Evaluating and Improving Quality of Colorectal Cancer Care

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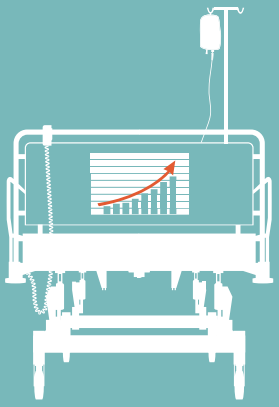

Chapter 1

Introduction and outline of this thesis

As health is considered one of the greatest goods for individuals and society as a whole, and the costs of the health care industry are growing fast, it is not surprising that quality and value of care is high on the political agenda these days. The ageing population, patients' increasing expectations, rapid innovations and growing costs are challenging the long-term sustainability of our health care system. All stakeholders in care have the same objective: higher quality and lower costs. This translates in a growing need for transparency of reliable information on (differences in) quality of care enabling patients to select their hospital of choice, health care insurers to contract more selectively and policy makers to monitor the value of care. Consequently, professionals become more accountable for their results and have an increased ability to improve their practice.

In 1999, the International Health Institute published an alarming report regarding the difference between what we consider good health care and what people actually receive[1]. There is a large difference in outcomes and care patterns between providers, indicating room for improvement. Six aims for quality improvement were set regarding patient safety, effectiveness, patient-centeredness, timing, efficiency and equitability.

Improving quality of care is a major challenge and demands effort and commitment of all professionals involved. Rapid innovations require continuous re-evaluation of what represents 'optimal care' and consequently adjusting clinical practice accordingly. Besides, also in daily routines, there may be room for improvement, leading to a reduction in preventable morbidity, more patient satisfaction and lower costs. How to get towards the best possible care?

Part I: Clinical auditing to evaluate and improve the quality of care

The idea of a hospital register to help doctors improve the quality of care was first discussed by the British doctor Sir Thomas Percival (1803): "*By the adoption of the register, physicians and surgeons would obtain clearer insight into the comparative success of their hospital and private practice; and would be incited to a diligent investigation of the causes of such difference*"[2]. Also, dr. Ernest Codman (1869–1940), an American surgeon, advocated clinical registries as he stated that evaluating outcomes of care in every patient is an intrinsic need and responsibility of every health care professional: "*Every hospital should follow every patient it treats long enough to determine whether the treatment has been successful, and then to inquire 'if not, why not' with a view to preventing similar failures in the future*"[3]. The systematic gathering of follow-up data provides the opportunity to identify errors and areas for improvement. Doctor Codmans' so-called end-result idea is considered the founder of modern clinical audits that have emerged internationally since the end of the 20th century[4].

A clinical audit is typically a continuous plan-do-check-act cycle: "a process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and the implementation of change"[5].

Following international examples of successful clinical audits, in 2009 Dutch colorectal surgeons developed the Dutch Surgical Colorectal Audit (DSCA)[6]. This nationwide clinical audit was initiated with the purpose to meet both the professional need to evaluate and benchmark quality of colorectal cancer care and simultaneously to provide reliable data for the public demand for transparency on quality of care. In chapter II, we reviewed whether international clinical audits have shown to improve outcomes of care and whether the implementation of improvement

projects focussing on specific outcomes have an additional effect. In chapter III, the initiation of the DSCA and its merits are elicited. Also, preliminary results after three years of auditing are shown.

Part II: Challenges in colorectal cancer care

Colorectal cancer is currently the third most common type of cancer worldwide and second in the Netherlands with 13,000 cases per year[7]. It is often a lifestyle disease or develops due to processes co-occurring ageing and its incidence is increasing every year (expected 20,000 cases by 2020)[8]. Treatment of patients with colorectal cancer typically involves cooperation of many different medical specialties. Due to rapid consecutive innovations and new insights, treatment of colorectal cancer increasingly demands specialisation of the doctor, multidisciplinary team and treatment facility, as up-to-date knowledge, experience and an adequate infrastructure are all necessary to provide optimal care.

Treatment of colorectal cancer is associated with substantial short- and long-term morbidity and mortality[9]. With an average age at time of diagnosis of 70 years, most patients are elderly and have one or more co-existent diseases. Treatment of colorectal cancer in these patients is even more challenging because of polypharmacy and decreased compensating mechanisms, which affect treatment effectiveness, risk of side effects and complications[10-12]. A high age and the presence of comorbidity are associated with worse short- and long-term outcomes. In chapter IV, the prevalence of co-morbidity and multi-morbidity and time trends of specific co-morbid diseases in colorectal cancer patients are described.

Another challenge in treating colorectal cancer is that patients may not present with one but multiple (hidden) tumours. Synchronous colorectal cancer may occur by accident or due to genetic disorders

or in the presence of ulcerative diseases (Crohns' disease and colitis ulcerosa)[13]. Identifying a secondary or even multiple other tumours before treatment is essential, as it may influence treatment strategy and especially the extent of surgery. A standard preoperative colonoscopy is performed to view the entire colon for tumour localisation and potential synchronous tumours. However, in acute circumstances or in case of an obstructive primary tumour, a (complete) colonoscopy may not be feasible preoperatively. Overlooking a synchronous tumour may lead to unintended reoperations or worse oncological outcomes[14]. The incidence of synchronous tumours and its effect on treatment and short-term postoperative outcomes is described in chapter V.

Part III Clinical decision-making and treatment outcomes

Optimal quality of care is personalised care: providing the right care, to the right patient, in the right setting at the right time[15]. The indicated diagnostic work-up and treatment are explicated separately for colon and rectal cancer in evidence-based guidelines[8]. Evidence based guidelines support medical decision-making. However, selecting patients for specific treatments is based on an individual situation. Herein, many variables including tumour characteristics, patients' condition, medical history and patient preferences should be taken into account. Weighing of possible advantages of (combinations of) treatments against risks for complications, short- and long-term functional and oncological outcomes and quality of life is therefore daily practice in colorectal cancer care.

Indication setting in preoperative radiotherapy

The optimal criteria for selection of patients with rectal cancer who would benefit from radiotherapy are increasingly debated and vary largely internationally[16,17]. Local recurrence has long been a frequent complication, leading to severe pain, morbidity and poor prognosis[18]. In

1987, the Swedish Rectal Cancer Trial showed that adding short-course preoperative radiotherapy to surgical resection of rectal cancer improved local recurrence rates from 27% to 11% compared to surgery alone[19] and increased 5-year overall survival from 48 to 58%. In the Dutch TME trial, a risk reduction from 11 to 5.6% was seen in patients receiving radiotherapy in addition to TME surgery[20]. Consequently, preoperative radiotherapy became standard treatment for rectal cancer. However, newer reports showed no benefit for 5-year overall survival and unfavourable long-term functional outcomes after radiotherapy[21,22]. Also, the absolute risk reduction of local recurrence in stage I and II rectal cancer appears limited[21]. Recently, major advances in imaging techniques have been accomplished. Standard use of high resolution MRI improved preoperative tumour staging enabling more tailored application of preoperative radiotherapy[23]. The ESMO guidelines (2010) recommended therefore that radiotherapy could be omitted in cT1-3aN0[24]. However, Dutch guidelines (2008-2013) still advised radiotherapy in all cT2-4 tumours[8]. In chapter VI, the use of preoperative radiotherapy in the Netherlands in 2011-2012 is evaluated and discussed. Were Dutch guidelines followed strictly or was the indication for radiotherapy already changing due to these new insights and international examples of decreased use?

Prognosis of different surgical techniques

At the time preoperative radiotherapy was introduced, also the influence of the circumferential resection margin (CRM) status and the quality of the resected specimen on local recurrence risks became better understood[25]. This led to the introduction of the standardized total mesorectal excision (TME) as opposed to the traditional blunt dissection of the rectum. Also, the role of the pathologist for quality assurance of surgical dissection became more appreciated. In 1991, the Dutch TME trial implemented the technique of TME surgery as a new standard in the Netherlands and trained surgeons and pathologists accordingly[20].

The type of resection, e.g. sphincter-preserving surgery or not, is based on tumour location, size, local involvement and preoperative continence. Low anterior resection (LAR) is often preferred over abdominoperineal excision (APE) by both doctors and patients, not only because of sphincter preservation, but because APE has widely been reported in association with a higher risk of CRM involvement and local recurrence[26]. Since APE is mainly performed in advanced and low rectal tumours in contrast to (often) smaller and more proximal tumours in LAR, the question is whether the more challenging circumstances or the APE technique itself underlies these inferior outcomes. Moreover, the introduction of better preoperative imaging by MRI and new extended APE techniques may help to acquire better resection planes today[27,28]. Is the APE currently associated with worse outcomes than LAR? In chapter VII, the LAR and APE are compared for CRM involvement with adjustment for differences in patient and tumour characteristics.

Defunctioning stoma

Anastomotic leakage is a feared complication in colorectal cancer surgery, as it is associated with high morbidity and mortality[29]. Although certain patient and tumour related factors associated with a higher risk of anastomotic leakage have been identified, it is still very challenging to predict this for an individual. Fragile patients, male gender and low anastomosis are risk factors, but leakage can occur in low-risk patients as well[30]. The construction of a defunctioning stoma proximal to an anastomosis has shown to reduce the severity and consequences of anastomotic leakage[31]. A defunctioning stoma is however burdensome for the patient, both socially and functional, and is associated with stoma related complications and reinterventions[32]. However, there is a growing use of defunctioning stomas in the Netherlands, without a decrease in anastomotic leakage rates[33]. So whether or not to construct a defunc-

tioning stoma? Clear guidelines on who should and should not receive a defunctioning stoma do not exist. Therefore, variation in risk selection strategies may exist between surgeons. Is a high tendency towards stoma construction a good strategy for preventing anastomotic leakage and mortality? Or can good results also be acquired with less stomas? In chapter VIII, variation between hospitals in the tendency towards stoma construction is evaluated and how these different strategies are associated with anastomotic leakage and mortality rates.

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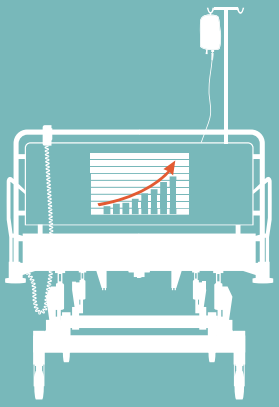
Part I

Clinical auditing to evaluate and improve the quality of care



Chapter 2

‘Clinical auditing’, a novel tool for quality assessment in surgical oncology

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ABSTRACT

Objective: To determine whether systematic audit and feedback of information about the process and outcomes improve the quality of surgical care.

Design: Systematic review.

Method: Embase, Pubmed, and Web of Science databases were searched for publications on 'quality assessment' and 'surgery'. The references of the publications found were examined as well. Publications were included in the review if the effect of auditing on the quality of surgical care had been investigated.

Results: In the databases 2415 publications were found. After selection, 28 publications describing the effect of auditing, whether or not combined with a quality improvement project, on guideline adherence or indications of outcomes of care were included. In 21 studies, a statistically significant positive effect of auditing was reported. In 5 studies a positive effect was found, but this was either not significant or statistical significance was not determined. In 2 studies no effect was observed. 5 studies compared the combination of auditing with a quality improvement project with auditing alone; 4 of these reported an additional effect of the quality improvement project.

Conclusion: Audit and feedback of quality information seem to have a positive effect on the quality of surgical care. The use of quality information from audits for the purpose of a quality improvement project can enhance the positive effect of the audit.

INTRODUCTION

'Clinical Auditing' is a relatively new quality instrument in the Dutch healthcare system. Where regular evaluation of processes and end products is common in most branches, this is not the case for healthcare. In 1915, dr. Ernest Amory Codman, surgeon at Harvard University, advocated implementation of auditing, 'the systematic and critical analysis of quality of care delivered, including the process of diagnosis, treatment and outcomes of care, by those who deliver it', in medical practice. However, his visionary ideas were not appreciated by his colleagues. Only a century later, the use of auditing for quality improvement, transparency and accountability was internationally appreciated. Clinical auditing is most commonly used in surgical oncology, as in this specialty, the relation between intervention and outcomes, or quality and costs is most obvious: a complication can result in repeated investigations, percutaneous interventions, reoperations, a long hospitalization and even treatment in an intensive care unit, all associated with substantial costs. Therefore, continuous improvement of quality of care is in the best interest of patients, but also of society.

In 2009 the 'Dutch Surgical Colorectal Audit' (DSCA, www.dica.nl) was initiated, following previous international examples such as the 'National Surgical Quality Improvement Program' (NSQIP; www.acsnsqip.org) in the United States and the 'National Bowel Cancer Project' (NBOCAP) in the United Kingdom (www.ic.nhs.uk/services/national- clinical-audit-support- programme-ncasp/cancer/bowel). The DSCA is a initiative of the Dutch Society for Surgical Oncology (NVCO), the Dutch Society for Gastro-intestinal Surgery (NVGIC) and the Dutch Colorectal Cancer Group (DCCG). By 2010, more than 20.000 patients are registered in this nationwide process and outcome registration for primary colorectal carcinoma. 98% of all Dutch hospitals participate, and from 2010 on,

participation in the DSCA is a national performance indicator. Purpose of this registration system is to realize demonstrable quality improvement by means of systematic registration and feedback of reliable, case-mix adjusted information on the processes and outcomes of care delivered.

Recently, various medical professional associations have been facilitated by the Dutch Institute for Clinical Auditing (DICA; www.dica.nl) to develop a clinical audit for breast, oesophagus, gastric and lung cancer, all according to the principles pioneered by the DSCA. These, and new developing audits now cover most of the surgical oncology field. However, clinical auditing also requires investments, not in the least from professionals, for whom the registration load is considerable. We therefore investigated the available evidence on whether measurement and feedback of information on process and outcome of surgical care result in improvement of process and outcomes of care by means of a systematic review of the available literature.

METHODS

Search strategy

We searched for relevant articles in Pubmed, Web of Science and Embase, published before May 15th 2011. In this search, combinations of the 'medical subject headings' (MeSH-terms) 'surgery' (subdivided in 'surgical care' and 'operative procedure') and 'outcome- and process assessment' (subdivided in 'medical audit', 'outcome assessment', 'clinical audit', 'quality assurance' and 'benchmarking') were used. Outcome measures were process and/or outcomes of care, or guideline adherence. There were no restrictions on publication language. In addition, relevant websites and reference lists of included articles were screened for relevant articles.

Article selection

Studies describing the effect of auditing on process and/or outcome indicators were selected. Auditing was defined as 'systematic measurement and feedback of structure, process and/or outcome information, in order to improve quality of care'; where needed, changes may be implemented at individual, team, hospital or national level and monitored by a new audit cycle.

Inclusion criteria were: a) at least one process or outcome indicator, or guideline adherence was measured, before and after the audit; b) the indicator or guideline was developed to evaluate quality of care, c) the indicator or guideline was focused on surgical care.

Relevant articles were selected by 2 independent researchers (NK en NvL), evaluating title and abstract of all retrieved publications. Discrepancies were discussed and when necessary, a third reviewer (MW) was consulted. Selected articles were included when all criteria were met. Included articles were subdivided in articles describing (a) the effect of auditing only, (b) the effect of auditing in combination with a quality improvement project and (c) comparing the effect of auditing with and without a quality improvement project. The level of evidence was assigned according to the CBO-guideline for 'Evidence-based Guideline development' (www.cbo.nl/thema/Richtlijnen/EBRO -handleiding/A-Levels- of- evidence/).

RESULTS

The search resulted in 2415 publications. After screening of titles and abstracts, 62 relevant articles were identified. After screening the reference lists of the selected articles, 9 more articles were selected. After reading

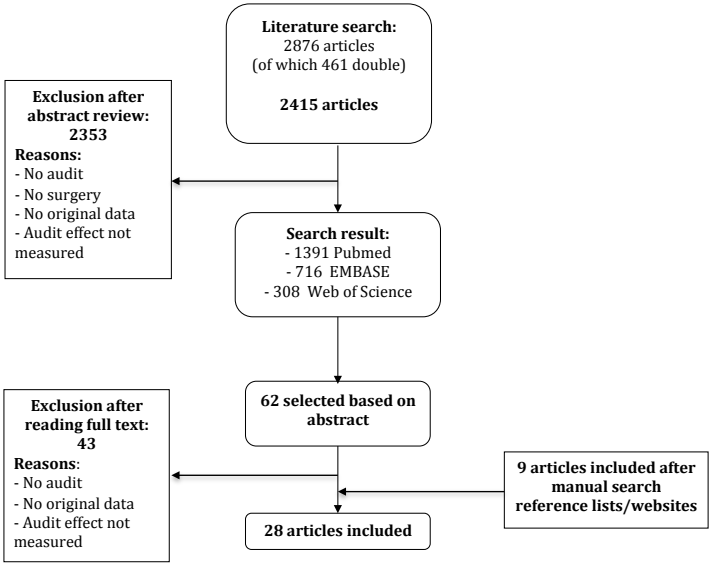

Figure 1. Process of selecting articles for systematic review.

the full text, 28 articles were included (figure 1). Reasons for exclusion after reading the full text were: the audit did not fit our definition; the article did not describe original data, or the effect of the audit was not quantified.

Tables 1, 2 and 3 give an overview of the selected articles. Most articles were prospective cohort studies. Comparative studies (comparing two interventions) were summarized in table 3. We found 2 randomized controlled trials (RCT) (table 3). Most studies were conducted in the United States in the last 5 years.

Table 1. Overview of prospective cohort studies investigating the effect of auditing in surgical interventions.

Author, year	Type of surgery	Setting	Feedback		Effect*	Level of evidence†
			Type	Frequency		
Antonacci, 2008[1]	All types of surgery	3 hospitals	Meeting Report	Weekly Annual	Improvement: • Decrease of no of incidents in theatre† (wound infections, conversion, waste of implants and cancelled procedures)	B
Duxbury, 2003[2]	Colorectal cancer surgery	1 hospital	Not specified	Once	Improvement: • Guideline adherence from 33 to 72%§	B
Freeman, 2002[3]	Hip fractures	10 hospitals	Not specified	Once	Improvement: • Process improved‡ • Morbidity decreased‡ • Mortality unchanged	B
Galandiuk, 2004[4]	Colorectal surgery	23 surgeons	Meeting Report, newsletter	Every month Annual Not specified	Improvement: • Guideline adherence improved‡	B
Hall, 2009[5]	All types of surgery	NSQIP	Report	2/year	Improvement: • In 66% of hospitals O/E mortality decreased ‡ • In 82% of hospitals O/E morbidity decreased ‡	B
Hammermeister, 1994[6]	Coronary bypass surgery	45 hospitals	Report	2/year	Improvement: • Decrease of O/E mortality ($p = 0,06$)	B
Henke, 2010[7]	All types of surgery	MSQC, NSQIP	'Real time'-interface Meeting	Continuous 4/ year	Improvement: • Morbidity decreased from 15,8 to 13,8%‡ • Mortality unchanged	B

Table 1. Overview of prospective cohort studies investigating the effect of auditing in surgical interventions. (continued)

Author, year	Type of surgery	Setting	Feedback		Effect*	Level of evidence†
			Type	Frequency		
Khuri, 2002[8]	All types of surgery	NSQIP	Report	2/year	Improvement: • Morbidity decreased 45%§ • Mortality decreased 27%	B
Khuri, 2008[9]	All types of surgery	NSQIP	Report	2/year	Improvement: • Mortality decreased with 8,7%‡ • Wound infections decreased with 9,1%‡ • Renal complications decreased with 23,7%‡	B

NSQIP = National Surgical Quality Improvement Program (VS); MSQC = Michigan Surgical Quality Collaboration, a part of NSQIP; O/E = Observed/Expected (standardized for case-mix)

*Compared to baseline measurement before audit.

†Level B: prospective cohort study insufficiently controlled for confounders.

‡$P < 0,05$.

§Statistical significance not investigated

Table 2. Overview of prospective cohort studies investigating the effect of auditing in combination with a quality improvement project in surgical interventions.

Author, Year	Type of surgery	Setting	Feedback		Improvement project	Effect*	Level of evidence
			Type	Frequency			
Aitken, 1997[10]	All types of surgery	LSA	Meeting Report	Weekly Annual	Specialized ward Introduction of new methods	Improvement: • Decrease of mortality and complications†	B
Aletti, 2009[11]	Treatment of ovary cancer	1 Hospital	Not specified	Not specified	seminars cadaver training	Improvement: • Increase radical resections: 63 to 79%‡	B
Dellinger, 2005[12]	All types of surgery	44 Hospitals	Report	4/year	Development of guidelines for prevention of surgical site infections	Improvement: • Decrease in wound infections: 2.3 to 1.7%‡	B
Doran, 1998[13]	All types of surgery	2 Hospitals	Report	Every 2 weeks	Development of guidelines Adjustments to process of care	Improvement • Detubation within 6 hours: 5% to 70% • Decreased costs $18.200 to $14.700 per patient • Decreased median hospital-stay: 8.6 to 6.0 days†	B
Forbes, 2008[14]	All types of surgery	1 Hospital	Report	Every month	Development of guidelines for prevention of surgical site infections	Improvement: • Guideline adherence improved‡ • Surgical site infections: unchanged	B

Table 2. Overview of prospective cohort studies investigating the effect of auditing in combination with a quality improvement project in surgical interventions. (continued)

Author, Year	Type of surgery	Setting	Feedback		Improvement project	Effect*	Level of evidence
			Type	Frequency			
Garnerin, 2007[15]	All types of surgery	1 Hospital	Presentations	4/year	Development of guidelines for prevention of 'wrong site/ patient surgery'	Improvement: • Increased guideline adherence from 32 to 63%	B
Haynes, 2009[16]	All types of surgery	3 Hospitals	Not specified	Once	surpass checklist	• Decreased mortality: 1.5 to 0.8%‡ • Decreased morbidity: 11 to 7%‡	B
Holman, 2004[17]	coronairy bypass surgery	21 Hospitals	Not specified	Once	Defining performance-indicators 'site-visits' Education	Improvement • Improved performance at most indicators‡ • Outcomes unchanged	B
O'Connor, 1996[18]	coronairy bypass surgery	5 Hospitals	Report	3/year	Annual meeting Quality training Site visits	Improvement: • Decreased mortality: 4.8 to 3.6%†	B
Potenza, 2009[19]	All types of surgery	1 Hospital	Meeting	Every month	Development of guidelines for safe surgery	Improvement: • Increased guideline adherence: from 80 to 91%	B
Richardson, 1998[20]	All types of surgery	1 Hospital	Not specified	Not specified	Development of guidelines for ordering packed cells to reduce the crossmatch/transfusion ratio	Improvement: 'crossmatch/ transfusion-ratio from 2.8 to 1.8†	B

Table 2. Overview of prospective cohort studies investigating the effect of auditing in combination with a quality improvement project in surgical interventions. (continued)

Author, Year	Type of surgery	Setting	Feedback		Improvement project	Effect*	Level of evidence
			Type	Frequency			
Tavris, 1999[21]	All types of surgery	15 Hospitals	Not specified	Once	Development of performance indicators for postoperative pain management	Improvement: • Improved performance on indicators 14 of 15 hospitals	B

LSA = Lothian Surgical Audit (Schotland).
*compared to baseline measurement before audit.
Level B: prospective cohort study insufficiently controlled for confounders.
† Statistical significance not investigated.
‡P < 0,05.

Table 3. Overview of studies comparing effect of auditing with auditing combined with an improvement project in surgical care.

Author, year	Design* (Comparison)	Type of surgery	Setting	Feedback		Improvement project	Effect
				Type	Frequency		
Berenguer, 2010[26]	Prospective cohort study (Audit + improvement project vs. audit)	Colorectal surgery	1 hospital in NSQIP	Report	2/year	Guideline for prevention of SSI	• Audit + improvement project: • Guideline adherence improved from 38 to 92%† • Decrease of SSI from 13,3 to 8,3%† • Audit only (NSQIP): • Increase of SSI from 9,7 to 10,5%
Campbell, 2010[27]	Prospective cohort study (Audit + improvement project vs. audit)	All types of surgery	MSQC	Meeting Report	4/year 2/year	MSQC: meetings and best practices in addition to audit and feedback	MSQC: decreased morbidity rate from 10,7 to 9,7%† NSQIP: no difference in morbidity rate (12,4%), no difference in mortality Odds ratio for complications (MSQC vs NSQIP): 0,90†
			NSQIP	Report	2/year	NSQIP: audit and feedback	
Ferguson, 2003[22]	RCT (Audit + improvement project vs. control ‡)	Coronary bypass surgery	NCD	Not specified	Not specified	Educational products, Presentations, Opinion leader, call to action letters	Larger improvement in preoperative bètablockade in intervention group than in control group† Other process indicator not improved

Table 3. Overview of studies comparing effect of auditing with auditing combined with an improvement project in surgical care. (continued)

Author, year	Design* (Comparison)	Type of surgery	Setting	Feedback		Improvement project	Effect
				Type	Frequency		
Guadagnoli, 2000[23]	RCT (Audit + improvement project vs. audit)	Breast cancer surgery	Not specified	Not specified	Once	Opinion leaders presentations and educational products	In both groups the possibility of a breast conserving treatment was more often discussed† In both groups the frequency of breast conserving surgery increased† no difference in effect between groups
Neumayer, 2000[24]	Prospective cohort study (Audit + improvement project vs. audit)	All types of surgery	NSQIP	Report	2/year	Guideline for prevention of SSI	Decrease in SSI from 5,5 to 2,9%† Hospital returned from negative outlier in NSQIP to average performing hospital
Reilly, 2002[28]	Prospective cohort study (Audit, then improvement project)	All types of surgery	1 hospital	Report	Every month	Guideline for prevention of SSI	SSI: Before audit 14% After audit 10%† After improvement project 8%†
Sheikh, 2003[25]	Prospective cohort study (Audit + improvement project vs. control ‡)	Prostate cancer surgery	Not specified	Not specified	Not specified	Presentations and information Treatment guideline	No difference in radical prostatectomy rates between groups

NSQIP = National Surgical Quality Improvement Program (VS); MSQC = Michigan Surgical Quality Collaboration, part of the NSQIP; NCD = National Cardiac Database SSI = Surgical Site Infections

*Level of evidence: A2 (comparative clinical studies such as Randomized controlled trials or large cohort studies sufficiently corrected for confounders).

†$P < 0,05$.

‡Control: no audit, no improvement project.

Interventions and outcome measures

Nine studies described the effect of auditing only (table 1).[1-9] Twelve studies described the effect of auditing in combination with a quality improvement project (table 2),[10-21] such as the development of guidelines or checklists, in combination with educational meetings or newsletters. For example, one of these studies described the effect of a protocol for prevention of wound infections.[12] Seven studies (2 RCT's and 5 prospective cohort studies, of which one longitudinal) described the effect of audits in combination with a quality improvement project compared with auditing only (table 3).[22-28] One of these studies compared results at three subsequent moments: before and after the start of the audit, and after the quality improvement project resulting from the audit.[28] The manner and frequency of feedback varied. Information was presented in newsletters, websites or during specialist meetings, once or on weekly or annual basis. Three articles did not describe method nor the frequency of feedback.[20,22,25] Most commonly described outcome measures were process indicators and guideline adherence (6 articles),[2,4,14,15,19,20] and the outcome indicators 'complications' and 'mortality' (13 articles),[1,5-12,18,22,23,28] or a combination of these (8 articles)[3,13,16,17,21,24,26,28]. Outcomes were often compared with a baseline measurement.

Effect of auditing

In 21 of 28 studies a statistically significant positive effect was described of auditing or of auditing in combination with a quality improvement project. In 5 studies, a positive effect was described, but no statistical tests were preformed.[5,8,10,13,15] In 1 study, the positive effect was not statistically significant ($p = 0.06$);[6] another study found no difference.[14] Six studies found a partial improvement, on some of the outcome measures investigated.[3,7,11,14,16,25]

Effect of auditing in combination with quality improvement project

Three studies, as a part of the NSQIP, compared the results of local improvement projects with other participants of the NSQIP (benchmarking).[24,26,27] Two of these studies described results of one hospital, which was a negative outlier in a previous report. In both studies, the improvement project resulted in the hospital returning to an average positioning in the NSQIP. This was interpreted as a faster improvement than the total group of participating hospitals. One RCT investigated the effect of auditing with or without a quality improvement project consisting of implementation of a treatment guideline.[23] The study described an overall increase of guideline adherence, but no additive effect was found of the improvement project. In 3 of 4 comparative prospective cohort studies, a statistically significant improvement was found in the group with an improvement project compared to the group with auditing only.

The second RCT investigated the effect of auditing in combination with a quality improvement project compared to no audit.[22] Auditing, combined with this improvement project resulted in a significant quality improvement. Another, observational study compared the effect of auditing or improvement projects with no intervention and found no differences.[25]

DISCUSSION

The results of our review suggest that the clinical auditing of process and outcomes of care, improves the quality of care. Clinical auditing can be combined with 'benchmarking', comparing own results with those of other hospitals, or with improvement projects. The improvement of

quality of care appears to be primarily accountable to the registration and feedback of information to professionals.

Previous reviews described similar results. A recent Cochrane review on the effect of auditing on the quality of care in a broader perspective than surgical care only, reported a positive effect of auditing on the outcome measures.[29] However, the magnitude of improvement varied strongly between studies. A larger effect of auditing was found when the baseline situation was poor, and the feedback was more frequent and combined with educational sessions. The Cochrane review was limited to RCT's of which only two described surgical patients.

A second review in 1991 also found a positive effect of auditing on quality of care, especially when a target for improvement was set before the start of the audit.[30] When the auditing process, including feedback, was build into the process of care, the effect was found to be greater. The present study supports the previous findings of a positive effect of auditing of quality of surgical care. By expanding our search beyond RCT's we were able to include more recent studies, reporting on various examples of clinical outcome registrations; apart from the RCT's we included 5 large prospective cohort studies with a level of evidence A2. However, most studies included had a longitudinal design, measuring the outcomes before and after implementation of the audit. A control group, in which no audit was conducted, was usually not available (level of evidence B). The observed improvements could therefore also be explained by autonomous evolvement of care instead of the clinical audit. Moreover, most studies only described short-term effects of clinical auditing. These effects could partly be explained by the Hawthorne-effect: the extra attention for the outcome measures brought on by the study, improves the medical practice for the duration of the study.

The value of clinical auditing

Although clinical auditing cannot resolve all challenges of surgical oncology, it may improve treatment and survival of cancer patients. Previous studies such as the Dutch 'Total mesorectal excision' (TME)-trial, in which quality of rectal surgery was standardized and reviewed, showed how quality assurance of the surgical procedure can improve local control and survival in the study population.[31] However, patients included in studies often represent a specific, more favourable selection of the full population. National clinical audits can be used to evaluate the effect of clinical practice on the full population, and to optimize practice when needed. Until recently, very little was known about the extent to which guidelines were followed, and the reasons for not adhering to guidelines. Clinical audits can be used as a platform for guideline evaluation, and implementation of new advances in technique or improvement projects. Based on information from these audits, best practices can be identified and implemented, and the effect of these best practices can be evaluated. In this way, professionals get more insight in the quality of care they deliver, but are also guided in how they can improve.

Quality instrument

Clinical auditing is preferably used where a large effect can be established such as diseases involving large groups of patients or procedures that involve a considerable risk at adverse events. The data set should be based on an up-to-date evidence-based guideline, and an expert committee should be responsible for the definition of outcome measures and relevant case-mix factors (patient or disease related factors influencing the probability for the outcome measure). In this way, doctors are in the lead to define the essential processes which lead to the perfect hospitalization, and which will serve as their benchmarks. The success of clinical auditing therefore depends on the involvement and dedication of professionals. For a frequent an timely feedback, short af-

ter the completion of the care process, data are collected from electronic patient files or by means of a 'web based' registration system.[7]

With a complete national database, uniform definitions and the possibility to adjust for differences in case-mix and random variation, clinical auditing is a valid and reliable instrument for measuring and reporting on hospital quality of care. The results are of great value, not only for providers but also for policy makers, healthcare insurance companies, and patients. National clinical audits could also be used to support and control the imminent advances in oncological care such as centralization, regionalization and risk-based referral. Therefore, the implementation of a continuous clinical auditing cycle, consisting of guideline development and implementation, subsequent auditing, followed by education and visitation and finally auditing of the results, is strongly advised in any medical profession.

CONCLUSION

Clinical auditing is a relatively new quality instrument in surgical oncology, which offers healthcare providers an insight in quality of care delivered. Clinical auditing may not only facilitate reviewing and benchmarking of providers' practices, but also offer insight in targets for quality improvement. Final goal is to assure that all Dutch patients receive optimal quality of surgical care.

Take home message

- 'Clinical auditing' is defined as the systematic measurement and feedback of quality of care delivered, concerning patients, diagnostics, treatment and outcomes.

- The value of clinical auditing for practitioners should outweigh registration load
- Clinical auditing is increasingly used to monitor and improve quality of surgical oncological care.
- Clinical audits for the surgical treatment of bowel cancer, breast cancer, oesophagus and gastric cancer and lung cancer are now implemented in the Dutch healthcare system.
- Clinical auditing has a positive effect on the quality and outcomes of surgical care.
- Combining clinical auditing with a targeted quality improvement project, such as concentration of oncological care, or development of a treatment guideline, enlarges the effect.

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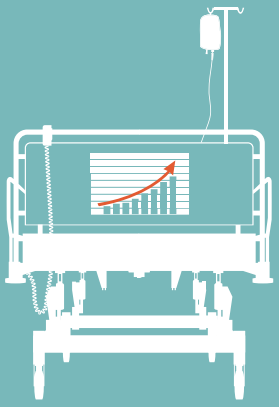

Chapter 3

The Dutch Surgical Colorectal Audit

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ABSTRACT

Introduction: In 2009, the nationwide Dutch Surgical Colorectal Audit (DSCA) was initiated by the Association of Surgeons of the Netherlands (ASN) to monitor, evaluate and improve colorectal cancer care. The DSCA is currently widely used as a blueprint for other audits, coordinated by the Dutch Institute for Clinical Auditing (DICA). This article illustrates key elements of the DSCA and results of three years of auditing.

Methods: Key elements include: a leading role of the professional association with integration of the audit in the national quality assurance policy; web-based registration by medical specialists; weekly updated online feedback to participants; annual external data verification with other data sources; improvement projects.

Results: In two years, all Dutch hospitals participated in the audit. Case-ascertainment was 92% in 2010 and 95% in 2011. External data verification by comparison with the Netherlands Cancer Registry (NCR) showed high concordance of data items. Within three years, guideline compliance for diagnostics, preoperative multidisciplinary meetings and standardised reporting increased; complication-, re-intervention and postoperative mortality rates decreased significantly.

Discussion: The success of the DSCA is the result of effective surgical collaboration. The leading role of the ASN in conducting the audit resulted in full participation of all colorectal surgeons. By integrating the audit into the ASNs' quality assurance policy, it could be used to set national quality standards. Future challenges include administrative burden; expansion to a multidisciplinary registration; addition of financial information and patient reported outcomes to the audit.

Introduction

Several clinical audits have been initiated internationally, acknowledging the importance of reliable and valid quality information in health care. Clinical auditing has been recognised as an important tool for quality assessment and improvement, consequently leading to demonstrable improvements in patient outcome[1-4]. Moreover, clinical audits are increasingly appreciated as a source of information for research on evidence based medicine as they provide 'real world' data on patients often not eligible for clinical trials.[5] However, the voluntary nature of existing audits may unintentionally lead to participation of mainly dedicated hospitals and underrepresentation of underperforming hospitals. Also, audit data are seldom transparent to other stakeholders involved in health care.

In 2009, the Dutch Surgical Colorectal Audit (DSCA) was initiated by the Association of Surgeons of the Netherlands (ASN) in collaboration with the Dutch Association for Surgical Oncology (NVCO), the Dutch Association for Gastrointestinal Surgery (NVGIC) and the Dutch Colorectal Cancer Group (DCCG). Their main goal was to evaluate and improve quality of care for primary colorectal cancer surgery in the Netherlands.

After one year of registration, participation in the audit had become a national performance indicator. Full participation of Dutch hospitals was realised within two years. Subsequent to this success, the Dutch Institute of Clinical Auditing (DICA) was founded in 2011 with the objective to facilitate and organise the start-up of new nation-wide audits. This article illustrates the introduction of the DSCA in the Netherlands by describing its main features and presenting the results of three years of auditing.

Methods

Main features of the DSCA

This section describes the organisational and structural key elements of the DSCA.

1. The initiator: the professional organisation of surgeons

All surgeons in the Netherlands are united in a professional organisation, the Association of Surgeons in the Netherlands (ASN). The ASN serves as a central protector of common interests of surgeons. Membership of the ASN is compulsory to all surgeons in the Netherlands. One of its main objectives is to assure that every surgical patient in the Netherlands receives high quality care. Furthermore, ASN continuously attempts to improve the quality of surgical care. The ASN uses different instruments to accomplish this, for example the development of evidence-based guidelines, surgical training programs and accreditation of surgeons in their surgical specialty. The initiation of clinical audits was necessary to facilitate the uniform measurement of quality of care and enhance the Association's quality improvement efforts.

2. Dataset: involvement of all experts in the field

The ASN formed a scientific committee of mandated clinical experts in colorectal cancer care (surgeons, oncologists, pathologists, epidemiologists) to initiate the first clinical audit. The scientific committee defined performance indicators and outcome measures, based on pre-existing evidence based guidelines, to highlight potential quality concerns, identify areas that need further investigation, and track changes over time. The committee defined a dataset using a Delphi method[6]. The dataset generally covers three aspects: case-mix variables (e.g. age, gender, co morbidity) necessary for hospital comparison; process variables (e.g.

wait times and number of patients discussed in a multidisciplinary team); and outcomes of care (e.g. morbidity and mortality).

3. Organizational structure

In accordance with the format of the DSCA, the Dutch Institute of Clinical Auditing (DICA) was founded to enhance other clinical audit initiatives in the Netherlands. The main goal of the DICA was to support other clinical audits by facilitating on legal, technical, methodological and logistic

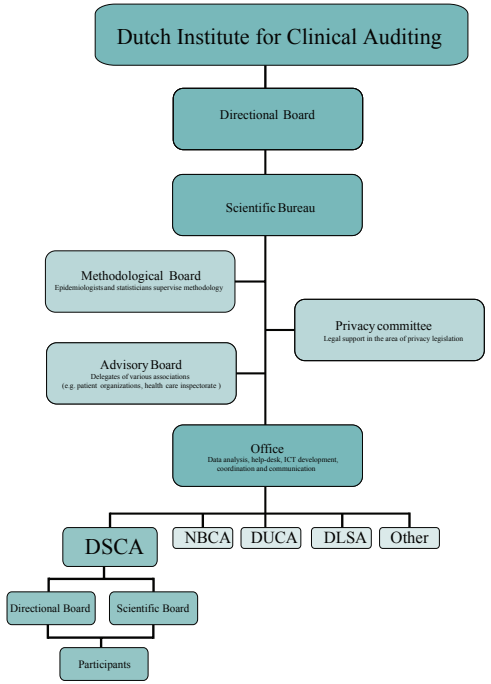

Figure 1. Organisational structure of the Dutch Institute for Clinical Auditing (DICA).
DSCA: Dutch Surgical Colorectal Audit; NBCA: Nabon Breast Cancer Audit; DUCA: Dutch Upper GI Audit; DLSA: Dutch Lung Surgery Audit.

issues. Three new audits have been initiated since the introduction of the DSCA: the breast cancer audit (NBCA), the upper GI cancer audit (DUCA) and the lung surgery audit (DLSA). The organization structure of the DICA is graphically presented in Figure 1.

4. Funding

The onset of the DSCA was funded by quality improvement grants donated by a health care insurance company. Since 2013, hospitals pay a subscription fee for participating in the DSCA. The subscription costs are returned to the hospitals as they are enclosed in the payments of treating patients with colorectal cancer. Costs of the data registration itself are not compensated and are borne by the hospitals.

5. Online data is self-registered in a secured web form

Each participating hospital appoints a surgeon responsible for (supervising) the data registration. The majority of the colorectal surgeons record the data themselves. The DSCA uses a generic internet based program to enable data entry in a secured web environment[7]. Depending on the complexity of the patient and perioperative course, a number of 56 to 179 variables have to be completed; registration time is approximately 20 to 30 minutes per patient. Data-entry can be entered either throughout patient's management or at the end of each admission. Data can be updated when necessary; for example when follow-up data is available. A third trusted party anonymises data regarding patient identification directly after data entry[8]. Definitions and helping texts are appointed to each variable in the dataset and are available during data entry. These guarantee that registration is performed uniformly. Also, frequently asked questions (FAQs) are available on the website and a front office can be contacted by data registrants for questions on both technical and content issues.

6. Internal and external data verification

Data validity is achieved and verified in various ways. The surgeon receives direct feedback on erroneous, missing or improbable data items during data entry through quality control tools that are build in the program. Hospitals receive feedback information on the number of patients and completeness of the data to encourage the participants to correct them when needed.

Data are annually compared with an external data registration, the National Cancer Registry (NCR), on completeness and accuracy.[1] The NCR registers all newly diagnosed malignancies in the Netherlands. Information on patient characteristics (e.g. age, gender) tumour characteristics (TNM stage, localization, histology) treatment (surgical procedure, chemo and/or radiation therapy, laparoscopy, urgency of procedure) hospital of diagnosis, hospital of treatment and outcomes (30-day mortality, anastomotic leakage, CRM, lymph nodes), are collected from the medical records by specially trained registrars 9 months after diagnosis[9,10]. The NCR has an automatic linkage to many important and solid databases, among which the Municipal Administration (GBA), which allow the full enrolment of patients eligible for registration and notification for postoperative mortality. Quality of the NCR data is high; completeness is estimated to be at least 95%.[11] The registration of the NCR is linked to the Municipal Administration, which by law receives notification on all patients that decease in the Netherlands. The quality of the data in comparison to the NCR is described elsewhere[12].

7. Online feedback is provided on a weekly basis

Information regarding volume, performance indicators and outcomes of care are presented online to individual hospitals. Each participating hospital has access to its own secured website. Data are weekly updated.

Results of the hospital are presented in relation to the national average and in relation to results of other anonymised hospitals.

8. Outcomes are adjusted for differences in case-mix

The methods to measure quality of care are described in detail elsewhere.[12,13] When comparing hospital outcomes differences in case-mix must be taken into account.[14] Therefore, a set of relevant case-mix variables specific for each outcome measure is embedded in the database. A standardised co morbidity module was developed using the Delphi method with incorporation of the Charlson Co morbidity Index.[15,16] Case-mix adjusted hospital outcomes are presented in funnel plots using 95% confidence limits that vary in relation to the hospital volume.[17]

9. Results and targets for quality improvement are presented in an annual report.

An extensive national report presenting the results of the audit is published annually.[12] This report focuses on various themes for improvements in the scope of recent literature. The results are presented in a yearly conference accessible to clinicians, patients, patient advocates, health insurers and policy makers, politicians. The conference functions as a platform for all parties to address their (common) interests and to discuss diverse health care topics.

Analysis of results of the DSCA

The completeness of the data on a national level is described by the percentage of participating hospitals and case ascertainment for each audit year. Patient, tumour and treatment characteristics are shown separately for patients with colon and rectal cancer. Then, the results of performance indicators on both process and outcomes of care were evaluated using a Chi square trend test was used to analyse changes over time. Last, hospital variation for preoperative multidisciplinary

team discussions for rectal cancer surgery are presented in a scatter plot, illustrating changes in variation over time.

RESULTS

Dataset

From 2009 to 2011, 26,511 patients undergoing surgical resection for colorectal carcinoma were registered by all 92 hospitals providing colorectal cancer care in the Netherlands (8 university, 47 teaching and 37 non-teaching hospitals). The national case ascertainment and completeness of the data per patient record was high. Compared with the data collected by the NCR, the DSCA included 80% of all eligible patients in 2009, 92% in 2010, and 95% in 2011**.** External data verification with the NCR showed nearly 100% completeness and high correspondence on almost all items of the dataset[12].

Patients

Information on tumour localisation, date of surgery and mortality are minimal requirements for analysis of patient records. In total, 752 patients (2.8%) were excluded for this reason. Hospitals that failed to register more than 10 patients were excluded to minimise selection bias. In 2009, this concerned 5 hospitals registering a total of 37 patients. In 2010 and 2011, none were excluded. In the results presented in this article, patients with multiple synchronous tumours (n = 894) were excluded as well. A total of 24,828 patients were included in the analysis. Patient, tumour and treatment characteristics are shown in Table 1, stratified by tumour location: colon (n = 17,729) and rectal cancer (n = 7,099). Patients in both groups differ in age, prevalence of preoperative complications, urgency of the resection and tumour stage. Treatment patterns differ as well. For example, the percentage of diverting stomas is 4% in colon can-

Table 1. Patient, tumour and treatment characteristics of patients included in the DSCA, stratified by colon and rectum

		Colon		Rectum	
		N	%	N	%
Total		**17729**		**7099**	
Age	>70	10192	57.5%	3155	44.4%
Gender	Male	9212	52.0%	4394	61.9%
ASA score	III	4064	22.9%	1133	16.0%
	IV-V	410	2.3%	65	.9%
	Missing	426	2.4%	168	2.4%
Charlson score	1	3965	22.4%	1409	19.8%
	≥ 2	4313	24.3%	1327	18.7%
Body Mass Index	25-30 kg/m^2	4701	26.5%	1935	27.3%
	>30 kg/m^2	4752	26.8%	2204	31.0%
	Missing	5982	33.7%	2073	29.2%
Abominal surgical history	Yes	6009	34.6%	2094	30.1%
Tumour location	Right colon	7917	44.7%	-	-
-	Transversum/left colon	2884	16.3%	-	-
	Sigmoid	6928	39.1%	-	-
Distance of tumour from anal verge	< 5 cm	-	-	2379	37.1%
	5 - 10 cm	-	-	2613	40.8%
	> 10 cm	-	-	1417	22.1%
	Missing	-	-	697	9.9%
Urgency of resection	Urgent	3567	20.1%	199	2.8%
Preoperative tumour complications	Tumour perforation	354	2.0%	41	.6%
	Abces	262	1.5%	33	.5%
	Ileus	2290	12.9%	176	2.5%
	Bleeding	983	5.5%	383	5.4%
Tumour stage (TNM)	I	2974	16.8%	2054	28.9%
	II	6410	36.2%	1804	25.4%
	III	5500	31.0%	2030	28.6%
	IV	2319	13.1%	566	8.0%
	X	365	2.1%	259	3.6%

Table 1. Patient, tumour and treatment characteristics of patients included in the DSCA, stratified by colon and rectum (continued)

		Colon		Rectum	
Surgical preoperative treatment	Stoma	182	9.6%	560	9.8%
	Stent	157	8.3%	16	0.3%
	Metastasectomy/RFA	35	1.8%	96	1.7%
	Other	24	1.3%	34	0.6%
Preoperative radiotherapy	5x5 Gy	-	-	3312	46.7%
	Long course isolated radiotherapy			595	7.9%
	Chemoradiation	-	-	2033	28.6%
Surgical procedure	Ileocoecal resection	258	1.5%	-	-
	Right hemicolectomy	7785	43.9%	-	-
	Transversal resection	553	3.1%	-	-
	Left hemicolectomy	1762	9.9%	-	-
	Sigmoid/(low) nterior esection	6489	36.6%	4371	61.6%
	Abdominoperineal resection	-	-	2168	30.5%
	Subtotal colectomy	159	0.9%	191	2.7%
	Panproctocolectomy	148	0.8%	43	0.6%
	Other	289	1.7%	126	1.8%
	Missing	286	1.6%	200	2.8%
Surgical approach	Laparoscopical	6606	37.4%	2690	38.1%
Anastomosis	Primary anastomosis	15556	87.7%	3252	45.8%
	No anastomosis (end-colostomy)*	2173	12.3%	3847	54.2%
Diverting stoma**	Yes	709	4.6%	2123	65.3%
Extended resections	Minimal local extended resection	1036	6.2%	258	3.9%
	Maximal local extended resection	810	4.8%	280	4.2%
	Metastasectomy	591	3.5%	202	3.0%

ASA: American Society of Anaesthesiologists risk score. RFA: radiofrequent ablation.
*includes abdominoperineal resections; **percentage is related to the performed anastomoses.

Table 2. Results of performance indicators for colorectal cancer care 2009 – 2011.

	Colon							Rectum						
	2009		2010		2011		P-value	2009		2010		2011		P-value
Process														
Cases discussed in preoperative MDT	2286	**46%**	3504	**56%**	4255	**68%**	**<0.01**	1625	**80%**	2249	**91%**	2400	**96%**	**<0.01**
Total colonoscopy	2931	**61%**	3816	**62%**	4149	**67%**	**<0.01**	1467	**76%**	1858	**77%**	2016	**83%**	**<0.01**
Preoperative MRI								1625	80%	2016	81%	2129	85%	**<0.01**
CRM reported in pathology rapport								980	**48%**	1472	**59%**	2066	**80%**	**<0.01**
>10 lymph nodes in sample	3623	**73%**	4902	**78%**	5423	**84%**	**<0.01**	1182	**58%**	1520	**61%**	1700	**68%**	**<0.01**
Outcomes														
All complications	1595	**33%**	2062	**33%**	1918	**31%**	**<0.01**	793	**40%**	1007	**41%**	945	**38%**	**<0.01**
Reintervention	706	**15%**	917	**15%**	699	**13%**	**<0.01**	351	**17%**	435	**18%**	352	**14%**	**<0.01**
Anastomotic leakage*	328	**7,5%**	429	**7,8%**	364	**6,4%**	**<0.01**	98	**11,5%**	144	**12,4%**	112	**9,1%**	**<0.01**
Hospital stay (mean in days)	13		12		11		**<0.01**	16		14		14		**<0.01**
CRM positive margin								138	**14%**	175	**12%**	168	**8,5%**	**<0.01**
30-day mortality	223	**4,5%**	255	**4,1%**	210	**3,4%**	**<0.01**	48	**2,4%**	48	**1,9%**	54	**2,2%**	**<0.01**
In-hospital mortality	232	**4,7%**	276	**4,4%**	230	**3,6%**	**0.02**	55	**2,7%**	55	**2,2%**	64	**2,5%**	**0.663**
In-hospital mortality/30 day mortality	289	**5,8%**	300	**4,8%**	256	**4,0%**	**<0.01**	77	**3,8%**	58	**2,3%**	69	**2,7%**	**0.035**
Total	**4960**		**6293**		**6263**			**2035**		**2484**		**2494**		

MDT: Multidisciplinary Team; MRI: Magnetic Resonance Imaging; CRM: Circumferential Resection Margin

* only for patients with a primary anastomosis.

cer surgery compared to 33% in rectal resections. Preoperative radiation therapy is applied in 84% of rectal cancer patients, which is very high from an international perspective.[17]

Performance indicators

A number of noticeable improvements on pre-defined performance indicators occurred since the introduction of the audit in 2009. These improvements concerned both processes as well as outcomes of care. Table 2 shows the results. Definitions of the various variables are provided in table 3.

Table 3. Definitions used in the DSCA.

Term	Definition
Tumour perforation	Preoperative tumour perforation with clinical signs of faecal peritonitis.
Abscess	Preoperative abscess formation in the intraperitoneal or extraperitoneal spaces.
Ileus	Preoperatieve presence of (partial) mechanical bowel obstruction with symptoms of abdominal cramping, abdominal distention, nausea, vomiting or failure to pass gas or stool.
Bleeding	Preoperative tumour related blood loss that requires an intervention (transfusion, urgent operation) or leads to anemia (Hb <7 mmol/L in male patients and <6.5 mmol/L in female patients).
Total colonoscopy	Preoperative visualization of the entire colon including the ascending colon by colonoscopy or CT colonography.
(Low) anterior resection	Rectosigmoid or rectal resection according to the TME principle with anastomosis of the colon to the intra- or extraperitoneal rectum or anal canal.
Multidisciplinary team	A team that consists of all mentioned specialists: a surgeon, an oncologist, a radiologist, a radiotherapist, and a gastroenterologist.
Urgent procedure	Non-elective colorectal resection that was required and performed within 24 hours of admission.
Anastomotic leakage	Clinically relevant anastomotic leak requiring a radiological or surgical reintervention.
Reintervention	An invasive (surgical, radiological or endoscopical) measure to treat a complication (excluding superficial drainage abscess of a wound abscess on the patient ward; introduction of a nasogastric tube; a central venous catheter; or tracheostomy).
Positive CRM	A circumferential resection margin of 1 mm or less.
Negative outlier	A hospital with a significantly worse (adjusted) outcome than the population average of all hospitals in the registration.

Hb = haemoglobin. CT = computed tomography. TME = total mesorectal excision. .

Process

From 2009 to 2011, the percentage of patients discussed in a preoperative multidisciplinary team increased significantly both in colon (46 to 68%, P<0.01) and rectal cancer surgery (80 to 96%, p<0.01). Moreover, the in-between hospital variation decreased during this time period (Figure 2). There was a significant increase in the implementation of guideline-recommended preoperative MR-imaging for rectal cancer surgery (80 to 83%, p<0.001), as well as an improved standard of pathological reporting of the circumferential resection margins (48% to 80%, p<0.01).

Outcomes

Postoperative morbidity, length of hospital stay and postoperative

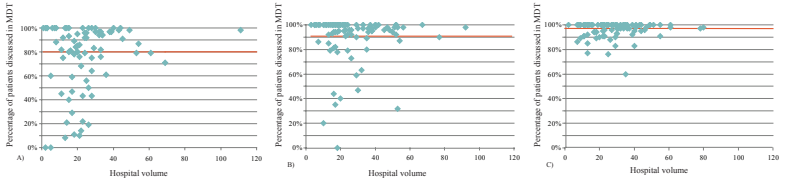

Figure 2. Variation between hospitals in the percentage of patients with rectal cancer that was preoperatively discussed in a multidisciplinary team. a) 2009; b) 2010; c) 2011. The red line represents the average percentage of patients.

mortality decreased significantly from 2009 to 2011 both for colon and rectal cancer surgery. The incidence of any postoperative complication decreased from 33 to 31% (p<0.01) after colon resections and from 40 to 38% (p<0.01) after rectal resections. The re-intervention rate decreased from 15 to 13% (p<0.001) after colon resections and from 17 to 14% (p<0.01) after rectal resections. Duration of hospital stay regressed with 2 days (both after colon and rectal resections). Postoperative mortality

rates (both in-hospital and 30-day mortality) decreased from 5.8 to 4.0% ($p = 0.012$) after colon resections and from 3.8 to 2.7% after rectal resections. The percentage of patients with a positive circumferential resection margin (CRM) after rectal cancer surgery (≤1 mm distance tumour to CRM) decreased from 14% to 8.5% ($p<0.001$).

DISCUSSION

This paper reports the key elements of the Dutch Surgical Colorectal Audit that have been crucial for its success. Quality of care regarding guideline compliance and clinical outcomes for colorectal cancer patients in the Netherlands improved significantly. Numerous international audit projects leading to substantial improvements in quality of care have preceded the DSCA. Many examples of successful clinical audits have been described in detail. [2,3,18-20] Often, the main goal of the audit is to generate valuable information for clinicians to receive feedback on the quality of care. A unique feature of the DSCA is the use of the audit data to support the effectuation of the national quality assurance policy of the surgical professional association, the ASN. There is a common need for evidence based, professionally supported consensus on what high quality care means in order to set standards of care. Benchmarking hospital performances can support surgeons in determining the minimal requirements of the provided care. On a national level, outliers can be identified. The ASN initiated an independent audit committee to provide consultative advice to hospitals identified as negative outliers in the DSCA. Furthermore, the ASN can use the data for board certification of surgeons, accreditation of hospitals, national and local improvement projects and the provisioning of valid quality information for patients, health care insurers and policy makers.

The engagement of colorectal surgeons to participate was mainly achieved by a strong plea for auditing in national meetings and conferences. The ASN strongly believed that for a valid measurement of quality of care, quality measures should be designed, registered, and interpreted by surgeons themselves. From the onset, the initiative was supported by the majority of Dutch colorectal surgeons, despite the investment in time and costs. One year later, participation became a quality indicator for the health care inspectorate, which ensured an almost 100% participation rate.

The contents of the DSCA dataset as well as the pre-defined process and outcome measures are generally supported by colorectal surgeons in the Netherlands, since they are based on evidence based guidelines and developed by representatives of their own professional organization, who are experts in the field. The leading role of the professional association and its expert members in the design, development and conduct of the audit has important advantages. It produces meaningful and feasible quality information, valid in the face of participating surgeons. This may also have led to the high participation rate among colorectal surgeons and their tremendous efforts to enter high quality data in the registry.

In three years, a trend towards better performance indicator results was objectified. A significant reduction in postoperative morbidity and mortality was observed, as well as a reduced duration of hospital stay. Although promising, the continuation of these trends needs a longer period of registration to be confirmed. Also, as was presented in Figure 2, the variation in guideline compliance between hospitals was reduced. Although, these improvements may have multifactorial causes, the active and integrated approach of the DSCA has at least resulted in increased awareness of surgeons for quality aspects of their practice and provided

insight in areas of improvement. The potential of clinical registries to improve health care outcomes and lowering related costs was recently demonstrated in a study by Larsson et al. [21] An important feature that supports the audit to function as a quality improvement tool, is the web based data collection system. This system facilitates timely registration of patients and automated feedback of benchmarked performance information on a weekly basis. These features may have contributed to the demonstrable improvements in quality of care presented here.

In recent years there has been an increasing demand for valuable and reliable information on the performance of health care providers from various perspectives. The ASN aimed at developing a system that responds to the exigencies of all major stakeholders in hospital care: patients, clinicians, managers, policy makers and insurance companies. Dutch surgeons have recently agreed to gradually publish publicly their hospital-specific audit results to provide transparency to all parties concerned. For the ASN, an important condition for external transparency is the validity and reliability of the data. This is assured by consistent quality checks on the registered data in the online system and the annual external validation with the National Cancer Registry.

A limitation of the DSCA concept is the administrative burden that is associated with data collection. The measurement of quality of care is complex, and requires the collection of multiple data points from different phases of the care process. The dataset is limited, but still entails detailed information to perform case-mix adjustment and in-depth analysis of observed variation in care processes. Structural data management support for the health care professionals is essential for a sustainable auditing process. Automated retrieval of data from electronic patient files is the logical next step. However, apart from the technical difficulties that have to be solved to extract data from the varying electronic systems in

Dutch hospitals, it is essential that synoptic reporting is implemented in the administrative process of hospitals. Links between other databases like the Dutch Pathological Anatomical District Automatized Archives (PALGA) are being established to minimise the registration burden and to automate as much as possible.

In the future, to reach full potential of the audit, information on outcomes of care should be linked to patient reported outcomes and financial information. Feedback to clinicians on patients' satisfaction and quality of life enables them to improve their practice, attitude, facilities and outcomes. Cancer patient organizations in the Netherlands have already committed themselves to collaborate in providing the clinical audits with patient reported outcomes in the near future.

In conclusion, we demonstrated the feasibility of nationwide surgical audit programs, with national coverage and high case-ascertainment, accomplished in a relatively short period of time. The Dutch Surgical Colorectal Audit shows that substantial improvements can be realized within a time period of 3 years. Success factors include: a leading role for medical specialists, external data verification, weekly updated online feedback of benchmarked and meaningful quality information, and embedded in the quality assurance program of the professional association. In the Netherlands, this has been the recipe for the initiation of several other clinical audits, with a generic format consistent with the blueprint of the DSCA.

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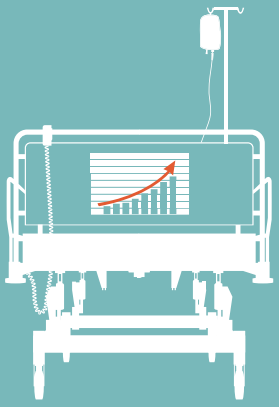
Part II

Challenges in colorectal cancer care



Chapter 4

Increasing prevalence of comorbidity in patients with colorectal cancer in the South of the Netherlands 1995-2010

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ABSTRACT

Comorbidity has large impact on colorectal cancer (CRC) treatment and outcomes and may increase as the population ages. We aimed to evaluate the prevalence and time trends of comorbid diseases in CRC patients from 1995-2010. The Eindhoven Cancer Registry registers comorbidity in all patients with primary CRC in the South of the Netherlands. We analyzed the prevalence of serious comorbid diseases in four time frames from 1995-2010. Thereby, we addressed its association with age, gender and socio-economic status (SES). The prevalence of comorbidity was registered in 27,339 patients with primary CRC. During the study period, the prevalence of comorbidity increased from 47% to 62%, multimorbidity increased from 20% to 37%. Hypertension and cardiovascular diseases were most prevalent and increased largely over time (respectively 16-29% and 12-24%). Pulmonary diseases increased in women, but remained stable in men. Average age at diagnosis increased from 68.3 to 69.5 years ($p = 0.004$). A low SES and male gender were associated with a higher risk of comorbidity (not changing over time). This study indicates that comorbidity among CRC patients is common, especially in males and patients with a low SES. The prevalence of comorbidity increased from 1995-2010, in particular in presumably nutritional diseases. Ageing, increased life expectancy and life style changes may contribute to more comorbid diseases. Also, improved awareness among health care providers on the importance of comorbidity may have resulted in better registration. The increasing burden of comorbidity in CRC patients emphasizes the need for more focus on individualized medicine.

INTRODUCTION

Comorbidity composes a great challenge when treating colorectal cancer (CRC) patients[1-4]. In the Netherlands, CRC represents the second most frequent cancer in terms of incidence with more than 12,000 newly diagnosed patients annually and a lifetime risk of more than 5%[5]. As more than half of CRC patients is aged older than 70 years, the diagnosis of CRC is often made amidst the presence of other chronic medical conditions. Treatment of patients with severe comorbidity is challenging because of polypharmacy and decreased compensating mechanisms, especially in older patients who also have normal age-related physiological changes[6]. The presence of a single or combination of chronic illnesses can affect both treatment effectiveness and tolerance, and is associated with worse short- and long-term outcomes after CRC surgery[1-4,7-11]. The prevalence of comorbidity is influenced by personal and environmental factors. Age, gender and socio-economic status (SES) have been described as interacting with the burden of specific comorbid ailments and influencing outcomes after CRC treatment[12-14].

Further, ageing, improved life expectancy and lifestyle habits in western countries will lead to a higher prevalence of (multiple) concomitant diseases among CRC patients[15,16]. Objectifying increases in the burden of comorbidity is essential to increase awareness in the medical community and urge additional research for improving treatment and outcomes in CRC patients with chronic diseases. There is however a paucity of epidemiological studies examining time trends in prevalence of comorbidity in CRC patients[2].

In this study, we evaluated the changing prevalence of chronic illnesses in a large cohort of unselected CRC patients over a time frame of 16

years. Thereby, we addressed the role of ageing, gender and SES in relation to the changing prevalence of comorbidity over time.

PATIENTS AND METHODS

The Eindhoven Cancer Registry

All patients newly diagnosed with CRC between 1995 and 2010 in the area of the population-based Eindhoven cancer registry (ECR) were included. The ECR collects data for all patients with cancer in the southern part of the Netherlands. It serves 10 community hospitals, 6 pathology departments, and 2 radiotherapy institutes in an area comprising 2.4 million inhabitants (16% of the Netherlands). Upon notification of these centers, trained registry personnel retrieves detailed data on demographics, diagnosis, staging and treatment from the medical records within 6 months after diagnosis[17]. The quality of the data is high because of thorough training of the registrars and computerized consistency checks at regional and national level. Completeness is estimated to be at least 95%[18]. Data on comorbidity have been recorded since 1993 by screening previous admissions, letters of referral from and discharge to general practitioners, the medical history, current medication, and preoperative assessments[19,20]. Internal validation studies were performed to evaluate the data quality by checking the completeness and accuracy of the registry personnel extracting comorbidity information from the medical records in random cases[21,25]. When underreporting was revealed, data registry personnel was educated and trained on specific issues to improve data extraction.

Definitions of variables

Comorbid diseases were defined as life shortening diseases present at the time of CRC diagnosis. If two or more chronic conditions co-existed

Table 1. Disease categories for comorbidity registered by Eindhoven Cancer Registry.

Disease category	Comorbid conditions
Other Cancer	Other malignancy in the last ≤5 years, 6-10 years, >10 years, not otherwise specified. Excluded: basal skin carcinoma and carcinoma *in situ* of the cervix
Pulmonary disease	Asthma, emphysema, chronic bronchitis, chronic obstructive pulmonary disease, lung fibrosis, lung transplantation,
Cardiovascular disease	Myocardial infarction, CABG, PTCA heart, cardiac decompensation, angina pectoris, heart valve disease, heart rhythm disorder, cardiomyopathy, pacemaker, heart transplantation
Vascular disease	Generalized arterial atherosclerosis, peripheral arterial disease, intermittent claudication, PTA, abdominal aneurysm, abdominal aortic surgery , arterial thrombosis, venous thrombosis, lung embolus
Cerebrovascular disease	Cerebrovascular accident, hemiplegia, hemiparesis, quadriplegia, carotid surgery (TIA excluded)
Hypertension	Systematic hypertension, portal hypertension
Diabetes mellitus	Insulin dependent, oral medication dependent, diet
Infectious disease	HIV, AIDS, tuberculosis
Digestive tract disease	Stomach ulcer, duodenum ulcer, reflux oesophagitis, (partial) stomach resection, chronic inflammatory bowel disease (Morbus Crohn, ulcerative colitis), liver cirrhosis, hepatitis, liver transplantation, diverticulitis Excluded: polyposis coli, irritable bowel syndrome
Genitourinary disease	Chronic glomerulonephritis, kidney failure, nephrotic syndrome, kidney transplantation, dialysis, pregnancy at time of diagnosis.
Muscle, connective tissue and joint disease	Connective tissue disease, sarcoidosis, Morbus Besnier Boeck, Wegener, periarteriitis nodosa, systematic lupus erythematosis, rheumatoid arthritis
Central and peripheral nervous system	Dementia, Alzheimer, Parkinson, serious psychiatric disease (severe depression, admittance in a psychiatric unit, psychosis, schizophrenia

CABG = coronary artery bypass grafting. PTCA = Percutaneous transluminal coronary angioplasty. PTA = Percutaneous Transluminal Angioplasty. TIA = Transient Ischaemic Attack. HIV = Human Immunodeficiency Virus. AIDS = acquired immune deficiency syndrome of acquired immunodeficiency syndrome CVA = cerebrovascular diseases

in at least two organ systems, this was referred to as multimorbidity. When assessing chronic obstructive pulmonary disease (COPD), and hypertension, these were only recorded if the patient received current medical treatment during admission. Cardiovascular (CVD), cerebrovascular (CVA), and other vascular diseases were also included after a circu-

latory event or vascular surgery. The Charlson Comorbidity Index is most widely used for recording and was validated in various studies[22]. We used a slightly modified version of this index for categorizing comorbidity as presented in table 1. For analyses of time trends four timeframes were defined: 1995-1998, 1999-2002, 2003-2006 and 2007-2010. Age at time of diagnosis was clustered: 18-60, 60-69, 70-79, 80-89, ≥90 years. The SES was based on average fiscal earnings and house prices per postal code area and calculated by Statistics Netherlands, a government funded organization responsible for collecting and processing data to publish statistics to be used by policymakers and for scientific research. Categories were low, intermediate, high and a fourth category represented a postal code in which an institute (nursing home e.g.) was situated.

Analyses

First, the prevalence of comorbidity was analyzed according to age, gender and SES. To evaluate comorbidity changes over time, the prevalence of comorbidity was estimated as a percentage per time period of four years and analyzed in different age groups, gender and SES. A chi square test was used for analysis of categorical variables; a student's t-test was performed to evaluate ageing during the study period. Last, the association between the presence of at least comorbidity or multimorbidity during the study period was examined by a multivariable logistic regression analysis, with adjustment for age, gender and SES. Data analysis was performed using SPSS 18.0.

RESULTS

Demographics and comorbidity

A total of 27,339 patients was diagnosed with primary CRC in the period 1995-2010 and included for analysis. The median age was 70 years

[18-100]; 4896 patients (18%) were older than 80 years; 400 patients (1.5%) were older than 90 years. The majority of patients was of male gender (54%). Fifty-five percent of patients suffered from at least one concomitant disease; in patients aged over 70, even 67%. In 29% of patients, two or more concomitant diseases were present (multimorbidity). Males suffered more often from comorbidity than females: respectively 57% versus 53% ($p<0.001$). Also, a high SES was associated with less comorbidity in comparison with patients with a low SES (51% vs. 63%, $p<0.001$). With increasing age the prevalence of comorbidity increased: 30% of patients <60 years suffered from comorbidity compared to 71% of patients aged over 80 years.

Specific comorbid diseases and age

The most common disease was hypertension, affecting 22% of the entire cohort and increasing with age from 11 up to 23%. Other common comorbid diseases were cardiac disease (19%), diabetes (11%) and other malignancies (15%). Infectious, neurologic, genitourinary and connective tissue diseases were least frequent, affecting only 5.4% of patients.

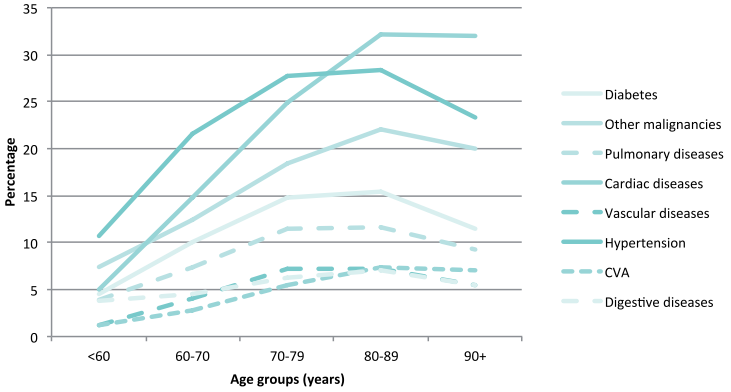

Figure 1. Prevalence of specific comorbid diseases for different age groups

Figure 1 presents the patterns of different comorbid diseases across the age spectrum. In general, the prevalence of comorbidity increased with age until the age of 80-89 years, whereas in the oldest patients (90+ years) a slight decrease was observed. In cardiac disease, the largest increase with age was observed: 5.0 to 32% (<60 versus 90+ years), accounting for a prevalence rate ratio (PRR) of 6.4. In digestive diseases, a minor increase was observed (3.8 to 5.5%, p<0.001, PRR 1.5).

Prevalence of comorbidity over time

The mean age of patients increased significantly within the time periods (68.3 to 69.5 year, p = 0.004). The prevalence of comorbidity and multimorbidity increased respectively from 47 to 62% and 20 to 37%. This increase was observed in all age groups, but was most pronounced in patients over 80 years (figure 2). Over time, an equal rise in comorbidity was observed in both genders and all SES categories (table 2).

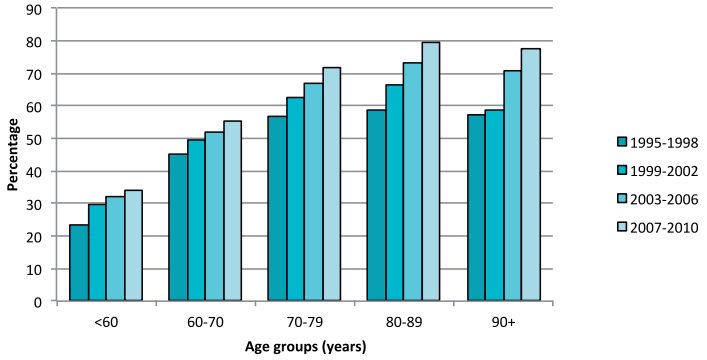

Figure 2. Prevalence of comorbidity for different age groups by time period.

Table 2. Percentage of colorectal cancer patients having comorbidity per time period stratified by gender and SES group .

	1995-1998	1999-2002	2003-2006	2007-2010	Relative change	p
Comorbid diseases						
1 or more	46.5%	51.7%	56.5%	61.6%	1.32	<0.01
2 or more	19.6%	25.0%	30.2%	36.5%	1.86	<0.01
Gender						
Male	48.7%	53.3%	58.4%	62.5%	1.28	<0.01
Female	44.0%	49.8%	54.3%	60.5%	1.38	<0.01
SES^						
Low	56.4%	59.7%	64.6%	70.1%	1.24	<0.01
Intermediate	49.5%	50.8%	54.3%	59.7%	1.21	<0.01
High	45.4%	45.9%	51.2%	56.1%	1.24	<0.01
Institutionalised	54.6%	63.6%	65.5%	74.0%	1.36	<0.01

^SES = social economic status

Variations in the trends of different comorbid diseases over time

In table 3, the prevalence of common comorbid diseases within different timeframes is presented. Especially, hypertension, cardiac disease, diabetes and other malignancies increased significantly over time in both genders. In contrast, the prevalence of CVA grew minimally. In pulmonary diseases, the prevalence of comorbidity remained unchanged in males in contrast to an increase in females. In multivariable logistic regression analysis to control for age, gender and SES, the last time period was associated with an increased risk of having comorbidity (OR 1.74) and multimorbidity (OR 2.56) compared to the first time period (table 4). Compared to 2003-2006, the odds of having comorbidity (OR 1.21) and multimorbidity (OR 1.32) in the last period were significantly higher as well.

Table 3. Percentage of patients with a specific comorbid diseases by gender and time period

	Male						Female					
	1995-1998	1999-2002	2003-2006	2007-2010	average change/year	p	1995-1998	1999-2002	2003-2006	2007-2010	average change/year	p
Diabetes	6.7%	8.9%	11.2%	13.8%	0.47	<0.01	9.1%	10.8%	12.6%	14.5%	0.36	<0.01
Other malignancies	13.9%	14.1%	14.1%	17.8%	0.26	<0.01	13.1%	13.6%	13.6%	16.9%	0.25	<0.01
Pulmonary diseases	10.1%	10.1%	10.4%	10.0%	-0.01	0.93	5.8%	6.4%	6.6%	7.6%	0.12	0.02
Cardiac diseases	14.6%	20.3%	24.9%	26.7%	0.81	<0.01	8.1%	13.7%	16.3%	19.4%	0.75	<0.01
Vascular diseases	4.4%	6.1%	6.9%	8.4%	0.27	<0.01	1.7%	2.6%	2.7%	3.8%	0.14	<0.01
Hypertension	12.4%	17.2%	21.2%	26.1%	0.91	<0.01	16.4%	21.2%	25.5%	31.7%	1.02	<0.01
Cerebrovascular Accidents	3.9%	4.6%	4.6%	5.4%	0.10	0.01	3.0%	3.7%	3.2%	3.8%	0.05	0.20
Digestive diseases	3.8%	6.1%	6.7%	6.5%	0.18	<0.01	2.5%	4.5%	4.8%	5.7%	0.21	<0.01

Table 4. Multivariate analysis on associations for having comorbidity (left) and multimorbidity (right).

	One or more comorbidities			Two or more comorbidities		
Factor	**OR**	**CI Low**	**CI High**	**OR**	**CI Low**	**CI High**
1995-1998	Ref.			Ref.		
1999-2002	1.20	1.11	1.29	1.48	1.36	1.62
2003-2006	1.40	1.31	1.50	1.87	1.72	2.03
2007-2020	1.70	1.58	1.81	2.47	2.28	2.67
<60 years	Ref.			Ref.		
60-70 years	2.33	2.17	2.50	3.08	2.77	3.43
70-80 years	4.32	4.02	4.63	6.22	5.62	6.88
>80 years	5.40	4.96	5.88	8.23	7.37	9.19
Male	Ref.			Ref.		
Female	0.76	0.72	0.80	0.68	0.65	0.72
SES low	Ref.			Ref.		
SES intermediate	0.79	0.74	0.84	0.78	0.73	0.83
SES high	0.70	0.65	0.75	0.65	0.60	0.70
Institutionalised	0.87	0.78	0.98	1.05	0.94	1.18

OR = odds ratio; CI = Confidence Interval; Ref = reference category; SES = social economic status

DISCUSSION

This large population-based study provides insight in the extent and nature of comorbidity in unselected CRC patients and its evolvement over time. The results indicate that comorbidity in CRC patients is common and has increased substantially during the last two decades. Also, the prevalence of multimorbidity has increased largely. The trends were most distinct among patients aged over 80 years, resulting in a 56 to 78% increase in single comorbid disease prevalence and a 26 to 54% increase for multiple chronic diseases concurrently present at time of CRC

diagnosis. Although the population as a whole has aged, this has only modestly attributed to the increased prevalence of chronic illnesses.

Increases in comorbidity prevalence were also observed by others. Iversen et al.[2] reviewed the prevalence of comorbidity in patients with CRC in Denmark in 1995-2006. Not only the percentage of patients with Charlson 0 decreased from 69 to 57%, also the prevalence of multimorbidity (Charlson 3+) increased from 6 to 11%. However, administrative changes during the study period may have influenced the registration. In our registration extraction methods have not been changed and clearly defined extraction methods were maintained; we worked with well-educated and trained registry personnel only and internally checked our results periodically. Under registration was however found in the first registration years (1993-1996) mainly for cardiac and other vascular diseases (20%), because terms such as CABG (coronary artery bypass grafting), and PTCA (percutaneous transluminal coronary angioplasty) were sometimes disregarded. The registration of these diseases was largely improved in the second validation study (1998-1999)[21]. However, under registration may have influenced our results in the first study period.

Trends for increasing (co)morbidity have also been observed in the general population. Uijen et al. described a doubling prevalence of chronic diseases in the patient files of 10 general practitioners in 1985-2005[23]. Also, the percentage of patients with at least 4 chronic diseases increased with approximately 300%. Tacken et al. reported that the prevalence of chronic pulmonary disease, cardiac disease or diabetes mellitus among patients over 65 years attending a general practitioner increased from 41.8% to 46.8% in 6 years (2003-2009)[24].

Most likely, multiple factors contributed to the increasing comorbidity among CRC patients we observed. First, due to demographic changes

the proportion of elderly among CRC patients is increasing. Second, improved care for patients with chronic diseases may help them survive in older age, subsequently becoming at risk of developing colorectal cancer. Third, unfavorable lifestyle, namely poor diets, lack of physical exercise and smoking habits (increasing among females), results in a raise in nutritional diseases.

Inevitably, registration effects may have influenced the trends we observed in time. Improved awareness of the importance of comorbidity among physicians may have resulted in a more active attitude in the registration and detection of comorbid diseases. Better detection of diseases by extensive preoperative screening for physical disabilities in elderly, may have attributed to this effect as well. Registration effects can however not completely explain the disproportionate increase in some specific illnesses (CVD) in contrast to the absence of positive trends in others (pulmonary diseases in men). Lifestyle related diseases (e.g. CVD, hypertension and diabetes) were largely accountable for the rising prevalence of comorbidity. Hypertension grew most strikingly, adding on 15 to 28% of patients. In earlier studies, the presence of CVD in patients with colorectal cancer led to a 1.1-1.8 higher risk of (adjusted) postoperative death compared to patients without CVD[11].

Remarkably, in pulmonary diseases no positive trends were observed in males, whereas in females the prevalence increased significantly. In the Continuous Morbidity Registration[25], similar observations were described: the prevalence of diabetes, hypertension and CVD increased largely; however for COPD a positive trend was observed for women and a negative trend for males. Most likely, increased smoking habits of females since the seventies explain these gender differences in pulmonary diseases[26].

Overall, the male gender was clearly associated with a higher risk of having a comorbid disease, and this gender difference was stable over time. Sexual hormones (in addition to smoking behavior) have been associated with differences in the prevalence of several comorbid diseases between males and females[27,28]. In this study, a low SES was also associated with having comorbid diseases. However, the number of comorbid diseases in different SES categories increased evenly over time. Extrapolating, this may indicate that differences between SES classes in lifestyle and access to care have been unchanged in CRC patients over time[29]. Frederiksen et al.[13] studied the role of SES in postoperative mortality after elective CRC surgery in a Danish cohort and found that low SES patients had an excess risk of death, which was mostly accounted for by comorbidity and lifestyle characteristics. The association of a low SES and a high prevalence of (multi) morbidity is also evident in the general population[30]. The inclusion of a large sample of unselected patients was one of the strengths of our study. Thereby, the registration of comorbidity in our database was limited to serious diseases, which precludes diseases of mild course. This contributed to the clinical relevance of our data to colorectal cancer patients. A limitation of this study is the absence of information on lifestyle characteristics (Body Mass Index, smoking and drinking habits), that may interfere with lifestyle related diseases.

The results of this study have many implications for current practice in colorectal cancer care. First, since cardiovascular disease, hypertension, and diabetes are among the most common comorbidities in our cohort, there is a need for clinical trials to include, or at least not unnecessarily exclude, colorectal cancer patients with these common comorbidities. It is well established that comorbidity in CRC patients leads to postoperative morbidity, mortality, less use of (neo-) adjuvant therapy and a worse prognosis[14,31-33]. Simultaneously, surgery is often performed regardless of age and comorbidity if only to avoid the consequences of tumor

obstruction[8]. Estimating the risk of (postoperative) adverse outcomes is important in establishing informed patient consent and shared decision-making[34,35] on the extent of intended surgery and appliance of adjuvant therapy. However, the development of personalized care programs is bothered by limited knowledge about the relation of comorbidity and cancer biology and what (combination of) chronic diseases are prone for complications and death. This gap in knowledge urgently needs to be bridged.

Second, clinical practice guidelines for colorectal cancer should address how care management may change in the context of these common comorbidities. Currently, clinical practice guidelines rarely account for elderly or patients with concurrent diseases[36] because of the paucity of clinical trials including elderly and patients with accompanying diseases. As a consequence disparity of care in vulnerable patients exists[33]. We are in need of research that focuses on the hazard/benefit ratio of treatment modalities in elderly patients and patients with comorbidity[37]. Subsequently, guidelines can be improved to support decision-making.

Third, health care providers need to remain vigilant for common comorbidities when trying to coordinate care for these patients. Both in the preoperative and peroperative phase increased care coordination among multiple disciplines is needed respectively to optimize preexistent conditions and to anticipate on vulnerability to specific complications.

Last, health care providers should be aware of potential drug-drug, drug-disease, and disease-disease interactions. The combination of age-related physiological changes with multimorbidity result in less compensatory capacity and multi-organ dysfunction. Subsequently, there is a higher susceptibility to polypharmacy and adverse drug effects.

Therefore, careful monitoring of side effects is indicated and alertness to identify symptoms as possible adverse drug effects.

In conclusion, with an increasing prevalence of comorbid diseases in CRC, patients will become more at risk of complications and in need of more specialized and individualized care. In order to accomplish better personalized medicine, more knowledge about and attention to the role of comorbidity in CRC in both research and care is needed. The emphasis in research on cancer therapy should therefore convert to the interaction of concomitant diseases and ageing on therapy. This will open the doors to more individualized specific treatment regimes.

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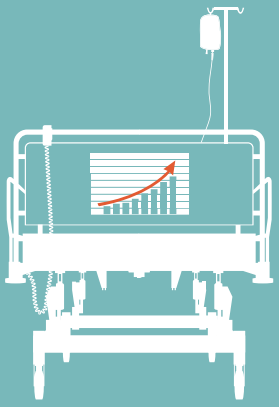

Chapter 5

Synchronous colorectal carcinoma: a risk factor in colorectal cancer surgery

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ABSTRACT

Objective: to evaluate clinical characteristics and treatment patterns of synchronous colorectal carcinoma and their influence on short-term postoperative outcomes in comparison with solitary colorectal carcinoma.

Design: Patients with primary colorectal carcinoma in the Dutch Surgical Colorectal Audit from 2009 to 2011 were included. Patient and tumor characteristics, treatment patterns and postoperative outcomes are described for patients with a solitary and synchronous colorectal carcinoma separately. Multivariable analysis is used to analyse the association between synchronous colorectal carcinoma and postoperative complications, reinterventions and mortality in comparison to solitary colorectal carcinoma.

Results: of 25.413 patients with colorectal cancer, 884 (3.5%) had synchronous colorectal tumors. Patients with synchronous colorectal carcinoma were older and more often of male gender compared to patients with solitary colorectal carcinoma. In at least 35% of cases an extended surgical procedure was conducted (n = 310). In multivariable logistic regression analysis, synchronous colorectal carcinoma were associated with a higher risk of severe postoperative complications (OR 1.40; CI 1.20 – 1.63) and reinterventions (OR 1.37; CI 1.14-1.65), compared to solitary colorectal carcinoma, but not with higher 30-day mortality (OR 1.34; CI 0.96 – 1.88).

Conclusions: synchronous colorectal carcinoma are prevalent in 3.5% of patients and require a different treatment strategy in comparison with solitary colorectal carcinoma. Postoperative outcomes are unfavourable, most likely due to extensive surgery.

INTRODUCTION

Colorectal cancer is the second most common cancer in terms of incidence in the Netherlands and its incidence is increasing.[1] In 1-8% of patients with colorectal cancer synchronous colorectal malignant tumors are present.[2-8] Known risk factors are familial polyposis and ulcerative colitis with dysplasia.[8] Preoperative diagnosis of synchronous colorectal cancer is important as it may influence clinical decision-making regarding type and extension of the surgical procedure and use of additional treatment modalities. Moreover, if overlooked, synchronous tumors may require additional surgery and may possibly grow into more advanced stages with risk of tumor spread. As the second cancer is often located in right colon, the risk of overlooking is conceivable especially in carcinoma causing obstruction. Therefore, most treatment guidelines include full colon examination in the preoperative phase (colonoscopy and CT colonography) parallel to the staging procedure aimed at identifying metastases.[9]

Current literature exists of mostly small series (less than 50 patients) in which epidemiology and clinicopathology are described. However, the influence of synchronous colorectal cancer on clinical decision-making and postoperative outcomes is less well studied.

In this study, we evaluate the impact of synchronous colorectal cancer on treatment and short-term postoperative outcomes in a large cohort of patients.

Methods

DSCA

About 90% of patients who underwent a resection for primary colorectal carcinoma in the Netherlands between 2009 and 2011 were registered in the DSCA.[10] All 92 Dutch hospitals providing colorectal cancer care, participated. The DSCA provides weekly feedback to participating hospitals on benchmarked performance indicators and establishes national improvement projects, an annual report and a conference on quality of colorectal cancer care. The dataset comprises detailed clinical information on all aspects of the treatment of colorectal cancer, including patient and tumor characteristics, diagnostics, surgical and (neo-) adjuvant treatment modalities, complications, 30-day postoperative mortality and pathology findings. Comorbidity was registered using a slightly modified version of the Charlson Comorbidity Index.[11] Details of this dataset regarding data collection and methodology have been published previously.[12] Both clinical and oncological data are validated on a yearly basis by comparison with the data registered in the Netherlands Cancer Registry.[13]

Patients

Patients undergoing surgery for primary colorectal cancer between January 1st 2009 and December 31th 2011 were included in this analysis. Patients undergoing local excision or resection for local recurrence of colorectal cancer are not included in the database, as are non-epithelial cancers (lymphomas, sarcomas, endocrine tumors). Synchronous colorectal cancer was defined as 2 or more malignant tumors present at time of surgical resection; the tumors had to be distinct and both evidently malignant (T1 carcinoma or higher according to TNM 5th edition) and the probability of one tumor being a metastasis of the other had to be excluded.

Variables

The diagnosis of synchronous caner was based on clinical findings during the primary treatment of colorectal cancer, either by diagnostics, intraoperative observation or pathology. The number of tumors found was registered. For two of these tumors, detailed clinical information on tumor characteristics, diagnostics, treatment and pathology information was registered. The most extensive tumor according to TNM stage was designated as the index tumor. The second tumor to be registered in detail was defined as the tumor most relevant for treatment (besides the index tumor). Patients were categorized into two groups accordingly: solitary CRC or synchronous CRC. According to national evidence based guidelines, all patients had a preoperative abdominal ultrasound or CT and a thoracic X-ray or CT. A total colonoscopy was defined as preoperative visualization of the entire colon including the entire ascending colon by colonoscopy or CT colonography. In case of an incomplete colonoscopy national guidelines advise a new colonoscopy within 3 months after surgery. No distinction was made between a 'standard' and an 'extended' colectomy during data collection. For 'combined resections' no information was available on whether more than one anastomoses was created. Postoperative complications were listed as 'severe' when they were accompanied with surgical or radiological reintervention, ICU readmission, length of hospital stay of 14 days or more, or postoperative mortality.

Statistical analysis

Baseline characteristics, treatment variables and outcomes were compared between both groups by either Chi Square test (categorical data) or student's t-test (continuous variables). A multivariable logistic regression analysis was performed to analyse whether the presence of synchronous tumors was associated with severe complications, reinterventions and 30-day postoperative mortality in comparison to

a solitary tumor, with adjustment for age, gender, ASA score, Charlson comorbidity index, disease stage and the urgency of surgery. Statistical significance was defined as $p<0.05$. All statistics were performed in PASW Statistics 20.

RESULTS

Patients

From 2009 to 2011, 25,413 patients with primary CRC were registered in the DSCA. Of these, 884 patients had synchronous CRC (3.5%). Patient and tumor characteristics are presented in Table 1. Patients with synchronous CRC were slightly older, more often had a male gender and had slightly more comorbidity when compared to patients with solitary CRC. Inflammatory bowel disease (ulcerative colitis or Crohns disease) was present in 211 patients, 0.8% of patients with solitary CRC and 0.6% of synchronous CRC, respectively. In 599 patients both tumors were localized in the colon (68%), in 38 patients both tumors were situated in the rectum (4.3%). Distribution of tumors in synchronous CRC in the (left and right hemi) colon and rectum are presented separately in Table 2.

Diagnostics

In 66% of all patients (n = 16,875), a total preoperative colonoscopy was performed. On hospital level, this percentage varied from 47-87%. In patients with synchronous CRC this was 72%. In 82% of patients with synchronous CRC (n = 712), two or more tumors were seen during total colonoscopy. In patients with synchronous CRC with at least one tumor in the rectum, (n = 285), 72% underwent a MRI; in solitary CRC, this was 82%.

Table 1. Patient and tumor characteristics of patients with synchronous and solitary colorectal carcinoma.

		Synchronous CRC	Solitary CRC	P
N		884	24.529	
Age	Mean	72.2 year (SD 10.1)	69.7 year (SD 11.5)	<0.001
Gender	Male	537 (61%)	13.319 (55%)	<0.001
BMI	Mean	26.2 (SD 4.3)	26.1 (SD 4.7)	0.90
Charlson Comorbidity Index	0	418 (48%)	13.567 (56%)	<0.001
	1	217 (25%)	5249 (22%)	
	2+	244 (28%)	5507 (23%)	
ASA score	I-II	632 (73%)	18334 (77%)	0.005
	III+	240 (27%)	5602 (23%)	
Ulcerative colitis/Crohn	yes	5 (0.6%)	206 (0.8%)	0.377
Urgency	Elective	787 (90%)	20742 (85%)	<0.001
	Urgent	93 (10%)	3727 (15%)	
Tumor stage	I	231 (26%)	5494 (22%)	0.045
	II	260 (29%)	8117 (33%)	
	III	273 (31%)	7437 (30%)	
	IV	95 (11%)	2858 (12%)	
	X	25 (2.8%)	620 (2.5%)	
Localisation*	Caecum	245 (14%)	3446 (14%)	<0.001
	Appendix	8 (0.5%)	124 (0.5%)	
	Ascending colon	243 (14%)	3159 (13%)	
	Hepatic flexure	79 (4,6%)	1102 (4.5%)	
	Transverse colon	169 (9.5%)	1264 (5.2%)	
	Splenic flexure	45 (2.7%)	551 (2.2%)	
	Descending colon	133 (7.4%)	1037 (4.2%)	
	Sigmoid colon	523 (29%)	6833 (28%)	
	Rectum	323 (19%)	7013 (29%)	

CRC = colorectal carcinoma. BMI = Body Mass Index. Crohn = Crohns disease. * for synchronous carcinoma a maximum of 2 tumors are counted per patient.

Table 2. Distribution of synchronous tumors over the colon and rectum

Synchronous colorectal tumors	N (%)
Right hemicolon – Right hemicolon	194 (22%)
Right hemicolon – Left hemicolon	245 (28%)
Right hemicolon – Rectum	111 (13%)
Left hemicolon - Left hemicolon	160 (18%)
Left hemicolon – Rectum	136 (15%)
Rectum - Rectum	38 (4.3%)

Right hemicolon = caecum to hepatic flexure
Left hemicolon = transverse colon to sigmoid colon

Treatment

Treatment variables are presented in table 3. For rectal tumours, short course radiotherapy schemes were similar in both groups, but the application of neo-adjuvant chemoradiation was lower for synchronous CRC (20%) when compared to solitary tumours (38%). In patients with synchronous CRC, extended surgery, in terms of length of intestine (e.g. subtotal colectomy, proctocolectomy or combined resection), were performed in at least 35% of cases (n = 310). For all different distributions of the synchronous tumors, the type of surgical resection are shown in figure 1. As expected, extended surgery was most often performed if synchronous tumors were located in the right hemicolon and rectum. Since, both hemicolectomy and extended hemicolectomy were registered as an "(extended) hemicolectomy", the actual percentage of extended operations may be even higher. Patients with synchronous CRC were less often treated by laparoscopy and during surgery more (permanent and deviating) stomas were constructed. There were no differences in the percentage of additional resections for metastasis or for tumor ingrowth into other organs between both groups.

Table 3. Treatment modalities in patients with synchronous and solitary CRC.

Variables	Categories	Synchronous CRC	Solitary CRC	P
Neo-adjuvant therapy*	Short course radiotherapy	140 (49%)	3362 (48%)	<0.001
	Chemoradiation	57 (20%)	2641 (38%)	
Type of surgery	Ileocaecal resection	6 (0.7%)	253 (1%)	<0.001
	(extended) Right hemicolectomy	205 (23%)	7645 (31%)	
	Transversectomy	10 (1.1%)	542 (2.3%)	
	(extended) Left hemicolectomy	111 (13%)	1737 (7.2%)	
	Sigmoid/anterior resection/ Hartmann	204 (23%)	10,657 (44%)	
	APE	38 (4.3%)	2145 (8.8%)	
	Subtotal colectomy	123 (14%)	337 (1.4%)	
	Proctocolectomy	61 (6.9%)	166 (0.7%)	
	Combined resections	126 (14%)	570 (2.3%)	
Additional resections	For metastasis	33 (3.7%)	782 (3.2%)	0.45
	For tumor ingrowth	79 (9.0%)	2,355 (9.6%)	0.13
Anastomosis or stoma	Anastomosis without stoma	536 (62%)	15,803 (67%)	0.02
	Stoma	200 (23%)	5041 (21%)	
	Anastomosis with deviating stoma	125 (14%)	2867 (12%)	
Laparoscopy	Open surgery	624 (73%)	15,092 (62%)	<0.001
	Laparoscopic	233 (27%)	9,102 (38%)	

CRC = colorectal carcinoma. APE = abdominal perineal excision.

* for rectal tumors only. n = 285 patients for synchronous CRC (323 tumors); for solitary CRC, n = 7013 patients.

Outcomes

Overall, the postoperative outcomes of synchronous CRC were less beneficial compared to the outcomes of solitary CRC (table 4). The percentages of postoperative complications, reinterventions and 30-day mortality were significantly higher in patients with synchronous CRC.

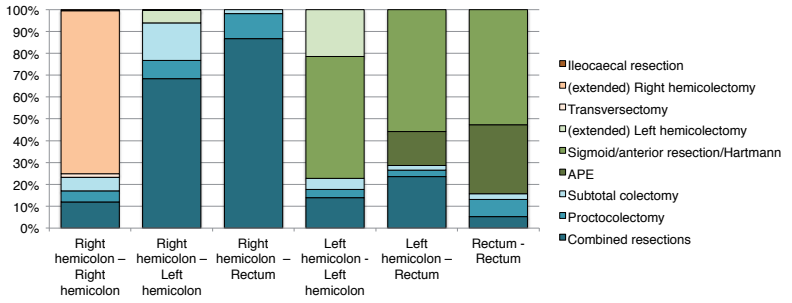

Figure 1: Type of surgical resection for the different distributions of the synchronous tumors. CRC = colorectal carcinoma. APE = abdominal perineal excision.

Also, time of hospital stay was significantly longer (14.0 versus 12.1 days respectively). After adjustment for patient and tumor related factors, having synchronous CRC was still associated with a higher risk of severe postoperative complications (OR 1.40, CI 1.20 – 1.63) and reinterventions (OR 1.37, CI 1.14 – 1.65), but not with a higher 30-day mortality (OR 1.34, CI 0.96 – 1.88) (table 5).

DISCUSSION

In this large population based study, synchronous CRC was prevalent in 3.5% of patients with CRC and was associated with a higher risk of severe postoperative complications and reinterventions after surgical resection compared to solitary CRC. The higher risk for worse short-term postoperative outcomes may be explained by the more extended surgical resection that is often required in synchronous CRC. The prevalence of synchronous CRC in our study was in concordance with earlier studies published on this subject.[6] However, many definitions have been used

Table 4. Outcomes of care in patients with synchronous and solitary CRC.

Variables	Categories	Synchronous CRC	Solitary CRC	P
Assessed lymph nodes	Mean	17.4	14.3	<0.001
Positive lymph nodes nodes	Mean	1.66	1.64	0.75
Any complication	Yes	355 (40%)	8320 (34%)	<0.001
Severe complications	Yes	271 (31%)	5687 (23%)	<0.001
Reintervention	Yes	164 (19%)	3426 (14%)	<0.001
Type of reintervention	Laparoscopy	5 (0.6%)	143 (0.6%)	0.973
	Laparotomy	116 (13%)	2380 (9.7%)	
	Radiologic	18 (2.0%)	364 (1.5%)	
	Other	34 (3.8%)	712 (2.9%)	
Complication requiring reintervention	Anastomotic leakage*	70 (10.6%)	1482 (8.0%)	0.01
	Abcess	33 (3.7%)	570 (2.3%)	0.39
	Bleeding	12 (1.4%)	193 (0.8%)	
	Ileus	9 (1.0%)	369 (1.5%)	
	Fascia dehiscence	16 (1.8%)	389 (1.6%)	
	Other	36 (4.1%)	829 (3.2%)	
	Blood transfusion	177 (20%)	3517 (14%)	<0.001
30 day mortality		42 (4.8%)	838 (3.4%)	0.03
Time of hospital stay	Mean	14.0	12.1	0.05

CRC = colorectal carcinoma. * represents percentage anastomotic leakage of patients with an anastomosis

Table 5. Multivariable logistic regression analysis for the risk for severe complications, reinterventions and 30-day postoperative mortality in patients with synchronous colorectal cancer.

		Severe complications	**Reinterventions**	**30-day mortality**
Variables	**Categories**	**OR [95% CI]**	**OR [95% CI]**	**OR [95% CI]**
Age	< = 65	Ref	Ref	Ref
	66-75	1.08 [1.00 – 1.17]	0.90 [0.82 – 0.99]	2.23 [1.68 – 2.95]
	76-85	1.24 [1.15 – 1.35]	0.92 [0.83 – 1.02]	4.57 [3.50 – 5.95]
Age	>85	1.43 [1.26 – 1.63]	0.70 [0.59 – 0.84]	8.73 [6.49 -11.73]
Gender	Male	Ref	Ref	Ref
	Female	0.65 [0.61 – 0.69]	0.66 [0.61 – 0.71]	0.75 [0.65 – 0.87]
ASA classification	I-II	Ref	Ref	Ref
	III+	1.65 [1.54 – 1.78]	1.19 [1.09 – 1.30]	3.21 [2.74 – 3.75]
Charlson Comorbidity Index	0	Ref	Ref	Ref
	1	1.17 [1.08 – 1.27]	1.23 [1.12 – 1.36]	1.34 [1.10 – 1.63]
	2+	1.31 [1.22 – 1.42]	1.22 [1.11 – 1.35]	1.73 [1.45 – 2.07]
Urgency	Elective	Ref	Ref	Ref
	Urgent	152 [1.40 – 1.65]	1.21 [1.09 – 1.35]	2.63 [2.23 – 3.09]
Laparoscopy	Open surgery	Ref	Ref	Ref
	Laparoscopic	0.69 [0.65 – 0.74]	0.86 [0.79 – 0.94]	1.33 [1.12 – 1.59]
TNM stage	I	Ref	Ref	Ref
	II	1.02 [0.94 – 1.11]	1.07 [0.97 – 1.18]	0.98 [0.79 – 1.22]
	III	0.96 [0.88 – 1.05]	0.99 [0.89 – 1.10]	0.98 [0.78 – 1.22]
	IV	0.96 [0.85 – 1.07]	0.81 [0.71 – 0.94]	1.88 [1.47 – 2.41]
	X	0.92 [0.75 – 1.14]	0.71 [0.54 – 0.94]	2.08 [1.38 – 3.14]
Synchronous CRC	No	**Ref**	**Ref**	**Ref**
	Yes	**1.35 [1.16 – 1.57]**	**1.35 [1.13 – 1.63]**	**1.31 [0.94 – 1.83]**

CRC = colorectal carcinoma. OR = odds ratio. CI = confidence interval. Ref = reference group.

in literature and often synchronous and metachronous CRC were used interchangeably, resulting in a wide range of described prevalence rates (1-8%).[3,5] The present study defined synchronous CRC as two or more malignant tumors present at time of surgery, as this was relevant for analysing associated postoperative outcomes.

Earlier studies on synchronous CRC focussed mainly on describing epidemiological and clinico pathological features.[5,6,8] These include predominance of male gender,[7] the presence of associated adenomas during colonoscopy, ulcerative colitis and Lynch syndrome.[6] The development of multiple synchronous tumors has been suggested to be largely due to somatic events arising by different molecular pathways. Microsatellite instability (MSI) and alterations in gene methylation have been described as possible pathways.[2,14] The origin of gender differences is presently unknown but most likely sexual hormones contribute.[10] With respect to age there is no clear consensus on its effect on the prevalence of synchronous colorectal cancer. In our study patients with multiple tumors were on average 3 years older than patients with solitary CRC. In most other studies these findings were supported, however there are also reports of younger and similar age of diagnosis in synchronous CRC. [7]

Although the pathological and epidemiological features have been described in multiple studies, clinical implications in terms of treatment and outcomes of care of synchronous CRC were seldom analysed. Information on differences in treatment and outcomes between solitary and synchronous CRC are relevant to evaluate the importance of identifying synchronous CRC preoperatively and to provide adequate preoperative counseling accordingly.

In this cohort, patient with synchronous CRC with at least one rectal tumor received less often neo-adjuvant therapy compared to solitary rectal tumors. Possibly, if a synchronous colon tumor is also present, chemoradiation therapy is more often omitted to avoid postponement of surgery. Otherwise, an unexpected intraoperative diagnosis of a synchronous rectal tumor may be the cause for a few cases for whom radiotherapy was omitted. Simultaneously, patients with synchronous CRC were more likely to receive a deviating or permanent stoma (respectively 37 versus 33%). At the same time, a lower percentage of patients with synchronous CRC underwent a laparoscopic surgical procedure. The type of surgical resection was extended in 35% of cases, most likely depending on the locations of the tumors and the presence of any underlying disease (Lynch syndrome or Familial Adenomatosis Polyposis). When deciding on the type of surgical resection for synchronous CRC (in absence of these underlying diseases), two groups can be distinguished:

(1) Tumors located in the same or adjacent segment (87% of patients in our population). In this group the choice for surgical resection is often simple: either a hemicolectomy or an extended colectomy with the adjacent segment. Reconstruction is achieved by means of one anastomosis and/or a stoma.

(2) Tumors not located in proximity to each other (13% of patients). If, for instance, one tumor is located in the right hemicolon and a synchronous tumor in the rectum, more extensive surgery is required. Either, two separate resections with two anastomoses can be performed, resulting in a higher risk of anastomotic leakage in return for preservation of the in between laying segments. Otherwise, a (sub) total (procto) colectomy is performed. Surgical decision-making is difficult in these cases and an individual approach is essential taking into account the patients preferences, physical performance status, number and location of tumors, the

extent of colon and/or rectal resection, the possible anastomoses and stomas.

The postoperative course after surgery was less beneficial in patients with synchronous CRC in our cohort. This was reflected in a significant longer time of hospital stay, more severe complications such as anastomotic leakage, reinterventions and postoperative mortality. Even after adjustment for differences in casemix, synchronous CRC appeared an independent risk factor for severe complications (OR 1.40; CI 1.20-1.63) and reinterventions (OR 1.37; CI 1.14-1.65). Thirty day postoperative mortality was however not significantly associated with synchronous CRC (OR 1.34; CI 0.96-1.88). In this database no information on long-term survival numbers was available unfortunately. In other studies, conflicting outcomes have been reported on the long-term prognosis of patients with synchronous CRC, likely caused by their limited sample size, but in larger studies no difference in survival rates were found. One study reported on a higher survival in females with synchronous CRC.[4] The results of this study indicate that patients with synchronous CRC should be informed on a higher risk of receiving a stoma during surgery and having a complicated postoperative course.

From a quality perspective, it is important to note that when comparing outcomes of care between hospitals providing CRC surgery, 'synchronous CRC' is seldom used for adjustment of differences in casemix. These data show that synchronous CRC is an independent determinant of a complicated postoperative course, indicating the relevance of this variable in such casemix adjustment models.

Synchronous CRC can constitute a clinical challenge in CRC surgery. Therefore, it needs to be identified in order to provide an optimal treatment. As 29% of tumors were located in the right colon (including

ascending colon), the importance of total colonoscopy cannot be overemphasized to prevent incomplete resection.
Earlier research shows a prevalence of metachronous CRC of 2.1% with a time interval ranging from 8 months to 20 years.[8] In another study, the authors found that early metachronous colorectal adenocarcinomas usually have a more advanced stage,[15] meaning that these carcinoma may have been missed during the first operation. A number of limitations of this study should be acknowledged. The data is self-reported, so selection bias cannot be completely excluded. However, the dataset is highly detailed and validated against data from the Netherlands Cancer registry and represents over 90% of patients operated on in all hospitals providing CRC surgery in the Netherlands (see methods). Another limitation concerns the risk adjustment. Although the DSCA collects a huge variety of potential casemix factors, there may have been unknown confounding casemix factors not included in the dataset, responsible for potential differences in outcome between solitary and synchronous CRC. Lastly, no information on long-term survival was present. Therefore, it is not known whether the initial unbeneficial outcomes after synchronous CRC surgery, actually resulted in worse outcomes on the long course as well. The strength of this study is the large population of synchronous CRC it presents. We believe it is the largest cohort published on this subject.

In conclusion, synchronous CRC are prevalent and require a different surgical treatment than solitary CRC. Postoperative complication and reintervention rates after surgery for synchronous CRC are unfavourable, most likely due to the extent of the resection.

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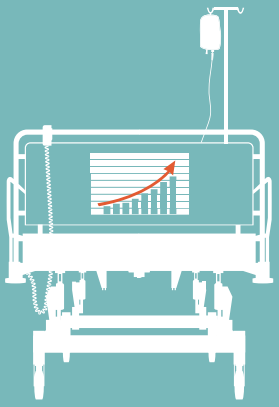

Chapter 6

Evaluating national practice of preoperative radiotherapy for rectal cancer based on clinical auditing

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ABSTRACT

Objectives: Internationally, the use of preoperative radiotherapy (RT) for rectal cancer varies largely, related to different decision-making based on the harm-benefit ratio. In the Dutch guideline, RT is indicated in all cT2-4 tumours. We aimed to evaluate the use of RT in the Netherlands and to discuss Dutch practice in the context of current literature.

Methods: Data of the Dutch Surgical Colorectal Audit (DSCA) were used and 6784 patients surgically treated for primary rectal cancer in 2009–2011 were included. The application and type of RT were described according to age, comorbidity, tumour localization and tumour stage at population level with analysis of hospital variation for specific subsets.

Results: In total, 85% of patients who underwent resection for rectal cancer received RT. Comorbidity (Charlson Comorbidity Index 2+) and older age (≥70 years) were associated with a slight decrease in application of RT (75 and 80% respectively). In stage I tumours, 77% of patients received RT, but large hospital variation existed (0-100%). The proportion chemoradiotherapy of the whole group of RT increased with increasing N-stage, increasing T-stage, decreasing distance from the anus, younger age and less comorbidity with hospital variation from 0-73%.

Conclusion: From a European perspective, a high percentage of rectal cancer patients is treated with RT in the Netherlands. Considerable hospital variation was observed for RT in stage I and the proportion of chemoradiotherapy among all RT schemes. Data from clinical auditing enable evaluation of national practice and current standards from both a scientific and international perspective.

INTRODUCTION

Preoperative radiotherapy (RT) has become an important modality in the treatment of rectal cancer. In the past, local recurrence was common after intentionally curative surgery for rectal cancer resulting in severe complaints, especially intractable pain, and poor prognosis[1,2]. After introduction of the technique of the total mesorectal excision (TME) technique in the 1980s, local recurrence rates were substantially reduced[3,4]. At the same time, combined modality treatment with radiotherapy gained interest[5,6]. In the late 1990s, the Dutch Colorectal Cancer Group performed a randomized controlled trial to evaluate the benefit of preoperative short course radiotherapy (SCRT) in addition to standardized TME compared to standardized TME alone[7]. As a result of preoperative SCRT, local recurrence rate dropped from 11 to 5%. Subsequently, a new standard for the treatment of rectal cancer with TME surgery, preoperative radiotherapy and standardized pathologic evaluation was set in the Netherlands.

However, reports on long term results of RT show unfavourable functional outcomes[8,9]. Also, the absolute risk reduction of local recurrence in stage I and II rectal cancer is limited[10,11]. The optimal criteria for selection of patients with rectal cancer who would benefit from RT are therefore increasingly debated. Due to major advances in imaging techniques, preoperative tumour staging has improved enabling tailored treatment[12]. In the Netherlands, current guidelines recommend RT for all stages of rectal cancer, except for T1N0 stage[13]. Preoperative treatment strategies for rectal cancer vary widely among Europe and even more worldwide[14].

Since 2009, all Dutch patients undergoing surgery for primary colorectal cancer are registered in the Dutch Surgical Colorectal Audit (DSCA).

The DSCA was initiated by the Dutch Surgical Society to monitor and improve the quality of surgical care in colorectal cancer patients on a national level. The aim of this study was to evaluate the application of RT in the Netherlands using the DSCA database and to discuss Dutch practice patterns in the context of the current literature. We focused on indication, guideline compliance and variation in treatment patterns among hospitals.

PATIENTS AND METHODS

Dataset

Data entry was web-based in a highly secured database. Each hospital appointed a surgeon responsible for data entry. The DSCA provides weekly online feedback to participating hospitals on benchmarked performance indicators and establishes national improvement projects, together with an annual report and conference on quality of surgical colorectal cancer care. Details of the dataset regarding data collection and methodology have been published previously[15]. Data completeness and accuracy are validated on a yearly basis by comparison with the data registered by the Netherlands Cancer Registry[16,17].

Patients and hospitals

In total, 90% of patients who underwent a resection for primary rectal cancer in the Netherlands from January 1th 2009 and December 31th 2011 were registered in the DSCA on March 1st 2012 and included for analysis. Patients who exclusively underwent a transanal local excision, were treated for local recurrence of rectal cancer or had multiple synchronous colorectal tumours were not registered in the DSCA. Patient records that did not contain information on tumour location, date of surgery or survival status at time of hospital discharge were excluded

(n = 229). All 92 Dutch hospitals involved in the surgical treatment of rectal cancer participated in the DSCA: 8 university hospitals, 46 teaching hospitals and 38 non-teaching hospitals.

Variables

The variables included were patient characteristics (age, gender, comorbidity according to the Charlson Comorbidity Index), tumour localization (<3, 3-4, 5-9 , ≥10 cm from the anal verge), tumour stage (TNM 5th edition), operative procedures (abdominoperineal excision (APE), low anterior resection (LAR) with primary anastomosis and Hartmann's procedure), diverting ostomy (yes/no) and type of preoperative radiotherapy. The latter was originally recorded as SCRT, chemoradiotherapy (CRT) and long course radiotherapy without concurrent chemotherapy (LCRT). Delaying surgery after SCRT is aimed at downstaging and/or downsizing in contrast to a short interval between SCRT and TME surgery[18]. Based on these two different treatment strategies, the following subsets were defined: (a) SCRT with a time interval to surgery of less than two weeks. When the time interval between SCRT and TME surgery was unknown (n = 977) it was considered less than 2 weeks (b), which is standard practice according to Dutch guidelines. Then, as only 3 percent of patients received LCRT and the indications being similar to CRT, both categories were combined and labelled as CRT (c). Postoperative radiotherapy was not included in the present analysis, because of the incidental use in the Netherlands (<1%).

Guidelines

Dutch evidence based guidelines for rectal cancer treatment, established in 2008, prescribe routine application of RT for all stages except cT1N0, regardless of the distance between the tumour and the anal verge. SCRT with short interval to surgery is standard preoperative treatment, but CRT is preferred in cT4 tumours, if a positive circumferential resection

margin (CRM) is expected, or if 4 or more lymph nodes appear to be tumour positive on preoperative imaging (cN2).

Analysis

Start date of radiotherapy and date of surgery are available in the DSCA database for the purpose of calculating time intervals. However, to calculate time interval to surgery from end of radiotherapy, time intervals between start date of radiotherapy and date of surgery were calculated and subsequently reduced with one week for SCRT and five weeks for CRT. The frequencies of the different types of RT were described according to age, gender, tumour localization, type of surgery and tumour stage. To evaluate guideline adherence, we calculated the percentage of patients with cT2-4 and cT1N1-2 tumours receiving RT, the percentage of patients with a cT1N0 tumour receiving RT, and the percentage of patients with a cT4 or cN2 stage treated with CRT. Hospital variation in the percentage of patients with stage I rectal cancer (cT1-2N0) treated with RT was presented in a scatterplot. Last, the ratio of CRT use to total use of RT was computed on hospital level and presented against hospital volume in a scatterplot as well. The relation between the proportion of CRT and hospital volume was analysed using Spearman's correlation coefficient. All statistics were performed in PASW Statistics, Rel. 18.0.2009. Chicago: SPSS Inc. Statistical significance was defined as $p<0.05$.

RESULTS

Patients and hospitals

A total of 6784 eligible patients were registered by 92 hospitals. Mean age was 67 years (range 18 to 95) and 62% of patients were males. Significant comorbidity (Charlson score ≥2) was recorded in 1252 patients (19%).

Preoperative staging

Preoperative imaging of the rectum consisted of MRI in 84% of patients (n = 5665), either with or without other imaging modalities. In the remaining patients, CT was performed in 6.1% (N = 415), transrectal ultrasound in 0.3% (N = 22), no imaging in 0.7% (n = 47), and imaging modalities were not registered in 9.4% of patients (n = 635). Patients were discussed in a preoperative multidisciplinary team meeting in 91%.

Preoperative radiotherapy

Of all patients with primary rectal cancer, 85% (n = 5745) received a certain type of RT: SCRT with short interval to surgery (<2 weeks) in 2970 patients (44%), SCRT with delayed surgery (interval >4 weeks) in 242 patients (3.6%), and CRT in 2533 patients (37%). For patients who underwent SCRT, the time interval to surgery was unknown in 30% of patients (n = 961). In Table 1, the use of the three types of RT according to patient-, tumour characteristics and treatment variables is listed. Older age (70+ years) and significant comorbidity was associated with a slightly lower application of RT: 80% and 77% respectively. Relatively less CRT and more SCRT were applied in these subgroups of patients. The distance from the anal verge was inversely related to the percentage of patients receiving RT and distal tumours were most often treated with CRT. This is also reflected in frequent application of RT and a high proportion of CRT in patients who subsequently underwent APR. Following CRT, a diverting stoma was constructed in 78% of patients with a primary anastomosis; the corresponding percentage after SCRT was 69%. The clinical TNM stage was registered in 83% of patients. In patients with stage I disease, the overall percentage of RT was 78% and CRT was applied in 6.6%. In stage IV rectal cancer, a relatively high percentage (10%) of patients received SCRT with delayed surgery. With each increasing tumour stage a larger part of patients were treated with RT and relatively more CRT was applied (figure 1). Also, with increasing

Table 1. Application of different types of preoperative radiotherapy according to age, comorbidity, distance of the tumour from the anal verge, surgical technique and clinical stage.

Variables	None (N = 1039)	SCRT TME< 2 weeks* (N = 2970)	SCRT TME> 4 weeks (N = 242)	CRT$ (N = 2533)
Age (years)**				
<70	450 (12)	1529 (40)	108 (2.8)	1708 (45)
≥70	588 (20)	1438 (48)	134 (4.5)	825 (28)
Charlson Comorbidity Index**				
2+	291 (23)	518 (41)	55 (4.4)	388 (31)
Distance to anal verge (cm)* *				
<3	73 (7.5)	334 (34)	46 (4.7)	520 (53)
3-4	55 (7.4)	307 (42)	28 (3.8)	349 (47)
5-9	189 (9.2)	968 (47)	79 (3.9)	809 (40)
10+	560 (23)	1136 (48)	75 (3.1)	623 (26)
Surgical technique**				
APE	163 (7.7)	744 (35)	92 (4.4)	1115 (53)
LAR/Hartmann	876 (19)	2226 (48)	150 (3.2)	1418 (30)
Diverting Ostomy**				
Yes #	195 (35)	1113 (69)	63 (64)	774 (78)
Clinical TNM stage**				
I	281 (22)	879 (69)	30 (2.4)	84 (6.6)
II	169 (11)	798 (52)	64 (4.1)	515 (33)
III	168 (7.2)	670 (29)	68 (2.9)	1417 (61)
IV	100 (20)	136 (27)	50 (10)	209 (42)

TME = total mesorectal excision; APE = abdominoperineal excision; SCRT = short course radiotherapy; CRT = chemoradiotherapy; LAR = low anterior resection; * including patients for whom the start date of radiotherapy was unknown. ** data registered for age (n = 6780), comorbidity (N = 6784), distance to the anal verge (n = 6151), surgical technique (n = 6784), ostomy (n = 6495), clinical TNM stage (n = 5638). # computed as the percentage of patients with different RT regimens that received a diverting stoma. $ including patients receiving long course radiotherapy without chemotherapy.

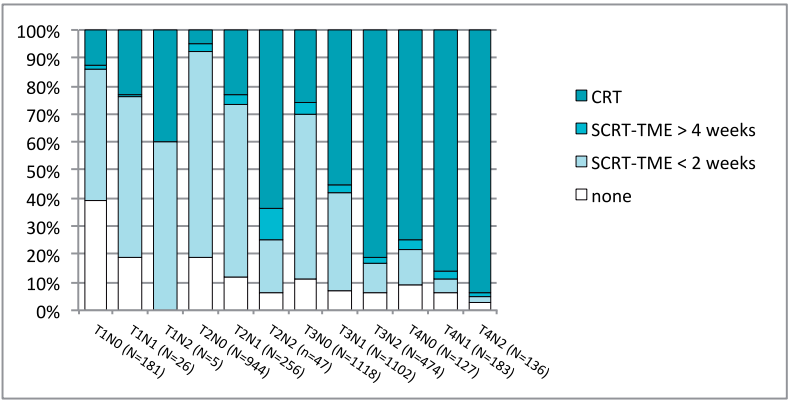

Figure 1. The use of different types of preoperative radiotherapy according to tumour and nodal stage (cM0). CRT = chemoradiotherapy SCRT = short course radiotherapy; TME = total mesorectal excision

cN stage, the number of patients treated with CRT increased markedly (OR 18.9, CI 15.15-23.50). Only 17% (n = 423) of all patients receiving CRT had a cT4 stage.

Guideline compliance

Of all patients with cT2-4Nx or T1N1-2 stage rectal cancer, who have an indication for RT according to Dutch guidelines, 88% received a certain type of RT. In cT1N0 stage, in which RT was not advised, 66% of patients received RT (figure 1). In cT4 and cN2 stage, 85% and 81% of patients were treated with CRT with an overall application of RT in 94% and 95% respectively (figure 3).

Hospital variation

Variation among different hospitals in application of RT for stage I rectal cancer ranged from 0 to 100%, though 96% of hospitals had a percentage of 50 or higher (figure 2). The ratio of CRT to total use of RT varied also between hospitals, with a percentage ranging between 0 and 73%

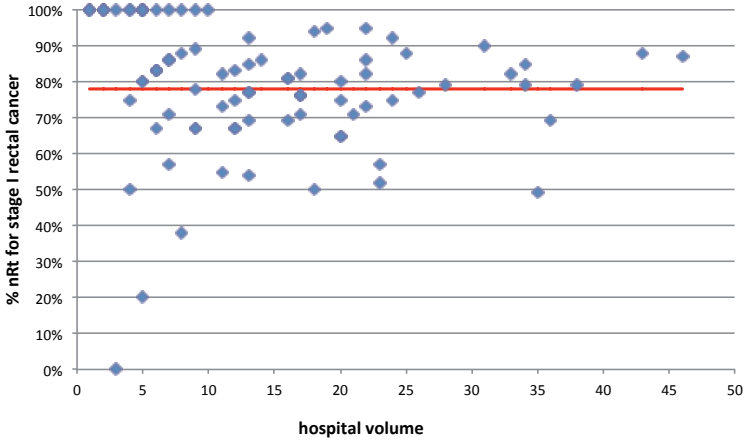

Figure 2. Hospital variation for the percentage of patients with clinical stage I rectal cancer who received preoperative radiotherapy. Each dot represents a hospital. The red line indicates mean on population level. nRT= preoperative radiotherapy.

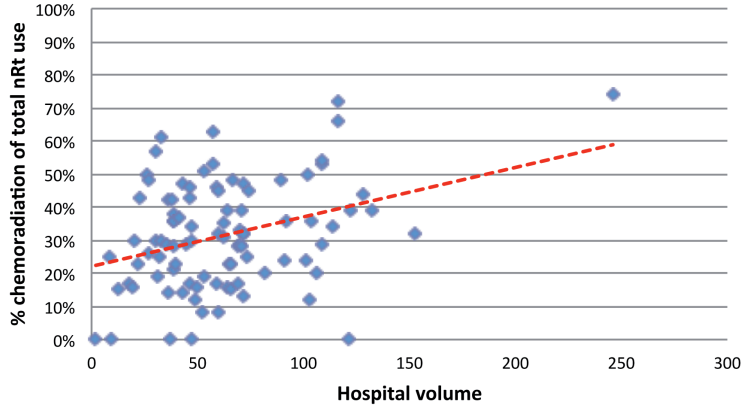

Figure 3. Hospital variation for the percentage of patients who received chemoradiotherapy of all patients receiving preoperative radiotherapy. Each dot represents a hospital. The dotted red line is a trend line for the correlation between chemoradiotherapy use and hospital volume. nRT= preoperative radiotherapy.

(figure 3). A weak correlation between hospital volume and the proportion of CRT was found ($r = 0.225$; $P = 0.031$).

DISCUSSION

Eighty-five per cent of Dutch patients surgically treated for rectal cancer in the period 2009 to 2011 underwent preoperative RT. In the Netherlands, preoperative radiotherapy seems to be considered as a routine part of treatment for rectal cancer, given the fact that even patients with cT1N0 disease received RT in 66%, which was decided by a multidisciplinary team in the majority of patients.

The percentage of RT use in the Netherlands is remarkably high compared to other European countries[14]. For example, the RT rate in Germany/Poland (41%) is half the Dutch RT rate. These figures reflect the broad indication as currently recommended in the Dutch guideline[13]. Substantial variation for both national evidence based guidelines and routine clinical practice regarding the application of RT is observed between countries[14,19].

An important reason for the lack of consensus is the rapid evolvement of diagnostic and treatment modalities, changing rectal cancer management and decreasing the applicability of evidence derived from large randomized controlled trials. None of the RT trials included routine MRI for clinical staging, which has become a cornerstone for patient tailored rectal cancer treatment.

Internationally, the indication for RT in early stage rectal cancer is currently under debate. Although a clear overall improvement in local recurrence rate was observed after the introduction of preoperative ra-

diotherapy, subgroup analyses showed that the absolute risk reduction of local recurrence depends on TNM stage. In stage I and II, the number needed to treat is about 30, though only 10 in stage III[10]. Also, the impact of RT on survival was found stage dependent. A significant overall survival benefit of radiotherapy was observed in stage III rectal cancer (10-year overall survival of 50 versus 40% for TME alone). However, in stage I and stage II disease, a non-significant trend towards excess mortality was seen in patients allocated to the RT group (respectively HR1.17, CI 0.86-1.59 and HR 1.19, CI 0.91-1.56)[10]. This suggests that a certain level of cancer specific survival benefit from RT is needed to compensate for non-rectal cancer related mortality related to RT.

The introduction of MRI for clinical staging has enabled better selection of patients who will benefit from RT. The MERCURY group and others extensively studied the sensitivity and specificity of preoperative staging by using MRI and its ability to determine prognostic factors for local recurrence[12,20-22]. With an optimal MRI technique, the distance of the tumour to the mesorectal fascia can be precisely determined and is strongly correlated to local recurrence risk[23]. Also, tumour growth into adjacent organs (cT4) and extramural invasion in cT3 tumours can be determined with high accuracy[12]. The latter is clinical important as extramural invasion of <5 mm (T3a, b) or >5mm (T3c, d) have similar prognosis as T2 and T4 tumours respectively[24]. By combining these prognostic factors into a risk profile, a subgroup of 'good prognosis' stage I-III rectal cancer representing 33% of patients from the MERCURY cohort, was treated by TME surgery alone. The local recurrence rate was only 3%[25]. More studies on MRI based risk profiling are needed to define subgroups of patients who can be safely treated by high quality TME surgery alone.

With the aim to reach more European uniformity in clinical practice of rectal cancer treatment, consensus meetings have been initiated by EURECCA[26]. It was concluded that patients with stage I rectal cancer receiving TME surgery do not require preoperative radiotherapy. This is almost complete in line with the guideline of the European Society of Medical Oncology in which TME surgery alone is advised for cT1-3aN0[27]. The considerable hospital variation regarding the use of RT in stage I rectal cancer in our study (0-100%) reflects an on-going debate in the Netherlands. The overall 66% RT use in cT1N0 tumours may be explained by the fact that MRI, which was performed in 86% of stage I patients, is not able to reliably discriminate cT1 from cT2 stage[28]. Consequently, advising to treat cT2N0 with RT in the current Dutch guideline has resulted in overtreatment of cT1N0 presumably by keeping on the safe side.

Discussing harm-benefit ratios of RT for rectal cancer is essential, because RT is associated with worse functional outcome compared to TME surgery alone. Herein, substantial increase in faecal incontinence is the most prominent, besides sexual dysfunction[8,9,29,30]. Patient preference studies showed that patients highly value functional outcomes and seem willing to accept a higher risk of local recurrence to achieve this [31,32].

The type of RT that is chosen is another clinically relevant discussion regarding treatment related toxicity[33,34]. The large variation between hospitals regarding the use of CRT (figure 3) may be indicative for this discussion. Considering the uniformly accepted indications for RT such as cT4 stage, a high level of guideline compliance was observed, with over 85% CRT use. Traditionally, CRT was used for irresectable tumours. Currently, the use of CRT is expanding rapidly given the fact that 83% of patients in our cohort had another indication than cT4. As no information on suspected CRM involvement on preoperative MRI is recorded in

the DSCA, a considerable percentage of patients who underwent CRT may have had a large T3 tumour with a threatened CRM. In addition, cN2 stage was often treated by CRT (overall 81%), independent of cT stage, as a result of the national guideline. However, the ability of MRI as a diagnostic tool for detection of tumour positive lymph nodes is limited[12,35] and not reliable according to European consensus[26].

Remarkably, CRT had been used in a substantial percentage in patients with cT1-2N0-1 tumours, which is not in accordance with the national guideline. This may reflect the growing attention for rectum saving surgery. Some hospitals participate in the CARTS study which enrols patients with cT1-3N0 tumours[36]. The treatment protocol consists of CRT followed by transanal endoscopic microsurgery (TEM) in case of good clinical response with subsequent 'wait and see' policy for ypT0-1 stages. It should be noted that local excisions were only registered in the DSCA if followed by completion TME surgery, not transanal resections alone.

Another interesting development we observed is the use of SCRT with delayed surgery (>4 weeks). The Stockholm III trial reported that this regimen increased the number of pathological complete responses from 0.8 to 12.5% compared to SCRT with surgery within a week[37]. This regimen is promising as it is also better tolerated than CRT in the elderly and patients with comorbidity while a similar downstaging effect is achieved[18,38,39]. In the M1 study, the feasibility of SCRT followed by systemic chemotherapy and finally resection of both primary and metastatic disease was demonstrated[40]. In our cohort, SCRT with delayed surgery was predominantly used for stage IV disease (10% of patients), which may indicate the implementation of the 'M1 study' protocol into routine practice. The effectiveness of this treatment schedule for locally advanced non-metastatic rectal cancer will be compared with CRT in

the RAPIDO study, which already started accrual in Sweden and the Netherlands[41].

In conclusion, from an international perspective, the use of RT for rectal cancer in the Netherlands is currently very high. In the light of international (consensus based) guidelines this can be interpreted as overtreatment. Existing evidence for seemingly less beneficial harm-benefit ratios for patients with early disease stages and the availability of better selection capabilities warn rapid modification of the Dutch evidence based guideline regarding the indication for RT. Most of all, these population based results underscore the importance of clinical auditing for gathering information on national practice, enabling us to evaluate our standards from both a scientific and international perspective.

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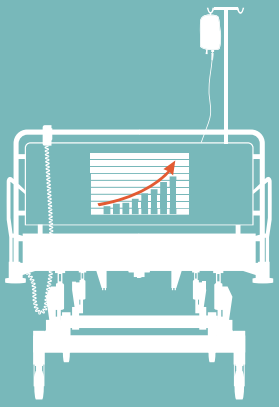
Part III

Clinical decision-making and treatment outcomes



Chapter 7

Differences in Circumferential resection margin involvement after abdominoperineal excision and low anterior resection no longer significant

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ABSTRACT

Objective: The aim of this study was to evaluate whether the abdominoperineal excision (APE) is associated with an increased risk of circumferential resection margin involvement (CRM) after rectal cancer surgery in comparison with low anterior resection (LAR).

Summary Background Data: The oncologic inferiority of the APE technique in comparison with LAR has been widely reported in literature. However, due to large evolvement in rectal cancer care, outcomes after APE may have improved since.

Methods: The population-based dataset of the Dutch Surgical Colorectal Audit (DSCA) was used selecting 5017 patients with primary rectal cancer undergoing surgery in 2010-2011. Propensity scores were calculated for the likelihood of performing an APE given relevant patient- and tumour characteristics, and used in the multivariate analysis of CRM involvement.

Results: The APE was associated with a slight, non-significant, increased risk of CRM involvement [OR 1•33; CI 0.93 – 1.90]. Absolute percentages of CRM involvement were 8 and 12 percent after LAR and APE respectively. In subgroup analysis, advanced rectal tumors (cT3,4) were associated to a higher risk of CRM involvement after APE (OR 1.61; CI 1.05-1.90), whereas smaller tumors (cT1,2) were not [OR 0.62, CI 0.27 – 1.40].

Discussion: The results suggest that on a national level the APE procedure itself is not a strong predictor anymore for CRM involvement after rectal cancer surgery. However, in advanced tumors, results after APE are inferior to LAR.

INTRODUCTION

In an era, when total mesorectal excision (TME) surgery was not standard, local recurrences occurred in up to 29% of patients[1,2] and were responsible for severe morbidity and poor prognosis[3]. The introduction of TME and preoperative radiotherapy reduced local recurrence rates significantly, resulting in improved oncological outcomes after rectal cancer surgery[4-6].

However, several studies have reported that relatively high rates of circumferential resection margins (CRM) involvement persist in patients undergoing an abdominoperineal excision (APE) and an associated worse survival is observed in these patients compared to patients undergoing sphincter saving surgery[7]. This may be explained by technical problems encountered during APE as was observed during pathological examination of specimens of the Dutch TME trial: more iatrogenic tumour perforations and positive resection margins occurred in APE surgery due to suboptimal resection planes[8]. Also, the characteristics of tumors that require an APE may be more challenging, since APE is indicated mainly in more advanced tumors in the lower rectum[7].

In a pooled analysis of 5 large European trials performed between 1987-2003 (n = 5187), Den Dulk et al. showed that independent of patient and tumour characteristics underlying the decision to perform an APE (age, gender and tumour localization), the surgical procedure of the APE itself was associated with an increased risk of CRM involvement, local recurrence rate and cancer specific death[9].

However, management of rectal cancer has evolved significantly in the last decades[10]. The finding that the APE technique was oncological inferior to LAR has led to increasing calls to improve APE surgery.

New extended surgical approaches have been developed which are believed to have increased radicality rates[11]. Also, the increased use of neoadjuvant chemoradiation has enabled downstaging and downsizing of advanced tumors, which also has helped to increase the radical CRM rate[12]. Even more, large advances in diagnostics have occurred with the implementation of standard preoperative high-resolution MRI. This has led to improved preoperative staging and visualization of the tumour, supporting surgeons in the selection of patients for neoadjuvant therapy and deciding which surgical technique to use and optimal dissection of the surgical plane[13].

Considering the enhancements in diagnostics and treatment modalities, one may question the applicability of results from earlier studies to current practice and whether the oncological outcomes after APE are still inferior in comparison with low anterior resection (LAR). Since 2009, all patients undergoing surgery for primary colorectal cancer are registered in the Dutch Surgical Colorectal Audit (DSCA) in the Netherlands. The DSCA was initiated by the Dutch Surgical Society to monitor and improve the quality of surgical care in colorectal cancer patients on a national level. We aimed to investigate whether APE is associated with a higher risk of CRM involvement after rectal cancer surgery in comparison with LAR using this population-based database.

PATIENTS AND METHODS

DSCA

About 94% of patients who underwent a resection for primary colorectal carcinoma in the Netherlands between 2010 and 2011 were registered in the DSCA[14,15]. All 92 Dutch hospitals participated. The DSCA provides weekly feedback to participating hospitals on benchmarked perfor-

mance indicators and establishes national improvement projects, an annual report and conference on quality of colorectal cancer care. Details of this dataset regarding data collection and methodology have been published previously[16]. The dataset was based on evidence-based guidelines and validated on a yearly basis by comparison with the data registered in the Netherlands Cancer Registry[15]. Patients undergoing surgery for primary rectal cancer between 1th of January 2010 and December 31th 2011 were included for this analysis. Patients treated for recurrent colorectal carcinoma and local excisions were not registered. Patient with an unknown distance of the tumour from the anal verge were excluded.

Endpoints and statistics

Patient, tumour, treatment and hospital characteristics as well as CRM involvement were described for patients who underwent an APE or LAR separately. TNM 5th edition was used. cTNM staging was based on diagnostics prior to neoadjuvant therapy. The CRM was considered positive if tumour cells were in 1mm or less distant from the resection margin. In patients for whom the CRM was registered, the distance of the tumour to the CRM was plotted against the tumour localisation and both cT and pT stage.

To evaluate whether the technique of APE is inferior to LAR concerning CRM involvement in the DSCA, the methods used in the fore mentioned pooled analysis of five randomized European rectal cancer studies[9] were carefully repeated. First, relevant patient- and tumour related characteristics were identified that could have influenced the choice for APE by preference over LAR. Subsequently, it was analysed whether involvement of the CRM was related to the type of surgery itself or to the patient- or tumour characteristics associated with the decision to perform a specific type of surgery. Age, gender, Charlson Co-morbidity

Index, tumour localization, cT stage, cN stage were considered as information on these factors was available at the time of surgery. Using univariate logistic regression analysis, these factors were evaluated for their association to the choice to perform an APE (statistical significance was set at $p<0.10$). The following factors were significant and included in multivariate logistic regression analysis: gender, tumour localization, cT stage and neoadjuvant therapy.

Then, a propensity score was calculated from the multivariate analysis as the predicted likelihood to perform an APE given these patient and tumour related risk factors[17]. A low score corresponds with a low probability of undergoing a specific type of surgery and a high score corresponds with a high probability. In a multivariate logistic regression model with inclusion of propensity scores, the type of surgery performed was assessed as a predictor for the risk of CRM involvement. Next, it was analysed whether the type of surgery was associated with CRM involvement independent of the surgical approach (laparoscopy or open). Therefore, a multivariate logistic regression analysis was performed, evaluating the association of APE and CRM involvement with inclusion of all above-mentioned factors in addition of surgical approach.

The multivariate analysis for CRM involvement comparing APE and LAR was repeated for selected subgroups of patients stratified by gender, cT stage, distance of the tumour to the anal verge and surgical approach. The derived odds ratios and confidence intervals were presented in a forest plot.

To evaluate whether experience on hospital level had an impact on CRM involvement after rectal cancer surgery, a pearson's correlation coefficient was calculated for hospital volume and CRM involvement.

All statistics were performed in PASW Statistics, Rel. 18.0.2009. Chicago: SPSS Inc.

RESULTS

Patients and Hospitals

In the DSCA, a total of 5017 patients were registered by all 92 Dutch hospitals. After exclusion for stage IV rectal cancer (n = 376), unknown distance of the tumour to the anal verge (n = 425) and, age ≤ 18 years (n = 2), 4214 patients were included for analysis. Mean age was 67 years [ranging from 18 to 95] and 62% of patients were males. Significant comorbidity (e.g. Charlson Comorbidity Index 1 or higher) was registered in 1688 patients (40%). A MRI was performed in 86% of patients, a pelvic CT in 6% and in 1% no pelvic imaging was performed (7% was unknown). Ninety four per cent of patients were discussed in a preoperative multidisciplinary team meeting. Neoadjuvant radiotherapy was applied in 85% of patients (n = 4256); 48% of patients received short course radiotherapy and 37% chemoradiation.

Treatment patterns

A LAR was performed in 2969 patients (71%), an APE in 1245 patients (29%). After LAR, a deviating ostomy was constructed in 68% of patients. In table 1, the frequency of different treatment modalities is outlined against patient and tumour characteristics and hospital volume. Factors associated with the performance of an APE, presented in table 2, were male gender, advanced cT stage, and tumors close to the anal verge (0-3 cm). The percentage of patients who underwent an APE or LAR in the different cT stages and distances from the anal verge is presented in figure 1. The percentage of resections in tumors 0-3 cm performed by an APE is 81%, and 33% of tumors 4-7cm from the anal verge. In 49% of all cT4

Table 1. Patient and tumour characteristics presented separately for patients treated with a LAR including Hartmann's procedure and an APE.

	Total **N**	**LAR** **N (%)**	**APE** **N (%)**
Total	4214	2969 (71)	1245 (29)
Gender*			
Female	1591	1161 (73)	430 (27)
Male	2623	1808 (69)	815 (31)
Age			
≤60 years	1076	737 (69)	339 (32)
61-70 years	1412	993 (70)	419 (30)
>70 years	1726	1239 (72)	487 (28)
Charlson Comorbidity Index			
0	2314	1618 (70)	696 (30)
≥ 1	1584	1130 (71)	454 (29)
Tumor distance to anal verge			
0-3 cm	921	173 (19)	748 (81)
4 -7 cm	1076	718 (67)	358 (33)
>7 cm	2217	2078 (94)	139 (6)
cT stage			
cT1/T2	1182	893 (76)	289 (24)
T3	2112	1479 (70)	633 (30)
T4	321	165 (51)	156 (49)
cTx	599	432 (72)	167 (28)
cN stage			
N0	1746	1234 (71)	512 (29)
N+	1756	1230 (70)	526 (30)
cNx	712	505 (71)	207 (29)
Preoperative radiotherapy			
None	566	473 (84)	93 (16)
5x5 Gy	2079	1580 (76)	499 (24)
Chemoradiation	1569	916 (58)	653 (42)

Table 1. Patient and tumour characteristics presented separately for patients treated with a LAR including Hartmann's procedure and an APE. (continued)

	Total N	LAR N (%)	APE N (%)
(y)pT stage	4181		
pT0/is/T1/T2	2083	1427 (69)	656 (31)
pT3	1926	1407 (73)	519 (27)
pT4	172	113 (66)	59 (34)
(y)pN stage	4108		
N0	2756	1919 (70)	837 (30)
N+	1352	979 (73)	340 (27)
Surgical approach			
Open	2439	1677 (69)	762 (31)
Laparoscopy	1775	1292 (73)	483 (27)
CRM involvement			
No	2745	1900 (69)	845 (31)
Yes	269	159 (59)	110 (41)
Unknown***	1200	910 (76)	290 (24)
Annual hospital volume			
<20 procedures	1058	757 (72)	301 (28)
20-50 procedures	2200	1532 (70)	668 (30)
>50 procedures	956	680 (71)	276 (29)

LAR = low anterior resection; APE = abdominoperineal excision; CRM = circumferential resection margin

Table 2. Multivariate logistic regression analysis for type of surgery (LAR/Hartmann's versus APE)

	APE	
Variables	**OR**	**95% CI**
Gender		
Female	1.00	
Male	1.24	1.03 – 1.49
Tumor distance to anal verge		
>7 cm	1.00	

Table 2. Multivariate logistic regression analysis for type of surgery (LAR/Hartmann's versus APE) (continued)

	APE	
Variables	**OR**	**95% CI**
4 -7 cm	7.39	5.87 – 9.29
0-3 cm	61.91	48.55 – 78.96
Tumor stage		
cT1/2	1.00	
cT3	1.12	0.89 – 1.40
cT4	2.58	1.79 – 3.73
cTx	1.16	0.87 – 1.56
Neoadjuvant therapy		
None	1.00	
5x5 Gy	1.09	0.79 – 1.50
Chemoradiation	1.65	1.19 – 2.30

LAR = low anterior resection; APE = abdominoperineal excision;
OR = odds ratio; CI = confidence interval

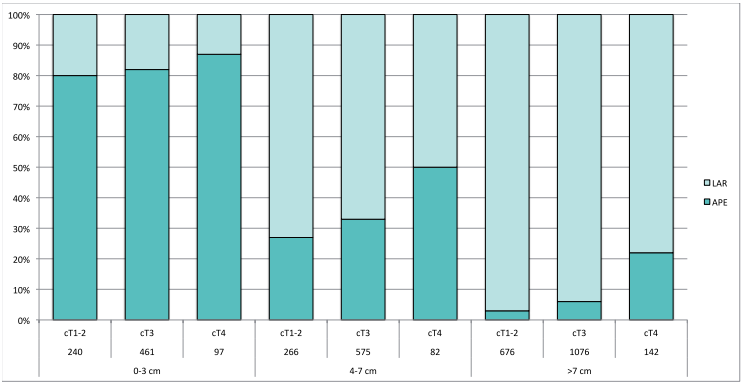

Figure 1. Percentage of resections performed by an APE or LAR by cT stage and distance of the tumor to the anal verge (cm). With exclusion of cTx tumors. APE = abdominoperineal excision;LAR = low anterior resection

tumors an APE was performed, but this was most pronounced in tumors close to the anal verge (0-3 cm).

CRM involvement

The analysis of CRM involvement was limited to 3014 patients for whom the CRM status was known. Tumour cells were found in 1mm or less distance from the mesorectal fascia in 269 patients (9% of patients for whom the CRM was known). A positive CRM was registered in 159 of 2059 patients (8%) treated with an LAR, 110 of 955 patients (12%) treated with an APE (table 1). In figure 2, the (distribution of) distances of the tumour to the circumferential resection margin is shown, according to tumour localisation and clinical (a) or pathological (b) tumour stage. Chemoradiation was applied in 12% of cT1-2 tumors, 47% of cT3 tumors and 83% of cT4 tumors. Positive margins were seen more frequently in distal tumors (0-3 cm) and in advanced tumour stages irrespective of tumour localization.

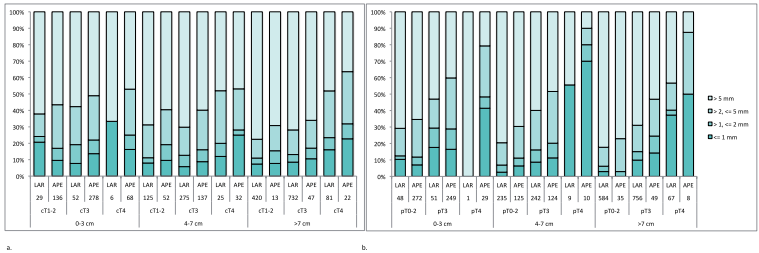

Figure 2. Percentage of resections with involvement of the circumferential resection margin after low anterior resection and abdominoperineal excision according to cT stage (a) or pT stage (b) and distance of the tumour to the anal verge (cm). With exclusion of cTx (a) and pTx (b) tumors. CRM+ = circumferential resection margin involvement. APE = abdominoperineal excision. LAR = low anterior resection

The multivariate prognostic factor analysis for CRM involvement is presented in table 3. The APE was associated with a higher, though not statistical significant increased, risk of CRM involvement (OR 1.33; 95% CI 0.93 – 1.90). In figure 3, the results are presented for subgroups of

Table 3. Multivariate logistic regression analysis for circumferential resection margin involvement

Variables	OR	95% CI low-high
a.		
Type of surgery		
LAR/Hartmann	1.00	
APE	1.33	0.93 – 1.90
Propensity scores	1.42	0.83 – 2.44
b.		
Type of surgery		
LAR/Hartmann	1.00	
APE	1.34	0.93 – 1.93
Gender		
Female	1.00	
Male	1.03	0.79 – 1.34
Tumor distance to anal verge		
>7 cm	1.00	
4 -7 cm	0.83	0.58 – 1.19
0-3 cm	1.19	0.78 – 1.80
Tumor stage		
cT0/1/2	1.00	
cT3	1.14	0•82 – 1.57
cT4	2.14	1.34 – 3.42
cTx	0.71	0.43 – 1.18

Table 3. Multivariate logistic regression analysis for circumferential resection margin involvement (continued)

Variables	OR	95% CI low-high
Neoadjuvant therapy		
None	1.00	
5x5 Gy	0.52	0.36 – 0.77
Chemoradiation	0.56	0.37 – 0.85
Surgical approach		
Open	1.00	
Laparoscopy	0.76	0.58 – 1.00

LAR = low anterior resection; APE = abdominoperineal excision; CRM = circumferential resection margin; OR = odds ratio; CI = confidence interval

a. multivariate logistic regression with propensity scores.

b. multivariate logistic regression with separate covariates and addition of the surgical approach.

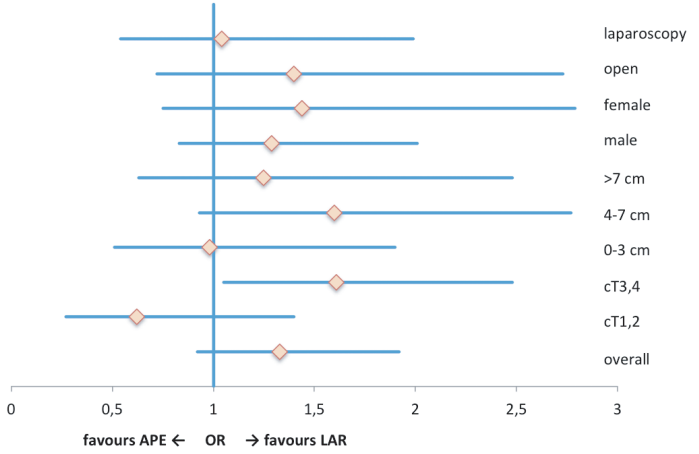

Figure 3. Forest plot representing the odds ratios and confidence intervals of low anterior resection (including Hartmann's) versus abdominoperineal excision for circumferential resection margin involvement seperately presented for subgroups as gender, distance of the tumour to the anal verge and cT stage.

APE = abdominoperineal excision; LAR = low anterior resection; OR = odds ratio

patients in a forest plot. Only in cT3 and cT4 tumors, the APE was significantly worse than LAR (OR 1.61; CI 1.05-1.90). In contrast, in cT1 and cT2 tumors, an OR of 0.62 (CI 0.27 – 1.40) was observed indicating a (non-significant) favour of the APE. In both laparoscopic and open surgery, the differences between APE and LAR were non-significant (respectively, OR 1.04 CI 0.52 – 1.99 and OR 1.41 CI 0.92 – 2.15). Analyses of correlation did not show a volume – outcome relation for CRM involvement on hospital level (Pearson Correlation Coefficient = -0.112, p = 0.29).

DISCUSSION

This population-based study indicates that the decision to perform an APE in patients with rectal cancer is associated with a slight increased risk of CRM involvement in comparison to LAR (OR 1.33; CI 0.92-1.92). Although the absolute percentage of CRM involvement was higher after APE than LAR (12 versus 8%), after adjustment for factors associated with the performance of an APE (advanced tumour stage, distal tumors, male gender and preoperative chemoradiation), the differences in outcomes between both techniques were diminished. In subgroup analysis of patients according to gender, tumour localization, cT stage and surgical approach, no significant differences between LAR and APE were observed except for cT3-4 tumors, in which the APE was associated with a higher risk of CRM involvement (OR 1.61; CI 1.05–2.48).

The oncologic inferiority of the APE technique has been widely reported in literature. However, often the data originated from trials, which were designed to address other endpoints, applied specific patient selection criteria, or were held in dedicated high volume centres. Also, outcomes after APE were often not corrected for tumour characteristics related to the decision to perform an APE. In a recent systematic review of litera-

ture, it could not be distinguished whether (unfavourable) selection bias of tumour characteristics or the operative technique itself was accountable for the inferior outcomes after APE[7].

In the analysis of Den Dulk et al., who adjusted outcomes for gender, age and distance of the tumour to the anal verge (but not T stage), the technique of APE was found to be inferior to LAR in CRM involvement (OR 2.52, CI 1.6-3.4), local recurrence and survival[18]. The analysis included aggregated data of five European trials performed between 1988-2003: Swedish Rectal Cancer Trial (SCRT)[19], Dutch TME trial[4], German CAO/ARO/AIO[20], EORTC 22921 trial (EORTC)[21], Polish Rectal Cancer Trial (PRCT)[22]. Since in 3 out of these 5 trials only advanced tumors were included, for the comparison of CRM involvement after LAR and APE by Den Dulk only cT3-4 tumors were included. In the present study, all cT stages were included. In subgroup analysis of cT3-4 tumors in this study, the difference between APE and LAR in terms of CRM involvement was also significant, although the odds ratio was much smaller in comparison with the results of the European trials (OR 1.61, CI 1.05-1.90).

Since CRM involvement is a strong predictor for local recurrence and an important marker for long-term oncological outcomes in rectal cancer surgery[23], our results may indicate an improvement of oncological outcomes after APE surgery in the last decade. Apart from that, the results of the European trials may not be representative anymore for current practice, because of the evolvement in rectal cancer management during the last two decades.

First, the emergence of standard preoperative high-resolution MRI has entailed more accurate preoperative staging and visualization of the tumour. The availability of detailed imaging information on the relationship of the tumour to the sphincter complex have supported surgeons

to choose appropriate surgical technique and dissection planes to achieve a negative CRM[13]. Especially in APE surgery, suboptimal dissection planes have been associated with tumour perforations and CRM involvement. In none of the 5 European trials, MRI was recommended or routinely performed. Today, preoperative MRI is considered routine diagnostics in rectal cancer surgery and performed in at least 86% of patients in the Netherlands[15]

Second, the role of neoadjuvant treatment has increased for obtaining local control. Especially, chemoradiotherapy is increasingly used for downsizing/down staging enabling radical surgery more often. Its indication has widened beyond T3-4 tumors[24]. Recently, studies have shown that MRI can be used for better selection of patients for neoadjuvant (chemo-) radiotherapy reducing under- and overtreatment of patients[25].

Third, the recognition that CRM involvement is associated with local recurrence has led to the standardization of TME resection and the conviction that colorectal cancer surgery should only be performed by specialized and experienced surgeons. Routine TME surgery for all rectal cancer surgery was applied only in two out of 5 European trials[8,14]. In the EORTC study, TME surgery was recommended, but only 6 years after starting accrual. Today, TME surgery is standard performed. Thereby, new extended surgical approaches to improve outcomes after APE have been developed which increase radicality rates. During the conventional APE the mesorectal plane, which tapers towards the distal rectum, is followed during resection. This results in formation of a 'waist' at the level of the levator sling. At this level, an increased risk of CRM involvement or tumour perforation exists. In new techniques such as the extralevator approach, the pelvic muscles are removed en-bloc with the specimen, which avoids tapering and subsequently results in a decrease of positive margins and iatrogenic tumour perforations. Various studies have dem-

onstrated that after an extralevator approach the number of positive resection margins can be reduced and may lead to similar results as for low anterior resection[11,26]. However, it is not clear to what extent these new techniques have been implemented in general practice and which results are achieved with this technique when performed outside clinical trials. In the DSCA, no information is available on the specific surgical technique of APE (e.g. extralevator or not), nor on the figure of the specimen. In a recent survey among 46 of Dutch hospitals participating in the DSCA, less than 5% of surgeons chose for the prone position as their standard approach. Therefore, it may be anticipated that positioning of the patient in prone position did not contribute to the results found[27].

Last, the focus on a multidisciplinary effort when treating rectal cancer has led to national evidence based multidisciplinary guidelines and the establishment of preoperative multidisciplinary team meetings in several countries. Although a survival benefit has not been proven, multidisciplinary team decisions have an impact on treatment strategies[28]. In the Netherlands, the performance of a MRI, preoperative multidisciplinary assessment and the use of neoadjuvant radiotherapy in T3-4 rectal cancer are defined as national quality indicators and are therefore mandatory for all rectal cancer patients.

The percentage of positive resection margins varies largely in literature[29]. In comparison with the Dutch TME trial, the CRM involvement in our study was lower both after APE (12 versus 29%), and LAR (8 versus 12%)[8]. In the present study, however, there was an under registration of CRM of 30% of patients. Although the nationwide availability of information on CRM involvement after rectal cancer surgery is exceptional to our knowledge, this was a limitation of our study. The under reporting was not related to tumour characteristics, e.g. it was seen both in tumors that were likely to have a positive CRM and those less likely (data not shown).

We therefore believe this only had a limited influence on our results. This issue also hampered the pooled analysis of European studies, in which information on the CRM was unknown in 25% of patients.

The frequent absence of information on the CRM is remarkable, especially since the CRM is known to be the most important factor predicting local recurrence. Furthermore, as a high correlation is observed between a positive CRM, poor quality of TME technique, local recurrence and a decreased 5-year survival[30,31], refinement on this issue could improve prognosis of patients. The pathologist has a very important task in quality assurance for rectal cancer surgery[32]. Using the DSCA, frequent feedback of missing information on CRM involvement was provided to surgeons, urging for standard reporting by pathologists. Furthermore, after the implementation of a national performance indicator for the registration of the CRM after rectal cancer surgery in the Netherlands, the percentage of registered CRMs improved largely (2010 to 2011, respectively 60 to 80%)[15]. These accomplishments underscore the importance of a nationwide approach to optimization of patient management with regard to oncological outcomes.

Although it appears that the results after APE in relation to the LAR have improved when compared to the European trials, comparing population-based data to the results of clinical trials warrants awareness of some limitations that might introduce bias. First, in the pooled analyses, a positive CRM was defined as the presence of tumour cells in the resection margin. In the present study we used the definition of Quirke and Dixon: tumour cells ≤1 mm of the surgical resection margin, which was validated for its ability to predict local recurrence and survival[23]. Therefore, absolute CRM percentages were not comparable between both studies. Second, due to in- and exclusion criteria of the trials, the distribution of patient and tumour characteristics may be different

from our population. Third, it is well known that the results of centres participating in clinical trials cannot always be extrapolated to general practice. Last, since the CRM is a strong, but not the only predictor for local recurrence, follow-up studies are needed to demonstrate whether oncological outcomes after APE as local recurrence rates and survival have been improved indeed.

A potential limitation of this study is that the cT stage, which was used as a casemix factor for comparing outcomes after LAR and APE, was registered prior to neoadjuvant therapy. Therefore, the actual cT stage at time of surgery may have been different due to possible downsizing and may have influenced clinical decision-making (e.g. choosing for a specific surgical technique). In this light, the pT stage may better represent the actual tumour size and ingrowth at time of surgery. This variable was not used in our initial analysis, as propensity scores do not allow adjusting for variables not known at time of surgery[17]. However, for the purpose of disproving any potential subsequent bias, we repeated the analysis for comparing the CRM involvement after APE and LAR using the pT stage as a casemix factor instead of the cT stage. The result was almost similar (OR 1.28, CI 0.90–1.82).

The strength of our study is the large cohort that was examined, including all Dutch hospitals and covering 94% of patients that underwent rectal cancer surgery in the audit period. It is therefore highly representative of the Dutch population and the quality of rectal cancer surgery in the Netherlands.

Conclusion

These results indicate that the technique of APE for rectal cancer surgery is not significantly inferior to LAR concerning CRM involvement. It appears that the results after APE have improved in relation to the

LAR when compared to the time when TME surgery was introduced. Both awareness of poor outcomes after APE and enhancements in diagnostics, neoadjuvant therapy use and surgical technique may have improved radicality rates. It does remain worrisome however that the pathologic reports in the Netherlands not always provide information on CRM involvement which limits good quality control. Optimal preoperative staging, a multidisciplinary approach of treatment and standardized surgery and pathology are critical to improving the prognosis of patients with rectal cancer. Quality of care for rectal cancer can be monitored and improved by clinical auditing.

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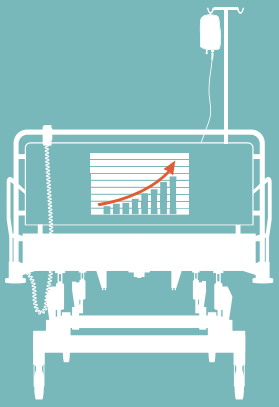

Chapter 8

Optimal treatment strategy in rectal cancer surgery; should we be cowboys or chickens?

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ABSTRACT

Background and purpose: Surgeons and hospitals are increasingly accountable for their postoperative complication rates, which may lead to risk averse treatment strategies in rectal cancer surgery. It is not known whether a risk-averse strategy leads to providing better care. In this study the association between hospitals' strategy regarding defunctioning stoma construction and postoperative outcomes in rectal cancer treatment was evaluated.

Methods: Population-based data of the Dutch Surgical Colorectal Audit including 3104 patients undergoing rectal cancer resection between January 2009 to July 2012 in 92 hospitals were used. Hospital variation in (casemix-adjusted) defunctioning stoma rates was calculated. Anastomotic leakage and 30-day mortality rates were compared in hospitals with high and low tendency towards stoma construction.

Results: Of all patients, 76% received a defunctioning stoma; 9.6% of all patients developed anastomotic leakage. Overall postoperative mortality rate was 1.8%. Hospitals' adjusted proportion of defunctioning stomas varied from 0-100%. There was no significant correlation between hospitals' adjusted stoma and anastomotic leakage rate. Severe anastomotic leakage was similar (7.0 versus 7.1%, $p = 0.95$) in hospitals with the lowest and highest stoma rates. Mild leakage and postoperative mortality rates were higher in hospitals with high stoma rates.

Conclusions: A high tendency towards stoma construction in rectal cancer surgery did not result in lower overall anastomotic leakage or mortality rates. It seems that not a risk averse strategy, but the ability to select patients for stoma construction is the key towards preferable outcomes.

INTRODUCTION

Surgical resection is the cornerstone of rectal cancer treatment. If tumour size, stage and location allow for a sphincter preserving resection, and bowel continuity is restored, the surgeon has to decide whether or not to defunction the anastomosis. The advantage of a defunctioning stoma can be that it decreases the consequences of anastomotic leakage, and may also decrease its incidence.[1,2] Anastomotic leakage is a serious complication causing re-operation, prolonged hospital stay, morbidity, mortality, and possibly worse oncological outcome.[3-5] On the other hand a stoma has evident disadvantages; defunctioning stomas can induce morbidity, discomfort (decreased quality of life), higher costs[6], longer hospitalisation[7] and even mortality from surgery to close the stoma. [8-12] Furthermore, 80% of defunctioning stomas is only reversed after 4 months and 20 % is never reversed.[13]

Nowadays quality of care has become a major topic and surgeons and hospitals are increasingly accountable for their postoperative complication rates. This may lead to risk adverse treatment strategies. Previous research suggests that differences in professional opinion may lead to variation in health care delivery.[14-21] The threshold for the decision to construct a stoma to avoid the risk for anastomotic leakage may also vary between surgeons. Some surgeons may be more risk-taking or risk-averse than others. However, the attempt to avoid or limit the risk for anastomotic leakage after colorectal surgery by frequent use of stomas is only in patients' interest if it in fact lowers clinically relevant anastomotic leakage and mortality rates.

The objective of this study was to investigate whether hospitals differ in their treatment strategy regarding construction of defunctioning stomas in rectal cancer surgery, and to assess if a hospital's treatment

strategy is related to its postoperative outcomes such as clinically relevant anastomotic leakage and mortality rates.

METHODS

Study cohort

Data was derived from the Dutch Surgical Colorectal Audit (DSCA). The DSCA contains data registered by 92 hospitals (representing all hospitals performing colorectal cancer surgery in the Netherlands). Over 90% of all eligible patients are included. The dataset is disease-specific for colorectal cancer and has shown a nearly 100% concordance on most items upon validation against the Netherlands Cancer Registry dataset.[22] All patients having undergone anterior resection for primary rectal cancer between the 1st of January 2009 and 31st of July 2012 were evaluated. Minimal data requirements for inclusion in the analysis were: information on tumour location, date of surgery, and mortality. Patients without an anastomosis, with metastasis at time of primary surgery, resections for multiple synchronous colorectal tumours, and patients with a tumour less than 5 cm from the anal verge were excluded, because these represent subgroups of patients with specific treatment perspectives and subsequent different expected outcomes.

Definitions

Overall anastomotic leakage, as used in the hospital comparisons, was defined as 'clinically relevant anastomotic leak requiring a re-intervention, either radiological (mild) or surgical (severe)'. Postoperative mortality was defined as 'in-hospital mortality or all deaths within 30 days after primary surgery'. The following casemix factors were considered: age, gender, ASA-classification, abdominal surgical history, tumour height, preoperative tumour complications, and urgency of the resection.

Considered treatment factors were surgical procedure (laparoscopic or open), and neoadjuvant treatment. Hospitals were stratified into non-teaching and teaching hospitals. Procedural volume in rectal cancer resections was calculated for each hospital before the aforementioned exclusion of patients and categorized into <25, 25–50 and >50 resections per year.

Statistical considerations

As patient and tumour related case-mix factors may be responsible for a large part of the hospital variation in the proportion of patients with a defunctioning stoma, we adjusted for these differences by calculating the Observed/Expected (O/E) stoma rate. The observed outcome was the number of patients with a defunctioning stoma in a hospital and the expected outcome is the sum of all patients' estimated probabilities for a defunctioning stoma. Patients' probability estimates were derived from a backwards-stepwise multivariate logistic regression model, fitted on the data of all included hospitals, and using all case-mix factors mentioned above. For an average performing hospital, the observed outcome will be equal to the expected outcome, resulting in an O/E outcome ratio of 1. Hospitals that construct more defunctioning stomas than average have an O/E outcome ratio higher than 1, while this ratio is lower than 1 in hospitals with lower than average stoma rates. The adjusted hospitals O/E ratios were plotted against their anastomotic leakage rates. The relation between the hospitals' strategy and its outcomes was analyzed by two methods.

First, to evaluate whether stoma rates were related to (lower) anastomotic leakage rates on a hospital level, a linear correlation was calculated using Pearson's correlation coefficient *R*. Second, to evaluate whether a risk adverse strategy (high stoma rates) is related to better postoperative outcomes on a hospital level, hospitals were grouped into equally-sized

groups based on quintiles of their case-mix adjusted rate of defunctioning stomas.

Differences between groups in outcomes (mild and severe anastomotic leakage and mortality rates) were analyzed using a chi-square test. The association of patient and tumour related case-mix factors, hospital factors (teaching status, volume) and treatment factors (neoadjuvant therapy, laparoscopic surgery) with being in the high stoma group was assessed with a chi-squared test and multivariate logistic regression analysis, considering the same case-mix factors as mentioned above All statistical analyses were performed in PASW Statistics, Rel. 18.0.2009. Chicago.

RESULTS

Between January 1 2009 and July 31 2012, 92 hospitals registered all rectal cancer patients in de the DSCA. After exclusion of ineligible patients, a total of 3104 patients were included in the analysis. Characteristics of the included patients and hospitals are shown in Table 1. Of all patients, 67% (n = 2080) received an anastomosis with a defunctioning stoma. In total, 302 patients (9.6%) developed anastomotic leakage. The majority (187 of 302, 62%) were severe leakages requiring a surgical reintervention. Anastomotic leakage rates were somewhat higher in patients with a defunctioning stoma (9.3 versus 10.4%), but this difference was not statistically significant (p = 0.35). Fifteen of 302 patients that developed anastomotic leakage, died during hospital stay or within 30 days after surgery (5%). Overall postoperative mortality rate was 1.8% (n = 187); anastomotic leakage caused one-fourth of overall mortality. There was no difference in overall mortality rate between both groups: 1.3% in patients without versus 2.1% in patients with stoma, p = 0.11).

Table 1. Patient, tumour and treatment characteristics of included patients.

		N	%
Total			
Age	Mean (range)	66	(15-97)
Gender	Male	1850	60%
ASA classification	I-II	2567	83%
	III+	369	12%
	Missing	168	5%
Abominal surgical history	Yes	808	26%
Tumor location	> = 10 cm	1149	14%
	<10 cm	1660	20%
Urgency	Acute/urgent	57	2%
Tumour stage	(Y) pT0/X	207	7%
	pT1	269	9%
	pT2	990	32%
	pT3	1533	49%
	pT4	105	3%
Surgical preoperative treatment	Stoma	162	5%
	Stent	8	0.3%
	Other	51	3%
Neoadjuvant treatment	5x5 Gy	1623	52%
	Chemoradiation	825	27%
Surgical procedure	Laparoscopic resection	1393	45%
Hospitals: type	Teaching hospital	2175	70%
	Non-teaching hospital	929	30%
Hospitals: volume	High volume (>50/year)	875	28%
	Medium volume (25-50 /year)	1490	48%
	Low volume (< 25/year)	739	24%

ASA: American Society of Anaesthesiologists risk score.

Hospitals

Relevant casemix factors were selected by backward stepwise logistic regression analysis. Relevant factors for the proportion of defunctioning stomas were gender, preoperative complications, tumour location, and laparoscopic surgery. Hospitals' adjusted proportion of defunctioning stomas varied considerably: percentages ranged from 0-100% (figure 1). Figure 2 shows the relation between the hospitals' adjusted proportion (O/E ratio) of defunctioning stomas and the hospitals' overall anastomotic leakage rate. Hospitals varied in anastomotic leakage rates (3-18%). There was a weak positive correlation between hospitals' adjusted O/E stoma ratio and anastomotic leakage rates ($r = 0.032$), this was not statistically significant ($p = 0.76$).

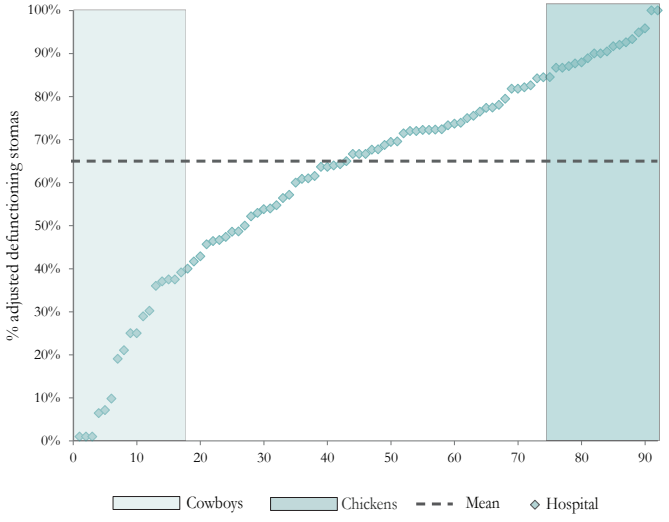

Figure 1. Hospitals ranked by their case-mix adjusted defunctioning stoma rate. Based on quintiles, groups of low (left) and high (right) stoma rates were identified.

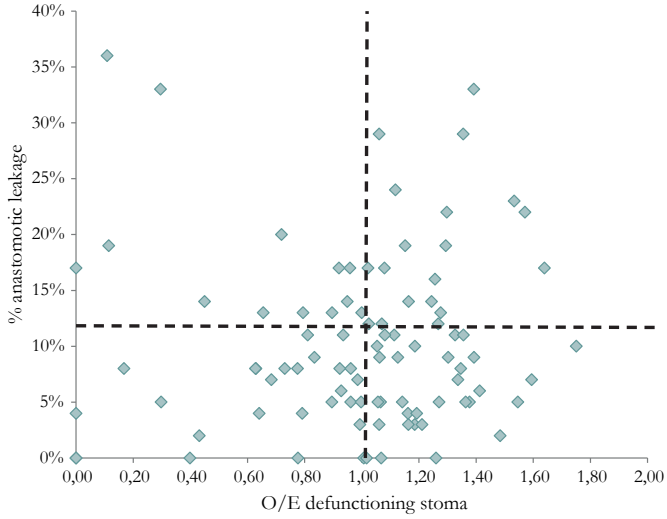

Figure 2. Hospitals' adjusted defunctioning stoma O/E rates plotted against their anastomotic leakage rates.

Low versus high stoma rate

Eighteen hospitals with a total number of 604 patients were identified as the group of low stoma rates. This group had a mean percentage of 26% of patients with a defunctioning stoma. The group of high stoma rates consisted of 18 hospitals, which treated 521 patients in total, had an 88% mean defunctioning stoma rate (Figure 3).

A slight difference in overall anastomotic leak rates was found between groups, although not statistically significant (8.4 vs 11.3%, $p = 0.11$). Severe anastomotic leakage rates were similar in both groups; 7.1 versus 7.5% ($p = 0.95$). Mild anastomotic leakage rates were significantly higher in the group with high stoma rates: 1.5 versus 3.8% ($p<0.001$). Postoperative mortality rates were significantly higher in the group with high stoma rates; 2.9 versus 1.0% ($P = 0.02$). The remaining hospitals formed a group with intermediate stoma rates (67%), and had outcomes

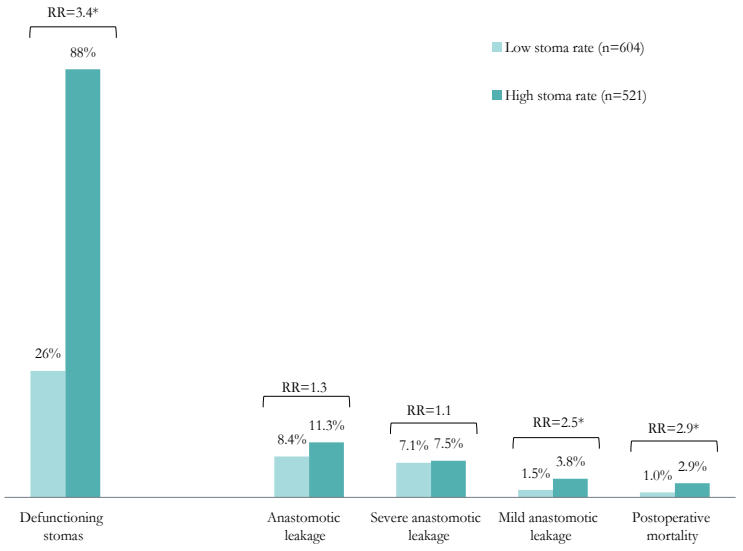

Figure 3: Comparison of outcomes between the groups identified as low and high stoma rates. Results with an * are considered statistically significant (P<0.05).

in between the low and high stoma groups (9.7% anastomotic leakage, 1.7% mortality). Table 2 shows the results of univariate and multivariate analysis for factors contributing to the odds of being in the group of high stoma rates. The percentage of patients treated with short course radiation therapy (SCRT) was higher in the group with high stoma rates, as well as the percentage of patients treated in teaching hospitals.

Also in multivariate analysis, these patients had higher odds of being in the group of high stoma rates. Urgent resections and volume were associated with a lower risk of being treated in a high stoma rate hospital in both univariate and multivariate analysis (Table 2). Other case-mix

Table 2: Univariate and multivariate analysis for factors contributing to being in the group of high stoma rates.

Factor		Univariate		Multivariate	
		Cowboys n (%)	**Chickens n (%)**	**OR***	**95 % CI**
Age	mean	66	66	0.99	0,98 - 1.01
Gender	female	247 (41)	210 (40)	0.88	0,68 - 1.14
Asa	1	157 (30)	149 (30)	1.0	ref
	2	297 (56)	307 (60)	1.13	0.76 – 1.36
	3+	79 (15)	52 (10)	0.81	0.55 - 1.30
Urgency	urgent operation	**18 (4)**	**4 (0.8)**	**0.29**	**0.09 - 0.89**
Preoperative surgery	Yes	24 (4)	25 (5)	1.19	0.64 - 2.24
T stage (p)	T0	22 (4)	32 (7)	1.0	Ref
	T1	53 (9)	55 (11)	1.35	0.36 - 5.00
	T2	193 (32)	165 (32)	1.02	0.29 - 3.61
	T3	314 (52)	260 (50)	1.08	0.31 - 3.78
	T4	22 (4)	9 (2)	0.62	0.14 - 2.74
Abdominal surgical history	yes	135 (22)	144 (28)	1.26	0.94 1.70
Tumour distance - anal verge	>10 cm	225 (37)	137 (33)	0.87	0.66 - 1.14
Neoadjuvant therapy	none	**171 (28)**	**100 (19)**	1.0	ref
	5x5 gy	**301 (50)**	**308 (60)**	**1.67**	**1.20 - 2.31**
	chemoradiation	132 (22)	133 (22)	1.13	0.72 - 1.69
Surgical treatment	laparoscopy	291 (50)	286 (55)	1.09	0.84 - 1.41
Hospital type	teaching	**259 (43)**	**269 (52)**	**2.88**	**2.04 - 4.10**
Volume	<25	191 (32)	141 (27)	1.0	ref
	25-50	222 (36)	274 (53)	1.18	0.86 - 1.62
	>50	**191 (32)**	**106 (20)**	**0.27**	**0.17 - 0.43**

*Odds ratios display the odds for being in the group of high stoma rates. Bold printed numbers are statistically significant ($p<0.05$).

factors, as age, ASA score and tumor characteristics, were not statistically different in both groups.

DISCUSSION

Overview of findings

This study demonstrates a large hospital variation in treatment strategy concerning defunctioning stoma construction after surgical resection of rectal cancer, even after adjustment for relevant casemix factors. Hospitals with a low threshold for defunctioning stoma construction after rectal cancer resection did not have lower anastomotic leakage rates in comparison with hospitals with an opposite strategy. Interestingly, mortality and anastomotic leakage rates requiring radiological drainage were even higher in hospitals with a high stoma rate. The latter may be partly due to the slight difference in short course radiation therapy (SCRT) between both groups. Although a direct correlation between clinically apparent anastomotic leakage and neoadjuvant therapy has not been demonstrated,[4,23-26] den Dulk et al showed SCRT to be a limiting factor for reversal of a (secondary) constructed stoma suggesting that it increases the risk for subclinical, or mild anastomotic leakage.[27] An explanation for the remarkable correlation between a risk adverse strategy and low hospital volume or teaching status cannot be provided within the scope of this article. Possibly, these hospitals may use other selection criteria for defunctioning stomas, or treat patients with an impaired condition for which could not be adjusted in this study.

Comparison with other studies

There is an on-going debate on differences in treatment approach despite ample data describing the direct correlation between the rate of both defunctioning stomas on the one hand, and anastomotic leakage

and postoperative mortality on the other hand. The discussion focuses mainly on whether defunctioning stomas should be used routinely after low anterior resection to decrease anastomotic leakage rates. A meta-analysis from Hüser et al[1], mainly based on the results of a randomized controlled trial from Mathiessen et al[2] clarifies the advantage of a defunctioning stoma on lowering anastomotic leakage rates. This is confirmed by a considerable amount of retrospective studies.[4,28-30] On the contrary, a study from Fielding et al. observed a higher leakage rate in patients with a defunctioning stoma (18% versus 7%) and suggested that surgeons with an individual anastomotic leakage rate less than 5% do not need to create a defunctioning stoma at all. Both Enker et al, and Matthiessen et al. showed that a defunctioning stoma did not reduce the incidence of anastomotic leakage in patients undergoing low or ultralow anterior resection.[7,31]

Strengths and limitations of study

We retrospectively evaluated a prospectively maintained, population-based database to determine the association between hospitals' strategy regarding defunctioning stoma construction and postoperative outcome in rectal cancer. It could be argued that comparing patient outcomes for patients with and without a stoma is not valid, because of confounding by indication: patients may have received a stoma because they were considered to be high risk patients and are therefore not comparable to patients that did not receive a defunctioning stoma. This bias could also explain the relatively high mortality in the group with high stoma rates. However, in our study this bias is largely overcome by comparing hospitals at both ends of the spectrum (either very high or very low defunctioning stoma rates). Defunctioning stoma rates of 88% and 26% respectively, reflect a strategic approach (standard a stoma or standard no stoma), which is only slightly based on individual decision-making concerning patient characteristics. It is likely that only

very high-risk patients received a stoma in both groups, and very low risk patients in both groups did not. For other patients, the decision was mainly based on the hospitals strategic approach. Therefore the method we used resembles a "pseudo randomization". This is supported by the fact that baseline characteristics were similar for both groups in our study.

These findings are very useful for clinical practice because they strengthen the concept that the decision of stoma formation after anterior rectal resection cannot be standardized but require a careful evaluation of individual risk factors. Data represent current surgical practice at a population level, since all hospitals participate in the DSCA and the percentage of eligible patients registered is over 90%. A limitation of this study is that analyses were performed at a hospital level, while the surgical strategy may differ between surgeons within a hospital. Information on a surgeons' level is not available in the DSCA and individual volumes may be low, introducing more impact of chance variation in the analyses.

Clinical implications

Should we then be cowboys or chickens; if the latter does not necessarily result in better outcomes? The results confirm that the protective effect of a defunctioning stoma is probably most apparent in high-risk patients, while the additional benefit for the rest of the population is limited or even non-existent. There have been numerous studies identifying risk factors for anastomotic leakage.[9-13] Dekker et al developed and tested the Colon Leakage Score (CLS) in which multiple risk factors were used to provide an objective prediction of the risk for anastomotic leakage.[32] They found that only 20% of their population could be considered as high risk. If we take into account the relative risk reduction of 64% that was found in the randomized trial of Matthiessen et al. (reduction in AL from 28% to 10%) for high-risk patients with an hypothetical a priori

risk of anastomotic leakage of 20%, this would mean an absolute risk reduction of 12.8% and so 8 defunctioning stomas would have to be constructed in order to prevent one anastomotic leak. In contrast, for patients with an a priori risk of 5%, (ARR 3.2%) 31 defunctioning stomas would have to be created to prevent one leak.

It should thereby kept in mind that stomas can induce morbidity, discomfort (quality of life), costs and even mortality. Stomal complications cause re-admission within two months after initial surgery in up to 17% of all patients, mostly due to de-hydratation[9,11,33,34]. Even when a defunctioning stoma is constructed, there is still is a considerable risk of (late) anastomotic leakage [2,4,35-37]. A recent study from our group on one year follow-up data shows a significant higher morbidity rate in patients with a defunctioning stoma when compared to patients without, due to unplanned re-admissions (18%) and re-interventions (12%) caused by anastomotic leakage and drainage of abscesses.[37] It is also recognized that 15-30% of defunctioning stoma's are never closed, resulting in a permanent stoma[10,38]. Future studies are important to gain more evidence on the possible benefits of defunctioning stomas in high and low risk patients.

Finally, we advocate that patients' preferences concerning the risk of morbidity and mortality of anastomotic leakage versus the consequences of a defunctioning stoma should be taken into account preoperatively.

Conclusions

In conclusion, a high tendency towards defunctioning stoma construction in rectal cancer surgery did not result in lower overall anastomotic leakage or mortality rates. The optimal treatment strategy can probably be found in hospitals with both low stoma rates and favourable postoperative outcomes. It seems that hospitals with low stoma rates were

better in selecting high-risk patients, and that stoma formation in more patients does not lead to better outcomes. Adequate identification of high-risk patients should be focus of future studies to facilitate decision-making.

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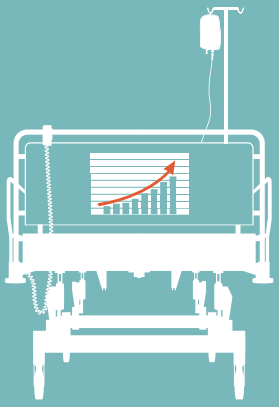

Chapter 9

General discussion and future perspectives

Colorectal cancer forms a major health burden. Annually, 13,000 patients are diagnosed with colorectal cancer in the Netherlands, which is equivalent to a 5% lifetime risk[1]. Although major improvements in survival after treatment for colorectal cancer have been achieved during the past decades, morbidity is still high and 4,000 patients die as a result of this disease every year[1]. The treatment of colorectal cancer is high-risk, complex and subject to rapid innovations and changing insights on what presents optimal care. Nevertheless, until recently, all Dutch hospitals provided colon and rectal cancer care[2].

In 2010, a report of the Signalling Committee of the Dutch Cancer Society revealed that large variation in colorectal cancer care existed between hospitals, resulting in an almost twofold higher risk of dying in one hospital compared to another[3]. Also, under- and overtreatment was identified in some hospitals regarding (neo-) adjuvant therapies. The committee considered differences in the care process, local preferences and delayed implementation of new therapeutic options underlying the variation between hospitals. To reduce variation and improve quality of care the authors recommended (1) the development of minimal quality standards (2) to implement clinical auditing on a national level (3) to centralise cancer care in those hospitals meeting the quality standards and showing high quality care processes and outcomes for their patients.

Prompted by this call for improvement, the Association of Surgeons in the Netherlands (ASN) developed a set of minimal procedural volume standards and requirements regarding institutional infrastructure and medical specialties available[4]. Furthermore, they initiated a nationwide clinical audit: the Dutch Surgical Colorectal Audit (DSCA)[2].

Clinical auditing

Clinical auditing is a quality improvement tool that is used to expose quality of care by continuous and meticulous evaluation of patients' outcomes and comparing these outcomes between hospitals (benchmarking) and providing feedback on their results to participants[5].

Internationally, many clinical audits have been initiated since the past three decades, especially in the surgical and oncological domain. Examples of national clinical audits are the National Surgical Quality Improvement Program (NSQIP) in the United States, the National Bowel Cancer Project (NBOCAP) in the United Kingdom, the Swedish Rectal Cancer Audit and the Norwegian Colorectal Cancer Project[6-9].

In chapter II, a literature review shows that clinical auditing has a positive effect on both the process and outcomes of care. Moreover, the effect on quality improvement is further amplified when improvement interventions are actively implemented next to clinical auditing **[this thesis]**. As underlying mechanisms for the effect of clinical auditing on quality improvement are considered: (1) feedback information enabling performance monitoring, benchmarking with peers and the identification of best practices. (2) the 'Hawthorne effect' [10,11]. Feedback information raises doctors' awareness and provides the opportunity to identify areas for improvement. The 'Hawthorne effect' is the psychological phenomenon that individuals improve in response to their awareness of being observed.

In addition to improving clinical outcomes, clinical auditing has also been associated with significant cost reduction, especially in high-risk procedures, such as colorectal cancer surgery[12]. As undesired outcomes, such as complications and unplanned reinterventions are very costly, it is credible that improved outcomes go hand-in-hand with cost reduction.

The Dutch Surgical Colorectal Audit

From its introduction in 2009, the DSCA has shown to be a valuable quality improvement tool. Within 2 years, high quality data has been collected as all hospitals participated and a near complete case ascertainment was established[13] **[this thesis]**. Quality improvement was stimulated by weekly online feedback to participating hospitals with a national benchmark, by discussing audit results in scientific medical conferences and reporting on areas for improvement in an annual report. Also, the ASN integrated the evaluation of audit results in their quality assurance program and provided counselling to negative outliers to improve their outcomes.

Within three years, hospital variation diminished remarkably and both the quality of the care process and postoperative outcomes improved[14] **[this thesis]**. Mortality after colon cancer surgery was reduced from 5.8 to 4.0%, a risk reduction of 31%. Today, after 6 years since the initiation of the DSCA, mortality rates are as low as 2.7%[15]. Another area of improvement is related to Circumferential Resection Margin (CRM) involvement after rectal cancer surgery. As CRM involvement is an important marker for local recurrence, the reporting of the CRM status became standard of care after the Dutch TME trial. At the start of the DSCA, the registration of the CRM status in the pathology report was only 48% and CRM involvement was seen in 14% of cases. After increased attention and feedback on this topic in the audit, reporting improved from 48 to 80% and the incidence of CRM positive margins after rectal cancer surgery decreased from 14 to 8.5% (39% risk reduction)[14]. Although CRM involvement after abdominoperineal excision (APE) was higher compared to low anterior resection (LAR), it was found that the risk of CRM involvement was not necessarily related to the chosen therapy (APE or LAR) **[this thesis]**, but associated with differences in quality of care as hospital variation in CRM

involvement is considerable and hospital factors such as annual volume and type of hospital are of influence[16,17].

It is difficult to prove a direct causal effect of clinical auditing on quality improvement, because time, as a proxy for innovation is a confounding factor.

However, there is consensual view that the awareness and continuous evaluation of doctors of their outcomes in relation to those of their peers, has led to a change in internal quality culture. The lead and intensive engagement of surgeons in the development of the database, the registration process and the evaluation of audit results, is therefore considered one of the largest merits of the DSCA. While technical aspects in care are certainly important, it is the cultural component that is perhaps the most critical element in quality improvement[18].

Measuring quality of care

To assess quality of care it is important to identify suitable performance indicators. Performance indicators are measurable aspects of care that reflect quality. There are three types of performance indicators, reflecting the organisational structure, the care process or outcomes of care. Examples are the presence of a specialised nurse (structure indicator), the percentage of patients discussed in a multidisciplinary team (process indicator) and the percentage of complications after surgery (outcome indicator).

Characteristics that make performance indicators suitable for quality evaluation are[19]:

1) Construct validity – it should be associated with quality of care.
2) Comparability – there should be little or no bias introduced by:
    a. Heterogeneity in the registration process (uniform definitions)

   b. Differences in the population treated (casemix adjustment)
   c. Differences in the sample tested (all patients are registered).
3) Discriminative capability – there should be variation in the performance on the indicator to identify good, average and underperformance. Also, a minimum event rate is necessary to be able to measure quality (and not random variation).
4) Measurability: the data should be retrievable in practice.

An important prerequisite for using clinical audit databases for quality evaluation is that the data is complete and the quality of the data is high. Thereby, doctors will only use the feedback information to implement change in practice, if they believe that the data are accurate. Incompleteness of data on a variable, patient or hospital level will introduce selection bias, which may interfere with valid quality measurement. For instance, when hospitals register some, but not all of their patients, it is possible that the patients who are not registered are not comparable with those registered (e.g. have worse outcomes), which may distort the estimate of the real hospitals' outcomes of care. Quality of data can be improved by uniform data gathering, using clear in- and exclusion criteria and definitions for each variable. Validation of the data to an external database or in-hospital verification by an independent registrar can be used to evaluate completeness and quality of the dataset.

Furthermore, when comparing outcomes between hospitals, it should be taken into account that besides the quality of the care process in a specific hospital, also patients' risk factors and random variation will influence results[20]. Therefore, a reliable clinical audit database needs to include at least both outcomes and patients' risk factors for these outcomes. Also, proper statistical methods are needed to apply adjustment for differences in casemix between hospitals and for random variation. Gathering outcome information is the first and most important objec-

tive in clinical auditing. However, it may take time to be able to assess outcomes, such as 5-year survival. Therefore, some outcome indicators don't reflect the quality of present care, but of the past. Measuring short-term intermediate outcomes can be proxy measures correlated with long-term results. For example, CRM involvement as a proxy measure for local recurrence after rectal cancer surgery. Importantly, the strength of the relation between the proxy measure and the long-term outcome (construct validity) should be taken into consideration when relating the performance on a proxy measure to quality of care. Process measures, although of secondary importance, are earlier and easier to act on. Also, insight in the care process may help to explain differences in outcomes. Recording of process measures in addition to outcome measures may therefore be valuable.

It is important to emphasize that data collection is not static in clinical auditing. As the concept of what presents state of the art care changes over the years, process measures change accordingly. New treatments are added to the registration and obsolete treatments are removed. Outcome measures are less susceptible to change over time.

Guideline adherence and quality of care

Today, clinical decisions are increasingly driven by evidence-based guidelines, which have become the standard of care. Also, the quality of care is increasingly assessed based on adherence to these recommendations. In colorectal cancer care, guideline adherence is high in the Netherlands and increases every year[21] **[this thesis]**. Although evidence-based guidelines are valuable for decision-support, have allowed standardisation of care and undeniably are a major determinant of improving outcomes for patients, there are reasons to be reluctant to use guideline adherence as a performance indicator:

1. Guideline adherence is not a guarantee for good outcomes in an individual patient

Evidence Based Medicine (EBM) can fall short in clinical decisions for the treatment of individual patients. It is for the most part based on clinical trials that determine effectiveness of a treatment in groups of patients (average outcomes), and those probabilities are not directly transferable to all individuals within the group[22]. Therefore, clinical reasoning in individual patients plays an important role in clinical decision-making: the individual patient is not the "average" patient[23]. Also, it is well known that trial results have limited external validity: results would apply only to individuals with characteristics identical to those studied. Last, empirical evidence on the relation between process and outcomes of care is very limited[24,25].

Especially, EBM lacks support for treatment of elderly and patients with co-morbidity. As elderly patients and patients with comorbid diseases are largely underrepresented in clinical trials, evidence based guidelines are lacking to support treatment decisions in these patients. In colorectal cancer, the urge for EBM in elderly patients and patients with co-morbidity is increasing as the population is ageing. Thereby, we see that the incidence of co-morbidity and multi-morbidity is increasing rapidly both in younger and older patients[26]**[this thesis]**. Especially, cardiovascular diseases and diabetes are more often co-existent in patients treated for colorectal cancer. Postoperative morbidity and mortality increases profoundly with advancing age and is further enhanced when one or more of co-morbidities co-exist. Thereby the effectiveness of (adjuvant) treatments can be largely influenced by altered physiology in these patients[27]. Adherence to general recommendations in guidelines in these fragile patients could therefore result in under- or overtreatment.

2. Evidence based guidelines can be out-dated and assessing quality based on guideline adherence may restrict innovation.

The development of guidelines takes significant time and in the last decades revision is performed only once in a few years. With the current pace at which new research articles are being published, there is the reality that critical evidence will appear in the interval between editions of a guideline. Evidently, the revision process needs to speed up to provide more actual EBM. The use of guideline adherence as a measure of quality also poses an ethical dilemma, as new therapeutic strategies that fall outside the guidelines may be difficult to test or implement[28].

A clarifying example is guideline adherence regarding the use of radiotherapy in rectal cancer. In the nineties, hallmark studies showed the benefit of radiotherapy regarding local recurrence rates in rectal cancer[29,30]. The use of radiotherapy was therefore incorporated in Dutch guidelines recommending it for all cT2-4 rectal tumours[31]. However, in recent years it was found that although local recurrence rates were reduced by preoperative radiotherapy, it did not lead to a 5-year overall survival benefit in addition to TME surgery[32]. Thereby, functional complications such as incontinence, and secondary malignancies can develop as a consequence of radiotherapy[33]. After the recent introduction of the high-resolution MRI, accuracy of staging and visualisation of the tumour increased and supported better clinical decision-making. The MERCURY study group showed that radiotherapy could safely be omitted in cT1-3a tumours, representing 33% of patients with rectal cancer[34]. However, in the Netherlands, 85% of all rectal cancer patients and even 78% of patients with cT1-2N0 tumours still received radiotherapy in 2011-2012[35] **[this thesis]**. The overuse of radiotherapy may be partly explained by the more extensive indication window in Dutch rectal cancer guidelines that were still based on the hallmark trials on radiotherapy that did not include MRI for staging at the time.

Last, it should be kept in mind that EBM is not available for many essential aspects of the care process that are important for outcomes in patients. For the majority of treatment decisions, no randomised controlled trials are available. This is partly because trials have just not been performed yet, and because performing a trial is considered unethical in the opinion of experts.

For example the use of defunctioning stomas in colorectal cancer surgery is not supported by EBM. There is limited evidence that defunctioning stomas decrease the risk of anastomotic leakage and it is not known which patients may benefit from a defunctioning stoma. Risk selection for defunctioning stomas is therefore partly based on personal experience and local preferences. This is exemplified by the large variation between hospitals on this topic[36]. Also, we see that anastomotic leakage rates and postoperative mortality are not higher in hospitals with a low tendency towards stoma construction **[this thesis]**. This may reflect the quality of patient selection (clinical decision-making) for stomas, rather than guideline adherence.

In conclusion, evidence-based guidelines are indispensible in current care, but adherence to guidelines in every patient is not per definition a sign of good quality. Using guideline adherence as a performance indicator could even have a perverse incentive: indicator driven practice. Outcome indicators therefore provide better information on the provided quality of care for each individual, and information on guideline adherence should be used to evaluate potential reasons for suboptimal outcomes. On the other hand, large hospital variation in guideline adherence in homogenous patient groups may be a sign of suboptimal quality of care. Using clinical auditing, the benchmark provided by all hospitals

treating a certain patient group may give meaning to the "performance" of an individual hospital regarding guideline adherence.

The value of population based data

The primary purpose for data collection in clinical auditing is to provide feedback information to participants on quality of care. Simultaneously however, in time a large database with detailed clinical data is generated that can be used for scientific research as well. An important feature of these databases is that it contains non-selected population based clinical data ("real life data") and therefore offers advantages in comparison to clinical trials [37]:

1. Outcomes will have a higher external validity, e.g. high applicability of the results to a defined population.
2. It allows the absolute estimation of distributions and prevalence rates of relevant variables in the population. Information on risk factors can for instance be used for the calculation of population attributable risks.
3. It is ideal to carry out unbiased evaluations of relations, not only of confounders to exposures and outcomes, but also among any other variables of interest, even those which were not specified in an original study hypotheses (which is not the case in clinical trials). When it comes to causal inference, clinical trials are superior as the reason for providing or withholding a certain therapy in a specific patient is often unknown in observational data. This reason may be a confounding factor when evaluating the effectiveness of that therapy in a population. In clinical trials on the contrary, the use of a therapy is merely based on randomisation and therefore a true causal relation between treatment and outcome can be assessed.
4. Because of the quantity of the data, evaluation of small subgroups (with uncommon conditions or therapies) is possible. In the DSCA

for instance, the effect of synchronous colorectal cancer (incidence of 3.4%) on short-term outcomes after surgery could be assessed, identifying this condition as a risk factor for complications and reinterventions[38] **[this thesis]**.

5. High-risk patients, including elderly patients and patients with co-morbidity, who are often excluded in clinical trials, are represented, allowing the evaluation of safety and effectiveness of care in this important patient group.

Altogether, population-based data from clinical registries are a valuable addition to the randomised controlled trials and may in time lead to the developments of algorithms that support clinical decision-making and personalized medicine.

FUTURE PERSPECTIVES

Towards outcomes that matter to patients

Notwithstanding its valuableness as a quality improvement tool, the data gathered for the DSCA provide only a limited view on quality of care: the clinical process and outcome measures that are important from a clinician's perspective with regard to safety and effectiveness of care. Not only are there many more ways to look at quality of care, for instance, patient-centeredness, timing, efficiency and equitability. Also, the perspective of patients may provide essential information to doctors to improve quality of care. In recent years, patient reported outcome measures (PROMs) have been introduced[39]. Although, critics question the validity of PROMs as they are prone to confounding factors, such as socioeconomic status, and the implementation of PROMs in the clinic flow (affecting accrual) are still burdensome, it may only be a matter of time before these barriers are overcome and the patient's

perspective will be fully incorporated in quality evaluation[40-43]. There are few nationwide PROM programs[44]. There are many factors that influence accrual rates. Among others, it requires an efficient infrastructure for data collection (supported by ICT), engaging patients and clinicians in the development of the PROMs program, integrating PROMs in clinical care pathways (similar as ordering a blood test), supporting the use of PROMs results in individual patients care and educating clinicians accordingly[45-47]. The joint evaluation of clinical data and patient's reported outcomes on a patient level may be the key to better interpretation of PROMs as demographics (such as socioeconomic status) and other confounding factors are available in the database to calculate risk-adjusted PROMs.

New movements state that not only should the patient take part in the registration process by registering PROMs. Also, the patient should pronounce which outcomes really matter to him/her when choosing a hospital, doctor or therapy, as these should be the similar outcomes doctors should strive for when treating patients[48]. In 2012, a joint force of Michael Porter at the Harvard Business School, the Boston Consulting Group and the Karolinska Institute in Sweden initiated the International Consortium for Health Outcomes Measurement (ICHOM)[49]. The purpose of this organisation is to define global standard sets of outcome measures that really matter to patients and drive adoption and reporting of these measures worldwide. The first sets are currently implemented in Dutch health care. By 2017, they aim to have published 50 standard sets covering more than 50 per cent of the global disease burden.

Naturally, these outcomes should be fully integrated in clinical auditing and quality assessments. This means incorporating these outcomes in the feedback information to clinicians and the identification of best practices based on the results. Also, public (transparent) performance

indicators should be based on outcomes that matter to patients. On an even broader scale: these outcomes should be used as a standard part of care when informing the patient about the expected results of an intended treatment, when making shared-decisions and when evaluating the treatment effect. Both on an individual level (how is this particular patient doing in comparison to others or to last year?) and on an aggregated level (what can my patient expect based on the results of comparable patients in the past?) very valuable information for doctors and patients.

Transparency on quality of care

Various international comparisons show that quality of care in the Netherlands is high[50,51]. However, incidents do occur and in the absence of publicly available quality information, the effects of individual cases may amplify and nurture public distrust. Worldwide, the call for transparency of quality information in health care has increased in recent years. The lack of availability of good outcome information has burdened the pace and ways at which this need is satisfied. In a recent report, it was shown that patients do not use the information that is currently available on quality of care for choosing their hospital[52]. Most likely, because the current information is not easily accessible, considered not reliable or difficult to interpret by the individual patient.

There is general consensus among doctors that transparency on quality information is indispensible and desirable to build trust. However, the main reasons to refrain from transparency are the suitability of indicators for public interpretation, distrust in the quality of quality information and anxiety for being punished (unjustly). The Association of Surgeons of the Netherlands has chosen for a stepped way towards transparency of results of the DSCA after its initiation. The first year, indicators regarding hospital structure and procedural volume were made publicly available.

The second year, information on guideline adherence and other indicators regarding the process of care were unlocked and after three years, outcome indicators as well. This strategy was successful as it allowed (1) a careful process of selecting suitable indicators, (2) an internal safety culture among doctors able to learn from their results before they became public, (3) thorough evaluation of the quality of data by in-hospital data verification performed by an independent third party and (4) the disclosure of extensive quality information.

Transparency of care is also an important driver of quality improvement. The Boston Consulting Group has shown how transparency of outcome information in Sweden led to large improvements in quality of care and reduction of costs[50].

On a negative side, reports have been published regarding defensive behaviour in doctors and "indicator-driven care", e.g. the effort to score high on an individual quality indicator, when this information is made public[53]. This raises the question whether the focus on process indicators, in which the relation with outcomes of care is often doubtful, might interfere with individual patients interests. Moreover, process measures are difficult to interpret by patients. Focus on outcome indicators that matter to patients on the other hand, visualizes the actual results of care, stimulates innovation, and most likely will enhance the actual use of quality information by patients. Also, besides focussing on unwanted outcomes (such as complications), positive formulated outcome indicators, such as gained quality of life, survival and functional outcomes will stimulate an integral approach towards the patient, especially in multidisciplinary care.

In the future, when outcomes that matter to patients are widely available, it may therefore be desirable to limit the use of process information

and specific technical outcomes to internal quality evaluation among medical professionals, stimulating both an internal quality culture and satisfying the patients' need for good quality information.

Towards value based health care

Finally, a short note on the emergence of value based health care. As costs of healthcare are growing stronger than the gross domestic product in the Netherlands (in 2009 accounting for 15%)[50], our current health care system is not sustainable in the future. Where current payment models incentivize volume, there is a growing movement aiming to tie reimbursements to the quality and the value of health care (cost per gained health). Porter advocates that competition between hospitals on quality of care (outcomes) will reduce costs due to diminishing preventable complications and overtreatment, and thereby will increase value of health care[54]. Recently, the Dutch Value Based Health Care study showed that the addition of in-hospital costs to DSCA data may provide benchmark information on the value of care, and as variation exists between hospitals, there may be an opportunity to learn from each other's results[55]. An integral view on clinical outcomes, patient reported outcomes and costs might be the holy grail to strive for in health care.

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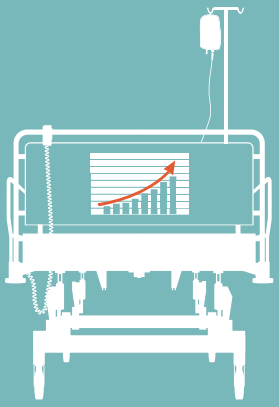

Nederlandse Samenvatting

HET EVALUEREN EN VERBETEREN VAN KWALITEIT VAN DARMKANKER ZORG

Darm- en endeldarmkanker heeft een grote impact op gezondheid. Jaarlijks worden 13.000 mensen met deze vorm van kanker gediagnosticeerd in Nederland, gelijk aan een risico van 5% per leven. Hoewel de overleving na behandeling sterk verbeterd is in de afgelopen jaren, is de morbiditeit onder deze patiënten nog steeds aanzienlijk en sterven jaarlijks 4.000 patiënten aan deze ziekte. De behandeling van (endel-) darmkanker is risicovol, complex en aan snelle innovatie onderhevig, waarbij de inzichten over wat optimale zorg betekent continu bijgesteld worden. Ondanks dat, werd tot voor kort door alle Nederlandse ziekenhuizen (endel-)darmkankerzorg aangeboden.

In 2010 publiceerde de signaleringscommissie van KWF Kankerbestrijding een rapport dat grote variatie in (endel-) darmkankerzorg tussen ziekenhuizen, wat resulteerde in een bijna dubbel zo hoog risico op sterfte in het ene ziekenhuis vergeleken met een ander ziekenhuis. Ook werd er onder- en overbehandeling met aanvullende behandelingen gezien in sommige ziekenhuizen. De commissie redeneerde dat verschillen in het zorgproces, lokale voorkeuren en verlate implementatie van nieuwe behandelingsmogelijkheden de oorzaak voor deze verschillen tussen ziekenhuizen waren. Om variatie te verminderen en kwaliteit van zorg te verbeteren bevolen zijn aan:

(1) de ontwikkeling van minimale kwaliteitsstandaarden
(2) het implementeren van clinical auditing op nationaal niveau

(3) het centraliseren van de kankerzorg tot alleen die ziekenhuizen die aan de kwaliteitsstandaarden voldoen en die hoge kwaliteit van het zorgproces en de zorguitkomsten van hun patiënten laten zien.

De Nederlandse Vereniging voor Heelkunde (NVvH) ontwikkelde hierop een set van minimale volumina per operatie en vereisten met betrekking tot de infrastructuur van de behandellocatie en het type medisch specialisten beschikbaar. Verder ontwikkelden ze een landelijke clinical audit: de Dutch Surgical Colorectal Audit (DSCA).

Clinical auditing

Clinical auditing is een kwaliteitsverbeteringsinstrument dat gebruikt wordt om de kwaliteit van zorg inzichtelijk te maken door continue en nauwkeurige evaluatie van zorguitkomsten bij patiënten en door deze uitkomsten te vergelijken tussen ziekenhuizen (benchmarking) en feedback hierover aan de deelnemers te geven.

Internationaal zijn er de afgelopen 30 jaar veel clinical audits geinitieerd, vooral in het chirurgische en oncologische domein. Voorbeelden van landelijke clinical audits zijn the National Surgical Quality Improvement Program (NSQIP) in de Verenigde Staten, de National Bowel Cancer Project (NBOCAP) in Groot Brittannië, de Swedish Rectal Cancer Audit en de Norwegian Colorectal Cancer Project.

In hoofdstuk II, wordt een literatuur overzicht weergegeven dat laat zien dat clinical auditing een positief effect op zowel het zorgproces als de uitkomsten van zorg heeft. Daarbij wordt het effect op kwaliteitsverbetering vergroot als er actief verbeterinitiatieven worden uitgezet naast clinical auditing **[dit proefschrift]**. De volgende factoren worden gezien als onderliggend mechanisme voor het verbetereffect van clinical auditing: (1) feedback informatie dat het mogelijk maakt om prestatie te

monitoren, vergelijking met collegae en identificatie van excellerende ziekenhuizen. (2) het 'Hawthorne effect'. Feedback informatie verhoogt bewustwording bij dokters en laat punten voor verbetering zien. Het 'Hawthorne effect' is het psychologische fenomeen dat individuen beter presteren doordat ze zich bewust zijn dat ze worden geobserveerd.

Naast het verbeteren van klinische uitkomsten, is clinical auditing ook gerelateerd aan significante kostenbesparingen, vooral bij hoog risico procedures, zoals bij (endel-) darmkanker chirurgie. Gezien ongewenste uitkomsten, zoals complicaties en ongeplande re-interventies, erg kostbaar zijn, is het geloofwaardig dat verbeterde uitkomsten hand in hand kunnen gaan met kostenreductie.

De Dutch Surgical Colorectal Audit

Vanaf het begin in 2009, heeft de DSCA zich een waardevol kwaliteitsverbeteringsinstrument getoond. Binnen 2 jaar werd data van hoge kwaliteit verzameld bij alle Nederlandse ziekenhuizen en werden vrijwel alle behandelde patiënten geregistreerd **[dit proefschrift]**. Kwaliteitsverbetering werd gestimuleerd door wekelijkse online feedback aan deelnemende ziekenhuizen met een landelijke benchmark, door resultaten te bespreken op wetenschappelijke congressen en aangrijpingspunten voor verbetering te beschrijven in een jaarrapport. Daarbij integreerde de NVvH de evaluatie van audit resultaten in hun kwaliteitsprogramma en bood begeleiding aan ondermaats presterende ziekenhuizen om hun resultaten te verbeteren. Binnen 3 jaar verminderde ziekenhuisvariatie aanzienlijk en zowel de kwaliteit van het zorgproces als postoperatieve uitkomsten verbeterden **[dit proefschrift]**. De sterfte na darmkanker chirurgie verminderde van 5,8% naar 4,0%, wat betekent een risico reductie van 31%. Op dit moment, 6 jaar na de start van de DSCA, sterfte percentages zijn zelfs 2,7%. Een ander onderwerp voor verbetering is gerelateerd aan de circumferentiële resectie marge (CRM)

na endeldarmchirurgie. Na de Nederlandse TME trial is het rapporteren van de CRM status standaard geworden, als belangrijke marker voor lokaal recidief. In het eerste registratiejaar werd echter slechts 48% van de gevallen de CRM status gerapporteerd en deze was positief bij 14% van de patiënten. Na extra aandacht en feedback op dit onderwerp, verbeterde dit van 48% naar 80% en het voorkomen van een positieve CRM verminderde van 14 naar 8,5% (39% risico reductie). Hoewel een positieve CRM na abdominoperineale resectie (APE) hoger was dan na laag anterieure resectie (LAR), was het risico op CRM positiviteit niet perse gerelateerd aan de keuze voor techniek (APE of LAR) **[dit proefschrift]**, maar geassocieerd met verschillen in kwaliteit van zorg gezien er behoorlijke variatie tussen ziekenhuizen was en ziekenhuisfactoren zoals volume en type ziekenhuis van invloed waren.

Het is lastig te bewijzen dat er een direct causaal verband bestaat tussen clinical auditing en kwaliteitsverbetering, omdat tijd –als een proxy voor innovatie- een verstorende (confounding) factor is. Echter, men is het eens dat bewustwording en continue evaluatie van uitkomsten door dokters en vergelijking met collegae heeft geleid tot een verandering in de interne kwaliteitscultuur. De sturing en intensieve betrokkenheid van chirurgen in de ontwikkeling van de database, het registratieproces en de evaluatie van resultaten van de audit, is daarom een van de belangrijkste voordelen van de DSCA te noemen. Hoewel technische aspecten zeker belangrijk zijn, is het culturele component mogelijk het meest essentiële element in kwaliteitsverbetering.

Meten van kwaliteit van zorg

Om kwaliteit van zorg vast te kunnen stellen, is het belangrijk geschikte kwaliteitsindicatoren te identificeren. Kwaliteitsindicatoren zijn meetbare aspecten van de zorg die kwaliteit reflecteren. Er zijn drie type kwaliteitsindicatoren, die respectievelijk de organisatie structuur, het

zorgproces en de uitkomsten van zorg weergeven. Voorbeelden zijn de beschikbaarheid van een gespecialiseerde verpleegkundige (structuurindicator), het percentage patiënten dat binnen een multidisciplinair team besproken wordt (procesindicator), en het percentage postoperatieve complicaties (uitkomstindicator).

Kenmerken die geschiktheid van kwaliteitsindicatoren voor kwaliteitsevaluatie weergeven zijn:

1) construct validiteit – het moet geassocieerd zijn met kwaliteit van zorg
2) vergelijkbaarheid – er moet weinig of geen bias optreden door:
   a. heterogeniteit in het registratieproces (uniforme definities)
   b. verschillen in de behandelde populatie (casemix correctie)
   c. verschillen in de geteste steekproef (alle patiënten moeten worden geregistreerd).
3) Discriminerend vermogen – er moet variatie zijn in de score op de indicator om goede, gemiddelde en ondermaatse kwaliteit van zorg te identificeren. Ook moet de (ongewenste) uitkomst voldoende vaak voorkomen om kwaliteit te meten (en niet random variatie).
4) Meetbaarheid: de data moet in de praktijk verkrijgbaar zijn.

Een belangrijke voorwaarde voor het gebruik van clinical audit data voor kwaliteitsevaluatie is dat de data compleet zijn en van hoge kwaliteit. Daarbij zullen artsen de feedback informatie alleen gebruiken om verandering in te zetten als ze geloven dat de data accuraat zijn. Incomplete data op variabele, patiënt of ziekenhuizeniveau geeft selectiebias, wat van invloed is op de validiteit van de kwaliteitsmeting. Bijvoorbeeld, als ziekenhuizen sommige, maar niet alle patiënten registreren, kan het zijn dat de patiënten die níet geregistreerd zijn, niet gelijk zijn aan de patiënten die wel geregistreerd zijn (m.a.w. hebben slechtere uitkomsten), wat de geschatte ware uitkomsten van dat ziekenhuis kan verstoren. Kwali-

teit van data kan verbeterd worden door uniforme data verzameling, het gebruik van in- en exclusiecriteria en variabelen definities. Validatie van de data op een externe database of via in ziekenhuis verificatie door een onafhankelijke registreerder kan gebruikt worden om de compleetheid en kwaliteit van de dataset te controleren.

Verder moet bij het vergelijken uitkomsten tussen ziekenhuizen rekening gehouden worden dat risico factoren van patiënten en toevalsvariatie de uitkomst kunnen beïnvloeden . Daarom moet een betrouwbare clinical audit ten minste uitkomsten en patiëntgebonden risicofactoren bevatten. Ook is correcte methodologie noodzakelijk om te corrigeren voor verschillen in patiënten casemix en toevalsvariatie. Het verzamelen van uitkomstinformatie is het eerste en belangrijkste doel van clinical auditing. Echter, het kan lang duren voordat uitkomsten vastgesteld worden, zoals 5-jaarsoverleving. Daarom reflecteren sommige uitkomstindicatoren niet de actuele kwaliteit van zorg, maar die van het verleden. Het meten van korte termijn tussenuitkomsten kan werken als proxy voor lange termijn resultaten. Bijvoorbeeld, CRM positiviteit is een proxy voor lokaal recidief naar endeldarmkanker chirurgie. Indien een proxy gebruikt wordt om kwaliteit te evalueren, is het wel belangrijk mee te laten wegen hoe sterk de correlatie is (construct validiteit) tussen de proxy en de uitkomstindicator. Procesmaten, hoewel van secundair belang, zijn tijdiger en makkelijker op te acteren. Ook kan inzicht in het zorgproces, verschillen in uitkomsten helpen verklaren. Het vastleggen van procesmaten naast uitkomstmaten kan daarom van waarde zijn.

Het is belangrijk om te benadrukken dat het dataverzamelingsproces niet statisch is bij clinical auditing. Wat nu als state-of-the-art zorg wordt gezien, verandert met de tijd en daarom zijn procesmaten ook aan verandering onderhevig. Nieuwe behandelingsmodaliteiten worden toegevoegd aan de registratie en obsolete behandelingen worden

verwijderd. Uitkomstmaten zijn minder gevoelig voor verandering door de tijd.

Richtlijnnaleving en kwaliteit van zorg

Besluitvorming in de kliniek is tegenwoordig steeds meer gebaseerd op wetenschappelijk onderbouwde richtlijnen, die de standaard zijn geworden. Daarbij wordt kwaliteit van zorg in toenemende mate gebaseerd op het naleven van de aanbevelingen in deze richtlijnen. Richtlijnnaleving is bij darmkanker zorg in Nederland hoog en wordt steeds hoger **[dit proefschrift]**. Hoewel richtlijnen waardevol zijn om besluitvorming te ondersteunen, meer standaardisatie in de zorg hebben gebracht en ontegenzeggelijk een belangrijke determinant voor verbetering van uitkomsten van patiënten zijn, zijn er ook redenen om terughoudend te zijn bij het gebruik van richtlijnnaleving als kwaliteitsindicator.

Richtlijnnaleving is geen garantie voor goede uitkomsten bij een individuele patiënt.

Evidence Based Medicine (EBM) kan tekort komen voor klinische besluitvorming voor de behandeling van de individuele patiënt. Het is vooral gebaseerd op klinische trials die de effectiviteit van een behandeling in een groep patiënten bepaald (gemiddelde uitkomsten), en die groepsgemiddelden zijn niet direct vertaalbaar naar alle individuele patiënten in de groep. Daarom speelt het klinisch redeneren bij individuele patiënten een belangrijke rol bij klinische besluitvorming: de individuele patiënt is niet de gemiddelde patiënt. Ten tweede is het bekend dat trial resultaten beperkte externe validiteit kennen: resultaten zijn alleen toepasbaar op die individuen die identieke eigenschappen hebben als de patiënten in de studie. Ten derde, is er weinig bewijs voor de relatie tussen het zorgproces en de uitkomsten van zorg.

Vooral bij de behandeling van ouderen en patiënten met co-morbiditeit schiet EBM tekort. Gezien ouderen en patiënten met veel verschillende ziekten niet goed gerepresenteerd worden in klinische trials, is er ook in de richtlijnen onvoldoende bewijs om behandelbeslissingen te ondersteunen bij deze patiënten. Met de toenemende vergrijzing is er bij (endel-) darmkanker steeds meer behoefte aan EBM voor ouderen en patiënten met co-morbiditeit. Daarbij wordt gezien dat de incidentie van co-morbiditeit en multimorbiditeit toeneemt in zowel jonge als oudere patiënten **[dit proefschrift]**. Vooral cardiovasculaire ziekten en diabetes komen vaker voor naast (endel-) darmkanker. Postoperatieve morbiditeit en mortaliteit nemen duidelijk toe met oplopende leeftijd en nog eens extra wanneer er een of meerdere andere ziekten aanwezig zijn. Daarbij kan de effectiviteit van (adjuvante) behandelingen beïnvloed worden door de bijbehorende veranderde fysiologie in deze patiënten. Het volgen van de algemene aanbevelingen in de richtlijnen kan bij deze fragiele patiëntengroep tot over- of onderbehandeling leiden.

Wetenschappelijk gebaseerde richtlijnen kunnen gedateerd zijn en het vaststellen van de kwaliteit van zorg op basis van richtlijnnaleving beperkt innovatie.

Het ontwikkelen van richtlijnen kost behoorlijk veel tijd en in de laatste decennia is deze steeds een keer per enkele jaren bijgewerkt. Nieuwe onderzoeksartikelen worden met een danig hoog tempo gepubliceerd dat het realistisch is dat nieuw bewijs ontstaat tussen twee edities van de richtlijn in. Het is duidelijk dat het revisieproces van de richtlijnen versneld moet worden om meer actuele EBM te verlenen. Het gebruik van richtlijnnaleving als maat voor kwaliteit brengt ook een ethisch dilemma met zich mee gezien nieuwe behandelstrategieën die buiten de richtlijnen vallen, moeilijker getest of geïmplementeerd kunnen worden.

Een verhelderend voorbeeld is de richtlijn naleving bij het gebruik van radiotherapie voor endeldarmkanker. In de jaren negentig hebben meerdere bekende studies het voordeel van radiotherapie ter voorkoming van lokaal recidief aangetoond. Het gebruik van radiotherapie werd daarom opgenomen in de Nederlandse richtlijn, die het aanraadde voor alle cT2-4 tumoren. Echter, later werd aangetoond dat hoewel het voorkomen van lokaal recidief verminderde na preoperatieve radiotherapie, had dit geen invloed op de 5-jaars overleving in vergelijking met alleen TME chirurgie. Daarbij kunnen allerlei functionele complicaties zoals incontinentie en secundaire maligniteiten ontwikkelen als gevolg van radiotherapie. Nu hoog-resolutie MRI beschikbaar is, is de preoperatieve stadiëring en visualisatie van de tumor veel beter en kan dit klinische besluitvorming voorafgaand aan de behandeling ondersteunen. De MERCURY studiegroep liet vervolgens zien dat radiotherapie veilig weggelaten kon worden bij cT1-3a tumoren, wat 33% van de patiënten betrof. In Nederland kreeg in 2011-2012 echter nog 85% van de patiënten met endeldarmkanker preoperatieve radiotherapie en zelfs 78% van de patiënten met cT1-2N0 tumoren **[dit proefschrift]**. Het te hoge gebruik van radiotherapie kan deels verklaard worden door het brede indicatiegebied dat in de Nederlandse richtlijnen gold, welke nog gebaseerd was op de studies die gehouden werden voor de implementatie van de MRI.

Als laatste moet men bewust zijn dat EBM niet beschikbaar is voor veel essentiële aspecten van het zorgproces die belangrijk zijn voor de uitkomsten van patiënten. Voor een meerderheid van de behandelbeslissingen is er geen gerandomiseerde gecontroleerde trial beschikbaar. Deels omdat deze gewoon nog niet is uitgevoerd, en deels omdat een trial uitvoeren als onethisch wordt gezien door experts.

Als voorbeeld is het gebruik van ontlastende stoma's bij (endel-)darmkanker chirurgie niet gebaseerd op EBM. Er is onvoldoende bewijs dat

een ontlastend stoma het risico op naadlekkage verminderd en het is niet bekend welke patiënten het meest voordeel hebben van zo'n stoma. Risico selectie voor het plaatsen van een ontlastend stoma wordt daarom vaak gebaseerd op persoonlijke ervaring en lokale voorkeuren. Dit is inzichtelijk in de grote variatie tussen ziekenhuizen op dit onderwerp. Ook zien we dat het percentage naadlekkage en mortaliteit niet hoger zijn in ziekenhuizen met minder neiging naar het aanleggen van stoma's **[dit proefschrift]**. Dit laat beter de kwaliteit van patiëntselectie (klinische besluitvorming) voor stoma's dan richtlijnnaleving.

Concluderend kan gesteld worden dat wetenschappelijk gebaseerde richtlijnen onvervangbaar zijn in de huidige zorg, maar ook dat richtlijnnaleving niet per definitie een teken van goede kwaliteit is. Het gebruik van richtlijnnaleving als kwaliteitsindicator zou zelfs een perverse prikkel geven: indicator gedreven zorg. Uitkomstindicatoren geven daarom betere informatie over de geleverde kwaliteit van zorg voor het individu, en de informatie over richtlijnnaleving zou gebruikt moeten worden voor het evalueren van mogelijke redenen voor suboptimale uitkomsten. Tegelijk kan grote variatie in richtlijnnaleving in een homogene patiëntengroep een teken zijn van suboptimale kwaliteit van zorg. Door clinical auditing te gebruiken, kan de benchmark met andere ziekenhuizen die een zeker patiëntengroep behandelen meer betekenis geven over het "presteren" van een individueel ziekenhuis in relatie tot richtlijnaleving.

De waarde van populatie data

Het primaire doel van dataverzameling bij clinical auditing is om feedback informatie aan deelnemers te geven over kwaliteit van zorg. Tegelijk wordt er een gedetailleerde klinische dataset ontwikkeld die ook voor gebruikt kan worden voor wetenschappelijk onderzoek. Een belangrijk kenmerk van deze databases is dat het data van een ongeselecteerde

populatie bevat ("real life data") en daarom voordelen biedt ten opzichte van klinische trials:

1. Uitkomsten hebben een hogere externe validiteit, met andere woorden een hoge toepasbaarheid van de resultaten op een gedefinieerde populatie.
2. Het laat absolute schattingen in de verdeling en prevalentie getallen van relevante variabelen in de populatie zien. Informatie over risicofactoren kunnen bijvoorbeeld gebruikt worden voor het berekenen van een populatie attributief risico.
3. Het is ideaal om relaties te evalueren zonder bias, niet alleen van confounders ten opzichte van determinanten en uitkomsten, maar ook van alle andere interessante variabelen, zelfs zonder dat hiervoor voorafgaand aan de dataverzameling een hypothese is opgesteld (wat bij klinische trials wel moet). Voor het aantonen van causale verbanden zijn klinische trials superieur gezien bij observationele data de reden voor het geven of niet geven van en bepaalde therapie bij een specifieke patiënt vaak onbekend is. Dit kan een confounder zijn bij het evalueren van de effectiviteit van een therapie in de populatie. Bij klinische trials is de keuze voor een therapie puur gebaseerd op randomisatie en daarom kan een echte causale relatie tussen behandeling en uitkomst worden vastgesteld.
4. Door de hoeveelheid data is het mogelijk kleine subgroepen (met zeldzame aandoeningen of therapieën) te evalueren. In de DSCA is bijvoorbeeld, het effect van synchrone (endel-)darmkanker (met een incidentie van 3,4%) op korte termijn uitkomsten onderzocht, waarbij deze aandoening als een risicofactor voor complicaties en reinterventies werd aangewezen **[dit proefschrift]**.
5. Hoog-risico patiënten, zoals ouderen en patiënten met co-morbiditeit, die vaak geëxcludeerd worden van klinische trials, zijn in deze databases wel aanwezig, waardoor de veiligheid en de effectiviteit

van zorg in deze belangrijke patiëntengroep geëvalueerd kan worden.

Samengenomen, zijn populatie data een waardevolle toevoeging op gerandomiseerde klinische trials en met de tijd zullen algoritmes ontwikkeld worden die klinische besluitvorming ondersteunen en gepersonaliseerde zorg.

TOEKOMSTPERSPECTIEF

Naar uitkomsten die er voor patiënten toe doen

Hoewel zeer waardevol als kwaliteitsverbeteringsinstrument, geven de data verzameld door de DSCA slechts een beperkt beeld op de kwaliteit van zorg: het klinische proces en de uitkomstmaten die belangrijk zijn vanuit behandelaars perspectief ten aanzien van veiligheid en effectiviteit van zorg. Er zijn niet alleen meer manieren om naar kwaliteit van zrog te kijken, zoals, patient-gerichtheid, tijdigheid, efficiëntie en gelijkheid. Daarbij kan het perspectief van de patiënt dokters ook essentiële informatie geven om de kwaliteit van zorg te verbeteren. Recentelijk zijn daarom patiënt gerapporteerde uitkomstmaten (PROMs) geïntroduceerd. Hoewel critici de validiteit van PROMs in twijfel trekken omdat deze gevoelig zijn voor confounders, zoals sociaal economische status, en de implementatie in de kliniek nog steeds moeizaam verloopt, is het waarschijnlijk een kwestie van tijd voordat deze barrières zijn overkomen en het patiëntenperspectief standaard onderdeel van de kwaliteitsevaluatie is. Er zijn enkele nationale PROM programma's. De responspercentages worden beïnvloed door vele factoren. Onder andere vraagt het een efficiënte infrastructuur van data collectie (ondersteund door ICT), het betrekken van patiënten en clinici in het ontwikkelen van het PROMs programma, het integreren van PROMs in de zorgpaden (zoals

het bestellen van een lab onderzoek), het ondersteunen van het gebruik van PROMs resultaten bij de individuele patiëntenzorg en het opleiden van clinici hiertoe. Het gezamenlijk evalueren van klinische en patiënt gerapporteerde uitkomsten zou de sleutel kunnen zijn voor een betere interpretatie van PROMs gezien demografische gegevens (zoals sociaal economische status) en andere confounding factoren beschikbaar zijn in de database om gecorrigeerde PROMs te berekenen.

Nieuwe bewegingen stellen dat de patiënt niet alleen deel zou moeten nemen aan het registratieproces door PROMs te registreren. Patiënten zouden daarnaast ook moeten uitspreken welke uitkomsten belangrijk zijn voor hem/haar bij het selecteren van een ziekenhuis, dokter of behandeling, gezien dat dezelfde uitkomsten zouden moeten zijn waar dokters naar streven bij het behandelen van patiënten. In 2012, hebben de gebundelde krachten van Michael Porter van Harvard Business School, de Boston Consulting Group en het Karolinska Instituut in Zweden geleid tot de start van het International Consortium of Health Outcomes Measurement (ICHOM). Het doel van deze organisatie is wereldwijde standaardsets te ontwikkelen van uitkomstmaten die er voor patiënten met het meest toe doen. De eerste sets worden momenteel geïmplementeerd in de Nederlandse zorg. Zij plannen in 2017 50 standaardsets te hebben gepubliceerd, die 50% van de universele ziektelast beslaan.

Deze uitkomsten zouden natuurlijk volledig opgenomen moeten worden in clinical auditing en kwaliteits vaststellingen. Dit houdt in het opnemen van deze uitkomsten in de feedback informatie aan clinici en het identificeren van best practices aan de hand van de resultaten. Ook publieke (transparante) kwaliteitsindicatoren zouden gebaseerd moeten zijn om uitkomsten die belangrijk zijn voor patiënten. Om zelfs een stap verder te gaan, zouden deze uitkomsten standaard onderdeel van

de zorg moeten zijn bij het informeren van de patiënt over de verwachte resultaten van een beoogde behandeling. Zowel op individueel niveau (hoe vergaat het deze specifieke patiënt in vergelijking met anderen of met vorig jaar?) en op geaggregeerd niveau (wat kan mijn patiënt verwachten gebaseerd op de resultaten van vergelijkbare patiënten in het verleden) is dit zeer waardevolle informatie zowel voor dokters als patiënten.

Transparantie van kwaliteit van zorg

Verschillende internationale vergelijkingen laten zien dat de kwaliteit van zorg in Nederland hoog is. Tegelijk doen incidenten zich voor en in de afwezigheid van publiek beschikbare kwaliteitsinformatie kan het effect van een individuele casus worden uitvergroot en wantrouwen voeden. De roep om transparantie kwaliteitsinformatie is de afgelopen jaren wereldwijd toegenomen. Het gebrek aan goede beschikbare uitkomstinformatie heeft de snelheid en wijze waarom aan deze roep wordt voldaan, belemmerd. In een recent rapport wordt aangegeven dat patiënten de huidig beschikbare kwaliteitsinformatie niet gebruiken voor het kiezen van hun ziekenhuis. Meest waarschijnlijk komt dit doordat de huidige informatie niet erg toegankelijk is, niet als betrouwbaar wordt beschouwd of moeilijk is te interpreteren voor de individuele patiënt.

Er is consensus onder dokters dat transparantie van kwaliteitsinformatie niet te voorkomen is en wenselijk om vertrouwen op te bouwen. Tegelijk is de geschiktheid van indicatoren voor publieke interpretatie, het wantrouwen van de kwaliteit van kwaliteitsinformatie en angst om (onterecht) gestraft te worden, redenen om van transparantie weg te blijven. De NVvH heeft gekozen voor een getrapt traject naar transparantie van resultaten van de DSCA. Het eerste jaar worden structuurindicatoren en operatievolumina publiek. Het tweede jaar komt informatie over

richtlijnnaleving en andere procesindicatoren vrij en het derde jaar ook uitkomstindicatoren. Deze strategie was succesvol omdat het mogelijk maakte: (1) een zorgvuldig selectieproces van geschikte indicatoren (2) een interne veiligheidscultuur onder dokters om te leren van de resultaten voordat ze publiekelijk beschikbaar worden, (3) uitgebreide evaluatie van de kwaliteit van data door verificatie in het ziekenhuis door een onafhankelijke partij en (4) het beschikbaar komen van uitgebreide kwaliteitsinformatie.

Transparantie van zorg is een belangrijke drijfveer voor kwaliteitsverbetering. De Boston Consulting Group heeft laten zien dat transparantie van uitkomstinformatie in Zweden geleid heeft tot grote verbeteringen in kwaliteit van zorg en kostenreductie.

Aan de andere kant hebben diverse rapporten ook laten zien dat het publiek maken van kwaliteitsinformatie leidt tot defensief gedrag onder dokters en "indicator gedreven zorg", m.a.w. het werken naar een hoge score op individuele kwaliteitsindicator. Hierdoor is het de vraag of de focus op procesindicatoren, waarbij de relatie met uitkomsten van zorg vaak twijfelachtig is, zou kunnen interfereren met het belang van een individuele patiënt. Ook zijn procesmaten moeilijk te interpreteren door patiënten. Het richten op uitkomstindicatoren die voor de patiënt belangrijk zijn, visualiseert de ware zorgresultaten, stimuleert innovatie, en zal waarschijnlijk het gebruik van kwaliteitsinformatie onder patiënten verhogen. Ook zou het focussen op positief geformuleerde uitkomstindicatoren, zoals toegenomen kwaliteit van leven, overleving en functionele uitkomsten, in plaats van het focussen op ongewenste uitkomsten (zoals complicaties) de integrale aanpak naar de patiënt toe stimuleren, vooral in multidisciplinaire zorg.

In de toekomst, wanneer uitkomsten die belangrijk zijn voor patiënten breed beschikbaar zijn, is het daarom wenselijk om het gebruik van procesinformatie en specifieke technische uitkomsten te beperken tot interne kwaliteitsinformatie voor medische professionals, wat zowel een interne kwaliteitscultuur zal stimuleren als het voldoen aan de behoefte van patiënten aan goede kwaliteitsinformatie.

Naar waarde gedreven zorg

Als laatste een korte notitie van het opkomen van waarde gedreven zorg (value based healthcare). Gezien de kosten van de zorg sterker toenemen dan het GDP in Nederland (in 2009 was dit al 15%)**,** is ons huidige zorgsysteem niet houdbaar in de toekomst. Het huidige betalingssysteem beloont volume, terwijl er een groeiende bewegingn is naar het verbinden van bekostiging aan kwaliteit en waarde van zorg (kosten per gewonnen gezondheid). Porter bepleit dat competitie tussen ziekenhuizen op kwaliteit van zorg (uitkomsten) kosten zal doen verminderen, en daarbij de waarde van de zorg zal verhogen. Recent liet de value based healthcare study zien dat de toevoeging van kosten gemaakt in het ziekenhuis aan de DSCA data benchmarkinformatie over de waarde van zorg kan opleveren, en gezien er variatie tussen ziekenhuizen bestaat zijn er mogelijkheden om van elkaars resultaten te leren. Een integrale blik op klinische uitkomsten, patiënt gerapporteerde uitkomsten en kosten zou de heilige graal zijn om voor te streven in de gezondheidszorg.

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To me, this thesis embodies much more than the articles it includes. It reflects my introduction to both scientific research, the start-up of an organization and management. And most of all, it stands for a period in which I changed my perspective on health care and decided to leave direct patient care to encounter other exciting opportunities in this fascinating industry. I have no regrets so far.

First, I want to thank my promotor, Rob Tollenaar. You have inspired me with your helicopter view and visionary leadership style. I have never met anyone that can simplify complexity and get directly to the real crux of the matter, like you do. And my co-promotor, Michel Wouters. You are a true innovator and scientist, having an infinite number of ideas and a solution to every problem. Besides discussing my papers, I have enjoyed our "innovation meetings" (especially when there is no agenda), duo presentations and project work enormously. Eric Hans Eddes, with your inexhaustible energy, optimism and humor, you are the engine of DICA. I want to thank all three of you for your guidance and trust in me and I am proud to have been working at your side while building DICA in its early stages.

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Curriculum Vitae

Nicoline van Leersum was born in Zeist on July 27th 1984 and grew up in The Hague. With a medical specialist and nurse as parents, her affection for health care started early. She obtained her medical degree in Leiden in 2008 after writing her graduation article on 'chronic post-sternotomy pain' with her father, drs. Rutger van Leersum (pain medicine), and supervised by dr. Henriette Verweij (cardiology) and Prof. dr. Klautz (thoracic surgery) at the Leiden University Medical Centre.

With the objective to becoming a surgeon, she worked as a surgical resident in Medical Centre Haaglanden in The Hague for two years. In 2010, during her surgical residency, she initiated a multicentre clinical trial aiming to recruit 2000 patients: the gum chewing trial. The pleasure of managing this trial with dr. Vincent van Weel, dr. Bert Bonsing dr. Hidde Kroon, dr. Joost van der Sijp and drs. Noortje de Leede, was immense. The trial was successfully completed recently and its article is written at this very moment.

To obtain a fulltime PhD position, she applied at Leiden University Medical Centre to professor dr. Rob Tollenaar and dr. Michel Wouters in 2011. This specific PhD project was of special interest to her, since it comprised both scientific research and pioneering: writing a thesis on colorectal cancer care and simultaneously coordinating a new national quality improvement project, the Dutch Surgical Colorectal Audit ("DSCA").

Evaluating quality of care on a national level changed her point of view from that of clinician on individual patient care to a more public health

point of view appreciating the importance of accountability, transparency and continuous self-evaluation of healthcare providers. The project was a real eye-opener to her as there were substantial differences between hospitals and potential for improvement of quality.

As the DSCA was a game changer in the Netherlands, DICA was founded to develop many more audits, using the DSCA as a blueprint. In 2012, Nicoline worked for 1,5 years at the DSCA as a PhD student when she was offered the opportunity to set up new registries and manage the medical department of DICA with supervision of the 3 founders: Rob Tollenaar, Eric Hans Eddes and Michel Wouters. With the intention of returning to patient care within two years, she accepted this challenge.

Soon she realized that this initiative could indirectly affect much more patients than she could ever treat as an individual doctor. Furthermore, the fulfilment of being a manager made her decide to continue her work at DICA and leave direct patient care behind. Currently, she works on innovative projects, for example she developed the concept of patient-centered registries, and leads the department for the development and implementation of Patient Reported Outcomes and Experiences registries (PROMs and PREMs).

In 2015, she was admitted to the Global Executive MBA at INSEAD, situated in France, Singapore and Abu Dhabi. Hereby, she works on her mission to improve health care and the ability to integrate her medical, scientific and business background to have an impact.

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