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Improved survival of patients with rectal cancer since 1980: a population-based study

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Abstract

The treatment of rectal cancer has changed over the last two decades as far as surgical techniques and radiotherapy are concerned. We studied the changes in patterns of care for patients with rectal cancer and the effect on prognosis. All patients with cancer of the rectum or rectosigmoid in South-east Netherlands, diagnosed in the period of 1980–2000, were included in our analyses ($n = 3635$). The use of surgery as the only treatment decreased from 62% in the period of 1980–1989 to 42% in the period of 1995–2000, whereas the combination of surgery and radiotherapy increased from 26 to 40%. The use of postoperative radiotherapy decreased from 25 to 4%, while preoperative radiotherapy increased from 1 to 35%. Patients aged 75 years or older were less likely to receive radiotherapy. After adjustment for age, gender, tumour stage and tumour site, significant improvements in the relative risk of death were observed between the periods of 1995–2000 and 1980–1989 for patients under 60 years of age (Relative Risk (RR) = 0.45; 95% Confidence Interval (CI) = 0.35–0.58) and those 60–74 years old (RR = 0.62; 95% CI 0.53–0.72). No improvement in the risk of death was found for patients aged 75 years and over. No improvements in the distribution of tumour stage were observed, making it very likely that the continuing increase in population-based survival among patients aged <75 years results from the shift from postoperative to preoperative radiotherapy, the development of the total mesorectal excision technique and the related tendency to subspecialisation of surgeons in colorectal cancer surgery.

Keywords: Rectal neoplasms; Patterns of care; Survival; Trend

1. Introduction

The treatment of patients with mobile cancer of the rectum and rectosigmoid has changed over the last few decades. In South-east Netherlands, close co-operation between oncological specialists developed in the 1980s and early 1990s. Retrospective analyses of population-based data were performed to evaluate the outcome of rectal cancer treatment [1–4]. In a study of 178 patients without residual disease or distant metastases, receiving adjuvant postoperative radiotherapy during the period of 1974–1989, the 5-year overall survival and disease-free survival rates were 42 and 37%, respectively [3]. The respective rates for Dukes' stage B2 (pT3, N0, M0) were 59 and 53%, and 25% for both for stage C2 (pT1-4, N+, M0). Five-year local relapse rates were 27% for Dukes' stage B2 and 40% for stage C2. In another study, including 232 patients from five community hospitals and treated surgically with curative intent between 1981 and 1986, adjuvant postoperative radiotherapy was given to 27% of all Dukes' stage B2 patients and to 50% of all stage C patients [4]. The surgical technique

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was not standardised and referral for adjuvant postoperative radiotherapy was at the surgeon's discretion. The 5-year survival rate was 58% and the local recurrence rate of 18% did not seem to be affected by application of postoperative radiotherapy. Furthermore, no significant difference was found between the participating hospitals, each of them with a surgical staff of 3–6 surgeons, of whom some had only just started to specialise in colorectal cancer surgery.

On the basis of our regional experiences and the results from the literature regarding the possibilities of pre-operative radiotherapy [5–7] and total mesorectal excision (TME) [8,9], steps were taken to improve locoregional control in patients with mobile rectal cancer. A new regional treatment protocol was developed, including preoperative radiotherapy for mobile rectal cancer and steps were taken to stimulate the use of total mesorectal excision (TME). Furthermore, intra-operative electron beam radiation therapy was developed for locally advanced and locally recurrent rectal cancer [10]. In view of these changes in the treatment of rectal cancer, we decided to determine their effect on the prognosis for patients with rectal cancer by performing a detailed analysis of 3635 patients with invasive rectal cancer diagnosed and treated in South-east Netherlands since 1980.

2. Patients and methods

2.1. Patients

Data were provided by the population-based Eindhoven Cancer Registry, which covers a well-defined area with approximately 900 000 inhabitants in South-east Netherlands. It has been recognised since 1978 by the International Association of Cancer Registries [11]. Registration is based on notification of newly-diagnosed cases by the three departments of pathology and the radiotherapy department and data were obtained from medical records in the eight community hospitals in the region and from specialised departments and hospitals outside the region. The distance to a hospital in most cases was less than 15 miles. Data are collected during regular visits to these institutions, generally within 6 months of diagnosis. A total of 3635 incident cases of invasive rectal cancer had been recorded in the period of 1980–2000 (International Classification of Diseases (ICD)-9 154). Of these patients, 2708 had a tumour in the rectum (154.1) and 927 in the rectosigmoid (154.0) (Table 1). Cancers of the anal canal (ICD-9 154.2; $n=24$) or the anus (ICD-9 154.3; $n=24$) as well as tumours overlapping the rectum and anus (ICD-9 154.8; $n=28$) were not included.

Table 1
Characteristics of patients with rectal cancer in South-east Netherlands, diagnosed in the period 1980–2000, according to age group ($n=3635$)

Characteristic	<60 years N (%)	60–74 years N (%)	75+ years N (%)	Total N (%)
Period of diagnosis				
1980–1989	383 (40)	646 (38)	388 (40)	1417 (39)
1990–1994	214 (22)	454 (27)	234 (24)	902 (25)
1995–2000	358 (37)	610 (36)	348 (36)	1316 (36)
Gender (one trans-sexual)				
Male	560 (59)	1062 (62)	506 (52)	2128 (59)
Female	395 (41)	648 (38)	463 (48)	1506 (41)
Stage (TNM)				
I	281 (29)	503 (29)	253 (26)	1037 (29)
II	222 (23)	451 (26)	253 (26)	926 (25)
III	259 (27)	372 (22)	191 (20)	822 (23)
IV	145 (15)	281 (16)	127 (13)	553 (15)
X	48 (5)	103 (6)	146 (15)	297 (8)
Subsite				
Rectosigmoid	218 (23)	437 (26)	272 (28)	927 (26)
Rectum	737 (77)	1273 (74)	698 (72)	2708 (74)
Primary treatment				
Surgery only	420 (44)	900 (53)	607 (63)	1927 (53)
Surgery + preoperative radiotherapy	161 (17)	269 (16)	86 (9)	516 (14)
Surgery + postoperative radiotherapy	227 (24)	311 (18)	98 (10)	636 (17)
Surgery + systemic treatment	82 (9)	79 (5)	5 (1)	166 (5)
Other/missing	37 (4)	84 (5)	74 (8)	195 (5)
None	28 (3)	67 (4)	100 (10)	195 (5)

TNM, tumor-node-metastases.

Stage at diagnosis was based on the surgical and pathological report, supplemented by information from the clinical examination, using the tumour node metastases (TNM) classification [12].

Traditionally, patients with mobile rectal cancer underwent either surgery alone or surgery with adjuvant postoperative radiotherapy for the group with Dukes' stage B2 (pT3, N0, M0) or C (pT1-4, N+, M0) disease. In November 1994, it was decided to perform preoperative instead of postoperative radiotherapy, as in the Swedish protocol: 5×5 Gy within 1 week, followed by surgery within 1 week of completion of radiotherapy. In 1996, a trial was started in The Netherlands by the Dutch Colorectal Cancer Study Group, comparing preoperative radiotherapy (5×5 Gy within 1 week) followed by TME within 10 days of the first radiation fraction versus TME surgery alone (i.e. the TME trial) [13]. Patients with mobile rectal cancer who were not included in this trial continued to receive 5×5 Gy preoperatively as standard treatment. During the study period, adjuvant chemotherapy was not recommended for patients with rectal cancer.

Patient and tumour characteristics and information on treatment, according to age group as well as for the total group, are shown in Table 1.

2.2. Statistical methods

The period of study ranged from 1980 through to 2000 and was divided into three periods: 1980–1989, 1990–1994 and 1995–2000. Primary treatment was analysed according to tumour stage and age group (<60 years, 60–74 years and 75+ years). The Chi-square test was used to detect differences in stage distribution and treatment between age groups and between subsequent periods.

The active follow-up of patients consisted of systematic checks on their vital status via hospitals, municipal population registries and the death registry of the Dutch Central Bureau of Genealogy. Follow-up was completed until 1 April 2002. Patients with incomplete follow-up were censored at the date of last follow-up. Survival time was defined as the period between the date of diagnosis and the date of death or last follow-up. Reliable information on the cause of death is often lacking in population-based studies. Therefore, a correction for mortality from competing causes of death was made, by computing the relative survival according to the Hakulinen approach, using the Finnish Cancer Registry survival software [14]. Relative survival is defined as the probability of a cancer patient surviving a defined short period divided by the probability that an age- and gender-matched individual will survive the same time period [15,16]. The latter figures were calculated from life-tables (supplied by Statistics Netherlands) compiled according to gender and year of diagnosis for the population of South-east Netherlands.

To compare the prognosis for patients from the three different periods (i.e. 1980–1989, 1990–1994 and 1995–2000), the Cox proportional hazards model was used to adjust for the potential confounding effect of the following factors: age at diagnosis (per year increase), gender (female versus male), subsite (rectosigmoid versus rectum) and stage of disease (II versus I, III versus I, IV versus I, and unknown versus I) [17].

3. Results

3.1. Stage distribution and patterns of care

No major shifts in the distribution of tumour stage occurred between 1980 and 2000, also when analysed for each age group separately (data not shown). The proportion of patients with positive lymph nodes remained stable: 73% in the period 1980–1989 and 71% in the following two periods. However, among the patients with positive lymph nodes, the proportion with more than three positive lymph nodes increased from 5.5% (21/383) in the period 1980–1989 to 30% (95/320) in the period 1995–2000.

The use of surgery as the sole treatment for rectal cancer decreased from 62 to 42% ($P<0.0001$) (Fig. 1), whereas an increase from 26 to 40% ($P<0.0001$) was found for the combination of surgery with radiotherapy. Patients of 75 years or older were less likely to receive radiotherapy (Table 1). The use of chemotherapy was restricted to patients with stage III or IV disease and increased from 0 to 9 to 10% and from 7 to

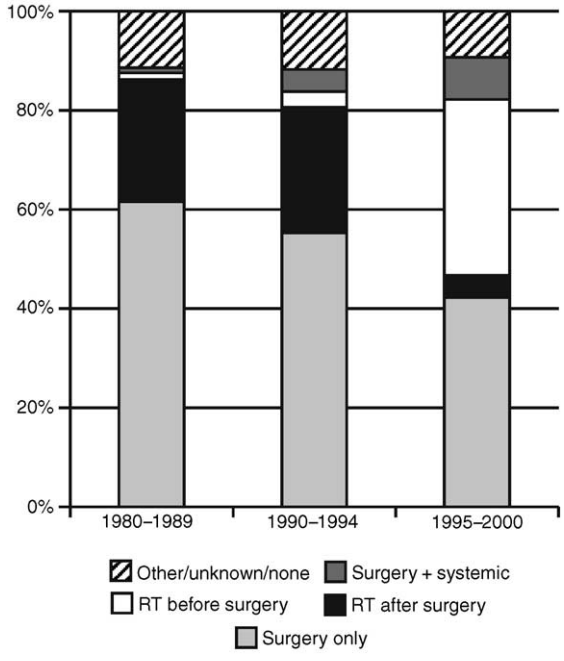

Fig. 1. Primary treatment of patients with rectal cancer, according to the period of diagnosis, 1980–2000. RT, radiotherapy.

Table 2
Relative survival rates (%) according to age group and period of diagnosis (95% confidence intervals (CI) between parentheses)

Age (years)	Period	No. at risk	Follow-up time			
			3 years (95% CI)	5 years (95% CI)	7 years (95% CI)	10 years (95% CI)
<60	1980–1989	383	60 (55–65)	51 (46–55)	49 (44–54)	46 (41–51)
	1990–1994	214	69 (62–74)	61 (54–68)	57 (50–63)	54 (46–61)
	1995–2000	358	77 (72–81)	69 (63–75)	64 (56–72)	–
60–74	1980–1989	646	56 (52–60)	49 (45–54)	44 (39–48)	40 (35–45)
	1990–1994	454	64 (59–69)	53 (48–59)	49 (44–55)	48 (42–55)
	1995–2000	610	71 (67–75)	63 (57–68)	61 (53–67)	–
75+	1980–1989	388	50 (44–57)	47 (39–54)	42 (33–51)	45 (33–59)
	1990–1994	234	58 (49–67)	54 (43–65)	52 (39–66)	37 (21–59)
	1995–2000	348	54 (47–61)	49 (40–60)	52 (36–70)	–
All	1980–1989	1417	56 (53–59)	49 (46–52)	45 (42–48)	42 (39–46)
	1990–1994	902	64 (60–67)	55 (51–59)	51 (47–56)	48 (43–53)
	1995–2000	1316	69 (65–72)	61 (57–65)	59 (54–64)	–

13 to 30%, respectively, in the three successive periods ($P<0.0001$). A significant decrease in the use of postoperative radiotherapy ($P<0.0001$) and a significant increase in pre-operative radiotherapy ($P<0.0001$) were observed in the period of 1995–2000. In the period of 1980–1989 25% of patients ($n=349$) received postoperative radiotherapy and only 1% ($n=20$) preoperative radiotherapy. For the period of 1990–1994, these percentages were 25% ($n=228$) and 3% ($n=29$), respectively. In the period of 1995–2000, the percentages were almost the opposite: 4% ($n=59$) and 35% ($n=467$), respectively. The switch from postoperative to preoperative radiotherapy occurred for all tumour stages and in all age groups.

3.2. Survival

Five-year relative survival for all patients with rectal cancer increased from 49% in the period of 1980–1989 to 55% in the period of 1990–1994, and 61% in the period of 1995–2000 (Table 2). Improvements in the relative survival rates were only seen for patients below 60 years of age and those 60–74 years of age, and not by patients aged 75 years or older (Table 2 and Fig. 2a and b).

The proportion of all patients dying within 1 year after the date of diagnosis decreased from 26.6% in the period of 1980–1989 to 23.0% in the period of 1990–1994 and 21.0% in the period of 1995–2000. One-year mortality decreased from 18.6 to 12.2% among patients younger than 60 years of age and from 25.5 to 17.2% among patients 60–74 years of age, but no decrease was observed among patients aged 75 years or older.

After adjustment for age, gender, subsite and tumour stage, significant improvements in the overall prognosis were found for patients below 60 years of age and those 60–74 years old (Table 3). In the group <60 years, the

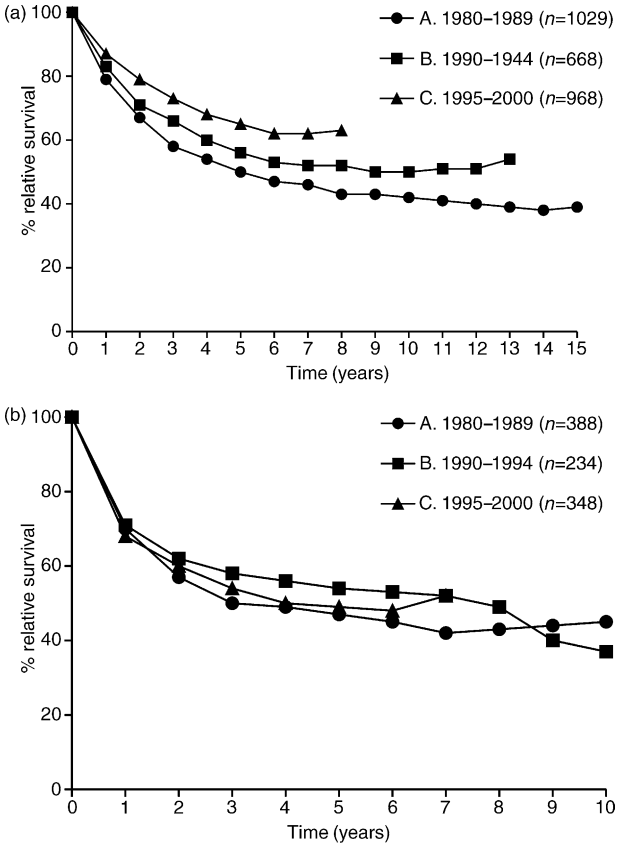

Fig. 2. (a) Relative survival of patients with rectal <75 years of age with rectal cancer, according to the period of diagnosis; (b) relative survival of patients 75 years of age or older with rectal cancer, according to the period of diagnosis.

relative risks (RR) of death for the 1990–1994 time period and the 1995–2000 time period were 0.72 (95% Confidence Interval (CI) (0.57–0.91) and 0.45 (95% CI 0.35–0.58) respectively, compared with the 1980–1989 time period. In the age group 60–74 years, patients

diagnosed in the period of 1990–1994, and 1995–2000 had a significantly lower relative risk of death compared with those diagnosed in the period of 1980–1989 (RR = 0.81; 95% CI 0.70–0.94) and (RR = 0.62; 95% CI 0.53–0.72). Among patients aged 60–74 years, women had a better prognosis than men (RR = 0.83; 95% CI 0.74–0.94). The relative risk of death for patients 75 years or older did not improve (Table 3).

4. Discussion

The data of a population-based cancer registry, covering eight general hospitals in South-east Netherlands, show that the management of and the prognosis for patients with rectal cancer have improved substantially since 1980, with the most striking changes taking place after 1994. The development of new regional guidelines and the participation in the TME trial of the Dutch Colorectal Cancer Study Group have brought quality of care to a higher level. These activities took place within the framework of a multidisciplinary study group, thus ensuring a broad basis for acceptance.

In South-east Netherlands, good access to sigmoidoscopy was established in the early 1980s. This may explain why the distribution of the stages of rectal cancer has barely changed between 1980 and 2000. According to a French study, the shift towards an earlier diagnosis of rectal cancer may already have taken place before 1980, when patients and general practitioners became more aware of the early symptoms of the disease and endoscopy was performed more frequently [18]. The proportion of patients with lymph node metastases remained stable. However, some upstaging of tumours seems to have taken place, in view of the higher proportion of patients with more than three positive lymph nodes. The shift towards more short-term, preoperative radiotherapy with 5×5 Gy will not have led to downstaging, provided the interval between the start of radiotherapy and surgery does not exceed 10 days [19].

In South-east Netherlands, the increase in the use of radiotherapy in combination with surgery from 26 to 40% was less striking than in the Cote-d'Or department and Burgundy region of France, where it increased from only 14% in 1976–1978 to 62% in 1994–1996 [20]. The shift from postoperative to preoperative radiotherapy in our region in 1995 was a direct result of the new regional guidelines, developed in 1994 within a multidisciplinary group. Although neither preoperative nor postoperative radiotherapy is indicated for TNM stage I patients, endorectal ultrasound was not available in most hospitals in our region, nor was it mandatory in the TME trial. This explains the use of preoperative radiotherapy in this group. To prevent a local recurrence in patients with disseminated disease (TNM stage IV), especially those with a low metastatic tumour burden, surgeons and radiotherapists agreed that preoperative irradiation should be considered for this group.

Chemotherapy was not widely applied until the end of the study period and its use remained limited to patients with TNM stage III or stage IV disease. Since adjuvant chemotherapy is not recommended for patients with rectal cancer, most of the observed increase in the use must be attributed to patients with TNM stage III cancer of the rectosigmoid region, who were treated like patients with stage III colon cancer, for whom adjuvant chemotherapy is standard treatment.

Between 1978 and 1989, the 5-year relative survival of rectal cancer patients in Europe increased from 38 to

Table 3
Results of multivariate analyses for overall survival of patients with rectal cancer diagnosed in the period of 1980–2000 according to their age group

Characteristics	<60 years		60–74 years		75+ years	
	HR 95% CI	*P* value	HR 95% CI	*P* value	RR 95% CI	*P* value
Age (per year increase)	1.01 (1.00–1.03)	0.06	1.04 (1.02–1.05)	<0.0001	1.04 (1.03–1.06)	<0.0001
Gender						
Female versus male	0.92 (0.76–1.11)	0.37	0.83 (0.74–0.94)	0.004	0.92 (0.80–1.00)	0.27
Subsite						
Rectosigmoid versus rectum	0.89 (0.72–1.10)	0.30	0.87 (0.76–1.00)	0.05	0.97 (0.83–1.13)	0.66
Tumour stage						
II versus I	2.40 (1.75–3.29)	<0.0001	1.75 (1.47–2.09)	<0.0001	1.31 (1.07–1.60)	0.010
III versus I	3.47 (2.58–4.68)	<0.0001	2.39 (2.00–2.86)	<0.0001	1.57 (1.27–1.95)	<0.0001
IV versus I	17.31 (12.47–24.03)	<0.0001	7.66 (6.31–9.30)	<0.0001	3.30 (2.59–4.20)	<0.0001
X versus I	2.98 (1.92–4.61)	<0.0001	2.25 (1.72–2.94)	<0.0001	2.00 (1.59–2.51)	<0.0001
Period of diagnosis						
1990–1994 versus 1980–1989	0.72 (0.57–0.91)	0.051	0.81 (0.70–0.94)	0.005	0.98 (0.82–1.17)	0.84
1995–2000 versus 1980–1989	0.45 (0.35–0.58)	<0.0001	0.62 (0.53–0.72)	<0.001	0.93 (0.78–1.10)	0.39
1995–2000 versus 1990–1994	0.63 (0.47–0.83)	0.001	0.76 (0.64–0.91)	0.0022	0.94 (0.78–1.15)	0.57

RR, relative risk; 95% CI, 95% confidence interval.

46%, with much better prognoses in the Nordic countries and the South-east Netherlands than in the United Kingdom and Denmark [21]. In a study of all patients with rectal cancer in Sweden between 1960 and 1989, the most pronounced improvement in survival was observed in the late 1980s in the county of Uppsala, the only region with a centre where the two major aspects of rectal cancer treatment, i.e. preoperative radiotherapy and TME surgery, were combined at that time [22]. The prognostic impact of interinstitution and intersurgeon variability on the outcome of rectal cancer treatment has been described in several studies [23–26], indicating the need for standardised surgical techniques. For one particular technique, the TME, a local recurrence rate as low as 5% has been reported [9]. This technique was prescribed in the Dutch TME trial [13]. In order to ensure homogeneity of the surgical procedure in this trial, 'instructor surgeons' were trained in the TME technique in special workshops and each surgeon participating in the trial had to perform the first five TME procedures under the supervision of an 'instructor surgeon'. This also led to a further concentration of rectal cancer treatment within surgical groups. Surgeons in the South-east Netherlands have been large contributors to the TME trial, with 49% of all their patients with rectal cancer entered in the trial in 1996 and 1997. In fact, quite a few surgeons had become convinced of the superiority of the TME technique over conventional non-standardised surgery before the start of the trial and also applied the technique on patients who did not enter in the TME trial. Together, these changes (i.e. standard short-term preoperative radiotherapy, standardised surgery with the TME technique and reduction of variability of outcomes between surgeons by concentration of rectal cancer treatment within surgical groups) are the most likely explanations for the improved survival rates in the periods of 1990–1994 and 1995–2000. The favourable effect of surgical training on the outcome of rectal cancer treatment has been substantiated by the study of Lehander Martling and colleagues [27], who showed a decrease of more than 50% in abdominoperineal procedures and the local recurrence rate, as well as a decline in rectal cancer mortality. In our study, information on the surgical technique was only available for the period of 1995–2000 and although the TME technique became widely used during these years, no decrease in abdominoperineal procedures was observed. Furthermore, the influence of local control on survival is supported by several studies. MacFarlane and colleagues reported a local recurrence rate of 5% and a recurrence-free survival rate of 78% [9], while the Swedish Rectal Cancer Trial, comparing non-TME surgery alone versus 5×5 Gy followed by TME surgery, showed a statistically significant decrease in the local recurrence rate from 22 to 11% and a significant increase in overall survival from 48 to 58% 9 years after treatment with curative intent [28]. Two very recent studies from The Netherlands and Norway [29,30] comparing the nationwide introduction of the TME technique with conventional surgical techniques, show an improvement in local control and survival in favour of the TME technique. The first results of the Dutch TME trial show a local recurrence rate at 2 years of 2.4% for the group with preoperative radiotherapy versus 8.2% for the group without radiotherapy ($P < 0.001$) [12]. The advantages of preoperative radiotherapy, as far as local control and overall survival are concerned, have been confirmed in two recent meta-analyses [31,32]. Although postoperative and preoperative radiotherapy both reduce the local recurrence rate, the latter seems more likely to influence survival favourably [33].

In a study in two French regions, a 3-fold reduction in the postoperative mortality (i.e. death within 30 days of surgery) was observed (from 7.7% during the years of 1978–1981 to 2.5% in the period of 1990–1993), which partly explained the improved survival in these regions [18]. In our study, we were not able to make a distinction between the date of diagnosis and the date of surgery, making it impossible to calculate postoperative mortality accurately. However, since 1980 a reduction of the 1-year mortality was observed for patients below 75 years of age, but not for patients 75 years or older.

In contrast to patients below 75 years of age, survival did not improve in the age group 75 years or older. Moreover, the relatively large number of deaths from causes independent of rectal cancer will have reduced the power to detect clinically relevant reductions in deaths due to rectal cancer in this age group [34].

5. Conclusion

The obvious sub-specialisation of surgeons in colorectal surgery, the shift from postoperative towards preoperative radiotherapy (5×5 Gy) for patients with mobile rectal cancer and the widespread use of TME surgery, within or outside the setting of randomised clinical trials, have been the most striking changes in the management of rectal cancer in South-east Netherlands during the last 20 years. No improvements in the distribution of tumour stage were observed, making it very likely that the continuing increase in population-based survival among patients <75 years of age results from the better management of rectal cancer.

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