Value of outcomes research in colorectal cancer care

Gietelink, L.

ISBN: 978-94-028-0821-6

COVER DESIGN AND LAY OUT: Tara Kinneging, PersoonlijkProefschrift.nl
PRINTING: Ipskamp Printing, www.proefschriften.net

This thesis was financially supported by:
Stichting DICA, Performation Healthcare Intelligence, Erbe and Coloplast.

VALUE OF OUTCOMES RESEARCH IN COLORECTAL CANCER CARE

PROEFSCHRIFT

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof.mr. C.J.J.M. Stolker,
volgens besluit van het College voor Promoties
te verdedigen op donderdag 30 november 2017
klokke 11.15 uur

door

Lieke Gietelink

geboren te Utrecht

in 1984

Promotor:
Prof. dr. R.A.E.M. Tollenaar

Co-promotores:
Dr. M.W.J.M. Wouters (Antoni van Leeuwenhoek, Amsterdam)
Dr. P.J. Tanis (Academisch Medisch Centrum, Amsterdam)

Leden promotiecommissie:
Prof. dr. E.W. Steyerberg
Prof. dr. L.P.S. Stassen (Maastricht Universitair Medisch Centrum, Maastricht)
Dr. N.J. van Leersum

CONTENTS

Chapter 1

GENERAL INTRODUCTION AND THESIS OUTLINE

GENERAL INTRODUCTION

Colorectal cancer is a major contributor to cancer-related deaths worldwide[1]. In the Netherlands over 15,000 patients get diagnosed with colorectal cancer every year, three-fourth of these patients qualify for curative surgical treatment.[2, 3] Treatment of colorectal cancer is shifting towards a patient-tailored approach and all patients should now be discussed in a multidisciplinary team.[4] As the heterogeneity of patients and tumor characteristics increases, there is a growing need for timely and reliable information that measures the quality of treatment in these populations; so-called real world and real time information.

Traditionally surgeons are concerned with measuring quality and outcomes of surgical interventions.[5] As a result multiple changes have been made in the past regarding the surgical treatment of colorectal cancer with a measurable effect on patient outcomes. In rectal cancer surgery for instance, implementation and standardization of the total mesorectal excision (TME) technique using surgical training programmes has led to major improvements in local disease control and survival rates.[6]

Next to adjustments in surgical technique we are currently involved in optimization of colorectal cancer care by reorganizing the way healthcare is provided. Procedural volume for example has gained much attention in relation to outcomes of surgery, as hospital volume is seen as a proxy for surgical experience and the expertise of the involved multidisciplinary team.[7] The Dutch Society of Surgery responded with an obligatory volume of at least 20 resections for rectal cancer per year per hospital, thereby stimulating centralisation of this procedure. Furthermore there is a development towards subspecialisation of surgeons and healthcare workers in colorectal cancer care. Due to this specialisation healthcare professionals are focussed to stay up to date with the latest developments in the field and are more likely to rapidly implement innovative techniques and ideas.

Outcomes research

Outcomes research is a type of public health research, which studies variation in end results (outcomes) of different providers and the differences in (infra)structure and care processes leading to better or

worse outcomes. It applies to clinical and population based research that studies and seeks to optimize the end results of healthcare in terms of benefits to the patient and society.

"Do no harm" is an important aim in medicine; all care provided should have a beneficial effect on a patient's well-being.[8] Healthcare is therefore captured in evidence-based guidelines, which dictate conditions for optimal care and form an important aspect of quality assurance. In the Netherlands the evidence-based guidelines on colorectal cancer surgery are developed by a multidisciplinary board and periodically revised.[9]

For a long time it was not exactly known to which extent hospitals followed these guidelines and if this lead to variation in outcomes between providers. As a result the Dutch Surgical Colorectal Audit (DSCA) was founded in 2009, a national audit that is developed and managed by colorectal surgeons and gets its input through a web-based system.[10] The DSCA provides risk-adjusted benchmarked feedback evaluating quality of care on a hospital level and compares hospitals with their peers. It gives medical teams information about their performance and stimulates processes that need to be developed or improved.[11] Furthermore the DSCA identifies hospital variation in the Netherlands on a structure – process and outcome level. Studying this hospital variation provides us with valuable information that can be used to improve healthcare.[12]

For instance data from the DSCA show that outcomes after colorectal cancer surgery have improved significantly since the start of the audit. There has been a significant reduction in postoperative morbidity and mortality for colorectal cancer patients as well as a reduced duration of postoperative admission time.[10, 13] Moreover as a result of clinical auditing variation in guideline compliance between hospitals reduced, which had a measurable effect on quality of care (chapter 4). Clinical audits include large numbers of patients and contain patients with a high risk for unfavourable outcomes due to the absence of exclusion criteria, which are normally encountered in randomized controlled trials (RCT's).[14] Due to these characteristics, clinical audits are rich databases that provide a unique source of real-time, real-world data and could complement the information from RCT's.

This thesis will describe different areas of medical research for which clinical audit data is used and will furthermore discuss the inherent statistical problems encountered in population studies.

THESIS OUTLINE

Part I: Risk-adjustment in clinical auditing

Valid comparisons between hospital outcomes are essential for the audit, especially when these outcomes become transparent to the public, healthcare insurers and healthcare authorities. The heterogeneity of patients and tumors affects hospital outcomes. In oncology there is a trend towards centralisation of specific patient subgroups based on the rarity and complexity of their disease. To analyse the effect of this centralisation on casemix correction for outcome comparisons, the first part of this thesis studies differences in the effect of variables in the currently used casemix model between referral and non-referral hospitals.

Part II: Quality improvement in the Dutch colorectal cancer care

The second part of this thesis focuses on quality improvement in Dutch colorectal cancer care. Chapter 3 shows how the audit is used to monitor a quality improving initiative. As mentioned before the ASN implemented a compulsory minimal volume standard for rectal cancer surgery per hospital. This study describes the influence of hospital volume on circumferential resection margin (CRM) involvement - the most significant prognostic factor for local recurrence, distant metastasis and survival - after rectal cancer surgery.

Chapter 4 evaluates the rates of CRM reporting by Dutch hospitals and CRM involvement after the implementation of the DSCA. Chapter 5 identifies changes in the use of preoperative radiotherapy for rectal cancer in the Netherlands after the revision of the national colorectal cancer guideline. This guideline revision was stimulated by data from the audit showing significant overtreatment of early stage rectal cancers.

Part III: Data from clinical audits as a supplement to RCT's

The third part of this thesis shows the complementary function of the clinical audit in providing data for clinically relevant research.

Chapter 6 analyses the rate of postoperative morbidity and mortality after open versus laparoscopic surgery for colorectal cancer in specific subgroups of patients, including patients with a high preoperative risk for adverse outcomes. This chapter shows a possible method to deal with the inherent statistical problems that accompany population studies.

Chapter 7 displays the quality of laparoscopic rectal cancer surgery in the Netherlands at present by comparing the data from the DSCA to the COLOR II trial. We performed a matched cohort study and show postoperative results after laparoscopic rectal cancer surgery a decade from start of the COLOR II trial.

Chapter 8 shows the outcomes of patients with locally advanced colon cancer in the Netherlands, a population that is underreported in literature. The clinical audit provides important information on the quality and outcomes of their care.

REFERENCES

1. Arnold M, Sierra MS, Laversanne M, et al. Global patterns and trends in colorectal cancer incidence and mortality. *Gut* 2017; 66(4):683-691.

2. http://www.cijfersoverkanker.nl.

3. https://http://www.dica.nl/jaarrapportage-2016/dsca.

4. Tanis PJ. Patient-tailored colorectal cancer care: a challenge within the context of evidence based guidelines. *Colorectal Dis* 2017; 19(6):521. Codman EA. The classic: A study in hospital efficiency: as demonstrated by the case report of first five years of private hospital. *Clin Orthop Relat Res* 2013; 471(6):1778-83.

5. Kapiteijn E, Putter H, van de Velde CJ. Impact of the introduction and training of total mesorectal excision on recurrence and survival in rectal cancer in The Netherlands. *Br J Surg* 2002; 89(9):1142-9.

6. Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. *N Engl J Med* 2002; 346(15):1128-37.

7. Kleisiaris CF, Sfakianakis C, Papathanasiou IV. Health care practices in ancient Greece: The Hippocratic ideal. *J Med Ethics Hist Med* 2014; 7:6.

8. http://www.oncoline.nl.

9. Van Leersum NJ, Snijders HS, Henneman D, et al. The Dutch surgical colorectal audit. *Eur J Surg Oncol* 2013; 39(10):1063-70.

10. Ivers N, Jamtvedt G, Flottorp S, et al. Audit and feedback: effects on professional practice and healthcare outcomes. *Cochrane Database Syst Rev* 2012; 6:CD000259.

11. Schreuder K, van Bommel ACM, de Ligt KM, et al. Hospital organizational factors affect the use of immediate breast reconstruction after mastectomy for breast cancer in the Netherlands. *Breast* 2017; 34:96-102.

12. Annual report 2013, the Dutch Surgical Colorectal Audit.

13. Benchmarking recent national practice in rectal cancer treatment with landmark randomized controlled trials. *Colorectal Dis* 2017; 19(6):O219-O231.

Chapter 2

DIFFERENCES IN EFFECT OF CASEMIX VARIABLES BETWEEN REFERRAL AND NON-REFERRAL HOSPITALS IN THE NETHERLANDS AND RELEVANCE FOR HOSPITAL COMPARISONS.

Lieke Gietelink, Perla J. Marang – van de Mheen, Claudia Fischer, Michel W.J.M. Wouters, on behalf of the Dutch Surgical Colorectal Cancer Audit Group.

Submitted

ABSTRACT

Background: Hospital comparisons based on outcome need to be adjusted for casemix. As there is a trend towards centralisation in oncology, patient population in specialized hospitals might differ from other hospitals to such an extent that the impact of casemix variables may be different for referral hospitals thereby affecting fair hospital comparisons. In addition, referral hospitals treat patients with paradoxical risk profiles e.g. young patients with advanced disease not adequately captured if no interactions are added. Therefore, our aim was to analyse whether the effect of variables used in the Dutch ColoRectal Audit (DCRA) casemix model are different between the referral and non-referral hospital population. Furthermore we added clinically relevant interactions to the standard model and evaluated their effect and added value on model performance.

Methods: Patients who underwent a surgical resection for colon cancer between 2009 and 2015 (n=39,604) were selected from the DCRA. 10 hospitals function as tertiary referral hospitals in the Netherlands and were selected as 'referral hospitals'. We analysed differences in effect of variables between referral versus non-referral hospitals in the currently used multivariate regression model for postoperative complicated course and tested the added value of added interactions between age and Charlson comorbidity index, pT4 tumor and metastatic disease (M1). Model performance was assessed by a C-statistic based on an ROC curve.

Results: Mean age of patients treated in referral hospitals is 3 years lower ($p<0.001$) than in non-referral hospitals. Patients treated in referral hospitals more often have pT4 disease or a Charlson comorbidity index of 2+ ($p<0.001$). The variables age, ASA score, tumor location, M1 disease, preoperative tumor complications, additional resection due to local tumor invasion or metastasis and pT classification have a significantly different effect (all $p\leq0.001$) on postoperative complicated course in referral hospitals. Added interactions had no significant effect on outcomes for the referral population. A separate model for referral hospitals showed the best model fit.

Conclusion: This study shows that referral hospitals treat a different patient population and that the effect of variables on postoperative complicated course is different in the casemix model. A specifically fitted casemix model to the referral population shows best model performance for referral hospitals.

INTRODUCTION

Patient populations treated for a specific condition significantly differ across hospitals.[1] Because patient and disease characteristics affect outcome, casemix is a confounder in between-hospital comparisons based on outcome. Therefore, casemix adjustment needs to be applied when comparing outcomes across hospitals with the aim to judge quality of hospital care. The most efficient way to execute risk adjustment is with a logistic regression model - in case of a binary outcome - that contains the most important predictors of the outcome parameter.

In oncology, there is a trend towards centralisation of treatment of specific patient subgroups particularly in case of rare disease or high complexity of treatment.[1, 2] Although colorectal cancer is one of the cancers with the highest incidence worldwide, specific patient groups with advanced stage of disease may benefit from treatment and thus cluster in expert centres. The patient population in such specialized hospitals might differ from the other hospitals to such an extent that the impact of different casemix variables (and thus also risk adjustment) may be different for referral hospitals.[1, 2]

The models for casemix adjustment in the DCRA are implicitly weighted more due to the majority of high volume non-specialised care hospitals, with a smaller contribution of the few referral hospitals. Furthermore, the models only contain main effects for casemix adjustment, and no interaction terms. In this way, the assumption is made that there are no interactions between the variables (e.g. comorbidities have the same effect on outcome across all ages), and it is uncertain whether these assumptions are actually met, especially in the case of paradoxical risk profiles – i.e. young patients with advanced disease - in some (referral) hospitals. Therefore, our aim was to analyse whether the effect of variables used in the DCRA casemix model is different within the referral versus non-referral hospital population and to evaluate the added value of a priori defined and clinically relevant interactions to the standard model.

METHODS

Patients

Data were derived from the DCRA, a disease specific national audit.[3] This audit collects information on patient, tumor and treatment characteristics of all patients undergoing a resection for primary colorectal cancer in the Netherlands and their postoperative outcomes. All Dutch hospitals participate, with approximately 97 percent completeness in 2012 based on comparison with the Netherlands Cancer Registry (NCR). Details of the DCRA regarding data collection and methodology have been published previously.[1, 3, 4] All patients with colon cancer registered from 1st of January 2009 until the 1st of September 2015 were included in this study. For the clarity of this study we excluded patients with rectal cancer, due to the different variables that influence postoperative outcomes in these two populations.[3]

Hospitals

In the Dutch healthcare system, there are 8 university hospitals and 2 non-university hospitals that function as tertiary referral hospitals for high-complex colorectal cancer care and therefore treat a selected patient group, of the total of 92 hospitals. These hospitals will be named 'referral hospitals' throughout the continuation of this manuscript. The population of all referral hospitals combined is referred to as "referral population", the population of all non-referral hospitals combined is referred to as "non-referral population".

Outcome Measures

We used the short-term postoperative outcome of complicated postoperative course for our analyses. Complicated postoperative course was defined as any complication leading to a reintervention (radiological/surgical), prolonged hospital stay (>14 days) or death, within 30 days from surgery.[1, 4-6]

Casemix correction model and interactions

Standard casemix correction model

We used the standard casemix correction model for colon cancer as currently used in the DCRA as reference model.[7] In short, this

multivariate regression model for outcomes after a resection for colon cancer includes several patient and tumor characteristics: age, gender, American Society of Anaesthesiologists (ASA) score, Charlson comorbidity index, Body Mass Index (BMI), tumor location, metastatic disease (M1), preoperative tumor complications, emergency surgery, additional resection due to local tumor invasion or metastasis and TNM classification (pT and c/pM classification). The 5th edition of the TNM classification is reported in the DCRA.

Interactions

Clinically relevant interactions were derived from expert opinion. Interactions between the variables age and Charlson comorbidity index, age and pT4 tumor, and age and metastatic disease were considered as potentially different in the referral versus non-referral population and therefore used in our analysis.

Statistical analysis

We first calculated differences between the referral and non-referral population for all variables included in the DCRA casemix model. Differences in casemix between patients treated in referral versus non-referral hospitals were tested using chi-square tests for categorical variables and t-tests for continuous variables. Hospital outcomes adjusted for casemix on postoperative complicated course per hospital in 2013-2014 were presented in a funnel plot using the standard casemix model, showing the overall average outcome with its 95% confidence limits, based on a Poisson distribution, varying in relation to the population size and indicating referral versus non-referral hospitals.

Then we estimated a casemix model separately for referral hospitals and non-referral hospitals, by including the same casemix variables as above in the model but only selecting the referral or non-referral population. In this way we show whether casemix variables have different effects on the outcome of postoperative complicated course in referral versus non-referral hospitals. In order to test whether casemix variables have a significantly different effect in the referral population compared to the non-referral population we added an interaction of each variable with the variable “referral hospital (yes/no) to the standard model. A significant interaction in this analysis indicates a significantly different

effect of the variable on the outcome of postoperative complicated course in the referral versus non-referral hospitals. To test the added value of interactions we extended the standard casemix model (for the total, non-referral and referral population) for the outcome of postoperative complicated course with clinically relevant interactions.

Model performance was assessed using a C-statistic based on a Receiving Operator Characteristic Curve (ROC curve), both for the standard model and for the models fitted for referral and non-referral hospitals separately and with or without clinically relevant interactions for the outcome of postoperative complicated course. We also analysed the model performance of the standard casemix model applied to referral hospitals; by saving the predicted values of the standard casemix model for the referral population and then calculate a c-statistic as above.

Statistical analyses were carried out with the statistical software packages SPSS version 18.0 (SPSS, Chicago, IL, USA). A p-value of 0.05 was considered significant in all analyses.

RESULTS

Patients and hospitals

Table 1 shows the percentages of patient and tumor characteristics for referral and non-referral hospitals. Referral hospitals more often treat younger patients and more often patients with comorbidity and advanced disease (i.e. pT4 tumor and metastasis). However, there is variance in patient characteristics among the referral hospitals, e.g. mean age for colon cancer varies from 62.8 to 71.2 years per hospital and the percentage of patients with a pT4 colon tumor from 13.0 to 26.0% (data not shown).

Figure 1 shows a funnel plot with the adjusted percentage of postoperative complicated course for colon cancer per hospital in 2013-2014, using the standard casemix model. None of the referral hospitals had significantly worse results compared to the other Dutch hospitals.

Casemix correction model and interactions

Table 2a shows the effect of the different casemix variables on postoperative complicated course after colon cancer resections fitted to respectively the total (general), non-referral and referral population. Overall, the estimated effects in the general model show most resemblance to the non-referral population (descriptive). The variables age, ASA score, tumor location, metastatic disease, preoperative tumor complications, additional resection due to local tumor invasion or metastasis and pT classification have a significantly different effect (all $p \leq 0.001$) on the outcome postoperative complicated course in referral hospitals compared to non-referral hospitals.

In table 2b the clinically relevant interactions are added to the casemix correction models for postoperative complicated course. The interaction effect of age with Charlson score and age with T4 tumor are significant in the total and non-referral population. None of these interactions were significant in the referral population. In the non-referral population, the age-T4 interaction and age-Charlson interaction were significantly associated with postoperative complication outcome. By adding the interactions, T4 was no longer independently associated with postoperative complications, whereas the independent effect of age remained. So T4 is only a significant predictor of the outcome in combination with age. The same was true for the interaction of age with Charlson comorbidity index.

Table 3 shows the C-statistic for each casemix correction model. The addition of interaction terms did not improve model performance. However, a separate model for referral hospitals showed better model fit for referral hospitals than the standard casemix correction model applied to referral hospitals (with saved predicted values) (C-statistic of 0.707 rather than 0.688 for postoperative complicated course). A separate model for non-referral hospitals did not improve model fit for non-referral hospitals compared with the standard model applied to non-referral hospitals (C-statistic of 0.674 for postoperative complicated course in both models).

DISCUSSION

The present study has shown that multiple casemix variables have a different effect on postoperative complicated course in referral hospitals than in non-referral hospitals. The currently used casemix model (general model) that is fitted in the total population performes equally well in the non-referral population as a casemix model specifically fitted in non-referral hospitals only. In contrast, the general model performes worse in the referral population when compared to a model specifically fitted in referral hospitals only. As hypothesized, casemix correction models based on the total population showed most resemblance to the non-referral population. However, the interactions that were added to the model were only significantly associated with the postoperative complication outcome in the non-referral population but not in the referral population. None of the added interactions resulted in better model performance.

The DRCA provides risk-adjusted benchmarks as feedback to evaluate hospital quality of care by comparing hospitals with their peers. It gives surgeons information about their performance and aims to thereby stimulate processes that need to be developed or improved.[8] In order to have the intended effect, healthcare providers need to trust their feedback and casemix correction should therefore be as adequate as possible. As this paper shows, referral hospitals seem to treat a different patient population. If casemix variables (e.g. age) would have the same effect on the outcome in both referral and non-referral hospitals, but only the distribution would differ (e.g. have more young patients), then performing casemix adjustment in one model will be adequate. However, if the effect of casemix variables differs as shown in this study, then casemix adjustment is likely to be inadequate and particularly in referral hospitals as the effect in the total model closely resembled that in the non-referral population. In addition, important information determining the caseload of this patient population may be lacking, i.e. detailed information about previous surgery, index surgery, intra-abdominal adhesions, multimodality treatments, and medication use (e.g. steroids) and thus cannot be taken into account in hospital comparisons. The addition of such variables would lead to fairer comparison but would increase the registration burden and these variables are often difficult to register unambiguously. A separate

model for referral centres might solve the before mentioned problem by creating a comparison with similar hospitals ('hospitals like mine') but might induce new questions. That is whether we are sure that any difference in average performance between these 2 groups of hospitals is based on the complexity of patients and not on a difference in quality of care and whether a hospital treats sufficient referral patients to be classified as a referral hospital.

In 2015 Walker at al. published a paper on casemix correction models in the field of hospital comparisons.[9] On the basis of previous literature they concluded that most publications described suboptimal methods for casemix model development, i.e by the usage of significance testing for the selection of risk factors, a small sample size, categorizing continuous risk factors and ignoring potential interactions between risk factors. They then developted a casemix correction model with casemix variables that were selected on clinical grounds and complemented the model with interaction terms. The only stable interaction - with a bootstrap method - was the interaction between age and metastases and was added to the casemix correction model. In our study we added interactions based on clinical relevance in accordance with the selection of the risk factors in the casemix correction model, but only age-T4 and age-comorbidity were found to be significantly associated and only in non-referral hospitals. Given that model fit also did not improve, it is not clear whether adding these interactions will be of added value for our hospital comparisons.

Our study has some limitations. The division into referral and non-referral hospitals was based on expert consensus. Over time, hospitals may be in one or the other group e.g. if hospitals merge with other hospitals. Furthermore it remains unclear whether referral hospitals have been insufficiently adjusted with the current casemix model, as the effect of some variables was higher in the referral population than in the general model but also lower for other variables so that the net effect remains unclear. Within the general model, none of the referral hospitals performed significantly worse compared to other hospitals on postoperative complicated course in the years 2013-2014. Nevertheless this study clarifies that some variables have a different effect on postoperative outcome in the referral population, and model performance does improve when the casemixmodel is specifically fitted to the referral population.

In conclusion, this study showed that referral hospitals treat a different population in which the effect of casemix variables on postoperative complicated course is different after a resection for colon cancer. Adding clinically relevant interactions did not improve model performance in referral hospitals as these were not signficantly associated with the outcome. A casemix model which was specifically fitted to the referral population showed the best model performance for referral hospitals.

Acknowledgements: The authors would like to thank all surgeons, registrars, physician assistants and administrative nurses that registered all the patients in the DCRA, as well as the Dutch ColoRectal Audit group.

Sources of funding: The authors received no funding.

REFERENCES

1. Kolfschoten NE, Marang van de Mheen PJ, Gooiker GA, et al. Variation in casemix between hospitals treating colorectal cancer patients in the Netherlands. Eur J Surg Oncol 2011; 37(11):956-63.

2. Friese CR, Earle CC, Silber JH, et al. Hospital characteristics, clinical severity, and outcomes for surgical oncology patients. Surgery 2010; 147(5):602-9.

3. Van Leersum NJ, Snijders HS, Henneman D, et al. The Dutch surgical colorectal audit. Eur J Surg Oncol 2013; 39(10):1063-70.

4. Henneman D, Snijders HS, Fiocco M, et al. Hospital variation in failure to rescue after colorectal cancer surgery: results of the Dutch Surgical Colorectal Audit. Ann Surg Oncol 2013; 20(7):2117-23.

5. Snijders HS, Bakker IS, Dekker JW, et al. High 1-year complication rate after anterior resection for rectal cancer. J Gastrointest Surg 2014; 18(4):831-8.

6. Kolfschoten NE, van Leersum NJ, Gooiker GA, et al. Successful and safe introduction of laparoscopic colorectal cancer surgery in Dutch hospitals. Ann Surg 2013; 257(5):916-21.

7. Gietelink L, Henneman D, van Leersum NJ, et al. The Influence of Hospital Volume on Circumferential Resection Margin Involvement: Results of the Dutch Surgical Colorectal Audit. Ann Surg 2014.

8. Lui CW, Boyle FM, Wysocki AP, et al. How participation in surgical mortality audit impacts surgical practice. BMC Surg 2017; 17(1):42.

9. Walker K, Finan PJ, van der Meulen JH. Model for risk adjustment of postoperative mortality in patients with colorectal cancer. Br J Surg 2015; 102(3):269-80.

TABLES AND FIGURES

Table 1. Patient and tumor characteristics of colon cancer patients in referral hospitals and non-referral hospitals.

	Non-referral		Referral		
	N	**%**	**N**	**%**	**P-value**
Total	36284		3320		
Age <= 60	5780	15.9	768	23.1	<0.001
Age (mean)	71		68		<0.001
Charlson 2+	9252	25.5	1069	32.2	<0.001
pT4	5920	16.4	683	20.8	<0.001
M1	4277	11.8	711	21.4	<0.001

Table 2a: Casemix correction models for postoperative complicated course after resection for colon cancer fitted to all hospitals, non-referral hospitals and referral hospitals. The interaction of each variable with the variable "referral hospital (yes/no) added to the standard model; the p-value of this interaction is displayed in the last column.

	Postoperative complicated course									
	ALL HOSPITALS			**NON-REFERRAL**			**REFERRAL**			**INTERACTION WITH REFERRAL**
	OR	**95%CI**		**OR**	**95%CI**		**OR**	**95%CI**		**p-value**
Female (ref male)	0.688	0.651	0.727	0.703	0.664	0.745	0.543	0.452	0.653	0.652
BMI										0.087
unknown	1.243	1.138	1.358	1.254	1.145	1.373	1.423	0.913	2.216	0.429
<18.5	1.498	1.239	1.811	1.489	1.216	1.825	1.600	0.911	2.812	0.532
18.5-25 (ref)										
25-29	1.026	0.963	1.094	1.034	0.967	1.105	1.015	0.826	1.247	**0.065**
30+	1.151	1.060	1.249	1.150	1.055	1.254	1.173	0.907	1.516	0.052
Age (continuous)	1.016	1.013	1.019	1.017	1.014	1.020	1.010	1.002	1.019	**0.001**
Charlson score (continuous)	1.099	1.078	1.120	1.101	1.079	1.125	1.071	1.013	1.132	0.133
ASA score										**<0.001**
I - II (ref)										
III	1.711	1.608	1.822	1.665	1.559	1.778	2.214	1.797	2.728	**<0.001**
IV - V	3.253	2.795	3.785	3.346	2.856	3.921	2.232	1.296	3.844	0.162

Continuation of Table 2a

Location tumor										**<0.001**
Caecum (ref)										
Appendix	1.025	0.725	1.447	0.728	0.458	1.155	1.434	0.795	2.588	**0.003**
Ascendens	1.043	0.955	1.139	1.055	0.962	1.157	0.935	0.694	1.260	0.487
Flexura hepatica	1.222	1.085	1.377	1.219	1.075	1.381	1.289	0.869	1.911	0.137
Transversum	1.484	1.334	1.652	1.526	1.364	1.707	1.143	0.801	1.630	0.731
Flexura splenica	1.461	1.263	1.690	1.584	1.362	1.843	0.611	0.350	1.066	**0.014**
Descendens	1.429	1.271	1.607	1.455	1.288	1.644	1.253	0.812	1.934	0.741
Sigmoid	0.969	0.898	1.046	0.967	0.892	1.048	1.011	0.787	1.298	**<0.001**
Preoperative tumor complication	1.131	1.062	1.205	1.099	1.028	1.175	1.384	1.136	1.686	**<0.001**
Setting										
urgent/emergency	1.658	1.539	1.785	1.705	1.577	1.844	1.519	1.179	1.956	0.155
Additional resection										**<0.001**
due to tumor invasion (extensive)	1.849	1.642	2.081	1.661	1.454	1.897	2.324	1.739	3.106	**<0.001**
due to tumor invasion (limited)	1.148	1.029	1.280	1.161	1.034	1.303	1.067	0.756	1.506	**0.020**
due to metastatic disease	1.366	1.187	1.571	1.168	0.989	1.381	1.576	1.168	2.126	**<0.001**

Continuation of Table 2a

	Postoperative complicated course									
	ALL HOSPITALS			NON-REFERRAL			REFERRAL			INTERACTION WITH REFERRAL
	OR	95%CI		OR	95%CI		OR	95%CI		p-value
Pathological T classification										**<0.001**
(y)pTX/unknown	1.572	1.175	2.103	1.599	1.164	2.197	1.141	0.532	2.449	0.666
(y)pT0-1 (ref)										
(y)pT2	1.118	0.980	1.275	1.111	0.966	1.277	1.213	0.808	1.821	**0.017**
(y)pT3	1.194	1.062	1.344	1.218	1.075	1.381	1.020	0.714	1.459	0.411
(y)pT4	1.380	1.208	1.576	1.383	1.201	1.594	1.418	0.950	2.117	**<0.001**
Metastatic disease	0.966	0.888	1.052	0.945	0.863	1.034	1.115	0.870	1.428	**<0.001**

Table 2b: Casemix correction models with added interactions for postoperative complicated course after resection for colon cancer fitted to all hospitals, non-referral hospitals and referral hospitals.

	Postoperative complicated course								
	ALL HOSPITALS			**NON-REFERRAL**			**REFERRAL**		
	AUC= 0.675			**AUC= 0.797**			**AUC= 0.797**		
	OR	**95%CI**		**OR**	**95%CI**		**OR**	**95%CI**	
Female (ref male)	0.688	0.651	0.727	0.704	0.664	0.745	0.544	0.452	0.654
BMI									
unknown	1.245	1.139	1.360	1.255	1.146	1.375	1.422	0.912	2.216
<18.5	1.503	1.243	1.818	1.493	1.219	1.830	1.610	0.917	2.827
18.5-25 (ref)									
25-29	1.027	0.963	1.094	1.034	0.966	1.105	1.018	0.828	1.252
30+	1.156	1.065	1.255	1.155	1.059	1.259	1.181	0.913	1.528
Age (continuous)	1.013	1.009	1.016	1.013	1.010	1.017	1.005	0.993	1.016
Charlson score (continuous)	0.919	0.796	1.062	0.921	0.785	1.080	0.859	0.604	1.221
ASA score									
I - II (ref)									
III	1.713	1.609	1823	1.668	1.562	1.781	2.214	1.795	2.729
IV - V	3.242	2.785	3774	3.341	2.850	3.916	2.186	1.262	3.786

Continuation of Table 2b

	Postoperative complicated course								
	ALL HOSPITALS			NON-REFERRAL			REFERRAL		
	AUC= 0.675			AUC= 0.797			AUC= 0.797		
	OR	95%CI		OR	95%CI		OR	95%CI	
Location tumor									
Caecum (ref)									
Appendix	1.029	0.729	1.453	0.728	0.459	1.155	1.461	0.808	2.643
Ascendens	1.044	0.956	1.140	1.056	0.963	1.158	0.939	0.697	1.265
Flexura hepatica	1.224	1.086	1.379	1.219	1.076	1.383	1.304	0.879	1.935
Transversum	1.485	1.334	1.652	1.527	1.365	1.708	1.139	0.798	1.626
Flexura splenica	1.462	1.264	1.692	1.586	1.363	1.845	0.609	0.349	1.064
Descendens	1.431	1.272	1.608	1.456	1.288	1.644	1.263	0.818	1.950
Sigmoid	0.968	0.897	1.046	0.966	0.891	1.047	1.013	0.788	1.301
Preoperative tumor complication	1.132	1.063	1.205	1.099	1.028	1.175	1.385	1.137	1.687
Setting									
urgent/emergency	1.655	1.536	1.782	1.703	1.575	1.842	1.512	1.173	1.948

Continuation of Table 2b

Additional resection									
due to tumor invasion (extensive)	1.858	1.650	2.093	1.667	1.459	1.905	2.351	1.756	3.146
due to tumor invasion (limited)	1.146	1.027	1.279	1.160	1.033	1.302	1.063	0.753	1.501
due to metastatic disease	1.371	1.191	1.578	1.177	0.996	1.392	1.023	0.288	3.631
Pathological T classification									
(y)pTX/unknown	1.561	1.166	2.088	1.589	1.157	2.183	1.121	0.522	2.404
(y)pT0-1 (ref)									
(y)pT2	1.118	0,980	1,276	1.113	0.976	1.280	1.209	0.805	1.815
(y)pT3	1.191	1.059	1.340	1.216	1.073	1.378	1.011	0.707	1.447
(y)pT4	0.835	0.521	1.338	0.763	0.456	1.274	0.812	0.226	2.913
Metastatic disease	1.058	0.628	1.780	0.895	0.500	1.603	1.023	0.288	3.631
Age by Charlson score	1.002	1.000	1.004	1.002	1.000	1.005	1.003	0.998	1.008
Age by pT4 tumor	1.007	1.001	1.013	1.008	1.001	1.015	1.008	0.990	1.026
Age by Metastatic disease	0.999	0.992	1.006	1.001	0.993	1.009	1.001	0.983	1.020

Table 3: Model performance of casemix correction models for postoperative complicated course calculated for the total, non-referral and referral population estimated by separate models per population with or without added interactions and estimated per population with saved predicted values.

	Colon	**Postoperative complicated course**
		C-statistic
No interactions	Total	0.675
	Non- referral	0.674
	Referral	0.707
With interactions	Total	0.675
	Non- referral	0.674
	Referral	0.707
Fixed model in	Total	0.675
	Non-referral	0.674
	Referral	0.688

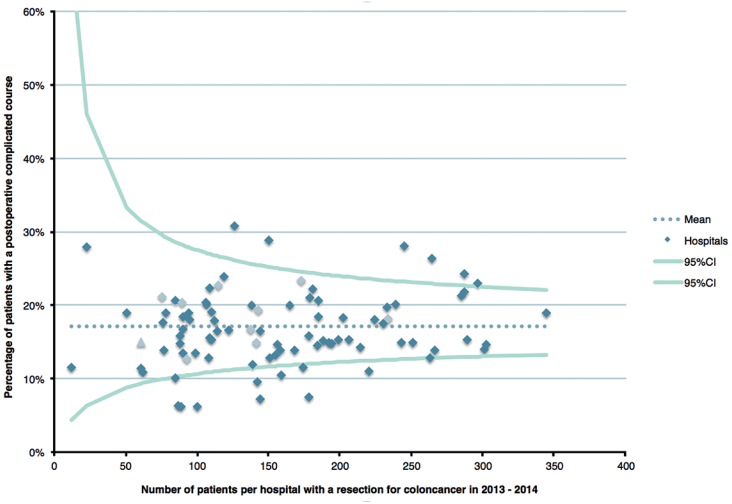


Figure 1: Funnel plot showing differences in risk-adjusted percentages of postoperative complicated course after resection for colon cancer between hospitals (2013-2014). Light dots are referral hospitals. 95%CI= 95 percent confidence interval.

Chapter 3

THE INFLUENCE OF HOSPITAL VOLUME ON CIRCUMFERENTIAL RESECTION MARGIN INVOLVEMENT: RESULTS OF THE DUTCH SURGICAL COLORECTAL AUDIT (DSCA).

Lieke Gietelink, Daniel Henneman, Nicoline J. van Leersum, Mirre E. de Noo, Eric Manusama, Pieter J. Tanis, Rob A.E.M. Tollenaar and Michel W.J.M. Wouters on behalf of the Dutch Surgical Colorectal Cancer Audit Group.

Ann Surg. 2016 Apr;263(4):745-50.

ABSTRACT

Objective: To evaluate the association between hospital volume and CRM involvement in rectal cancer surgery.

Summary Background Data: To guarantee the quality of surgical treatment of rectal cancer, the Association of Surgeons of the Netherlands (ASN) has stated a minimal annual volume standard of 20 procedures per hospital. The influence of hospital volume has been examined for different outcome variables in rectal cancer surgery. Its influence on the pathological outcome (CRM) however remains unclear. As long-term outcomes are best predicted by the CRM status, this parameter is of essential importance in the debate on the justification of minimal volume standards in rectal cancer surgery.

Methods: Data from the Dutch Surgical Colorectal Audit (2012) was used. Hospital volume was divided into three groups and baseline characteristics were described. The influence of hospital volume on CRM involvement was analysed, in a multivariate model, between low and high volume hospitals, according to the minimal volume standards.

Results: This study included 5161 patients. CRM was recorded in 86 percent of patients. CRM involvement was 11 percent in low volume group versus 7,7 and 7,9 percent in the medium and high volume group (p=<0.001). After adjustment for relevant confounders, the influence of hospital volume on CRM involvement was still significant (OR 1.54; 95% CI 1,12-2,11).

Conclusions: The outcomes of this pooled analysis support minimal volume standards in rectal cancer surgery. Low hospital volume was independently associated with a higher risk of CRM involvement (OR 1.54; 95% CI 1,12-2,11).

INTRODUCTION

Improving the outcomes of oncologic surgery has been widely discussed over the last decades.[1] In this context, hospital differences regarding quality of care have received much attention in recent years.[2]

In rectal cancer surgery, implementation and standardization of the technique of total mesorectal excision (TME) using surgical training programmes, as well as the introduction of preoperative (chemo) radiotherapy has led to major improvements in local disease control and survival rates.[3-5] Despite this evolution, a lower though significant proportion of these patients will develop local recurrences.[6, 7] The status of the circumferential resection margin (CRM) is a significant prognostic factor for local recurrence and distant metastasis and the most accurate predictor of survival after rectal cancer surgery.[7-10]

Several patient, tumor and treatment related factors have been associated with a higher risk of CRM involvement, such as tumor stage, response to neo-adjuvant radiotherapy and abdominoperineal excision (APR).[7, 11] Consequently, hospital variation in outcomes may be influenced by differences in patient- and tumor related factors.[2] Hospital characteristics, like procedural volume, have also proven to be important factors influencing outcomes in oncologic surgery, including rectal cancer treatment.[12-14] Hospital volume seems to be a proxy for the experience of the multidisciplinary team (MDT) and more specifically the surgical quality with respect to a specific procedure.

In the Netherlands a standard was set at 20 resections for rectal cancer per hospital per year. The relation between hospital volume and specific pathological outcome measures, such as CRM involvement, is less well defined with contradictory findings in literature.[15-18] Therefore, the objective of this study was to evaluate the effect of hospital volume on CRM involvement in rectal cancer surgery in the Netherlands, based on data from a national clinical registry.

METHODS

Data were derived from the Dutch Surgical Colorectal Audit (DSCA), a disease specific national audit.[19] This audit collects information on patient, tumor, treatment and outcome characteristics and contains approximately 97 percent of all patients with a resection for primary colorectal carcinoma in the Netherlands in 2012. The dataset is based on evidence-based guidelines and compared on a yearly basis with the data registered in the Netherlands Cancer Registry (NCR).[20] The registered CRM rate in the DSCA was 80 percent in 2011 and 92 percent in 2012 with a high level of concordance with the NCR. Details of this dataset regarding data collection and methodology have been published previously.[2, 19]

Patients

For this study, no ethical approval or informed consent was required under Dutch law. All patients (n=5552) undergoing surgical resection for primary rectal cancer between January 1st 2011 and December 31th, 2012, and registered in the DSCA before March 15, 2013, were evaluated. Minimal data requirements to consider a patient eligible for analyses were information on tumor location, date of surgery and 30-day mortality (n=5534). All these patients, except those treated with a transanal resection (n=140), were included for the calculation of annual hospital volume. However, to create a homogenous cohort, patients with multiple synchronous colorectal tumors (n=233) were excluded from the analysis.

CRM involvement

CRM was considered positive if tumor cells were in a distance of ≤1mm from the inked margin according to the definition of the Royal college of Pathologists. CRM involvement was only calculated for patients with a recorded CRM. The percentage of CRM involvement per hospital was presented in a funnel plot, showing the overall average CRM involvement with its 95% confidence limits, based on a Poisson distribution, varying in relation to the population size. The plot allowed for identification of hospitals with a CRM involvement rate that was significantly higher or lower than average.

Hospital volume

The mean annual operative caseload was calculated for each hospital based on their respective numbers of rectal cancer cases, including patients with multiple synchronous colorectal tumors. Volume was stratified in two groups (< 20 and ≥ 20 cases/year), based on the mandatory annual volume of rectal cancer surgery per hospital in the Netherlands and three groups (< 20, 20-40, ≥ 40 cases/year) to evaluate the influence of a higher hospital volume than is currently required. Patients with an unknown CRM status were not excluded from this calculation.

Potential patient- and tumor specific risk factors (casemix) for CRM involvement were selected from the dataset and, together with treatment characteristics, compared between the three volume groups using the chi-square test. Subsequently, a univariable analysis was performed to determine the effect of hospital volume on CRM involvement. The significance level was set at a two-tailed p-value of 0.05. Factors were entered in the multivariable analysis at a p-value of 0.10 using an ENTER model. No process or treatment characteristics were included in the multivariable analysis for adjustment.

Statistical analyses were performed in PASW Statistics, version 20 (SPSS inc., Chicago, IL).

RESULTS

Patient characteristics

A total of 5,161 patients, registered by 91 hospitals, met the inclusion criteria. Hospitals were categorized into three volume groups; low volume (n=25), medium volume (n=47) and high volume hospitals (n=19). Patient, tumor, treatment and outcome characteristics were displayed by hospital volume category in table 1. In medium and high volume hospitals, there was a higher proportions of advanced tumors (cT3-4: 68 and 66 versus 59%, p=< 0.001) and elective surgery (1,8 and 1,1 versus 3,7%). There was an uneven distribution in preoperative pelvic imaging; high volume hospitals showed a significantly higher percentage of patients with no recorded type of imaging. (7.0 versus 3.1 and 2.1%, p=< 0.001). Significant differences in type of neo-adjuvant treatment were observed between hospital categories with increasing use of chemoradiotherapy and decreasing use of short course radiotherapy (SCRT) with increasing volume. As for the type of surgical procedure, there was no

difference in APR rate, but medium volume hospitals treated more patients by laparoscopy than the other volume categories did (58 versus 50 and 40%, p=<0.001). Medium and high volume hospitals showed a higher percentage of patients with more than 10 examined lymph nodes. There was no significant difference between these groups for sex, age, ASA classification, Body Mass Index, distance from the tumor to the anal verge, registered CRM and postoperative morbidity and mortality.

CRM involvement

CRM was recorded in 86 percent of all included patients, with no marked differences between the volume categories. Univariable analysis showed 8 factors with a significant influence on CRM involvement (table 2). The significance level was set at a two-tailed p-value of 0.10. Sex, non-elective surgery, distance between tumor and the anal verge, a preoperative MRI, clinical T classification, preoperative (chemo) radiotherapy, laparoscopic surgery and the APR procedure were of significant influence.

Hospital volume significantly influenced the rate of CRM involvement. A positive CRM was more frequently encountered in low volume hospitals compared to medium and high volume hospitals (p=0.026). However, no difference was seen between medium and high volume hospitals (OR 0.69 and 0.71). When CRM rate was analysed using a cut-off level of 20 procedures per year, hospitals with high volume had significantly lower rates of CRM involvement than hospitals treating <20 patients annually (OR 0.70, CI 0.52 - 0.94).

Forrest plot

The influence of hospital volume (low volume vs medium/high volume) on CRM involvement in specific subgroups was plotted in a forest plot (figure 1). This figure shows that there is a marked influence of hospital volume in certain subgroups of patients. Low hospital volume has, like was already apparent in the whole group, in most groups a negative effect on CRM involvement, as is shown by the different odds ratio's.

Multivariable analysis

With adjustment for sex, clinical T classification and the distance from the tumor to the anal verge, hospital volume was still of significant

influence on CRM involvement (table 3). The risk of CRM involvement was 1.5 times as high in patients operated in a low volume setting (OR 1.54, CI 1.12-2.11). Furthermore, clinical T classification was an independent predictor for CRM involvement (cT3; OR 1.31, CI 1.00-1.72, cT4; OR 2.99, 2.08-4.31 when compared to cT1-2).

Funnelplot

Figure 2 shows the CRM involvement rate, after adjustment for casemix, of 91 hospitals varying between 0 and 50 percent. All hospitals, except for 3, were within the upper 95 percent confidence limit of the average. Nine hospitals showed significantly lower rates than average.

DISCUSSION

This population-based study is the first to analyse and demonstrate a casemix adjusted association between hospital volume and CRM involvement in rectal cancer resections. The relation remained significant after adjustment for clinical T classification, distance from the tumor to the anal verge and whether or not the resection took place in an elective setting. Patients treated in low-volume hospitals had a 1.5-fold higher risk of CRM involvement than patients operated in high-volume hospitals. Treatment strategy related factors that were both inherently related to hospital preferences or experience as well as to outcome (e.g. preoperative (chemo) radiotherapy, preoperative MRI, surgical procedure and approach) were not adjusted for.

Many studies have evaluated the influence of procedural volume on clinical outcomes like morbidity, mortality and survival.[12-14] Only few studies evaluated the influence of this factor on oncological outcome parameters like CRM.[15-18] Supportive evidence for the influence of hospital volume on CRM involvement has been scarce. Harling et al. included over 5,000 patients and found no influence in univariable analysis of hospital volume on pathological outcome.[17] Another smaller (n=302) more recently published study by Kennely et al. showed no relationship either by analysing the influence of unit APR volume (≤5, >5 per year) on CRM involvement.[18] Cornish et al. included over 7,000 patients and did find a significant relationship in univariable analysis.

High volume trusts (annual volume ≥190 colorectal procedures, rectal procedures were not mentioned) were more likely to have a negative CRM than trusts with a lower volume of cases. They did not investigate this relationship in a multivariable analysis. A higher volume per surgeon was not associated with improved CRM rates.[16] Borowski et al analysed the influence of both hospital and surgeon volume on CRM involvement; high volume surgeons had better outcomes, though hospital volume was not associated with this outcome.[15]

The definition of a high volume hospital differs between countries; minimal volume standards seem to be introduced on a rather arbitrary basis.[15] Numbers required to qualify a hospital as 'high volume' varied widely between studies. Cut off points for low volume hospitals ranged between 5 and 20 and for high volume hospitals between 10 and 40 cases a year.[21] National audits like the DSCA make continuous verification of these volume standards possible, which is important as it has substantial implications for healthcare delivery. Extensive population based audit registrations with feedback adjusted for casemix would be the ideal alternative and could make rigid minimal volume standards obsolete. However, until this is fully realised, minimal volume standards can result in better care for patients with colorectal cancer.[14, 22]

Our study has some limitations. As it is known from other national audits, the status of the CRM is not registered for every patient.[23] The proportion of reported CRM, however, did not differ significantly between the hospital volume groups. Eighty percent of the patients had a registered CRM in 2011, which increased to 92 percent in 2012. This is a high percentage compared to the audits in our neighbouring countries like the UK (60%) and Belgium (88%).[23, 24] The rate of MRI documented threatened CRM (distance to the mesorectal fascia < 1 mm) was not registred for 71 percent of all patients. Therefore, this variable was excluded from analysis. The available data revealed that high volume hospitals treated more patients with a threatened CRM (8.2% versus 7.3%) and achieved higher percentages of a negative CRM in these patients (92% versus 78 %). This suggests that MRI documented threatened CRM would not significantly have changed outcomes.

Furthermore, as the level of expertise in high volume hospitals could lead to better patient selection, diagnostic procedures and therapeutic strategies, translating into better outcomes for patients, we did not

adjust for treatment strategy related factors such as a preoperative MRI and neoadjuvant treatment. Nevertheless, we explored the potential impact of the use of 'pre-treatment MRI' and 'neoadjuvant treatment' on CRM positivity. Inclusion of these two additional variables in the multivariable model resulted in a persisting, significant and independent effect of hospital volume on CRM positivity (OR 1,58; 95% CI 1,15 – 2,17).

As the DSCA provides no results on long-term outcomes, we were only able to analyse CRM involvement as a surrogate endpoint. Nonetheless, it seems reasonable to extrapolate these outcomes to the overall quality of care for rectal cancer patient as the status of the CRM gives an accurate estimation of long-term oncological outcomes.[25]

The influence of volume on the outcomes of rectal cancer surgery has been analysed for procedural volume per surgeon and per hospital.[12, 15] The working mechanism has been described in great detail.[26] A large volume per surgeon results in greater experience but on top of that it is generally believed that volume is to be seen as a 'proxy' for other important structural and process factors in the chain of multidisciplinary treatment.[13, 22] This study underlines the importance of a high quality care process, extending beyond the surgical part of the treatment. The quality of these factors is more likely to be realised and sustained in high volume hospitals.[27, 28] By this means, the Association of Surgeons of the Netherlands decided to dictate minimal volume standards per hospital instead of minimal annual volume standards per surgeon. It is important however to conclude that individual small volume hospitals can provide the same standard of care compared to high volume hospitals as shown in figure 2. In this way, hospital volume does not guarantee quality.

In conclusion, this article supports the minimal annual volume standard of 20 rectal cancer resections a year, implemented by the Association of Surgeons of the Netherlands, by showing an independent and significant relationship between volume and CRM involvement. The question is whether there is a need for further centralisation of rectal cancer surgery in the Netherlands, since there were no marked differences in CRM involvement rates between medium and high volume hospitals and CRM status alone may not be the only outcome measure to determine optimal volume.

Acknowledgment: The authors would like to thank all surgeons, registrars, physician assistants and administrative nurses that registered all the patients in the DSCA, as well as the Dutch Surgical Colorectal Audit group.

REFERENCES

1. Verdecchia A, Francisci S, Brenner H, et al. Recent cancer survival in Europe: a 2000-02 period analysis of EUROCARE-4 data. *Lancet Oncol* 2007; 8(9):784-96.

2. Kolfschoten NE, Marang van de Mheen PJ, Gooiker GA, et al. Variation in casemix between hospitals treating colorectal cancer patients in the Netherlands. *Eur J Surg Oncol* 2011; 37(11):956-63.

3. Kapiteijn E, Putter H, van de Velde CJ. Impact of the introduction and training of total mesorectal excision on recurrence and survival in rectal cancer in The Netherlands. *Br J Surg* 2002; 89(9):1142-9.

4. Martling AL, Holm T, Rutqvist LE, et al. Effect of a surgical training programme on outcome of rectal cancer in the County of Stockholm. Stockholm Colorectal Cancer Study Group, Basingstoke Bowel Cancer Research Project. *Lancet* 2000; 356(9224):93-6.

5. van Gijn W, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *Lancet Oncol* 2011; 12(6):575-82.

6. McCall JL, Cox MR, Wattchow DA. Analysis of local recurrence rates after surgery alone for rectal cancer. *Int J Colorectal Dis* 1995; 10(3):126-32.

7. Russell MC, You YN, Hu CY, et al. A Novel Risk-Adjusted Nomogram for Rectal Cancer Surgery Outcomes. *JAMA Surg* 2013:1-9.

8. Adam IJ, Mohamdee MO, Martin IG, et al. Role of circumferential margin involvement in the local recurrence of rectal cancer. *Lancet* 1994; 344(8924):707-11.

9. Nagtegaal ID, Marijnen CA, Kranenbarg EK, et al. Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma: not one millimeter but two millimeters is the limit. *Am J Surg Pathol* 2002; 26(3):350-7.

10. Wibe A, Rendedal PR, Svensson E, et al. Prognostic significance of the circumferential resection margin following total mesorectal excision for rectal cancer. *Br J Surg* 2002; 89(3):327-34.

11. Rullier A, Gourgou-Bourgade S, Jarlier M, et al. Predictive factors of positive circumferential resection margin after radiochemotherapy for rectal cancer: the French randomised trial ACCORD12/0405 PRODIGE 2. *Eur J Cancer* 2013; 49(1):82-9.

12. Archampong D, Borowski D, Wille-Jorgensen P, et al. Workload and surgeon's specialty for outcome after colorectal cancer surgery. *Cochrane Database Syst Rev* 2012; 3:CD005391.

13. Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. *N Engl J Med* 2002; 346(15):1128-37.

14. van Gijn W, Gooiker GA, Wouters MW, et al. Volume and outcome in colorectal cancer surgery. *Eur J Surg Oncol* 2010; 36 Suppl 1: S55-63.

15. Borowski DW, Bradburn DM, Mills SJ, et al. Volume-outcome analysis of colorectal cancer-related outcomes. *Br J Surg* 2010; 97(9):1416-30.

16. Cornish JA, Tekkis PP, Tan E, et al. The national bowel cancer audit project: the impact of organisational structure on outcome in operative bowel cancer within the United Kingdom. *Surg Oncol* 2011; 20(2): e72-7.

17. Harling H, Bulow S, Moller LN, et al. Hospital volume and outcome of rectal cancer surgery in Denmark 1994-99. *Colorectal Dis* 2005; 7(1):90-5.

18. Kennelly RP, Rogers AC, Winter DC. Multicentre study of circumferential margin positivity and outcomes following abdominoperineal excision for rectal cancer. *Br J Surg* 2013; 100(1):160-6.

19. Van Leersum NJ, Snijders HS, Henneman D, et al. The Dutch surgical colorectal audit. *Eur J Surg Oncol* 2013; 39(10):1063-70.

20. Dutch Institute for Clinical Auditing. Annual Reports 2012. http://www.clinicalaudit.nl.

21. Iversen LH, Harling H, Laurberg S, et al. Influence of caseload and surgical speciality on outcome following surgery for colorectal cancer: a review of evidence. Part 1: short-term outcome. *Colorectal Dis* 2007; 9(1):28-37.

22. Finlayson SR. The volume-outcome debate revisited. *Am Surg* 2006; 72(11):1038-42; discussion 1061-9, 1133-48.

23. National Bowel Cancer Audit Programme (NBOCAP). Annual reports 2013. http://www.acpgbi.org.uk/content/uploads/Bowel-Cancer-Audit-2013_INTERACTIVE-PDF_01-07-13.pdf. Assessed on 2/3/2014.

24. Demetter P, Vandendael T, Sempoux C, et al. Need for objective and reproducible criteria in histopathological assessment of total mesorectal excision specimens: lessons from a national improvement project. *Colorectal Dis* 2013; 15(11):1351-8.

25. Birbeck KF, Macklin CP, Tiffin NJ, et al. Rates of circumferential resection margin involvement vary between surgeons and predict outcomes in rectal cancer surgery. *Ann Surg* 2002; 235(4):449-57.

26. Mesman R, Faber MJ, Westert GP, et al. [Volume standards: quality through quantity? relationship between treatment volume and outcomes not well founded]. *Ned Tijdschr Geneeskd* 2013; 157(33):A5466.

27. Hohenberger W, Merkel S, Hermanek P. Volume and outcome in rectal cancer surgery: the importance of quality management. *Int J Colorectal Dis* 2013; 28(2):197-206.

28. Donabedian A. Evaluating the quality of medical care. *Milbank Mem Fund Q* 1966; 44(3):Suppl:166-206.

TABLES AND FIGURES

Table 1: Patient, tumor, treatment and outcome characteristics categorised per hospital volume. Complicated postoperative course: a complication leading to a surgical, endoscopic or radiological re-intervention, to an in-hospital stay of more than 14 days, or to death. MDT=Multidisciplinary team meeting; SCRT=Short course radiotherapy; CRT=Chemoradiotherapy; LAR=Low anterior resection; APR=Abdominoperineal resection.

	< 20 / year		**20-40 / year**		**> 40 / year**		χ^2
No. of patients	618	12%	2607	50%	1936	38%	
No. of hospitals	25		47		19		
Patient							
Sex							0.780
male	390	63%	1609	62%	1192	62%	
female	228	37%	998	38%	744	38%	
Age							0.751
<75 yrs	232	72%	993	73%	729	74%	
>75 yrs	91	28%	364	27%	257	26%	
ASA classification							0.500
I - II	519	84%	2141	82%	1603	83%	
III	90	15%	445	17%	320	17%	
IV - V	6	1.0%	15	0.6%	12	0.6%	
Body mass index							0.509
<20	8	1.7%	53	2.7%	44	3.2%	
20-25	155	34%	620	32%	427	31%	
25-29	207	45%	879	45%	655	47%	
>30	89	19%	393	20%	260	19%	
Tumor							
Clinical T classification							<0.001
cT 1-2	237	41%	810	32%	617	35%	
cT3	309	53%	1531	60%	965	54%	
cT4	35	6.0%	210	8.2%	205	12%	

Continuation of Table 1

Distance tumor to anal verge							0.112
<=5 cm	229	40%	900	36%	697	40%	
6-10 cm	230	40%	1035	42%	677	39%	
>10 cm	116	20%	558	22%	382	22%	
Diagnostics							
Preoperative MRI pelvis							<0.001
No	41	6.6%	197	7.6%	127	6.6%	
Yes	558	90%	2356	90%	1674	87%	
Unknown	19	3.1%	54	2.1%	135	7.0%	
Preoperative MDT meeting	592	96%	2524	97%	1896	98%	0.009
Treatment							
Preoperative (chemo) radiotherapy							<0.001
None	88	14%	409	16%	412	21%	
SCRT	306	50%	1205	46%	743	38%	
CRT	224	36%	993	38%	781	40%	
Procedure							0.356
LAR	420	70%	1782	70%	1245	68%	
APR	182	30%	766	30%	587	32%	
Laparoscopic surgery	310	50%	1522	58%	763	40%	<0.001
Non-elective surgery	23	3.7%	46	1.8%	22	1.1%	<0.001
Pathology							
More than 10 harvested lymph nodes	412	67%	1885	72%	1394	72%	0.017
Registred circumferential resection margin	527	85%	2241	86%	1662	86%	0.907
Postoperative course							
Complicated postoperative course	167	27%	621	24%	436	23%	0.071
30-day mortality	19	3.1%	53	2.0%	43	2.2%	0.288

Table 2: Prevalence of CRM involvement in various casemix factors and univariate analysis of the influence of these casemix factors on CRM involvement. CRM+ = CRM involvement, MDT = Multidisciplinary team, SCRT=Short course radiotherapy, CRT=Chemoradiotherapy, LAR=Low anterior resection; APR=Abdominoperineal resection.

	CRM +	OR	95% CI	95% CI
Patient				
Sex				
male	8.7%	ref		
female	7.2%	0.81	0.65	1.02
Age				
< 75 yrs	8.1%	ref		
> 75 yrs	7.4%	0.92	0.65	1.29
ASA classification				
I - II	7.8%	ref		
III	9.7%	1.26	0.95	1.66
IV - V	12%	1.60	0.48	5.39
Body mass index				
<20	11%	1.21	0.61	2.42
20-25	9.3%	ref		
25-29	8.0%	0.85	0.64	1.12
≥30	7.6%	0.80	0.56	1.14
Tumor				
Clinical T-classification				
cT 1 and 2	6.4%	ref		
cT3	7.8%	1.23	0.95	1.60
cT4	17%	2.91	2.06	4.11
Distance tumor to anal verge				
≤ 5 cm	9.6%	1.17	0.87	1.56
6-10 cm	6.7%	0.80	0.59	1.09
> 10 cm	8.3%	ref		

Continuation of Table 2

Diagnostics				
Preoperative MRI pelvis				
no	14%	1.84	1.29	2.62
yes	7.9%	ref		
unknown	4.2%	0.51	0.22	1.16
Preoperative MDT meeting				
yes	10%	1.26	0.67	2.37
no	8.1%	ref		
Treatment Preoperative (chemo) radiotherapy				
None	12%	ref		
SCRT	5.7%	0.45	0.33	0.61
CRT	9.6%	0.80	0.60	1.06
Procedure				
LAR	7.1%	ref		
APR	10%	1.49	1.19	1.86
Approach				
Open	9.8%	ref		
Laparoscopic	6.5%	0.64	0.51	0.79
Setting				
Elective	7.9%	ref		
Urgent	24%	3.63	2.01	6.54
Hospital volume				
Volume in 2 groups				
low volume	11%	ref		
high volume	7.8%	0.697	0.517	0.939
Volume in 3 groups				
low volume	11%	ref		
medium volume	7.7%	0.69	0.50	0.94
high volume	7.9%	0.71	0.51	0.99

Table 3: Assessment of the influence of hospital volume on CRM involvement in a multivariate analysis. CI=Confidence interval; OR=Odds ratio.

	Sig.	OR	95% CI	95% CI
Sex				
Male				ref
Female	.112	0.82	0.65	1.05
Clinical T classification				
cT 1 and 2				ref
cT3	.050	1.31	1.00	1.72
cT4	.000	2.99	2.08	4.31
Distance tumor - anal verge				
≤ 5 cm	.654	1.07	0.79	1.45
6-10 cm	.230	0.83	0.60	1.13
> 10 cm				ref
Hospital volume				
low volume	.008	1.54	1.12	2.11
high volume				ref

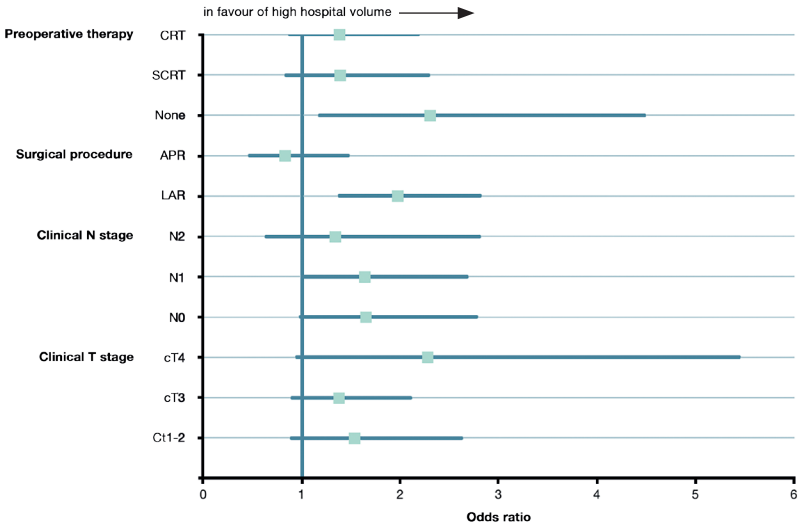


Figure 1: Forest plot representing the OR and CI of the influence of low hospital volume versus high hospital volume on CRM involvement, seperately presented for different subgroups (hier subgroepen beschrijven?) cT=clinical T classification, cN=clinical N classification, LAR=Low anterior resection, APR=Abdominoperineal resection, SCRT=Short course radiotherapy, CRT=Chemoradiotherapy).

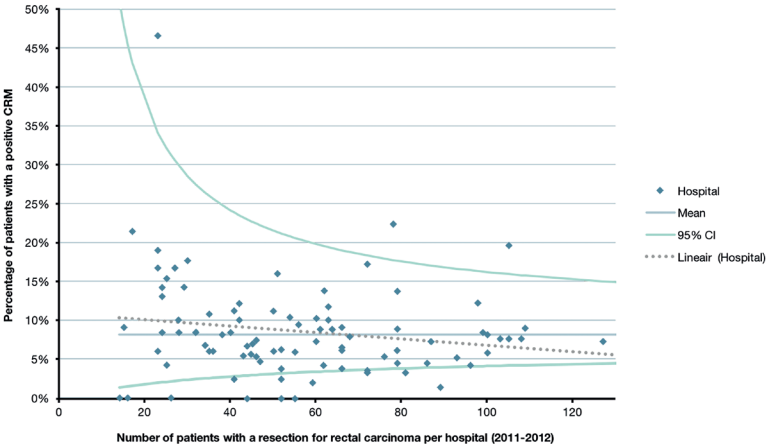


Figure 2: Funnel plot showing differences in risk-adjusted CRM involvement rates between hospitals (2011-2012). Casemix adjustments were made for sex, clinical T classification and the distance from tumor to the anal verge.

Chapter 4

REDUCED CIRCUMFERENTIAL RESECTION MARGIN INVOLVEMENT IN RECTAL CANCER SURGERY; RESULTS OF THE DUTCH SURGICAL COLORECTAL AUDIT.

Lieke Gietelink, Michel W.J.M. Wouters, Pieter J. Tanis, Marion M. Deken, Martijn G. ten Berge, Rob A.E.M. Tollenaar, Han J. van Krieken and Mirre E. de Noo, on behalf of the Dutch Surgical Colorectal Cancer Audit Group.

J Natl Compr Canc Netw. 2015 Sep;13(9):1111-9.

ABSTRACT

Background: The circumferential resection margin (CRM) is a significant prognostic factor for local recurrence, distant metastasis and survival after rectal cancer surgery. Therefore, availability of this parameter is essential. Although the Dutch TME trial raised awareness about CRM in the late 1990s, quality assurance on pathologic reporting was not available until the Dutch Surgical Colorectal Audit (DSCA) started in 2009. This study describes the rates of CRM reporting and CRM involvement since the start of the DSCA and analyses whether improvement of these parameters can be attributed to the audit.

Methods: Data of the DSCA (2009 - 2013) was analysed. Reporting of CRM and CRM involvement was plotted for successive years and variation of these parameters were analysed in a funnelplot. Predictors of CRM involvement were determined in univariable analysis and the independent influence of year of registration on CRM involvement was analysed in multivariable analysis.

Results: A total of 12,669 patients were included for analysis. The mean percentage of patients with a reported CRM increased from 52.7 to 94.2 percent (2009-2013) and interhospital variation decreased. The percentage of patients with CRM involvement decreased from 14.2 to 5.6 percent. In multivariable analysis, the year of DSCA registration remained a significant predictor of CRM involvement.

Conclusion: After the introduction of the DSCA, there has been a dramatic improvement in CRM reporting and a major decrease of CRM involvement after rectal cancer surgery. This study suggests that a national quality assurance program has been the driving force behind these achievements.

INTRODUCTION

Surgical resection remains the cornerstone of curative treatment in rectal cancer.(1) The implementation and standardization of the total mesorectal excision technique (TME) and the introduction of preoperative (chemo) radiotherapy have led to improved oncological outcomes.(2, 3) The circumferential resection margin (CRM) indicates the distance from the tumor to the resection plane in a transverse section through the TME specimen. Tumour negative, non-involved, CRM is defined as the absence of microscopic tumor cells within 1 mm of the inked resection margin, This is the most significant prognostic factor for local recurrence, distant metastasis and survival after rectal cancer surgery.(4) Therefore this parameter provides both important information on the quality of surgical resection and on the prognosis of the patient.

Because of its prognostic value, the CRM has been frequently used as a surrogate endpoint in randomised controlled trials (RCT's).(5,6) In the Netherlands, a standard pathology protocol to examine a TME specimen was introduced in the 1990s related to the start of the Dutch TME trial.(5) Due to this standardization, 97 percent of patients included in this trial had a reported CRM.(2) In subsequent years, until the start of the Dutch Surgical Colorectal Audit (DSCA) in 2009, there was no national quality assurance on histopathological reporting and the CRM was presumably less frequently reported in routine practice outside a trial setting.

The DSCA evaluates and reports on the quality of care of primary colorectal cancer surgery.(7) It provides periodic feedback to all hospitals in the Netherlands on a set of quality measures, including two indicators regarding the CRM in rectal cancer surgery. The objective of this study was to evaluate the rates of CRM reporting and CRM involvement throughout the successive years of the DSCA registration. Secondly, it analyses changes in these CRM related quality indicators over time and investigates the potential contribution of the DSCA to observed changes in a multivariable model.

METHODS

Data were derived from the DSCA, a disease specific national audit. This audit collects information on patient, tumor, treatment and outcome characteristics and containes data on approximately 97 percent of all patients who underwent a resection for primary colorectal carcinoma in the Netherlands.(8) The dataset is based on evidence-based guidelines and compared on a yearly basis with the data registered in the Netherlands Cancer Registry (NCR). Details of this dataset regarding data collection and methodology have been published previously.(7,9)

Patients

For this study, no ethical approval or informed consent was required under Dutch law. All patients (n=13,029) undergoing surgical resection for primary rectal cancer between January 1st 2009 and December 31th, 2013, and registered in the DSCA before March 15, 2014, were evaluated. Patients with multiple synchronous tumors with at least one tumor located in the rectum were included. Patients who underwent a local excision with or without completion TME surgery were excluded (n=241). In addition, patients with a complete pathological response (ypT0) on neo-adjuvant (chemo)radiotherapy were excluded as well (n=610). Minimal data requirements to consider a patient eligible for analyses were information on tumor location and date of surgery. Baseline characteristics of the study population and treatment characteristics are displayed per year in table 1.

Circumferential resection margin

The mean percentage of reported CRM as well as the reported CRM rate per hospital for each year of the study period were calculated. CRM was considered positive if tumor cells were present within 1mm from the inked margin according to the definition of the Dutch guideline.(10) CRM involvement was only calculated for patients with a reported CRM. The mean percentage of CRM involvement as well as the percentage of CRM involvement per hospital was calculated for each year.

Statistical analyses

Differences in baseline characteristics between different years of the study period were analyzed using a Chi square test. A p-value of less

than 0.05 was considered statistically significant. Potential predictors of CRM involvement were determined in a univariable analysis. Variables with a significance level of $p<0.1$ in univariable analysis were subsequently included in a multivariable logistic regression model as categorical variables. To analyze the possible effect of the DSCA on CRM involvement, the year of DSCA registration was added as an ordinal variable to the multivariable model. A scatterplot with each dot representing an individual hospital was used to visualize the hospital variation in CRM reporting for the years 2009, 2011 and 2013. The number of patients who underwent a resection for rectal cancer is plotted on the x-axis and the percentage of patients with a reported CRM on the y-axis. The overall mean percentage is represented as a horizontal line.

A funnel plot was used to visualize the hospital variation in casemix corrected CRM involvement for the years 2009, 2011 and 2013. Variables included in this casemix correction for CRM involvement included type of resection, laparoscopic resection, emergency surgery and pathological T classification. The number of patients with a reported CRM is plotted on the x-axis and the percentage of CRM involvement on the y-axis. The overall average CRM involvement is represented by a horizontal line with its 95% and 99% confidence limits, based on a Poisson distribution, varying in relation to the population size of each hospital. To evaluate the linear effect of year of registration on CRM involvement, we performed a linear-by-linear association test. Statistical analyses were performed in PASW Statistics, version 20 (SPSS inc., Chicago, IL).

RESULTS

Patient and treatment characteristics

A total of 12,178 patients, registered by 91 hospitals, were included for analysis. Patient, tumor and treatment characteristics are displayed in table 1. There was a decrease in unspecified clinical T-classification ($p<0.001$). The use of MRI as preoperative imaging technique increased ($p<0.001$) and so did the percentage of patients who were preoperatively discussed in a multidisciplinary team (MDT) meeting

(p<0.001). There was a peak incidence in the use of neoadjuvant therapy in 2011, and was still above 80% in 2013. There was an increase in the use of short course radiotherapy with delayed (>3 weeks) surgery (SCRT-DS) and chemoradiotherapy (CRT), both with a potential downsizing effect. The use of laparoscopic surgery doubled during this 5-year period; from 33 percent in 2009 to 66 percent in 2013 (p<0.001). Non-elective resections decreased to 1.5 percent (p<0.001).

Reporting of CRM

Figure 1 shows the mean percentage of patients with a reported CRM per year and displays the variation on this parameter between hospitals in 2009, 2011 and 2013. In 2009, the mean reported CRM rate was 52.7 percent, which varied from 0 to 100 percent between individual hospitals. The mean percentage of patients with a reported CRM increased to 94.2 percent in 2013 and inter-hospital variation decreased (range 33 to 100% in 2013). Baseline characteristics between patients with a reported and unreported CRM are displayed in Table 2, which shows the percentage of patients without a reported T and N classification is higher amongst patients without a reported CRM than amongst patients with a reported CRM.

CRM involvement

In 2009, the mean rate of CRM involvement was 14.2 percent in patients with a reported CRM (Table 3). In 2013, the mean percentage of CRM involvement was 5.6 percent in the 94 percent of patients with a reported CRM. Figure 2a-c shows the variation of CRM involvement among the Dutch hospitals in the years 2009, 2011 and 2013. The mean percentage of patients with an involved CRM was significantly lower in 2013 compared to 2009 (p<0.001). Furthermore, inter-hospital variation has decreased since the start of the DSCA (range 0 – 90 % in 2009, range 0 – 22 % in 2013). None of the hospitals were a negative outlier, however, due to low annual numbers of rectal cancer resections per hospital per year, confidence intervals are wide. There was a significant effect of year of DSCA registration on CRM involvement in the linear by linear association test (p=0.005).

Predictors of CRM involvement

Table 4 displays the univariable and multivariable analysis of potential predictors for CRM involvement, including the year of DSCA registration.

In multivariable analysis the year of DSCA registration remained a significant influence on CRM involvement, with an odds ratio of 0.47 for registration year 2013 compared to 2009. Together with the year of DSCA registration, clinical T classification, procedure, approach, setting and pathological T classification were of significant influence on CRM involvement. To consider the correlation in the multivariate model between clinical and pathological T classification we repeated the multivariable analysis without pathological T classification; results however remained unchanged (data not shown).

DISCUSSION

After the introduction of the DSCA as a quality assurance initiative in the Netherlands, there has been a dramatic improvement in the percentage of patients with a reported CRM in rectal cancer surgery. Alongside this improvement there has been a major decrease of CRM involvement, which is known to have a significant effect on the long-term outcomes of patients with rectal cancer. Such a substantial progress in the quality of rectal cancer care has not been observed since the introduction and standardization of the TME technique and the concomitant use of neo-adjuvant therapy.(3) Improvement in CRM reporting is almost exclusively attributable to the national audit, and the present multivariable analysis also suggests that the DSCA was a driving force behind the significant increase in tumor free resection margins.

Population based studies and other national audits on rectal cancer confirmed that the CRM, as an important measure for the quality of surgical resection, was often lacking in the pathology report.(11-14) Swellengrebel et al. performed a population study on the value of multidisciplinary team meetings in the Netherlands between 2006 and 2008, right before the start of the DSCA, and showed that only 61 percent of patients had a reported CRM.(15) This is substantially lower than the 97 percent reported CRM rate in the Dutch TME trial (1996-1999), confirming again that a trial setting does not represent routine daily practice. But why was the standardized pathology reporting from the TME trial not implemented in the Netherlands? This is especially

important to ask given the numerous publications from our country at that time showing that CRM is one of the most important outcome parameters in rectal cancer.(4, 16-19) Apparently, confronting the individual hospitals with their data, benchmarking their outcome, and making CRM reporting a quality indicator that is made available to external parties is what eventually does lead to practice changing. The present analysis shows that quality indicators play an important role in identifying quality concerns and variation, and enable targeting quality improvement projects.

Other countries with a national audit on rectal cancer, for example the United Kingdom, also reported on CRM related quality indicators.(20) A decrease in CRM involvement have been observed by the National Bowel Cancer Audit Programme (NBOCAP) in the UK, although only a minor improvement in CRM reporting was found with still more than 30 percent of patients without a reported CRM in 2013. Remarkably similar results as observed in the Netherlands were found by a regional Quality Initiative in Canada in a population of 1.3 million inhabitants for whom colorectal cancer surgery is provided in eight community hospitals and three teaching hospitals.(21) During 2-yearly voluntary workshops, quality markers were selected by the participating surgeons, together with the commencement of improvement interventions such as auditing and feedback, preoperative multidisciplinary consultation and a system event reporting system. In the period between 2006 and 2012, CRM reporting improved from 55 to 93 percent and CRM involvement decreased from 14 to 6 percent. In the limitations of this study, the authors question the generalizability of their findings. Our study proves that almost identical improvements can be achieved by just auditing, even at a national level with more than 16 million inhabitants.

This positive effect of feedback on CRM involvement has been described before. In the MRC CR07 trial, quality of the resection specimen was prospectively assessed and reported to the surgeons. As the study proceeded, the percentage of CRM involvement decreased significantly from 21 to 10 percent.(22) Evaluation of the TME specimen by the pathologist and CRM provide direct feedback towards the surgeon on the technical performance of the resection and, therefore, should be dedicated team members participating in multidisciplinary meetings in which patients are discussed postoperatively.(19) Furthermore, Quirke et al also pointed out the possible influence of the introduction of

standard preoperative MDT meetings and local staging with MRI which both could have led to the lowered percentage of CRM involvement in the MRC CR07 study. The DSCA included preoperative MR imaging and the discussion of patients in a preoperative MDT meeting as quality indicators, and improvements in both indicators have been observed (Table 1). As both preoperative MRI and MDT meetings were already an obligatory part of the diagnostic pathway for rectal cancer patients according to the Dutch national guidelines, the improvements can also be seen as an effect of the DSCA. Both factors were significantly associated with CRM involvement in univariable analysis, but lost their significance in multivariable analysis. Other changes during the study period that may have contributed to the decrease of CRM involvement in our study period are the increased use of downstaging radiotherapy regimens (SCRT-DS and CRT), which indeed revealed to be related to the risk of an involved CRM in univariable analysis, but not in multivariable analysis. The above-mentioned factors could also have slightly influenced CRM reporting. A multivariate analysis (data not shown) however showed a significant and independent effect of the year of registration on CRM reporting, when the effect was corrected for all these factors. The positive impact of an increased use of minimally invasive techniques on CRM involvement is difficult to interpret, as meta-analysis of randomized controlled trials revealed no difference in CRM involvement between laparoscopic and open TME surgery.(19) This finding could reflect the use of laparoscopic surgery by more specialized colorectal surgeons within more dedicated teams, but it might also be influenced by the inherent risk of selection bias within population studies. Although the influence of the approach on CRM involvement was analyzed in a multivariate model, there could be unmeasured factors that influenced the decision between open en laparoscopic resection.

There have not been other important changes in the treatment of rectal cancer in the Netherlands during the years covered by the present study. The multivariable analysis demonstrates the independent significant influence of the registration year on the risk of CRM involvement, which strenghtens the believe that the DSCA has been one of the leading factors in the major improvement of CRM involvement in the Netherlands in only a five year time period.

The limitation of this study is that it remains difficult to estimate to what extend the audit has influenced the improved outcome of CRM reporting and CRM involvement. Although we think we addressed the most important clinical changes we can't exclude the possibility of other clinical changes that could have influenced these improvements and are not captured in the DSCA database. Furthermore we cannot exclude some reporting bias. Table 1 shows a disproportionate increase of mid-rectal tumors and LAR procedures and some hospitals with low numbers of patients with a reported CRM might have reported relatively more patients with CRM involvement in the first registration years. However, this seems unlikely as a population based study from the Netherlands showed equal CRM involvement in that period.(15) Furthermore, the 14 percent CRM involvement at the start of the DSCA is even favorable if compared to the 16 percent CRM involvement in the Dutch TME trial, especially considering the fact that the audit also includes locally advanced rectal cancer.(2)

In conclusion, there has been a marked improvement in the percentage of patients with a reported CRM since the start of the DSCA as a national quality assurance program. Furthermore, there has been a significant decrease of patients with CRM involvement, which attributes to a better prognosis for these patients. Few other interventions in the care of rectal cancer patients have led to such magnitude of improvements in a relatively short period of time and it shows the value of national auditing as a tool for quality improvement.

Acknowledgment: The authors would like to thank all surgeons, registrars, physician assistants and administrative nurses that registered all the patients in the DSCA, as well as the Dutch Surgical Colorectal Audit group.

REFERENCES

1. Weitz J, Koch M, Debus J, Hohler T, Galle PR, Buchler MW. Colorectal cancer. Lancet. 2005 Jan 8-14;365(9454):153-65. PubMed PMID: 15639298. Epub 2005/01/11. eng.

2. van Gijn W, Marijnen CA, Nagtegaal ID, Kranenbarg EM, Putter H, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. The lancet oncology. 2011 Jun;12(6):575-82. PubMed PMID: 21596621. Epub 2011/05/21. eng.

3. den Dulk M, Krijnen P, Marijnen CA, Rutten HJ, van de Poll-Franse LV, Putter H, et al. Improved overall survival for patients with rectal cancer since 1990: the effects of TME surgery and preoperative radiotherapy. European journal of cancer (Oxford, England : 1990). 2008 Aug;44(12):1710-6. PubMed PMID: 18573654. Epub 2008/06/25. eng.

4. Nagtegaal ID, Quirke P. What is the role for the circumferential margin in the modern treatment of rectal cancer? Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2008 Jan 10;26(2):303-12. PubMed PMID: 18182672. Epub 2008/01/10. eng.

5. Kapiteijn E, Kranenbarg EK, Steup WH, Taat CW, Rutten HJ, Wiggers T, et al. Total mesorectal excision (TME) with or without preoperative radiotherapy in the treatment of primary rectal cancer. Prospective randomised trial with standard operative and histopathological techniques. Dutch ColoRectal Cancer Group. The European journal of surgery = Acta chirurgica. 1999 May;165(5):410-20. PubMed PMID: 10391155. Epub 1999/07/03. eng.

6. Sebag-Montefiore D, Stephens RJ, Steele R, Monson J, Grieve R, Khanna S, et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. Lancet. 2009 Mar 7;373(9666):811-20. PubMed PMID: 19269519. Pubmed Central PMCID: PMC2668947. Epub 2009/03/10. eng.

7. Van Leersum NJ, Snijders HS, Henneman D, Kolfschoten NE, Gooiker GA, Ten Berge MG, et al. The Dutch Surgical Colorectal Audit. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2013 Jul 18. PubMed PMID: 23871573. Epub 2013/07/23. Eng.

8. Annual report 2013, the Dutch Surgical Colorectal Audit. Available from: http://www.clinicalaudit.nl/jaarrapportage/2013/ - dica_rapportages_dsca.

9. Kolfschoten NE, Marang van de Mheen PJ, Gooiker GA, Eddes EH, Kievit J, Tollenaar RA, et al. Variation in casemix between hospitals treating colorectal cancer patients in the Netherlands. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2011 Nov;37(11):956-63. PubMed PMID: 21944049. Epub 2011/09/29. eng.

10. http://www.oncoline.nl.

11. Bernstein TE, Endreseth BH, Romundstad P, Wibe A. Circumferential resection margin as a prognostic factor in rectal cancer. The British journal of surgery. 2009 Nov;96(11):1348-57. PubMed PMID: 19847867. Epub 2009/10/23. eng.

12. National Bowel Cancer Audit Programme (NBOCAP). Annual reports 2013. http://www.acpgbi.org.uk/content/uploads/Bowel-Cancer-Audit-2013_INTERACTIVE-PDF_01-07-13.pdf.

13. Demetter P, Vandendael T, Sempoux C, Ectors N, Cuvelier CA, Nagy N, et al. Need for objective and reproducible criteria in histopathological assessment of total mesorectal excision specimens: lessons from a national improvement project. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland. 2013 Nov;15(11):1351-8. PubMed PMID: 23865820. Epub 2013/07/20. eng.

14. Jorgren F, Johansson R, Damber L, Lindmark G. Risk factors of rectal cancer local recurrence: population-based survey and validation of the Swedish rectal cancer registry. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland. 2010 Oct;12(10):977-86. PubMed PMID: 19438885. Epub 2009/05/15. eng.

15. Swellengrebel HA, Peters EG, Cats A, Visser O, Blaauwgeers HG, Verwaal VJ, et al. Multidisciplinary discussion and management of rectal cancer: a population-based study. World journal of surgery. 2011 Sep;35(9):2125-33. PubMed PMID: 21720869. Pubmed Central PMCID: PMC3152708. Epub 2011/07/02. eng.

16. Nagtegaal ID, Marijnen CA, Kranenbarg EK, van de Velde CJ, van Krieken JH. Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma: not one millimeter but two millimeters is the limit. The American journal of surgical pathology. 2002 Mar;26(3):350-7. PubMed PMID: 11859207. Epub 2002/02/23. eng.

17. Gosens MJ, Klaassen RA, Tan-Go I, Rutten HJ, Martijn H, van den Brule AJ, et al. Circumferential margin involvement is the crucial prognostic factor after multimodality treatment in patients with locally advanced rectal carcinoma. Clinical cancer research : an official journal of the American Association for Cancer Research. 2007 Nov 15;13(22 Pt 1):6617-23. PubMed PMID: 18006762. Epub 2007/11/17. eng.

18. den Dulk M, Collette L, van de Velde CJ, Marijnen CA, Calais G, Mineur L, et al. Quality of surgery in T3-4 rectal cancer: involvement of circumferential resection margin not influenced by preoperative treatment. Results from EORTC trial 22921. European journal of cancer (Oxford, England : 1990). 2007 Aug;43(12):1821-8. PubMed PMID: 17627809. Epub 2007/07/14. eng.

19. Nagtegaal ID, van Krieken JH. The role of pathologists in the quality control of diagnosis and treatment of rectal cancer-an overview. European journal of cancer (Oxford, England : 1990). 2002 May;38(7):964-72. PubMed PMID: 11978521. Epub 2002/04/30. eng.

20. National Bowel Cancer Audit Programme (NBOCAP). Annual reports 2014. http://www.tripartite2014.org/content/uploads/2013/05/NBOCAP-2014-Progress-Report.pdf.

21. Simunovic M, Stephen W, Kelly S, Forbes S, Cadeddu M, Thabane L, et al. Quality improvement in colorectal cancer in local health integration network 4 (LHIN 4) project (QICC-L4): integrated knowledge translation in a large geographic region. Ann Surg Oncol. 2013 Dec;20(13):4067-72. PubMed PMID: 23975323. Epub 2013/08/27. eng.

22. Quirke P, Steele R, Monson J, Grieve R, Khanna S, Couture J, et al. Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomised clinical trial. Lancet. 2009 Mar 7;373(9666):821-8. PubMed PMID: 19269520. Pubmed Central PMCID: PMC2668948. Epub 2009/03/10. eng.

TABLES AND FIGURES

Table 1: Baseline characteristics of patients with a resection for rectal cancer registered in the Dutch Surgical Colorectal Audit, 2009 – 2013.

	Year of DSCA registration					
	2009	**2010**	**2011**	**2012**	**2013**	**X^2**
Male	61.5%	62.2%	63.7%	61.1%	63.1%	0.291
Age						0.311
75+	28.9%	27.0%	28.2%	28.1%	29.6%	
ASA score						0.884
III	16.9%	16.8%	17.6%	17.8%	17.3%	
BMI						0.005
30+	13.5%	16.6%	15.2%	17.9%	16,0%	
Clinical T classification						<0.001
cT1	3.5%	3.8%	3.8%	2.7%	2.3%	
cT2	19.2%	23.3%	23.3%	24.0%	21.2%	
cT3	47.0%	46.6%	52.1%	55.7%	61.9%	
cT4	9.9%	8.7%	7.9%	8.6%	9.1%	
cTx/unknown	20.4%	17.5%	12.9%	8.9%	5.5%	
Distance tumor - anus						<0.001
<=5 cm	35.8%	32.3%	34.9%	33.3%	36.2%	
6-10 cm	35.6%	39.0%	38.5%	38.9%	39.0%	
>10 cm	20.1%	20.9%	20.3%	23.0%	21.1%	
unknown	8.5%	7.8%	6.2%	4.8%	3.7%	
MRI						<0.001
yes	78.4%	83.7%	88.0%	90.2%	91.9%	
unknown	11.3%	6.7%	3.2%	1.7%	1.8%	
MDT						<0.001
yes	79.0%	90.4%	95.9%	98.1%	98.7%	
Neo-adjuvant therapy						<0.001
none	21.3%	16.9%	14.1%	18.2%	18.6%	
SCRT	41.9%	45.4%	45.7%	39.2%	35.9%	
SCRT-ds	3.5%	3.7%	4.4%	6.3%	8.8%	

Continuation of Table 1

CRT	33.0%	33.9%	35.5%	36.3%	36.5%	
other	0.3%	0.1%	0.3%	0.0%	0.2%	
Procedure						<0.001
LAR	58.0%	61.5%	65.8%	70.5%	68.9%	
APR	31.6%	29.4%	29,4%	26.6%	28.6%	
other/non-specified	10.4%	9.2%	4.8%	2.8%	2.6%	
Approach						<0.001
Laparoscopic	33.2%	36.2%	43.2%	54.7%	65.5%	
Setting						<0.001
Non-elective	5.4%	2.6%	1.7%	2.3%	1.5%	
Pathological T classification						<0.001
(y)pT1	7.4%	7.1%	8.3%	8.5%	8.8%	
(y)pT2	28.5%	32.0%	33.9%	32.8%	33.3%	
(y)pT3	46.8%	47.7%	49.1%	51.9%	51.9%	
(y)pT4	6.6%	5.8%	5.2%	4.9%	4.6%	
(y)pTX/unknown	10.6%	7.3%	3.5%	2.0%	1.5%	
Pathological N classification						<0.001
pN0	58.7%	61.5%	61.0%	62.6%	63.0%	
pN1	20.2%	23.8%	25.8%	23.8%	24.5%	
pN2	12.8%	11.6%	10.4%	12.6%	11.8%	
pNx/unknown	8.3%	3.0%	2.7%	1.1%	0.8%	
Metastatic disease	8.3%	7.8%	7.5%	8.2%	7.5%	0.806

Table 2: Baseline characteristics of tumors with and without a reported CRM.

	Reported CRM		
	No	**Yes**	**X2**
Clinical T classification			<0.001
cT1	5.5%	2.5%	
cT2	21.2%	22.7%	
cT3	39.2%	57.0%	
cT4	7.8%	9.1%	
cTx/unknown	26.2%	8.7%	
Neo-adjuvant therapy			<0.001
none	29.9%	14.2%	
SCRT	37.9%	42.6%	
SCRT-ds	2.9%	6.2%	
CRT	29.0%	36.9%	
other	0.3%	0.2%	
Procedure			<0.001
LAR	62.9%	66.0%	
APR	24.1%	30.4%	
other/non-specified	13.0%	3.6%	
Pathological T classification			<0.001
(y)pT1	10.2%	7.4%	
(y)pT2	29.5%	33.0%	
(y)pT3	38.7%	52.8%	
(y)pT4	6.8%	5.0%	
(y)pTX/unknown	14.9%	1.8%	
Pathological N classification			<0.001
pN0	61.4%	61.5%	
pN1	21.0%	24.5%	
pN2	9.4%	12.5%	
pNx/unknown	8.1%	1.4%	
Metastatic disease	8.1%	7.8%	0.631

Table 3. Reported CRM and CRM involvement from 2009 to 2013.

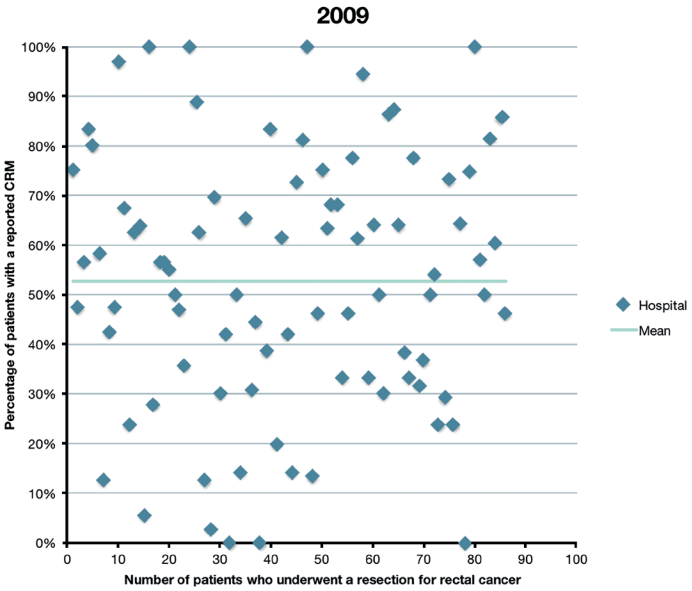
Year	Total*		Reported CRM		CRM+
	n	n	%	n	%
2009	2056	1084	52.7	154	14.2
2010	2447	1531	62.6	185	12.1
2011	2462	1956	79.4	177	9.0
2012	2692	2480	92.1	197	7.9
2013	2521	2375	94.2	134	5.6

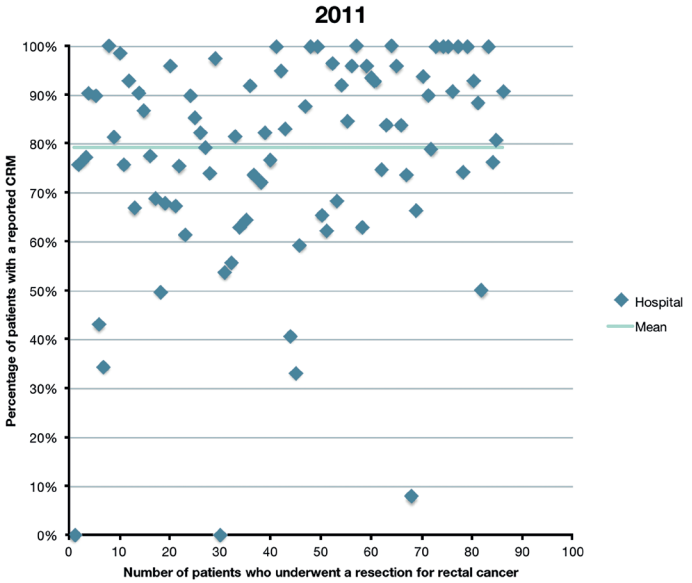
Table 4. The influence of the year of DSCA registration on CRM involvement in a multivariable analysis.

Variable (ref)	Univariate	Multivariate		
	p	OR	CI	
			Lower	Upper
Clinical T-classification (cT1)	<0.001			
cT2		1.33	0.67	2.65
cT3		1.21	0.62	2.36
cT4		1.33	0.65	2.68
cTx		0.95	0.47	1.96
Distance tumor - anus (>10cm)	<0.001			
≤ 5 cm		1.16	0.90	1.51
6-10 cm		0.95	0.76	1.18
unknown		1.09	0.75	1.59
MRI (no)	0.059			
yes		1.04	0.80	1.35
MDT (no)	0.055	0.96	0.68	1.36
yes				
Down-sizing radiotherapy (no)	<0.001			
yes		1.15	0.96	1.37
Procedure (LAR)	<0.001			
APR		1.49	1.21	1.84
other / non-specified		1.49	1.02	2.16
Approach (open)	<0.001			
laparoscopic		0.82	0.70	0.97
Setting (elective)	<0.001			
urgent		2.22	1.43	3.47
Pathological T-classification ((y)pT1)	<0.001			
(y)pT2		1.52	0.82	2.81
(y)pT3		6.35	3.54	11.40
(y)pT4		29.19	15.68	54.33
(y)pTx		2.43	1.00	5.90

Continuation of Table 4

Year of DSCA registration (2009)	<0.001			
2010		0.97	0.75	1.25
2011		0.75	0.58	0.96
2012		0.67	0.52	0.86
2013		0.47	0.35	0.61


2009
Percentage of patients with a reported CRM
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
10
20
30
40
50
60
70
80
90
100
Number of patients who underwent a resection for rectal cancer
Hospital
Mean


2011
Percentage of patients with a reported CRM
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
10
20
30
40
50
60
70
80
90
100
Number of patients who underwent a resection for rectal cancer
Hospital
Mean

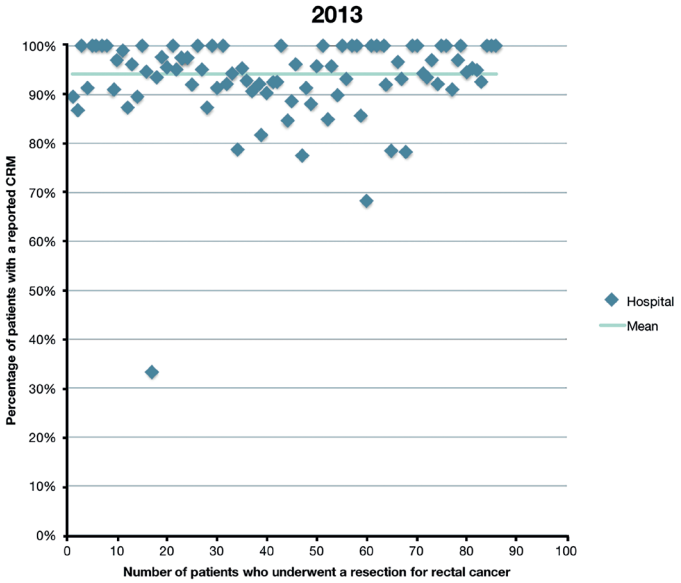
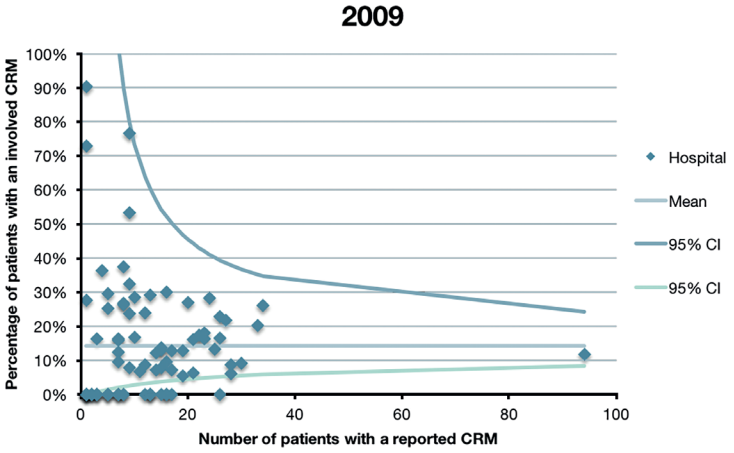
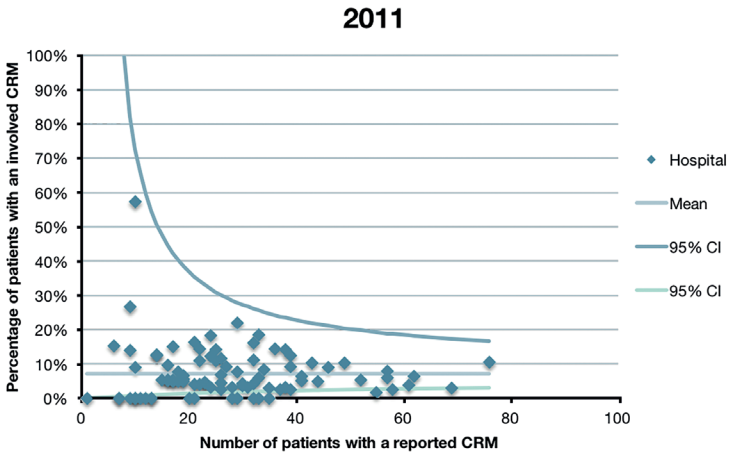


Figure 1a-c. Scatterplots showing the mean percentage and hospital variation of patients with a reported CRM, 2009(a), 2011(b), 2013(c).


2009
Percentage of patients with an involved CRM
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
20
40
60
80
100
Number of patients with a reported CRM
Hospital
Mean
95% CI
95% CI


2011
Percentage of patients with an involved CRM
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
20
40
60
80
100
Number of patients with a reported CRM
Hospital
Mean
95% CI
95% CI

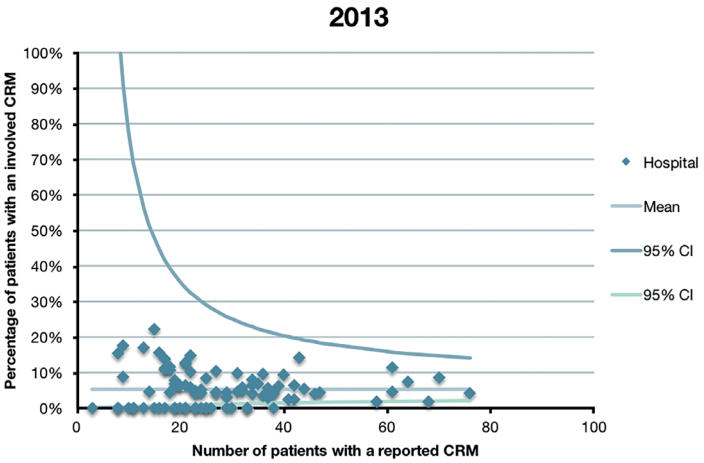


Figure 2a-c. Funnelplot showing the case-mix corrected percentage of patients with an involved CRM per hospital, 2009(a), 2011(b), 2013(c).

Chapter 5

CHANGES IN NATIONWIDE USE OF PREOPERATIVE RADIOTHERAPY FOR RECTAL CANCER AFTER REVISION OF THE NATIONAL COLORECTAL CANCER GUIDELINE.

Lieke Gietelink, Michel W.J.M. Wouters, Corrie A.M. Marijnen, Julia van Groningen, Nicoline J. van Leersum, Regina G.H. Beets-Tan, Rob A.E.M. Tollenaar, and Pieter J. Tanis, on behalf of the Dutch Surgical Colorectal Cancer Audit Group.

Eur J Surg Oncol. 2017 Jul;43(7):1297-1303.

ABSTRACT

Background: The rate of preoperative radiotherapy (RT) for rectal cancer in the Netherlands has been the highest among European countries. Revision of the national guideline on colorectal cancer, officially published in 2014, specifically focussed on the indication for RT and MRI criteria to evaluate mesorectal lymph nodes. The objective of this study was to evaluate implementation of the revised guideline using a national audit.

Methods: Data of the Dutch Surgical Colorectal Audit (DSCA) between 2009 and 2014 were used to evaluate RT use and RT regimen for relevant subgroups of cM0 rectal cancer patients, as well as accuracy of preoperative MRI.

Results: 14,018 patients were included for analysis. Overall RT use in cT1-4N0-2M0 stage ranged from 81.4% to 84.2% between 2009 and 2013, and decreased to 64.4% in 2014. The absolute decrease in RT use from 2013 to 2014 for cT1N0, cT2N0 and cT3N0 stage was 32.8%, 43.5% and 31.6%, respectively. Short course RT with delayed surgery was used as an alternative to chemoradiotherapy up to 2013 in 30.6% of patients over 80 years, and in 12.1% of patients with an ASA score > 2; these percentages increased to 45.8% and 19.9% in 2014, respectively. Specificity of MRI for N-stage decreased from 82.9% in 2009 to 62.9% in 2013, with an increase to 73.2% in 2014.

Conclusion: The revised national guideline on colorectal cancer was rapidly implemented in the Netherlands with a substantial decrease in RT use for low risk resectable rectal cancer, and increased specificity of MRI for N-staging.

INTRODUCTION

Preoperative radiotherapy (RT) in rectal cancer patients has been shown to reduce local recurrence rates, but this oncological improvement should be weighed against radiotherapy related morbidity.[1, 2] The use of RT in rectal cancer management in the Netherlands was published by van Leersum et al. in 2013.[3] RT use in the Netherlands appeared to be high compared to other countries, with an overall rate of more than 80%. Even the majority of stage I rectal cancer patients received preoperative RT.[3, 4]

In 2012, a revision of the national guideline on colorectal cancer was initiated with RT indications as one of the primary topics. The revised guideline was sent to all the members of the involved national societies with the possibility to comment on this version before September 2013. The revised guideline was officially published in June 2014.[5] RT is not recommended for low risk resectable rectal cancer in the revised guideline, defined as a cT1-3N0 stage with extramural invasion ≤5 mm and a distance to the mesorectal fascia (MRF) >1 mm based on the preoperative MRI. In order to reduce overtreatment with RT based on false-positive cN+ stage, MRI criteria to evaluate mesorectal lymph nodes were adapted. Furthermore, the use of short course radiotherapy with delayed surgery (SCRT-ds) was recommended as an alternative to chemoradiotherapy (CRT) for the older, more fragile patient.

The Dutch Surgical Colorectal Audit (DSCA) was founded in 2009 and evaluates and reports on the quality of care of primary colorectal cancer surgery. It provides periodic feedback to all hospitals in the Netherlands on patient, tumor, and treatment characteristics and a set of predefined national quality measures.[6] The objective of this study was to evaluate the use of preoperative RT for rectal cancer in the Netherlands and the impact of the revised national guideline through an analysis of the DSCA data by comparing data of 2014 with data in the period between 2009 and 2013. Furthermore, the aim was to determine the diagnostic accuracy of preoperative MRI for nodal staging during the study period by comparing cN and pN stage in patients without down-staging therapy.

METHODS

Data were derived from the Dutch Surgical Colorectal Audit (DSCA), a disease specific national audit.[6] This audit collects information on patient, tumor, treatment and 30 day and in-hospital outcome characteristics of all patients undergoing a resection for primary colorectal carcinoma in the Netherlands. The dataset is based on evidence-based guidelines and has been cross-checked on a yearly basis with data from the Netherlands Cancer Registry (NCR).[7] All Dutch hospitals participate and the dataset contains approximately 97% of all patients that are surgically treated for a primary colorectal carcinoma in the Netherlands. Details of the DSCA regarding data collection and methodology have been published previously.[6, 8]

Patient selection

For this study, no ethical approval or informed consent was required under Dutch law. All patients (n=16,238) undergoing surgical resection for primary rectal cancer between January 1st, 2009 and December 31th, 2014, and registered in the DSCA before April 15th, 2015, were evaluated. Minimal data requirements to consider a patient eligible for analysis were information on tumor location, date of surgery and 30-day mortality (n=16,128). For the purpose of this study, patients who underwent a transanal resection (n=392) were excluded. Furthermore, the heterogenous group of patients with synchronous distant metastases (n=1177) and multiple synchronous colorectal tumors (n=616) were excluded, resulting in 14,018 patients with a solitary tumor in the rectum and a cM0 stage.[9]

Preoperative therapy

The DSCA registers different regimens of RT: short course radiotherapy (SCRT), chemoradiotherapy (CRT), and long course radiotherapy without concomitant chemotherapy (LCRT). As indications of LCRT are similar to CRT, we added these patients (n=315) to the CRT group for our analyses. Because of its clinical implications, the interval from SCRT to surgery was determined and a subgroup of delayed surgery was defined when the interval from end of RT to surgery was more than 2 weeks (SCRT-ds). Because only the start date of RT is available in the DSCA, the time interval between end of RT and surgery was calculated

by subtracting 7 days from the interval between start of RT and surgery. When the interval to surgery for patients with SCRT was unknown (n=1335, 9.5%) it was considered as less than 2 weeks as it is standard practice to proceed to surgery within a few days after the last dose of SCRT.[5, 10] SCRT-ds and CRT both have a downsizing effect on the tumor. Therefore, these modalities are referred to as down-staging therapy.[11]

Statistical analysis

The draft version of the revised colorectal cancer guideline became publicly accessible in September 2013 and was already used in the few months thereafter by many MDTs before the definitive version was published in June 2014. Therefore, we choose January 2014 as the cut-off to determine the impact of the revised colorectal cancer guideline. The overall percentage of RT use in patients with a cT1-4N1-2M0 stage was determined for each year throughout the study period, as well as the use of SCRT, SCRT-ds and CRT for different cTN categories separately. Extramural invasion is not registered in the DSCA, which did not allow for separate analyses for cT3a-d stages. Furthermore, the use of CRT and SCRT-ds was analysed in patients with locally advanced rectal carcinoma (cT3 with a distance to mesorectal fascia of less than 1 mm, or cT4, and/or cN2 according to the MRI) within stratified subgroups based on age and ASA score.

Revised MRI criteria to determine cN stage were evaluated in patients in whom no down-staging effect was expected (TME surgery alone or SCRT with short interval to surgery). Patients without preoperative MRI were excluded. The cN stage was compared with pN stage as golden standard, and sensitivity, specificity, positive and negative predictive value were calculated for each year and plotted to analyse time trends during the study period. We calculated 95% and 99% confidence intervals for each of these values in order to detect significant changes of these values throughout the years. P-values are displayed accordingly ($p<0.05$ or $p<0.01$). For the purpose of this analysis, cN1 and cN2 were grouped together as cN+, and patients with an unknown cN or cT stage were excluded. Clinical suspicion of a positive lymph node on MRI was defined as a diameter > 5 mm in the old guideline. The revised criteria are: diameter ≥ 9 mm; diameter 5-9 mm and two of three morphological criteria consisting of irregular border, heterogeneous texture and round shape; diameter < 5 mm and all three morphological criteria. In case of

doubt, the revised guideline recommends to classify as cN0. Statistical analyses were performed in PASW Statistics, version 20 (SPSS inc., Chicago, IL)

RESULTS

Patient, tumor and treatment characteristics

A total of 14,018 eligible rectal cancer patients were registered by 92 hospitals between January 2009 and December 2014. Table 1 shows the baseline characteristics of the study population. A majority of 11,989 (85.5%) patients had a registered cT and cN stage; 1362 (9.7%) and 1707 (12.2%) patients did not have a registered cT or cN stage, respectively. cT stage was not registered for 18.6% of patients in 2009, which improved to 3.5% in 2014 (p=<0.001). For pT stage, these percentages were 10.7% and 1.0% (p=<0.001), respectively. cN stage was not registered for 24.6% of patients in 2009, which improved to 3.9% in 2014 (p=<0.001). For pN stage, these percentages were 7.8% and 0.7% (p=<0.001), respectively. The use of preoperative MRI increased during the study period from 81.1% in 2009 to 94.6% in 2014 (p=<0.001).

Trends in time for preoperative radiotherapy

The overall percentage of RT use in cT1-4N0-2M0 stage was 81.4% to 84.2% between 2009 and 2013 and decreased to 64.4% in 2014 (p=<0.001) (Figure 1). This decrease was mainly seen in low risk resectable rectal cancer. Figure 1 shows that use of RT increased until 2011 for cT1-4N0-2M0 stages, with decreasing RT rates since 2012 that became most pronounced in 2014. The absolute decrease in RT use from 2013 to 2014 was 32.8%, 43.5% and 31.6% for cT1N0, cT2N0 and cT3N0 (p=<0.001), respectively.

Figure 2 shows preoperative therapy for all cTN categories for patients without metastasized disease in the period from 2009 -2013 and 2014. The use of SCRT decreased for almost all stages, with the greatest decrease in the use of SCRT for patients with a cT1-3N0 tumor. SCRT-ds was used more frequently for cT3-4N0-2 stages in 2014 (p=<0.001).

Overall CRT use increased from 34.7% in 2009 up to 41.3% in 2013 (p=<0.001); MRI based diagnosis of cN2 stage increased from 10.5% to 24.4% during this period (p=<0.001). There was a deviation from this trend in CRT use with a decrease to 34.3% in 2014 (p=<0.001); clinical diagnosis of N2 stage slightly decreased to 23.1% in 2014 (ns).

For patients with locally advanced rectal carcinoma the use of SCRT-ds instead of CRT increases for patients of higher age and with an ASA score of III+ (figure 3a and b). Up to 2013, 30.6% of these patients that were older than 80 years received SCRT-ds; this percentage was 12.1% for these patients with an ASA score of three or higher. In 2014 these percentages increased to 45.8% and 19.9% (p=<0.001).

Clinical N stage on preoperative MRI

Up to 2013, a 20% increase in clinical diagnosis of cN1-2 disease was observed, from 41.4% to 61.4% (p=<0.001). After guideline revision, the opposite trend was seen with an increase of cN0 from 38.6 to 45.5% in 2014, and a corresponding decrease in patients with cN1-2 disease (p=<0.001). The sensitivity of MRI to determine cN1-2 disease showed a steady increase from 37.4% in 2009 to 55.4% in 2014 (p<0.01). The positive predictive value showed a decrease up to 2013 and a reversed deviation from this trend in 2014 with an increase from 42.7% to 47.8% after guideline revision (figure 4) (ns). The specificity decreased from 82.9% to 62.9% in 2013 with an increase to 73.2% in 2014 (p<0.01). The negative predictive value slightly improved from 73.8% in 2013 to 78.8% after guideline revision (p<0.05).

DISCUSSION

This population-based study on radiotherapy use for non-metastatic rectal cancer revealed a clear impact of the revised national colorectal cancer guideline immediately after it became available to the community. The most remarkable change in daily practice was abolishing the use of RT in cT1N0 rectal cancer in the Netherlands, with significant reductions in cT2-3N0 stages. A deviation from the trend in the use of RT in low-risk resectable rectal cancer was already observed

in 2012 (figure 1), based on increased insight by auditing and raising awareness of being a European exception regarding RT use for this patient group.[3] Guideline revision appeared to be the ultimate tool to rapidly change clinical practice. Besides adapted indications, the overall reduction in RT use can also be attributed to the adapted criteria for evaluation of the mesorectal lymph nodes on MRI, which resulted in a decrease of false-positive results in 2014 (figure 4).

Multiple European countries have initiated rectal cancer audits. Subsequent improvements in rectal cancer care were achieved at a national level by going through the audit cycle of measuring performance, giving feedback and initiation of interventions, and by identification of best practices and underperforming hospitals.[12-15] In addition, comparisons between these audits provided also valuable information by showing substantial variation in outcomes and treatment strategies between countries.[4, 16, 17] DSCA data confirmed that rectal cancer patients in the Netherlands were more often treated with preoperative RT compared to other European countries.[3] This was based on the previous Dutch rectal cancer guideline from 2008, which recommended SCRT for all patients with resectable rectal cancer except for T1N0 and proximal T2N0 tumors. The Dutch TME trial with quality controlled implementation of TME surgery, radiotherapy and pathological examination in the Netherlands in the 1990s dictated the treatment of rectal cancer in the decade thereafter and constituted the basis of the national guideline. The experimental arm of the TME trial became routine rectal cancer management. In the absence of reliable methods to diagnose a cT1N0 stage, even these early cancers were irradiated with increasing rates of up to 66% in 2011, which was not in accordance with the guideline.

Before MRI became a standard part of the preoperative work up, the risk of local recurrence was difficult to estimate, which hampered implementation of a patient tailored use of RT. The Mercury trial showed that the risk of local recurrence could preoperatively be estimated by MRI and demonstrated that low risk resectable rectal cancer was safely treated by TME surgery alone given a 3% 5-year local recurrence rate.[18] Especially in light of these published data, Dutch practice stressed the need for a revision of the national guideline. The discrepant policy regarding RT use in early stages of rectal cancer in the Netherlands was published in an international journal, presented at

national gatherings and broadly discussed in the annual report of the DSCA.[3, 15] This is most likely the explanation for the observed break in the trend in 2012 and explains why the multidisciplinary rectal cancer teams were able to rapidly implement the renewed national guideline in 2014. National auditing is therefore not only useful as a benchmarking tool but also creates an informed professional environment in which new guidelines can be introduced and thereafter tested on their implementation.

Oncological benefit of RT has to be weighed against short and long-term negative effects of radiotherapy.[19-21] For older patients or patients with comorbidity it is especially important to weigh the potential oncological benefit and consider the risks of acute toxicity. The Stockholm III trial introduced a new downstaging regimen; short course radiotherapy with delayed surgery (SCRT-ds). This is an alternative down-staging regimen with less acute toxicity compared to CRT and is now mentioned as such in the revised guideline. However, SCRT-ds was already used for several indications including elderly frail people with locally advanced rectal cancer before that time (Figure 3), showing that changes in clinical practice sometimes precede guideline recommendations. After guideline revision, the use of SCRT-ds in high-risk patients further increased to a substantial level.

In contrast to the Mercury study group, clinical N stage is still an important factor when deciding on preoperative RT in the Netherlands. Being aware of the restricted accuracy of MRI for nodal staging, it was decided to define more strict criteria for suspicion of lymph node involvement in order to reduce the risk of over-staging.[22, 23] Our results show that the adapted MRI protocol for lymph node assessment in the national guideline did seem to have an influence on the amount of patients with false positive lymph nodes at clinical staging, leading to less patients with low-risk rectal cancer undergoing RT. Compared to 2013, the specificity, positive predicted value, and negative predictive value increased, while the sensitivity remained at the same level. The percentage of cN2 was steadily increasing up to 2013, but slightly decreased in 2014. This could be, amongst others, the explanation for the decrease in the percentage of CRT use from 2013 to 2014. In the near future, higher accuracy of MRI based nodal staging is expected from lymph node-specific contrast agents such as ultrasmall superparamagnetic particles of iron oxide (USPIO).[24] At present however, the FDA and EMEA have not approved USPIO contrast.

Limitations of the present study are related to the limitations of the DSCA dataset. It would have been interesting to analyse the use of RT in patients with a cT3 tumor depending on the extent of extramural invasion in 2014, because this has become an additional criterion in the revised guideline. The DSCA unfortunately does not register whether extramural invasion was seen on preoperative MRI, but this will be added to the dataset of 2016. Similarly, the distance of the tumor to the MRF based on the preoperative MRI was only registered from 2012 on, with registration rates of 57.8% in 2012 and still only 73.9% in 2014. Availability of these data would have enabled more detailed analysis of guideline adherence in cT3 stage rectal cancer.

In conclusion the revised national guideline on colorectal cancer was rapidly implemented in the Netherlands and led to a fast decrease in the use of RT for patients with low risk resectable rectal cancer and a decrease in patients with false positive cN1-2 disease on preoperative MRI. It is believed that the national clinical audit has played an important role in the observed changes in clinical practice. The rapid implementation of the revised national guideline on colorectal cancer is a good example of the usage of audit data to instigate national practice change and to check its implementation afterwards.

REFERENCES

1. Adjuvant radiotherapy for rectal cancer: a systematic overview of 8,507 patients from 22 randomised trials. Lancet 2001; 358(9290):1291-304.

2. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 2001; 345(9):638-46.

3. van Leersum NJ, Snijders HS, Wouters MW, et al. Evaluating national practice of preoperative radiotherapy for rectal cancer based on clinical auditing. Eur J Surg Oncol 2013; 39(9):1000-6.

4. Mroczkowski P, Ortiz H, Penninckx F, et al. European quality assurance programme in rectal cancer--are we ready to launch? Colorectal Dis 2012; 14(8):960-6.

5. http://www.oncoline.nl.

6. Van Leersum NJ, Snijders HS, Henneman D, et al. The Dutch surgical colorectal audit. Eur J Surg Oncol 2013; 39(10):1063-70.

7. Dutch Institute for Clinical Auditing. Annual Reports 2012. http://www.clinicalaudit.nl.

8. Kolfschoten NE, Marang van de Mheen PJ, Gooiker GA, et al. Variation in casemix between hospitals treating colorectal cancer patients in the Netherlands. Eur J Surg Oncol 2011; 37(11):956-63.

9. van Leersum NJ, Aalbers AG, Snijders HS, et al. Synchronous colorectal carcinoma: a risk factor in colorectal cancer surgery. Dis Colon Rectum 2014; 57(4):460-6.

10. Marijnen CA, Nagtegaal ID, Klein Kranenbarg E, et al. No downstaging after short-term preoperative radiotherapy in rectal cancer patients. J Clin Oncol 2001; 19(7):1976-84.

11. Pettersson D, Holm T, Iversen H, et al. Preoperative short-course radiotherapy with delayed surgery in primary rectal cancer. Br J Surg 2012; 99(4):577-83.

12. Bulow S, Harling H, Iversen LH, et al. Improved survival after rectal cancer in Denmark. Colorectal Dis 2010; 12(7 Online):e37-42.

13. Wibe A, Moller B, Norstein J, et al. A national strategic change in treatment policy for rectal cancer--implementation of total mesorectal excision as routine treatment in Norway. A national audit. Dis Colon Rectum 2002; 45(7):857-66.

14. Pahlman L, Bohe M, Cedermark B, et al. The Swedish rectal cancer registry. Br J Surg 2007; 94(10):1285-92.

15. Annual report 2013, the Dutch Surgical Colorectal Audit.

16. van den Broek CB, van Gijn W, Bastiaannet E, et al. Differences in preoperative treatment for rectal cancer between Norway, Sweden, Denmark, Belgium and the Netherlands. Eur J Surg Oncol 2014; 40(12):1789-96.

17. De Angelis R, Sant M, Coleman MP, et al. Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE--5-a population-based study. Lancet Oncol 2014; 15(1):23-34.

18. Taylor FG, Quirke P, Heald RJ, et al. Preoperative high-resolution magnetic resonance imaging can identify good prognosis stage I, II, and III rectal cancer best managed by surgery alone: a prospective, multicenter, European study. Ann Surg 2011; 253(4):711-9.

19. Chen TY, Wiltink LM, Nout RA, et al. Bowel function 14 years after preoperative short-course radiotherapy and total mesorectal excision for rectal cancer: report of a multicenter randomized trial. Clin Colorectal Cancer 2015; 14(2):106-14.

20. Marijnen CA, van de Velde CJ, Putter H, et al. Impact of short-term preoperative radiotherapy on health-related quality of life and sexual functioning in primary rectal cancer: report of a multicenter randomized trial. J Clin Oncol 2005; 23(9):1847-58.

21. Stephens RJ, Thompson LC, Quirke P, et al. Impact of short-course preoperative radiotherapy for rectal cancer on patients' quality of life: data from the Medical Research Council CR07/ National Cancer Institute of Canada Clinical Trials Group C016 randomized clinical trial. J Clin Oncol 2010; 28(27):4233-9.

22. Lahaye MJ, Engelen SM, Nelemans PJ, et al. Imaging for predicting the risk factors--the circumferential resection margin and nodal disease--of local recurrence in rectal cancer: a meta-analysis. Semin Ultrasound CT MR 2005; 26(4):259-68.

23. Bipat S, Glas AS, Slors FJ, et al. Rectal cancer: local staging and assessment of lymph node involvement with endoluminal US, CT, and MR imaging--a meta-analysis. Radiology 2004; 232(3):773-83.

24. Lahaye MJ, Engelen SM, Kessels AG, et al. USPIO-enhanced MR imaging for nodal staging in patients with primary rectal cancer: predictive criteria. Radiology 2008; 246(3): 804-11.

TABLES AND FIGURES

Table 1: Baseline characteristics of patients with a resection for rectal cancer registered in the Dutch Surgical Colorectal Audit, 2009 – 2014. ASA = Association of Anaesthesiologists; BMI = Body Mass Index; MRI = Magnetic Resonance Imaging; MDT = Multidisciplinary team meeting; SCRT = Short course radiotherapy; SCRT-ds = Short course radiotherapy with delayed surgery; LAR = Low anterior resection; APR = Abdominoperineal resection.

	Count	Percentage
Male	8713	62.2
Age		
75+	3955	28.2
ASA score		
III+	2329	16.6
BMI		
30+	2050	16.7
Clinical T classification		
cT1	478	3.4
cT2	3305	23.6
cT3	7713	55.0
cT4	1160	8.3
cTx	1362	9.7
Clinical N classification		
cN0	5761	41.1
cN1	4172	29.8
cN2	2378	17.0
cNx	1707	12.2
Distance tumor - anus		
<=5 cm	5001	36.3
6-10 cm	5270	38.2
>10 cm	2939	21.3
MRI		
yes	12559	89.6

Continuation of Table 1

MDT		
yes	13268	94.6
Neo-adjuvant therapy		
none	2695	19.2
SCRT	5278	37.7
SCRT-ds	774	5.5
CRT	5271	37.6
Procedure		
LAR	9244	65.9
APR	4213	30.1
other	561	4.0
Setting		
Non-elective	257	1.8
Pathological T classification		
(y)pT0-1	1984	14.2
(y)pT2	4537	32.4
(y)pT3	6382	45.5
(y)pT4	565	4.0
(y)pTX	550	3.9
Pathological N classification		
pN0	9302	66.4
pN1	3041	21.7
pN2	1356	9.7
pNx	319	2.3
CRM involvement	776	6.7
10+ retrieved lymphnodes	10079	71.9

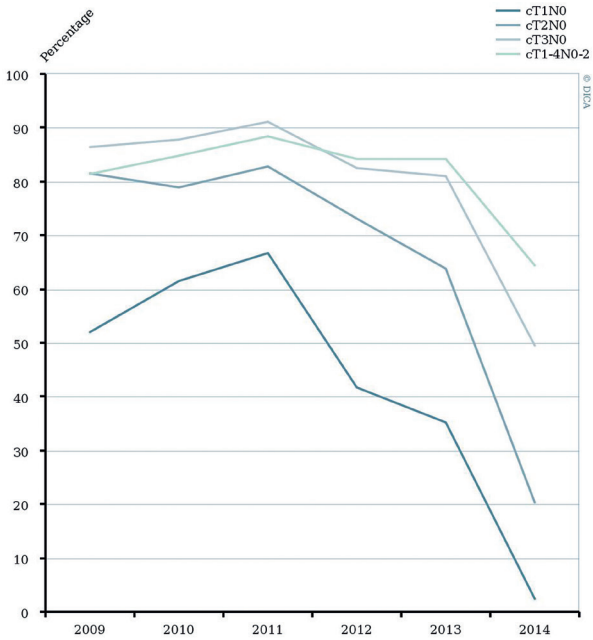


Figure 1: Use of preoperative radiotherapy for rectal cancer in the Netherlands for different clinical stages, 2009 – 2014.

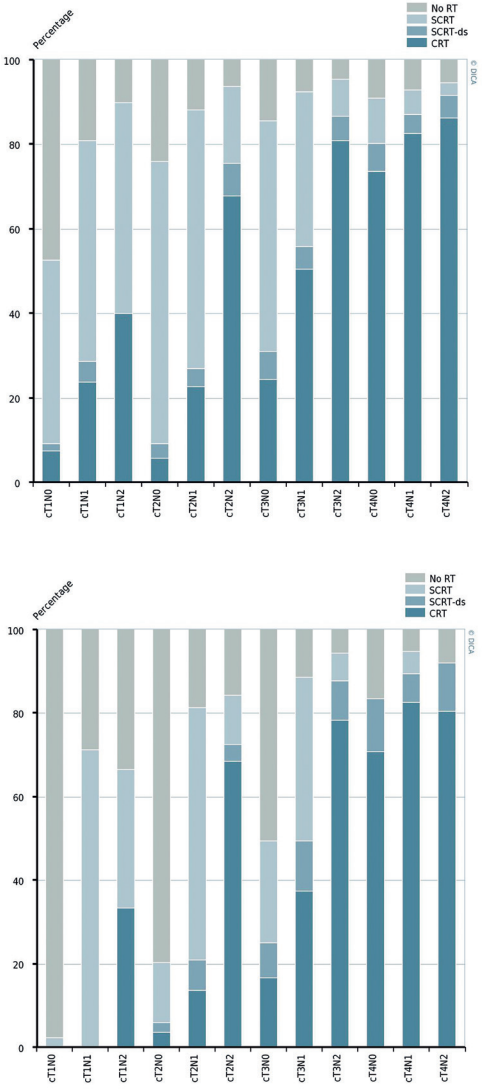


Figure 2a, b: Use of preoperative radiotherapy according to tumor and nodal stage (cM0) in the period between 2010 -2013(a) and in 2014(b). SCRT = short course radiotherapy; SCRT-ds = short course radiotherapy with delayed surgery; CRT = chemoradiotherapy.

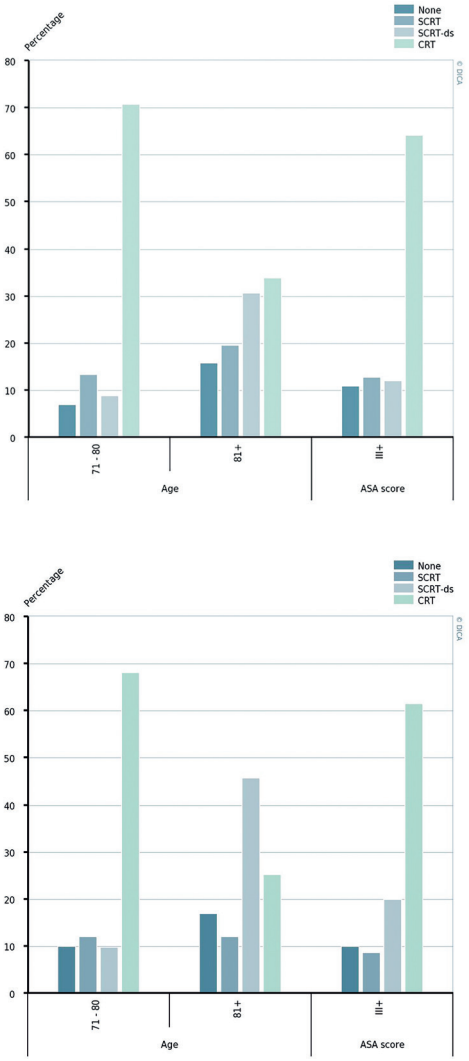


Figure 3a and b: Use of preoperative therapy in stratified groups based on age and ASA classification in 2009-2013 (a) and 2014 (b).

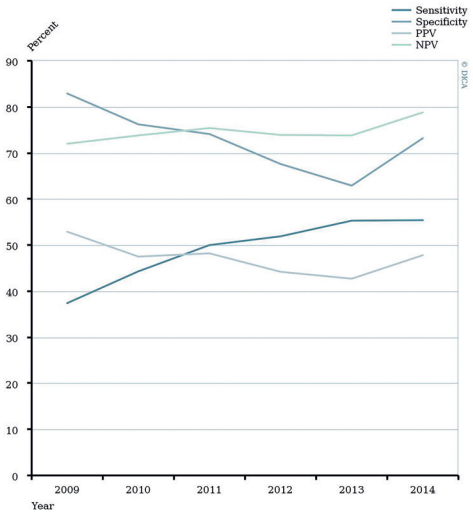


Figure 4: Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for clinical mesorectal lymph node staging based on MRI (cN0 and cN1-2 versus pN0 and pN1-2 in patients not undergoing downstaging therapy) for each year in the period from 2009 to 2014.

Chapter 6

REDUCED 30 DAY MORTALITY AFTER LAPAROSCOPIC COLORECTAL CANCER SURGERY: A POPULATION BASED STUDY FROM THE DUTCH SURGICAL COLORECTAL AUDIT (DSCA).

Lieke Gietelink, Michel W.J.M. Wouters, Willem A. Bemelman, Jan Willem Dekker, Rob A.E.M. Tollenaar and Pieter J. Tanis on behalf of the Dutch Surgical Colorectal Cancer Audit Group.

Ann Surg. 2016 Jul;264(1):135-40

ABSTRACT

Objective: To evaluate the impact of a laparoscopic resection on postoperative mortality after colorectal cancer surgery.

Summary background data: The question whether laparoscopic resection (LR) compared to open resection (OR) for colorectal cancer influences the risk of postoperative mortality remains unresolved. Several meta-analyses showed a trend, but failed to reach statistical significance. The exclusion of high-risk patients and insufficient power might be responsible for that. We analyzed the influence of LR on postoperative mortality in a risk-stratified comparison and secondly we studied the effect of LR on postoperative morbidity.

Methods: Data from the Dutch Surgical Colorectal Audit (2010 - 2013) was used. Homogenous subgroups of patients were defined based on factors influencing the choice of surgical approach and risk factors for postoperative mortality. Crude mortality rates were compared between LR and OR. The influence of LR on postoperative complications was evaluated using both univariable and multivariable analysis.

Results: In patients undergoing elective surgery for non-locally advanced, non-metastasized colon cancer, LR was associated with a significant lower risk of postoperative mortality compared to OR in 20/22 subgroups. LR was independently associated with a lower risk of cardiac (OR 0.73, 95% CI 0.66-0.82) and respiratory (OR 0.73, 95% CI 0.64-0.84) complications.

Conclusions: LR reduces the risk of postoperative mortality compared to OR in elective setting in patients with non-locally advanced, non-metastasized colorectal cancer. Especially elderly frail patients seem to benefit because of reduced cardiopulmonary complications. These findings support widespread implementation of LR for colorectal cancer, also in patients at high operative risk.

INTRODUCTION

The reduction of surgical trauma by minimally invasive techniques in both colon and rectal cancer surgery has been shown to result in faster postoperative recovery compared to conventional open surgery, without compromising oncological outcome.[1, 2] This has been demonstrated with the highest level of evidence by meta-analyses of randomized controlled trials (RCTs). Long-term benefits of laparoscopic resection for colorectal cancer are better cosmetics, less incisional hernias due to preserved abdominal wall integrity, and less adhesion related small bowel obstruction.[3-5] Considering costs, laparoscopic colorectal surgery seems to be cost-effective because of reduced hospital stay despite higher intra-operative costs, which may become even more pronounced in the long run given the lower rate of readmissions and re-operations for small bowel obstruction and incisional hernia.[5, 6]

A still unresolved question is whether a laparoscopic approach influences the risk of postoperative mortality after colorectal cancer surgery. Several meta-analyses of RCTs showed a trend towards lower postoperative mortality in favor of laparoscopic resection, but failed to reach statistical significance.[1, 7, 8] The inclusion of relatively low risk patients and the lack of sufficient power are probably responsible for that.

Population studies can solve this problem because of higher numbers of patients. In addition, high-risk patients with higher event rates are included in these studies reflecting daily practice.[9-12] Therefore, the purpose of this population-based analysis was to compare postoperative mortality between laparoscopic and open resection of colorectal cancer in homogenous subgroups based on known operative risk factors. By using a risk-stratified comparison, it was intended to minimize the inherent risk of selection bias in population studies. Secondly we studied the effect of laparoscopic surgery on postoperative morbidity, especially cardiopulmonary complications, in order to investigate one of the mechanisms by which laparoscopic resection could lead to lower postoperative mortality.

METHODS

Data were derived from the Dutch Surgical Colorectal Audit (DSCA), a disease specific national audit.[13] This audit collects information on patient, tumor, treatment and 30 day and in-hospital outcome characteristics of all patients undergoing a resection for primary colorectal carcinoma in the Netherlands. The dataset is based on evidence-based guidelines and is cross-checked on a yearly basis with data from the Netherlands Cancer Registry (NCR).[14] All Dutch hospitals participate, with approximately 97 percent completeness in 2012 based on comparison with the NCR. Details of the DSCA regarding data collection and methodology have been published previously.[13, 15]

Patients

For this study, no ethical approval or informed consent was required under Dutch law. All patients (n=37,871) undergoing surgical resection for primary colorectal cancer between January 1st, 2010 and December 31th, 2013, and registered in the DSCA before April 15th, 2014, were evaluated. Minimal data requirements to consider a patient eligible for analysis were information on tumor location, date of surgery and 30-day mortality (n=37,636). For the purpose of this study, patients who underwent transanal resection (n=244) were excluded. Furthermore, the heterogenous group of patients with multiple synchronous colorectal tumors (n=1396) were excluded.[16] One hospital did not have reliable outcomes of postoperative mortality in 2010 and 2011 due to incorrect electronic input of data and corresponding patients were excluded (n=274). One hospital closed during 2011 and the registered 8 patients from that year were also excluded (n=8).

Surgical approach at hospital level

Practice patterns of surgical approach for resection of colorectal cancer in the Netherlands in 2010 based on the DSCA have been published previously.[12] A mean laparoscopic resection rate of 44% at patient level was found, with a laparoscopic resection rate ranging between 0% and 96% at hospital level. In order to be informed about hospital variation in use of laparoscopic resection since then, the proportion of laparoscopic resections for colorectal cancer per hospital per year was calculated, with conversion to open surgery being included in the

laparoscopic group. Six hospitals didn't have results for the full study period; two due to hospital closure, three hospitals had incompatible datasets for specific years which could not be implemented in the DSCA database and one due to the earlier mentioned non-plausible outcome on postoperative mortality. Hospitals were categorized into three groups; low- (0-33%), medium- (33-67%) and high- (67-100%) rate laparoscopic resection hospitals, according to the percentage of laparoscopic colorectal cancer resections in these hospitals. Potential differences in baseline characteristics of patient populations between these three categories were assessed in order to be aware of confounding factors determining the surgical approach.

Data analysis and risk stratification

For the purpose of analyzing the primary aim of this study, homogenous subgroups were defined based on potential factors influencing the choice of surgical approach (locally advanced tumor, previous abdominal surgery, elective or emergency setting), and known risk factors for postoperative mortality (elective or emergency setting, age, ASA classification, tumor stage). Analyses were performed separately for colon and rectal cancer. Type of previous abdominal surgery is not specified in the DSCA. This may entail for example laparoscopic appendectomy or prior open bowel resection. For this reason, analyses were performed with and without including patients with previous abdominal surgery. Procedures were defined as an open resection (OR) or a laparoscopic resection (LR) based on the intentional approach of the resection. In this way, converted LR was included in the LR group. Crude mortality rates were compared between OR and LR in the predefined subgroups. This analysis was chosen as an alternative to casemix adjusted comparison between OR and LR in the whole group of patients, because we wanted to determine if the impact of surgical approach differs among groups of patients with different operative risk.

Differences in postoperative mortality rates were analyzed using a chi-square test with a significance level of 0.05. A relative risk of postoperative mortality with 95% confidence interval and corresponding relative risk reduction was calculated for each subgroup. This analysis was repeated for the same subgroups, excluding patients with a converted laparoscopic resection. The influence of laparoscopic resection on different postoperative complications that may contribute

to the risk of postoperative mortality were evaluated using both univariable and multivariable analysis. The significance level of univariable analysis was set at a two-tailed p-value of 0.05, but factors were entered in the multivariable analysis at a p-value of less than 0.10 using an ENTER model. The following factors were included in multivariable analysis to adjust for differences in casemix between OR and LR; sex, age, ASA classification, BMI, previous abdominal surgery, emergency surgery, additional resection for locally advanced/metastatic disease, pT-classification, and metastatic disease. No process or treatment characteristics were included in the multivariable analysis for risk-adjustment. Statistical analyses were performed in PASW Statistics, version 20 (SPSS inc., Chicago, IL).

RESULTS

Patients and hospitals

A total of 35,714 patients, registered by 92 hospitals, met the inclusion criteria. Annual laparoscopic resection rates at hospital level were calculated. This showed hospitals still performing laparoscopic resection on an incidental basis, hospitals with laparoscopic resection being already fully implemented at the start of the study period, and in between several stable, increasing or decreasing levels of application of laparoscopic resection. The overall laparoscopic resection rate increased from 37 percent in 2010 to 58 percent in 2013. The percentage of converted laparoscopic resections decreased from 13.6 percent in 2010 to 13.3 percent in 2013. Categorization by the rate of laparoscopic resection per hospital resulted in 29 low-rate laparoscopic resection (LRL) hospitals, 46 medium-rate laparoscopic resection (MRL) and 17 high-rate laparoscopic resection (HRL) hospitals, in which 11,579, 18,191 and 5,944 patients were treated, respectively. Table 1 shows the distribution of casemix factors among LRL, MRL and HRL hospitals. Patient characteristics were similar among the three types of hospitals, but LRL hospitals treated up to 5 percent more patients with locally advanced disease and up to 4.5 percent more patients with metastatic disease compared to MRL and HRL hospitals.

Risk stratified comparison of postoperative mortality

The overall percentage of postoperative mortality for this study period was 3.3 percent; 3.9 percent for patients with colon carcinoma and 2.0 percent for patients with rectal carcinoma.

Emergency surgery, T4 stage and M1 stage were excluded for the purpose of the primary analysis of postoperative mortality after laparoscopic and open approach, based on the observed casemix differences among the three hospital categories and the generally considered relative contraindications for a laparoscopic approach. Within the total group of patients undergoing elective surgery for non-locally advanced, non-metastasized colorectal cancer (T1-3N0-2M0 stage), 22 different subgroups were defined based on age (<70, ≥70 and ≥80 years), ASA score (1-2 and 3-4), and previous abdominal surgery.

Postoperative mortality was lower after LR compared to OR in all 22 subgroups after elective resection of T1-3N0-2M0 colon cancer (Table 2), with an absolute risk reduction ranging from 0.4% (<70 years, ASA 1-2) to 4.6% (≥80 years, ASA 3-4). The lower relative risk of postoperative mortality after LR was statistically significant in 20 of 22 subgroups, with a range between 0.18 (95% confidence interval (CI) 0.05-0.66) and 0.64 (95% CI 0.45-0.90). After elective surgery for T1-3N0-2M0 rectal cancer, postoperative mortality differed significantly in 4 of 22 subgroups. In patients of 70 years and older, with or without previous abdominal surgery, LR resulted in an absolute risk reduction of mortality of 1.8 and 2.4 percent and a relative risk of 0.58 (95% CI 0.41-0.82) and 0.53 (95% CI 0.35-0.81), respectively. The other two subgroups consisted of patients of 70 years and older, and ASA 3-4 with or without previous abdominal surgery: absolute risk reduction of 4.0 and 4.7 percent and relative risk of 0.57 (95% CI 0.35-0.92) and 0.56 (95% CI 0.32-0.98), respectively.

Emergency surgery and advanced disease were analyzed in a secondary analysis with a relatively high risk of bias. Significantly different mortality rates were found for elective colon surgery for T4 stage and emergency colonic surgery, with or without previous abdominal surgery, in favor of LR (Table 2).

The analysis was repeated for all the above-mentioned subgroups excluding patients with a converted laparoscopic resection. This showed

nearly equal results, with an equal amount of subgroups in which laparoscopic resection led to a significantly lowered percentage of postoperative mortality (data not shown).

Surgical approach and postoperative complications

Table 3 shows the surgical and non-surgical postoperative complication rates after OR and LR. In univariable analysis, surgical complications and any type of non-surgical complications were significantly higher in the OR group. Multivariable analysis showed an OR of 0.66 (95% CI 0.63 – 0.70) for overall postoperative complications in favor of LR. A laparoscopic approach was also independently associated with a lower risk of surgical complications (OR 0.88; 95% CI 0.83 – 0.94), pulmonary complications (OR 0.73; 95% CI 0.66 – 082), cardiac complications (OR 0.73; 95% CI 0.64 – 0.84), infectious complications (OR 0.74; 95% CI 0.66 – 0.84), and other complications (OR 0.72; 95% CI 0.65 – 0.79).

DISCUSSION

This population-based study demonstrates the significantly reduced risk of postoperative mortality after laparoscopic resection compared to open surgery in patients with non-locally advanced, non-metastatic colon cancer in an elective setting. The relative risk reduction was approximately 50% for all risk categories, but this translated into an absolute lower mortality rate of 0.4 percent in a priori low risk patients (<70 years, ASA 1-2) and 4.6 percent in a priori high risk patients (≥80 years, ASA 3-4). These observations were similar in rectal cancer, but differences in mortality were less often statistically significant due to lower numbers of patients and events. In contrast to what is often believed, our data shows that especially high-risk patients benefit from laparoscopic surgery. The present finding of a significant reduction of non-surgical complications associated with laparoscopic surgery, e.g. cardiopulmonary complications, demonstrates the clinical implications of reduced surgical stress response that becomes most apparent in the elderly frail patients.

The effect of laparoscopic surgery on postoperative mortality has been studied previously. Meta-analyses of RCTs showed a trend towards

lower postoperative mortality for laparoscopic resection compared to an open approach. The recently updated Cochrane analysis showed a relative risk of 0.81 in favor of laparoscopic resection, but with a wide confidence interval (95% CI 0.50-1.32).[17] A meta-analysis published in 2012 included 3 RCTs in ERAS setting and showed an OR for postoperative mortality of 0.33 (95% CI 0.09-1.18) in favor of laparoscopic resection.[7] All these meta-analyses, however, lacked sufficient power to demonstrate a significant relationship between laparoscopic surgery and lowered postoperative mortality in the relatively healthy study populations that were included in the individual trials.

Population studies on the subject are able to include higher numbers of patients from daily clinical practice with different operative risk levels, compared to RCTs with strict selection criteria. In 2012, we reported a lower casemix corrected mortality rate after laparoscopic surgery compared to open resection (2.4% versus 4.0%; OR 0.63; P<0.01) based on all patients registered in the DSCA in 2010.[12] Other population studies have confirmed these findings.[9-11] The question remained to what extend the results of these analyses were subject to selection bias and which specific patient groups would benefit most from a minimally invasive approach. While casemix correction reduces the effect of confounding factors, it is not likely that a multivariable model in a heterogeneous population will sufficiently correct for the whole range of factors that may influence the decision to perform open or laparoscopic surgery. To deal with these inherent methodological problems of non-randomized comparisons in a different way, we tried to gain more insight by using a risk-stratified comparison between relatively homogenous subgroups. Analysis of the laparoscopic resection rate at hospital level revealed that selection bias was most likely related to advanced disease while the other casemix factors were remarkably comparable among the low, medium and high laparoscopy hospitals. Apparently, low and high laparoscopy hospitals are treating similar patients, except for a small subgroup. This led us to conclude that the decision on the surgical approach in non-metastatic localized colorectal cancer seems to be hospital driven, depending on the availability of adequate equipment and surgeons experienced in the technique. Based on this conclusion, one may also hypothesize that better results after a laparoscopic approach are not only explained by the technique itself,

but also by the quality of the surgeons and hospital setting. However, it is difficult to prove that laparoscopy is performed by 'better' surgeons in 'better' hospitals.

Although a RCT is considered to provide the highest level of evidence, its restrictions become more and more apparent. National health registries are a unique source of data, due to the absence of preselected populations and large numbers of patients. In this way, research questions that are unlikely to be answered in RCTs can be analyzed with high external validity because it reflects daily clinical practice. The comparison between laparoscopic and open surgery for colorectal carcinoma is a good example of its usage.

The largest reduction in absolute mortality rate by the use of laparoscopic surgery was found in subgroups comprising high-risk patients. The reduction of the surgical stress response caused by laparoscopic surgery could, theoretically speaking, lead to the reduction of postoperative complications. A pooled analysis of 11 studies, analyzing the use of laparoscopic resection in an elderly population, showed a significant difference in pulmonary and cardiac complications.[18] Elderly patients who underwent open surgery showed a doubled rate of cardiopulmonary complications compared to patients of similar age who underwent laparoscopic resection. Initially, elderly patients with increased cardiopulmonary risk were considered a contraindication for a laparoscopic approach, because of high intra-abdominal pressure and extreme Trendelenburg positioning during laparoscopic surgery with negative impact on ventilation and hemodynamics related to reduced venous return.[19] However, the postoperative risk of open surgery with a higher stress response and pain might be more likely to influence the outcome rather than the intra-operative risk which can often be adequately managed during anesthesia. Support for this mechanism is found in the Dutch LAFA study which describes the inflammatory response in four study arms; laparoscopic or open resection with or without ERAS perioperative care.[20] Human Leukocyte Antigen (HLA-DR) expression, indicating immune competence, showed the highest levels in patients undergoing a laparoscopic resection with ERAS care. Interleukin 6 (IL-6), indicating inflammatory response, showed the highest levels in patients undergoing an open procedure without ERAS.[21] Wang et al. confirmed this finding in 2012.[22] The relationship between the systemic

inflammatory response after surgery and the prognosis of the patient has been widely studied in oncologic surgery. The validated Glasgow prognostic score, consisting of preoperative CRP and albumin has an independently predicting value for cancer specific survival.[23, 24] In the light of the lowered postoperative inflammatory response caused by laparoscopic surgery, minimal invasive surgery could be of positive effect on cancer specific survival as well, although long-term results of RCTs do not support this.

Limitations of the present population bases analysis are the methodological issues related to a non-randomized comparison with risk of selection bias, as already mentioned. Differences in postoperative care among the hospitals may have contributed to the present findings, although recent meta-analyses showed that ERAS has no impact on postoperative mortality and that laparoscopy has independent advantages beyond ERAS care.[25, 26] Furthermore, the DSCA only provides 30-day and in-hospital mortality rates, while 90-day or even 1-year mortality rates may be more appropriate, especially in the elderly frail patients. In the near future, we plan to match the two databases of the DSCA and national cancer registry at an individual patient level, which enables similar analyses on long-term outcome.

In conclusion, this population-based analysis demonstrates a reduced mortality risk after elective minimally invasive surgery for localized colorectal cancer compared to an open approach, especially in a priori high-risk patients. The implication of these findings are further implementation of laparoscopic colorectal surgery by facilitating adequate training of colorectal surgeons and providing an adequate infrastructure in hospitals and countries in which open surgery is still standard of care.

Acknowledgment: The authors would like to thank all surgeons, registrars, physician assistants and administrative nurses that registered all the patients in the DSCA, as well as the Dutch Surgical Colorectal Audit group.

REFERENCES

1. Ohtani H, Tamamori Y, Arimoto Y, et al. A meta-analysis of the short- and long-term results of randomized controlled trials that compared laparoscopy-assisted and open colectomy for colon cancer. *J Cancer* 2012; 3:49-57.

2. Trastulli S, Cirocchi R, Listorti C, et al. Laparoscopic vs open resection for rectal cancer: a meta-analysis of randomized clinical trials. *Colorectal Dis* 2012; 14:e277-96.

3. Taylor GW, Jayne DG, Brown SR, et al. Adhesions and incisional hernias following laparoscopic versus open surgery for colorectal cancer in the CLASICC trial. *Br J Surg* 2010; 97:70-8.

4. Burns EM, Currie A, Bottle A, et al. Minimal-access colorectal surgery is associated with fewer adhesion-related admissions than open surgery. *Br J Surg* 2013; 100:152-9.

5. Bartels SA, Vlug MS, Hollmann MW, et al. Small bowel obstruction, incisional hernia and survival after laparoscopic and open colonic resection (LAFA study). *Br J Surg* 2014; 101:1153-9.

6. Keller DS, Champagne BJ, Reynolds HL, Jr., et al. Cost-effectiveness of laparoscopy in rectal cancer. *Dis Colon Rectum* 2014; 57:564-9.

7. Li MZ, Xiao LB, Wu WH, et al. Meta-analysis of laparoscopic versus open colorectal surgery within fast-track perioperative care. *Dis Colon Rectum* 2012; 55:821-7.

8. Breukink S, Pierie J, Wiggers T. Laparoscopic versus open total mesorectal excision for rectal cancer. *Cochrane Database Syst Rev* 2006:CD005200.

9. Byrne BE, Mamidanna R, Vincent CA, et al. Population-based cohort study comparing 30- and 90-day institutional mortality rates after colorectal surgery. *Br J Surg* 2013; 100:1810-7.

10. Panis Y, Maggiori L, Caranhac G, et al. Mortality after colorectal cancer surgery: a French survey of more than 84,000 patients. *Ann Surg* 2011; 254:738-43; discussion 743-4.

11. Faiz O, Haji A, Bottle A, et al. Elective colonic surgery for cancer in the elderly: an investigation into postoperative mortality in English NHS hospitals between 1996 and 2007. *Colorectal Dis* 2011; 13:779-85.

12. Kolfschoten NE, van Leersum NJ, Gooiker GA, et al. Successful and safe introduction of laparoscopic colorectal cancer surgery in Dutch hospitals. *Ann Surg* 2013; 257:916-21.

13. Van Leersum NJ, Snijders HS, Henneman D, et al. The Dutch surgical colorectal audit. *Eur J Surg Oncol* 2013; 39:1063-70.

14. Dutch Institute for Clinical Auditing. Annual Reports 2012. http://www.clinicalaudit.nl.

15. Kolfschoten NE, Marang van de Mheen PJ, Gooiker GA, et al. Variation in casemix between hospitals treating colorectal cancer patients in the Netherlands. *Eur J Surg Oncol* 2011; 37:956-63.

16. van Leersum NJ, Aalbers AG, Snijders HS, et al. Synchronous colorectal carcinoma: a risk factor in colorectal cancer surgery. *Dis Colon Rectum* 2014; 57:460-6.

17. Vennix S, Pelzers L, Bouvy N, et al. Laparoscopic versus open total mesorectal excision for rectal cancer. *Cochrane Database Syst Rev* 2014; 4:CD005200.

18. Grailey K, Markar SR, Karthikesalingam A, et al. Laparoscopic versus open colorectal resection in the elderly population. *Surg Endosc* 2013; 27:19-30.

19. Weber DM. Laparoscopic surgery: an excellent approach in elderly patients. *Arch Surg* 2003; 138:1083-8.

20. Vlug MS, Wind J, Hollmann MW, et al. Laparoscopy in combination with fast track multimodal management is the best perioperative strategy in patients undergoing colonic surgery: a randomized clinical trial (LAFA-study). *Ann Surg* 2011; 254:868-75.

21. Veenhof AA, Vlug MS, van der Pas MH, et al. Surgical stress response and postoperative immune function after laparoscopy or open surgery with fast track or standard perioperative care: a randomized trial. *Ann Surg* 2012; 255:216-21.

22. Wang G, Jiang Z, Zhao K, et al. Immunologic response after laparoscopic colon cancer operation within an enhanced recovery program. *J Gastrointest Surg* 2012; 16:1379-88.

23. Guthrie GJ, Roxburgh CS, Farhan-Alanie OM, et al. Comparison of the prognostic value of longitudinal measurements of systemic inflammation in patients undergoing curative resection of colorectal cancer. *Br J Cancer* 2013; 109:24-8.

24. Guthrie GJ, Roxburgh CS, Richards CH, et al. Circulating IL-6 concentrations link tumor necrosis and systemic and local inflammatory responses in patients undergoing resection for colorectal cancer. *Br J Cancer* 2013; 109:131-7.

25. Lv L, Shao YF, Zhou YB. The enhanced recovery after surgery (ERAS) pathway for patients undergoing colorectal surgery: an update of meta-analysis of randomized controlled trials. *Int J Colorectal Dis* 2012; 27:1549-54.

26. Spanjersberg WR, van Sambeeck JD, Bremers A, et al. Systematic review and meta-analysis for laparoscopic versus open colon surgery with or without an ERAS programme. *Surg Endosc* 2015.

TABLES

Table 1: Baseline characteristics of low- (LRL), medium- (MRL) and high-rate laparoscopy (HRL) hospitals. ASA; American Society of Anesthesiologist classification, BMI; Body Mass Index, M1; Metastatic disease

	Colon				**Rectum**			
	Laparoscopic Rate				**Laparoscopic Rate**			
	LRL	**MRL**	**HRL**	**χ2**	**LRL**	**MRL**	**HRL**	**χ2**
Patient								
Male	52%	52%	53%	0.559	63%	62%	62%	0.667
Age 70+	58%	58%	57%	0.714	43%	45%	43%	0.047
ASA III+	25%	27%	26%	0.027	16%	18%	15%	0.001
BMI 30+	15%	15%	14%	0.212	15%	15%	14%	0.859
Previous abdominal surgery	35%	35%	35%	0.898	32%	31%	28%	0.010
Tumor								
Pathological T4	19%	17%	14%	<0.001	6.6%	3.7%	3.5%	<0.001
M1	15%	12%	12%	<0.001	10%	6.1%	5.5%	<0.001
Surgery								
Non-elective surgery	20%	20%	19%	0.313	1.7%	1.7%	1.4%	0.590
Additional resection				0.002				<0.001
due to tumor invasion, extensive	5.3%	4.4%	3.8%		6.9%	2.1%	2.9%	
due to tumor invasion, limited	6.0%	6.4%	6.8%		3.6%	3.2%	4.0%	
Additional resection due to metastasis	5.2%	3.0%	3.3%	<0.001	5.3%	1.8%	2.1%	<0.001

Table 2a: Percentage of postoperative mortality for open and laparoscopic surgery in different subgroups of patients stratified by perioperative risk. ARR; absolute risk reduction, RR; relative risk, RRR; relative risk reduction, ASA; American Society of Anesthesiologist classification, T4; pathological T4, M1; metastatic disease.

Risk group	Mortality N (%) Open	Mortality N (%) Laparoscopy	ARR %	RR (95% CI)	RRR %	P-value
Colon cancer, elective, T1-3N0-2M0						
<70	26/2436 **(1.1)**	18/4120 **(0.4)**	0.7	0.41 (0.22-0.74)	59	0.003
>70	238/4481 **(5.3)**	152/5137 **(3.0)**	2.3	0.54 (0.44-0.67)	46	<0.001
>80	160/1950 **(8.2)**	91/1900 **(4.8)**	3.4	0.56 (0.43-0.73)	44	<0.001
ASA 1-2	98/5005 **(2.0)**	75/7325 **(1.0)**	1.0	0.52 (0.38-0.70)	48	<0.001
ASA 3-4	166/1893 **(8.8)**	96/1924 **(5.0)**	3.8	0.55 (0.42-0.71)	45	<0.001
<70, ASA 1-2	14/2107 **(0.7)**	11/3670 **(0.3)**	0.4	0.45 (0.20-0.99)	55	0.042
>70, ASA 1-2	84/2898 **(2.9)**	64/3655 **(1.8)**	1.1	0.60 (0.43-0.83)	40	0.002
>80, ASA 1-2	59/1098 **(5.4)**	38/1170 **(3.2)**	2.2	0.59 (0.39-0.90)	41	0.012
<70, ASA 3-4	12/319 **(3.8)**	7/445 **(1.6)**	2.2	0.41 (0.16-1.05)	59	0.055
>70, ASA 3-4	154/1574 **(9.8)**	88/1478 **(6.0)**	3.8	0.58 (0.45-0.77)	42	<0.001
>80, ASA 3-4	101/851 **(11.9)**	53/728 **(7.3)**	4.6	0.58 (0.41-0.83)	42	0.002
Rectal cancer, elective, T1-3N0-2M0						
<70	12/2228 **(0.5)**	15/2694 **(0.6)**	-0.1	1.03 (0.48-2.21)	-3	0.931
>70	80/1823 **(4.4)**	53/2050 **(2.6)**	1.8	0.58 (0.41-0.82)	42	0.002
>80	33/562 **(5.9)**	28/601 **(4.7)**	1.2	0.78 (0.47-1.31)	22	0.354

Continuation of Table 2a

ASA 1-2	40/3306 **(1.2)**	35/4050 **(0.9)**	0.3	0.71 (0.45-1.12)	29	0.142
ASA 3-4	51/732 **(7.0)**	33/690 **(4.8)**	2.2	0.67 (0.43-1.05)	33	0.810
<70, ASA 1-2	9/1988 **(0.5)**	11/2497 **(0.4)**	0.1	0.97 (0.40-2.35)	3	0.951
>70, ASA 1-2	31/1318 **(2.4)**	24/1553 **(1.5)**	0.9	0.65 (0.38-1.12)	35	0.116
>80, ASA 1-2	15/354 **(4.2)**	14/396 **(3.5)**	0.7	0.83 (0.39-1.74)	17	0.619
<70, ASA 3-4	2/236 **(0.8)**	4/196 **(2.0)**	-1.2	2.49 (0.44-13.45)	-149	0.291
>70, ASA 3-4	49/496 **(9.9)**	29/494 **(5.9)**	4.0	0.57 (0.35-0.92)	43	0.019
>80, ASA 3-4	18/206 **(8.7)**	14/205 **(6.8)**	1.9	0.77 (0.37-1.58)	23	0.470
Colorectal cancer, advanced disease, non-elective surgery						
Colon, elective, T4	79/1745 **(4.5)**	21/1027 **(2.0)**	2.5	0.44 (0.27-0.72)	56	0.001
Colon, Elective, M1	53/1352 **(3.9)**	22/767 **(2.9)**	1.0	0.72 (0.44-1.20)	28	0.208
Colon, emergency	362/4379 **(8.3)**	28/648 **(4.3)**	4.0	0.50 (0.34-0.74)	50	<0.001
Rectum, elective, T4	7/319 **(2.2)**	5/122 **(4.1)**	-1.9	1.91 (0.59-6.12)	-91	0.272
Rectum, elective, M1	6/459 **(1.3)**	3/228 **(1.3)**	0.0	1.01 (0.25-4.06)	-1	0.993
Rectum, emergency	17/119 **(14.3)**	2/46 **(4.3)**	10.0	0.27 (0.06-1.23)	73	0.073

Table 2b: Percentage of postoperative mortality for open and laparoscopic surgery in different subgroups of patients, excluding patients with previous abdominal surgery, stratified by perioperative risk. ARR; absolute risk reduction, RR; relative risk, RRR; relative risk reduction, ASA; American Society of Anesthesiologist classification, T4; pathological T4, M1; metastatic disease.

Risk group	Mortality N (%) Open	Mortality N (%) Laparoscopy	ARR %	RR (95% CI)	RRR %	P-value
Colon cancer, elective, T1-3N0-2M0						
<70	22/1569 **(1.4)**	10/2996 **(0.3)**	1.1	0.24 (0.11-0.51)	76	<0.001
>70	130/2430 **(5.3)**	99/3225 **(3.1)**	2.2	0.56 (0.43-0.73)	44	<0.001
>80	86/1011 **(8.5)**	58/1139 **(5.1)**	3.4	0.58 (0.41-0.81)	42	0.002
ASA 1-2	58/2986 **(1.9)**	45/4990 **(0.9)**	1.0	0.46 (0.31-0.68)	54	<0.001
ASA 3-4	94/1022 **(9.2)**	64/1225 **(5.2)**	4.0	0.54 (0.39-0.76)	46	<0.001
<70, ASA 1-2	12/1383 **(0.9)**	7/2674 **(0.3)**	0.6	0.30 (0.12-0.76)	70	0.007
>70, ASA 1-2	46/1603 **(2.9)**	38/2316 **(1.6)**	1.3	0.57 (0.37-0.87)	43	0.009
>80, ASA 1-2	33/574 **(5.7)**	22/712 **(3.1)**	2.6	0.52 (0.30-0.91)	48	0.019
<70, ASA 3-4	10/199 **(5.0)**	3/319 **(0.9)**	4.1	0.18 (0.05-0.66)	82	0.004
>70, ASA 3-4	84/823 **(10.2)**	61/906 **(6.7)**	3.5	0.64 (0.45-0.90)	36	0.009
>80, ASA 3-4	53/437 **(12.1)**	36/425 **(8.5)**	3.6	0.67 (0.43-1.05)	33	0.078

Continuation of Table 2b

Rectal cancer, elective, T1-3N0-2M0						
<70	7/1616 **(0.4)**	11/2068 **(0.5)**	-0.1	1.23 (0.48-3.18)	-77	0.670
>70	57/1103 **(5.2)**	39/1380 **(2.8)**	2.4	0.53 (0.35-0.81)	47	0.003
>80	23/312 **(7.4)**	20/383 **(5.2)**	2.2	0.69 (0.37-1.29)	31	0.242
ASA 1-2	26/2244 **(1.2)**	24/2974 **(0.8)**	0.4	0.69 (0.39-1.21)	31	0.197
ASA 3-4	37/466 **(7.9)**	26/472 **(5.5)**	2.4	0.68 (0.40-1.14)	32	0.137
<70, ASA 1-2	4/1447 **(0.3)**	8/1929 **(0.4)**	-0.1	1.50 (0.45-5.00)	-50	0.504
>70, ASA 1-2	22/797 **(2.8)**	16/1045 **(1.5)**	1.3	0.55 (0.29-1.05)	45	0.066
>80, ASA 1-2	10/188 **(5.3)**	9/248 **(3.6)**	1.7	0.67 (0.27-1.68)	33	0.392
<70, ASA 3-4	2/165 **(1.2)**	3/138 **(2.2)**	-1.0	1.81 (0.30-11.00)	-81	0.513
>70, ASA 3-4	35/301 **(11.6)**	23/334 **(6.9)**	4.7	0.56 (0.32-0.98)	44	0.038
>80, ASA 3-4	13/122 **(10.7)**	11/135 **(8.1)**	2.6	0.74 (0.32-1.73)	26	0.490
Colorectal cancer, advanced disease, non-elective surgery						
Colon, elective, T4	39/1084 **(3.6)**	13/713 **(1.8)**	1.8	0.50 (0.26-0.94)	50	0.028
Colon, elective, M1	24/852 **(2.8)**	16/541 **(3.0)**	-0.2	1.05 (0.55-2.00)	-5	0.878
Colon, emergency	250/3001 **(8.3)**	20/474 **(4.2)**	4.1	0.49 (0.30-0.77)	51	0.002
Rectum, elective, T4	4/175 **(2.3)**	4/94 **(4.3)**	-2.0	1.90 (0.46-7.78)	-90	0.365
Rectum, elective, M1	3/262 **(1.1)**	2/157 **(1.3)**	-0.2	1.11 (0.18-6.74)	-11	0.906
Rectum, emergency	13/80 **(16.2)**	1/30 **(3.3)**	12.9	0.18 (0.02-1.42)	82	0.070

Table 3: Postoperative complications after OR and LR for colorectal cancer. The following factors were included in the multivariable model to correct for differences in casemix between the two surgical approaches; sex, age, ASA classification, BMI, previous abdominal surgery, emergency surgery, additional resection for locally advanced/metastatic disease, pT-classification, metastatic disease.

	Complication n (%)	**Complication n (%)**	**Odds ratio (CI)**	
Complication type	**Open (n=18861)**	**Laparoscopy (n=16705)**	**Univariable**	**Multivariable**
Postoperative complications	7033 **(37)**	4389 **(26)**	0.60 (0.57-0.63)	0.66 (0.63-0.70)
Surgical complication	3082 **(16)**	2309 **(14)**	0.82 (0.78-0.87)	0.88 (0.83-0.94)
General complication				
Pulmonary	1196 **(6.3)**	660 **(4.0)**	0.61 (0.55-0.67)	0.73 (0.66-0.82)
Cardiac	751 **(4.0)**	404 **(2.4)**	0.60 (0.53-0.68)	0.73 (0.64-0.84)
Thromboembolic	142 **(0.8)**	86 **(0.5)**	0.68 (0.52-0.89)	0.85 (0.63-1.13)
Infectious	838 **(4.4)**	476 **(2.8)**	0.63 (0.56-0.71)	0.74 (0.66-0.84)
Neurologic	267 **(1.4)**	179 **(1.1)**	0.75 (0.62-0.91)	0.94 (0.77-1.16)
Other	1446 **(7.7)**	842 **(5.0)**	0.64 (0.59-0.70)	0.70 (0.63-0.76)

Chapter 7

QUALITY OF LAPAROSCOPIC RECTAL CANCER RESECTION IN THE NETHERLANDS, A DECADE FROM START OF THE COLOR II TRIAL; A MATCHED COHORT STUDY.

Lieke Gietelink, Charlotte L. Deijen, Jurriaan B. Tuynman, Susan van Dieren, Willem A. Bemelman, Michel W.J.M. Wouters, Jaap H. Bonjer and Pieter J. Tanis.

Submitted

ABSTRACT

Background: Laparoscopic surgery for rectal cancer has become routine practice in the Netherlands 10 years after initiation of the COLOR II trial. As rectal cancer surgery evolved, one might question whether this trial is still representative for current national performance. Therefore, this study aimed to compare recent DCRA data with the COLOR II trial, using circumferential resection margin (CRM) as main quality indicator.[14]

Methods: All Dutch patients included in the laparoscopic arm of the COLOR II trial were matched (1:2) to patients registered in the DCRA after laparoscopic resection for primary rectal cancer (2013- 2014) on the variables; sex, age, tumor distance from anal verge, pT-classification, ASA physical status, and type of operation.

Results: A total of 103 Dutch patients were selected from the COLOR II trial, and matched with 206 patients from the DCRA. The percentage of involved CRM was 3.4% in the DCRA patients, which was significantly lower compared to 10.7% in the Dutch COLOR II patients (P=0.018). Conversion rate was significantly lower in the DCRA compared to the COLOR II trial: 9% vs. 18% (P=0.049). The DCRA group had a significantly higher mean number of examined lymph nodes (11.6 vs. 13.8; P=0.038) and a lower median postoperative hospital stay (7 vs. 8 days; P=0.007). Postoperative complication, reintervention and mortality rates were not significantly different.

Conclusion: Routine implementation of laparoscopic surgery for rectal cancer in the Netherlands after the COLOR II trial was accompanied by substantially lower CRM positivity rates, besides lower conversion rates and shorter hospital stay. This study shows that the rapid evolution in rectal cancer management over time requires real-time data and underpins the importance of national audits.

INTRODUCTION

Laparoscopic surgery for colorectal cancer started in the early 1990s and evolved to routine practice in several institutes worldwide over the last decades.[1] There were concerns on the oncological quality of the resection with early reports of port-site tumor metastases.[2, 3] Early conducted trials mainly included patients with colon cancer and demonstrated improved postoperative recovery while maintaining comparable oncologic outcomes for laparoscopic surgery (LS) compared to open surgery (OS).[4-7]

Further research was needed to evaluate whether these outcomes could also be achieved for the technically more challenging resection of rectal cancer. The COlorectal cancer Laparoscopic or Open Resection (COLOR II) trial included 1044 patients and showed similar short-term benefits of LS as were seen in colon cancer. In 2015, the COLOR II study group published the long-term outcomes and reported that LS results in comparable survival and recurrence rates as OS at 3 years postoperative.[8, 9]

LS for rectal cancer has been rapidly and safely implemented in the Netherlands and has become routine practice in most recent years based on data from the Dutch ColoRectal Audit (DCRA), the former DSCA.[10, 11] It has been over 10 years that the COLOR II trial was initiated and the results of this trial, amongst others, are commonly quoted. As LS has a steep learning curve and rectal cancer surgery is presently concentrated with a minimal hospital volume of 20, one might question whether the COLOR II data are still representative for current national performance. Furthermore, two recent trials again raised questions about the quality of the oncological resection of LS for rectal cancer.[12, 13] Therefore, this study aims to analyse current oncological quality of LS for rectal cancer by matched comparison of data from the DCRA and the COLOR II trial, using circumferential resection margin (CRM) as main quality indicator.[14]

METHODS

For the purpose of this matched comparative cohort study, all Dutch patients included in the laparoscopic arm of the COLOR II trial between 2004 and 2010 were selected from the original database. All patients registered in the DCRA after laparoscopic resection for primary rectal cancer between January 1st 2013 and December 31th, 2014, were eligible matches. Patients with an unreported CRM and those with a complete pathological response after preoperative radiotherapy were excluded from analyses. Furthermore, exclusion criteria of the COLOR II trial were also applied to the DCRA population, and registered local excision or emergency procedures in the DCRA were also excluded.

The primary outcome parameter was CRM involvement. CRM involvement was defined as CRM < 2 mm in the COLOR II trial and as CRM ≤ 1 mm in the DCRA which is according to the definition of the current Dutch colorectal cancer guideline.[15] Secondary outcomes were conversion to open surgery, lymph node retrieval, postoperative complications (in specific anastomotic leakage and cardiopulmonary complications), reintervention, length of hospital stay, and mortality. Anastomotic leakage was defined as leakage leading to a reintervention. Postoperative complications and mortality were registered within 28 and 30 days postoperatively in the COLOR II trial and DCRA, respectively, or within the period of admission following the resection.

COLOR II trial

The COLOR II trial was a non-inferiority phase 3 trial randomizing patients with non-metastatic, non-locally advanced rectal cancer between laparoscopic and open surgery in a 2:1 ratio. Exclusion criteria were: age <18 years, distance from tumor to anal verge > 15cm, metastatic disease, tumor histologically not proven adenocarcinoma, T1 tumors eligible for local excision, T4 tumors, T3 tumors with a threatened circumferential margin (distance < 2 mm), signs of obstruction, patients categorised as ASA (American Society of Anesthesiologists) classification > III and planned simultaneuous colorectal surgery. The primary outcome was locoregional recurrence at 3 years after surgery and was published in 2015.[8]

DCRA cohort

Data for the matched cohort were derived from the DCRA, a disease specific national audit. This audit collects information on patient, tumor, treatment and outcome characteristics and containes approximately 97 percent of all patients with a resection for primary colorectal carcinoma in the Netherlands.[16] Details of this dataset regarding data collection and methodology have been published previously.[17, 18]

Statistical analyses

Dutch patients included in the COLOR II trial that were randomised in the laparoscopic group were matched to patients who underwent laparoscopic surgery in the DCRA on a 1:2 ratio on the following variables; sex, age (continuous; years), distance tumor-anus (continuous; cm), pathological T classification, ASA physical status (I/II/III) and type of operation (simplified to APR/no APR). A predefined maximal deviation (fuzz factor) was set: sex, identical; age, ±10 years; distance tumor to anal verge, ±5 cm; pathological T-classification, identical; ASA physical status, identical; type of operation, identical. For every case, the most homologous control was chosen. Patients from the COLOR II with missing data of matching variables were matched on the remaining variables.

Differences in baseline characteristics between the two cohorts were analysed with paired analyses. Categorical variables were compared using a conditional logistic regression analysis (Wald test). Continuous variables, both normally and not normally distributed, were compared using a general linear model (F-test). Outcomes were compared between COLOR II and DCRA with the previously mentioned statistical tests. A p-value of less than 0.05 was considered statistically significant. Statistical analyses were performed in SPSS and R.

Ethical approval and informed consent

For this study, no ethical approval or informed consent was required according to national legislation.

RESULTS

A total of 103 patients were selected from the COLOR II trial and matched with 206 patients of the DCRA. Table 1 shows the baseline characteristics of patients included in the COLOR II trial and DCRA after matching in a 1;2 ratio. Eighty percent of the patients included in the COLOR II population underwent a form of preoperative radiotherapy compared to 74 percent in the DCRA population. After matching for APR/no APR, a higher percentage of patients in the DCRA received a low anterior resection with diverting stoma or Hartmann's procedure compared to the Dutch COLOR II patients. The conversion rate was significantly lower in the DCRA group: 9.2% vs. 17.5% (p=0.049).

Tabel 2 shows the pathological outcomes of the matched pair analysis. The pathological N classification was not significantly different between the groups (p=0.549). CRM involvement was 10.7% in the COLOR II trial and 3.4% in the DCRA matched cohort (p=0.018). The number of examined lymph nodes was significantly higher in the DCRA cohort compared to the COLOR II patients: 13.8 vs 11.6 (p=0.038). The median postoperative hospital stay was one day shorter in the DRCA population (p=0.007). Other postoperative outcomes did not show significant differences between the two populations. Table 3 shows the postoperative outcomes of the COLOR II and DCRA population.

DISCUSSION

This matched cohort study demonstrates that the oncological quality of laparoscopic surgery for rectal cancer in the Netherlands has been improved over the last decade. The percentage of patients with an involved CRM was significantly lower in the DCRA population (2013-2014) compared to the Dutch COLOR II patients (2004-2010). Furthermore, other improvements have been achieved within a ten-year period in which laparoscopic resection became part of routine daily practice, as reflected by lower conversion rate and one day shorter hospital stay. Our study shows the time related development of laparoscopic rectal cancer surgery and the implementation of the technique in non-expert centres by providing real-time data on Dutch national performance.

Laparoscopic surgery for rectal cancer was quickly implemented in rectal cancer care in the Netherlands. At the time the COLOR II trial complete accrual in 2010, 37% of rectal cancer resections were already performed laparoscopically. This percentage was high compared to other countries and accompanied by a relatively low conversion rate (13%).[19] The percentage of laparoscopic rectal cancer resections in the Netherlands increased in recent years to 83% in 2015, which is still high compared to surrounding countries.[20, 21] As multiple studies found a relationship between surgical experience with laparoscopic colorectal resection and improving outcomes, both intraoperative and postoperative, a specific time driven influence on the quality of laparoscopic resections in the Netherlands can thus be expected after a decade of experience.[25] The relatively low conversion rate in the DCRA population in our matched analysis (9.2%) combined with the high percentage of rectal cancer patients undergoing laparoscopic surgery in the Netherlands overall is a clear example of this learning curve.[4]

Other changes in colorectal cancer care have positively influenced the outcomes for patients with colorectal cancer.[18] The implementation of Enhanced Recovery After Surgery (ERAS) care, which involves a small surgical incision, adequate pain management, short period of immobility, and quick return to normal diet, has gained ground and shows positive results for both open and laparoscopic surgery.[31] Centralisation of the technically more challenging resection of rectal cancer was stimulated by evidence of a relationship between volume and quality of colorectal cancer surgery.[22-24] In the Netherlands this has led to the introduction of a mandatory annual volume of 20 rectal cancer resections per hospital, as stated by the Dutch Society of Surgery. Together with a larger volume per surgeon leading to more experience, it is generally believed that volume is to be seen as a 'proxy' for other important structural and process factors in the chain of multidisciplinary treatment.[23, 24] Laparoscopy encouraged the formation of subspecialized colorectal surgeons in order to gain specific experience. This could have further enhanced quality improvement in both expert and non-expert centres, explaining the overall improvement at a population level. It has been shown that such specialization ultimately translates into better survival of colorectal cancer patients.[26] Therefore, the current matched comparison illustrates both influences of time related development of a surgical technique and adhering

processes and structure as well as implementation of the technique in non-expert centres.

Our study has some limitations. We decided to include only the Dutch patients from the COLOR II trial, for which reason the number of matched patients was relatively low with less statistical power. Nevertheless, we think that this study gives a good overview on how far laparoscopic surgery has advanced and that renowned quoted studies show different results compared to more recent data. Furthermore, we only recently added the variable 'macroscopic completeness of the TME specimen' to the DCRA dataset, another important item of quality of rectal cancer surgery. Therefore this variable was not available for our study population. The COLOR II study defined involvement of CRM as tumor cells within 2mm (<2mm) between the outermost part of the tumor and the CRM, whereas the DCRA regards the CRM involved if the tumor-free margin is 1 mm or less (≤1mm). This discrepancy benefits the result of the DSCA population. However as CRM is usually not measured/registered in decimals, the difference should be small and does not undermine the conclusion of this study.

In conclusion, this study shows that laparoscopic surgery in patients with rectal cancer in the Netherlands has evolved and improved over the years, implicating that laparoscopic surgery has been successfully implemented in the Netherlands. The percentage of patients with an involved CRM was significantly lower in the DCRA population compared to the COLOR II population. This study shows once again the value of national audits because they are able to provide us with real-time data and an accurate representation of national performance.

REFERENCES

1. Tanis PJ, Buskens CJ, Bemelman WA. Laparoscopy for colorectal cancer. *Best Pract Res Clin Gastroenterol* 2014; 28(1):29-39.

2. Berends FJ, Kazemier G, Bonjer HJ, et al. Subcutaneous metastases after laparoscopic colectomy. *Lancet* 1994; 344(8914):58.

3. Walsh DC, Wattchow DA, Wilson TG. Subcutaneous metastases after laparoscopic resection of malignancy. *Aust N Z J Surg* 1993; 63(7):563-5.

4. Jayne DG, Guillou PJ, Thorpe H, et al. Randomized trial of laparoscopic-assisted resection of colorectal carcinoma: 3-year results of the UK MRC CLASICC Trial Group. *J Clin Oncol* 2007; 25(21):3061-8.

5. Lacy AM, Garcia-Valdecasas JC, Delgado S, et al. Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomised trial. *Lancet* 2002; 359(9325):2224-9.

6. Veldkamp R, Kuhry E, Hop WC, et al. Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. *Lancet Oncol* 2005; 6(7):477-84.

7. Nelson H, Sargent DJ, Wieand HS, et al. A comparison of laparoscopically assisted and open colectomy for colon cancer. *N Engl J Med* 2004; 350(20):2050-9.

8. Bonjer HJ, Deijen CL, Abis GA, et al. A randomized trial of laparoscopic versus open surgery for rectal cancer. *N Engl J Med* 2015; 372(14):1324-32.

9. van der Pas MH, Haglind E, Cuesta MA, et al. Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial. *Lancet Oncol* 2013; 14(3):210-8.

10. Kolfschoten NE, van Leersum NJ, Gooiker GA, et al. Successful and safe introduction of laparoscopic colorectal cancer surgery in Dutch hospitals. *Ann Surg* 2013; 257(5):916-21.

11. Annual report 2015, the Dutch Surgical Colorectal Audit.

12. Stevenson AR, Solomon MJ, Lumley JW, et al. Effect of Laparoscopic-Assisted Resection vs Open Resection on Pathological Outcomes in Rectal Cancer: The ALaCaRT Randomized Clinical Trial. *JAMA* 2015; 314(13):1356-63.

13. Fleshman J, Branda M, Sargent DJ, et al. Effect of Laparoscopic-Assisted Resection vs Open Resection of Stage II or III Rectal Cancer on Pathologic Outcomes: The ACOSOG Z6051 Randomized Clinical Trial. *JAMA* 2015; 314(13):1346-55.

14. Nagtegaal ID, Marijnen CA, Kranenbarg EK, et al. Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma: not one millimeter but two millimeters is the limit. *Am J Surg Pathol* 2002; 26(3):350-7.

15. http://www.oncoline.nl.

16. Annual report 2013, the Dutch Surgical Colorectal Audit.

17. Kolfschoten NE, Marang van de Mheen PJ, Gooiker GA, et al. Variation in casemix between hospitals treating colorectal cancer patients in the Netherlands. *Eur J Surg Oncol* 2011; 37(11):956-63.

18. Van Leersum NJ, Snijders HS, Henneman D, et al. The Dutch Surgical Colorectal Audit. *Eur J Surg Oncol* 2013.

19. Dobbins TA, Young JM, Solomon MJ. Uptake and outcomes of laparoscopically assisted resection for colon and rectal cancer in Australia: a population-based study. *Dis Colon Rectum* 2014; 57(4):415-22.

20. Nationell patientrapport 2015, Sweden.

21. National Bowel Cancer Audit Report 2015, UK.

22. Archampong D, Borowski D, Wille-Jorgensen P, et al. Workload and surgeon's specialty for outcome after colorectal cancer surgery. *Cochrane Database Syst Rev* 2012; 3:CD005391.

23. Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. *N Engl J Med* 2002; 346(15):1128-37.

24. van Gijn W, Gooiker GA, Wouters MW, et al. Volume and outcome in colorectal cancer surgery. *Eur J Surg Oncol* 2010; 36 Suppl 1:S55-63.

25. Heroor A, Panjwani G, Chaskar R. A Study of 101 Laparoscopic Colorectal Surgeries: a Single Surgeon Experience. How Important Is the Learning Curve? *Indian J Surg* 2015; 77(Suppl 3):1275-9.

26. Oliphant R, Nicholson GA, Horgan PG, et al. Contribution of surgical specialization to improved colorectal cancer survival. *Br J Surg* 2013; 100(10):1388-95.

27. Gietelink L, Henneman D, van Leersum NJ, et al. The Influence of Hospital Volume on Circumferential Resection Margin Involvement: Results of the Dutch Surgical Colorectal Audit. *Ann Surg* 2014.

28. Benchmarking recent national practice in rectal cancer treatment with landmark randomized controlled trials. *Colorectal Dis* 2017; 19(6):O219-O231.

29. Mol L, Koopman M, van Gils CW, et al. Comparison of treatment outcome in metastatic colorectal cancer patients included in a clinical trial versus daily practice in The Netherlands. *Acta Oncol* 2013; 52(5):950-5.

30. Morris EJ, Jordan C, Thomas JD, et al. Comparison of treatment and outcome information between a clinical trial and the National Cancer Data Repository. *Br J Surg* 2011; 98(2):299-307.

31. Vlug MS, Wind J, Hollmann MW, et al. Laparoscopy in combination with fast track multimodal management is the best perioperative strategy in patients undergoing colonic surgery: a randomized clinical trial (LAFA-study). *Ann Surg* 2011; 254(6):868-75.

TABLES

Table 1: baseline characteristics of the COLOR II trial population and matched DCRA population. Distance T-A=distance tumor – anal verge; Preoperative Rtx/Ctx= preoperative (chemo)radiotherapy; ASA=American Society of Anaesthesiologists; APR=Abdominoperineal resection; LAR+DS=Low anterior resection and diverting stoma, LAR+ no DS=Low anterior resection without a diverting stoma.

	COLOR N=103		**DCRA N=206**		**P-value**	**Missing Color/DCRA**
	N	**%**	**N**	**%**		**N/N**
Sex (male)	65	63.1	130	63.1	1.000	0/0
Age *mean* (95%CI)	65.5(65.3-65.8)		65.7(65.5-65.9)		0.226	0/0
Distance T-A *mean* (95%CI)	7.4 (7.2-7.7)		7.3 (7.1-7.5)		0.368	18/0
Preop Rtx/Ctx (yes)	82	79.6	153	74.3	0.304	0/0
ASA					1.000	
I-II	73	70.9	156	75.7		5/0
III+	25	24.3	50	24.3		
Type of surgery					0.007	
APR	34	33.0	69	33.5		0/0
LAR + no DS	37	35,9	38	18.4		
Hartmann	6	5.8	30	14.6		
LAR + DS	21	20.4	68	33.0		
Other	5	4.9	1	0.5		
Conversion	18	17.5	19	9.2	0,049	0/8

Table 2: Pathology outcomes of the COLOR II and DCRA population. pT= pathological T classification. pN=pathological N classification; lnn=lymphnodes; CRM= circumferential resection margin.

	COLOR N=103		**DCRA N=206**		**P-value**	**Missing Color/ DCRA**
	N	**%**	**N**	**%**		**N/N**
pT classification					0.997	0/0
pT0	2	1.9	0	0.0		
pT1	3	2.9	8	3.9		
pT2	40	38.8	83	40.3		
pT3	55	53.4	115	55.8		
pT4	3	2.9	0	0.0		
pN classification					0.549	2/1
N0	65	63.1	140	68.0		
N1+	36	35	65	31.6		
No. of lnn harvested *mean* (95%CI)	11.6(10.4-12.8)		13.8(12.9-14.6)		0.038	0/1
CRM involvement	11	10.7	7	3.4	0.018	0/0

Table 3: The postoperative outcomes of the COLOR II and DCRA population.

	COLOR N=103		DCRA N=206		P-value	Missing Color/ DCRA
	N	%	N	%		N/N
Admission time (median)	8.0(IQR 6.0-14.0)		7.0(IQR 6.0-14.0)		0.007	3/1
Postop complications *any*	46	44.7	77	37.4	0.234	0/0
Reintervention	18	17.5	27	13.1	0.139	0/0
Anastomotic leakage	14	13.6	17	8.3	0.139	0/0
Cardiac complication	1	1.0	5	2.4	0.403	0/0
Pulmonary complication	2	1.9	8	3.9	0.381	0/0
Postoperative mortality	2	1.9	0	0.0	0.999	0/0

Chapter 8

LOCALLY ADVANCED COLON CANCER; EVALUATION OF CURRENT CLINICAL PRACTICE AND TREATMENT OUTCOME AT POPULATION LEVEL.

Charlotte E.L. Klaver, Lieke Gietelink, Willem A. Bemelman, Michel W.J.M. Wouters, Theo Wiggers, Rob A.E.M. Tollenaar and Pieter J. Tanis; on behalf of the Dutch Surgical Colorectal Audit Group.

J Natl Compr Canc Netw. 2017 Feb;15(2):181-190

ABSTRACT

Background: The aim of this study was to evaluate current clinical practice and treatment outcomes regarding locally advanced colon cancer (LACC) at population level.

Patients/Methods: Data from the Dutch Surgical Colorectal Audit (DSCA) from 2009 to 2014 were used. A total of 34,527 patients underwent resection for non-LACC and 6,918 for LACC. The latter was defined as cT4 and/or pT4 stage. LACC was divided into those with multivisceral resection (LACC-MV (n=3,385)) and without (LACC-noMV (n=1,595)). Guideline adherence, treatment strategy, and short term outcomes were evaluated.

Results: Guideline adherence regarding preoperative imaging was more than 90% and 80% regarding preoperative multidisciplinary team discussion. In the elective setting, neoadjuvant (chemo)radiotherapy was applied in 6.2% of the cT4 cases and neoadjuvant chemotherapy in 4.0%. R0 resection rates were 99%, 91% and 87% in non-LACC, LACC-noMV and LACC-MV patients, respectively ($p<0.001$). A postoperative complicated course occurred in 17%, 25% and 29% ($p<0.001$), and the 30 day/in-hospital mortality was 3.6%, 6.0%, and 5.4% ($p<0.001$) in the non-LACC, LACC-noMV and LACC-MV groups, respectively.

Discussion/Conclusion: This population based study suggests that there is room for improvement in the treatment of LACC, with regard to short term surgical outcomes as well as oncological outcomes, i.e. radicality of resection. Improvement might be expected from optimized preoperative imaging, routine MDT discussions, and further specialisation and centralisation of care. Optimized use of neoadjuvant treatment strategies based on already available and upcoming evidence is likely to result in a better margin status and related to that a better long-term prognosis. Furthermore, lower R0 resection rates in emergency setting suggest a potential role for bridging strategies in order to enable optimal staging, neoadjuvant treatment and elective surgery by a surgical team most optimally qualified for the procedure.

BACKGROUND

Colon cancer is highly prevalent world-wide and a major public health problem.[1] A substantial group of patients (10-15%) presents with locally advanced colon cancer (LACC), which has an important impact on the management and prognosis of the disease.The standard curative intent treatment of LACC is a complete resection of the tumor (R0 resection) followed by adjuvant systemic chemotherapy depending on the age and clinical condition of the patient.[2,3]

LACC can be subdivided into T4a stage with serosal ingrowth and T4b stage with ingrowth into nearby tissues or organs (TNM, 7th edition). In order to achieve a R0 resection of the latter tumors, the surgical approach should include a multivisceral resection with or without neoadjuvant down staging.[4,5] Despite the prevalence of LACC and the relatively poor prognosis, treatment of LACC is still an underexposed area in the field of colorectal cancer care when compared to, for example, the extensive literature on locally advanced rectal cancer.

The Dutch Surgical Colorectal Audit (DSCA) has been evaluating and reporting on the quality of care of primary colorectal cancer surgery since 2009.[6,7] The aim of this study was to evaluate current clinical practice regarding short-term outcomes of the treatment of LACC at population level using DSCA data.

METHODS

Dataset

Data were derived from the DSCA, a disease specific national audit. The audit collects information on patient, tumor, treatment characteristics and outcomes and contains data from approximately 97 percent of all patients who underwent a resection for primary colorectal cancer in the Netherlands. Data-entry is obligatory and data are stored in a highly secured online database. All 92 Dutch hospitals participate and appoint a surgeon who is responsible for data-entry. The dataset is cross-checked several times with data registered in the Netherlands Cancer Registry (NCR) to ensure completeness. Detailed information on the validity, collection and methodology of the dataset has been published previously.[6,7]

Patients

For this study, no ethical approval or informed consent was required under Dutch law. All patients who underwent surgery between January 1st 2009 and December 31st 2014 and were registered before March 15, 2015, were evaluated. Patients with multiple synchronous tumors within the colon were included, but patients with a second tumor in the rectum were excluded. Patients were considered eligible for this study if at least the following data were available: location of the tumor, date of surgery and survival status at the time of hospital discharge. Based on these criteria, 98.7 percent (n=39,491) of all registered patients were available for analysis. Furthermore, for the purpose of the present analysis, all patients with metastatic disease were excluded.

Definitions

In the DSCA, both clinical and pathological T stage were available, but without subdivision in T4a and T4b. LACC was defined as all patients with a registered clinical and/or pathological T4 stage. The extent of surgery for the primary tumor was registered in the DSCA as no, limited or extensive additional resections for local ingrowth. Limited additional resections were defined as resections of the abdominal wall, the omentum or the ovaries. Extensive additional resections referred to resections of the pancreas, spleen, kidney, liver, stomach,

bladder, ureters, uterus or additional bowel resections. The organs involved or the exact locations of the additional resections are not specified. The variable "additional resections for local ingrowth" was used to define two subgroups: LACC without additional/multivisceral resections (LACC-noMV) and LACC with limited or extended additional/multivisceral resections (LACC-MV). All other colon cancer resections were referred to as non-LACC. In short, the following three subgroups were used in this study: LACC-noMV: patients who underwent a resection of a cT4 and/or pT4 colon carcinoma without the need for a multivisceral resection; LACC-MV: patients who underwent a multivisceral resection of a cT4 and/or pT4 colon carcinoma; Non-LACC: patients who underwent a resection for a T1-3 colon cancer (i.e. a tumor that was not classified as either cT4 or pT4).

Emergency surgery was defined as surgery performed within 12 hours after the procedure was scheduled. Urgent surgery referred to semi-urgent procedures that were scheduled more than 12 hours before being performed, but outside of the elective program. Surgical approach was either open, laparoscopic or converted laparoscopic surgery. Hospital volume was defined as the number of resections performed for LACC-MV per hospital per year.

The outcome variables were guideline adherence (see below for the guidelines), radicality of resection and postoperative course. The subcategories for radicality of resections were: R0: complete tumor resection with all margins histologically uninvolved; R1: incomplete resection with microscopic surgical resection margin involvement; R2: incomplete tumor resection with gross residual tumor that was not resected. A complicated course referred to a postoperative complication leading to a re-intervention, hospital stay longer than 14 days, or death. Surgical complications were complications directly related to the surgical procedure (i.e. anastomotic leakage, abscess, bleeding, ileus). Non-surgical complications were not directly related to the surgery (i.e. postoperative pneumonia). Mortality was defined as 30 day or in-hospital mortality.

Treatment for LACC according to the Dutch guidelines

The Dutch colorectal guideline used until June 2014 advised to routinely perform a preoperative CT scan for colon cancer. In case

of LACC, this was aimed at optimizing the surgical approach with 'en bloc' multivisceral resection and at considering neoadjuvant therapy. Preoperative (chemo)radiotherapy had to be considered if R0 resection was not found to be achievable based on CT imaging or intraoperative findings from explorative laparotomy. Postoperative (chemo)radiotherapy had to be considered in cases of R2 resection with clipping of the operative field. In the revised guideline of June 2014 (www.oncoline.nl), preoperative imaging as well as multidisciplinary team (MDT) discussion was recommended in order to select the optimal treatment strategy. Preoperative systemic therapy is added as a neoadjuvant treatment option, besides (chemo)radiotherapy. Postoperative (chemo)radiotherapy for LACC is no longer advised.

Statistical analysis

Differences in baseline characteristics and outcome variables between patients with non-LACC, LACC-noMV and LACC-MV were analyzed using a Chi square test or Fisher's exact test in the case of categorical variables. The Kruskal-Wallis one-way analysis of variance was used for continues (nonparametric) variables. R0 resection proportions were compared between different subgroups based on the type of resection, surgical approach, neo-adjuvant treatment and hospital volume. To determine potential improvement in quality of care over time, outcome parameters were plotted against year of registration. The trend over time was analyzed using the Chi square for linearity. A p-value of less than 0.05 was considered statistically significant. Statistical analyses were performed in PASW Statistics, version 22 (SPSS inc., Chicago, IL).

RESULTS

Patients

Of all colon cancer patients registered between the 1st of January 2009 and the 31st of December 2014 in 92 Dutch hospitals, 39,491 were eligible for analysis. A total of 4,964 patients were staged as M1 and excluded from this analysis. Clinical T stage was known in only 27% of the remaining 34,527 patients and cT4 stage was registered in 578 patients. A total of 4730 patients had a pathological T4 tumor. There

was an overlap between these two groups in the case of 328 patients who had both a cT4 and pT4 classified tumor. This resulted in a total of 4,980 patients with a cT4 and/or pT4 stage (LACC) and the remaining 29,547 (86%) were non-LACC patients (figure 1). In the LACC group, 3,385 patients (68%) were classified as LACC-noMV and 1,595 patients (32%) as LACC-MV. Limited and extensive additional resections were performed in 53% and 47% of the LACC-MV patients, respectively.

Baseline characteristics and surgery

Baseline characteristics of the three subgroups are outlined in table 1. Compared to non-LACC patients, patients with LACC-noMV as well as those with LACC-MV experienced more preoperative tumor complications (34% vs. 51% and 52% respectively). The percentage of procedures in emergency/urgent setting was 14% for non-LACC and 33% and 29% for LACC-noMV and LACC-MV patients, respectively. LACC was associated with a higher proportion of nodal positivity compared to non-LACC. Within the LACC group, nodal positivity was higher for LACC-noMV compared to LACC-MV (60% vs. 47%).

The surgical procedure commenced laparoscopically in 53% of patients with non-LACC, in 36% of those with LACC-noMV and in 21% of those with LACC-MV. Conversion rates were 13%, 19% and 52%, respectively. The proportion of primary anastomoses was considerably lower in LACC-MV patients compared to LACC-noMV and non-LACC patients (table 1).

Guideline adherence

Preoperatively, a CT-abdomen at the least was performed in 92% of patients with LACC-noMV and in 95% of the patients with LACC-MV (table 2). These percentages were slightly higher (94% and 96%, respectively) if emergency/urgent procedures are excluded. Patients undergoing elective surgery were discussed during a MDT meeting in 80% and 82% of LACC-noMV and LACC-MV patients, respectively. Considering cT4 stage in the elective setting only, 6.2% (n=22) of patients with LACC (either no-MV or MV) received neoadjuvant (chemo) radiotherapy and 4.0% (n=14) neoadjuvant systemic therapy.

Outcome variables

As compared to non-LACC, the overall R0 resection proportion was lower in LACC patients (99% vs. 90% respectively) (table 3). A higher proportion of R1/R2 resections was found for LACC-MV as compared to LACC-noMV ($p < 0.001$), also in the elective setting only ($p<0.001$). R0 resection proportions were significantly higher in the elective setting as compared to the emergency and urgent settings for both LACC-noMV (93 vs. 87%; $p<0.001$) and LACC-MV (90% vs. 81%; $p<0.001$). In the LACC-noMV group, the R0 resection proportion was significantly lower in converted procedures than in laparoscopically completed resections (89% vs. 96%; $p<0.001$) though similar R0 resection proportions were found in the LACC-MV group (90% after conversion vs. 93% after laparoscopy). The R0 resection proportions following any form of neoadjuvant treatment did not significantly differ from the overall groups.

In table 4, data on the postoperative course are displayed. The length of stay was the longest for the LACC-MV subgroup. Additionally, complications occurred most often in the LACC-MV group. 30 day / in-hospital mortality rate was significantly higher for LACC compared to non-LACC (5.8% vs. 3.6%; $p<0.001$) without significant impact of multivisceral resection ($p=0.606$) in LACC patients (table 4).

Patients with LACC-MV were treated in all 92 hospitals. Based on the number of LACC-MV patients treated, the hospitals were subdivided into low (≤5 procedures annually) and high (>5 procedures annually) volume hospitals. There were 82 low volume hospitals (median volume 2.3; range 0.2-5.0) and 10 high volume hospitals (median volume 6.9; range 5.2-8.2). The R0 resection proportion was 86% in low volume hospitals, as compared to 91% in high volume hospitals ($p=0.024$).

When looking at the development of the quality of surgical care throughout the years, a significantly positive trend in completeness of resection, postoperative complicated course and 30 days / in-hospital mortality could be observed in the non-LACC and LACC-noMV groups in figure 2. These improvements were less clear (and non-significant) in the LACC-MV group (figure 2).

DISCUSSION

This population study reports on clinicopathological characteristics, treatment strategy and short-term outcomes after resection of M0 LACC in 4,980 patients, who comprise 13% of the registered patients who underwent resection for colon cancer during a 6-year study period in the Netherlands. Only a small proportion of LACC patients was treated with neoadjuvant chemo- and/or radiotherapy. The overall R0 resection proportion was 90% in LACC patients, with the lowest proportion being 81% for patients who underwent a multivisceral resection in a non-elective setting. LACC patients had a slightly worse postoperative outcome compared to non-LACC patients. Short-term outcomes improved over time for LACC-noMV with the R0 resection proportion exceeding 95%. For LACC-MV, improvement over time was less clear and the R0 resection proportion in 2014 was 88%.

An R1 resection of a primary colon cancer has a strong and stage independent negative prognostic impact on the survival and recurrence rate.[8] In a recent single institutional cohort study, recurrence rates were 56% and 19% for R1 and R0 resection, respectively, with corresponding 5-year survival rates of 25% and 60%.[9] Similar to our findings, the risk of incomplete resection was related to the T stage. R0 resection proportions were remarkably low: 65% for T4a and 50% for T4b. Another population based study reported a 75% R0 resection proportion in 861 patients with T4a stage colon cancer.[10] These data from literature and our findings suggest that there is room for improvement in LACC surgery. This will have a positive impact on prognosis given its independent association with recurrence and survival. Furthermore, the postoperative mortality for LACC of 5.8% also suggests room for improvement. This mortality rate is comparable to published series on LACC (3.3 – 8.9%)[11–13]. However, this is a population-based study of unselected patients including emergency surgery and non-expert centers. The volume-outcome relationship in the present analysis suggests the potential benefit of further specialization and centralization of care in high volume centers. The small differences in absolute numbers of procedures between ‘low’ and ‘high’ volume hospitals (2.3 vs. 6.9 respectively), as well as the relatively low median volume in the ‘high’ volume group (6.9), show that LACC surgery has not yet been centralized in the Netherlands. Further improvement might

be expected when annual volumes exceed 15 to 20[14]. The low hospital volumes for LACC-MV might also explain the absence of improvement over time for LACC-MV. Furthermore, lower R0 resection proportions in the emergency and urgent settings suggest a potential role for bridging strategies, such as a decompressing stoma. This would enable optimal staging, potential neo-adjuvant treatment and elective surgery by an optimal surgical team.

A multivisceral resection is essential to achieve a R0 resection in pT4b stage colon cancer and has been associated with improved outcome at population level.[15] However, preoperative as well as intraoperative assessment of organ involvement is often inaccurate, because of the difficulty in distinguishing between true tumor invasion and inflammatory adhesions.[16,17] Reported 'true' pT4 rates in multivisceral resections were 55, 36 and 34% in three studies. [12,18,19] Therefore, multivisceral resection often turns out to be overtreatment. This is a clinically relevant problem because of the increased morbidity rates as shown by our results and others.[13,17] Despite its drawbacks, a multivisceral resection seems to be preferred over a less radical approach in clinically adherent tumors with uncertainty regarding the extent of malignant invasion, bearing in mind the negative prognostic impact of an irradical resection.[20–22]

In addition to extensive surgery, neoadjuvant therapies could optimize R0 resection proportions in LACC.[23,24] In contrast to other types of gastrointestinal cancer, administration of neoadjuvant therapy in colon cancer remains uncommon.[10,13,25,26] Incidental use of a variety of neoadjuvant therapy schedules has been described. In the phase-II Foxtrot trial,[5] 150 patients with LACC were randomized (2:1) between an experimental arm with preoperative chemotherapy (FOLFOX) and a second randomization in RAS wild type for an anti-EGFR antibody, and a control arm with routine adjuvant chemotherapy only. Preoperative systemic therapy was shown to reduce tumor size and resulted in a significant improvement of R0 resection proportion (96% vs. 80%). The need for emergency or urgent surgery, complication rate and toxicity were comparable across both groups. These findings were confirmed in another phase II study including 22 patients and the PRODIGE 22-ECKINOXE trial with a similar design is currently recruiting. [27,28] In the present study, neoadjuvant therapy was not associated with a higher percentage of R0 resections. This may be the result of both small sample

size (n=77) and allocation bias, since the most advanced tumors were probably allocated to neoadjuvant therapy.

Due to concerns regarding radiation toxicity, mainly concerning the small bowel, the use of (chemo)radiotherapy for LACC remains controversial.[29] One study, in which 33 patients were retrospectively analyzed, suggested that neoadjuvant (chemo)radiotherapy combined with en bloc multivisceral resection results in high R0 resection proportions and excellent local control, with acceptable morbidity and mortality.[16] In 64% of these patients, the T4 tumor was located in the sigmoid. The sigmoid was also the main tumor location (68%) in patients who received neoadjuvant (chemo) radiotherapy in the present study.

Decisions on neoadjuvant therapy strategies should be based on preoperative imaging, but the accuracy is limited and over staging rates of up to 50% have been described.[12,30] In this study a comparable discrepancy between cT4 and pT4 was found; in 833 of the pT4 patients, clinical T stage was registered with 61% being classified as cT1-3. Only 57% of the 578 cT4 tumors was classified as pT4 tumor. Despite its limited accuracy, preoperative imaging seems to be essential when considering neoadjuvant treatment and surgical planning. Therefore, further improvement can be expected from optimal guideline adherence with respect to preoperative imaging and MDT discussion. LACC is often considered to be a contra indication for laparoscopic surgery, due to oncological concerns. In this series, laparoscopic surgery was performed in 31% of LACC overall and 21% of LACC-MV with conversion rates of up to 52%. Conversion did not lower the R0 resection proportion in LACC-MV patients, which suggests that it can be considered safe to initiate surgery laparoscopically. In contrast, conversion did result in lower R0 resection proportions in the LACC-noMV group. The latter finding is remarkable and was not confirmed in the literature. Several non-randomized comparative studies have been published on laparoscopy in LACC.[10,13,25,26,31,32] The laparoscopic group often had favorable baseline characteristics with regard to factors such as previous abdominal surgery and emergency setting. Additionally, resections were less often multivisceral. Conversion rates ranged between 7% and 24% and R0 resection proportions were mostly similar to the open surgery groups. These data are most likely skewed by allocation bias. Increasing the rate of laparoscopic surgery for LACC might contribute to a lower morbidity rate, but this may never jeopardize oncological safety.

This is a large population based cohort study, which provides the best available evidence of the nationwide current clinical practice regarding LACC. However, several limitations of this design should be kept in mind. The availability of data is dependent on the self-reported data from the DSCA database, which is subject to registration bias and incomplete data registration. Nonetheless, data were validated on a yearly basis using the Dutch National Cancer Registry, in order to show accuracy and completeness of data[6]. Also, the variable set is chosen for the purpose of clinical auditing and several variables relevant to the aim of this study such as subdivision in T4a/b subgroups and organ involvement based on pathology reports are lacking. Additionally, the clinical T stage was unknown in a substantial number of patients, resulting in a small sample size of clinical T4 tumors, which is the relevant group to assess for neoadjuvant strategies. Furthermore, differences in patient and tumor characteristics between subgroups should be recognized when comparing outcome variables between the relevant subgroups.

In conclusion, amongst patients who undergo surgery for LACC there is a lower R0 resection proportion and they are at higher risk of postoperative complications and mortality as compared to patients who receive surgery for less invasive colon cancer. Neoadjuvant therapy for colon cancer is still rarely applied in the Netherlands and prospective randomized studies have to be awaited in order to confirm the observation of more radical resections in phase 2 studies. Considering the relatively low R0 resection proportion, there is an opportunity for improvement. This may be achieved by optimizing preoperative imaging, the application of neoadjuvant therapy schedules and centralization and specialization.

REFERENCES

1. Ferlay J, Soerjomataram I I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int. J. Cancer. 2014;136(5):E359–86.

2. Izbicki JR, Hosch SB, Knoefel WT, et al. Extended resections are beneficial for patients with locally advanced colorectal cancer. Dis. Colon Rectum. 1995;38(12):1251–6.

3. Saha AK, Smith KJE, Sue-Ling H, et al. Prognostic factors for survival after curative resection of Dukes' B colonic cancer. Colorectal Dis. 2011;13(12):1390–4.

4. Larkin JO, O'Connell PR. Multivisceral resection for T4 or recurrent colorectal cancer. Dig. Dis. 2012;30 Suppl 2:96–101.

5. Foxtrot Collaborative Group. Feasibility of preoperative chemotherapy for locally advanced, operable colon cancer: the pilot phase of a randomised controlled trial. Lancet. Oncol. 2012;13(11):1152–60.

6. van Leersum NJ, Snijders HS, Wouters MWJM, et al. Evaluating national practice of preoperative radiotherapy for rectal cancer based on clinical auditing. Eur. J. Surg. Oncol. 2013;39:1000–6.

7. Kolfschoten NE, Marang van de Mheen PJ, Gooiker GA, et al. Variation in casemix between hospitals treating colorectal cancer patients in the Netherlands. Eur. J. Surg. Oncol. 2011;37(11):956–63.

8. Amri R, Bordeianou LG, Sylla P, Berger DL. Association of Radial Margin Positivity With Colon Cancer. JAMA Surg. 2015;150:890–898.

9. Khan MAS, Hakeem AR, Scott N, Saunders RN. Significance of R1 resection margin in Colon Cancer Resections in the Modern Era. Colorectal Dis. 2015;17(11):943–953.

10. Elnahas A, Sunil S, Jackson TD, Okrainec A, Quereshy FA. Laparoscopic versus open surgery for T4 colon cancer: evaluation of margin status. Surg. Endosc. 2015;

11. Campos FG, Calijuri-Hamra MC, Imperiale AR, et al. Locally advanced colorectal cancer: results of surgical treatment and prognostic factors. Arq. Gastroenterol. 48(4):270–5.

12. Gezen C, Kement M, Altuntas YE, et al. Results after multivisceral resections of locally advanced colorectal cancers: an analysis on clinical and pathological t4 tumors. World J. Surg. Oncol. 2012;10:39.

13. Hoffmann M, Phillips C, Oevermann E, et al. Multivisceral and standard resections in colorectal cancer. Langenbeck's Arch. Surg. 2012;397(1):75–84.

14. Gietelink L, Henneman D, van Leersum NJ, et al. The Influence of Hospital Volume on Circumferential Resection Margin Involvement: Results of the Dutch Surgical Colorectal Audit. Ann. Surg. 2014;

15. Govindarajan A, Coburn NG, Kiss A, et al. Population-based assessment of the surgical management of locally advanced colorectal cancer. J. Natl. Cancer Inst. 2006;98(20):1474–81.

16. Cukier M, Smith AJ, Milot L, et al. Neoadjuvant chemoradiotherapy and multivisceral resection for primary locally advanced adherent colon cancer: a single institution experience. Eur. J. Surg. Oncol. 2012;38(8):677–82.

17. Mohan HM, Evans MD, Larkin JO, Beynon J, Winter DC. Multivisceral resection in colorectal cancer: a systematic review. Ann. Surg. Oncol. 2013;20(9):2929–36.

18. Gebhardt C, Meyer W, Ruckriegel S, Meier U. Multivisceral resection of advanced colorectal carcinoma. Langenbecks. Arch. Surg. 1999;384(2):194–9.

19. Darakhshan A, Lin BPFC, Chan C, et al. Correlates and outcomes of tumor adherence in resected colonic and rectal cancers. Ann. Surg. 2008;247(4):650–8.

20. Cirocchi R, Partelli S, Castellani E, et al. Right hemicolectomy plus pancreaticoduodenectomy vs partial duodenectomy in treatment of locally advanced right colon cancer invading pancreas and/or only duodenum. Surg. Oncol. 2014;23(2):92–8.

21. Zhang J, Leng J, Qian H, et al. En bloc pancreaticoduodenectomy and right colectomy in the treatment of locally advanced colon cancer. Dis. Colon Rectum. 2013;56(7):874–80.

22. Croner RS, Merkel S, Papadopoulos T, et al. Multivisceral resection for colon carcinoma. Dis. Colon Rectum. 2009;52(8):1381–6.

23. Stojadinovic A, Nissan A, Wainberg Z, et al. Time-dependent trends in lymph node yield and impact on adjuvant therapy decisions in colon cancer surgery: an international multi-institutional study. Ann. Surg. Oncol. 2012;19(13):4178–4185.

24. Scott N, Jamali A, Verbeke C, et al. Retroperitoneal margin involvement by adenocarcinoma of the caecum and ascending colon: What does it mean? Color. Dis. 2008;10(3):289–293.

25. Vignali A, Ghirardelli L, Di Palo S, Orsenigo E, Staudacher C. Laparoscopic treatment of advanced colonic cancer: A case-matched control with open surgery. Color. Dis. 2013;15(8):944–948.

26. Shukla PJ, Trencheva K, Merchant C, et al. Laparoscopic resection of T4 colon cancers: Is it feasible? Dis. Colon Rectum. 2015;58(1):25–31.

27. Arredondo J, Pastor C, Baixauli J, et al. Preliminary outcome of a treatment strategy based on perioperative chemotherapy and surgery in patients with locally advanced colon cancer. Colorectal Dis. 2013;15(5):552–7.

28. Karoui M, Rullier A, Luciani A, et al. Neoadjuvant FOLFOX 4 versus FOLFOX 4 with Cetuximab versus immediate surgery for high-risk stage II and III colon cancers: a multicentre randomised controlled phase II trial - the PRODIGE 22 - ECKINOXE trial. BMC Cancer. 2015;15:511.

29. Hallet J, Zih FS, Lemke M, et al. Neo-adjuvant chemoradiotherapy and multivisceral resection to optimize R0 resection of locally recurrent adherent colon cancer. Eur. J. Surg. Oncol. 2014;40(6):706–12.

30. van Santvoort HC, Braam HJ, Spekreijse KR, et al. Peritoneal carcinomatosis in t4 colorectal cancer: occurrence and risk factors. Ann.Surg.Oncol. 2014;21(5):1686–1691.

31. Huh JW, Kim HR. The feasibility of laparoscopic resection compared to open surgery in clinically suspected T4 colorectal cancer. J. Laparoendosc. Adv. Surg. Tech. A. 2012;22(5):463–7.

32. Kim IY, Kim BR, Kim YW. The short-term and oncologic outcomes of laparoscopic versus open surgery for T4 colon cancer. Surg. Endosc. 2015;

TABLES AND FIGURES

Table 1. Baseline characteristics. LACC: Locally advanced colon cancer, MV: multivisceral resection required.

		non-LACC		LACC- noMV		LACC-MV		
		n	%	*n*	%	*n*	%	χ^2
Sex	Male	15502	52	1669	49	708	44	<0.001
	Female	14044	48	1716	51	886	56	
Age	≤ 60	4600	16	526	15	259	16	0.005
	61-70	8405	28	939	28	462	29	
	71-80	10520	36	1140	34	527	33	
	≥ 81	6014	20	780	23	347	22	
ASA score	I - II	21866	75	2357	71	1146	72	<0.001
	III	6844	23	886	27	408	26	
	IV - V	534	1.8	98	2.9	36	2.3	
Preoperative complications caused by the tumor	None	19470	66	1658	49	759	48	<0.001
	Perforation with faecal peritonitis	334	1.1	180	5.4	69	4.4	
	Abscess	214	0.7	90	2.7	94	5.9	
	Obstruction	3236	11	805	24	324	21	
	Blood loss / anaemia	4649	16	419	13	176	11	
	Other	1416	4.8	209	6.2	162	10	

Continuation of Table 1

Operative setting	Elective (incl. following stent placement)	25349	86	2250	67	1125	71	<0.001
	Emergency / urgent	4151	14	1132	33	470	29	
Pathologic N-stage	N0	19328	66	1336	40	847	54	<0.001
	N1	6733	23	1081	33	436	28	
	N2	3035	10	907	27	294	19	
	Nx	325	1.1	44	1.3	15	0.9	
Surgical approach	Open	13999	47	2175	64	1247	78	<0.001
	Laparoscopic	13587	46	982	29	166	10	
	Laparoscopic – converted	1961	6.6	228	6.7	182	11	
Surgical procedure	Ileocecal resection	325	1.1	61	1.8	21	1.3	<0.001
	(Extended) right hemicolectomy	13316	45	1679	50	677	42	
	Transverse resection	774	2.6	79	2.3	75	4.7	
	(Extended) left hemicolectomy	3186	11	383	11	215	14	
	(Low) anterior / sigmoid resection	10970	37	1038	31	548	34	
	Subtotal colectomy	545	1.8	77	2.3	37	2.3	
	Panproctocolectomy	174	0.6	10	0.3	5	0.3	
	Other	257	0.9	58	1.7	17	1.1	
Anastomosis	Anastomosis	25562	88	2611	79	1131	73	<0.001
	Anastomosis with diverting ostomy	1076	3.7	144	4.3	123	7.9	
	End ostomy	2352	8.1	567	17	300	19	

Table 2. Guideline adherence. LACC: Locally advanced colon cancer, MDT: multidisciplinary team discussion, MV: multivisceral resection required. *In the DSCA database, preoperative imaging is registered for the abdomen and thorax separately. The imaging modality is further specified for both compartments, and only the one with highest accuracy is registered in case of multiple modalities. **Analysed as fulfilling guideline recommendation for preoperative imaging.

				LACC-noMV		LACC-MV	
				n	%	n	%
Elective, emergency and urgent procedures	**Preoperative imaging***	**Abdomen**	**none**	93	2.8	18	1.2
			ultrasound	184	5.6	61	3.9
			CT	2912	89	1406	91
			MRI-liver**	31	0.9	15	1.0
			PET-CT**	63	1.9	47	3.0
		Thorax	**none**	305	9.1	86	5.5
			X-thorax	2292	68	1062	68
			CT	694	21	373	24
			PET-CT**	65	1.9	47	3.0
Elective procedures only	**Preoperative imaging***	**Abdomen**	**none**	18	0.8	3	0.3
			ultrasound	128	5.8	44	4.0
			CT	1982	90	993	91
			MRI-liver**	26	1.2	11	1.0
			PET-CT**	57	2.6	40	3.7
		Thorax	**none**	79	3.5	30	2.7

Continuation of Table 2

		X-thorax	1561	70	740	67
		CT	538	24	294	27
		PET-CT*	58	2.6	39	3.5
	MDT		1784	80	919	82
Elective procedures cT4	**Neoadjuvant therapies**	**chemotherapy**	2	1.1	12	6.7
		(chemo)radiotherapy	5	2.9	17	9.5

Table 3. Radicality of resection. CT: chemotherapy; (C)RT: (chemo)radiotherapy; LACC: locally advanced colon cancer, MV: multivisceral resection required, R0: complete tumor resection with all margins histologically uninvolved, R1: incomplete resection with microscopic surgical resection margin involvement, R2: incomplete tumor resection with gross residual tumor that was not resected.*Only elective procedures included. ** Analysed using Fisher's exact test.

		non-LACC		LACC-noMV		LACC-MV		
		n	%	*n*	%	*n*	%	χ^2
Overall	R0	28605	99	2981	91	1363	87	<0.001
	R1	222	0.8	190	5.8	135	8.7	
	R2	51	0.2	93	2.8	62	4.0	
Elective procedures	R0	24618	99	2040	93	990	90	<0.001
	R1	146	0.6	95	4.3	79	7.2	
	R2	32	0.1	50	2.3	29	2.6	
Emergency/urgent	R0	3949	98	938	87	373	81	<0.001
procedures	R1	72	1.8	95	8.8	56	12	
	R2	18	0.4	43	4.0	33	7.1	
Open	R0	13453	99	1855	89	1049	86	<0.001
	R1	132	1.0	142	6.8	111	9.1	
	R2	32	0.2	78	3.8	57	4.7	
Laparoscopic	R0	13257	99	926	96	153	93	<0.001
	R1	65	0.5	31	3.2	10	6.1	
	R2	12	0.1	7	0.7	1	0.6	

Continuation of Table 3

Laparoscopic - converted	R0	1895	98	200	89	161	90	<0.001
	R1	25	1.3	17	7.6	14	7.8	
	R2	7	0.4	8	3.6	4	2.2	
Neoadjuvant CT*	R0			22	85	47	92	0.429**
	R1			2	7.7	3	5.9	
	R2			2	7.7	1	2.0	
Neoadjuvant (C)RT*	R0			9	90	40	83	0.321**
	R1			0	0.0	6	13	
	R2			1	10	2	4.2	

Table 4. Postoperative course and complications. LACC: locally advanced colon cancer, MV: multivisceral resection required. Complicated course: postoperative complication leading to a re-intervention, hospital stay longer than 14 days, or death. Mortality: 30-day / in-hospital mortality. *Median (IQR); **Analysed using Kruskal-Wallis one-way analysis of variance.

	non-LACC		**LACC-noMV**		**LACC-MV**		
	n	***%***	***n***	***%***	***n***	***%***	χ^2
Length of stay (days)	7 (5-11)*		8 (5-14)*		10 (7-16)*		<0.001**
Complicated course	5509	17	837	25	460	29	<0.001
Non-surgical complications	3859	13	561	17	254	16	<0.001
Surgical complications	3698	13	494	15	290	18	<0.001
Surgical re-intervention	2816	9.5	355	11	185	12	0.007
Radiological re-intervention	270	0.9	47	1.4	40	2.5	<0.001
Mortality	1070	3.6	201	6.0	86	5.4	<0.001

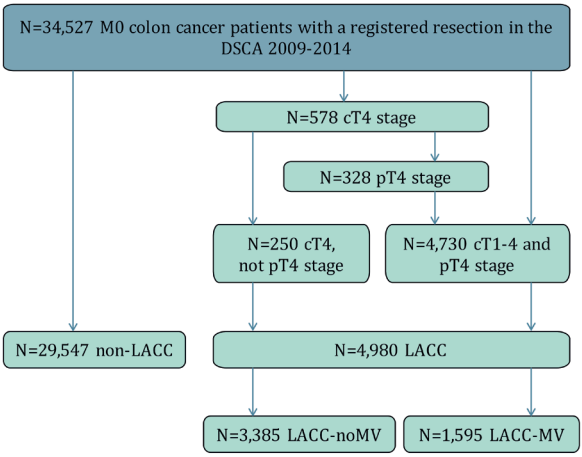


Figure 1. Subdivision of patients into non-LACC, LACC-noMV and LACC-MV. LACC: locally advanced colon cancer, MV: multivisceral resection required.

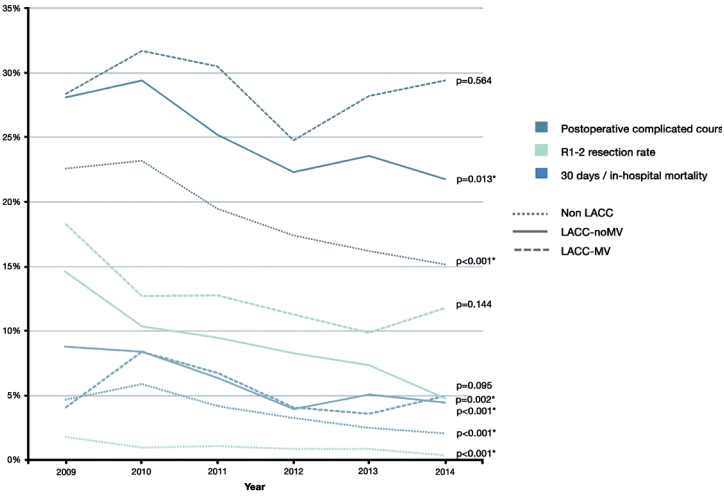


Figure 2. The development of the quality of surgical care for LACC throughout the years. LACC: locally advanced colon cancer, MV: multivisceral resection required. R1: incomplete resection with microscopic surgical resection margin involvement, R2: incomplete tumor resection with gross residual tumor that was not resected. Postoperative complicated course: postoperative complication leading to a re-intervention, hospital stay longer than 14 days, or death.

Chapter 9

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

PART I: RISK-ADJUSTMENT IN CLINICAL AUDITING

Patient populations treated for a specific condition usually differ across hospitals.[1] Casemix is a confounder for between-hospital comparisons based on outcomes and therefore, casemix adjustment needs to be applied when comparing outcomes across hospitals with the aim to judge quality of hospital care. The casemix correction models are logistic regression models that include the most important predictors of the outcome parameter that are available in the audit.[2] Despite incorporating casemix adjustment, many risk adjustment models could be considered suboptimal.[3] In casemix adjustment we come across several problems. When comparing hospitals there is always random variation; fluctuations in outcomes of hospitals based on chance.[4] Random variation becomes smaller when the study population and frequency of events (the studied outcome) increases. This is specifically important regarding the fact that some serious but infrequent adverse events – like mortality rates - gain much attention in colorectal cancer care. The frequency of postoperative mortality, especially after rectal cancer resections is low and hospital variation could be due to random variation instead of a difference in performance.

Another problem associated with casemix adjustment is the low frequency of specific patient populations in the majority of hospitals, while these are overrepresented in a few centres. The population of referral centres consist of a carefully selected group of patients based on the rarity of the disease or the high complexity of the treatment. These referral centres have a significantly different patient population, but are compared with general hospitals in one casemix correction model (this thesis). In chapter 2 we demonstrated that variable effects of predictors that are included in the currently used casemix model differed between referral and non-referral centres when we created separate casemix models for these two populations. As we hypothesized casemix correction models based on the total population showed the most resemblance with the non-referral population. The currently used casemix model (general model) that is fitted in the total population performs equally well in the non-referral population as a casemix model specifically fitted in non-referral hospitals only. In contrast, the general model performs worse in the referral population when compared to a model specifically fitted in referral hospitals only. It remains unclear

if the differences in casemix correction caused undercorrection for referral centres (this thesis). However no referral hospital was an outlier on the outcomes that were studied within the time frame of this study.

It seems plausible that a bigger gain lies in the registration of typical characteristics of the referral population as the DSCA casemix models only include the most frequently occurring factors of influence.[2] For hospitals with a specific patient population, like referral centres, it seems plausible that the registration of certain factors that are typical for this group of complex patients; i.e. detailed information about previous surgery, index surgery, multimodality treatments, and medication use therefore could be of influence on the correction of postoperative outcomes. Furthermore factors dictating the technical difficulty of the procedure are difficult to register with clear definitions – such as the detailed information about previous surgery – leading to suboptimal correction of postoperative outcomes. The possible solutions to these problems have their own disadvantages. Adding more variables to the dataset would make the registration burden bigger and the DSCA wants to keeps the dataset compact for users. Creating two separate casemix correction models would raise the question which hospital should be added to which population group. Beside from all university hospitals and two other hospitals that are generally seen as referral centres it is complex to decide whether hospitals treat a sufficiently different population in order to be compared to referral centres.

Interpretation of hospital comparisons

A certain amount of unmeasured confounding in casemix correction of outcomes will remain, meaning that even casemix adjusted outcome rates should always be interpreted with caution. This is especially important as there is a growing demand for public transparency of hospital outcomes. Hospitals and surgeons are naturally held responsible for their outcomes and transparency to a public that is not informed on how to interpret this data could lead to unwanted reactions, such as the avoidance of high-risk surgery.[5] Healthcare providers are less willing to register openly if this leads to adverse reactions and this disturbs the audit cycle. Therefore it is important that transparency is carefully introduced with the necessary information to interpret the data. Herein lies an important task for the national audits.

PART II: QUALITY ASSURANCE AND IMPROVEMENT IN DUTCH COLORECTAL CANCER CARE

Quality assurance is an important aspect of the healthcare industry. All components of the patient's healthcare process are of importance and influence the overall quality of treatment. Ernest J. Codman already noted at the beginning of the 20th century that careful registration of healthcare processes and patient outcomes would provide important feedback information. He wanted an end-results system to track the outcomes of his patient's treatments as an opportunity to identify clinical misadventures that would serve as the foundation for improving the care of future patients.[6] Doctor Codman was ahead of his time and was expelled from the staff of the Massachusetts General Hospital.[7] Fortunately his ideas on quality of care are regarded as highly relevant nowadays.[8, 9]

Hospital volume

New thoughts on quality assurance at the beginning of this century were largely focussed on the relationship between hospital or surgeon's volume and quality.[10-16] This relationship was also analysed in the Netherlands with multiple papers describing the positive relationship between hospital volume and patient outcomes.[17-19]

The Netherlands is a small country with 90 hospitals. As a result low-volume high-risk procedures could be centralized in a smaller number of hospitals, with acceptable travelling distances for patients.[17] Besides the fact that a larger volume per surgeon will lead to more experience, it is generally believed that volume is a 'proxy' for other important structural and process factors in the chain of multidisciplinary treatment.[20]

This further enhanced centralisation of technically challenging procedures such as rectal-, pancreas-, oesophageal- and bladder cancer resections. The Association of Surgeons of the Netherlands (ASN) set an obligatory minimal volume standard of 20 resections per hospital per year.[21] Hospitals with lower annual volumes of rectal cancer resections are no longer allowed to carry out this procedure. With data from the DSCA this decision could further be substantiated (this thesis). Chapter 3 shows the significant influence of hospital

volume on CRM involvement in the Netherlands. In the light of these results an obligatory volume for rectal cancer care seems justifiable. It is however important to conclude that hospital volume is merely a proxy for healthcare processes and that hospital volume does not guarantee quality.[22] Individual small volume hospitals can provide the same standard of care compared to high volume hospitals as shown in this thesis. Over the last years focus has shifted towards value of care instead of volume of care.[23, 24]

Clinical auditing

Amongst other initiatives the DSCA was founded in 2009 and provides risk-adjusted benchmarked feedback evaluating quality of surgical colorectal cancer care on hospital level and compares hospitals with their peers. It gives surgeons and their teams information about their performance and stimulates the development or improvement of hospital processes.[2] Amongst other great improvements in the field of colorectal cancer surgery the introduction of clinical auditing has been successful.[2, 25] Important aspects of surgical colorectal cancer care improved significantly since the start of the audit. As clinical auditing provides healthcare professionals with essential information on their performance in comparison to their peers, multiple improvements can be made. There are several requirements for surgical audits to provide valuable information.[26] The definitions used in the surgical audit should be unambiguous and feedback information should be reliable, accompanied by a risk-adjusted benchmark. Furthermore the information has to be up to date and easily accessible to involved healthcare providers. Most importantly the feedback information should be relevant, meaningful and actable which necessitates the formation of the surgical audits content by those personally engaged in the surgical activity concerned.[6] In addition, the effect of clinical auditing in hospitals is probably influenced by the attitude of the healthcare providers towards the national audit. Are surgical teams learning from their data and are they keen to start improvement projects or are they merely collecting this information as an obligatory burden? In the Netherlands, 86% of colorectal surgeons discuss their results periodically with their colleagues and 76% started improvement projects in response to the DSCA. The majority of colorectal surgeons are content with the DSCA.[27]

The basis of clinical auditing is an intrinsic motivation of medical professionals to improve the care they provide. Nevertheless it is known that intrinsic motivation is subject to daily change, it lies in the human nature. The so-called Hawthorne effect is a type of reactivity in which individuals modify an aspect of their behaviour in response to their awareness of being observed.[28] This is a bothersome effect in the interpretation of results of medical research but a welcome effect in clinical auditing. Due to this effect the DSCA stimulates the quality of care that is measured. If problems in healthcare processes get identified, the national audit can give extra attention to these aspects (this thesis). Awareness usually leads to quality improvement projects and in depth investigation of underlying problems.[27] When this action has led to the aimed results – i.e better national mean outcome and decreased hospital variability - the raised awareness can be loosened and registration of the item could be stopped to keep the registration burden manageable (figure 1). Sometimes this loosened awareness causes old hiatus to come back. When data sources are linked in the future it might get easier to periodically bring these aspects back to the attention, as this would not imply greater registration burden.

CRM registration and involvement

At the start of the DSCA the percentage of patients with a resection for rectal cancer that had a reported CRM was only 50 percent (chapter 4). The CRM is a significant prognostic factor for local recurrence, distant metastasis and survival after rectal cancer surgery.[29, 30] Before – at the time of the Dutch TME trial (1996-1999) - the availability of the CRM due to a standard pathology report, which included the CRM, had been an important aspect of the study.[31] During this period reporting of CRM was therefore high (97%) in participating centres.[32] We can conclude that focus on registering the CRM greatly diminished after the Dutch TME trial had finished. Another conclusion we can extract from this information is that trial data not always represent real life data. Only 3 years after the start of the DSCA CRM reporting improved to 94.2 percent nationally (chapter 4). We think that this improvement in CRM reporting is almost exclusively attributable to the increased awareness of the healthcare providers raised by national audit (this thesis). Due to renewed focus in each hospital this valuable information on the quality of surgery and on the long-term prognosis of the patient became available again to the healthcare providers.

During the first five years of the DSCA registration incidence of CRM involvement decreased from 14 to 6 percent; an absolute reduction of more than fifty percent (chapter 4). Clinical auditing lays tremendous focus on the outcome of the CRM, which was, to our opinion, a driving force for the significant improvement of this outcome parameter leading to better long-term outcomes for rectal cancer patients. Furthermore the DSCA stimulated guideline adherence leading to a higher percentage of patients that were preoperatively discussed in a multidisciplinary team (MDT) meeting.[2] The stimulated guideline adherence led to a higher percentage of patients in whom local staging by MRI was performed. Both improvements could have attributed to the quality of rectal cancer surgery (this thesis). The present analysis shows that quality indicators play an important role in identifying quality concerns and variation, and enable targeted quality improvement projects. Few other interventions in the care of rectal cancer patients have led to such magnitude of improvements in a relatively short period of time and it shows the value of national auditing as a tool for quality improvement. Furthermore, centralisation of the technically challenging rectal cancer surgery has had significant influence on CRM involvement (chapter 3). The minimal annual volume of 20 rectal cancer resections has had a positive influence on CRM involvement.

International comparisons

The information from the DSCA makes it easier to compare current national practice in the Netherlands with international peers. As described in chapter 5 of this thesis, van Leersum et al. found that the use of radiotherapy for patients with stage I / low-risk stage II rectal cancer (cT1-3N0) in the Netherlands was high compared to other European countries.[33] The national audit therefore increased national insight on this subject and raised awareness in Dutch hospitals of being the European exception regarding RT-use. This laid the foundation for guideline revision and the fast implementation by healthcare providers afterwards (chapter 5). Our study shows the impact of the revised national colorectal cancer guideline immediately after it became available to the community. The use of radiotherapy in patients with cT1N0 disease was abandoned and radiotherapy treatment in patients with cT2-3N0 disease significantly decreased within one year (this thesis). In addition to guideline revision as the ultimate tool to rapidly change clinical practice, it appears to be very important to create a well-informed

medical field. Secondly the audit is a useful tool to verify whether the changed indication for radiotherapy altered postoperative outcomes. This thesis shows that CRM involvement did not increase after RT-use radically changed (figure 2). Clinical auditing in this case proves to be a useful tool for quality control after guideline revision.

PART III: DATA FROM CLINICAL AUDITS AS A SUPPLEMENT TO RCT'S

Hospital outcome variation can be the result of differences in the structural and procedural differences between hospitals.[34] The higher the degree of variation between hospitals on a particular subject the more we can usually learn from this information. The national audit is a rich source that can be used for such research. The audit provides us with "real-time" information as the data is frequently updated and it provides us with "real-world" data as all patients are included, meaning all patients who underwent resection of colorectal cancer in case of the DSCA. This part of the thesis provides examples of how clinical audit data is used to answer several clinically relevant questions in the field of surgical treatment of colorectal cancer.

Laparoscopic colorectal surgery

Laparoscopic surgery has been a major change in abdominal surgery.[35] The technique was introduced by gynaecologists and in the 90's adapted by other specialists.[36, 37] In colorectal cancer surgery, laparoscopic surgery resulted in faster postoperative recovery compared to conventional open surgery, without compromising oncological outcomes.[38, 39] Long-term benefits of laparoscopic surgery for colorectal cancer are better cosmetics, less incisional hernias due to preserved abdominal wall integrity, and less adhesion related small bowel obstruction.[40-42] Due to these results laparoscopic surgery makes up for the majority of colorectal cancer surgery in present times.[43]

Randomized controlled trials can provide solid prove on non-inferiority of new techniques. But this type of research comes with some drawbacks; i.e. they take a long time to conduct, handle strict inclusion criteria and usually do not include large numbers of patients.[44] These

issues can cause clinically relevant questions to remain unanswered.[35] In chapter 6 we describe an example; is laparoscopic surgery in colorectal cancer care influencing postoperative mortality? This remains unanswered because mortality was a rare event in most RCT's including a relatively low-risk population. As the technique is already widely introduced and next to the earlier mentioned unwanted characteristics of the RCT regarding this subject, the effectuation of an RCT on the matter would no longer be regarded ethically sound. This chapter shows that population studies are able to include higher numbers of patients with different operative risk levels from daily clinical practice showing interesting results. It demonstrates the significantly reduced risk of postoperative mortality after laparoscopic surgery compared to open surgery in patients with non-locally advanced, non metastatic colon cancer in an elective setting. Moreover it endorses the hypothesis of the positive influence of laparoscopic surgery on postoperative outcomes in elderly patients with or without comorbidity.[45-47] To deal with the inherent methodological problems of non-randomized comparisons, a risk-stratified comparison between relatively homogenous subgroups using raw data was used, thereby minimizing selection and allocation bias.

Ideally all developments in medicine should be extensively tested before they are introduced to patient care. However development is an important element of quality assurance and healthcare professionals in all area's need to keep up with latest developments. There is a thin line between fast introduction of new techniques and providing evidence-based medicine. In reality techniques are already implemented while large randomized or prospective studies are still running.[48] A national audit can be used to monitor the implementation of new techniques providing regular feedback of patient outcomes to the surgical teams. If a relatively high number of adverse events would be observed, the professional society and their members can take actions.

Kolfschoten et al. analysed the introduction of laparoscopy for colorectal cancer in the Netherlands and concluded that the introduction had been completed safely.[49] In the Netherlands the percentage of laparoscopic colorectal cancer resections is high, especially compared to the surrounding countries. We may therefore expect that the learning curve in the Netherlands has been passed through with better postoperative

outcomes at present.[50] Furthermore, laparoscopy encouraged the subspecialisation of colorectal surgeons, further enhancing surgical quality. Moreover laparoscopic surgery became available for the technically more challenging patients, and now those are also profiting from its short- and long-term advantages (this thesis). Frequently quoted outcomes after laparoscopic surgery however are from older RCT's such as the COLOR II trial.[51] Chapter 7 complements older studies by showing the current outcomes of a comparable population, matched to the Dutch population of the COLOR II trial. This study demonstrates that patient outcomes after laparoscopic surgery for rectal cancer largely improved and that older RCT's do not provide representative outcomes anymore. It shows once again the value of national audits because they are able to provide us with real-time data and an accurate representation of national performance.

High-risk patients

Healthcare industry is naturally ever changing. Due to the aging population, patients with colorectal carcinoma are older and have a higher perioperative risk.[46] Furthermore there is growing interest for patient-tailored treatment.[52] Different patients and tumor characteristics benefit from tailored treatment. Not surprisingly, this has an effect on the treatment of colorectal cancer patients. With these changes there is a need for real-time and real-life data, providing us with end results after specific treatment schedules, changed processes and providing us with data on specific patient groups. A significant proportion of colorectal cancer patients are underreported. They are excluded from RCT's due to advanced disease, multiple-comorbidity or their age. For instance, if you apply the exclusion criteria of the COLOR II trial (chapter 7) to the DSCA population in 2014, only 70% of patients with a laparoscopic resection for rectal cancer would have been included in the COLOR II trial.

Chapter 8 describes the clinical-pathological characteristics, treatment strategies and short-term outcomes after resection of 6,918 patients with locally advanced colon carcinoma (LACC), comprising 17.5% of the registered patients who underwent resection for colon cancer during a 6-year study period in the Netherlands. Hospital variation regarding this oncological high-risk frail patient population is informative. Best practices might be able to educate us on improving outcomes for this

fragile patient population that deserves more attention.[53] As high-risk patients are underreported in large RCT's shared decision-making is difficult in this population. LACC patients for instance had worse postoperative outcomes compared to non-LACC patients regarding length of hospital stay, complication rate, re-intervention rate and mortality rate (chapter 8). There has been much more interest in rectal cancer surgery during the past decades, and it is only in recent years that focus on LACC is increasing. Audit data can be used in this way to provide information for identifying areas for potential improvement and knowledge gaps that necessitate new research. From a patient perspective, these data can help in shared decision making and managing of expectations.

FUTURE PERSPECTIVES

Due to the accomplished successes of clinical auditing the need for clinical feedback information of healthcare providers will grow. This thesis shows the usefulness of real-world and real-time data provided by clinical audits. It not only serves as risk-adjusted feedback to healthcare providers, it serves other important causes as well by providing clinical information of a merely non-selected group of patients. Growth in these areas of usage is needed and expected.[44]

Clinical audits already provide information on specific groups of patients that are underreported in literature. Outcomes research in this patient population is providing important information for shared decision-making in the clinical setting. The inclusion of patient reported outcome measurements (PROMS) can potentially deepen this information by linking on patient level to structure – process and outcome data. This information should be at hand in daily clinical practice and patients could then be informed on the clinical outcomes and patient reported functional outcomes of patients like them who received different types of treatment. Although interpretation of such data might still be difficult due to, for example, relevant inter-individual variability in perceiving treatment effects.

This thesis provides a clear example of how international treatment variation can lead to practice change in the Netherlands. Through

international comparison we became aware of the overuse of radiotherapy in rectal cancer treatment, which led to the revision of the national guideline on the treatment of rectal cancer (chapter 5). International benchmarking will bring forth extensive practice variation – regarding structural, process and outcome measurements - making it a rich source of valuable clinical feedback information and outcomes research. Orientation towards international clinical auditing is growing with the set up of multiple European initiatives like EURopEan CanCer Audit (EURECCA) or European Reference Networks (ERNs).[54, 55] International audits should be erected with unambiguous definitions, which is challenging due to existence of multiple national initiatives. The ICHOM colorectal cancer set is a good example of an internationally available compact set of outcome measurements composed by professionals and patients, which can be implemented in every hospital around the globe.[56] This does not only apply to audit data; all data in healthcare should be reusable for other parties in order to get the most out of it. The FAIR data principles act facilitated by a broad community of international stakeholders is a good example of the lobby for the reusability of data holdings for sharing knowledge around the globe.[57] FAIR data pleas for good data stewardship with findable, accessible, interoperable and reusable data.

The fast spread and implementation of (future) innovations necessitates reliable data registration systems. Clinical audits, connected to other data systems, should be part of such registration systems, connecting registered new techniques to clinical outcomes and PROMs. As not all changes can be extensively tested – i.e in RCT's – these registration systems could play a part in the safe implementation of new techniques and enabling timely intervention in the case of adverse events.[58] Connection to other data systems will give insight in the influence of clinical changes on healthcare costs and provide information on costs effectiveness of clinical innovations.[59] In this way clinical auditing could play a major role in providing value based healthcare.

There is an on-going transition from intervention-centered clinical audits to multidisciplinary, patient-centered clinical audits. The DSCA started as a monodisciplinary clinical audit in 2009, concentrated around the surgical resection for patients with colorectal cancer and is slowly changing to a multidisciplinary audit. Now gastro-enterologists, radiologists, radiotherapists and medical oncologists joined the audit

changed its name recently to the multidisciplinary Dutch ColoRectal Audit (DCRA). A full transition to a patient-centered audit is yet to be completed, as only patients with a resection for colorectal cancer are currently registered. In order to create the ultimate patient-centered clinical audit patients receiving only adjuvant treatment or no treatment at all should be included. Only then the audit will provide us with complete information on clinical care and outcomes without the current blind spot of patients that fall behind the inclusion criteria of the clinical audits. This will create the true basis for shared decision-making as patients can get all the information that is available on patients like them who underwent different types of treatment or no treatment. Moreover such a system would create a rich resource for further outcomes research bringing valuable new insights to the whole medical community.

An extensive patient-centered registration system will not be able without far-going connection between multiple data-systems. Again this underlines the importance of data that is recorded once at its source that is suitable for data connection and for re-use in different settings. In this way information is gathered with minimal registration burden for healthcare providers. The DCRA started recently with the inclusion of synoptic reporting of surgical resections in the clinical audit. Furthermore the structural input of pathology reports in the audit is already effectuated by a connection to PALGA (the national archive of pathology data).

END CONCLUSION

This thesis shows the value of outcomes research with clinical audit data. Real-world and real-time data of clinical audits complement RCT's due to large numbers of patients and the inclusion of high-risk patients. Furthermore they provide a basis for international comparison and valuable information on patients that are excluded from RCT's and underreported in literature. The evolution of clinical audits to patient-centered registrations and the connection with multiple other data registrations will lay the basis for a registration system that can be used for shared-decision making, providing value-based healthcare and further extensive outcomes research.

REFERENCES

1. Kolfschoten NE, Marang van de Mheen PJ, Gooiker GA, et al. Variation in casemix between hospitals treating colorectal cancer patients in the Netherlands. *Eur J Surg Oncol* 2011; 37(11):956-63.

2. Van Leersum NJ, Snijders HS, Henneman D, et al. The Dutch surgical colorectal audit. *Eur J Surg Oncol* 2013; 39(10):1063-70.

3. Walker K, Finan PJ, van der Meulen JH. Model for risk adjustment of postoperative mortality in patients with colorectal cancer. *Br J Surg* 2015; 102(3):269-80.

4. van Dishoeck AM, Lingsma HF, Mackenbach JP, et al. Random variation and rankability of hospitals using outcome indicators. *BMJ Qual Saf* 2011; 20(10):869-74.

5. Frankish H. UK league table reveals variations in mortality rate after heart surgery. *Lancet* 2001; 358(9295):1790.

6. Codman EA. The classic: A study in hospital efficiency: as demonstrated by the case report of first five years of private hospital. *Clin Orthop Relat Res* 2013; 471(6):1778-83.

7. nl.wikipedia.org.

8. Lui CW, Boyle FM, Wysocki AP, et al. How participation in surgical mortality audit impacts surgical practice. *BMC Surg* 2017; 17(1):42.

9. Kodeda K, Johansson R, Zar N, et al. Time trends, improvements and national auditing of rectal cancer management over an 18-year period. *Colorectal Dis* 2015; 17(9):O168-79.

10. Borowski DW, Kelly SB, Bradburn DM, et al. Impact of surgeon volume and specialization on short-term outcomes in colorectal cancer surgery. *Br J Surg* 2007; 94(7):880-9.

11. Ko CY, Chang JT, Chaudhry S, et al. Are high-volume surgeons and hospitals the most important predictors of in-hospital outcome for colon cancer resection? *Surgery* 2002; 132(2):268-73.

12. Schrag D, Panageas KS, Riedel E, et al. Hospital and surgeon procedure volume as predictors of outcome following rectal cancer resection. *Ann Surg* 2002; 236(5): 583-92.

13. Harling H, Bulow S, Moller LN, et al. Hospital volume and outcome of rectal cancer surgery in Denmark 1994-99. *Colorectal Dis* 2005; 7(1):90-5.

14. Harmon JW, Tang DG, Gordon TA, et al. Hospital volume can serve as a surrogate for surgeon volume for achieving excellent outcomes in colorectal resection. *Ann Surg* 1999; 230(3):404-11; discussion 411-3.

15. Iversen LH, Harling H, Laurberg S, et al. Influence of caseload and surgical speciality on outcome following surgery for colorectal cancer: a review of evidence. Part 1: short-term outcome. *Colorectal Dis* 2007; 9(1):28-37.

16. Birkmeyer JD, Finlayson EV, Birkmeyer CM. Volume standards for high-risk surgical procedures: potential benefits of the Leapfrog initiative. *Surgery* 2001; 130(3):415-22.

17. Wouters MW, Karim-Kos HE, le Cessie S, et al. Centralization of esophageal cancer surgery: does it improve clinical outcome? *Ann Surg Oncol* 2009; 16(7):1789-98.

18. Poeze M, Verbruggen JP, Brink PR. The relationship between the outcome of operatively treated calcaneal fractures and institutional fracture load. A systematic review of the literature. *J Bone Joint Surg Am* 2008; 90(5):1013-21.

19. de Wilde RF, Besselink MG, van der Tweel I, et al. Impact of nationwide centralization of pancreaticoduodenectomy on hospital mortality. *Br J Surg* 2012; 99(3):404-10.

20. In: Hewitt M, Petitti D, eds. Interpreting the Volume-Outcome Relationship in the Context of Cancer Care. Washington DC: 2001 by the National Academy of Sciences; 2001.

21. Normering chirurgische behandelingen 5.0. http://www.minimumkwaliteitsnormen.nl.

22. Birkmeyer JD, Dimick JB, Birkmeyer NJ. Measuring the quality of surgical care: structure, process, or outcomes? *J Am Coll Surg* 2004; 198(4):626-32.

23. Lee VS, Kawamoto K, Hess R, et al. Implementation of a Value-Driven Outcomes Program to Identify High Variability in Clinical Costs and Outcomes and Association With Reduced Cost and Improved Quality. *JAMA* 2016; 316(10):1061-72.

24. Porter ME. What is value in health care? *N Engl J Med* 2010; 363(26):2477-81.

25. Annual report 2013, the Dutch Surgical Colorectal Audit.

26. de Groot S, van der Linden N, Franken MG, et al. Balancing the Optimal and the Feasible: A Practical Guide for Setting Up Patient Registries for the Collection of Real-World Data for Health Care Decision Making Based on Dutch Experiences. *Value Health* 2017; 20(4):627-636.

27. J.C.B.H.M. Luijten dAJAB, dr. N. Wijffels, prof. dr. J.H.W. de Wilt. Een objectieve evaluatie van de DSCA-registratie. *NTvH* 2017; Jaargang 26(nummer 4).

28. McCarney R, Warner J, Iliffe S, et al. The Hawthorne Effect: a randomised, controlled trial. *BMC Med Res Methodol* 2007; 7:30.

29. Nagtegaal ID, Marijnen CA, Kranenbarg EK, et al. Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma: not one millimeter but two millimeters is the limit. *Am J Surg Pathol* 2002; 26(3):350-7.

30. Bernstein TE, Endreseth BH, Romundstad P, et al. Circumferential resection margin as a prognostic factor in rectal cancer. *Br J Surg* 2009; 96(11):1348-57.

31. Kapiteijn E, Kranenbarg EK, Steup WH, et al. Total mesorectal excision (TME) with or without preoperative radiotherapy in the treatment of primary rectal cancer. Prospective randomised trial with standard operative and histopathological techniques. Dutch ColoRectal Cancer Group. *Eur J Surg* 1999; 165(5):410-20.

32. van Gijn W, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *Lancet Oncol* 2011; 12(6):575-82.

33. van Leersum NJ, Snijders HS, Wouters MW, et al. Evaluating national practice of preoperative radiotherapy for rectal cancer based on clinical auditing. *Eur J Surg Oncol* 2013; 39(9):1000-6.

34. de Ridder M, Balm AJ, Baatenburg de Jong RJ, et al. Variation in head and neck cancer care in the Netherlands: A retrospective cohort evaluation of incidence, treatment and outcome. *Eur J Surg Oncol* 2017.

35. Vennix S, Pelzers L, Bouvy N, et al. Laparoscopic versus open total mesorectal excision for rectal cancer. *Cochrane Database Syst Rev* 2014; 4:CD005200.

36. Gangal HT, Gangal MH. Laparoscopic appendicectomy. *Endoscopy* 1987; 19(3):127-9.

37. Semm K. [Laparoscopy in gynecology]. *Geburtshilfe Frauenheilkd* 1967; 27(11):1029-42.

38. Trastulli S, Cirocchi R, Listorti C, et al. Laparoscopic vs open resection for rectal cancer: a meta-analysis of randomized clinical trials. *Colorectal Dis* 2012; 14(6):e277-96.

39. Ohtani H, Tamamori Y, Arimoto Y, et al. A meta-analysis of the short- and long-term results of randomized controlled trials that compared laparoscopy-assisted and open colectomy for colon cancer. *J Cancer* 2012; 3:49-57.

40. Taylor GW, Jayne DG, Brown SR, et al. Adhesions and incisional hernias following laparoscopic versus open surgery for colorectal cancer in the CLASICC trial. *Br J Surg* 2010; 97(1):70-8.

41. Burns EM, Currie A, Bottle A, et al. Minimal-access colorectal surgery is associated with fewer adhesion-related admissions than open surgery. *Br J Surg* 2013; 100(1):152-9.

42. Bartels SA, Vlug MS, Hollmann MW, et al. Small bowel obstruction, incisional hernia and survival after laparoscopic and open colonic resection (LAFA study). *Br J Surg* 2014; 101(9):1153-9.

43. Annual report 2016, the Dutch ColoRectal Audit.

44. Faraoni D, Schaefer ST. Randomized controlled trials vs. observational studies: why not just live together? *BMC Anesthesiol* 2016; 16(1):102.

45. Lim SW, Kim YJ, Kim HR. Laparoscopic surgery for colorectal cancer in patients over 80 years of age: the morbidity outcomes. *Ann Surg Treat Res* 2017; 92(6):423-428.

46. Moon SY, Kim S, Lee SY, et al. Laparoscopic surgery for patients with colorectal cancer produces better short-term outcomes with similar survival outcomes in elderly patients compared to open surgery. *Cancer Med* 2016; 5(6):1047-54.

47. Chesney T, Acuna SA. Do elderly patients have the most to gain from laparoscopic surgery? *Ann Med Surg (Lond)* 2015; 4(3):321-3.

48. Smith LE, Ko ST, Saclarides T, et al. Transanal endoscopic microsurgery. Initial registry results. *Dis Colon Rectum* 1996; 39(10 Suppl):S79-84.

49. Kolfschoten NE, van Leersum NJ, Gooiker GA, et al. Successful and safe introduction of laparoscopic colorectal cancer surgery in Dutch hospitals. *Ann Surg* 2013; 257(5):916-21.

50. Bennett CL, Stryker SJ, Ferreira MR, et al. The learning curve for laparoscopic colorectal surgery. Preliminary results from a prospective analysis of 1194 laparoscopic-assisted colectomies. *Arch Surg* 1997; 132(1):41-4; discussion 45.

51. Bonjer HJ, Deijen CL, Abis GA, et al. A randomized trial of laparoscopic versus open surgery for rectal cancer. *N Engl J Med* 2015; 372(14):1324-32.

52. Tanis PJ. Patient-tailored colorectal cancer care: a challenge within the context of evidence based guidelines. *Colorectal Dis* 2017; 19(6):521.

53. Ugolini G, Ghignone F, Zattoni D, et al. Personalized surgical management of colorectal cancer in elderly population. *World J Gastroenterol* 2014; 20(14):3762-77.

54. Breugom AJ, Bastiaannet E, Boelens PG, et al. Adjuvant chemotherapy and relative survival of patients with stage II colon cancer - A EURECCA international comparison between the Netherlands, Denmark, Sweden, England, Ireland, Belgium, and Lithuania. *Eur J Cancer* 2016; 63:110-7.

55. Parker S. The pooling of manpower and resources through the establishment of European reference networks and rare disease patient registries is a necessary area of collaboration for rare renal disorders. *Nephrol Dial Transplant* 2014; 29 Suppl 4: iv9-14.

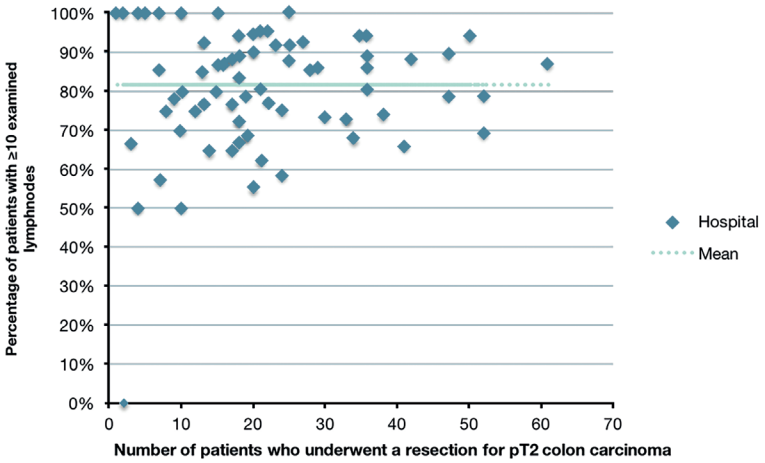
56. Zerillo JA, Schouwenburg MG, van Bommel ACM, et al. An International Collaborative Standardizing a Comprehensive Patient-Centered Outcomes Measurement Set for Colorectal Cancer. *JAMA Oncol* 2017; 3(5):686-694.

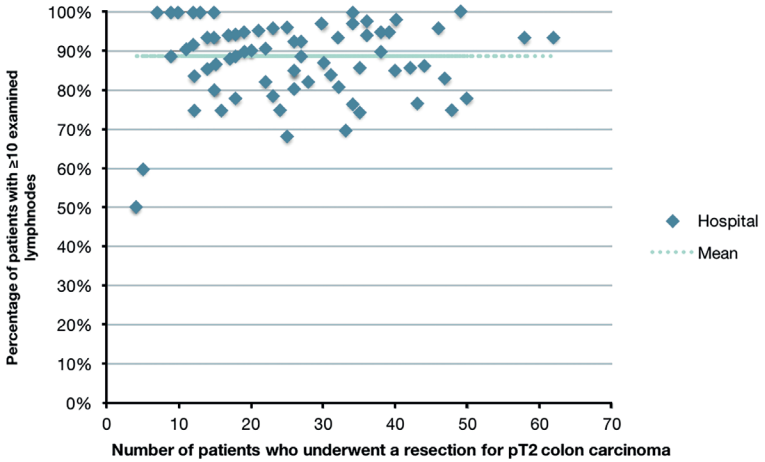
57. Wilkinson MD, Dumontier M, Aalbersberg IJ, et al. The FAIR Guiding Principles for scientific data management and stewardship. *Sci Data* 2016; 3:160018.

58. http://www.dica.nl/dbir.

59. Johansen NJ, Saunders CM. Value-Based Care in the Worldwide Battle Against Cancer. *Cureus* 2017; 9(2):e1039.

FIGURES


100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
10
20
30
40
50
60
70
Percentage of patients with ≥10 examined lymphnodes
Number of patients who underwent a resection for pT2 colon carcinoma
Hospital
Mean


100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
10
20
30
40
50
60
70
Percentage of patients with ≥10 examined lymphnodes
Number of patients who underwent a resection for pT2 colon carcinoma
Hospital
Mean

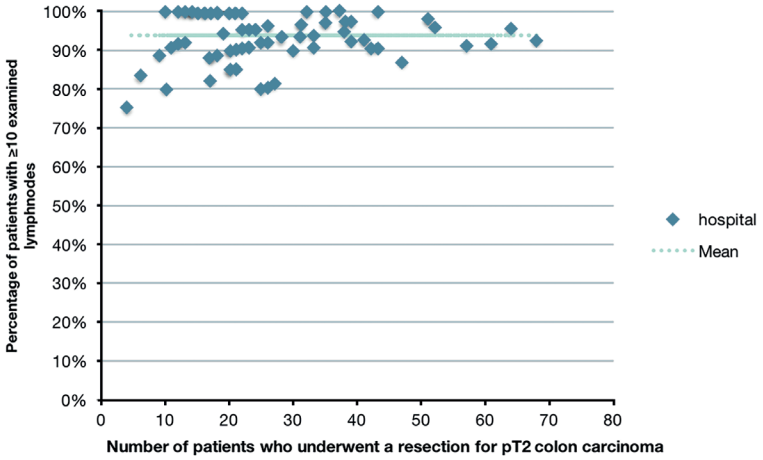


Figure 1a,b, and c. Patients with pT2 colon carcinoma with a minimum of 10 examined lymphnodes by a pathologist per hospital in 2009, 2011, and 2013.

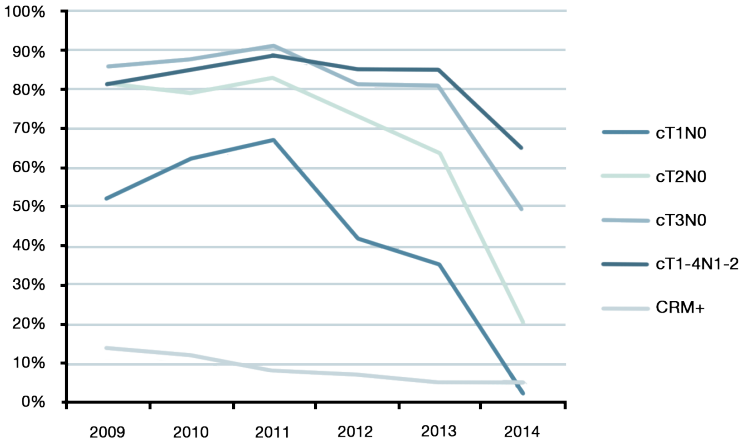


Figure 2. Use of preoperative radiotherapy for rectal cancer in the Netherlands for different clinical stages and the percentage of patients with an involved CRM (2009 – 2014).

Chapter 10

SUMMARY
SAMENVATTING

SUMMARY

Colorectal cancer is a major contributor to the health burden worldwide. As the heterogeneity of patients and tumor characteristics increases, there is a growing need for timely and reliable information that measures the quality of treatment in these populations; so-called real-world and real-time information. In 2009 the Dutch Colorectal Audit (DCRA), formerly known as the DSCA, started, which includes all patients undergoing a resection for colorectal cancer. Clinical audits are rich databases that provide a unique source of up to date information without the strict inclusion criteria that apply to randomised controlled trials (RCT's) and therefore complement the latter. This thesis describes the value of clinical audit data in colorectal cancer care and furthermore discusses the inherent statistical problems encountered in population studies.

Part I: Risk-adjustment in clinical auditing

When hospital outcomes are compared the validity of these comparisons is essential. Hospital outcomes are corrected for casemix. A casemix model is a tool designed to measure patient complexity by using a system of identifiable patient/tumor factors applied to a weighted scoring system in relation to the postoperative outcome. In this way the outcome of hospitals can be corrected for the complexity of their patient population for fairer comparisons. In oncology there is a trend towards centralisation of specific patient subgroups based on the rarity and complexity of their disease in so called referral hospitals. At this moment outcomes of non-referral and referral hospitals are corrected for casemix with the same casemix correction model. Chapter 2 shows that referral hospitals treat a significantly different population and that the effect of casemix variables on postoperative complicated course differs in weight between non-referral and referral hospitals. The study demonstrates that the currently used casemix model is mostly dictated by non-referral hospitals and thereby shows most resemblance to the non-referral hospitals. A casemix model specifically fitted to the referral population performs better then the currently used casemix model in the referral population. Whether it would be advisable to use two separate casemix models for non-referral and referral hospitals is not clear and further research is required.

Part II: Quality improvement in the Dutch colorectal cancer care

Changes in colorectal cancer surgery over the last years include amongst other things the implementation of minimum volume standards for colorectal cancer surgery and the start of the DCRA providing regular casemix corrected benchmarked feedback to the medical team. In order to detect areas that request further improvement audit data can be used for international comparison.

Chapter 3 analyses the effect of hospital volume on the outcome of circumferential resection margin (CRM) involvement. The CRM is a significant prognostic factor for local recurrence, distant metastasis and survival after rectal cancersurgery.

From 2014 the Dutch Society of Surgery stated a compulsory minimal volume standard of 20 rectal cancer resections per hospital, following the multiple publications on the positive relationship between volume and postoperative outcomes. This chapter shows an independent and significant relationship between volume (<20) and CRM and demonstrates that patients treated in low-volume hospitals had a 1.5-fold higher risk of CRM involvement than patients operated in high-volume hospitals. Therefore it supports the minimal annual volume standard for rectal cancer surgery, leading to better oncological outcomes, attributing to a better prognosis for these patients.

Chapter 4 shows that there has been a dramatic improvement in CRM reporting and a major decrease of CRM involvement after rectal cancer surgery since the start of the DCRA. Population based studies and other national audits on rectal cancer confirmed that the CRM, as an important measure for the quality of surgical resection, was often lacking in the pathology report. This study describes that the mean percentage of patients with a reported CRM increased from 52.7 to 94.2 percent (2009-2013) and interhospital variation decreased. The percentage of patients with CRM involvement decreased from 14.2 to 5.6 percent. Improvement in CRM reporting is almost exclusively attributable to the national audit, and the multivariable analysis included in this study also suggests that the DSCA was a driving force behind the significant increase in tumor free resection margins.

International comparison of audit data can identify differences in treatment modalities between countries. The rate of preoperative

radiotherapy (RT) for rectal cancer in the Netherlands has been the highest among European countries. Data from the national audit showed significant overtreatment of early stage rectal cancers, which encouraged the revision of the national guideline on rectal cancer treatment. This revision specifically focussed on the indication for RT and MRI criteria to evaluate mesorectal lymph nodes in order to reduce overtreatment for patients with false positive cN1-2 disease. Chapter 5 evaluates the implementation of the new guideline in the Netherlands and determines the diagnostic accuracy of preoperative MRI for nodal staging. The revised national guideline on colorectal cancer was rapidly implemented in the Netherlands with a substantial decrease in RT use for low risk resectable rectal cancer. The specificity of MRI for N staging increased, resulting in a decrease of false-positive results in 2014, leading to fewer patients with low-risk rectal cancer undergoing RT. It is believed that the national clinical audit has played an important role in the observed changes in clinical practice. The rapid implementation of the revised national guideline on colorectal cancer is a good example of the usage of audit data to instigate national practice change and to check its implementation afterwards.

Part III: Data from clinical audits as a supplement to RCT's

The third part of this thesis shows how clinical audit data is used for clinically relevant research. Due to the absence of preselected populations and large numbers of patients, clinical audits can analyse research questions that are unlikely to be answered in RCTs due to insufficient power. Furthermore it provides up to date information on the present-day quality of care and is able to evaluate care of patients that are underreported in literature.

Chapter 6 analyses the rate of postoperative morbidity and mortality after open versus laparoscopic surgery for colorectal cancer in specific subgroups of patients, including patients with a high preoperative risk for adverse outcomes. Several meta-analyses of RCTs showed a trend towards lower postoperative mortality in favour of laparoscopic resection, but failed to reach statistical significance. The inclusion of relatively low risk patients and the lack of sufficient power are probably responsible for that. This study demonstrates a reduced mortality risk after elective LR compared to OR in patients with non-locally advanced, non-metastasized colorectal cancer. Especially elderly frail

patients (a priori high-risk patients) seem to benefit because of reduced cardiopulmonary complications. These findings support widespread implementation of LR for colorectal cancer, also in patients at high operative risk.

LR for rectal cancer has been rapidly and safely implemented in the Netherlands, increasing to 83% of all rectal cancer patients in 2015. The results of older randomised trials, i.e. COLOR II trial, are commonly quoted and as LS has a steep learning curve one might question whether the COLOR II data are still representative for current national performance. Chapter 7 analyses current oncological quality of laparoscopic surgery for rectal cancer in the Netherlands by performing a matched comparison of data from the DCRA and the COLOR II trial, using the CRM as main quality indicator. This study demonstrates improved oncological quality of laparoscopic surgery for rectal cancer in the Netherlands with a significantly lower percentage of CRM involvement, higher mean harvested lymph nodes and lower admission time, implicating that LS has been successfully implemented in the Netherlands. Secondly it provides an accurate representation of national performance regarding the laparoscopic resection of rectal carcinoma.

Chapter 8 shows the outcomes of patients with locally advanced colon cancer (LACC) in the Netherlands. The curative intent treatment for these patients is a complete resection of the tumor (R0 resection) followed by adjuvant systemic chemotherapy. An incomplete resection has a negative prognostic impact on long-term outcomes. Treatment of LACC is still an underexposed area in the field of colorectal cancer care and is not centralised in expert centres. Our study demonstrates a lower R0 resection proportion for patients with LACC and a higher risk of postoperative complications and mortality as compared to patients with less invasive colon cancer. Data from literature and our findings suggest room for improvement for patients with LACC. Improvement might be expected from optimized preoperative imaging, routine MDT discussions, bridging to surgery in emergency setting, and further specialisation and centralisation of care. Optimized use of neo-adjuvant treatment strategies based on already available and upcoming evidence is likely to result in a better margin status and related to that a better long-term prognosis.

SAMENVATTING

Darmkanker draagt in belangrijke mate bij aan de wereldwijde ziektelast. Met de toenemende heterogeniteit van patiënt- en tumorkarakteristieken is er meer en meer behoefte aan tijdige en betrouwbare informatie die de kwaliteit van de behandeling in verschillende populaties meet en terugkoppelt; zogenaamde real-world en real-time informatie. In 2009 is de Dutch Colorectal Audit (DCRA), eerder bekend als de Dutch Surgical Colorectal Audit (DSCA), opgericht, die alle patiënten includeert die een resectie voor darmkanker ondergaan. Clinical audits zijn waardevolle databases die unieke actuele informatie bevatten omdat zij niet de strikte inclusiecriteria hanteren die van toepassing zijn op gerandomiseerd onderzoek (RCT's). Hierdoor vormt audit data een belangrijke aanvulling op gerandomiseerd onderzoek. Dit proefschrift beschrijft de waarde van audit data in de darmkankerzorg en bespreekt daarnaast de inherente statistische problemen die populatie studies met zich mee brengen.

Deel I: Correctie voor zorgzwaarte in clinical audits

Bij het vergelijken van ziekenhuisuitkomsten is de validiteit van deze vergelijking van essentieel belang. Ziekenhuisuitkomsten worden gecorrigeerd voor casemix, de zorgzwaarte van een patiëntenpopulatie. Een casemix model is een instrument dat de complexiteit van een patiëntenpopulatie berekend op basis van een gewogen scoringssysteem bestaande uit identificeerbare patiënt- en tumorkarakteristieken, waarvan het gewicht in relatie tot postoperatieve uitkomst gemeten wordt. Op deze manier kan de uitkomst van ziekenhuizen gecorrigeerd worden voor de complexiteit van hun patiëntenpopulatie, wat leidt tot eerlijkere vergelijkingen. In de oncologie is er centralisatie gaande van specifieke subgroepen patiënten in zogenaamde verwijsziekenhuizen op basis van de zeldzaamheid en complexiteit van de ziekte. Op dit moment worden resultaten van niet-verwijs en verwijsziekenhuizen gecorrigeerd voor casemix in hetzelfde casemix correctie model. Hoofdstuk 2 laat zien dat verwijsziekenhuizen een significant verschillende populatie behandelen en dat het effect van casemixvariabelen op de uitkomst "postoperatief gecompliceerd beloop" verschilt tussen niet-verwijs en verwijsziekenhuizen. Uit onze studie blijkt dat het casemixmodel dat momenteel gebruikt wordt, overwegend gedicteerd wordt door

de niet-verwijspopulatie en dat het gewicht van de variabelen in het model in relatie tot de uitkomst het meest lijken op de situatie in niet-verwijsziekenhuizen. Een casemixmodel dat specifiek op de verwijspopulatie is gefit, presteert beter dan het momenteel gebruikte standaard casemixmodel in de verwijs populatie. Of het raadzaam is om twee aparte casemixmodellen te gebruiken voor het terugkoppelen van de gecorrigeerde uitkomsten van niet-verwijs en verwijsziekenhuizen valt uit deze studie niet te concluderen; verder onderzoek is nodig.

Deel II: Kwaliteitsverbetering in de Nederlandse darmkankerzorg

In de afgelopen jaren heeft de darmkankerchirurgie in Nederland veranderingen doorgemaakt; zo is er een volumenorm voor darmkanker resecties geïmplementeerd en is de DCRA van start gegaan die zorgprofessionals voorziet van tijdige en casemix gecorrigeerde gebenchmarkte terugkoppelingen. Verder wordt in deel II besproken hoe er, door middel van internationale vergelijking van audit data, gebieden in de zorg geïdentificeerd worden die aandacht behoeven.

Hoofdstuk 3 analyseert het effect van ziekenhuisvolume op een oncologische uitkomst; de circumferentiële resectie marge (CRM). De CRM is een significant voorspellende factor voor lokaal recidief, afstandsmetastasen en overleving na een resectie voor rectumcarcinoom. Vanaf 2014 stelde de Nederlandse Vereniging voor Heelkunde (NVvH) een verplicht minimaal jaarlijks volume van 20 rectumcarcinoom resecties per ziekenhuis in, op basis van wetenschappelijke studies die een positieve invloed van een hoger ziekenhuisvolume op postoperatieve resultaten aantoonden. Dit hoofdstuk toont een onafhankelijke en significante relatie tussen laag volume (<20) en een positieve CRM en beschrijft een 1,5 keer hoger risico op een positieve CRM voor patiënten die in een laag volume ziekenhuis zijn geopereerd vergeleken met zij die werden geopereerd in een hoog volume ziekenhuis. Dit onderzoek ondersteunt daarmee de volumenorm voor de chirurgische behandeling van rectumcarcinoom aangezien het leidt tot betere oncologische resultaten, wat samenhangt met een betere prognose voor de patiënt.

Hoofdstuk 4 toont de verbetering van het percentage gerapporteerde CRM en de begeleidende afname van het percentage positieve CRM na resectie van rectumcarcinoom na de start van de DCRA in 2009.

Populatiestudies en andere nationale audits toonden ook dat de CRM, een belangrijke maat voor de oncologische kwaliteit van de rectumresectie, vaak ontbreekt in het pathologie rapport. Dit onderzoek beschrijft dat het gemiddelde percentage patiënten met een gerapporteerde CRM in de DCRA steeg van 52,7 naar 94,2 procent (2009-2013) en dat de variatie tussen ziekenhuizen op het gebied van deze rapportage is afgenomen. Het percentage patiënten met een positieve CRM daalde van 14,2 tot 5,6 procent in diezelfde jaren. De verbetering van CRM rapportage is bijna uitsluitend toe te schrijven aan de nationale audit. Verder suggereert de multivariabele analyse in deze studie dat de audit een drijvende kracht is geweest achter de significante afname van het percentage patiënten met een positieve CRM.

Internationale vergelijkingen van audit data kunnen verschillen in behandelingsstrategieën tussen landen inzichtelijk maken. Zo is gebleken dat het percentage preoperatieve (chemo)radiotherapie voor patiënten met rectumcarcinoom in Nederland hoog was in vergelijking met andere Europese landen. Gegevens uit de nationale audit toonden een substantiële overbehandeling van laag stadium (laag risico) rectumcarcinoom. Dit heeft ertoe geleid dat de nationale richtlijn colorectaal carcinoom is herzien. De gereviseerde versie heeft met name aandacht besteed aan de indicatie voor preoperatieve (chemo) radiotherapie. Tevens zijn MRI criteria om mesorectale lymfeklieren te beoordelen aangepast om daarmee de overbehandeling te verminderen van patiënten gediagnosticeerd met vals positieve cN1-2 ziekte. Hoofdstuk 5 evalueert de implementatie van de gereviseerde richtlijn in Nederland en analyseert de diagnostische nauwkeurigheid van de preoperatieve MRI voor het bepalen van het N-stadium. De gereviseerde nationale richtlijn colorectaal carcinoom is snel geïmplementeerd in Nederland en heeft geleid tot een aanzienlijke daling van het aantal patiënten dat preoperatieve radiotherapie ondergaat voor laag stadium rectumcarcinoom. De specificiteit van MRI voor N stagering is toegenomen, wat heeft geresulteerd in een daling van patiënten met vals positieve cN1-2 ziekte in 2014, wat heeft geleid tot minder patiënten met laag risico rectumcarcinoom dat onnodig preoperatieve radiotherapie onderging. De nationale audit heeft naar alle waarschijnlijkheid een belangrijke rol gespeeld in de waargenomen veranderingen in de klinische praktijk. De snelle implementatie van

de gereviseerde richtlijn is een goed voorbeeld van het gebruik van de audit om nationale beleidswijzigingen in te zetten en de implementatie ervan voorts te controleren.

Deel III: Gegevens uit clinical audits als aanvulling op RCT's

Het derde deel van dit proefschrift toont hoe audit data gebruikt kan worden als aanvulling op gerandomiseerd onderzoek. Zo kan je met audit data, door de afwezigheid van voorgeselecteerde patiënten populaties en grote aantallen patiënten, vraagstukken analyseren die niet beantwoord kunnen worden met RCT's vanwege een tekort aan statistische power. De audit maakt verder de actuele kwaliteit van zorg inzichtelijk en biedt daarnaast informatie over patiënten populaties waarover normaliter weinig gerapporteerd wordt in literatuur.

Hoofdstuk 6 vergelijkt postoperatieve morbiditeit en mortaliteit tussen open en laparoscopische resectie voor colorectaal carcinoom in gestratificeerde subgroepen patiënten, waaronder hoog-risico patiënten. Verschillende meta-analyses van RCT's toonden een trend van lagere postoperatieve mortaliteit in het voordeel van de laparoscopische resectie, deze resultaten waren echter niet statistisch significant. Dit zou verklaard kunnen worden door de inclusie van relatief laag risicopatiënten en het gebrek aan statistische power. Deze studie toont een lagere postoperatieve mortaliteit na electieve laparoscopische resecties in vergelijking met een open resectie voor patiënten met niet lokaal uitgebreid en niet gemetastaseerd colorectaal carcinoom. Ook oudere kwetsbare patiënten (a priori hoog-risico patiënten) lijken te profiteren door verminderde cardiopulmonale complicaties. Deze bevindingen ondersteunen de wijdverspreide implementatie van laparoscopische chirurgie voor colorectaal carcinoom, ook voor hoog-risico patiënten.

Laparoscopische chirurgie voor rectumcarcinoom is vlot en veilig geïmplementeerd in Nederland. Het percentage patiënten met een rectumcarcinoom dat in 2015 een laparoscopische resectie onderging is naar 83 procent gestegen. De postoperatieve resultaten van oudere gerandomiseerde studies, zoals de COLOR II trial, worden nog vaak geciteerd. Aangezien laparoscopische chirurgie een steile leercurve kent zou men zich kunnen afvragen of die data nog steeds representatief is voor de huidige nationale resultaten. Hoofdstuk 7

analyseert de huidige oncologische kwaliteit van laparoscopische resecties voor rectumcarcinoom in Nederland door middel van een gematchte vergelijking tussen de populatie van de DCRA en de COLOR II trial, met de CRM als primaire oncologische uitkomst. De studie toont de succesvolle implementatie van laparoscopische chirurgie voor rectumcarcinoom in Nederland met een significant lager percentage positieve CRM's, een hoger gemiddeld aantal onderzochte lymfeklieren en lagere totale opnametijd. Het artikel geeft met behulp van audit data een accurate weergave van de huidige staat van de oncologische kwaliteit van resecties voor rectumcarcinoom.

Hoofdstuk 8 toont de resultaten van patiënten met lokaal uitgebreid coloncarcinoom (LACC) in Nederland. De in opzet curatieve behandeling bestaat voor deze patiënten uit een volledige resectie van de tumor (R0 resectie) gevolgd door adjuvante systemische chemotherapie. Een niet radicale resectie heeft een negatieve prognostische impact op de lange termijn resultaten van deze patiënten. Behandeling van LACC is een nog onderbelicht gebied in de colorectale kankerzorg en is niet gecentraliseerd in expertcentra. Onze studie toont een lager percentage radicale resecties bij patiënten met LACC en een hoger risico op postoperatieve complicaties en mortaliteit in vergelijking met patiënten met minder vergevorderde dikke darmkanker. Deze resultaten tezamen met gegevens uit de literatuur suggereren ruimte voor verbetering van de behandeling van patiënten met LACC. Geoptimaliseerde preoperatieve beeldvorming, standaard multidisciplinair overleg, strategieën ter overbrugging in de spoedsetting tot aan de definitieve resectie, en verdere specialisatie en centralisatie van zorg zou de zorg voor deze patiënten kunnen verbeteren. Daarnaast kan op basis van huidige kennis en aanstaand onderzoek het gebruik van neoadjuvante behandelingsstrategieën geoptimaliseerd worden wat naar alle waarschijnlijkheid zal resulteren in minder irradicale resecties en daarmee een betere langetermijnprognose.

Chapter 11

CURRICULUM VITAE
AUTHOR'S LIST OF PUBLICATIONS
ACKNOWLEDGEMENTS

CURRICULUM VITAE

Lieke Gietelink was born on the ninth of July 1984 in Utrecht, the Netherlands. In 2002 she finished her secondary school at Stedelijk Gymnasium in Breda. With a gynaecologist and nurse as parents, her affection for health care started early. In 2003 she got accepted to Amsterdam University Medical School. During her studies Lieke worked with prof. Maher in Brisbane, Australia, who introduced her to scientific research. Before obtaining her medical degree in 2010 she worked in the Surgical and the Gynaecological and Obstetrics department of a rural hospital in Hlabisa, South Africa.

Lieke obtained clinical experience as a resident not in training at the Gynaecology and Obstetrics department of former Kennemer Gasthuis (Spaarne Gasthuis) and at the Urology department of Diaconessenhuis in Leiden.

Her close friend Heleen Snijders introduced her to the Dutch Institute of Clinical Auditing (DICA), where she started a PhD project under the supervision of professor R.A.E.M. Tollenaar. At DICA she combined 3 years of scientific research with the data of the Dutch ColoRectal Audit (DCRA) with daily work for multiple national audits, especially the DCRA and the Dutch Gynaecological Oncology Audit (DGOA). With her colleagues she cycled Tour for Life, a bicycle benefit for cancer research.

In 2016 she started her postgraduate training in urology with two years of general surgical training in Zaans Medical Center under program director dr. den Boer. In January 2018 she will start her academic part of urology training in VU Medical Center guided by dr. Nieuwenhuijzen.

AUTHOR'S LIST OF PUBLICATIONS

Changes in nationwide use of preoperative radiotherapy for rectal cancer after revision of the national colorectal cancer guideline. Gietelink L, Wouters MWJM, Marijnen CAM, van Groningen J, van Leersum N, Beets-Tan RGH, Tollenaar RAEM, Tanis PJ; Dutch Surgical Colorectal Cancer Audit Group. Eur J Surg Oncol. 2017 Jul;43(7):1297-1303.

Locally Advanced Colon Cancer: Evaluation of Current Clinical Practice and Treatment Outcomes at the Population Level. Klaver CE, Gietelink L, Bemelman WA, Wouters MW, Wiggers T, Tollenaar RA, Tanis PJ; Dutch Surgical Colorectal Audit Group. J Natl Compr Canc Netw. 2017 Feb;15(2):181-190.

Reduced 30-Day Mortality After Laparoscopic Colorectal Cancer Surgery: A Population Based Study From the Dutch Surgical Colorectal Audit (DSCA). Gietelink L, Wouters MW, Bemelman WA, Dekker JW, Tollenaar RA, Tanis PJ; Dutch Surgical Colorectal Cancer Audit Group. Ann Surg. 2016 Jul;264(1):135-40.

Comparison of a low Hartmann's procedure with low colorectal anastomosis with and without defunctioning ileostomy after radiotherapy for rectal cancer: results from a national registry. Jonker FH, Tanis PJ, Coene PP, Gietelink L, van der Harst E; Dutch Surgical Colorectal Audit Group. Colorectal Dis. 2016 Aug;18(8):785-92.

Nationwide Outcomes Measurement in Colorectal Cancer Surgery: Improving Quality and Reducing Costs. Govaert JA, van Dijk WA, Fiocco M, Scheffer AC, Gietelink L, Wouters MW, Tollenaar RA. J Am Coll Surg. 2016 Jan;222(1):19-29.e2.

Reduced Circumferential Resection Margin Involvement in Rectal Cancer Surgery: Results of the Dutch Surgical Colorectal Audit. Gietelink L, Wouters MW, Tanis PJ, Deken MM, Ten Berge MG, Tollenaar RA, van Krieken JH, de Noo ME; Dutch Surgical Colorectal Cancer Audit Group. J Natl Compr Canc Netw. 2015 Sep;13(9):1111-9.

The Influence of Hospital Volume on Circumferential Resection Margin Involvement: Results of the Dutch Surgical Colorectal Audit. Gietelink L, Henneman D, van Leersum NJ, de Noo M, Manusama E, Tanis PJ, Tollenaar RA, Wouters MW; Dutch Surgical Colorectal Cancer Audit Group. Ann Surg. 2016 Apr;263(4):745-50.

The introduction of mid-urethral slings: an evaluation of literature. Hogewoning CR, Gietelink L, Pelger RC, Hogewoning CJ, Bekker MD, Elzevier HW. Int Urogynecol J. 2015 Feb;26(2):229-34. doi: 10.1007/s00192-014-2488-5. Epub 2014 Aug 21. Review. Erratum in: Int Urogynecol J. 2015 Sep;26(9):1403-4.

Renal ultrasound to detect hydronephrosis: a need for routine imaging after radical hysterectomy? Hazewinkel MH, Gietelink L, van der Velden J, Burger MP, Stoker J, Roovers JP. Gynecol Oncol. 2012 Jan;124(1):83-6.

Anterior vaginal mesh sacrospinous hysteropexy and posterior fascial plication for anterior compartment dominated uterovaginal prolapse. Feiner B, Gietelink L, Maher C. Int Urogynecol J. 2010 Feb;21(2):203-8.

ACKNOWLEDGEMENTS

A large number of people have contributed to this thesis.
Thank you all.

A special thanks goes out to:

Heleen Snijders
My promotor; professor Rob Tollenaar
My co-promotores; Michel Wouters and Pieter Tanis
All my colleagues at DICA and LUMC
All my colleagues at the Department of Surgery at Zaans Medical Center
Dutch colorectal surgeons for patient registration in DCRA
All my co-authors
Tara Kinneging for the design
My dear DICA friends
My paranymphs
My parents and grandparents