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Actionable indicators for short and long term outcomes in rectal cancer

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ABSTRACT

Aim of the study: Although patient and tumour characteristics are the most important determinants for outcomes in rectal cancer care, *actionable* factors for improving these are still unclear. Therefore, the purpose of this study was to assess the impact of surgeon and hospital factors which can actually be influenced to improve on postoperative complications, disease-free survival (DFS) and relative survival (RS) in rectal cancer.

Methods: For 819 curatively operated rectal cancer patients, staged I–III and diagnosed between 2001 and 2005, data were derived from the population-based Cancer Registry of the Comprehensive Cancer Centre North East and supplemented by medical record examination. (Multilevel) Logistic regression analysis was performed to examine the influence of relevant factors on postoperative complications and time from diagnosis to first treatment. Besides, Cox regression analysis for DFS and relative survival analysis was performed.

Results: Postoperative complications were dependent on type of surgery ($p = 0.024$) and hospital volume ($p = 0.029$). DFS was mainly influenced by stage ($p < 0.001$) and time to treatment ($p = 0.018$). Actionable indicators related to RS were type of surgery ($p = 0.011$) and time to treatment ($p = 0.048$). Time to treatment was found to be related to co-morbidity ($p = 0.007$), preoperative radiotherapy ($p = 0.003$) and referral for operation ($p = 0.048$). Nevertheless, 18.2% unexplained variation in time to treatment remained on hospital level.

Conclusions: We conclude that optimal outcomes for rectal cancer care can be achieved by focusing on early detection and timely diagnosis, as well as adequate choice and timeliness of treatment in hospitals with optimal logistics for rectal cancer patients.

1. Introduction

The management of rectal cancer has changed in many aspects during the last few decades, which has positively affected several outcomes.[1] Especially the introduction of the Total Mesorectal Excision (TME) technique and the use of preoperative radiotherapy have significantly reduced local recurrence rates with improvement of long-term survival after

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curatively intended surgery.[2,3] Neo-adjuvant chemotherapy has recently been introduced for a better control of locally advanced disease and is currently combined with radiotherapy for optimal results.[4,5] Despite these irrefutable improvements, there is still a large variation in both short- and long-term outcomes. Complications after surgery, including anastomotic leakage, range widely.[6,7] Local recurrence, with its tremendous impact on the quality of life and a marked decline in survival, also varies considerably.[8,9] Besides, several studies showed a wide variation in 5-year relative survival between different countries, partly reflecting differences in quality of care.[10,11] Patient and tumour characteristics, including age, co-morbidity, tumour stage and tumour location still are the most important determinants for outcomes of rectal cancer. However, from an improvement perspective it is unclear which *actionable* factors, i.e. factors amenable to change, are related to short- and long-term outcomes.[12] In rectal cancer, for which surgery is technically demanding and coordinating multiple interventions is challenging, predictive actionable factors are expected to be found on surgeon as well as hospital level.

Surgeon and hospital volume are often considered as actionable factors, as more specialised and experienced care providers and concentration of services seem beneficial for outcomes.[13] For rectal cancer however, studies on the effect of surgeon and hospital volume report conflicting and non-conclusive results.[14] It is generally recognised that there is a lack of understanding the determinants of the volume–outcome relationship. Several authors state that volume is a side issue, as other aspects may be more important.[15,16] These aspects include the organisation and coordination of care, e.g. the implementation of clinical pathways and multidisciplinary team working.

This study aims to assess the impact of actionable factors on postoperative complications, disease-free survival (local recurrence and distant metastases) and 5-year relative survival in rectal cancer patients. We focused on the impact of surgeon and hospital volume and on organisational aspects reflected by time from diagnosis to first treatment.

2. Patients and methods

2.1. Data collection

For this study, rectal cancer patients diagnosed in the northern part of the Netherlands were selected from the Cancer Registry of the Comprehensive Cancer Centre North East (CCCNE). This population based registry contains data of all newly diagnosed cancer patients.[17] The northern part of this region covers a predominately rural area with about 2.2 million inhabitants and is served by 1 university hospital, 3 teaching and 12 non-teaching hospitals, four radiotherapy facilities and 7 pathology laboratories. In addition to the cancer registry data, medical records of these patients were examined for detailed information on patient and tumour characteristics, diagnosis, treatment, pathological evaluation and follow-up. These additional data were registered on a standardised registration form by specially trained registration clerks.

2.2. Patients

All patients diagnosed from January 2001 to January 2005 in the above-mentioned region who underwent a curatively intended rectal resection for a histologically proven invasive rectal cancer, without distant metastases (pTNM according to UICC classification stages I–III) were included. Patients with previous or coexisting invasive cancer other than non-melanoma skin cancer or *in situ* cervical cancer, and those with another invasive cancer within 3 months after rectal cancer diagnosis were excluded. In total, 948 patients were eligible for this study. Cases of which medical records were unavailable ($n = 18$) or incomplete ($n = 8$) were excluded, as well as patients who underwent non-elective surgery ($n = 14$). We also excluded patients treated by polipectomy, transanal surgery, including Transanal Endoscopic Microsurgery (TEM) or unknown type of surgery ($n = 53$) and in case distance from tumour to anal verge was unknown ($n = 32$). Patients referred to hospitals outside the region after diagnosis were also excluded because of the unavailability of treatment data ($n = 4$). The final cohort consisted of 819 patients operated by 76 different surgeons in 16 hospitals.

2.3. Variables

Standard patient and tumour characteristics were derived from the cancer registry, including gender, age and stage. Type of operation was recorded as abdominoperineal resection (APR), low anterior resection (LAR) or Hartmann procedure, as well as the hospital where the operation was performed. Co-morbidity was registered using a modified Charlson Index.[18] The American Society of Anesthesiologists (ASA) physical score[19] was also recorded, but was not included in our analysis due to incompleteness (39% incomplete). Multidisciplinary team discussion and specialised stoma nurse involvement was listed, but not documented in the medical records in 45.2% and 32.7% of the patients, respectively. Therefore, these items were not included in the analyses. Start date of first treatment (radiotherapy or surgery) was registered and the interval from date of incidence to start of first treatment was calculated. Time from diagnosis to treatment (ttt) was dichotomised based on the maximum acceptable waiting times in the Netherlands, which indicates that cancer treatment should start at the latest within 7 weeks (www.treeknorm.nl).

These national standards were established in the Netherlands in 2000 by hospitals and medical specialists from the Dutch healthcare system. The standard targets offer the maximal acceptable waiting time for elective diseases, based on social acceptability rather than medical urgency.[20]

Serious surgical complications as described in the medical records occurring within 30 days after surgery were recorded, such as anastomotic leakage, (presacral) abscess, serious peritonitis, wound dehiscence, serious postoperative bleeding, stoma-bowel necrosis and fistula.

Information on local recurrence, distant metastases, vital status and cause of death was mainly obtained from the medical records and completed with information from the Municipality Administration Database (GBA), and the central death register of the Central Bureau of Genealogy. Follow-up was

complete until 1st March 2008. The median follow-up was 4.4 years (inter quartile range 3.2–5.6 years).

2.4. Hospital and surgeon volume

Hospital volume was defined as average annual number of operated rectal cancer patients between 2001 and 2005. Nine hospitals were defined as low-volume (<20 patients/year), four as mid-volume (20–40 patients/year) and three as high-volume (⩾40 patients/year) hospitals. These hospital volume groups consisted of, respectively, 237 (28.9%), 241 (29.4%) and 341 (41.6%) patients. Both leading and assisting surgeons were recorded and surgeon volume was calculated as the average annual number of rectal cancer operations both leading and assisting in the study population between 2001 and 2005. The 76 surgeons were classified into three volume groups based on their mean annual number of rectal cancer resections; 57 were defined as low-volume surgeons (<5 resections/year), 12 as mid-volume surgeons (5–10 resections/year) and 7 as high-volume surgeons (⩾10 resections/year). Patients were relatively equally distributed among the low, mid and high surgeon volume groups, respectively, 32.6%, 35.9% and 31.5%. The distribution of the surgeon volume over the different hospital volume groups is shown in Table 1. In our study, 4 of 19 (21%) surgeons in high-volume hospitals are high-volume surgeons, while 57% (11/19) of the surgeons in high-volume hospitals only occasionally perform rectal cancer surgery. This lack of task differentiation within the surgical domain is also seen in low and mid-volume hospitals.

2.5. Statistics

For postoperative complications and time to treatment, the hierarchical structure of the data was examined with multilevel logistical analysis in an empty model (null model).[21] For complications, the influence of the structure was not significant, and standard logistic regression analysis was performed and odds ratios (ORs) were calculated. For time to treatment, the hierarchical structure of the data could not be ignored because of significant variation on surgeon and hospital level, and multilevel logistic regression was performed. For disease-free survival (DFS) analysis, patients without tumour free margins after surgery ($n = 31$), those who developed metastases within 3 months after resection ($n = 6$) and patients who died within 30 days after surgery ($n = 26$) were excluded. In the remaining 755 eligible patients DFS was calculated from the date of surgery to the date of recurrence or follow-up. The Cox proportional Hazard model was used for multivariate analysis of factors affecting the risk of disease recurrence, expressed in Hazard Ratios (HRs).

Relative survival,[22] as estimation of disease-specific survival, was calculated for all 819 patients and risk factors were expressed in Relative Excess Risks (RERs). Factors associated with time to treatment were investigated using multilevel logistic regression analysis.

For all analyses, the variables in table 2 and surgeon and hospital volume were entered into univariate analyses. For time to treatment we added the variable referral to other hospital for operation into analysis. Significant factors were entered into multivariate analyses. Confidence intervals (CIs) were set at 95% and (individual) p-values < 0.05 were considered statistically significant (two-sided). STATA 10.0 (Stata Corporation, College Station, TX) was used, including generalised linear latent and mixed models (gllamm) programme for multilevel analyses.

Table 1 – Task differentiation among surgeons within hospitals concerning rectal cancer surgery.

Surgeon volume	Hospital volume					
	Low		Mid		High	
	N of surgeons	%	N of surgeons	%	N of surgeons	%
Low	31	54	15	26	11	19
Mid	4	33	4	33	4	33
High	1	14	2	29	4	57

Table 2 – Patient characteristics.

Characteristics	N	%
Total	819	100
Gender		
Male	506	61.8
Female	313	38.2
Age		
<70	476	58.1
70+	343	41.9
Stage (TNM)		
I	262	32.0
II	249	30.4
III	308	37.6
Tumour location (cm from anal verge)		
Low (0–5)	246	30.0
Mid (5–10)	304	37.1
High (⩾10)	269	32.8
Co-morbidity		
0	359	43.8
1	236	28.8
2+	224	27.4
Period of diagnosis		
2001–2002	390	47.6
2003–2004	429	52.4
Preoperative radiotherapy		
No	139	17.0
Yes	680	83.0
Type of surgery		
APR	324	39.6
LAR	344	42.0
Hartmann	151	18.4
Time to treatment		
>7 weeks	241	29.4
⩽7 weeks	578	70.6

3. Results

3.1. General

Table 2 shows the characteristics of the 819 patients included in this study. More than half of the patients were male (61.8%), median age was 68.4 (range 25.6–92.4) years. Most tumours were classified as pTNM stage III (37.6%). According to the modified Charlson classification, 43.8% of the patients had no co-morbidity, 28.8% had one and 27.4% had two or more co-morbid conditions. Preoperative radiotherapy was given to 83.0% ($n = 680$) of the patients. Patients underwent a LAR (42.0%), an APR (39.6%) or a Hartmann procedure (18.4%). Forty-one patients (5.0%) were referred to another hospital within the region for operation.

3.2. Complications

Twenty three percent of the patients ($n = 193$) developed one or more serious complications after surgery. In regular univariate logistic regression analysis, time to treatment did not have an influence on complications, nor did gender, age, co-morbidity, stage, tumour location and preoperative radiotherapy. As type of surgery and hospital volume were significant variables, these were entered into multivariate analysis.

Multivariate analysis (Table 3) showed that patients from the highest hospital volume group had a significant lower complication risk (OR = 0.65, 95% CI = 0.44–0.96) and LAR had the lowest complication risk (OR = 0.67, 95% CI = 0.46–0.97). There was no interaction between hospital volume and type of surgery.

3.3. Disease-free survival

Overall, 3-year disease-free survival (DFS) was 78.8%. During follow-up, 9.8% of the patients ($n = 74$) developed a local recurrence, and 20.3% ($n = 153$) distant metastases. Median time to recurrence, locally or distantly, was 20.7 months after surgery. The univariate analysis revealed that stage, surgeon volume and ttt were strong predictors for DFS; other variables had no significant impact on recurrence rate. The multivariate analysis (table 3) showed that the effect of surgeon volume was no longer significant ($p = 0.109$), while stage (stage II: HR = 3.42, stage III: HR = 6.61, $p < 0.001$) and ttt (HR = 0.69, $p = 0.018$) had an independent impact on DFS.

3.4. Relative survival

Overall, 5-year relative survival (RS) was 79.2%. During follow-up, 282 (34.4%) patients died, median time to death was 26.1 months after surgery. In univariate analysis, neither

Table 3 – Multivariate analyses of outcomes.

Characteristics	Complications			DFS			RS		
	OR	95% CI	*p*-value	HR	95% CI	*p*-value	RER	95% CI	*p*-value
Age (years)									
<70									
70+									
Stage (TNM)				1.0		<0.001	1.0		<0.001
I				3.42	2.02–5.79		2.90	1.26–6.64	
II				6.61	4.06–10.76		4.68	2.17–10.14	
III									
Co-morbidity									
0									
1									
2+									
Surgery							1.0		0.011
APR	1.0		0.024				0.49	0.31–0.80	
LAR	0.67	0.46–0.97					0.99	0.60–1.65	
Hartmann	1.17	0.76–1.81							
Surgeon volume									
Low < 5				1.0		0.109			
Mid 5–10				1.02	0.73–1.42				
High ⩾ 10				0.70	0.47–1.03				
Hospital volume			0.092						
Low < 20	1.0								
Mid 20–40	0.79	0.52–1.20							
High ⩾ 40	0.65	0.44–0.96							
Time to treatment									
>7 weeks				1.0		0.018	1.0		0.048
⩽7 weeks				0.69	0.51–0.94		0.66	0.44–0.99	

DFS, disease-free survival; RS, relative survival; OR, odds ratio; HR, hazard ratio, RER, relative excess risk and 95% CI, 95% confidence interval.

surgeon volume nor hospital volume had an effect on RS. By contrast, higher stage was associated with lower survival and patients treated with a LAR had better survival. Patients receiving treatment within 7 weeks after diagnosis had significant better survival. Multivariate analysis (table 3), demonstrated ttt (RER = 0.66, $p = 0.048$) as an independent predictor of survival, even as stage (stage II: RER 2.90, stage III RER = 4.68, $p < 0.001$) and type of surgery (LAR: RER = 0.49, Hartmann: RER = 0.99, $p = 0.011$). Interactions between the variables were tested, but none of them were significant.

3.5. *Time to treatment*

In 70.5% of the patients, first treatment started within 7 weeks after diagnosis.

Median ttt was 40 days (inter quartile range 28–53 d). Multilevel analysis (Table 4) showed that most of the variation in ttt was attributable to the patient level (80.8%), while the other 19.2% of the variance was attributable to the hospital. In multilevel regression analysis, surgeon and hospital volume were not associated with ttt. Significant patient variables related to ttt were co-morbidity and tumour location. Other influencing factors are preoperative radiotherapy, type of surgery, and referral for operation. In multivariate analysis, from the different types of surgery, only patients receiving a Hartmann procedure were significantly less likely to receive a timely treatment (OR = 0.58, 95% CI 0.37–0.93). For patients with two or more co-morbid conditions, the likelihood of early treatment was almost two times lower (OR = 0.54, $p = 0.003$). Treatment was less likely to start within 7 weeks if first treatment was radiotherapy (OR = 0.46, $p = 0.003$) and when patients were referred for operation (OR = 0.48, $p = 0.048$). However, significant variation on hospital level remained (18.2%), indicating the need for other explanatory variables on hospital level.

4. Discussion

In this study we examined *actionable* factors for short- and long-term outcomes in rectal cancer care. Regarding postoperative complications, our results show that higher hospital volume was related to a lower complication risk. This is in line with several studies,[23] but not with others.[24] In addition, we found fewer complications after LAR than APR, as was also reported elsewhere.[25] This indicates the importance of choice of treatment. Although choice of treatment is or should be largely dependent on patient and tumour characteristics, previous studies pointed out that more sphincter saving procedures are being performed in high caseload hospitals or in the hands of experienced surgeons.[23,24] Although in our study APR rates were lower in high-volume hospitals and for high-volume surgeons (data not shown), only type of surgery and hospital volume were independent predictors for postoperative complications.

Regarding disease-free and relative survival, a very interesting finding is that besides stage, time to treatment was significantly associated with both long-term outcomes. To our knowledge, this publication is the first to show that time to treatment is an independent predictor for DFS and RS in rectal cancer. Although the association between treatment delay

Table 4 – Multilevel analysis on time to treatment.

	Null model			Full model		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Fixed part						
Co-morbidity						
0				1.0		0.007
1				0.62	0.41–0.92	
2+				0.54	0.36–0.81	
Surgery						
APR				1.0		0.074
LAR				0.85	0.58–1.26	
Hartmann				0.58	0.37–0.93	
Preoperative radiotherapy						
No				1.0		0.003
Yes				0.45	0.27–0.75	
Referral for operation						
No				1.0		0.048
Yes				0.48	0.24–0.99	
Random part	*B*	SE	%[a]	*B*	SE	%[a]
Hospital level	0.781	0.197	19.2	0.733	0.203	18.2
Surgeon level	$7.54e^{-18}$	$6.72e^{-10}$	0.0	$2.17e^{-23}$	$1.08e^{-12}$	0.0
Patient level ($\pi^2/3$)	3.290		80.8	3.290		81.8

OR, odds ratio, 95% CI, 95% confidence interval.

[a] Relative share of total variance: the lowest level variance is fixed to the variance of a logistic distribution ($\pi^2/3$), therefore, the surgeon and hospital level variances can only be interpreted as a proportion of the total variance.

and stage has been researched,[26] multiple centre studies that directly relate time between diagnosis and first treatment to outcomes in rectal cancer care were generally lacking. Regarding hospital volume, we did not find an association with either DFS or RS. Adjusted for stage, surgeon volume was associated with better DFS, which is in agreement with current literature.[27] However, this association was no longer significant after adjustment for time to treatment. So, an important implication of our study is that early stage and time to treatment, rather than volume alone should be the major focus for improving outcomes.

To formulate improvement actions on time to treatment, we examined factors influencing delay in first treatment after diagnosis. Our analyses showed that, apart from the patient level, variation in time to treatment is attributable to the hospital level. This indicates that for shortening time from diagnosis to treatment, the hospital should be the major focus.

We did not find a relationship between surgeon volume and ttt, as one might have expected from the results of the DFS analysis. This finding relates to the hierarchical structure of the data and the dependency of the observations in the dataset. Our results showed that the likelihood to receive timely treatment was lower when first treatment was radiotherapy, pointing out possible deficits in the coordination in surgical treatment and radiotherapy, likely related to planning of the patient journey. Although type of treatment (i.e. preoperative radiotherapy and Hartmann procedure) was associated with ttt, choice of treatment is not an improvement action for ttt, as type of treatment should be dependent on patient and tumour characteristics.

Besides, a time lag for referred patients before start of treatment was found, most likely related to the handover of the patient and the diagnostics test results. Hospital volume did not have a significant effect and it did not reduce the variation on hospital level. Large unexplained variation in time to treatment remained on hospital level, as was also found by Schulz et al. in their analysis of waits for lung cancer treatment.[28] Apparently, other hospital factors contribute to a timely treatment. From management literature, logistical and planning factors are shown to play an important role in shortening waiting times.[29] This pleads for further research into, e.g. the effective implementation of care pathways, multidisciplinary team work, and adequate planning and coordination of different departments involved in the rectal cancer patient journey.

We dichotomised the time from diagnosis to treatment based on the general Treek norms for socially acceptable waits. Since this study has shown the importance of ttt for medical outcomes, further research can contribute to determining a threshold in waits related to medical outcomes.

We are aware that time from diagnosis to treatment is only a part of the total delay before start of treatment for rectal cancer. Unfortunately, we could not assess the delay before referral and between referral and pathological confirmed diagnosis after rectal- or coloscopy. Delay on the part of the patient and general practitioner is a considerable problem. Most patients do not consider cancer as a possible cause of their often vague and non-specific symptoms and they often delay consulting their doctor until the symptoms become more severe or more persistent.[30] Improved awareness on symptoms of rectal cancer in the population and effective screening on colorectal cancer could contribute to the detection of rectal cancer in an earlier stage. Besides, waiting time for coloscopy is an acknowledged problem, as a shorter diagnostic delay is associated with a less advanced disease in rectal cancer.[31] For the hospitals in our study this delay is estimated to be at least 6 weeks. Nevertheless, this stresses even more the importance of the focus on the hospital for improving waiting and lead times for optimal outcomes in rectal cancer care.

Concluding, our results do not support the general assumption that the concentration of services in high volume hospitals is necessarily attributing to high-quality outcomes, at least for long-term outcomes. Based on the results of this study, we conclude that optimal outcomes for rectal cancer can be achieved by focusing on early detection and timely diagnosis, as well as adequate choice and timeliness of treatment in hospitals with optimal logistics for rectal cancer patients. So, the organisation of care on hospital level should be considered as important opportunity for improvements in outcomes of rectal cancer care. As hospital volume is not predictive on hospital level, further research into additional indicators on hospital level, e.g. clinical pathways, is needed.

Conflict of interest statement

None declared.

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