018.

4. Discussion

In this nationwide cohort of patients with non-metastatic rectal cancer from 2013 to 2018, a continuing decrease in surgical resection rates was observed. The distribution of clinical tumor stage changed over time, in favor of those with early-stage disease. Furthermore, an increase in organ preserving and minimally invasive procedures was observed.

The incidence of rectal cancer had increased for the past 25 years until the start of the colorectal cancer screening program that was initiated in 2014 in the Netherlands [1]. In this cohort, the numbers seem to stabilize after an increase in the first year of the screening program. This increase in incidence is also observed in other European countries as demonstrated in a recent study and is followed by a decrease in age standardized incidence [14]. The initial increase seems to be to be mainly attributable to detection of more asymptomatic early-stage disease [15,16]. This can also be observed in the present cohort where the proportion of patients with clinical stage I disease has doubled over time. Early-stage rectal cancer can often be treated by endoscopic resection only, which can, in part, explain the reduction in the resection rates [17].

The proportion of organ preserving procedures in stage 1 disease increased over time. Local excision is an attractive alternative to TME due to a substantially lower risk of morbidity [18]. The risk of local recurrence can be significant especially in those with high risk T1 tumors or T2 tumors [19,20]. In another Dutch cohort more than two-thirds of patients who underwent local excision for high risk T1 tumors did not undergo the indicated completion TME [21]. Future studies should determine whether an increased quality of life associated with rectal sparing treatment outweighs the oncological risks. In this study the histopathological risk factors to determine the risk in T1 tumors were not available.

Several randomized trials have demonstrated that also in patients with T2-3 rectal cancer, organ sparing procedures after successful neo-adjuvant chemo-radiotherapy show similar oncological outcomes compared to radical surgery [22,23]. The stable proportion of local surgery in stage 2 disease within the present cohort suggests that these treatment strategies are not yet implemented on a large scale for these patients in the Netherlands. This might change in the near future, especially since long term results of these studies have recently been published [22,23]. Furthermore, in stage 1 rectal cancer high levels of organ preservation can be achieved by short course radiotherapy combined with local excision [24]. The results of ongoing randomized trials will demonstrate whether this could also be safely applied in patients with larger rectal cancers [25].

There was a decrease in resection rates in stage III disease. The majority of these “unresected” patients underwent neo-adjuvant therapy and indeed the decrease in resection rate was more pronounced in patients treated with neo-adjuvant chemo-radiotherapy. Although the use of a watchful waiting strategy is not registered as a variable in the Netherlands Cancer registry for our total study population, it is very likely that this is the primary reason for the reduced resection rate in stage III disease.

A lower resection rate was found in patients older than 75 years in the present cohort. There was a similar decrease in number of resections compared to the rest of the study population. A recent report with numbers from the NHS et al. reported resection rates as low as 30% in patients above 80 years old [5]. Older patients have a higher postoperative mortality and morbidity rate after major rectal resection. However, the 1-year mortality rate seems to decrease over time and it should be noted that cancer specific survival does not seem to be related so much to age [26,27] Despite improvements in postoperative outcomes for older patients, the

possibility to avoid a major surgical resection remains of high interest in this group of patients. A recent report shows excellent outcomes in patients of 75 years and older who were followed in a watch and wait protocol [28].

The use of neo-adjuvant radiotherapy decreased over time, especially in early-stage disease. After the publication of the Dutch TME trial, neoadjuvant radiotherapy was recommended to reduce local recurrences by the Dutch guideline for all resectable rectal cancers except for T1N0 tumors [29]. A more recent report demonstrated low risk rectal cancers can be identified with use of high-quality MRI and safely treated without neoadjuvant treatment [30]. Furthermore, the use of neoadjuvant radiotherapy in the Netherlands was much higher compared to other countries with a similar local recurrence rate [31]. As a result, the guideline was revised in 2014 recommending a more restrictive use of radiotherapy. This probably explains the clear decrease in the use of neo-adjuvant radiotherapy after 2014 and is in line with a previous report [32].

Laparoscopic resection has become the standard of care for rectal cancer surgery. In the present study, the rate of minimally invasive surgery increased to 93% with a decrease in conversation rates. Several studies have shown a faster time to recovery after laparoscopic rectal cancer surgery with similar oncological outcomes [33].

The present study has some limitations mostly related to the retrospective study design. No information was available for the total study population regarding the exact reason why patients did not undergo surgery, such as a watchful waiting policy. The strength of this nationwide study is the large number of patients and the use of real-world data by including all patients diagnosed with rectal cancer in the Netherlands over a six-year period.

In conclusion, there seems to be a trend toward less invasive treatment strategies for rectal cancer over the study period. After the introduction of the screenings program an increase in Stage I disease is noted. Surgical resection rates for rectal cancer have fallen over time. Endoscopic resections due to more early-stage disease probably accounts for a large part of this decline. Furthermore, a watch and wait approach after neo-adjuvant chemo-radiotherapy may play an important role as well.

CRediT authorship contribution statement

L.J.X. Giesen: Conceptualization, Visualization, Writing – original draft, Writing – review & editing, Project administration, Investigation. **P.B. Olthof:** Methodology, Validation, Formal analysis, Writing – review & editing, Writing – original draft, Investigation, Data curation. **M.A.G. Elferink:** Writing – review & editing, Validation. **H.L. van Westreenen:** Writing – review & editing, Supervision. **G.L. Beets:** Writing – review & editing, Supervision. **C. Verhoef:** Writing – review & editing, Supervision, Resources. **J.W.T. Dekker:** Conceptualization, Writing – review & editing, Supervision, Project administration.

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