

# Laparoscopic surgery as treatment for rectal cancer

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Laparoscopic surgery as treatment for rectal cancer  
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*To my mother Lena, who left us all too soon  
and to my beloved children Isabell and Artur.*

*I have made this longer than usual because I have not had  
time to make it shorter.*

Blaise Pascal, 1657



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## ABSTRACT

### Introduction

Colorectal cancer is the third most common cancer worldwide, with nearly 1.4 million new cases annually, of which about one third suffer from rectal cancer. Laparoscopic surgery has in several surgical fields shown faster recovery, shorter hospital stay, and less pain than open surgery. In rectal cancer surgery firm evidence is lacking regarding oncological safety. Moreover, patient-reported Health Related Quality of Life (HRQL) has become an important outcome in clinical trials, complementing clinically driven endpoints.

### Aim

The aim of this thesis was to assess if laparoscopic rectal cancer surgery is non-inferior to open surgery in terms of loco-regional recurrence, disease specific and overall survival, as well as to compare the outcome regarding health related quality of life and genitourinary dysfunction. We also analysed if there are factors that determine global quality of life.

### Patients and method

The four papers were analysed within the only large randomised international multicentre trial comparing laparoscopic and open surgery for rectal cancer – the COLOR II trial - an open label non-inferiority trial. Between 2004-2010, 1044 patients from 30 centres in 8 countries were included. The HRQL sub-study was optional and included 385 patients.

### Results

In paper I, the primary outcome in COLOR II showed that laparoscopic surgery was non-inferior to open surgery with a loco-regional recurrence rate of 5% in both groups with a difference of 0% (90% CI of -2.6 to 2.6). In paper II and III we showed that there were no differences in HRQL and genitourinary dysfunction between the surgical techniques. In paper IV we discovered pain and fatigue as possible important factors of global quality of life.

### Conclusion

The overall conclusion was that laparoscopic rectal cancer surgery is non-inferior to open surgery in rectal cancer in terms of oncological safety. Based on earlier results showing benefits of laparoscopic rectal resection, now is the time to widely implement the technique.

**Keywords:** Rectal Neoplasms, Laparoscopy, Quality of Life

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# SAMMANFATTNING PÅ SVENSKA

Tjock- och ändtarmscancer (kolorektal cancer) med tumör i tjocktarm eller ändtarm är den tredje vanligaste cancerformen i världen sett till hur många som insjuknar. Dödligheten är hög. I ungefär en tredjedel av fallen sitter tumören i ändtarmen (rektum). Prognosen har förbättrats påtagligt de senaste 30 åren när det gäller överlevnad och också återfall i det ursprungliga tumörområdet (lokalrecidiv), vilket tidigare var ett stort problem för både patienter och kirurger med stort lidande som följd och med tekniska svårigheter vid försök till behandling. Den förbättrade prognosen är framför allt ett resultat av förfinad och mer noggrann kirurgi och tillskrivs till stor del införandet av total mesorektal excision (TME) – en metod där man tar med hela den fettvävnad som omger ändtarmen och där lymfsystem och kärlförsörjning ligger. Detta innebär också att man opererar i ett kärlfritt skikt. Vidare har införandet av strålbehandling och i viss mån cellgiftsbehandling innan och efter operation också bidragit till den förbättrade prognosen.

Titthålskirurgi (laparoskopisk kirurgi), där man använder sig av videoteknik genom små öppningar (porthål) i bukhålan, har blivit den gängse standarden inom flertalet områden inom kirurgi och gynekologi. Anledningen är att tekniken innebär mindre smärta, snabbare återhämtning, kortare vårdtid, kortare sjukskrivning och förbättrad livskvalitet för patienterna jämfört med vid öppen kirurgi.

Inom kolorektal kirurgi avstannade utvecklingen efter att det kommit oroande rapporter om dottertumörer (metastaser) i porthålen efter operationen. Fyra stora randomiserade studier, jämförande laparoskopisk och öppen kirurgi vid tjocktarmscancer, kunde avfärda oron och visa att dessa porthålsmetastaser var lika vanliga som metastaser i ärren efter konventionell öppen kirurgi. De kunde också bekräfta de ovan beskrivna fördelarna med laparoskopisk kirurgi jämfört med öppen kirurgi.

En av de fyra stora studierna – CLASSIC – hade även med patienter med ändtarmscancer, men studien var för liten för att man skulle kunna dra hållbara slutsatser om fördelen av laparoskopisk kirurgi vid ändtarmscancer.

Både hälsa och livskvalitet är begrepp som är svåra att definiera, men i båda fallen kan de flesta av oss ha en intuitiv uppfattning om vad som avses. När det gäller hälsa är den mest använda definitionen den från WHO från 1946: ”ett tillstånd av fullständigt fysiskt, psykiskt och socialt välbefinnande och

inte bara frånvaro av sjukdom”. Denna definition känns i det närmaste utopisk och för tankarna till trafikverkets 0-vision om att ingen skall skadas i trafiken. Dock tydliggör den att det hälsa handlar om är olika delar; flera dimensioner. När det gäller livskvalitet är det ett mycket vitt begrepp. För att försöka avgränsa det område som avser livskvalitet som konsekvens av sjukdom eller skada och dess behandling, använder man oftast termen hälsorelaterad livskvalitet - HRQL.

Precis som WHO:s hälsodeklaration ser man HRQL som ett multidimensionellt begrepp med olika domäner. Förutom ett mått på global livskvalitet (ett totalmått) brukar åtminstone dimensioner för fysisk, psykisk/emotionell och social hälsa tillsammans med olika symptomskalor ingå.

Det vanligaste sättet att studera HRQL är att använda enkäter. Detta ger fördelen att man kan få ett mått som kan upprepas över tid och att man kan följa utvecklingen samt jämföra olika behandlingsmetoder.

COLOR II är den enda stora internationella randomiserade studie som jämför laparoskopisk och öppen kirurgi vid ändtarmscancer. COLOR II är en öppen, randomiserad, non-inferiority studie.

Med non-inferiority menas att man kan visa att en behandling inte är sämre jämfört med en annan inom ett fördefinierat intervall där man accepterar statistisk osäkerhet. Detta skall inte förväxlas med att visa likhet.

Syftet med denna avhandling är att presentera huvudresultatet för COLOR II samt de patientrapporterade utfallsmåtten i studien gällande livskvalitet och sexuell hälsa. Dessa är de huvudsakliga områden där man uttryckt oro för laparoskopisk kirurgi vid rektalcancer. Dessutom görs en ansats att kartlägga huruvida det finns faktorer som är viktiga för den globala livskvaliteten hos patienter med rektalcancer.

I delarbete 1 visas att laparoskopisk kirurgi inte är sämre än öppen kirurgi med avseende på återfall i cancersjukdomen. Frekvensen av lokalrecidiv var 5 % i båda grupperna. Den statistiska osäkerheten låg väl inom det fördefinierade intervall som satts upp för att studien skulle anses som lyckad.

Avseende cancer-specifik och total överlevnad fanns inte heller någon statistiskt signifikant skillnad mellan grupperna.

I delarbete 2 visas att hälsorelaterad livskvalitet (HRQL) inte skiljer sig mellan grupperna när man mäter med enkäterna EQ-5D, EORTC C30 och de

flesta domäner från EORTC CR38 efter 1, 6 och 12 månader. Eftersom konfidensintervallen var mycket smala och de faktiska skillnaderna var små, drog vi slutsatsen att det med stor sannolikhet inte finns någon skillnad när man använder dessa enkäter och mäter vid dessa tidpunkter.

I delarbete 3 fann vi inte heller någon säkerställd skillnad mellan risken att drabbas av sexuell dysfunktion eller urininkontinens när man jämför laparoskopisk och öppen kirurgi. Vi fann att frekvensen av problem skiljer sig mycket beroende på om man frågar den sjukvårdspersonal som följt upp patienten eller om man frågar patienten själv. Vidare visade vi att urinfunktionen påverkas i mindre grad än den sexuella funktionen.

Slutligen fann vi i delarbete 4 att patientfaktorer som ålder eller kön samt kliniska variabler såsom typen av ändtarmscancer och operation samt komplikationer spelar mindre roll för global livskvalitet än vad andra domäner inom livskvalitet gör. Vi fann att patientrapporterade värden för smärta och fatigue (ett begrepp svåröversatt från engelska innefattande både fysisk och mental trötthet samt uttrötthet) sannolikt är viktiga faktorer för global livskvalitet. Fler studier krävs för att se om dessa går att påverka för att förbättra patienternas globala livskvalitet. Det förefaller som att några få frågor skulle kunna användas i det kliniska arbetet för att identifiera dessa patienter.

Sammanfattningsvis konkluderar vi att laparoskopisk kirurgi är säkert med avseende på risk för återfall i cancer uttryckt som lokalrecidiv samt på cancerspecifik och total överlevnad. Tiden är nu mogen för breddinförande i klinisk praxis, men detta kommer att kräva utbildningsinsatser.



## LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

**I. A Randomized Trial of Laparoscopic versus Open Surgery for Rectal Cancer**

H. Jaap Bonjer, Charlotte L. Dreijen, Gabor A. Abis, Miguel A. Cuesta, Martijn H.G.M. van der Pas, Elly S.M. de Lange-de Klerk, Antonio M. Lacy, Willem A. Bemelman, John Andersson, Eva Angenete, Jacob Rosenberg, Alois Fuerst, Eva Haglind.

*New England Journal of Medicine 2015; 372(14): 1324-32.*

**II. Health-related quality of life after laparoscopic and open surgery for rectal cancer in a randomized trial**

Andersson J, Angenete E, Gellerstedt M, Angerås U, Jess P, Rosenberg J, Fuerst A, Bonjer J, Haglind E.

*British Journal of Surgery 2013; 100: 941–949.*

**III. Patient-reported genitourinary dysfunction after laparoscopic and open rectal cancer surgery in a randomized trial (COLOR II)**

Andersson J, Abis G, Gellerstedt M, Angenete E, Angerås U, Cuesta M A, Jess P, Rosenberg J, Bonjer, H J, Haglind E.

*British Journal of Surgery 2014; 101: 1272–1279*

**IV. Determinants of global quality of life in patients with rectal cancer**

John Andersson, Eva Angenete, Ulf Angerås, Martin Gellerstedt, Eva Haglind.

*Submitted manuscript*



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## ABBREVIATIONS

ASA	American Society of Anaesthesiologists classification
COLOR	Colorectal Laparoscopic or Open Resection, trial addressing colonic cancer
COLOR II	Sequel to COLOR addressing rectal cancer.
COLOR III	Possible trial addressing trans-anal TME
CRF	Clinical Record Form
CRM	Circumferential Resection Margin
CT	Computed Tomography
EORTC C30	European Organization of Research and Treatment for Cancer Quality of life Questionnaire Core 30
EORTC CR38	European Organization of Research and Treatment for Cancer Quality of life Questionnaire ColoRectal 38
MID	Minimal clinical Important Difference
MRI	Magnetic Resonance Imaging
RCT	Randomised Controlled Trial
TME	Total Mesorectal Excision

# 1 INTRODUCTION

## 1.1 Rectal cancer

Colorectal cancer is the third most common cancer worldwide with nearly 1.4 million new cases each year. The incidence is increasing and 700000 people die annually from colorectal cancer<sup>1</sup>. About one third of the patients with colorectal cancer suffer from rectal cancer with the tumour situated in the last 15 cm of the bowel.

Surgery is still the only curative treatment but adjuvant treatment with radiotherapy and chemotherapy are important.

Historically the prognosis for rectal cancer has been worse than for colon cancer, but since the beginning of the 1980's the prognosis has improved and in recent years it has become comparable between the groups, with a 5-year survival of over 60%<sup>2,3</sup>.

This improvement is mainly due to more accurate surgery. The introduction and implementation of total mesorectal excision (TME) by Heald<sup>4, 5</sup> is probably one of the most important factors, but adjuvant treatment with radiation and/or chemotherapy before and after surgery are also important to the achievement of loco-regional control and increased survival<sup>6,7</sup>.

## 1.2 Laparoscopic surgery

Laparoscopic surgery is the gold standard in a variety of surgical fields, and today it is the technique of choice for gallbladder surgery, obesity surgery<sup>8</sup>, gynaecological surgery<sup>9</sup>, and diagnostic surgical procedures. It results in shorter recovery time, less pain, shorter hospital stay and shorter sick leave<sup>10, 11</sup>. There is also data suggesting that the incidence of small-bowel obstruction is less common after laparoscopic surgery<sup>12</sup>.

After an enthusiastic start in laparoscopic colorectal surgery in the beginning of the 1990's by Jacobs and others<sup>13</sup>, reports on port site metastases retained the development<sup>14</sup>. Three large randomised trials in laparoscopic colonic surgery (Barcelona<sup>15</sup>, COST<sup>16</sup>, COLOR<sup>17</sup>) and one in laparoscopic colorectal surgery (CLASSIC<sup>18</sup>) showed that the incidence of such port site metastases were not more common than surgical wound metastases after open surgery. These trials also showed the expected short-term benefits of laparoscopic

surgery. In the CLASSIC trial, however, no firm conclusions about patients suffering from rectal cancer were possible due to the small study population<sup>18</sup>. Since then there have been small randomised single-institution trials<sup>19, 20</sup> and one medium sized randomised national trial<sup>21</sup> investigating the effects of laparoscopic technique in the treatment of rectal cancer. In 2004, the study group responsible for the COLOR trial initiated a trial aiming to evaluate laparoscopic surgery in rectal cancer. The COLOR II is the only large international randomised trial comparing laparoscopic and open surgery, designed to study efficacy and safety<sup>22</sup>.

### **1.3 Health related quality of life**

The term ‘Quality of life’ was introduced in the early 50’s by researchers in Economics due to fear of ecological aspects of unlimited economical growth<sup>23</sup> and difficulties of explaining the lack of correlation between satisfaction with life and the increasing wealth in terms of average income in the United States<sup>24</sup>.

It is still a concept without a clear-cut definition even though most people have an intuitive understanding of its meaning.

Another similar and to some extent vague concept is ‘health’. The definition of health suggested by the World Health organisation in 1946: “a state of complete physical, mental and social well-being and not merely the absence of disease” is still valid, but could be seen as a utopian ideal. However, the WHO definition stresses that health is a wide concept with several dimensions.

In an attempt to define the quality of life aspects in relationship to disease and their treatments many researchers have used the term “Health related quality of life” (HRQL)<sup>25</sup>. In contrast to most research, HRQL is based on direct subjective information retrieved from patients. Proxy assessment is only accepted in cases where direct communication with the patient is difficult, such as in the case of infants or the mentally impaired<sup>26</sup>.

The subjective information from the patients should not be seen as an alternative to traditional “hard endpoints” but rather as a complement and as an addition of another dimension. Recently the term patient-reported outcome measures (PROM) has been widely adopted. PROM includes all data derived directly from patients. HRQL is one of the most commonly used PROM.

Despite sometimes vague and ill-defined, HRQL research is nowadays an accepted field of research, adding important information and understanding of treatment effects in trials. After great improvements in several medical fields, new treatments can often add only mild to moderately improved effects on the disease. As a result, the comparisons of other benefits e.g. better compliance or fewer side effects have increased. One of these benefits is an improvement in HRQL. The early adoption of HRQL studies in palliative medicine is not surprising since symptom relief and improvement in HRQL may be the most important endpoints in this field.

The assessment of patient reported quality of life is often performed through questionnaires. Questionnaire-based research is a large field with a variety of forms giving different perspectives and enabling different degrees of generalizability and specificity. Questionnaires can roughly be divided into “generic” – used to compare different diseases and to compare with cross sectional data in the general population, “disease-specific” – addressing the specific problems that a patient with a certain disease has, and “symptom centred” – addressing the aspects of a certain symptom.

The European Organisation of Research and Treatment of Cancer offers a concept with a disease specific core questionnaire, the Quality of life Questionnaire - Core 30 (EORTC C30), validated for patients with different types of cancer<sup>27</sup>. In combination with this questionnaire there are disease specific supplements, for example Colorectal 38 (CR38) for colorectal cancer<sup>28</sup> and H&N35 for Head and Neck malignancies<sup>29</sup>. These supplements have additional questions addressing specific symptoms and problems depending on type of cancer.

The EORTC C30 and its add-ons are widely used in clinical trials and have been translated and validated in 81 languages<sup>30</sup>.

## 1.4 Summing up

In the current situation of improved prognosis in rectal cancer and more patients surviving, there has been an increasing interest in the morbidity and patient reported outcomes after rectal cancer surgery. In the setting of the COLOR II trial this thesis explores whether the laparoscopic approach in rectal cancer surgery results in an outcome similar to the open approach, and if there are any benefits in HRQL between patients undergoing open or laparoscopic surgery.



## 2 AIM

- To determine if laparoscopic rectal cancer surgery is non-inferior to open surgery in terms of loco-regional recurrence.
- To explore if there is a difference in patient-reported health related quality of life after laparoscopic and open rectal cancer surgery.
- To explore if there is a difference in sexual and urinary dysfunction after laparoscopic and open rectal cancer surgery.
- To explore determinants of importance for patient-reported global quality of life in patients with potentially curable rectal cancer.

## 3 PATIENTS AND METHODS

### 3.1 COLOR II

The COlorectal Laparoscopic or Open Resection (COLOR) II trial is a sequel to the COLOR trial. While the COLOR trial examined laparoscopic surgery in colonic cancer, the COLOR II addressed laparoscopic surgery in rectal cancer<sup>22</sup>.

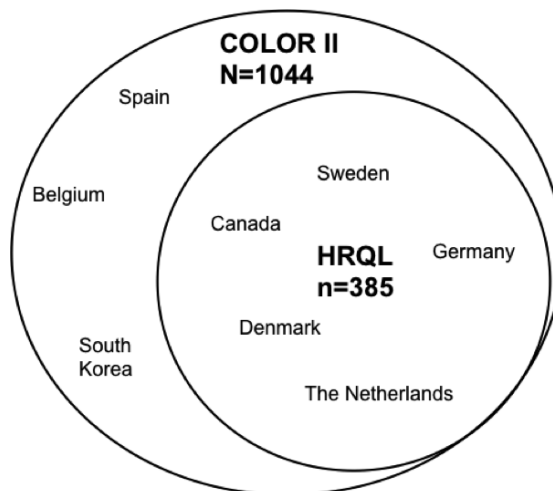
The trial was set up in 2003 before the results of COLOR were finished. The design was an open-label randomised non-inferiority trial. Thirty centres from Belgium, Canada, Denmark, Germany, the Netherlands, South Korea, Spain and Sweden participated with an accrual of 1044 patients. The patients were included from January 2004 until May 2010.

Participants were randomised between laparoscopic and open surgery in a 2:1 ratio in favour of laparoscopy.

The primary endpoint was loco-regional recurrence at a 3-year follow-up.

Secondary outcomes were short-term morbidity and mortality, disease free and overall survival after 3 and 5 years, quality of the resected specimen, HRQL, and costs.

In the HRQL sub-study, which was optional, twelve centres in five countries (Canada, Denmark, Germany, the Netherlands and Sweden) chose to participate. Out of 617 eligible patients included from these centres in COLOR II, 385 were finally included in the HRQL analysis.



### 3.1.1 Non-inferiority design

The empirical background of the study design implicated that there would be small differences between laparoscopic and open surgery in terms of loco-regional recurrence. It was suggested that laparoscopic surgery in rectal cancer would lead to the common benefits of faster recovery, shorter hospital stay etc. Hence the appropriate method was a non-inferiority trial<sup>31</sup>.

In a non-inferiority trial you have to define the accepted maximal clinical difference between treatments. In 2003, when the study protocol was defined, the consensus in the COLOR II-trial group was that an acceptable level of loco-regional recurrence was 10 %. At that time the population based rate of 5-year overall loco-regional recurrence in Sweden was 9.5%, and recurrence in patients with a curative intent resection was 7.9%<sup>32</sup>.

Consensus was also that most of the loco-regional recurrences develop in the first three years after surgery. Later it has been suggested that the introduction of neo-adjuvant treatment may lead to later recurrences<sup>33</sup>.

The maximal accepted difference between treatments was decided to be 5% units.

The initial power calculation was based on the assumption that 1275 (850 laparoscopic and 425 open) patients were required to detect a difference of 5% units between the treatments with 80% power. This is based on a two-sided 95% confidence interval. It was estimated that the inclusion would be met in 2008.

Later, in 2009, realising that accrual was slower than expected, the study committee decided to recalculate the power calculation, using a one-sided test of 95% confidence interval (corresponds to a two-sided with 90% confidence interval). The new power calculation resulted in the need of 1000 patients (670 laparoscopic and 330 open). The study committee reached the decision to aim for 1100 patients.

### 3.1.2 Blinding

Blinded studies are considered to yield the highest degree of evidence in medical research, but they are still rare in the field of surgery. Obviously it is not possible to blind the operating surgeon, but some studies have shown that the staff caring for the patient in the postoperative period, as well as the patient, could be blinded. For example the use of the same wound dressing in all patients could achieve blinding<sup>34, 35</sup>. This would have been possible in the

postoperative period of the COLOR II trial. However, since scarring after laparoscopic and open surgery would have been evident in the 3-year follow-up period, blinding of the primary endpoint would have been virtually impossible. Theoretically, but not ethically feasible, there could have been complementing sham-surgery with skin incisions mimicking the other technique. The result, however, would have been additional trauma to all participating patients.

The reason of blinding is to assure that the participants in the trial will not consciously or unconsciously affect the result and exaggerate differences between the treatment and the control.

In a non-inferiority trial blinding has certain drawbacks compared with a superiority trial, as the goal of the non-inferiority trial is to show “similarity”.

One of the methods to ascertain adequate blinding is to make the study design unknown to both participants and researchers, i.e. they do not know if it is a superiority or non-inferiority trial, or to include a non-inferiority margin in a superiority trial<sup>36</sup>.

### **3.1.3 Choice of primary outcome**

While many still believe that the development of distant metastases is influenced by more factors than surgical technique, loco-regional recurrence has been reported to be a marker of good surgical technique<sup>5, 37</sup>. This is supported by historically high rates of loco-regional recurrences, which has declined after the introduction of more accurate and standardised surgery by TME<sup>5</sup>. This was the first and main reason to choose loco-regional recurrence as primary outcome in the COLOR II trial.

The definition of loco-regional recurrence in the COLOR II trial was cancer recurrence in the pelvis or perineal area detected by physical examination and visible with rectoscopy or in CT scan or MRI.

There are, however, other measures that reduce the risk for local recurrence. Since the introduction of TME, pre-operative radiotherapy and chemotherapy have become a standard part of treatment with curative intent. In particular radiotherapy has been shown to decrease the risk of local recurrence<sup>32, 37</sup>.

Secondly, a local recurrence is a surgical challenge, with high risks of unwanted outcomes after surgical treatment of recurrence, in terms of postoperative morbidity such as faecal, urinary and sexual dysfunctions and with high mortality<sup>38</sup>.

Thirdly and most importantly – the patients’ suffering from local recurrence is often characterised by severe symptoms and dysfunctions and impaired quality of life<sup>39,40</sup>.

### **3.1.4 1 or 2 mm as negative CRM**

At the time when the study protocol was written a topic of discussion was the definition of a “negative circumferential margin” (a microscopic term defining a radical resection). The question was whether a one or two mm margin free of cancer cells was the appropriate margin. A recent report by Nagtegaal on the subject had been published, showing that pathological specimens with a CRM of 1-2mm lead to a higher rate of local recurrences and lower survival than specimens with >2 mm<sup>41</sup>. The protocol committee decided to use a 2 mm margin free of cancer cells as definition of “negative circumferential margin”, in the belief that it would be fully accepted within a fairly short time. However it has yet to be accepted as the normative definition. Since the CRF also included a question on the actual CRM-margin (in mm), a post-hoc analysis with 1 mm as definition was performed but did not change the results<sup>42</sup>.

### **3.1.5 Randomisation**

The ratio of 2 laparoscopic versus 1 open was set to collect as much information as possible on the “new treatment” (laparoscopic resection of rectal cancer). It also meant a higher possibility to detect rare adverse effects in the group of patients receiving the new treatment.

Another intent was to increase the speed with which the surgeons gained experience in the laparoscopic technique. Even though there was an initial quality control assessment of the participating centres, a development in skills was anticipated as the learning curve would be on-going for most participating surgeons. The COLOR II study group will later analyse the centre and surgeon caseload versus risk of adverse events and outcome in general.

### **3.1.6 Intention-to-treat**

The analysis was performed by intention-to-treat. Thus, patients randomised to laparoscopic surgery but receiving or perioperatively converted to open surgery were analysed in the laparoscopic group. Some of the patients randomised to laparoscopic surgery received open surgery when there was no laparoscopic surgeon available.

Many countries have health care systems where hospitals compete, making it important to have satisfied customers. This may explain why three patients in our trial received laparoscopic surgery by “own choice”, in violation of the protocol. These patients were analysed within the group they were randomly assigned to (“intention to treat”). The conclusion, which could be drawn, is that the now widespread use of laparoscopic rectal cancer surgery will make it nearly impossible to repeat this trial since patients today are well informed and are demanding laparoscopy.

### **3.1.7 Importance of per-protocol analysis**

The opposite of “intention to treat” is the per-protocol or “as treated”-analysis where patients are analysed within the group of the actual treatment they received. In non-inferiority trials the per-protocol analysis is more important and is in fact the more conservative statistical estimate than intention to treat. The reason is that in a conventional superiority trial, the per-protocol analysis may exaggerate the differences of treatments in favour of the studied one. But in the non-inferiority trial this possible exaggeration will lead to a more conservative testing of the hypothesis since the main goal is to show “similarity”.

In the “as treated”/per-protocol analysis of COLOR II, the differences between laparoscopic or open surgery were even smaller or more in favour of laparoscopy albeit with no statistical significant difference (paper I).

## **3.2 HRQL**

### **3.2.1 HRQL Optional**

The HRQL sub-study of COLOR II was optional for the including centres. This fact was debated during the set-up of the trial. The advocates pointed out that there might be a correlation between the workload with each patient and the centres’ willingness to join the trial and undertake inclusion. Questionnaires were to be administrated before surgery and at several time points during follow-up (1, 6, 12 and 24 months).

The centres that chose to participate in the HRQL-sub-study included 617 patients in the main trial but only 385 patients in the HRQL sub-study. We interpret this as being due to logistic difficulties in distributing and retrieving the preoperative questionnaires.

There may also have been a difference in awareness of the importance of HRQL and other PROM among different surgeons.

### **3.2.2 Inclusion time**

Despite the large number of centres the inclusion time of the trial was 6 years. During this time there were several changes in the treatment regimens of rectal cancer as for example an increasing use of preoperative radiotherapy, introduction of long-term radio-chemotherapy and rectal washout, all reported to reduce the risk of local recurrences<sup>43-45</sup>. This could of course be considered a limitation of the trial. However, when looking at other trials in surgery this is an acceptable time period. The COST trial had an inclusion time of 7 years (1994-2001) resulting in inclusion of 863 patients of the goal of 1200<sup>16</sup>. The CLASSIC trial included 794 of the aim at 1000 patients during 6 years (1996-2002). In the perspective of these trials the COLOR II was a success including 1044 in 6 years, meeting the goal of 1000 patients.

The set-up did not affect local decisions regarding preoperative treatment such as radiotherapy or postoperative treatment such as chemotherapy. The focus was that both the laparoscopic and open group should receive the same perioperative care according to the local protocol.

### **3.2.3 Choice of questionnaires**

#### **Specificity to change versus transferability**

Since the number of available questionnaires is nearly indefinite the key is to choose an instrument that is sensitive to the problems that are most likely to occur in the studied cohort of patients.

At the same time it is important to use a questionnaire, which is easy to use and has adequate psychometric properties. It is also important that it is validated in the actual study population and available in the required languages as the translation is a time-consuming process. Since the COLOR II was an international study we chose three of the most common questionnaires in the field: EQ-5D, EORTC C30 and EORTC CR38.

The benefit of using a commonly used generic questionnaire (EQ-5D) is the possibility to compare with other diseases and population-based controls.

The drawback is that generic questionnaires may have difficulties addressing the typical problems in the actual patient group and also difficulties in discriminating among many disease-specific problems. EQ-5D is therefore

most useful in treatments that are supposed to have a large impact on HRQL. It has also problems with floor and ceiling effects – easily demonstrated by looking in table 3 in paper II where very few patients assess their function as level 3 in all questions. EQ-5D has later been revised in order to improve these shortcomings by adding additional steps in the scale<sup>46</sup>.

Disease-specific questionnaires address the typical symptoms and functions at risk in a certain disease. EORTC C30 takes an intermediate place as it has been constructed to discriminate and evaluate typical symptoms and treatment effects in patients suffering from cancer. Thus the result can be compared with patients with other types of cancer but hardly those with completely different diseases.

There are also disease-specific instruments like the EORTC CR38 focusing on the more specific symptoms common in patients with colorectal cancer as for example stoma related problems or defecation problems.

### **Questions – items**

In questionnaire-based research a question is often called ”item”. The question has to be carefully expressed and much work is inquired to assure that patients and researchers have the same interpretation of the question. Often an item has to be tested several times with rephrasing before the question is valid.

Questionnaires often have several items analysing the same field in order to gather enough information on the subject. Another reason is to evaluate the degree of problems in the same subject. One example is the physical function, which often consists of several items addressing different levels of physical problems – one question could be about walking short distances and one about long distances and yet another could be about carrying heavy objects etc.

The different questions/items are analysed together in a “domain”/functional scale or symptom scale. As an example the domain “Physical function” in EORTC C30 consists of five questions.

### **Validity of questionnaires**

There are several important concepts in validating a questionnaire, often expressed as psychometric evaluation.



*Content validity* analyses if the domains truly measure what they set out to measure, for example if all the items (questions) in a domain really concern that subject.

*Criterion validity* compares the test against a gold standard. One good example is the Montgomery Åsberg Depression Rating Scale (MADRS), shown to correlate well with clinical depression<sup>47</sup>.

In the field of HRQL there is no gold standard, thus the criterion validity has to be calculated by indirect methods. Often the test is compared to other questionnaires that are already accepted in the research field.

*Construct validity* addresses the question of how effective the item is in measuring the latent variable or “true value”. Do included questions cover all aspects of the domain? Are other aspects of the domain missing?

Construct validity also considers whether the scale is appropriate. Are all steps in the scale used? Are there floor or ceiling effects – meaning that most patients use the same steps and the scale is poor at discriminating in lower functioning/symptoms (floor effects) or higher degree of functioning/symptoms (ceiling effects).

The concept also addresses if there are questions that have missing values, for example sexual problems, or other questions that might be considered to be of a private nature.

*Reliability* is the concept of whether a scale is reproducible, i.e. gives the same result at different occasions of testing. Reliability is often measured by Cronbach  $\alpha$  or test-retest. It is important not to re-test too soon because the participants may remember their previous answers. On the other hand, if there is a long time span between the two assessments, there may be changes in the actual variable measured.

*The internal consistency* addresses whether the separate items in the same domain are correlated. Items within the same domain should correlate with each other but not to a high degree with items from other domains.

*Sensitivity* is the scale’s ability to detect differences between groups while *responsiveness* is the ability of the domain or symptom scale to detect changes over time.

## **EORTC C30**

Psychometric evaluation of the EORTC has been extensive and it has gone to major revision three times. The latest version, 3.0, which we also used in the COLOR II trial, have shown acceptable psychometric properties<sup>48</sup>.

## **EORTC CR38**

In the psychometric evaluation of the EORTC CR 38 several problems were found later leading to the revision to EORTC CR 29<sup>49</sup>. A psychometric evaluation was performed in 2009 showing that it is a valid and reliable tool in international trials but still with concerns in the section of sexuality<sup>50</sup>.

It has also been suggested that the EORTC CR38 have trouble in discriminating problems with bowel function<sup>51</sup>.

## **Imputation**

All questionnaire-based studies have the problem of missing answers, especially when using several questionnaires and subsequent assessments over time. Imputation is when these missing values are replaced by estimated values from the observed data. There are a number of statistical methods with different degrees of complexity that attempt this estimation.

The EORTC manual recommends the simplest method, avoiding imputation but using multi-item scales if at least half of the items were answered. Hence if, for example, a two-item scale has one missing answer the scale could be calculated implying that the missing answer is the same as the answered item. As a consequence, single item scales would be set as missing if the single question lacked an answer. No other imputation was made.

## **Sexual dysfunction**

Patient-reported HRQL regarding sexual function is an area with specific pitfalls. The response rates are often low, which probably reflects the private nature of the topic.

Another reason might be that the definition of sexual activity is rather narrow in most questionnaires, often with heterosexual intercourse as the norm and many questions implying partners in the sexual act<sup>52,53</sup>.

It might, however, be problematic to suggest homosexual or masturbating behaviour in the questions<sup>54</sup>.

There are obviously gender differences in the experiences of sex. Because of this, the EORTC CR38 has problems with conditional questions that may lead to lower response rates, especially in women<sup>55</sup>.

As shown in paper III, response rates regarding sexual function and sexual enjoyment differed between men and women. The response rates for Male sexual problems and Female sexual problems were even lower, with the latter so low that analysis was not possible.

One of the instruments that could have been used is the international Index of Erectile Dysfunction (IIEF), an instrument assessing erectile dysfunction in male patients and also briefly addressing other parts of male sexual problems. Pfizer developed the instrument during the research on Sildenafil (Viagra). Later it has become one of the most commonly used and accepted instruments in male sexual function, with good cross-cultural validity, and it has also been used in rectal cancer. At the time of finalising the study protocol in 2003, reports of its use in rectal cancer trials were scarce<sup>56, 57</sup>.

Regarding female sexual function in rectal cancer the literature was even more absent in 2003. Since then the Female Sexual Function Index (FSFI) has become a popular instrument in analysis of female sexual function after rectal cancer resection<sup>58</sup>.

### **3.2.4 Clinically meaningful differences**

#### **MID**

The vast number of variables in questionnaire based research lead to the risk of finding statistical significant differences by chance (mass significance). Hence it is important to determine if a statistically significant difference implies a clinically meaningful difference, recognised by the patients.

There are several methods to assess a clinically meaningful difference. They could be divided into anchor-based methods, populations-based comparisons, and pure statistical methods.

In the anchor-based methods the studies try to define the minimal clinically important difference (MID). In this case patients do not only assess their HRQL at several time points, but also complete separate questions on any experience of change in functions or symptoms. The results are then compared with levels in the questionnaires, and an interval is calculated in the population.

Most of these reports show that the MID is in the interval 5-10, meaning a small difference. A difference of 10-20 means a moderate effect and >20 means a large and clinically meaningful effect.

The pure statistical, data-driven methods are for example “effect size” and calculation of “standard response mean” (SRM). Both consider the random variability of the collected data.

Although still a subject of some controversy, the methods result in roughly the same conclusion of a MID of 5-10%, or 5-10 in a 100 point scale. This should work as a rule of thumb, but there may be differences in the symptom scales and further research is needed<sup>59</sup>.

In the assessment of HRQL in the COLOR II trial we used the accepted definition of MID.

### **3.2.5 Choice of measuring time points**

The COLOR trial showed a decrease in several HRQL domains with a significant difference between laparoscopic and open surgery in role function after 2 weeks and social function after 2 and 4 weeks.

The reason for not measuring at 2 weeks in the COLOR II trial was that surgery for rectal cancer, with curative intent, was regarded as more traumatic. We assumed that 2 weeks would be too early to be able to detect differences between the groups, and as always there is a discussion about recall bias and repeated questionnaires. We eventually decided to wait until 4 weeks with the first post-operative assessment of HRQL. With the results at hand, this was possibly an unfortunate error in timing.

## **3.3 Complications**

In the construction of a trial’s clinical record form there are certain problems. Questions that are absolutely clear to the study committee constructing the CRFs may prove to be hard to interpret for local investigators and research nurses. You are also tempted to have an “other” alternative with plain text. In the phase of analysis this has often proved to be difficult. One way to address this problem is to face-to-face validate the CRF, i.e. let the clinicians and nurses fill in a dummy CRF to identify problems and questions.

The trial was planned and started before the Clavien-Dindo assessment of complications was published<sup>60</sup>. In the surgical literature Clavien-Dindo is

now more or less the gold standard of assessing complications. Using this classification in our trial could have made it easier to interpret the result regarding complications. We decided to not perform a post hoc classification of the registered complications according to the Clavien-Dindo, in accordance with the clinical protocol.

Lessons learned from working with the database and the CRF are several. We suggest; always perform both expert validation and face-to-face validations, and preferably use the CRF in a pilot before the actual trial. Further, be careful about definitions and in an international study: agree upon the language to be used in all answers. One problem regarding definitions is that few countries use the NOMESCO classification of surgical procedures<sup>61</sup>, and instead describe the additional surgical procedures in open text fields.

## **3.4 Statistical considerations**

### **3.4.1 Continuous versus ordinal data**

The data from the questionnaires are derived from rigid answering alternatives and are by definition ordinal data. The construction of multi item scales with mean values of two or more questions and recalculation into scales of 0-100, makes it convenient to treat data as continuous allowing tests with higher precision to be performed. This could of course be criticised by the orthodox but is often performed by convention. Hence, in paper IV we treated the data from EORTC as continuous variables. Since this is an exploratory analysis, the result should be interpreted with care.

### **3.4.2 Mass significance**

Multiple testing of a large number of variables as in questionnaire-based research will inevitably lead to the problem with the risk of detecting statistically significant differences by chance. One method to address this problem is the Bonferroni correction, in which the significance level rises with the number of tests. But this is a highly conservative method leading to the risk of making type II errors, i.e. missing true effects/differences.

Another way of addressing the problem is to compare the result with the empirical knowledge and literature.

The HRQL study (paper II) showed small actual differences between the two treatments in all variables and they were below the interval of MID. Since the confidence intervals were also really narrow, we concluded that there were probably no differences to find.

Paper IV was an explorative study; hence the result should be interpreted with care. But since the finding of pain and fatigue, as possible factors important to global quality of life, was consistent in all different time points during follow-up and the level of significance was high ( $p=0.005$ ), we suggest that the result is valid. This is also concordant with the literature where at least Fatigue is a well documented determinant of global quality of life in a number of cancer types<sup>62-65</sup>.

### **3.5 Ethical approvals**

The appropriate ethics committees approved the COLOR II protocol and informed consent was retrieved from all patients<sup>22</sup>. For the Swedish part of the trial the regional ethics board of Västra Götaland approved the trial in February 3<sup>rd</sup> 2003 (Dnr: S 619-02). An additional approval was made in October 5<sup>th</sup> 2009 (Dnr: 480-09).

## 4 RESULTS

The focus of this thesis (apart from the primary endpoint of the COLOR II trial) is the patient-reported secondary outcome – HRQL.

### 4.1 Paper I

In the first paper the main outcome of COLOR II showed that laparoscopic surgery is non-inferior to open surgery regarding oncological safety, expressed as loco-regional recurrence, disease-specific and overall survival.

Out of 1103 randomised patients 1044 was included. Follow-up data was retrieved for 1009 patients.

Loco-regional recurrence in the intention-to-treat analysis was 5.0% in both groups after 3 years with a difference of 0% (90% CI, -2.6 to 2.6). The upper limit of the confidence interval was below the non-inferiority margin of a difference of 5% points. To check the robustness of the result we then performed an as-treated (per-protocol) analysis showing that the difference in loco-regional recurrence was -2.0 (90% CI -4.7 to 0.7) in favour of the laparoscopic group, but not statistically significant.

Disease-free survival was 74.8% in the laparoscopic group and 70.8% in the open group, with a difference of 4.0% (95% CI -1.9 to 9.9).

Overall survival was 86.7% in the laparoscopic group and 83.6% in the open group with a difference of 3.1% (95% CI -1.6 to 7.8).

### 4.2 Paper II

In the second paper we analysed the overall HRQL and its sub-domains in EQ-5D, EORTC C30 and most of the aspects of EORTC CR38.

We found that there was a negative effect on HRQL in most of the domains studied after rectal cancer surgery, but that most of them had recovered during the 12-month follow-up.

Compared to patients with colonic cancer in the COLOR trial, where there was an additional time point 2 weeks after surgery, we could conclude that the HRQL was affected during a longer time after rectal cancer. In the COLOR trial the impact on HRQL was highest after 2 weeks and patients

had started to recover after 4 weeks. In our study the level of impact after 4 weeks was comparable to the impact after 2 weeks in the COLOR trial regarding physical and role functioning.

There was no statistically significant difference between laparoscopic and open surgery in any of the HRQL measurements during the follow-up period. The confidence intervals were also narrow and the magnitude of the differences excluded clinically meaningful differences, expressed as MID. Therefore we suggest that there is no difference at 4 weeks after surgery between laparoscopic and open surgery, at least when using these questionnaires.

### 4.3 Paper III

Since there have been concerns that there is a higher degree of problems in sexual and urinary function after laparoscopic surgery we performed a separate analysis on this matter in paper III. We also compared the clinical evaluation of sexual dysfunction and urinary incontinence in the follow-up section of the CRF, with the patient-reported HRQL in the subject.

There were very few cases reported in the CRF with substantial differences from what patients reported in the questionnaire. This stresses the possible doctor-patient bias<sup>66</sup>, which has been described as the “I want to please my surgeon” effect. The patient will not describe problems to the doctor, in fear of making the surgeon unhappy.

Both sexual function and micturition symptoms were affected by the treatment and recovered during the first year, but some specific male sexual problems were persistent.

This analysis found that sexual function and urinary function was similar in the two groups with no significant difference. Again, taking into consideration the statistical uncertainty, the level of possible differences was below the level of MID.

We analysed the two separate questions which concern sexual function: Sexual interest and Sexual activity. We found a gender difference with men rating both sexual activity and sexual interest higher than women did.

The overall result showed that there was no difference in either sexual or urinary dysfunction between the groups of laparoscopic or open surgery.



## 4.4 Paper IV

The first step in improving patient-reported HRQL is to understand if there are functions or domains that have a greater impact on quality of life than others. To further understand and explore the different part of HRQL and the correlation between global quality of life and the common clinical variables in patients with rectal cancer, we conducted the analysis in paper IV.

In this paper we performed an explorative analysis with several models of linear regression. We found that common clinical variables like patient characteristics and complications only explained a small part of the variation in global quality of life. When examining the different domains and symptom scores, two symptoms stood out: pain and fatigue. Pain and fatigue correlated with global quality of life at all time points.

All models were adjusted for baseline (preoperative) global quality of life, since previous reports have concluded this to be the most important factor.

## 5 DISCUSSION

This thesis addresses some of the most important concerns that have been raised regarding the efficacy of laparoscopic surgery in rectal cancer.

The first and most important question is the one about oncological safety. As shown in paper I we can now conclude that laparoscopy in rectal cancer surgery is non-inferior to open surgery in terms of one of the most important quality marker of good surgery: loco-regional recurrence.

Disease specific and overall survival did not show any difference between the groups after 3 years. There will be further reports since the follow-up continues up to 5 years, adding information on this subject.

Another concern has been early reports on increased sexual dysfunction after laparoscopic as compared to after open surgery. In paper III we address this question and conclude that this fear is probably over-rated.

High-level evidence in surgery is still unusual compared to in other parts of medicine. This is probably due to the difficulty of running large randomised trials in this field, since many of these diseases and conditions and their treatments are complex, and in part subject to individual assessments of surgeons. The surgical work has also historically been a solitude work, and standardisation of operations has arisen late in history. In addition, differences in health care systems and funding sometimes influence the choice of treatment.

Laparoscopic colorectal surgery has been scrutinised from the start and met early setbacks, but laparoscopic colonic surgery is now one of the exceptions in terms of evidence. The COLOR II trial is also an exception being a large international trial meeting its inclusion goal and reaching the goal of the non-inferiority margin.

Surgery has for a long time been like the Wild West with new treatment strategies randomly introduced and with non-existing follow-up or questionable reports on “my best series” with low external validity. The introduction of robotic surgery is not an exception.

At the same time there has to be progress, which requires early pioneers performing feasibility studies and exploring the boundaries of what can be accomplished in the field of surgery.

In my opinion, when new treatments are adopted they should always be within prospective studies. The national quality registers in Sweden is one of the best ways to follow new treatment modalities with the aim to improve treatment, but this clearly demands certain changes with inclusion of new variables to be registered. This process is sometimes time-consuming.

## **5.1 Quality of data**

The COLOR II trial had a high follow-up rate and a total of 1036, out of the original 1044 patients, could be included in the long-term analysis.

Missing values were generally low, thanks to the endeavour of Kevin Druhan and Karen Inglis, gathering and processing data at the coordination centre in Halifax, Canada.

In the HRQL sub-study there were generally high answering rates in the HRQL measurements with rather few lost questionnaires, but with missing values in single items as described in paper II and paper III.

## **5.2 If I could choose again**

In retrospect, after the findings in paper IV, with results of pain, fatigue and emotional function (preoperatively and after 1 month), it would have been interesting to choose more symptom-specific instruments focusing on pain and fatigue.

### **5.2.1 Pain**

Pain is a complex symptom with both physiological and psychological components. The common method of assessing pain is by using the visual analogue scale (VAS).

A more detailed instrument is the Short form McGill Pain Questionnaire (SF-MPQ)<sup>67</sup>. It consists of several measures and characterisation of pain also including a VAS as one of the scales.

It would have been interesting to evaluate in detail whether the type of pain differs between the small incisions in laparoscopic surgery and the midline incision in open surgery, or if the visceral part of the pain is more pronounced.

## 5.2.2 Fatigue

Fatigue is a complex symptom holding both physical and mental components. Multidimensional Fatigue Inventory (MFI-20) is a widely adopted questionnaire addressing fatigue. Smets et al developed MFI-20 in 1995<sup>68</sup>. It consists of five dimensions addressing different parts of fatigue: general fatigue, physical fatigue, reduced motivation, reduced activity, and mental fatigue.

Its psychometric properties have shown that it could be used to assess fatigue in both patients and healthy individuals, resulting in comparability<sup>69</sup>.

Since we found that fatigue was one of only two factors with a significant impact on global quality of life in paper IV, it would be interesting to have assessed patients with this instrument, giving more information on in which one of the dimensions patients experienced most problems.

## 5.2.3 Sexual function

At least, a combination of IIEF in male patients and FSFI in female patients would have been a better choice than the EORTC CR38 with its shortcomings, in order to address the complex issue of sexual dysfunction after laparoscopic rectal cancer resection. The two instruments combined would have provided more detailed information on the subject.

## 5.3 Other measuring time points

Since most of the benefits of laparoscopic surgery occur in the early postoperative period, it would have been interesting to assess HRQL earlier than 4 weeks after surgery.

Intuitively, it seems that the significantly lower use of epidural analgesia in the laparoscopic group reported in the short-term results, suggests that there could have been a difference in patient reported HRQL of pain between the two groups, if it had been measured after one or two weeks. On the other hand, the correlation between HRQL and common clinical variables are often not correlated, making them complementary to each other.

Since epidural analgesia is often planned and executed preoperatively, there might also have been a selection bias. An anticipation of more pain in the open surgery group might have resulted in a higher use of epidural analgesia, since the trial was not blinded.

## 5.4 External validity

The 30 participating centres in the COLOR II trial represent both different countries from Europe, the American continent, and Asia, as well as different types and sizes of hospitals with expertise in laparoscopic surgery for rectal cancer<sup>42</sup>.

One important way of assuring the external validity is to keep track of all eligible patients, i. e. keeping screening-logs, which is often mandatory in trials of pharmaceuticals.

In the Nordic countries monitoring of screening logs are facilitated by the fact that there is a central patient administration in each hospital. In other countries the health care system is instead based on the individual surgeon/consultant, keeping his or her separate patient register. However, screening logs are still rare in surgical trials. The COLOR II trial did not use screening logs.

In the HRQL sub-study population there was a selection bias with the included patients somewhat healthier and with fewer patients receiving preoperative radiotherapy than in the population of the main COLOR II trial. However, comparison of the laparoscopic and the open groups did not show any statistically significant differences in baseline characteristics. Hence we suggest that the main results within paper II and paper III are valid.

The result from paper IV is harder to interpret but since this is an explorative analysis, the result should already be interpreted with great care. Possibly the lesser rate of preoperative radiotherapy and lower ASA score may lead to an underestimation of these two factors' effect on global quality of life. But since both these factors are fixed factors, the result is concordant with the literature showing lesser impact from fixed factors such as common clinical variables than from modifiable factors such as HRQL domains and symptoms<sup>70</sup>.

## 5.5 Clinical implication

One of the participating hospitals in Sweden, the NU Hospital group, continued with laparoscopic rectal cancer surgery after the inclusion in the COLOR II. Figures from the Swedish Colorectal cancer registry show that they now perform almost 60% of rectal cancer surgery laparoscopically<sup>3</sup>.

In Denmark there has been a centralisation of treatment. Laparoscopic colorectal cancer surgery has been adopted and structured training programmes have been initiated. A recent decision by the Danish government makes it mandatory for all treating centres to offer laparoscopic colorectal surgery. There have also been organised educational efforts with external mentors and continuous evaluation. This has recently been tried in Malmö in Sweden with reportedly good results. However, many mentors require at least 40 cases per year prior to implementation of laparoscopic surgery, making it difficult to achieve in low volume centres.

In Sweden there is still much work to be done. Laparoscopic colonic cancer surgery is still uncommon but increasing. In 2013, only 17% of resection for colonic cancer was performed laparoscopically<sup>3</sup>. This is a figure far from the 50-60% as suggested by Jansson in his thesis 2006 (the article was published in 2009)<sup>71</sup>. As a rule of thumb, the same rate should be possible to accomplish in rectal cancer patients in Sweden, with the NU hospital group as a leading example, but with the need of implementation by training programmes.

## 5.6 Development in HRQL research

In questionnaire-based research there are always patients suffering from the same disease who have a wide range of problems in regard to the same domain of function or symptom. Ceiling and floor effects are common as well as difficulty in discriminating changes for individual patients.

The rigid alternatives in the questionnaire limit the degree of detail. For example, if you are in a wheelchair you have trouble answering questions about “walking on stairs”. The questionnaire-based form of research implies that the patient should still answer that question.

There is an exciting evolvment in HRQL research with computer adaptive testing (CAT). In CAT there is a large item bank of questions and the patients are asked different questions depending on their level of functioning or symptoms, where the computer programme tailors new questions based on the previous answer, refining the degree of details. This enhances the probability to detect changes in functions and symptoms over time.

The computer programme also remembers the individual patients and addresses their specific details in subsequent testing, thus increasing the possibility to discriminate between changes. The answers can still be

compared on the group level since the questions are validated and respond to different alternatives on the same scale.

The EORTC is currently working with CAT versions of the different domains and symptom scales in the EORTC C30 with the intention of ensuring retrospective comparability<sup>72</sup>.

Patient-Reported Outcomes Measures Information System (PROMIS) is another initiative in constructing web-based questionnaires. It was started in 2004 and is supported by National Institute of Health (NIH), building an item bank and a domain structure that will be used in CAT<sup>73</sup>.

## 6 CONCLUSION

- Laparoscopic rectal cancer is oncologically safe in terms of loco-regional recurrence.
- Health related quality of life measured by EQ-5D, EORTC-C30 and EORTC CR38 after one month up to one year is similar to open surgery. Even considering statistical uncertainty and the size of difference, there is probably no difference due to narrow confidence intervals and the absence of clinically meaningful differences.
- Sexual dysfunction and micturition symptoms are similar after laparoscopic and open surgery. Earlier fears of worse outcome after laparoscopic surgery are probably not true.
- Pain and fatigue are important determinants of global quality of life in patients recently diagnosed with potentially curable rectal cancer. Simple questions could identify patients with risk of facing lower global quality of life and more research on possible interventions is needed.

### 6.1 Overall conclusion

- I suggest that laparoscopic surgery should from now on be the routine treatment and open surgery the exception in treatment of rectal cancer. To reach this goal training programmes in laparoscopic rectal cancer surgery are needed. There are several examples which prove that such training is feasible, such as the introduction of TME surgery or the introduction of laparoscopic colorectal surgery in Denmark and England.



## 7 FUTURE PERSPECTIVES

### 7.1.1 HE-COLOR II

The health economic evaluation in COLOR II (HE-COLOR II) is ongoing. The method is cost minimisation, as there was no difference concerning the primary outcome. This analysis will use both a hospital and a societal perspective and the time frame will be 3 years from index surgery<sup>74</sup>.

### 7.1.2 COLOR III

Trans-anal TME has been described as a new way of making the pelvic dissection easier in order to improve outcome in low rectal cancer<sup>75</sup>. The introduction of this hypothetically better technique, using a combination of abdominal and trans-anal laparoscopy is recent. An initiative of a trial (COLOR III) has come from the principal investigator of COLOR and COLOR II. It is an interesting perspective but too early for anything but a hypothesis of improved results.

### 7.1.3 QoliRECT

The QoliRECT-study<sup>76</sup> has a different approach. This trial examines a large number of specific questions and will hopefully determine the specific questions which are most important to patients with rectal cancer in different stages of the disease. It might prove to be a new fundamental resource in later trials.

### 7.1.4 Robotics

Robot-assisted laparoscopy was introduced about one decade ago. The number of robots in the world has increased explosively, but so far the main area for robot-assisted laparoscopy is in radical prostatectomy. The implementation has taken place without any high level evidence of it being superior. Sweden has probably one of the highest numbers of Da Vinci™ robots per capita.

The market for robots in urology is probably close to filled, and now rectal cancer surgery is another new field. It is important not to repeat the mistakes of the past and allow implementation to be “industry driven” rather than motivated by high level evidence of improvement for patients. The results from the first RCT on robot-assisted laparoscopic versus laparoscopic surgery for rectal cancer will be presented in the near future (ROLARR)<sup>77</sup>.

One of the early advances of robotic surgery was the functional three-dimensional representation of the operating field. This is nowadays easy to accomplish in the setting of conventional laparoscopy and at a much lower cost.

The health care systems in the Western world, irrespective of model of funding, are facing increasing costs from expensive treatments and an aging population. My personal opinion (patient-centred and not technology-driven) is that investment in a costly technique such as robot-assisted surgery is questionable.

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# **APPENDIX**

**7.2 EORTC QLQ C30**

**7.3 EORTC QLQ CR38**





## EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:

--	--	--	--	--

Your birthdate (Day, Month, Year):

--	--	--	--	--	--	--	--	--	--

Today's date (Day, Month, Year):

31 

--	--	--	--	--	--	--	--	--	--

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a <u>long</u> walk?	1	2	3	4
3. Do you have any trouble taking a <u>short</u> walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

### During the past week:

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

**During the past week:**

	<b>Not at All</b>	<b>A Little</b>	<b>Quite a Bit</b>	<b>Very Much</b>
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your <u>family</u> life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your <u>social</u> activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

**For the following questions please circle the number between 1 and 7 that best applies to you**

29. How would you rate your overall health during the past week?

1            2            3            4            5            6            7

Very poor

Excellent

30. How would you rate your overall quality of life during the past week?

1            2            3            4            5            6            7

Very poor

Excellent





## **EORTC QLQ – CR38**

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

<b>During the past week :</b>	<b>Not at All</b>	<b>A Little</b>	<b>Quite a Bit</b>	<b>Very Much</b>
31. Did you urinate frequently during the day?	1	2	3	4
32. Did you urinate frequently during the night?	1	2	3	4
33. Did you have pain when you urinated?	1	2	3	4
34. Did you have a bloated feeling in your abdomen?	1	2	3	4
35. Did you have abdominal pain?	1	2	3	4
36. Did you have pain in your buttocks?	1	2	3	4
37. Were you bothered by gas (flatulence)?	1	2	3	4
38. Did you belch?	1	2	3	4
39. Have you lost weight?	1	2	3	4
40. Did you have a dry mouth?	1	2	3	4
41. Have you had thin or lifeless hair as a result of your disease or treatment?	1	2	3	4
42. Did food and drink taste different from usual?	1	2	3	4
43. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
44. Have you been feeling less feminine/masculine as a result of your disease or treatment?	1	2	3	4
45. Have you been dissatisfied with your body?	1	2	3	4
46. Were you worried about your health in the future?	1	2	3	4

<b>During the past <u>four</u> weeks:</b>	<b>Not at All</b>	<b>A Little</b>	<b>Quite a Bit</b>	<b>Very Much</b>
47. To what extent were you interested in sex?	1	2	3	4
48. To what extent were you sexually active (with or without intercourse)?	1	2	3	4
49. Answer this question only if you have been sexually active: To what extent was sex enjoyable for you?	1	2	3	4

Please go on to the next page

**During the past four weeks:**

Not at All    A Little    Quite a Bit    Very Much

**For men only:**

50. Did you have difficulty getting or maintaining an erection?	1	2	3	4
51. Did you have problems with ejaculation (e.g., so-called "dry ejaculation")?	1	2	3	4

**Only for women who have had intercourse:**

52. Did you have a dry vagina during intercourse?	1	2	3	4
53. Did you have pain during intercourse?	1	2	3	4

54. Do you have a stoma (colostomy bag)?

No

**Please answer questions 55 to 61**

(Please circle No or Yes)

Yes

**Please skip questions 55 to 61 and answer questions 62 to 68****During the past week:**

Not at All    A Little    Quite a Bit    Very Much

**Only for patients WITHOUT a stoma (colostomy bag):**

55. Did you have frequent bowel movements during the day?	1	2	3	4
56. Did you have frequent bowel movements during the night?	1	2	3	4
57. Did you feel the urge to move your bowels without actually producing any stools?	1	2	3	4
58. Have you had any unintentional release of stools?	1	2	3	4
59. Have you had blood with your stools?	1	2	3	4
60. Have you had difficulty in moving your bowels?	1	2	3	4
61. Have your bowel movements been painful?	1	2	3	4

**Only for patients WITH a stoma (colostomy bag):**

62. Were you afraid that other people would be able to hear your stoma?	1	2	3	4
63. Were you afraid that other people would be able to smell your stools?	1	2	3	4
64. Were you worried about possible leakage from the stoma bag?	1	2	3	4
65. Did you have problems with caring for your stoma?	1	2	3	4
66. Was your skin around the stoma irritated?	1	2	3	4
67. Did you feel embarrassed because of your stoma?	1	2	3	4
68. Did you feel less complete because of your stoma?	1	2	3	4