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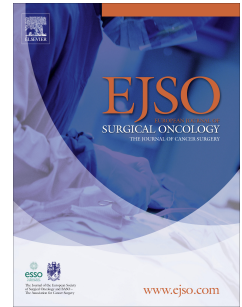
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**Quality assurance in rectal cancer treatment in the Netherlands: a catch up compared to colon cancer treatment**

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**Abstract**

*Background:* In the Netherlands, the Total Mesorectal Excision (TME) surgical technique for rectal cancer was introduced together with pre-operative radiotherapy in a quality controlled manner within the framework of the TME trial (1996-1999). The aim of this study is to examine the effects of the structural changes in rectal cancer care on survival compared to colon cancer for patients treated before, during and after the TME trial.

*Method:* We compared overall survival of all patients with curatively resected colon (n=15266) and rectal cancer (n=5839) in the regions of Comprehensive Cancer Centres South and West between 1990 and 2005, adjusting for prognostic variables.

*Results:* In the pre-trial period, rectal cancer had a significant lower survival compared to colon cancer (HR 1.248,  $P < 0.01$ ). However, in the post-trial period, survival after rectal cancer was similar to colon cancer (HR 0.987, n.s.).

*Conclusion:* Although survival improved significantly for both colon and rectal cancer in the last 15 years, the substantially worse results after rectal cancer have been eliminated. This study shows the lasting effects that structural surgical training and quality assurance can have on survival outcome.

## Introduction

In the last two decades, treatment of rectal cancer has been substantially improved by the introduction of the Total Mesorectal Excision (TME) surgical technique in combination with preoperative treatment. In the Netherlands, TME surgery was implemented in a structural way within the framework of the TME trial (1996-1999)<sup>1</sup>. This trial was performed to study the effects of preoperative radiotherapy in patients who underwent TME surgery. All participating surgeons were trained in the TME technique by workshops and videotapes. At least five procedures of each participating surgeon were supervised by an instructor surgeon. Pathologists were trained to examine the specimens according to the protocol of Quirke et al. regarding the circumferential resection margin (CRM), lymph nodes and dissection plane<sup>2</sup>. This is of importance for adequate staging and adjuvant treatment as well as for essential feedback to the surgeons. The TME trial resulted in a five-year local recurrence rate of 5.6% with and 10.9% without preoperative radiotherapy and a five-year overall survival of 64% in both groups<sup>3</sup>.

The transition from conventional surgery to a quality-controlled multidisciplinary treatment regimen was not limited to the trial population. For all rectal cancer patients treated in the Comprehensive Cancer Centres South and West in the Netherlands survival increased substantially. Before the TME trial (1990-1995), five-year overall survival after rectal cancer was 56%, during the trial (1996-1999) 62%, and after the TME trial (2000-2002) 65%<sup>4</sup>. The majority of patients in this study did not participate in the TME trial proving the lasting positive effects which quality assurance in surgical oncology can have.

Nevertheless, not only the operative treatment of rectal cancer improved. For instance, postoperative chemotherapy was introduced in the treatment schedule of colon cancer in the late 1990s. While there are similarities between colon and rectal cancer, there are also striking differences in treatment and tumour characteristics. For example, local recurrence is an important complication for rectal cancer patients, whereas it is less an issue for colon cancer. Traditionally, survival after rectal cancer was inferior compared to survival after colon cancer<sup>5</sup>. Although there were improvements in the treatment of colon cancer, surgery for colon cancer is not standardised or quality controlled as it is for rectal cancer. The aim of this study is to examine the effects of quality assurance measures on survival for patients treated for rectal cancer compared to survival of patients treated for colon cancer before, during and after the TME trial.

## **Patients and methods**

### **Patients**

The Comprehensive Cancer Centres South and West register all newly diagnosed malignancies in the southern and western part of the Netherlands with a population of approximately 4 million inhabitants. Trained registration clerks extract primary and follow-up data from hospital records while survival data are synchronized with the municipal personal records databases. The regional cancer registries have shown to have a coverage exceeding 95%<sup>6</sup>. We selected all patients with primary invasive colon or rectal cancer diagnosed between 1990 and 2005. All patients have a complete follow-up until 1 January 2008. Patients with clinical or pathological distant metastases (TNM stage IV) were excluded as well as patients that did not undergo surgery. Patients were

classified in three groups depending on their year of diagnosis relative to the inclusion period of the TME trial: 1990-1995 (pre-trial period), 1996-1999 (trial period) and 2000-2005 (post-trial period). Rectosigmoid tumours, including proximal rectal cancers and distal sigmoid cancers, were categorised as a separate group, as these tumours form a heterogeneous group with respect to treatment.

### **Statistical analysis**

Data were analysed using SPSS software (SPSS 16.0 for Windows; SPSS Inc., Chicago, IL). Univariate comparisons between the three study periods were performed by ANOVA for age and by Chi-square test for categorical variables. Five-year survival and median follow-up time were calculated with the Kaplan Meier method. Log rank tests were used to calculate significance. In a multivariate analysis, a Cox proportional hazards model for survival was used to calculate Hazard Ratio's adjusted for age, gender and tumour stage. Interaction was tested to compare improvements in survival between colon cancer and rectal cancer. Two-sided p-values  $\leq 0.05$  were considered statistically significant.

## **Results**

### **Patient characteristics**

A total of 23 078 patients were included in the study: 15 266 colon cancer patients, 1973 rectosigmoid cancer patients and 5839 rectal cancer patients. Patient characteristics are shown in table 1. The median follow-up is 15.13 years (range 12-18 yr) for the pre-trial period, 9.93 years (range 8-12 yr) for the trial period and 4.87 years (range 2-8 yr) for the post-trial period. For colon and rectal cancer, a clear increase in patient numbers is

noticeable when comparing the first time period (1990-1995) with the last period (2000-2005). Rectal cancer patients were significantly younger than colon cancer patients (66.6 yrs vs 69.9 yrs,  $p < 0.01$ ). Female / male ratio changed to a more equal distribution for colon cancer while for rectal cancer, the proportion of males increased over time. For rectal cancer, there is an evident switch from postoperative to preoperative radiotherapy while for colon cancer patients there is an increase in the use of chemotherapy. The use of both radiotherapy and chemotherapy in the 'rectosigmoid' group shows the mix of colon and rectal cancer present in this category.

### **Survival**

In table 2, overall five-year survival is given per tumour stage and period of diagnosis. In the pre-trial period, uncorrected five-year survival was 56.2% for colon cancer and 56.1% for rectal cancer whereas in the post-trial period both colon and rectal cancer improved significantly to 59.1% for colon cancer and 64.8% for rectal cancer. Notwithstanding the improvements for colon and rectosigmoid cancer, the greatest and most significant survival rise in all stages was made for rectal cancer. In a Cox proportional hazards model adjusting for age, gender and tumour stage, rectal cancer had a significant lower survival in the pre-trial period (1990-1995) compared to colon cancer: HR 1.248, 95% confidence interval 1.17-1.33,  $P < 0.01$  (Table 3, figure 1). However, in the post-trial period (2000-2005), survival after rectal cancer was similar to colon cancer: HR 0.987, 95% confidence interval 0.91-1.07, n.s. (Table 4, figure 1). After testing of interaction, the magnitude of improvement showed significant greater for rectal cancer than for colon cancer ( $P < 0.01$ ) which is visualized in figure 1.



## Discussion

In the past 15 years, survival improved markedly for both colon and rectal cancer. Remarkably, the substantial survival backlog of rectal cancer compared to colon cancer has been completely caught up through the introduction of standardised TME surgery combined with preoperative radiotherapy. In our opinion, this is an example of the lasting effects that structural surgical training and quality assurance can have on survival outcome. Similar results were found for training and quality assurance measures within the Dutch gastric cancer D1-D2 trial (1986-1989) which have led to lasting improvements in surgical quality in the region of Comprehensive Cancer Centre West<sup>7</sup>. Quality assurance can be summarized as “the complete set of systematic actions that is required to achieve a treatment result that meets a certain standard”<sup>8</sup>. Compared to other fields such as chemotherapy and radiotherapy, quality assurance in surgical oncology is relatively new. For a long time, surgery was thought to have too much unexpected variation to be feasible for standardisation and quality control. However, the conception of surgery steadily shifted from being a non-definable craftsmanship to a transparent and well-defined skill.

Nowadays many quality assurance programs have been successfully enrolled in surgical oncology with encouraging results, in particular for rectal cancer. The succeeding Eurocare studies match with the European efforts to improve rectal cancer care. Between 1978 and 1989, five-year relative survival in Europe was 43% (95% CI: 42-44) for rectal cancer and 47% (95% CI: 46-48) for colon cancer<sup>5</sup>. Between 1995 and 1999, European five-year relative survival for rectal cancer (53.6%) was similar to colon

cancer (54.3%)<sup>9</sup>. While for both rectal and colon cancer survival increased, rectal cancer treatment caught up from a survival backlog compared to colon cancer. Although our study lacks data on cost-effectiveness, it is plausible that surgical quality assurance is a cost-effective instrument to improve quality of care. In the Nordic countries, rectal cancer care is monitored by national audit registrations that provide casemix-adjusted feedback to all hospitals performing rectal cancer surgery. All these audit projects are successful in improving nationwide quality of care<sup>10</sup>. The Norwegian Rectal Cancer Project includes more than 99% of patients operated for rectal cancer and showed to be very cost-effective with the costs of every saved life being less than €700<sup>11;12</sup>. Compared to most chemotherapy regimes these costs are extraordinary. For instance, for colon cancer patients, every life year gained with fluorouracil, levamisole and folinic acid costs more than € 50.000<sup>13</sup>.

### **Study limitations**

It might be possible that more emergency surgery is performed for (obstructive) colon cancer than for rectal cancer. This could have an effect on short-term survival because emergency surgery is associated with higher post-operative mortality. Unfortunately, we lacked data on emergency status of primary surgery, making it impossible to further analyse or correct for urgency.

In the multivariate Cox regression model, we did not analyse the ‘rectosigmoid’ group. Because of the uncertain mix of colon and rectal cancer patients we decided to leave this group out of consideration.

### **Future improvements of surgical quality**

In a recent study of West et al, only 32% of the resections for colon cancer were performed in the appropriate surgical plane (mesocolic plane) whilst in the recently published MRC CR07 rectal cancer study the percentage of resections in the appropriate surgical plane (mesorectal plane) was 52%<sup>14;15</sup>. Though in both study populations no quality assurance measures were taken, their results clearly show the improvements that can be made in surgical oncology and this especially applies to colon cancer. Although our study shows that positive effects of quality assurance within a clinical trial reaches much further than the trial population alone, a continuous nationwide audit program such as the Nordic countries provides the best data for adequate casemix-adjusted feedback and quality control. Therefore, nationwide rectal cancer audit programs are set up in several European countries (Norway, Sweden, Denmark, UK and Belgium). In the Netherlands, the Dutch Surgical Colorectal Audit started in January 1<sup>st</sup> 2009 and in the first 7 months 3200 patients were included<sup>16</sup>. Despite the positive results of quality control initiatives from clinical trials and audit programs on a national level, there remain striking differences in treatment outcome in Europe. For colorectal cancer, the Eurocare IV study showed five-year relative survival varying between 32% and 64% between European registrations<sup>9</sup>. The conclusion is that a European audit registration is needed to ameliorate the treatment of cancer even further and decrease variation in the quality of not only rectal cancer care but all solid malignancies. Urged by these arguments, the European Society of Surgical Oncology (ESSO) initiated an international, multidisciplinary, outcome-based quality improvement program which is fully embraced by the European CanCer Organisation (ECCO).

In this study, quality assurance in surgical oncology has shown to be an excellent instrument to raise quality of care and decrease outcome variation. A European audit could advance future improvements and spread these to every cancer patient in Europe. The ECCO has recognised the importance of quality assurance and has created a framework to develop a European audit. All information about this project can be found on the webpage: [www.canceraudit.eu](http://www.canceraudit.eu).

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Table 1: Patient Characteristics by period of diagnosis.  
RT = radiotherapy

	1990-1995	1996-1999	2000-2005	P-value
Colon	N= 5037	N= 3688	N= 6544	
Median Follow-up (yr)	15.17	9.99	4.93	
Age (yr)	69.8 ± 11.9	70.0 ± 11.7	69.9 ± 11.5	n.s.
Gender (%)				<0.01
M	45.7	47.6	49.4	
F	54.3	52.4	50.6	
Stage (%)				<0.01
I	19.5	18.7	19.1	
II	51.2	49.7	47.2	
III	29.4	31.6	33.7	
Chemotherapy (%)	6.1	14.1	19.9	<0.01
Preoperative RT (%)	0.0	0.2	0.6	<0.01
Postoperative RT (%)	1.1	0.7	0.4	<0.01
Rectosigmoid	N= 779	N= 428	N= 766	
Median Follow-up (yr)	15.17	9.69	4.99	
Age (yr)	68.6 ± 11.5	68.7 ± 10.5	68.5 ± 10.9	n.s.
Gender (%)				n.s.
M	56.4	57.5	56.4	
F	43.6	42.5	43.6	
Stage (%)				n.s.
I	25.9	25.2	26.2	
II	43.6	40.2	37.1	
III	30.4	34.6	36.7	
Chemotherapy (%)	4.5	13.1	20.0	<0.01
Preoperative RT (%)	0.4	6.1	24.8	<0.01
Postoperative RT (%)	19.0	9.3	3.1	<0.01
Rectum	N= 1853	N= 1370	N= 2616	
Median Follow-up (yr)	15.04	9.90	4.75	
Age (yr)	66.7 ± 11.8	66.6 ± 11.8	66.5 ± 11.5	n.s.
Gender (%)				n.s.
M	55.5	56.4	58.8	
F	44.5	43.6	41.2	
Stage (%)				<0.01
I	38.2	36.5	38.2	
II	34.3	30.1	31.0	
III	27.6	33.4	30.8	
Chemotherapy (%)	3.7	5.3	12.9	<0.01
Preoperative RT (%)	3.3	28.5	69.0	<0.01
Postoperative RT (%)	34.3	11.9	5.5	<0.01

Table 2: Five-year overall survival (in percent) by period of diagnosis and TNM stage calculated with Kaplan Meier survival tables. Significance calculated with Log rank test.

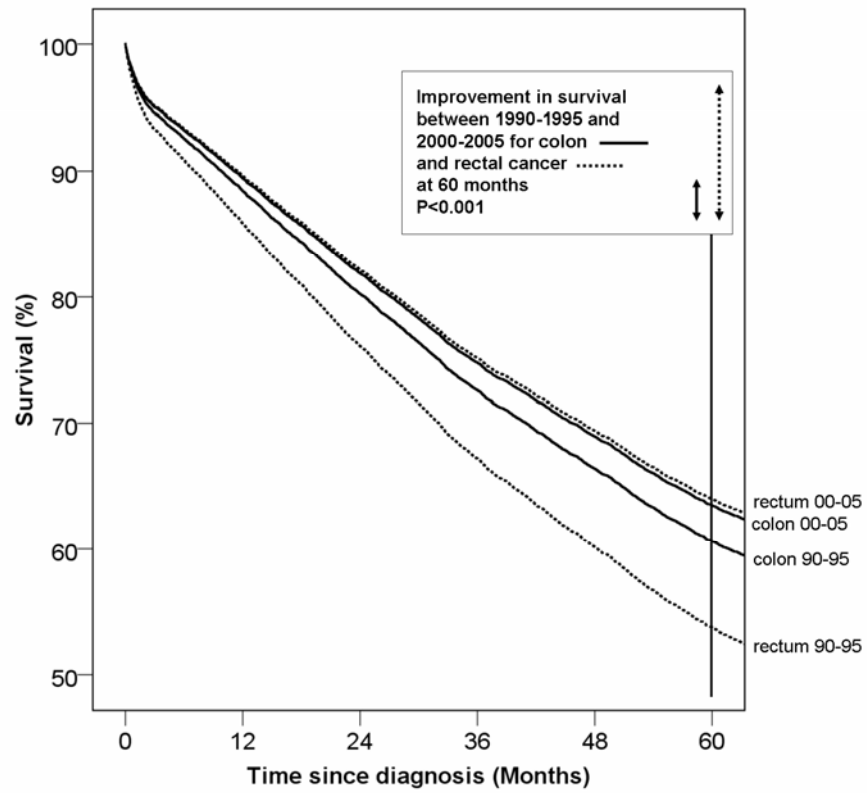
	Stage	1990-1995	1996-1999	2000-2005	P-value
Colon	I	73.4	72.4	75.1	n.s.
	II	58.3	60.3	62.6	n.s.
	III	41.2	41.5	45.4	<0.01
	All	56.2	56.6	59.1	0.02
Rectosigmoid	I	76.7	66.7	75.5	0.01
	II	54.4	60.5	58.3	n.s.
	III	36.9	41.9	52.4	<0.01
	All	54.9	55.6	60.6	n.s.
Rectum	I	71.5	79.0	75.2	<0.01
	II	54.0	56.9	65.5	<0.01
	III	37.2	42.8	50.9	<0.01
	All	56.1	60.3	64.8	<0.01

Table 3: Multivariate Cox regression analysis for overall survival adjusted for age, gender, and tumour stage (\* reference group = Colon 1990-1995)

	Hazard Ratio	95% CI	P-value
Colon 1990-1995*	1.000	-	-
Rectum 1990-1995	1.248	1.17 – 1.33	<0.01
Colon 1996-1999	0.998	0.95 – 1.05	n.s.
Rectum 1996-1999	1.068	0.99 – 1.16	n.s.
Colon 2000-2005	0.907	0.86 – 0.96	<0.01
Rectum 2000-2005	0.896	0.83 – 0.97	<0.01

Table 4: Multivariate Cox regression analysis for overall survival adjusted for age, gender, and tumour stage (\* reference group = Colon 2000-2005)

	Hazard Ratio	95% CI	P-value
Colon 1990-1995	1.102	1.05 – 1.16	<0.01
Rectum 1990-1995	1.376	1.28 – 1.47	<0.01
Colon 1996-1999	1.100	1.04 – 1.17	<0.01
Rectum 1996-1999	1.177	1.09 – 1.28	<0.01
Colon 2000-2005*	1.000	-	-
Rectum 2000-2005	0.987	0.91 – 1.07	n.s.



ACCEPTED