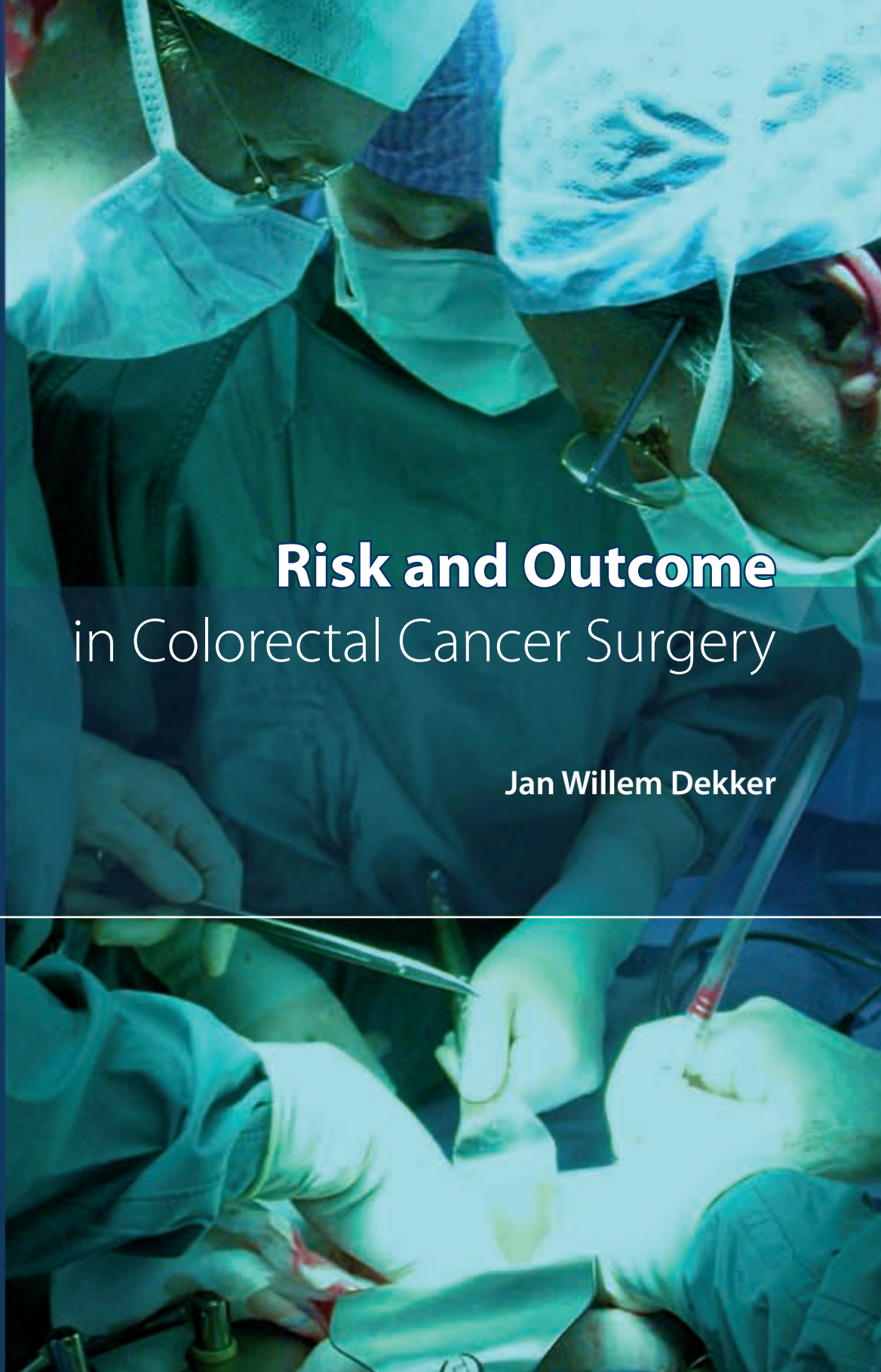

Risk and Outcome
in Colorectal Cancer Surgery

Jan Willem Dekker

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A good physician treats the disease, a better physician treats the patient that has the disease.
(William Ossler)

Aan mijn ouders
Voor Kim, Tim, Anne Jet en Hidde

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Chapter 1

General Introduction

General Introduction

Colorectal carcinoma has a high and growing incidence in the Western world. It is the second most commonly diagnosed cancer in the Netherlands, with an incidence of over 57 per 100 000 per year (European Standardized Rate)1.

Over the years an expanding arsenal of treatment options has improved survival. The EUROCARE Working Group has reported five-year relative survival of elderly (70–84 years) and middle-aged cancer patients (55–69 years)[2]. They observed a significant survival improvement from 1988 to 1999 for all cancers combined and for almost every cancer site, including colon cancer.

Surgery remains the mainstay of colorectal cancer treatment. Although colorectal cancer surgery is common, it is hazardous and can be considered high risk surgery. Colorectal surgery accounts for a disproportionate share of the morbidity, mortality and excess length of stay (LOS) in general surgery [3]. Therefore, with its increasing frequency, colorectal cancer surgery is an important focus for quality enhancement programs.

To improve outcomes we can focus on improvement of the quality of care, and also on better patient selection with subsequent tailored treatment.

Currently on a national level different quality enhancement strategies are being used. Firstly, the adherence to evidence based checklists and guidelines is stimulated to induce a high standard of organised care.
Secondly, selective referral is promoted. This concerns centralisation of medical care to dedicated centres of excellence. However, for colorectal surgery the literature on centralisation is not univocal. Some studies underline the importance of caseload and specialisation[4-7], while others find no significant differences in outcome between different categories of care providers[8-10]. Thirdly, outcome registration is used to measure and subsequently enhance the quality of care. Outcome

registration with feedback has been shown to improve results of surgery. Rigorous and timely feedback about surgeon and hospital outcomes relative to peers can enhance quality as it helps to identify opportunities for improvement and stimulates according action. There is strong evidence this can reduce both overall mortality and variation between health care providers[11-13]. In 2006, in the Midwestern part of the Netherlands a regional audit for colorectal cancer care (KIC) was started in the nine affiliated hospitals of the Leiden Cancer Registry. The data collection of the cancer registry was extended to data that reflected quality of care and case mix factors. The prospectively collected data were used for benchmarking and feedback, ultimately to improve the quality of colorectal cancer care in the entire region. The definite results concerning a measurable improvement of colorectal cancer care have to be awaited. However, a similar program for breast cancer has shown a clear improvement of care [14]. In 2009 a nationwide audit has started with the ultimate goal to improve the care for colorectal cancer patients in the Netherlands. The audit started as a surgical audit, but will be multidisciplinary in the near future. It intends both to increase the transparency of colorectal cancer care and to collect valuable data for quality enhancement through the same principles as outlined before.

Quality of care

Quality of care can be viewed from different perspectives. Policy makers often consider it to have five dimensions. Good quality care must be safe, effective, patient centred, accessible and efficient. From a clinical perspective, a sound preoperative workup, meticulous operative technique, early detection of postoperative complications and adequate action when indicated are elementary to good surgical care and the mainstay of surgical quality. A more used analytic approach of describing the quality of care is in terms of structure of care, process of care and outcomes [15]. The structure of care concerns surgeon and hospital factors, such as case load, specialisation, the level of intensive care unit and other dedicated facilities.

The process of care concerns patient selection and evaluation, the intra-operative

care and last but not least prevention, recognition and management of complications. Three recent studies of Ghaferi et al. showed that the difference in deaths following major complications was the primary determinant of variation in mortality between hospitals [16-18]. *This failure to rescue phenomena indicates that effective management of postoperative complications can reduce postoperative mortality and improve patient outcomes.*

Finally, to describe quality of care, outcomes have to be defined such as complications and mortality. There is a growing recognition that the variations in surgical outcome are not completely contributable to variation in surgical quality of care. Variations in surgical outcome can also be attributed to chance and case mix [19]. Surgical outcomes can vary simply due to chance, resulting in statistically imprecise estimates of performance. Furthermore, differences in patient factors (case mix) also contribute to variation in outcomes.

Risk stratification

Surgery always concerns the balance of risk and benefit. Both risk and benefit can vary immensely among patients. For instance a right hemicolectomy in a sixty year old otherwise healthy woman does not compare to a low anterior resection in an eighty five year old man with serious cardiopulmonary co morbidity. Likewise a patient with stage IV disease and an asymptomatic colon tumour will not benefit from surgery as a symptomatic patient with stage II disease does. Outcome and prognosis are determined by several patient, tumour and treatment characteristics. In order to achieve the best outcomes for colorectal cancer patients, detailed and objective information on risk profiles is indispensible. For the individual patient this should guide clinical judgment and the administration of tailored care. On a hospital or population level knowledge of risk factors can lead to adjusted (better tailored) treatment protocols and better information on case mix influences adding to an improved care for colorectal cancer patients.

Outline of this thesis

In this thesis different risk factors and outcome measures for colorectal cancer patients are studied. More objective information on risk could improve patient selection and with subsequent better tailored treatment this has the potential to improve the quality of care for colorectal cancer patients. Outcome and prognosis are determined by patient, tumour and treatment characteristics.

Accurate staging is indispensable for a balanced decision on further treatment and an accurate estimation of prognosis. Currently, the UICC/AJCC TNM staging system[20-21] is considered the most robust tool for prediction of prognosis and for decisions on the delivery of adjuvant treatment. However, some criticism is raised towards the validity of this system[22] and the usefulness of other tools such as nomograms is being explored [23]. In addition to the UICC / AJCC TNM stage[20], the metastatic lymph node ratio (i.e. the ratio of metastatic to retrieved lymph nodes) was found to be an important independent prognostic factor in various malignancies [24-27]. In ***chapter 2*** the prognostic capacity of the metastatic lymph node ratio is assessed for rectal cancer.
If it has a predictive value in addition to the UICC / AJCC TNM stage [21], it could improve identification of high risk patients and may also have the advantage to be less dependent on the number of retrieved lymph nodes than N stage. Especially in rectal cancer adequate retrieval of lymph nodes may be troublesome.

Patient and treatment characteristics are main determining factors for risk and outcome in colorectal cancer surgery. Often these factors interact.
Anastomotic leakage is a major problem in colorectal surgery. It often results in serious morbidity, increased healthcare costs and even death. Anastomotic leaks are also associated with local recurrences and reduced survival[28-30]. It has been reported that clinical risk assessment for anastomotic leakage by the operating surgeon has a low predictive value and underestimates leakage risk [31]. ***Chapter 3*** describes the development and testing of a risk score for anastomotic leakage, to help identify high risk patients. Such a risk score could facilitate the intra-operative

decision regarding whether or not to construct a (non functional) stoma.

As cancer treatment improves and cancer screening programs develop, the number of patients with multiple metachronous malignancies is increasing [32-35].
Chapter 4 investigates the prognostic importance of a previous non-colorectal primary malignancy for colorectal cancer patients.
The presence of comorbidity effects treatment decisions[36-39] and the prognosis of patients receiving colorectal cancer treatment [40-44]. In colorectal cancer research, several validated comorbidity measures are used to predict mortality after treatment [45-48]. However, the comparability of these different comorbidity measures in predicting postoperative mortality remains unclear. ***Chapter 5*** compares frequently used comorbidity measures and their additional value in models predicting the outcome of colorectal cancer.

Colorectal cancer has a large incidence peak around 74-80 years and approximately half of colorectal patients are over seventy years of age [1]. ***Chapters 6 and 7*** address old age as a risk factor for impaired survival and elaborate on what constitutes age related survival differences.

An important outcome measure for surgery is postoperative mortality. This is usually described as mortality within thirty days after surgery. However, earlier studies have shown that 30-day mortality after surgery is not an appropriate measure of surgical risk, as a significant proportion of patients die in the months that follow [49-51]. This suggests that there may be a prolonged impact of the insult of surgery. ***Chapter 8*** and ***chapter 9*** look into the aetiology of the excess mortality in the first postoperative year. ***Chapter 8*** identifies risk factors and ***chapter 9*** looks into causes of death.

Finally, in ***chapter 10*** the thesis is summarised. This chapter also contains a general discussion with future directives.

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Chapter 2

Metastatic lymph node ratio in stage III rectal cancer; prognostic significance in addition to the 7th edition of the TNM classification

JWT Dekker
KC Peeters
H Putter
AL Vahrmeijer
CJH van de Velde

European Journal of Surgical Oncology 2010 dec; 36(12): 1180-6.

Abstract

Aims: Optimal staging in rectal cancer is indispensable for the decision on further treatment and estimation of prognosis. This study assesses the prognostic capacity of the metastatic lymph node ratio (LNR) in addition to the new TNM classification.

Methods: LNR was determined, in stage III patients from the Dutch TME trial. Six year median follow up data from the trial database were used to analyse the relation of LNR to overall survival (OS) and local recurrence (LR). The relation of LNR to lymph node yield was assessed and appropriate cut off values of LNR for clinical use were determined.

Results: 605 patients were analyzed. 278 underwent preoperative radiotherapy. 82 patients developed a local recurrence and 289 distant metastases. LNR was an independent risk factor for OS, hazard ratio 2.10 (95%CI 1.35-3.27) (in addition to age >= 65 years, involved circumferential resection margin (CRM) and new TNM stage) and LR, hazard ratio 2.25 (95%CI 1.02-4.56) (in addition to pre operative radiotherapy and involved CRM). LNR is predictive of OS and LR from a lymph node yield of more than one and more than five respectively. A LNR value of 0.60 offers the best cut off to identify high risk patients.

Conclusions: LNR is an independent risk factor for OS and LR in addition to the 7th edition of the TNM classification. It can aid in predicting prognosis and identifying patients that should be considered for adjuvant treatment.

Introduction

Rectal cancer still poses many challenges to oncologists. Major advantages in surgical technique with complete removal of the mesorectum under vision have led to a significant drop in local failure and improvement of overall survival[1-2]. Also the use of (neo-) adjuvant therapy has contributed to improved prognosis with a tendency towards pre- in stead of postoperative radiation[3-5].

Using TME surgery and pre-operative radiotherapy the problem of local recurrence seems to be contained (5.6% at five years[6]). However, as in colon cancer, distant recurrences are still a matter of concern and occur in 25-30% of patients at five years [6]. Adjuvant chemotherapy can possibly aid, but there is still no strong evidence that its benefits in rectal cancer are comparable to those in colon cancer patients [7-10]. Although there are some studies that show a minor benefit of adjuvant chemotherapy in rectal cancer patients[11-13] a recent European consensus conference failed to reach consensus on its use[14].

Optimal patient stratification is important to identify patients who will most likely benefit from adjuvant therapy. In this manner, overall morbidity from cytotoxic regimens will be reduced and health care costs are cut down by targeted delivery of expensive chemotherapeutic drugs.

Currently, the UICC/AJCC TNM staging system[15-16] is considered the most robust tool for prediction of prognosis and for decisions on the delivery of adjuvant treatment. However, some criticism is raised towards the validity of this system[17] and the usefulness of other tools such as nomograms is being explored[18].

In addition to the UICC / AJCC TNM stage[15], the metastatic lymph node ratio (i.e. the ratio of metastatic to retrieved lymph nodes) was found to be an important independent prognostic factor in various malignancies [19-22]. Also in colon cancer some studies show a strong association of metastatic lymph node ratio (LNR) with

disease recurrence and survival [23-26]. In rectal cancer the evidence is still limited.

If the LNR can be considered as a prognostic factor it may also have the advantage to be less dependent on the number of retrieved lymph nodes than N stage. Especially in rectal cancer adequate retrieval of lymph nodes may be troublesome as it is dependent on many factors such as age over 60, obesity, female sex, small tumour size and localisation, poor differentiation grade, the absence of a lymphoid reaction and neo-adjuvant therapy [27-29].

Some questions remain unanswered. To what extend can the LNR be considered a reliable prognostic indicator? What is the effect of lymph node yield is on the predictive capacity of LNR? Which LNR cut off values have the best discriminative power? Most importantly, very recently the UICC / AJCC TNM system was updated [16] and T stage and N stage were further specified to improve its prognostic capacity. More emphasis is made to the number of retrieved malignant lymph nodes. Considering the inherent correlation between LNR and the number of positive lymph nodes it is not clear whether LNR remains an independent predictor prognosis in addition to this 7th edition of the TNM classification.

The aim of this study is to assess the prognostic capacity of the metastatic lymph node ratio in stage III rectal cancer in addition to the 7th edition of the TNM classification and to identify high risk patients.

Methods

From the database of the Dutch TME-trial, a prospective multicentre randomized trial investigating the value of neo-adjuvant short term radiotherapy applying 5x5 Gy, all UICC / AJCC stage III patients were selected for this study. Inclusion and exclusion criteria for the TME-trial have been published previously by Kapiteijn et al. [30-31]. Tumours had to be below the level of S1/S2 with the inferior tumour margin being 15 centimetres or less from the anal verge as measured during withdrawal of a flexible coloscope.

Surgery was performed between 1996 and 1999. Patients that died in the postoperative phase and patients that did not have adenocarcinoma on definitive pathological examination were excluded. The total number of retrieved lymph nodes and the number of metastatic lymph nodes were recorded and the metastatic lymph node ratio (LNR) was calculated. This was defined as the number of metastatic lymph nodes divided by that of retrieved lymph nodes.

Classic prognostic data were available from the Dutch TME-trial records.

Follow up was registered within the Dutch TME-trial. For the purpose of this study outcome data with a median follow up of 6 years were used (earlier reported by Peeters et al.[6]).

Statistics

Overall survival (OS) was calculated from surgery to all cause mortality or end of follow up (censoring). Local recurrence time (LR) was defined from surgery to the time of evidence of tumour within the pelvic or perineal area, or death (censoring) or end of follow up (censoring).

Univariate and multivariate analyses (of all univariate relations with $p <= 0.1$) were performed using a Cox regression analysis. Since the objective of the multivariate

analysis was to assess the independent prognostic value of LNR, first a multivariate model was constructed using forward selection with the selected ($p < 0.1$ at univariate analysis) covariates. To this model, LNR was then added.

For all Cox regression analyses, hazard ratios were calculated including 95 % confidence intervals (95% CI).

Furthermore LNR was stratified on quartiles and again survival analyses were conducted using Cox regression analyses. Overall survival probabilities were estimated using the Kaplan-Meier method, while for LR the cumulative incidence was estimated accounting for death as competing risk [32].

To determine the best cut off values for LNR, the p-value from a log-rank test comparing LNR < cut off with LNR >= cut off were calculated for every possible cut off value. The smallest p-value was identified indicating the most significant cut off. It is known that such a minimum p-value approach yields biased p-values[33].
Adjusted p-values suggested in that paper, were calculated (based on leaving out the smallest and largest cut off points.

Finally the minimal number of retrieved lymph nodes needed for a reliable LNR was evaluated using a Cox model with number of retrieved lymph nodes (log-transformed), LNR and their interaction. From the estimated coefficients and covariance matrix of this model, for each number of retrieved lymph nodes, the implied hazard ratios and 95% confidence intervals were determined.

For all tests statistical significance was stated as two tailed $p< 0.05$.

Results

Six hundred five patients were included in the present analysis. There was a complete registration of lymph node harvest and survival data for all patients. For two patients information on local recurrence was unknown.

Patients had an average age of 63 years (range 26-92). Preoperative radiotherapy was given to 278 patients (46.0%). Baseline characteristics are shown in **table 1**.

Table 1.
Baseline characteristics of patients from dataset
(605 stage III rectal cancer patients)

variable	characteristics	number
Age, years	< 65	312
	>= 65	293
sex	Male	370
	Female	235
Preoperative Radio Therapy	PRT+	278
	PRT-	327
Largest tumour diameter	< 5 cm	370
	>= 5 cm	221
	missing	14
pT stage	<=T2	115
	T3	458
	T4a	17
	T4b	12
pN	N1a	190
	N1b	185
	N2a	116
	N2b	114
Tumour stage	III A (T1-2/N1, T1/N2a)	85
	III B (T3-4a/N1, T2-3/N2a, T1-2/N2b)	405
	III C (T4a/N2a, T3-4/N2b, T4b/N1-2)	115
Involved CRM	No	427
	Yes	175
	missing	3
Retrieved lymph nodes	< 12	378
	>=12	227
Adjuvant treatment	Chemotherapy	99
	Radiotherapy*	53
	Chemo radiation*	14

The pT stage, pN stage and tumour stage were defined according to the 7th edition of the UICC / AJCC TNM staging.
CRM, circumferential resection margin
* Patients receiving adjuvant radiotherapy/ chemo radiation had an involved CRM according to the pathology report (Marijnen et al. reported on this group (43)).

The median number of retrieved lymph nodes was 9 (range 1-47). The median number of malignant lymph nodes was 2 (range 1-40).

During the follow up period 306 patients (50.7%) had a recurrence, 82 (13.6%) had a local recurrence and 289 (47.8%) developed distant metastases. Sixty three patients (10.4%) developed both local and distant recurrences. Three hundred twenty eight patients (54.2%) died during follow up. Two hundred sixty (43.6%) patients died of disease recurrence. Median follow up time for patients still alive at the end of study (n=277) was 6 years (range 1-9 years).

Univariate Cox regression analyses incorporating baseline characteristics showed that LNR, pN-stage, tumour-stage, number of malignant lymph nodes and involved circumferential resection margin (CRM) were significantly correlated to overall survival (OS) and local recurrence (LR). Age of 65 or more years, pT-stage and retrieved lymph nodes < 12 were significantly related to OS, but not to LR. Pre operative radiotherapy significantly decreased LR, but not OS.

Multivariate analysis is shown in **table 2**. When LNR was added, it was found to be an independent risk factor for OS and LR (hazard ratio 2.10 (95% CI 1.35-3.35 and 2.25 (95% CI 1.02-4.96) respectively).

Table 2

Multivariate Cox regression analysis for OS and LR

		Overall Survival		Local Recurrence	
variable	**characteristics**	**HR (95%CI)**	**P- value**	**HR (95%CI)**	**P-valuel**
Age, years	>= 65	1.77 (1.41-2.22)	<0.01	n.a.	
Preoperative Radio Therapy	PRT+	n.a.		0.43 (0.27-0.70)	<0.01
pT stage	T<=2		0.15	n.a.	
	T3			n.a.	
	T4a			n.a.	
	T4b			n.a.	
pN	N1a		0.82		0.86
	N1b				
	N2a				
	N2b				
Tumour stage	III A		<0.01		0.55
	III B	1.78 (1.18-2.67)			
	III C	2.88 (1.73-4.78)			
Involved CRM	Yes	1.52 (1.20-1.93)	<0.01	2.30 (1.46-3.62)	<0.01
Retrieved lymph nodes	< 12		0.86	n.a.	
Malignant lymph nodes		1.02	0.08		0.71
LNR		2.10 (1.35-3.27)	<0.01	2.25 (1.02-4.96)	0.04

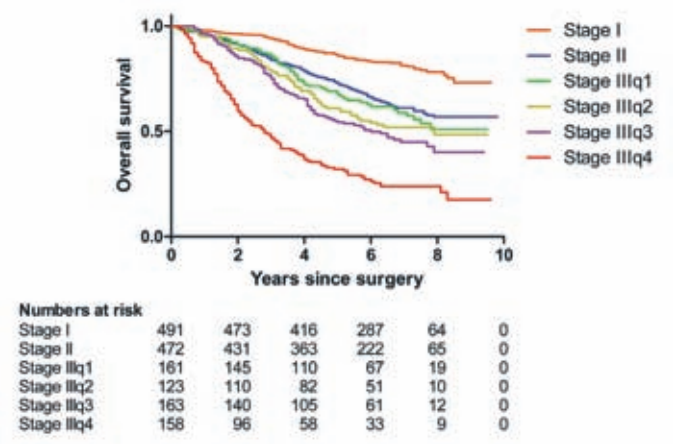
Covariates with trend-significance (p<0.10) in univariate analysis were entered in multivariate analysis.
HR, hazard ratio; CI, confidence interval; CRM, circumferential resection margin; n.a., variables not selected for multivariate analyses because they were not trend significant in univariate analysis.

Influence of lymph node yield

The Cox model used to determine the influence of the number of retrieved lymph nodes on the predictive capacity of LNR showed that LNR is predictive of OS from a lymph node yield of two nodes or more (**figure 2A**). For a significant prediction on LR at least six lymph nodes had to be retrieved **(figure 2B)**

Figure 1

Kaplan-Meier estimates of overall survival according to stage I, II and III divided by LNR-quartiles; q1, q2, q3, q4.



Numbers at risk						
Stage I	491	473	416	287	64	0
Stage II	472	431	363	222	65	0
Stage IIIq1	161	145	110	67	19	0
Stage IIIq2	123	110	82	51	10	0
Stage IIIq3	163	140	105	61	12	0
Stage IIIq4	158	96	58	33	9	0

Cut off values

To determine cut off values for LNR further analyses were performed. First LNR was stratified on quartiles (LNR 0-0.17, 0.17- 0.33, 0.33-0.60, 0.60-1).

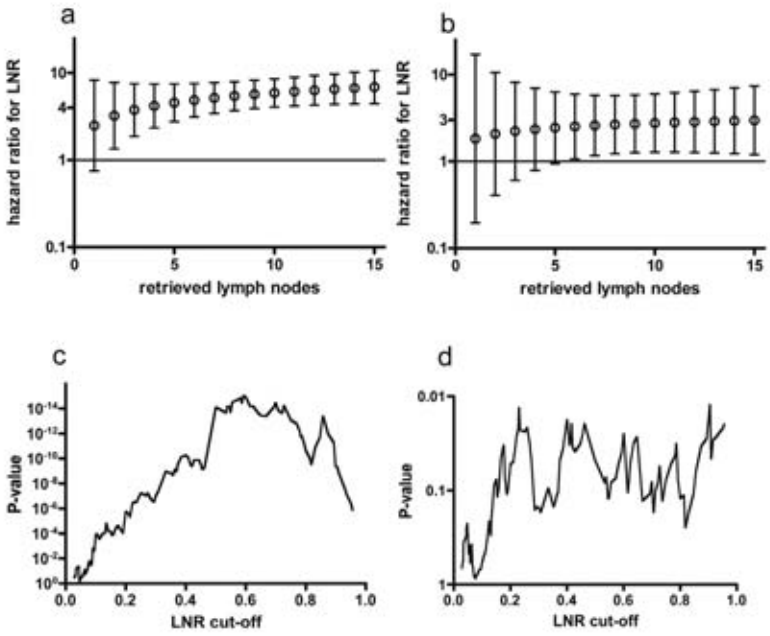
Univariate and multivariate analyses were repeated for LNR quartiles. LNR-quartile groups were independent risk factors for OS ($p<0.04$), but not for LR ($p=0.62$).

Kaplan-Meier curves for OS according to quartiles are shown in **figure 1**. Kaplan-Meier curves for stage I and stage II patients (from TME trial records) are added. Stage II patients did not have different outcomes from the lowest LNR quartile group (HR 1.15 (95% CI 0.85-1.55)

Figure 2

a/b Influence of number of retrieved lymph nodes on predictive capacity of LNR for OS (a) and LR (b)

c/d Inverse unadjusted p-values for LNR cut offs for OS (c) and LR (d), indicating discriminative value of all possible cut off values. Lowest p-value indicating best discriminative power (= highest point on curve)

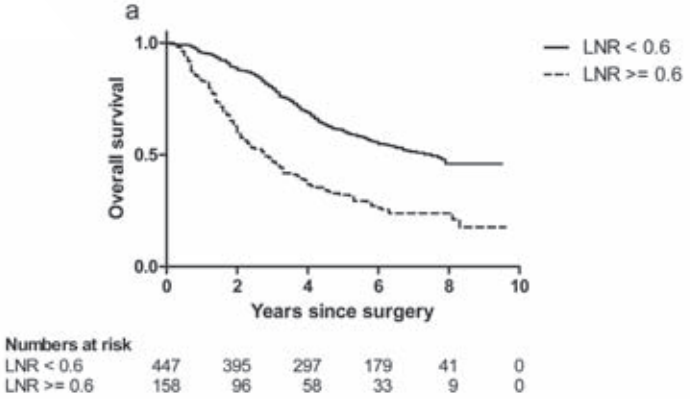


Figures 2C and **D** show the p-values of the log-rank test comparing low (LNR < cut off) and high (LNR >= cut off) LNR according to all cut off values in the data.

Only patients with a sufficient lymph node yield (>1 and >5 respectively) were entered into this model. For OS the lowest p-value indicating the best cut off was found for LNR=0.60. The adjusted minimum p-value found was 2.3*10-13. For LR p-values were not so small. Here no distinct cut off value could be identified **(figure 2d)**; the adjusted minimum p-value found was 0.34.

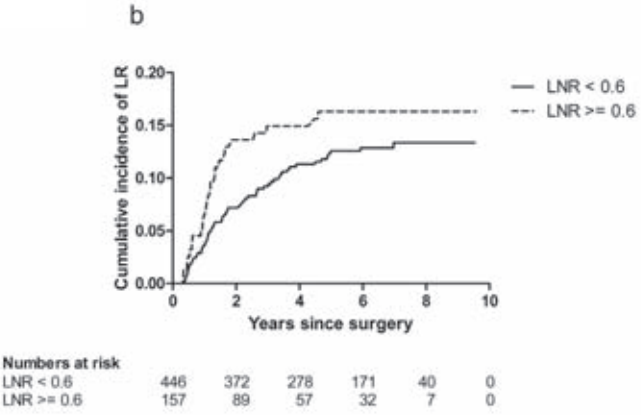
When patients were stratified on LNR < 0.60 and >=0.60, 5-years OS was 61 vs. 32%, HR 2.45 (95% CI 1.96-3.08) and 5-years LR rate 12.6 versus 16.3%, HR 1.65 (95% CI 1.03-2.64). Kaplan-Meier and cumulative incidence curves are shown in **figure 3**.

Figure 3
Kaplan-Meier curves of OS (a) and cumulative incidence curve of LR (b) for Stage III patients subdivided by LNR cut off value 0.60 and Kaplan-Meier curves of OS for Stage III patients subdivided by TNM stage IIIA, IIIB, IIIC and within sub-stage by LNR cut off value 0.60 (c)



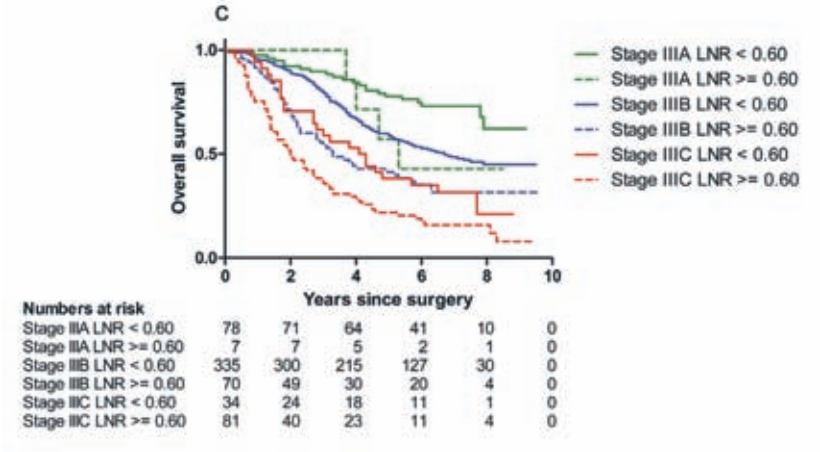
Numbers at risk

LNR < 0.6	447	395	297	179	41	0
LNR >= 0.6	158	96	58	33	9	0



Numbers at risk

LNR < 0.6	446	372	278	171	40	0
LNR >= 0.6	157	89	57	32	7	0



Numbers at risk

Stage IIIA LNR < 0.60	78	71	64	41	10	0
Stage IIIA LNR >= 0.60	7	7	5	2	1	0
Stage IIIB LNR < 0.60	335	300	215	127	30	0
Stage IIIB LNR >= 0.60	70	49	30	20	4	0
Stage IIIC LNR < 0.60	34	24	18	11	1	0
Stage IIIC LNR >= 0.60	81	40	23	11	4	0

Discussion

The present study investigated the predictive capacity of metastatic lymph node ratio (LNR) in stage III rectal cancer. LNR was, in addition to the updated (7th) edition of the UICC/ AJCC TNM staging, an independent prognostic factor for LR and OS. Furthermore we determined the minimum number of retrieved lymph nodes required to ensure that LNR is a prognostic factor (two for prediction of OS and six for prediction of LR rate). Finally a cut off value of 0.60 was calculated for which LNR is most discriminating.

For rectal cancer the prognostic significance of the metastatic LNR was earlier addressed in four studies [34-37]. All these studies determined the predictive capacity of LNR in addition to the previous (6th edition) TNM classification. In comparison to the present (7th edition) TNM classification the earlier classification contained less detailed information on the number of malignant nodes and thus less prognostic information. This could mean these studies found a larger effect of LNR than they would have in addition to the updated TNM classification. The present study shows that even with the 7th edition of the TNM classification, LNR can still improve patient stratification.

Influence of lymph node yield

The use of preoperative radiotherapy may alter the prognostic impact of clinical parameters among which the LNR. Only in the study by Moug et al. [37] neo-adjuvant radiotherapy was used and then only in 21 patients.

Neo-adjuvant therapy diminishes the number of retrieved lymph nodes [27-29-38]. The influence of lymph node yield on the predictive capacity of LNR has been a matter of debate. It is argued that the poor prognosis in patients with a high LNR might be attributed to an inadequate LN dissection [39].

After all, if the denominator (the number of retrieved lymph nodes) is smaller the LNR will be higher and an inadequate LN dissection itself is associated with poor survival [40]. However Derwinger et al. [41] found that in colorectal cancer at least part

of this association is due to stage migration. Interestingly this is exactly where LNR can be useful. Reports on gastric cancer [19-42] show, that LNR-based staging can halve the incidence of stage migration.

In this study inadequate lymphadenectomy as defined by the UICC and AJCC as the retrieval of less than 12 lymph nodes was not independently related to OS and LR. Furthermore there was no interaction between LNR and the retrieval of less than 12 or 12 and more lymph nodes in relation to OS and LR (p=0.41 and p=0.84).

For a more specific answer to the question whether lymph node yield affects the predictive capacity of LNR, the present study tried to quantify this effect for every lymph node harvested.

LNR showed to be predictive for OS for a lymph node yield of more than one (figure 2A). This means it is a reliable predictor for OS in the vast majority of patients (594 out of 605 patients (98%) in this study). For a significant prediction on LR more than five lymph nodes need to be retrieved (figure 2B), which was the case in 474/605 patients (78%).

As expected the number of retrieved lymph nodes was lower in patients that received preoperative radiotherapy compared to the other patients (median 8 and 11 respectively, $p<0.01$). As a consequence the LNR was higher (median 0.39 and 0.29, $p<0.01$). However, this had no effect on the predictive capacity of the LNR. A test for interaction showed no interaction between LNR and radiotherapy in relation to OS and LR (p=0.94, p=0.50 respectively).

Cut off values

Previous studies have stratified patients according to LNR in different ways. Methods to determine the cut off varied and different cut off values are used. Stocchi et al. [34] stratified by the percentage of positive nodes (0-25%, 25-50%, 50-75%, 75-100%).

Most studies, including the other studies in rectal cancer [35-37], stratified on quartiles. After stratifying in quartiles, overall the LNR lost its value for predicting LR. Only the highest quartile remained strongly associated with LR. All quartiles were prognostic for OS.

Interestingly stage II patients did not have a different prognosis from patients in the lowest quartile group (0-0.16). This is probably due to inadequate staging for stage II patients. When stage II patients were subdivided to adequacy of lymph node yield (<12 versus >=12), adequately sampled stage II patients (>=12 lymph nodes retrieved) had a better prognosis than stage III patients (p=0.04; data not shown). However, inadequately sampled patients (<12 lymph nodes retrieved) had no different survival than stage III patients in the lower two quartile groups (p=0.82 and p=0.13 respectively; data not shown).

The actuarial overall survival data in the lowest 3 quartiles (0-0.60) are comparable, while there is an apparent difference with the highest quartile (0.60-1) (figure 1).

These findings do not match the results of Peng et al.[35], Kim et al.[36] and Moug et al.[37] They all found that only OS in the middle quartiles was comparable and Peng suggested combining them for stratification. These different findings could be based on differences in distribution of quartiles. In this study cut off values between quartiles seem to be somewhat higher than in the previous studies. This could be the effect of preoperative radiotherapy (46% of patients) resulting in a higher LNR as outlined above. In patients that did not receive preoperative radiotherapy quartile distribution was 0-0.14; 0.14-0.29; 0.29-0.50; 0.50-1, in accordance with Peng's data. Kaplan Meier curves for these patients also match the previous studies (not shown). However it should be stressed again that neo-adjuvant radiotherapy has proven its value and it is the standard of care in the Netherlands and many Northern European countries. Therefore the distribution of quartiles in the present study is probably more applicable to patients treated in these countries.

Figures 2C and D show the p-values of the log-rank test comparing low (LNR < cut off) and high (LNR >= cut off) LNR according to all cut off values in the data. In search of the cut off value with the best discriminative power for OS we found the LNR value of 0.60 (figure 2c). For LR rate no discriminating cut off value was found (figure 2d). The cut off value of 0.60 produces absolute differences for 5-years OS and LR (figures 3A and B). Using one cut off is very practical for modifying existing staging practices. Applying it in addition to the 2009 TNM stage it can modify patient stratification to more accurately reflect the impact on prognosis (figure 3C).

A possible limitation of this study could be the fact we used data from a trial that was designed to study the effect of preoperative short course radiotherapy and did not have LNR as a covariate or outcome measure. However, this multicentre study with contributions of more than 80 hospitals reflects common practice among radiation oncologists, surgeons and pathologists throughout the Netherlands. Furthermore the data were gathered under extensive quality control within the framework of the TME trial [30]. Therefore, we believe that this study provides useful information that may improve rectal cancer treatment.

Conclusions

Accurate staging in rectal cancer is indispensable for a balanced clinical decision on further treatment and an accurate estimation of prognosis. This study shows that in addition to the 7th edition of the UICCC / AJCC TNM classification the metastatic lymph node ratio (LNR) is an independent prognostic factor for overall survival and local recurrence in stage III rectal cancer. LNR is a reliable measure for OS from a lymph node yield of two or more. For adequate prediction of LR at least six lymph nodes need to be retrieved. Stratification of patients is possible by dividing them in quartiles, but the LNR value with the best discriminating power is 0.60. This cut off value can improve TNM staging per stage and identify high risk patients. This could add to the discussion on further (adjuvant) treatment in the multidisciplinary team meeting.

Acknowledgements

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Chapter 3

Predicting the risk of anastomotic leakage in left-sided colorectal surgery using a colon leakage score

JWT Dekker
GJ Liefers
JCA de Mol van Otterloo
H Putter
RAEM Tollenaar

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Abstract

Aims: Anastomotic leakage following colorectal surgery still occurs all too frequently, and this complication is difficult to predict. A nonfunctional stoma may reduce the risk of clinically relevant leaks but is overtreatment for most patients. More accurate assessments of the risk of anastomotic leakage would be very helpful in tailoring treatment in colorectal surgery. Therefore, a Colon Leakage Score (CLS) was developed and tested.

Methods: The CLS was developed based on information from the literature and expert opinions. It was tested in a retrospective cohort of consecutive patients undergoing left-sided colorectal surgery with primary anastomosis in a teaching hospital in the Netherlands.

Results: the test cohort, 10 of 121 patients that were not treated with a nonfunctional stoma experienced anastomotic leakage. The mean CLS in the leakage group was 16 versus 8 in the group that did not have a leak ($p<0.01$). Using receiver-operating characteristics, the area under the curve (AUC) showed that the CLS was a good predictor (AUC=0.95, CI 0.89 - 1.00) of anastomotic leakage. Furthermore, logistic regression analysis with CLS as a predictor for anastomotic leakage showed an odds ratio of 1.74 (95% CI 1.32 – 2.28, $P < 0.01$).

Conclusions: The CLS can predict the risk of anastomotic leakage following left-sided colorectal surgery. After further validation, this score may help the surgeon make a more individualized, safer decision regarding whether to perform an anastomosis or a make a (nonfunctional) stoma.

Introduction

Anastomotic leakage after colorectal surgery is a major and potentially life-threatening complication. Unfortunately, it still occurs all too frequently. The incidence rate, especially after low anterior resections, has been reported to be as high as 15 to 20% in some series [1-2].

Over the years, many studies have identified risk factors for anastomotic leakage [1-48]. However, to date, it is not possible to predict the likelihood of leakage in an individual patient. Few of the risk factors are conditionally independent, so combining these factors is methodologically unsound. In addition, multiple regression analysis does not seem to offer the solution. In studies with less than ten cases of anastomotic leakage per variable entered into the model, this technique lacks the required sample size and regression coefficients, such that the results are likely to be imprecise [49]. Judging by the plethora of risk factors identified in the literature, anastomotic leakage has multiple overlapping etiologies. Therefore, studies that use multiple regression analysis are not useful if they only identify a small number of independent risk factors. Combining the odds ratios for these risk factors with odds ratios for risk factors identified in other studies is methodologically hazardous. Therefore, the clinical decision about whether to perform a colonic anastomosis or a stoma remains difficult.

Clinical risk assessment for anastomotic leakage by the operating surgeon has a low predictive value and underestimates leakage risk [50]. There has been a recent trend to create more (nonfunctional) stomas to counteract the problem of anastomotic leakage. However, unnecessary stoma's can also induce morbidity and discomfort and increase healthcare costs [51]. In addition, continuity is never restored in many patients.

There is a need for patient stratification. However, in absence of large and detailed datasets that can overcome the methodological problems described above, ap-

propriate stratification criteria cannot be identified through logistic regression analysis of risk factors. Therefore, this study used an alternative approach. The aim was to develop a risk score for anastomotic leakage based on information from the literature and expert opinion, after which we planned to test the predictive value of the scoring system.

Methods

Construction of the Colon Leakage Score (CLS)

A systematic search for English language literature published between January 1990 and September 2010 was undertaken on the biomedical bibliographical databases Pubmed and the Cochrane Library to identify risk factors for anastomotic leakage.

The search headings "anastomotic leakage and colorectal surgery" in combination with the keywords "risk factor" were used. The "related articles" function was used to broaden the search. Reference lists from each study were used to obtain more studies that were eligible. Letters, reviews without original data, non-English language papers, overlapping patient populations and animal studies were excluded. Initial searches focused on studies that analyzed risk factors associated with the occurrence of leaks in colorectal anastomosis. These clinical studies were required to have primary or secondary goals of identifying risk factors for anastomotic leakage.

The definitions used in the reviewed literature were not always well defined. The clinical signs and symptoms most frequently described were localized or generalized peritonitis, but fecal or purulent discharge from the wound and pelvic or anal drainage were also considered signs of anastomotic leakage. Some studies also included patients in whom anastomotic leak was discovered only on routine radiological examination; these were excluded from our study.
For practical reasons, a set of easily accessible clinical items was chosen. The literature does not offer practical combinations of clinical factors with quantified

impacts. Therefore, the contribution of various risk factors was weighted by the collective expertise of three dedicated colorectal surgeons, analogous to the Delphi-method[52], with multiple iterations. Points were attributed to each factor, resulting in a "Colon Leakage Score" (CLS).

Patients in the test set

The CLS was tested in a retrospective cohort of all consecutive patients that underwent left-sided colorectal surgery with primary anastomosis at Medical Center Haaglanden (a teaching hospital in the Netherlands) in 2005 and 2006. Left-sided colorectal surgery was defined as left colectomy, sigmoid resection or rectal resection. The CLS was calculated from information on patient charts and hospital computer records. Patients that received a nonfunctional stoma were analyzed both separately and in combination with the other patients. Patients with colonic and rectal anastomoses were analyzed as one group and as separate groups. Some patients had laparoscopic surgery. To rule out any possible influences of laparoscopic surgery, these patients were compared to patients that had open surgery.

Patients that underwent an elective rectal resection had an enema prior to surgery. During the study period, the hospital protocol was not to use further mechanical bowel preparation.

The type of anastomosis - i.e., stapled or hand sewn and single- or double-layered - was not recorded in our series.

Anastomotic leakage was defined by clinically relevant operative and / or radiological findings. Postoperative pyrexia or septicemia with localized or generalized peritonitis and fecal or purulent discharge from the wound or pelvic drains were considered signs of anastomotic leakage. Patients whose leak was only detected on radiological examination and was not clinically relevant were not considered to have an anastomotic leak. Routine contrast enema was not performed after the operation.

Statistics

The mean total-scores for patients with and without anastomotic leakage were compared using a student's t-test for equality of means. Fisher's exact test was used to identify differences in occurrence of anastomotic leakage between groups. The strength of the CLS in predicting anastomotic leakage was assessed by the receiver-operating characteristics (ROC). Furthermore logistic regression analysis was used to determine the correlation between the CLS and the presence or absence of anastomotic leakage. In addition, the predicted probability of anastomotic leakage per CLS value was determined. For all tests, statistical significance was stated as two-tailed $p< 0.05$.

Results

Our search of the literature resulted in a total of 221 studies, of which 64 were eligible for inclusion [1-48] [53-68]. Consensus was reached on inclusion of risk factors and their relative weight after four iterations.

The constructed Colon leakage Score (CLS) system is shown in **Table 1**. The minimum possible total-score for left-sided colorectal surgery = 0, and the maximum total-score = 43 points.

In 2005 and 2006 at Medical Center Haaglanden, a total of 139 consecutive patients underwent left-sided colorectal surgery with primary anastomosis (101 colons and 38 rectums). Eighteen patients had a nonfunctional stoma. Operations were performed by nine different surgeons and residents. Data collection resulted in a complete list of items for all but two patients. In these two patients, the only missing data were perioperative blood loss. Here, the mean blood loss for all patients was used as a value to compute the CLS. These two patients had average operative times. Furthermore, the difference between their pre- and postoperative hemoglobin levels did not exceed 1.0 mmol/l. Neither patient received a blood transfusion.

Table 1
Colon Leakage Score (CLS) points per variable
Between brackets references are shown for each variable

	score
Age (years) [2;29;57]	
< 60	0
60-69	1
70-79	2
>= 80	4
Gender [3;17;19;29;30;37;41;43;44;67;68]	
Female	0
Male	1
ASA [10;28;42;45;67]	
I	0
II	1
III	3
IV	6
BMI [10;13;16;30;34]	
19-< 25	0
25-30	1
> 30/< 19 or weight loss (> 5 kg/6 months)	3
Intoxication	
No	0
smoking (any) [2;23;32;37;56]	1
alcohol (> 3U/day) [2;13;56;59]	1
steroids (present use, excluding inhalers) [3;21;46]	4
Neoadjuvant therapy	
No	0
Radiotherapy [15;17;28;35]	1
Chemoradiation [39;43;58;66]	2
Emergency surgery [2;11;13;21;34;45-47]	
No	0
Bleeding	2
Obstruction	3
Perforation	4
Distance of anastomosis to anal verge (cm)	
[9;15;17;19;20;22;24;26;28;29;31;32;37;39;41;47;48;54;57;64]	
> 10	0
5-10	3
< 5	6
Additional procedures	
no	0
yes	1
Blood loss (cc) [28;37;41;57;68] blood transfusion	
[11;13;22;36;46;47]	0
< 500	1
500-1000	3
1001-2000	6
> 2000	
Duration of operation (hours:minutes) [3;13;21;40;42;65]	
< 2:00	0
2:00 - 2:59	1
3:00 - 3:59	2
>= 4:00	4

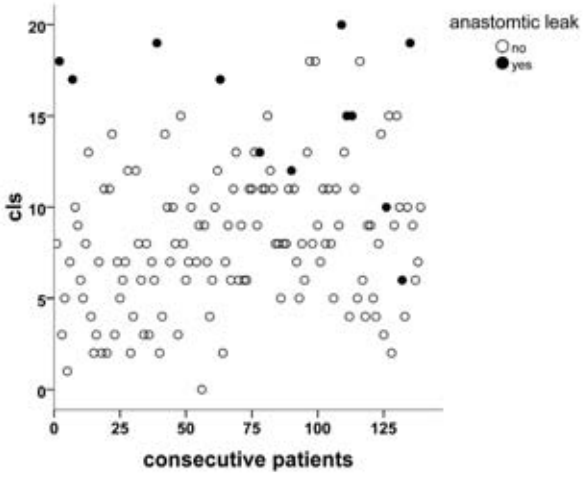
The patient, treatment and outcome-characteristics of the validation set are shown in **Table 2**. CLS values and anastomotic leak data for all 139 consecutive patients are shown in **Figure 1**. In one patient, primarily undetected stapler failure occurred. On the first postoperative day, urgent relaparotomy revealed dehiscence of the complete stapled anastomosis. This patient is the one outlier in Figure 1 with a CLS of six. Anastomotic leakage occurred in 10 of 121 cases (8.3%) that did not receive a nonfunctional stoma and in two of 18 cases with a nonfunctional stoma (p=0.66). After colon resections, the incidence of anastomotic leakage was 4/101, and after rectal resections, it was 8/38 (p<0.01).

Table 2
Patients, Treatment and Outcome Characteristics of Validation-set. (n=121)
The number of patients is given for binary and ordinal variables.
Median and range are given for continuous variables.

characteristics		number	continuous
Patients			
Age (years)	Median		66
	Range		25 - 93
Gender	female	52	
	male	69	
ASA	I	26	
	II	65	
	III	25	
	IV	5	
BMI	<19	2	
	19- < 25	52	
	25-30	52	
	>30	15	
Smoking (any)		31	
Alcohol (> 3 U/day)		6	
Steroids		3	

characteristics		number	continuous
Treatment			
preop. Radiotherapy		7	
preop. Chemoradiation		2	
Emergency surgery		20	
Bleeding		1	
Obstruction		7	
Perforation		12	
Laparoscopic surgery		46	
conversions		11	
Additional intervention		29	
Colonic anastomosis		95	
Rectal anastomosis		26	
Distance to anal verge (cm)	median		5
(for rectal anastomoses)	Range		3 - 12
Blood loss (cc)	Median		300
	Range		20 – 14 000
Duration of operation (hours:minutes)	Median		2:45
	range		0:50 – 9:00
Outcome			
Anastomotic leakage		10	
Mortality		4	
	anastomotic leakage	1	
	pneumonia	1	
	mycardial infarction	1	
	bleeding gastric ulcer	1	
CLS	Median		8
	range		0 - 20

Figure 1
Scatter-plot of CLS for all 139 consecutive patients that had left sided colorectal surgery with and without anastomotic leakage.

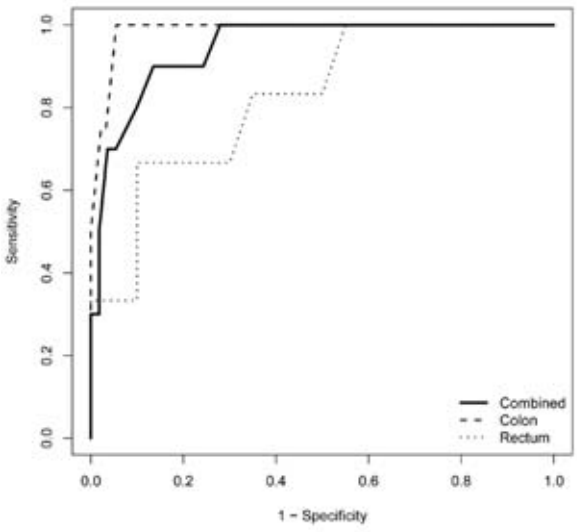


Patients without a nonfunctional stoma

For all patients without a nonfunctional stoma, the mean computed CLS for patients with anastomotic leakage was 15.7 versus 7.6 for those without this complication (p<0.01, mean difference 8.1 (CI 5.7 - 10.5)). When colon and rectum cases were analyzed separately, the equivalent mean computed CLS values were 7.0 versus 16.0 for colonic (p<0.01, mean difference 9.0 (CI 5.6 - 12.3)) and 10.2 versus 15.5 for rectal anastomoses (p<0.01, mean difference 5.3 (CI 1.5 - 9.0)), respectively. The mean difference for colonic anastomoses was not significantly higher than that for rectal anastomoses (p=0.12), so there is no evidence suggesting a difference in the association between CLS and anastomotic leakage based on site of anastomosis. No differences were found in CLS values between colon and rectum patients (p=0.26).

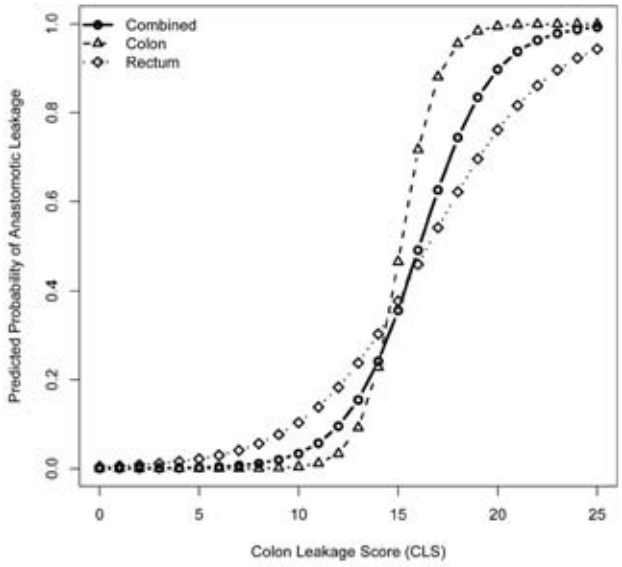
Using the receiver-operating characteristics curve, the area under the curve (AUC) showed the CLS to be an excellent predictor (AUC=0.95, CI 0.89 - 1.00) for the occurrence of anastomotic leakage **(Figure 2)**. When they were analyzed separately, different ROC-curves were found for colon (AUC=0.99, CI 0.96 - 1.00) and rectum patients (AUC=0.83 (CI 0.64 - 1.00) **(Figure 2)**.

Figure 2
ROC curve for CLS versus Anastomotic Leakage for all patients with primary anastomosis without a defunctioning stoma (n=121) and patients that had colonic or rectal surgery separately.



Logistic regression analysis using CLS as predictor of anastomotic leakage revealed an odds ratio of 1.74 (CI 1.32 - 2.28, P < 0.01). For patients who underwent colonic anastomosis, the CLS was 2.92 (CI 1.16 - 7.39, p=0.02), and for patients who underwent a rectal anastomosis, it was 1.39 (CI 1.04 -1.86, p=0.02). The predicted probability of anastomotic leakage versus CLS for all unprotected anastomosis, and for colon and rectum separately, is shown in **Figure 3**.

Figure 3
CLS versus predicted probability of anastomotic leakage for all patients with primary anastomosis without a defunctioning stoma (n=121) and patients that had colonic or rectal surgery separately.



Patients with a nonfunctional stoma

When patients with a nonfunctional stoma (n=18) were included in the analyses, the mean CLS in the leakage group was 15.1 versus 8.0 in patients without a leak (mean difference 7.1, CI 4.80 - 9.32, p<0.01). The ROC revealed an AUC= 0.89 (CI 0.77 - 1.00, p<0.01). Logistic regression analysis including patients with a nonfunctional stoma showed an odds ratio of 1.55 (CI 1.27 - 1.88, p<0.01). The mean CLS value for patients with a nonfunctional stoma was different from the mean CLS for patients that only underwent primary anastomosis (10.9 vs. 8.3; difference 2.66 (CI 0.56 -

4.75; p=0.01)). However, there was no difference in the incidence of anastomotic leakage between the nonfunctional group and the other patients (2/18 vs. 10/121; difference 2.8% (CI -12.5 - 18.2; p=0.79)).

Laparoscopic surgery

Laparoscopic surgery was not a risk factor for anastomotic leakage (5/56 in laparoscopy versus 7/83 in open surgery (p=0.919) for all patients and 4/46 versus 6/75 (p=0.893) for nonfunctional stoma patients). There was no difference in the mean total CLS values for the open versus the laparoscopic groups (respectively 9.0 versus 8.1; difference 0.9 (CI -0.64 - 2.28; p=0.27) for all patients and 8.7 versus 7.6; difference 1.1 (CI -0.44 – 2.70) for patients with a stoma).

Discussion

Anastomotic leakage is a major problem in colorectal surgery. It often results in serious morbidity, increased healthcare costs and even death. Though there have been numerous studies on the subject, no evidence-based tools exist to predict anastomotic leakage. Judging by the plethora of risk factors identified in the literature, anastomotic leakage is thought to have many causes. Therefore, creation of a predictive model that takes all these factors into account requires a very large and detailed database. For example, if there are less than ten cases of anastomotic leakage available per variable in a multivariate model, the regression coefficients will likely be imprecise [49]. To test a predictive model that would take into account the 16 items we address in this study (on the basis of our overall leakage percentage of 8.6%), a cohort of 1860 patients would be needed to overcome this problem.

Therefore, we pursued an alternative approach for this study. Instead of using a statistically-derived predictive model, we created a risk score system by a heuristic combination of risk factors identified from the literature. This risk score, the CLS, was then tested in a retrospective cohort of patients from a teaching hospital in

the Netherlands. Although the CLS was generated by a well-structured process, it is subjective. Ultimately, however, the essence of a risk score is that it can predict risk. As long as it can be objectively applied, any subjectivity in the design is inconsequential.

In this study, the CLS accurately predicted the risk of anastomotic leakage following left-sided colorectal surgery. Application of this score correctly predicted which patients should undergo primary anastomosis and which should receive a proximal nonfunctional stoma or a definitive stoma.

To our knowledge, this is the first attempt to construct a scoring system that could predict a patient's risk of anastomotic leakage. The various surgical risk scores that have been developed focus on mortality or overall postoperative morbidity and do not offer straightforward guidance for the intra-operative decision on whether or not to perform an anastomosis. An enormous and detailed database such as the one from the American College of Surgeons National Surgical Quality Improvement Program could possibly help, but we were unable to determine if this database contained all of the necessary information from the publication of Cohen et al. on the ACS NSQIP colorectal risk calculator [69].

Ideally, the CLS would be calculated pre-operatively. However, intra-operative blood loss and duration of the operation are important predictive factors [3-13-21-28-37-40-42-57-65-68]. They can be considered surrogate markers of technical difficulties during the operation. Since an anastomosis is made at the end of a procedure, this information will be available and can be incorporated in the CLS to facilitate clinical decision making in the operating room. All of the other necessary information will be available pre-operatively. This can provide information for patients and their family. In anticipation of the final score, their personal preferences concerning risk of morbidity and mortality versus (temporary) stomata can be taken into account.

Cohort

To test the CLS, we selected a cohort of consecutive patients that underwent left-sided colorectal surgery. Using any cohort of patients to test a predictive score for anastomotic leakage presents a methodological problem when some patients receive a nonfunctional stoma.

Inclusion of these stoma patients could confound the analysis. In patients that receive a nonfunctional stoma (even though they are likely high risk patients), the risk of anastomotic leakage is reduced by a temporary stoma. There is accumulating evidence for similar risk reduction by a nonfunctional stoma in low rectal resections [70-71]. Therefore, the association between the CLS and anastomotic leakage becomes confounded. This methodological problem is not solved if the nonfunctional stoma patients are left out of the analysis, because then the residual group of patients would not be representative of the population for which the CLS would be used in clinical practice. This issue would arise even in a prospective trial unless stomas were only performed when indicated by the risk score under investigation. This policy is unethical in the absence of evidence that the risk score is a reliable predictor of outcome. Therefore, we accepted this problem and decided to perform analyses both with and without the nonfunctional stoma patients.

In our cohort, the decision about whether or not to construct a nonfunctional stoma was made by the surgeon. As expected, the stoma patients had a higher mean CLS. However, the surgeons did not identify patients according to CLS. There were no differences in the incidence of anastomotic leakage between the nonfunctional stoma group and the other patients. This could be because patients that were regarded as high-risk were treated with a nonfunctional stoma, thereby reducing the risk of anastomotic leak. Ultimately the CLS could accurately predict the risk of anastomotic leakage in all patients irrespective of inclusion or exclusion of patients with a nonfunctional stoma.

Patients with colon resections and rectal resections were analyzed as one group

and as separate groups because of potential differences in surgical complexity and risk. These analyses should be interpreted with caution. Although it seems that CLS has a better predictive capacity for colon than rectum patients, there were no statistical differences between colon and rectum patients for the association between CLS values and anastomotic leakage. This could be due to small sample size, so a difference may still exist. It is possible that certain risk factors are not equally distributed between colon and rectum patients. For instance, acute surgery occurred more often in colon cases. It is also possible that within the rectum group, the chosen cut off values for height of the anastomosis did not differentiate enough between high or low risk. Unfortunately these subgroups are too small for reliable analyses of possible differences.

A possible limitation of this study is that the operations in our series were performed by nine different surgeons and residents. Although they all had training in colorectal surgery, it is possible that this introduced some bias. Unfortunately, the numbers are too small for further analysis. However, because this series consists of consecutive patients it represents routine practice.

Cut off values for routine practice

The purpose of the CLS is patient stratification. It could help to define subgroups with high, intermediate and low risks of anastomotic leakage. But which cut off values are useful? On the ROC-curve, the cut off point that best discriminates between groups is the point closest to the left upper corner of the graph. In our study, this is a CLS of 11. One of the interesting features of the ROC, however, is the ability to choose a suitable cut off point, depending on the emphasis on sensitivity or specificity. Therefore, if you want to minimize the risk of anastomotic leakage, you can choose a lower CLS cut off. If, on the other hand, you want to avoid unnecessary stomata you can use a higher CLS cut off.

With logistic regression analysis **(Figure 3)** it is possible to determine the risk of anastomotic leakage per CLS value and thus for the individual patient. This forces

us to determine what risk we consider acceptable. For instance, in our opinion, a risk of anastomotic leakage of lower then 3% does not justify a nonfunctional stoma. A stoma can also cause problems (morbidity, discomfort and higher cost). If a 3% risk of anastomotic leakage is accepted as a cut off, a CLS value of more than 11 indicates that a stoma should be made. It should be noted here that in our series, less than 20% of patients had a CLS value of more than 11, so 80% of patients would not be considered high-risk for leakage.

In the end, it is up to the surgeon and patient to determine their own cut off CLS value considering their preferences concerning the risk of anastomotic leakage versus (temporary) stomata. The receiver-operating characteristics curve and the logistic regression curves offer a perfect tool to guide this clinical decision.

Since it is a simple formula and all of the necessary information is easily available in standard clinical practice, the CLS could be very useful for the intra-operative decision regarding whether or not to construct a nonfunctional stoma. Confirmation of the value of this scoring system in a larger multi-center series offers the potential to solve a difficult clinical problem.

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Chapter 4

Mortality of patients diagnosed with colorectal cancer as second primary malignancy

SLE Lambooij
JWT Dekker
E Bastiaannet
RAEM Tollenaar
RGJ Westendorp
AJM de Craen

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Abstract

Aims: Patients with colorectal cancer followed by an extracolonic primary tumour, have a shorter survival. However, the influence of colorectal cancer as a second primary tumour on survival is not clear. We assessed the mortality of colorectal cancer patients with a colorectal cancer as a second primary versus a first primary malignancy.

Methods: Sixty-two patients with a second primary colorectal cancer were compared to a control series of 220 patients with colorectal cancer from the regional Comprehensive Cancer Center matched for age, sex, year of diagnosis and tumour size, and as well to 409 patients from the Leiden Colorectal Database with a first primary colorectal cancer. Cox proportional hazard analysis was used to assess the association of second primary colorectal cancer versus primary colorectal cancer and all cause mortality.

Results: All cause mortality after a second primary colorectal cancer was significantly increased when compared to both the matched controls (HR 1.6, 95% CI 1.2-2.3, $p<0.01$) and to the controls from the remaining patients of the Leiden Colorectal Database with colorectal cancer as a first malignancy (HR 1.7, 95% CI 1.2-2.3, $p<0.01$). The difference in mortality was not explained by differences in stage or treatment.

Conclusions: Patients with a second primary colorectal cancer have a higher mortality compared to patients with a primary colorectal cancer.

Introduction

Life expectancy in western societies is still increasing. Therefore, the number of people with colorectal cancer, as for other age-related tumours, is rising [1-3]. The incidence of invasive colorectal tumours in the Netherlands has increased from 376/100.000 patients in 1989 to 437/100.000 in 2007 according to the Dutch Cancer Registration[1]. Cancer survivors may increasingly develop a second primary tumour because cancer treatment improves and cancer screening programs develop [4-7]. The proportion of second- or higher order invasive cancers reported to the US International Cancer Institutes Surveillance, Epidemiology and End Results Program (SEER) has increased to over 10% in 2008 [4].

Patients with colorectal cancer followed by an extracolonic primary tumour, have a shorter survival [2, 8-10]. Several studies have shown that subjects with ovarian, endometrial, breast, renal and urethral cancer have a higher incidence of colorectal cancer as a second primary tumour [11-17]. However, the influence of colorectal cancer as a second primary tumour on survival is not clear. To our knowledge two studies have assessed the survival of patients with colorectal cancer as a second primary malignancy compared to patients with non-colon cancer as primary tumour [18-19]. One study showed better survival for patients with colorectal cancer as a second primary malignancy [18] while the other study found a similar survival [19]. These results seem contradictory to studies that show that co-morbidity is a strong prognostic factor for survival in colorectal cancer [20-21]. Therefore, the objective of our study was to assess the mortality of colorectal cancer patients with a colorectal tumour as a second primary versus first primary malignancy.

Methods

Study group selection

All 531 consecutive patients undergoing surgical treatment for colorectal cancer between 1991 and 2002 at the Leiden University Medical Center, the Netherlands were included in our study. According to hospital protocol, pre- and postoperative staging was performed using the TNM classification [22]. For this research all clinico-pathological records were examined for patients' medical history and prognostic factors of colorectal cancer such as sex, location, TNM classification, and year of diagnosis. To compare severity of co-morbidity, the Adult Co-morbidity Evaluation-27 (ACE-27) was derived from the medical history [23]. Patients who had a carcinoma in situ in a polyp or adenoma and patients who had previous treatment for colorectal cancer were excluded, leading to 471 patients for the current analysis. From this database, the Leiden Colorectal Database (LCD), we identified all patients with extracolonic metachronous or synchronous primary malignancies. Synchronous tumours were defined as those diagnosed simultaneous or within an interval of 3 months. Cancers were considered metachronous when the second malignancy was diagnosed more than three months after the first. All skin cancers except melanomas, neuro-endocrine tumours and benign brain tumours were excluded as previous primary malignancies. A total of 62 patients with a previous cancer were identified.

Control series

Patients with a second primary colorectal cancer were matched with patients with a first primary colorectal cancer as identified in our regional Comprehensive Cancer Center. For each case a maximum of 5 controls were selected, ranging from 0 control (n=1) to 5 controls (n=20). A total number of 220 controls were found. The mean number of controls was 3.6. All control patients were surgically treated for their colorectal cancer and were matched for age within a decade (+/- 5 years), sex, tumour location, year of diagnosis (+/- 1 year or with less than 3 matches +/- 2 years).

In addition to the control group from the regional Comprehensive Cancer Center, we used the remaining 409 patients with colorectal cancer as a first primary malignancy from our Leiden Colorectal Database as a second control group. This control group was used to prevent possible selection bias because the matched controls were also diagnosed in general hospitals within our region.

Mortality

Mortality data on all subjects were obtained form our regional Comprehensive Cancer Center. The Comprehensive Cancer Center does not record cause of death. The censor date for all cases and controls was 31 December 2008.

Statistical analysis

Statistical analysis was performed using SPSS 16.0 statistical software. Differences in characteristics of patients from our study group and the control groups were assessed using chi-square tests. Cox proportional hazard analysis was used to assess the association between individual factors and all cause mortality. Moreover, cause specific mortality was also assessed between cases and controls from the Leiden Colorectal Database. This information was obtained from ONCDOC, a patient follow up system within our hospital maintained by professional data-managers.

Results

Patient characteristics

Of the 471 patients included in this study, 62 patients had a history of a previous extracolonic malignancy. These 62 patients had 76 previous tumours (12 patients had 2 previous tumours and 1 patient had 3 previous tumours). The most prevalent initial tumours were breast cancer, head and neck cancer, urothelial cancer and melanoma **(table 1)**. No patients were known to have a familial colon cancer syndrome. Eleven patients had first or second grade family members with a gastrointestinal tumour. Of the 62 patients with colorectal cancer as a second primary tumour, 32 patients had the most recent primary tumour less than five years ago and 30 patients more than five years ago. Eleven tumours were found synchronous to

Table 1
Previous malignancies in study group

Type of cancer	Total group (n=76)*	%
Breast	20	26.3
Head and neck	9	11.8
Urothelial	7	9.2
Melanoma	7	9.2
Cervical and endometrial	**6**	**7.9**
Lymphoma/leukemia	6	7.9
Renal cell	5	6.6
Prostate	5	6.6
Seminoma	3	4.0
Lung	3	4.0
Ovarian	2	2.6
Gastric	2	2.6
Vaginal	1	1.3

* there were 76 malignancies in 62 patients

colorectal cancer, five of which were renal cell cancers. Within the group of patients with a second primary colorectal cancer, no significant differences in survival times were found between type of first cancer and type of treatment.

The distribution of age, sex, tumour location, tumour stage, and year of diagnosis in our study population as well as the matched control group and the Leiden Colorectal Database (LCD) control group is shown in **table 2**. Patients were similar in all baseline characteristics in all three groups except for the mean age (p=0.01) and ACE-27 score (p<0.0001) of patients in the LCD control group. Of the 409 LCD controls 11 patients had a familial cancer syndrome and a further 66 patients had first or second grade family members with a gastro-intestinal tumour.

Table 2
Baseline characteristics of patients

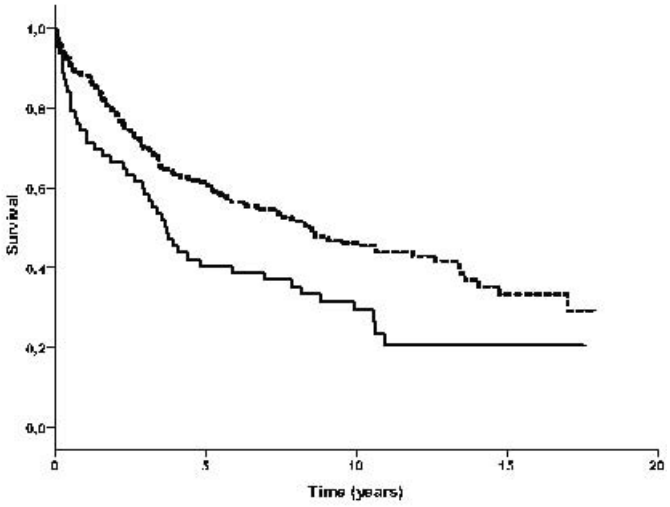
	Study group (N=62)	Matched controls (N=220)	LCD controls (N=409)	LCD controls (N=409)	p-value study group vs LCD controls
Age (mean, SD)	69.7 (10.1)	69.5 (9.4)	65.1 (13.1)	0.94	0.01
Gender					
Males	31 (50)	108 (49)	207 (51)	0.90	0.98
Females	31 (50)	112 (51)	202 (49)		
Location					
Colon	44 (71)	168 (76)	271 (66)	0.39	0.57
Rectum	18 (29)	52 (24)	138 (34)		
Classification					
Stage 1	13 (21)	76 (35)	86 (21)	0.10	0.44
Stage 2	16 (26)	62 (28)	155 (38)		
Stage 3	15 (24)	66 (30)	109 (27)		
Stage 4	17 (27)	16 (7)	59 (14)		
unknown	1 (2)	-	-		
Year of diagnosis					
1991-1995	20 (32)	72 (33)	186 (46)	0.87	0.07
1996-2001	42 (68)	148 (67)	223 (54)		
ACE-27					
0	-	NA	189 (46)	NA	<0.0001
1	25 (40)		130 (32)		
2	21 (34)		63 (15)		
3	16 (26)		16 (6)		
unknown	-		1		

Study group are patients from Leiden Colorectal Database (LCD) with a previous malignancy, matched controls from the regional Comprehensive Cancer Center and a control group consisting of remaining patients from Leiden Colorectal Database (LCD).
All data are presented in n(%) unless otherwise stated
NA= not applicable. SD= standard deviation

Study group versus matched control group

Five-year mortality in patients with a second primary colorectal cancer was 60% compared with 39% in the matched control patients with a first primary colorectal cancer. This resulted in an increased overall mortality of the patients with a second primary cancer (HR 1.6, 95% CI 1.2-2.3, p<0.01) **(figure 1)**. Adjustment for tumour

Figure 1
Overall survival of 62 patients with colorectal cancer as second primary cancer compared to 220 matched patients with colorectal cancer as a first primary tumour from the regional Comprehensive Cancer Center with colorectal cancer.



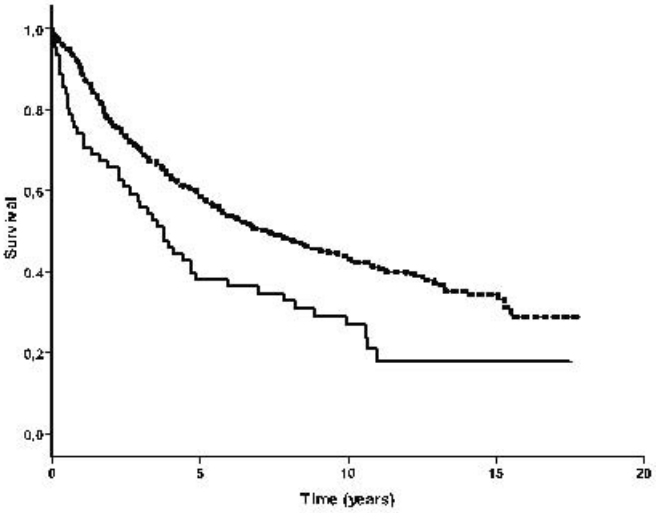
classification stage or removal of patients from the database with tumour classification stage 4 did not affect the hazard ratio. Mortality of patients who had their first primary tumour more than five years ago was similar to the mortality of patients who had their first primary tumour less than five years ago (HR 1.1, 95% CI 0.6-2.0, p=0.75).

Study group versus LCD control group

Overall mortality of patients with a second primary colon cancer compared to patients with colorectal cancer as a primary tumour from the Leiden Colorectal Database was also significantly increased (HR 1.7, 95% CI 1.3-2.3, p<0.01) **(figure 2).** After adjustment for age, tumour classification stage, and year of diagnosis the increased mortality risk remained (HR 1.7, 95% CI 1.2-2.3, p<0.01).

Mortality was not affected by possible differences in treatment: adjuvant chemotherapy (9.7% versus 14.9%, p=0.27), adjuvant radiotherapy (1.6% versus 4.2%,

Figure 2
Overall survival of 62 patients with colorectal cancer as second primary cancer compared to 409 patients from the Leiden Colorectal Database with colorectal cancer as a first primary tumour.



p=0.33) or surgical radicality (82.2% versus 80.6%, p=0.72), since further adjustment for these factors did not affect the observed hazard ratio. The increased mortality risk in patients with a second primary colorectal cancer could also not be explained by a survival benefit in patients with familial cancer syndromes as the overall mortality of the second primary group was similar after removal of patients with familial cancer syndromes from the LCD control group (HR 1.6, 95% CI 1.2-2.2, p<0.01).

Discussion

This study shows that mortality in patients with a secondary primary colorectal tumour is increased compared to patients with colorectal cancer as a primary tumour. Differences in mortality were not explained by differences in age, tumour classification stage, year of diagnosis, and treatment.

The five-year mortality in patients with a second primary colorectal cancer was 60% compared with 39% in the control patients with a first primary colorectal cancer, matched for stage, age, sex, tumour location and year of diagnosis. The interval between first and second cancer had also no influence on mortality. The reduction in survival may be attributable to an increased co-morbidity caused by the first primary tumour or its treatment [24]. Furthermore, life style and genetic factors could also be involved [25-28].

Our results are not in line with two previously published studies assessing the survival of patients with colorectal cancer as a second primary malignancy compared to patients with non-colon cancer as primary tumour [18,19]. One study showed better survival for patients with colorectal cancer as a second primary malignancy[18] while the other study found a similar survival [19]. Results from both studies were unexpected because co-morbidity is a strong prognostic factor for mortality of colorectal cancer [20-21], although some studies have reported better survival for patients with multiple primary malignancies [29]. Furthermore, a better survival has also been shown in studies with familial cancer syndromes [30]. However, after excluding patients with known familial cancer syndromes from our study, results remained unchanged.

There are some differences between the two previously reported studies and our study. The mean age of the patients in the study by Varty et al. [18] was 73 years compared to 70.5 years in our study. Additionally, that study seems similar in material and methods to our study but their control group was formed only by the remain-

ing patients from the database. Furthermore, 5.3% of the patients of their database had colorectal cancer second to a previous extracolonic malignancy compared to 13% in our study. The difference in frequency could be explained by improved case finding and treatment or by the fact that our database had its origin in a tertiary hospital. The study by Sankila et al. [19] was based on data from the population-based Finnish Cancer Registry and only included women with a previous diagnosis of breast cancer. The overall uncorrected ratio of relative risk was 1.0 for patients with colon carcinoma and prior breast cancer compared with patients with colon carcinoma and no prior breast cancer. The corresponding overall corrected ratio of relative risk (corrected for the excess mortality related to the first breast cancer) was .87. They concluded that, the combined risk of death from breast cancer and colorectal carcinoma is similar to that from colorectal carcinoma only.

The number of patients with multiple malignancies is increasing. It is a challenge to seek a differentiated individual treatment in these cases because of differences in co-morbidity and prognosis. This study showed that patients with a previous extracolonic cancer have a higher mortality compared to patients with colorectal cancer as a first primary tumour.

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Chapter 5

Use of different comorbidity scores for risk adjustment in the evaluation of quality of care for colorectal cancer surgery: does it matter?

JWT Dekker*
GA Gooiker*
LGM van der Geest
NE Kolfschoten
H Struikmans
H Putter
MWJM Wouters
RAEM Tollenaar

On behalf of the steering committee of the 'Quality Information System Colorectal Cancer' project**
* Both authors contributed equally to this article
** Collaborators of the steering committee who contributed to this article: Andreas Marinelli, Willem Hans Steup, Robert Vree

In revision for to European Journal of Surgical Oncology

Abstract

Aims: Comorbidity affects outcomes after colorectal cancer surgery. However, its importance in risk adjustment is unclear and different measures are being used. This study aims to assess its impact on postoperative outcomes.

Methods: All 2204 patients who were operated on for stage I-III colorectal cancer in the Midwestern region of the Netherlands between January 1, 2006 and December 31, 2008 were analyzed. A multivariate two-step enter-model was used to evaluate the effect of the American Society of Anesthesiologists Physical Status classification (ASA) score, the sum of diseased organ systems (SDOS), the Charlson Comorbidity Index (CCI) and a combination of specific comorbidities on 30-day mortality, surgical complications and a prolonged length of stay (LOS). For each retrieved model, and for a model without comorbidity, a ROC curve was made.

Results: High ASA score, SDOS, CCI, pulmonary disease and previous malignancy were all strongly associated with 30-day mortality and a prolonged LOS. High ASA score and gastro-intestinal comorbidity were risk factors for surgical complications. Predictive values for all comorbidity measures were similar with regard to all adverse postoperative outcomes. Omitting comorbidity only had a marginal effect on the predictive value of the model.

Conclusions: Irrespective of the measure used, comorbidity is an independent risk factor for adverse outcome after colorectal surgery. However, the importance of comorbidity in risk-adjustment models is limited. Probably the work and costs of data collection for auditing can be reduced, without compromising risk-adjustment.

Introduction

Almost 60% of newly diagnosed colorectal cancer patients aged 65 years and older suffer from at least one comorbid condition. [1-2] The presence of comorbidity affects treatment decisions [3-6] and the prognosis of patients receiving colorectal cancer treatment. [7-12] Consequently, comorbidity is believed to be an important confounder in the analysis of postoperative adverse events and omitting riskadjustment for comorbidity is argued to introduce bias in studies that do not take it into account. The growing emphasis on comparative effectiveness research and hospital quality rankings has revived the discussion on the importance of comorbidity as a confounding factor.[13]

Surgical audits are introduced to measure variations in care process and outcomes between hospitals, and to feed back detailed information related to a benchmark to care givers, to improve the quality of care. The drawback of these programs is that the amount of variables needed for analysis, make them time consuming and costly. A reduction in the number of variables needed for risk-adjustment could significantly relieve this burden.

However, despite the growing number of studies addressing comorbidity, the role of different comorbidity-scores in models predicting mortality after colorectal cancer is not clarified. It is also unknown if different comorbidity scores are similar in predicting other postoperative adverse events, such as postoperative complications.

In colorectal cancer research, the Charlson Comorbidity Index (CCI) and the sum of diseased organ systems (SDOS) (i.e., NIA/NCI or Elixhauser lists) are randomly used in prediction models for postoperative adverse outcomes after colorectal surgery. [14-17] Also, the American Society of Anaesthesiologists Physical Status classification (ASA) score, is used for this purpose. The ASA- score, SDOS and CCI have the advantage that the required data are readily available. More detailed indices may cor-

relate better with outcome, but have the disadvantage that not all required items can be easily obtained for clinical registration and auditing.
The aim of this study is to assess the impact of comorbidity, estimated by three different scores, on postoperative mortality, surgical complications and length of stay (LOS) after colorectal cancer surgery. The second aim is to compare the predictive value of these scores with a set of specific comorbidities, and a model with no riskadjustment for comorbidity at all.

Methods

Data source
In the Netherlands, all newly diagnosed malignancies are registered in the nationwide population based Netherlands Cancer Registry (NCR). Independent trained data managers collect data from the original patient files after receiving an automatic report from the Dutch pathology reporting system "PALGA." Completeness of the cancer registry is crosschecked with the Dutch National Registry of Hospital Discharge Diagnosis, which is a near complete registry of hospital discharge data. Information on patient characteristics, tumour characteristics, hospital of diagnosis and/or treatment and follow-up are routinely recorded. Tumour site and morphology are coded according to the International Classification of Diseases for Oncology (ICD-0).[18] All cancers are staged by the NCR according to the TNM classification of Malignant Tumours, 6th edition.[19] The quality of the data is high, and completeness is estimated to be at least 95%.[20-21]

The Leiden Cancer Registry, which is part of the NCR, collects data on all cancer patients diagnosed in one of the nine affiliated hospitals of the comprehensive cancer centre west (CCCW) in the Midwestern part of the Netherlands. This region comprises of one university hospital, six teaching hospitals and two non-teaching hospitals and serves a population of 3.5 million.

In 2006, a regional audit for colorectal cancer surgery (KIC) was started. The data collection was extended to data that reflected quality of care, such as postop-

erative surgical complications. These prospectively collected data were used for benchmarking and reflection, ultimately to improve the quality of care in the entire region.

Patients

All patients who were diagnosed with a neoplasm of the colon (C18), the rectosigmoid (C19) or the rectum (C20) from January 1, 2006 to December 31, 2008 in one of the affiliated hospitals of the CCCW were identified from the cancer registry. Patients with a stage IV tumour, those with a tumour of the appendix, and those who did not undergo a surgical resection of the tumour were excluded.
Data were collected on patient demographics (age, sex, comorbidities, ASA score), tumour characteristics (localization, TNM staging) and type of treatment (neo-adjuvant treatment, type of surgery, urgency of the operation, and hospital of treatment).

All comorbidities present at time of diagnosis were registered and categorized according to the NCR guideline (appendix I).
For each patient, the CCI was calculated. Patients were categorized as CCI 0, 1, or CCI >1. In addition, the SDOS was calculated for each patient. Patients were categorized as no comorbidity, 1 or 2 diseased organ systems, and > 2 diseased organ systems. For the ASA score, patients were categorized as ASA 1 or 2 and ASA 3 or higher. Missing data from the ASA score were included as a separate category in multivariate analysis.[22]

Outcomes

Postoperative mortality was defined as 30-day mortality: death from any cause between date of surgery and 30 days thereafter. Vital status of all patients was obtained actively on a regular basis through linking with the integrated database of the municipal registry and the central bureau for genealogy. Surgical complications were classified as wound infections (both superficial and deep), wound dehiscence (including all abdominal wall problems) and abdominal problems, including all intra-abdominal complications such as bleeding, ileus, infections, abscess or anastomotic leaks. There were no data available on non-surgical complications. Instead,

a prolonged LOS was used as a proxy for postoperative complications in general. In this study, a prolonged LOS was defined as a stay of more than 14 days. A LOS more than 14 days is associated with the occurrence of complications and an uneventful postoperative period is unlikely to result in a longer hospital stay. Therefore a LOS of longer than 14 days can function as a proxy for complications in general.

Statistics

Descriptive statistics were calculated for all variables. The possible influences of patient-, tumour-, and treatment characteristics were analyzed by means of univariate logistic regression analysis. A multivariate two-step enter-model was used to evaluate the effect of comorbidity on postoperative mortality, surgical complications and a prolonged LOS for colorectal cancer patients and for colon and rectal cancer patients separately.

For each outcome, four different models were made and compared. In each model a fixed set of parameters were included in the first step irrespective of statistical significance: age, gender, urgency, T stage, neo-adjuvant therapy and hospital of surgery. In the second step of each model, one of the scores was added: the ASA score, the SDOS, the CCI or a combination of specific comorbidities, selected with univariate analysis (comorbidities with $P < 0.05$ were selected).

For each retrieved model, an ROC curve was made, and the area under the curve (AUC) was calculated.[23] The retrieved AUC curves were compared to each other and with the AUC curve of the model without comorbidity. The overlap of 95%-confidence intervals of the AUC's was compared to calculate statistical significance. For all analyses, PASW statistics® version 18 software (SPSS inc, Chicago, Illinois, USA) was used.

Results

Patients

Between January 1, 2006 and December 31, 2008, 2204 patients were diagnosed and surgically treated for stage I-III colorectal cancer in one of nine affiliated hospitals of the CCCW, of which 1435 patients had colon cancer and 769 had rectal cancer. The mean age was 70 years. All patient characteristics are shown in **table 1**.

Table 1
Baseline characteristics of 2204 stage I - III colorectal cancer patients from the Comprehensive Cancer Center West region the Netherlands (2006-2008)

		Colon cancer patients (n=1435)		Rectal cancer patients (n=769)		All patients (n=2204)	
Variable	**Characteristic**	**Number**	**%**	**Number**	**%**	**Number**	**%**
Gender	Male	689	48.0	435	56.6	1124	51.0
	Female	746	52.0	334	43.4	1080	49.0
Age	< 65	378	26.3	279	36.3	657	29.8
	65-74	397	27.7	257	33.4	654	29.7
	75-84	504	35.1	192	25.0	696	31.6
	> 85	156	10.9	41	5.3	197	8.9
	Mean (range)	71 (24-96)		68 (22-94)		70.3 (22-96)	
pT	0	8	0.6	30	3.9	38	1.7
	1	78	5.4	46	6.0	124	5.6
	2	203	14.1	242	31.5	445	20.2
	3	951	66.3	423	55.0	1374	62.3
	4	195	13.6	28	3.6	223	10.1
Stage	1	237	16.5	220	28.6	457	20.7
	2	672	46.8	237	30.8	909	41.2
	3	518	36.1	282	36.7	800	36.3
Neo-adjuvant treatment	Yes	6	0.4	473	61.5	479	21.7

		Colon cancer patients (n=1435)		Rectal cancer patients (n=769)		All patients (n=2204)	
Variable	**Characteristic**	**Number**	**%**	**Number**	**%**	**Number**	**%**
Urgency	Elective	1247	86.9	752	97.8	1999	90.7
	Urgent/ acute	188	13.1	17	2.2	205	9.3
ASA	1	154	10.7	124	16.1	278	12.6
	2	488	34.0	301	39.1	789	35.8
	3	267	18.6	120	15.6	387	17.6
	4	31	2.2	9	1.2	40	1.8
	missing	495	34.5	215	28	710	32.2
SDOS	None	615	42.9	400	52.0	1015	46.1
	1 or 2	710	49.5	334	43.4	1044	47.4
	> 2	110	7.7	35	4.6	145	6.6
CCI	0	769	53.6	474	61.6	1243	56.4
	1	365	25.4	170	22.1	535	24.3
	>1	301	21.0	125	16.3	426	19.3
Particular	Cardiac	367	25.6	150	19.5	517	23.5
comorbidities	Hypertension	424	29.5	204	26.5	628	28.5
	Pulmonary	179	12.5	74	9.6	253	11.5
	Malignancy	204	14.2	90	11.7	294	13.3
	Gastro-intestinal	85	5.9	25	3.3	110	5.0
	Uro-renal	34	2.4	13	1.7	47	2.1
	Reumatologic	22	1.5	8	1.0	30	1.4
	Neurologic	38	2.6	19	2.5	57	2.6
	Diabetes	211	14.7	79	10.3	290	13.2
	Infectious	18	1.3	9	1.2	27	1.2
	CVA	61	4.3	19	2.5	80	3.6
	Thrombosis	47	3.3	18	2.3	65	2.9
	Vascular disease	82	5.7	46	6.0	128	5.8

The majority of patients had at least one comorbid disease (54%): 145 patients (6.6%) had three or more affected organ systems, and 426 patients (19.3%) had a CCI of 2 or higher. The most frequent comorbid diseases were hypertension (28.5%),

cardiac disease (23.5%), pulmonary disease (11.5%), a previous malignancy (13.3%) and diabetes (13.2%). The presence of comorbidity increased with age, although patients older than 85 years had a lower percentage of comorbidities.
The prevalence of comorbidity was higher in patients with colon cancer compared to patients with rectal cancer (57% versus 48%, p <0.001).

Outcomes

In total, 106 patients (4.8%) died within 30 days after surgery **(table 2)**. The 30-day mortality was 6.2% in the patients with colon cancer and 2.2% in the patients with rectal cancer (p<0.001). In approximately 20% of all patients, postoperative surgical complications occurred, 14 which the majority were abdominal events (14%). The median LOS was 10 days, and 671 patients (30.4%) had a prolonged LOS.

Table 2
Crude outcomes of 2204 stage I – III colorectal cancer patients from the CCCW region the Netherlands (2006-2008)

		Colon cancer patients	%	Rectal cancer patients	%	All patients	%
30- day mortality		89	6.2	17	2.2	106	4.8
Surgical Complications	None	1181	82.3	597	77.6	1778	80.7
	1	232	16.2	159	20.7	391	17.7
	2	22	1.5	13	1.7	35	1.6
	Wound infection	62	4.3	48	6.2	110	5.0
	Abdominal problem	183	12.8	123	16.0	306	14.1
	Wound dehiscence	31	2.2	14	1.8	45	2.0
Length of Stay	> 14 days	423	29.5	248	32.2	671	30.4
	Median (days)	9	(1-230)	11	(2-374)	10	(1-374)

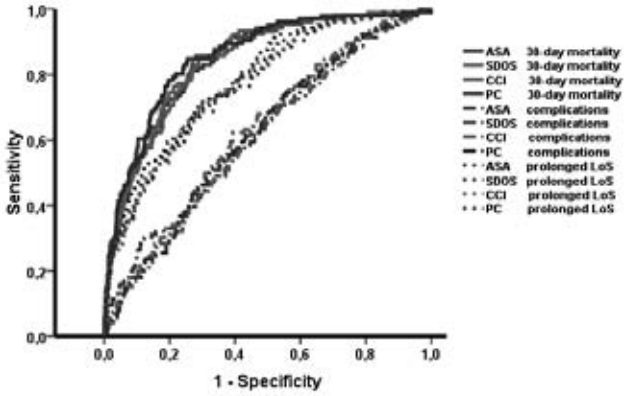
Impact of comorbidity on postoperative mortality

In the model, a high ASA score, SDOS and CCI were all strongly associated with 30-day mortality **(table 3)**. Pulmonary disease and a previous malignancy were independent risk factors as well. A history of thrombosis was a significant independent risk factor in rectal cancer patients. The ROC curves of all retrieved models are shown in **figure 1**. The AUC of the model with the ASA score was 0.843 (0.806-0.880), with the SDOS 0.838 (0.800-0.876), with the CCI 0.846 (0.810-0.882), and with a combination of specific comorbidities 0.853 (0.817-0.890). There was no significant difference in AUC between the models.

Table 3
Multivariable logistic regression analysis of the association of different comorbidity measures with 30-day mortality *(Factors included in each model were age, gender, urgency, T stage, neo-adjuvant therapy and hospital of surgery)*

		Colon cancer patients		Rectal cancer patients		All patients	
Variable		**OR (95%CI)**	**p-value**	**OR (95%CI)**	**p-value**	**OR (95% CI)**	**p-value**
ASA	1 or 2	1	**0.002**	1	0.148	1	**<0.001**
	3 or 4	3.18 (1.59-6.36)		3.73 (0.95-14.73)		3.25 (1.76-5.99)	
	missing	3.02 (1.49-6.11)		3.39 (0.64-17.88)		2.93 (1.55-5.53)	
SDOS	0	1	0.141	1	**0.046**	1	**0.014**
	1 or 2	1.32 (0.78-2.24)		14.04 (1.71-115.60)		1.75 (1.07-2.87)	
	> 2	2.15 (1.01-4.61)		17.23 (1.19-249.44)		2.71 (1.33-5.51)	
CCI	0	1	**0.014**	1	**0.025**	1	**< 0.001**
	1	1.30 (0.72-2.34)		5.24 (1.14-24.19)		1.63 (0.95-2.78)	
	>1	2.27 (1.30-3.98)		8.10 (1.73-38.01)		2.73 (1.63-4.57)	
Specific comorbidities	Cardiac	0.59 (0.34-1.04)	0.066	1.64 (0.52-5.24)	0.401	0.70(0.43-1.14)	0.155
	Hypertension	1.44 (0.87-2.40)	0.160	1.89 (0.55-6.49)	0.309	1.50 (0.94-2.37)	0.087
	CVA	1.70 (0.70-4.09)	0.239	6.09 (0.85-43.43)	0.072	1.87 (0.86-4.09)	0.115
	Pulmonary	2.39 (1.36-4.20)	**0.002**	2.77 (0.58-13.28)	0.202	2.23 (1.33-3.73)	**0.002**
	Diabetes	1.44 (0.78-2.67)	0.248	0.68 (0.10-4.51)	0.688	1.37 (0.78-2.43)	0.276
	Previous Malignancy	1.84 (1.03-3.29)	**0.041**	1.46 (0.34-6.30)	0.612	1.72 (1.02-2.90)	**0.042**
	Uro-renal	1.26 (0.34-4.72)	0.731	2.81 (0.30-26.03)	0.363	1.68 (0.59-4.79)	0.336
	Thrombosis	2.03 (0.75-5.50)	0.164	9.39 (1.28-69.04)	**0.028**	2.31 (0.99-5.40)	0.054

Figure 1
ROC-curves of prediction-models of 30-day mortality, surgical complications and prolonged LOS (>14 days) with different comorbidity measures added to the model. Abreviations: ASA, American Society of Anaesthesiologists Score; SDOS, Sum of Diseased Organ Systems; CCI, Charlson Comorbidity Index; PC, Preselected Specific Comorbidities.



Impact of comorbidity on surgical complications

In univariate analysis ASA score ≥ 3, SDOS >2, CVA and gastro-intestinal disease were identified as risk factors for surgical complications. In multivariate analysis, only ASA score and gastro-intestinal disease remained significant **(table 4)**.

The ROC curves of all retrieved multivariable models are shown in **figure 1**. The AUC of the model with the ASA score was 0.621 (0.592-0.650), with the SDOS 0.614 (0.584-0.643), with the, CCI 0,615 (0.586-0.644) and with a combination of specific comorbidities 0.619 (0.589-0.648). There was no significant difference in AUC between the models.

Table 4
Multivariable logistic regression analysis of the association of different comorbidity measures with surgical complications *(Factors included in each model were age, gender, urgency, T stage, neo-adjuvant therapy and hospital of surgery)*

		Colon cancer patients		Rectal cancer patients		All patients	
Variable		**OR (95%CI)**	**p-value**	**OR (95%CI)**	**p-value**	**OR (95% CI)**	**p-value**
ASA	1 or 2	1	0.124	1	0.099	1	**0.019**
	3 or 4	1.34 (0.93-1.93)		1.72 (1.05-2.82)		1.49 (1.11-1.99)	
	missing	0.89 (0.62-1.28)		1.23 (0.76-2.00)		1.02 (0.77-1.36)	
SDOS	0	1	0.708	1	0.508	1	0.696
	1 or 2	1.13 (0.84-1.53)		1.11 (0.77-1.61)		1.09 (0.86-1.36)	
	2	1.06 (0.62-1.84)		0.63 (0.23-1.75)		0.94 (0.58-1.51)	
CCI	0	1	0.349	1	0.637	1	0.422
	1	0.99 (0.70-1.40)		1.23 (0.80-1.89)		1.05 (0.81-1.37)	
	>1	1.27 (0.90-1.81)		1.12 (0.67-1.88)		1.21 (0.91-1.62)	
Specific comorbidities	CVA	1.49 (0.81-2.73)	0.201	1.45 (0.52-4.04)	0.481	1.51 (0.90-2.52)	0.119
	Gastro-intestinal	1.87 (1.13-3.10)	**0.015**	1.20 (0.45-3.15)	0.718	1.63 (1.05-2.55)	**0.030**

Impact of comorbidity on prolonged LOS

In multivariate analysis, high ASA score, SDOS and CCI were all strongly associated with a prolonged LOS **(table 5)**. CVA, pulmonary disease and a previous malignancy were also identified as independent risk factors

The ROC curves of all retrieved multivariable models are shown in **figure 1**. The AUC of the model with the ASA score was 0.695 (0.672-0.718), with the SDOS 0.696 (0.672-0.719), with the CCI 0,690 (0.666-0.713), and with a combination of specific comorbidities 0.702 (0.678-0.725). There were no significant differences in AUC of the different models.

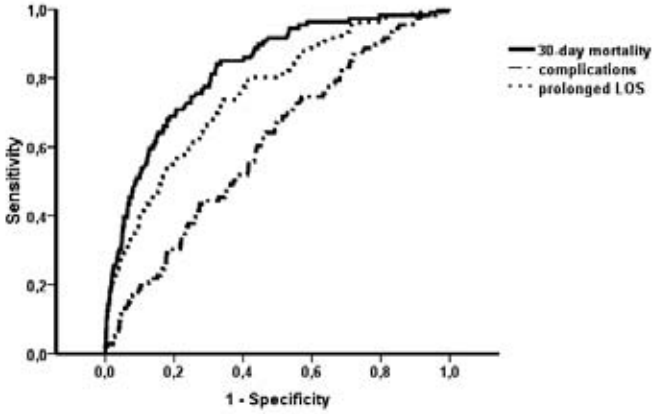
Table 5
Multivariable logistic regression analysis of the association of different comorbidity measures with prolonged LOS (> 14 days) *(Factors included in each model were age, gender, urgency, T stage, neo-adjuvant therapy and hospital of surgery)*

		Colon cancer patients		Rectal cancer patients		All patients	
Variable		**OR (95%CI)**	**p-value**	**OR (95%CI)**	**p-value**	**OR (95% CI)**	**p-value**
ASA	1 or 2	1	**<0.001**	1	**0.009**	1	**<0.001**
	3 or 4	1.89 (1.37-2.60)		1.88 (1.19-2.98)		1.90 (1.47-2.46)	
	missing	1.14 (0.82-1.57)		1.77 (1.06-2.65)		1.30 (1.00-1.69)	
SDOS	0	1	**< 0.001**	1	**0.006**	1	**< 0.001**
	1 or 2	1.52 (1.17-1.98)		1.43 (1.01-2.03)		1.44 (1.17-1.78)	
	> 2	2.26 (1.43-3.56)		3.18 (1.47-6.90)		2.39 (1.62-3.52)	
CCI	0	1	**0.007**	1	0.254	1	**0.004**
	1	1.31 (0.98-1.76)		1.31 (0.88-1.96)		1.28 (1.01-1.62)	
	>1	1.63 (1.20-2.22)		1.36 (0.86-2.15)		1.51 (1.17-1.94)	
Specific comorbidities	Cardiac	1.16 (0.87-1.54)	0.321	1.56 (1.03-2.37)	**0.035**	1.23 (0.98-1.55)	0.080
	Hypertension	1.18 (0.91-1.54)	0.213	1.36 (0.59-3,14)	0.427	1.18 (0.95-1.46)	0.139
	CVA	1.10 (0.61-1.96)	0.756	6.79 (2.08-22.19)	**0.002**	1.67 (1.02-2.72)	**0.040**
	Pulmonary	1.62 (1.14-2.30)	**0.007**	1.60 (0.93-2.72)	0.087	1.57 (1.17-2.09)	**0.002**
	Previous Malignancy	1.46 (1.04-2.05)	**0.027**	1.60 (0.95-2.70)	0.076	1.46 (1.10-1.92)	**0.008**
	Uro-renal	1.69 (0.80-3.54)	0.167	1.19 (0.33-4.23)	0.792	1.75 (0.94-3.28)	0.080
	Thrombosis	1.79 (0.94-3.40)	0.077	1.17 (0.42-3.24)	0.770	1.59 (0.93-2.73)	0.094
	Vascular	1.54 (0.93-2.53)	0.091	1.40 (0.71-2.77)	0.332	1.46 (0.98-2.16)	0.062

Additional value of comorbidity for the predictive value of the models

When comorbidity was removed from the multivariable models, the AUC of the different ROC curves did not change (figure 2). Indicating a marginal contribution of comorbidity to the predictive value of the models for 30-day mortality, surgical complications and prolonged LOS.

Figure 2
ROC-curves of prediction-models of 30-day mortality, surgical complications and prolonged LOS (>14 days) without comorbidity added to the model.



Discussion

Comorbidity is an independent risk factor for 30-day mortality and a prolonged LOS after colorectal cancer surgery. All used comorbidity measures (ASA score, the SDOS, the CCI) had similar predictive values. For the occurrence of postoperative surgical complications, the only predictive comorbidity measure was ASA score and the only specific risk factor was gastro-intestinal comorbidity. Apparently, any of these measures can be used in predicting adverse outcome in colorectal cancer surgery.

However, the importance of comorbidity in models predicting the risk of postoperative adverse events is limited.

Different comorbidity measures

The results of the present study show that all used models are similar in predicting postoperative adverse events after colorectal cancer surgery. This goes for all three examined outcomes. The predictive values of the ASA score, the SDOS and the CCI on postoperative mortality of colorectal cancer patients have been previously studied .[10-24-26] These studies showed a strong correlation with postoperative mortality and moderate correlation with postoperative morbidity, which compares to our findings.

However, few studies compared the predictive value of different comorbidity scores. Hines and colleagues evaluated the impact of the choice of comorbidity measure on long-term survival after colorectal cancer surgery.[27] They found similar results for the Adult Comorbidity Evaluation-27 score (ACE-27), the NIA/NCI comorbidity index and the CCI. Dimick et al evaluated if reduction in the number of variables for risk-adjustment would alter the predictive value of the models predicting postoperative outcome in data of the National Surgical Quality Improvement Program (NSQIP).[28-29] Their results demonstrated that a reduced set of case mix variables could be used without compromising risk-adjustment. The authors conclude that risk-adjustment could be simplified, thus lowering the registration burden.

Comorbidity and risk adjustment

In the present study, adding comorbidity to the model only slightly increased the predictive value of the model. This contradicts the common believe that extensive risk-adjustment for comorbidity, is always important. Although comorbidity represents an important risk domain, it adds little to the predictive value of the model. This can be explained by the fact that the influence of comorbidity is already captured by other variables in the model, such as age and emergency surgery.

Nevertheless, also in the present study, comorbidity remains a significant risk factor for postoperative mortality and prolonged LOS, independent of the choice of comorbidity measure. Although the association with postoperative surgical com-

plications was limited, a strong association was seen with a prolonged LOS, implying that comorbidities do have an impact on postoperative non-surgical complications. This confirms previous evidence showing the impact of comorbidities on the occurrence of complications and LOS. [30-32]

However, only patients with severe comorbidities seemed to be at higher risk of adverse events. In this study, only patients with severe comorbidity (ASA III or higher, SDOS >2 and CCI > 1) were at greater risk. This could mean that limited comorbidity does not necessarily have to influence treatment decisions.

It should be noted that the registration of comorbidities and risk-adjustment for comorbidities has several advantages. First, it increases the face validity and prevents gaming of quality measurement efforts. Omitting risk adjustment for comorbidities could lead to more defensive treatment regimes and even avoidance of high risk patients.

Also, when individual hospitals receive feedback on their performance, insight in the characteristics of their patient population, including comorbidities, could guide quality improvement initiatives. Lastly, the registration of comorbidities allows for the identification of procedure specific and outcome specific comorbidities, that represent a greater post-operative risk in large population based databases.

Strengths and weaknesses

The present study has several strengths. Clinical, accurate data of the Netherlands Cancer Registry are used, and variables included an extensive registration of comorbidities and other relevant case mix factors such as the urgency of the operation and tumour stage.

Nevertheless, the results of this study should be interpreted with regard of several limitations to the dataset. The number of missing data regarding the ASA score is large. However, patients with missing ASA scores formed a distinct category in

multivariate analysis. In all analyses, the missing ASA category showed outcomes between the outcomes for ASA I-II and ASA III-IV; therefore, it could be assumed ASA data were randomly missing, and missing data did not interfere with the outcome of this study.

Also, only data on postoperative surgical complications were available. A prolonged LOS was used as a substitute of postoperative complications in general. In this study, a prolonged LOS was defined as a stay of more than 14 days. An uneventful postoperative period is unlikely to result in a longer hospital stay. Therefore, it can be used as a substitute measure for overall complications. This assumption is supported by a study of Cohen et al, who demonstrated a mean LOS after colorectal surgery of 16 days in the presence of complications versus 6 days when no complications occurred.[30] In the present study 30.4% of the patients had a prolonged LOS. This is also consistent with findings in literature.[30-31]

Acknowledging these limitations, the findings of this study can have important implications for current and future audit initiatives, as the number of variables may be reduced.[33-34] The results are especially important for the 'European Registration of Cancer Care' (EURECCA) framework, an initiative of the European CanCer Organisation (ECCO), to develop a European colorectal audit structure.[33] In this dataset, the universal ASA score may be sufficient to assure both adequate risk adjustment and face validity.

Conclusion

This study demonstrates that comorbidity is a significant risk factor for postoperative adverse events after colorectal cancer surgery. However, the role of comorbidity in risk adjustment for colorectal cancer surgery is limited. Obviously risk adjustment for case mix influences remains elementary, but the effect of comorbidity in predictive models seems only marginal. These findings suggest that the workload and costs of data collection could be reduced. Nevertheless, advantages of extensive risk-adjustment for comorbidities should be considered in the decisions to re-

duce the number of variables collected. Further efforts should be made to identify the most important clinical comorbid factors to minimize the amount of necessary data, without compromising risk-adjustment.

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Chapter 6

The survival gap between middle-aged and elderly colorectal cancer patients. Time trends in treatment and survival.

CBM van den Broek
JWT Dekker
E Bastiaannet
P Krijnen
AJM de Craen
RAEM Tollenaar
CJH van de Velde
GJ Liefers

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Abstract

Aims: For several types of cancer, including colon cancer, the survival gap between middle-aged patients and elderly patients widened between 1988 and 1999 in Europe. The aim of our study was to describe treatments and compare survival rates over time (1991-2005) between middle-aged (<65 years), aged (65-74 years) and elderly (≥75 years) colon cancer patients in the mid-western part of the Netherlands to assess whether this survival gap further increased.

Methods: All 8926 patients with invasive colon cancer diagnosed between 1991 and 2005 were selected from the Comprehensive Cancer Centre West. Relative survival was calculated. Relative Excess Risks of death (RER) were estimated using a multivariable generalized linear model with a Poisson distribution.

Results: There were no significant changes in the treatment for stage I and II colon. Patients with stage III and IV more often received chemotherapy over time (from 9.6% to 54.3% and from 7.5% to 44.2% for all ages, respectively), while less stage IV patients were operated on (from 73.1% to 55.2%). Relative 5-year survival increased significantly for middle-aged patients (RER=0.97, 95%CI=0.95-0.98, p<0.001), borderline significantly (RER=0.98, 95% CI=0.97-0.99, p=0.05) for elderly patients and not significantly for aged patients (RER=0.99, 95%CI=0.97-1.00, p=0.08) after adjustment for sex, age, grade, stage, and treatment.

Conclusions: The survival gap earlier found by the EUROCARE is confirmed for the mid-western part of the Netherlands, even after adjustment for age, sex, grade, stage and treatment. However, present study does not show an increase in the survival gap between middle-aged and elderly patients.

Introduction

Colorectal cancer is the second most commonly diagnosed cancer in the Netherlands.[1] The incidence in the Netherlands is more than 57 per 100 000 persons per year (European Standardized Rate) and increases with age. There is an incidence peak around 74-80 years and approximately half of colorectal patients are over 70 years of age.

The EUROCARE Working Group has compared five-year relative survival between elderly (70–84 years) and middle-aged cancer patients (55–69 years).[2] They observed a significant survival improvement between 1988 and 1999 for all cancers combined and for almost every cancer site including colon cancer. Survival increased at a slower rate in the elderly. As a result the gap in survival between middle-aged and elderly patients widened. In particular middle-aged women showed more marked improvements than elderly women for colon cancer.[2] Differences in survival for colon cancer may be explained by variations in tumour factors, patient characteristics and therapy. Elderly patients receive adjuvant chemotherapy less frequently and more often discontinue treatment.[3] Moreover, the administration of adjuvant treatment for elderly stage III colon cancer patients is influenced by socioeconomic status, gender, and co-morbidity.[4] Besides, co-morbidity also influences surgical eligibility and other treatment options.

In recent years the focus on elderly colon cancer patients has increased. Several studies have concluded that age per se is not a contraindication for more aggressive or adjuvant treatment.[5] Therefore, the past ten years more elderly patients are considered for extensive therapy in routine clinical practice.[5] As a consequence an improved outcome for elderly patients might be expected. We hypothesized that the gap in survival between middle-aged and elderly patients as observed in the EUROCARE data between 1988 and 1999 might be decreasing. Hence, the aim of our study was to describe treatments and compare survival rates over time between middle-aged (<65 years), aged (65-74 years) and elderly (≥75 years) colon cancer patients.

Methods

Patients and follow-up

Patients were selected from the regional cancer registry of the Comprehensive Cancer Centre West (CCCW) covering the mid-western part of the Netherlands. The nationwide Dutch network and registry of histo- and cytopathology (PALGA) regularly submits reports of all diagnosed malignancies to the cancer registries. The national hospital discharge databank, which receives discharge diagnoses of admitted patients from all Dutch hospitals, completes case ascertainment. After notification, trained registry personnel collect data on diagnosis, staging, and treatment from the medical records, including pathology and surgery reports, using the registration and coding manual of the Dutch Association of Comprehensive Cancer Centres. Cancer registry data show actual variations in patterns of staging, treatment and survival by age. Therefore, these data offer a scope for improvement of care and for creating guidelines, in addition to randomized clinical trials.[6]

From the regional cancer registry, patients with their first primary invasive colon cancer were selected (International Classification of Diseases for Oncology (ICD-O) code C18.0), diagnosed between 1991 and 2005 (n = 8926). CCCW established vital status either directly from the patients' medical record or through linkage of cancer registry data with the municipal population registries which record information on their inhabitants' vital status (last linkage at December 31st 2009). Stage was based on pathological information; clinical information was used if pathology data were missing.

Statistical analyses

Patients were divided into middle-aged (younger than 65 years), aged (65-74 years) and elderly (75 years and older). We chose to divide the patients into those three age groups, so differences between middle-aged and elderly patients would be more pronounced. Differences between age groups were tested with Chi-Square tests. Statistical significance was defined as $p \leq 0.05$. The study period was divided

into three 5-year strata for the analyses of the treatment data; 1991-1995, 1996-2000, and 2001-2005. Treatment was divided into no treatment, surgery only, surgery and chemotherapy, chemotherapy only, and other (radiotherapy, in combination with surgery and/or chemotherapy). Changes over time were assessed for stage at diagnosis and age.

For survival analyses, relative survival is the preferred way to describe the prognosis of elderly cancer patients, as it takes into account the risk of dying from other causes than the cancer of interest.6 Relative survival was calculated by the Hakulinen method as the ratio of the observed survival among the cancer patients and the survival that would have been expected based on the corresponding (age, sex and year) general population. National life tables were used to estimate expected survival. Patients diagnosed between 1991 and 2004 were selected for 5-years survival analyses (n=8197). Patients diagnosed in 2005 were excluded from survival analyses by year, because five year follow-up was not available. Relative Excess Risks of death (RER) were estimated using a multivariate generalized linear model with a Poisson distribution, based on collapsed relative survival data, using exact survival times. Relative Excess Risks of death over time were calculated according to age and according to year of incidence stratified for age groups, with their 95% confidence interval (95%CI). The RER was adjusted for sex, age, grade, and stage. Models with and without adjustment for treatment are shown to assess the effect of therapy on the RER. Model fit was assessed for each multivariable analysis. Based on the model fit, continuous or categorical data were selected for the analyses.

Results

Patient characteristics

Between 1991 and 2005, 8926 patients with incident primary colon cancer were registered in the database of the Comprehensive Cancer Centre West (CCCW) in the Netherlands. The characteristics of the patients are shown in **Table 1**.

Table 1
Characteristics of patients diagnosed in the period 1991-2005 according to age.

		Age Groups			
		<65 years (n=2570)	**65-74 years (n=2564)**	**≥75 years (n=3792)**	**p-value**
Sex	Male	1311 (51.0)	1328 (51.8)	1571 (41.4)	p<0.001
	Female	1259 (49.0)	1236 (48.2)	2221 (58.6)	
Year	1991-1995	794 (30.9)	829 (32.3)	1162 (30.6)	p=0.08
	1996-2000	791 (30.8)	844 (32.9)	1240 (32.7)	
	2001-2005	985 (38.3)	891 (34.8)	1390 (36.7)	
Grade	I	151 (5.9)	158 (6.2)	219 (5.8)	p<0.001
	II	1466 (57.0)	1610 (62.8)	2212 (58.3)	
	III	428 (16.7)	396 (15.4)	649 (17.1)	
	Unknown	525 (20.4)	400 (15.6)	712 (18.8)	
Stage	I	320 (12.5)	386 (15.1)	480 (12.7)	p<0.001
	II	799 (31.1)	922 (36.0)	1502 (39.6)	
	III	644 (25.1)	634 (24.7)	819 (21.6)	
	IV	619 (24.1)	488 (19.0)	590 (15.6)	
	Unknown	188 (7.3)	134 (5.2)	401 (10.6)	
Surgery	No	271 (10.5)	242 (9.4)	630 (16.6)	p<0.001
	Yes	2299 (89.5)	2322 (90.6)	3162 (83.4)	
Chemotherapy	No	1760 (68.5)	2125 (82.9)	3661 (96.6)	p<0.001
	Yes	810 (31.5)	439 (17.1)	131 (3.4)	

Number displayed are n (%)

The male to female ratio changed over time from 0.8 to 1.0. The age distribution was stable from 1991 to 2005 (p=0.08). The distribution between men and women changed with age, with relatively more elderly women diagnosed than men. The median age at diagnosis was 72 years (range 7-101 years) and stable over time. Patients between 65 and 75 years at time of diagnosis were more often diagnosed with grade II, and less often with unknown grade (p<0.001). Stage distribution was associated with age, with more elderly patients having an unknown stage of disease.

Elderly patients did not have more advanced disease at time of diagnosis. Elderly patients were less frequently operated on their colon cancer compared with middle-aged and aged patients, while use of chemotherapy gradually declined over the age strata.

Treatment

Changes in treatment over time for the three age groups are shown in **Figure 1**.

During the study period, almost all patients with stage I to III colon cancer underwent resection of their primary tumour (98.5%). Over time, there were no significant changes in treatment for stage I and II in all age groups. Patients with stage III colon cancer received significantly more often surgery with adjuvant chemotherapy over time: from 31% to 85% among the middle-aged patients (p<0.001), from 8% to 59% among the aged patients (p<0.001), and from 2% to 13% for the oldest patients (p<0.001). Resection rates of stage IV colon cancer patients (with or without chemotherapy) decreased over time: from 73% to 60% among middle-aged patients (p=0.02), from 73% to 64% among aged patients (p=0.2), and from 67% to 51% among elderly patients (p=0.004). The use of chemotherapy only for stage IV colon cancer increased: from 10% to 26% in the middle-aged patients (p<0.001), from 6% to 17% in the aged patients (p=0.002), and from 0% to 7% in the elderly patients (p<0.001). Elderly patients with stage IV colon cancer received more often no treatment compared to middle-aged patients, 17% in the middle-aged and aged group compared to 38% in the elderly group(p<0.001).

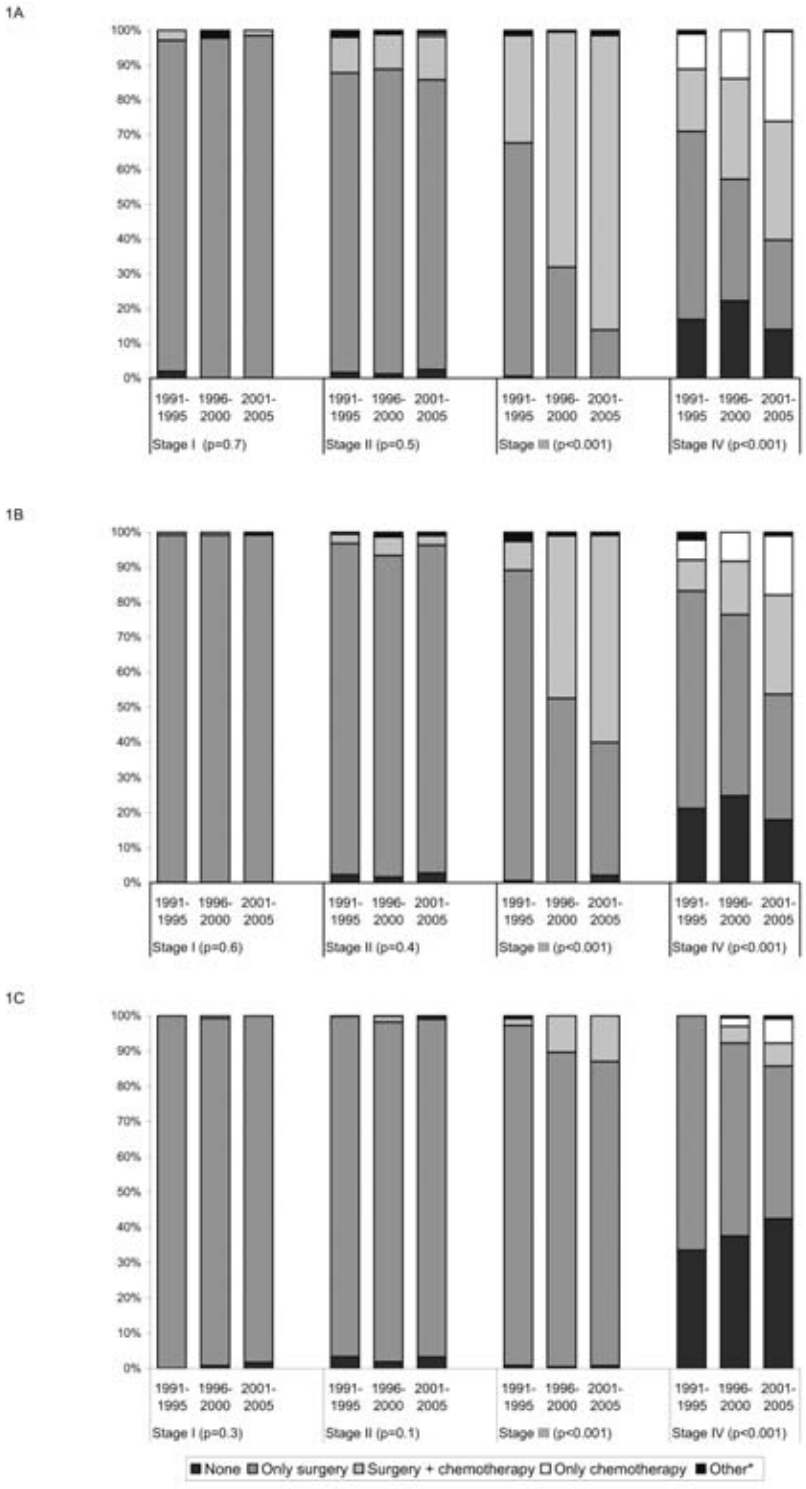


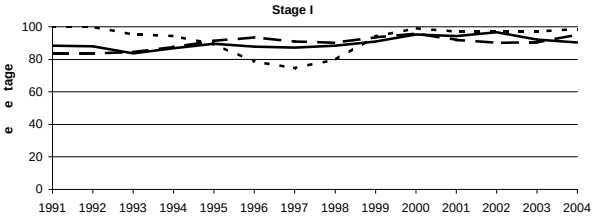
Figure 1
Changes in treatment over the years according to age: (A) Middle-aged patients (<65 years, (B) Aged patients (65-74 years), and (C) Elderly patients (75 years and older).

Survival

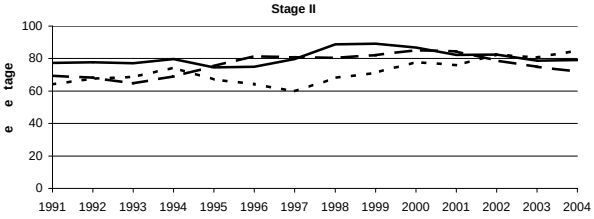
Overall, there was a significant increase in the 5-year relative survival from 54.9% in 1991-1995, to 56.5% in 1996-2000, and to 57.9% in 2001-2004 (p=0.03). The 5-year relative survival of men increased from 52.5% in 1991-1995 to 58.9% in 2001-2004(p=0.02), the 5-year relative survival of women remained stable in the same period from 56.7% to 57.0% (p=0.5). After adjustment for age (as a continuous variable in the model), grade, and stage, men showed a significant increase in 5-year relative survival over time with a RER of 0.98 (95%CI=0.97-0.99, p<0.001). Women did not show a significant increase in their 5-year relative survival with a RER of 0.99 (95%CI=0.98-1.00, p=0.1). After additional adjustment for treatment, both men and women showed a small, but significant increase in 5-year relative survival over time with a RER of 0.99 (95%CI=0.97-1.00, p=0.02) for men and a RER of 0.99 (95%CI=0.98-1.00, p=0.03) for women.

Stratified for stage, relative survival did not increase for stage I colon cancer **(Figure 2)**. In stage II colon cancer both aged and elderly showed a significant improvement in their unadjusted relative survival. After adjusting for sex, age, and grade, only aged patients still showed a significant improvement in their relative survival, while after additional adjustment for treatment, both aged and elderly patients showed an improved relative survival. In stage III colon cancer for all age groups unadjusted relative survival increased significantly. After adjustment for sex, age, and grade both middle-aged and elderly patients showed an increased relative survival, and after additional adjustment for treatment, only elderly patients showed an increased relative survival. Unadjusted relative survival in stage IV colon cancer did not increase in any of the age groups, after adjustment for sex, age and grade only middle-aged patients had an increased relative survival, which remained after additional adjustment for treatment.

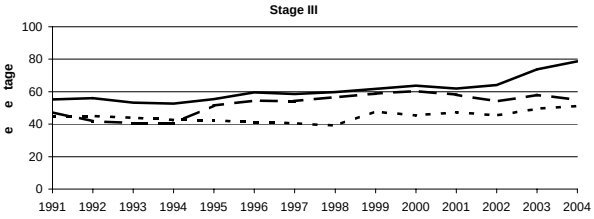
Figure 2
Unadjusted relative 5-year survival per stage and per age group in 3-year moving means, combined with tables with unadjusted and adjusted RER.



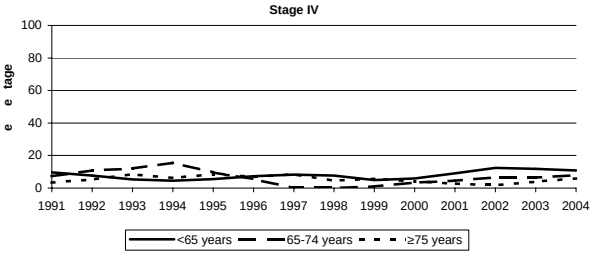
Stage I	RER		
	Unadjusted	Adjusted (1)	Adjusted (2
< 65 years	0.96	0.95	0.94
65-74 years	0.93	0.88	0.99
≥ 75 years	0.97	0.97	0.97



Stage II	RER		
	Unadjusted	Adjusted (1)	Adjusted (2
< 65 years	0.97	0.96	0.96
65-74 years	***0.95****	***0.95****	***0.95****
≥ 75 years	***0.97****	0.97	***0.97****



Stage III	RER		
	Unadjusted	Adjusted (1)	Adjusted (2
< 65 years	***0.94****	***0.94****	0.98
65-74 years	***0.97****	0.97	1.02
≥ 75 years	***0.97****	***0.96****	***0.97****



Stage IV	RER		
	Unadjusted	Adjusted (1)	Adjusted (2
< 65 years	0.99	***0.98****	***0.97****
65-74 years	0.99	0.98	0.99
≥ 75 years	1.01	1	1.01

* p≤0.05
(1) adjusted for sex, age, and grade
(2) adjusted for sex, age, grade, and treatment

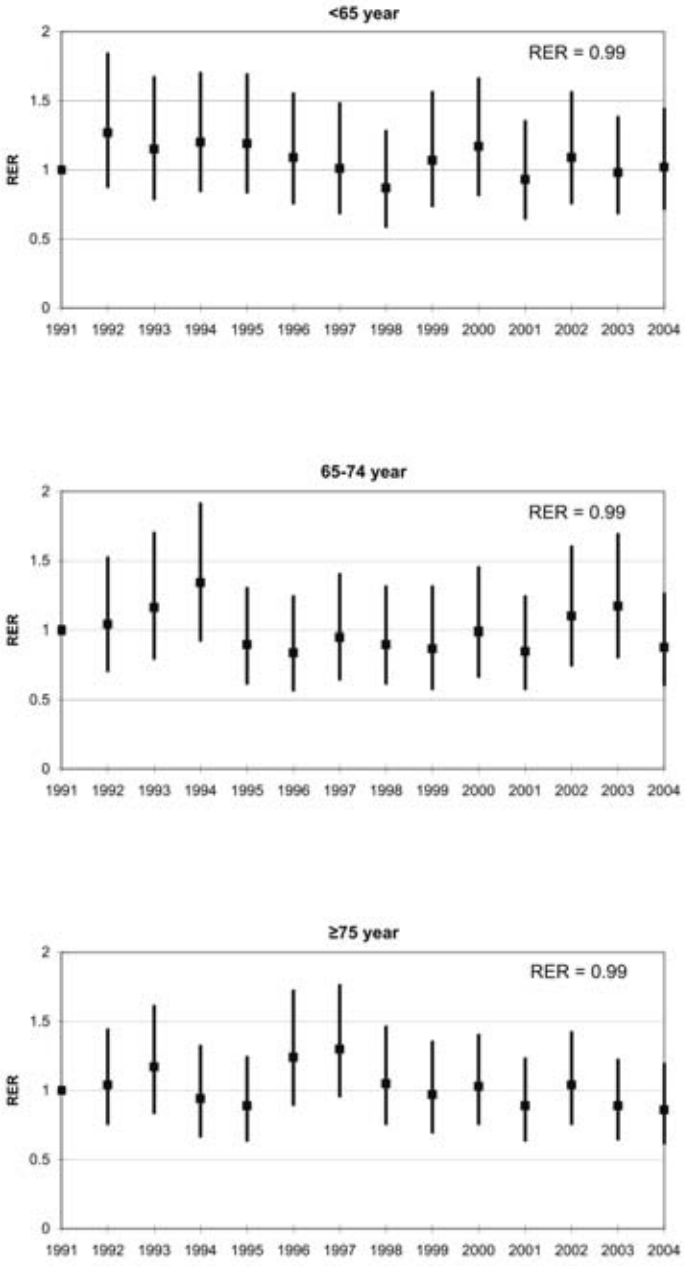
For comparison with the EUROCARE study, which showed a widening survival gap between 1988 and 1999, we calculated the adjusted RER over time, with 1991 as reference, stratified by age groups. **(Figure 3(A))** None of the age groups showed a significant increase in their adjusted relative survival between 1991 and 2004 after adjustment for sex, age, grade, and stage. After additional adjustment for treatment **(Figure 3(B))** both middle-aged patients (< 65 years) and elderly patients (≥ 75 years) showed a significant increase in their adjusted relative survival between 1991 and 2004 (RER=0.97, 95%CI=0.95-0.98, p<0.001 and RER=0.98, 95% CI=0.97-0.99, p=0.05, respectively). There was no significant increase in adjusted relative survival for patients aged between 65 and 75 years (RER=0.99, 95%CI=0.97-1.00, p=0.08).

We calculated the RERs over time per age group adjusted for sex, grade, and stage without treatment **(Table 2A)** and with treatment **(Table 2B)**, with middle-aged patients (<65 years) as reference. Aged and elderly patients always showed a lower survival than middle-aged patients in all years. When there is a significant difference in the RERs, the survival of the aged or elderly patients is significant worse than the survival of the middle-aged patients. The higher the RER is, the larger the difference in survival between age groups. Looking at the study period of the EUROCARE, until 1999, we see a gap between the survival of middle-aged patients and elderly patients, which is the largest in 1997 and 1998. In more recent years, the gap between middle-aged and elderly patients is still present, with 2001 and 2002 comparable with 1997 and 1998, even when adjusted for treatment, but the gap has not further increased.

Figure 3
Adjusted RER and 95% CI per age group over time, with 1991 of each age group as a reference. (A) Adjusted for sex, age, grade, and stage, (B) Adjusted for sex, age, grade, stage, and treatment.

* p≤0.05.

3A



* p≤0.05.

3B

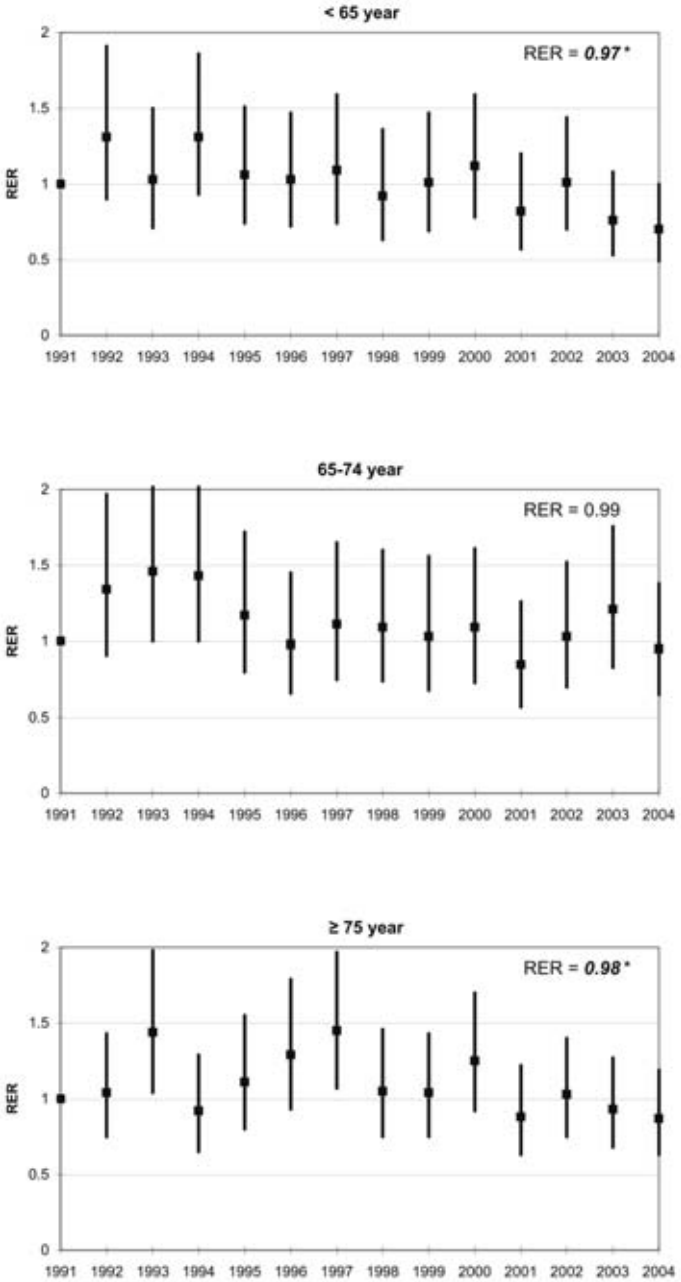

< 65 year
RER = 0.97*
RER
2
1.5
1
0.5
0
1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004
65-74 year
RER = 0.99
RER
2
1.5
1
0.5
0
1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004
≥ 75 year
RER = 0.98*
RER
2
1.5
1
0.5
0
1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004

Table 2

RER over time per age group, with middle-aged patients (<65 years) as reference.

(A) Adjusted for sex, grade and stage

			1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
All stages	**Reference**	**<65 years**	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
	Adjusted RER	**65-74 years**	1.4	1.2	1.4	**1.6***	1.0	1.2	1.4	**1.5***	**1.6***	1.2	**1.7***	1.4	**1.9***	1.4
	Adjusted RER	**≥75 years**	**2.7***	**1.5***	**2.1***	**1.5***	**1.9***	**2.0***	**3.0***	**2.7***	**2.4***	**2.0***	**3.2***	**2.9***	**2.0***	**2.3***

* p≤0.05

(B) Adjusted for sex, grade, stage and treatment

			1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
All stages	**Reference**	**<65 years**	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
	Adjusted RER	**65-74 years**	1.4	1.2	1.5	1.3	1.2	1.1	1.1	1.4	1.4	1.0	1.4	1.1	**1.5***	1.2
	Adjusted RER	**≥75 years**	**2.2***	1.3	**1.6***	1.1	**1.8***	**1.6***	**2.1***	**2.2***	**1.5***	1.2	**1.8***	**2.0***	**1.5***	1.3

* p≤0.05

Discussion

In this population-based study covering the mid-western region of the Netherlands over a period of 15 years, substantial changes in treatment of colon cancer were found. Adjuvant chemotherapy for patients with stage III disease increased over time, resection rates remained stable over time for patients with stage I, II, and III disease in all age groups, while resection rates among metastatic patients decreased, and administration of chemotherapy for stage IV colon cancer patients increased for all age groups. Moreover, survival increased significantly over time for middle-aged and elderly patients after adjusting for age, sex, grade, stage and treatment. The adjusted survival of aged patients did not increase significantly over the years. However, the present study did not show a further increase in the survival gap between middle-aged and elderly patients.

Treatment

During the study period, some major changes in the adjuvant treatment of colon cancer have occurred. After Moertel et al.[7] published the first clinically important survival benefit of one year adjuvant therapy with fluorouracil and levamisole for patients with stage II and III colon cancer, the United States quickly adopted this as standard therapy for stage III colon cancer patients. However, in the Netherlands adjuvant chemotherapy for stage III colon cancer was incorporated in the guidelines from the mid 1990's and since 2005 the guideline also includes adjuvant chemotherapy for high risk stage II patients.[8] The changes in the guidelines for treating patients with colon cancer are visible in the data; in the period 1996-2000, for all age groups a large increase in the adjuvant treatment of stage III colon cancer patients was visible (from 31% to 68%, from 8% to 47%, and from 2 to 10% for middle-aged, aged, and elderly patients respectively), although this showed much smaller survival benefit in the cohort than expected. During the study period stage IV colon cancer patients were increasingly treated with chemotherapy and less often with surgery. Over the past three decades, stage IV colon cancer has turned from a lethal, incurable disease, into a potentially curable disease for a selected group of patients.[9]

The surgical technique for colon cancer has not changed in the Netherlands during the study period. However, in 2009 Hohenberger et al. presented their promising results about the complete mesocolic excision for patients with colon cancer.[10] Possibly with use of this technique local recurrence rates might decrease and 5-year survival rates might increase further in the future. Also centralisation and auditing are relatively new for colon cancer in the Netherlands which might improve survival in the future.[11]

Survival

Overall we found a small increase in relative survival for colon cancer patients over the years. However, stage migration could have influenced this study. More advanced diagnostic tools have been used in the recent years,[12-13] possibly leading to detecting a more advanced stage of disease. Furthermore, a more extensive search for affected lymph nodes could have had a similar effect. The harvesting of more lymph nodes could also have contributed directly to an improved survival.[14-15]
Another factor that might have influenced the survival results, is the improvement of peri-operative care.[16] With the hypothesis that survival would not increase over time when adjusted for sex, age, grade, stage, and treatment, the data in this paper show that there are residual influences related to outcome. Even after adjusting for sex, age, grade, stage, and treatment, a significant improvement was found in relative survival of elderly patients with stage III and of middle-aged patients with stage IV colon cancer.

Changes in treatment and improvements in survival of colon cancer in the midwestern region of the Netherland found in this study, are in line with the results of a previous study covering national data.[17] Notable is that the improvement in survival and the increase in use of adjuvant treatment are more visible in middle-aged patients than in aged and elderly patients. One of the main problems found in the treatment of elderly patients is that current guidelines are based on randomized controlled trials, in which elderly patients or patients with severe co-morbidity are underrepresented or excluded. The improvement in survival of middle-aged colon

cancer patients over time has mostly been due to a decrease in operative mortality and an increase in the resection rate, possibly coupled with a more aggressive approach to the treatment of local and distant recurrences.[18-21] Elderly patients on the other hand usually present with more advanced stage and tend to undergo more emergency surgery. Although, in the present study we could not confirm the higher stage at diagnosis, but more elderly patients were registered with an unknown stage of disease which could include undiagnosed stage III and IV. Elderly patients are also less likely to receive adjuvant treatment and receive "suboptimal" management.[22-27] Adjuvant chemotherapy has shown to be an effective treatment for elderly patients with stage III colon cancer, but the benefit is lower with older age.[18-28-29] However, elderly patients do not necessarily experience greater chemotherapy-related toxicity.[19-29]

Gap in survival between younger and elderly

EUROCARE recently reported that for colon cancer, as well as other cancer types, the survival gap between elderly (70-84 years) and middle-aged (55-69 years) patients was widening in the period between 1988 and 1999.[2] Due to the information available in the EUROCARE study, adjusting for several factors, like stage, was not possible. In the present study we were able to adjust for sex, age, grade, stage, and treatment. Besides, we were able to analyze more recent data. Patients were divided into three age groups instead of two; this would make the difference between middle-aged and elderly patients more visible. We found a significant difference in survival between patients middle-aged and elderly patients over all the years, even after adjusting for sex, age, grade, stage, and treatment. The largest difference in survival was between 1997 and 1998 and between 2001 and 2002. Besides the gap between 1997 and 1998, which is similar to the gap shown by the EUROCARE, we also show a more recent survival gap in 2001 and 2002, which is similar in size to the gap in 1997 and 1998. However, the survival differences between middle-aged and elderly patients are not consistent over time. The survival gap is mainly caused by an increase in survival of middle-aged patients and a stable survival of elderly patient. In the present study, this gap did not widen any further, but is stabilising.

Hopefully in the future aged and elderly patients will also benefit of the increased survival, possibly due to improved treatment.

Stage distribution differs between several countries in Europe.[13] As tumour stage is one of the most important prognostic factors in most cancer types, survival rates for several countries are difficult to compare. A new initiative is needed and founded in EURECCA, which aims to collect prospective information about colorectal cancer patients in several countries in Europe.[30]

Conclusions

In the mid-western region of the Netherlands no changes in treatment have occurred for stage I and II colon cancer during the study period. Patients with stage III and IV were treated with significantly more adjuvant chemotherapy over time, although less prominent for elderly patients, while the resection rate of patients with stage IV decreased for all age groups. The survival gap earlier found by the EUROCARE is confirmed for the mid-western part of the Netherlands, even after adjusting for several confounders. However, the present study did not show a further increase in the survival gap between middle-aged and elderly patients. The near future will have to show if a more extensive and hopefully better tailored treatment can help elderly to close this gap.

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Chapter 7

Importance of the first postoperative year in the prognosis of elderly colorectal cancer patients.

JWT Dekker
CBM van den Broek
E Bastiaannet
LGM van de Geest
RAEM Tollenaar
GJ Liefers

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Abstract

Aims: Elderly colorectal cancer patients have a worse prognosis than younger patients. Age related survival differences may be cancer or treatment related, but also due to death of other causes. This study aims to compare population based survival data for young (<65 years), aged (65-75 years) and elderly (≥75 years) colorectal cancer patients

Methods: All patients operated for stage I-III colorectal cancer, between 1991 and 2005 in the Western region of the Netherlands were included. Crude survival, relative survival and conditional relative survival curves, under the condition of surviving 1-year, were made for colon and rectal cancer patients separately. Furthermore, 30-day, 1-year and 1-year excess mortality data were compared.

Results: A total of 9 397 stage I-III colorectal cancer patients were included in this study. Crude survival curves showed clear survival differences between the age groups. These age related differences were less prominent in relative survival and disappeared in conditional relative survival (CRS). Only in stage III disease, elderly patients had a worse CRS than young patients. Furthermore, significant age related differences in 30-day and 1-year excess mortality were found. Thirty-day mortality vastly underestimated 1-year mortality for all age groups.

Conclusions: Elderly colorectal cancer patients that survive the first year, have the same cancer related survival as younger patients. Therefore, decreased survival in the elderly is mainly due to differences in early mortality. Treatment of elderly colorectal cancer patients should focus on peri-operative care and the first postoperative year.

Introduction

The number of elders in the population and the incidence of colorectal cancer are increasing. Therefore, it is to be expected that the number of elderly colorectal cancer patients will further increase. Various population-based studies show that survival of elderly colorectal cancer patients is worse compared to younger patients. Differences in survival by age groups in colorectal cancer may be explained by variations in tumour factors, patient characteristics and therapy. Elderly colorectal cancer patients tend to have a more advanced stage of disease.[1] Besides, they have more co-morbidity and are treated less aggressive than their younger counterparts.[2] Co-morbidity influences surgical eligibility and other treatment options.[3] Furthermore, it represents a greater risk of non cancer related mortality. Elderly patients less frequently receive adjuvant chemotherapy and more often discontinue treatment before completion. [4]

Notwithstanding all these differences, several studies found a similar disease specific survival for elderly and young colorectal cancer patients.[5-7] This would indicate the excess mortality in elderly colorectal cancer patients is due to competing causes of death. To gain a better insight in survival differences between age groups, the present study aims to compare population-based survival data of colorectal cancer patients for different age groups. It will not only regard overall and relative survival but also conditional relative survival under the condition of surviving one year. Furthermore, this study will focus on age related differences in 30-day and 1-year mortality.

Methods

Patients were selected from the regional cancer registry of the Comprehensive Cancer Centre West (CCCW) covering the Western part of the Netherlands. The nationwide Dutch network and registry of histo- and cytopathology (PALGA) regularly

submits reports of all diagnosed malignancies to the cancer registries. The national hospital discharge databank, which receives discharge diagnoses of admitted patients from all Dutch hospitals, completes case ascertainment. After notification, trained registry personnel collect data on diagnosis, staging, and treatment from the medical records, including pathology and surgery reports, using the registration and coding manual of the Dutch Association of Comprehensive Cancer Centers. Cancer registry data show actual variations in patterns of staging, treatment and survival by age and therefore offer a scope for improvement of care and for creating guidelines, in addition to randomized clinical trials.[8]

From the regional cancer registry, patients diagnosed between 1991 and 2005 with their first primary colon or rectal cancer stage I, II or III and surgically treated were selected. Vital status was established either directly from the patient's medical record or through linkage of cancer registry data with the municipal population registries which record information on their inhabitant's vital status. Stage was based on pathological information; clinical information was used if pathology data were missing.

Statistics

Patients were divided into younger than 65 years, 65-74 years and 75 years and older. Differences between characteristics were tested with Chi-Square tests. Overall Survival was calculated with death due to any cause as event. Relative survival is the preferred way to describe the prognosis of elderly cancer patients, as it takes into account the risk of dying from other causes than the disease of interest.[8] Relative survival was calculated by the Hakulinen method as the ratio of the survival observed among the cancer patients and the survival that would have been expected based on the corresponding (age, sex and year) general population. National life tables were used to estimate expected survival. Conditional relative survival was calculated for patients who survived the first year. Relative Excess Risks of death (RER) were estimated using a multivariate generalized linear model with a Poisson distribution, based on collapsed relative survival data, using exact survival times.

Finally, 30-day and 1 year overall mortality were calculated as well as the 1-year excess mortality (observed – expected deaths / number of patients).

Results

From January first 1991 trough December 31st 2005 in the CCCW region 9 611 stage I -III colorectal cancer patients were diagnosed and 9 397 (97.8%) were operated, 6 405 patients with colon cancer and 2 992 rectal cancer patients. These patients had a median age of 72 years (range 7-100) for colon cancer and 69 years (range 18-98) for rectal cancer patients. Patient characteristics according to age groups for colon and rectum separately are shown in **Table 1**. The percentage of female patients was significantly higher in the oldest age groups, especially for colon cancer patients. The number of treated colon cancer patients increased over the years. Tumor grade is evenly divided for rectal cancer but not for colon cancer patients, with more grades III in the elderly. In this cohort younger patients had higher tumor stages than the elderly, although the percentage of patients with an unknown stage of disease was higher in the elderly (data not shown). The use of adjuvant chemotherapy decreased with advancing age groups. Radiotherapy for rectal cancer patients was comparable for the young and aged groups and was lower in the elderly group.

Figure 1 shows survival curves for overall survival **(a)**, relative survival **(b)** and conditional relative survival **(c)** for colon and rectal cancer patients in the different age groups. Differences in survival between age groups for colorectal cancer patients disappear when a correction is made for death of other causes under the condition of surviving one year. As shown in **Table 2** the elderly patients had a RER of 1.6 (95%CI 1.4-1.9; $p<0.001$) as compared to the young patients for colon cancer and 1.4 (95%CI 1.2-1.7; $p<0.001$) for rectal cancer. When relative survival was calculated for the patients who survived the first year relative excess risks were around 1.0 (RER 1.1; $p=0.2$ for colon and RER 1.1; $p=0.3$ for rectal cancer). Going into more de-

Table 1
Characteristics of patients operated for colon and rectal cancer, diagnosed in the period 1991-2005 according to age

		Colon cancer				Rectal cancer			
		<65.0 years Number (%)	**65-75 years Number (%)**	**≥75 years Number (%)**	**p-value**	**<65.0 years Number (%)**	**65-75 years Number (%)**	**≥75 years Number (%)**	**p-value**
Sex	Male	889 (51.1)	964 (50.3)	1123 (40.8)	<0.001	603 (57.6)	513 (57.5)	523 (49.7)	<0.001
	Female	851 (48.9)	952 (49.7)	1626 (59.2)		444 (42.4)	379 (42.5)	530 (50.3)	
Year	1991-1995	539 (31.0)	624 (32.6)	831 (30.2)	0.02	307 (29.3)	295 (33.1)	342 (32.5)	0.2
	1996-2000	531 (30.5)	642 (33.5)	930 (33.8)		326 (31.1)	281 (31.5)	343 (32.6)	
	2001-2005	670 (38.5)	650 (33.9)	988 (36.0)		414 (39.6)	316 (35.4)	368 (34.9)	
Grade	Grade I	123 (7.1)	129 (6.7)	184 (6.7)	0.02	62 (5.9)	44 (4.9)	56 (5.3)	0.4
	Grade II	1150 (66.1)	1326 (69.2)	1808 (65.8)		720 (68.8)	652 (73.1)	768 (72.9)	
	Grade III	284 (16.3)	276 (14.4)	505 (18.3)		169 (16.1)	122 (13.7)	149 (14.2)	
	Unknown	183 (10.5)	185 (9.7)	252 (9.2)		96 (9.2)	74 (8.3)	80 (7.6)	
Stage	Stage I	317 (18.2)	386 (20.1)	476 (17.3)	<0.001	310 (29.6)	333 (37.3)	380 (36.1)	<0.001
	Stage II	782 (44.9)	902 (47.1)	1459 (53.1)		318 (30.4)	285 (32.0)	363 (34.5)	
	Stage III	641 (36.9)	628 (32.8)	814 (29.6)		419 (40.0)	274 (30.7)	310 (29.4)	
Treatment	Only surgery	1219 (70.1)	1610 (84.0)	2661 (96.8)	<0.001	447 (42.7)	471 (52.8)	750 (71.2)	<0.001
	Surgery + RT	12 (0.7)	18 (0.9)	4 (0.2)		449 (42.9)	370 (41.5)	295 (28.0)	
	Surgery + CT	504 (28.9)	287 (15.0)	84 (3.0)		68 (6.5)	34 (3.8)	7 (0.7)	
	Surgery+CT+RT	5 (0.3)	1 (0.1)	0 (0.0)		83 (7.9)	17 (1.9)	1 (0.1)	
Overall		**1740 (27.2)**	**1916 (29.9)**	**2749 (42.9)**		**1047 (35.0)**	**892 (29.8)**	**1053 (35.2)**	

tail and considering different stages a significant difference in conditional relative survival remains for stage III patients for both colon and rectal cancer.

Figure 1a
Overall Survival according to age for stage I - III patients operated for colon and rectal cancer

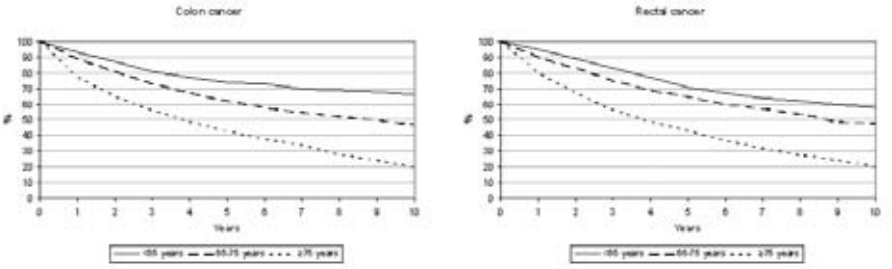

Figure 1b
Relative Survival according to age for stage I -III patients operated for colon and rectal cancer

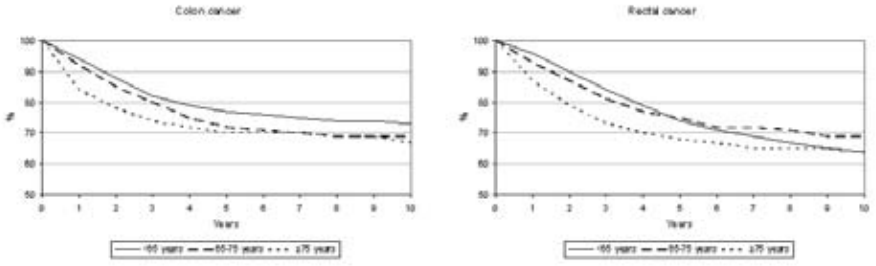

Figure 1c
Conditional Relative Survival (conditioning on patients who survived 1 year) according to age for stage I -III patients operated for colon and rectal cancer

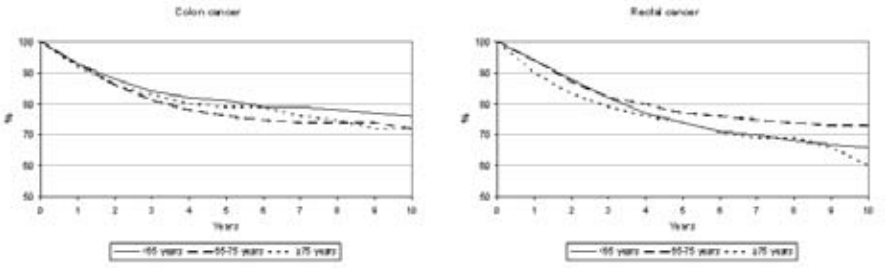

Table 2
Relative and Conditional survival of operated stage I-III patients

COLON CANCER	**All stages**		**Stage I**		**Stage II**		**Stage III**	
	RS	**CS**	**RS**	**CS**	**RS**	**CS**	**RS**	**CS**
<65	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
65-74	1.2 (1.0-1.4)	1.2 (1.0-1.4)	1.2 (0.6-2.4)	1.2 (0.6-2.5)	1.2 (0.9-1.5)	1.3 (1.0-1.8)	1.4 (1.2-1.7)	1.3 (1.0-1.6)
p-value	**0.01**	**0.03**	0.7	0.5	0.2	**0.04**	**<0.001**	**0.02**
75+	1.6 (1.4-1.9)	1.1 (0.9-1.4)	1.2 (0.5-2.8)	N.A.	1.8 (1.4-2.2)	1.3 (0.9-1.8)	2.0 (1.6-2.3)	1.4 (1.1-1.8)
p-value	**<0.001**	0.2	0.7	0.99	**<0.001**	0.1	**<0.001**	**0.003**

RECTAL CANCER	**All stages**		**Stage I**		**Stage II**		**Stage III**	
	RS	**CS**	**RS**	**CS**	**RS**	**CS**	**RS**	**CS**
<65	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
65-74	1.0 (0.8-1.2)	0.9 (0.7-1.1)	0.8 (0.4-1.8)	0.6 (0.3-1.5)	1.2 (0.8-1.6)	1.1 (0.8-1.7)	1.2 (0.9-1.5)	1.1 (0.8-1.4)
p-value	0.8	0.2	0.6	0.3	0.4	0.6	0.1	0.6
75+	1.4 (1.2-1.7)	1.1 (0.9-1.4)	1.7 (0.8-3.6)	0.3 (0.1-7.0)	1.6 (1.1-2.2)	1.4 (0.9-2.2)	1.8 (1.4-2.3)	1.5 (1.2-2.0)
p-value	**<0.001**	0.3	0.2	0.5	**0.009**	0.1	**<0.001**	**0.002**

RS=relative survival, CS=conditional survival, N.A.=not addressed due to small numbers

Table 3 shows overall 30-day, 1-year and 1-year excess mortality according to type of tumor in reference to baseline factors. Gender was a significant factor for first year mortality in rectal cancer, with more male patients dying. Age was the most significant factor for all three mortality endpoints for both colon and rectal cancer patients. Tumor grade did not influence 30-day mortality but was a significant factor for 1 year mortality for both colon and rectal cancer patients. Tumor stage also influenced 30-day mortality for colon cancer patients, but not for rectal cancer patients. Thirty-day and 1-year mortality rates decreased over the years (data not shown). For colon cancer patients this was only significant ($p<0.05$) for 1-year mortality rates for all age groups (lowest RER 0.94). For rectal cancer patients 30-day mortality was significantly reduced ($p<0.01$) for the elderly (RER 0.89). One-year mortality for the young and aged patients (lowest RER 0.93) was significantly improved ($p= 0.03$), however not for the elderly patients ($p=0.3$; RER 0.98).

Table 3
Overall 30-day and 1-year mortality and 1-year excess mortality rates in percentages according to type of tumor

	COLON CANCER				RECTAL CANCER			
	Overall mortality			Excess mortality	Overall mortality			Overall mortality
	N	† ≤30 d	† 1st year	† 1st year	N	† ≤30 d	†1st year	† 1st year
Sex								
Male	2976	4.6	15.7	11.3	1639	2.1	**13.2**	**9.4**
Female	3429	4.1	14.5	10.9	1353	1.3	**9.9**	**6.9**
Age (years)								
<65	1740	**1.4**	**6.8**	**6.1**	1047	**0.2**	**5.1**	**4.4**
65-75	1916	**2.4**	**10.8**	**8.5**	892	**1.4**	**9.5**	**7.2**
≥75	2749	7.5	**23.2**	**16.0**	1053	**3.7**	**20.1**	**13.1**
Grade								
I	436	2.1	**9.9**	**6.0**	162	3.1	**8.0**	**4.9**
II	4284	4.4	**12.6**	**8.5**	2140	1.8	**10.2**	**6.6**
III	1065	4.7	**25.2**	**21.3**	440	1.6	**22.3**	**19.5**
Unknown	620	4.8	**18.2**	**14.8**	250	1.2	**8.4**	**5.2**
Stage								
I	1179	**1.7**	**8.0**	**4.0**	1023	1.5	**7.6**	**3.8**
II	3143	**5.0**	**13.5**	**9.2**	966	2.4	**12.7**	**9.1**
III	2083	**4.8**	**21.4**	**18.0**	1003	1.5	**14.9**	**12.1**

Discussion

Crude survival is a solid outcome measure that shows evident age related differences. However, crude survival will overestimate the impact of cancer on survival, because it also includes mortality due to other causes. To adjust for this, relative survival is used, defined as the ratio of observed to expected survival. This reduces age related differences in colorectal cancer survival. However, the results of age related relative survival are still largely influenced by early mortality (defined as mortality in the first postoperative year). Postoperative complications are a more probable cause for early mortality than the colorectal cancer itself in stage I to III patients (who in general had curative surgery). Therefore, in order to get a clear image of the impact of colorectal cancer on survival for different age groups, we used conditional relative survival under the condition of surviving one year. As a result age related differences in survival disappeared, indicating that probably colorectal cancer itself is not the main cause of age related differences in survival. This is in line with earlier studies that found no age related differences in cancer specific survival.[5-7] However, this remains intriguing since many papers indicate that differences in survival between the young and the elderly can be attributed to undertreatment in the elderly.[1-9] Our study confirms these variations in treatment and conditioned survival in stage III patients is indeed significantly worse in the elderly. Nonetheless, the excess mortality in the first postoperative year was the main determining factor for age related survival differences.

Postoperative mortality

The 30-day mortality rates for the different age groups in the present study are in accordance with earlier findings by other studies.[10-11] However, the most striking finding of this analysis is the fact that 30-day mortality vastly underestimates 1-year mortality for all age groups. Apparently, the impact and consequences of treatment have a prolonged effect on mortality. This effect is very strong even for patients in the youngest group. With increasing age, also the excess mortality increases. It has been shown earlier that with age not only mortality, but also postop-

erative morbidity increases.[12-14] Furthermore, Manku et al.[15] showed that in hospital complications had a prognostic significance. In five hundred seventeen patients who underwent non-cardiac surgery, they found that postoperative complications caused mortality up to 3 months after surgery, with a sustaining effect on survival. Greenblatt et al.[16] studied stage I to III colon cancer patients from the Surveillance, Epidemiology, and End Results-Medicare database and found that readmission was strongly associated with 1-year mortality. The same variables that predicted readmission in this study also predicted 1-year mortality (male gender, comorbidity, emergent admission, prolonged hospital stay, blood transfusion, ostomy and discharge to a nursing home). Kunitake et al.[17] showed that patients older than eighty years were readmitted almost twice as much as patients younger than sixty five years. Furthermore, in their study 75% of readmittances were not related to the surgery itself. With the present study, all these studies seem to imply that for a significant number of patients the assault of surgery has delayed effects that can cause mortality outside the scope of the surgeon.

Stage III patients

Only in stage III patients we found age related differences in conditional relative survival. Here differences in (neo-) adjuvant therapy between the age groups were most apparent. This is in line with earlier studies, that show that elderly patients are undertreated.[4] This undertreatment of elderly patients could explain the age related differences in conditional relative survival for stage III patients. However, also in stage III patients, first year mortality remains a crucial factor for survival. The difference in conditional relative survival between young and elderly stage III patients was 10.4% for colon and 5.6% for rectal cancer, while the differences in 1-year excess mortality rates were 17.2 and 12.0% respectively.

Limitations

An obvious limitation of this study is the lack of information on emergency surgery, and comorbidity. Both are associated with increased postoperative complications and mortality. They will not only have had a prominent influence on early mortality

for all age groups, but they probably account for the differences between the age groups as well. Elderly patients are more likely to undergo emergency surgery and also the incidence of comorbidity increases with age.[10] Nevertheless, the strength of this study is that it shows the essence of age related survival and early mortality differences in a large population based cohort.

Clinical Implications

The results of this study could provide a focus for future studies and have implications for the clinical setting. As age related differences in mortality are most apparent the first postoperative year, this is where the focus must be in treating elderly colorectal cancer patients. Although some risk factors may not be modifiable, others relate to the processes of care. More attention should be given to patient selection and careful preoperative evaluation, followed by medical optimization, proper timing of surgery and planning of peri-operative care. Furthermore, appropriate referral to high volume or dedicated centers should be considered if anticipated that patients will require higher level of resources and care following surgery. Quality enhancement programs could focus on particular complications. These should not only try to prevent the occurrence of peri-operative complications, but also focus on early identification and adequate treatment of complications to avoid related mortality.[18]

The excess mortality of the first postoperative year forms a clear indication of the prolonged impact of the peri-operative period, especially when complications occur. Therefore, we should anticipate preoperatively on the level of functioning after discharge.[13] The targets of treatment for elderly patients should extend beyond the in-hospital period and continued attention should be given to comorbidity and complications in the post-hospital period.

The prolonged impact of the peri-operative period could also have a profound effect on functional status and quality of life. For elderly patients these issues should be evaluated with care, especially when they have limited life expectancies. How-

ever, for the majority of patients, age per se is not a contra indication for surgery. Not in the least because surgery for colorectal cancer is often the best way to ensure palliation.

Conclusions

This study can help to comprehend the challenge of treating elderly colorectal cancer patients. When survival data for colorectal cancer are corrected for expected death of other causes and first year mortality, age differences disappear. Therefore, decreased survival in the elderly is mainly due to differences in early mortality. Only for stage III disease elderly patients fare worse, probably as a result of less extensive adjuvant treatment. The overall difference between the younger and elderly age groups is that within the elderly group there is an excess mortality of about 10 % the first year. Further studies are necessary to elucidate the etiology of these differences and whether they may be modifiable. This study implies that in treating elderly stage I-III colorectal cancer patients the focus should be on the peri-operative process and the first postoperative year.

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Chapter 8

Risk factors for excess mortality in the first year after curative surgery for colorectal cancer

GA Gooiker*
JWT Dekker*
E Bastiaannet
LGM van der Geest
JWS Merkus
CJH van de Velde
MWJM Wouters
RAEM Tollenaar
GJ Liefers

On behalf of the steering committee of the 'Quality Information System Colorectal
* Both authors contributed equally to this article

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Abstract

Aims: Thirty-day mortality after surgery for colorectal cancer may vastly underestimate 1-year mortality. This study aims to quantify the excess mortality in the first postoperative year of stage I-III colorectal cancer patients and to identify risk factors for excess mortality.

Methods: All 2131 patients who were operated with curative intent for stage I-III colorectal cancer in the Western region of the Netherlands, between January 1 2006 and December 31 2008, were analyzed. Thirty-day mortality and relative survival were calculated. Also Relative Excess Risks of death (RER) were estimated using a multivariable model.

Results: Thirty-day mortality was 4.9%. One-year mortality was 12.4%. Risk factors for Excess Mortality (EM) in the first postoperative year for colon cancer patients were emergency surgery (EM 29.7%, RER (Relative Excess Risk) 2.5 (95%CI 2.5-5.0), a Charlson score >1 (EM 12.6%, RER 2.3 (1.5-3.7)), stage II or III disease (EM 14,9%, RER 3.9 (1.9-8.1)) and postoperative adverse events (EM 22,6%, RER 2.1 (1.4-3.2)).

Conclusions: The 30-day mortality rate highly underestimates the risk of dying in the first year after surgery, with excess 1-year mortality rates varying from 15 to 30%. This excess mortality was especially prominent in patients with co-morbidities, higher stages of disease, emergency surgery, and postoperative surgical complications.

Introduction

Adverse postoperative events are most often recorded as 30-day mortality and postoperative complications. Large studies show that colorectal cancer surgery can be considered as high risk with reported postoperative mortality and complication rates around 5% and 20-40% respectively. [1-4]

For the prognosis of colorectal cancer patients that undergo curative surgery, adverse postoperative events constitute a determining factor. Several studies showed that complications are of prognostic importance, because they can cause delayed mortality. [5,-6] Furthermore, specific complications such as anastomotic leaks are associated with local recurrences and reduced survival.[7-9] Elderly patients with severe co-morbidities, lower social economic status, a stage III tumor or preoperative tumor complications, have been shown to be at higher risk for postoperative adverse events.[10-12]

Earlier studies have shown that 30-day mortality after surgery for colorectal cancer vastly underestimates 1-year mortality,[13-14] even in young colorectal cancer patients that were operated with curative intent. Furthermore, Dekker et al showed that 1-year excess mortality (1-year mortality adjusted for expected mortality in the general population) was the main determining factor for age related survival differences: after surviving the first year, elderly had the same cancer related survival as younger patients.[14] This suggests that there may be a prolonged impact of the assault of surgery. Up to date little information exists on the etiology of the excess mortality in the first postoperative year. Because of the lack of reported determinants of excess mortality in the contemporary literature, we set out to determine the role of co-morbidity, emergency surgery and postoperative complications, expecting that these factors are main determinants for 1-year excess mortality. Especially in elderly patients where the incidence of co-morbidity is higher and emergency surgery and postoperative complications occur more frequently.

The identification of risk factors would help to stratify patients according to their risk. Moreover, risk factors may be modifiable and targeted optimization of care may result in an improved prognosis.

Therefore, the first aim of this study was to quantify the excess mortality in the first postoperative year of stage I-III colorectal cancer patients operated with curative intent according to several patient and tumor characteristics. The second aim of this study is to identify risk factors for excess mortality in the first postoperative year.

Methods

Data

In the Netherlands, all newly diagnosed malignancies are registered in the nationwide population based Netherlands Cancer Registry (NCR). The Leiden Cancer Registry, part of the NCR, collects data on all cancer patients diagnosed in one of the nine affiliated hospitals in the Midwestern part of the Netherlands. This region comprises one university hospital, six teaching hospitals and two non-teaching hospitals and serves a population of 1.7 million inhabitants.

Independently trained data managers collect data from the original patient files after receiving an automatic report from the Dutch pathology reporting system "PALGA." Information on patient characteristics, tumor characteristics, treatment, hospital of diagnosis and/or treatment and follow-up are recorded. Tumor site and morphology are coded according to the International Classification of Diseases for Oncology (ICD-0).[15] Cancers are staged according to the TNM classification of Malignant Tumors, 6th edition.[16] The quality of the data is high, and completeness is estimated to be at least 95%.[17-18]

In 2006, a regional audit for colorectal cancer surgery (KIC) was started in the nine

affiliated hospitals of the Leiden Cancer Registry. The data collection was extended to data that reflected quality of care and case mix factors. These prospectively collected data were used for benchmarking and feedback on each hospitals process, ultimately to improve the quality of care in the entire region. Data were collected on patient demographics (age, sex, co-morbidities and socio-economic status (SES)), tumor characteristics (localization, TNM staging) and treatment characteristics ((neo-) adjuvant treatment, type of surgery, emergency, hospital of treatment, surgical complications and length of stay). Apart from ASA scores, completeness of data was more than 98%.

Patients

All patients who had a resection of stage I, II or III tumor of the colon (C18), the recto-sigmoid (C19) or the rectum (C20) from 1 January 2006 to 31 December 2008 in one of the affiliated hospitals, were identified (patients with a stage IV tumor, with a tumor of the appendix and patients who did not undergo a resection of the tumor, were excluded). Age was categorized in younger than 65 years, 65 to 74 years and 75 years and older. Co-morbidity was recorded according to a slightly modified version of the Charlson index, used by the Dutch Cancer Registry. ASA scores were categorized as ASA I and II or ASA III and IV. Missing data from the ASA score were included as a separate category. SES was categorized as low, intermediate and high, based on area-based data concerning income, employment and education, provided by the Netherlands Institute for Social Research.[19] Surgical complications comprised superficial wound infections, abdominal wall problems (i.e., dehiscence), deep infections, and intra-abdominal complications including bleeding, ileus, abscess or anastomotic leaks. As a substitute for overall complications (both surgical and non-surgical such as pulmonary or cardiac events), a prolonged length of stay was used, which was defined as a hospital admission of 15 days or longer after surgery. Vital status of all patients was obtained actively on a regular basis through linkage of the cancer registry data with the integrated database of the municipal registry and the central bureau for genealogy. Follow-up was completed until January 1 2010.

Statistical analysis

All analyses were done for colon and rectum cancer patients separately. Stratified by several characteristics, 30-day mortality, 1-year overall mortality (all causes) and 1-year excess mortality rates were calculated. Excess mortality was calculated by (Observed number of deaths in the 1st year – Expected number of deaths in the matched general population) / Number of patients. Expected number of deaths was calculated using national life tables matched on age, sex and year of incidence. Survival curves of the relative survival in the first year were constructed. Relative survival is the preferred way to describe the prognosis of elderly cancer patients as it takes into account the risk of dying of other causes than the disease of interest in the absence of cause of death in the database. Relative survival was calculated as the ratio of the observed survival among the cancer patients and the expected survival. Relative Excess Risks of death (RER) with p-value were estimated using a multivariable generalized linear model with a Poisson distribution, based on collapsed relative survival data, using exact survival times.

Results

From January 1, 2006 until December 31, 2008, 2131 patients had a colorectal resection in one of the nine affiliated hospitals of the CCCW, for stage I-III colorectal cancer; 1407 for colon cancer and 724 for rectal cancer. **Table 1** shows characteristics of the study population for colon and rectal cancer patients. Colon patients were older, more often female, had more comorbidity and more often required emergency surgery.

30-day mortality, 1-year mortality and excess mortality

The overall observed 30-day mortality was 4.9%, the 1-year mortality 12.4%. Median follow-up time was 24.6 (range 0.03-47.9) months. All patients had follow up for at least one year unless they died previously. **Table 2** shows crude overall mortality and excess mortality rates of stage I-III colon and rectal cancer patients in the first year after surgery, according to several characteristics. The observed 1-year

Table 1
Characteristics of the population according to localization

Variables		Colon cancer		Rectal cancer	
Age (years)	<65	371	26.4	264	36.5
	65-74	390	27.7	236	32.6
	≥75	646	45.9	244	30.9
Sex	Male	672	47.8	406	56.1
	Female	735	52.2	318	43.9
Stage	I	234	16.6	214	29.6
	II	661	47.0	231	31.9
	III	512	36.4	279	38.5
Emergency	Emergent	188	13.4	17	2.4
	Elective	1219	86.6	707	97.6
ASA	I / II	633	45.0	45.0	56.8
	III / IV / V	297	21.1	21.1	17.0
	Unknown	477	33.9	33.9	26.2
Charlson	0	757	53.8	444	61.3
	1	358	25.4	160	22.1
	2 or more	292	20.8	120	16.6
Complications	No	1155	82.1	559	77.2
	Yes	252	17.9	165	22.8
Hospital stay	< 15 days	956	67.9	471	65.0
	≥ 15 days	419	29.8	238	32.9
	Unknown	32	2.3	15	2.1
SES	High	449	31.9	243	33.6
	Intermediate	480	34.1	241	33.3
	Low	478	34.0	240	33.1
Total		**1407**	**100%**	**724**	100%

Table 2

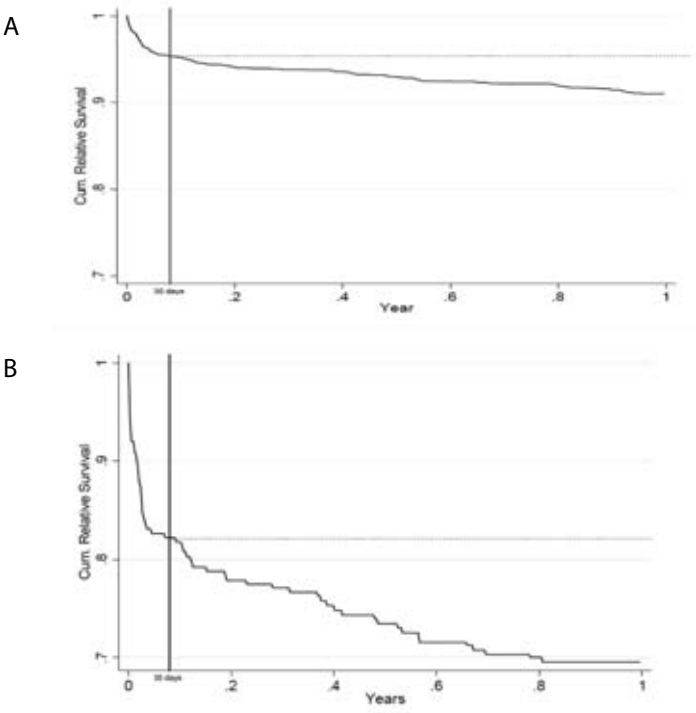
Overall 30-day and 1-year mortality, and 1-year excess mortality.

	Colon			Rectal		
	30-day mortality	**1-year overall mortality**	**1-year excess mortality**	**30-day mortality**	**1-year overall mortality**	**1-year excess mortality**
Overall	6.3	14.8	10.9	2.4	7.9	4.8
Sex						
Male	***7.7***	16.2	12.1	***3.5***	9.6	6.2
Female	***4.9***	13.5	9.8	***0.9***	5.7	3.2
Age						
<65	***1.6***	***5.9***	***5.3***	***0.4***	***2.3***	***1.6***
65-74	***4.1***	***12.3***	***10.2***	***0.4***	***6.8***	***4.5***
≥75	***10.2***	***21.4***	***14.6***	***6.7***	***15.6***	***8.9***
SES						
High	***4.7***	12.9	9.0	2.5	7.0	3.5
Intermediate	***8.5***	15.2	11.5	2.9	9.1	6.7
Low	***5.4***	16.1	12.1	1.7	7.5	4.2
ASA						
I/II	***1.9***	***7.9***	***4.4***	***1.0***	***5.1***	***2.3***
III/IV	***11.1***	***24.9***	***19.9***	***6.5***	***14.6***	***10.2***
Unknown	***9.0***	***17.6***	***13.8***	***2.6***	***9.5***	***6.6***
Stage						
I	6.8	***9.8***	***6.1***	1.9	4.7	1.3
II	5.9	***13.8***	***9.5***	3.0	8.2	5.4
III	6.5	***18.4***	***14.9***	2.2	10.0	7.1
Emergency						
Emergent	***18.1***	***32.9***	***29.7***	N.A.		
Elective	***4.4***	***11.9***	***8.0***			
Comorbidity						
No	***4.3***	***10.5***	***7.7***	***0.3***	***4.4***	***1.7***
Yes	***7.7***	***17.8***	***13.2***	***4.5***	***11.5***	***8.0***
Charlson						
0	***4.1***	***10.8***	***7.5***	***0.7***	***4.7***	***1.8***
1	***6.7***	***17.0***	***12.6***	***3.8***	***10.0***	***6.9***
2 or more	***11.3***	***22.3***	***17.5***	***6.7***	***16.7***	***13.0***
Complications						
No	***5.2***	***12.4***	***8.3***	***1.4***	***6.1***	***2.9***
Yes	***11.1***	***25.8***	***22.6***	***5.5***	***13.9***	***11.2***
Hospital stay						
< 15 days	5.4	***9.8***	***6.2***	2.3	***5.5***	***3.0***
≥ 15 days	8.4	***26.5***	***22.0***	**2.5**	***11.3***	***7.2***
Unknown	3.1	***9.4***	***5.0***	**0**	***26.7***	***24.3***

Bold and italic: p-value<0.05 for the different value within a variable. .

mortality rates of patients older than 75, were 21% and 16% for colon and rectal patients respectively. High excess mortality rates were observed in colon cancer patients with ASA III/IV (19.9%), a stage III tumor (14.9%), a Charlson score of 2 or higher (17.5%) and in patients with postoperative surgical complications (22.6%) or a prolonged length of stay (22%). Of all colon cancer patients with an emergency resection, 33% died in the first year, an excess mortality of 30%. In rectal cancer patients high excess mortality rates were observed in elderly (8.9%), patients with a Charlson 2 or higher (13%) and patients with postoperative complications (11.2%). **Figure 1** shows relative survival curves of all patients in the cohort (a) and an example of relative survival in a specific subgroup: colon cancer patients treated in an emergency setting (b).

Figure 1
Relative Survival in the first year: all patients (a) and colon patients treated in emergency setting (b). The red line marks the 30th day after surgery.
The blue line represents the relative survival in the first year. The space between the red dotted line and the blue line represents the excess mortality after 30 days and within the first year after surgery.



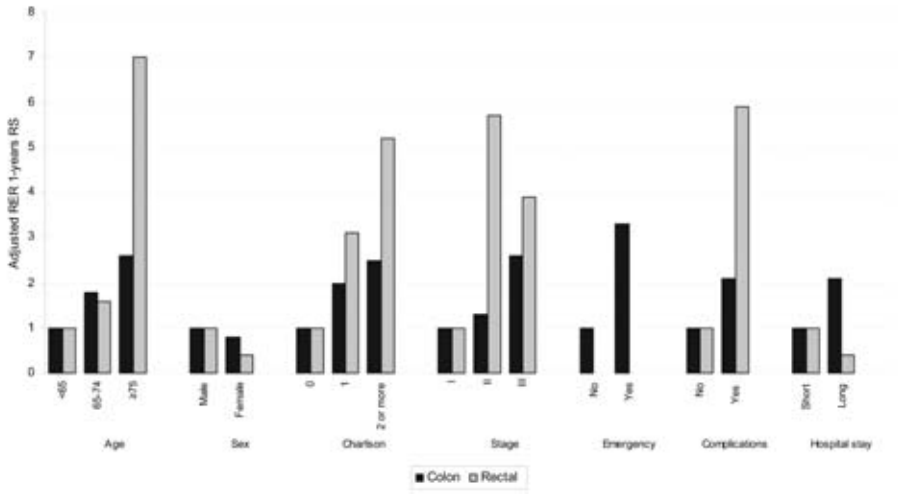
Risk factors for excess mortality in the first year

Figure 2 shows all identified risk factors for 1-year mortality for colon and rectal cancer patients separately. The effect is represented as adjusted relative excess risk (RER) for 1-year mortality. In table 3 (supplementary) the results of univariate and multivariable analysis for risk factors for excess mortality in the first year are shown.

For colon cancer patients, significant risk factors for excess mortality in the first year after surgery, were a stage III tumor (RER 2.6 (1.3-5.3), p <0.001), a Charlson score > 1 (RER 2.5 (1.6-4.0) p = 0.001), an emergency resection (RER 3.3 (2.5-5.0), p < 0.001) and postoperative surgical complications (RER 2.1 (1.4-3.3) p < 0.001). Particular co-morbidities, that increase the risk of excess mortality, were a previous tumor (RER 1.8 (1.2-2.8) p = 0.009), pulmonary disease (RER 2.1 (1.3-3.2) p =0.001), gastro-intestinal disease (RER 2.0 (1.1-3.6) p=0.02) and neurological disease (RER 1.7 (1.0-2.8) p= 0.04).

For rectal cancer patients risk factors for excess mortality in the first year, were age ≥ 75years (RER 7.0 (1.8-27.4) p=0.009), Charlson score > 1 (RER 5.2 (1.7-15.9) p =0.01), and postoperative surgical complications (RER 5.9 (1.3-26.8). Particular co-morbidities that increase the risk were, hypertension (RER 2.4 (1.1-5.5) p=0.04), vascular disease (RER 3.4 (1.3-9.3) p=0.02), kidney disease (RER 7.9 (2.4-26.5) p=0.001) and neurological disease (RER 3.3 (1.0-10.4) p=0.04).

Figure 2
Factors associated with 1-year Relative Survival in multivariable analysis for colon and rectal cancer patients separately. *At the Y-axis, the effect size is represented as adjusted relative excess risk (RER) for 1 year mortality, compared to the reference group, which always has a RER of 1.*



Supplementary table to figure 2

Multivariable One-year Relative Survival, expressed as relative excess risk (RER) for colon and rectal cancer patients separately. *Multivariable analyses include all variables with p-value of 0.1 or smaller. Besides, gender, stage & treatment were also entered into the model.*

EVENT = DOD AT 1 YEAR

		Colon				**Rectal**			
		Univariate		**Multivariable**		**Univariate**		**Multivariable**	
		RER (95%CI)	**p-value**	**RER (95%CI)**	**p-value**	**RER (95%CI)**	**p-value**	**RER (95%CI)**	**p-value**
Age	<65	***1***	***0.0001***	***1***	***0.004***	***1***	***0.01***	***1***	***0.009***
	65-74	***2.0 (1.1-3.6)***		***1.8 (1.0-3.3)***		***2.8 (0.7-11.0)***		***1.6 (0.4-7.6)***	
	≥75	***3.2 (1.9-5.4)***		***2.6 (1.5-4.5)***		***6.2 (1.7-22.0)***		***7.0 (1.8-27.4)***	
Sex	Male	1	0.2	1	0.3	1	0.2	1	0.1
	Female	0.8 (0.5-1.1)		0.8 (0.6-1.2)		0.5 (0.2-1.3)		0.4 (0.1-1.3)	
Charlson	0	***1***	***0.0001***	***1***	***0.0004***	***1***	***0.004***	***1***	***0.01***
	1	***1.8 (1.1-2.8)***		***2.0 (1.3-3.2)***		***3.8 (1.0-14.1)***		***3.1 (0.8-11.3)***	
	2 or more	***2.6 (1.7-4.0)***		***2.5 (1.6-4.0***		***7.7 (2.3-26.3)***		***5.2 (1.7-15.9)***	
Hospital	cont	1.1 (1.0-1.2)	0.1	1.0 (1.0-1.1)	0.3	1.0 (0.8-1.2)	0.7	1.0 (0.8-1.2)	0.7
Stage	I	***1***	***0.006***	***1***	***0.0002***	1	0.3	1	0.2
	II	***1.6 (0.8-3.2)***		***1.3 (0.6-2.6)***		4.4 (0.4-48.8)		5.7 (0.9-36.2)	
	III	***2.5 (1.3-5.1)***		***2.6 (1.3-5.3)***		5.8 (0.5-62.4)		3.9 (0.7-24.1)	
Emergency	No	***1***	***<0.001***	***1***	***<0.001***				
	Yes	***5.0 (3.3-10.0)***		***3.3 (2.5-5.0)***					
Resection	Right sided	***1***	***0.01***	***1***	***0.03***				
	Left sided	***1.4 (0.9-2.2)***		***0.7 (0.4-1.2)***					
	Sigmoid	***0.6 (0.4-1.0)***		***0.5 (0.3-0.9)***					
Complications	No	***1***	***<0.001***	***1***	***<0.001***	***1***	***0.001***	***1***	***0.02***
	Yes	***3.1 (2.1-4.4)***		***2.1 (1.4-3.3)***		***4.2 (1.8-9.9)***		***5.9 (1.3-26.8)***	
Hospital stay	Short	***1***	***<0.001***	***1***	***0.003***	***1***	***0.002***	***1***	***0.002***
	Long	***4.0 (2.7-5.9)***		***2.1 (1.4-3.2)***		***2.5 (1.0-6.3)***		***0.4 (0.1-2.1)***	
	Unknown	***0.8 (0.1-6.6)***		***0.7 (0.1-6.5)***		***9.9 (2.7-35.9)***		***8.6 (2.4-31.7)***	

Discussion

The excess mortality in the first year after surgery for stage I-III colorectal cancer is high. Overall, 12.4 % of all patients died within the first year, compared to a 4.9 % 30- day mortality rate. Thus, the 30-day mortality rate highly underestimates the risk of dying in the first year after surgery. After adjustment for expected mortality in the general population, patients with co-morbidities, patients with stage III tumors, patients requiring emergency resection, and patients with postoperative surgical complications were at higher risk for excess mortality, with excess 1-year mortality rates varying from 15 to 30%.

The present study is the first detailed population based study, quantifying excess mortality after colorectal cancer surgery with curative intent, and examining risk factors for excess mortality within the first year. Clinical, accurate data of the Netherlands Cancer Registry were used, and variables not only comprised age and stage, but also data on co-morbidities, emergency and postoperative complications were available. Moreover relative survival and excess mortality rates were used as outcome measures. This also takes into account mortality which is not attributable to the examined disease or the treatment of the disease.

The results in this study should be interpreted with regard to several limitations inherent to its observational design. In the univariate and multivariable analysis potential confounders were examined and added to the model (shown in supplementary table). In calculations of expected mortality, patients with severe comorbidity may not match well with the general population. This could have led to a slight underestimation of the expected mortality in this group, resulting in a lower excess mortality.

Furthermore, only data on postoperative surgical complications were available. To estimate the impact of both surgical and non-surgical complications (for example pneumonia, delirium, cardiac event or urinary tract infection), a prolonged length

of stay was used as a substitute of postoperative complications in general. In this study, a prolonged length of stay was defined as a stay of 15 days or longer. An uneventful postoperative period is unlikely to result in a longer hospital stay, and therefore, it can function as a proxy for overall complications. This assumption is in line with a study of Cohen et al, who demonstrated a mean length of stay after colorectal surgery of 16 days in the presence of complications versus 6 days when no complications occurred.[20] In the present study a prolonged length of stay occurred in 30.4% of the patients. This is also consistent with findings in literature. [20-21]

Acknowledging these limitations, the present study provides valuable information, showing that 30-day mortality underreports postoperative mortality after colorectal surgery. This is consistent with previous studies. [13-14] Visser et al reported a doubling of 30-day mortality to 9.1% at 90 days after surgery. A previous study from our group showed that 1-year excess mortality was the main determinant for age related survival differences. [14] In the present data, the steepest decline in relative survival was observed during the first 7 to 11 months after surgery. The excess mortality was especially high in patients with comorbidities, stage III disease, emergency surgery and postoperative surgical complications or a prolonged length of stay. These risk factors have been described before as risk factors for postoperative mortality and survival.[11-12-22-23] However, these reports did not adjust for expected mortality in the general population, thereby not taking into account the risk of dying of other causes than colorectal cancer.
The aim of identifying risk factors for 1-year excess mortality was to find targets for improvement of patient care. However, these risk factors may not be easily malleable.

Comorbidity

The prevalence of comorbid disease is increasing with the aging population and improvements in modern medicine.[24-25] Patients with comorbidity may have less biological reserve and comorbidities alter organ functions.[26] More research is needed on these mechanisms and the influence of comorbidities on postopera-

tive outcomes. Obviously, optimizing peri-operative care to reduce surgical risk by thorough preoperative assessment and by additional supportive measures may improve the prognosis of patients. A multidisciplinary approach with integrated chronic disease management in cancer patients also in the post-hospital period seems warranted.

Stage III disease

Patients with stage III disease had an increased risk of excess 1-year mortality. This could be due to cancer recurrences. Although it is unlikely a large part of early mortality is due to cancer recurrences in patients operated with curative intent. An earlier study on relapses in these patients showed that only a very limited number of patients had a recurrence within the first year. Furthermore, only ten percent of patients with a recurrence die within one year.[27]

Emergency surgery

Emergency surgery has consistently been demonstrated to be a major risk factor for adverse outcome in colorectal surgery. Efforts should be made to reduce the number of patients in need of an emergent intervention. In this respect national screening programs could be helpful. If colorectal cancer could be identified at an earlier (asymptomatic) stage, it could be expected the need for emergent surgery can be reduced.

Postoperative surgical complications or a prolonged length of stay

Also patients with postoperative surgical complications or a prolonged length of stay had an increased risk for excess mortality in the first year. These results compare to a recent study of Greenblatt et al.[5] They showed that readmission after colectomy, due to a postoperative complication, was predictive for 1-year mortality. Two recent studies of Ghaferi et al showed that differences in death after major complications were the primary determinant of variation of mortality between hospitals.[28-29] This indicates that effective management of postoperative complications may reduce postoperative mortality and improve patient outcomes. This

provides a potential target for improvement of the quality of cancer care. Not only prevention of complications, but also early recognition and aggressive treatment of complications can improve patient outcomes. Identifying structures, processes and best practices to reduce the occurrence of complications and improve the management of complications should have priority. Although randomized controlled trials are pivotal for determination of efficacious interventions, large cohort studies and comparative effectiveness research are essential to fill critical gaps in defining optimal strategies for complication management. [30]

Conclusions

In conclusion the excess mortality in the first postoperative year after colorectal cancer surgery is high and reflects postoperative risk more accurate than 30-day mortality. The presence of co-morbidities, a stage III tumor, emergency resection, and postoperative surgical complications were predictive for excess mortality, with excess 1-year mortality rates as high as 15 to 30%. These risk factors may not be easily modifiable. Nevertheless, their identification is important to develop tailored management of high risk patients. Moreover, identifying effective strategies for both prevention and treatment of complications could have the potential to improve patient outcomes.

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Chapter 9

The prolonged impact of the insult of surgery in elderly patients.

JWT Dekker
GA Gooiker
E Bastiaannet
CBM van den Broek
LGM van der Geest
CJH van de Velde
RAEM Tollenaar
GJ Liefers

On behalf of the steering committee of the 'Quality Information System Colorectal

Submitted to Journal of the American Geriatrics Society

Abstract

Background: Especially in elderly patients mortality after colorectal cancer surgery is not limited to the immediate postoperative period. The excess 1-year mortality explains age related differences in colorectal cancer survival. To gain better insight in its etiology, causes of death were studied in a population based cohort of stage I-III colorectal cancer patients.

Methods: All 1924 patients who had a resection for stage I-III colorectal cancer in 2006, 2007 and 2008 in the Western region of the Netherlands were identified. Data were merged with causes of death data from the Central Bureau of Statistics Netherlands. Cause of death according to patient and tumour characteristics were assessed. To calculate excess mortality as compared to the general population, national data were used.

Results: Overall 13.2% of patients died within the first postoperative year. One-year mortality increased with age. It was as high as 43% in elderly patients that underwent emergency surgery. In 75% of patients, death was attributed to the colorectal cancer. In 25% of all patients, registered deaths were attributed to post-operative complications. Elderly patients with comorbidity more frequently died due to complications ($p<0.01$). Death of other causes was similar to background mortality according to age group.

Conclusion: In the presently studied cohort of stage I to III colorectal cancer patients that died within one year of surgery, cause of death was predominantly attributed to colorectal cancer. Because it is not to be expected that in this cohort the number of deaths from recurrences is very high, the excess 1-year mortality signifies the prolonged impact of the insult of surgery. Especially in elderly patients it has a large impact on colorectal cancer survival. Therefore, in elderly patients the aim should be to limit the physiological insult of surgery, with a prolonged involvement in the post-hospital period.

Introduction

Recently there has been an increasing emphasis on peri-operative risk in colorectal surgery.

In this respect the surgical management of the elderly patient forms one of the most prominent issues. The elderly population is very heterogeneous and although excellent results of colorectal cancer surgery in these patients are reported [1-2], co-morbidity and frailty challenge surgical management in these patients.

An important outcome measure for surgery is postoperative mortality. This is usually described as mortality within thirty days after surgery. However, recent studies have shown that 30-day mortality after surgery is not an appropriate measure of surgical risk, as a significant proportion of patients die beyond this period [3-5]. Especially in elderly patients a significant proportion fails to thrive in the months that follow colorectal surgery. The excess mortality beyond thirty days has been shown to sustain up to one year after surgery. It is the single most important explanation for age related differences in colorectal cancer survival [6]. But even in younger colorectal cancer patients that underwent curative surgery a significant 1-year excess mortality exists. In high risk patients this can even increase to 15-30% [7]. This shows that the deleterious physiological impact of surgery and postoperative complications is not limited to the immediate postoperative period. Considering the large impact on overall and disease-specific survival, information on the etiology of the 1-year excess mortality is important. Earlier studies identified risk factors such as high age, emergency surgery, postoperative complications and re-admittance [7-9]. However, up to date information on the cause of death for these patients is limited.

To improve overall care for elderly colorectal cancer patients it is important to know whether patients die as a consequence of their cancer, the treatment they receive or by competing causes of death. This could allow for improvements in the

care for and counseling of elderly colorectal cancer patients. It could also provide important information for outcome registrations and audits.
The aim of this study is to gain a better insight in the etiology of the 1-year excess mortality by studying causes of death in a population based cohort of stage I-III colorectal cancer patients, with a special emphasis on elderly patients.

Methods

Data

In the Netherlands, all newly diagnosed malignancies are registered in the nationwide population based Netherlands Cancer Registry (NCR). The Leiden Cancer Registry, part of the NCR, collects data on all cancer patients diagnosed in one of the nine affiliated hospitals in the western part of the Netherlands. This region comprises one university hospital, six teaching hospitals and two non-teaching hospitals and serves a population of 1.7 million inhabitants.

Independently trained data managers collect data from the original patient files after receiving an automatic report from the Dutch pathology reporting system "PALGA". Information on patient characteristics, tumor characteristics, treatment, hospital of diagnosis and/or treatment and follow-up are recorded. Tumor site and morphology are coded according to the International Classification of Diseases for Oncology (ICD-0)[10]. Cancers are staged according to the TNM classification of Malignant Tumors [11]. The quality of the data is high, and completeness is estimated to be at least 95% [12-13].

In 2006, a regional audit for colorectal cancer care (KIC) was started in the nine affiliated hospitals of the Leiden Cancer Registry. The data collection was extended to data that reflected quality of care and case mix factors. These prospectively collected data were used for benchmarking and feedback on each hospitals process, ultimately to improve the quality of care in the entire region. Data were collected

on patient demographics (age, sex, co-morbidities and socio-economic status (SES)), tumor characteristics (localization, TNM staging) and treatment characteristics ((neo-) adjuvant treatment, type of surgery, emergency, hospital of treatment, surgical complications and length of stay). Apart from ASA scores, completeness of data was more than 98%.

Patients

All patients who had a resection of stage I, II or III tumor of the colon (C18), the recto-sigmoid (C19) or the rectum (C20) from January 1st 2006 to December 31st 2008 in one of the affiliated hospitals, were identified (patients with a stage IV tumor, with a tumor of the appendix and patients who did not undergo a resection of the tumor, were excluded). Vital status of all patients was obtained actively on a regular basis through linkage of the cancer registry data with the integrated database of the municipal registry and the central bureau for genealogy. Follow-up was completed until January 1 2010.

Data of patients who died in the first year after surgery, were merged with causes of death data from the Central Bureau of Statistics Netherlands that records data on the primary and three underlying causes of death according to ICD-9. Cause of death was grouped into:

1) Died of colorectal cancer: colorectal cancer as primary cause of death or metastases as primary cause of death with colorectal cancer as underlying cause of death. Death due to complications (in the group died of colorectal cancer) were coded as yes if one of the underlying codes indicated complications as cause of death.

2) Died with colorectal cancer: patient died of other causes than colorectal cancer, but with colorectal cancer as underlying cause.

3) Died of other causes: patients died of other causes than colorectal cancer (colorectal cancer not mentioned in primary or underlying causes).

Age was divided into <65, 65-74 and 75 years or older. Co-morbidity was recorded according to a slightly modified version of the Charlson index, used by the Netherlands Cancer Registry. ASA scores were categorized as ASA I and II or ASA III and IV. Missing data from the ASA score were included as a separate category. Surgical complications comprised superficial wound infections, abdominal wall problems (i.e., dehiscence), deep infections, and intra-abdominal complications including bleeding, ileus, abscess or anastomotic leaks. As a substitute for overall complications (both surgical and non-surgical such as pulmonary or cardiac events), a prolonged length of stay was used, which was defined as a hospital admission of 15 days or longer after surgery.

Cause of death according to patient and tumour characteristics were assessed; differences were tested with chi-squared or Fischer's exact, where appropriate. Analyses were stratified for colon and rectal cancer. To calculate excess mortality as compared to the general population, national data were used. They were matched on sex, year and age. Data concerning recurrences was not available in this dataset.

Results

From January 1st 2006 through December 31st 2008, 1924 patients had a resection in one of the nine affiliated hospitals of the Leiden Cancer Registry, for stage I-III colorectal cancer; 1279 for colon cancer and 645 for rectal cancer. **Table 1** shows the characteristics of the study population. Overall 13% of patients died within the first postoperative year. Besides gender and year of surgery all depicted characteristics were associated with 1-year mortality. Among patients aged 75 years or older, patients that underwent emergency surgery, patients with a high comorbidity burden (Charlson >1; ASA III/IV) and patients that had a prolonged length of stay (LOS) 1-year mortality rates were as high as 20-33 %. For elderly patients that underwent emergency surgery the 1-year mortality rate was even 43%.
Most patients that did not survive the first year died beyond 30-days (61% of all

Table 1
Mortality of 1924 patients who had a resection in one of the nine affiliated hospitals of the Leiden Cancer Registry, for stage I-III colorectal cancer from January 1st 2006 through December 31st 2008 (1279 colon cancer patients and 645 rectal cancer patients), according to patient, tumor and treatment characteristics.

Characteristics		N	Alive %	Died in the 1st year %	p-value
Sex	Male	981	85.5	14.5	0.1
	Female	943	88.0	12.0	
Age	<65	530	94.7	5.3	<0.001
	65-74	581	89.5	10.5	
	75+	813	79.6	20.4	
Year	2006	677	86.6	13.4	0.5
	2007	610	85.7	14.3	
	2008	637	87.9	12.1	
Stage	I	408	92.4	7.6	<0.001
	II	816	86.6	13.4	
	III	700	83.6	16.4	
Tumor	Colon	1279	84.4	15.6	<0.001
	Rectal	645	91.5	8.5	
Emergency Surgery	Yes	183	67.8	32.2	<0.001
	No	1741	88.7	11.3	
Charlson	0	1088	90.6	9.4	<0.001
	1	467	84.8	15.2	
	2 or more	369	77.8	22.2	
Comorbidity	No	856	91.0	9.0	<0.001
	Yes	1068	83.3	16.7	
ASA	I/II	951	92.7	7.3	<0.001
	III / IV	381	76.6	23.4	
	Unknown	592	83.6	16.4	
Surgical Complications	No	1540	89.0	11.0	<0.001
	Yes	384	77.6	22.4	
Age	<65	530	94.7	5.3	<0.001
	65-74	581	89.5	10.5	
	75+	813	79.6	20.4	

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Surgical Complications	No	1540	89.0	11.0	<0.001
	Yes	384	77.6	22.4	
Length of Stay	regular	1276	91.2	8.8	<0.001
	prolonged	605	77.5	22.5	
	Unknown	43	83.7	16.3	

patients). We found no age related differences here (p=0.4). The proportion of patients that died beyond 30-days increased with tumor stage (p<0.01), lower comorbidity burden (p=0.02), elective surgery (for colon cancer p=0.02) and prolonged length of stay (p<0.01).

Table 2 shows the causes of death that were registered for the patients that died within 1-year of surgery for colon and rectal cancer patients. About 65% of patients that died within 1-year of surgery were 75 years or older. Deaths in the first year after colorectal surgery were predominantly attributed to the colorectal cancer. Distribution of causes of death was similar for different age groups. The incidence of 1-year mortality and death due to colorectal cancer increased with age.

Table 2
One-year mortality and cause of death, for patients with colon cancer (A) and rectal cancer (B).

COLON (A)		**Cause of death**			
	1-year mortality	Colon cancer*	With colon cancer**	Other causes#	Unknown cause
	n=200 (15.6%)	n=149 (74.5%)	n=9 (4.5%)	n=35 (17.5%)	n=7 (3.5%)
<65 years	22	16	1	3	2
	11.0%	72.7%	4.6%	13.6%	9.1%
65-74 years	47	34	1	9	3
	23.5%	72.4%	2.1%	19.1%	6.4%
75+ years	131	99	7	23	2
	65.5%	75.6%	5.3%	17.6%	1.5%
RECTAL (B)					
	1-year mortality	Rectal cancer*	With rectal cancer**	Other causes#	Unknown cause
	n=55 (8.5%)	n=35 (63.6%)	n=7 (12.7%)	n=10 (18.2%)	n=3 (5.5%)
<65 years	6	4	1	1	0
	11.0%	66.6%	16.7%	16.7%	
65-74 years	14	6	2	4	2
	25.5%	42.9%	14.3%	28.5%	14.3%
75+	35	25	4	5	1
	63.5%	71.4%	11.4%	14.3%	2.9%
p-value	<0.001	<0.001	0.3	0.2	0.4

*Colon or rectal cancer as primary cause of death, or other cancer with colorectal cancer with underlying cause of death, **Other causes as primary cause of death with colon or rectal cancer as underlying cause of death, #Other causes as primary cause of death without colon or rectal cancer as underlying cause of death

When excess 1-year mortality (observed / expected deaths) was compared to the general population, death of other causes was similar to background mortality (standardized mortality ratio of general population) according to age group. No differences were found here between colon and rectal cancer patients.

Death certificates in the Netherlands also register whether death was due to complications. **Table 3** shows 1-year mortality that was attributed to complications. With increasing age death in the first postoperative year is more frequently attributed to complications. In elderly patients 25% of early mortality is due to complications. No clear association was found between comorbidity and death due to complications for all patients. However, elderly colon cancer patients with comorbidities more frequently died due to complications ($p<0.01$). Especially elderly patients with neurologic disease, diabetes and cardiac disease more frequently died due to complications.

Table 3
Mortality in the first postoperative year attributed to complications

Complications	**<65**	**65-74**	**75+**
No	23 (82.1%)	53 (86.9%)	125 (75.3%)
Yes	5 (17.9%)	8 (13.1%)	41 (24.7%)
Total*	28 (100%)	61 (100%)	165 (100%)

Difference between the age categories $p<0.001$.
*Total number of patients who died in the first postoperative year.
Incidence of death due to complications: 0.9% <65 years (5/530), 1.4% 65-74 years and 5.0% in 75 and older.

No association was found for LOS and death due to complications.

There was a strong association between the occurrence of surgical complications and death due to complications, which increased with age **(table 4)**. It seems that the significance of having a surgical complication increases with age. In elderly

patients whose deaths were attributed to complications, the incidence of surgical complications was 40-71%. Within this group the type of surgical complication was predominantly abdominal (ileus, abcess, anastomotic leak). For elderly colon cancer patients also abdominal wall problems (i.e. dehiscence) were significantly associated with mortality due to complications.

Table 4
Association between surgical complications and death due to complications in the 1st year, by age

	Colon			Rectal		
	Surgical complications	Died of complications (%)	p-value	Surgical complications	Died of complications (%)	p-value
<65	No	9.1	0.3	No	25.0	0.7
	Yes	27.3		Yes	0	
65-74	No	6.7	0.05	No	0	0.3
	Yes	29.4		Yes	20.0	
75-79	No	7.4	0.02	No	0	0.04
	Yes	40.0		Yes	62.5	
80-84	No	20.0	0.047	No	12.5	0.07
	Yes	55.6		Yes	75.0	
85-89	No	11.1	0.004	No	20.0	0.7
	Yes	71.4		Yes	25.0	
90+	No	0	0.1	No	No patients	
	Yes	50.0		Yes	One patient	

Discussion

In this study we found that deaths in the first year after colorectal cancer surgery were predominantly attributed to the colorectal cancer. The incidence of this early mortality increased with age. It was as high as 43% in elderly patients that underwent emergency surgery. Distribution of causes of death was similar for different

age categories. Up to 25% of all registered deaths were attributed to postoperative complications. This underlines the impact the surgery has on the excess 1-year mortality, especially in elderly patients with a decreased functional reserve and a reduced ability to cope with the physiological challenges of the surgery and its consequences.

The reliability of cause of death coding in The Netherlands has been shown to be high for major causes of death such as cancer and myocardial infarction, but for chronic diseases it can be low [14]. The accuracy of cause of death statements has been debated in many investigations [15-17]. The attribution of the cause of death depends on data from the physician completing the death certificate. He may not know the patient or may not be aware of the earlier diagnosis of cancer. It also depends on subjective judgments of the possible pathway of morbid events leading directly to death by both the physician and the coding medical registry clerk. The attribution of deaths to specific causes can be confusing. Should deaths within one month after surgery be attributed to surgery or to the cancer for which the surgery was performed? It seems that conventionally treatment-related deaths are not being attributed to cancer. Brown et al. found that non-cancer mortality was considerably higher in cancer patients than in the general population 16. In population based studies nowadays this problem is usually countered by the use of relative survival as an outcome measure. In an earlier publication of our group we used this technique to show that there is a significant excess mortality the first year after colorectal surgery [6]. In the present study early mortality was predominantly categorized as caused by the colorectal cancer. This suggests that among physicians and moreover medical registry clerks in the Midwestern part of The Netherlands there is consensus on how to code treatment related deaths of patients with cancer. There is certainly an argument for coding deaths from cancer treatment as cancer mortality. The World Health Organization defined the cause of death as "the disease or injury which initiated the train of morbid events leading directly to death" [18]. Furthermore, by including treatment related deaths cancer mortality can serve as a reliable measure for the progress against cancer[19].

Apart from confusions in attributing deaths to treatment or cancer, difficulties have been shown in classifying deaths from other causes but with colorectal cancer [17]. This makes it difficult to interpret the group of patients that have died due to other causes but with CRC in the present study. This group is fairly small (1% of all patients). In a cohort of stage I to III colorectal cancer patients operated with curative intent, it is to be expected that early recurrences will be limited. Although a limited number of patients could have been under-staged. They could have already had occult metastases at the time of surgery. Since most patients in the present cohort had a preoperative abdominal CT-scan and a chest X-ray (elective patients that had no CT-scan underwent an abdominal ultrasound before surgery) and 28% also had a chest CT-scan, this is not likely to be a significant group of patients. Earlier population based studies on colorectal cancer prognosis show that in patients undergoing curative resections, recurrences within the first year are rare 20. Even in these patients, only a small number of recurrences will cause mortality within 1-year.

This argument is also important for interpreting the group of colorectal cancer deaths in the present study. Since it is not likely that more than a very small number of deaths attributed to the colorectal cancer are in fact attributable to cancer progression, they will have to be attributed to the cancer treatment. This would imply that the vast majority of colorectal cancer deaths within the first year will have to be attributed to the impact of the surgery and its consequences, although the administration of chemotherapy may have been of influence here.

For the majority of these patients the physician coding the cause of death saw no apparent complication that lead directly to their death. Probably the physiological insult of the surgery initiated a chain of events that eventually caused a failure to thrive in these patients, without an apparent causal event other than the debilitating effect of the surgery itself.

Death certificates showed that up to 25% of colorectal cancer deaths are attributed to postoperative complications. This illustrates that in a significant number of cases

coded as death due to colorectal cancer it was apparent that death occurred as a direct consequence of postoperative complications. This is an interesting group. In this study we found no clear association between comorbidity and death due to complications for all patients. However, elderly patients with comorbidity did more frequently die of complications. This could be a result of the fact that comorbidity has a relatively more severe impact in patients with limited physiological resources.

Surprisingly we found no association between prolonged LOS and death due to complications. It has been shown that prolonged LOS is related to the occurrence of (medical) complications [21]. Possibly a prolonged LOS also depicts the efforts made to rescue patients from the consequences of complications, thereby neutralizing its association with death due to complications.

The strong association of surgical (especially abdominal) postoperative complications and death due to complications may seem logical. However, it is often assumed that the larger part of postoperative deaths in the elderly is caused by medical complications. As Iversen et al. showed, postoperative medical complications are the main cause of early death after emergency surgery for colonic cancer. Possibly surgical complications are relatively more apparent for the coding physician at the time of death. The importance of surgical complications seems to increase with age. A surgical complication in itself may be a manifestation of the decreased potential to recover from surgery in the elderly. Moreover, surgical complications may have a relatively more severe impact in elderly patients with limited physiological resources.

Limitations and strength

The limitations of this study are consequential to limitations in the accuracy of coding the cause of death as discussed above. Its strength is the fact that this study uses reliable population based data. Furthermore, this study is the first to study cause of death in patients that did not survive the first year after curative colorectal cancer resection. It could help to elucidate the etiology of the 1-year excess mor-

tality in the elderly, that has been shown to be the major influence on age related differences in cancer survival [6].

Clinical implications

This study implies that we have to concentrate on improving the outcome of colorectal cancer surgery as it is the primary influence on early cancer mortality especially in elderly patients.

The very finely balanced physiological resources in the frail elderly colorectal cancer patient demand extra care to optimise their cardiopulmonary, nutritional and performance status. Active participation of a multidisciplinary team is hereby required, aimed to maximise the physiological reserve and minimise the impact of the surgery. Possibly minimally invasive surgery could be of use here.

Although there are concerns that elderly patients tolerate poorly the cardiovascular changes associated with pneumoperitoneum, laparoscopic surgery has been shown to be safe and beneficial in the elderly [22-25]. Moreover, the benefits of laparoscopic colorectal resection were found to be more pronounced in the elderly [26]. Less tissue trauma, early mobilisation and faster recovery that could limit the impact of the surgery may be especially helpful in elderly patients with limited reserves.

It has been shown that better physical performance status and serious postoperative complications consistently predicted recovery. Substantial numbers of patients, especially elderly, have a protracted recovery. Even six months after abdominal surgery performance based measures such as timed walk, functional reach and grip strength does not returned to preoperative levels in 40-60% of patients [27]. A prehabilitation programme to improve or at least maintain functional capacity preoperatively may play a role in decreasing complication rates after colorectal surgery [28].

The high 1-year excess mortality we found after colorectal cancer surgery not only highlights the importance of the peri-operative period, where complications and

re-admittance seem important determining factors [8-9]. It also turns our attention to the post-hospital period as a potential new area for quality improvement. Further studies are necessary to elucidate the aetiology of the 1-year excess mortality and whether modifiable risk factors exist. However, it seems clear that further efforts should be made to minimise the physiological insult of surgery but also its consequences. A continued attention to comorbid conditions after surgery and appropriate medical follow up may be helpful. This may decrease the number of hospital readmissions as approximately 75% of readmissions within the first 90 days were not related to the surgery itself [29]. Analogue to the enhanced recovery principle [30-31], there is an argument for developing a sustained enhanced recovery program for elderly colorectal cancer patients.

Conclusions

Cause of death statements on death certificates should be interpreted with care. In the presently studied cohort of stage I to III colorectal cancer patients that died within one year of surgery, cause of death was predominantly attributed to colorectal cancer. Because it is not to be expected that in this cohort the number of deaths from recurrences is very high, the excess 1-year mortality signifies the prolonged impact of the insult of surgery. This is supported by the finding that up to 25% of deaths was attributed to postoperative complications. Considering the high mortality in the first postoperative year, the focus in the surgical treatment of elderly colorectal cancer patients should be on limiting the physiological insult of surgery, with a prolonged involvement in the post-hospital period.

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Chapter 10

Summary, general discussion and future directives

Summary

The incidence of colorectal cancer is high and expected to grow in the Western world [1]. Colorectal cancer surgery can be considered high risk surgery. It accounts for a disproportionate share of the morbidity, mortality and excess length of stay (LOS) in general surgery [2]. Therefore, it is a very important focus for quality enhancement programs.

For an optimal quality of care it is elementary to study what constitutes the risk of adverse outcome in colorectal cancer surgery and to identify chances for improvement. Objective information on risk profiles is indispensible both in the care for an individual patient and for comparative analyses on a hospital or population level. It can provide better information on prognosis and opens possibilities for more tailored treatment. It can also allow for adjusted treatment protocols for different risk groups.

In this thesis different risk factors and outcome measures for colorectal cancer patients are studied.

Accurate staging in colorectal cancer is important for a balanced clinical decision on further treatment and an accurate estimation of prognosis. In **chapter 2** the prognostic capacity of the metastatic lymph node ratio (LNR) is assessed in stage III rectal cancer in addition to the 7th edition of the TNM classification [3]. The use of LNR could improve identification of high risk patients and may also have the advantage to be less dependent on the number of retrieved lymph nodes than N stage. Especially in rectal cancer adequate retrieval of lymph nodes can be troublesome. This study shows that the LNR is an independent prognostic factor for overall survival and local recurrence in stage III rectal cancer. We demonstrate LNR is a reliable measure for overall survival from a lymph node yield of two or more. Our study shows that for an adequate prediction of local recurrence, at least six lymph nodes need to be retrieved. Stratification of patients is possible by dividing them in

quartiles. However, in this study, the LNR cut off point with the best discriminating power was 0.60, this means patients with lower LNR values can be considered low risk and patients with a LNR value above 0.60 should be considered high risk patients. We found this cut off value could improve prediction of prognosis per stage in addition to the TNM stage. It could add to the discussion on further (adjuvant) treatment in the multidisciplinary team meeting.

Patient and treatment characteristics are main determining factors for risk and outcome in colorectal cancer surgery. Often patient and treatment factors interact.
Anastomotic leakage is a major problem in colorectal surgery, which unfortunately occurs all too frequently. It often results in serious morbidity, increased healthcare costs and even death. Anastomotic leaks are also associated with local recurrences and reduced survival[4-6]. It has been reported that clinical risk assessment for anastomotic leakage by the operating surgeon has a low predictive value and underestimates leakage risk [7]. **Chapter 3** describes the development and testing of a risk score for anastomotic leakage. A validated easy to use risk score could facilitate the intra-operative decision regarding whether or not to construct a (non-functional) stoma. However, anastomotic leakage is thought to have many causes. Creation of a predictive model that takes all these factors into account requires a very large and detailed database. Therefore, we pursued an alternative approach for this study. Instead of using a statistically-derived predictive model, we created a risk score through a heuristic combination of risk factors identified from the literature. This Colon Leakage Score (CLS) was then tested on a consecutive series of patients undergoing a left-sided colorectal resection with primary anastomosis. Our study shows that the CLS can determine the risk of anastomotic leakage for the individual patient. What risk of anastomotic leakage is acceptable is of course debatable. In our opinion, a risk of anastomotic leakage of lower than 3% does not justify a non-functional stoma, because a stoma can also cause problems (morbidity, discomfort and higher cost). If we choose to accept a 3% risk of anastomotic leakage as a cut off, only less than 20% of patients would be considered high risk and we would not have to worry about 80% of patients.

In the end, it is up to the surgeon and patient to determine their own cut off CLS value considering their preferences concerning the risk of anastomotic leakage versus (temporary) stomata. The receiver-operating characteristics curve and the logistic regression curves displayed in chapter 3 could offer a useful tool to guide this clinical decision. After confirmation by larger multi-centre series the CLS potentially solves a difficult clinical problem.

The number of patients with multiple malignancies is increasing. Because cancer treatment improves and cancer screening programs develop cancer survivors may increasingly develop a second primary tumour[8-10]. The proportion of second- or higher order invasive cancers reported to the US International Cancer Institutes Surveillance, Epidemiology and End Results Program (SEER) has increased to over 10% in 2008 [11]. However, the influence of an earlier non-colorectal cancer on survival of colorectal cancer patients is not clear. **Chapter 4** investigates its prognostic importance. This study showed that patients with a previous non-colorectal cancer have a higher mortality compared to patients with colorectal cancer as a first primary tumour. However, further analyses that were not published in the article of chapter 4, showed that the difference in survival was not explained by a difference in disease specific mortality. This suggests that a second primary colorectal cancer has the same clinic pathological behaviour as a primary colorectal cancer. Therefore, an earlier malignancy in the history of colorectal cancer patients could just be regarded as comorbidity. In this respect, it is presently not clear whether a previous malignancy should be a regarded as marker for a higher inherent risk of cancer (cancer biology) and harmful lifestyle factors, or whether it is the damage caused by the previous malignancy or its treatment that determines its consequences.

The presence of comorbidity effects treatment decisions[12-15] and the prognosis of patients receiving colorectal cancer treatment [16-20]. Consequently, comorbidity is believed to be an important confounder in the analysis of postoperative adverse events and omitting risk adjustment for comorbidity is argued to induce bias in studies that do not take it into account. However, despite the growing number of

studies addressing comorbidity, the added value of comorbidity in models predicting the outcome of colorectal cancer is not clarified. It is also unknown whether different comorbidity measures are comparable in predicting mortality, and if these measures can equally predict other postoperative adverse events, such as postoperative complications. **Chapter 5** compares frequently used comorbidity measures and their additional value in models predicting the outcome of colorectal cancer. It shows that, all used comorbidity measures (ASA score, the Sum of Diseased Organ Systems, the Charlson Comorbidity Index and specific comorbidities) had similar predictive values. Thus, any of these measures can be used for predicting 30-day mortality and prolonged length of stay. For the occurrence of postoperative surgical complications, only a high ASA score and gastro-intestinal comorbidity were found to be risk factors.

Although comorbidity is an independent risk factor for 30-day mortality and prolonged length of stay after colorectal cancer surgery, the additional value of comorbidity in models predicting postoperative adverse events seems only marginal.
To optimise efficiency with regard to audits and quality improvement programs, only the most important comorbid factors should be identified to minimize the burden and costs of data collection, without compromising risk-adjustment.

Chapters 6 and 7 address old age as a risk factor for impaired survival and elaborate on what constitutes age related survival differences.

The EUROCARE Working Group (EUROpean CAncer REgistry-based study on survival and CARE of cancer patients) observed a significant survival improvement from 1988 to 1999 for all cancers combined and for almost every cancer site, including colon cancer [21]. However, survival increased at a slower rate in the elderly, so that the gap in survival between younger and older patients widened. Elderly patients less frequently receive adjuvant chemotherapy and more often discontinue treatment [22]. The administration of adjuvant treatment for elderly stage III colon cancer patients was found to be influenced by socioeconomic status, gender, and

comorbidity [12]. Besides, comorbidity also influences surgical eligibility and other treatment options. However, in recent years the focus on elderly colorectal cancer patients has increased. Several studies concluded that age per se is not a contraindication for more aggressive or adjuvant treatment [23]. Therefore, nowadays more elderly patients are considered for extensive therapy in routine practice. As a consequence an improved outcome for elderly patients could be expected. We hypothesized that the gap in survival between young and elderly patients shown in the EUROCARE data might be decreasing. So, the aim of the study in **chapter 6** was to describe treatments and compare survival rates over time between elderly (≥75 years), aged (65-75 years) and younger (<65 years) colon cancer patients.
In this population-based study covering the mid-western region of the Netherlands over a period of 15 years, substantial changes in treatment of colon cancer were found; use of adjuvant chemotherapy for patients with stage III disease increased over time, resection rates remained stable over time for patients with curable disease in all age groups, while resection rates among metastatic patients decreased, and administration of chemotherapy for stage IV colon cancer patients increased for all age groups.

Survival increased significantly over time for younger patients after adjusting for confounders (such as sex, age, grade, and stage and treatment). The survival of aged patients also improved after adjusting for sex, age, grade, and stage, but not after adjusting for treatment as well. The survival of elderly patients did not improve after either of the adjustments. This leaves a gap in survival between young and elderly similar to the EUROCARE data.

The near future will have to show if a more extensive and hopefully better tailored treatment can help elderly to close this gap.

The number of elderly colorectal cancer patients is high and expected to increase in the future. If survival of elderly colorectal cancer patients is worse compared to younger patients it is important to know what constitutes this difference.

Differences in survival by age groups in colorectal cancer may be explained by variations in tumour factors, patient characteristics and therapy. Notwithstanding these differences, several studies found a similar disease specific survival for elderly and young colorectal cancer patients. This would indicate that the excess mortality in elderly colorectal cancer patients is due to competing causes of death. To gain a better insight in survival differences between age groups, the study in **chapter 7** aims to compare population-based survival data of colorectal cancer patients for different age groups. It not only regards overall and relative survival but also conditional relative survival under the condition of surviving one year. Furthermore, to comprehend the challenge of treating elderly colorectal cancer patients this study focuses on age related differences in 30-day and 1-year mortality. We found that when survival data for colorectal cancer are corrected for expected death of other causes and first year mortality, age differences disappear. Therefore, decreased survival in the elderly is mainly due to differences in early mortality. Only for stage III disease elderly patients fare worse, probably as a result of less extensive adjuvant treatment. The overall difference between the younger and elderly age groups is that within the elderly group there is an excess mortality of about 10 % the first year. This study implies that in treating elderly stage I-III colorectal cancer patients the focus should be on the peri-operative process as well as the first postoperative year.

Postoperative mortality is one of the most important outcome measures for surgery. This is usually described as mortality within thirty days after surgery. However, earlier studies have shown that 30-day mortality after surgery is not an appropriate measure of surgical risk, as a significant proportion of patients die in the months that follow [24-26]. This suggests that there may be a prolonged impact of the insult of surgery. **Chapter 8** and **Chapter 9** look into the aetiology of the excess mortality in the first postoperative year.

Chapter 8 identifies risk factors. We found that the excess mortality in the first year after surgery for stage I-III colorectal cancer is high. Overall, 12.4 % of all patients

died within the first year, compared to a 4.9 % 30- day mortality rate. After adjustment for expected mortality in the general population, patients with comorbidities, patients with stage III tumours, patients requiring emergency resection, and patients with postoperative surgical complications were at higher risk for excess mortality, with excess 1-year mortality rates varying from 15 to 30%.

The identification of these risk factors provides potential targets for improvement of patient outcomes. Moreover, identifying effective strategies for both prevention and management of complications must have priority.

Chapter 9 investigates cause of death for patients that do not survive the first postoperative year. Cause of death statements on death certificates should be interpreted with care. In the studied cohort of stage I-III colorectal cancer patients that died within one year of surgery, cause of death was predominantly attributed to colorectal cancer. Because it is not to be expected that the number of deaths from recurrences or faulted diagnoses -i.e. under staged stage IV patients- is very high in this cohort, the excess 1-year mortality signifies a prolonged impact of the insult of surgery. This is supported by the finding that up to 25% of deaths was also attributed to postoperative complications. Therefore, in the surgical treatment of colorectal cancer patients the focus should be on limiting the physiological insult of surgery, with prolonged involvement in the post-hospital period.

General discussion and future directives

Risk assessment to enhance quality of care

The outcome and prognosis for colorectal cancer patients after surgery is determined by a plethora of interacting factors. These factors can be divided into tumour/ stage related, treatment related and patient related subcategories. Ideally, for an optimal informed treatment, knowledge of all these factors and their interaction should be available. Alas, it is impossible to appreciate the complete scale of multi-factorial interaction of effects and uncertainties will remain on this issue. It is not the aim of this thesis to produce a final overview of all important risk factors or outcome measures for colorectal cancer patients. We chose to investigate the possibilities of risk stratification and hopefully identify some modifiable risk factors. A better insight in peri-operative risk is important. For an individual patient this should guide clinical judgment and the administration of tailored care. Furthermore, in modern practise there is a high demand for individualised risk assessment to be shared with the patient at the time of consenting. On a hospital or population level knowledge of risk factors can lead to adjusted (better tailored) treatment protocols and better information on case mix influences. The identification and optimisation of modifiable risk factors has the potential to improve the overall care for patients.

Risk assessment in general surgery has greatly advanced over the last two decades. In 1991 the Department of Veterans Affairs (VA) has systematically collected and analysed risk-adjusted surgical data in VA hospitals, the National Surgical Quality Improvement Program (NSQIP). Based on observed hospital variations in outcome structural changes have been implemented that have led to a significant reduction of complications, 30-day mortality and length of hospital stay together with an increased patient satisfaction[27]. The program has now been adopted by the American College of Surgeons and the implementation of the ACS-NSQIP demonstrated improvements in surgical outcome similar to the VA experience. In the Netherlands different quality enhancement programs have been started. A region-

al multidisciplinary audit for colorectal cancer care (KIC) in the Midwestern part of the Netherlands supplied some of the data used in this thesis. In 2009 a nationwide audit (DSCA) has started with the ultimate goal to improve the care for colorectal cancer patients in the Netherlands. The audit started as a surgical audit, but will be multidisciplinary in the near future. It intends both to increase the transparency of colorectal care and to collect valuable data for quality enhancement as it can help to identify opportunities for improvement and stimulates according action. Now in its third year the DSCA offers a large database used for research. Targeted quality enhancement projects are being offered to negative outliers. For short term outcomes positive trends are already starting to outline, for instance in the increasing number of harvested lymph nodes. Long term effects have to be awaited but based on experiences in other countries, reduction of adverse events after colorectal cancer surgery could be anticipated in the future.

Anastomotic leakage

Anastomotic leakage is a major problem in colorectal cancer surgery, causing morbidity, worse cancer outcome and death. Although it is still widely regarded as technical failure, a vast literature on the comparison of different techniques has not shown clear differences in leak rate [28-30]. In this thesis we show that patient factors play an important role in the occurrence of anastomotic leaks. In combination with tumour location (height), intra-operative blood loss and the duration of the surgery, they could predict the risk of an anastomotic leak.

The importance of blood loss and the duration of the surgery within the colon leakage score (CLS), described in chapter 3, is interesting. These items could be considered surrogate markers for the skill and training of the surgeon. However, there could also be a direct relation with the operations stress response and the wound healing process.

One of the appealing assets of the CLS is its logic. It is based upon the notion that it is the inherent healing power of a patient (depicted by several patient factors) and

the severity of the physiological insult of the surgery (operation factors) that determine the outcome. The problem remains that presently we do not exactly know what determines the impact of the physiological challenges the surgery poses and what constitutes a patients physical capacity to recover. Focussed research especially on high risk groups is warranted.

Recently, there has been a trend to create more non-functional stomas to counteract the problem of anastomotic leakage. In the Dutch Surgical Colorectal Audit the number of non-functional stomas was as high as 70% in rectal resections (unpublished data). The problem is that unnecessary stoma's also induce morbidity and discomfort and increase healthcare costs [31]. In addition, continuity is never restored in many patients. In the future predictive scores like the CLS should be used to guide appropriate use of non-functional stomas.

Comorbidity

Comorbidity is of critical importance in the care for an individual patient. The presence of comorbidity effects treatment decisions[12-15] and the prognosis of patients undergoing colorectal cancer treatment [16-20].

To ensure favourable outcomes, on a hospital level great efforts should be made to optimise peri-operative evaluation and subsequent treatment of comorbidities. However, in this thesis we found that, although comorbidity is an important risk factor for 30-day mortality and a prolonged length of stay after colorectal cancer surgery, the importance of comorbidity in models predicting postoperative adverse events, is only marginal. This means that for risk-adjustment in colorectal cancer surgery comparisons, comorbidity is not as important as often considered. With regard to audits and quality improvement programs this could mean only the most important clinical comorbid factors have to be taken into account so that the burden and costs of data collection can be minimised, without compromising risk-adjustment. However, if audits are to be including long term outcome measures in the future, then comorbidity can be expected to be an important parameter, as it

represents a greater risk of non cancer related mortality. For the DSCA a long-term oncologic evaluation is scheduled.

Emergency surgery

Emergency surgery has consistently been demonstrated to be a major risk factor for adverse outcome in colorectal surgery. Prior resuscitation and stabilisation are elementary to reduce this risk. However, in some cases the risk of delaying surgery for medical stabilisation is higher than any potential gain (for instance with imminent blow-out). Therefore, efforts should be made to reduce the number of patients in need of an emergent intervention. In this respect the intended national screening program, which is to be implemented in 2012, could be helpful. If colorectal cancer could be identified at an earlier (asymptomatic) stage, the need for emergent surgery will probably be lower.

Elderly patients more frequently undergo emergency surgery. This could be an effect of less aggressive diagnostics and treatment in the elderly. A more liberal policy to consider elderly for well prepared elective surgery, could lower the number of emergency operations, leading to a better overall outcome for elderly patients. Also a faster trajectory from diagnosis to surgery for patients with imminent obstruction could diminish the need for emergency surgery.

Complications

Peri-operative risk factors are directly linked to postoperative complications. Different studies showed that variations in preoperative status are related to operative outcomes [32], hospital length of stay [33] and hospital costs [34]. Furthermore, the occurrence of postoperative complications itself is among the most important predictors of further adverse outcome after colorectal surgery. Therefore, developing strategies to reduce postoperative complications is critical. In three ACS-NSQIP studies Ghaferi et al. showed that while rates of individual complications did not vary significantly among hospitals with differing mortality rates, mortality in patients with major complications was almost twice as high in hospitals with very

high overall mortality as in those with very low overall mortality[35-37]. This failure to rescue phenomena suggests that the quality of peri-operative care once complications occur is just as important as the efforts to prevent them. To improve the outcome of colorectal cancer surgery in the future both prevention and management of complications is critical.

Old age

In recent years the focus on elderly colorectal cancer patients has increased. Octogenarians and nonagenarians are a rapidly growing segment of the population. It is important to realise that the elderly population forms a very heterogeneous group. The onset and severity of the progressive functional inadequacy of physiological systems, that comes with senescence is variable from individual to individual. Age alone is therefore not the primary influence on the outcome after surgery for colorectal cancer. Rather the combination of comorbid status and an impaired physical capacity to recover from adverse events that may occur before, during and after surgery determines the outcome in elderly patients [38]. This is also referred to as frailty. Although frailty is defined variably it is likely to be correlated with disability, comorbidity and self rated health, and should identify a group that is vulnerable to adverse outcomes.[39]

Notwithstanding the fact that increasing age is an independent risk factor for postoperative adverse events, even after adjustment for comorbid conditions, several studies concluded that age per se is not a contraindication for more aggressive or adjuvant treatment [23]. Therefore, nowadays more elderly patients are considered for extensive therapy in routine practice. However, elderly colorectal cancer patients tend to have a more advanced stage of disease [23]. They have more comorbidity and are treated less aggressive than their younger counterparts[19]. Comorbidity for its part influences surgical eligibility and other treatment options[18]. Furthermore, it represents a greater risk of non cancer related mortality. Elderly patients less frequently receive adjuvant chemotherapy and more often discontinue treatment before completion[22].

In this thesis we found that although the survival of aged patients (65-75 years) improved, the survival of elderly patients (older than 75 years) did not improve in the period of 1990-2005. From this thesis we can deduce two possible explanations. Firstly, there is still an under-treatment of elderly, especially in stage III colon patients. This may not be entirely modifiable due to frailty and comorbidity precluding the use of adjuvant chemotherapy. Secondly, in elderly patients there is a higher excess mortality. This is possibly due to a more profound and prolonged impact of the insult of surgery in the elderly. Elderly tend to have a decreased functional reserve and a reduced ability to cope with the physiological challenges of the surgery and its consequences. In this thesis we showed that after adjusting for the expected mortality in the population and for mortality in the first year, age related survival differences disappeared. This underlines that the deleterious physiological impact of surgery and postoperative complications is not limited to the immediate postoperative period. A significant proportion of these patients potentially fail to thrive in the months that follow colorectal surgery [26].

In order to improve survival in the elderly, in the future more focus should be on non cancer specific (neo)adjuvant treatment, not only on the (neo)adjuvant cancer treatment. The very finely balanced physiological resources in the frail elderly colorectal cancer patient demand extra care to optimise their cardiopulmonary, nutritional and performance status. Also the timing of the surgery should be discussed. Active participation of a multidisciplinary team is hereby required, aimed to maximise the physiological reserve and minimise the impact of the surgery. Possibly minimally invasive surgery could be of use here. Although there are concerns that elderly patients tolerate poorly the cardiovascular changes associated with pneumoperitoneum, laparoscopic surgery has been shown to be safe and beneficial in the elderly [40-43]. Moreover, the benefits of laparoscopic colorectal resection were found to be more pronounced in the elderly [44]. Less tissue trauma, early postoperative mobilisation and faster recovery that could limit the impact of the surgery may be especially helpful in elderly patients with limited reserves.
The near future will have to show if a more extensive and hopefully better tailored

multidisciplinary treatment, with extra focus on the peri-operative and post-hospital period, can help elderly to close the gap.
However, we have to keep in mind that, for very old people in particular, the quality of life after surgery is of overriding importance. Before undertaking surgery we must first understand what can be accomplished with our operation, what the physiologic cost will be for the patient, and what each patient wants and can tolerate.

Prolonged impact of surgery

An important finding in this thesis is the fact that 30-day mortality, a widely used outcome measure, vastly underestimates 1-year mortality. Thereby it underestimates the true impact of surgery on survival of colorectal cancer patients. It has been shown that physical performance status and serious postoperative complications consistently predicted recovery. Substantial numbers of patients, especially elderly, have a protracted recovery. Even six months after abdominal surgery performance based measures such as timed walk, functional reach and grip strength have not returned to preoperative levels in 40-60% of patients [45]. A prehabilitation programme to improve or at least maintain functional capacity preoperatively may play a role in decreasing complication rates after colorectal surgery [46]. It has also been suggested that preoperative cognitive status and depression may be related to recovery. This is interesting since depression is treatable and there is some evidence that postoperative delirium can be prevented [47]. There is a growing literature on mind-body interventions that use mindfulness-based stress reduction to decrease anxiety and sleep disturbances to attenuate stress response [48].

The high 1-year excess mortality we found after colorectal cancer surgery not only highlights the importance of the peri-operative period, where complications and re-admittance seem important determining factors [49-50], it also turns our attention to the post-hospital period as a potential new area for quality improvement and auditing. Further studies are necessary to elucidate the aetiology of the 1-year excess mortality and whether modifiable risk factors exist. However, it seems clear that further efforts should be made to minimise the physiological insult of surgery but

also its consequences. A continued attention to comorbid conditions after surgery and appropriate medical follow up may be helpful. This may decrease the number of hospital readmissions, because approximately 75% of readmissions within the first 90 days are not related to the surgery itself [51]. Analogue to the enhanced recovery principle [52-53], there is an argument for developing a sustained enhanced recovery program.

The responsibility of the surgeon

In addressing risk and outcome in colorectal cancer surgery tension exists between considering large cohorts and the care for an individual patient. Population based risks of adverse outcomes are often difficult to interpret and translate to a clinical situation. It is up to the surgeon to make an educated judgement of a patient's risk. He must provide for appropriate well organised peri-operative care, up standard surgical skill and dedicated counselling of the patient. All these factors are necessary for a well balanced treatment, considering personal preferences and reducing risk to allow for the best possible outcome. This work can not be done without the support and contribution of a dedicated multidisciplinary team. Therefore, the surgeon has to be a team player. Improvement of surgical care is the result of team effort, rather than individual technical brilliance.

Finally, it is the responsibility of the surgeon to focus on continued education and development, dedication to the patient and the willingness to confront his actual outcomes and hold them up against relevant bench-marks.

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Chapter 11

Nederlandse samenvatting, discussie en aandachtspunten voor de toekomst

Nederlandse samenvatting

De incidentie van darmkanker is hoog in de westerse wereld en zal naar verwachting door de vergrijzing nog toenemen [1]. Darmkanker chirurgie is hoogrisico chirurgie. Het zorgt voor een buiten proportionele morbiditeit, mortaliteit en verlengde opnameduur binnen de algemene chirurgie [2]. Daarom vormt darmkanker chirurgie een belangrijk aandachtsgebied voor kwaliteitsverbetering.
Voor een optimale kwaliteit van zorg is het van groot belang te weten welke risicofactoren een rol spelen bij het ontstaan van ongewenste uitkomsten en welke mogelijkheden er zijn om deze te beïnvloeden. Objectieve informatie ten aanzien van risicoprofielen is onmisbaar, zowel in de zorg voor de individuele patiënt als voor vergelijkend onderzoek op ziekenhuis en populatie niveau. Meer inzicht in risicoprofielen kan zorgen voor een betere inschatting van prognose en opent mogelijkheden voor zorg op maat. Deze kennis kan ook aanleiding geven om behandel protocollen aan te passen aan specifieke risicogroepen.

In dit proefschrift worden verschillende risico factoren en uitkomstmaten voor darmkanker patiënten bestudeerd.

Nauwkeurige stadiering van darmkanker is essentieel voor een evenwichtige klinische beslissing over verdere behandeling en voor een betrouwbare schatting van de prognose. De studie in **hoofdstuk 2** beoordeelt de voorspellende waarde van de metastatische lymfeklier ratio (LNR; aantal uitgezaaide gedeeld door het aantal gevonden lymfeklieren) in stadium III endeldarm kanker, in aanvulling op de nieuwste TNM classificatie [3]. Het gebruik van LNR zou de identificatie van hoogrisico patiënten kunnen verbeteren, met als bijkomend voordeel dat LNR minder afhankelijk is van het gevonden aantal lymfklieren dan het N stadium. Vooral in endeldarm kanker kan het terugvinden van een adequate hoeveelheid lymfeklieren lastig zijn. Onze studie toont aan dat LNR een onafhankelijke voorspellende factor is voor overleving en lokaal recidief in stadium III endeldarm kanker. LNR gaf een betrouwbare inschatting van de overleving vanaf een lymfeklier opbrengst van

twee of meer. Voor een adequate voorspelling van lokaal recidief, moeten minstens zes lymfeklieren worden teruggevonden. Indeling van patiënten naar risico is mogelijk door hen in kwartielen te verdelen. In deze studie echter, was de LNR waarde met het beste onderscheidend vermogen 0.60. Dit betekent dat patiënten met een lagere LNR beschouwd kunnen worden als laagrisico en de patiënten met een LNR waarde boven 0.60 als hoogrisico. Deze afkapwaarde kon de voorspelling van prognose per stadium verbeteren, in aanvulling op het TNM stadium. De LNR kan daarom bijdragen aan de discussie in de multidisciplinaire bespreking van patiënten.

Patiënt en behandeling karakteristieken zijn bepalende factoren voor risico en uitkomst in darmkankerchirurgie. Deze factoren zijn vaak met elkaar verbonden.
Naadlekkage is een belangrijk probleem in de darmchirurgie, dat jammer genoeg maar al te vaak voorkomt. Het leidt vaak tot ernstige morbiditeit, verhoogde gezondheidszorgkosten en zelfs sterfte van de patiënt. Naadlekkages zijn tevens geassocieerd met lokaal recidief en verminderde overleving [4-6]. Er is beschreven dat klinische inschatting van het risico op naadlekkage door de betrokken chirurg een lage voorspellende waarde heeft en het risico op naadlekkage wordt onderschat [7].
Hoofdstuk 3 beschrijft de ontwikkeling en evaluatie van een risicoscore voor naadlekkage bij darm operaties. Een gevalideerde eenvoudig te gebruiken risicoscore kan de intra-operatieve beslissing om al dan niet een (deviërend) stoma aan te leggen vergemakkelijken. Naadlekkage heeft waarschijnlijk vele oorzaken. Voor het maken van een voorspellend model dat met al deze factoren rekening houdt is een zeer groot en gedetailleerd gegevensbestand nodig (meer dan 1860 patiënten). Daarom gebruiken wij een alternatieve benadering voor deze studie. Wij maakten een risicoscore door een intuïtieve combinatie van risicofactoren die in de literatuur beschreven worden. Deze Colon Lekkage Score (CLS) werd vervolgens toegepast op een opeenvolgende reeks patiënten die een linkszijdige colorectale resectie met primaire anastomosis ondergingen. Onze studie toont aan dat de CLS het risico van naadlekkage kan vaststellen voor de individuele patiënt. Wij kunnen discussiëren over welk risico op naadlekkage acceptabel is, maar naar onze men-

ing is het bij een risico kleiner dan 3% niet verstandig om een deviërend stoma aan te leggen, omdat een stoma ook problemen (morbiditeit, ongemak en hogere kosten) kan veroorzaken. Als we een risico op naadlekkage van 3% accepteren als afkapwaarde, dan zijn in onze serie slechts 20% van de patiënten hoogrisico en zouden we ons dus over 80% van de patiënten geen zorgen hoeven te maken.

Uiteindelijk is het aan de chirurg en zijn patiënt om hun eigen afkapwaarde te bepalen, gebaseerd op persoonlijke preferenties ten aanzien van de afweging van het risico op naadlekkage tegen een (tijdelijke) stoma. De ROC curve en de logistische regressie curve uit hoofdstuk 3 kunnen een handvat bieden om de besluitvorming te ondersteunen. Als de waarde van de CLS bevestigd wordt in grotere multi-centre studies kan deze score helpen een moeilijk klinisch probleem op te lossen.

Het aantal patiënten met meerdere maligniteiten neemt toe. Omdat de behandeling van kanker verbetert en screenings programma's zich ontwikkelen, kunnen overlevenden in toenemende mate een tweede tumor ontwikkelen [8-10]. De proportie patiënten met meerdere invasieve kankers in de US International Cancer Institutes Surveillance, Epidemiology and End Results Program (SEER) is toegenomen tot boven de 10% in 2008 [11]. De invloed van een eerdere andere maligniteiten op de overleving van darmkanker patiënten is echter niet duidelijk. **Hoofdstuk 4** gaat hierop in. Deze studie laat zien dat patiënten met een eerdere niet-darmkanker een hogere sterfte hebben dan patiënten met darmkanker als eerste maligniteit. Echter, verdere analyses die niet in het artikel van hoofstuk 4 gepubliceerd zijn, tonen aan dat het verschil in overleving niet verklaard wordt door een verschil in ziekte specifieke overleving. Dit lijkt te suggereren dat darmkanker als tweede maligniteit hetzelfde klinisch pathologische gedrag heeft als een darmkanker als eerste maligniteit. Een eerdere maligniteit in de anamnese van darmkanker patiënten zou daarom beschouwd kunnen worden als comorbiditeit. Het is tot op heden niet duidelijk of een eerdere maligniteit dan beschouwd moet worden als een marker voor een verhoogd kanker risico (kanker biologie) en een risicovolle levensstijl, of dat schade door de eerdere kanker of de behandeling hiervan haar consequenties bepaald.

De aanwezigheid van comorbiditeit beïnvloed behandelbeslissingen[12-15] en de prognose van patiënten die behandeld worden voor darmkanker[16-20]. Daarom wordt comorbiditeit gezien als belangrijke verstorende factor in de analyse van postoperatieve uitkomsten en het weglaten van comorbiditeit in risicocorrectie zou studies minder betrouwbaar maken. Ondanks het toenemend aantal studies naar comorbiditeit is de toegevoegde waarde van comorbiditeit, in modellen voor het voorspellen van de uitkomsten van darmkanker, niet opgehelderd. Het is ook onbekend of verschillende comorbiditeitsscores vergelijkbaar zijn in het voorspellen van sterfte en of deze scores net zo goed andere postoperatieve uitkomsten kunnen voorspellen, zoals postoperatieve complicaties.

Hoofdstuk 5 vergelijkt veelgebruikte comorbiditeitsscores en hun toegevoegde waarde in modellen die de uitkomsten van darmkanker chirurgie voorspellen. Het toont aan dat alle gebruikte comorbiditeitsscores (ASA score, de Sum of Diseased Organ Systems, de Charlson Comorbidity Index en specifieke comorbiditieten) dezelfde voorspellende waarde hebben. Dus elk van deze scores zou gebruikt kunnen worden om 30-dagen sterfte en een verlengde opnameduur te voorspellen. Voor het optreden van postoperatieve chirurgische complicaties waren alleen hoge ASA score en gastrolintestinale comorbiditeit risicofactoren.

Hoewel comorbiditeit een onafhankelijke risicofactor was voor 30-dagen sterfte en een verlengde opnameduur na darmkanker chirurgie, bleek de aanvullende waarde van comorbiditeit in voorspellende modellen slechts marginaal. Om de efficiëntie van audits en verbetertrajecten te optimaliseren zouden alleen de allerbelangrijkste comorbiditeits factoren geïdentificeerd moeten worden. Dit vermindert de administratie last en de kosten van het vergaren van relevante gegevens, zonder de mogelijkheden van risicocorrectie te beperken.

De **hoofdstukken 6 en 7** behandelen hoge leeftijd als risicofactor voor verminderde overleving en gaan in op de oorzaken van leeftijdsgebonden verschillen in overleving.

De EUROCARE Working Group (EUROpean CAncer REgistry-based study on survival and CARE of cancer patients) vond,tijdens de periode van1988 tot 1999, significante verbeteringen in de overleving voor alle vormen van kanker inclusief darmkanker [21]. Echter de overleving verbeterde langzamer voor de ouderen (≥ 75 jaar), zodat de al bestaande overlevingsachterstand voor ouderen toenam ten opzichte van de jongere patiënten. Oudere patiënten krijgen minder vaak adjuvante chemotherapie en maakten hun kuren vaker niet af[22]. Het is aangetoond dat het toedienen van adjuvante behandeling aan oudere stadium III darmkanker patiënten beïnvloed wordt door socio-economische status, geslacht en comorbiditeit [12]. Tegelijk beïnvloed comorbiditeit ook de chirurgische mogelijkheden en andere behandelopties. De aandacht voor oudere darmkanker patiënten is de laatste jaren toegenomen. Verschillende studies hebben vastgesteld dat leeftijd op zich geen contra-indicatie is voor meer agressieve of adjuvante behandeling [23]. Daarom komen tegenwoordig in de dagelijkse praktijk meer ouderen in aanmerking voor uitgebreide behandeling. Als een gevolg hiervan zou een verbeterde uitkomst voor ouderen dan ook te verwachten zijn. Wij verwachtten dat de achterstand in overleving van ouderen ten opzichte van jongeren, zoals getoond in de EUROCARE data, kleiner zou worden. Het doel van de studie in **hoofdstuk 6** was om de behandelingen en verschillen in overleving te beschrijven tussen oudere oudere (≥75 jaar), jongere oudere (65-75 jaar) en jongere (<65 jaar) darmkanker patiënten, over een periode van 15 jaar.

In deze populatiestudie van de regio van het Integraal Kanker Centrum West, vonden we substantiële veranderingen in de behandeling van darmkanker; het gebruik van adjuvante chemotherapie voor stadium III patiënten nam over de tijd toe, resectie percentages bleven gelijk voor patiënten met curabele ziekte in alle leeftijdsgroepen, terwijl resectie percentages bij gemetastaseerde patiënten afnamen. De toediening van chemotherapie voor stadium IV darmkanker patiënten nam toe voor alle leeftijdsgroepen. Er was een significante toename in overleving voor jongere patiënten na correctie voor verstorende factoren (zoals geslacht, leeftijd, differentiatie graad, stadium en behandeling). De overleving van jongere ouderen verbeterde eveneens na correctie voor geslacht, leeftijd, differentiatie

graad en stadium, maar niet na correctie voor behandeling. De overleving van oudere ouderen verbeterde niet, ook niet na correctie voor verstorende factoren. Dit resulteerde in het achterblijven van de overleving van oudere ouderen vergelijkbaar met de EUROCARE data.

De nabije toekomst zal moeten uitwijzen of uitgebreidere en hopelijk beter aangepaste zorg op maat, de ouderen zal helpen deze overleving achterstand in te lopen.

Naar verwachting neemt het hoge aantal oudere darmkanker patiënten de komende jaren nog toe. Als de overleving van oudere darmkanker patiënten achterblijft, is het belangrijk om te weten hoe dat komt.

Verschillen in overleving van darmkanker tussen verschillende leeftijdsgroepen zou verklaard kunnen worden door verschillen in tumorfactoren, patiëntfactoren en behandelingsfactoren. Ondanks deze verschillen vonden verschillende studies een vergelijkbare ziektespecifieke overleving voor oudere en jongere darmkanker patiënten. Dit zou betekenen dat de oversterfte van ouderen veroorzaakt wordt door andere doodsoorzaken dan de darmkanker.

Om een beter inzicht te krijgen in overlevingsverschillen tussen leeftijdsgroepen, was het doel van de studie in **hoofdstuk 7** om populatiebreed overlevingsgetallen van darmkanker patiënten te vergelijken tussen verschillende leeftijdsgroepen. De studie keek niet alleen naar algemene en relatieve overleving, maar ook naar conditionele relatieve overleving onder de conditie dat het eerste jaar overleefd wordt. Om beter te begrijpen waarin de uitdaging ligt voor de behandeling van oudere darmkanker patiënten, keek onze studie verder naar leeftijdsgebonden verschillen in 30-dagen en 1-jaar sterfte. Wij vonden dat als overlevingsgetallen van darmkanker patiënten gecorrigeerd werden voor de verwachte sterfte aan andere doodsoorzaken (de achtergrond sterfte in de populatie) en sterfte in het eerste jaar, leeftijdsgebonden verschillen in overleving verdwenen. Het bleek dus

dat de verminderde overleving van de ouderen vooral berust op vroege sterfte. Alleen bij stadium III ziekte deden ouderen het slechter, mogelijk als resultaat van minder uitgebreide adjuvante behandeling. Het algemene verschil in de prognose van jongere en oudere darmkanker patiënten kwam dus neer op een oversterfte van 10 % in de oudere groep in het eerste jaar. Onze studie impliceert dat bij het behandelen van oudere darmkanker patiënten de aandacht gericht moet zijn op het peri-operatieve proces en het eerste jaar na de operatie.

Postoperatieve sterfte is een van de belangrijkste uitkomstmaten binnen de chirurgie. Meestal wordt deze beschreven als sterfte binnen 30 dagen. Zoals verschillende studies echter hebben aangetoond, is 30-dagen sterfte geen goede maat voor chirurgisch risico, want een significant deel van de patiënten sterft alsnog in de maanden die volgen[24-26]. Dit lijkt te suggereren dat er een verlengd effect uitgaat van de impact van de chirurgische behandeling. **Hoofdstuk 8 en 9** gaan verder in op de etiologie van de oversterfte in het eerste jaar na de operatie.

Hoofdstuk 8 identificeert risicofactoren. We vonden dat de oversterfte in het eerste jaar na chirurgie voor stadium I-III darmkanker hoog was. Over het geheel ging 12.4 procent van alle patiënten dood binnen het eerste jaar na de operatie, ten opzichte van 4.9% 30-dagen sterfte. Na correctie voor de verwachte sterfte in de populatie, hadden patiënten met comorbiditeit, stadium III ziekte, spoedoperaties en patiënten met postoperatieve chirurgische complicaties een hogere 1-jaar sterfte, die varieerde van 15 tot 30%. De identificatie van deze risicofactoren kan handvatten bieden voor het verbeteren van de uitkomsten van darmkanker chirurgie. Het ontwikkelen van strategieën om complicaties te voorkomen en effectief te behandelen moet daarbij prioriteit hebben.

Hoofdstuk 9 onderzoekt de doodsoorzaken van darmkanker patiënten die het eerste jaar na de operatie niet overleven. Overlijdensaktes moeten met enige terughoudendheid beschouwd worden. In onze studie van stadium I-III darmkanker patiënten werd de sterfte in het eerste jaar na de operatie voornamelijk toege-

schreven aan de darmkanker. Omdat het niet voor de hand ligt dat veel van deze patiënten stierven aan een recidief of een foute stadiering (patiënten die eigenlijk al stadium IV hadden), benadrukt de 1-jaar oversterfte dat er een verlengd effect uitgaat van de impact van de operatie. Dit wordt ondersteund door het feit dat tot 25% van de sterfte werd toegeschreven aan postoperatieve complicaties. Hierom moet in de chirurgische behandeling extra aandacht gegeven worden aan het beperken van de fysiologische impact van de operatie en moet er meer betrokkenheid zijn bij de periode na ontslag.

Discussie en aandachtspunten voor de toekomst

Het gebruik van risico inschatting om de kwaliteit van zorg te verbeteren

De uitkomst en prognose van geopereerde darmkanker patiënten wordt bepaald door uiteenlopende en onderling verbonden factoren. Deze risico factoren zijn onder te verdelen in tumor/ stadium, behandeling en patiënt factoren. Idealiter zouden voor een optimale behandeling al deze factoren en hun interacties bekend moeten zijn. Helaas is het onmogelijk om een compleet overzicht te verkrijgen van alle risicofactoren en hun oorzaken en gevolgen. Er zal altijd een zekere mate van onzekerheid blijven. Het is niet de bedoeling van dit proefschrift om een definitief overzicht te geven van alle risico's en uitkomsten van darmkanker chirurgie. We hebben ervoor gekozen om de mogelijkheden van risicostratificatie te onderzoeken en hopelijk enkele risico factoren te identificeren, die te beïnvloeden zijn. Een beter inzicht in peri-operatieve risico's is belangrijk. Voor de individuele patiënt kan dit een leidraad zijn voor de klinische besluitvorming en zorg op maat. Op ziekenhuis en populatie niveau kan kennis van risicofactoren leiden tot op maat aangepaste behandelingsprotocollen en betere informatie over case mix invloeden. De identificatie en optimalisatie van beïnvloedbare risico factoren kan een belangrijke verbetering betekenen in de zorg voor darmkanker patiënten.

Het vaststellen van risico's voor patiënten heeft de laatste twintig jaar een grote

vlucht genomen. Vanaf 1991 heeft de Department of Veterans Affairs (VA) systematisch risicogecorrigeerde chirurgische gegevens verzameld en geanalyseerd, in het National Surgical Quality Improvement Program (NSQIP). Op basis van verschillen in uitkomsten tussen ziekenhuizen werden structurele veranderingen doorgevoerd, die hebben geleid tot een significante afname van het aantal postoperatieve complicaties, 30 dagen sterfte en opnameduur, tegelijk met een grotere tevredenheid bij patiënten[27]. Het programma is ondertussen overgenomen door de American College of Surgeons en de implementatie (ACS-NSQIP) heeft geleid tot dezelfde verbeteringen in chirurgische uitkomst als bij de VA ziekenhuizen. In Nederland zijn verschillende kwaliteit verbetertrajecten gestart. Een deel van de data uit dit proefschrift is afkomstig van een multidisciplinaire regionale audit van de zorg voor darmkanker patiënten in de IKW-regio (KIC). In 2009 is een nationale audit (DSCA) gestart met het uiteindelijke doel de zorg voor darmkanker patiënten in Nederland te verbeteren. Deze audit is begonnen als een chirurgische audit, maar zal in de nabije toekomst multidisciplinair worden. De bedoeling is dat de transparantie van de zorg hierdoor verbetert en dat het tegelijkertijd waardevolle informatie verkregen wordt die kan helpen de kwaliteit van de zorg te verbeteren. Door het vaststellen van verbeterpunten en het stimuleren van passende initiatieven. In zijn derde jaar levert de DSCA ondertussen een grote database die gebruikt wordt voor onderzoek. Klinieken die het slechter lijken te doen dan verwacht, worden nader bekeken en krijgen verbeter initiatieven aangeboden. Voor korte termijn uitkomsten worden al positieve trends waargenomen, zoals het toenemende aantal lymfeklieren dat geoogst wordt. Lange termijn effecten moeten nog afgewacht worden, maar gelet op de ervaringen in andere landen, is een afname van ongewenste uitkomsten na darmkanker chirurgie te verwachten.

Naadlekkage

Naadlekkage is een groot probleem in de darmkanker chirurgie, dat kan leiden tot morbiditeit, slechtere kanker uitkomst en sterfte. Hoewel naadlekkage nog steeds vaak wordt beschouwd als technisch falen, laat de literatuur geen verschillen in uitkomsten zien tussen verschillende technieken[28-30]. In dit proefschrift laten we zien

dat patiënt factoren een belangrijke rol spelen in het optreden van naadlekkage. Gecombineerd met de afstand tot de anus, het intra-operatieve bloedverlies en de duur van de operatie, konden zij het risico op naadlekkage voorspellen.

Het belang van bloedverlies en duur van de operatie in de Colon Lekkage Score (CLS), zoals beschreven in hoofdstuk 3 is interessant. Deze onderdelen zouden beschouwd kunnen worden als afgeleiden van de behendigheid en training van de chirurg. Er zou echter ook een directe relatie kunnen zijn met de lichamelijke stress respons op de operatie en het wondgenezingsproces.

Een van de aansprekende onderdelen van de CLS is zijn logica. De score is gebaseerd op het besef dat de genezingspotentie van de patiënt (weergegeven als verschillende patiënt factoren) en de ernst van de fysiologische impact van de operatie (operatie factoren), de uitkomst bepalen. Het probleem is dat we tot op heden niet goed weten wat de impact bepaald van de fysieke uitdagingen die het chirurgische trauma veroorzaakt en waaruit de fysieke genezingspotentie van een patiënt bestaat. Verder onderzoek hiernaar is nodig, in het bijzonder bij hoog risico groepen.

De laatste tijd is er een trend ontstaan om meer ontlastende stoma's aan te leggen, om zo het probleem van naadlekkage tegen te gaan. In de DSCA is het aantal ontlastende stoma's 70% bij rectum chirurgie (ongepubliceerde data). Het probleem is dat onnodige stoma's morbiditeit en ongemak opleveren en de kosten hierdoor stijgen[31]. Bij veel patiënten worden de stoma's ook nooit meer opgeheven. In de toekomst zouden voorspellende scores zoals de CLS kunnen helpen om meer gepast gebruik van ontlastende stoma's te maken.

Comorbiditeit

Comorbiditeit is van essentieel belang in de zorg voor de individuele patiënt. De aanwezigheid van comorbiditeit beïnvloedt de besluitvorming ten aanzien van de behandeling[12-15] en ook de prognose van darmkanker patiënten[16-20].

Om te zorgen voor gunstige uitkomsten moet op ziekenhuis niveau de peri-operatieve evaluatie en behandeling van comorbiditeit geoptimaliseerd worden. Echter, in dit proefschrift vonden wij dat, hoewel comorbiditeit een significante risicofactor is voor 30-dagen sterfte en verlengde opnameduur na darmkanker chirurgie, het belang van comorbiditeit in modellen die postoperatieve ongewenste uitkomsten voorspellen slechts marginaal is. Dit betekent dat bij risicocorrecties voor vergelijking in darmkanker chirurgie comorbiditeit niet zo belangrijk is als vaak gedacht wordt. Met het oog op audits en kwaliteit verbetertrajecten kan dit betekenen dat alleen de allerbelangrijkste comorbiditeit meegenomen hoeft te worden. Dit zou kunnen leiden tot het minimaliseren van de registratielast zonder dat dit gevolgen heeft voor risicocorrectie. Als audits echter ook voor de lange termijn uitkomsten willen registreren dan zal comorbiditeit wel weer een belangrijke factor zijn, omdat ze een groter risico op niet kanker gerelateerde sterfte tot gevolg heeft. Voor de DSCA is lange termijn oncologische evaluatie overigens gepland.

Spoedoperaties

Spoedoperaties vormen een belangrijke risicofactor voor ongewenste uitkomsten bij darmkanker chirurgie. Het voor een spoedoperatie eerst resusciteren en stabiliseren van een patiënt is van elementair belang om het risico te verlagen. In sommige gevallen is het risico van uitstel van de operatie echter groter dan het potentiële voordeel (bijvoorbeeld bij dreigende blow-out). Daarom moet het streven zijn om het aantal patiënten te verminderen dat een spoedoperatie nodig heeft. Hierbij zou het voorgenomen nationale screenings programma, dat in 2012 ingevoerd zal worden, kunnen helpen. Als darmkanker eerder (asymptomatisch) gevonden kan worden, zou dit de noodzaak voor spoedoperaties kunnen verminderen.

Ouderen ondergaan vaker spoedoperaties. Mogelijk is dit het gevolg van minder agressieve diagnostiek en behandeling bij oudere patiënten. Dan zou een meer liberaal (laagdrempelig) beleid om bij ouderen, gepland en goed voorbereid, darmkanker te opereren, het aantal spoedoperaties mogelijk kunnen verminderen. Ook een versneld traject van diagnose naar operatie bij patiënten met een dreigende obstructie zou kunnen bijdragen aan het verminderen van het aantal spoedoperaties.

Complicaties

Peri-operatieve risicofactoren zijn direct verbonden met postoperatieve complicaties. Meerdere studies hebben laten zien dat pre-operatieve verschillen tussen patiënten gerelateerd zijn aan postoperatieve uitkomsten[32], opnameduur[33] en ziekenhuiskosten[34]. Daarnaast is het optreden van postoperatieve complicaties zelf een van de belangrijkste oorzaken van verdere ongewenste uitkomsten na darmchirurgie. Daarom is het ontwikkelen van strategieën om postoperatieve complicaties te verminderen erg belangrijk. In drie ACS-NSQIP studies hebben Ghaferi et al. laten zien dat, hoewel het percentage complicaties niet significant verschillend was tussen ziekenhuizen met een hoge en een lage postoperatieve sterfte, de sterfte na complicaties in ziekenhuizen met een hoge sterfte bijna twee keer zo hoog was als in ziekenhuizen met een lage sterfte[35-37]. Dit fenomeen wordt ook wel het failure to rescue genoemd. Het suggereert dat de kwaliteit van de peri-operatieve zorg wanneer complicaties optreden minstens zo belangrijk is als de pogingen om complicaties te voorkomen. Om de uitkomsten van darmkanker chirurgie in de toekomst te verbeteren moeten zowel het voorkomen als vroeg opsporen en agressief behandelen van complicaties prioriteit hebben.

Ouderdom

De laatste jaren is de aandacht voor oudere darmkanker patiënten toegenomen. Tachtig- en negentigjarigen vormen een snel groeiend segment van de bevolking. Het belangrijk te bedenken dat de oudere populatie een heterogene groep is. Zowel het optreden als de ernst van het toenemend tekortschieten van fysiologische systemen, zoals die bij veroudering optreden, wisselt van individu tot individu. Leeftijd op zich is daarom niet de belangrijkste factor die de uitkomst na darmkanker chirurgie bepaald. Het is meer de combinatie van comorbiditeit en een verminderde fysieke capaciteit om te herstellen van de tegenslagen die kunnen optreden voor, tijdens en na een operatie, die de uitkomst voor oudere patiënten bepaald[38]. Dit wordt ook wel aangeduid met het Engelse begrip frailty (kwetsbaarheid). Hoewel dit begrip wisselend wordt gedefinieerd, is het meestal gecorreleerd aan lichamelijke gebreken, comorbiditeit en verminderd welbev-

inden. Het zou patiënten moeten aanduiden die kwetsbaar zijn en een verhoogd risico hebben op ongewenste uitkomsten [39].

Hoewel toenemende leeftijd een onafhankelijke risicofactor is voor ongewenste uitkomsten, zelfs na correctie voor comorbiditeit, hebben verschillende studies geconcludeerd dat leeftijd op zich geen reden is om af te zien van agressieve of adjuvante behandeling[23]. Daarom komen tegenwoordig meer ouderen in de dagelijkse praktijk in aanmerking voor een uitgebreide behandeling. Toch hebben oudere darmkanker patiënten vaker een meer gevorderd stadium van de ziekte[23]. Ze hebben meer comorbiditeit en worden nog steeds minder agressief behandeld dan jongere patiënten[19]. Comorbiditeit op zijn beurt beïnvloed of iemand in aanmerking komt voor een operatie of een andere behandeling[18]. Daarnaast geeft comorbiditeit een groter risico op niet kanker gerelateerde sterfte. Oudere patiënten krijgen minder vaak adjuvante chemotherapie en maken vaker hun kuren niet af[22].

In dit proefschrift vonden wij dat hoewel de overleving van patiënten van 65 tot 75 jaar verbeterde, de overleving van patiënten boven de 75 jaar gelijk bleef tussen 1990 en 2005.

In dit proefschrift kunnen we twee verklaringen hiervoor vinden. Ten eerste is er nog steeds een onderbehandeling van ouderen (>75), vooral bij stadium III patiënten. Dit is mogelijk niet helemaal te voorkomen als gevolg van zwakte of comorbiditeit die het gebruik van adjuvante chemotherapie in de weg staat.

Ten tweede is er bij ouderen een hogere oversterfte. Dit is mogelijk het gevolg van een zwaardere en meer langdurige aanslag die de operatie vormt voor de oudere patiënt. Ouderen hebben vaak verminderde functionele reserves en afgenomen mogelijkheden, om te gaan met de fysiologische uitdagingen van de operatie en zijn gevolgen. In dit proefschrift hebben we laten zien dat na correctie voor de verwachte mortaliteit in een populatie en voor de sterfte in het eerste jaar, leeftijds-

gebonden verschillen in overleving na darmkanker chirugie verdwenen. Dit onderstreept het feit dat het verwoestende fysiologische effect van een darmkanker operatie en postoperatieve complicaties niet beperkt blijft tot directe postoperatieve periode. Een significant deel van de patiënten komt er na een darmkanker operatie uiteindelijk niet meer boven op[26].

Om de overleving van ouderen te verbeteren zouden we ons in de toekomst meer moeten richten op niet kanker specifieke voorbehandeling en niet alleen op de kanker specifieke neo-adjuvante behandeling. Het zeer subtiele evenwicht van fysiologische marges bij fragiele oudere darmkanker patiënten vereist extra zorg om hun cardiopulmonale toestand, hun voedingstoestand en hun fysieke prestaties te optimaliseren. Ook een optimale timing van de operatie zou bediscussieerd moeten worden. Actieve betrokkenheid van een multidisciplinair team is hierbij noodzakelijk, gericht op het optimaliseren van fysiologische reserves en het minimaliseren van de impact van de operatie. Mogelijk zou minimaal invasieve chirurgie hierbij van nut kunnen zijn. Hoewel er zorgen bestaan dat ouderen slecht opgewassen zijn tegen de cardiovasculaire en pulmonale gevolgen van een pneumperitoneum, is aangetoond dat laparoscopie veilig is en van voordeel kan zijn bij ouderen[40-43]. De voordelen van laparoscopie lijken zelfs meer uitgesproken bij ouderen[44]. Minder weefsel beschadiging, sneller postoperatief mobiliseren en een sneller herstel van de patiënt zou de impact van de operatie kunnen beperken. Dit kan vooral nuttig zijn bij oudere patiënten met beperkte reserves.

De nabije toekomst zal moeten tonen of uitgebreidere en hopelijk meer op de patiënt aangepaste multidisciplinaire behandeling, met extra aandacht voor de peri-operatieve zorg ook na de opname, kan helpen om de achterstand van oudere darmkanker patiënten goed te maken.
We mogen echter niet vergeten dat, in het bijzonder voor hele oude mensen, de kwaliteit van leven na een operatie het allerbelangrijkste is. We moeten daarom steeds goed bedenken wat er met een operatie te bereiken is, wat de gevolgen hiervan voor de patiënt kunnen zijn, en wat elke patiënt wil en aankan.

Verlengde impact van de operatie

Een belangrijke bevinding in dit proefschrift is het feit dat 30-dagen sterfte, een veel gebruikte uitkomstmaat, een ernstige onderschatting geeft van 1-jaar sterfte. Hierdoor onderschat de 30 dagen sterfte de werkelijke impact van de operatie op de overleving van darmkanker patiënten. Het is aangetoond dat fysieke fitheid en serieuze postoperatieve complicaties het herstel na een operatie kunnen voorspellen. Veel patiënten, vooral ouderen, hebben een vertraagd herstel. Zelfs 6 maanden na een buikoperatie zijn prestatiematen, zoals loopsnelheid, functionele reikwijdte en knijpkracht nog niet terug op het niveau van voor de operatie bij 40-60% van de patiënten[45]. Een trainingsprogramma om preoperatief de functionele capaciteit te verbeteren of tenminste op niveau te houden, zou een rol kunnen spelen bij het verminderen van complicaties na darmoperaties[46]. Het is ook gesuggereerd dat preoperatieve cognitieve toestand en depressie gerelateerd zijn aan herstel. Dit is interessant omdat depressie behandelbaar is en er is enig bewijs dat een postoperatief delier verkomen kan worden[47]. Er verschijnt steeds meer literatuur over lichaam en geest interventies die met behulp van op mindfulness gebaseerde stress reducerende therapie angst en slaap stoornissen behandelen om zo de lichamelijke stress reactie te verminderen[48].

De hoge 1-jaar oversterfte die wij vonden na darmkanker chirurgie, benadrukt niet alleen het belang van de peri-operatieve periode, waar complicaties en heropname belangrijke factoren lijken[49-50], maar richt ook onze aandacht op de periode na de opname in het ziekenhuis, als een nieuw terrein voor kwaliteit verbetertrajecten en audits. Meer studies zijn nodig om meer te weten te komen over de oorzaken van oversterfte het eerste jaar na een darmkanker operatie en of deze factoren te beïnvloeden zijn. Echter, het lijkt duidelijk dat verdere inspanningen nodig zijn om de fysiologische impact van de operatie en zijn gevolgen te minimaliseren. Een voortdurende aandacht voor comorbiditeit ook na de operatie en hierbij passende follow up zou hierbij kunnen helpen. Hierdoor zou mogelijk ook het aantal heropnames verminderd kunnen worden, omdat 75% van de heropnames in de eerste 90 dagen niet gerelateerd zijn aan de operatie zelf[51]. Analoog aan het enhanced

recovery principe, zou je kunnen pleiten voor een sustained enhanced recovery programma[52-53].

De verantwoordelijkheid van de chirurg

Bij het bespreken van risico's en uitkomsten bij darmkankerchirurgie bestaat er een spanningveld tussen het beschouwen van grote groepen en de zorg voor de individuele patiënt. In populaties vastgestelde risicofactoren zijn vaak moeilijk te vertalen naar een klinische situatie. Het is aan de chirurg om zich een onderbouwd oordeel te vormen van het risico van zijn patiënt, dit te bespreken en te vertalen in een toegewijd advies. Hij moet zorgen voor aangepaste, goed georganiseerde peri-operatieve zorg en zijn chirurgische vaardigheden op niveau houden. Al deze factoren zijn nodig voor een uitgebalanceerde behandeling, die rekening houdt met persoonlijke voorkeuren en tegelijk het risico op ongewenste uitkomsten beperkt om zo de optimale uitkomst mogelijk te maken.

Dit werk kan niet gedaan worden zonder de steun en bijdrage van een toegewijd multidisciplinair team. Daarom moet de chirurg een teamspeler zijn. Verbeteringen in de chirurgische zorg zijn vooral het gevolg van teamwork en niet zozeer van individueel technisch uitblinken.

Tot slot is het de verantwoordelijkheid van de chirurg om zich voortdurend te scholen en te ontwikkelen, toegewijd te zijn aan de patiënt en bereid te zijn om zijn daadwerkelijke uitkomsten onder ogen te zien en ze te spiegelen aan relevante bench-marks.

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Appendices

Dankwoord

Een proefschrift!
De weg en het doel, alle clichés zijn waar.
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Curriculum Vitae

Jan Willem Dekker was born on may 31st 1972 in Veenendaal, the Netherlands, as the son and grandson of local general physicians. He graduated from the Christelijk Lyceum Veenendaal in1990. The same year he started medical school at the University of Leiden, where he graduated in1998.
After graduation he started working as a house officer in the obstetrics and gynaecology department of the Westeinde Hospital in The Hague, under supervision of Dr. J.P. Dörr. Here he learned what it means to be a medical doctor.
In 2000 he decided to take up surgery at the Bronovo Hospital in The Hague under supervision of Dr. A.B.B. van Rijn who was a great stimulus to make a career in surgery.
In 2001 he started working at Medical Center Haaglanden in The Hague where he began his surgical training under supervision of Dr. J.C.A. de Mol van Otterloo.
He continued his training at the Leiden University Medical Center, under supervision of Prof.Dr. O.T.T. Terpstra and later Prof.Dr. J.F. Hamming who made a compelling argument to become a PhD student.
After finishing his training in 2008 he took up a fellowship (CHIVO) in Surgical Oncology at the Leiden University Medical Center under supervision of Prof.Dr. R.A.E.M. Tollenaar who also supervised his scientific career. In 2010-2011 he worked as a gastro-intestinal surgeon at the Onze Lieve Vrouwe Gasthuis in Amsterdam.
Since January 1st 2012 he is practising gastro-intestinal surgery at the Reinier de Graaf Gasthuis in Delft.
He is happily married to Kim Boers and has three wonderful children: Tim, Anne Jet and Hidde.

List of publications:

CBM van den Broek, E Bastiaannet, ***JWT Dekker***, JEA Portielje, AJM de Craen, MAG Elferink, CJH van de Velde, GJ Liefers, E Kapiteijn Time trends in chemotherapy (administration and costs) and relative survival in stage III colon cancer patients - a large population-based study from 1990 to 2008. Submitted to European Journal of Cancer

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Risk and Outcome
in Colorectal Cancer Surgery

Surgery always concerns the balance of risk and benefit. Both risk and benefit can vary immensely among patients. Outcome and prognosis are determined by several patient, tumour and treatment characteristics. In order to achieve the best possible outcomes for colorectal cancer patients, detailed and objective information on risk profiles is indispensible. For the individual patient it should guide clinical judgment and the administration of tailored care. On a hospital or population level knowledge of risk factors can lead to adjusted (better tailored) treatment protocols and better information on case mix influences adding to an improved care for colorectal cancer patients.

Jan Willem Dekker