Health economic aspects of minimally invasive surgical techniques

Jacob Gehrman

Department of Surgery
Institute of Clinical Sciences
Sahlgrenska Academy, University of Gothenburg

UNIVERSITY OF GOTHENBURG

Gothenburg 2018

Cover illustration by Peter Gehrman

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jacob.gehrman@gu.se

ISBN 978-91-629-0503-3 (PRINT)
ISBN 978-91-629-0504-0 (PDF)
http://hdl.handle.net/2077/55382

Printed in Gothenburg, Sweden 2018
Printed by BrandFactory AB

To Emma

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Jacob Gehrman

Department of Surgery, Institute of Clinical Sciences
Sahlgrenska Academy at University of Gothenburg
Gothenburg, Sweden

ABSTRACT

The aim of this thesis was to compare minimally invasive- with traditional open surgical techniques for various diseases with regards to cost-effectiveness. Health economic evaluations were performed using data from clinical trials and routine care data from registers. The healthcare perspective was represented in all four studies and the societal perspective (including sick-leave costs) was represented in three out of four studies.

Paper I included a cost-minimization analysis of laparoscopic and open surgery as treatment for rectal cancer within the randomized, controlled COLOR II trial. From the healthcare perspective laparoscopic surgery was costlier while from the societal perspective no significant long-term difference was observed. Paper II included a cost analysis of laparoscopic lavage versus Hartmann's procedure as treatment for complicated diverticulitis with purulent peritonitis within the randomized, controlled DILALA trial. Laparoscopic lavage was considered less costly both at 12 months and throughout patients' expected life, from the healthcare perspective. Paper III was a cost analysis of robot-assisted laparoscopic prostatectomy (RALP) versus open surgery for prostate cancer within the prospective trial LAPPRO. RALP was associated with a higher mean cost than open surgery from both the healthcare and societal perspective at 24 months. Paper IV was a prospective cohort study of cost-effectiveness for laparoscopic versus open surgery as treatment for colorectal cancer, with resource use data and unit costs derived from Swedish national registers. Laparoscopic surgery was associated with better clinical and cost outcomes from both healthcare and societal perspectives at 12 months after primary surgery.

Minimally invasive surgery can be cost saving compared to conventional open surgery. It is advisable to perform economic evaluations in routine care, as cost-effectiveness of surgical techniques most likely will change over time.

Keywords: Minimally invasive surgery, health economic evaluation, register-based, trial-based, colorectal cancer, prostate cancer, diverticulitis

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SAMMANFATTNING PÅ SVENSKA

Minimalinvasiv kirurgi har under de senaste decennierna vuxit fram som ett alternativ till traditionell öppen kirurgi. Tekniken innebär att man genom flera mindre snitt för in ett laparoskop samt kirurgiska instrument och därigenom orsakar mindre trauma för patienten under operationen och åstadkommer en snabbare återhämtning efter operationen. Förutom laparoskopisk kirurgi, kan minimalinvasiv kirurgi utföras med hjälp av en robot, vilket innebär att kirurgen sitter i en konsol och styr roboten samt instrumenten. Laparoskopisk- och robot-assisterad laparoskopisk kirurgi har visats ha i stort sett liknande fördelar för patienten. I denna avhandling har olika hälsoekonomiska utvärderingar av minimalinvasiv kirurgi och traditionell öppen kirurgi gjorts för tjock- och ändtarms samt prostatacancer och vid brusten tarmficka med varig bukhinneinflammation.

Hälsoekonomiska utvärderingar ämnar att i samma analys jämföra de kliniska och ekonomiska konsekvenserna av en ny teknik med en beprövad behandling. Dessa kan utföras med information inhämtad från kliniska prövningar eller genom register som fångar klinisk vardag. Skillnaden utgörs främst av hur man bestämmer vilka patienter som får en viss behandling; i en klinisk prövning används ofta lottning (randomisering) och i klinisk vardag bestämmer kliniska och demografiska egenskaper eller kirurgens preferenser vilken behandling patienten får. Att använda nationella register för hälsoekonomiska utvärderingar ger tillgång till en stor datamängd som kan behövas för att fånga verkliga skillnader mellan teknikerna.

I det första delarbetet jämfördes laparoskopisk och öppen kirurgi för ändtarmscancer och klinisk resursförbrukning samlades in från den randomiserade kliniska prövningen COLOR II. Från hälso- och sjukvårdens perspektiv var laparoskopisk kirurgi mer kostsam medan det från samhällets perspektiv inte förelåg en statistiskt säkerställd skillnad i kostnader vid tre år. I det andra delarbetet genomfördes en kostnadsanalys av laparoskopisk och öppen kirurgi vid brusten tarmficka med varig bukhinneinflammation där kliniska data inhämtades i den randomiserade kliniska prövningen DILALA. Laparoskopisk operation gav upphov till färre reoperationer och var mindre kostsam än öppen operation, både under ett år och under patienternas förväntade livslängd. I det tredje delarbetet jämfördes kostnader mellan robotassisterad laparoskopisk operation och öppen operation vid prostatacancer där klinisk resursförbrukning inhämtades i den kliniska studien LAPPRO. Robotassisterad laparoskopisk operation var associerad med högre kostnader såväl från hälso- och sjukvårdens som samhällets perspektiv vid 24

månader. Det fjärde delarbetet var en studie av kostnadseffektivitet mellan laparoskopisk och öppen operation vid kolorektalcancer. Klinisk resursförbrukning samlades in med hjälp av flera svenska nationella register. Laparoskopisk kirurgi var associerad med lägre kostnader och bättre kliniska utfall från både hälso- och sjukvårdens som samhällets perspektiv upp till och med ett år efter primäroperationen.

Resultaten i denna avhandling tyder på att minimalinvasiv kirurgi kan vara kostnadsbesparande i jämförelse med traditionell kirurgi vid tjock- och ändtarmscancer samt vid brusten tarmficka med varig bukhinneinflammation. Det är viktigt att använda register för att följa upp kliniska och hälsoekonomiska utfall i klinisk vardag eftersom kostnadseffektivitet kan förändras över tid, framförallt för kirurgiska tekniker som innebär en inlärningskurva för kirurgen och en implementering i hälso- och sjukvården.

LIST OF PAPERS

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

I. **Health economic analysis of costs of laparoscopic and open surgery for rectal cancer within a randomized trial (COLOR II).**
Gehrman J, Björholt I, Angenete E, Andersson J, Bonjer J, Haglind E. *Surgical endoscopy* 2017;31:1225-34.

II. **Health economic analysis of laparoscopic lavage versus Hartmann's procedure for diverticulitis in the randomized DILALA trial.**
Gehrman J, Angenete E, Björholt I, Bock D, Rosenberg J, Haglind E. *The British journal of surgery* 2016;103:1539-47.

III. **Health economic analysis of open and robot-assisted laparoscopic surgery for prostate cancer within the prospective multi-centre LAPPRO trial.**
Forsmark A, Gehrman J, Angenete E, Bjartell A, Björholt I, Carlsson S, Hugosson J, Marlow T, Stinesen-Kollberg K, Stranne J, Wallerstedt A, Wiklund P, Wilderäng U, Haglind E.
Submitted manuscript

IV. **Laparoscopic surgery was associated with fewer complications and lower costs in routine Swedish care.**
Gehrman J, Angenete A, Björholt I, Lesén E, Haglind E. *Manuscript*

CONTENT

ABBREVIATIONS

CBA	Cost-benefit analysis
CEA	Cost-effectiveness analysis
CUA	Cost-utility analysis
CMA	Cost-minimization analysis
DILALA	DIverticulitis – LAparoscopic LAvage versus resection (Hartmann's procedure) for acute diverticulitis with peritonitis
ICER	Incremental cost-effectiveness ratio
MIS	Minimally invasive surgery
PPP	Purchasing power parity
QALY	Quality adjusted life year
RALP	Robot-assisted laparoscopic radical prostatectomy
SCRCR	Swedish Colorectal Cancer Register (Svenska kolorektalcancerregistret)
TLV	Tandvårds- och läkemedelförmånsverket (The Dental and Pharmaceutical Benefits Agency)

1 INTRODUCTION

Swedish municipalities and counties spent at least 22 billion SEK in 2016 on medical devices and according to TLV (Tandvårds- och läkemedelförmånsverket) spending is increasing. In comparison, the cost for subsidizing pharmaceuticals in Sweden was 25 billion SEK the same year. Surgery, anesthesia and intensive care make up 14% of the market for medical devices. It is mainly at the discretion of the Swedish municipalities and counties themselves to decide which medical devices to invest in, whereas the pharmaceutical and consumables industries face demands to submit evidence of clinical and cost effectiveness to relevant government agencies to get their products approved. According to TLV, some municipalities and counties do their own evaluation of the clinical research, but often there is a lack of a formal evaluation of cost-effectiveness[1].

Minimally invasive surgical procedures stem from the ambition to cause less trauma for the patient, and to improve clinical outcomes and post-operative recovery. Laparoscopic surgery originated as a diagnostic tool and became a technique used in surgical procedures in the 1980's, but did not receive widespread use until the 1990's[2]. The first surgical robot was approved by the U.S. Food and Drug Administration (FDA) in the early 2000's[3] and has since been implemented for several disease conditions. According to 2017 data almost 4500 robotic systems exist worldwide[4]. Intuitive Surgical Inc. (Sunnyvale, California) has dominated the market for abdominal surgical robots since the FDA approval. This could be about to change; some patents have recently expired and in 2017 a new surgical robot was demonstrated and more are ready to enter the market[5].

1.1 BACKGROUND

Health economic evaluations of laparoscopic and open surgery as treatment for colorectal cancer have been studied in multiple settings and countries for nearly 30 years and as a result a vast body of literature exists. Some studies have utilized data from single randomized, controlled trials and included costs as a secondary end-point[6,7], while others have had health economic evaluation as the primary aim[8-12]. The two randomized, controlled, multicentre studies by Janson et al and Franks et al both used the health economic methodology recommended by most guidelines. Resource use and unit costs were presented separately, indirect costs were included, reporting was transparent and the possibility of including clinical effectiveness in the analysis was discussed,

although not performed because no differences were evident. Both studies analysed costs accumulated during three months after index surgery and the studies showed no significant differences. Franks et al found that resource use in the operating theatre was costlier for laparoscopic surgery, but total hospital cost was lower. Janson et al found that productivity loss was less costly for laparoscopic colon surgery, but operating room cost was higher.

Most literature about economic evaluations of minimally invasive surgery for colorectal cancer is based on non-randomized data[13-27]. Two prospective, non-randomized studies with standard health economic methodology were performed in the U.K., using data from a prospective trial. The study by Dowson and colleagues[19] included 201 patients with colorectal cancer, polyps, Crohn's disease and ulcerative colitis. The study by Jordan et al.[15] utilized data from the same study, but focused solely on 95 patients with colon cancer and polyps. In both studies important and relevant resource use was identified, measured and valued in accordance with the aim and perspective of each study. Sick-leave cost was not included in either of the two studies because of practical difficulties in retrieving relevant information. There was no need for adjustments due to differential timing as resource use was assigned unit costs at the end of the study and patient follow-up was 6 weeks. Dowson and colleagues did not assess selection bias or confounding but concluded this was not necessary as baseline characteristics between treatments were the same. A non-significant total cost difference between laparoscopic and open surgery was found. The study by Jordan and colleagues used the same resource use and unit costs as Dowson et al. but utilized quality of life data (EQ-5D) collected within 28 days after index surgery. While total costs were not significantly different between the groups, a difference in QALYs (quality-adjusted-life-years) of 0.011 in favour of laparoscopy was observed over the first 28 days. This difference made an analysis of the incremental cost per incremental QALY possible. The incremental cost-effectiveness ratio was £12375 per QALY, and at a threshold of £20,000, cost-effective compared to open surgery. This is the standard outcome measure in health economics to compare a new treatment with a conventional treatment.

Some non-randomized studies that have utilized data from databases and/or registers for analysis have been identified[28-33]. Govaert and colleagues[29] used a population-based database in the Netherlands and included 6530 patients with colorectal cancer surgery during 2010-2012. Laparoscopic surgery for rectal cancer was associated with a higher cost, but not for colon cancer surgery. The authors did not adjust for potential influence of confounding variables and sick-leave costs were not measured. In a third study[30] a nationwide inpatient database was reviewed to find patients undergoing colorectal surgery

(colorectal cancer, polyps, diverticulitis, etc) during 2013 in the U.S.A propensity-score matching technique was used to match 6343 patients operated by laparoscopic and open surgery. Laparoscopic surgery was associated with lower mean costs than open surgery. One limitation of the study was the mix of different diseases. Sheetz and colleagues[31] analysed Medicare expenditures associated with laparoscopic and open colorectal surgery, including colon cancer, diverticular disease and inflammatory bowel disease. An instrumental variables approach was used as the direct effect of laparoscopic surgery (exposure) on costs (the outcome) was expected to be biased by unobserved confounding. Use of laparoscopic surgery in the region where the patient was operated on was chosen as instrument for laparoscopic surgery. First, the unbiased part of laparoscopic surgery was isolated, then the isolated part was used to estimate the local treatment effect of laparoscopic surgery on Medicare expenditures. The study included 428,799 Medicare beneficiaries undergoing laparoscopic surgery (133,528) or open surgery (295,271) between early 2010 and late 2012. In one analysis laparoscopic surgery was associated with significantly lower costs; when using the instrumental variable approach the difference between open and laparoscopic surgery was less but still significant. One limitation of the study was that it did not include patients with rectal cancer.

A few model-based economic evaluations of laparoscopic compared to open surgery exist[34,35], where data is synthesized from different sources and a decision analytic model is used to estimate costs and effects for different clinical pathways. De Verteuil and co-authors[35] constructed a Markov-model to illustrate cost-effectiveness covering 25 years. After a review and meta-analysis of the literature, they found a small difference in survival, no difference in quality of life, but slightly higher cost (£300) after laparoscopic colorectal cancer surgery than after open surgery. However, they concluded that laparoscopic and open surgery are most likely similar in terms of long-term survival and disease-free survival, but demonstrated some short-term benefits of laparoscopic surgery, which were not captured in their model. With only a modest gain of 0.01 in QALYs, laparoscopic surgery would be considered as cost-effective at a threshold value of £30,000.

RALP for prostate cancer is by most accounts costlier than both laparoscopic and open surgery. According to a recent, comprehensive literature review[36], 17 of 18 studies found a higher cost for RALP from the healthcare perspective, 12 out of 16 studies from the payer's perspective, while 4 studies conducted from the societal perspective had mixed results. Two studies from the societal perspective assessed the additional cost/additional health effect as A$24,000/QALY gained and €78,000/successful treatment; one study found

medical spending to be higher after RALP and the other found a cost reduction. Further, the systematic review concluded that the quality of evidence was in general moderate to low and all included studies were observational.

Economic evaluations of laparoscopic lavage, as treatment for complicated diverticulitis, are scarce. To date there are only two and one is included in this thesis (paper II). The other study[37] found that laparoscopic lavage compared to sigmoid resection was less costly, although the difference was not statistically significant. One other alternative exists as treatment for complicated diverticulitis with purulent peritonitis; primary anastomosis with or without a temporary ileostomy. One randomized controlled trial compared the costs of primary anastomosis with stoma formation and Hartmann's procedure and found the former less costly than the latter[38].

1.2 HEALTH ECONOMIC EVALUATION

One of the definitions of economics infers that choices about resource allocation must be made as resources are scarce and have alternative uses[39]. In health economics, a sub-discipline of economics, this definition is particularly true. Healthcare resources are limited and decisions regarding allocation of resources must be made. The cost of a resource is best valued in its best alternative use (i.e. opportunity cost).

One tool to guide decision-makers on the best way to allocate healthcare resources is health economic evaluation. The perhaps most widely used definition of economic evaluation is defined by Drummond and co-authors (p. 4) as *"the comparative analysis of alternative courses of action in terms of both their costs and consequences"*[40]. This is done by comparing the opportunity costs and health effects of two or more alternatives and can be done in four different frameworks, where the main difference is what measure of health effect is the focus:

- Cost-effectiveness analysis (CEA): the health effect is common to both treatments evaluated and is expressed as a physical unit of effect, for example life-years gained.
- Cost-utility analysis (CUA) uses a generic measure of health effect that takes into account both time spent in a health-state and the health-related quality of life for that health-state, known as quality-adjusted life-years (QALY)
- Cost-minimization analysis (CMA) implies that two treatments achieve equivalent health effects

- Cost-benefit analysis (CBA) involves that health effect are valued in monetary terms.

The implications of a CUA compared to a CEA is that the resulting cost per QALY can be compared across all different disease conditions as it uses a generic measure of health effect, whereas the result of a CEA can only compare treatments with the same specific measure of health effect. While both CEA and CUA values health effects in terms of nonmonetary units, a CBA values it in monetary units. The advantage of a CBA is that the results of healthcare programmes or interventions can be compared to other programmes and interventions in different sectors of society. Traditionally CBA has not been used as extensively as CEA/CUA in healthcare, but more often in the evaluation of environmental programmes[41].

One framework to illustrate the results from a CUA or a CEA is the incremental cost-effectiveness ratio (ICER), the incremental cost divided by the incremental effect results in the added cost of the added effect. If a new treatment A, is compared to the conventional alternative B, and the measurement of health effect is QALYs the ICER can be compared to a threshold value, λ. This represents what a decision-maker is willing to pay for one additional QALY; if the ICER is equal to or below this value the new treatment can be recommended to be adopted.

$$\text{ICER} = \frac{\text{Cost}_\text{A} - \text{Cost}_\text{B}}{\text{QALY}_\text{A} - \text{QALY}_\text{B}} = \frac{\Delta\text{Cost}}{\Delta\text{QALY}} \leq \lambda$$

The threshold in Figure 1. is represented by the slope of the straight line (λ), in this case one additional unit of effect is valued (cost/QALY) at 500,000 SEK. There are roughly four outcomes of both a CEA and a CUA, indicating that the new treatment compared to the conventional treatment is:

- More effective and costlier (1a and 1b)
- Less effective and costlier (2.)
- Less effective and less costly (3.)
- More effective and less costly (4.)

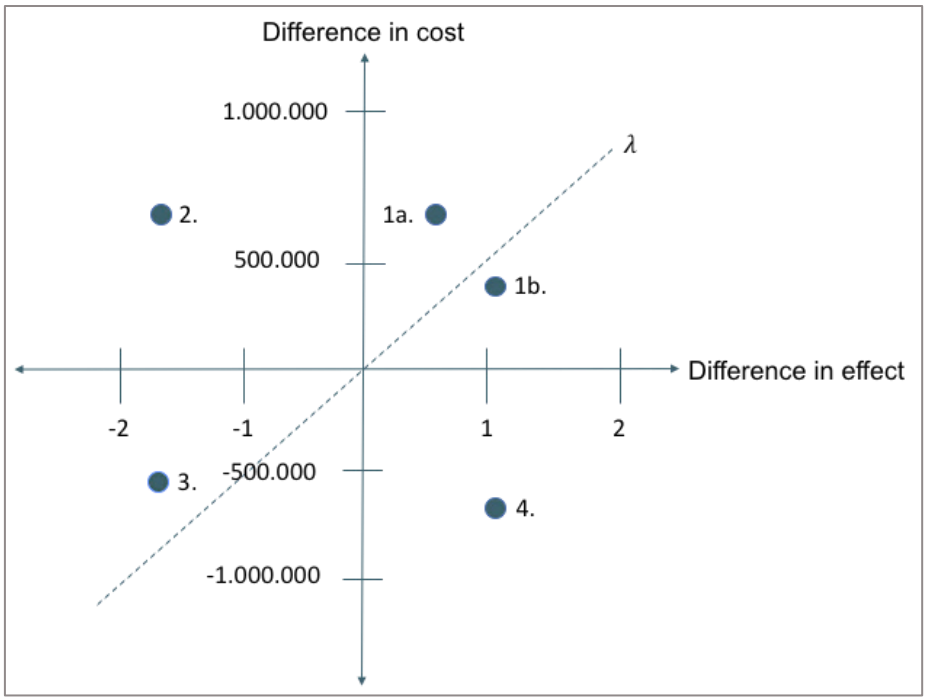

Figure 1. The cost-effectiveness plane, with difference in effect on the x-axis and difference in cost on the y-axis. The incremental cost-effectiveness ratios are represented by the dots and the threshold by the straight line, λ.

If the point estimate of the ICER falls into the upper left corner (2.) in Figure 1 the recommendation to decision-makers is that the new therapy should not be implemented, it is costlier and does less. In the lower right quadrant (4.), the new treatment costs less and does more, and should be recommended to be implemented. If the point estimate falls into the upper right (1a. and 1b.) or lower left (3.) it is desirable to compare cost and effect jointly, as there is a trade-off between cost and effect. Assuming that the threshold value (λ) in Figure 1. is true, the dots situated below the threshold (1b. and 4.) are considered cost-effective compared to the alternative treatments, and dots above (1a., 2. and 3.) are not considered cost-effective relative to the comparison treatment.

CMA is a debated form of economic evaluation (sometimes addressed as a partial economic evaluation), as it is not often the case that two treatments are truly equivalent. Some have pointed out that a CMA is only relevant, if it is conducted alongside an non-inferiority trial[42]. The rationale is that non-inferiority or equivalence trials are designed to evaluate the hypothesis that one

treatment is non-inferior to another treatment, i.e. not the regular two-sided hypothesis test. Further, because cost and clinical effectiveness should be tested jointly to investigate uncertainty, others suggest that CMA is not relevant even then[43]. Dakin et al[43], concluded that CMA can still have a role to play if the difference in cost is "sufficiently" large between treatments that plausible values of effectiveness as analysed in uncertainty analysis would not change this.

1.2.1 COST ANALYSIS

Regardless of whether CUA, CEA, CMA or CBA is the appropriate method, the basic task of costing is common to all methods:

1. Identify which type of resource use to include

2. Measure how many resource units are used per patient/treatment

3. Value resource use in monetary units (price weight/ unit cost)

The perspective of the analysis is important when identifying the resource use categories to include in the study, as a cost to one stakeholder can be a saving to another. Society is generally the preferred viewpoint of a health economic analysis[44]; it is the most comprehensive perspective and costs can be divided into sub-categories such as healthcare or patient costs. If all relevant treatments are compared, those common to all treatments can be eliminated and the focus can be on collecting data on resource use that is expected to differ between treatments. As it is the difference between treatments that is of primary interest, all costs common to both treatments will cancel each other out. Furthermore, it is not as important to spend time on collecting data on relatively small amounts of resource use, as they will make little or no difference to the result of the study[40].

Micro-costing implies that each item of interest is quantified at the patient-level, for example all resources consumed in an operating room during surgery. At the other end of the spectrum is gross-costing, where resources are aggregated into a meaningful unit. An example of this is a cost per diagnosis-related group (DRG). This will typically capture the cost per average patient with the same diagnosis, but not that of the actual inpatient stay for the patient in question. Which method to use typically depends upon the trade-off between precision and time available to spend and the relative importance of the resource use category itself[45].

Obtaining the value of a resource use category involves multiplying the resource use by the value (price weight/unit cost). As unit costs reflecting opportunity costs are often not readily available, the pragmatic solution is to use the best obtainable unit costs. Considerations include: the level of resource use collected (national, local or international), the perspective of the analysis (society, healthcare etc.), the time it takes to collect and the type of resource that is costed (inpatient vs. outpatient)[46]. Often used unit costs are DRG-payments, centre-specific unit costs (from one or several centres), the average wholesale price for pharmaceuticals and trial-specific unit costs (including accounting data). If patients are followed-up or enrolment carries on beyond year one in a study, it is common to adjust costs and health effects for differential timing and inflation. The first means that resource consumption is valued differently depending on when it is consumed and the latter refers to the fact that prices generally increase over time[45].

1.3 FRAMEWORK FOR HEALTH ECONOMIC EVALUATION

A health economic evaluation can be conducted based on data from a single randomized clinical trial or observational study. Alternatively, data can be synthesised from different sources including several clinical trials and/or observational studies, expert opinions and/or surveys. A model that suits the conditions in a specific region or a specific decision problem can then be applied. More common is a combination of collecting data within a single trial or study and collecting data from different sources. As an example, if the time horizon in a single clinical trial is not long enough to estimate the full health effect and cost of treatment, then modelling cost and clinical effectiveness beyond the cessation of the trial is warranted[47,48].

In this thesis clinical resource use and clinical effectiveness were based mainly on a single clinical trial in papers I-III, while unit costs were derived from several sources. In paper II a model to analyse cost beyond the clinical trial was used in a secondary analysis. Paper IV is a register-based study where clinical resource use, unit costs and clinical effectiveness were derived from several register-based sources. Various aspects relating to performing health economic evaluations alongside single clinical trials or register-based studies, e.g. randomized and observational study design, sample size and length of follow-up, are presented below.

1.3.1 TRIAL-BASED

The gold standard for clinical study design is the randomized controlled trial (RCT). It accomplishes high internal validity as randomisation balances both observable and unobservable patient characteristics between treatments. Randomisation is used to identify causal inference and to ascertain that a relationship is causal[49]. Non-randomized controlled trials do not allow for identifying causal inference, but still hold merit as, for example, they include a relevant control group and an identical way of comparing outcomes[50].

The advantages of clinical trials could, at least in theory, be applied to health economic evaluations alongside a randomized clinical trial.[40,45] A randomized study design means that patient-level data of clinical effectiveness have high internal validity[40]. Moreover, data from randomized clinical trials typically comprise the latest available evidence, especially early or before implementation of a treatment. It is also relatively inexpensive to add a study objective of health economic evaluation to a clinical trial, as data retrieval of clinical efficacy or effectiveness can be accompanied by additional questions regarding important clinical resource use and facilitate an economic evaluation[40,47,51].

There are, however, several challenges when conducting an economic evaluation alongside a single clinical trial[52]. It is desirable that a relevant comparator treatment is given to the control group as an alternative to the treatment being investigated. Omitting such an alternative can entail that the new treatment is not compared to the most cost-effective treatment, and the results are not informative. Furthermore, there are often several treatment options in place at the same time and randomized clinical trials rarely incorporate all treatments in one trial.

Another implication for health economic evaluation is that clinical trials more commonly capture intermediate health outcomes that do not necessarily translate into final outcomes such as morbidity or mortality, which is desirable in economic evaluations. There are no willingness-to-pay standards for intermediate health effects and thus not relevant for policy decisions[45]. Follow-up is another potential shortcoming of clinical trials, as it is often too short to capture all meaningful economic considerations[51].

Furthermore, sample size calculation in clinical trials is based on the primary clinical end-point and may be underpowered to detect meaningful differences in economic outcomes such as resource use and health-related quality of life. Moreover, resource use data (and costs) are typically right-skewed as many

patients incur no resource use (e.g. readmission or reoperation) and some patients incur very high resource use (e.g. several reoperations). Analysing arithmetic mean costs is desirable from both a budgetary and social efficiency perspective, but the arithmetic mean in a small sample with non-normal distribution can potentially bias the analysis[45].

The fact that trial patients are often more closely monitored and examined can create "protocol-driven resource use". As an example, if protocol stipulated that patients enrolled in a trial should be examined by a doctor once a month it would probably lead to discovery and consequently treatment of more diseases than would be the case in routine care[45].

1.3.2 REGISTER-BASED

Using observational data, in health economic evaluations as well as in clinical research has gained increased attention during the last decade[49,53,54]. The umbrella term for these kinds of data is real-world data and is defined differently by different entities. The most common definition is data collected outside of conventional RCTs; examples include registers, electronic health records, and social media. Register-based data and observational study design is the most common source and study design respectively, when the term real-world data is used in literature, according to a recent review[55].

It is widely recognized among clinical researchers and health economists that data from other sources than clinical trials can provide important complementary information. When clinical trials enrol too few patients or do not have an appropriate follow up to register late occurring or rare adverse events or when disease epidemiology is examined, registers are often used[49,56]. Healthcare registers can also be linked together from different sources and provide information for large numbers of patients. Compared to randomized clinical trials, the use of healthcare registers allows for more refined statistical methods as additional clinical and demographic information for a wide range of patients is available to account for risk factors and comorbidities[49,54].

Some of the potential benefits of using healthcare registers could be attributed to surgical interventions rather than pharmaceuticals. The learning curve of individual surgeons and the uptake of a surgical technique could have a potential impact on both outcomes and costs. While some might argue that the learning curve should be incorporated in the cost of adopting a new technique, others might want evidence of the cost-effectiveness when the learning curve has reached a plateau. Randomized, controlled trials are typically performed in the beginning of the learning curve, when uptake is limited, and the cost-

effectiveness reported might not be representative of the technique at a later stage[57]. Furthermore, a new surgical technique may result in improvements to patients progressively, e.g. minimally invasive surgery improves short-term recovery that could improve longer-term outcomes, but randomized controlled trials may have too short follow-up or include too small a sample to capture this.

All the above is dependent upon the registers' validity and degree of coverage. Register-based studies lack the stringency of RCTs which makes it difficult to handle problems associated with causal inference such as confounding, which compromises internal validity. Further limitations are the lack of prospective planning and collection of data[58-60]. Different statistical methods have been utilized to handle measured confounding, including regression analysis and matching[61]. Regression analysis aims to adjust clinical or economic outcomes, according to baseline differences in clinical and demographic characteristics. Matching tries to find a matching pair of patients in the treatment and control group, with similar observed characteristics that affect the outcome. Propensity score implies that the probability for a patient to receive one treatment over another (or no treatment) is estimated by applying clinical and demographic variables. Patients' outcomes can then be compared by matching or other techniques using the propensity score[62]. A recent Cochrane review[63] concluded that observational studies and RCTs lead to comparable results in terms of healthcare outcomes even after accounting for a difference in study design. The authors evaluated methodological reviews that compared observational studies and RCTs that addressed the same outcomes.

1.4 MINIMALLY INVASIVE SURGERY

Below is a brief description of the evidence base for minimally invasive surgery as treatment in the fields of colorectal and prostate cancer as well as diverticulitis.

1.4.1 COLORECTAL AND PROSTATE CANCER

Among new cancer cases worldwide prostate and colorectal cancer are the second and third most common in men, while colorectal cancer is the second most common among women. In 2012 there were 1.4 million new colorectal cancer cases and 694,000 died from the disease, while for prostate cancer the corresponding numbers were 1.1 million and 307,000 respectively[64].

The median age of patients with colorectal cancer was 70 years at diagnosis, and relative 5-year survival was 65% in the western world, but this varies

according to disease stage. In the U.S., for example, the distribution across disease stages were 90%, 69% and 12% for localised, regional and distant spread of the disease respectively[65]. In lower income countries relative 5-year survival was below 50%. Surgery is the primary curative treatment sometimes combined with radio(chemo)therapy. Open, laparoscopic and robot-assisted laparoscopic surgery techniques are used. Robot-assisted laparoscopic surgery and laparoscopic surgery seems to offer similar benefits to rectal cancer patients, according to the only large, randomized, controlled trial[66]. There is one colon cancer RCT which compares the two techniques and concludes that robotic assisted surgery is effective, but provides no clinical benefit compared to laparoscopic surgery[67]. Several randomized, controlled trials have concluded that laparoscopic surgery for colon cancer offers benefits such as less use of analgesics after surgery[68,69], earlier return of bowel function[12], less intraoperative blood loss[68], shorter length of hospital stay[68] and higher quality of life 30 days after surgery[70]. Clinical trials have also established no significant difference in long-term overall survival and recurrence[69,71,72]. Concerning rectal cancer, laparoscopic surgery has been shown to be as safe and effective as open surgery[71,73] with similar positive short-term outcomes as for colon cancer[74]. Two smaller RCTs have failed to demonstrate non-inferiority of laparoscopic surgery as compared to open surgery[75,76].

Treatments for localised prostate cancer vary substantially according to the prognosis. Low-risk disease can be actively surveilled and treatment can be avoided entirely, with only a 1% risk of prostate cancer-related death in 10 years. Men with intermediate to high-risk disease can undergo radical prostatectomy, although erectile dysfunction and urinary incontinence are common complications affecting quality-of-life[77]. Furthermore, brachytherapy and external-beam radiotherapy can also be used to treat intermediate to high risk disease. Advanced disease is not treated with surgery, but other options exist[78]. Laparoscopic radical prostatectomy has been concluded to be inferior to robot-assisted laparoscopic radical prostatectomy (RALP) [79,80] in two review articles. Open retropubic radical prostatectomy (RRP) and RALP were compared in one large prospective, controlled trial and a difference in erectile function was found, 75% vs. 70% at one year and 74% vs. 68% at two years. No statistically significant difference in surgical margins or urinary continence was found one and two years after index surgery[81,82].

1.4.2 DIVERTICULITIS

Diverticulosis of the colon is common in the western world; prevalence increases with age. It is most often asymptomatic (70%), but inflammation (10-25%) can lead to perforation and consequent peritonitis, a life-threatening

condition. The risk of developing diverticulitis following diverticulosis has been reported to be 4.8%[83] and 7%[84], or 4.8 to 6 detected cases in 1000 follow-up years.

Diverticulitis can be split into complicated and uncomplicated; the former sometimes requires surgery (20-25%). Complicated diverticulitis is classified according to disease severity according to several different classifications such as the Hinchey classification[85]. Emergency surgery is required for Hinchey grades III and IV and standard treatment has been colon resection with creation of a stoma (Hartmann's procedure)[86]. Five RCTs have evaluated a new technique involving laparoscopically rinsing of the abdominal cavity with saline until return of clear fluid[86], a method first described by O'Sullivan[87].

2 AIM

The overall aim of this thesis was to compare minimally invasive surgical methods with conventional open surgery in terms of clinical effectiveness and cost. The particular aims of the studies included in this thesis were:

- To compare the cost of laparoscopic and open surgery for rectal cancer within a randomized controlled trial COLOR II (Paper I)
- To evaluate the cost-effectiveness of laparoscopic lavage versus Hartmann's operation for complicated diverticulitis (Paper II)
- To analyse the cost-effectiveness of robot-assisted laparoscopic surgery as compared to open prostatectomy for curative prostate cancer surgery (radical prostatectomy) (Paper III)
- Using data from routine care to compare the cost-effectiveness of laparoscopic and open surgery for colorectal cancer. (Paper IV)

3 PATIENTS AND METHODS

3.1 CLINICAL STUDIES AND EFFECTIVENESS

Papers I and II were conducted alongside two randomized, multicentre, controlled trials: one large (COLOR II) and one smaller (DILALA). Paper III was based on one large non-randomized, multicentre, controlled, trial (LAPPRO) and paper IV was designed using one large observational, register-based, prospective study. In a health economic evaluation it is desirable to include the health effects and their costs in one analysis, e.g. cost-effectiveness or cost-utility analysis. This was not required in this thesis as measures of quality-of-life and clinical outcomes, such as mortality and morbidity, were not different between the techniques. An overview of the clinical studies and patients included in paper IV is available in Table 1.

In paper I resource use data collected in the COLOR II-trial was applied in the analysis. The trial enrolled 1044 patients with rectal cancer who were randomized 2:1 laparoscopic and open surgery respectively. Data on time in anesthesia and recovery room was collected retrospectively from the Swedish patients in the study, who were operated on at Sahlgrenska university hospital (n=105). Sick-leave data from the Swedish insurance agency were collected for the sub-set of COLOR II patients, who were included in Sweden and who were working at the time of onset of disease (n=251). The COLOR II-trial was based on demonstrated non-inferiority between the two techniques in local recurrence. No differences in survival, morbidity or quality of life outcomes were observed[73,74,88,89].

In paper II resource use was derived from the DILALA-trial, randomising patients with perforated diverticulitis with purulent diverticulitis to laparoscopic lavage (43 patients) and Hartmann's operation (40 patients). The DILALA-trial demonstrated a statistically significant difference in patients with at least one reoperation in favour of laparoscopic lavage (28% vs. 63%). No difference in survival or quality of life outcomes were observed compared to open surgery (Hartmann's procedure)[86,90].

In paper III clinical resource use was collected as part of the LAPPRO trial. Patients with prostate cancer were recruited to undergo robot-assisted laparoscopic radical prostatectomy (RALP) and open retropubic radical prostatectomy (RRP). To avoid learning-curve effects, only patients operated by a urologist, who had performed at least 100 operations, were included in the base case analysis. In total 2638 patients was eligible for the health economic

evaluation, 803 in the RRP group and 1835 in the RALP group. Secondary analysis included all operations regardless of the operating urologists' experience and included 916 patients and 2700 patients in the RRP and RALP group respectively.

Table 1. Information on clinical studies and patients in Paper I-IV

Paper	Study design/ follow-up	Surgical technique/ disease	Sample size	Clinical effectiveness
I	RCT (COLOR II)/ 3 years	Laparoscopic versus open surgery/ rectal cancer	1044: 699 lap 345 open	Non-inferiority was demonstrated in local recurrence, comparable levels of overall and disease-free survival and morbidity as well as health-related quality of life
II	RCT (DILALA)/ 1 year	Laparoscopic lavage versus open surgery/ complicated diverticulitis with purulent peritonitis	83: 43 lap 40 open	Lavage was more effective in terms of patients with at least one reoperation, no significant difference in survival or health-related quality of life
III	Non-randomized prospective, controlled, trial (LAPPRO)/ 2 years	Robotic versus open surgery / prostate cancer	2638: 1835 robot 803 open	A difference in erectile dysfunction 70 vs 75% at 12 months after surgery and 68% vs. 74% at 24 months after surgery
IV	Non-randomized prospective, register-based, study/1 year	Laparoscopic versus open surgery / colorectal cancer	7764: 1647 lap 6060 open	A difference in clinical effectiveness (composite end-point) was demonstrated

Abbreviations: RCT= randomised controlled trial, lap=laparoscopic surgery, robot=robot-assisted laparoscopic surgery

In paper III results after two-year follow-up indicated a difference in erectile dysfunction 68% vs. 74%[82]. Thus, a cost-effectiveness analysis of the cost per avoided case of erectile dysfunction between 0 and 24 months could have been

possible. It was, however, decided that this analysis was not meaningful due to the small difference in treatment effect relative to the large number of patients experiencing the complication of prostate cancer surgery in both groups. Further, although the difference in erectile dysfunction was observed, self-assessed quality-of-life outcomes did not differ between the surgical techniques at 3, 12 or 24 months[77].

In paper IV the basis for clinical resource use between open and laparoscopic surgery was collected from the Swedish Colorectal Cancer Registry (SCRCR), for patients with colorectal cancer undergoing surgery in 2013 and 2014. After exclusion of locally advanced tumours, 7707 patients were included; 6060 in the open surgery group and 1647 in the laparoscopic surgery group. A composite clinical end-point including resource-consuming events in inpatient care, readmissions and mortality was chosen as a measure of clinical effectiveness. From 90 days and up to 365 days only events predefined as related to colorectal cancer surgery were included This end-point was statistically significantly different in favour of laparoscopic surgery. The cost analysis also showed that costs were significantly different in favour of laparoscopic surgery. Quality of life was not included in the register at the time of the study. Laparoscopic surgery was dominant in both clinical end-point and cost and no joint analysis was therefore warranted.

3.2 METHODOLOGICAL CONSIDERATIONS

Some advantages and limitations of conducting a health economic evaluation alongside a single clinical trial or register-based study were described in chapter 1. These aspects are discussed below with reference to the papers in this thesis.

3.2.1 FRAMEWORK

A strength of a trial-based economic evaluation based on randomized data is that randomisation allows for causal inference regarding clinical effectiveness and resource use. Furthermore, they comprise the first or latest evidence for clinical resource use and effectiveness, as they are typically conducted to prove efficacy and safety before approval in routine care. In the case of paper I and II both laparoscopic rectal resection and laparoscopic lavage were somewhat novel treatments, which had been performed for some time, but not evaluated in randomized settings. Thus, both papers offer high quality evidence on clinical effectiveness. They were conducted in a multicentre setting, which improves the external validity of the results. In paper III and IV, the health economic evaluations were not based on a randomized clinical study design.

In the case of the LAPPRO trial it was not feasible to randomize patients, because they were allocated to each treatment according to what surgical technique was performed in the region where patients resided. However, it is the largest, interventional, prospective study involving robot-assisted surgery for prostate cancer. In paper IV, the aim was to compare laparoscopic and open surgery in routine care, and it was not possible to apply randomized allocation of patients.

A limitation of health economic evaluations conducted alongside a randomized controlled trial is that not all comparators are always included. It can be argued that not all relevant comparators were included in the papers in this thesis, such as robot-assisted surgical technique in papers I and IV, primary anastomosis with or without temporary ileostomy for complicated diverticulitis in paper II and conventional laparoscopic technique in paper III. However, at the time that data collection started in paper I (2004), robot-assisted laparoscopic colorectal surgery was not performed. In paper IV the Swedish Colorectal Cancer Register had not yet began to distinguish robot-assisted laparoscopic from conventional laparoscopic procedures until the second year of the study (2014). It was decided to include robot-assisted procedures as conventional laparoscopic for the first year. Primary anastomosis with or without the creation of a temporary ileostomy was not included as treatment for complicated diverticulitis in the DILALA trial. It has previously been included in one cost analysis[37], and was shown to be costlier for the index surgery than Hartmann's procedure and laparoscopic lavage. Costs accumulated during one year after index surgery was not presented for Hartmann's procedure and primary anastomosis separately. It was therefore not possible to determine whether it was less costly than Hartmann's operation at one year follow-up. However, laparoscopic lavage was less costly than both procedures, but the difference was not significant. In another randomized controlled trial primary anastomosis with diverting ileostomy was compared with Hartmann's procedure for patients with Hinchey grade III and IV and resulted in lower hospital costs, although the difference was not statistically significant. Based on available evidence, it is uncertain whether primary anastomosis with or without ileostomy, is less costly than Hartmann's procedure. Conventional laparoscopic surgery exists as treatment for prostate cancer, however it is not extensively used. As a result, the two most relevant surgical techniques for prostate cancer are included in paper III.

Patients are often subject to more rigorous follow-up during a trial than in routine care and the cost of this should not inflate resource use in trial-based economic evaluations compared to routine care. As an example, if several diagnostic tests are a product of the need to monitor patients and not likely to

be performed in routine care, they should be excluded from the health economic evaluation. Inflated resource use involves two considerations: which resource use categories should be included and, if they are included, what kind of resources should be collected. For example, should time in anesthesia be included in the cost for the operating theatre? The latter is discussed in detail later in this thesis and the former could be ruled out by considering if a kind of resource use is likely to be included in routine care or if it is a product of the need to monitor patients more closely during the trial. This was deliberated on in the designing of papers I through III. In paper IV the costing level did not allow for such considerations, because resource use was collected at an aggregated level. It could be argued that it was not necessary as paper IV was based on routine care data and protocol-induced cost was not present.

Economic evaluation should include final health outcomes, such as morbidity or mortality. Ideally patient follow-up should last as long as clinical or economic outcomes can be associated with the initial treatments studied, or when resource use returns to its preoperative levels. Because all economic evaluations in this thesis aim to compare treatments affecting survival, it is relevant to consider whether extending follow up beyond the clinical trial would be relevant. For colorectal cancer, no robust evidence is available on differences between surgical techniques on the impact of mortality. For example, when COLOR II was initiated it was hypothesised that laparoscopic surgery could lead to increased survival compared with open surgery. This has not been confirmed in any of the large randomized, controlled, multicentre trials that have presented their long-term results and the same applies to long-term morbidity. In papers I and IV the analyses assume the difference in health outcomes and costs occur during the clinical study periods and no extrapolation of data is carried out. In paper II, on the other hand, costs are estimated during the patients' expected lifetime, since stoma appliances are influenced by which technique is initially chosen and is expected to continue to differ after the cessation of the trial. Further, because laparoscopic lavage is a novel treatment without long-term clinical data and since affected bowel segment are not resected, initial concerns were raised regarding the possibility of missing a cancer. A model was utilized to estimate future expected costs of sigmoid resection for patients in the laparoscopic lavage group.

The sample size of a trial-based economic evaluation is often smaller than in a study using register-based data. In paper I, although the overall sample size was 1044 patients (699 in the laparoscopic group and 345 in the open surgery group), sick-leave data was only collected for a sub-set of trial patients (n=261). It was hypothesized after the health economic study that the sample size was too small to detect a difference in sick-leave. Further, the difference

in incidence of colostomy (a costly resource use category) diffused the results and was a product of a too small sample size, due to a numerical difference between surgical techniques in abdominoperineal resections. In papers III and IV sick-leave was examined in larger sample sizes; it was an important contributor to total cost in paper III, but not in paper IV. Abdominoperineal resection (which inherently leaves the patient with a colostomy) was included in paper IV and did not skew the results of the health economic evaluation in the same way as in paper I.

The effects of the learning curve and uptake of a new surgical technique can have impact on both health effect and costs. This was not studied explicitly in paper I and IV, but a case can be made that it was to some degree implicitly included. In paper I, laparoscopic surgery for rectal cancer was a relatively new technique and not implemented to a large degree in routine care, at least not in Sweden. The COLOR II trial required assessment of either recorded images or live observations of at least five laparoscopic cases. The centre, not the individual surgeon, was then invited to participate in the trial. In paper IV, on the other hand, uptake of the laparoscopic technique in Sweden had increased to 25% of all operations and the learning curve had come close to levelling out. In paper III the primary analysis included only operations performed by urologists with prior experience of at least 100 operations to avoid learning curve effects having a differential treatment effect on the two techniques. In secondary analysis all operations, regardless of the urologists' experience, were included and the difference between analysis one and two approximates at least a part of the learning curve effect.

3.2.2 COSTING

Paper I derived resource use from 8 different countries and 30 centres and paper II from nine centres in Sweden and Denmark, while paper III derived resource use data from 14 centres in Sweden. Paper IV utilized data for both resource use and unit costs from various Swedish registries with almost complete coverage. Both the healthcare and societal perspective were represented in papers I, III and IV as it was hypothesized that minimally invasive surgery could have impact on post-operative sick-leave cost. In designing paper II, it was concluded that the sample size was too small (n=83) and high median age implied that a large share of patients were not of working age, with no sick-leave costs, so a healthcare perspective was adopted. When differences between treatments in resource use were expected or when it made up a large share of total resource use, it was included in the health economic evaluation. Minimally invasive surgery is routinely associated with costlier basic equipment and surgical instruments, a longer operating time (skin-to-skin

time) including longer time in anesthesia, shorter time in the recovery room, shorter post-operative hospital stay, shorter sick leave and less need for transfusions. Reoperation, readmission and stoma appliances (not in paper III) were expected to make up a large share of total cost.

In the design of the health economic evaluation in paper I, considerations were given to limit the effect of resource-use variables caused by differences in healthcare systems within and across countries[91]. The same rationale was applied in papers II and III. On principle, costly resources were only allowed to differ in incidence and not by the exact amount and type of resource use. For example, if standard protocol stipulated that the treatment of a reoperation included nine days of hospital stay in one country and only three days in another, or if there were four members of different staff categories in the operating theatre in one country but only three in another, these differences were eliminated by only recording the NOMESCO-code and then applying the Swedish unit cost. This allowed for use of data based on the total patient population, whatever the location. One potential limitation of this method is that the frequency can be influenced by different healthcare systems: some conditions might require a surgical procedure in some countries or regions and not in others. However, it is unlikely that this affects the two treatments in an unequal way.

Throughout this thesis the same unit costs have been applied to different surgical techniques studied in each paper, except for surgical instruments and the basic laparoscopic and robot equipment. This limits bias in inter-treatment comparisons. In papers I through III, a specific basic set of instruments, determined by two surgeons, was used in all surgeries. A surgeon's choice of instruments is typically based on personal preference or determined by hospital procurement decisions, but not necessarily associated with the surgical technique being studied. The alternative would have been to collect such information in clinical record forms, which was regarded as allowing for randomness. Another aspect is that surgical instruments used during operations performed early during the trial would probably no longer be in use when analysis were conducted five or ten years later. The same reasoning can be applied to basic laparoscopic equipment: similar components were needed to perform the same type of laparoscopic surgery around the world, but manufacturers and prices differ between hospitals, regions and countries.

Unit costs are based on sources of different scales; national (e.g. reoperation); regional (e.g. basic robot- and laparoscopic equipment); and local (e.g. minutes in the operating theatre). The rationale is to collect unit costs from the largest available source, when the resource use category is expected to have a large

impact on the result, as for example the cost-per-patient database for reoperations in papers I-III and resource consuming events in paper IV. Unit costs are derived from Swedish sources, not necessarily generalizable to other countries. Clinical trials conducted in different countries can lose the connection between resource use and unit cost because they are not collected from the same sources; this applied to paper I and II. However, as different jurisdictions, regions, and countries are faced with different relative prices, it is generally recommended to present separately unit costs and resource use. In paper IV the patient cohort, resource use and unit costs were collected at a national level, the level of all three was the same and the link between resource use and unit cost was maintained.

3.3 STATISTICAL ANALYSES

In papers I, II and III, the null hypothesis of no difference in mean costs between treatments was compared using a two sample t-test. Because cost data typically are skewed with a heavy right tail, a non-parametric bootstrap was used to calculate percentile-based 95% confidence intervals.

In paper II and IV two methods were used to adjust for censoring because of loss to follow-up as well as death, proposed by Lin[92] as well as Bang and Tsiatis[93]. Both methods imply that the follow up period be divided into shorter time intervals (in this case: months). The Lin-approach referred to also calculates the probability of survival to the beginning of each month, as well as the mean cost of those who were not censored or dead. The mean cost for each month was weighted with the probability of survival and lastly mean total cost was calculated by summation of the weighted mean costs. The method proposed by Bang and Tsiatis altered the Lin approach by weighting the cost for uncensored patients in each month by the inverse probability of a patient not being censored. Then mean total cost is the sum of cost over all intervals divided by both censored and uncensored patients.

In papers III and IV, baseline clinical characteristics were compared using Fisher's exact test and Pearson's χ^2 test (categorical variables), as well as Mann-Whitney U test (continuous variables).

Ordinary least squares regression (OLS) was used in papers III and IV and generalized linear models (GLM) was used in paper IV. Confounding variables was accounted for by adjustment by including the variables in the regression models.

3.4 ETHICS

In paper I, the COLOR II-trial was approved by the local ethics committee (Dnr: 480-09), specific to the health economic evaluation was an amendment regarding collection of sick-leave data (Dnr: T741-13).

In paper II, the DILALA- trial was approved by the local ethics committee (Dnr: 378-09).

In paper III, the LAPPRO- study was approved by the local ethics committee (Dnr: 277-07), specific to the health economic evaluation was an amendment regarding collection of sick-leave data (Dnr: T611-13).

In paper IV, the study was approved by the local ethics committee (Dnr: 661-16).

4 RESULTS

4.1 MAIN RESULTS

The main results (Table 2) supported the use of minimally invasive surgery as compared to open surgery in papers II and IV, was inconclusive in paper I and did not support its use in paper III. To enable comparisons between all four papers costs from paper I were adjusted for inflation to 2016-year value and costs were converted to purchasing power parity U.S. dollar 2016-year value. The latter was also done for costs from paper II.

In paper I the prospective cost-minimization analysis showed that laparoscopic surgery was significantly costlier for the healthcare sector than open surgery, both at 28 days (short-term analysis) PPP$1380 (95% CI: 495 to 2256) and 3 years (long-term analysis) after surgery PPP$2784 (95% CI: 1077 to 4373). Adding sick-leave cost as part of the societal analysis had little impact in the short-term analysis as almost no difference in sick-leave was observed within the period of the short-term analysis PPP$1338 (95% CI: 282 to 2247). The long-term difference between the techniques became non-significant when sick-leave was included, PPP$494 (95% CI: -4116 to 5241). Main cost-driving variables were surgical instruments, sick-leave and stoma appliances (colostomy).

In paper II a prospective cost analysis was performed using data on clinical resource use collected in the RCT DILALA. Healthcare costs accumulated during the study period (12 months) and throughout the patients' expected life time were analysed (long-term analysis). Resource use specific to the long-term analysis was included because of a concern of future sigmoid resection in the laparoscopic lavage group and future consumption of stoma appliances after Hartmann's procedure. The short-term analysis (12 months) showed a cost difference between laparoscopic lavage and open surgery of PPP$-8994 (95% CI: -11628 to -1571). In the long-term analysis an even larger difference PPP$-19818 (95% CI: -24520 to -3935) was found. The differences were composed of longer duration of anaesthesia, more stoma appliances and reoperation during follow up and future consumption of stoma appliances all in favour of laparoscopic lavage, and future sigmoid resections in favour of the open group.

Table 2. Difference in mean cost in each paper

Paper	Perspective/ follow-up	Difference (minimally invasive surgery- open) $PPP	95% CI Lower	95% CI Upper
I	**Healthcare:**			
	28 days	1380	495	2256
	3 years	2784	1077	4373
	Society:			
	28 days	1338	282	2247
	3 years	494	-4116	5241
II	**Healthcare:**			
	1 year	-8994	-11628	-1571
	>1 year	-19818	-24520	-3935
III	**Healthcare:**			
	2 years	5109	4692	5527
	Society:			
	2 years	3837	2747	4928
IV	**Healthcare:**			
	1 year	-4480	-6203	-2739
	Society:			
	1 year	-4504	-6799	-2257

Abbreviations: PPP=Purchasing Power Parity, CI=Confidence interval. Results from paper I were adjusted for inflation to SEK 2016 and then costs in paper I and II were converted to purchasing power parity U.S. dollar 2016-year value (1 $PPP=9.08 SEK) per OECD.

In paper III resource-use associated with robot-assisted laparoscopic prostatectomy (RALP) as compared to open surgery was prospectively collected within the LAPPRO-study. To avoid results potentially being affected by the learning curve of the technique, the study included only surgeries performed by urologists that had performed at least 100 procedures at the beginning of the trial. Thus, the groups comprised 803 patients in the open surgery group and 1835 patients in the robot-assisted laparoscopic group, in total 2638 patients. The difference in mean healthcare cost expressed in terms of purchasing power parity at two years was PPP$5109 (95% CI: 4692 to 5527) for RALP versus open surgery. Including sick-leave costs decreased the difference between the techniques to PPP$3837 (95% CI: 2747 to 4928). Main cost-driving factors were operating time, sick-leave and the cost of robotic equipment including maintenance.

In paper IV resource use, clinical effectiveness and costs were prospectively collected using nationwide sources to analyse the cost-effectiveness of laparoscopic versus open surgery for colorectal cancer. As clinical effectiveness measure a composite end-point was chosen comprising all-cause resource consuming events in inpatient care, readmissions and deaths up to 90 days. Costs included costly events in inpatient care, readmissions and sick-leave. Both clinical effectiveness and costs were adjusted according to differences in baseline TNM-stage, ASA-grade, sex, age and tumour location. The adjusted analysis of clinical effectiveness showed a mean difference of 0.23 events (95% CI: 0.12 – 0.33), in favour of laparoscopic surgery. The adjusted difference at one year in mean healthcare costs was PPP$4480 (95% CI: 2739 – 6203) and the equivalent societal cost was PPP$4504 (95% CI: 2257 – 6799), in favour of laparoscopic surgery. The main cost-driving resource-use category was costly events in inpatient care.

4.2 COMMON FINDINGS

The short-term cost categories in Table 3 are associated with the first admission. Data in paper IV was not detailed enough that these cost categories could be separated and compared between the laparoscopic and open techniques. The longer-term resource use categories in Table 4 occurred after index admission.

The extra resource use categories of minimally invasive surgery in the four papers comprised the purchasing price for basic laparoscopic equipment in paper I and II and the robot (including maintenance fee) in paper III, as well as some surgical instruments in paper I, II and III. In papers I and II the basic surgical equipment was not a significant cost-driving variable, only 1 % of total cost of the technique in each study, while in paper III, when robot-assisted laparoscopic technique was used, it made up around 17 % of the total cost of the technique (results not shown). The difference between laparoscopic ($PPP203 and $PPP197) and robotic basic equipment ($PPP2713) was around $PPP 2500, in favour of laparoscopic technique.

Table 3. Short-term cost categories during the first admission, expressed as relative percentage difference between minimally invasive surgery and open surgery

Cost category	Paper	Minimally invasive surgery $PPP	Open surgery $PPP	Relative percentage difference
Basic Equipment	I	203	0	N/A
	II	197	0	N/A
	III	2713	0	N/A
Surgical instruments	I	1419	634	124%
	II	236	231	2%
	III	1468	102	1339%
Operating time	I*	3049	2495	22%
	II**	3193	5541	-42%
	III	4169	2454	70%
Length of hospital stay	I	4909	5141	-5%
	II	5549	6260	-11%
	III	1617	2074	-22%
Transfusions	II	39	56	-30%
	III	27	83	-67%

*Abbreviations: PPP=Purchasing Power Parity, N/A=Not Applicable *Duration of anesthesia and skin-to-skin time. ** Duration of anesthesia. All results adjusted for inflation to SEK 2016-year value if necessary and then converted to purchasing power parity U.S. dollar 2016-year value (1 $PPP=9.08 SEK) per OECD*

The relative percentage difference between minimally invasive surgery and open surgery in Table 3 shows that cost of surgical instruments was 124 % higher in laparoscopic than open surgery in paper I, while it was comparable to the open technique in paper II (2% more) and more costly in paper III, 1339% higher in the robot-assisted laparoscopic group versus the open surgery group. Operating room costs were less in paper II for laparoscopic lavage, but costlier in the other two papers. Length of hospital stay was less costly for minimally invasive surgery in all three papers.

The long-term outcomes regarding sick-leave, reoperations and readmission are displayed in Table 5. In paper I, evidence was inconclusive, mainly because of the small sample size. In papers III and IV, a difference in sick-leave was found; significantly different in paper III but not in paper IV. The difference in cost of reoperations was higher in paper I in favour of open surgery, but the opposite was observed in papers II-IV. Readmission was not separated from

reoperation in paper I, but was more costly after laparoscopic than after open surgery in papers II and III, while in paper IV it was less costly.

Table 4. Long-term cost categories after the first admission accumulated during the follow up time, expressed as relative percentage difference between minimally invasive surgery and open surgery

Cost category	Paper	Minimally invasive surgery $PPP	Open surgery $PPP	Relative percentage difference
Reoperation	I	4264	3845	11%
	II	5631	11891	-53%
	III	1003	1206	-17%
	IV	24811	30876	-20%
Sick- leave	I	16466	18757	-12%
	III	4615	5886	-22%
	IV	7271	7457	-2%
Readmission	II	2574	865	198%
	III	364	333	9%
	IV	1437	1885	-24%

All results adjusted for inflation to SEK 2016-year value if necessary and then converted to purchasing power parity U.S. dollar 2016-year value (1 $PPP=9.08 SEK) per OECD.

5 DISCUSSION

To assess the value of new and established surgical interventions, it is important to take into consideration both the costs and the consequences of the techniques in comparison to the conventional (alternative) treatment(s). Resources spent on one intervention cannot be spent elsewhere; consequently one should always consider the alternative uses of that resource. Economic evaluation is one tool used to assess if limited resources are spent where they provide the most value to society and patients. A few Swedish agencies are evaluating cost-effectiveness of surgical techniques: SBU (Statens beredning för medicinsk och social utvärdering) and to some extent TLV. It is mostly up to Swedish counties and healthcare regions to decide what surgical techniques are implemented. In the last few years TLV has had a short-term assignment from the Swedish government to evaluate medical devices; this could include evaluation of minimally invasive surgical techniques. It is important that TLV's contract is made permanent in the hope that health economic evaluations of medical devices used in surgical interventions will be performed more routinely. In conclusion, economic evaluations of surgical techniques are not performed in a systematic way in Sweden. This could lead to considerable waste of healthcare resources and potentially health benefits forgone.

This thesis evaluates surgical techniques from a health economic perspective using data from different sources, including randomized and non-randomized trials as well as registers. In clinical research as well as in health economics it is important to first generate evidence on the efficacy in a selected group of patients, and then show that this evidence is applicable to routine care. In randomized, controlled trials including patients with colorectal cancer laparoscopic surgery was either costlier than open surgery or not significantly different, as showed in paper I in this thesis. Paper IV and the literature show the impact of implementing a new technique, i.e. surgeons' learning curve and uptake of the technique. Overall, laparoscopic surgery appears to be associated with lower mean cost[28-33].

Clinical trials rarely have health economic evaluation as the primary objective. Therefore, the study design, including sample size, is in general not optimized for economic evaluations. Register-based sources enable the collection of data from a larger sample of patients and might remedy these problems. Another property of a larger sample size is the ability to find small differences between surgical techniques in quality of life. Quality of life was measured in a subset of patients in paper I, in the entire sample in paper II and paper III, but did not show any statistical, significant differences between minimally invasive and

open surgical techniques. One potential explanation for this could be that the surgery or disease itself has such a large impact on experienced quality of life that surgical technique does not make enough difference to be shown when using generic quality-of-life instruments. It has, however, particularly important implications in health economic evaluations when the preferred measure of clinical benefit is the QALY. It enables the comparison of healthcare interventions between different diseases. When neither length nor quality of life is different, the results of an economic evaluation cannot be compared to other healthcare interventions.

One limitation of register-based studies is the presence of observed and unobserved confounding and selection bias. There are methods to address observed confounding, but few to adjust for unobserved confounding. One article included in the background section adjusted for unobserved confounding by using a instrumental variable approach and found that the difference in cost was still significant, but smaller than when only adjusting for observable confounding. Indeed, these statistical methods come with their own difficulties and limitations, for example the potential difficulty of finding a good instrumental variable. A common challenge when using data from registers is the quality of the data; there might be data entry errors and data missing. Swedish registers are generally of high quality and both the Swedish Colorectal Cancer Register and the Swedish Patient register have published validation studies[94,95] presenting good results. The Swedish cost-per-patient register is the basis for calculation of the national DRG-system and is used as one source for the reporting of quality and efficiency published annually ("öppna jämförelser") and is used in research. Furthermore, it seems reasonable to expect that errors in data entry would affect different surgical techniques in a similar way, and if sample sizes are large, this should not bias results.

It has long been suggested that shorter sick-leave and length of hospital stay could compensate for the higher initial costs of the basic equipment and surgical instruments for both laparoscopic and robot-assisted laparoscopic technique, but this was not concluded in this thesis. In paper III and paper IV sick-leave was investigated in two large cohorts of patients and a statistically significant difference between the techniques was found in paper III, but not in paper IV. One reason for this finding could be that median age was higher than retirement age in paper IV. Thus, benefits from early recovery may not have translated into measurably shorter sick-leave because of the low percentage of patients of working age. Patients with prostate cancer are younger than patients with colorectal cancer and sick-leave seemed to have a larger impact on cost in this group in paper III, although not enough to offset

the higher initial cost entirely. Another explanation could be that sick-leave was measured in a different way in paper III than in papers I and IV. In paper III two weeks of sick leave was allocated at discharge after the first admission. If additional sick-leave was required, it was allocated after a phone call to the patient's doctor, seven days each time for maximum 6 weeks. In paper I and IV, sick leave was administered at the discretion of the doctor and the patient and it could be hypothesised that more standardized and less individualized sick leave was given. This means that patients, who were ready to return earlier to work, most likely did not do so or at least it did not show in the data extracted. However, sick leave was administered as part of routine care in paper IV, which was not the case in paper III. If future research confirms that at least part of the difference in sick leave between the approaches in paper III and paper IV could result in lower sick leave cost, it might inform decision-making when it comes to guidelines. Further implications for measuring sick leave alongside a clinical trial is that sick leave depends on the kind of work, e.g. comparing manual labour to office work. Furthermore, sick leave is only estimated for people employed and discounts unemployment.

Laparoscopic lavage seems to be both more effective and less costly than Hartmann's procedure for complicated diverticulitis with purulent peritonitis. However, outcomes in routine care in a larger cohort of patients is still to be reported on and it is too early to conclude if it is beneficial from both a clinical and economic perspective. Moreover, the need for stoma appliances in the Hartmann's procedure group, and the fear of future bowel resection in the laparoscopic lavage group, have not been completely resolved. In this thesis the expected future cost for stoma appliances outweighed the expected future cost for bowel resection.

6 CONCLUSIONS

Implications for decision-makers and health care providers:

As the cost-effectiveness of a treatment can change over time, it is important, especially in the case of a new surgical technique where learning curve effects are present, that the cost-effectiveness is re-evaluated in routine care.

Laparoscopic surgery for colorectal cancer seems to be associated with lower costs from the healthcare perspective in routine care, contrary to what has been showed in earlier literature.

At the current acquisition cost for basic equipment and maintenance, robot-assisted laparoscopic surgery for prostate cancer seems to be associated with higher cost, especially from the healthcare perspective, according to paper III in this thesis as well as literature. There is some additional health benefit associated with robot-assisted laparoscopic surgery for prostate cancer and it is up to decision-makers to decide if it motivates the additional cost.

Future perspectives:

In the future, a cost-effectiveness analysis of robot-assisted laparoscopic technique for colorectal cancer could be included in a comparison with both open and laparoscopic surgery.

With the finding that laparoscopic colorectal cancer surgery became more cost-effective over time, it could be of interest to see if robot-assisted laparoscopic surgery for prostate cancer could exhibit the same pattern.

Laparoscopic lavage as treatment for complicated diverticulitis (Hinchey III) could be included in future analysis of cost-effectiveness compared to primary anastomosis, with or without diverting ileostomy, and Hartmann's procedure.

The finding of fewer costly events in inpatient care after laparoscopic colorectal surgery as compared to open surgery needs to be analysed further.

ACKNOWLEDGEMENT

This thesis had not been possible to write without the contributions, support and inspiration from many people, of whom I would especially like to extend my sincere gratitude to:

Eva Haglind, my supervisor, for including a health economist as a member of the research group and sharing your knowledge, expertise and vast experience regarding research in general and surgery in particular. All your stories and advice I will bring with me throughout my career.

Ingela Björholt, my co-supervisor, for sharing your deep knowledge of applied health economic research. Thank you for constantly challenging me during discussions regarding the different projects in this thesis, it has made me grow in my professional role.

Eva Angenete, my co-supervisor, your energy is contagious and your capabilities are truly inspiring. Thank you for sharing your knowledge regarding surgical techniques and clinical research as well as providing valuable input on all projects in this thesis.

David Bock, my co-worker, for guidance regarding statistics and input on manuscript writing but also for interesting lunch discussions.

Sofia Erestam, my Ph.D-colleague, for helping me to identify various surgical instruments and equipment and also for much needed coffee breaks to talk about cats.

My past Ph.D-colleagues: **John Andersson**, **Anders Thornell**, **Mattias Prytz** and **Dan Asplund**, providing me with examples of well-written theses and excellent defences.

My present Ph.D-colleagues: **Jennifer Park, Sofie Walming**, **Aron Onerup**, **Anton Sterner**, **Bodil Gessler**, **Adiela Correa Marinez** and **Andreas Samuelsson.** I wish you all the best of luck with your theses.

All my co-authors of whom I would especially like to mention **Annabelle Forsmark** and **Eva Lesén**.

My beloved co-workers being with me throughout the whole thesis project: **Ingrid Höglund Karlsson, Jane Heath**, **Elisabeth González**, **Kira**

Bröndum, Carolina Ehrencrona, Hanna Nilsson, **Carina Rosander** and **Anette Wedin**, for much love, laughter and for making SSORG a truly great place to work.

My past and present co-workers: **Kajsa Holm, Elin Grybäck Gillheimer, Marie Kärrman**, **Louise Karlsson, Emma Setterberg Degerskär**, **Annelie Olofsson, Anette Engström**, **Daniel Andersson** and **Sara Kürcman**.

My mother **Ann**, my father **Kenneth**, my sisters **Malin** and **My**, my brother **Peter**. You have always been there and provided me with support and my love for all of you is infinite and unconditional. My niece **Nora** and my nephew **Albert**, I look forward to seeing you grow. My brother-in-law **Peter**, for taking such good care of my sister and nephew.

My dear friends, **Jocke** & **Anna**, **Emelie**, **Jesper** & **Anna** for all the fun times.

My love and best friend **Emma** for making it possible on so many levels for me to write this thesis and my dear old cat **Orlando** for being the character that you are. Both provide me with one of the greatest gift of all, a loving home to come to after a hard day's work.

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