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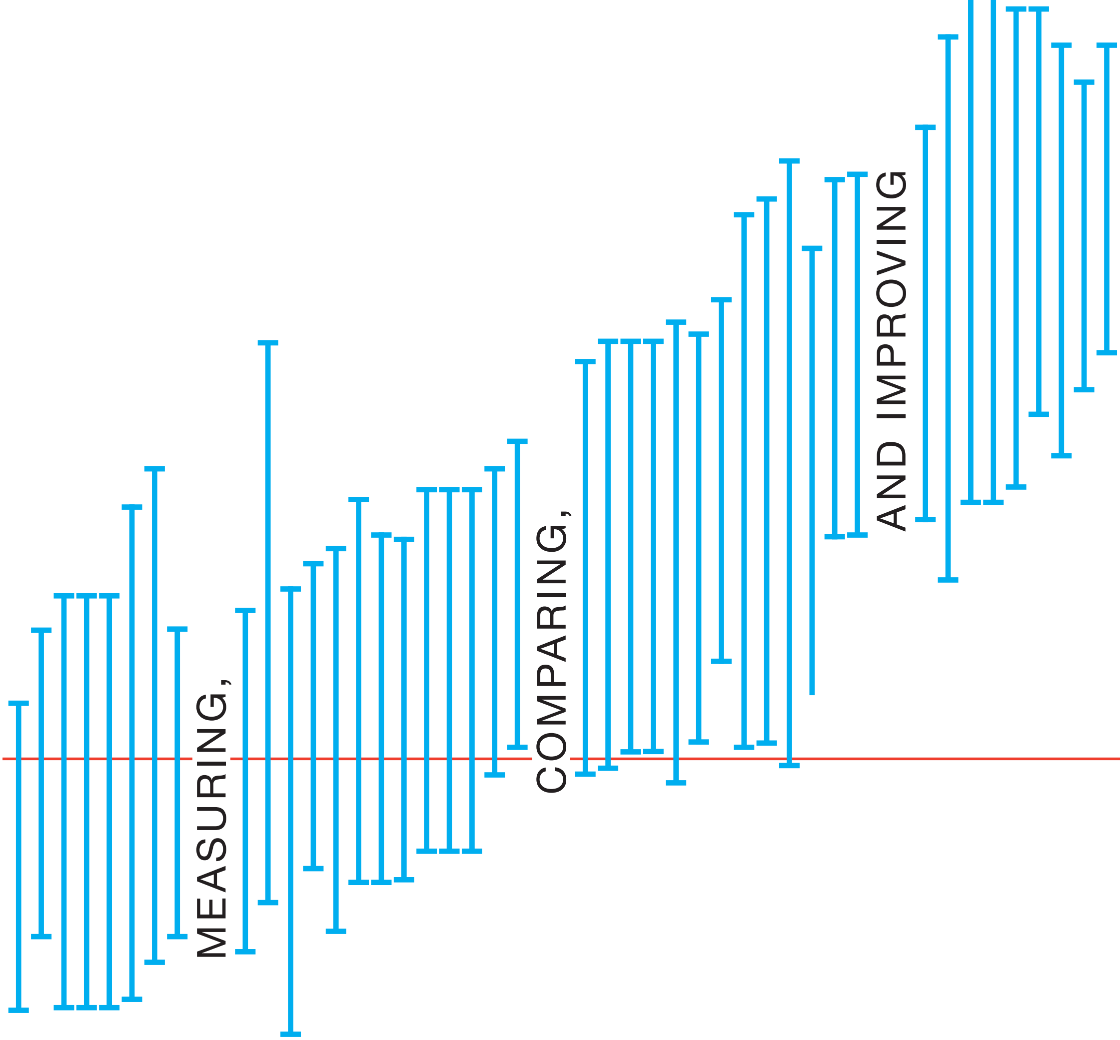

MEASURING, COMPARING, AND IMPROVING

Clinical Outcomes in Gastrointestinal Cancer Surgery

DANIEL HENNEMAN

Measuring, comparing and improving clinical outcomes in gastrointestinal cancer surgery

Daniel Henneman

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Measuring, comparing and improving clinical outcomes in gastrointestinal cancer surgery

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CHAPTER 1

Introduction and outline of this thesis

D. Henneman

GENERAL INTRODUCTION

As healthcare expenditures keep rising and technological advances in healthcare continue, guiding and canalizing efforts aiming at improvement of effectiveness and efficiency of care remains high on the political agenda throughout the Western world. Particularly, the field of oncological care becomes more and more complex, with an increasingly multidisciplinary approach to cancer treatment, advances in staging methods, surgical- and multimodality treatment, and an ongoing centralization of care towards referral centers for many types of cancer treatment. One of the major challenges is the ageing population, leading to a higher proportion of cancer patients that is susceptible for complications secondary to cancer treatment, as a result of prevalent comorbid illnesses[1,2].

High-risk surgery

A successful treatment for a patient consists of a right diagnosis, followed by a proper and adequately performed treatment, and the avoidance of adverse events associated with the treatment. Perhaps, the processes and outcomes of surgical treatment are the most straightforward to measure among oncological treatments. Postoperative clinical outcomes are important for both patients and caregivers, and adverse events like postoperative complications and mortality remain a major concern in intestinal oncological procedures. Of all intestinal surgical oncological procedures, colorectal resections are performed most commonly. They account for a disproportionate share (24%) of all adverse events within the spectrum of general surgery[3]. For instance, anastomotic leakage after low anterior resection is reported in literature to be approximately 9%[4] and 30-day postoperative mortality after colorectal cancer surgery is reported to be between 3-6% in larger series[5-8]. Oesophageal cancer surgery is a classic example of high-complex, low-volume surgery with reported postoperative mortality rates as high as 9%[9]. In esophageal cancer surgery, there is compelling evidence of better results and lower morbidity and mortality rates when surgery is performed in high-volume referral centres[10,11]. Although esophageal cancer care is now centralized in the Netherlands[12], postoperative morbidity and mortality (4.5%) is still high and esophageal cancer patients still have an unfavorable prognosis[13].

Hospital variation

With this background, hospital variation regarding quality of care received much attention in recent years. In the Netherlands, the 2010 'Quality of Cancer Care' report[14,15] by the Signaling Committee of the Dutch Cancer Society described the marked presence of variability of treatment patterns, as well as outcomes, between hospitals in the treatment of bladder-, lung-, colorectal- and breast cancer. A major theme was the volume-outcome relationship. Centralization of highly complex, low volume care- treating patients in centers that are experienced in a certain treatments, with a high annual number of procedures, has been shown to improve outcomes and reduce adverse events[13,16,17]. However, according to the report, a higher annual number of patients receiving a certain treatment per caregiver proved to be only a part of the explanation of variation in outcomes between hospitals. Several studies showed that centralization based on outcomes is more effective than volume-based referral[13,18,19]. The report highlighted the need for further defining quality of care and focusing research on the observed differences between hospitals, thereby appealing to the increasing demand of patients, policy makers and payers for transparency of treatment and outcome information. This paved the way for various Dutch clinical audits after international examples[20,21]. Not surprisingly, gastrointestinal cancers surgeons, especially colorectal surgeons, were among the first to embrace clinical registries in the Netherlands.

Clinical registry

The Dutch Surgical Colorectal Audit (DSCA) was initiated in 2009 as a nationwide continuous quality improvement program, registering all patients undergoing resections for primary colorectal cancer in the Netherlands. One of its main focus points is reduction of adverse event rates through feedback to participants of results with the national average as a benchmark[22]. The Association of Surgeons of the Netherlands agreed on a process in which outcomes of the DSCA will become publicly available in a stepwise fashion throughout the years. With a high rate of case-ascertainment and participation of all Dutch hospitals performing colorectal cancer resections, it is a valuable source of information on outcomes of everyday practice of colorectal cancer surgery in the Netherlands. Risk factors for adverse outcomes can be identified, with inclusion of patients that are usually not enrolled in clinical trials because of advanced age or comorbidity. The DSCA dataset forms the basis for most chapters in this thesis.

OUTLINE OF THIS THESIS

In this thesis, hospital variation concerning various outcomes is illustrated, thereby exploring the usability of these outcomes for hospital comparisons, both from a clinical and methodological point of view. Moreover, the studies provide insight in risk factors for adverse events in colorectal and oesophageal cancer surgery, focusing on the mechanism behind postoperative complications leading to mortality or not.

When hospital-specific outcomes are made available for the public, explicit ranking of hospitals based on specific outcomes may be attempted to compare quality of care, as is rather popular in the lay press[23-25]. Postoperative mortality may be considered one of the most delicate outcomes, and unjustly stigmatizing a hospital as having a high mortality rate may have great impact on its reputation. In rankings, besides differences in casemix, chance variation may play a role. The study described in **chapter 2** aims to determine to what extent chance variation and differences in casemix between hospitals have an impact on rankings; and whether postoperative mortality is an appropriate outcome to be used for hospital rankings in colorectal cancer surgery.

When comparing hospitals on outcomes, there is an important role for risk-adjustment, as observed variation between hospitals may be influenced by differences in patient- and tumor characteristics (casemix) between hospitals. It has been shown, for instance, that patients at high risk for postoperative mortality after colorectal cancer resections are not evenly distributed among hospitals[26]. It may be valuable to identify outcomes that accurately reflect actual differences in quality of care, but are not much influenced by patient characteristics. In **chapter 3**, it is explored to which extent hospital variation in anastomotic leak rates can be attributed to differences in casemix, in comparison with postoperative mortality.

Another well-known outcome measure in colorectal surgery is ‘unplanned reoperations’. In the Netherlands, it has long been a compulsory quality indicator for hospitals, traditionally collected by the Dutch Healthcare Inspectorate. On a patient level, reoperations are obviously associated with adverse outcomes such as complications, a prolonged length of hospital stay and postoperative mortality[7,27,28].

Less is known, however, about the correlation between reoperation rates and other outcomes on a hospital level. In fact, a low threshold for a reoperation in case of a suspected surgical complication may be part of an effective strategy to reduce postoperative mortality[29]. **Chapter 4** studies the value of reoperation rate as a marker for quality of care in elective colorectal cancer surgery.

As postoperative mortality is usually preceded by postoperative complications, hospitals with high postoperative mortality rates will intuitively have higher complication rates. However, there is increasing evidence that high postoperative mortality rates in certain centres is better explained by the way they recognize and rescue patients from postoperative complications once they emerge[6,30] - reflected by the 'failure to rescue' rate: the postoperative mortality rate among patients with a postoperative complication[31]. The study described in **chapter 5** investigates whether high-mortality centers are characterized by higher complication rates or by higher failure to rescue rates and explores its value for quality improvement programs.

Hospital type (e.g., academic or non-academic hospital) and annual hospital caseload (volume) are well-known proxies for surgical experience, perioperative care, and availability of resources. The environment in which a surgical team works may influence the ability of the team to keep patients alive when severe complications occur. Another seemingly important hospital characteristic, the level Intensive Care facilities available in a hospital, was not studied before in this context. **Chapter 6** studies the association between these three hospital characteristics and failure to rescue rates after colorectal cancer resections.

The study presented in **chapter 7** of this thesis concerns oesophageal cancer resections. As mentioned above, there is a clear volume-outcome relationship in oesophageal cancer surgery and minimum volume standards are now introduced in various countries. In literature, usually arbitrary volume categories are compared and as a result, these minimums vary from country to country. In this study, the relationship between hospital volume and 6-month and 2-year mortality following oesophagectomy in a non-categorical, non-linear fashion was determined, exploring how far centralization should go to be most effective. The discussion in **chapter 7**, as well as the general discussion of this thesis elaborates whether this should be achieved through a higher volume standard or through another process.

In order to reduce morbidity and mortality, it is important to understand the mechanisms behind the development of complications and the way they lead to fatal outcomes. **Chapter 8** studied rates of anastomotic leak and associated mortality in left-sided and right-sided colectomies, assessing the burden and impact of leaks in various types of colon cancer resections. Besides anastomotic leak, associated non-surgical complications may be an important determinant of postoperative mortality. The impact of these may be more related to patient factors. In the DSCA as well as the British National Bowel Cancer Audit Program[32], postoperative complication- and reoperation rates appear to be higher after rectal cancer resections than after colon cancer resections. However, postoperative mortality rates are higher in the latter[22]. This suggests the risk of dying once a postoperative complication has emerged is higher for patients undergoing a colon cancer resection. **Chapter 9** investigates differences in failure to rescue associated with major complications between elective colon- and rectal cancer resections, adjusting for differences in patient- and tumour- characteristics.

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CHAPTER 2

Ranking and rankability of hospital postoperative mortality rates in colorectal cancer surgery

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ABSTRACT

Objectives: To examine to what extent random variation and variation in casemix influence hospital rankings based on mortality rates; to determine the suitability of mortality for ranking hospitals in colorectal surgery.

Background: Comparing and ranking postoperative mortality rates between hospitals becomes increasingly popular. Differences in hospital case-mix, and chance variation related to caseload, may influence rankings. The suitability of mortality for rankings remains unclear.

Methods: Data were derived from the Dutch Surgical Colorectal Audit. Hospital rankings based on fixed (FE) and random effects (RE) logistic regression models, unadjusted and adjusted for casemix were compared with the percentile expected ranks (PCER; the chance that a hospital performs better than a random hospital). Rankability, measuring which part of variation between hospitals is not due to chance, was calculated.

Results: Some 25,591 patients undergoing colorectal resections in 92 hospitals were evaluated. Postoperative mortality rates ranged between 0 and 8.8%. Adjustment for casemix with an FE model caused large changes in rankings. A smaller additional effect on changes in rankings occurred after adjusting with an RE model, with lower volume hospitals moving towards the mean. PCERs ranged between 10% and 85%. Rankability was 38%, meaning that 62% of hospital variation in mortality was due to chance.

Conclusions: Hospital ranks changed after casemix adjustment and random effect models, compared to unadjusted analysis. A large proportion of hospital variation in mortality was due to chance. Caution should be warranted when interpreting hospital rankings

based on postoperative mortality. Percentiles of expected ranks may help to identify hospitals with exceptional performance.

INTRODUCTION

Colorectal cancer surgery is performed commonly, but colorectal resections remain associated with morbidity and mortality, accounting for 24% of all adverse events in general surgery[1]. Hence, complications and mortality are widely used outcomes in colorectal surgery[2-5]. At the same time, society focuses increasingly on effectiveness and efficiency in healthcare. Variations in hospital performances have become subject to research[6] and various quality improvement projects aim at reducing adverse event rates[7].

The Dutch Surgical Colorectal Audit (DSCA) is a nationwide continuous quality improvement program. One of its main focus points is reduction of postoperative mortality rates by providing feedback of results to participating hospitals, with the national average as a benchmark[8]. The Association of Surgeons of the Netherlands agreed on a process in which outcomes of the DSCA will become publicly available in a stepwise fashion throughout the years.

With outcomes made available for the public, explicit ranking of hospitals based on specific outcomes may be attempted to compare quality of care, as is rather popular in the lay press[9-11]. Postoperative mortality may be considered one of the most delicate outcomes, and unjustly stigmatizing a hospital as having a high mortality rate may have great impact on hospital reputation. It is therefore crucial that hospital comparisons, especially rankings, are based on sound methodology and should be reliable. After all, when information becomes public, allocation of reimbursements by insurers and certification by policy makers might be based on such rankings.

Two issues have to be addressed when comparing hospital performances. First, the occurrence of postoperative death may depend on the patient’s age, preoperative condition and disease severity. There is an increasing body of evidence that case-mix of different hospitals varies[12,13]. Second, chance variation may play an important role. For hospitals with a small number of cases, it is difficult to know whether extremely high or low mortality rates are due to chance or caused by actual differences in quality of care. Random Effect (RE) regression models can be fitted to account for the fact that part of the variation in outcomes between hospitals is due to chance[14-16].

Previous studies have examined the influence of random variation and differences in casemix on hospital variation and ranking in performance indicators for various types of treatments[13,17,18], including wound infections and reoperation rates in colorectal surgery. Only one study investigated the effect of adjustment for chance variation on 30-day mortality after colectomy[15], finding a large impact on rankings.

With this background, we aimed to determine to what extent random variation and differences in casemix between hospitals have an impact on hospital comparisons in mortality rates after colorectal cancer resections in the context of the DSCA; and to explore whether postoperative mortality is an appropriate outcome to be used for hospital rankings in colorectal cancer surgery.

METHODS

Data source

Data were derived from the Dutch Surgical Colorectal Audit (DSCA), a continuous national quality improvement project in which many variables concerning patient and disease-specific details, diagnostics, treatment, and outcomes are collected prospectively. Since part of the dataset of the DSCA was designed with the objective of performing casemix adjustment for postoperative mortality, variables were determined as risk factors for postoperative mortality at an early stage of development of the dataset. These factors were based on existing evidence concerning potential risk factors for mortality and determined by an expert panel using a Delphi method[8,12].

The DSCA contains data registered by all 92 Dutch hospitals performing colorectal cancer surgery[8]. The dataset shows a high level of completeness on most items and a case-ascertainment of approximately 95% when compared to the Netherlands Cancer Registry [8,19]. All information concerning individual patients and hospitals are made anonymous, making it possible to compare hospitals without identifying them.

Primary outcome

The primary outcome was 30-day and/or in-hospital postoperative mortality (death within 30 days after the operation, or during the index admission).

Statistical methods

To assess hospital's performance with respect to mortality, patient- and treatment characteristics (casemix) were included in the logistic regression analysis. Both fixed effect (FE) and random effect (RE) models were investigated. The case-mix factors age, gender, American Society of Anaesthesiologists (ASA) score, Charlson comorbidity index, body mass index, TNM stage, preoperative conditions related to the tumor, tumor location, procedure, preoperative (chemo/radio)therapy, urgent operations, additional resections and multiple synchronous colorectal tumors were included in the models. Details concerning the use of relevant casemix factors have been described elsewhere [12,20].

Fixed effect model

The FE logistic regression model is a classical regression model in which hospitals were included as a categorical variable by considering the situations without and with adjustment for case-mix. From these two models the log odds of mortality, with and without adjustment for differences in casemix between hospitals, and related standard errors for each hospital were estimated. Results from the FE models are referred to as FE estimates in this article.

Random effect model

Random effect (RE) models were used to represent the different source of variation in observed hospital-specific mortality rate. These models were employed to evaluate to what extent hospital variation in postoperative mortality can be attributed to chance. The estimated log odds adjusted for casemix between hospitals were computed along with a model parameter that describes the between-hospital variance (also called heterogeneity). As for the FE model, results from the RE are denoted as RE estimates, also known as Empirical Bayes (EB) estimates. The Bayesian approach, as introduced by Laird and Lewis and Thomas et al., produces shrinkage estimates of individual hospital mortality rates towards the national average and produces a more stable estimator[21,22]. In hospitals with a small number of cases, shrinking is bigger. The confidence intervals produced by the Bayesian methods account for the multiple comparisons problem that arises when identifying hospitals with an exceptional outcome among all hospitals. The variation in hospital-specific mortality rates not due to small sample fluctuations or measureable differences in severity of casemix can be quantified. Previous studies have also looked at the existence of such variation[16,23].

Ranking and rankability

To account for the effect of chance variation on rankings, the expected rank (ER)[21] was used. The ER represents the probability that the performance of a specific centre is better than a randomly chosen hospital. The ER can be transformed in percentiles based on expected ranks (PCER) to scale them between 0% and 100%.

By fitting a RE model, an estimation of the variability between hospitals can be obtained while the FE model provides an estimation of the variance for each hospital as it has been described in the Fixed Effects section. These quantities can be compared to measure which part of the variation between the hospitals is due to true differences. This leads to the measure called rankability, which indicates which part of variation between hospitals is due to true difference, and which part is due to chance[24]. Rankability is computed by relating heterogeneity between hospitals to uncertainty between and within centres. From this definition it follows that rankability can be used to express how reliable the ranking procedure is.

All statistical analyses were performed using R version 2.14. (http://cran.r-project.org/).

RESULTS

Patients

A total of 25,591 patients that underwent colorectal cancer resections in 92 Dutch hospitals between January 1st, 2009 and December 31st, 2011 were evaluated. The average hospital case volume in the study period was 278 patients (standard deviation 125,2). Patient, tumor and treatment characteristics are displayed in table 1.

Table 1: patient-, tumor- and treatment characteristics.

Characteristic		**N**	**%**
Gender	Male	14072	55%
Age	Mean (standard deviation)	70	11
Body Mass Index	Kg/m^2, mean (standard deviation)	26	4,8
Charlson co-morbidity index	0	14189	55%
	1	5555	22%
	2	3419	13%
	3 or higher	2428	10%
ASA classification	I	5132	20%
	II	13968	55%
	III	5389	21%
	IV	481	1,90%
	V	15	0,10%
	Unknown	606	2%
Pathological TNM stage	X	943	4%
	I	5270	21%
	II	8472	33%
	III	7934	31%
	IV	2972	11%
Preoperative tumor conditions	Perforation	409	2%
	Obstruction	2507	10%
	Anaemia/blood loss	1389	5%
Location of tumor	Right hemicolon	8207	32%
	Left hemicolon	3021	12%
	Sigmoid colon	7104	28%
	Rectum	7259	28%
Preoperative treatment	Short course radiotherapy	3417	13%
	Chemoradiotherapy	2067	8%
	Other	564	2%
Procedure	Ileocaecal resection	267	1%
	Right hemicolectomy	8026	32%
	Transverse colectomy	567	2%

Table 1: patient-, tumor- and treatment characteristics. *Continued*

Characteristic		N	%
	Left hemicolectomy	1854	7%
	Sigmoid colectomy/low anterior resection	11092	44%
	Subtotal colectomy	400	2%
	Abdominoperineal resection	2240	9%
	Panproctocolectomy	245	1%
	Other	622	3%
Urgency of procedure	Urgent/emergency procedure	3840	15%
Additional resections	Locally advanced tumor	2448	10%
	Metastasectomy	821	3%

ASA= American Society of Anesthesiologists

Estimating hospital differences

The average mortality was 4.3% (range 0 - 8,8%). The individual hospital effects are displayed as a sequence of 95% confidence intervals (95% CI) (figures 1a-1b). The 95% CI's represent the estimated range in which the true effect size for each hospital lies with a likelihood of 95%. Similarly, in figure 1c, posterior probability intervals (estimated from the RE model) for the true hospital effects are shown. In these three figures, one specific hospital with no mortality cases is not shown due to the extreme effect sizes and corresponding confidence interval. Although not shown, this hospital was included in the analyses.

Figure 1a shows unadjusted log odds for mortality of all hospitals, ranked from the lowest to the highest mortality rate. In this unadjusted analysis, five hospitals had significantly lower (low outliers) and nine hospitals had significantly higher (high outliers) mortality rates than average (figure 1a). These are hospitals of which the 95% CI's do not cross 0 (horizontal black line). For illustrative purposes, ten arbitrarily chosen hospitals with unadjusted ranks 1, 11, 21, 31

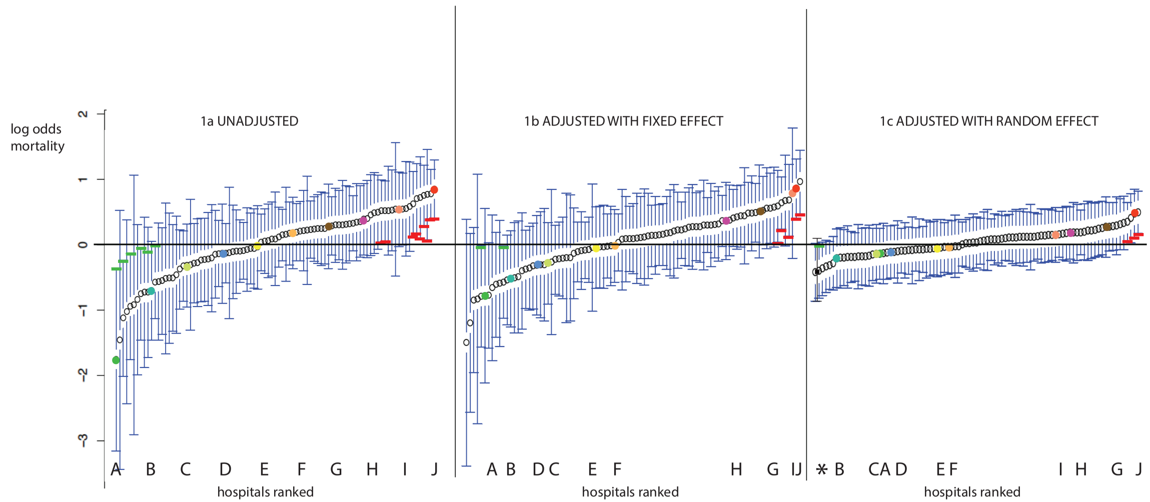

Figure 1: Hospital effect size in mortality and 95% confidence intervals; unadjusted analysis (1a), adjusted for casemix with a fixed effect model (1b), adjusted for casemix with a random effect model (1c). Hospitals A through J, in unadjusted analysis ranked 1st, 11th, 21st, 31st etc., are marked for illustration purposes.

* Hospital with no mortality cases, only displayed in figure c.

etc. up to 91 are marked with a specific colour and letter (A through J).

After adjustment for case-mix by fitting a FE model, hospitals changed ranks, as can be seen by tracking the positions of hospitals A-J in figure 1b compared to figure 1a. Only two hospitals remained low (significantly lower mortality than average) and five hospitals remained high outliers (figure 1b). Hospital A appeared to perform better than the average in the unadjusted analysis (figure 1a), but this proved to be partly due to a favourable casemix as the hospital was not a low outlier after fixed effect adjustment for casemix (figure 1b). After adjustment using a RE model with hospitals as a random effect, confidence intervals shrunk and only three high and one low outlier remained (figure 1c). Hospital J consistently remained a high outlier (significantly higher mortality than average) in all three models.

Ranking

Table 2 shows a quantification of change in ranks between unadjusted analysis and after adjustment for casemix with a FE model (A), and the extent of change in ranks between the FE and RE model analysis (B).

After adjustment for casemix in the FE model, 4 hospitals moved more than 30 places in the ranking. One of these hospitals moved from the lowest 20% (rank 79) to the middle 20% (rank 44), and two hospitals moved from the middle 20% to the bottom 20% (i.e. from the 51st to the 78th place, and from the 56th to the 85th place, respectively). One specific hospital moved from the 57th to the 15th rank. Four other hospitals changed between 21 and 30 ranks, and 23 hospitals changed between 11 and 20 ranks. Overall, three of the 18 'best' hospitals (top 20% in rank) moved out of the top 20%, and six of the 18 'worst' (lowest 20% in rank) moved out of the bottom 20%.

Table 2

	A Difference in rank between unadjusted and FE model	B Difference in rank between FE and RE model
>30 ranks higher	3	0
21-30 ranks higher	1	1
11-20 ranks higher	11	1
6-10 ranks higher	9	12
1-5 ranks higher	24	32
same rank	3	11
1-5 ranks lower	17	20
6-10 ranks lower	8	11
11-20 ranks lower	12	2
21-30 ranks lower	3	1
>30 ranks lower	1	1

Table 2: Change of ranks a) between results from unadjusted analysis and analysis with casemix adjustment in fixed effect (FE) model; b) between results from FE and random effect (RE) model.

By fitting a RE model, three top-20% hospitals moved out of this group, and three of the bottom-20% hospitals moved out of this group. One hospital moved down 45 ranks from the 43rd place to the 88th place; one changed from the 4th to the 29th place; and another one from the 89th to the 68th rank. Eventually three hospitals changed between 11 and 20 ranks, and for 11 hospitals the rank remained as in the FE model analysis.

For illustrative purposes, table 3 shows the respective ranks for postoperative mortality for hospitals A – J with the three different models as used in figure 1a-1c. In addition, the PCER for these specific hospitals are displayed. The PCER can be interpreted as the

Table 3

hospital	unadjusted rank	FE adjusted rank	RE adjusted rank	ER	Percentile ER
A	1	6	19	31.3	65,6%
B	11	13	7	24.1	73,8%
C	21	23	18	30.2	67,6%
D	31	20	22	33.1	64,2%
E	41	36	35	40.6	56,2%
F	51	41	38	41.5	55,4%
G	61	81	82	67.3	27,3%
H	71	72	72	60.2	35,2%
I	81	89	68	57.3	38,1%
J	91	90	90	83.1	9,9%

Table 3: ranks on postoperative mortality of hospitals A-J (ranked 1st, 11th, 21st, 31st and so on in unadjusted analysis) based on results from different models. FE= fixed effect; RE=random effect; ER= expected rank.

probability that a specific hospital has a better performance than a randomly selected hospital *i*.

Hospital A was highest in rank in unadjusted analysis, but moved to the 6th and 19th place in adjusted analysis and in the RE model analysis. Hospital A had PCER equal to 66%; this means that there is 66% probability that hospital A would have better mortality rates than a randomly selected hospital. Hospitals A, C, and D, in unadjusted analysis ranked 1, 21, and 31 had quite similar PCERs (64%-68%).

The distribution of the PCERs for all hospitals is shown in figure 2. As Figure 2 shows none of the hospitals could be classified as the worst or the best hospital (0% or 100%). Hospitals' percentiles of all hospitals ranged from 10% to 85%. PCER for hospital B was 74%, implying that there is 74% probability that hospital B performs better than a randomly selected hospital. On the other hand, hospital J with a PCER of 10% still had a 10% chance of not being the worst perform-

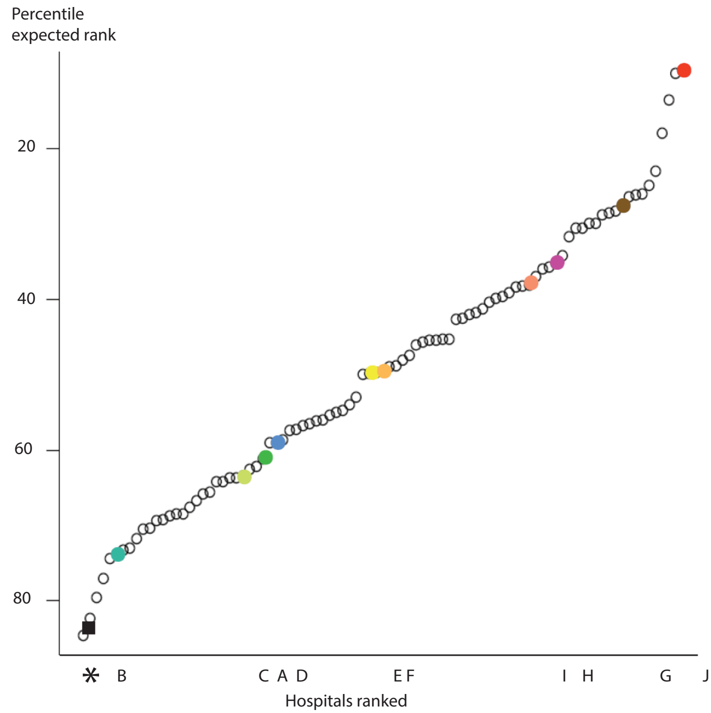

Figure 2: percentiles expected rank (PCER) on postoperative mortality for all hospitals. Hospitals A through J, in unadjusted analysis ranked 1st, 11th, 21st, 31st etc., are marked for illustration purposes.

* Hospital with no mortality cases.

ing hospital. The hospital with the highest PCER of all 92 hospitals was ranked 12th in unadjusted analysis (not shown in table 2).

Rankability

Rankability without and with adjustment for case-mix was equal to 44% and 38% respectively. Rankability can be interpreted as part of the observed differences between centres not due to chance; while the rest is due to natural variations or chance. A value of rankability equal to 38% implies that 62% of the variation in postoperative mortality between hospitals was due to chance while 38% may be considered due to true differences in hospital performance.

DISCUSSION

Our study is the first to look at the rankability concept of postoperative mortality in colorectal surgery. In our study we estimated that 62% of the variation in postoperative mortality between hospitals was due to chance. We found that the differences in hospitals' ranks between unadjusted and FE adjusted analysis were considerable. To a lesser extent, rankings changed again after fitting RE models. Finally, we illustrated the differences between rankings on mortality rates based on FE and RE models and compared these rankings to result from the PCER measure, which estimated the probability that a hospital has a better mortality rate than a randomly chosen hospital.

Dimick et al., assessing mortality rates in 18,454 colectomy patients from 181 hospitals participating in the American National Surgical Quality Improvement Program (NSQIP), found large differences between hospital rankings based on FE and RE models[15]. In our study, we also detected effect of the RE model on rankings, although in our study, drastic relevant changes in rank (e.g. moving from the top or bottom 20% in comparison with ranking based on FE modelling) only occurred in 3 of the bottom-20% and 3 of the top-20% hospitals when comparing ranks based on the FE model with the RE model results. Dimick et al. found that the FE model ranking potentially misclassified 25% of the top-20% hospitals and 25% of the bottom-20%

hospitals when comparing with the RE model ranking. Our dataset might be more homogenous in terms of variation in hospital volumes and mortality rates between hospitals, which could be a possible explanation for the different findings. Both studies suggest the use of EB methodology when ranking hospital outcomes and this method should still be preferred over the more traditional FE models.

The novelty of our work concerns the use of rankability, as introduced by van Houwelingen et al.[24], for postoperative mortality in colorectal surgery. Rankability gives an idea of how a specific outcome accurately reflects hospitals' performance. Previous studies have looked at rankability in different outcomes. Van Dishoeck et al. studied seven performance indicators[18]. For the performance indicator 'unplanned reoperations after colorectal surgery', rankability was relatively high (71%), but for all the other remaining indicators rankability was lower (e.g., 58% for in-hospital mortality following myocardial infarction, 38% for pressure ulcer incidence). Unfortunately, the authors were unable to perform adjustments for casemix in this study. In a similar study, looking at surgical site infections for various procedures in 34 Dutch hospitals, the same authors found a rankability of only 8% for this outcome when all procedures were combined; however for colectomies, the rankability for surgical site infections was 80%. An exact rule that can be used to assess the reliability of a specific ranking does not exist. Lingsma et al. suggest that any ranking is meaningless when rankability is smaller than 50%, and that ranking can be used if rankability is bigger than 75% [25]. In our study, the rankability for postoperative mortality after colorectal surgery was rather low, 38%, suggesting that this measure is not appropriate for ranking hospitals. Should it be attempted, the PCER can be used. The PCER can be interpreted as an estimate of the probability that the mortality rate of a specific hospital is smaller than the mortality rate of a randomly selected hospital. In this study the PCERs ranged from 10% to 85%.

The necessity of adjusting for casemix factors when comparing outcomes between hospitals is well established[13,26]. Kolfschoten at al. showed differences in patient characteristics between hospitals in the DSCA dataset, leading to different expected mortality rates[12]. Siregar et al. showed that hospital rankings on mortality following cardiac surgery are greatly influenced by adjustment for casemix with an RE model.

We came to the same conclusion for colorectal cancer surgery. We furthermore showed that outlier status (ie. hospitals having a significantly lower or higher mortality rate than average) changes after adjusting for case-mix factors.

Our study has some limitations. Firstly, although many casemix variables were available, there may have been unknown confounding variables not available in the dataset that may have influenced variation in outcomes between hospitals. However, colorectal cancer surgery experts constructed the DSCA dataset, and special attention was given to case-mix variables necessary for fair hospital comparisons[8,27].

One specific hospital had no observed cases of mortality. In unadjusted and adjusted FE analysis this hospital had an enormous (negative) effect size with extraordinarily large confidence intervals. For this reason, the estimates for this hospital were not displayed in the figures. This example illustrates the shortcomings of a FE model when there are no observed events in a hospital, which is not unlikely to happen in a sample with many hospitals. Arguably this hospital may perform well since there were no postoperative deaths in three years. Nonetheless, it is difficult to draw statistically valid conclusions from this observation in FE analysis. The EB methodology overcomes this problem and an estimated hospital effect can be found in hospitals with no events. The PCER for this specific hospital was equal to 83% with an ER of 16.7.

In this study, we used pooled data from three registration years of registration. The longitudinal aspect of the data is beyond the scope of this manuscript, but in a future work it will be investigated whether results based on correlation across years might be used to make predictions about center effects.

There is an on-going debate whether outcome measures such as postoperative mortality adequately reflect quality of care. Some advocate using process measures (e.g. guideline adherence) in measuring quality of care, because these factors can be improved more concretely by hospitals with poor performance. However, what counts for patients are outcomes. Most probably, quality of care is best expressed as a combination of process and outcome measures, or even composite measures comprising both[28]. For this study, postoperatively mortality was chosen because it is well defined and may be considered quite delicate: unjustly stigmatizing a hospital as having high postoperative mortality may have a dramatic impact on hospital reputation and reimbursements. We found that 62% of variation in mortality between hospitals is due to chance, which implies that great caution should be used when interpreting hospital comparisons and rankings on this outcome. However, since this is an important outcome for patients, it seems worthwhile to continue measuring postoperative mortality rates. Another important reason to continue collecting and reporting postoperative mortality information is that evidence shows that feedback of surgical outcomes to physicians can lead to improvement[29,30]. Recently, in the UK, postoperative mortality data per surgeon has become publicly available on the Internet. Presumably, the influence of chance variation is even greater in that situation, since the number of patients for each surgeon is rather small.

Measuring quality of care may have internal and external purposes. The DSCA is used as a system for benchmarking: surgical teams from the participating hospitals can compare results and improve in relation to the national average. This is an internal purpose. With an increasing demand for transparency of quality information, however, more information becomes public. Eventually, (risk-adjusted) outcome information will become public too. In this situation, third parties may compare outcomes between hospitals. Payers have limited resources and want to allocate them to the best performers. Ranking can be used in this context and therefore people should be aware of the reliability of such lists. The magnitude of differences between two hospitals is lost: one hospital is simply higher in rank than the other. Moreover, a hospital can move down on a ranking list as a result of another one moving up, even when performance remains the same. The advantage of the PCER measure is that it can be interpreted on its own, and it can be very useful in helping payers and patients to make decisions. The uncertainty concerning the outcome is included in the percentage ascribed to each hospital: the chance that the selected hospital has a better outcome than a randomly selected hospital. We suggest that when outcome information such as postoperative mortality becomes public, PCERs should be published with them. Reliable information on specific performance indicators may be extremely useful, if properly analysed and interpreted.

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CHAPTER 3

Anastomotic leakage as an outcome measure for quality of colorectal cancer surgery

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ABSTRACT

Introduction: When comparing mortality rates between hospitals to explore hospital performance, there is an important role for adjustment for differences in casemix. Identifying outcome measures that are less influenced by differences in casemix may be valuable. The main goal of this study was to explore whether hospital differences in anastomotic leakage (AL) and postoperative mortality are due to differences in casemix, or to differences in treatment factors.

Methods: Data of the Dutch Surgical Colorectal Audit were used. Casemix factors and treatment related factors were identified from the literature, and their association with anastomotic leakage and mortality were analyzed with logistic regression. Hospital differences in observed anastomotic leakage and mortality rates; and adjusted rates based on the logistic regression models were shown. The reduction in hospital variance after was adjustment was analyzed with a Levene's test for equality of variances.

Results: 17 out of 22 case-mix factors and 4 out of 11 treatment factors related to anastomotic leakage derived from literature were available in the database. Variation in observed AL rates between hospitals was large with a maximum rate of 17%. This variation could not be attributed to differences in casemix, but more to differences in treatment factors. Hospital variation in observed mortality rates was significantly reduced after adjustment for differences in casemix.

Conclusions: Hospital variation in anastomotic leakage is relatively independent of differences in casemix. In contrast to 'postoperative mortality' the observed anastomotic leakage rates of hospitals evaluated in our study were only slightly affected after adjustment for case-mix factors. Therefore, anastomotic leakage rates may be

suitable as an outcome indicator for measurement of surgical quality of care.

INTRODUCTION

Nowadays there's a growing public interest in quality of medical and surgical care, with an increasing urge for outcome measures that represent hospital performance. The outcome measure postoperative mortality is often used to benchmark surgical performance.[1-3] When comparing mortality rates between hospitals, there is an important role for risk adjustment.[4, 5] Observed variations in mortality may be caused by differences in patient and tumor characteristics (casemix), and high risk patients may not be evenly distributed between hospitals.[6]

However, valid casemix adjustments require a substantial amount of reliable data collected on a patient level. These data are rarely available and require a substantial registration effort. Therefore, it may be valuable to identify outcome measures that are less influenced by differences in casemix and represent the actual differences in quality of care processes.

Colorectal cancer is a significant source of mortality with nearly 10,000 new cases diagnosed in the Netherlands each year.[7] The cornerstone of this treatment is surgical resection. Patients undergoing surgical resection have a considerable risk for postoperative complications, which can lead to significant morbidity, mortality and large costs. Internationally, several quality improvement programs have therefore been initiated to reduce postoperative complications after colorectal surgery.

Anastomotic leakage is one of the most feared complications after colorectal surgery, often causing prolonged hospital stay, morbidity, mortality and possibly worse oncological outcomes.[8] The percentage of patients developing anastomotic leakage depends on multiple factors. In literature, several elements have been identified as risk factors. These can be patient- or tumor-related, often referred to as casemix, such as height of the anastomosis, a malnourished status, steroid use and male gender.[9-13] Treatment related factors such as surgeons' experience, operative duration, blood loss, preoperative radiation and a defunctioning stoma have also demonstrated to be associated with the occurrence of anastomotic leakage.[9-13]

The aim of this study was to explore whether hospital differences in anastomotic leakage rates are related to differences in casemix. We compared the role of casemix adjustment for anastomotic leakage and postoperative mortality. With this objective, the following research questions were drawn:

1. Which casemix and treatment related risk factors are associated with anastomotic leakage and postoperative mortality after colorectal surgery?
2. What are differences in anastomotic leakage and mortality rates between hospitals and are these due to differences in casemix or due to differences in treatment-patterns?

METHODS

Patients

Data was derived from the Dutch Surgical Colorectal Audit (DSCA), a national quality improvement project in which over 200 variables concerning the patient, comorbidity, diagnostics, disease-specific details, treatment, and outcomes are collected prospectively. The DSCA contains data of patients registered by 92 hospitals (all hospitals performing colorectal cancer surgery). The data set is disease-specific for colorectal cancer and shows a nearly 100% accordance on most items, including anastomotic leakage on validation against the National Cancer Registry (NKR) data set.[14] All patients undergoing resection for primary colorectal cancer between the 1st of January 2009 and 31st of December 2011 and registered in the DSCA before March 15th 2012 were evaluated. Minimal data requirements for inclusion in analyses were information on tumor location, date of surgery and mortality. Patients with metastases at time of primary surgery and resections for multiple synchronous colorectal tumours were excluded, because these represent subgroups of patients with other treatment perspectives and subsequent different expected outcomes. Also, patients in which a primary end-colostomy was constructed were excluded from analysis.

Risk Factors

Since part of the dataset of the DSCA was designed with the objective of performing casemix adjustment particularly for postoperative mortality, variables have been determined as risk factors for postoperative mortality in an early stage of conduction of the dataset. These factors were based on existing evidence on potential risk factors for mortality and determined by an expert panel using a Delphi method.[6] To assess whether there are additional casemix and treatment related risk factors that need to be taken into account when adjusting for anastomotic leakage, we performed a systematic search for literature published between 1990 and 2012 on biomedical bibliographical databases Pubmed and the Cochrane Library. The search headings “anastomotic leak and colorectal surgery” were used in combination with the keyword “risk factor”. The “related articles” function was used to expand the search. References from the articles were also used when appropriate. Letters, reviews without original data, non-English language papers, overlapping patient populations and animal studies were excluded. From the articles retrieved from the literature search, different risk factors for anastomotic leakage were selected. A distinction was made between patient and tumor related factors (casemix factors) and treatment related factors. We selected risk factors with a statistical significance of $p < 0.05$, which were analyzed with multivariate logistic regression.

Outcomes

Various definitions of AL have been previously presented.[15] The definition of anastomotic leakage in this study was 'a clinically relevant anastomotic leak requiring a re-intervention'. Both radiological and surgical re-interventions were included. Postoperative mortality was defined as 'death during postoperative hospital stay or within 30 days after the date of surgery'.

Analyses

The association of casemix and treatment factors and both anastomotic leakage and mortality were tested with multivariate logistic regression models. Separate models were used for each outcome. To analyze the differences in anastomotic leakage and mortality between hospitals and investigate whether these were due to differences in case-mix or due to differences in treatment-patterns we applied 3 different models. model 1: unadjusted (observed) variation in outcome; model 2: adjusted for patient (casemix) characteristics; model 3: 'adjusted' for casemix and treatment characteristics. Adjustment was performed by calculating expected outcomes (E) using casemix (model 2) and both casemix and treatment (model 3) coefficients from the regression analysis. Next, for each hospital, the observed percentage (O) was divided by the expected value (E) and multiplied by the overall mean (observed/E * mean) to obtain the adjusted percentages.

Hospital differences in anastomotic leakage and mortality rates before and after adjustment were plotted in a graph; a summary measure of the between hospital variance was given with ranges and standard deviations. The reduction in between center variance after adjustment for (model 2) casemix and (model 3) casemix and treatment factors was analyzed with a Levene's test for equality of variances. A p-value <0,05 was considered statistically significant. Furthermore, a mixed logistic regression model with hospitals as random effects was performed A likelihood ratio test was used to test whether the variance of the random effects was statistically significant after adjustment for casemix and treatment factors. Hospitals with more than 15% missing casemix factors were excluded from multivariate analyses. All statistical analyses were performed in PASW Statistics, Rel. 18.0.2009. Chicago: SPSS and R version 2.14.[16]

RESULTS

On March 15th 2012, 92 hospitals (8 university, 47 teaching and 37 non-teaching hospitals) registered a total of 25,555 eligible primary colorectal cancer patients with a date of surgery between January 1st 2009 and December 31 2011 in the DSCA. Nine hospitals had more than 15% missing case-mix factors in total, and were therefore excluded (n=1,460). After additional exclusion of patients with multiple synchronous tumors (n=598), distant metastases (n=2,032) and without an anastomosis (n=5,480), a total of 15,236 patients were included in the analysis. Characteristics of the included patients are shown in Table 1.

Of all patients, 1207 patients (8%) developed anastomotic leakage and 525 patients (3.4%) died within 30 days or during hospital admission.

Risk factors

The literature search gave a total of 39 studies describing risk factors for anastomotic leakage.[8, 10-13, 17-49] In total, 22 casemix factors and 11 treatment related factors for were identified. Table 1 shows the results. Casemix factors described most frequently were gender, American Society of Anesthesiologists (ASA) score and location of the tumor and/or anastomosis. Treatment factors often described were blood loss/transfusion, duration of the operation and the use of a defunctioning stoma.

Of the 22 casemix factors for anastomotic leakage identified in literature, 17 were available in the DSCA. The database had no information on the factors weight loss, nutrition status, alcohol abuse, smoking and leukocytosis. Treatment factors were less often available; 4 out of 11 were available in the dataset.

The casemix and treatment related risk factors that were found for anastomotic leakage in literature were similar to those that have been used for risk adjustment for postoperative mortality in the DSCA dataset.

A multivariate analysis has been performed to investigate the association of casemix and treatment factors with anastomotic leakage and postoperative mortality; results of the analysis are shown in table 2.

Individual casemix factors predicting anastomotic leakage were male gender, urgency of the resection, renal disease and tumor location. Treatment related factors associated with anastomotic leakage were short preoperative radiotherapy, the absence of a defunctioning stoma and postoperative blood transfusion. For postoperative mortality the case-mix factors age, gender, ASA score, pulmonary disease, tumor location sigmoid, urgency of the resection were individual predicting factors. Treatment related factors were chemo-radiotherapy and blood transfusion.

Table 1: Risk factors for AL described in literature and available patient and treatment characteristics of included patients in the DSCA. ASA= American Society of Anesthesiologists score. BMI= Body Mass Index.

		DSCA (n=15.236)		**Literature (n=39)**
Factor		N	%	Author
Casemix factors				
Age	>75	5464	37.8%	Hun Yung et al (2006)
Gender	Male	8034	52.7%	Van 't Sant (2010); Bertelsen (2010); Peng (2010); Lee (2008); Jestin (2008); Hun Yung (2006); Lipska (2006); Yuh Yeh (2005); Rudinskaite (2005); Peeters (2005); Law (2004); Mathiessen (2003); Poon (1999); Rulier (1998).
ASA score	3+	3268	21.4%	Van 't Sant (2010); Wang (2010); Eberl (2008); Bucher (2007); Jestin (2008); Choi (2006); Makela (2003); Alves (2002); Tang (2001)
BMI	<25	4048	26.6%	Kim (2009); Biondo (2005); Makela (2003);
	25-30	4327	28.4%	
	>30	1964	12.9%	
	Unknown	4897	32.1%	
2 or more comorbidities	Yes	6456	42.4%	Iancu (2008); Makela (2003)
Cardiovascular disease	Yes	6408	42.1%	Iancu (2008); kruschewski (2007); Makela (2003); Tang (2001)
Pulmonary disease	Yes	1858	12.2%	Akasu (2009); Iancu (2008); Makela (2003)
Diabetes	Yes	2186	14.3%	Iancu (2008); kruschewski (2007); Benoist (2000); Vignali (1997)

Table 1: Risk factors for AL described in literature and available patient and treatment characteristics of included patients in the DSCA. ASA= American Society of Anesthesiologists score. BMI= Body Mass Index. (continued)

		DSCA (n=15.236)		Literature (n=39)
Factor		N	%	Author
Crohn's disease	Yes	107	0.7%	Lipska (2006)
Preoperative anemia	Yes	846	5.6%	Iancu (2008);
Renal failure	Yes	461	3.0%	Alves (2002)
Steroid treatment	Yes	1174	7.7%	Konoshi (2006); Alves (2002)
Previous abdominal surgery	Yes	5037	33.1%	Lipska (2006)
Weight loss	N.a.			Iancu (2008); Makela (2003)
Hypoproteinemia/ nutritial status	N.a.			Iancu (2008); Makela (2003)
Alcohol abuse	N.a.			Nickelsen (2005); Makela (2003)
Smoking	N.a.			Bertelsen (2010); Iancu (2008); Kruschewksi (2007)
Leukocytosis	N.a.			Iancu (2008); Alves (2002)
Tumor stage	Stage 0/I	1156	7,60%	Eberl (2008)
	Stage II	3068	20,10%	
	Stage III	8940	58,70%	
	Stage IV	1588	10,40%	
Additional resection	Locally	1126	7,40%	Yuh Yeh (2005)

Table 1: Risk factors for AL described in literature and available patient and treatment characteristics of included patients in the DSCA. ASA= American Society of Anesthesiologists score. BMI= Body Mass Index. (continued)

		DSCA (n=15.236)		Literature (n=39)
Factor		N	%	Author
Tumor location	Right-sided	5966	11,80%	Bertelsen (2010); Peng (2010); Cong (2009); Kim (2009); Lee (2008); Eberl (2008); Bucher (2008); Jestin (2008); Hun Yung (2006); Lipska (2006); Yuh Yeh (2005); Rudinskaite (2005); Law (2004); Matthiessen (2003); Marush (2002); Rulier (1998); Vignali (1997)
	Transverse/ descending	2003	39,20%	
	Sigmoid	4468	13,10%	
	Rectum	2799	29,30%	
Urgent resection	Acute	1799	11,80%	Choi (2006)
Treatment factors				
Neoadjuvant therapy	5x5 GY	1508	18,40%	Eriksen (2005); Alves (2002);
	Chemoradiation	830	9,90%	
Defunctioning stoma	Yes	2467	16,20%	Matthiessen (2007); Rullier (1998); Peeters (2005); Pakkastie (1997); Cong (2009)
Blood loss/transfusion	Yes	2042	13,40%	Alves (2002); Sorensen (1999); Law (2004); Yuh Yeh (2005); Nesbakken (2002); Tang (2001); Akasu (2009); Boccola (2009); Telem (2010);
Intra-operative contamination	N.a.			Alves (2002); Makela (2003); Konishi (2006)
Intra-operative adverse events	N.a.			Matthiessen (2003)
Pelvic drain	N.a.			Peeters (2005); Tang (2001); Yuh Yeh (2005); Boccola (2010); Cong (2009)

Table 1: Risk factors for AL described in literature and available patient and treatment characteristics of included patients in the DSCA. ASA= American Society of Anesthesiologists score. BMI= Body Mass Index. (continued)

	DSCA (n=15.236)		Literature (n=39)
Factor	N	%	Author
Incomplete donut	N.a.		Makela (2003); Schmidt (2003)
Stapling device	N.a.		Boccola (2010)
Duration of operation	N.a.		Vignali (1997); Marusch (2002); Alves (2002);Konishi (2006); Bucher (2007); Choi (2010); Telem (2010)
Specialization surgeon	N.a.		Cong (2009)
After-hours' surgery	N.a.		Komen (2009)

Table 2: Casemix and treatment factors included in the multivariate logistic regression model for AL and mortality after colon and rectal carcinoma resections. Age and BMI were analyzed as continuous variables. AL= anastomotic leakage; CI= confidence interval; OR= odds ratio; ASA= American Society of Anesthesiologists score; BMI = Body Mass Index. Bold printed numbers are significant odds ratios ($p < 0.05$).

		AL			Mortality		
		OR	**95% C.I.**		**OR**	**95% C.I.**	
Casemix factors							
Age		0.99	0.98	1.02	**2.65**	**2.33**	**3.04**
Gender	male	**1.31**	**1.11**	**1.55**	**1.82**	**1.39**	**2.37**
ASA	2	1.01	.84	1.22	**3.09**	**1.54**	**6.17**
	3+	1.00	.80	1.24	**6.44**	**3.46**	**13.12**
BMI		.91	.74	1.13	.99	.97	1.02
2 or more comorbidities		.88	.70	1.10	1.17	.82	1.67
Cardiovascular disease		.85	.70	1.04	1.21	.90	1.62
Pulmonary disease		.92	.71	1.20	**1.44**	**1.06**	**1.97**
Diabetes		.99	.77	1.28	1.12	.81	1.55
Crohn's disease		1.06	.43	2.60	1.35	.36	4.98
Preoperative blood loss		.72	.42	1.25	.68	.23	2.00
Steriod treatment		1.27	.81	2.00	1.25	.72	2.15
Renal disease		**1.34**	**1.01**	**1.78**	.91	.62	1.34
Abdominal surgical history		1.03	.87	1.22	.87	.67	1.14
T-stage	T3	1.03	.87	1.21	1.05	.81	1.36
	T4	1.13	.78	1.64	1.22	.71	2.10
Additional resection		1.20	.88	1.64	.96	.59	1.55
Urgent resection		**1.32**	**1.01**	**1.73**	**2.18**	**1.60**	**2.98**
Tumor location	Transverse colon	**1.93**	**1.49**	**2.50**	1.25	.89	1.76
	Sigmoid	**1.68**	**1.33**	**2.11**	**.70**	**.50**	**1.00**
	Rectum	**2.22**	**1.49**	**3.29**	1.04	.52	2.04
Treatment factors							
Neo-adjuvant therapy	5x5	**1.70**	**1.13**	**2.54**	.88	.42	1.85
	Chemoradiotherapy	1.33	.84	2.09	**.30**	**.09**	**.98**
Defunctioning Stoma		**.54**	**.42**	**.70**	1.15	.69	1.89
Transfusion		**4.27**	**3.56**	**5.12**	**4.06**	**3.14**	**5.25**

Hospital variation

Anastomotic leakage

Unadjusted hospital variation in anastomotic leakage rates was large: the hospital with the lowest percentage had an anastomotic leakage rate of 0% (n=0/166); the hospital with the highest percentage had an anastomotic leakage rate of 18% (n=12/70) (SD 0.036, Figure 1a). After adjustment for casemix, there was still a large variation between hospitals: the adjusted anastomotic leakage rates per hospital ranged from 0 to 17% (SD 0.033). The reduction in variation after adjustment for casemix was not statistically significant (p=0.52). The variance in anastomotic leakage rates significantly decreased after including treatment factors in the adjustment model (p<0.01). Casemix and treatment adjusted anastomotic leakage rates varied from 0 to 12% (SD 0.024).

For 60% of the hospitals (50/83), the unadjusted anastomotic leakage rate was similar to the casemix adjusted anastomotic leakage rate. In 36% of the hospitals, anastomotic leakage rates slightly in-or decreased with 1%, and in 4% of the hospitals with 2% (Figure 2a). For 75% of the hospitals (63/83), unadjusted anastomotic leakage rate altered after adjustment for treatment factors with at least 1%; for 32% of the hospitals, the unadjusted rate altered with more than 3% and for 10% with more than 5%.

Although hospital variance decreased after adjustment for casemix and treatment factors, there was still variability between hospitals as a likelihood ratio test showed that the variance of the random effects was statistically significant in all models.

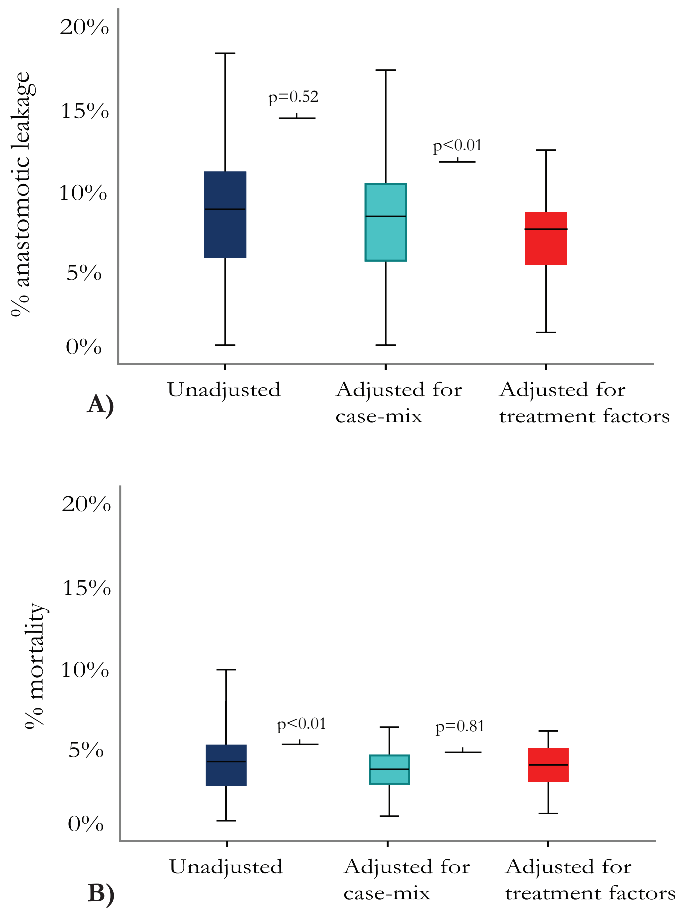

Figure 1: Boxplots presenting the range in hospitals' anastomotic leakage rates (A) and mortality rates (B). The unadjusted range (left), the range after adjustment for case-mix (center), and the range after adjustment for case-mix and treatment factors (right) are shown. P-values describe the statistical significance of the reduction in variance (Levene's test); a p-value of <0.05 was considered statistically significant.

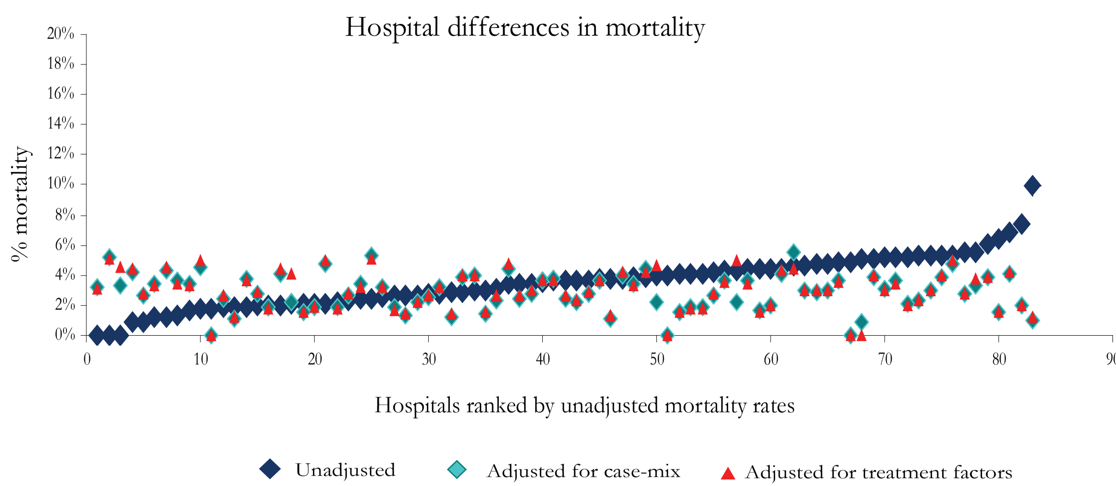

Figure 2: Scatterplots showing the effect of adjustment for casemix (model 2) and both casemix and treatment factors (model 3) for anastomotic leakage (A) and mortality (B) on an individual hospital level. Each scatter represents a single hospital's unadjusted, case-mix adjusted, and case-mix and treatment adjusted rate. On the x-axis, hospitals are ranked according to their unadjusted anastomotic leakage or mortality rate.

Postoperative mortality

Hospitals' unadjusted mortality rates ranges from 0 to 10% (SD 0.017). The variance in postoperative mortality significantly decreased after casemix adjustment (p<0.01) (range 0-6%, SD 0.012, Figure 1b).

The variance in postoperative mortality rates slightly increased (range 0-6%, SD 0.013) after including treatment factors in the adjustment model, although not statistically significant (p=0.81).

For 84% of the hospitals (70/83), the unadjusted postoperative mortality rate altered after adjustment for treatment factors with at least 1%; for 24% of the hospitals, the unadjusted rate altered with more than 3% and for 6% with more than 5% (Figure 2b).

Adjustment for treatment factors had a slight effect on two hospitals when compared to the casemix adjusted mortality rate. In these hospitals, case-mix adjusted mortality rate altered with 1% after adjustment for treatment factors.

Hospital variability in postoperative mortality was still significant after adjustment for casemix and treatment factors, as a likelihood ratio test showed that the variance of the random effects was statistically significant in all models.

DISCUSSION

The present study suggests that 'anastomotic leakage rate' is an outcome indicator for measurement of surgical quality of care that is relatively independent of differences in casemix between hospitals. We found a large variation in anastomotic leakage rates between Dutch hospitals, which confirm the ability of this outcome indicator to be discriminative. In contrast to 'postoperative mortality' the observed anastomotic leakage rates of hospitals evaluated in our study could not be explained by differences in casemix. In addition, we found that the influence of treatment factors on the variation in anastomotic leakage rates was substantial. These findings imply that anastomotic leakage rates may be much more related to treatment factors and in hospital care processes, than to characteristics of the patient population treated in a certain hospital. Anastomotic leakage rates may therefore be a good reflection of the quality of care provided.

Outcome measures

Optimizing surgical outcomes can be seen as 'the bottom line' of what surgeons do, and outcome indicators have the advantage that they have 'face validity' for surgeons as well as for their patients. Also, measurement in itself may improve surgical outcomes – as suggested by the so-called Hawthorne effect.[4] As shown in our study, outcome indicators can present meaningful differences between hospitals. However, there was still significant variability in both anastomotic leakage and mortality rates, after adjustment for case mix factors and treatment factors in our study. This suggests that there are other characteristics of the hospital, its staff and the care they deliver, which may explain the observed differences. Although outcomes of care are important, process and structure information is essential to identify which area is susceptible for innovation. Therefore, adopting to the Donabedian paradigm[50], a balanced indicator set needs to include information on structures, processes and outcomes.

Limitations

The results presented in this study should be interpreted in the light of some important limitations. First, despite the fact that most patient-related risk factors were available in the database of the DSCA, it lacked data on some important host-related factors, such as smoking, alcohol consumption, nutrition status and preoperative leukocytosis. Although unlikely, it is possible that a strong casemix adjustment model for AL could have been made when exactly those four missing factors would have been available from the data set. Also, high risk patients according to the surgeons' preoperative risk judgment or patients with impaired continence at baseline may not have been selected for a primary anastomosis, and therefore excluded which may have caused a potential selection bias. It is not exactly clear how these differences in patient selection might affect the between hospital comparisons. Moreover, due to a lack of clear agreements on definitions, the factors we used may not have been identical to the ones we found in literature.

Although we found that casemix adjustment does not seem to play a large role when comparing hospitals' anastomotic leakage rates, there are some limitations of using it as an outcome indicator that deserve mentioning. It may unintentionally lead to the perverse incentive of aiming for the lowest possible anastomotic leakage rate by constructing more end-colostomies or defunctioning stomas. This defensive attitude would not immediately contribute to a higher quality of care, as a surgeon or clinic that has zero AL rates at the cost of constructing defunctioning stomas or end-colostomies in all patients will not be regarded as the best practice. Obviously, anastomotic leakage rates are only calculated over patients in whom an anastomosis has been created. Therefore hospitals, with lower rates of patients with anastomoses could automatically have better scores, without immediately better quality of care, as the stoma itself may cause morbidity, lead to a higher need for readmissions[51, 52] and may be associated with morbidity at the time of surgical removal of the stoma.[53] In reality, there is probably an optimum percentage of defunctioning stoma's and end-colostomies to be created, and AL rates should always be seen in the light of these percentages. However, the exact optimum is unclear and it may vary between different surgeons or clinics. Auditing programs like the DSCA may help to clarify in what range this optimum should be. A composite quality measure might be a solution, that is a metric which includes whether or not AL occurred, creation of a defunctioning stoma or end-colostomy, readmissions or mortality. Patient reported outcomes are of additive value in this context. The choice between an anastomosis with or without a defunctioning stoma or an end-colostomy can and should always be influenced by patient preferences.

Improvement of outcomes

When anastomotic leakage is used in hospital comparisons, it should be under the condition that practices with higher anastomotic leakage rates have the opportunity to improve their performance. Unfortunately, the actual cascade of factors resulting in anastomotic leakage still remains a 'black box'. Our findings suggest that this black box consists of factors that represent multiple elements of the care processes taking place within a hospital. Per-operative factors, such as blood loss and duration of the operation have been described as important predictors for AL by several authors.[9-13] Longer duration, more blood loss than anticipated, an increased anastomotic strain and limited vascular supply at the anastomotic sites may be a proxy of a more complicated procedure, suggesting that anastomotic leakage rates might be related to surgical technical skill and experience. Additionally, factors more related to perioperative care than to surgical skill, such as oliguria during the operation, are are also said to enhance the risk for leakage.[54]

The ultimate challenge for outcome researchers is to understand the complex clinical mechanisms that lead to success or failure, so that the excellence of best practices can be transferred to all hospitals performing these procedures.

Definition of AL

Comparison of AL between hospitals also requires the use of standard definitions and methods of measurement of AL. It has however been stated before that the definition of AL varies; a systematic review done by Bruce et al. found 56 separate definitions for AL used in literature.[15] A valuable feature of an audit registration system is that it applies one definition that is used by all participants. In the DSCA; only clinical apparent leaks requiring re-intervention have been registered, and a distinction has been made between radiological and surgical re-intervention. Further (international) agreement on a standard definition that is valid and reliable, and can distinguish between clinical minor and major anastomotic leaks are explicitly important when using anastomotic leakage as an outcome indicator.

Conclusions

Hospital variation in anastomotic leakage rates is relatively independent of differences in case-mix. Differences in treatment factors contributed more to the variation of anastomotic leakage rates. Further exploration of in-hospital factors may give insight in further improvement possibilities and understanding the multifactorial process that underlies anastomotic leakage. Audit programs may provide data for targeted visitation of clinics with bad outcomes, as well as best practices, aiding in identification of the most important areas for improvement.

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CHAPTER 4

Benchmarking clinical outcomes in elective colorectal cancer surgery: the interplay between institutional reoperation- and mortality rates

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ABSTRACT

Background: "Unplanned reoperations" has been advocated as a quality measure in colorectal cancer surgery as it is correlated with complications and postoperative mortality at a patient level. However, little is known about the relation between reoperation rates and postoperative mortality rates at a hospital level.

Methods: Data were derived from the Dutch Surgical Colorectal Audit 2009-2012 database. Hospitals with significantly higher and lower reoperation rates than average were identified and grouped accordingly. Postoperative mortality rates were compared between the groups.

Results: Some 28,667 patients who underwent elective colorectal cancer resections in 92 hospitals were analyzed. Fourteen hospitals had significantly higher (mean 14.6%) adjusted reoperation rates than average (10%), 20 had lower (5.3%) rates than average. Adjusted mortality rates were similar in groups with high reoperation rates and the majority cohort (3,5-3,2%) and significantly lower in hospitals with low reoperation rates (2,3%). However, individual hospitals with relatively high reoperation rates had low mortality rates and vice versa.

Conclusions: Reoperation rates after elective colorectal cancer resections varied. Hospitals with significantly higher reoperation rates than average did not have higher mortality rates. The group with lowest reoperation rates also had lower postoperative mortality rates; however, this did not apply to all hospitals in the group. In conclusion, 'reoperations' seems suitable as benchmark information to hospitals but less suitable to detect poor performers. Best practices should be identified as hospitals with both low reoperation- and mortality rates.

INTRODUCTION

There is an increasing demand for transparency of information that aids in rating hospitals' performance, both from policy makers and patients. At the same time, clinical outcome registries are becoming more widespread, helping caregivers to improve by generating benchmark information[1]. As a result, measuring and comparing quality of surgical care has become increasingly important in the last decades, and in several quality improvement projects, quality indicators have been defined[2]. Quality indicators measure a certain aspect (structure, process, or outcome[3]) of care and are compared against a standard or average. They may be used for internal purposes (feedback and quality improvement) as well as external purposes (making public of information on hospital performance).

Colorectal surgery is associated with relatively high surgical postoperative morbidity rates[4] and accounts for a disproportionate share of reoperations within the spectrum of general surgery[5]. "Unplanned reoperation" is a well-accepted quality measure for colorectal surgery. In the Netherlands, it is a compulsory quality indicator collected by the Dutch Healthcare Inspectorate. Many publications have concluded that the measure is suitable as a quality measure because it is a factor independently associated with other adverse outcomes such as prolonged hospital stay and postoperative mortality[5-7]. Obviously, this is because of the close relationship between reoperations and surgical complications such as anastomotic leak or haemorrhage. An advantage over postoperative mortality as an outcome indicator would be that in elective surgery, postoperative mortality is less frequent and may therefore not discriminate worse performing hospitals from better performing hospitals. On the other hand, timely reoperations in case of complications may save the patients' life and higher reoperation rates may in fact be associated with lower postoperative mortality rates[8]. Although on a patient level the association between reoperations and postoperative mortality is well established, little is known about the relation between reoperation rate and postoperative mortality rate at a hospital level.

This study aims to investigate the value of reoperation rates as a marker for quality of care in elective colorectal cancer surgery by exploring hospital variation, the presence of hospitals with significantly lower or higher reoperation rates than average (low and high outliers) and the association with postoperative mortality rates.

MATERIALS AND METHODS

Data

Data was derived from the Dutch Surgical Colorectal Audit (DSCA), a nationwide clinical registry and continuous quality improvement project in which a wide range of variables concerning patient and disease-specific details, diagnostics, treatment, and outcomes are collected prospectively. The dataset is disease-specific for colorectal cancer and shows a case ascertainment of >95% and high accuracy level on comparison against the Netherlands Cancer Registry (NCR) dataset[9,10].

Patients

For this study, no ethical approval or informed consent was required under Dutch law. All patients undergoing a surgical resection for primary colorectal cancer between the 1st of January 2009 and 31st of December 2012, and registered in the DSCA before March 15th 2013, were evaluated. Minimal data requirements to consider a patient eligible for analyses were information on tumor location, date of surgery, and mortality. In total, 35,749 patients were eligible.

Patients undergoing non-elective surgery (n=5546), local tumor excisions (n=393), and surgery for multiple synchronous colorectal tumors (n=1122) were excluded from analysis. The total number of patients diagnosed with stage I-IV colorectal cancer in the Netherlands during the study period was 52,046; increasing from 12,423 in 2009 to 13,408 in 2012[11].

Outcomes

Primary outcomes

Reoperations were defined as unplanned operations within 30 days from the primary operation. Postoperative mortality was defined as death within 30 days from the primary operation and/or during the index admission.

Statistical analysis

Categorical variables were compared using a chi-square test, and continuous variables using the independent samples t-test. A 2-sided $p \leq 0.05$ was considered statistically significant.

Potential, clinically relevant risk factors for adverse events were selected from the dataset and logistic regression models were employed to estimate expected outcomes. The variables age, gender, ASA score, Charlson comorbidity index, BMI, TNM stage, neoadjuvant therapy, type of index procedure and extended resections were incorporated in the model. Data were aggregated at a hospital level and observed-to-expected rates were multiplied with the average outcome in the study population in order to obtain casemix-adjusted outcomes for each hospital.

Hospital variation in adjusted reoperation rates is illustrated in a funnel plot, showing the overall average reoperation rate with its 95% confidence limits, based on a Poisson distribution, varying in relation to the population size. The funnel plot was used to identify hospitals with reoperation rates that were significantly higher or lower than the national average (high and low outliers, hospitals that are outside the 95% confidence limits). Hospitals were grouped accordingly (higher reoperation rate than average; lower reoperation rate than average; and the majority cohort with reoperation rates within the 95% confidence limits). Outcomes were compared between these groups.

Also after aggregating the data on a hospital level, comparison of outcomes between the three hospital groups was performed. This was done by applying the analysis of variance (ANOVA). Pairwise comparisons between the hospitals groups were carried out by using one-way multiple comparisons with Bonferroni correction. All statistical analyses were performed in PASW Statistics, version 20 (Chicago, IL, USA).

RESULTS

Some 28,667 patients undergoing elective colorectal cancer resections were included in the analysis. Patient characteristics are displayed in table 1. The average reoperation rate was 9.7%, ranging from 0.7% to 20.9% among the 92 hospitals.

Outlier hospitals concerning reoperation rates

Adjusted reoperation rates for all hospitals are shown in figure 1. Fourteen hospitals had adjusted reoperation rates that were higher than average (two hospitals had similar caseloads and reoperation rates and cannot be distinguished from each other in this figure). Twenty hospitals had adjusted reoperation rates that were lower

Table 1. Patient-, tumor- and treatment characteristics.

characteristic		n	%
gender	male	15,839	55.3%
Age	mean, SD	70	11
BMI	mean, SD	26	4.4
Charlson comorbidity index	0	15,584	54.4%
	1	6,295	22.0%
	2	3,954	13.8%
	3 or higher	2,834	9.9%
ASA score	I - II	22,314	77.8%
	III	5,687	19.8%
	IV - V	314	1.1%
	unknown	352	1.2%
TNM stage	X/missing	1,049	3.7%
	1	6,738	23.5%
	2	9,566	33.4%
	3	8,629	30.1%
	4	2,685	9.4%
tumor location	right colon	8,912	31.1%
	transverse/left colon	2,889	10.1%
	sigmoid colon	7,481	26.1%
	rectum	9,385	32.7%
neoadjuvant therapy	none	20,655	72.1%
	short course RT	4,390	15.3%
	CRT	3,014	10.5%
	other	608	2.1%
procedure	ileocecal resection	233	0.8%
	right hemicolectomy	8,937	31.2%
	transverse colectomy	574	2.0%
	left hemicolectomy	1,791	6.2%
	LAR/sigmoid colectomy	13,212	46.1%
	subtotal colectomy	396	1.4%

Table 1. Patient-, tumor- and treatment characteristics. (continued)

characteristic		n	%
	APR	2,923	10.2%
	panproctocolectomy	163	0.6%
	other	438	1.5%
extended resection	locally advanced tumor	2,419	8.4%
	metastasectomy	849	3.1%

BMI: body mass index; SD: standard deviation; ASA: American Society of Anesthesiologists; TNM: tumor, node metastasis classification (5th edition); RT : radiotherapy; CRT: chemoradiotherapy; LAR: low anterior resection; APE: abdominoperineal resection

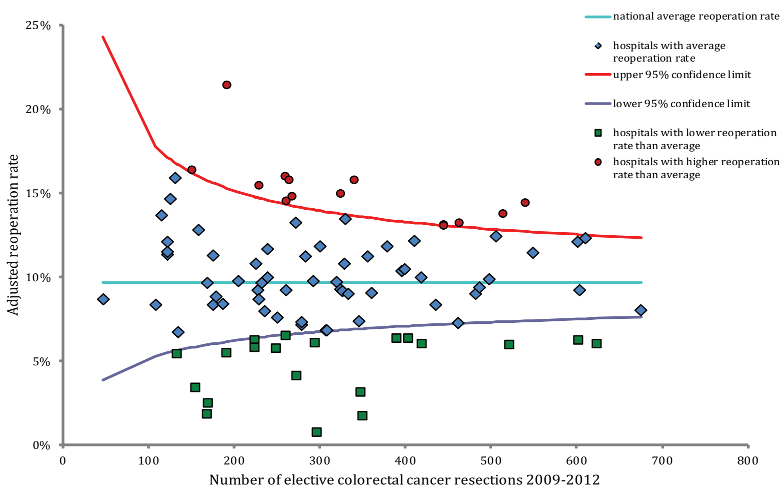

Figure 1: Funnel plot of risk-adjusted reoperation rates in 92 hospitals in the Netherlands

Table 2. stoma rates and outcomes for patients operated in hospitals with high, average and low reoperation rates (as identified in figure 1). * percentage in relation to all patients in the group ** percentage in relation to all re-interventions (reoperations and percutaneous re-interventions)

		High reoperation rates	**Average reoperation rates**	**Low reoperation rates**	**p**
patients		4691	17410	6566	
anastomosis	without fecal diversion	3012 (65.4%)	11298 (67.2%)	4321 (66.8%)	0.094
	with fecal diversion	678 (14.7%)	2232 (13.3%)	899 (13.9%)	
	no anastomosis	914 (19.9%)	3279 (19.5%)	1246 (19.3%)	
reoperations	any	685 (14.6%)	1743 (10%)	350 (5.30%)	<0.001
anastomotic leak		325 (6.9%)	831 (4.8%)	158 (2.4%)	<0.001
bleeding		35 (0.7%)	98 (0.6%)	25 (0.4%)	0.034
ileus		75 (1.6%)	164 (0.9%)	37 (0.6%)	<0.001
fascial dehiscence		82 (1.7%)	194 (1.1%)	42 (0.6%)	<0.001
iatrogenic bowel injury		23 (0.5%)	62 (0.4%)	9 (0.1%)	0.003
bladder/urethral injury		6 (0.1%)	17 (0.1%)	2 (0%)	0.171
other		98 (2.1%)	291 (1.7%)	62 (0.9%)	<0.001
negative relaparotomy		12 (0.3%)	14 (0.1%)	3 (0.0%)	<0.001
postoperative mortality		160 (3.4%)	559 (3.2%)	155 (2.4%)	0.001
percutaneous reinterventions *		92 (2.0%)	206 (1.2%)	74 (1.1%)	<0.001
proportion of percutaneous reinterventions**		92/777 (11.8%)	206/1945 (10.6%)	74/424 (17.6%)	<0.001
blood transfusion postoperatively		658 (14.8%)	2540 (15.8%)	684 (11.5%)	<0.001
length of stay	> 14 days	981 (21.2%)	3430 (20.1%)	1023 (15.8%)	<0.001

than average. The remaining hospitals had reoperation rates that were within the 95% confidence limits (the 'majority cohort').

Table 2 compares outcomes between the groups (high and low rates and the majority cohort as identified in the funnel plot in figure 1). As reoperation rates may be influenced by the construction of a an anastomosis and/or a defunctioning stoma, anastomosis- and stoma rates are displayed as well. The proportion of patients receiving an unprotected primary anastomosis, an anastomosis with a diverting stoma, or an end-colostomy did not differ significantly between the groups. The majority cohort had slightly but significantly lower rates of laparoscopically completed procedures.

Most reoperations were performed for anastomotic leaks. For all indications except bladder- or urethral injury, reoperation rates were different between the groups. The number of registered negative reoperations was very small, but did differ between the groups and was highest in the group with high reoperation rates.

Postoperative mortality

Unadjusted postoperative mortality rates were 3,4% in hospitals with high reoperation rates, 3,2% in the majority cohort and lower (2,4%) in hospitals with lowest reoperation rates. Figure 2 displays postoperative mortality rates, adjusted for case-mix, for the three hospital groups, based on the aggregated data on a hospital level. The group of hospitals with high reoperation rates had an adjusted mortality rate of 3,5%. The majority cohort had an adjusted postoperative mortality rate of 3,2% and the group with low reoperation rates had an adjusted postoperative mortality rate of 2,3%. The ANOVA showed a significant difference between the groups ($p=0.009$). The group with low reoperation rates had significantly lower mortality rates than the group with high reoperations ($p=0.022$), and also than the majority cohort ($p=0.019$). Mortality rates were not significantly

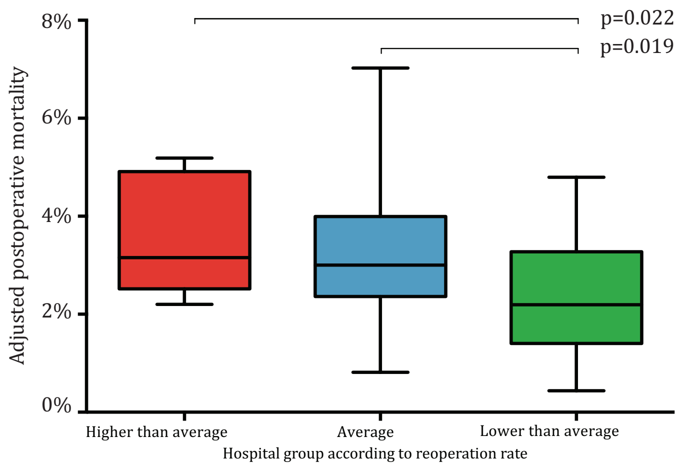

Figure 2: Risk-adjusted postoperative mortality in hospitals grouped according to reoperation rates (higher than average, average and lower than average). P values are derived from one-way multiple comparisons with Bonferroni correction.

different when comparing hospitals with high reoperation rates and the majority cohort.

Postoperative mortality: individual hospitals

The funnel plot in figure 3 displays postoperative mortality rates, adjusted for casemix, for all 92 hospitals marked with different colours corresponding with high or low reoperation rates or the majority cohort. It shows a variation between 0,5% and 7% postoperative mortality around the average of 3%. Figure 2 showed that the hospitals with low reoperation rates have lowest mortality rates when compared as groups of hospitals, figure 3 shows that individual hospitals with low reoperation rates had mortality rates that were higher than some hospitals with high reoperation rates. Also, some hospitals with high reoperation rates had postoperative mortality rates that

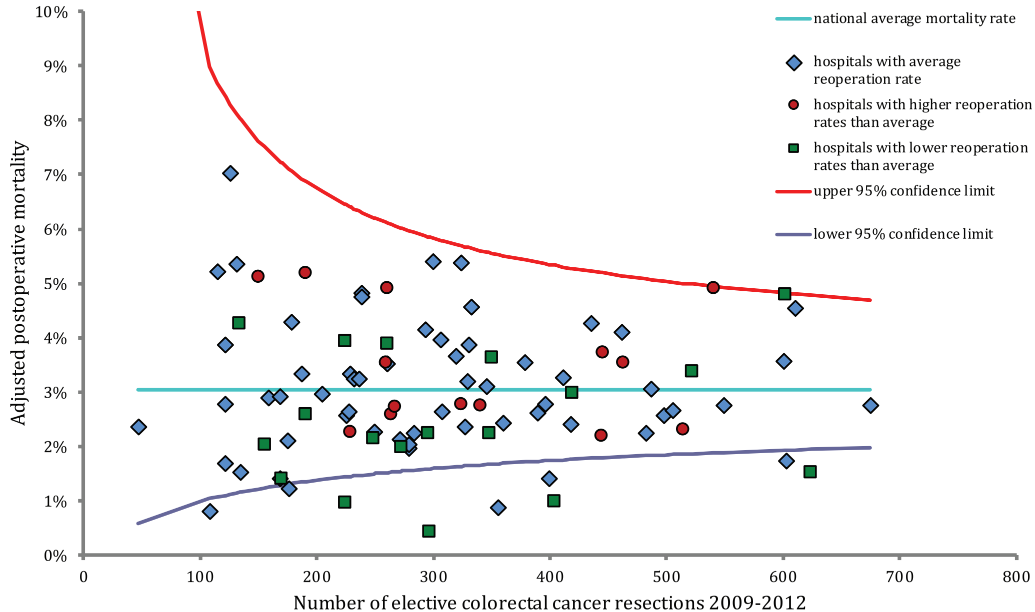

Figure 3: Funnel plot for risk-adjusted postoperative mortality rates. Hospitals are marked according to reoperation rates (higher than average, average and lower than average).

were as low as 2%. Nine hospitals had postoperative mortality rates that were significantly lower than average, 5 of which were hospitals with reoperation rates within the 95% confidence limits.

The low reoperation group also had significantly lower rates of percutaneous re-interventions than the other groups (table 2). However, the ratio between percutaneous re-interventions and all re-interventions (reoperations and percutaneous procedures altogether) was significanlty higher in the low reoperation group, with 17.6% of all re-interventions being a percutaneous procedure.

The high reoperation group had a relatively high percentage of laparoscopy in case of a reoperation (10.7% of all reoperations, vs. 6.0 and 6.6% in the majority cohort and the low reoperation rate groups).

DISCUSSION

This study evaluated the value of reoperation rates as a marker of surgical quality of care in colorectal cancer surgery. A large hospital variation was found, with many hospitals having significantly higher or lower reoperation rates than the national average. The group of hospitals with high reoperation rates had similar outcomes as the majority cohort with reoperation rates within the 95% confidence limits. The group of hospitals with low reoperation rates had a lower rate of postoperative mortality. However, when comparing all hospitals on an individual basis, lower reoperation rates than average could go together with relatively high mortality rates, although no hospitals had mortality rates that were significantly higher than average. Merkow et al., analyzing over 20,000 elective colorectal surgery cases from the American College of Surgeons NSQIP dataset, found a large hospital-by-hospital variation (ranging from 0% to

38%) in reoperation rates with the presence of many high and low outlier institutions[12]. Because of this hospital variation, the authors conclude that reoperation rates are valuable as mirror information for institutions participating in a quality improvement project. Burns et al. report national reoperation rates after colorectal resections in England derived from the Hospital Episode Statistics database[7]. These authors found a large variation in reoperation rates between hospitals/trusts, using a database with various pathologies and indications for colorectal resections, both emergent and elective. One study demonstrated the correlation between reoperation- and mortality rates after colorectal resections on a hospital level[13]. This study found a weak correlation between reoperation rate and mortality rate on the whole. Importantly, for individual hospitals the performance on reoperation rate could be the exact opposite of the performance on postoperative mortality: one high mortality outlier trust had a lower reoperation rate than average and one low mortality unit had a reoperation rate above the 2 standard deviation limit.

Our study builds on these publications, confirming the large hospital variation and the presence of outlier institutions. We showed that lower reoperation rates than average are, on the whole, associated with a lower postoperative mortality. However, hospitals with higher reoperation rates than the national average perform similarly to the institutions with average reoperation rates when it concerns postoperative mortality. We confirm the findings of Almoudaris et al[13] that group outcome patterns do not apply to all individual hospitals in the group (in this case, reoperation rate outlier status).

The 30-day reoperation rate we found in this study is relatively high when compared to the rates in the abovementioned American and English cohorts. Differences in patient populations may prohibit direct comparison, however the reoperation rate of 5.9% in the subset of elective colorectal cancer resections that Burns et al. describe still compares favourably to the 9.7% we found. The single-centre series of van Westereenen et al., reporting a 12.5% reoperation rate, is the only publication from the Netherlands we can use as a reference, but this study included benign indications as well[14]. Perhaps the differences between our findings and the English publication reflect differences between a clinical registry and administrative data.

The present study focused on elective surgery. We also did a sub analysis on the patients undergoing urgent/emergency resections (n=5546). In this group, the reoperation rate was slightly higher than in the elective group (12.2% vs 9.8%), but postoperative mortality was three times higher in this group (9.3% vs 3%). Although hospital variation in reoperation rates and mortality rates proved wide (reoperations: range 0-27%; mortality: range 0-29%), it is hard to draw conclusions concerning individual hospital performance and correlation between each other, as numbers break down quickly and confidence intervals become extremely wide in this relatively small cohort. Future research on a larger (international) database may focus on this subject.

There are some limitations to this study. The data is self-reported, so selection bias cannot be completely excluded. However, the dataset is highly detailed and validated against data from the Netherlands Cancer registry. Moreover, the relatively high registered reoperation rates do not suggest under-reporting of this outcome. Unfortunately, our database only contains information concerning patients who underwent surgical resection of colorectal cancer. The percentage of patients selected for surgery may vary per region or hospital. In future research, requiring linkage of Cancer Registry data to Audit data, it would be interesting to study whether differences in the preoperative selection process are related to the found variation in outcomes.

Another limitation concerns the risk adjustment. The DSCA dataset was designed with the objective of performing adjustment for differences in casemix between hospitals, and relevant risk factors were included in the dataset at an early stage of development of the dataset based on a Delphi method by an expert panel[15,16]. The included variables are therefore mainly risk factors for mortality which may or may not be the same as risk factors for reoperations- although from a clinical point of view they seem relevant for this outcome, too, and compare with the confounders adjusted for in other publications[6,7,12,17]. Although adjustment was made for many variables, a large variation in outcomes between hospitals remains after adjustment; which may be due to true differences in performance as well as possible limitations of the adjustment model. Thirdly, we conclude that high outliers have mortality rates similar to hospitals with reoperation rates within the 95% confidence limits. This only concerns 30-day and/or in-hospital mortality, whereas reoperations may be associated with a higher risk of 1-year mortality[14]. It is unknown to what extent hospital reoperation rates correlate with longer-term mortality rates.

Hospitals with lowest reoperation rates had a relatively high rate of percutaneous reinterventions compared to the two other groups. This may be due to less severe complications or due to other factors such as improved radiological support or a better selection for percutaneous solutions for surgical complications in these hospitals.

"Reoperation" is a measure that reflects many factors in the postoperative process. There are, however, no guidelines concerning return to the operating room. Decisions regarding postoperative management remain at the surgeon's discretion and surgeons may differ in their threshold for performing a reoperation on a patient with a suspected surgical complication. As a timely reoperation may be an effective measure to rescue a patient with a postoperative complication, a low threshold for a reoperation is not necessarily a reflection of a low quality of surgical care. A problem that may be associated with this outcome, is that the threshold for reoperation may rise when it is being used as an outcome indicator. For the individual patient, it may have dramatic results when the surgeon does not re-operate or waits too long, as a timely intervention may result in better outcomes[18]. Our study shows that some individual hospitals with high reoperation rates have relatively low postoperative mortality rates, well below the national average. Some majority cohort hospitals even had mortality rates that were significantly lower than average. Apparently, the surgical teams in these hospitals have a good ability to rescue patients with a surgical complication. On the other hand, a high reoperation rate puts a low mortality rate in perspective: clearly the low mortality comes at a high cost. Conversely, some hospitals with significantly lower reoperation rates than the national average had quite high postoperative mortality rates. Best practice should be sought in hospitals with both low reoperation and mortality rates. Another valuable outcome indicator relating to both complications and postoperative mortality is "failure to rescue (FTR)", defined as the mortality rate among patients with a serious complication[19]. Almoudaris et al. introduced the outcome measure "failure to rescue-surgical (FTR-S)" : the mortality among patients that underwent a reoperation[20], reflecting the ability of a surgical team to effectively manage surgical complications. They found that high-mortality hospitals were characterized by high FTR-S rates rather than high reoperation rates. For the DSCA, FTR is defined as the mortality rate among patients with a serious complication (leading to a reintervention or a prolonged in-hospital stay)[21]. Regardless of the definition, such a FTR measure takes away possible hesitations to intervene in case of a surgical complication, as a successful intervention will merely lower

FTR rates. In our opinion, this is an important outcome measure to consider alongside the outcome indicator reoperation rate.

In conclusion, the results of this study show a wide hospital variation in reoperation rates after colorectal cancer resections in the Netherlands. Although several high outlier institutions could be identified, this could not be linked to worse mortality rates. Conversely, hospitals with low reoperation rates did perform better on other outcomes and it can be concluded that the outcome is suitable as feedback information to hospitals in quality improvement projects but not to stigmatize hospitals with high reoperation rates as poor performers. Best practices with regard to clinical outcomes should be identified as hospitals with both low reoperation rates and low mortality rates.

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CHAPTER 5

Hospital variation in failure to rescue after colorectal cancer surgery: results of the Dutch Surgical Colorectal Audit

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ABSTRACT

Background: Postoperative mortality is frequently used in hospital comparisons as marker for quality of care. Differences in mortality between hospitals may be explained by varying complication rates. A possible modifying factor may be the ability to let patients with a serious complication survive, referred to as *failure to rescue (FTR).*

Purpose of this study is to evaluate how hospital performance on postoperative mortality is related to severe complications or to FTR and to explore the value of FTR in quality improvement programs.

Methods: All patients operated for colorectal cancer from 2009-2011, registered in the Dutch Surgical Colorectal Audit, were included. Logistic regression models were used to obtain adjusted mortality- complication- and FTR rates. Hospitals were grouped into 5 quintiles according to adjusted mortality. Outcomes were compared between quintiles.

Results: 24 667 Patients were included. Severe complications ranged from 19% in the lowest to 25% in the highest mortality quintile (OR=1,5; 95% CI 1,37-1,67). Risk-adjusted FTR rates showed a marked difference between the quintiles, ranging from 9 to 26% (OR=3.0; 95% CI 2,29-3,98). There was significant variability in FTR rates. Seven hospitals had significantly lower FTR rates than average.

Conclusions: High-mortality hospitals had slightly higher rates of severe complications than low-mortality hospitals. However, FTR was three times higher in high-mortality hospitals than in low-mortality hospitals. In quality improvement projects, feedback to hospitals of FTR rates- along with complication rates- may illustrate shortcomings (*prevention* or *management* of complications) per hospital, which may be an important step in reducing mortality.

INTRODUCTION

Increasingly, society focuses on effectiveness and efficiency in healthcare, and differences in hospital performances have become subject to research. Recent studies have shown great differences in hospital (surgical) mortality rates[1,2] even after adjustment for differences in case-mix[3]. One of the explanations of these differences is sought in the handling of postoperative complications, eg. '*failure to rescue*' (FTR).

The term, introduced by Silber et al.[4] is defined as "the mortality rate among patients with complications". These authors found that hospital rankings based on adjusted complication rates did not correlate with rankings based on adjusted mortality rates. Ghaferi et al. defined FTR as "mortality among patients with serious complications" and found that hospitals with high mortality rates had higher FTR rates rather than higher complication rates[5-7]. Almoudaris et al. introduced the term "failure-to-rescue-surgical", defined as death among patients that underwent reoperation. These authors found that hospitals with high mortality rates had higher death rates among patients that underwent reoperation after colorectal surgery, while reoperation rates were the same in high- and low-mortality hospitals[8].

Colorectal surgery is considered high-risk surgery as it brings along a relatively high risk of complications. Patients that experience a complication have a substantial increase in risk of dying[9]. Hence, mortality and complication rates are considered important outcome measures in colorectal surgery.

Many publications on FTR used administrative data, in which the risk of identifying preoperative conditions as a postoperative complication is substantial[10,11]. The valuable insight into "failure to rescue" that the publication based on the National Surgical Quality Improvement Program (NSQIP) clinical dataset provided, lacked details on procedure-specific complications such as anastomotic leak[5]. After the example of the NSQIP and other international audits, in 2009 the Dutch Surgical Colorectal Audit (DSCA) was introduced[12], in which approximately 95% of patients undergoing surgery for colorectal cancer in the Netherlands are included. By clarifying the hospital variation of FTR on a national level, its potential value in quality improvement programs is explored.

The aims of this study are to evaluate:

1. to what extent mortality rates after colorectal surgery vary between Dutch hospitals, when adjusted for casemix
2. whether, and to what extent, hospitals with higher mortality rates have higher severe complication rates
3. whether, and to what extent, hospitals with higher mortality rates have higher FTR rates
4. the variability in FTR after colorectal surgery between Dutch hospitals and the presence of positive and negative outliers

METHODS

Data was derived from the DSCA, a national quality improvement project in which over 200 variables concerning patient and tumor characteristics, treatment, and outcomes are collected prospectively. All 92 hospitals performing colorectal cancer surgery participate. The dataset shows a high level of completeness on most items, including anastomotic leakage on validation against the National Cancer Registry (NKR) dataset[13,14]. Information concerning individual patients and hospitals are made anonymous, making it possible to compare hospitals without identifying them.

Patients

For this study, no ethical approval or informed consent was required under Dutch law.

All patients (n=26 410) undergoing surgical resection for primary colorectal cancer between the 1st of January 2009 and 31st of December 2011, and registered in the DSCA before March 15th 2012, were evaluated.

Minimal data requirements to consider a patient eligible for analyses were information on tumor location, date of surgery, complications and mortality (25 591 eligible patients). To minimize the risk of selection bias, patients from hospitals that failed to register more than 10 patients in a year were excluded (36 patients from nine hospitals in 2009, none in 2010 and 2011). To analyze a clinically homogenous patient cohort, patients with multiple synchronous tumors (n=888) were excluded.

From the subset of patients operated in 2011 (n=8885), a detailed description of both surgical and non-surgical complications was available.

Mortality

The definition of mortality is shown in panel 1. Potential patient- and disease-specific risk factors (casemix) for mortality were selected from the dataset. The methods used to calculate the expected mortality have been described in an earlier publication by the Dutch Surgical Colorectal Audit group[3]. In univariate analysis, categorical variables were compared by χ^2 tests, while 2-sample *t* tests were used for continuous variables. A 2-sided $P \leq 0.05$ was considered statistically significant, but casemix factors were selected for multivariate analysis when reaching a significance of $p<0.10$. Backward stepwise logistic regression models were employed to estimate the final model and calculate expected rates of mortality. The casemix factors age, sex, American Society of Anesthesiologists (ASA) classification, Charlson co-morbidity index, body mass index (BMI), emergency surgery, tumor location, preoperative complications from the tumor, oncologic stage and neoadjuvant therapy proved to be contributing to the correction model. Data were aggregated on hospital level and observed-to-expected rates were multiplied with the average mortality in the study population in order to obtain casemix-adjusted mortality rates. Hospitals were grouped into five equally sized, risk-adjusted quintiles of mortality according to previous publications[5,8].

Severe complications

With the same methods, adjusted severe complication (see panel 1 for definitions) rates were calculated for each hospital. The casemix factors sex, ASA classification, Charlson co-morbidity index, BMI, emergency surgery, tumor location, pre-operative complications, oncologic stage and additional resections for extended disease were significant contributors to the model. Adjusted severe complication rates were compared between the mortality quintiles.

Failure-to-rescue

For FTR, the casemix factors age, sex, ASA score, Charlson co-morbidity index, emergency surgery, oncological stage and neoadjuvant therapy contributed to the model. Adjusted FTR rates were compared between the mortality quintiles.

Hospital variation and outliers in FTR

A mixed logistic regression model with hospitals as random effects was employed to account for the presence of variability between hospitals.

The fixed effects predictors in the model are the same as employed in the first model for FTR described before. The variance in the random effects model quantifies the degree of variation in the outcome between hospitals after adjustment for case mix. The likelihood ratio test was used to assess whether the variance of the random effect was significant.

The adjusted FTR rates per hospital are presented in a funnel plot, showing the overall average FTR rate with its 95% confidence limits, based on a Poisson distribution, varying in relation to the population size. The plot allows to identify hospitals with FTR rates that are significantly higher or lower than average.

Statistical analyses were performed in PASW Statistics, Rel. 20.0.2012 (SPSS inc., Chicago, Il) and R 2-14 (http://cran.r-project.org/).

RESULTS

Patient characteristics

A total of 24 667 patients, registered by 92 hospitals met the inclusion criteria and were included in the study. Hospitals were grouped according to adjusted mortality rates and the total group of hospitals was divided into quintiles. Patient characteristics are displayed in table 1. There was no evidence of systematic differences in case mix across hospital quintiles, as reflected by quite similar overall expected rates of death per quintile, based on casemix. Average mortality was 4.3% and the percentage of patients with a severe complication was 23%.

Table 1: Patient characteristics by risk-adjusted-mortality quintile

Mortality Quintile		**1st**	**2nd**	**3rd**	**4th**	**5th**
Number of patients		4841	4879	5134	4988	4825
Number of hospitals		20	18	16	19	18
Sex	Males (%)	2632 (54.4%)	2677 (54.9%)	2810 (54.7%)	2769 (55.5%)	2625 (54.4%)
Age	mean	69.2	69.9	69.8	69.8	69.8
Body Mass index	kg/m^2, mean	25.9	26.2	25.9	25.9	26.2
Charlson co-morbidity index	2 or higher	1083 (22.4%)	963 (19.7%)	1260 (24.5%)	1155 (23.2%)	1129 (23.4%)
Pathological TNM stage	X	137 (2.8%)	174 (3.6%)	195 (3.8%)	140 (2.8%)	243 (5.0%)
	I	1013 (20.9%)	1042 (21.4%)	989 (19.3%)	1048 (21.0%)	957 (19.8%)
	II	1638 (33.8%)	1538 (31.5%)	1804 (35.1%)	1668 (33.4%)	1562 (32.4%)
	III	1478 (30.5%)	1544 (31.6%)	1602 (31.2%)	1515 (30.4%)	1508 (31.3%)
	IV	575 (11.9%)	581 (11.9%)	544 (10.6%)	617 (12.4%)	555 (11.5%)

Table 1: Patient characteristics by risk-adjusted-mortality quintile (continued)

Mortality Quintile		**1st**	**2nd**	**3rd**	**4th**	**5th**
Number of patients		4841	4879	5134	4988	4825
Number of hospitals		20	18	16	19	18
Procedure	ileocaecal resection	53 (1.1%)	44 (0.9%)	44 (0.9%)	65 (1.3%)	52 (1.1%)
	right hemicolectomy	1509 (31.2%)	1512 (31.0%)	1577 (30.7%)	1608 (32.2%)	1541 (31.9%)
	transverse colectomy	100 (2.1%)	117 (2.4%)	113 (2.2%)	92 (1.8%)	128 (2.7%)
	left hemicolectomy	358 (7.4%)	330 (6.8%)	383 (7.5%)	372 (7.5%)	316 (6.5%)
	sigmoid colectomy/low anterior resection	2283 (47.2%)	2102 (43.1%)	2117 (41.2%)	2202 (44.1%)	2079 (43.1%)
	subtotal colectomy	39 (0.8%)	22 (0.5%)	194 (3.8%)	28 (0.6%)	65 (2.3%)
	abdominoperineal resection	387 (8.0%)	374 (7.7%)	520 (10.2%)	450 (9.0%)	450 (9.4%)
	panproctocolectomy	28 (0.6%)	19 (0.4%)	48 (0.9%)	48 (1.0%)	47 (1.0%)
	other	84 (1.7%)	359 (7.4%)	138 (2.7%)	123 (2.5%)	147 (3.0%)
Urgency of the procedure	urgent/emergency	680 (14.0%)	742 (15.2%)	819 (16.0%)	837 (16.8%)	663 (13.7%)
Approach	laparoscopic	1891 (39.1%)	1822 (37.3%)	2270 (24.2%)	1418 (28.5%)	1798 (37.3%)
Mortality	Expected (based on casemix)	4.0%	4.3%	4.3%	4.3%	4.1%

Mortality

After adjustment for casemix, a marked variation in mortality rates between hospitals was observed ranging from 1 to 9 %. Figure 1 shows the hospitals grouped in risk-adjusted mortality quintiles (left series).

Each quintile represents a group of hospitals with a different (adjusted) mortality rate, the first mortality quintile having the lowest casemix-adjusted mortality (2 %), with adjusted mortality increasing stepwise per quintile to 6.6% in the 5th (highest) quintile. The OR for mortality of the highest quintile was 3,5 (95% confidence interval 2,79 – 4,54; p<0,001) compared to the lowest quintile. The other

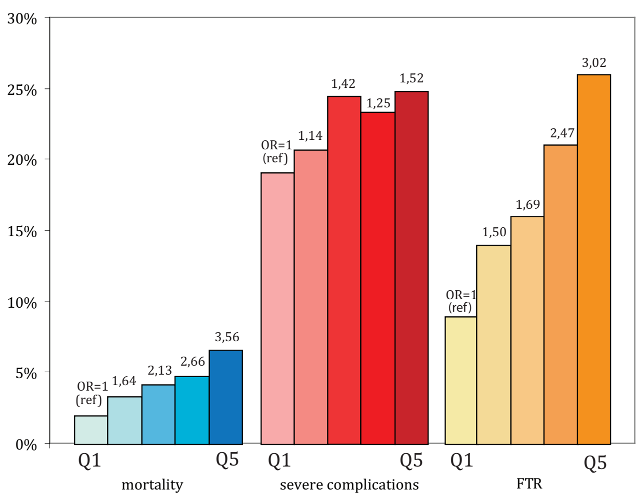

Figure 1: risk-adjusted mortality, severe complication, and FTR rates per quintile. Odds ratios are given, compared to quintile 1 (reference). RR=relative risk; Q= mortality quintile; FTR= failure to rescue

quintiles had significantly higher adjusted mortality rates than the first quintile as well.

Severe complications

An increase in adjusted percentage of patients with a severe complication was observed when comparing the lowest to the highest mortality quintile (figure 1, middle series). The percentages ranged from 19% in the lowest to 25 % in the highest mortality quintile- with the OR for severe complications of the highest being 1,5 (95% confidence interval 1,37 – 1,67; $p<0,001$) compared to the lowest quintile. The

Table 2: details of the severe complications in the subset of patients operated in 2011.

Total no. of patients (2011)		**8885 (100%)**
Any severe complication		1882 (21,2%)
Surgical complications		
	anastomotic leak	440 (5,0%)
	intra-abdominal abcess	139 (1,6%)
	postoperative haemorrhage	51 (0,5%)
	ileus	106 (1,2%)
	fascial dehiscence	99 (1,1%)
	iatrogenic bowel injury	34 (0,4%)
	iatrogenic injury to ureter/bladder	11 (0,1%)
	other	187 (2,1%)
General complications		
	Pulmonary	415 (4,6%)
	Cardiac	222 (2,4%)
	Thrombo-embolic	45 (0,5%)
	Septic/infectious (non-pulmonary, non-surgical)	216 (2,4%)
	Neurologic	74 (0,8%)
	Other	367 (4,1%)

other quintiles had significantly higher adjusted severe complication rates than the lowest quintile as well.

Details of the severe complications in the subset of patients operated in 2011 are displayed in table 2.

Failure-to-rescue

The OR of FTR in the highest mortality quintile was 3.0 (95% confidence interval 2,29 – 3,97, p<0.001) compared to the lowest mortality quintile, with an incremental increase per quintile (figure 1, right series). The difference in FTR rate was also significant for the other quintiles when compared to the lowest quintile.

Hospital variation and outliers

The variance in the random effects model quantified the degree of variation in FTR between hospitals; this was 0.09 with a standard error of 0.038. A likelihood ratio test showed that the variance of the random effects was statistically significant.

Figure 2 shows that the adjusted FTR rates of the 92 hospitals varied between 0 and 39%. For 85 hospitals (92%), results were within the 95%-confidence limits of the average. Seven hospitals showed statistically significant lower percentages than average. Each hospital is colored according to mortality quintile: the hospitals in the lower mortality quintiles fill the lower regions of the funnel plot, and the hospitals in the higher mortality quintiles are displayed on the higher part of the funnel plot.

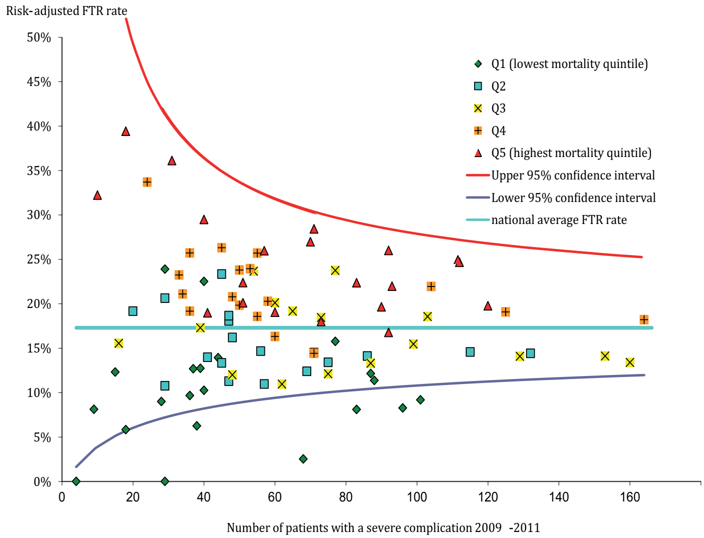

Figure 2: funnel plot showing differences in risk-adjusted failure to rescue (FTR) rates between hospitals

DISCUSSION

Colorectal surgery is not without adverse events. This study acknowledges the fact that postoperative casemix-adjusted mortality rates after colorectal surgery vary by hospital. Our study shows that higher mortality rates seem to be only partially explained by higher rates of severe complications: the 1,5-fold increase in severe complication rate seems insufficient to explain the 3-fold increase in mortality between the first and fifth quintile. Failure to rescue seems to play a role as modifying factor, with a vast increase in failure to rescuebetween the lowest and highest mortality quintile. Moreover, we demonstrated that there was variability in FTR between individual hospitals, after adjusting for casemix.

High- and low-mortality hospitals were distinguished by their ability to treat and save patients with severe complications. These findings are consistent with recent literature[5-8].

Our study adds that in a specific, homogeneous group of surgical procedures, colorectal cancer surgery, failure to rescue plays an important role in explaining the variability in hospital mortality. The dataset we used was disease-specific and did, unlike some other studies, include anastomotic leak. Therefore we were able to accurately characterize the impact of failure to rescue on mortality in patients that underwent colorectal surgery. Secondly, this paper is the first from the European continent that describes hospital variation in FTR, whereas most publications concerning FTR originate from the United States[4-7] or United Kingdom[8]. Despite differences in health care systems, FTR seems to be the main determinant of differences in hospital mortality after colorectal surgery in populations from different countries. Moreover, we found that FTR rates vary significantly between hospitals, with some hospitals having a significantly lower FTR rate than average ("best practices").

The study has some limitations. Firstly, since data are self-reported, registration bias cannot be excluded. However, the dataset is validated against the independently collected data of the Dutch National Cancer Registry, showing a very high rate of case-ascertainment, completeness and accuracy in terms of patient demographics, tumor stage, comorbidity, treatment and mortality[14]. The dataset consists of detailed, prospectively collected clinical data, registered by or under direct responsibility of colorectal surgeons. This avoids the problem that the use of administrative data brings along: difficulties in correctly distinguishing a comorbid illness from a postoperative complication[11].

The definition of a severe complication used in this study is arbitrary but it is believed to exclude the minor complications such as simple urinary tract infections or minor wound problems not hindering the postoperative course. However, it cannot be ruled out that some patients with a minor complication, who spent more than 14 days in the hospital due to other reasons, were incorrectly identified as having a severe complication. On the other hand, with the definition used in this study, a small number of mortality cases were not covered by our definition of a severe complication. Therefore we performed additional analyses using alternative definitions of severe complications (1. with all mortality cases included in the "severe complication" measure; 2. with exclusion from the data set of the 62 mortality cases with no postoperative complication), showing very similar results. However, the severity of illness associated with complications like anastomotic leak may vary widely. These differences may level out in larger groups of patients treated per hospital. However, we cannot exclude that differences in severity of complications between hospitals may have influenced the variation in FTR rates.

A possible form of bias may have emerged from complicated patients transferred to another hospital, dying after transfer. However, as a minimum of facilities (e.g. ICU) is mandatory for hospitals performing colorectal surgery in the Netherlands, patients with complications are rarely transferred. In this uncommon situation the mortality is ascribed to the hospital that performed the initial operation.

A drawback of using FTR is that it is a short-term outcome, whereas patients that experienced a complication following colorectal surgery are known to have a higher risk of mortality up to a year after the procedure[15-17]. The post-discharge period may be just as important as the immediate postoperative period, when aiming at improving mortality rates.

Nonetheless, the hospital variation in FTR rates may reflect differences in the postoperative care process. What these differences are, is beyond the scope of this study. Probably, FTR is affected by many factors including the usual postoperative care at each hospital, availability of resources like interventional radiology or a high level of Intensive Care facilities, staffing factors and equipment. Suggested factors related to FTR are nurse-to-patient ratios[18-19], high-technology status of a hospital (i.e., does the hospital perform organ transplant surgery open-heart surgery)[19], higher case-volume[6] and teaching status[6]. Probably as important as these structural factors are preoperative risk-assessment and appropriate case-selection, multidisciplinary treatment of patients with comorbid illnesses and timely recognition of complications. An active surveillance protocol has been shown to reduce the delay in diagnosis of anastomotic leak[20]. Whether the hospitals with lower FTR rates had a shorter delay between the onset of symptoms and the start of treatment of the complication is unknown and should be subject of further research- ideally not only focusing on anastomotic leakage but also on non-surgical complications. In the context of quality improvement, feedback of complications and FTR rates to hospitals illustrates shortcomings (*management* or *prevention* of complications), allowing targeted improvement efforts. Based on the results of this study, the DSCA started using FTR as feedback information to participating hospitals, enabling surgeons to evaluate detection and treatment of complications. Best practices can be identified and knowledge can be shared between surgical teams from different hospitals.

In conclusion, although the incidence of severe postoperative complications differed slightly across mortality quintiles, the adjusted rate of death in patients with a severe complication (failure to rescue) was markedly higher in hospitals with higher overall mortality. The chance that a patient dies once a severe complication has emerged was three times higher in a high-mortality hospital than in a low-mortality hospital. FTR rates show a wide, significant variation between hospitals, with seven hospitals having a significantly lower FTR rate than average. More research is needed to identify the underlying mechanisms and structural factors that account for differences in FTR rates between hospitals.

DEFINITIONS

Severe complication: a complication leading to a surgical, endoscopic or radiological reintervention or to a in-hospital stay of more than 14 days, or to death.

Mortality: A patient that died within 30 days after the operation or within the same admission.

Failure to rescue: The percentage of patients with a severe complication that dies. (Number of patients that died secondary to a severe complication) / (total number of patients that experienced a severe complication)

Panel 1: definitions used in the current study

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CHAPTER 6

Failure to rescue after colorectal cancer surgery and the association with three structural hospital factors

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ABSTRACT

Background: Evidence suggests that a large hospital variation in failure to rescue (FTR) in colorectal surgery is causing hospital differences in mortality rates. Which structural hospital factors are associated with better FTR rates remains largely unclear. The purpose of this study is to evaluate the association between FTR and hospital volume, teaching status and level of Intensive Care facilities, in colorectal cancer surgery.

Methods: All patients undergoing colorectal cancer surgery from 2009 through 2011 in 92 Dutch hospitals were analysed. Univariate and multivariate logistic regression models including casemix, hospital volume, teaching status and different levels of ICU facilities were used to analyse risk-adjusted FTR rates.

Results: 25591 patients from 92 hospitals were included. The average failure-to-rescue rate was 17% [0-39]. In univariate analysis, high hospital volume (>200 patients/year versus <=200/year), teaching status (academic versus teaching versus non-teaching hospitals) and high level of ICU facilities (highest level 3 versus lowest level 1) were associated with lower FTR rates. Only the higher levels of ICU facilities (2 or 3 compared to level 1) were independently associated with lower FTR rates (OR 0.72 (95% CI 0.65 – 0.88) in multivariate analysis.

Conclusions: Hospital type and annual hospital volume were not independently associated with FTR rates in colorectal cancer surgery. Instead, the lowest level of ICU facilities was independently associated with higher rates. This suggests that a more advanced ICU may be an important factor that contributes to better FTR rates, although individual hospitals perform well with lower ICU levels.

INTRODUCTION

Hospital differences regarding quality of care have received much attention in recent years. Complications and mortality are outcomes frequently used to compare hospital performance in colorectal cancer surgery. *Failure to rescue* (FTR) is another outcome measure that indicates the ability of a surgical team to keep patients alive when severe complications occur. The term, introduced by Silber et al.[1] is defined as "the mortality rate among patients with complications". These authors found that hospital rankings based on complication rates did not correlate with rankings based on mortality rates. Recent literature suggests that high hospital mortality after colorectal surgery is best explained by higher FTR rates rather than by higher complication rates[2,3]. Hence it may be considered an outcome that is actionable, reflecting the ability of a surgical team to timely recognize and treat major complications once they emerge.

The fact that higher FTR rates, and not higher complication rates are the main determinant of higher mortality rates was recently confirmed by the Dutch Surgical Colorectal Audit (DSCA) group[4]. Dutch hospitals showed variability between 0 and 40% in FTR rates. It remains largely unclear which factors account for this variation. Some potential factors have been suggested. Surgical teams may vary in the ability to adequately and timely recognize and treat postoperative complications by differences in expertise, experience with the procedure, and by more advanced resources.

The number of procedures performed annually, might be a proxy for the experience of a surgical team with a specific procedure and its perioperative care. Increasing hospital volume is associated with better outcomes in many surgical procedures including colorectal surgery[5]. An American study using Medicare data showed that lower postoperative mortality rates after gastrectomy, esophagectomy and pancreatectomy in higher volume hospitals were strongly related to lower FTR rates[6]. Yet, the association between hospital volume and FTR in colorectal surgery remains largely unexplored.

Another hospital-related factor that has been associated with differences in outcome, is its teaching status. University hospitals have been associated with favorable outcomes compared to non-teaching hospitals for many procedures and conditions like prostatectomy[7], cystectomy[8] and cardiovascular events[9,10]. Teaching status has been mentioned as a factor inversely related to FTR[11]. It has been suggested that this association may be related to more advanced resources in university hospitals. A logical next step is to explore the relation between intensive care (ICU) capacity and outcomes. The relationship between level of care in ICU facilities and FTR after colorectal cancer surgery has not been investigated yet but higher ICU staffing has been associated with lower mortality in critically ill medical, surgical and pediatric patients[12]. In the Netherlands, ICU units are classified into three levels according to capacity, staffing and resources[13] (table 1), making it possible to study the influence of enhanced ICU facilities on outcomes.

This study looks at the association between three major structural hospital factors and failure-to-rescue rates in colorectal cancer surgery:

1. Annual hospital volume in colorectal cancer procedures
2. Teaching status (Academic-, teaching- and non-teaching hospitals)
3. Level of Intensive Care (ICU) facilities

Table 1: main differences between the three levels of ICU care[13].

	ICU level 1	level 2	level 3
Medical responsibility for patient	Responsibility not transferred to intensivist	Responsibility transferred to intensivist	Responsibility transferred to intensivist
Continuity of care	Intensivist available during working hours	Intensivist available exclusively for ICU 7x24 hours / week	Intensivist available exclusively for ICU 7x24 hours / week
Intensivist staffing	0,1 - 0,15 fte / bed	0,35 - 0,42 fte / bed	0,45 - 0,55 fte / bed
Other medical staff	5 -6 fte ICU-trained doctors working in hospital	0,55 fte / bed	0,6 - 0,9 fte / bed
ICU nurse staffing	2,7 fte / bed	3,5 fte / bed	4,2 fte / bed
Minimum no. of ventilation days / year	.	1250	1500
Minimum no. of beds	6	12	12

METHODS

Data was derived from the DSCA, a nationwide, continuous quality improvement project in which a wide range of variables concerning patient and disease-specific details, diagnostics, treatment, and outcomes are collected prospectively. The dataset is disease-specific for colorectal cancer and shows a nearly 100% completeness on most items, and high accuracy level on comparison against the Netherlands Cancer Registry (NCR) dataset. The latter is constructed with data retrieved from chart review by independent, trained researchers[14,15].

Patients

For this study, no ethical approval or informed consent was required under Dutch law.

All patients (n=26 410) undergoing surgical resection for primary colorectal cancer between the 1st of January 2009 and 31st of December 2011, and registered in the DSCA before March 15th 2012, were evaluated. Minimal data requirements to consider a patient eligible for analyses were information on tumor location, date of surgery, complications and mortality. For calculation of average annual hospital volume, no cases were excluded.

Definitions

Hospital volume

Hospital volume was divided into five groups: <51 cases/year, 51-100 cases/year, 101-150 cases/year, 151-200 cases/year and more than 200 cases/year. Subsequently, we used five different cutoff points for volume (0-50 versus more than 50 cases/year; 0-100 versus more than 100 cases/year, and so on). The groups were formed around 100 cases per year, as the average hospital volume was 99 cases per year, with most hospitals performing between 50 and 200 procedures annually.

Hospital type

Hospitals were categorized as either academic hospitals, teaching hospitals or non-teaching hospitals. In the Dutch healthcare system there are eight university hospitals, which function as referral centers for high-complex, low-volume care like surgery for locally advanced tumors and synchronous metastasectomies[16]. Each university hospital is affiliated with a number of teaching hospitals, providing the surgical residency programs together. The remaining hospitals were defined as non-teaching hospitals.

ICU facilities

According to the guidelines "organization of ICU departments for adults in the Netherlands"[17], three levels of ICU facilities are defined. Table 1 displays the main differences per level, as described by the guideline.

The level of ICU facilities is a quality indicator that hospitals must provide to the Dutch healthcare inspectorate on a yearly basis. For this study, the level of ICU facilities for each hospital was derived from the website with the databank of these quality indicators[13]. If a hospital had changed levels within the study period of 2009-2011, the category noted in most of these years was used.

Failure to rescue

The definition of FTR is displayed in panel 1 and was formulated in accordance with the definition in a previous study[4]. Unadjusted FTR rates were compared between different hospital volumes, hospital types and between hospitals with different levels of ICU facilities with the X^2 test. Subsequently, multivariate logistic regression analysis was used for risk adjustment and to determine whether the structural hospital factors were independently associated with differences in FTR rates. Risk adjustment was done for age, sex, ASA score, location of the tumor, Charlson co-morbidity index, urgency of the operation, TNM stage, additional resections, multiple synchronous colorectal tumours and neoadjuvant therapy.

A 2-sided $P \leq 0.05$ was considered statistically significant. Statistical analyses were performed in PASW Statistics, version 20 (SPSS inc., Chicago, Il, USA) and R 2-14 (The R Project for Statistical Computing and The Comprehensive R Archive Network; http://cran.r-project.org/).

DEFINITIONS

Mortality: A patient that died within 30 days after the operation or during the index hospital admission.

Severe complication: a complication leading to a surgical, endoscopic or radiological reintervention, to an in-hospital stay of more than 14 days, or to death

Failure to rescue: The pecentage of patients with a severe complicaion that died in-hospital or within 30 days after the resection; (Number of patients that died secondary to a severe complication) / (total number of patients that experienced a severe complication)

Panel 1: definitions used in the current study

Table 2: hospital,- patient-, tumor- and treatment characteristics

		Total patient group	Non-teaching hospitals	Teaching hospitals	University hospitals
Hospital characteristics					
Annual hospital volume	Mean (range)		74 (20-118)	144 (41-287)	78 (41-115)
ICU level 3 (highest)	Number of hospitals		0	16	8
ICU level 2	Number of hospitals		2	23	0
ICU level 1 (lowest)	Number of hospitals		36	7	0
Patient characteristics					
Sex	Male	14072 (55%)	55%	55%	58%
Age	Mean (standard deviation)	70 (11)	70 (11)	70 (11)	67 (12)
BMI	kg/m^2, mean (standard deviation)	26 (4,8)	26 (4,6)	26 (4,8)	26 (4,6)
Charlson co-morbidity index	0	14189 (55%)	55%	56%	53%
	1	5555 (22%)	23%	21%	22%
	2	3419 (13%)	13%	13%	15%
	3 or higher	2428 (10%)	9%	10%	11%
ASA classification	I -II	19100 (75%)	72%	76%	76%
	III	5389 (21%)	22%	20%	21%
	IV-V	496 (2,0%)	3%	2%	2%

Table 2: hospital,- patient-, tumor- and treatment characteristics (continued)

		Total patient group	Non-teaching hospitals	Teaching hospitals	University hospitals
	Unknown	606 (2%)	3%	4%	1%
Pathological TNM stage	X	943 (4%)	3%	4%	4%
	I	5270 (21%)	22%	20%	18%
	II	8472 (33%)	32%	34%	30%
	III	7934 (31%)	32%	31%	30%
	IV	2972 (11%)	11%	11%	18%
Location of tumor	Right hemicolon	8207 (32%)	34%	32%	29%
	Left hemicolon	3021 (12%)	12%	12%	10%
	Sigmoid colon	7104 (28%)	29%	28%	23%
	Rectum	7259 (28%)	26%	28%	38%
Procedure	Ileocaecal resection	267 (1%)	1%	1%	1%
	Right hemicolectomy	8026 (32%)	33%	31%	29%
	Transverse colectomy	567 (2%)	2%	2%	1%
	Left hemicolectomy	1854 (7%)	8%	7%	6%
	Sigmoid colectomy/low anterior resection	11092 (44%)	45%	43%	42%
	Subtotal colectomy	400 (2%)	1%	2%	1%
	Abdominoperineal resection	2240 (9%)	7%	9%	15%
	Panproctocolectomy	245 (1%)	1%	1%	2%
	Other	622 (3%)	2%	3%	4%
Urgency	Urgent/emergency resection	3840 (15%)	17%	15%	13%

RESULTS

Patients

A total of 25591 patients, registered by 92 hospitals were included in this study. Patient, tumor and treatment characteristics are displayed in table 2. Average mortality was 4.3% and the percentage of patients with a severe complication was 23%, with an average FTR rate of 17%. University hospitals treated a higher proportion of patients with rectal cancer. Patients treated in university hospitals were younger, but had slightly more comorbidity and more often stage IV disease. Consequently, additional resections and metastasectomies were performed more often in university hospitals, and patients in these hospitals were treated with preoperative chemoradiotherapy more frequently. Non-elective surgery was slightly less common in university hospitals, compared to other hospital types.

Hospital volume

The average annual number of colorectal cancer resections per hospital was 99 and ranged between 20 and 206 procedures per year (table 2).

In univariate analysis, there was no difference in FTR rate between the five hospital volume groups, especially not between the lowest (<50 patients/year) and highest volume (more than 200 patients/year) group (data not shown). With the cutoff at 0-200 cases/year versus more than 200/year there was a significantly lower FTR rate in the higher volume group (table 3). Four hospitals had an average annual volume of more than 200 colorectal cancer resections. Adjusted for casemix, the difference in FTR between hospitals with more than 200 cases/year and the lower volume hospitals was 17% versus 14%; p=0.07 (figure 1).

Table 3: unadjusted and adjusted failure-to-rescue (FTR) rates per hospital type and ICU level.

Factor		Unadjusted FTR	Univariate OR (95% CI)	Multivariate OR (95% CI)*
Hospital volume				
	low (<=200 cases/yr)	18%	1 (ref)	(1 ref)
	high (more than 200 cases/yr)	13%	**0.69 (0.51-0.95)**	0.75 (0.53 -1.06)
Hospital type				
	Non-teaching hospital	21%	**1.34 (1.15 - 1.55)**	0.99 (0.76-1.3)
	Teaching hospital	17%	1 (ref)	1 (ref)
	University hospital	12%	**0.72 (0.54 - 0.98)**	0.84 (0.60-1.16)
Level of ICU facilities				
	ICU level 1	21%	**1.54 (1.31-1.83)**	**1.39 (1.06-1.83)**
	ICU level 2	15%	1 (ref)	1(ref)
	ICU level 3	16%	1.14 (0.96 -1.35)	1.16 (0.95-1.40)

Bold printed numbers are statistically significant ($p<0.05$). FTR= failure to rescue ICU= Intensive Care
* casemix factors, hospital volume, hospital type and ICU level are included in the model

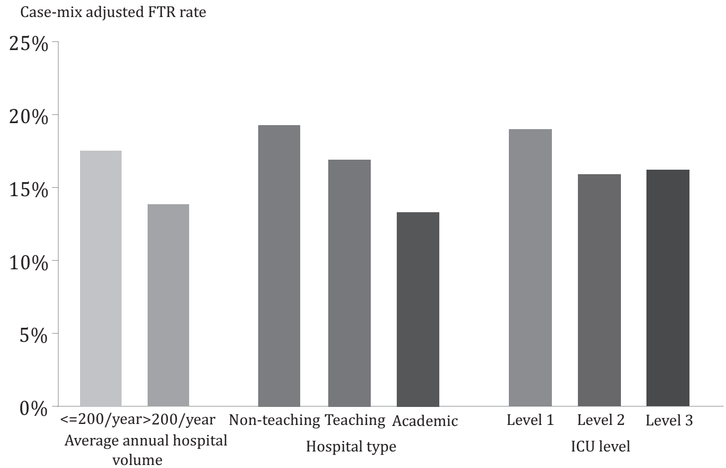

Figure 1: failure to rescue (FTR) rates, adjusted for casemix, per volume group, hospital type and ICU level.

Hospital type and ICU level

All Dutch hospitals performing colorectal cancer surgery were included in the study: eight university hospitals; 46 teaching hospitals and 38 non-teaching hospitals.

In 43 hospitals only basic (level 1) ICU facilities were available, 25 hospitals had a level 2 ICU, and 24 hospitals had an ICU of the highest level 3. Hospital characteristics are displayed in table 2.

Differences in FTR rates between the different hospital types and levels of ICU facilities, derived from univariate- and multivariate analysis are displayed in table 3. Unadjusted FTR rates were significantly lower in university hospitals and significantly higher in non-teaching hospitals, compared to teaching hospitals.

Also, level 1 ICU hospitals had significantly higher FTR rates than hospitals with level 2 ICU capacity; there was no difference in FTR rates between level 2 and 3 ICU hospitals.

Adjusted for casemix, FTR rates were 19% (0-39%) in non-teaching hospitals, 17% (2-26%) in teaching hospitals and 13% (6-20%) in university hospitals. When stratified according to ICU level, casemix-adjusted FTR rates were 19% (0-39%) in level 1 ICU hospitals, 16% (8- 26%) in level 2 and 16% (6-23%) in level 3 ICU hospitals (figure 1).

As can be seen in table 4, the relation between teaching status and FTR lost its statistical significance when the factors hospital volume, hospital type and ICU level were entered as variables in the logistic regression model. Only ICU level proved to be independently related to FTR rates, with level 1 (lowest) ICU level being associated with sig-

Table 4: incidence of and failure-to-rescue (FTR) from various complications per level of ICU

postoperative complication	**incidence (n/%)**	**FTR from complication (%)**			**p for difference**
		ICU level 1	ICU level 2	ICU level 3	
anastomotic leak	1315 (5%)	17%	14%	16%	ns
abscess	606 (2,4%)	9%	6%	7%	ns
hemorrhage	205 (1%)	23%	17%	10%	0.05*
ileus	380 (2%)	15%	5%	4%	0.006* / 0.003 **
fascial dehiscence	409 (2%)	12%	6%	9%	ns
iatrogenic bowel injury	109 (0%)	29%	13%	22%	ns
other surgical complications	759 (3%)	18%	14%	12%	ns
non-surgical complications	2330 (9%)	27%	22%	22%	0.021* / 0.016**

* ICU level 1 vs level 3

** ICU level 1 vs level 2

nificantly lower FTR compared to a level 2 ICU (reference category). When level 2 and 3 ICU hospitals were combined in one group, the OR for FTR was 0,72 (95% CI 0,65 – 0,88; p<0,001) when compared to level 1 ICU hospitals.

Complication types

A characterization of FTR per complication type is displayed in table 4. Anastomotic leak, intra-abdominal abscess and non-surgical complications occurred most often. FTR rates were lower for all complications in ICU level 2 and level 3 hospitals when compared to hospitals with level 1 ICUs. This difference was significant for FTR from postoperative haemorrhage, ileus, and non-surgical complications.

DISCUSSION

This study is the first to directly evaluate the association between FTR and hospital characteristics in colorectal cancer surgery. FTR was lower in patients operated in high volume hospitals, in university hospitals and in hospitals with higher levels of ICU facilities in univariate analysis. A higher level of ICU facilities was the only factor associated with lower FTR rates in multivariate analysis. Differences in level of ICU facilities might be a part of the explanation of the differences in FTR rates between hospitals.

Ghaferi et al. found higher hospital volume to be significantly associated with favourable FTR rates[6], however this association concerned patients undergoing surgery that may be considered more challenging than colorectal cancer surgery (pancreatic and upper gastrointestinal surgery). In another study, teaching hospitals and overall hospital size of >200 beds were independently associated with lower FTR rates after pancreatic resections[11]. In this study, "high technology" (transplantation and cardiac surgery performed in the hospital) was also associated with lower FTR. Arguably, "high technology" may be a proxy for better ICU facilities. Almoudaris et al. describe a higher number of high-dependency unit beds in the quantile of hospitals with lowest postoperative mortality after colorectal surgery; however the number of ICU beds did not differ between quantiles[3].

Colorectal cancer surgery is performed in the majority of Dutch hospitals, typically in a medium-volume setting (average 99 cases/year), though with many lower volume centers being present as well. Only a small number of hospitals perform more than 200 procedures/year, which may make it hard to reach significance.

Although we found that unadjusted FTR rates were lower in university hospitals and higher in non-teaching hospitals, these differences lost statistical significance when casemix factors and the three hospital characteristics were analyzed together in multivariate analysis. The availability of at least a level 2 ICU was the only structural hospital factor independently associated with better FTR rates.

Patients operated in hospitals with level 2 ICUs had a similar risk of FTR as patients from level 3 ICU hospitals. The differences in characteristics between ICUs of level 2 and 3 (table 1) appear relatively modest whereas differences between level 1 and 2 ICUs seem more distinct. The biggest differences between level 1 ICUs and level 2 or 3 ICUs are the exclusive 24 hours a day availability of an intensivist, the transfer of responsibility for the patient to the intensivist, and more intensive care staffing (table 1). Our findings suggest that these staffing factors of an ICU may be important factors that contribute to better FTR rates in colorectal surgery. Surgical complications such as anastomotic leak may lead to single or multiple organ dysfunction. Non-surgical complications may carry an additional risk of mortality in this relatively old and frail patient group. Therefore, adequate availability of ICU support seems essential in management of patients with severe complications after colorectal surgery.

The positive effects of higher ICU staffing and 24-hour coverage by an intensivist on ICU- and hospital mortality have been described before[12,18,19]. Our study builds on this, showing an association between these staffing factors and lower FTR rates in a specific surgical population.

Many Dutch hospitals with lower-level ICUs have regional agreements with hospitals with higher levels of ICU care on, for instance, teleconferencing. Although regional collaboration undoubtedly has a positive impact on outcomes, our study shows that despite these initiatives a lower level of ICU facilities was associated with higher FTR rates. However, some hospitals with low level ICUs performed well.

There are some limitations in this study. The data is self-reported, so selection bias cannot be completely excluded. However, the dataset is highly detailed and validated against data from the Netherlands Cancer registry (see methods). Secondly, the definition of severe complications (complications followed by a reintervention, a prolonged in-hospital stay of more than 14 days or to death) may be considered arbitrary. However, this definition distinguishes major complications from less severe complications that do not hinder the postoperative course[20].

The variability of FTR rates within each group of hospitals' structural factors suggest that there must be other factors as well playing a role in explaining hospital differences in FTR rates. Firstly, these may be factors associated with timely recognition of complications[21]. For instance, higher nurse-to-patient ratios have been associated with lower FTR rates[22]. An in-depth study concerning factors reflecting differences concerning in-hospital processes should be conducted, evaluating the daily ward rounds, responsibility for the ward patients, staffing outside office hours, vital sign collection and reporting, the level of experience in a surgical team, team communication, guideline adherence and quality of care from nurses. Secondly, hospital differences in FTR rates may be sought in differences in delay until the start of treatment of complications. For instance, early reintervention for anastomotic leak may prevent clinical deterioration and death. Alves et al. found lower mortality after reoperations performed before postoperative day five, although this difference was not significant[23].

With identification of specific care processes that account for differences in hospital FTR rates, quality improvement initiatives can aim at reducing postoperative mortality by addressing the most important factors in the postoperative care process. Safeguarding adequate ICU capacity to support patients with complications after colorectal surgery seems one of these factors.

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CHAPTER 7

Centralization of esophagectomy: how far should we go?

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ABSTRACT

Objective: To define a statistically sound and clinically meaningful cutoff point for annual hospital volume for esophagectomy.

Background: Higher hospital volumes are associated with improved outcomes after esophagectomy. However, reported optimal volumes in literature vary, and minimal volume standards in different countries show considerable variation. So far, no research was done on studying the non-categorical, non-linear volume-outcome relationship in esophagectomy.

Methods: Data were derived from the Netherlands Cancer Registry. Restricted cubic splines were used to investigate the non-linear effects of annual hospital volume on 6-month and 2-year mortality rates. Outcomes were adjusted for year of diagnosis, case-mix and (neo)adjuvant treatment.

Results*:* Between 1989 and 2009, some 10,025 patients underwent esophagectomy for cancer in the Netherlands. Annual hospital volumes varied between 1/year to 83/year, increasing over time. Increasing annual hospital volume showed a continuous, non-linear decrease in HR (Hazard Ratio) for mortality along the curve. Increasing hospital volume from 20/year (baseline, HR = 1.00) to 40/year and 60/year was associated with decreasing 6-month mortality, with a HR of 0.73 (95% Confidence Interval (0.65-0.83) and 0.67 (0.58-0.77) respectively. Beyond 60/year, no further decrease was detected. Higher hospital volume was also associated with decreasing 2-year mortality until 50 esophagectomies/year with a HR of 0.86 (0.79-0.93).

Conclusions: Centralization of esophagectomy to a minimum of 20 resections/year has been effectively introduced in the Netherlands. Increasing annual hospital volume was associated with a non-linear decrease in mortality up to 40-60 esophagectomies/year,

after which a plateau was reached. This finding may guide quality improvement efforts worldwide.

INTRODUCTION

Surgical resection is the cornerstone of curative treatment for esophageal cancer. Postoperative mortality remains a challenge with reported mortality rates as high as 8.9% in the Western world[1], with a 5-year survival rate after esophagectomy of around 50%[2].

There is compelling evidence that patients have better short- and long-term outcomes when operated in hospitals with a high annual caseload of esophagectomies[3,4,5].

To improve outcomes after esophagectomy, many countries introduced minimum hospital volume standards [1,6,7], but it remains unclear, how high this minimum volume standard should be. Many different definitions of a 'high-volume hospital' have been proposed in the recent literature, ranging from more than 5 to over 86 esophageal cancer resections annually[1,3,8-34]. Consequently, there is no consensus what should be considered a 'high-volume' hospital and minimum volume standards for esophagectomies vary per country or region. The American Leapfrog group set the standard at a minimum of 13 esophagectomies per hospital annually[35,36], whereas in the Netherlands, the minimum was recently set at 20 esophagectomies per year[37]. In Great Britain and Ireland, AUGIS advises at least 60 esophagogastric cancer resections per unit per year[38].

The majority of volume-outcome studies in esophagectomy analyze hospital volume as a categorical variable. Hospitals are grouped in volume categories and casemix adjusted outcomes are compared between the highest and the lowest group. Therefore, the definition of a 'high-volume' hospital is based on the predefined hospital volume categories, based on the available data or are chosen arbitrarily. Non-linear statistical modeling techniques allow analysis of annual hospital volume as a continuous variable, thus providing support in defining a meaningful cutoff point. So far, these statistics have not been used for volume-outcome studies in esophagectomy.

The purpose of this study is to define a meaningful cutoff point for annual hospital volume for esophagectomy, using non-linear statistical modeling techniques on a large dataset with a broad range in annual hospital volumes.

METHODS

Dataset

Data were derived from the Netherlands Cancer Registry (NCR), which routinely collects information on all newly diagnosed malignancies in all Dutch hospitals 6-18 months after diagnosis. Topography and morphology were coded according to the International Classification of Diseases for Oncology (ICD-O)[39]. ICD-O morphology codes were used to classify tumors as adenocarcinoma (8140-8145, 8190, 8201-8211, 8243, 8255-8401, 8453-8520, 8572, 8573, 8576), squamous cell carcinoma (SCC) (8032, 8033, 8051-8074, 8076-8123), and other/unknown histology (8000-8022, 8041-8046, 8075, 8147, 8153, 8200, 8230- 8242, 8244-8249, 8430, 8530, 8560, 8570, 8574, 8575). Staging was according to the International Union Against Cancer (UICC) Tumor Node Metastases (TNM) classification in use in the year of diagnosis. Vital status was initially obtained from municipal registries, and from 1994 onwards from the nationwide population registries network, which provides complete coverage of all deceased Dutch citizens. Follow-up was complete for all patients until 31st December 2009. The study was approved by the NCR Review Board.

Patients

Between January 1989 and December 2009, 37,560 patients with esophageal or gastric cardia cancer were diagnosed in the Netherlands. Esophagectomies were defined as resections for cancers of the esophagus (C15.0-15.9) and gastric cardia (C16.0). Patients who did not undergo surgery (N = 26,521) were excluded, leaving 11,039 resections available to calculate annual hospital volumes. Annual hospital volumes, defined as the number of esophagectomies per hospital per year, were determined for each year of surgery and may have changed per year for individual hospitals.

Subsequently, patients with in situ and M1 disease (N = 1,014) were excluded, leaving 10,025 patients with non-metastatic invasive carcinoma available for volume–outcome analyses.

Statistical analyses

Differences in baseline characteristics between hospital volume categories were calculated with the Chi-square test. The main outcomes were 6-month and 2-year overall mortality (OM). These were calculated using Cox regression, adjusted for sex, age, socioeconomic status, tumor stage, morphology, preoperative therapy use, postoperative therapy use (only for 2-year mortality) and year of diagnosis. To adjust for possible correlation due to clustering of patients in hospitals, robust standard errors were obtained using sandwich estimators. Frailty models with random hospital effects were used as sensitivity analysis. OM was calculated from the day of diagnosis until death, because the date of surgery was not available before 2005. Six-month OM was calculated unconditionally, while 2-year OM was calculated conditionally on surviving the first 6 months after diagnosis.

The relationship between annual hospital volume and outcomes was calculated using Cox regression with annual hospital volume modeled through restricted cubic splines[40], adjusted for the above-mentioned patient and treatment factors. Restricted cubic splines statistics allow investigation of non-linear effects of continuous covariates and have been described as a method for threshold identification [41,42]. The current Dutch minimum volume standard of 20 esophagectomies per year was taken as a reference and given a hazard ratio (HR) of 1.

Analyses were performed with SPSS (version 17.0.2) and R (version 2.12.2).

RESULTS

Patient characteristics

Patient, tumor, and treatment characteristics are displayed in table 1. The majority of patients were males (76%). The median age was 64 years. Hospitals in the higher volume categories (>40/year) operated a slightly lower percentage of patients aged 75 years and older. Preoperative therapy use was significantly different between the volume categories.

Hospital volumes

From 1989 to 2009, the annual number of esophagectomies performed in the Netherlands doubled from 352 to 723. The percentage of esophagectomies performed in hospitals with an annual volume of more than 20 esophagectomies per year increased from 7% to 64%. From 1998 on, 18.2% of patients were operated in hospitals performing more than 60 esophagectomies per year. Overall, throughout the study period the mean hospital volume was 20.7 esophagectomies per year. In 2009, 44 of 92 Dutch hospitals performed esophagectomies.

Table 1. Patient characteristics for patients treated in different annual hospital volume categories. SES= socio-economic status; SCC= squamous cell carcinoma; pTNM= pathological tumor, nodal, metastasis staging. * χ^2 test

Patient characteristics		Total patient group		Hospital volume category 1-20/year		21-40/year		41-60/year		>60/year		P-value*
	Total	10025	100%	7103	100%	865	100%	890	100%	1167	100%	
Gender	male	7650	76%	5401	76%	684	79%	669	75%	896	77%	0.193
Age category	<60 years	3439	34%	2407	34%	292	34%	337	38%	403	35%	0.007
	60-75 years	5532	55%	3900	55%	486	56%	481	54%	665	57%	
	>75 years	1054	11%	796	11%	87	10%	72	8%	99	8%	
SES	Low	1006	10%	747	11%	105	12%	69	8%	85	7%	<0.001
	Medium	7878	79%	5747	81%	592	68%	775	87%	764	65%	
	High	426	4%	311	4%	29	3%	44	5%	42	4%	
	Unknown	715	7%	298	4%	139	16%	2	0%	276	24%	
Tumor morphology	Adenocarcinoma	7541	75%	5407	76%	679	78%	610	69%	845	72%	<0.001
	SCC	2255	22%	1523	21%	177	20%	260	29%	295	25%	
	Other	229	2%	173	2%	9	1%	20	2%	27	2%	
pTNM stage	I	1941	19%	1419	20%	146	17%	137	15%	239	20%	<0.001
	II	3898	39%	2830	40%	328	38%	325	37%	415	36%	
	III	3575	36%	2463	35%	316	37%	367	41%	429	37%	
	IV	108	1%	83	1%	4	0%	9	1%	12	1%	
	Unknown	503	5%	308	4%	71	8%	52	6%	72	6%	
Preoperative therapy	Yes	1704	17%	766	11%	347	40%	182	20%	409	35%	<0.001
Postoperative therapy	Yes	531	5%	380	5%	53	6%	54	6%	44	4%	0.053

Volume outcome analysis

The results of the cubic splines analyses are shown in Table 2 and in Figures 1 and 2. In Figure 1, the volume-outcome curve for 6-month mortality showed a steep decrease in HR in volumes above 20. At 40 resections per year, the HR was 0.73 (95% confidence interval 0.65-0.83). From this point, the curve became less steep but the HR decreased to 0.68 (0.60-0.78) at 50 resections per year and to a HR of 0.67 (0.58-0.77) at 60 per year. Beyond this point, no further decrease in HR was observed. Figure 2 displays the volume-outcome curve for 2-year conditional mortality. The curve was similar to Figure 1: the HR for death after 2 years strongly decreased between 20 and 40 esophagectomies per year, with a HR of 0.88 (0.83-0.93) at 40 resections per year. At 50 resections per year, the HR was 0.86 (95% CI 0.79-0.93)- similar to the HR at 60 resections per year (HR 0.85 (0.75-0.97)). Sensitivity analyses using frailty models did not qualitatively change these hazard ratios or confidence intervals (data not shown).

Table 2. Volume-outcome analyses

6-months mortality			**Conditional 2-year mortality**		
Annual hospital volume	HR	95% CI	Annual hospital volume	HR	95% CI
20	1	REFERENCE	20	1	REFERENCE
30	0.83	(0.76-0.91)	30	0.92	(0.89-0.96)
40	0.73	(0.65-0.83)	40	0.88	(0.83-0.93)
50	0.68	(0.60-0.78)	50	0.86	(0.79-0.93)
60	0.67	(0.58-0.77)	60	0.85	(0.75-0.97)
70	0.67	(0.54-0.83)	70	0.86	(0.71-1.05)
80	0.68	(0.49-0.94)	80	0.88	(0.66-1.16)

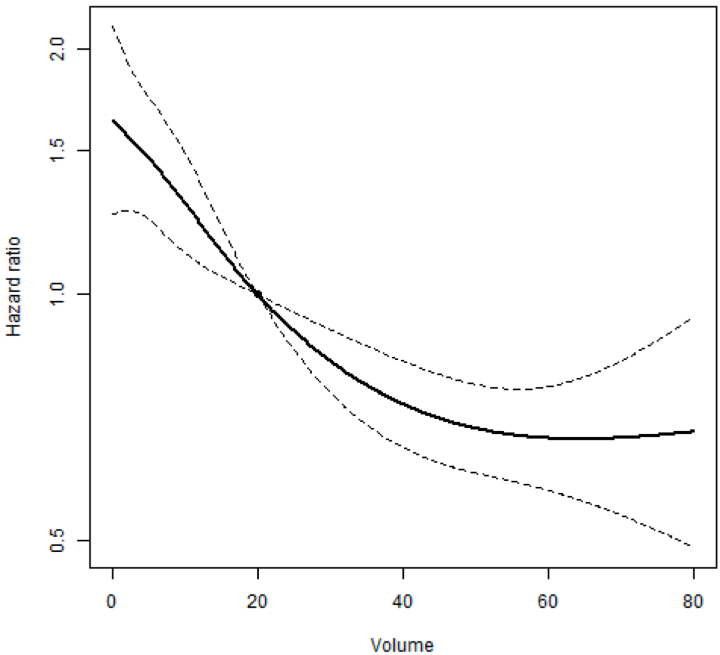

Figure 1: Volume-outcome curve for 6-month mortality (black line) with 95 percent confidence intervals (dotted line). Note that the vertical axis has a logarithmic scale.

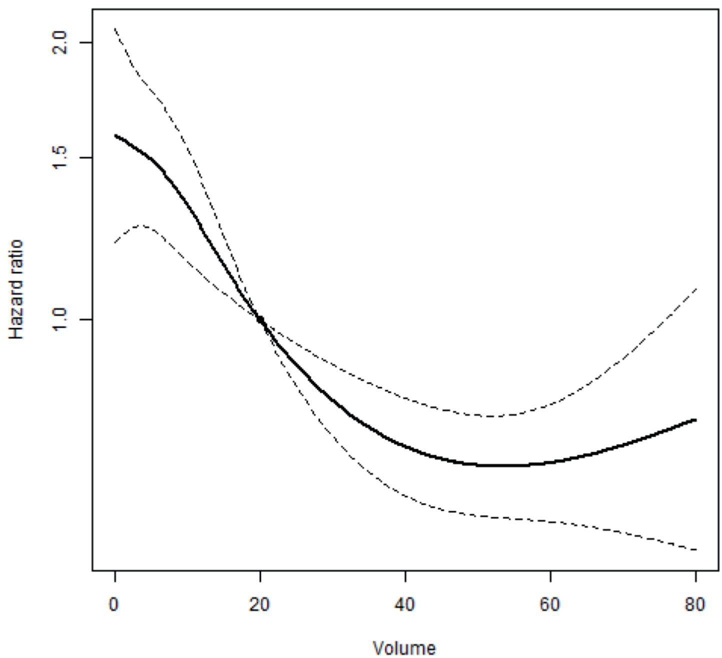

Figure 2: Volume-outcome curve for conditional 2-year mortality (black line) with 95 percent confidence intervals (dotted line). Note that the vertical axis has a logarithmic scale.

DISCUSSION

In the current study, the volume-outcome relationship in esophagectomy was assessed in a non-categorical fashion, using non-linear statistical modeling techniques on a large dataset with reliable case-mix information. It was found that further centralization of esophagectomy beyond the current Dutch minimum volume standard of 20 resections per year can have a beneficial effect on mortality rates. A continuous decrease in HRs for 6-month and 2-year mortality was observed until hospital volumes of up to 40-60 esophagectomies per year. Beyond this point, no further improvement was detected.

Increasing annual hospital volume is associated with better outcomes after esophagectomy[1,3,4,5,34,43]. So far, little research has been performed on defining the optimal hospital volume threshold for esophagectomy. In an American study, analyzing 4080 esophagectomy patients from the Nationwide Inpatient Sample, a cutoff point of 15 resections per year showed the largest difference in postoperative mortality between hospitals with a volume below and above this threshold[44]. However, mean and maximum hospital volumes were small with 4 and 33 esophagectomies per year respectively.

Another study, investigating 1634 esophagectomies from the 1999-2000 UHC clinical database found the greatest difference in mortality between hospitals at the volume threshold of 22 esophagectomies per year [45]. However, this analysis did not go beyond a threshold of 25.

A meta-analysis of relevant literature available between 1990 and 2003[46] showed that differences in postoperative mortality after esophagectomy were best discriminated using a volume threshold of at least 20 esophagectomies. However, no analyses were performed for hospital volumes above 20. In contrast to the abovementioned studies, the current study aimed to define the annual hospital volume above which no further improvement in outcomes can be detected.

A potential bias when analyzing outcomes over a long period is that preoperative staging and (perioperative) care generally improved over time, while at the same time most high-volume resections were performed in the more recent years. Therefore, high volume resections may be intrinsically associated with better outcomes. To offset this effect, we adjusted for year of diagnosis among other covariates. The surgery hospital was not available for part of the patients treated before 2005. Instead, the hospital of diagnosis was used in this case. Although referral of esophageal cancer patients to another hospital for surgery was uncommon in the earlier years of the study period, it may have influenced the analyses in the time period between 2000 and 2004.

The results of the current study are representative for the entire population as case ascertainment of the Netherlands Cancer Registry is high[47].

Due to the high number of registered variables, case-mix adjustments could be made, in all survival analyses, although it is possible that some confounding factors not available in the dataset may have influenced differences in outcomes between hospitals. However, after adjusting for age, tumor stage and SES, the added value of other confounding factors like comorbidity may be limited, especially in more aggressive types of cancer.

Worldwide, programs to concentrate esophageal cancer surgery towards high-volume hospitals take place, which has led to decreasing mortality rates in, for instance, the United States,[1, 35,] and the United Kingdom [9, 43].

Because of the minimum volume standard in the Netherlands (10 per hospital per year as of 2006, 20 per year as of 2011), the majority of Dutch patients are currently operated in centers performing 20 or more resections per year[48]. The current results suggest that further centralization up to 40-60 esophagectomies per hospital per year may further improve both short-term mortality and long-term survival. The recent increase in hospital volumes can mainly be attributed to hospitals performing 20-40 procedures per year as of 2005, whereas the highest volume category remained the same size since approximately 2000. Therefore, the learning curve of the hospitals that became referral centers after 2005 might have influenced results: it may have taken some time for these hospitals to arrange care in such a way that they could achieve results similar to the higher volume centers (performing >60 resections/year) that existed already a longer time. However, by adjusting for year of diagnosis, there is also adjusted for the potential presence of learning curves.

Moreover, it is possible that a greater effect of volumes above 60 resections/year would have been detected with more hospitals in this higher end of the spectrum.

In the Netherlands, a small country with a good infrastructure, further centralization will not likely lead to unreasonable travel burdens or problems in continuity of post-surgical care. The right number for a small, densely populated country might differ from that of larger countries with less densely populated areas.

Hospital volume may be a reflection of a variety of factors in the process of care, such as multidisciplinary approach, patient selection, and protocols; as well as resources. Arguably, lower volume hospitals may achieve excellent results with a similar approach and environment. Volume-based referral carries the risk that high-volume hospitals with unfavorable outcomes are selected as referral centers[34,36] but identification of the processes and structural factors that account for superior results remains challenging [49]. Outcome-based referral avoids this problem by selecting referral centers based on outcomes[50]. Identification of centers of excellence requires valid, reliable, complete, and adequate risk-adjusted registration of outcomes through audits[51,52], which provide insight in care patterns, and allow clinicians to benchmark their hospital on outcomes, thereby stimulating improvement[53].

In conclusion, the current study showed a continuous, non-linear decrease in HRs for 6-month and 2-year mortality, until hospital volumes of up to 40-60 esophagectomies per year, implicating that centralization of esophageal cancer resections to hospitals performing 40-60 resections per year may lead to an improved 6-month mortality and 2-year survival. These findings may guide national and regional centralization efforts worldwide.

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CHAPTER 8

Risk factors for anastomotic leakage and leak-related mortality after colon cancer surgery in a nationwide audit

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ABSTRACT

Background: Surgical resection with restoration of bowel continuity is the cornerstone of treatment for colon cancer patients. The aim of this study is to identify risk factors for anastomotic leakage (AL) and subsequent mortality in colon cancer surgery.

Methods: Data were retrieved from the Dutch Surgical Colorectal Audit. Patients undergoing a colon cancer resection with creation of an anastomosis between January 2009 to December 2011, were included. Outcomes were AL requiring a re-intervention and post-operative mortality following AL.

Results: AL occurred in 7.5 per cent of a total of 15 667 included patients. Multivariate analyses identified male gender, high ASA classification, extensive tumour resection, emergency surgery and surgical resection types as transverse resection, left colectomy and subtotal colectomy, as independent risk factors for anastomotic leakage. In a small group of patients a defunctioning stoma was created, leading to a lower leakage risk. Overall mortality was 4.1 per cent, and mortality was significantly higher in patients with AL compared to patients without leakage (16.4 vs 3.1 per cent $P<0.001$). Multivariate analyses showed a higher age, high ASA classification, high Charlson score and emergency surgery, as independent risk factors for mortality after AL. Moreover, the adjusted risk of mortality after AL was twice as high in right colectomy compared to left colectomy.

Conclusions: Elderly and patients with comorbidity have higher mortality after anastomotic leakage. Despite a lower adjusted risk of AL after right colectomy compared to left colectomy, the risk of mortality after AL was higher after right colectomies. Of importance is accurate preoperative patient selection, intensive postoperative

surveillance for AL and early and aggressive treatment of AL once suspected, especially in patients undergoing right colectomy.

INTRODUCTION

Surgical resection is the cornerstone of treatment for colon cancer patients. Generally, restoration of bowel continuity with a primary anastomosis is pursued in uncomplicated colon resections. The most serious complication of colonic surgery with restoration of bowel continuity is anastomotic leakage (AL)[1], which is associated with the possible need for reinterventions, increased mortality[2,3] and possibly a worse oncological outcome[4,5]. The reported incidence of AL in colonic anastomosis varies between 3 and 6.4 per cent, depending on patient and tumor characteristics, definition criteria, site of the anastomosis and possibly by case-load per surgeon[6-9]. Several risk factors including co-morbidity, higher American Society of Anesthesiologists (ASA) classification, stage of disease, type of surgery, surgery in emergency setting and intraoperative complications have been associated with AL[7,10-12]. Furthermore, concentration of surgery in high-volume centers has been considered as a strategy to improve quality of care, surgical outcomes and mortality[13,14]. Therefore, hospital procedural volume could also be a possible risk factor for AL. Although AL has long been subject of debate, the prediction for the risk of AL for the individual patient remains difficult. The Dutch Surgical Colorectal Audit (DSCA), a clinical outcome registry in which all Dutch hospitals participate, was initiated in 2009 to monitor and improve outcome of surgical care for colorectal cancer patients. The DSCA facilitates individual hospitals in quality improvement projects but is also used to identify treatment and outcome patterns for different patient groups. In the DSCA, AL after colorectal resections was appointed as an outcome indicator for surgical quality of care[15]. In rectal cancer surgery, the practice of routine construction of defunctioning stomas may play a large role in measuring this outcome and determining risk factors[16]. Stoma construction may be of lesser importance in colon cancer resections. Moreover, among all colorectal surgical procedures, patients undergoing colon cancer resections may be considered a specifically vulnerable patient group, being at risk for morbidity and mortality because of advanced age and co-morbidity[17]. Risk factors for AL and related postoperative mortality have not yet been investigated in this particular group. The aim of the present study is to identify risk factors for AL after colon cancer resection and factors influencing mortality associated with AL with patient information from a national audit database.

METHODS

Study Population

The dataset was retrieved from the DSCA, a web-based national database, in which all patients undergoing surgical resection for colorectal cancer were entered[18]. Data on patient and tumor characteristics, diagnostics, treatment and outcome, were collected. The dataset contained data registered from 92 hospitals with a high concordance on validation against the National Cancer Registry (NKR). In 2009, 89 per cent of the Dutch hospitals participated, increasing to 99 per cent in 2010 and 2011[19]. Medical ethics committee approval was not required for this study as all patients and hospital information in the DSCA was de-identified. Individual patient data was collected in the treating hospital and encrypted transferred to the database of the DSCA.

Inclusion and Exclusion Criteria

All Dutch patients who underwent a colon cancer resection in the Netherlands from January 2009 to December 2011, were included in this study. Rectal cancer patients, patients with multiple synchronous tumors, patients without a primary anastomosis or with an unknown surgical resection type, were excluded from analysis. Surgical resections were categorized in ileocecal resection, right colectomy, transverse resection, left colectomy, sigmoid resection and subtotal colectomy.

Outcome

Primary outcome measures were AL, defined as clinically significant AL requiring surgical or radiological re-interventions, and mortality after AL, defined as in-hospital mortality or within 30 days after primary surgery. Potential risk factors for postoperative complications including patient factors (age, gender, Body Mass Index (BMI), Charlson co-morbidity Score[20,21], ASA classification, previous abdominal surgery), tumor factors (tumor stage, tumor location, preoperative tumor complications) and treatment factors (preoperative surgical procedures (stoma or other), type of surgical resection, emergency surgery, extensive resections, fashioning of a defunctioning stoma) were extracted from the database. Hospitals were categorized as low- (< 50), medium- (51 -100) or high-volume (>100) center, based on the number of surgically treated colon cancer patients per year for the years 2010 and 2011 (in 2009 not all hospitals completed registration). These categories reflect the present situation in the Netherlands with 50 percent of the clinics performing between 50-100 colon cancer resections annually[22].

Statistical Analysis

Univariate analyses were performed to test the association between the above-mentioned patient, tumor, treatment and hospital factors and the occurrence of AL and mortality after AL, with a Chi-square test. Logistic multivariate analyses were performed to correct for possible confounders. A manual stepwise model was used for the variables with a P-value <0.05 in univariate analysis. Clinically relevant variables were added to the statistical model. The variables 'timing of surgery (elective/emergency)' and 'preoperative tumor complications' were assumed to indicate the same clinical situation. To check for colinearity when both variables ('timing of surgery (elective/emergency)' and 'preoperative tumor complications') were incorporated in the model, the variance inflation factor was computed. To check our model, we repeated the multivariate analysis with outcome AL, first without the variable 'preoperative tumor complications' and including 'time of surgery'. Thereafter we performed the same analysis conversely (including 'preoperative tumor complications' and without 'timing of surgery'). Results are reported as odds ratios (OR) and 95 per cent confidence intervals (95 per cent c.i.). Analyses were considered to be statistically significant with a 2-sided P-value <0.05. All data was analyzed using PASW Statistics, Release 20.0.0.1 (SPSS inc, Chicago, IL).

RESULTS

From 2009 to 2011 data from 27 259 patients were included in the database of the DSCA (Figure 1). After exclusion of 7614 rectal cancer patients and 943 patients with multiple synchronous tumors, 18 702 colon cancer patients were eligible. After excluding another 2581 patients without a primary anastomosis and 454 patients who underwent another surgical resection (total colectomy or unknown resection type), 15 667 colon cancer patients were included for analysis (tables 1-3). From all included patients there were 240 ileocecal resections, 7788 right colectomies, 527 transverse resections, 1601 left colectomies, 5354 sigmoid resections and 157 subtotal colectomies. Surgery was performed in 92 hospitals, with 15.3 per cent of

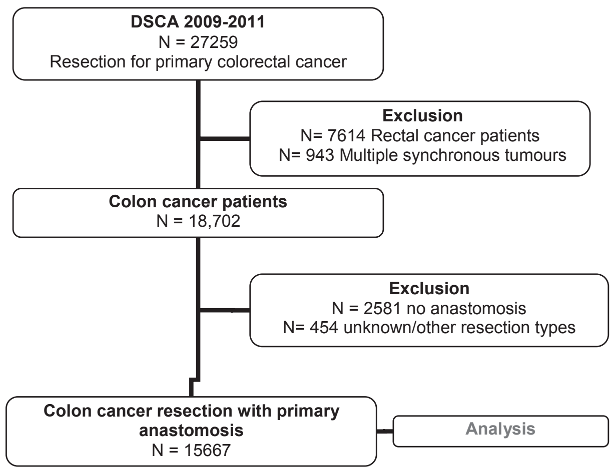

Figure 1: Patient inclusion chart.

Table 1: Patient characteristics of patients operated for colon cancer, and univariate analyses of possible variables associated with anastomotic leakage and with mortality after anastomotic leakage

Patient Characteristics			**Anastomotic Leakage**			**Mortality after AL**		
Patient factors	N	%	N	%	P-Value	N	%	P-Value
	15667		1176	7.5		145	15.7	
Gender								
Female	7605	48.5	477	6.3	<0.001	80	16.8	0.783
Male	8062	51.5	699	8.7		113	16.2	
Age (years)								
<65	4825	30.8	386	8.0	0.284	20	5.2	<0.001
65-80	7616	48.7	551	7.2		101	18.3	
>80	3211	20.5	239	7.4		72	30.1	
BMI								
<20	623	5.0	54	8.5	0.643	11	20.4	0.535
20-25	4922	39.0	366	7.4		59	16.1	
25-30	4986	49.5	389	7.8		54	13.9	
>30	2079	16.5	169	8.1		29	17.2	
ASA								
I -II	11638	74.3	822	7.1	<0.001	94	11.4	<0.001
III-IV	3713	23.7	249	9.2		96	28.2	
Unknown	316	2.0	10	4.4		3	21.4	
Charlson Score								
0	8335	53.2	583	7.0	0.032	56	9.6	<0.001
I	3579	22.8	285	8.0		59	20.7	
≥II	3753	24.0	308	8.2		78	25.3	
Previous abdominal surgery								
Yes	5309	33.9	425	8.0	0.090	81	19.1	0.065
No	10358	66.1	751	7.3		112	14.9	

BMI= Body Mass Index; ASA= American Society of Anesthesiologists

Table 2: Tumour characteristics and univariate analyses of possible variables associated with anastomotic leakage and with mortality after anastomotic leakage

Patient Characteristics			**Anastomotic Leakage**			**Mortality after AL**		
	N	%	N	%	P-Value	N	%	P-Value
Tumour factors								
Preoperative tumour complications								
None	11968	76.4	820	6.9	<0.001	130	15.9	0.100
Perforation	356	2.3	43	12.1		8	18.6	
Obstruction	1557	9.9	175	11.2		30	17.1	
Blood loss	951	6.1	65	6.8		6	9.2	
Other	835	5.3	73	8.7		19	26.0	
TNM Stage								
0	153	1.0	13	8.5	0.176	3	23.1	0.782
1	2811	17.9	180	6.4		31	17.2	
2	5769	36.8	461	8.0		67	14.5	
3	4918	31.4	376	7.6		67	17.8	
4	1784	11.4	131	7.3		23	17.6	
Unknown	232	1.5	15	6.5		2	13.3	
Tumor Location								
Caecum	3513	22.4	216	6.1	<0.001	45	20.8	0.225
Ascending colon	3085	19.7	199	6.5		35	17.6	
Hepatic Flexure	1064	6.8	70	6.6		15	21.4	
Transverse colon	1168	7.5	122	10.4		20	16.4	
Splenic Flexure	448	2.9	54	12.1		9	16.7	
Descending colon	887	5.7	93	10.5		11	11.8	
Sigmoid colon	5502	35.1	422	7.7		58	13.7	

Table 3: Treatment characteristics and univariate analyses of possible variables associated with anastomotic leakage and with mortality after anastomotic leakage. Hospital Volume: low: <50 patients per year, medium: 51-100 patients per year, high: >101 patients per year.

Patient Characteristics			Anastomotic Leakage			Mortality after AL		
	N	%	N	%	P-Value	N	%	P-Value
Treatment factors								
Preoperative surgical procedures								
None	15285	97.6	1133	7.4	0.015	188	16.6	0.383
Stoma formation	118	0.8	15	12.7		3	20.0	
Other	264	1.7	28	10.6		2	7.1	
Surgical Resection								
Right colectomy	7788	1.5	495	6.4	<0.001	101	20.4	0.029
Ileocecal resection	240	49.7	18	7.5		3	16.7	
Transverse resection	527	3.4	57	10.8		10	17.5	
Left colectomy	1601	10.2	172	10.7		20	11.6	
Sigmoid resection	5354	34.2	413	7.7		58	14.0	
Subtotal colectomy	157	1.0	21	13.4		1	4.8	
Time of surgery								
Elective	13139	83.9	925	7.0	<0.001	145	15.7	0.028
Emergency	1625	10.5	159	9.6		37	23.3	
Unknown	869	5.5	92	10.6		11	12.0	
Stoma								
No stoma	15061	96.1	1137	7.5	0.308	187	16.4	0.860
Defuncioning stoma	606	3.9	39	6.4		6	15.4	
Extensive resections								
No	14216	90.7	1025	7.2	<0.001	164	16.0	0.321
Yes	1451	9.3	151	10.4		29	19.2	
Hospital factors								
Hospital Volume								
Low	2680	17.1	180	6.7	0.225	38	21.1	0.162
Medium	8461	54.0	653	7.7		99	15.2	
High	4525	28.9	343	7.6		56	16.3	

the patients being treated in a low-volume center, 55.5 per cent in a medium-volume center and 29.2 per cent in a high-volume center.

Anastomotic leakage

AL leading to re-intervention occurred in 1176 patients (7.5%). The re-interventions were laparotomy (82.1%), laparoscopy (2.8%), radiological drainage (8.2 %) or other interventions for example wound drainages or wound abscesses (6.9 %). During the primary operation a defunctioning stoma was made in 606 patients (3.9 %), usually after a sigmoid resection. From all anastomoses created after a sigmoid resection, 8.7 % was deviated. There was no difference in AL rate between the patients with and without defunctioning stoma, 6.4 vs 7.5 % respectively (P=0.308). Compared to the other types of resections, the incidence of AL was significantly higher after resection of the transverse colon, left colectomy and subtotal colectomy. In 805 patients (69 %) requiring a surgical or radiological re-intervention for AL, a secondary stoma was created.

Risk Factors for anastomotic leakage

Tables 1-3 show univariate analyses of possible risk factors for the occurrence of AL. In univariate analyses, patient factors associated with an increased risk of AL were male gender, higher ASA classification and higher Charlson Score. Of the analyzed tumour factors, preoperative tumour complications (mostly tumor perforation or obstruction) and tumor location were associated with an increased risk of AL. Treatment factors associated with a higher risk of AL, were preoperative surgical procedures (e.g. preoperative construction of a defunctioning stoma), extensive resections (resections of other organs during surgery), emergency surgery, and type of resection, especially transverse resection, left colectomy and subtotal colectomy. Multivariate analyses confirmed that male gender and

Table 4: Risk factors for anastomotic leakage; multivariate analyses of all patients who underwent colonic surgery with a primary colonic anastomosis

Characteristics		OR	95% CI	P-value
Gender	Female	Ref		
	Male	1,378	1,219-1,558	<0.001
ASA classification	I-II	Ref		
	III-IV	1,261	1.088-1.449	0.002
	Unknown	0,59	0,343-1,016	0.075
Charlson Score	0	Ref		
	I	1,11	0,954-1,291	0,178
	≥II	1,102	0,944-1,287	0,218
Preoperative surgical procedures	None	Ref		
	Stoma	1,52	0,873-2,647	0,139
	Other	1,209	0,805-1,814	0,361
Surgical Resection	Right colectomy	Ref		
	Ileocecal resection	1,129	0,690-1,848	0,63
	Transverse resection	1,689	1,262-2,261	<0.001
	Left colectomy	1,69	1,404-2,034	<0.001
	Sigmoid resection	1,276	1,109-1,468	0.001
	Subtotal colectomy	2,281	1,421-3,661	0.001
Extensive resection	No	Ref		
	Yes	1,431	1,191-1,720	<0,001
Stoma	No stoma	Ref		
	Defunctioning stoma	0,682	0,486-0,956	0,026
Time of surgery	Elective	Ref		
	Emergency	1,327	1,107-1,592	0,002
	Unknown	1,553	1,232-1,957	<0,001

ASA= American Society of Anesthesiologists a high ASA classification remained independent risk factors for AL (table 4). Treatment factors that remained associated with a higher AL risk were types of resection (mainly transverse resection, left colectomy and subtotal colectomy compared to right colectomy as reference group), extensive resections during surgery and surgery in emergency setting. On clinical grounds, the variable 'defunctioning stoma' was added to the model and adjusted data also showed less AL in patients with a defunctioning stoma (OR 0.682). In order to check for the presence of colinearity between the two clinical associated variables 'timing of surgery (elective/emergency)' and 'preoperative tumor complications', the variance inflation factor was computed. Results indicated no colinearity between these variables.

Repeated analysis of our multivariate model including the variable 'preoperative complication' instead of 'time of surgery' showed a significant higher risk for AL in patients with preoperative tumor complications as perforation or obstruction (OR 1.684 and 1.629 respectively).

Mortality

Of all included patients, 648 (4.1 %) died within 30 days postoperatively (3.4 % after elective surgery vs 7.2 % after emergency surgery $P<0.001$). In 193 of all deceased patients, AL was diagnosed postoperatively (29.8 %). The mortality in patients with AL was significantly higher than in patients without AL (16.4 vs 3.1 %, $P<0.001$). There was no significant association between the number of patients treated yearly per hospital and mortality after AL ($P=0.162$).

Risk Factors for mortality after anastomotic leakage

Univariate analyses revealed that patient factors associated with mortality after AL were higher age, high ASA classification and a high

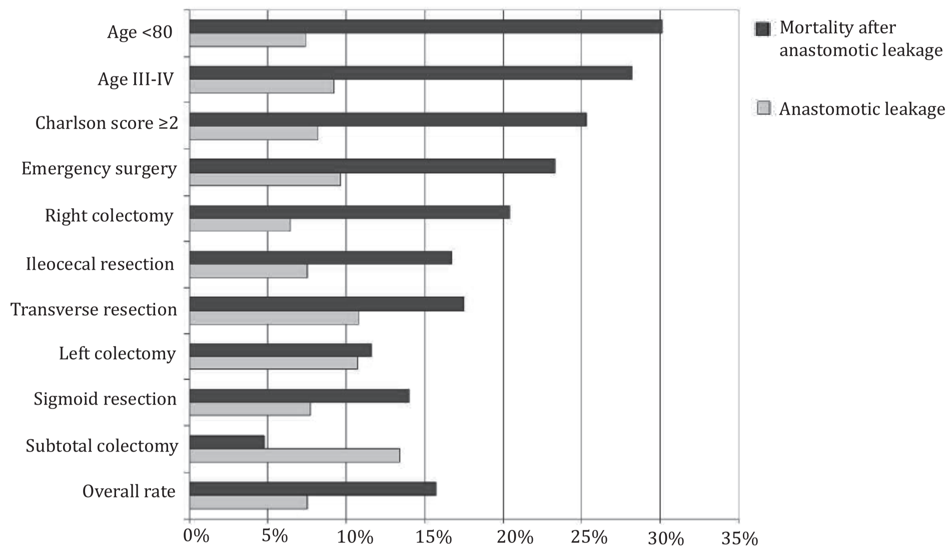

Figure 2: Anastomotic leakage and subsequent mortality rates of the different risk factors for mortality after anastomotic leakage. Results of univariate analysis, with overall rates as a reference.

Charlson score (table 1). Moreover, surgery in emergency setting and type of surgical resection were associated with a higher risk.

Especially patients undergoing a right colectomy, transverse resection or ileocecal resection, had high mortality rates after occurrence of AL (figure 2). After adjustment for possible confounders, multivariate analyses showed that higher age, high ASA classification, higher Charlson score and surgery in an emergency setting were independent risk factors for mortality in patients diagnosed with AL. Multivariate analysis also showed lower mortality associated with AL after left colectomy compared to other surgical resection types (table 5).

Table 5: Risk factors for mortality after anastomotic leakage, multivariate analyses of all patients diagnosed with anastomotic leakage

Characteristics		OR	95% CI	P-value
Age	<65	Ref		
	65-80	3.154	1.887-5.271	<0.001
	>80	5.162	2.976-8.956	<0.001
ASA classification	I-II	Ref		
	III-IV	1.771	1.244-2.521	0.002
	Unknown	1.891	0.479-7.473	0.363
Charlson Score	0	Ref		
	I	1.764	1.156-2.693	0.008
	≥II	2.23	1.474-3.373	<0.001
Surgical resection	Right colectomy	Ref		
	Ileocecal resection	1.002	0.254-3.944	0.998
	Transverse resection	0.802	0.377-1.706	0.566
	Left colectomy	0.538	0.313-0.924	0.025
	Sigmoid resection	0.745	0.513-1.084	0.124
	Subtotal colectomy	0.284	0.036-2.235	0.232
Time of surgery	Elective	Ref		
	Emergency	1.749	1.121-2.730	0.014
	Unknown	0.778	0.386-1.568	0.483

DISCUSSION

The present study on risk factors for anastomotic leakage and mortality following colon cancer resection with an anastomosis showed a 7.5 % leak rate for all patients. There was an overall mortality rate of 4.1 %, which was significantly higher for patients with anastomotic leakage than in those without (16.4 vs 3.1 %).

The leak rate found in the present study is higher than the leak rate reported in recent literature (3-6.4 %)[6-8]. This might be attributed to the complete registration in a clinical audit. Reported results from a nationwide study on leak in Denmark also showed a rather high percentage of 6.4 %[7]. Other publications with lower percentages usually are from dedicated centers. Adjusted data for confounding factors indicated male gender and high ASA classification as independent risk factors for anastomotic leakage, which is consistent with the literature[7,23,24]. Other reported predictors for anastomotic leakage such as previous abdominal surgery[24] or high BMI[3,25], could not be confirmed in our analysis. Another well-known risk factor for anastomotic leakage is co-morbidity[8,11,24], in the present study reflected in the Charlson score and ASA classification. Both scores were associated with anastomotic leakage in univariate analyses and ASA score remained a significant predictor for anastomotic leakage in multivariate analyses.

Adjusted analysis in the present study indicated that treatment factors such as extensive resections and type of surgical resection were independent risk factors for anastomotic leakage. The incidence of anastomotic leakage differs per tumour location and subsequent type of surgical resection. Right-sided colectomy is associated with a lower leakage rate compared to left sided colectomy[3,26], and the occurrence of anastomotic leakage is higher after transversectomy[11]. Vascularization of the anastomotic site may be explanatory in this as in a right-sided hemicolectomy a well-vascularized ileal bowel loop is anastomosed to an adequately vascularized transverse colon loop. While in transverse or left colic resection, where the middle colic artery or inferior mesenteric artery is divided, vascularization of the anastomotic site might be compromised[27,28]. Another explanation is the lack of full mobilization of one or both flexures. The poorer outcome after a transverse resection in the present study, emphasize the importance of careful surgical decision-making.

In patients requiring a transverse resection, an extended colectomy could be a better alternative than a transverse resection.

Data of other known risk factors as loss of weight[26], intraoperative complications, operative time, blood loss and fecal contamination[8,11] were not available in our database.

The overall mortality of 4.1 % in the present analysis is in range with population based studies in the literature (3.0-7.4 per cent)[6,29,30]. The 16.4 per cent mortality following AL is high and related to old age and co-morbidity, as is also known from the literature (12.0-18.6 %)[6,11]. The mortality rate after AL is described to be much higher after a colon resection compared to patients undergoing a rectal resection (0.7-4 per cent)[9,31,32]. This dissimilarity might be explained by differences in anatomy. Anastomotic leakage after colon resection often results in a generalized peritonitis, compared to more local, extra peritoneal abscess formation after a rectum resection. For early detection of anastomotic leakage after rectal surgery, leakage scores are developed[29,33]. It is of upmost interest to validate these scores also for colonic resections, since severity of the consequences of leakage from a colonic anastomosis is underestimated.

To reduce incidence of anastomotic leakage or its clinical sequelae, a defunctioning stoma could be constructed. In rectal anastomoses, temporary defunctioning stomas are made to reduce the clinical consequences of anastomotic leakage[10,34]. In our series most of the defunctioning stomas were constructed after a sigmoid resection. The present analysis showed no significant decrease of anastomotic leakage in univariate analysis, but after adjustments for patient and tumour characteristics, multivariate analysis showed a protective effect of a defunctioning stoma for anastomotic leakage. Apparently, there was a good patient selection for fecal diversion, based on the preoperative or intraoperative surgeons' judgment concerning the risk for anastomotic leakage. Emergency surgery is also considered as a risk factor for both anastomotic leakage[12,35] and postoperative mortality[12.30,36]. A poor general condition and nutritional state, is associated with higher morbidity and mortality risks in these patients[36,37]. In the present study, emergency surgery was an independent risk factor for both anastomotic leakage and mortality following anastomotic leakage. Our repeated multivariate analysis also confirmed that patients with preoperative complications as tumour perforation and obstruction had a higher odds for postoperative anastomotic leakage occurrence.

Emergency surgery is frequently performed in evening and night shifts. Studies from different medical fields also reported worse postoperative outcome after surgeries performed in late hours[38-40]. Surgical procedures in late hours are sometimes performed by surgeons with a lower disease-specific caseload. Some studies suggested that experience and caseload of the individual surgeon are predictors for postoperative mortality[9,41.] Unfortunately, our database does not contain individual data of surgeons.

The strength of this study is that results are based on a complete and large nationwide dataset, which contained registered data from all Dutch hospitals performing colorectal surgery. Validation of the registered data showed a high concordance against the national cancer registry. Therefore a valid analysis of colon cancer surgery in the Netherlands could be made. However, several limitations are worth mentioning. A somewhat heterogeneous study population is included for analysis. All colon cancer patients undergoing resection are included, including patients with stage IV disease, who may represent both curative and palliative resections and operations in emergency setting. Though the analysis of such a complete cohort leads to fair results, the heterogeneity is also accompanied by confounding factors and might lead to bias. In order to control for bias we also performed a multivariate analysis model stratified for time of surgery (elective and emergency). The main results of the analysis for the subgroups did not differ significantly, compared to the presented results of the total study population (data not shown). Therefore, we used 'time of surgery' as possible risk factor for anastomotic leakage and subsequent mortality in our multivariate model. Another limitation of this dataset is that only patients treated for malignancy could be analyzed, while there are also benign indications for colon surgery. Furthermore, little intraoperative information is recorded. The dataset contains no data regarding duration of operation, blood loss and surgical techniques. Intraoperative information could be a valuable contribution for the identification of risk factors for anastomotic leakage. The same also applies to information regarding caseload per surgeon. Colon cancer resections are common surgical procedures. Although for the individual patient the exact mechanism leading to the development of anastomotic leakage is often unknown, and the clinical risk assessment by the operating surgeon is of low predictive value[44], it is important to understand that tumour and treatment factors may play an important role.

Mortality rates after the occurrence of anastomotic leakage are high, and mainly determined by patient factors as high age and comorbidity. Therefore, it is important to monitor patients postoperatively according to standardized postoperative surveillance, perhaps incorporating colon leakage scores designed for left sided colorectal surgeries[29,33]. Future research projects should be focused on further evaluation of these leakage scores in colon resections, and on continuous monitoring through clinical auditing.

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CHAPTER 9

Safety of elective colorectal cancer surgery: non-surgical complications and colectomies are targets for quality improvement.

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ABSTRACT

Background: Mortality following severe complications (failure to rescue, FTR) is targeted in surgical quality improvement projects. Rates may differ between colon- and rectal cancer resections.

Methods: Analysis of patients undergoing elective colon and rectal cancer resections registered in the Dutch Surgical Colorectal Audit in 2011 – 2012. Severe complication- and FTR rates were compared between the groups in univariate and multivariate analysis.

Results: Colon cancer (CC) patients (n=10184) were older and had more comorbidity. Rectal cancer (RC) patients (n=4906) less often received an anastomosis and had more diverting stomas. Complication rates were higher in RC patients (24.8% vs. 18.3%, P<0.001). However, FTR rates were higher in CC patients (18.6% vs 9.4% p<0.001). Particularly, FTR associated with anastomotic leakage, postoperative bleeding and infections was higher in CC patients. Adjusted for casemix, CC patients had a two-fold risk of FTR compared to RC patients (OR 1.89, 95% CI 1.06-3.37).

Conclusions: Severe complication rates were lower in CC patients than in RC patients; however, the risk of dying following a severe complication was twice as high in CC patients, regardless of differences in characteristics between the groups. Efforts should be made to improve recognition and management of postoperative (non-)surgical complications, especially in colon cancer surgery.

INTRODUCTION

Ever since the Institute of Medicines report 'to err is human', patient safety is a number one priority in many western health care systems. Colorectal cancer surgery is performed commonly, though it remains associated with relatively high morbidity and mortality rates[1,2], in part because colorectal cancer patients often have a high age and comorbid illnesses[3]. As a result, colorectal cancer surgery is the subject of many national quality improvement programs in Europe[4] and the United States[5], with complication- and mortality rates being widely used outcomes for comparisons of quality of surgical care. *Failure to rescue (FTR)* - the mortality rate in patients with a severe complication - is another outcome measure that indicates the ability of a surgical team to keep patients alive when severe complications occur[6-8]. FTR is seen as a good quality indicator as it evaluates both complication recognition and treatment.

Following the example of audits in other European countries, the nationwide Dutch Surgical Colorectal Audit (DSCA) was introduced in the Netherlands in 2009[9]. One of the main objectives of these audit programs is to reduce morbidity and mortality after colorectal surgery. To reach this objective, it is important to understand the mechanisms behind the development of adverse events and the way they lead to fatal outcomes. In the DSCA, postoperative mortality appears to be higher after colon cancer resections than after rectal cancer resections, despite higher complication rates in the latter[9], suggesting higher FTR rates in colon cancer surgery. These differences in FTR may be partly due to a higher proportion of non-elective surgery in colon cancer patients, which carries a higher risk of adverse events[10], though may also exist in elective cases. A similar pattern was observed in the British National Bowel Cancer Audit Program, with higher postoperative mortality rates after colon resections than after rectal cancer resections, both in elective and non-elective cases, despite higher reoperation rates in rectal cancer patients[11].

Differences in patient characteristics, such as age, comorbidity, and tumor stage between colon and rectal cancer patients may also play a role in the differences in outcomes between the two patient groups. Moreover, possible differences in treatment characteristics, such as neoadjuvant therapy, fecal diversion and minimally invasive surgery may play a role.

The purpose of this study was to evaluate differences in FTR rates between elective colon and rectal cancer resections in relation to the characteristics of these patient groups and differences in treatment patterns between colon and rectal cancer patients.

PATIENTS AND METHODS

Data source

A retrospective review of prospectively collected clinical data was undertaken. Data were provided by the DSCA, a national quality improvement project in which all hospitals performing colorectal cancer surgery participate and in which a variety of characteristics concerning patient demographics, comorbidity, diagnostics, disease-specific details, treatment and outcomes are collected prospectively. Inclusion criteria for registration are patients undergoing a resection for primary colorectal cancer. External data verification with the dataset of the Netherlands Cancer Registry (NCR), showed a 95% case-ascertainment of the DSCA in 2011[9] which increased to 97% in 2012[12].

Patients

For this study, no ethical approval was required under Dutch law. Patients undergoing any surgical resection for primary colorectal cancer between the 1st of January 2011 and 31st of December 2012, and registered in the DSCA before March 15th 2013, were evaluated. Minimal data requirements to consider a patient eligible for analyses were information on tumor location, date of surgery, complications and mortality. Patients undergoing non-elective surgery were excluded since these patients represent a subgroup of patients with other treatment perspectives and subsequent different expected outcomes[13]. Finally, patients treated for multiple synchronous colorectal tumors were excluded to make sure a clear distinction between colon and rectal cancer patients could be made.

Outcomes

Postoperative complications were defined as all surgical or non-surgical postoperative complications. In the DSCA, surgical complications (e.g. anastomotic leak, hemorrhage) are only registered when a reintervention was performed.

Failure to rescue was, in accordance with previous publications, defined as the mortality rate among patients with a severe complication[8,14]. Severe complications were defined as complications leading to ICU admission (longer than 2 days), to a reintervention, to a prolonged hospital stay of more than 14 days, or to postoperative mortality. This is consistent with previous publications in which data from the DSCA were analyzed[8,15], except for the ICU criterion which was added for a more precise characterization of severe complications. The reason this criterion was not used in previous publications is that data on ICU admission were lacking from the DSCA database before 2011. Patients with a prolonged hospital stay, in which no complication was registered, were not included in the definition of a severe complication.

Anastomotic leakage was defined as clinically apparent leakage or an abscess in the proximity of the anastomosis. Intra-abdominal abscesses were registered as such when not evidently associated with anastomotic leakage. Infectious/septic complications were all infections not meeting other (pulmonary, urinary tract, intra-abdominal etc.) criteria, for instance central venous catheter related infections, or wound infections.

Postoperative mortality was defined as death within 30 days from surgery or within the same hospital admission as the resection.

Statistical analysis

Categorical variables were compared between colon cancer and rectal cancer patients by Chi-square tests, while 2-sample t tests were used for continuous variables.

The risk of FTR after severe complications, adjusted for patient- and tumor related risk factors, was calculated with multivariable logistic regression with addition of patient category (colon or rectal cancer patients) as a variable in the model. A random effects model adjusted for the presence of variability in outcomes between hospitals.

To assess whether differences in hospital characteristics of hospitals treating colon- and rectal cancer patients influenced differences in outcomes between colon- and rectal cancer patients, we repeated our analysis in a fixed effects model with the addition of the variables teaching status, hospital volume, and level of ICU facilities according to a previous study[14].

A 2-sided $P \leq 0.05$ was considered statistically significant. Statistical analyses were performed in PASW Statistics version 20 (SPSS inc., Chicago, Il, USA) and R 2-14 (The R Project for Statistical Computing and The Comprehensive R Archive Network; http://cran.r-project.org/).

RESULTS

Patients

A total of 15,090 patients undergoing elective colon or rectal cancer resections in 92 hospitals were included. Patient characteristics are displayed in table 1.

Colon cancer patients were less often male, were older and had higher Charlson comorbidity scores and ASA classifications compared to rectal cancer patients. TNM stage was also higher in colon cancer patients. A primary anastomosis was constructed less often in rectal cancer patients, with more often fecal diversion in case of an anastomosis, compared to colon cancer patients. Laparoscopic resection rates were quite similar in both patient groups.

Outcomes

The overall postoperative complication and reintervention rates were lower in colon cancer patients than in rectal cancer patients. Median length of stay was one day longer in rectal cancer patients with a higher proportion of patients with a length of stay longer than 14 days compared to colon cancer patients. Duration of postoperative ICU admission did not differ much between colon and rectal cancer patients.

Severe complication (see definitions in the methods section) rates were higher in rectal cancer patients than in colon cancer patients ($p<0.001$) (table 2). Colon cancer patients with a severe complication met the ICU criterion more often. The majority of colon and rectal cancer patients with a severe complication had a prolonged hospital

Table 1: Patient characteristics of colon and rectal cancer patients.

Patient characteristics		**Colon cancer**		**Rectal cancer**		**p for difference**
Number of patients		10184		4906		.
Gender	male	5299	52%	1596	63%	p<0.001
Age	mean, standard deviation	71	11	67	11	p<0.001
Body mass index	mean, standard deviation	26,3	4,5	26,2	4,3	n.s.
Charlson comorbidity score	charlson 0	4979	48,9%	2837	57,8%	p<0.001
	charlson 1	2445	24,0%	1058	21,6%	
	charlson 2	1572	15,4%	609	12,4%	
	charlson 3 or higher	1189	11,7%	402	8,2%	
ASA classification	I	1961	19,3%	1271	25,9%	p<0.001
	II	5834	57,3%	2826	57,6%	
	III or higher	2366	23,2%	802	16,3%	
	unknown	23	0,2%	6	0,1%	
TNM stage	X	100	1,0%	22	0,4%	p<0.001
	I	2229	21,9%	1879	38,3%	
	II	3719	36,5%	1224	24,9%	
	III	3107	30,5%	1444	29,4%	
	IV	1029	10,1%	337	6,9%	

Table 1: Patient characteristics of colon and rectal cancer patients. (continued)

Patient characteristics		Colon cancer		Rectal cancer		p for difference
Number of patients		10184		4906		.
Procedure	Ileocecal resection	111	1,1%	.	.	.
	Right hemicolectomy	4741	46,6%	.	.	
	transverse colectomy	293	2,9%	.	.	
	left hemicolectomy	971	9,5%	.	.	
	sigmoid colectomy	3819	37,5%	.	.	
	Low anterior resection	.	.	3334	68,0%	
	Subtotal colectomy / panproctocolectomy	184	1,8%	33	0,7%	
	Abdominoperineal resection	.	.	1463	29,8%	
	Other	55	0,5%	75	1,5%	
Approach	laparoscopic	5396	53,0%	2511	51,2%	n.s.
Anastomosis	primary anastomosis	9022	88,6%	745	15,2%	p<0.001
	anastomosis with defunctioning stoma	389	3,8%	1709	34,8%	
	no anastomosis	581	5,7%	2280	46,5%	

N.s.=not significant

Table 2: Outcomes in colon and rectal cancer patients.

	Colon cancer		Rectal cancer	
	n (patients)	%	n (patients)	%
Any complication	2760	27.4%*	1775	36.5%*
Reintervention	1075	10.6%*	687	14.0%*
Length of stay				
Median	7 days		8 days	
>14 days	1553	15.4%*	1075	22.1%*
ICU admission				
0-1 day	8624	84.7%*	4121	84.0%*
2 days	328	3.2%*	213	4.3%*
3-7 days	405	4.0%*	196	4.0%*
8-14 days	150	1.5%*	58	1.2%*
> 14 days	138	1.4%*	53	1.1%*
unknown	539	5.3%*	265	5.4%*
Severe complication	1863	18,3%*	1218	24,8%*
Reason:				
Postoperative mortality	347	18,6%**	114	9,4%**
ICU admission > 2 d	693	37,2%**	307	25,2%**
Reintervention	1075	57,7%**	687	56,4%**
Complication + hospital stay >14 d	1268	68,8%**	834	68,5%**
Number of severe complications				
1	1217	12.0%*	902	18.4%*
2	437	4.3%*	221	4.5%*
3	164	1.6%*	73	1.5%*
4 or more	44	0.4%*	22	0.4%*
Failure to rescue	347	18,6%**	114	9,4%**
Postoperative mortality		3,4%*		2,3%*

*percentage of all patients ** percentage of all patients with a severe complication. Note that patients may have met multiple criteria for a severe complication

Table 3: incidence of and failure to rescue (FTR) from serious complications, displayed per complication type. Note that patients may have had more than one complication and that numbers add up to more than the total.

	colon cancer		rectal cancer		
	severe complication	FTR (%)	severe complication	FTR (%)	p for difference
anastomotic leakage	576	72 (12,5%)	215	11 (5,1%)	p=0.003
intra-abdominal abscess	16	2 (12,5%)	80	3 (3,8%)	n.s.
postoperative bleeding	51	11 (21,6%)	35	1 (2,9%)	p=0.014
ileus	84	9 (10,7%)	84	3 (3,6%)	n.s.
fascial dehiscence	105	7 (6,7%)	59	4 (6,8%)	n.s.
pulmonary complication	448	115 (25,7%)	199	45 (22,6%)	n.s.
cardiac complication	262	97 (37%)	111	31 (27,9%)	n.s.
infection/septic complication	235	49 (20,9%)	140	14 (10%)	p=0.007

stay but only in 20 and 27% of patients with a severe complication, respectively, a prolonged hospital stay following a complication was the sole reason for inclusion in the severe complication group.

FTR from severe complications – the mortality rate among the patients defined as having a severe complication – was higher in colon cancer patients, resulting in a higher overall postoperative mortality rate in colon cancer patients ($p<0.001$ for both outcomes).

Table 3 shows the most important severe complications for colon and rectal cancer patients. In colon cancer patients, the most frequent complications were anastomotic leakage (5.6% of all colon cancer patients and 6.1% of colon cancer patients with an anastomosis), pulmonary complications (4.8%) and cardiac complications (2.6%). In rectal cancer patients, the most common severe complications were anastomotic leak (4.4% of all rectal cancer patients and 8.7% of rectal cancer patients with anastomosis), pulmonary complications (4.1%) and infections/septic complications (2.9%).

Overall, FTR from severe complications was highest in both patient groups when associated with pulmonary and cardiac complications. FTR was higher in colon cancer patients than in rectal cancer patients when associated with anastomotic leakage (12.5% vs 5.1% p=0.003), postoperative bleeding (21.6% vs. 2.9%, p=0.014) and infections/ septic complications (20.9% vs. 10.0%, p=0.007). FTR rates associated with other complication types were not significantly different between the two patient groups.

Most patients had one severe complication, but some had several (table 2). FTR rates increased with the number of severe complications that a patient experienced postoperatively. In colon cancer patients this increased from 15.7% in patients that had one severe complication to 36.4% in patients that experienced four or more

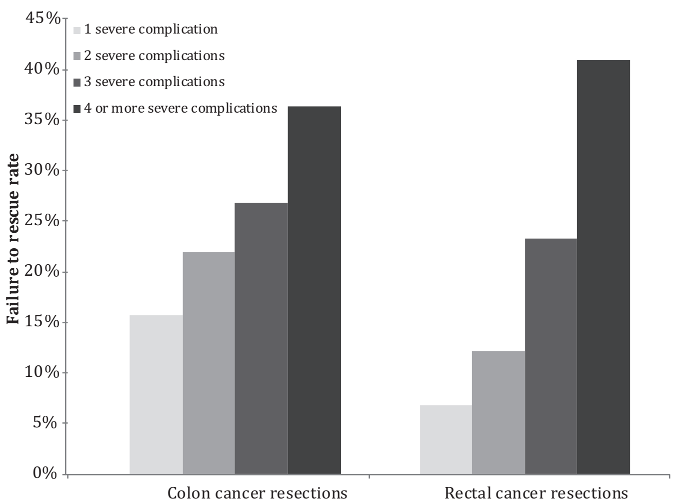

Figure 1: Failure to rescue rates according to the number of severe complications

Table 4: Multivariate analysis for the risk of failure to rescue in patients with a severe complication.

Variable		Odds Ratio	95% CI
Gender	male	1	ref
	female	0.84	0.66-1.08
Age	<=70 years	1	ref
	>70 years	**2.86**	**2.09-3.89**
Body mass index	<20	1.06	0.64 -1.74
	20-24.9	1	ref
	25-29.9	**0.75**	**0.57-0.98**
	30 or higher	**0.71**	**0.50-0.99**
Charlson comorbidity score	0	1	ref
	1	**1.42**	**1.03-1.95**
	2	1.03	0.71-1.48
	3 or higher	**1.97**	**1.38-2.82**
ASA classification	I	1	ref
	II	**1.97**	**1.51-2.58**
	III or higher	**4.07**	**2.26-7.32**
TNM stage	I	1	ref
	II	0.87	0.64-1.19
	III	0.94	0.86-1.31
	IV	1.23	0.79-1.92
Neoadjuvant therapy	none	1	ref
	short course RT	1.28	0.71-2.31
	chemoradiotherapy	0.80	0.40 -1.60
Approach	open	1	ref
	laparoscopic	1.04	0.80 -1.36
Additional resections	none	1	ref
	limited*	0.89	0.50 – 1.58
	extensive**	0.94	0.56 – 1.58
Anastomosis	primary anastomosis	1	ref
	anastomosis with defunctioning stoma	0.74	0.47 -1.17
	no anastomosis	1.07	0.74-1.55
Resection type	rectal cancer resection	1	ref
	colon cancer resection	**1.89**	**1.06-3.37**

ASA=American Society of Anesthesiologists CI=confidence interval. Bold printed numbers are significant associations (P<0.05). *abdominal wall, omentum, posterior vaginal wall, ovaries. **organ resection (pancreas, small bowel, spleen, kidney, liver, stomach, sacrum, bladder/urethra/ureters/prostate, uterus) severe complications. In rectal cancer patients this increased from 6.8% to 41% (figure 1).

Risk factors

Table 4 displays the results of the multivariable regression analysis for the association between patient-, tumor-, and treatment factors and the association with FTR in patients who had a severe complication. Adjusted for these variables, colon cancer patients had an almost two-fold higher risk of dying secondary to a severe complication than rectal cancer patients.

Other independent predictors of FTR were advanced age and higher Charlson comorbidity and ASA scores. Higher body mass index was associated with a lower risk of FTR. Gender, neoadjuvant therapy, additional organ resections, laparoscopic resections and stoma construction were not significantly associated with outcome.

In a repeated analysis with adjustment for the hospital characteristics in the model, the difference in FTR between colon and rectal cancer patients remained the same (colon vs. rectal cancer resection: adjusted OR 1.88; 95% CI 1.04 – 3.39). There was no significant effect of volume or teaching status on FTR rates but better ICU facilities were associated with better FTR rates (level 2 vs. level 1; OR 0.54, 95% CI 0.35 – 0. 84 and level 3 vs. level 1; OR 0.83, 95% CI 0.53 – 1.31).

DISCUSSION

This is the first study comparing FTR rates between patients undergoing a resection for colon cancer and rectal cancer. FTR was higher in colon cancer patients than in rectal cancer patients. This was partly because colon cancer patients were older, and had more comorbidity and higher ASA classifications; although adjusted for the differences in patient- and treatment characteristics, the risk of FTR remained twice as high in colon cancer patients.

Schilling et al. described that colectomies account for a disproportionate share of morbidity, mortality and excess length of stay among all general surgical procedures. Colectomies account for 24% of all adverse events in general surgery with an adverse event rate of 29%[1]. In a Dutch study with data from the Eindhoven Cancer registry, it was shown that patient characteristics differ between colon- and rectal cancer patients, and that rectal cancer patients have a higher risk of postoperative complications, even though they are younger and less often have comorbid diseases than colon cancer patients[3]. Our study confirms the relatively high adverse event rate in colorectal surgery, and confirms that this rate is higher in rectal cancer surgery than in colon cancer surgery. Our study adds that the risk of dying given a severe complication is higher following a colon cancer resection than after a rectal cancer resection, even after adjustment for other relevant factors. Due to the nature of the database, our study provides a realistic image of outcomes of everyday practice in elective colorectal cancer surgery in the Netherlands.

Our study has some limitations. Firstly, as data are self-reported, registration bias cannot be excluded. However the dataset is validated against the independently collected data of the Netherlands Cancer Registry, showing a high rate of case-ascertainment, completeness and accuracy[12]. The direct involvement of clinicians in the registration leads to a robust database and avoids coding problems that may occur when using an administrative database. Secondly, although the definition of a severe complication we used is arbitrary, it excludes the less severe complications that did not hinder the postoperative course. Since ICU admission, reinterventions and prolonged hospital stay are objective criteria, FTR rates are not influenced by differences in the way hospitals register minor complications. However, it cannot be excluded that some patients with a serious complication were not included in the definition. All (complications leading to) mortality cases were considered severe complications, regardless of reinterventions, ICU admission or prolonged hospital stay. We performed a sub analysis in only those patients who underwent a reintervention, had ICU admission or a complication with a prolonged hospital stay, and the difference in FTR rates between rectal and colon cancer patients remained the same (adjusted OR 2.1; 95% CI 1.06-4.37). Finally, with regards to the analysis of FTR rates associated with different complication types, we cannot exclude that patients who were registered as having experienced non-surgical complications might also have had undiscovered underlying surgical complications.

Anastomotic leakage is considered the most dreadful complication in colorectal surgery and accounts for a large proportion of overall postoperative mortality[16]. Indeed, in our study anastomotic leak was the most common severe complication. The proportion of leaks that lead to mortality was significantly higher in colon cancer patients, although the anastomotic leak rate was higher in rectal cancer patients (given an anastomosis was constructed). A part of the explanation may be found in the larger proportion of anastomoses with a defunctioning stoma in rectal cancer patients compared to colon cancer patients. Also, a large proportion of rectal cancer patients did not receive a primary anastomosis, and therefore the group of colon cancer patients was a priori more susceptible for mortality following anastomotic leak as well as possible associated non-surgical complications. However, diverting stomas and end-colostomies were not significantly associated with FTR. Moreover, adjusted for stoma rates, FTR remained higher in colon cancer patients. Early recognition and treatment of anastomotic leak may be associated with lower mortality associated with leakage[17]. Arguably, as the anastomosis following rectal resections lies in the pelvic region, anastomotic leaks following rectal cancer resections often will have a more chronic course, developing a presacral sinus or pelvic abscess[18], whereas colonic anastomotic leaks might have a higher risk of fecal peritonitis due to the intra-abdominal location. Whether a longer delay or a more fulminant course of anastomotic leak in colon cancer patients has contributed to the differences in FTR between the two patients groups cannot be retrieved from the DSCA dataset, but should be the focus of future in-depth studies as a reduction in delay of diagnosing anastomotic leak may prove a potential target for improvement[19].

Cone et al. reported a high risk of mortality following postoperative non-surgical complications such as pneumonia and renal insufficiency in colorectal surgery patients[20]. Friese et al. described mortality rates and their relation with complications in 25,957 patients that underwent a surgical resection for colorectal- and other types of cancer[21]. Mortality was most frequently secondary to respiratory compromise (37% of postoperative mortality) and pneumonia (26%). Our study confirms that cardiopulmonary complications are often associated with postoperative mortality, although it is not possible to make a clear distinction between surgical and non-surgical complications as surgical complications may start a chain of non-surgical adverse events, leading to clinical deterioration and eventually death. It does however underline the importance of a high postoperative vigilance for non-surgical complications besides the intuitively important surgical complications such as anastomotic leak. Aggressive, multidisciplinary treatment of complications such as pneumonia, arrhythmias or central venous catheter sepsis may prevent postoperative death from non-surgical complications. Arguably, adequate preoperative optimization of the patient's condition may be an even more important step in reducing mortality from non-surgical complications. Fuchshuber et al. describe how a hospital drastically improved the number of patients on a ventilator for >48 hours, and achieved a zero postoperative pneumonia rate in patients undergoing thoracoabdominal surgery during seven months by strictly adhering to a few perioperative steps[22]. Similar achievements have been published about reducing the number of acute bloodstream infections related to central venous catheters[23]. A recent meta-analysis showed that measuring the C-reactive protein on postoperative day 4 has a pooled negative predictive value of 89% for predicting postoperative infectious complications after colorectal surgery, allowing safe discharge of patients not at risk[24].

In the last decade, improvement of clinical outcomes for complex, low-volume gastrointestinal cancer surgery such as pancreatic, esophageal and rectal cancer resections has received much attention in the western world[25-30]. In the Netherlands, specialization of caregivers, focused improvements to infrastructure, specific interventions to perioperative management and selective referral have led to dramatic improvements in outcomes of patients undergoing these particular procedures[31-35]. In contrast, CC surgery received less attention and is, as a result, often performed in a non-focused setting. In a previous study, we found no association between FTR and hospital volume or teaching status in colorectal cancer patients, but better FTR rates in patients operated in hospitals with better ICU facilities[14]. We therefore repeated our analyses including these hospital characteristics, confirming the association between ICU facilities and FTR rates. However, the difference in FTR between colon and rectal cancer patients remained the same in this second analysis and we cannot conclude that the difference in FTR between colon and rectal cancer patients can be attributed to differences in hospital characteristics in which colon- and rectal cancer patients are treated. Surgeons' differentiation may play a role- rectal cancer resections are usually performed by specialized gastrointestinal surgeons, whereas colon cancer resections are often performed by surgeons without gastrointestinal specialization- but our study has no data on a surgeon level to support this. Recently, the Association of Surgeons of the Netherlands started with certification of surgeons performing colon cancer procedures.

In conclusion, the incidence of severe postoperative complications was lower in colon cancer patients than in rectal cancer patients; however, the risk of dying when a severe complication had occurred (FTR) was twice as high in colon cancer patients, even after adjustment for differences in patient-, tumor-, and treatment characteristics between the two patient groups. In particular, FTR associated with anastomotic leak, postoperative bleeding and non-surgical infectious complications was higher in colon cancer patients than in rectal cancer patients. Given the results of our study, efforts should be made to improve recognition and management of postoperative surgical and non-surgical complications in order to reduce postoperative mortality. Especially patients undergoing colon cancer surgery should receive full attention.

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CHAPTER 10

General discussion and summary of this thesis

D. Henneman

With the ever-expanding technological advances, the boundaries of healthcare continue to be moved. Especially, oncological care is developing rapidly. As staging methods, surgical-, medical- and non-medical care evolve, the patient with cancer is increasingly approached in a multidisciplinary fashion. The ageing population leads to a higher proportion of cancer patients that is susceptible for complications secondary to cancer treatment, as a result of prevalent comorbid illnesses.

In this era of expanding indications and increasing complexity of treatments, healthcare providers are more and more conscious of the need for evaluating the processes and outcomes of the care they provide. These developments are accelerated by the fact that doctors are progressively confronted with payers and policy makers demanding information that should enable them to allocate resources towards cost-efficient providers with the best outcomes. Patients, nowadays increasingly organized in- and represented by- patient associations, also call for information concerning safety and effectiveness of treatments in different hospitals.

COMPARING HOSPITALS

With the growing societal demand for quality information on healthcare providers, the lay press increasingly publishes reports on presumed quality of health care of providers. For instance, in the Netherlands, everyone is familiar with the league tables provided each year by some journals (Elsevier's best hospitals, AD hospital top 100). Focusing on outcome, the hospital standardized mortality rate (HSMR) is calculated annually. In 2014, it became mandatory for Dutch hospitals to publish their HSMR. The HSMR comprises of an average mortality in-hospital rate from 50 main diagnoses. These rates are merged into one hospital-wide mortality rate, adjusted for secondary diagnosis codes. A problem with this method is that secondary diagnosis codes are insufficient for a comprehensive and reliable risk adjustment, as they do not allow procedure-specific risk-adjustment[1]. Moreover, the mortality rate itself is an average hospital-wide mortality rate, and not procedure- or diagnosis specific. HSMRs are often displayed as simple rankings, which are unsubtle and arguably unreliable[2].

Both the lay press league tables as well as the HSMR lack face validity for doctors[3,4].

This lack of face validity with doctors is important, because without it, it is less likely to result in actual improvement of quality of care. Recent studies from the Netherlands show that patients so far aren't using available quality information for choosing a hospital[5,6].

MEASURING QUALITY OF CARE

Measuring quality of care classically comprises three overlapping aspects; structure (the environment in which the provision of care takes place), process, and outcomes. This triad is referred to as the 'Donabedian paradigm'[7]. Measuring quality of care information in a comprehensive manner, and feeding this back to the participating healthcare providers can enhance the quality of delivered care[8].

In 2010 and 2011, the Boston Consulting Group published two reports elaborating on a comparison between the Dutch and Swedish healthcare systems[9,10]. The main conclusion was that the quality of care is generally high in the Netherlands, but that costs can be reduced and outcomes improved when compared to Sweden. The main recommendation was to initiate nationwide clinical registries, with a focus on generation of meaningful outcome indicators, which is common practice in Sweden for years.

Dutch Surgical Colorectal Audit

Initiated by the Association of Surgeons of the Netherlands, the Dutch Surgical Colorectal Audit (DSCA) started in 2009 as a nationwide quality improvement program auditing the surgical treatment of patients with primary colorectal cancer in the Netherlands. One of the main focus points of this initiative is reduction of adverse event rates. Colorectal cancer surgery was considered a logical starting point: colorectal surgery accounts for a disproportionate share of morbidity, mortality and excess length of stay among all general surgical procedures. It accounts for roughly a quarter of all adverse events in general surgery[11].

In contrast to other initiatives and registrations, the DSCA is characterized as doctor-driven with a high face-validity among surgeons. This is important, as it assures a high participation rate, case-ascertainment and accuracy of data, as well as a smooth implementation of improvement projects once targets for improvement have been signalled. A main feature is a quick feedback loop to the participating surgeons, enabling quality assurance and improvement. This is done through web-based feedback of outcomes with the national average as a benchmark to participating clinics[12]. Importantly, the audit was designed to capture many patient- and disease related risk factors that may add to hospital variation in outcomes when they would be unevenly distributed among hospitals[13]. Where possible, outcomes are adjusted for these factors so comparisons are as fair as possible. Accumulative evidence shows the benefits of such a program[8]. A well-known example of improvement through measurement and feedback is from Canada: in 1999, pancreatic cancer surgery was centralized in two Canadian provinces. In Quebec, the regionalization was accompanied by an audit cycle, feeding back mortality data to hospitals, whereas Ontario did not have an additional audit program. As a result, mortality decreased dramatically in Quebec (from 10 to 2%) but remained constant in Ontario[14]. Similarly, the American National Quality Improvement Project (NSQIP) is a large-scale clinical registry that provides feedback of outcomes to participating hospitals. Initiated in Veteran's Affairs hospitals and later adopted by the American College of Surgeons, the project has led to a significant decrease in postoperative adverse events[15,16].

In the DSCA improvement cycle, a team of experts led by the Association of Surgeons of the Netherlands helps clinics with morbidity or mortality rates that are significantly higher than the national average ('outlier hospitals') to initiate targeted improvement projects. Already after a few years of auditing, the first improvements in terms of higher standards and reduced variation in guideline adherence, as well as a reduction in the number of adverse outcomes are becoming apparent[12]. After the example of the DSCA, various (surgical) clinical audits were initiated in the Netherlands: the Dutch Upper GI Cancer Audit (DUCA; 2011), the NABON Breast Cancer Audit (NBCA, 2011) and the Dutch Lung Surgery Audit (DLSA, 2012). Quite recently, this number has increased even more. After Swedish example, the Association of Surgeons of the Netherlands has set the goal to make outcomes of the audits publicly available. To reach this goal, a process in which outcomes of the audits will become publicly available in a stepwise fashion throughout the years was initiated.

OUTCOMES RESEARCH

In programs like these audits, determining outcomes that measure and represent actual quality of care remains challenging and depends on the condition of interest and the patient population. In surgical oncology, outcomes can be roughly divided into 'achieving goal', i.e. performing a resection with tumor-free margins and harvesting enough lymph nodes; and 'avoiding adverse events' on the other hand. With a good performance on both aspects, the ultimate goal of long-term survival and quality of life can be pursued. Quality of care for procedures that are relatively high-risk, as is the case with surgery for cancer of the digestive tract, is often assessed using adverse event outcome measures such as morbidity or mortality rates.

In order to identify good and bad performers, outcomes reflecting hospital performance must be investigated. The specific value or usability of such outcome indicators is not always clear. Outcome indicators should represent meaningful differences between caregivers. This thesis, focusing on clinical adverse event outcomes associated with surgical oncological procedures, should be seen in the light of the recent developments around the Dutch nationwide outcome registries. The studies contribute to the knowledge about the meaning of, and interaction between certain clinical outcome indicators that are used in hospital comparisons. This may contribute to more targeted feedback to hospitals and a better understanding of results from the audits, which is especially important when outcomes become publicly available. Moreover, these studies add to the knowledge concerning risk factors and outcomes, which may aid in directing improvement efforts for the care of surgical patients on a national and local level.

HOSPITAL VARIATION

Postoperative mortality

Postoperative mortality is considered a very important outcome in major oncological surgical procedures like colorectal cancer surgery. It also may be considered one of the most delicate outcomes. Recently, in the United Kingdom, postoperative mortality rates per hospital and per surgeon became publicly available from the internet[17]. This development is laudable from a societal perspective. However, transparency of this kind of information should be well thought of. It is crucial that comparisons of caregivers are reliable as this information may influence the patients' trust and choice, as well as allocation of reimbursements by insurers and certification by policy makers. Unjustly stigmatizing a hospital as having a high mortality rate may have great impact on hospital reputation. Simple mortality league tables that may arise from this data may not be reliable[18,19].

One of the drawbacks of rankings on this measure is that differences between hospitals may be influenced by the fact that hospitals treat patients with different characteristics

(" casemix"), associated with a different a priori risk of mortality (e.g., a hospital treating many elderly patients is likely to have a higher operative mortality rate because of this)[13]. Secondly, chance variation may play an important role. For hospitals with a small number of cases, it is difficult to know whether extremely high or low mortality rates are due to chance or caused by actual differences in quality of care. In this thesis, we showed the importance of adjustment for case-mix as well as statistical reliability adjustment[20] in rankings on postoperative mortality. Moreover, we found that 62% of variation between hospitals in mortality after colorectal cancer resections is due to chance (a 'rankability'[21] of 38%) **[chapter 2]** which can be attributed to a relatively low 'event rate' from a statistical point of view.

This implies that great caution should be used when interpreting hospital rankings on this outcome. Outcomes with a higher event rate may have a higher rankability. Lingsma et al. suggest that rankings are meaningless when rankability is lower than 50%[22]. Should rankings be attempted anyway, we suggest the percentile expected rank (PCER) should be used: the chance that the selected hospital has a better outcome than a randomly selected hospital **[chapter 2]**[23]. This way, the uncertainty concerning the outcome is included in the single percentage ascribed to each hospital. Future work will focus on inclusion of confidence intervals in displaying of ranks and on assessing the possibility to predict a hospital' s future rank based on previous years. The rankability of other outcomes should be determined.

Moreover, in the context of outcome indicators becoming public, it should be investigated whether measures like the PCER are comprehensible and usable for the general public.

Anastomotic leakage

The abovementioned study underlines the need for case-mix adjustment in hospital comparisons on postoperative mortality. This is achievable, but it requires a substantial registration effort to collect all possible confounding factors. Hence, it would be valuable to find outcomes that reflect differences in quality of care rather than differences in casemix. One of the most dreadful complications in colorectal surgery is anastomotic leakage[24]. The findings of this thesis suggest that hospital variation in anastomotic leak rates is relatively independent of patient- and tumor characteristics, and may be more related to treatment factors and in-hospital care processes when compared to mortality as an outcome indicator **[chapter 3].** A drawback of using anastomotic leak rates as an outcome indicator is that it is only useful for patients that had a primary anastomosis created.

Reoperation rates

Another often suggested outcome indicator in colorectal surgery is 'unplanned reoperations'. The indicator, a compulsory indicator collected by the Dutch Healthcare Inspectorate, is said to be useful because it discriminates more than mortality rates, especially in elective surgery where mortality rates are lower. It correlates with postoperative surgical complications, a prolonged hospital stay and mortality[25-27]. Not unimportant, it may be relatively easily obtained, for example from financial data or procedure codes. The problem is that most of the abovementioned evidence is based upon studies performed on a patient level. This thesis sought to determine the value of reoperation rates after colorectal cancer resections on a hospital level. It turns out that high reoperation rate outlier institutions (significantly higher rates than average) have similar outcomes as the hospitals with average reoperation rates **[chapter 4]**. The group of hospitals with lower reoperation rates had low mortality rates. Interestingly, when all hospitals are compared on an individual basis, results may be the other way around: high reoperation rates combined with low mortality or vice versa.

Defensive behaviour

Benchmarking hospitals on outcome indicators such as anastomotic leakage or reoperation rates to compare hospital performance may potentially lead to defensive behaviour among surgeons. For instance, surgeons may increasingly decide to construct a defunctioning ileostomy or colostomy proximal to the large bowel anastomosis in order to limit the rate of clinically relevant anastomotic leaks and subsequent reoperations. In the Netherlands, the number of defunctioning stomas after rectal resection with anastomosis has already increased over the last decade to more than 70%[28]. As such a stoma itself causes short-term but also longer-term morbidity for the patient[29,30], there is increasing evidence that a more critical application of faecal diversion may be warranted. Auditing short-term outcomes such as anastomotic leakage may maintain a certain defensive attitude among surgeons, which may not always be in the interest of patients.

'Reoperation rate' as an outcome indicator has a similar ambiguity. A reoperation is a marker for surgical complications and has, by itself, a high impact on a patient. However, using reoperation rates as an outcome indicator may theoretically raise the threshold for a reoperation in case of a suspected surgical complication- while in fact, a surgical team that recognizes complications early in the process may save patients' lives by adequately performing reoperations. In a publication by Almoudaris et al., hospitals with low mortality rates after upper gastrointestinal cancer surgery were the ones with higher reoperation rates[31].

So, reoperation rates are discriminative but do not tell the whole story when used in isolation **[chapter 4]**. A surgical team with high reoperation rates but a low mortality rate is at least able to rescue a patient with a surgical complication. The same thing applies to analyzing mortality rates in isolation: if mortality rates are low, though come at the cost of very high rates of reoperations, there is probably room for improvement.

Failure to rescue

An outcome indicator that may be of additional value is failure to rescue (FTR): the mortality rate among patients with a severe complication[32]. This outcome indicator reflects the ability of a surgical team to *manage* postoperative complications once they have occurred. This thesis explored the applicability of FTR as an outcome measure, finding a wide variation between hospitals **[chapter 5]**. Hospitals with high mortality rates will intuitively have higher complication rates. Although rates of severe complications differed between low- and high-mortality hospitals, this difference was too small to explain the large difference in mortality. Instead, high- and low-mortality hospitals were distinguished by high and low FTR rates: their ability to treat and save patients with severe complications. These findings are consistent with recent international literature[33-35]. Hence, an important area for improvement of mortality rates may be found in early detection and aggressive treatment of postoperative complications.

So, FTR reflects processes in the perioperative care. It may explain why some teams or centers are able to prevent serious complications to lead to mortality. The rationale of using FTR is to help institutions understand and prevent this. Intuitively, using FTR as an outcome indicator would remove any hesitations to reintervene in case of a complication, as a successful reoperation will merely lower FTR rates. A limitation of this outcome indicator is that event rates are relatively low, as is the denominator: only complicated cases are used for calculation. This may increase chance variation and lower the strength of statistical modelling (and thus risk adjustment) in smaller datasets.

HOSPITAL CHARACTERISTICS AND OUTCOMES

Surgical teams differ in their ability to save patient's lives once complications occur. Why do FTR rates differ? Identification of the processes that account for superior results remains challenging[36]. Therefore, some argue to focus on exploring which hospital characteristics are associated with better outcomes. For instance, it has been suggested that a higher caseload per hospital is associated with lower FTR rates[37]. Similarly, in Anglo-Saxon literature, university hospitals or teaching hospitals have been described to have lower FTR rates than non-teaching hospitals[38], which may very well be related to intensive care (ICU) characteristics. We found that in unadjusted analysis, a case volume of >200 patients/year, teaching status and higher level of ICU facilities were all associated with favorable FTR rates after colorectal cancer resection **[chapter 6].** After adjustment for each other, as well as for other confounders, only a higher level of ICU facilities remained significantly associated with better FTR rates. A beneficial effect of a higher standard of ICU care on FTR rates is in keeping with the fact that ICU treatment is an essential element of postoperative care in high risk patients: 15% of all patients undergoing elective colorectal cancer surgery receive ICU treatment postoperatively[39]. This rate is probably even higher in patients undergoing surgery in an urgent setting. In the Netherlands, standards of ICU care have traditionally been divided into three levels. A level 3 ICU is the highest level, comprising of a closed format ICU, with highest number of beds (12 minumum), nurses per bed, number of ventilator days per year, among other quality standards. On an ICU level 1, responsibility for the patient is not necessarily transferred to an intensivist, an intensivist is not exclusively available 24 hours a day, has less beds (6 minimum) and no minimum of ventilator days per year. A level 2 ICU is a closed format ICU with lower minimum standards of ventilator days, treatment days per year compared to a level 3 ICU[40].

In the study in **chapter 6**, levels 2 and 3 had a similar beneficial odds ratio for FTR when compared to level 1. A main difference between the levels is the 24-hour availability of an intensivist in levels 2/3. In the upcoming revised Dutch national ICU guidelines, the level classification is abolished and 24-hour intensivist staffing becomes a standard element of ICU care. Of note, this research focusing on hospital characteristics, aims to identify possible mechanisms behind differences in outcomes between hospitals. From **[chapter 6]** it follows that one of the possible factors may be a difference in standard of ICU care. These differences in ICU level may reflect differences in clinical processes and resources, and further research in 'best practices' as well as the lesser performing centers should be aimed at unraveling the processes leading to better or worse outcomes. Combining data from the national Intensive Care registration (NICE) with DSCA data may be a valuable first step in this process.

Centralization

There is no consensus for concentration of care for common oncological procedures like colorectal cancer surgery[41,42]. A Cochrane review showed a volume-outcome relationship in colorectal cancer surgery, but not between postoperative mortality and hospital volume[43]. The review acknowledges that results vary per country or region. In a recent Dutch publication, no differences in mortality were seen between high- and low volume hospitals performing colon cancer surgery[44]. The absence of association between hospital volume and FTR in this thesis **[chapter 6]** is in line with this study.

In contrast, the volume-outcome relationship is more convincing for high-complex low-volume procedures like pancreatic or upper gastrointestinal cancer surgery[45]. In esophageal cancer surgery, there is compelling evidence that patients have better short- and long-term outcomes when operated in a hospital with a high annual caseload of esophagectomies, including some evidence from Dutch studies[46,47,48]. Therefore, around the world there is a growing consensus to centralize esophageal cancer surgery to high-volume centers. However, many different definitions of a 'high-volume hospital' are proposed in the recent literature, ranging from more than 5 to more than 86 esophageal cancer resections annually[45,46,49-75]. No research was done to define to what extent the volume-outcome relationship remains. Consequently, minimum volume standards for esophagectomies vary per country or region[76-78]. The current Dutch minimum volume standard, set arbitrarily in 2007, is 20 esophageal cancer resections per hospital per year[79]. From **chapter 7** it follows that further centralization of esophagectomies may lead to a decrease in postoperative mortality and survival. Better outcomes in hospitals with a higher hospital volume may be a reflection of a variety of factors in the process of care, such as an integrated multidisciplinary approach, improved patient selection, and protocols; as well as superior resources.

In contrast to the well-established relationship between hospital volume and postoperative mortality, this association is less established in colorectal cancer surgery. In a meta-analysis by van Gijn et al., non-significant results were found in both rectal cancer surgery and colon cancer surgery, although the result became significant in favor of high-volume hospitals with exclusion of the study that did not adjust for confounders[42]. This excluded study was the only Dutch study in the analysis. Of note, the relationship between hospital volume and longer-term survival was in fact significantly in favor of high volume.

An original study from the Netherlands also did demonstrate no relationship between volume and postoperative mortality in colon cancer surgery[44]. This notable difference between Upper GI cancer surgery and colorectal cancer surgery remains subject of speculation. A factor may be that esophagectomy and gastric tube reconstruction is perhaps technically more challenging and a physically more demanding procedure for the patient compared to a segmental colectomy. As (surgically treatable) esophageal cancer is far less common than colon cancer, treatment in a high-volume would then be more important for esophageal cancer patients compared to colon cancer patients. Contradicting this theory is that postoperative mortality rates after colectomies in the Netherlands are comparable to those of esophagectomies. Perhaps case volume is less an issue in colorectal cancer surgery, but when compared to esophageal cancer surgery, dedication of the team to this type of surgery may be. In esophageal cancer, a high degree of dedication came along with the introduction of the minimum volume standards. Perhaps the introduction of the DSCA reflects an increasing awareness in the field of colorectal cancer surgery that more dedication with multidisciplinary teams, enhanced perioperative care protocols and a smoother run-through time from diagnosis to surgery- thereby avoiding surgery in the urgent setting- is the way to go in order to further improve outcomes for colorectal cancer patients. Moreover, a drawback of using case volume as a proxy for quality of care is that nothing can be learnt from it[80,81]. In both esophageal cancer surgery and colorectal cancer surgery, in order to reduce morbidity and mortality, it is important to understand the mechanisms behind the development of complications and the way they lead to fatal outcomes. Nationwide audits have the potential to indicate areas for improvement, enabling surgical teams to move forward.

Outcome based referral

Nonetheless, in upper GI cancer surgery in the Netherlands, the centralization- and thereby case-volume- discussion continues. Patient advocates and some opinion leaders plea for further centralization; some go as far as advocating centralization towards a maximum of 5-7 upper GI cancer centers, like is the case in Denmark.

Hospital volume and other structural factors reflect a certain environment in which the chance that caregivers can achieve optimal results for their patients is high. Maintaining a minimum volume standard is therefore likely to be beneficial for the outcomes of the whole group of patients. However, hospitals with less favorable characteristics or lower annual caseloads may achieve excellent results with a similar approach and environment. Moreover, pure volume-based referral carries the risk that high volume hospitals with unfavorable outcomes are selected as referral centers[45,76]. In contrast to volume-based referral, outcome-based referral can avoid this problem by selecting hospitals as referral centers based on their outcomes. As an example, postoperative mortality after esophagectomy dropped from 11.6% to 3.1% in the western part of the Netherlands after the region started to selectively refer patients to the three best performing hospitals in the region instead of the original 11 hospitals[82]. The additional benefit of feedback besides pure volume based centralization was illustrated in the centralization process of pancreatic cancer surgery in Canada, with mortality decreasing in the province in which outcomes were monitored; and mortality remaining constant in Ontario, where only volume-based centralization took place[14].

Identification of centers of excellence, which should become the referral centers, requires valid, reliable, complete, and adequate risk-adjusted registration of outcomes through audits. Auditing of upper gastrointestinal cancer surgery treatment is for example performed in the ACS-NSQIP[83] in the US, and various similar projects for upper gastrointestinal cancer run in Europe on a national level in Denmark[84], Sweden, United Kingdom and the Netherlands. An additional effect in improvement of outcomes may be expected from such audits, which provide insight in care patterns and allows surgical teams to benchmark their outcomes[85]. Further quality improvement through centralization may come at the cost of increased waiting times which are already a problem for patients undergoing esophageal surgery in the Netherlands, with the median waiting time between diagnosis and treatment for resectable esophageal cancer being 6 weeks[86]. It is a challenge for the Dutch hospital system to rearrange referral and care patterns on a relatively short notice in this dynamic field.

Patients at risk

In order to reduce morbidity and mortality, it is important to understand the mechanisms behind the development of complications and the way they lead to fatal outcomes. Besides enabling individual hospitals to improve care through benchmarking of outcomes, audits help with identification of areas for improvement, enabling surgeons nationwide to move forward. From the DSCA for example, it became evident that elderly patients undergoing colon cancer surgery in an emergency setting for colonic obstruction or tumor perforation have a risk of postoperative mortality as high as 41%[87]. Fortunately, the majority of patients are operated in an elective setting; but also elective colorectal cancer surgery is not without risks[11].

In a detailed analysis of patients undergoing colon cancer resections, we found lower anastomotic leak rates in patients undergoing left-sided resection compared to right sided colectomies. However, the risk of dying when a leak has occurred is twice as high following a right-sided leak **[chapter 8].** Additionally, in this thesis, a further investigation into the differences in postoperative events between patients undergoing rectal and colonic resections was performed. Even though severe postoperative complications occured more often in rectal cancer patients than in colon cancer patients, the chance of dying secondary to a severe complication is twice as high in the latter group **[chapter 9].** Part of the explanation for this is the fact that colon cancer patients are on average four years older and have more comorbidity, though adjusted for these factors the difference remained.

Importantly, non-surgical complications such as cardiac and pulmonary events appear to have a great impact on mortality. Friese et al. described mortality rates and their relation with complications in 25,957 patients that underwent a surgical resection for colorectal- and other types of cancer[88]. Mortality was most frequently secondary to respiratory compromise (37% of postoperative mortality) and pneumonia (26%). Surgical complications may start a chain of non-surgical adverse events, leading to quick clinical deterioration of patients. Failure to rescue rates increased drastically with the number of postoperative complications **[chapter 9].** It seems that a further reduction in mortality may come from prevention of, and aggressive treatment of cardiopulmonary complications and non-surgical infections besides the already intuitive vigilance for anastomotic leak. Fuchshuber et al. describe how a hospital drastically decreased the number of patients on a ventilator for >48 hours, and achieved a zero postoperative pneumonia rate in patients undergoing thoracoabdominal surgery during seven months by strictly adhering to a few perioperative steps[89]. Similar achievements have been published about reducing the number of acute bloodstream infections related to central venous catheters[90].

Perioperative care

Unraveling the mechanisms leading to complications and mortality as well as perioperative care processes associated with best practice should be investigated in-depth and shared in order to initiate improvement widely.

Adequate patient selection and preoperative optimization of the patient's condition may be an important step. Carlisle et al. analyzed the effect of a specialized, anesthesiologist-led preoperative high-risk clinic in colorectal cancer patients[91]. The introduction of this high-risk clinic led to a drastic improvement of 1-year mortality in patients that were older and had more comorbidity. The authors emphasize that part of the success may be explained by the higher percentage of patients with planned ICU admissions postoperatively.

Furthermore, factors associated with timely recognition of complications should be explored[92]. Higher nurse-to-patient ratios, associated with lower FTR rates, may be related to this[93]. Although some patient-related risk factors for anastomotic leak were identified **[chapter 8]**, for the individual patient the exact mechanism leading to the development of leakage is mostly unknown. As the clinical assessment by the surgeon is of low predictive value for leakage[94], different algorithms to detect anastomotic leakage have been developed for left-sided large bowel anastomoses[95-97]. These algorithms may aid in standardized postoperative monitoring of patients and in selecting patients for defunctioning stoma creation at the end of the procedure. As this thesis underlines the higher risk of mortality associated with right-sided leakage, future studies should focus on further evaluation of these leakage scores in right-sided colectomies.

Also, less specific clinical scoring systems such as the early warning score (EWS) may improve clinical detection of postoperative complications[98]. Furthermore, measuring the C-reactive protein on postoperative day 4 has a pooled negative predictive value of 89% for predicting postoperative infectious complications after colorectal surgery, allowing safe discharge of patients not at risk[24].

Further in-depth studies in high and low performing centers concerning factors reflecting differences concerning in-hospital processes should be performed. This is probably a complex interaction between many factors e.g. the daily ward rounds, responsibility for the ward patients, staffing outside office hours, vital sign collection and reporting, the level of experience in a surgical team, team communication, guideline adherence and quality of care from nurses.

The apparently large burden of non-surgical complications may be sought in improvement of intra-operative factors such as intra-operative volume load, hypotension, ventilator techniques, blood loss, and duration of surgery. So far, the clinical audits contain little intra-operative factors but linking postoperative outcomes to intra-operative data may reveal new opportunities for improvement.

Secondly, hospital differences in FTR rates may be sought in differences in delay until the start of treatment of a complication. For instance, early reintervention for a surgical complication may prevent clinical deterioration and death. Alves et al. found lower mortality after reoperations performed before postoperative day five, although this difference was not significant[99]. Almoudaris et al. did not find a difference in time interval to reoperation between low- and high-mortality hospitals but the median day of reoperation was late, being posotoperative day 8 in both groups[34]. Ideally, improvement of (surgical) FTR rates would not imply higher reoperation rates, but earlier reoperations. However, slightly higher reoperation rates in order to prevent postoperative mortality secondary to surgical complications may prove acceptable.

The presence of rapid response teams[100] in a hospital may influence failure to rescue after colorectal surgery and should be investigated in this context.

With identification of specific care processes that account for differences in hospital FTR rates, local and national quality improvement initiatives can aim at reducing postoperative mortality by addressing the most important factors in the postoperative care process.

MOVING FORWARD

The introduction of the DSCA reflects a change in mind-set among colorectal surgeons in the Netherlands, characterized by – more than ever- increasing efforts to learn, to improve and to share in order to assure quality throughout the field. Already, within a few years after initiation, it has brought many improvements in the outcomes of surgical care for colorectal cancer patients[12], and continues to do so. In other gastrointestinal tumours, much attention still goes to case volume, which historically has brought along many improvements. However, in order to take the next step in quality improvement, a change in paradigm- from volume-based to outcome-based quality assurance- is essential. Focus on 'best practice' should play a pivotal role.

Following the DSCA, clinical audits have been introduced in, among others, the fields of gastro-oesophageal and pancreatic cancer, aiming at further improving outcomes of care for these patients.

Selecting outcomes

This thesis has explored outcome indicators concerning adverse events. We showed that these outcomes, when used in isolation, do not entirely reflect quality of care (for instance, when assessing anastomotic leakage rates, stoma rates should not be ignored **[chapter 3]**). Moreover, indicators like surgical resection margins or lymph node yield are important predictors for long term survival but do not necessarily correlate with clinical outcomes[101]. Therefore, summarizing measures for outcome indicators, representing the number of patients in which all desired (short-term) goals are achieved may better reflect quality of surgical care. Kolfschoten et al. found that only half of colorectal cancer patients have a so-called ' textbook outcome' (hospital survival, radical resection, no reintervention, no ostomy, no adverse event, hospital stay <14 days) with a marked hospital variation. A quality measure like this may be an impetus for improvement on all separate components of the indicator.

Finally, medium term outcomes (90 days, 1 year) instead of the traditional in-hospital or 30-day outcomes may improve sensitivity for adverse events[102-105]. As medium-term events are less likely to be directly surgery-related[106], their use in clinical audits should be further explored.

Patient preferences

Ultimately, with transparency of outcomes comes the possibility for patients to use outcome information for selecting the hospital of choice for a certain treatment. So far there is little evidence that patients actually use such information. A survey among Dutch surgical patients revealed that quality information is not often used for choosing a hospital. Most mentioned reasons were 'hospital reputation', ' friendly atmosphere' and 'ease of access by (public) transportation'[6]. Only 3% of patients had used quality information. In another study, it was shown that even patients who had actively compared quality information of hospitals, mostly relied on their own and other peoples' experiences[5]. For future reference, patients most often (52%) would prefer a summary measure (textbook outcome) over more detailed, procedure-specific outcome measures[6].

The Dutch clinical audits bring together all stakeholders, including patients, doctors and payers in order to facilitate all with meaningful information. Importantly, this includes patient-related outcome measurements (PROMS). The DSCA is currently running a pilot project involving patients reporting their (functional) outcomes. With definitive incorporation of PROMS, a big step will be taken in participation of patients in monitoring quality of care, with potentially meaningful information for patients being generated.

CONCLUSIONS

The recent introduction of clinical audits in the Netherlands has already brought many improvements in the field of surgical oncology, reflecting the beginning of a new era of quality measurement and improvement. With tangible results after the first few years, they are promising tools for further nationwide quality improvement. With consolidation of their role in quality policy of individual hospitals and the Association of Surgeons of the Netherlands, and increasing participation of patients and other stakeholders, further refinement of outcome measures is warranted.

This thesis explored the value of clinical outcome indicators in gastrointestinal cancer surgery on a hospital level. Interactions between outcome indicators are complex and measuring single outcomes in isolation do not seem to adequately reflect quality of care as related areas remain underexposed.

Rankings are not suitable for displaying hospital postoperative mortality rates in colorectal cancer surgery. Ranking caregivers on outcomes should only be done when rankability is high. Adjustments for casemix and reliability (sample size) should be made and preferably, rankings should be displayed as PCERs as this takes into account the uncertainty of the rank. The rankability of other outcomes should be explored. Measuring and comparing certain outcomes such as anastomotic leakage or reoperations between surgical teams may induce defensive behaviour, which is not always in the patient's interest. The indicator 'failure to rescue' is an interesting outcome measure that reflects the ability of a surgical team to detect and treat complications, thereby keeping patients alive. Identification of related hospital characteristics like procedural volume or level of ICU facilities, as well as identification of patient groups at risk may aid in further understanding the mechanisms leading to adverse events. Guided by clinical data, further in-depth research should focus on the differences in the perioperative care process between hospitals, accounting for superior results in some hospitals and suboptimal outcomes in others, ultimately leading identification and sharing of 'best practice' and improvements throughout the field.

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CHAPTER 11

Samenvatting en beknopte discussie

D. Henneman

Met de toenemende mogelijkheden en groeiende complexiteit van behandelingen is de medische wereld in toenemende mate bewust van het belang van het evalueren en verbeteren van de processen en uitkomsten van geleverde zorg. Dat is bij uitstek het geval in de oncologische zorg. Dit is niet in de laatste plaats vanwege de toenemende behoefte aan kwaliteitsinformatie vanuit patiënten, tegenwoordig toenemend verenigd in patiëntenverenigingen, en vanuit instanties zoals zorgverzekeraars en beleidsmakers. Het bekendste voorbeeld van de behoefte aan kwaliteitsinformatie is wel de ranglijstjes vanuit de Elseviers beste ziekenhuizen en de AD ziekenhuis top-100; een ander bekend voorbeeld is het cijfer over (ziekenhuisbrede) sterftecijfers die Nederlandse ziekenhuizen tegenwoordig moeten publiceren (de hospital standardized mortality rates, HSMR). Het probleem is dat deze initiatieven voor medici onvoldoende betekenisvolle informatie over kwaliteit van zorg genereren waardoor de beroepsgroepen geen instrument hebben om kwaliteit van zorg werkelijk te evalueren en verbeteren[1,2]. In het eerste geval gaat het veelal over subjectieve zaken en over processen, maar wordt er weinig op uitkomsten gefocusd. In het geval van de HSMR is het getal dermate overkoepelend voor het gehele ziekenhuis, dat de uitkomst weinig zegt over individuele behandelteams in dat ziekenhuis. Tot slot zijn veel specialisten van mening dat de correctie voor verschillen in zorgzwaarte tussen ziekenhuizen inadequaat is. Ook bij patiënten sluit deze informatie niet aan: patiënten gebruiken nog steeds nauwelijks dergelijke informatie bij de keuze voor een bepaalde zorgverlener[3,4].

In navolging van Zweden[5,6] werd in Nederland begonnen met het opzetten van klinische uitkomstregistraties, met als doel kwaliteit van zorg inzichtelijk te maken door naast structurele factoren (type ziekenhuis, aantal verrichtte procedures) en processen (bijvoorbeeld verschillende vlakken van richtlijnnaleving) te focussen op uitkomsten van zorg (tumor radicaal verwijderd, complicaties, sterfte etc.)

volgens het paradigma van Donabedian[7]. Het doel hiervan is een kwaliteitsimpuls te initiëren. De chirurgen lopen in Nederland hierin voorop, met de Dutch Surgical Colorectal Audit die in 2009 als eerste succesvolle klinische registratie van start ging[8]. Hierin worden van alle chirurgisch behandelde patiënten met colorectaal carcinoom gegevens met betrekking tot het zorgproces en de uitkomsten hiervan geregistreerd. Een ruime hoeveelheid geregistreerde gegevens over onder andere comorbiditeit waarborgen uitgebreide correcties voor zorgzwaarte[9], waardoor uitkomsten van verschillende ziekenhuizen eerlijker vergeleken kunnen worden.

Een van de doelen van de DSCA is het reduceren van postoperatieve complicaties en mortaliteit door middel van terugkoppelen van spiegelinformatie aan de participerende centra. Hierdoor kunnen op lokaal zowel als landelijk niveau verbeterpunten worden gesignaleerd en aangepakt. Omdat de audit door chirurgen zelf is bedacht en opgezet, heeft deze bij hen meer '*face validity*' dan andere projecten, waardoor het uiteindelijke kwaliteitsbevorderende potentieel veel groter is.

De uitkomsten in de DSCA leveren veel informatie op over de prestaties van de Nederlandse colorectale chirurgie. In hoeverre de uitkomstindicatoren daadwerkelijk iets over de geleverde zorg zeggen en wat we er mee kunnen, is echter niet altijd even duidelijk. Dit proefschrift draagt bij aan kennis over de betekenis van, en de (on) mogelijkheden van diverse klinische uitkomsten die gebruikt worden in de gastrointestinale oncologische chirurgie. Bovendien zoomen een aantal studies in op de risico's op ongewenste uitkomsten in een aantal verschillende patiëntengroepen. Dit alles om tot gerichtere en betere feedback binnen de klinische registraties te komen, om een maximaal kwaliteit bevorderend effect te behouden. Bovendien is meer inzicht in hoe de uitkomsten gebruikt kunnen worden essentieel wanneer deze openbaar zullen worden.

In **hoofdstuk 2** wordt onderzocht wat de invloed van correctie voor zorgzwaarte en correctie voor toeval ("*reliability adjstment*")[10,11] is op rangorde van 92 ziekenhuizen op postoperatieve mortaliteit na colorectale chirurgie. Het belang van beiden wordt onderstreept door verandering van rang na toepassing van verschillende modellen. De 'rankability' bleek laag bij deze uitkomst in deze patientengroep: 62% van de gevonden ziekenhuisverschillen in rangorde is toe te schrijven aan toeval. Rankability moet worden meegenomen wanneer ranglijsten worden getoond en in dit geval is het maken van een ranglijst niet juist. Indien dit toch wordt gedaan, is het percentiel "*expected rank*"[12] een duidelijker alternatief, dat in èèn getal de kans aangeeft dat een ziekenhuis beter presteert op deze uitkomst dan een willekeurig ander ziekenhuis.

In **hoofdstuk 3** wordt geconcludeerd dat de uitkomst naadlekkage na colorectale resectie relatief minder afhankelijk is van patiënt- en ziektegebonden factoren zoals leeftijd en comorbiditeit, en meer van behandeling gebonden factoren, wanneer vergeleken wordt met mortaliteit. Een nadeel van de uitkomst is dat het alleen van toepassing is op patiënten met een anastomose.

Vervolgens wordt in **hoofdstuk 4** ingegaan op de wisselwerking tussen heroperatie- en mortaliteitscijfers na colorectale chirurgie. Hoewel patiënten die een heroperatie moeten ondergaan een hogere kans hebben op overlijden postoperatief, is het niet zo dat de ziekenhuizen die meer heropereren dan gemiddeld, ook een hoger sterftecijfer hebben dan gemiddeld. De ziekenhuizen met weinig heroperaties hadden gemiddeld genomen echter wel lagere sterftecijfers. Dit is van belang bij de interpretatie van deze indicator, die ook door de Inspectie voor gezondheidszorg wordt uitgevraagd. Bovendien hebben zowel de uitkomst 'heroperaties' als 'naadlekkages' de potentie om tot meer defensief gedrag (aanleggen van stoma's om naadlekkages en heroperaties te voorkomen) te leiden bij chirurgen, wat niet altijd in het belang van de patiënt zal zijn.

Een uitkomst die dit nadeel niet heeft is '*failure to rescue*': het aantal overleden patiënten binnen de groep patiënten met een (ernstige) postoperatieve complicatie. Dit zegt dus iets over het vermogen van een chirurgisch team om een patiënt met een complicatie adequaat te behandelen, waardoor de complicatie niet fataal afloopt. **Hoofdstuk 5** exploreert de ziekenhuisvariatie op deze uitkomst en concludeert dat ziekenhuizen met hoge en lage mortaliteit zich eerder onderscheiden door meer of minder '*failure to rescue*' dan dat er grote verschillen in aantal ernstige complicaties zijn. In terugkoppelingen kan deze uitkomst dan ook erg inzichtgevend zijn. Een nadeel is dat ook hier het toeval een rol speelt wanneer kleinere datasets worden gebruikt, omdat zowel de teller (aantal overleden na een complicatie) als de noemer (aantal patiënten met een ernstige complicatie) relatief klein is vanuit statistisch oogpunt.

Waarom een patiënt in het ene ziekenhuis een grotere kans heeft om een ernstige complicatie te overleven dan in het andere ziekenhuis, is grotendeels onbekend. In **hoofdstuk 6** wordt de correlatie tussen 'failure to rescue' en een drietal ziekenhuisfactoren onderzocht. In multivariate analyse blijkt dat ziekenhuizen met een level 2 of 3 Intensive care lagere failure to rescue rates hebben dan ziekenhuizen met een intensive care van de laagste categorie. Aantal operaties en type ziekenhuis (academisch, opleidings- of sytreekziekenhuis) waren niet significant van invloed. De bevindingen zijn slechts een associatie en hangen waarschijnlijk samen met een groot aantal structurele en procesmatige factoren, die bij nader onderzoek naar verschillende processen bij de goed presterende ziekenhuizen ('best practices') en de minder presterende ziekenhuizen, onder loep moeten worden genomen. Wel ligt het voor de hand dat dergelijk vervolgonderzoek in elk geval ook naar de processen op de IC, en de wisselwerking met de rest van het ziekenhuis (bijvoorbeeld de kwaliteit van de spoed interventie teams in het ziekenhuis)[13-15] zal kijken.

Bij oncologische chirurgie hoger in de tractus digestivus, zoals chirurgie bij oesophaguscarcinoom, ligt in de literatuur de nadruk nu nog erg op de associatie tussen volume (aantal verrichte procedures) en uitkomsten zoals mortaliteit. Bij dit type chirurgie is deze relatie dan ook duidelijk aanwezig[16,17]. In **hoofdstuk 7** wordt gezien dat verdere centralisatie een verdere daling in postoperatieve mortaliteit tot gevolg kan hebben. Hierbij geldt dat het verhogen van de volumenorm slechts èèn van de middelen is om tot verdere centralisatie te komen. Van een volumenorm kan niets geleerd worden en het gevaar bestaat dat niet (alleen) ziekenhuizen met goede resultaten worden aangezewen als verwijscentrum . Een andere strategie is 'outcome-based referral' , waarbij gecentraliseerd wordt op basis van uitkomsten. Een klinische audit heeft de potentie om te laten leren van 'best practice' en de zorg te centraliseren naar die centra die zichzelf bewijzen met goede uitkomsten na feedback van de resultaten[18].

In **hoofdstuk 8** wordt nader ingegaan op factoren die samenhangen met de kans om te overlijden wanneer een naadlekkage optreedt na een colonresectie. In linkszijdige colonresecties is de kans op lekkage verhoogd, maar de kans om te overlijden wanneer deze complicatie is opgetreden, is twee keer zo hoog in rechtszijdige resecties.

In **hoofdstuk 9** wordt vervolgens een gedetailleerde analyse gedaan naar het optreden van verschillende complicaties en overlijden secundair hieraan, bij patiënten die een rectum- danwel een colonresectie ondergingen. Ernstige complicaties komen vaker voor bij patiënten met rectumcarcinoom, maar *failure to rescue*- dus het aantal overleden patiënten als percentage van het totaal aantal patiënten met een ernstige complicatie- was twee keer zo hoog bij patiënten die een colonresectie ondergingen in vergelijking met patiënten die een rectumresectie ondergingen. Naast naadlekkage lijken cardiopulmonale complicaties een groot aandeel in het fatale verloop van complicaties te hebben, waarbij de kans op overlijden fors toeneemt met het aantal optredende complicaties.

In conclusie kan gesteld worden dat de recente introductie van de klinische audits in Nederland de gastrointestinale chirurgische oncologie al veel heeft gebracht, met tastbare resultaten na reeds een aantal jaar. Het lijkt het begin in te luiden van een nieuw tijdperk waarin kwaliteitscontrole door medici zelf, maar ook door middel van transparantie naar buiten toe, voorop staat. Met de toenemende rol van de uitkomstregistraties is het van belang dat uitkomstindicatoren worden geëvalueerd en daar waar nodig aangescherpt. Dit zal een continu proces zijn, waarbij jaarlijks bruikbaarheid en relevantie moet worden beoordeeld. De onderzoeken zoals beschreven in dit proefschrift exploreren de waarde en toepasbaarheid van een aantal klinische uitkomstindicatoren. Het gevaar van ranglijsten maken wordt aangestipt: van belang is dan de *rankability* om te beoordelen in hoeverre toeval een rol speelt.

De interactie tussen uitkomsten onderling kan complex zijn en wanneer ze op zichzelf worden bekeken bestaat het risico dat er andere aspecten onderbelicht blijven. Bovendien zouden uitkomsten als 'naadlekkage' en 'heroperaties' defensief gedrag, zoals het aanleggen van stoma's, tot gevolg kunnen hebben. Een interessante uitkomstmaat is daarom 'failure to rescue', die aangeeft in hoeverre chirurgische teams in staat zijn patiënten met een ernstige complicatie in leven te houden. Associatie tussen uitkomsten en structuurfactoren geven richting aan het begrijpen waarom prestaties beter zijn in het ene ziekenhuis dan in het andere. Echter, diepte-onderzoek naar verschillen in het zorgproces tussen ziekenhuizen- bijvoorbeeld bij '*best practices'* en bij minder presterende centra- is van belang om werkelijk te achterhalen welke mechanismen een rol spelen bij het optreden en het fataal aflopen van complicaties. Dergelijke kennis zal de gehele chirurgie helpen om ongewenste uitkomsten nog verder te reduceren.

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APPENDICES

Dankwoord
Curriculum Vitae
List of Publications

DANKWOORD

Mijn promotietijd was een dynamische tijd. Als promovendus een radertje in het geheel van een jonge, groeiende organisatie die zich hard maakt de kwaliteit van zorg inzichtelijker en beter te maken. Zonder dit framewerk geen promotietraject en geen proefschrift. Het werk van (o.a.) mijn promotor Rob Tollenaar en Eric Hans Eddes heeft dit mogelijk gemaakt en hen wil ik dan ook bedanken.

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Tot slot wil ik iedereen die de moeite heeft genomen dit proefschrift te lezen hiervoor bedanken.

CURRICULUM VITAE

Daniel Henneman was born in Amsterdam on April 19th, 1985. After graduating from the Montessori Lyceum Amsterdam in 2003, he started to study Medicine at the University of Amsterdam in the same year. In highschool and college, Daniel enjoyed rowing fanatically on national and international waters. In 2008 he finished the theoretical part of his curriculum with a research project on adrenal surgery at the Massachusetts General Hospital, a Harvard University teaching affiliate. This led to his first academic publication (surpervision of dr. D.L. Berger). His interest in science and surgery was wakened.

After having worked through his clinical rotations at the Academic Medical Centre in Amsterdam and affiliated hospitals, he received his medical degree in November 2010. During his rotations, he coached freshman's rowing crews and participated in research concerning adrenal incidentalomas (Dr. E.J. Nieveen van Dijkum). Following his clinical rotations, Daniel worked at the surgery department at the St. Lucas Andreas Hospital under supervision of dr. E. Ph. Steller and dr. B.C. Vrouenraets.

In 2012, he got the opportunity to become part of the research team of the Dutch Institute For Clinical Auditing in Leiden, engaging in a Ph. D. program at the Leiden University Medical Center. Under supervision of Prof. Dr. R.A. Tollenaar and Dr. M.W. Wouters, he spent two years working with the scientific committees of the Dutch Surgical Colorectal Audit and the Dutch Upper GI Cancer Audit, analyzing data from the outcome registries, co-authoring the annual reports and helping consolidating the Dutch surgical clinical audits. During this period he was also involved in the start-up of the Dutch Pancreatic Cancer Audit as well as the Dutch Lung Radiotherapy Audit. His work in Leiden led to many publications regarding outcomes research- mainly focusing on colorectal cancer surgery- a vast majority of which are incorporated in this thesis.

After two years, it was time to move on from full-time research back to the surgical clinic, but not before he was awarded a Dutch Cancer Society (KWF) grant, ensuring progress of the current research project towards more in-depth study of *best practice* in surgery. In January 2014, he started his training to become a general surgeon at the Alrijne Hospital, Leiderdorp (the former Rijnland hospital) under supervision of dr. A.M. Zeillemaker.

When he is not at the clinic, Daniel can be found boating the canals of Amsterdam, running alongside the river Amstel, cycling the French Alps or relaxing at home with his girlfriend Digna.

LIST OF PUBLICATIONS

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