ON EFFECTIVENESS IN COLORECTAL SURGERY

Mechanical bowel preparation or not in elective colonic surgery and treatment options for elderly patients with rectal cancer.

Bärbel Jung

Umeå 2008

Department of Surgical and Perioperative Sciences,
Fakulty of Medicine
University of Umeå, Umeå, Sweden
To Bo, Michaela and Joachim

”För har vi inte frågorna så är vi inte öppna för svaren, och dem behöver vi om vi vill växa”

Mark Levengood 2006
ABSTRACT

The management of patients undergoing colorectal surgery has changed in recent decades. Efforts have been made to show that perioperative physiological stress to the patient can be minimised with standardised care programmes and thus improve short term outcome after colorectal surgery. Mechanical bowel preparation (MBP), for instance, has been questioned as part of standard management.

There are studies highlighting the effect of cancer treatment and its side effects in the elderly, showing that geriatric patients benefit from oncological therapy in much the same way as younger patients. The impact of this information on surgical and oncological practice in Sweden today is not known.

To assess the effectiveness of colorectal surgery we need both randomised controlled trials and population-based cohort studies. We have performed a trial on colonic surgery with and without preoperative mechanical bowel preparation, as well as a nationwide register study comparing treatment and outcome of rectal cancer in two age groups.

In a randomised controlled trial 1505 patients from 21 hospitals were randomised to MBP or no-MBP prior to open elective colonic resection. There were no differences in overall complication rates between the groups: cardiovascular 5.1% with MBP vs. 4.6% without MBP; general infection 7.9% vs. 6.8%; and surgical site complications 15.1% vs. 16.1%. The proportion of patients reaching at least one primary endpoint was 24.5% vs. 23.7% respectively.

The patients experience of and postoperative recovery after MBP or no-MBP was evaluated in 105 of the patients in the bowel preparation trial at three of the participating hospitals. Sixty-five patients received MBP and 40 patients did not. In the MBP group 52% needed assistance with bowel preparation. Day 4 postoperatively patients in the no-MBP group perceived more discomfort than patients in the MBP group, p<0.05. Bowel emptying occurred significantly earlier in the no-MBP group than in the MBP group, p<0.05.
In an experimental study the effect of MBP on intramucosal bacterial count was evaluated. Macroscopically normal colon mucosa was collected from 37 patients (20 MBP and 17 No-MBP) undergoing elective colorectal surgery at three hospitals. MBP did not influence the median colony count of E. coli, Bacteroides, or total median colony count, information that was previously unknown.

These three studies imply that MBP can be omitted before elective colonic resection.

In a population-based register study, treatment for rectal cancer in patients $\geq 75$ years and those $< 75$ years was evaluated using data from the Swedish Rectal Cancer Register 1995-2004 ($N=15104$). This study revealed that preoperative radiotherapy was used less in patients $\geq 75$ years. There was also a higher threshold for surgery in this group, and they more often received a permanent stoma compared to younger patients. Outcome in terms of 5-year local recurrence rate and 5-year cancer-specific survival differed very little between the older and younger patient groups who underwent abdominal tumour resection with curative intent.

We suggest future studies focusing on ways of reducing surgical and perioperative stress and on quality of life when assessing suitable treatment modalities for rectal cancer.
# LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBP</td>
<td>Mechanical bowel preparation</td>
</tr>
<tr>
<td>HNPCC</td>
<td>Hereditary non-polyposis colorectal cancer</td>
</tr>
<tr>
<td>FAP</td>
<td>Familial adenomatous polyposis</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>ERUS</td>
<td>Endorectal ultrasonography</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>TNM</td>
<td>Tumour Node Metastasis</td>
</tr>
<tr>
<td>AJCC</td>
<td>The American Joint Commission of Cancer</td>
</tr>
<tr>
<td>UICC</td>
<td>Union Internationale Contre le Cancer</td>
</tr>
<tr>
<td>APE</td>
<td>Abdominoperineal excision</td>
</tr>
<tr>
<td>HA</td>
<td>Hartmann’s procedure</td>
</tr>
<tr>
<td>AR</td>
<td>Anterior resection</td>
</tr>
<tr>
<td>TME</td>
<td>Total mesorectal excision</td>
</tr>
<tr>
<td>RT</td>
<td>Radiotherapy</td>
</tr>
<tr>
<td>MDT</td>
<td>Multidisciplinary team</td>
</tr>
<tr>
<td>SRCR</td>
<td>Swedish Rectal Cancer Registry</td>
</tr>
<tr>
<td>ASA</td>
<td>American Society of Anestesiologists</td>
</tr>
</tbody>
</table>
LIST OF PAPERS

This thesis is based on the following four papers, which will be referred to by their Roman numerals:

I Multicentre randomized clinical trial of mechanical bowel preparation in elective colonic resection. 
Jung B, Påhlman L, Nyström PO, Nilsson E; Mechanical Bowel Preparation Study Group 
Br J Surg. 2007 Jun;94(6):689-95
Copyright British Journal of Surgery Society Ltd. Reproduced with permission. Permission is kindly granted by John Wiley & Sons Ltd on behalf of the BJSS Ltd.

II Preoperative mechanical preparation of the colon: the patient’s experience. 
Jung B, Lannerstad O, Påhlman L, Arodell M, Unosson M, Nilsson E 
BMC Surgery 2007;7(1):5

III Does Mechanical Bowel Preparation Affect the Intramucosal Bacterial Colony Count? 
Submitted

IV Rectal cancer treatment in the elderly, an audit based on the Swedish rectal cancer register 1995-2004 
Jung B, Påhlman L, Johansson R, Nilsson E
Submitted
CONTENTS

Introduction 13

Aims of the Study 15

Background 17

Methods and Methodological Considerations 27

Results and Discussion 36

General Conclusion 49

Summary in Swedish
(Sammanfattning på svenska) 51

Acknowledgements 57

References 59

Papers I-IV
INTRODUCTION

Colorectal resection became feasible following the introduction of anaesthesia\(^1\), antibacterial therapy\(^2\) and antiseptic preparation of the operating field. In the early 20\(^{th}\) century mortality rates after colorectal resection were as high as 40\% but have improved and are today 1-3\% in elective cases. Focus on the development of surgical techniques has been a major issue during the past 20 years, and has clearly changed long-term survival after surgery for rectal cancer\(^2\)-\(^5\). Long-term survival after colorectal cancer has also improved due to the introduction of adjuvant and neo-adjuvant chemo-and radiotherapy\(^6\)-\(^13\). Introduction of the multidisciplinary team will almost certainly optimise care of colorectal cancer patients in the future\(^4\),\(^14\),\(^15\).

Early observational studies and clinical experience came to the conclusion that removal of faeces from the bowel was associated with lower postoperative morbidity\(^16\), and MBP became self-evident in colorectal practice throughout the 20\(^{th}\) century. In a survey of members of the American Society of Colon& Rectum Surgeons, published in 2003, Zmora and colleagues showed that 99\% of respondents used MBP prior to colorectal surgery\(^17\).

Studies have shown that short-term outcome after colorectal surgery is improved and perioperative physiological stress to the patient is minimised using standardised care programmes which include early feeding and mobilisation as well as restriction of intravenous fluids perioperatively\(^18\)-\(^21\). In these programmes mechanical bowel preparation has been questioned as part of standard care.

Most of the studies on changes in perioperative care for both colorectal cancer and benign lesions have not included geriatric patients. In the Swedish National Population Register 2005 the proportion of habitants older than 75 years was 8.9\% and for those older than 80 years 2.5\%\(^22\). These figures are expected to increase in the future. There are studies highlighting the effect of cancer treatment and it’s side-effects in the elderly population showing that geriatric patients benefit from surgery and chemo- and radiotherapy in much the same way as younger patients, but that in some instances older patients suffer more pronounced side-effects\(^23\)-\(^25\). The impact of this information on surgical and
oncological practice in Sweden today is not known, but we do know that elderly patients are seldom included in clinical trials investigating the effect of cancer treatment. As in all other fields of health care, treatment of colorectal cancer should follow the fundamental principles of medical ethics. This means that clinical practice guidelines and other recommendations must be based upon judgements of quality of evidence and strength of recommendations. A systematic approach in the judgement of quality of evidence, which takes into account not only randomised controlled trials but also observational (cohort) studies, such as register audit, has been presented. Before making a recommendation it is necessary to consider the balance between benefit and harm, as well as cost and resource utilisation. This has special implications for populations with increasing age where the demand for surgical services is expected to increase. This thesis is based upon information from a multicentre randomised controlled trial scrutinising evidence for mechanical bowel preparation as routine practice prior to elective colonic surgery, and from prospectively collected data from a nation-wide register covering all patients with the diagnosis of rectal cancer in Sweden.

Effectiveness - performance in more general routine practice
Nat Inst Med 1985
AIMS OF THE STUDY

The general aim of this work was to contribute to improvement of some aspects of colorectal surgery, the specific aims were

- to assess whether or not preoperative mechanical bowel preparation (MBP) is necessary for safe elective colonic surgery

- to assess patients’ experience of, and acceptance of preoperative MBP in elective colonic surgery

- to determine whether or not MBP affects intra mucosal bacterial growth in the colon

- to assess the influence of age on treatment for rectal cancer and outcome
BACKGROUND

Preoperative considerations in colorectal surgery

Colonic surgery is performed for both benign and malignant disorders. In 2005 the number of colonic resections performed in Sweden was 5346 (5228 open and 118 laparoscopic) according to statistics of The National Board of Health and Welfare, Sweden. The postoperative complication rate is high, comprising both infectious and cardiovascular events, which leads to suffering for patients and increased costs for society. Lowering the complication rate has been a guiding principle for current research as well as evaluation of new surgical and oncological methods in colorectal cancer treatment.

Prophylactic antibiotic therapy and venous thromboembolism prophylaxis have a well-documented effect and today are included in every treatment protocol for colonic surgery. There are data suggesting that enhanced recovery programmes where normal activities are encouraged early and invasive monitoring is restricted, facilitates postoperative mobilisation and lowers the risk for both cardiopulmonary and infectious complications, but there are still questions as to how to implement these findings in general practice.

Mechanical bowel preparation in colonic surgery

MBP

Mechanical bowel preparation (MBP) refers to clearing the bowel of faecal contents. This can be achieved by a variety of methods. Bowel irrigation with saline where a large quantity of warm (37°C) isotonic saline is perfused through the stomach until clear liquid is passed rectally. This method results in water and sodium retention and is contraindicated in patients with cardiac disease.
**Oral mannitol preparation** is given orally as an iso- or hypertonic solution. The bowel does not absorb the mannitol and the osmotic action of mannitol facilitates irrigation and cleansing of the bowel. This method leads to dehydration and might increase the risk for postoperative infection due to excessive production of gas under the influence of mannitol\(^{37,38}\).

*Polyethylene Glycol solution* is a non-absorbable osmotic agent in an isotonic electrolyte solution. The solution is taken orally and large quantities are needed (4 L) for faecal clearance of the large bowel. This is one of two preferred MBP methods today. There are no known serious side-effects, but many patients dislike the large quantities of fluid combined with its salty taste\(^{37,39-41}\).

*Sodium Phosphate solution*, like polyethylene glycol solution is taken orally. Osmotic diarrhoea is provoked by small quantities of the solution (90 mL). Sodium phosphate solutions have been shown to be effective and well tolerated by patients\(^{42,43}\) and is the most commonly used MBP today. The method is contraindicated in patients with congestive heart failure, renal failure or ascites. In these cases polyethylene glycol may be used instead.

In addition to these cathartic solutions bowel cleansing can be achieved by *preoperative fasting, preoperative enema or peroperative colonic lavage*. These methods are not regarded as standard bowel preparation when bowel cleansing is desired, because Polyethylene Glycol and Sodium Phosphate are more effective, more economic and better tolerated by the patient.\(^{39,44}\)

**Anastomotic healing**

MBP has historically been considered one of the most important procedures if one is to avoid postoperative septic complications in all kinds of abdominal surgery. In colorectal surgery an empty bowel has been regarded crucial for optimal anastomotic healing\(^{45,46}\).
In emergency and trauma surgery primary anastomosis can be safely performed without pre- or intra-operative preparation (on table lavage)\textsuperscript{47-49} but animal studies investigating anastomotic healing have yielded conflicting data \textsuperscript{50-54}.

The most feared postoperative complication in colonic and rectal surgery is anastomotic dehiscence, which leads to considerable morbidity and elevated postoperative mortality rates, efforts have been made to understand the mechanism of anastomotic healing and the causes of anastomotic dehiscence. Some authors have suggested that anastomotic dehiscence is dependent on a diversity of risk factors \textsuperscript{45, 55-60} some of which can be influenced by specific treatment modalities applied perioperatively.

The phases of anastomotic healing in the gastrointestinal tract are defined as\textsuperscript{60, 61}:

1. \textit{Lag phase} (0-3 days) with cytokine release and infiltration of inflammatory cells
2. \textit{Proliferative phase} (day 4-) with angiogenesis, increase in fibroblastic activity and epithelial cell migration.
3. \textit{Remodelling} with collagen fibre organisation and decrease in numbers of inflammatory cells.

The importance of intrinsic and extrinsic factors for successful anastomotic healing are not completely understood and it is therefore difficult to anticipate which clinical factors are truly important to avoid anastomotic dehiscence.

Mechanical bowel preparation was first questioned as an independent factor in the prevention of anastomotic dehiscence in 1972 by Hughes \textsuperscript{62} and since then several randomised trials and meta-analyses have suggested that MBP is not important to diminish the rate of postoperative septic complications\textsuperscript{63-75}. However, these studies are all of limited size and have had little effect in causing colorectal surgeons to abandon MBP prior to elective colonic surgery\textsuperscript{17, 76, 77}.  

Bacteriology of the colon

The interactions between host and colonic bacteria are important for normal life. The colonic flora comprises vast numbers of bacteria (\(10^{12}\) bacteria/gram faeces) of which approximately 500 species are detectable by methods used today. There is spatial organisation of the bacterial compartments, where the intramucosal and intraluminal compartments are divided by the mucus layer\(^78\). The microbial ecosystem of the colon shows great individual stability but can be altered by intake of antimicrobial drugs and major changes in diet. The stability of the microflora is maintained by host factors such as cellular and humoral immunity, the mucus layer between the mucosal and intraluminal compartments, peristalsis and secretions to the gastrointestinal tract such as pancreatic enzymes and bile acids\(^78,79\).

Intraluminal bacteria of the colon promote energy utilisation by fermentation with break-down of carbohydrates resulting in short-chain fatty acids which are mainly metabolized as an energy source for enterocytes but also appear to be a possible energy source for patients with severe malnutrition or short bowel syndrome\(^80,81\).

Very few bacterial strains are identified in the colonic mucosa of healthy individuals. In colorectal cancer patients, however, the colonic mucosa is shown to be colonised by intracellular E.coli\(^82\), and in patients with inflammatory bowel disease multiple mucosa-invading bacteria are found, mainly anaerobes\(^83,84\).
Rectal cancer treatment in the elderly

Epidemiology and aetiology

Colorectal cancer is one of the most common cancers in the world. The incidence of rectal cancer in Sweden in 2006 was 1995 patients, overall, of which 767 (39.2%) were 75 years or older, according to The National Board of Health and Welfare, Sweden\textsuperscript{22}. The incidence of rectal cancer, as with colonic cancer, shows geographical variations and is most frequent in the western world\textsuperscript{85} where the incidence is increasing due to an ageing population. Environmental factors, especially life-style factors are important in the aetiology of adenocarcinoma of the rectum\textsuperscript{86-90}. Although the specific causes of cancer development have not been established there is evidence that low intake of dietary fibre, high intake of animal fat, tobacco and alcohol are factors that facilitate rectal cancer development. About 5-10\% of colorectal cancer cases are attributed to two high-penetrance genetic disorders: hereditary non-polyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP)\textsuperscript{91-93}. The total proportion of rectal cancers caused by hereditary factors is difficult to establish due to limited knowledge about the effect of low-penetrance genetic mutations as well as uncertainty about the impact of familial genetic contra environmental factors.

Diagnosis and staging

Diagnostic procedures are undertaken either because of patient symptoms or positive screening results. Screening for colorectal cancer is not general practice in Sweden today but is the subject of discussion following recent data\textsuperscript{94-96}. The diagnosis of cancer is verified by biopsies taken through an endoscope. If the tumour is located in the lower part of the rectum, digital examination gives valuable information about possible
fixation of the tumour to adjacent tissues. Magnetic resonance imaging (MRI) and/or endo-rectal ultrasound (ERUS) are valuable tools when evaluating the extent of local tumour growth and local lymph node status preoperatively. To screen for possible distant metastases, computered tomogram (CT) of the thorax and abdomen or contrast-enhanced ultrasonography combined with a chest x-ray are undertaken.

Table 1. The TNM classification and the relation to the tumour stage defined by the AJCC/UICC system

<table>
<thead>
<tr>
<th>AJCC/UICC stage (Dukes classification)</th>
<th>TNM system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I (A) T1-2 N0 M0</td>
<td>T1 = Invasion of submucosa</td>
</tr>
<tr>
<td></td>
<td>T2 = Invasion of muscularis propria</td>
</tr>
<tr>
<td></td>
<td>N0 = No nodal metastases</td>
</tr>
<tr>
<td></td>
<td>M0 = No distant metastases</td>
</tr>
<tr>
<td>Stage II (B) T3-4 N0 M0</td>
<td>T3 = Invasion of subserosa or perirectal fat</td>
</tr>
<tr>
<td></td>
<td>T4 = Invading other organ (T4A) and/or visceral peritoneum(T4B)</td>
</tr>
<tr>
<td></td>
<td>N0 = No nodal metastases</td>
</tr>
<tr>
<td></td>
<td>M0 = No distant metastases</td>
</tr>
<tr>
<td>Stage III (C) Any T N1-2 M0</td>
<td>N1 = 1-3 regional nodes involved</td>
</tr>
<tr>
<td></td>
<td>N2 = ≥ 4 regional nodes involved</td>
</tr>
<tr>
<td></td>
<td>M0 = No distant metastases</td>
</tr>
<tr>
<td>Stage IV (D) Any T N0-2 M1</td>
<td>M1 = Distant metastases</td>
</tr>
</tbody>
</table>

Correct staging (according to the TNM classification, Table 1) is crucial for planning treatment since patients with advanced rectal tumours are shown to benefit from neo-adjuvant oncological treatment (radiotherapy and/or chemotherapy). Furthermore, an accurate preoperative staging process facilitates planning of the
surgical strategy. A multi disciplinary team (MDT) recommends a treatment strategy for each patient, a recommendation the attending surgeon or oncologist discusses with the patient before deciding on the final treatment plan\textsuperscript{104}. Postoperatively the tumour status is evaluated and described according to the residual tumour classification (Table 2) proposed by Union Internationale Contre le Cancer (UICC).

Table 2 Residual Tumour Classification

<table>
<thead>
<tr>
<th>Tumour status</th>
</tr>
</thead>
<tbody>
<tr>
<td>R 0</td>
</tr>
<tr>
<td>R 1</td>
</tr>
<tr>
<td>R 2</td>
</tr>
</tbody>
</table>

Treatment for rectal cancer

Surgery is the only proven curative treatment for rectal cancer although there are reports demonstrating long term-survival with oncological treatment alone\textsuperscript{105,106}. Several studies have shown an additive beneficial effect on local recurrence rate and/or long-term survival with neoadjuvant radiotherapy\textsuperscript{8,9,107} and chemotherapy\textsuperscript{101,108} in primarily resectable rectal cancer.

Surgery

Surgical removal of the tumour and regional lymph nodes draining the rectal segment via an abdominal approach is the recommended surgical option. For patients at great risk for postoperative morbidity and mortality with a Stage I tumour local excision is an option. The long-term oncological results of local excision, however, are inferior to the results of abdominal rectal cancer surgery\textsuperscript{109}.

In 1908 Miles described a new surgical procedure in rectal cancer surgery: abdominoperineal excision (APE) with a permanent stoma\textsuperscript{110}. The APE method was developed in the early 20\textsuperscript{th} century.
and remained the method of choice for all rectal cancer surgery for many decades. APE is today reserved for selected cases, mainly low tumours close to the anal sphincter. The Frenchman H. Hartmann suggested in 1921 a two-stage operation for cancer of the distal part of colon\textsuperscript{111}. In the first stage the large bowel (i.e. sigmoid) was divided proximal to the tumour and the proximal bowel externalised as an end-colostomy. After recovery from the first operation a relaparotomy was employed with closure of the rectum distal to the tumour and removal of the rectal segment including the tumour. The Hartmann procedure (HA) has been refined and is today employed as a one-stage procedure preferably in cases where a low colorectal anastomosis is not considered safe or functional.

In the 1970s sphincter-saving surgery with restored bowel continuity, anterior resection (AR), gained popularity following the introduction of mechanical staplers\textsuperscript{112} and the work by Parks describing how to suture a low colo-anal anastomosis\textsuperscript{113}. Regardless of the choice of surgical technique the 5-year survival remained 40-50\%\textsuperscript{114} and local recurrence rate nearly 40\%\textsuperscript{115} until a change of paradigm was initiated with the introduction of total mesorectal excision (TME) by professor Heald in 1982\textsuperscript{3}. Until then rectal cancer surgery was performed by removing the bowel segment without any serious consideration of the local lymphatic system. In his work Heald recognised the importance of understanding the embryological development of the rectum in order to obtain radical surgery with removal of the local pathways for lymphatic spread and intact fascial coverage to achieve adequate local control of the tumour disease. The superiority of TME (compared to older techniques) was emphasised by the work of the pathologist Quirke. He showed that clinical outcome in terms of local recurrence rate was better when TME was employed\textsuperscript{116} since TME increases the chance of circumferential margins clear of tumour cells. This work led to a close collaboration between surgeons and pathologists in order to improve surgical techniques. Pathologists are today important participants in the multidisciplinary team. The TME technique is often associated with AR but is also applicable and important when performing HA or APE.
Radiotherapy

Radiotherapy (RT) using a radiation dose tolerated by adjacent organs in the pelvis has not convincingly been shown to cure rectal cancer as a single treatment modality, but adjuvant RT increases the chance of local control in resectable rectal cancer. RT can be administered preoperatively, postoperatively or intra-operatively. In resectable rectal cancer, preoperative adjuvant RT has been shown to be superior to postoperative RT as adjuvant treatment and also compared to surgery alone. The effect of intra-operative in addition to preoperative RT has been analysed in locally advanced rectal cancer and seems to offer an additive effect in very advanced cancers due to less damage to adjacent organs despite the high radiation dose. The side-effects of preoperative adjuvant RT are known to affect the quality of life due to bowel dysfunction and impairment of sexual function, these probably being more pronounced in elderly patients. This emphasises the importance of sound knowledge when selecting patients that benefit from adjuvant RT if one is to avoid over treatment and thus conceivable side-effects. Preoperative staging and MDT conferences are important for adequate selection of patients for preoperative RT.

Chemotherapy

Postoperative adjuvant chemotherapy has been shown to improve outcome in Stage III colonic cancer but there is still no single study demonstrating the same benefit in rectal cancer patients. Based on current scientific data, the Swedish national treatment programme for rectal cancer does not recommend postoperative adjuvant chemotherapy for rectal cancer as standard treatment. Neoadjuvant chemotherapy has been shown to be beneficial when down-staging is desired either to gain resectability of a locally advanced tumour
or to improve the chance of successful sphincter-saving surgery in low tumours.  

Rectal cancer treatment in the elderly

Rectal cancer is predominantly a disease of elderly people who, in many cases, suffer from concurrent disease and decreased physical and physiological function. There are studies showing that age influences selection of cancer treatment. The rationale for this is unclear since elderly patients seem to benefit from surgery and chemotherapy in much the same way as younger patients and without serious side-effects. There are though data suggesting that elderly patients might not benefit from preoperative RT in the same way as their younger counterparts.

Swedish Rectal Cancer Register

The Swedish Rectal Cancer Register (SRCR) was launched by the Swedish Board of Health and Welfare and in 1995 and every department of surgery agreed to deliver data to the register. Since then the register has been validated. Registered data includes preoperative staging, neoadjuvant therapy, type of surgery, residual tumour status, postoperative complications and adjuvant therapy. Since a unique social security number identifies all patients, data in the SRCR can be matched with data in the Swedish Cancer Register and Cause of Death Register.
METHODS AND METHODOLOGICAL CONSIDERATIONS

This thesis is based on four papers. Two reports are based upon a multicenter randomised controlled trial (Papers I-II), one investigational study compares the effect of two treatment options on intramucosal bacterial count (Paper III), and one register study evaluates prospectively collected data from the Swedish Rectal Cancer Register (Paper IV).
Patients in study I consisted of 1505 patients undergoing elective colonic resection allocated to MBP or no-MBP (Figure 1). Patients 18-85 years-of-age, undergoing elective, open surgery for cancer, adenoma or diverticular disease with an ASA score I-III and life expectancy >6 months were eligible for inclusion. The study was designed as a multicentre trial and included patients from January 1999 through March 2005. Primary endpoints were cardiovascular-, general infectious- and surgical site complications 30 days postoperatively. Secondary endpoints were postoperative mortality and reoperation rate 30 days postoperatively. Data were registered in a study form and sent to the study centre in Motala, Sweden, stored in a database and processed. One hundred and sixty-two patients were excluded, thus leaving 1343 patients for final analysis (686 MBP, 657 No-MBP), described in Table 3. Thirty-two (19 MBP, 13 No-MBP) were not treated according to allocation but remained in their allocation groups for intention-to-treat analysis. The Oncology Centre in Linköping, Sweden performed the central allocation and the material was stratified for each of the 21 participating units. The patients were allocated in blocks of permutations of four using random numbers, and the size of the block was not known to any of the participants. The external validity of the study was assessed by review of all eligible patients in three of the participating units and the internal validity was assessed by review of hospital charts of 10% of the patients included. A statistician and a surgeon not participating in the study reviewed the safety of the study every 6 months, and the hospital charts of patients who died and/or underwent reoperation within 30 days of surgery were reviewed by a surgeon not involved in the study design.
The objective was to assess if there is a difference in postoperative complication rate between MBP or No-MBP regimens prior to elective colonic surgery.

The planned inclusion number was determined according to a power calculation based on historical data describing postoperative complication rates in the literature. Preoperative management such as type of MBP (when appropriate) and antibiotic prophylaxis was administered according to local routines at each unit. The same was true for the choice of anastomotic technique. This was considered acceptable since the allocation was stratified for each participating unit and the number of inclusions planned was large. The allocation procedure was simple and completely carried out by a unit not involved in the design or implementation of the study in order to avoid any selection bias.

**Table 3 Demographic data and diagnosis (Paper I)**

<table>
<thead>
<tr>
<th></th>
<th>MBP (n=686)</th>
<th>No-MBP (n=657)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range)</td>
<td>69 (35–85)</td>
<td>69 (28–86)</td>
<td>0.82</td>
</tr>
<tr>
<td>Male (%)</td>
<td>306 (44.6)</td>
<td>317 (48.2)</td>
<td>0.18</td>
</tr>
<tr>
<td>Diagnosis Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>560</td>
<td>518</td>
<td>0.28</td>
</tr>
<tr>
<td>Adenoma</td>
<td>104</td>
<td>108</td>
<td>0.17</td>
</tr>
<tr>
<td>Diverticular disease</td>
<td>101</td>
<td>93</td>
<td>0.56</td>
</tr>
<tr>
<td>Diabetes, insulin dependent (%)</td>
<td>28 (4.1)</td>
<td>23 (3.5)</td>
<td>0.34</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>25.7 (6.0)</td>
<td>26.4 (15.5)</td>
<td>0.27</td>
</tr>
</tbody>
</table>
Paper II

One hundred and five patients in the Bowel preparation study (Paper I) at three units were asked to complete a questionnaire regarding perceived health including experience with bowel preparation. There were 39 questions, each having 3 – 10 answer alternatives, dealing with food intake, pain, discomfort, nausea/vomiting, gas distension, anxiety, tiredness, need of assistance with bowel preparation, and willingness to undergo the same preoperative procedure again if necessary (Tables 4 and 5). Comparisons were made between patients receiving mechanical bowel preparation (MBP group, n=60) and patients without mechanical bowel preparation (No-MBP group, n=45) prior to surgery.

The number of inclusions was predetermined to a minimum of 100 without any power-calculation due to scanty knowledge on this topic. Every separate question was designed according to validated questionnaire models.

Paper III

The study population in Paper III consisted of 37 patients undergoing elective colorectal surgery at three hospitals (20 with MBP and 17 No-MBP). A small full-thickness biopsy was taken from macroscopically normal bowel wall and the biopsy was stored at -20°C before transport to the laboratory for analysis. The biopsies were then thawed and incubated at 35°C and cultured. Colonies were identified by standard culture methods. This study aimed to answer the question whether or not MBP affects intramucosal bacterial count.

The material in study III was not randomised nor was it preceded by a power-calculation due to the explorative nature of the study. The most critical element in the study was deemed to be the culture of bacteria and this was therefore done at the same microbiological laboratory.
Table 4 The Patient’s experience preoperatively. Description of questionnaire (Paper II)

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Describe your appetite the week before surgery?</td>
<td>Very good/ Good/ Fairly good/ Fairly poor/ Poor/ Very poor</td>
</tr>
<tr>
<td>Did your diet change during the days prior to surgery?</td>
<td>Ate more than normal/ Did not change/ Ate less than normal</td>
</tr>
<tr>
<td>Were you able to complete your bowel preparation?</td>
<td>Yes, completely/ to some extent</td>
</tr>
<tr>
<td>If you had difficulty in completing bowel preparation – which were the two most important reasons?</td>
<td>Free text</td>
</tr>
<tr>
<td>How would you describe your experience of your preoperative preparation?</td>
<td>0-10 on a Numerical Rating Scale where 0 = not difficult at all and 10 = extremely difficult</td>
</tr>
<tr>
<td>Did you experience pain from the abdomen/bowel the day before surgery?</td>
<td>0-10 on a Numerical Rating Scale where 0 = no pain and 10 = worst conceivable pain</td>
</tr>
<tr>
<td>Did you experience discomfort in the abdomen/bowel the day before surgery?</td>
<td>0-10 on a Numerical Rating Scale where 0 = no discomfort and 10 = worst conceivable discomfort</td>
</tr>
<tr>
<td>Did you experience hunger the day before surgery?</td>
<td>Not at all/ A little/ Quite a lot/ Very much</td>
</tr>
<tr>
<td>Did you feel tired the day before surgery</td>
<td>Not at all/ A little/ Quite a lot/ Much/ Very much</td>
</tr>
<tr>
<td>Did you experience a sense of fullness the day before surgery?</td>
<td>Not at all/ A little/ Quite a lot/ Very much</td>
</tr>
<tr>
<td>Did you experience nausea the day before surgery?</td>
<td>Not at all/ A little/ Quite a lot/ Much/ Very much</td>
</tr>
<tr>
<td>Did you experience abdominal distension the day before surgery?</td>
<td>Not at all/ A little/ Quite a lot/ Much/ Very much</td>
</tr>
<tr>
<td>Did you experience anxiety the day before surgery?</td>
<td>Not at all/ A little/ Quite a lot/ Much/ Very much</td>
</tr>
<tr>
<td>Did you feel sick the day before surgery?</td>
<td>Not at all/ Quite a lot</td>
</tr>
<tr>
<td>Did you experience sleeping disturbance the day before surgery?</td>
<td>Not at all/ A little/ Quite a lot/ Much/ Very much</td>
</tr>
<tr>
<td>Did you experience disturbance in your daily routine the day before surgery?</td>
<td>Not at all/ A little/ Quite a lot/ Much/ Very much</td>
</tr>
<tr>
<td>Did you experience extensive sweating the day before surgery?</td>
<td>Not at all/ A little/ Quite a lot/ Much</td>
</tr>
<tr>
<td>How many times did you visit the toilet the day before surgery?</td>
<td>None/ 1-2/ 3-4/ 5-6/ 7-8/ 9-10/ 10 or more</td>
</tr>
<tr>
<td>If you had bowel preparation, did you need assistance?</td>
<td>No assistance/ Assistance from a relative/ Assistance from hospital staff/ assistance from other person</td>
</tr>
<tr>
<td>Could You consider the same preoperative preparation again?</td>
<td>Absolutely/ Possibly/ Absolutely not</td>
</tr>
</tbody>
</table>
Table 5 The Patient’s experience postoperatively. Description of questionnaire (Paper II)

<table>
<thead>
<tr>
<th>Questions</th>
<th>Answer alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Describe the extent of pain you experienced during the first, fourth and seventh postoperative day.</td>
<td>A ten point Numerical Rating Scale where 0=no pain and 10 = worst conceivable pain</td>
</tr>
<tr>
<td>How many times did you take pain medication during the seventh postoperative day?</td>
<td>Zero/ Once/ Twice/ Three times/ More than three times</td>
</tr>
<tr>
<td>Describe the extent of discomfort you experienced during the first, fourth and seventh postoperative day.</td>
<td>A ten point Numerical Rating Scale where 0 = no discomfort and 10 = worst conceivable discomfort</td>
</tr>
<tr>
<td>Describe the extent of nausea you experienced during the first, fourth and seventh postoperative day.</td>
<td>A ten point Numerical Rating Scale where 0 = no discomfort and 10 = worst conceivable discomfort</td>
</tr>
<tr>
<td>Do you experience constipation now on the seventh postoperative day?</td>
<td>Yes/ No</td>
</tr>
<tr>
<td>Do you have diarrhoea now on the seventh postoperative day?</td>
<td>Yes/ No</td>
</tr>
<tr>
<td>How would you describe your appetite now, on the seventh postoperative day?</td>
<td>Very good/ Good/ Fairly good/ Fairly poor/ Poor/ Very poor</td>
</tr>
<tr>
<td>If you compare your appetite now with your appetite preoperatively, how would you describe it today on the seventh postoperative day?</td>
<td>Improved a lot/ Improved/ Improved to some extent/ Not affected/ Slightly worse / Worse/ Very much worse</td>
</tr>
<tr>
<td>When did you drink for the first time postoperatively?</td>
<td>The day of surgery/ The day after surgery/ two days after surgery/ More than two days after surgery</td>
</tr>
<tr>
<td>When did you have solid food for the first time postoperatively?</td>
<td>The day after surgery/ two days/ three days/ four days/ five days/ six days/ More than six days after surgery</td>
</tr>
<tr>
<td>When did you experience the movement of gas in the bowel postoperatively?</td>
<td>The day after surgery/ two days after surgery/ three days after surgery/ four days after surgery/ more than four days after surgery</td>
</tr>
<tr>
<td>When did you have your first bowel movement postoperatively?</td>
<td>The day after surgery/ two days after surgery/ three days after surgery/ four days after surgery/ more than four days after surgery</td>
</tr>
<tr>
<td>Where were you when you completed this form?</td>
<td>In the surgical department/ in another hospital department/ at home/ with a relative</td>
</tr>
</tbody>
</table>
**Paper IV**

Paper IV was a register study based on prospectively collected data in the Swedish Rectal Cancer Register (SRCR). Comparisons were made between two groups of patients: $\geq 75$ years and $< 75$ years at diagnosis in order to study the influence of age on choice of therapy and outcome in abdominal rectal cancer treatment. All 15104 patients who were identified in SRCR diagnosed with rectal cancer from 1995 through 2004 were analysed for occurrence of distant metastases.

**Fig 2 Patients with rectal cancer included in paper IV**
Tumour stage was analysed for 11725 patients treated with abdominal tumour resection stated as anterior resection (AR), abdominoperineal excision (APE) or Hartman’s procedure (HA). For 11510 patients data was available about curative or non-curative surgery, of these patients 9705 were identified as curatively treated and this cohort was analysed for tumour location, occurrence of preoperative radiotherapy, re-operation within 30 days and relative survival 90 days postoperatively. Of 6557 patients with abdominal tumour resection, diagnosed 1995-2001, 5590 were curatively treated. These 5590 patients were analysed for cancer-specific 5-year survival. Data about local recurrence were available for 6771 patients diagnosed 1995-2000 of which 5590 were curatively treated. (Figure 2)

This was an audit of a validated register comparing prospectively collected data of two age-cohorts in order to gain information about possible differences in treatment and outcome between the cohorts during the study period. Since the study was retrospective we could not influence the data input.

**STATISTICAL METHODS**

The sample size in Paper I was determined by a power calculation (80% power and 5% significance level) where the estimated proportion of subjects reaching a primary endpoint was an based on published data. The chi-square test (Papers I, II and IV) or Fisher exact test (Papers II and III) were used to test differences between proportions. T test (Paper I) or Mann-Whitney U test (Papers I, II and III) were used for comparison of continuous variables. Two tailed p-values <0.05 were considered statistically significant.
Relative survival is the ratio of the observed survival rate of the patients to the survival rate expected in the general population with the same sex- and age distribution. The programme “Relsurv” was used to calculate the relative survival 90-days after surgery in Paper IV.

Relative risk is defined as the ratio of the incidence rates (incidence exposed/ incidence unexposed). In Paper IV the Cox regression model was used to calculate the relative risk for local recurrence for three surgical methods using one of the surgical procedures (AR) as a reference. The patient material was in this aspect adjusted for sex, tumour stage, radiotherapy, proportion of low tumours and age within each age-group.

The cancer-specific 5-year survival in Paper IV was calculated using data from SRCR matched with data from The National Board of Health and Welfare’s Cause of death Register. Kaplan Meyer survival analysis was used for log rank significance tests.
RESULTS AND DISCUSSION

Multicentre randomised clinical trial of mechanical bowel preparation in elective colonic resection (Paper I)

MBP has been questioned as preoperative management many years prior to this trial\textsuperscript{16, 63-71, 73-75}, but was still considered standard treatment despite indications that MBP does not lower postoperative complication rate\textsuperscript{17, 77}. In the majority of randomised trials authors discussed the possibility of underpowered study size, and meta-analyses identified the heterogeneity of included studies as a possible source of misinterpretation of the results. The present trial was therefore planned to include enough subjects to cover for a type II statistical error.

Postoperative complications
The choice of primary endpoints was based on previous research and clinical experience. Complications were classified in three groups: cardiovascular-, general infectious- and surgical site complications. There was no statistically significant difference between the groups studied concerning any of these endpoints (Table 6), nor was there any difference concerning the secondary endpoints postoperative mortality (P=0.94) or reoperation rate (P=0.42).

In the study form and subsequent registration we created subgroups of these primary endpoints (Table 6) and tested the significance of differences between these subgroups, showing a significantly higher rate of postoperative haemorrhage in the no-MBP group (1.8% vs. 0.4%, p<0.05). No other subgroup analysis yielded significant differences between the groups. The information provided by these subgroup analyses is interesting, but must be interpreted with caution since the trial was not designed to test for differences in these aspects. This also applies to the rate of postoperative anastomotic dehiscence, which, by many authors, is regarded a primary endpoint when comparing outcome after colonic resection with and without MBP.

36
However, the present trial did not reveal any difference in the rate of anastomotic dehiscence, nor in the secondary endpoints (mortality and reoperation rate), which suggests there is no clinically significant benefit from MBP in this aspect.

Table 6 Postoperative complications within 30 days.

<table>
<thead>
<tr>
<th></th>
<th>MBP (n=686)</th>
<th>no-MBP (n=657)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of complication</td>
<td>192</td>
<td>181</td>
<td>0.55</td>
</tr>
<tr>
<td>Cardiovascular (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>8</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>14</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>General infectious (%)</td>
<td>54 (7.9)</td>
<td>45 (6.8)</td>
<td>0.44</td>
</tr>
<tr>
<td>Septicaemia</td>
<td>9</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>10</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>17</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Fever of unknown origin</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Surgical site (%)</td>
<td>103 (15.1)</td>
<td>106 (16.1)</td>
<td>0.62</td>
</tr>
<tr>
<td>Wound infection</td>
<td>54</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Postoperative haemorrhage</td>
<td>3</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Deep abscess</td>
<td>5</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Anastomotic dehiscence</td>
<td>13</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Wound disruption</td>
<td>10</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Ileus /bowel paralysis</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>13</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No of patients reaching at least one primary endpoint (%)</td>
<td>168 (24.5)</td>
<td>156 (23.7)</td>
</tr>
</tbody>
</table>
**Multicentre trials**
The trial was a multicentre one where one German and all Swedish colorectal units were invited to participate. The reason for choosing the multicentre setting was to ensure a sufficient number of inclusions in a reasonable time period and to get high generalisability of the results. The number of participating units was 21 with a mean number of inclusions per unit of 72 (range 2-246) patients over a time period of six years. An inclusion period of many years could decrease the homogeneity in the study population if new methods with potentially confounding factors are introduced. In this trial we registered antibiotics used and type of anastomosis (hand-sewn/stapled). Analysis of possible changes in these parameters showed that there were differences in antibiotics used between the units, but not over the study period. On the other hand there was a trend towards a higher proportion of hand-sewn anastomoses with time. This trend was similar at all participating units, thus leading to a trial population comparable between the randomisation groups.

Retrieving data for all eligible patients in three participating units tested the generalisability of conclusions. We found that 64.5% of eligible patients were included and there were no significant differences in age, sex or diagnosis between randomised and non-randomised patients. The high proportion of non-inclusions (36.5%) as well as the time consumed to get a sufficient number of inclusions emphasises the ongoing discussion about how to incorporate clinical research, as an essential part of clinical practice, in order to get rapid and reliable answers to questions addressed in clinical studies.

Retrieving the hospital charts of a random sample of 134 patients tested the internal validity of the trial. We found registration errors in 20.9% but only 6.7% concerned primary endpoints. In order to improve these figures and the proportion of inclusions in future multicentre studies it is important to recognise the need for staff dedication and research nurses.
Conclusion
This large multicentre trial demonstrated no benefit from MBP regarding postoperative complication rate in colonic surgery. Similar results have recently been shown in a trial from the Nederlands\textsuperscript{136}. Our advice is to abandon this routine practice prior to elective colonic surgery.

Preoperative mechanical preparation of the colon: The patient’s view and early outcome (Paper II)

Patient experience of various forms of MBP have been reported\textsuperscript{39, 43, 137,138,141,142}. In Paper II we addressed the patient’s experience and early recovery comparing MBP to no-MBP in a randomised study. The study population comprised 105 patients (60 receiving MBP and 45 not receiving MBP) randomised in the Bowel Preparation Study described in Paper I. The two groups of patients were comparable regarding age, gender and diagnosis.

Health economics
The present study revealed that 52\% of patients receiving MBP needed help with the preoperative preparation and that 16\% of patients having MBP reported more than 10 bowel movements the day before surgery (compared to none in the no-MBP group). This might necessitate admission to hospital for MBP patients early the day before surgery, thus increasing the nursing staff workload and poor utilisation of hospital bed capacity. Health economic considerations are important when changing general practice in medicine, since financial resources are not sufficient to support the increased cost of effective and expensive new methods without redirecting resources. In this aspect it is equally important to scrutinise new and old treatment options regarding cost-effectiveness in professional analyses made by specialists in health.
economics together with the clinical profession in order to provide decision makers with adequate information 139, 140.

**Early mobilisation**

Time to first bowel movement was significantly shorter in the group with no-MBP compared to the MBP group (p=0.03) and the patients in the no-MBP group also experienced a significantly higher degree of discomfort on the fourth postoperative day (p=0.02). There was no difference in perceived discomfort on the first or seventh postoperative day, neither was there any inter group difference concerning postoperative pain during the first week. The short time to bowel movement in patients not receiving MBP can be explained by prolonged postoperative paralysis in patients receiving MBP and/or as a consequence of the presence of stools in the bowel in patients not having MBP. Early bowel movement offers a likely explanation for the sensation of discomfort on the fourth postoperative day when MBP is omitted. Regarding other questions in the questionnaire, there were no significant differences between the study groups. In the present study more than half of the patients in the whole material experienced some degree of nausea on postoperative Days 1 (54%) and 4 (52%), decreasing to one third on postoperative Day 7 (28%). When patients were asked to rate the degree of pain on a 10 grade numerical rating scale, 65% reported a pain score exceeding 3 on Day 1, the corresponding numbers for Days 4 and 7 were 52% and 26% respectively. These are discouraging figures implying there is need for improvement in the postoperative management of pain and nausea. Standardised care programmes with ongoing follow-up monitored by nurses are one way to improve the quality of postoperative care. The protocols used to implement enhanced recovery programmes19, 21, 36 are good examples of such quality management where the engagement and dedication of all members of staff is essential.
Different forms of MBP
The MBP performed comprised 28 sodium phosphate, 31 polyethylene glycol and in one case enema. Four of the patients in the MBP group (two given sodium phosphate and, two polyethylene glycol) could not complete the intended MBP because of inability to drink the required amount of fluids. The patients were asked if they could consider the same preoperative preparation again in order to compare results between the study groups (MBP vs. no-MBP). The proportion of missing answers was 42% in the no-MBP group compared to 5% in the MBP group, which probably reflects the fact that many patients without MBP, thought (correctly) that they had not received any “preoperative procedure”. Therefore no conclusions can be drawn between possible differences in this aspect. In a subgroup analysis, of willingness to have the same MBP again, comparing sodium phosphate and polyethylene glycol, a similar proportion in each group could consider the same preoperative preparation again which is not consistent with the findings of previous studies (Table 7). This emphasises the importance of methodological strictness and caution when interpreting subgroup analyses.

Table 7 Proportion of patients stating willingness to have the same preoperative bowel preparation again.

<table>
<thead>
<tr>
<th>Author</th>
<th>Reference</th>
<th>Year</th>
<th>Sodium phosphate</th>
<th>Polyethylene glycol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oliveira</td>
<td>43</td>
<td>1997</td>
<td>65/100 (65%)</td>
<td>25/100 (25%)</td>
</tr>
<tr>
<td>Hwang</td>
<td>41</td>
<td>2005</td>
<td>26/40 (68%)</td>
<td>30/40 (75%)</td>
</tr>
<tr>
<td>Lichtenstein</td>
<td>141</td>
<td>2007</td>
<td>218/240 (91%)</td>
<td>164/241 (68%)</td>
</tr>
<tr>
<td>Kastenberg</td>
<td>137</td>
<td>2007</td>
<td>379/418 (91%)</td>
<td>280/417 (67%)</td>
</tr>
<tr>
<td>Paper II</td>
<td></td>
<td></td>
<td>24/28 (86%)</td>
<td>25/31 (81%)</td>
</tr>
</tbody>
</table>
Conclusion
This study demonstrates that MBP delays the return of normal bowel movements and underlines the incentive to omit mechanical bowel preparation prior to elective colonic surgery.

Does Mechanical Bowel Preparation Affect the Intramucosal Bacterial Colony Count? (Paper III)

MBP is known not to affect the intraluminal bacterial count/ml\textsuperscript{142}. The aim of this experimental study was to investigate if MBP affects the intramucosal bacterial colony count.

Intramucosal bacterial count
The study revealed no difference in intramucosal bacterial colony count between the two groups (MBP vs. no-MBP) for any of the bacteria identified, described in Table 8. The two bacterial species identified in the majority of postoperative clinical infections, E. coli and Bacteroides, were analysed in the study in addition to the total bacterial count. The selection was based on published data\textsuperscript{143, 144} and was made because the design of the present study was linked to the question whether or not MBP alters the postoperative complication rate in colorectal surgery as addressed in Paper I. There are few bacterial strains identified in the colonic mucosa of healthy individuals\textsuperscript{145}, in contrast to pathological conditions such as colorectal cancer and inflammatory bowel disease\textsuperscript{82-84}. The clinical implication of these findings is not completely understood, but an aetiological role for intramucosal bacterial growth cannot be ruled out. It is thus of interest that the present study did not find any influence of MBP, which is frequently used prior to colonoscopy and rectal cancer surgery, on intramucosal bacterial growth.
Table 8
Bacterial species identified in colonic mucosa. Colonies were counted and identified by standard methods used in clinical practice.

<table>
<thead>
<tr>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. Coli</td>
</tr>
<tr>
<td>Klebsiella /Enterobacter</td>
</tr>
<tr>
<td>Diphteroids</td>
</tr>
<tr>
<td>Enterococci</td>
</tr>
<tr>
<td>Alfa Streptococci</td>
</tr>
<tr>
<td>Staphylococci-group</td>
</tr>
<tr>
<td>Clostridium</td>
</tr>
<tr>
<td>Bacteroides</td>
</tr>
<tr>
<td>Propioni bacteria</td>
</tr>
</tbody>
</table>

**Antibiotic regimens**
Antibiotic prophylaxis has been shown to reduce the postoperative complication rate in colorectal surgery\(^{35, 146, 149}\) and is standard preoperative treatment in Sweden. The use of prophylactic antibiotic therapy is associated with adverse events and increases the total burden of antibiotics used in society and facilitates the evolution of multiresistant bacterial strains\(^ {148}\). It is therefore of great importance to employ effective short-term prophylactic antibiotic regimens.

In the present study two different prophylactic antibiotic regimens were used: oral sulfamethoxazole-trimethoprim + metronidazole (STM) or intravenous cephalosporin + metronidazole (CM), both effective in reducing both anaerobic and aerobic postoperative infections\(^ {148, 150}\). There was a significantly higher colony count of intramucosal E. coli in patients receiving prophylactic STM compared to those given CM (p=0.02). No corresponding difference was seen in total bacterial count in the biopsies. To evaluate this finding the database of the Bowel Preparation Study (Paper I) was searched for patients receiving preoperative STM (n=618) or CM (n=443), regardless of MBP or no-MBP. There was no significant difference in postoperative general septic (7.0 % STM and 7.4% CM) or surgical site complication rate (15.3 % STM and 15.1 % CM) between the two prophylactic antibiotic
regimens. The clinical implication of higher colony counts of E.coli colonies in patients receiving STM compared to CM is thus unclear, and both regimens can be regarded effective as prophylaxis.

**Conclusion**
This investigational study demonstrated that MBP does not affect intramucosal bacterial colony count, which is a novel finding.

**Rectal cancer treatment in the elderly, an audit of the Swedish rectal cancer register 1995-2004 (Paper IV)**

Paper IV describes the results of a register study, and as such it generates rather than tests hypothesis. The aim of the present study was to identify any differences in treatment and outcome between two age groups (≥ 75 vs. < 75 years of age) in Sweden during a defined time period.

**Tumour stage**
Distant metastases in the present audit were significantly less frequent among patients older than 75 years at diagnosis compared to their younger counterparts (14.8 vs. 17.8%, P=0.001). One explanation for this finding could be occult metastases due to inadequate tumour staging in older patients. These findings can be compared to the results from a survey of the Norwegian Rectal Cancer Register where Stage IV disease was found in 15 % of patients > 65 years, with an equal proportion amongst the studied age groups. It is noteworthy that the Norwegian study included patients older than 65 years and thus a majority of the rectal cancer patients, but showed no age related difference in the occurrence of stage IV rectal cancer as compared
to results of the present study. Data in both surveys are based on national registers aiming at a description of the clinical verity of the panorama of rectal cancer patients in two Scandinavian populations. Since the Swedish and Norwegian populations could be expected to be similar in many aspects, the difference in results highlights the need for internationally accepted definitions of data input and for continuous validation of registers in order to obtain valid register data. Among patients treated with abdominal tumour resection older patients were less likely to have Stage IV disease than their younger counterparts (10.4% vs. 13.4%, P=0.001).

Surgery
Abdominal resection was performed less frequently (68.5%) on patients ≥75 years than on patients <75 years (84.4%) and thus a high proportion of elderly patients were excluded from surgery. This could have been because of poor clinical status, expectation of poor outcome or presence of comorbidity in the elderly. The importance of appropriate surgical treatment does not diminish with age. Modern perioperative treatment and surgical techniques has made major surgery safe for elderly patients if careful selection is employed, especially with respect to cardiopulmonary comorbidity. The surgical strategy for abdominal resection varied with patient age. AR was less commonly performed among elderly patients, whereas the reverse was true for HA. These age-related differences were more pronounced in curative surgery. The percentage of APE was similar in the two age groups both for curative and non-curative operations. The majority of low rectal tumours (0-6 cm from anal verge) in both age groups were treated with APE as surgical strategy (87.5 vs. 87.1%, P=0.86), and one may therefore conclude that tumour height above the anal verge was the main reason for surgical choice in these patients. The preference for HA in elderly patients might be due to concern about an expected higher postoperative complication rate after restorative surgery compared to surgery with a permanent stoma in elderly and frail patients. In the present study the reoperation rate
within 30 days of curative surgery was significantly lower for older patients compared to their younger counterparts (P=0.036), which might support this strategy. Mortality rate was higher in the elderly measured as relative survival 90 days postoperatively following curative abdominal tumour resection [0.96 (0.95-0.97) vs. 0.99 (0.987-0.993)], a difference that might have been more pronounced if the rate of restorative surgery had been similar between the groups. To understand the real implications of these figures, data input into the register should have to be expanded regarding preoperative ASA classification and postoperative morbidity registration over a defined time-period. This would provide specific information about postoperative morbidity after different surgical procedures.

Another reason why HA was favoured as surgical strategy in the elderly might have been concern about the functional result after restorative surgery. There are data demonstrating favourable results after AR in elderly patients and age alone should not exclude patients from restorative rectal cancer surgery.

Besides short-term postoperative outcome there are several aspects to be considered when a permanent stoma is created, such as the risk for stomal hernia and prolapse, as well as skin problems. Available studies comparing quality of life in patients treated for rectal cancer with HA and AR do not demonstrate a significant difference between the two alternatives. Further prospective studies on this aspect are therefore important since the long-term survival did not differ between these two surgical procedures in our audit. The long-term survival figures should be validated when data on detailed tumour stage assessment are available for each patient.

Radiotherapy
The extent to which preoperative radiotherapy should be used in rectal cancer treatment is controversial. Preoperative radiotherapy is known to improve local control but it also increases the probability of faecal incontinence, sexual dysfunction and late hospital admission. Negative side-effects are expected to be more pronounced in older patients as shown in The Stockholm I and II trials. In the present study older patients had...
preoperative radiotherapy less frequently than younger patients regardless of which surgical technique was used, overall 34.3% versus 67.2%, P<0.001. Preoperative radiotherapy was used in 47% of patients ≥75 years as compared to 82% in younger patients treated with APE (mostly low rectal tumors). The 5-year cancer-specific survival was significantly better for patients <75 years compared to their older counterparts. However, there was no difference in 5-year local recurrence rate after APE, which indicates that preoperative radiotherapy alone, cannot explain the 5-year cancer-specific survival differences. There is an ongoing discussion about surgical techniques employed in APE which might improve the long-term outcome after APE to a level comparable with AR and HA\textsuperscript{158,159}.

**Summary**

This audit of a population-based rectal cancer register showed that older patients have less distant metastases at diagnosis, an abdominal procedure have less frequently, and AR less often than younger patients. The relative survival 90 days postoperatively was slightly lower among older patients. They also received radiotherapy less often with slightly worse oncological outcome measured as 5-year cancer-specific survival, but not in terms of local recurrence rate. Further studies, investigating appropriate treatment options for elderly patients are needed to assess the special needs of geriatric patients.
GENERAL CONCLUSION

The present thesis has provided firm evidence from a large multicentre randomised controlled trial that routine use of mechanical bowel preparation before colonic surgery can safely be omitted. This has important consequences for effectiveness and cost of colorectal surgery. The thesis has also demonstrated significant differences in treatment of rectal cancer between patients 75 years or older and those younger than 75 years. Future studies may reveal to what extent these differences should and can be made even.
SAMMANFATTNING PÅ SVENSKA

Introduktion


Kirurgi

Den engelska kirurgen Bill Heald har beskrivit vikten av en mycket precis kirurgi vid ändtarmscancer, vilket har lett till förbättrad teknik och överlevnadsvinster. Förändringarna i operationsstrategier vid ändtarmscancer har successivt genomförts i Sverige och studier i vårt land har kunnat påvisa förbättrade behandlingsresultat. En korrekt kirurgisk behandling är grunden för bot vid cancer i grovtarmen och ändtarmen. Vårdprogram för behandling av cancer i ändtarmen genomgår en fortlöpande förnyelse baserad på aktuell forskning.

Mekanisk tarmrengöring (MTR)

MTR har använts före kirurgi i grovtarmen sedan början av 1900-talet och har ansetts vara nödvändig för att undvika postoperativa infektiösa komplikationer. Detta har dock ifrågasatts sedan slutet av 1980-talet. MTR innebär att patienten får dricka en saltlösning som inducerar diarré och därmed minskar innehållet av avföring i tarmen. MTR har visats ge påverkan på patienternas saltbalans och kräver ofta inläggning på vårdavdelning tidigt dagen innan operation.
En optimal handläggning av patienten före och efter operationen är viktig för att minimera den fysiologiska påfrestningen i samband med det kirurgiska ingreppet och därmed minska de postoperativa komplikationerna. Detta har visats av den danska kirurgen Henrik Kehlets forskargrupp.

En fruktad komplikation till grovtarmskirurgi, där man utfört en tarmanastomos (tarmskarv), är läckage i anastomosen. Mekanismen bakom anstomosläckage är idag inte klarlagt. Det har diskuterats om förekomst av bakterier i operationsområdet ger en ökad risk för läckage. Det är tidigare visat att andelen bakterier/ml tarminnehåll inte påverkas av MTR. Djurexperimentella studier har pekat på att bakteriefloran skiljer sig mellan tarminnehåll och i själva tarmslemhinnan, vilket gör frågan om MTR påverkar bakteriefloran i slemhinnan intressant.

### En åldrande befolkning

Val av kirurgisk och medicinsk cancerbehandling (cellgifter eller strålbehandling) samt en skonsam handläggning i samband med operationen påverkar den postoperativa utgången för äldre patienter i en högre grad än för yngre individer. Detta bör uppmärksammas eftersom befolkningen i Sverige blir allt äldre, vilket påverkar medelåldern för patienter med cancer i grovtarmen och ändtarmen.

### Avhandlingens syfte

Den här avhandlingen har två huvudsakliga syften. För det första undersökes om mekanisk tarmrengöring (MTR) jämfört med ingen MTR påverkar det postoperativa förloppet och korttids överlevnad för patienter som opereras med borttagande av hela eller delar av

Delarbete I


Sammanlagt 1505 patienter randomiserades i studien varav 1343 patienter utgjorde den slutgiltiga studiegruppen (686 som fått MTR och 657 som inte fått MTR). Nästan en fjärdedel av alla patienter (24.5% för dem som fått MTR och 23.7% för de som inte fått MTR) hade minst en komplikation efter grovtarmskirurgi. Vi kunde inte visa någon skillnad mellan behandlingsgrupperna avseende några av de beskrivna komplikationerna.

Detta är en stor studie, där antalet patienter är tillräckligt för att visa att MTR kan överges som praxis inför kirurgisk behandling av sjukdom i grovtarmen utan att detta påverkar det postoperativa förloppet negativt.
Delarbete II

I detta arbete utgick vi från patienter från tre sjukhus i studien beskriven i delarbete I. Syftet med denna studie var att undersöka om MTR påverkar patientens välbefinnande före och efter grovtarms operation samt att undersöka om MTR påverkade återhämtningen efter operationen avseende matlust, smärta, välbefinnande och återgång av tarmfunktion. Mellan februari 2000 och mars 2002 fick 105 patienter, som vid tre sjukhus opererades, en enkät med frågor som berörde smärta, oro, trötthet, illamående och patientens allmänna välbefinnande före och efter operationen. Sextio patienter fick MTR och 45 ingen MTR.

Resultatet av denna undersökning visar att patienter som inte fått MTR fick en snabbare återhämtning av tarmfunktionen men hade en högre grad av obehag på fjärde dagen efter operationen. För övrigt fann vi inga skillnader mellan grupperna. Denna undersökning, baserat på patientens upplevelse ger inget stöd för fortsatt bruk av MTR inför kirurgi av grovtarmen.

Delarbete III

I detta delarbete analyserades bakteriehalten i tarmslehminnan med och utan MTR. Tre sjukhus deltog i undersökningen, där 37 patienter (20 MTR och 17 ingen MTR) som opererades med borttagande av delar av grovtarmen eller ändtarmen undersöktes. I samband med operationen togs små bitar av tarmslehminnan till vara för bakteriologisk analys. Analyserna utfördes med standard odlingsteknik på ett laboratorium. Samtliga bakterier som odlades fram registrerades, men i analysen redovisas bara de vanligt förekommande sjukdomsalstrande bakterierna (Escherichia Coli och Bacteroides) samt totalantalet bakterier.

Resultatet visar att MTR inte påverkar bakteriehalten i tarmslehminnan, vilket inte tidigare varit känt.
Delarbete IV

I det sista delarbetet har behandlingen vid ändtarmscancer hos äldre (≥75 år) jämförts med behandlingen hos yngre patienter. Studien är en registerstudie där prospektivt registrerade data från Svenska Rektalcancer Registret analyserades. Alla som under åren 1995-2004 genomgått abdominell operation (operation genom öppnande av buken) för ändtarmscancer ingick i undersökningen (N=11725). De operationsmetoder som använts är: AR (bortoperation av den del av ändtarmen där tumör finns med ihopkoppling av tarmen), APE (bortoperation av hela ändtarmen med permanent stomi) samt HA (bortoperation av den del av ändtarmen där tumör finns med permanent stomi). Materialet delades in i två grupper baserat på patientens ålder, 75 år eller äldre och yngre än 75 år. Äldre patienter med tumörer högre upp än 6 cm från ändtarmsöppningen opererades oftare än yngre med Hartmanns operation, dvs. fick permanent stomi. Om tumören var belägen inom 6 cm från ändtarmsöppningen sågs det ingen skillnad i val av operationsmetod mellan äldre och yngre (87.1% respektive 87.5% opererades med APE).

Äldre patienter fick bara hälften så ofta strålbehandling innan operation (33.1%) jämfört med yngre patienter (66.7%). Överlevnaden på kort sikt (90 dagar efter operationen) var sämre för de äldre i jämförelse med yngre. Detta pekar på att äldre patienter är känsligare för den påfrestning som orsakas av stor kirurgi.

Fem års cancer specifik överlevnad (andelen patienter med ändtarmscancer som inte dött av sin cancersjukdom inom 5 år) skiljde sig mellan åldersgrupperna bara för dem som opererats med APE. För denna operationstyp förefaller valet av operationsmetod vara likvärdig mellan åldersgrupperna (tumörer inom 6 cm från ändtarmsöppningen). Den enda skillnaden mellan åldersgrupperna var den låga benägenheten att behandla äldre med strålbehandling före operationen, vilket skulle kunna förklara våra fynd. Strålbehandling anses dock i första hand påverka risken för lokalt återfall i cancersjukdomen (jämfört med risk för dottersvulster i andra organ), vilket inte noterades bland de äldre. Orsakerna till denna överlevnads skillnad mellan åldersgrupperna bör studeras vidare.
Denna studie visar att det finns en skillnad i behandling av ändtarmscancer mellan äldre och yngre patienter. Vidare studier som fokuserar på livskvalitet och fysiologiska faktorer i stället för kronologisk ålder vore av värde för att bäst studera effekten av behandling hos både äldre och yngre patienter med ändtarmscancer.

Sammanfattning

I delarbete I påvisades att MTR kan överges inför grovtarms kirurgi utan påverkan på den postoperativa komplikationsfrekvensen, vilket debatterats av kirurger i flera år. Det har tidigare visats att bakteriehalten i tarmen/ml inte påverkas av MTR och i delarbete III har påvisats att bakteriehalten i tarmslemhinnan inte heller påverkas av MTR. Delarbete II visar att tarmfunktionen normaliseras tidigare hos patienter som inte fått MTR. Resultaten av dessa tre undersökningar styrker rekommendationen att avstå från MTR som praxis inför grovtarmskirurgi.

Den åldrande befolkningen i vårt samhälle gör att allt flera som behandlas för ändtarmscancer är över 75 år. I den utförda registerstudien noterades en klar skillnad i val av operationsmetod och benägenhet att ge strålbehandling för äldre patienter jämfört med yngre. Detta bör studeras ytterligare för att ge denna ökande grupp en optimal behandling.
ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to everyone who has contributed to this work. My special thanks to

Erik Nilsson, my tutor and mentor in colorectal surgery, a surgeon who has devoted his work to quality improvement in many areas of surgery. I thank him for his never failing enthusiasm and patience when discussing ethical aspects of this thesis. Without him this thesis would not have been made.

Lars Påhlman, my co-tutor and chairman of the SRCR, who insightfully and willingly has helped me in the art of writing a scientific paper.

Per-Olof Nyström, my co-tutor for inspiring discussions about surgical techniques and quality assessment, also for teaching me about the beauty of good surgery many years ago.

Björn Bäckstrand and Eva Orusild, my former and present head of the department of surgery, for generously giving me the opportunity to finish this research project.

Gunnel Nordberg (in memoriam), for creating a database and for help with the design of a study form. I miss you.

Gunnar Arbman and Lennart Gustafsson for safety analysis.

Anita Fredäng for help with data collection and registration.

Anders Kald for introducing me to the fascinating world of surgery and Harald Bång, a brilliant general surgeon, for a never failing faith in me, and for being there to support me for so many years.

Peter Cox for valuable linguistic guidance.

Peter Naredi for the warm welcome to the University of Umeå.
Robert Johansson, co-author and statistician who has spent many hours trying to let me in to the world of statistics.

Ulrika Ransjö, co-author for shearing of her knowledge in clinical bacteriology.

Malin Arodell and Mitra Unosson, co-authors for collaboration.

Olof Lannerstad, co-author, for validation of a randomized trial and for interest and enthusiasm in this research project.

Peter Matthiessen and Kenneth Smedh, co-authors, for shearing the interest in this research and for help with collecting biopsies.

Hans Stenlund for help with statistical calculations even on holidays.

Anna Lundgren for help with the final preparation of this thesis.

FORSS for generous grants supporting this project and Oncological centre in Linköping for help with randomization.

My colleagues at the Department of Surgery, Visby Hospital for support and many great laughs.

My mother Aagot for always believing in me and my “aunts” Anne and Lusse for always supporting me.

Bo, Michaela and Joachim, my family and best friends for your love, sacrifice and understanding during my work with the thesis. I love you.

This project was supported by grants from Health Research Council of South-East of Sweden (FORSS), The Lion's Cancer Research Foundation at the University of Umeå, The Swedish Cancer Society and the regional agreement on medical training and clinical research (ALF), Umeå. SRCR is funded by The Swedish Association of Local Authorities and Regions (SALAR).
REFERENCES

22. www.socialstyrelsen.se/Statistik/


