

**EVALUATING SURGICAL OUTCOMES: A SYSTEMATIC COMPARISON OF  
EVIDENCE FROM RANDOMIZED TRIALS AND OBSERVATIONAL STUDIES IN  
LAPAROSCOPIC COLORECTAL CANCER SURGERY**

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## **ABSTRACT**

*Background:* Laparoscopic surgery for colorectal cancer is a novel healthcare technology, for which much research evidence has been published. The objectives of this work were to compare the oncologic outcomes of this technology across different study types, and to define patterns of adoption on the basis of the literature.

*Methods:* A comprehensive systematic review of the literature was conducted using 1) existing systematic reviews, 2) randomized controlled trials (RCTs), and 3) observational studies. Outcomes of interest were overall survival, and total lymph node harvest. Outcomes were compared for congruence. Adoption was evaluated by means of summary expert opinions in the literature.

*Results:* 1) Existing systematic reviews were of low to moderate quality and displayed evidence of overlap and duplication. 2) Laparoscopy was not inferior to open surgery in terms of oncologic outcomes in any study type. 3) Oncologic outcomes from RCTs and observational studies were congruent. 4) Expert opinion in the literature has been supportive of this technology, paralleling the publication of large RCTs.

*Conclusions:* The evaluation of laparoscopic surgery for colorectal cancer in RCTs and observational studies suggests that it is not inferior to open surgery. Adoption of this technology has paralleled RCT evidence.

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## **CHAPTER ONE: INTRODUCTION**

### **DEFINITION OF THE CLINICAL PROBLEM**

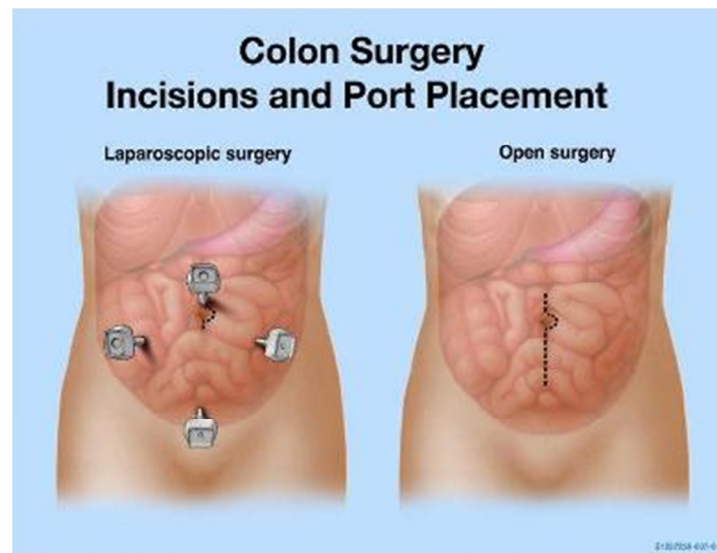
Colorectal cancer represents a significant burden of disease worldwide. It is the third commonest cancer in men and women, and the second leading cause of cancer-related death in Canada and the United States [1, 2]. The mortality rate associated with colorectal cancer continues to improve, with annual improvements of approximately -1.5% for males and -1.8% for females since 1997 [1]. The five-year survival rate for colorectal cancer in Canada is 63% [1].

Despite tremendous improvements in chemotherapeutic agents over the past decade, the cornerstone of therapy for a vast majority of patients with this illness remains the surgical resection of the colonic or rectal primary tumor. In performing this procedure, the surgeon must resect the segment of colon or rectum involved by tumor with sufficient normal bowel margins, and must reconnect the remaining healthy ends. As well, the surgeon must remove lymph nodes found along blood vessels feeding the particular piece of colon or rectum being resected. Each harvested lymph node is subsequently analyzed for evidence of tumor metastasis, a step which is critical in providing a final disease stage for the patient. The number of harvested lymph nodes has become an oncologic surrogate marker of good surgery, and it is included in guidelines on the care of colorectal cancer [3].

The traditional approach to colon and rectum surgery has been that of a generous mid-abdominal laparotomy incision. This maximally-invasive technique allows excellent direct visualization of all abdominal organs, and allows the surgeon to resect the colon or rectum manually. Since 1991, an alternative laparoscopic approach to abdominal colorectal surgery has been described [4, 5], whereby the surgeon fashions only a few one-centimeter abdominal incisions, through which working trocars can be inserted. These ports allow the insertion of long stick-like working instruments and a video-endoscope, which produces an

image of the abdominal cavity on a screen. As such, laparoscopy allows the resection of abdominal organs such as the colon or rectum utilizing small skin incisions and with minimal tissue manipulation (figure 1).

**Figure 1.** Comparison of abdominal incisions with laparoscopic and open surgery <sup>i</sup>



The controversial and theoretical benefits of laparoscopic surgery over traditional open surgery include reduced blood loss, faster recovery of postoperative intestinal function, reduced rates of wound infection, reduced pulmonary complications, reduced postoperative pain and narcotics requirements, reduced length of stay in hospital, reduced rates of long-term adhesions formation, reduced rates of incisional hernia, reduced intraabdominal inflammation, and improved cosmesis [6]. Similarly, claimed disadvantages of laparoscopy include increased operative theater time, increased costs, and long learning curves for individual providers [6]. Given the above list, it is not surprising that this surgical technology has been highly controversial among surgeons in the years following its original description. Making matters worse, reports from the mid-1990s also raised the possibility of worsened

<sup>i</sup> From <http://pinoy picks.blogspot.com/2011/03/minimally-invasive-and-robotic.html>, accessed August 2011

oncologic outcomes associated with trocar-site tumor recurrence following laparoscopic colorectal cancer surgery [7]. In contrast, other groups have reported a survival advantage with laparoscopy over laparotomy, and have speculated that this finding may result from preserved immune function with a less traumatic operation [8, 9]. Needless to say, these claims and others have generated controversy among surgeons, but have also provided a useful case study highlighting the importance of understanding the process of surgical innovation and technology adoption.

## **SURGICAL INNOVATION AND TECHNOLOGY ADOPTION**

Surgical innovation and the adoption of surgical procedures or technologies into clinical practice is a complex process. Many novel surgical technologies have been rapidly adopted into routine surgical practice, sometimes on the basis of limited evidence from randomized controlled trials (RCTs), as was the case for laparoscopic cholecystectomy [10]. In contrast, other procedures, such as laparoscopic surgery for colorectal cancer, have exhibited a much more complex adoption history [6]. Reasons behind these varied patterns of adoption into surgical practice are multifactorial, and include matters of group dynamics, surgical politics, timing, patient demands, and, of course, clinical research evidence. At different time points, and for different surgical technologies, each of the above-mentioned variables takes on a varying degree of importance in driving adoption by practitioners.

Most healthcare practitioners and decision-makers would readily argue that judgements regarding the usefulness and adoption of technologies – whether in surgery or other branches of medicine – ought to be based upon robust evidence from clinical research. In this context, RCTs are widely understood to provide the highest standard of research evidence in evaluating healthcare interventions. While surgical research has attracted much criticism in recent years [11], there is no doubt that the hierarchy of research evidence is now common knowledge among surgeons. Despite this fact, RCTs have

accounted for as little as 3-9% of clinical studies in surgery [12], with surgeons being traditionally reticent to carry out RCTs. Indeed, observational studies, particularly uncontrolled case series, have represented the mainstay of surgical research for many years. As indicated earlier, laparoscopic surgery for colorectal cancer is a prolific example of a relatively novel surgical technology, for which both RCTs and numerous observational studies have been published concomitantly.

## **THESIS RATIONALE**

There is currently very little empiric work in the literature pertaining to the complex continuum of surgical innovation to technology adoption [13]. While many groups have provided clinical summaries of results pertaining to technologies such as laparoscopic surgery for colorectal cancer, very few have examined the process of knowledge translation by which evidence is synthesized for surgeons. As well, only few studies have provided empirical comparisons of RCT and observational data in surgery [14, 15], a fact that is highly relevant given the traditional reliance upon observational data in this branch of medicine. Finally, much work remains to be done to understand the process by which novel technologies are adopted by practicing surgeons. It is indeed unclear at present whether adoption relies upon evidence in the surgical literature, and, if so, whether it relies upon RCT and/or observational evidence.

As the proportion of healthcare expenditures allocated to surgical departments continues to grow, it will become increasingly important to address these questions in a rigorous fashion. Doing so will provide the surgical community with an important appraisal of its current evidence base and knowledge translation processes, from innovation to adoption.

## **THESIS OBJECTIVE**

The global objective of this work was to provide a critical appraisal of the processes of evaluation and adoption of laparoscopic and open surgery for colorectal cancer, as an example of a novel surgical technology. The following specific objectives have been addressed in this thesis:

1. To compare the short-term surrogate and long-term oncologic outcomes of laparoscopic and open surgery for colorectal cancer obtained from RCTs, observational studies, and existing systematic reviews/meta-analyses;
2. To define the risk of bias associated with each study design and its association with each outcome ;
3. To define patterns of acceptance of laparoscopic surgery for colorectal cancer in the literature, and to compare it to summary evidence.

## **REFERENCES**

1. Canadian Cancer Society's Steering Committee on Cancer Statistics. Canadian Cancer Statistics 2011. Toronto, ON: Canadian Cancer Society; 2011. Available from [[http://www.cancer.ca/Canada-wide/Publications/Alphabetical%20list%20of%20publications/Canadian%20Cancer%20Statistics.aspx?sc\\_lang=en](http://www.cancer.ca/Canada-wide/Publications/Alphabetical%20list%20of%20publications/Canadian%20Cancer%20Statistics.aspx?sc_lang=en)], accessed August 2011
2. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin* 2010;60:277-300
3. Smith AJ, Driman DK, Spithoff K, Hunter A, McLeod RS, Simunovic M, Langer B, Expert Panel on Colon and Rectal Cancer Surgery and Pathology. Guideline for optimization of colorectal cancer surgery and pathology. *J Surg Oncol* 2010;101:5-12

4. Fowler DL, White A. Laparoscopy-assisted sigmoid resection. *Surg Laparosc Endosc* 1991;1:183-8
5. Jacobs M, Verdeja JC, Goldstein HS. Minimally invasive colon resection (laparoscopic colectomy). *Surg Laparosc Endosc* 1991;1:144-50
6. Martel G, Boushey RP. Laparoscopic colon surgery: past, present and future. *Surg Clin N Am* 2006;86:867-97
7. Wexner SD, Cohen SM. Port site recurrences after laparoscopic colorectal surgery for cure of malignancy. *Br J Surg* 1995;82:295-298
8. Lacy AM, Garcia-Valdecasas JC, Delgado S, Castells A, Taura P, Pique JM, Visa J. Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomized trial. *Lancet* 2002;359:2224-2229
9. Poulin EC, Mamazza J, Schlachta CM, Gregoire R, Roy N. Laparoscopic resection does not adversely affect early survival curves in patients undergoing surgery for colorectal adenocarcinoma. *Ann Surg* 1999;229:487-492
10. Barkun JS, Barkun AN, Sampalis JS, Fried G, Taylor B, Wexler MJ, et al. Randomised controlled trial of laparoscopic versus mini-cholecystectomy: the McGill gallstone treatment group. *Lancet* 1992;340:1116-1119
11. Horton R. Surgical research or comic opera: questions, but few answers. *Lancet* 1996;347:984

12. Solomon MJ, McLeod RS. Surgery and the randomised controlled trial: past, present and future. *Med J Aust* 1998;169:380-383
  
13. Barkun JS, Aronson JK, Feldman LS, Maddern GJ, Strasberg SM. Surgical innovation 1: evaluation and stages of surgical innovation. *Lancet* 2009;374:1089-96
  
14. Shikata S, Nakayama T, Noguchi Y, Taji Y, Yamagishi H. Comparison of effects in randomized controlled trials with observational studies in digestive surgery. *Ann Surg* 2006;244:668-676
  
15. Abraham NS, Byrne CJ, Young JM, Solomon MJ. Meta-analysis of well-designed nonrandomized comparative studies of surgical procedures is as good as randomized controlled trials. *J Clin Epidemiol* 2010;63:238-245

## **CHAPTER TWO: OVERVIEW OF SYSTEMATIC REVIEWS**

### **THE QUALITY OF RESEARCH SYNTHESIS IN SURGERY: THE CASE OF LAPAROSCOPIC SURGERY FOR COLORECTAL CANCER**

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## INTRODUCTION

Any field of active investigation in healthcare requires that the overwhelming volume of cumulative information generated by individual researchers be condensed and summarized into a usable product. This synthesis must be simple, yet comprehensive, so as to inform decisions and policies carried out by physicians and surgeons, hospital administrators, healthcare payers, funding agencies, and other end-users of research and outcomes data. Systematic reviews are widely considered to be the most comprehensive and unbiased method to do so [1]. On the basis of their completeness, such reviews should remain unique in the literature and be updated frequently, rather than duplicated or compartmentalized. In this context, some authors have recently advocated for the open registration of systematic reviews [2-4].

Laparoscopic colorectal surgery was first described in 1991 by Fowler and White [5] and by Jacobs and colleagues [6]. This technology has since been applied to almost every disease process – whether benign or malignant – involving the colon and rectum [7]. The use of laparoscopy rather than traditional open laparotomy to treat colorectal cancer has generated tremendous controversy in the surgical literature, particularly regarding the oncologic adequacy of this technique. Many investigators have attempted to address this issue, and have thus generated a large body of literature over the past twenty years. Published studies have included the entire spectrum of research data, ranging from small personal case series to large nationally-funded multicenter randomized controlled trials (RCT). This work presents an excellent opportunity for a case study of research synthesis and knowledge translation processes in surgical research, an area which has traditionally lacked investigative rigor [8].

Numerous systematic reviews and meta-analyses pertaining to laparoscopic surgery for colorectal cancer have been published. Informal examination of these reviews would suggest significant overlap and possible duplication. The utility of this body of work is

unclear at this time. As such, we set out to examine and appraise all existing systematic reviews of laparoscopic colorectal surgery for cancer, both in terms of clinical outcomes and their relative completeness, methodological quality, and overlap.

## **MATERIALS AND METHODS**

This overview of systematic reviews was carried out using the framework for umbrella reviews described by the Cochrane Collaboration [9]. This approach consisted of identifying all existing systematic reviews and meta-analyses pertaining to laparoscopic surgery for colorectal cancer. This work was part of a larger review effort addressing both primary publications and review papers, the results of which will be presented separately. A review protocol was utilized for the project as a whole.

### ***Criteria for considering reviews for inclusion***

All inclusion and exclusion criteria were defined a priori. All systematic reviews and meta-analyses addressing laparoscopic and open surgery for colorectal cancer were included. For this purpose, all reviews were allowable if they were self-described as systematic, whether in the title, abstract, or methods of the paper. Alternatively, a citation was also allowable if the authors presented a meta-analysis of primary papers or utilized meta-analytic techniques to pool primary data. These criteria were utilized regardless of the quality or comprehensiveness of the review. The type of primary data papers included in the citations could be RCTs, observational studies, or both.

All included citations reviewed primary papers addressing the curative resection of colon and/or rectal cancer. Patients with colorectal cancer did not have to be the sole population under review. Laparoscopic resection for colorectal cancer was the intervention under study. Included reviews had to present a comparison to an open resection control group.

The primary outcome of interest was overall survival. Secondary endpoints were also considered if they were included in a review of interest: operative outcomes, short-term postoperative outcomes, oncologic surrogate outcomes, long-term oncologic outcomes, other long-term outcomes, and quality of life. A review could be included in this overview even if no data pertaining to survival was presented, as identification of review deficits was a pre-specified objective of our work. Reviews addressing exclusively cost or immune function were excluded.

### ***Search methods for identification of reviews***

Systematic reviews and meta-analyses were identified as part of a broader comprehensive search strategy designed to identify primary comparative literature pertaining to laparoscopic and open surgery for colorectal cancer. The final search algorithm was devised in conjunction with an experienced information specialist from the Ottawa Hospital Library (appendix 1). This search strategy was designed to be highly sensitive, and was modified from previously published work [10]. Six major databases were searched for relevant citations from 1991-2008 (Ovid MEDLINE, Ovid EMBASE, Cochrane Library, Science Citation Index Expanded, BIOSIS Preview, and BIREME LILACS). An additional thirteen databases were also searched for relevant citations (Database of Abstracts of Reviews of Effectiveness, Health Technology Assessment Database, National Health Service Economic Evaluation Database, National Institute for Health Research Health Technology Assessment Programme, TRIP Database, Clinicaltrials.gov, Controlled-trials.com, National Guidelines Clearinghouse, Canadian Medical Association Infobase: Clinical Practice Guidelines, National Institute for Health and Clinical Excellence (NICE), Scottish Intercollegiate Guidelines Network, National Health and Medical Research Council (Australia), New Zealand Guidelines Group). The reference lists of all included citations were also screened to identify missing reviews. No language limitation was applied to the

search strategy. All citation records were retrieved and downloaded electronically using Reference Manager 10 (ISI ResearchSoft, Berkeley, CA), and were then de-duplicated.

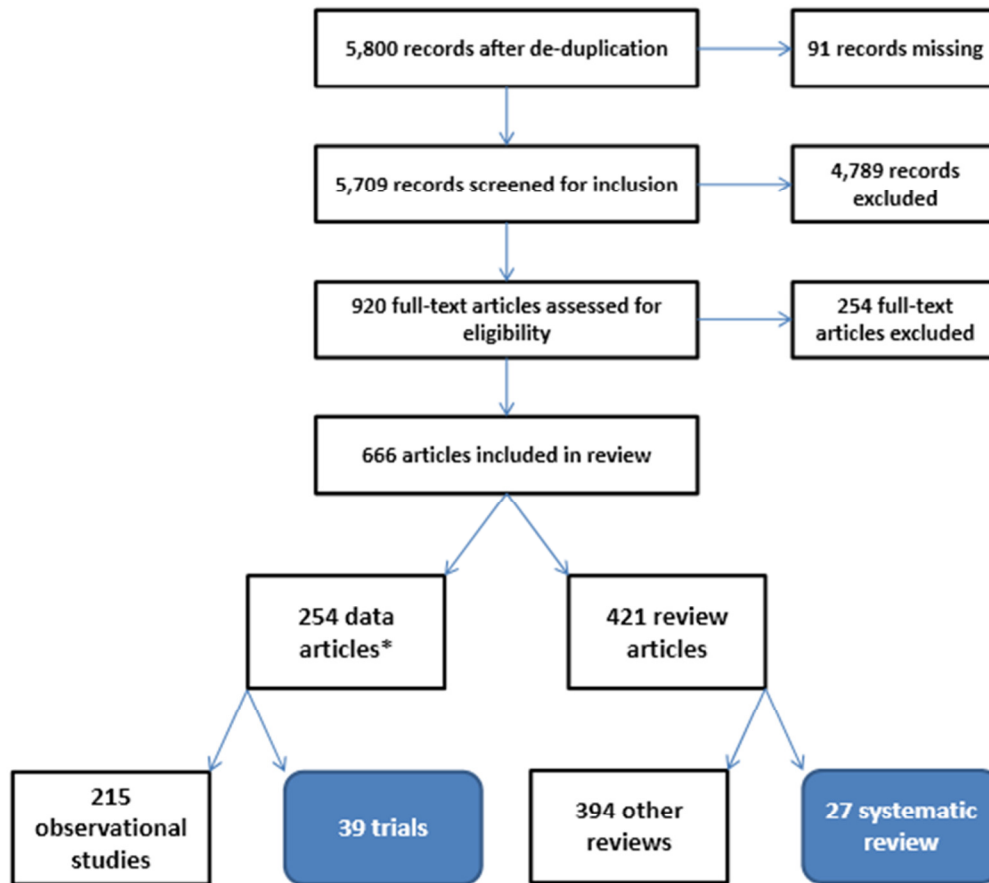
### ***Selection of reviews***

All citations were first screened for inclusion by one reviewer (GM) on the basis of titles and abstracts (figure 2). All retained citations were then retrieved in full text. Papers which could not be obtained after extensive interlibrary searching were considered missing. Papers published in languages other than English, French, or Spanish were translated in full using Google Translate (Google Inc., Mountain View, CA). Full-text articles were evaluated for inclusion by one reviewer (GM). Included articles were then classified as 1) data papers or 2) review papers. Review papers were then further divided as systematic reviews/meta-analyses, narrative reviews, textbook chapters, and guidelines/position papers. Only systematic reviews/meta-analyses were considered in the current work, while all other included paper types were set aside for a separate research project. All included systematic reviews were further evaluated for inclusion by a second reviewer (SD), and disagreements between the two reviewers was resolved by discussion and consensus.

### ***Data extraction and management***

A total of 6 study characteristics and 19 pre-specified outcomes of interests were extracted by two reviewers (GM, SD) onto data tables designed a priori. All discrepancies were resolved by discussion and consensus. Relative outcomes were always recorded as a comparison of laparoscopic to open surgery. Where papers compared open to laparoscopic surgery, the appropriate reciprocal relative measure of effect and reciprocal measure of significance were calculated and recorded. The relative measures of effect were maintained in the statistical format provided by the authors of individual citations.

**Figure 2.** PRISMA diagram [94].



\* Total number of data and review articles does not add up to 666, as 9 papers were included in both categories.

### ***Assessment of methodological quality of included reviews***

The methodological quality of individual reviews included in this overview was assessed using the AMSTAR (Assessment of Multiple Systematic Reviews) instrument [11]. This tool consists of 11 individual items, which were developed from pre-existing instruments, empirical evidence, and expert consensus. It has been shown to be valid, reliable, and relatively easy to use [11-13]. Each item within the instrument can receive one point for a possible range of AMSTAR scores of 0-11. The AMSTAR instrument was

administered independently by two reviewers (GM, SD) and discrepant scores were resolved by discussion and consensus.

### ***Data synthesis***

The data extracted from each included systematic review was incorporated into summary tables and figures. The resulting data were synthesized in narrative form and correlated qualitatively with methodological AMSTAR scores. The congruence of pooled summary estimates for outcomes of interest across reviews was evaluated qualitatively.

As a means of evaluating the appropriateness of included reviews, a bibliographic analysis was carried out. Citation matrices [14] were generated that cross-linked individual reviews with 1) previously published systematic reviews identified in this work, and 2) published RCTs of laparoscopic vs. open colorectal cancer surgery also identified in this work. This technique was used to determine whether the authors of included reviews made use of other pre-existing systematic reviews, and whether the identification of relevant RCTs was comprehensive. A one year lag time to publication was incorporated into the citation matrices and calculations. To account for the growing number of publications in time, the ratio of cited to total preexisting publications was calculated for each systematic review. The mean ratios and 95% confidence interval were calculated for citation of both preexisting systematic reviews and RCTs. Finally, citation ratios for individual systematic reviews were compared to AMSTAR scores and 5-year impact factors [15] using Pearson correlation coefficients.

All calculations and statistical analyses were performed using Microsoft Excel 2010 (Microsoft Corporation, Richmond, WA) and SAS 9.2 (SAS Institute Inc., Cary, NC).

**Table 1.** Characteristics of included systematic reviews.

Review (Origin)	Last Update	Population / Intervention*	Study Types	Notes / Limitations
Bernard / ANDEM 1994 [16] (France)	Jul 1993	Any colorectal pathology and other abdominal pathologies (appendicitis, biliary disease, reflux, inguinal hernia)	Case series, no RCT or observational study found	In French Paucity of available comparative literature Broad review addressing all laparoscopic techniques (biliary, hernia, etc.)
Chapman / ASERNIP-S 2000 [17] (Australia)	Jul 1999	Colon cancer (right, left/sigmoid) and animal studies of in vitro/in vivo tumor spread <u>Excluded</u> transverse colectomy, APR, total colectomy	RCTs Observational Animal studies	Limited to English Inclusion/exclusion of high and mid-rectal cancer is not clearly specified Chose not to pool data Overlap with Chapman 2001
Vardulaki / NICE 2000 [18] (UK)	2000	Colorectal cancer <u>Excluded</u> case series of <10 patients	RCTs Observational	Extensive methodological description Rigorous assessment of heterogeneity Pooling of RCTs and observational data done separately to avoid bias (for some outcomes) Statistical manipulations to overcome data limitations
Chapman 2001 [19] (Australia)	Jul 1999	Colon cancer (right, left/sigmoid) <u>Excluded</u> transverse colectomy, APR, total colectomy	RCTs Observational	Limited to English Inclusion/exclusion of high and mid-rectal cancer is not clearly specified Chose not to pool data Overlap with Chapman 2000
Yong 2001 [20] (UK)	Mar 1997	Any colorectal pathology (all operation types)	Observational No RCT found	Modification of inclusion / exclusion criteria from protocol based on available studies Only 13/42 studies had only malignant disease Pooled certain outcomes by calculating weighted means

Korolija 2003 [21] (Croatia)	Jan 2000	“Colorectal procedures”, unclear	RCTs Observational	No inclusion / exclusion criteria provided Not mentioned whether RCTs included (2 identified in reference list) Chose to pool outcomes from RCTs, observational studies, case series together (no mention of appropriateness)
Abraham 2004 [22] (Australia)	Dec 2002	Colorectal cancer (right hemicolectomy, left hemicolectomy, rectosigmoid resection, APR, others)	RCTs	Limited to English Study selection on basis of reported outcomes
Reza / UETS 2004 [23] (Spain)	Sep 2004	Colorectal cancer Excluded combination of benign and malignant pathologies, immune outcomes	RCTs Systematic reviews Meta-analyses	In Spanish Pre-2000 RCTs not included No pooling of outcomes except survival and recurrence (reason unclear)
Poutignat / Haute Autorité de Santé 2005 [24] (France)	2003	Colorectal cancer <u>Excluded</u> metastatic disease, combined benign and malignant pathologies, non-intention-to-treat studies or those excluding converted patients	RCTs Observational Meta-analysis	In French, limited to English and French Unclear from text whether inclusion/exclusion criteria chosen a priori or after literature search by group of expert Chose not to pool outcomes, qualitative analysis
Manterola 2005 [25] (Chile)	Dec 2002	Colon cancer (right, transverse, left, sigmoid) <u>Excluded</u> : rectal cancer, perforated or obstructing cancer, metastasis, recurrent cancer, invasion into adjacent bowel/organs, polyps	RCTs Observational	In Spanish, limited to English, Spanish, French, Italian Methodology score created by review authors Controlled series and RCTs broken down into individual case series yielding 6 lap and 11 open series in total
Schwenk 2005 [26] (Germany)	Jan 2005	Colorectal pathologies (benign or malignant, for curative or palliative resection)	RCTs	Cochrane Review, protocol published in 2001 Extensive methodological description Results for different pathologies pooled together
Aziz 2006 [27] (UK)	2004	Rectal cancer (described as anterior resection or APR)	RCTs Observational	Extensive quantitative assessment of heterogeneity Results for RCTs and observational studies pooled (no sensitivity analysis comparing RCT to observational data)
Tjandra 2006 [28] (Australia)	Sep 2005	Colon and rectosigmoid cancer <u>Excluded</u> : rectal cancer, distant metastases	RCTs	Limited to English Effect of heterogeneity on results not clear/not documented

Reza 2006 [29] (Spain)	Nov 2005	Colorectal cancer  <u>Excluded:</u> papers with mixed malignant/benign populations, immune function as outcome	RCTs Systematic reviews	Pre-2000 RCTs not included  Limited description of methodology  No pooling of outcomes except survival and recurrence (reason unclear)
Breukink 2006 [30] (Netherlands)	Aug 2006	Rectal cancer (undergoing TME)	RCTs Observational	Cochrane Review, protocol published in 2005  Primary outcome: disease-free survival  Chose not to pool survival data; qualitative analysis
Gao 2006 [31] (China)	Jun 2005	Rectal cancer	RCTs Observational	Outcomes considered were selected posthoc after reviewing selected literature  Meta-analysis of RCT and observational data  Incomplete assessment of heterogeneity
Murray 2006 [10] (UK)	May 2005	Colorectal cancer (including laparoscopic or HALS, excluding palliative surgery)	RCTs IPD meta-analyses	HTA report (commissioned), protocol published in 2005  Pre-2000 RCTs identified from existing systematic reviews  Extensive description of methodology, rigorous assessment of heterogeneity  Academic-in-confidence data obtained from other authors removed from final report  Includes economic evaluation
Kahnamoui 2007 [32] (Canada)	2004	Colorectal cancer (right, left, sigmoid, anterior resection, APR)	RCTs	Defined primary outcome: cancer-related mortality  Extensive methodological description  Quality appraisal list designed by authors
Noel 2007 [33] (US)	Jan 2005	Colorectal cancer, IBD, diverticular disease	RCTs Observational (controlled)	Limited to English  Excluded historical controls with <50% overlap in accrual periods  Combination of RCT and non-RCT data  No assessment of methodological quality

Bonjer 2007 [34] (Netherlands)	2006	Colon cancer (rectal cancer included in at least one of trials)	RCTs	Minimum 150 patients with primary outcomes of survival Authors of review are primary investigators in 4 included trials Meta-analysis of individual patient data with 3 years of follow-up data
Jackson 2007 [35] (US)	Feb 2006	Colorectal cancer (colon and rectosigmoid as per inclusion criteria, but selected RCTs include rectal cancers)  <u>Excluded</u> : benign pathologies	RCTs	Primary outcome: survival and recurrence Inclusion/exclusion of mid and low rectal cancer is not clearly specified Meta-analysis of survival outcomes using time-to-event data Significant assessment of heterogeneity
Abraham 2007 [36] (Australia)	Dec 2003	Colorectal cancer (non-metastatic, treated with intention to cure)  <u>Excluded</u> uncontrolled series	Observational	Limited to English Limited to end of 2003 Quality assessment of papers done but not utilized in analysis (to be reported separately) Limited assessment of heterogeneity
Kuhry 2007 [37] (Norway)	Apr 2006	Colorectal cancer	RCTs	In Norwegian, limited to English Very limited methodological description
Kuhry 2008 [38] (Norway)	Jan 2008	Colorectal cancer (reporting long-term result, non-metastasized carcinoma)	RCTs	Cochrane review, protocol published 2002 Meta-analysis of survival outcomes using time-to-event data Sensitivity analyses done separately for colon and rectum
Lourenco 2008 [39] (UK)	May 2007	Colorectal cancer  <u>Excluded</u> patients undergoing palliative treatment	RCTs IPD meta-analyses	Pre-2000 RCTs identified from existing systematic reviews Extensive description of methodology Overlap with Murray 2006
Anderson 2008 [40] (US)	Nov 2007	Rectal cancer  <u>Excluded</u> tumors invading adjacent organs, previous pelvic surgery, contraindications to pneumoperitoneum, obstruction, perforation, studies which did not report rectal cancer outcomes separately	RCTs Observational	Limited to English language RCT and observational studies pooled together

Liang 2008 [41] (China)	Jan 2007	Colorectal cancer  <u>Excluded</u> emergency surgery (obstruction, perforation), known prohibitive adhesions, studies for which colorectal cancer patients could not be analyzed separately from patients with benign pathologies	RCTs	Limited to English  Extensive assessment of heterogeneity
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\*Laparoscopic vs. open radical oncologic resection is the intervention under study unless stated otherwise.

Abbreviations – ANDEM: Agence nationale pour le développement de l'évaluation médicale; APR: abdominoperineal resection; ASERNIP-S: Australian Safety and Efficacy Register of New Interventional Procedures – Surgical; HALS: hand-assisted laparoscopic surgery; HTA: health technology assessment; IBD: inflammatory bowel disease; IPD: individual patient data; NICE: National Institute for Health and Clinical Excellence; RCT: randomized controlled trials; UETS: Unidad de Evaluación de Tecnologías Sanitarias; UK: United Kingdom; US: United States.

## RESULTS

### *Description of included reviews*

A total of 5,800 single citation records were screened for inclusion (figure 2). After applying a two-step screening process, a total of 27 full-text systematic reviews and/or meta-analyses [10, 16-41] were included in this overview. One Chinese-language review, which based on its English abstract would have been included, was excluded from the final analysis due to resource limitations [42]. Another systematic review was excluded, as it focused solely on the methodological quality of RCTs identified in a Cochrane Review by the same author [43]. Finally, two more reviews were excluded as they addressed cost outcomes [44] and hand-assisted vs. standard laparoscopic colorectal surgery [45], respectively. Other primary data papers and reviews identified in figure 2 have also been included, and will form the basis for a separate publication. The full list of citations is available from the authors upon request.

The characteristics of all included reviews are provided in table 1. Included reviews were published between 1994 and 2008, of which 19/27 (70%) were published in 2005 or later. Three groups published updates of their own reviews, but did not label them as such [10, 17, 19, 23, 29, 39]. A majority of reviews (n=18, 67%) were published in traditional print journals, while the remainder comprised commissioned reports (n=4, 15%) [16, 17, 23, 24], Cochrane Reviews (n=3, 11%) [26, 30, 38], and Health Technology Assessment (HTA) report (n=2, 7.4%) [10, 18]. The mean 5-year impact factor associated with published reports was 4.02 (n=20, 95% CI: 3.07, 4.96). These originated in 12 countries, with Europe (n=14, 52%) and Australia (n=5, 19%) accounting for a majority of papers. Five reviews were presented in non-English languages, including French (n=2), Spanish (n=2), and Norwegian (n=1).

Among included reviews, four (15%) addressed exclusively rectal cancer [27, 30, 31, 41], one (3.7%) reviewed only colon cancer [25], whereas the remainder were less specific

and identified “colorectal cancer” as their population of choice (table 1 and 2). This descriptor led to contradictions in certain papers, as the authors sometimes specifically excluded rectal cancer, but then went on to include papers with “rectosigmoid cancers” or “anterior resections” [17, 19, 34]. A total of 4 (15%) reviews were wide in scope and addressed the laparoscopic treatment of all colorectal pathologies, of which colorectal cancer was a subset of patients [16, 20, 21, 33]. All reviews sought to find studies comparing laparoscopic and open radical resection for cancer. One early paper found no controlled study, and was thus limited to case series of laparoscopic surgery for colorectal cancer [16]. Right hemicolectomy, left hemicolectomy, and sigmoid resection were the most commonly included types of colonic resections. All publications not limited exclusively to rectal cancer included those three procedures. In contrast, studies including transverse colectomies were frequently excluded by review authors [17, 19, 22, 32].

All reviews except one set out to include RCTs as part of their analyses (table 1). One group chose to focus solely upon observational studies [36]. A total of 13 (48%) reviews allowed only RCTs as part of their inclusion criteria. Of these, 77% were published in 2006 or later. One such group selected only 4 larger RCTs, and carried out a meta-analysis of individual patient data [34]. Two reviews whose last literature searches were in 1993 [16] and 1997 [20], respectively, were unable to identify any published RCTs. As a result, both groups presented only observational studies.

Table 2 provides an overview of the purposes, disease processes, and outcomes addressed by each systematic review. The self-described purposes were highly comparable, with most papers choosing to address issues of efficacy or effectiveness in broad terms. Long-term oncologic outcomes were sought by 19/27 reviewers (70%), while oncologic surrogates were found in 22 (81%) reviews. Similarly, operative and short-term postoperative outcomes were analyzed in 74% (n=20) and 78% (n=21) of reviews, respectively. A total of 13 (48%) reviews addressed all four outcomes types, while 18 (67%)

included at least three of the four. Visual inspection of table 2 reveals significant overlap in study purposes and outcomes. In contrast, long-term operative outcomes (n=4, 15%) and perioperative quality of life (n=6, 22%) were much less frequently included in the current group of systematic reviews.

### ***Methodological quality***

The included systematic reviews were generally of low to moderate quality. The mean AMSTAR methodological quality score was 5.8 (95% CI: 4.6, 7.0). A total of 8 reviews (30%) achieved a score of 9 or greater, and can be considered of high methodological quality. The quality of reviews appears to have improved in time (figure 3), with all but one high-quality review having been published in 2005 or later. Among high-quality reviews, three were published in traditional journals [32, 35, 39], three were Cochrane Reviews [26, 30, 38], and two were HTA reports [10, 18].

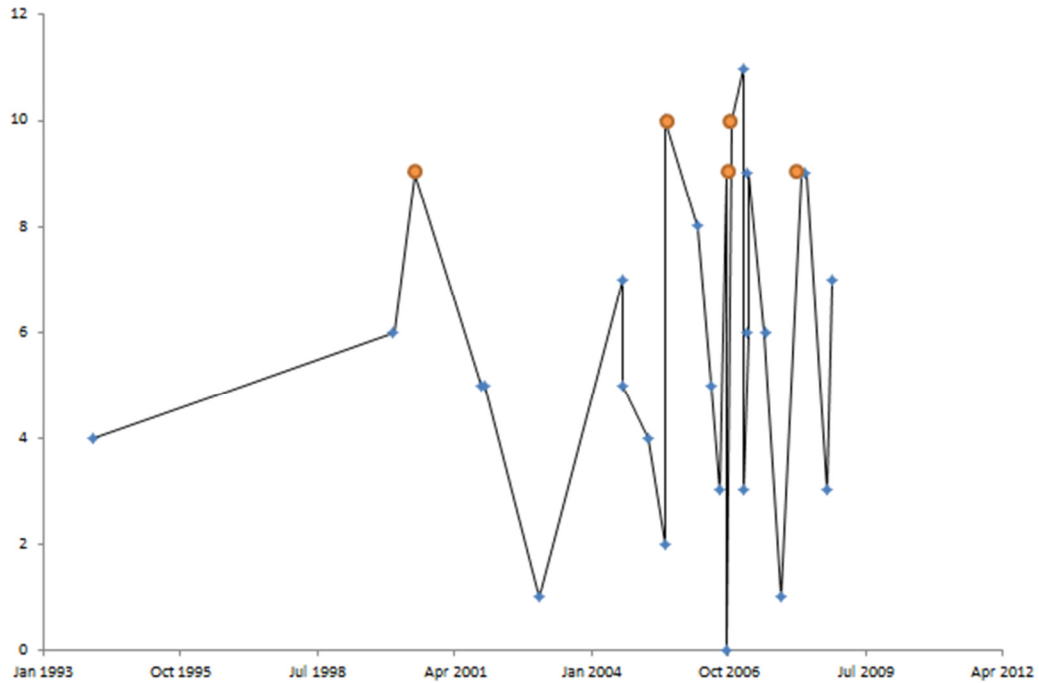
The composite of individual items within the AMSTAR score is presented in figure 4. Most review groups defined their research question and inclusion criteria a priori (20/27, 74%), and documented the evaluation of the scientific quality of included studies (20/27, 74%). Similarly, 70% of systematic reviews used appropriate methods to combine individual study results (n=19), and can be considered to have reached appropriate conclusions that reflected the methodological quality assessment of their selected papers (n=19). In contrast, few groups addressed the possibility of publication bias (7/27, 26%), provided evidence of a duplicate study selection and data extraction process (10/27, 37%), listed all included and excluded studies (10/27, 37%), or avoided limiting their search or inclusion of studies on the basis of publication status (9/27, 33%).

**Table 2.** Summary of systematic review purposes, populations, and outcomes.

Reviews	Purpose	Disease Process			Outcomes Reviewed					
		Colon CA	Rectal CA	Other	Operative	Short-term Postop	Oncologic Surrogate	Long-term Oncologic	Long-Term Other	QoL
Bernard 1994 [16]	Safety, efficacy	√	√	√	√	√	√	√		
Chapman 2000 [17]	Safety, efficacy	√	*		√	√	√	√		
Vardulaki 2000 [18]	Effectiveness, cost-effectiveness	√	√		√	√	√	√		
Chapman 2001 [19]	Safety, efficacy	√	*		√	√	√	√		
Yong 2001 [20]	Effectiveness	√	√	√	√	√	√	√		
Korolija 2003 [21]	Extent of oncologic resection	√	√	√			√			
Abraham 2004 [22]	Safety, efficacy (short-term)	√	√		√	√	√			
Reza 2004 [23]	Safety, efficacy	√	√		√	√	√	√		√
Poutignat 2005 [24]	Safety, efficacy	√	√		√	√	√	√		√
Manterola 2005 [25]	Identify best therapeutic option	√				√		√		
Schwenk 2005 [26]	Short-term benefits	√	√		√	√				√
Aziz 2006 [27]	Short/long-term results (rectal)		√		√	√	√		√	
Tjandra 2006 [28]	Update short-term results	√	√		√	√	√			
Reza 2006 [29]	Safety, efficacy	√	√		√	√	√	√		
Breukink 2006 [30]	Safety, efficacy (rectal)		√		√	√	√	√		√
Gao 2006 [31]	Safety, efficacy, benefits (rectal)		√		√	√	√			
Murray 2006 [10]	Effectiveness, cost-effectiveness	√	√		√	√	√	√	√	√
Kahnamoui 2007 [32]	Noninferiority survival/periop results	√	√		√	√	√	√		
Noel 2007[33]	Safety, efficacy (short-term)	√	√	√	√	√				
Bonjer 2007 [34]	Safety (oncologic)	√	*				√	√		
Jackson 2007 [35]	Compare oncologic results	√	√				√	√		
Abraham 2007 [36]	Safety, efficacy (non-RCT, short-term)	√	√		√	√	√			
Kuhry 2007 [37]	Not stated	√	√		√	√	√	√		
Kuhry 2008 [38]	Evaluate long-term outcomes	√	√				√	√	√	
Lourenco 2008 [39]	Update, effectiveness	√	√		√	√	√	√	√	√
Anderson 2008 [40]	Compare oncologic outcomes (rectal)		√				√	√		
Liang 2008 [41]	Evaluate recurrence outcomes	√	√					√		

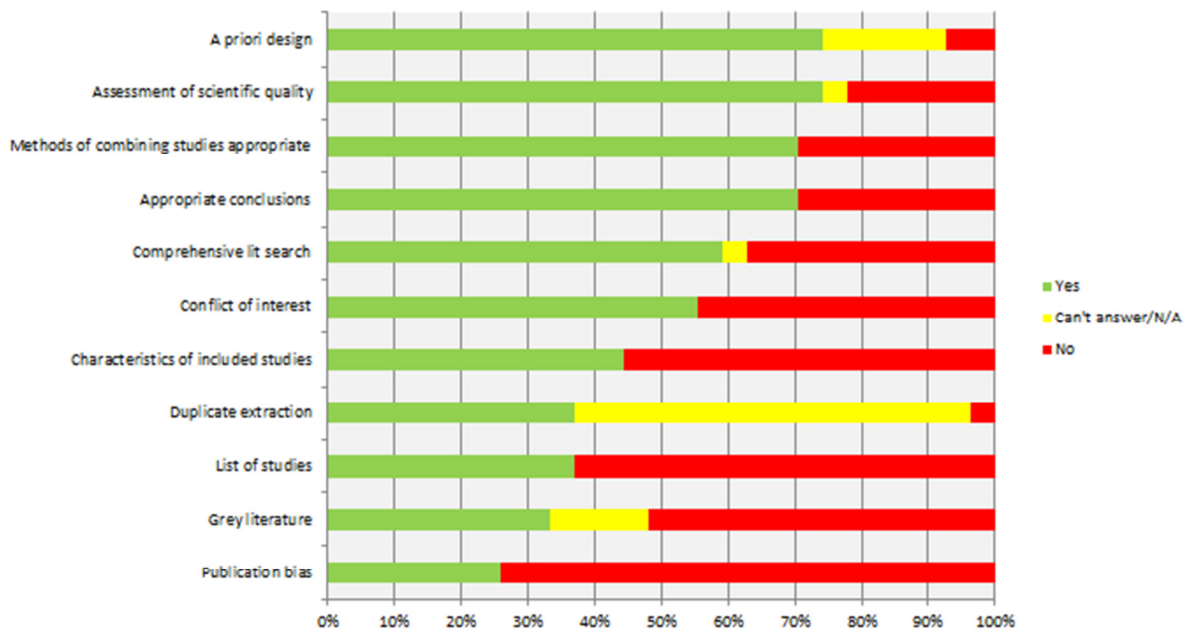
\* Unclear from descriptions whether includes high rectal cancers.

**Figure 3.** Change in AMSTAR methodological quality scores of systematic reviews in time.



\*Red circles represent Cochrane reviews and HTA reports.

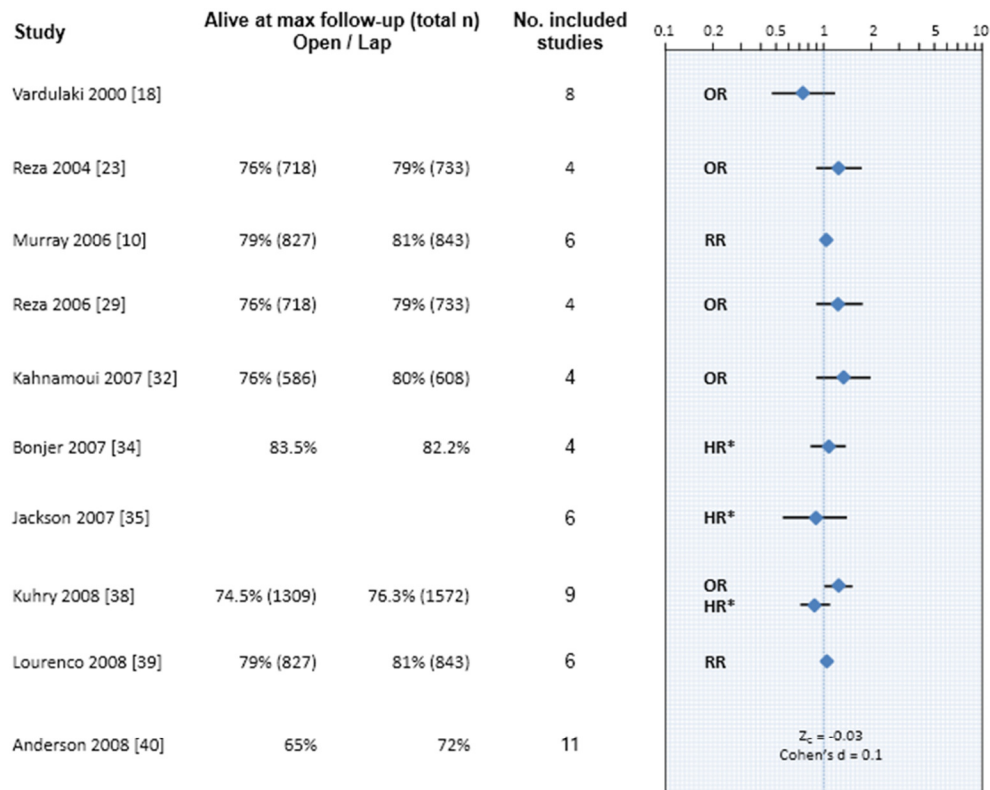
**Figure 4.** Methodological quality of included systematic reviews on the basis of individual AMSTAR items.



### Synthesis of reviewed outcomes

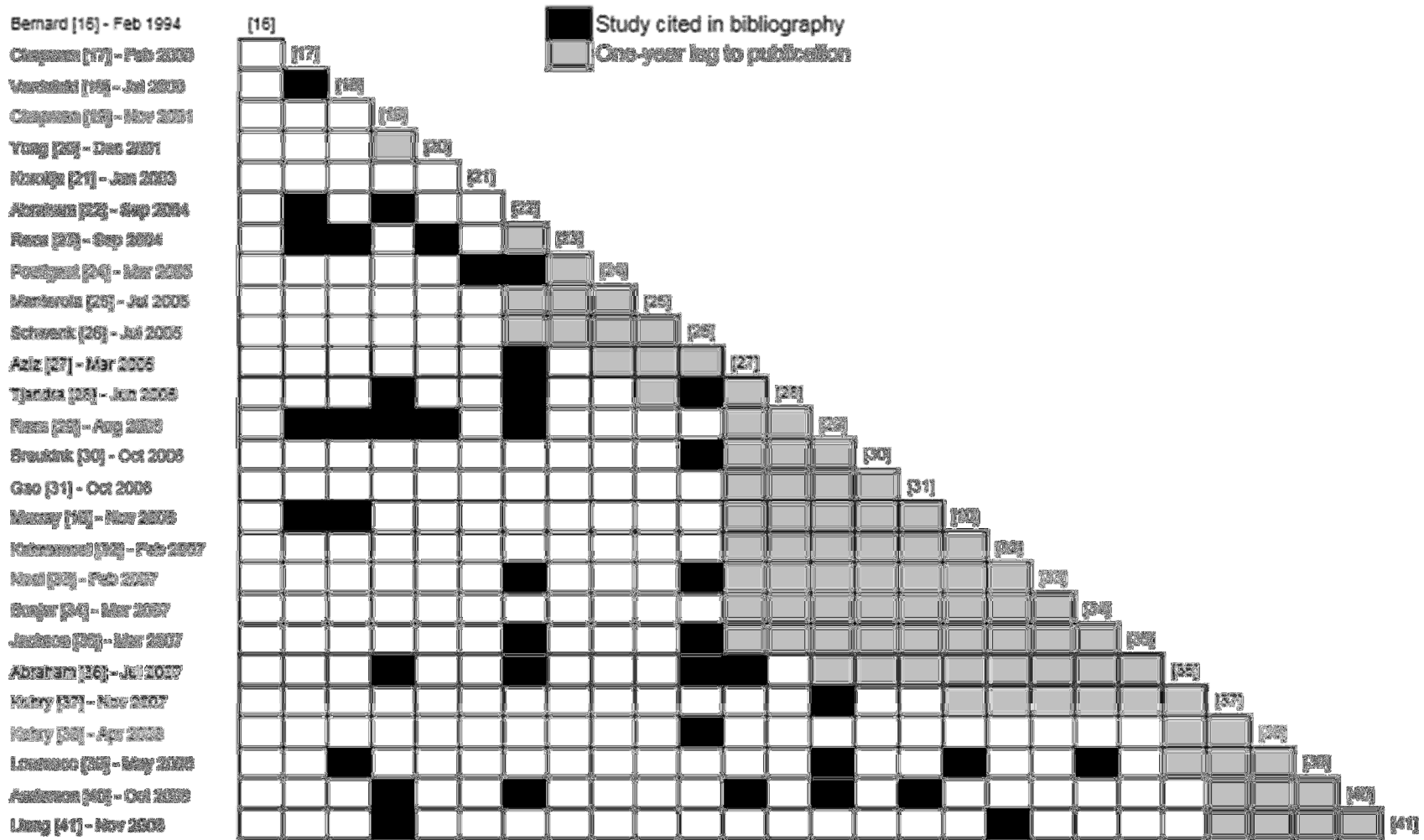
The primary outcome of overall survival was pooled quantitatively in 10 reviews (figure 5). Most authors presented this data as a dichotomous outcome (alive/dead) at maximum follow-up. After meta-analysis, this data was presented as odds ratios (OR), risk ratios (RR), and Stouffer's composite Z ( $Z_C$ ). Two groups presented this outcome as time-to-event data by pooling hazard ratios (HR), using methods relying on the estimation of HR from Kaplan-Meier curves. Finally, another group also presented a HR which was derived from an individual patient data meta-analysis. No significant difference in overall survival was found between laparoscopic and open surgery for colorectal cancer across all meta-analytic comparisons. The direction of effect for all analyses favored laparoscopy, except for one which was conducted exclusively on observational studies.

**Figure 5.** Synthesis of overall survival across systematic reviews.

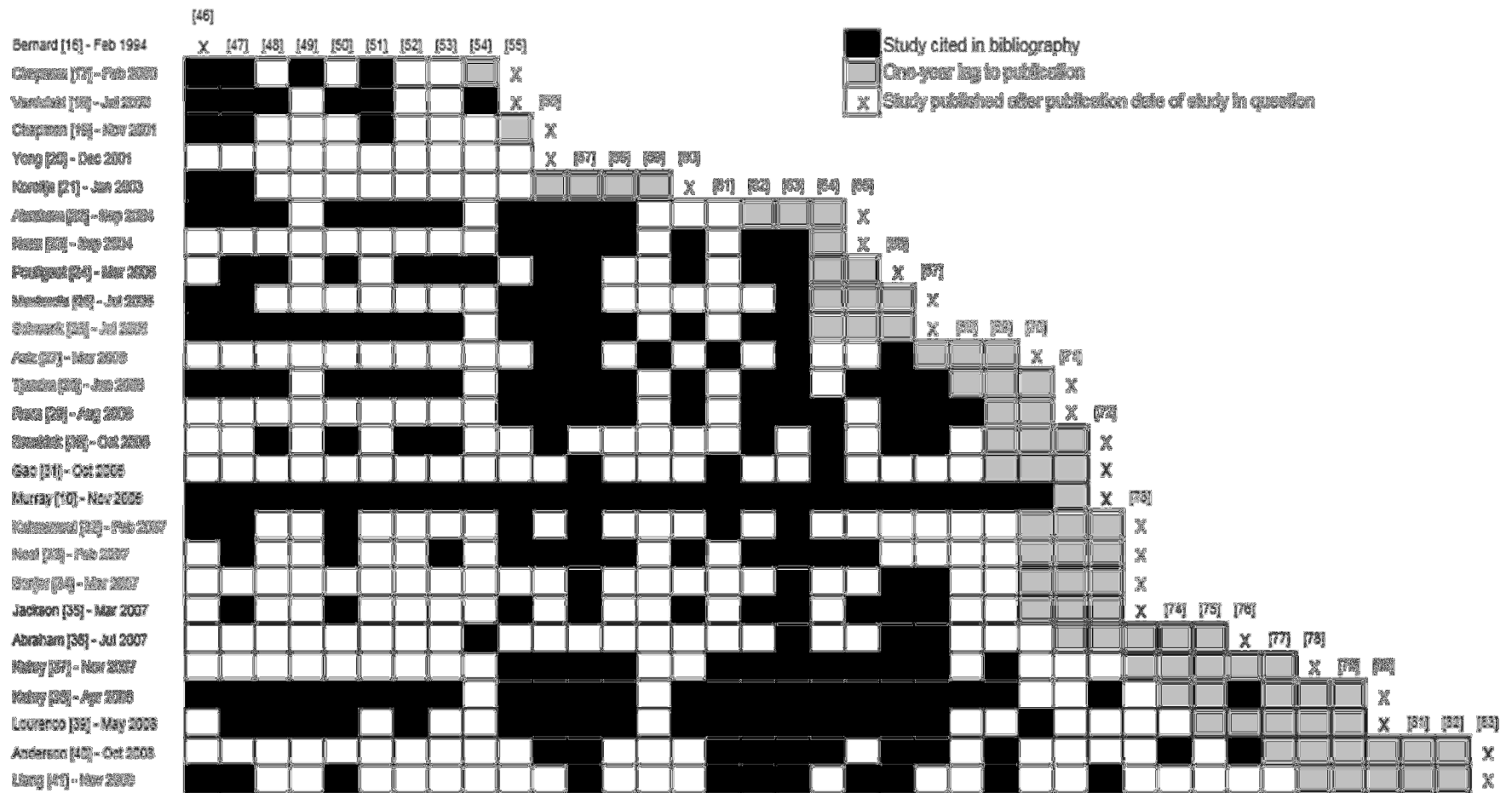


\* Hazard ratios <1 favor laparoscopic surgery, as the hazard function compares the risk of death for each study group.

**Figure 6.** Citation of previously published systematic reviews.



**Figure 7.** Citation of previously published randomized controlled trials.



All other pooled outcomes, both long-term and surrogate, yielded comparable non-significant results. These findings are not presented in the main text, but are available in appendix 2.

### ***Bibliographic analysis***

The pattern of citations of previously published systematic reviews is presented in figure 6. In total, 9 (33%) reviews did not cite any preexisting work. The maximum number of cited systematic reviews was 5, which was found in two studies [29, 40]. All other studies cited 0-4 preexisting systematic reviews. The mean number of cited existing reviews was 1.6 (95% CI: 1.0, 2.2). The mean ratio of cited to total existing systematic reviews was 0.16 (95% CI: 0.093, 0.22), ranging from 0 to 0.5. All three Cochrane Reviews (0, 0.048, 0.091) and the more recent HTA report (0.18) had citation ratios that were less than 0.2. There was no correlation between the citation ratio and the AMSTAR score ( $r=0.047$ ) or the journal's 5-year impact factor ( $r=-0.099$ ) for individual reviews. In total, 13/26 preexisting reviews were cited at least once, with 5 of these accounting for 71% of all citations (29/41) [17-19, 22, 26]. Visual inspection of figure 6 confirms that 5 reviews were cited disproportionately more frequently, and that all five reviews were published in the earlier portion of the literature review.

The current overview protocol identified 38 publications pertaining to 23 individual RCTs comparing laparoscopic and open surgery for colorectal cancer [46-83]. The patterns of citations of these RCTs are presented in figure 7. Two systematic reviews did not cite any RCTs. In the case of Bernard et al. [16], there were no RCTs yet published in the literature. In the case of Yong et al. [20], a total of 10 RCT publications could have been cited. The mean ratio of cited to total published RCT reports was 0.45 (95% CI: 0.35, 0.54), ranging from 0-1. Excluding Abraham et al. [36], which sought to analyze only observational studies, yielded a comparable mean ratio of 0.46 (95% CI: 0.36, 0.56). Given that certain RCTs were

published over multiple papers, the ratio of cited to total published RCT reports was recalculated using each trial as the denominator rather than individual papers. This analysis yielded a mean ratio of 0.56 (95% CI: 0.46, 0.65). A total of only 4 reviews identified at least 75% of RCT publications, of which 2 were Cochrane Reviews and one was an HTA report [10, 26, 28, 38]. Reviews that selected rectal cancer as their sole patient population had generally low citation ratios, ranging from 0.13 to 0.39 [27, 30, 31, 40]. Among all RCT publications, two were cited disproportionately more frequently than others. Indeed, the Barcelona trial by Lacy et al. [57] and the Clinical Outcomes of Surgical Therapy (COST) trial [63] were both cited by 90% of systematic reviews. Finally, the correlation between the citation ratios and the AMSTAR scores ( $r=0.43$ ), and between the ratios and the journal's 5-year impact factors were moderate at best ( $r=0.46$ ).

## **DISCUSSION**

In this work, we have presented an overview of published systematic reviews and meta-analyses comparing laparoscopic and open surgery for colorectal cancer. We have conducted an extensive review of the literature using a highly sensitive search algorithm, and utilized the framework proposed by the Cochrane Collaboration [9] to synthesize 27 systematic reviews and meta-analyses published between 1994 and 2008. We have summarized the major oncologic outcome of overall survival, and provided a methodological appraisal of the reviews. Finally, we have analyzed the citation patterns of all included reviews in an attempt to understand the perceived redundancy of this body of work.

The first major finding of this overview pertains to the startling number of systematic reviews and meta-analyses identified in the literature on laparoscopic colorectal cancer surgery. There were more reviews than clinical trials, and 19 reviews were published within the span of four years (2005-2008). Given that systematic reviews are typically meant to be comprehensive in nature, this result is particularly surprising. This finding can be explained

in part by the decision of certain reviewers to address only a subset of outcomes. That being said, inspection of table 2 would suggest that there is significant overlap between papers in terms of review purpose and outcomes. This argument is further supported by the large number of pooled analyses identified for the primary survival outcome in figure 5, in addition to the consistency and congruence of this result across reviews.

In addition to variation in outcomes, other authors have limited their review protocols with respect to disease subsets such as rectal cancer. This distinction may also account for a portion of the large volume of published systematic reviews, although it is unlikely to be a major factor as only four groups have focused solely on this population. More importantly, we argue that the limitation of review protocols to rectal cancer is artificial, as definitions and inclusion of rectal cancer in primary trials are highly variable. Indeed, high rectal lesions have been inconsistently defined both as rectosigmoid and rectal cancers, and this variation in terminology has been translated to different inclusion and exclusion criteria in systematic reviews. Given that high rectal cancers are typically treated in a manner that is more similar to sigmoid colon cancers, we argue that rectal cancer is best considered as part of broader reviews addressing colorectal cancer as a whole. Sensitivity analyses can then be carried out to identify outcome differences between colon and rectal cancer populations.

In addition to the above mentioned patient population and outcomes factors, it is possible that the large number of systematic reviews be a result of a duplication of research efforts on the part of individual investigators. The analysis of citation patterns of preexisting systematic reviews presented in figure 6 supports this hypothesis. Indeed, we have identified that, on average, only 1.6 preexisting reviews were referenced by individual systematic reviews. More strikingly, this corresponds to a mean ratio of cited to existing reviews of 0.16, indicating that, on average, 84% of existing systematic reviews in the literature were not found or ignored by individual review authors. This finding would support the argument that review authors either carry out poor literature evaluations or choose not to

take into account preexisting work in performing or analyzing their own reviews. Individual explanations are likely to vary, but it remains that our findings provide evidence of a duplication of research efforts in the literature.

Other examples of overlapping systematic reviews and meta-analyses can be found in the literature. In one such case, 10 reviews pertaining to the use of N-acetylcysteine for the prevention of contrast-associated nephropathy were published within a three-year span [84]. In that particular case study, the authors documented varying quality and inconsistent recommendations. Another such analysis was published in the field of orthopedic surgery, in which different methods of anterior cruciate ligament repair were compared [85]. A total of 11 overlapping systematic reviews were identified in this case, with varying conclusions. Interestingly, this group also identified evidence of incomplete citation of preexisting systematic reviews.

Several academics have recently called for the registration of systematic reviews and their protocols [3, 4]. Although the Cochrane Library currently acts as a central repository of high-quality systematic reviews and meta-analyses, it is clear from our analysis that most reviewers publish their work in traditional print journals. This interpretation is supported by Moher and colleagues who reported that approximately 2,500 new systematic reviews are published annually, of which over 90% are found in specialty journals [2]. As such, a freely-accessible registration system would have several advantages, including the early identification of preexisting, ongoing, or unpublished reviews, the prioritization of research funding, and the enhancement of collaboration between review groups, while minimizing the possibility of research duplication. This body of information would be of particular use to practicing surgeons who would now have access to systematic reviews and meta-analyses through a single portal. Duplication of systematic reviews may be minimized with the existence of such an open-access registry, and identification of preexisting work would likely be enhanced.

The continuous publication of new trials in time leads to the production and dissemination of new systematic reviews as a means to provide a synthesis of the literature that relies upon the latest data. For systematic reviews to be considered useful for end-users, they must be up to date. In the current study, at least three groups of reviewers have provided updates of their own work in subsequent publications [10, 17, 19, 23, 29, 39]. However, these were not specifically labeled as such, a finding which may lead to confusion on the part of the reader. In contrast, all three Cochrane Reviews documented having undergone substantive amendments since their original publication, as a result of new data pertinent data in the literature [26, 30, 38]. This difference between Cochrane and non-Cochrane reviews is not surprising. Indeed, Jadad et al. have previously demonstrated that only 3% of systematic reviews published in traditional journals underwent update within two years of publication, compared with 38% of Cochrane Reviews [86]. Although the timing at which systematic reviews should be updated remains controversial, it seems intuitive that, in a rapidly-progressing field of healthcare such as laparoscopic surgery for colorectal cancer, existing systematic reviews should be updated frequently [87, 88]. The case for updating systematic reviews becomes particularly compelling when one considers the large number of overlapping reviews identified in this study, and when registration of systematic reviews is considered.

The methodological quality of systematic reviews included in this study was low to moderate. As indicated, the mean AMSTAR score was 5.6, although 8/27 reviews achieved a score of 9 or greater. It is noteworthy that all Cochrane reviews and HTA reports in this study were classified as high-quality reviews. This result is supported by existing work in the literature, which demonstrated that Cochrane reviews have greater methodological rigor than traditional print reviews [86].

Although many systematic reviews in this work were deemed to have a comprehensive literature search (n=16, 59%) on AMSTAR methodology scoring, few

incorporated the grey literature (n=9, 33%). As a result, many reports fell short in their identification of published trials. Indeed, the mean ratio of cited to existing RCT reports was only 0.46 across reviews. It was only marginally better at 0.56 if one considered actual trials rather than individual reports of trials which were sometimes multiple (38 reports on 23 RCTs). Only one HTA report [10] managed to identify all reports of existing trials. This finding is concerning in that well-conducted systematic reviews are meant to be comprehensive and commonly believed to provide the highest degree of healthcare evidence [4]. Many factors may explain this finding, including the differing patient populations and outcomes examined in each review. It is also likely that the time between systematic review search completion and dissemination in electronic or print format may account for a portion of the poor citation of trials. We have attempted to avoid this form of time lag bias by allowing for a reasonable one-year grey zone between citation of RCTs and publication (figure 6 and 7). However, several systematic reviews had time lags to publication in excess of two years [19-21, 25, 32, 36] (table 1), which may partially account for a failure to identify more recent RCTs. In addition to the above factors, it is also likely that individual search strategies were not as comprehensive as should be, in order to identify all available trials. In the current study, we have modified the highly sensitive search algorithm developed by Murray and colleagues [10] and have identified at least two recent trials that have not been cited in of the existing reviews [71, 73]. Moreover, at least four other reports of RCTs were cited much less frequently than other reports of trials published around the same time period [49, 54, 59, 68, 70]. In contrast, two well-known RCTs were cited by almost all reviews [57, 63]. Putting together the above patterns of trials citations, we argue that the identification of trial evidence was incomplete in most retrieved systematic reviews, due at least in part to inadequate search strategies.

Our overview of all systematic reviews presenting data on oncologic outcomes reveals several important findings. First, we found no evidence of a consistent or congruent

difference in overall survival between patients with colon cancer treated by laparoscopy or open surgery. Similar conclusions can be drawn from other oncologic outcomes (data not shown, appendix 2). This result is likely to be extendable to patients with high rectal cancer as many large trials included this pathology [62, 66, 76]. However, our analysis cannot be extrapolated to those with mid or low rectal cancer, as too few trials have included these patients. Results from the large multicenter and multinational COLOR II (Colon Cancer Laparoscopic or Open Resection) [89], ACOSOG (American College of Surgeons Oncology Group) Z6051 [90] trials will shed light onto this area of uncertainty. That being said, it is important to note that the above conclusion is limited by the lack of proper analysis of time-to-event data. Indeed, only three meta-analyses addressing overall survival presented their data in the form of HR [34, 35, 38]. Instead, many authors simply used pooled OR, which incorporate the proportion of patients alive or dead at a given point in time in each study. While this approach provides some information on survival, it is potentially biased by variable lengths of follow-up, different trial maturity, and the incomplete utilization of available data from patient censoring [38]. Because many RCT authors do not report HR, statistical methods exist to generate such estimates from Kaplan-Meier curves [91-93]. We advocate that review groups should attempt to gather this type of data when addressing survival or other oncologic outcomes.

## **CONCLUSION**

A large number of overlapping systematic reviews and meta-analyses comparing laparoscopic and open surgery for colorectal cancer can be identified in the literature. The methodological quality of systematic reviews is generally low to moderate, as evidenced by the incomplete identification of published trials. On the whole, Cochrane Reviews and Health Technology Assessment reports demonstrate higher quality indices than most traditional print reviews. Survival outcomes are inconsistently reported and time-to-event

data are infrequently included in pooled estimates. That being said, all pooled estimates of overall survival comparing laparoscopic and open surgery for colorectal cancer are congruent and demonstrate no significant difference. There appears to be evidence of duplication of research efforts among review groups, as evidenced by overlapping review purposes, populations, and outcomes, as well as by the poor citation of pre-existing systematic reviews. Further systematic reviews or meta-analyses are unlikely to be justified without specifying a significantly different research objective. This work lends support to the registration and updating of systematic reviews.

## **REFERENCES**

1. Mulrow CD. Rationale for systematic reviews. *BMJ* 1994;309:597-599
2. Moher D, Tetzlaff J, Tricco AC, Sampson M, Altman DG. Epidemiology and reporting characteristics of systematic reviews. *PLoS Med* 2007;4(3):e78
3. Straus S, Moher D. Registering systematic reviews. *CMAJ* 2010;182:13-14
4. Booth A, Clarke M, Gherzi D, Moher D, Petticrew M, Stewart L. An international registry of systematic-review protocols. *Lancet* 2011;377:108-109
5. Fowler DL, White A. Laparoscopy-assisted sigmoid resection. *Surg Laparosc Endosc* 1991;1:183-8
6. Jacobs M, Verdeja JC, Goldstein HS. Minimally invasive colon resection (laparoscopic colectomy). *Surg Laparosc Endosc* 1991;1:144-50

7. Martel G, Boushey RP. Laparoscopic colon surgery: past, present and future. *Surg Clin N Am* 2006;86:867-97
8. Barkun JS, Aronson JK, Feldman LS, Maddern GJ, Strasberg SM. Surgical innovation 1: evaluation and stages of surgical innovation. *Lancet* 2009;374:1089-96
9. Becker LA, Oxman AD. Chapter 22: Overviews of reviews. In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester (UK): John Willey & Sons, 2008, pp. 607-631
10. Murray A, Lourenco T, de Verteuil R, Hernandez R, Fraser C, McKinley A, Krukowski Z, Vale L, Grant A. Clinical effectiveness and cost-effectiveness of laparoscopic surgery for colorectal cancer: systematic reviews and economic evaluation. *Health Technol Assess* 2006;10(45)
11. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, Porter AC, Tugwell P, Moher D, Bouter LM. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol* 2007;7:10
12. Shea BJ, Bouter LM, Peterson J, Boers M, Andersson N, Ortiz Z, Ramsay T, Bai A, Shukla VK, Grimshaw JM. External validation of a measurement tool to assess systematic reviews (AMSTAR). *PLoS One* 2007;2:e1350
13. Shea BJ, Hamel C, Wells GA, Bouter LM, Kristjansson E, Grimshaw JM, Henry DA, Boers M. *J Clin Epidemiol* 2009;62:1013-20

14. Fergusson D, Glass KC, Hutton B, Shapiro S. Randomized controlled trials of aprotinin in cardiac surgery: could clinical equipoise have stopped the bleeding? *Clinical Trials* 2005;2:218-232
15. Journal Citation Reports 2009. Available through ISI Web of Knowledge, Thompson Reuters. [www.wokinfo.com]. Accessed on 31 January 2011
16. Bernard A, Durieux P. Evaluation des methods coelioscopiques en chirurgie digestive. Agence Nationale pour le Développement de l'Évaluation Médicale, Paris, France, 1994. Available at [<http://www.has-sante.fr/portail/upload/docs/application/pdf/coeliodigestive%20.pdf>], accessed August 2008
17. Chapman A, DeNichilo D, Babidge W, Maddern G, Hewett P, Levitt M, Sheiner H, Woods R. Systematic review of laparoscopic-assisted resection of colorectal malignancies. ASERNIP-S Report No. 8. ASERNIP-S, Adelaide, South Australia, 2000. Available at [<http://www.surgeons.org/racs/research-and-audit/asernip-s/asernip-s-publications/systematic-reviews/laparoscopic-assisted-resection-of-colorectal-malignancies>], accessed August 2008
18. Vardulaki KA, Bennett-Lloyd BD, Parfitt J, Normond C, Paisley S, Darzi A, Reeves BC. A systematic review of the effectiveness and cost-effectiveness of laparoscopic surgery for colorectal cancer. National Institute for Health and Clinical Excellence, 2000. Report no longer available on NICE website, full-text obtained from [<http://www.bristolsurgery.com/Documents/HTAreportonlapsurgcoloreccanc.pdf>] on 5 February 2011

19. Chapman AE, Levitt MD, Hewett P, Woods R, Sheiner H, Maddern GJ. Laparoscopic-assisted resection of colorectal malignancies: a systematic review. *Ann Surg* 2001;234:590-606
20. Yong L, Deane M, Monson JRT, Darzi A. Systematic review of laparoscopic surgery for colorectal malignancy. *Surg Endosc* 2001;15:1431-1439
21. Korolija D, Tadic S, Simic D. Extent of oncological resection in laparoscopic vs. open colorectal surgery: meta-analysis. *Langenbecks Arch Surg* 2003;387:366-371
22. Abraham NS, Young JM, Solomon MJ. Meta-analysis of short-term outcomes after laparoscopic resection for colorectal cancer. *Br J Surg* 2004;91:1111-1124
23. Reza MM, Blasco JA. Eficacia y seguridad de la cirugía laparoscópica vs cirugía abierta en el cancer colorrectal. Unidad de Evaluación de Tecnologías Sanitarias (UETS), Área de Investigación y Estudios Sanitarios Agencia Laín Entralgo, Madrid, Spain, 2004. Available from [[http://www.madrid.org/cs/Satellite?cid=1142494649964&language=es&pagename=PortalSalud%2FPPage%2FP TSA\\_pintarContenidoFinal&vest=1142494649964](http://www.madrid.org/cs/Satellite?cid=1142494649964&language=es&pagename=PortalSalud%2FPPage%2FP TSA_pintarContenidoFinal&vest=1142494649964)], accessed January 2009
24. Poutignat N, Bataille N, Obrecht O, Zaleski ID. Comparison of laparoscopic and open surgery in colorectal cancer. Haute Autorité de Santé, Saint-Denis La Plaine, France, 2005. Available from [[http://www.has-sante.fr/portail/jcms/c\\_272421/coelioscopie-en-chirurgie-du-cancer-colo-rectal](http://www.has-sante.fr/portail/jcms/c_272421/coelioscopie-en-chirurgie-du-cancer-colo-rectal)], accessed August 2008

25. Manterola C, Pineda V, Vial M. Resección abierta frente a laparoscópica en el cancer de colon no complicado. Revisión sistemática. *Cir Esp* 2005;78:28-33
26. Schwenk W, Haase O, Neudecker JJ, Müller JM. Short term benefits for laparoscopic colorectal resection. *Cochrane Database Syst Rev* 2005;CD003145
27. Aziz O, Constantinides V, Tekkis PP, Athanasiou T, Purkayastha S, Paraskeva P, Darzi AW, Heriot AG. Laparoscopic versus open surgery for rectal cancer: a meta-analysis. *Ann Surg Oncol* 2006;13:413-424
28. Tjandra JJ, Chan MKY. Systematic review on the short-term outcome of laparoscopic resection for colon and rectosigmoid cancer. *Colorectal Dis* 2006;8:375-388
29. Reza MM, Blasco JA, Andradas E, Centero R, Mayol J. Systematic review of laparoscopic versus open surgery for colorectal cancer. *Br J Surg* 2006;93:921-928
30. Breukink S, Pierie JP, Wiggers T. Laparoscopic versus open total mesorectal excisionfor rectal cancer. *Cochrane Database Syst Rev* 2006;CD005200
31. Gao F, Cao YF, Chen LS. Meta-analysis of short-term outcomes after laparoscopic resection for rectal cancer. *Int J Colorectal Dis* 2006;21:652-656
32. Kahnamoui K, Cadeddu M, Farrokhyar F, Anvari M. Laparoscopic surgery for colon cancer: a systematic review. *Can J Surg* 2007;50:48-57

33. Noel JK, Fahrbach K, Estok R, Cella C, Frame D, Linz H, Cima RR, Dozois EJ, Senagore AJ. Minimally invasive colorectal resection outcomes: short-term comparison with open procedures. *J Am Coll Surg* 2007;204:291-307
34. Bonjer HC, Hop WC, Nelson H, Sargent DJ, Lacy AM, Castells A, Guillou PJ, Thorpe H, Brown J, Delgado S, Kuhri E, Haglind E, Pålman L; Transatlantic Laparoscopically Assisted vs Open Colectomy Trials Study Group. Laparoscopically assisted vs open colectomy for colon cancer: meta-analysis. *Arch Surg* 2007;142:298-303
35. Jackson TD, Kaplan GG, Arena G, Page JH, Rogers SO Jr. Laparoscopic versus open resection for colorectal cancer: a metaanalysis of oncologic outcomes. *J Am Coll Surg* 2007;204:439-446
36. Abraham NS, Byrne CM, Young JM, Solomon MJ. Meta-analysis of non-randomized comparative studies of the short-term outcomes of laparoscopic resection for colorectal cancer. *ANZ J Surg* 2007;77:508-516
37. Kuhry E, Sætnan E, Græslie H, Gaupset R. Laparoskopipi ved kolorektal kreft. *Tidsskr Nor Lægeforen* 2007;127:2946-2949
38. Kuhry E, Schwenk W, Gaupset R, Romild U, Bonjer HJ. Long-term results of laparoscopic colorectal cancer resection. *Cochrane Database Syst Rev* 2008;CD003432
39. Lorenzo T, Murray A, Grant A, McKinley A, Krukowski Z, Vale L. Laparoscopic surgery for colorectal cancer: safe and effective? – A systematic review. *Surg Endosc* 2008;22:1146-1160

40. Anderson C, Uman G, Pigazzi A. Oncologic outcomes of laparoscopic surgery for colorectal cancer: a systematic review and meta-analysis of the literature. *Eur J Surg Oncol* 2008;34:1135-1142
41. Liang Y, Li G, Chen P, Yu J. Laparoscopic versus open colorectal resection for cancer: a meta-analysis of results of randomized controlled trials on recurrence. *Eur J Surg Oncol* 2008;34:1217-1224
42. Li J, Ding K, Zhang S. Meta-analysis of short-term efficacy and safety after laparoscopic resection for colorectal cancer. *Natl Med J China* 2006;86:2485-2490
43. Schwenk W, Haase O, Günther N, Neudecker J. Methodological quality of randomised controlled trials comparing short-term results of laparoscopic and conventional colorectal resection. *Int J Colorectal Dis* 2007;22:1369-1376
44. Aalbers AG, Biere SS, van Berge Henegouwen MI, Bemelman WA. Hand-assisted or laparoscopic-assisted approach in colorectal surgery: a systematic review and meta-analysis. *Surg Endosc* 2008;22:1769-1780
45. Dowson HM, Huang A, Soon Y, Gage H, Lovell DP, Rockall TA. Systematic review of the costs of laparoscopic colorectal surgery. *Dis Colon Rectum* 2007;50:908-919
46. Lacy AM, Garcia-Valdecasas JC, Pique JM, Delgado S, Campo E, Bordas JM, Taura P, Grande L, Fuster J, Pacheco JL, Visa J. Short-term outcome analysis of a randomized study comparing laparoscopic vs open colectomy for colon cancer. *Surg Endosc* 1995;9:1101-1105

47. Stage JG, Schulze S, Moller P, Overgaard H, Andersen M, Rebsdorf-Pedersen VB, Nielsen HJ. Prospective randomized study of laparoscopic versus open colonic resection for adenocarcinoma. *Br J Surg* 1997;84:391-39
48. Schwenk W, Böhm B, Haase O, Junghans T, Müller JM. Laparoscopic versus conventional colorectal resection: a prospective randomized study of postoperative ileus and early postoperative feeding. *Langenbecks Arch Surg* 1998;383:49-55
49. Schwenk W, Bohm B, Muller JM. Influence of laparoscopic or conventional colorectal resection on postoperative quality of life. *Zentralbl Chir* 1998;123:483-490
50. Milsom JW, Böhm B, Hammerhofer KA, Fazio V, Steiger E, Elson P. A prospective, randomized trial comparing laparoscopic versus conventional techniques in colorectal cancer surgery: a preliminary report. *J Am Coll Surg* 1998;187:46-54
51. Lacy AM, Delgado S, Garcia-Valdecasas JC, Castells A, Pique JM, Grande L, Fuster J, Targarona EM, Pera M, Visa J. Port site metastases and recurrence after laparoscopic colectomy: a randomized trial. *Surg Endosc* 1998;12:1039-1042
52. Schwenk W, Bohm B, Muller JM. Postoperative pain and fatigue after laparoscopic or conventional colorectal resections. *Surg Endosc* 1998;12:1131-1136
53. Schwenk W, Bohm B, Witt C, Junghans T, Grundel K, Muller JM. Pulmonary function following laparoscopic or conventional colorectal resection: a randomized controlled evaluation. *Arch Surg* 1999;134:6-12

54. Delgado S, Lacy AM, Garcia-Valdecasas JC, Balague C, Pera M, Salvador L, Momblan D, Visa J. Could age be an indicator for laparoscopic colectomy in colorectal cancer. *Surg Endosc* 2000;14:22-26
55. Curet MJ, Putrakul K, Pitcher DE, Josloff RK, Zucker KA. Laparoscopically assisted colon resection for colon carcinoma: prospective results and long-term outcome. *Surg Endosc* 2000;14:1062-1066
56. Weeks JC, Nelson H, Gelber S, Sargent D, Schroeder G. Short-term quality-of-life outcomes following laparoscopic-assisted colectomy vs open colectomy for colon cancer: a randomized trial. *JAMA* 2002;287:321-328
57. Lacy AM, Garcia-Valdecasas JC, Delgado S, Castells A, Taura P, Pique JM, Visa J. Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomized trial. *Lancet* 2002;359:2224-2229
58. Winslow ER, Fleshman JW, Birnbaum EH, Brunt LM. Wound complications of laparoscopic vs open colectomy. *Surg Endosc* 2002;16:1420-1425
59. Quah HM, Jayne DG, Eu KW, Seow-Choen F. Bladder and sexual dysfunction following laparoscopically assisted and conventional open mesorectal resection for cancer. *Br J Surg* 2002;89:1551-1556

60. Hasegawa H, Kabeshima Y, Watanabe M, Yamamoto S, Kitajima M. Randomized controlled trial of laparoscopic versus open colectomy for advanced colorectal cancer. *Surg Endosc* 2003;17:636-640
61. Araujo SE, da Silva e Sousa AH Jr, de Campos FG, Habr-Gama A, Dumarco RB, Caravatto PP, Nahas SC, da Silva J, Kiss DR, Gama-Rodrigues JJ. Conventional approach x laparoscopic abdominoperineal resection for rectal cancer treatment after neoadjuvant chemoradiation: results of a prospective randomized trial. *Rev Hosp Clin Fac Med Sao Paulo* 2003;58:133-140
62. Leung KL, Kwok SP, Lam SC, Lee JF, Yiu RY, Ng SS, Lai PB, Lau WY. Laparoscopic resection of rectosigmoid carcinoma: prospective randomized trial. *Lancet* 2004;363:1187-1192
63. Clinical Outcomes of Surgical Therapy Study Group. A comparison of laparoscopically assisted and open colectomy for colon cancer. *N Engl J Med* 2004;350:2050-2059
64. Zhou ZG, Hu M, Li Y, Lei WZ, Yu YY, Cheng Z, Li L, Shu Y, Wang TC. Laparoscopic vs open total mesorectal excision with anal sphincter preservation for low rectal cancer. *Surg Endosc* 2004;18:1211-1215
65. Kaiser AM, Kang JC, Chan LS, Vukasin P, Beart RW Jr. Laparoscopic-assisted vs. open colectomy for colon cancer: a prospective randomized trial. *J Laparoendosc Adv Surg Tech A* 2004;14:329-334

66. Guillou PJ, Quirke P, Thorpe H, Walker J, Jayne DG, Smith AM, Heath RM, Brown JM. Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. *Lancet* 2005;365:1718-1726
67. Colon Cancer Laparoscopic or Open Resection Study Group. Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. *Lancet Oncol* 2005;6:477-484
68. Jayne DG, Brown JM, Thorpe H, Walker J, Quirke P, Guillou PJ. Bladder and sexual function following resection for rectal cancer in a randomized clinical trial of laparoscopic versus open technique. *Br J Surg* 2005;92:1124-1132
69. Braga M, Frasson M, Vignali A, Zuliani W, Civelli V, Di Carlo V. Laparoscopic vs. open colectomy in cancer patients: long-term complications, quality of life, and survival. *Dis Colon Rectum* 2005;48:2217-2223
70. King PM, Blazeby JM, Ewings P, Franks PJ, Longman RJ, Kendrick AH, Kipling RM, Kennedy RH. Randomized clinical trial comparing laparoscopic and open surgery for colorectal cancer within an enhanced recovery programme. *Br J Surg* 2006;93:300-308
71. Arteaga Gonzalez I, Diaz Luis H, Martin Malagon A, Lopez-Tomassetti Fernandez EM, Arranz Duran J, Carrillo Pallares A. A comparative clinical study of short-term results of laparoscopic surgery for rectal cancer during the learning curve. *Int J Colorectal Dis* 2006;21:590-595

72. Liang JT, Huang KC, Lai HS, Lee PH, Jeng YM. Oncologic results of laparoscopic versus conventional open surgery for stage II and III left-sided colon cancers: a randomized controlled trial. *Ann Surg Oncol* 2007;14:109-117
73. Pechlivanides G, Gouvas N, Tsiaoussis J, Tzortzinis A, Tzardi M, Moutafidis M, Dervenis C, Xynos E. Lymph node clearance after total mesorectal excision for rectal cancer: laparoscopic versus open approach. *Dig Dis* 2007;25:94-99
74. Braga M, Frasson M, Vignali A, Zuliani W, Capretti G, Di Carlo V. Laparoscopic resection in rectal cancer patients: outcomes and cost-benefit analysis. *Dis Colon Rectum* 2007;50:464-471
75. Janson M, Lindholm E, Anderberg B, Haglind E. Randomized trial of health-related quality of life after open and laparoscopic surgery for colon cancer. *Surg Endosc* 2007;21:747-753
76. Jayne DG, Guillou PJ, Thorpe H, Quirke P, Copeland J, Smith AMH, Heath RM, Brown JM. Randomized trial of laparoscopic-assisted resection of colorectal carcinoma: 3-year results of the UK MRC CLASICC trial group. *J Clin Oncol* 2007;25:3061-3068
77. Fleshman J, Sargent DJ, Green E, Anvari M, Stryker SJ, Beart RW Jr, Hellinger M, Flanagan R Jr, Peters W, Nelson H. Laparoscopic colectomy for cancer is not inferior to open surgery based on 5-year data from the COST Study Group Trial. *Ann Surg* 2007;246:655-664

78. Chung CC, Ng DCK, Tsang WWC, Tang WL, Yau KKK, Cheung HYS, Wong JCH, Li MKW. Hand-assisted laparoscopic versus open right hemicolectomy: a randomized controlled trial. *Ann Surg* 2007;246:728-733
79. Ramacciato G, D'Angelo F, Aurello P, Nigri G, Valabrega S, Pezzoli F, Ravaioli M, Cescon M, Cucchetti A, Lauro A, Del Gaudio M, Ercolani G. Right hemicolectomy for colon cancer: a prospective randomised study comparing laparoscopic vs open technique. *Chir Ital* 2008;60:1-7
80. Lacy AM, Delgado S, Castells A, Prins HA, Arroyo V, Ibarzabal A, Pique JM. The long-term results of a randomized clinical trial of laparoscopy-assisted versus open surgery for colon cancer. *Ann Surg* 2008;248:1-7
81. King PM, Blazeby JM, Ewings P, Kennedy RH. Detailed evaluation of functional recovery following laparoscopic or open surgery for colorectal cancer with an enhanced recovery programme. *Int J Colorectal Dis* 2008;23:795-800
82. Ng SSM, Leung KL, Lee JFY, Yiu RYC, Li JCM, Teoh AYB, Leung WW. Laparoscopic-assisted versus open abdominoperineal resection for low rectal cancer: a prospective randomized trial. *Ann Surg Oncol* 2008;15:2418-2425
83. Hewett PJ, Allardyce RA, Bagshaw PF, Frampton CM, Frizelle FA, Rieger NA, Smith JS, Solomon MJ, Stephens JH, Stevenson ARL. Short-term outcomes of the Australasian randomized clinical study comparing laparoscopic and conventional open surgical treatments for colon cancer: the ALCCaS trial. *Ann Surg* 2008;248:728-738

84. Biondi-Zoccai GGL, Lotrionte M, Abbate A, Testa L, Remigi E, Burzotta F, Valgimigli M, Romagnoli E, Crea F, Agostoni P. Compliance with QUOROM and quality of reporting of overlapping meta-analyses on the role of acetylcysteine in the prevention of contrast associated nephropathy: case study. *BMJ* 2006;332:202-209
85. Poolman RW, Abouali JAK, Conter HJ, Bhandari M. Overlapping systematic reviews of anterior cruciate ligament reconstruction comparing hamstring autograft with bone-patellar tendon-bone autograft: why are they different? *J Bone Joint Surg Am* 2007;89:1542-1552
86. Jadad AR, Cooks DJ, Jones A, Klassen TP, Tugwell P, Moher M, Moher D. Methodology and reports of systematic reviews and meta-analyses. A comparison of Cochrane reviews with articles published in paper-based journals. *JAMA* 1998;280:278-80
87. Moher D, Tsertsvadze A, Tricco AC, Eccles M, Grimshaw J, Sampson M, Barrowman N. When and how to update systematic reviews. *Cochrane Database Syst Rev* 2008;(1):MR000023
88. French SD, McDonald S, McKenzie JE, Green SE. Investing in updating: how do conclusions change when Cochrane systematic reviews are updated? *BMC Med Res Methodol* 2005;5:33
89. COLOR II Study Group, Buunen M, Bonjer HJ, Hop WC, et al. COLOR II. A randomized clinical trial comparing laparoscopic and open surgery for rectal cancer. *Dan Med Bull* 2009;56:89-91

90. American College of Surgeons Oncology Group. Laparoscopic-assisted resection or open resection in treating patients with stage IIA, stage IIIA, or stage IIIB rectal cancer. 2011. Available at [[www.clinicaltrials.gov](http://www.clinicaltrials.gov)], identifier NCT00726622. Accessed 12 February 2011
91. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007;8:16
92. Williamson PR, Smith CT, Hutton JL, Marson AG. Aggregate data meta-analysis with time-to-event outcomes. *Statist Med* 2002;21:3337-3351
93. Parmar MKB, Torri V, Stewart L. Extracting summary statistics to perform meta-analysis of the published literature for survival endpoints. *Statist Med* 1998;17:2815-2834
94. Moher D, Liberati A, Tetzlaff J, Altman D, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6(7):e1000097

## **BRIDGE**

In the previous chapter of this work, we have provided a global overview of oncologic outcomes of laparoscopic and open surgery for colorectal cancer, as derived from existing systematic reviews and meta-analyses in the literature. As well, we have provided a critical analysis of methods pertaining to research data synthesis in surgery, which is highly important in understanding adoption patterns of novel technologies.

In the next chapter, we carry out our own rigorous systematic review and meta-analysis of oncologic data pertaining to laparoscopic colorectal cancer surgery. In addition, we derive estimates of the degree of adoption of this technology by quantifying summary expert opinions in the literature.

## **CHAPTER THREE: RANDOMIZED CONTROLLED TRIALS**

### **ONCOLOGIC OUTCOMES OF LAPAROSCOPIC AND OPEN COLORECTAL CANCER SURGERY: SYSTEMATIC REVIEW OF RANDOMIZED TRIALS AND CORRELATION WITH EXPERT OPINION**

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## INTRODUCTION

Laparoscopic surgical techniques were first introduced as a treatment for colorectal pathologies in 1991 [1, 2]. Since this pioneering work by Fowler & White and Jacobs and colleagues, an abundance of literature has been published detailing the application of this novel technology to both benign and malignant colorectal disorders [3]. In the early days, surgeons were quick to embrace laparoscopic surgery for benign colorectal conditions such as diverticulitis and inflammatory bowel disease, on the basis of perceived improvements in length of stay in hospital, postoperative pain, bowel function, and return to normal activities, as well as obvious cosmetic advantages [3-5]. On the other hand, the adoption of laparoscopic surgery to treat colorectal cancer has lagged behind that of benign conditions, and has been highly controversial over the last twenty years.

As with any other malignant disorder, novel surgical technologies used to treat patients with curable colorectal cancer must be demonstrated to achieve improved or, at a minimum, equivalent survival outcomes. While surgical innovation has traditionally lacked in research rigor and utilized a trial-and-error approach, many surgeon-scientists now argue that novel technologies must be scrutinized carefully and tested using robust research methods [6]. It is widely agreed that randomized controlled trials (RCTs) provide the highest standard of evidence in evaluating healthcare interventions. In this context, it is not surprising that several RCTs comparing laparoscopic and open surgery for colorectal cancer have been conducted over the years, many of which have now yielded long-term oncologic outcomes.

In spite of an abundance of published data, both RCTs and observational studies, very few groups have attempted to synthesize survival data pertaining to laparoscopic and open surgery for colorectal cancer using robust statistical methods. In addition, it remains unclear whether surgeons have chosen to adopt this novel technology on the basis of published high-level survival evidence. As such, the objective of this study was to

synthesize survival outcomes from all published randomized controlled trials of laparoscopic and open colorectal cancer surgery. As well, we sought to identify patterns in expert acceptance of this technology in the literature and to correlate it with survival data evidence obtained in our synthesis of clinical trials.

## **MATERIALS AND METHODS**

The global methodological approach to this work was that of a comprehensive systematic review of the literature pertaining to laparoscopic and open surgery for colorectal cancer. This study was then further subdivided into two main methodological stages. In the first stage, a synthesis and meta-analysis of oncologic outcomes derived from existing RCTs was carried out. In the second stage, review articles were utilized to generate a measure of expert opinion pertaining to the acceptability of laparoscopy in treating colorectal cancer. As such, review authors' opinions on this topic in the literature were used as a surrogate indicator of the general acceptability and uptake of this technology among surgeons. Finally, a temporal evaluation of this information was generated and correlated with the results of the meta-analysis of oncologic outcomes. This work was part of a larger review effort addressing both primary publications and review papers, the results of which will be presented over several publications. A systematic review protocol was developed for the project.

### ***Eligibility criteria***

All inclusion and exclusion criteria were defined a priori and specified in the review protocol. Both primary data and review publications were included in this work. Specifically, allowable primary study designs included RCTs, controlled observational studies, and uncontrolled observational studies. Among these, only RCTs are addressed further in the current report. Review articles included narrative reviews, systematic reviews and meta-

analyses, textbook chapters, and guidelines/policy statements. All types of review citations were included in this study.

All included citations pertained to patients with primary carcinoma of the colon or rectum of any stage. The primary intent of the citation had to be to address the treatment of colorectal cancer specifically. Included patients had to undergo a segmental resection of the colon (ileocecal, right, extended right, transverse, left, extended left, or sigmoid colon resection) or rectum (anterior, low anterior, or abdominoperineal resection) by laparoscopic, laparoscopic-assisted, or hand-assisted laparoscopic surgery. The control intervention was traditional open surgery (laparotomy/celiotomy or mini-laparotomy). To be considered for inclusion, citations had to provide data on the primary outcome of overall survival, or on at least one of the secondary endpoints: other measures of survival, operative outcomes, short-term postoperative outcomes, long-term postoperative outcomes, quality of life.

Primary data papers were excluded from consideration if they were published before 1991, if they included any patients with benign colorectal conditions (eg. diverticular disease, volvulus) or non-carcinoma tumors (eg. neuroendocrine, lymphoma), or if they included patients undergoing interventions other than laparoscopy (eg. robotic-assisted resection, transanal resection). Other criteria by which citations were excluded were other types of non-segmental colorectal resections (eg. total colectomy), emergency operations, purely palliative procedures, observational studies providing data on fewer than 10 patients undergoing laparoscopic resection, other study designs not covered in the inclusion criteria, and animal or laboratory studies not involving patients. Conference abstracts and other unpublished trials were considered acceptable for inclusion if sufficient data could be extracted based on inclusion and exclusion criteria mentioned above.

For review papers, inclusion criteria were purposely less strictly defined so as to capture the entire spectrum of publications pertaining to the laparoscopic treatment of colorectal cancer published since 1991. Reviews on laparoscopic surgery for colorectal

cancer were included if they were not limited to single specific outcomes other than oncologic outcomes (eg. postoperative pain). All reviews addressing the surgical care of colorectal cancer in general terms were included, as a lack of discussion of laparoscopy would indicate that the authors do not consider it relevant.

### ***Search methods for identification of citations***

A comprehensive search strategy was designed to identify both primary comparative literature and review citations pertaining to laparoscopic and open surgery for colorectal cancer. The final search algorithm was devised in conjunction with an experienced information specialist from the Ottawa Hospital Library (appendix 1). This search strategy was designed to be highly sensitive, and was modified from previously published work [7]. Six major databases were searched for relevant citations from 1991-2008 (Ovid MEDLINE, Ovid EMBASE, Cochrane Library, Science Citation Index Expanded, BIOSIS Preview, and BIREME LILACS). An additional thirteen databases were also searched for relevant citations (Database of Abstracts of Reviews of Effectiveness, Health Technology Assessment Database, NHS Economic Evaluation Database, NIHR Health Technology Assessment Programme, Trip Database, Clinicaltrials.gov, Controlled-trials.com, National Guidelines Clearinghouse, CMA Infobase: Clinical Practice Guidelines, NICE England, SIGN Scotland, NHMRC Australia, New Zealand Guidelines Group). In addition, all editions of nine major surgical textbooks published since 1991 were included for consideration (Schwartz's Principles of Surgery, Sabiston Textbook of Surgery, Greenfield's Surgery, Cameron's Current Surgical Therapy, Shackelford's Surgery of the Alimentary Tract, Mastery of Surgery, Gordon's Surgery of the Colon, Rectum and Anus, Corman's Colon and Rectal Surgery, and Fazio's Current Therapy in Colon & Rectal Surgery).

The reference lists of all included citations were screened to identify missing trials and reviews. No language limitation was applied to the search strategy. All citation records

were retrieved and downloaded electronically using Reference Manager 10 (ISI ResearchSoft, Berkeley, CA), and were then de-duplicated manually.

### ***Selection of citations***

All citations were first screened for inclusion on the basis of titles and abstracts (figure 2). All retained citations were then retrieved in full text. Papers which could not be obtained after extensive international interlibrary searches were considered missing. Papers published in languages other than English, French, or Spanish were translated in full using Google Translate (Google Inc., Mountain View, CA). Despite our lack of language restrictions, citations in Asian languages included after the first screen had to be excluded from further consideration due to translation resource limitations. Full-text articles were then evaluated for inclusion. Included articles were then classified as 1) primary studies or 2) review papers. Review papers were further divided as systematic reviews/meta-analyses, narrative reviews, textbook chapters, and guidelines/position papers. All paper types were considered in the current review, except for observational studies, which will form the basis of a future publication.

### ***Risk of bias assessment***

Each included trial was examined for its risk of bias using the approach advocated by the Cochrane Collaboration [8]. Using this framework, each trial was appraised using seven common items: 1) random sequence generation, 2) allocation concealment, 3) blinding of participants and personnel, 4) blinding of outcome assessment, 5) incomplete outcome data, 6) selective reporting, and 7) other potential sources of bias. In accordance with Cochrane methodology, we chose to examine blinding in components, as it is more appropriate to do so in surgical research, where the blinding of patients and surgeons is commonly thought to be impractical. In contrast, blinding of outcome assessors is generally

more feasible. In addition to the above items, “provider expertise bias” was also evaluated as an eighth important source of potential bias specific to surgical procedures. This item was pre-defined in the review protocol, as it is clear that issues pertaining to surgical skill acquisition and learning curves can influence outcomes in procedures-based trials [9].

All eight risk of bias items were assessed for each trial. Where trials had more than one publication, the trial as a whole as evaluated using all included reports. As well, referenced trial protocols or partial publications not included in this review were also read in an attempt to minimize trial reporting issues. All items were graded as “low risk of bias”, “high risk of bias”, or “unclear risk of bias”. These data were synthesized using descriptive figures. Trials with five or more items with a low risk of bias were arbitrarily defined as high-quality studies.

### ***Data abstraction and management***

Data from included RCTs and review papers were extracted onto data abstraction forms designed a priori (appendix 2 and 3, respectively). Both data abstraction forms were piloted independently with ten citations each prior to utilization. Data points were checked for accuracy by a second reviewer and discrepancies were resolved by consensus. Relative outcomes were always recorded as a comparison of laparoscopic to open surgery. Where papers compared open to laparoscopic surgery, the appropriate reciprocal relative measure of effect and reciprocal measures of significance were calculated and recorded. The relative measures of effect were maintained in the statistical format provided by the authors of individual citations. Where means were provided without standard deviations, the standard deviation was derived from standard errors, confidence intervals, or p-values. Medians were abstracted as such, as no assumption was made about the underlying data distribution. Although each citation was abstracted separately, trials with multiple publications were identified and labeled so as to avoid duplication of patients within this systematic review.

Individual trial authors were contacted selectively whenever questions arose during data abstraction about trial outcomes, or to check whether individual citations overlapped. All abstracted data were transferred into a spreadsheet for analysis.

#### *Abstraction of outcome data*

Data pertaining to the primary outcome of overall survival and the surrogate outcome of lymph node harvest were primarily abstracted in the same statistical format provided in individual reports. When hazard ratios (HR) for survival and their measures of significance were not provided in individual papers, available data in the reports were utilized to estimate appropriate hazard ratios for each trial using published methods [10-12]. This technique allows one to derive the  $\ln(\text{HR})$  and  $\text{var}(\ln(\text{HR}))$  from published data using a hierarchy of techniques, from simple to more complicated, making an increasing number of assumptions depending on the data presented by the authors. Whenever available, the HR and 95% confidence interval were utilized to derive the  $\text{var}(\ln(\text{HR}))$  using simple computations:

$$\text{var}(\ln(\text{HR})) = \left[ \frac{\ln(\text{upper CI}) - \ln(\text{lower CI})}{2 \times Z \text{ score for upper CI boundary}} \right]^2.$$

Where this information was unavailable, Kaplan-Meier curves were used to generate estimates of HR. To do so, curves were divided into smaller time intervals of 6-12 months. For each interval, the proportion of event-free patients at the start of the interval was calculated, along with an estimate of the number of censored patients, and the number of events during the interval. Censoring was estimated based on the available data on follow-up, and was assumed to occur at a constant rate and to be non-informative for each interval. The number of censored patients was calculated using the following formula:

$$\text{censored} = \text{at risk during interval} \times \left( \frac{1}{2} \times \frac{(\text{End of time interval} - \text{Start of time interval})}{(\text{Maximum follow-up} - \text{Start of time interval})} \right).$$

When a precise count of the number of patients at risk was provided by the authors at specific time points along the Kaplan-Meier curve, these were utilized to derive more

accurate estimates of censoring. For each interval, the number of patients at risk was adjusted for censoring, and used to compute the HR, variance, and O-E using the relative risk formula:

$$HR = \left( \frac{Events\ research/At\ risk\ research}{Events\ control/At\ risk\ control} \right).$$

Finally, the HR for the entire study was calculated by summing all intervals:

$$HR = exp \left[ \frac{\sum O-E}{\sum V} \right].$$

HR estimates for survival were generated from individual Kaplan-Meier curves after generating a full-page high-quality printout of each curve, and manually plotting out survival percentages at each smaller time intervals. Such time intervals were determined on a convenience basis on each curve, and ranged from 6-12 months. A Microsoft Excel (Microsoft Corporation, Richmond, WA) macro designed by Sydes and Tierney was utilized to facilitate all computations [12, 13].

#### *Abstraction of expert opinion*

Expert opinion in the literature was abstracted from review papers separately for colon and rectal cancers. The author's global conclusion regarding the acceptability of laparoscopic surgery to treat colon or rectal cancer was extracted. Where multiple conclusions were provided within a single review, the expert author's opinion regarding the primary outcome of overall survival was considered.

The review paper's conclusion was graded on a seven-point asymmetric scale. The scale is presented in figure 8. It ranges from 1, whereby laparoscopy is not mentioned in a review paper pertaining to colorectal cancer surgery, to 7, whereby laparoscopy is deemed the standard of care. Option 3 indicates that the author would only allow for laparoscopy in the context of a clinical trial, whereas options 4-6 provide various levels of equivalency with open surgery. For the purpose of data synthesis, options 1-2 on the scale were considered

to indicate that laparoscopy was “inferior” to open surgery, whereas options 4-6 were deemed to indicate that laparoscopy was “equivalent” to open surgery. This scale was piloted independently by two reviewers using ten distinct review articles for ease of use and congruence among reviewers.

**Figure 8.** Asymmetric grading scale of review authors’ opinion regarding the value of laparoscopy in treating colorectal cancer

Not mentioned	Inferior to open	Only acceptable in trials	Equivalent with anatomic limitations	Equivalent for experts	Equivalent in general practice	Standard of care
1	2	3	4	5	6	7

**Data synthesis**

Individual trials were synthesized narratively and using summary tables. The primary outcome of overall survival and the surrogate outcome of lymph node harvest were further analyzed using meta-analytic techniques. Derived ln(HR) for individual trials were pooled using the inverse variance method and random effects models. Random effects models were preferred in this work because of the often non-standardized nature of surgery across trials, the variability in trial quality, and the added statistical conservatism provided by this approach. Where multiple publications of the same RCT were identified, only the most mature survival data were used in this meta-analysis. In contrast, a continuous random effects meta-analysis of the primary outcome was also carried out using the earliest available survival data set for each trial, so as to assess the evolution of this outcome in time. For lymph nodes harvest, weighted mean differences were also pooled using random effects models. For each pooled outcome, statistical measures of heterogeneity (Cochran’s Q and I<sup>2</sup>) were obtained from fixed effects models. Clinical heterogeneity among studies

included in this meta-analysis of overall survival was explored using sensitivity and subgroup analyses. Pre-specified sensitivity analyses were carried out based on the inclusion of colon and/or rectal cancer patients, and based on the risk of bias assigned to each trial. All analyses were carried out using RevMan 5.1 (The Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark) and Comprehensive Meta-Analysis 2.2 (Biostat, Englewood, NJ).

Grades of opinion for individual review paper were synthesized as yearly proportions, and plotted as a time series. Changing trends in expert opinions were then evaluated visually from these graphs and correlated qualitatively with overall survival data derived from RCTs, as well as compared to the temporal data obtained from the cumulative meta-analysis of overall survival.

**Table 3.** Characteristics of included randomized controlled trials.\*

Trial (Origin)	Study Years	Study Size (Lap/Open)	Population	Providers	Outcomes	Follow-Up
Lacy (Spain) [14, 19, 22, 25, 48]	1993-1998	219 (111/108) ITT	Colon cancer, 15 cm above anal verge Excluded: transverse colon, distant mets, organ invasion, obstruction, prior colonic surgery	Single center Team with "wide" experience in advanced laparoscopy Center described as "laparoscopy-devoted"	Primary: cancer-related survival Operative Short-term postop Oncologic surrogates Long-term oncologic	Median 95 months (77-133 months)
Stage (Denmark) [15]	Before May 1996	34 (15/14) Non-ITT	Colorectal cancer Excluded: LAR, APR, signs of extensive local tumor growth	Single center "All surgery performed by senior surgeons trained in both open and laparoscopic colorectal surgery"	Primary: not defined Operative Short-term postop Oncologic surrogates	Median 14 months (7-19 months)
Schwenk (Germany) [16, 17, 20, 21]	1995-1996	60 (30/30) ITT	Colorectal cancer (elective right hemicolectomy, sigmoid resection, AR, APR) Excluded: rectal cancer below 12 cm from anal verge for sphincter salvage, transverse colon/flexures tumor, adjacent organ infiltration, tumor diameter >8 cm, ASA>3, flap reconstruction, BMI>32, pronounced adhesions, synchronous extracolonic tumors, uncorrectable coagulopathy, abscess or sepsis, obstruction, immunopathy, pregnancy, age<18, chronic analgesic/alcohol use	Single center "Experienced" laparoscopic team Same team for open and laparoscopic surgery	Primary: each reference provides different primary endpoint (pain, respiratory function, recovery of bowel function, and global quality of life), and each with sample size calculation based on different outcome but with same set of 60 patients Operative Short-term postop Quality of life	Interview at 3 months
Milsom (US) [18]	1993-1997	113 (59/54) Non-ITT	Colorectal cancer (right/sigmoid, upper or lower rectum), elective, curative surgery, ASA 1-3, age>18 Excluded: emergency, disseminated disease, organ invasion, tumor >8 cm, transverse/left colon tumor, middle rectum tumor, BMI>32	Single center Same team carried out both procedure types and postop care Trained for several years with lap for benign disease/oncologic resections in animals and cadavers Improved "skill and efficiency" for laparoscopy during trial period	Primary: pulmonary recovery Operative Short-term postop Oncologic surrogate Long-term oncologic	Median 20.4 months (1.5-48 months)
Curet (US) [23]	1993-1995	43 (25/18) Non-ITT	Colorectal cancer Excluded: age<18, pregnancy, obstruction, malignant fistulization, fixation to adjacent tissue, colostomy	Single center Attending surgeons and residents under direct supervision. All attendings had performed multiple lap-assisted	Primary: not specified Operative Short-term postop Oncologic surrogate	Median 4.9 years (2.5-6.3 years)

			placement/reversal alone	colectomies for benign disease and palliation of malignancy	Long-term oncologic	
COST (US) [24, 26, 31, 45]	1994-2001	872 (435/428) Partial ITT	Colon cancer (right, left, sigmoid), age>18, able to communicate in English  Excluded: T4 or metastatic cancer, rectal or transverse colon, prohibitive adhesions, obstruction or perforation, severe medical illness, IBD, familial polyposis, pregnancy, concurrent or previous malignant tumor, ASA 4 or 5	48 centers in the US and Canada  Surgeons had to have performed at least 20 lap-assisted colectomies  Videotape submitted by surgeons to assess oncologic technique (mesenteric ligation, avoidance of tumor handling, identification of critical adjacent structures, thoroughness of exploration)  Ongoing random audit of tapes and assessment of bowel margins, among first 500 trial cases	Primary: tumor recurrence  Operative Short-term postop Oncologic surrogate Long-term oncologic Quality of life Long-term other	Median 7 years (5-10 years)
Quah (Singapore) [27]	1997-1999	170 (86/84) ITT	Rectal cancer, age >18, suitable for elective surgery  Excluded: other tumor sites, contraindications to pneumoperitoneum, obstruction, malignancy in previous 5 years, synchronous multiple adenocarcinomas, pregnancy	Single center  All surgeons performing lap rectal resection were experienced laparoscopic surgeons proficient in TME	Primary: T cell count  Operative Quality of life Immune function (reported in separate paper, not included in this review)	Questionnaire at 1 year
Hasegawa (Japan) [28]	1998-2000	59 (26/24) Non-ITT	Colorectal cancer, preop diagnosis of T2 or T3 (N0) lesion, curative surgery  Excluded: Tis/T1 lesions (lap considered standard of care), T3 in upper or lower rectum, T3 in transverse colon	Single center  Operated on "hundreds of early colorectal cancers cases [laparoscopically] (and hence passed the learning curve)"  Started lap for Tis/T1 in 1992, when minimal risk of LN metastases. Included T2 in 1996, then T3 in 1997	Primary: not specified  Operative Short-term postop Oncologic surrogate	Median 20 months (6-34 months)
Araujo (Brazil) [29]	1997-2000	28 (13/15) ITT	Rectal cancer, distal only, incomplete response to neoadjuvant therapy, staging favorable to radical resection by APR  Excluded: non specified	Single center  Some progress with the learning curve in colorectal surgery, good results with lap APR  Sufficient experience with laparoscopy that male gender, obesity, previous surgery are no longer contraindicated	Primary: not specified  Operative Oncologic surrogate Short-term postoperative Long-term oncologic Long-term other	47.2 months
Leung (Hong Kong) [30]	1993-2002	403 (203/200) ITT	Rectosigmoid cancer  Excluded: distal tumors needing anastomosis below 5 cm from dentate line, tumor >6 cm, infiltration of adjacent	Single center  All operations done or supervised by surgeons skilled in both laparoscopic and open colorectal surgery	Primary: 5-year survival  Operative Short-term postop Oncologic surrogate	Median 52.7/49.2 months (lap/open)

			organs, prior abdominal operations near colorectal operation, lack of consent, obstruction, perforation	Most experienced with rectosigmoid tumors due to most volume	Long-term oncologic Long-term other	
Zhou (China) [32]	2001-2003	171 (82/89) ITT	Rectal cancer below peritoneal reflection (1.5-8 cm from dentate line)  Excluded: other pathological types (eg. lymphoma), tumor below 1.5 cm from dentate line, emergencies, Duke D with local infiltration into other organs, no consent	Single center  Surgeons with adequate experience of open TME and laparoscopic technique  One surgeon for lap procedures (Zhou)	Primary: not specified  Operative Short-term postoperative Long-term oncologic Quality of life	1-24 months
Kaiser (US) [33]	1995-2001	49 (15/20) Non-ITT	Colon cancer (right, left, sigmoid), elective, curative, age >18, ASA 1-3, ability to participate in follow-up  Excluded: emergency, stage IV tumors, rectal or transverse colon cancer, prohibitive adhesions, ASA 4 or 5, associated GI disease (IBD, FAP), pregnancy	Single center  Surgical teams headed by 2 surgeons with "previously demonstrated extensive experience" with lap colon surgery for benign and malignant disease	Primary: cancer-specific survival  Operative Short-term postoperative Oncologic surrogate Oncologic long-term	Median 35 months (3-69 months)
CLASICC (UK) [34, 36, 44]	1996-2002	794 (526/268) ITT	Colorectal cancer (right, left, sigmoid, AR, APR)  Excluded: transverse colon cancer, contraindication to pneumoperitoneum, obstruction, malignancy in past 5 years, synchronous adenocarcinoma, pregnancy, associated GI tract disease needing surgical intervention	27 centers in the United Kingdom 32 surgeons  Both procedure types performed by same surgeon locally  Each had undertaken as least 20 laparoscopic-assisted resections	Primary: 3-year overall and disease-specific survival  Operative Short-term postoperative Oncologic surrogate Long-term oncologic Quality of life	Median 36.8/49.5 months (lap/open)
COLOR (Netherlands) [35, 43, 52]	1997-2003	1248 (536/546) ITT	Colon cancer, single tumor (right or sigmoid colon above peritoneal reflection), age >18  Excluded: rectal cancer, transverse colon or splenic flexure cancer, mets to liver or lung, obstruction, multiple primary colonic tumors, synchronous intraabdominal surgery, preop evidence of invasion into adjacent organs, previous ipsilateral colon surgery, previous cancer, absolute contraindication to general anesthesia or pneumoperitoneum	29 centers in Western Europe  For lap, all surgical teams had done at least 20 lap-assisted colectomies  An unedited videotape of laparoscopic colectomy was submitted before a center participated in trial, to assess safety and thorough technique  All open cases done by team with a surgeon with credentials in colon surgery	Primary: 3-year disease-free survival  Operative Short-term postoperative Oncologic surrogate Long-term oncologic Quality of life	Median 52/55 months (lap/open)
Braga (Italy) [37, 42]	2000-2001 ?	391 (190/201) ITT	Colorectal cancer, age >18, suitable for elective surgery  Excluded: cancer infiltrating adjacent organs, NYHA class >3, respiratory	Single center  "Well-trained in both laparoscopic and open colorectal surgery" surgical team of 3 surgeons	Primary: postoperative complication rate  Operative Short-term postoperative	Median 54.2 months

			dysfunction (PaO <sub>2</sub> <70), hepatic dysfunction (Child C), ongoing infection, neutrophils <2x10 <sup>9</sup> /L	Learning curve said to be completed before start of trial, reported in another paper (3 month trial period with lap colorectal)	Oncologic surrogate Long-term oncologic Quality of life Long-term other	
King (UK) [38, 49]	2002-2004	60 (41/19) ITT	Colorectal cancer  Excluded: non-elective admission, preop evidence of mets, age <18, pregnancy, no consent, patient unable to have epidural anesthesia	Single center	Primary: postoperative hospital length of stay  Operative Short-term postop Quality of life	12 months
Arteaga (Spain) [39]	2003-2004	40 (20/20) ITT	Rectal cancer, <15 cm from anal verge  Excluded: obstruction, perforation, preoperative diagnosis of T4 tumor, tumor >7 cm, candidate for local surgery	Single center  3 lap surgeons (2 experienced with advanced lap and open CRC surgery, and 3 <sup>rd</sup> one with training at centers of excellence of lap CRC surgery  All lap cases performed by 2 surgeons, team established November 2002  Lap cases performed "during the learning" curve  3 open surgeons, >5 years of experience with open rectal cancer surgery	Primary: not specified  Operative Short-term postoperative Oncologic surrogate	Unclear
Liang (Taiwan) [40]	2000-2004	286 (135/134) ITT	Colorectal cancer, stage 2 or 3, curative left hemicolectomy (distal transverse colon, splenic flexure, left, sigmoid colon requiring mobilizing splenic flexure), ASA 1-3, age >18  Excluded: other colorectal locations, emergency, palliation, disseminated disease or involvement of adjacent organs, mass >8 cm, BMI>40, previous major abdominal surgery	Single center  Technique for laparoscopic colon cancer surgery was well established; single surgeon  Started medial-to-lateral approach in 2000 for takedown of splenic flexure	Primary: cancer recurrence  Operative Short-term postoperative Oncologic surrogate Long-term oncologic	Median 40 months (18-72 months)
Pechlivanides (Greece) [41]	Unclear (before 2007)	74 (34/39) ITT	Low rectal cancer (distal 12 cm from anal verge)  Excluded: tumors extending to the pelvic walls or organs	3 centers in Greece  All procedures performed or supervised by most experienced surgeon	Primary: lymph nodes harvest  Oncologic surrogate	Immediate postoperative stay
Chung ** (Hong Kong) [46]	2001-2006	86 (41/40) ITT	Colon cancer (right), age >18  Excluded: no consent, unfit for surgery, emergency, obstruction, peritonitis, abscess, metastatic disease on preop	Single center  Two surgeons involved in all cases	Primary: postoperative pain  Operative Short-term postoperative	Median 30/28 months (lap/open) (2-60 months)

			work-up, synchronous tumor/polyp, tumor >6.5 cm Colon cancer (right)		Oncologic surrogate Long-term oncologic	
Ramacciato (Italy) [47]	2001-2005	66 (33/33) ITT	Excluded: obstruction, perforation, prior major abdominal surgery, clinical contraindication to surgery, infiltration of adjacent organ, more than one hepatic met >1 cm	Single center	Primary: not specified  Operative Short-term postoperative Oncologic surrogate	Median 6.4 months (2-60 months)
Ng (Hong Kong) [50]	1994-2005	99 (51/48) ITT	Low rectal cancer (within 5 cm from anal verge)  Excluded: tumor >6 cm, tumor infiltrating adjacent organs, recurrent disease, no consent, obstruction, perforation	Single center  Performed or supervised by surgeons experienced in both laparoscopic and open colorectal surgery	Primary: analgesic requirement and postoperative recovery  Operative Short-term postoperative Oncologic surrogate Long-term oncologic	Median 87.2/90.1 months (lap/open) (22.8-150 months)
Hewett (Australia) [51]	1998-2005	601 (294/298) ITT	Colon cancer (right, left, sigmoid), age >18  Excluded: advanced local disease >8 cm, mets, rectal or transverse colon cancer, emergency, BMI >35, ASA 4 or 5, associated GI disease requiring extensive operative evaluation or intervention, pregnancy, other cancer in past 5 years	31 centers in Australia and New Zealand  "Stringent credentialing criteria", as with COST trial  Audited videotape of lap colorectal procedure and 20 operative reports describing oncologically appropriate laparoscopic procedures  Participating surgeons "already experienced"; introduction of less experienced surgeons over duration of study	Primary: 3- and 5-year disease-free and overall survival  Operative Short-term postoperative Oncologic surrogate	Immediate postoperative stay

\*All studies were RCTs and compared laparoscopic to open surgery. \*\*Compared hand-assisted laparoscopic to open surgery.

Abbreviations: ASA: American Society of Anesthesiologists score; APR: abdominoperineal resection; AR: anterior resection; BMI: body mass index; CRC: colorectal cancer; FAP: familial adenomatous polyposis; GI: gastrointestinal; IBD: inflammatory bowel disease; ITT: intention to treat analysis; lap: laparoscopic; LAR: low anterior resection; LN: lymph node; mets: tumor metastases; NYHA: New York Heart Association; TME: total mesorectal excision; UK: United Kingdom; US: United States.

## RESULTS

### *Description of included studies*

A total of 5,800 single citations were screened for inclusion (figure 2). After applying a two-step screening process, a total of 38 reports pertaining to 23 individual RCTs were included [14-51]. An additional report of long-term data pertaining to a trial already included in this review became available a few weeks after study selection [52]. This report was also included in the current work, thus accounting for 39 included citations (table 3). Included trials were published between 1995 and 2009, and conducted in 15 countries. Trials conducted in Western Europe (43%, n=10), Asia (30%, n=7), North America (17%, n=4), Australia/New Zealand (4%, n=1), and South America (4%, n=1). All trials were published in English, except for one Italian RCT [47].

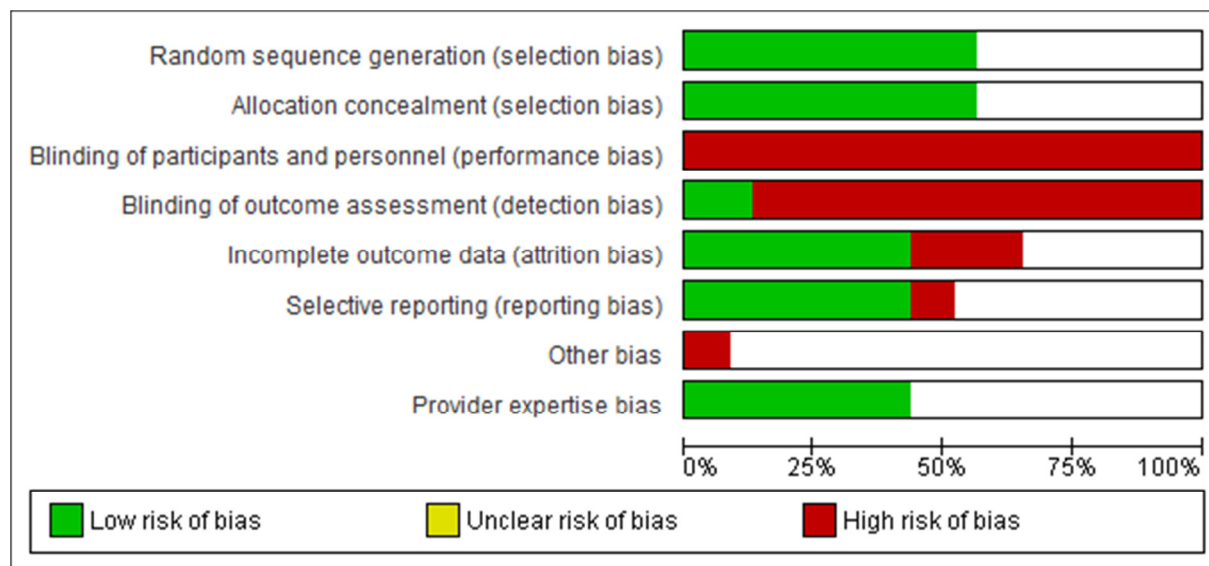
Among 23 individual RCTs, 5 (22%) were multicenter in design. The smallest multicenter study recruited 3 centers in Greece [41], whereas the largest multinational RCT included 48 centers across the United States and Canada [24, 26, 31, 45]. Patient recruitment varied widely across RCTs, ranging from 28 patients for the smallest study from Brazil [29] to 1,082 patients for the European COLOR trial [35, 43, 52]. In total, 5,782 patients were randomized between laparoscopic (n=3,031) and open (n=2,751) surgery as a primary treatment for colorectal cancer. Among these patients, 58% (n=3,336) were included as part of trials addressing only colon cancer, whereas 10% (n=582) took part in trials limited to rectal cancer. The remainder of patients (32%, n=1,864), were included in trials addressing colorectal cancer in general, with varying definitions as it pertains to the inclusion of rectal cancer patients (table 3).

### *Risk of bias assessment*

A total of eight risk of bias items were assessed individually (figure 9). Both items pertaining to selection bias (random sequence generation and allocation concealment), demonstrated the lowest overall risk of bias, with each item being addressed adequately by

57% of trials (n=13), and all other trials lacking sufficient information to render judgment. Similarly, the issue of provider expertise was addressed satisfactorily by 43% of trials (n=10), with inadequate reporting in the remainder of studies. Incomplete outcome reporting and selective reporting both also yielded a low risk of bias in 43% of trials, but these items also generated a high risk of bias in 22% and 9% of trials, respectively. In contrast, blinding – whether of patients, study personnel, or outcome assessors – was almost universally not attempted, yielding a high risk of bias in all trials except for three (13%) groups that employed blinded assessors of their primary outcomes. Two trials also demonstrated high risks of “other bias”, as they elected to carry out a diagnostic laparoscopy prior to randomization so as to determine whether individual patients could undergo a formal oncologic colorectal resection by laparoscopy [16-18, 20, 21].

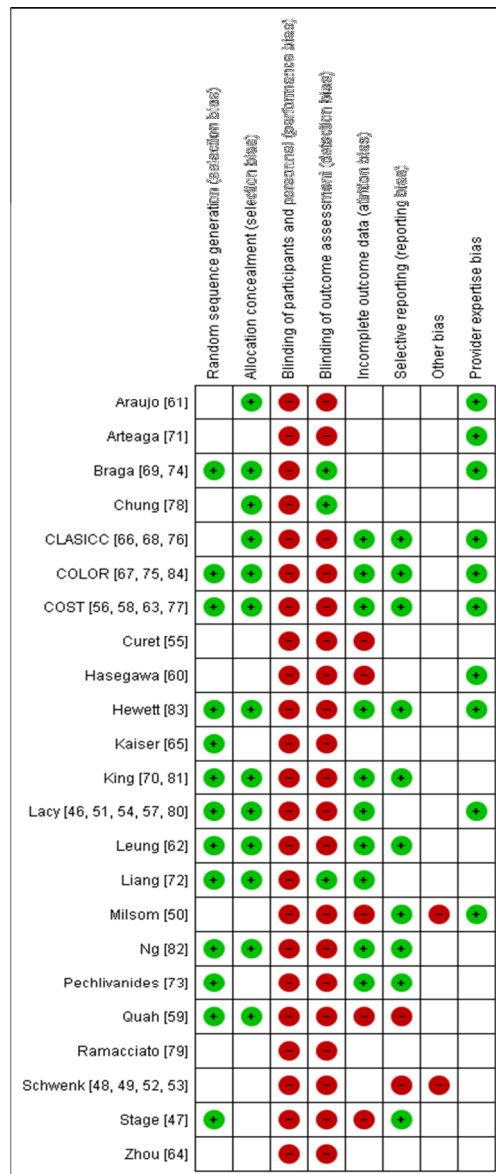
**Figure 9.** Global risk of bias assessment divided by individual items



Analysis of risk of bias judgments at the individual trial level identified three groups that achieved “low risk of bias” marks for at least five items [24, 26, 31, 35, 43, 45, 51, 52] (figure 10). These three trials are all large-scale multicenter multinational RCTs, and they contributed a

total of 2,721 patients to this review. Seven trials obtained four “low risk of bias” marks, as certain items could not be adequately assessed from available trial reports, study protocols, or adjunct publications. Finally, 11 trials obtained a total of two or less “low risk of bias” marks, highlighting a greater overall risk of bias based on reported information. Among these, six trials obtained at least three “high risk of bias” marks [15-18, 20, 21, 23, 27, 28], of which five trials did not carry out intention-to-treat analyses.

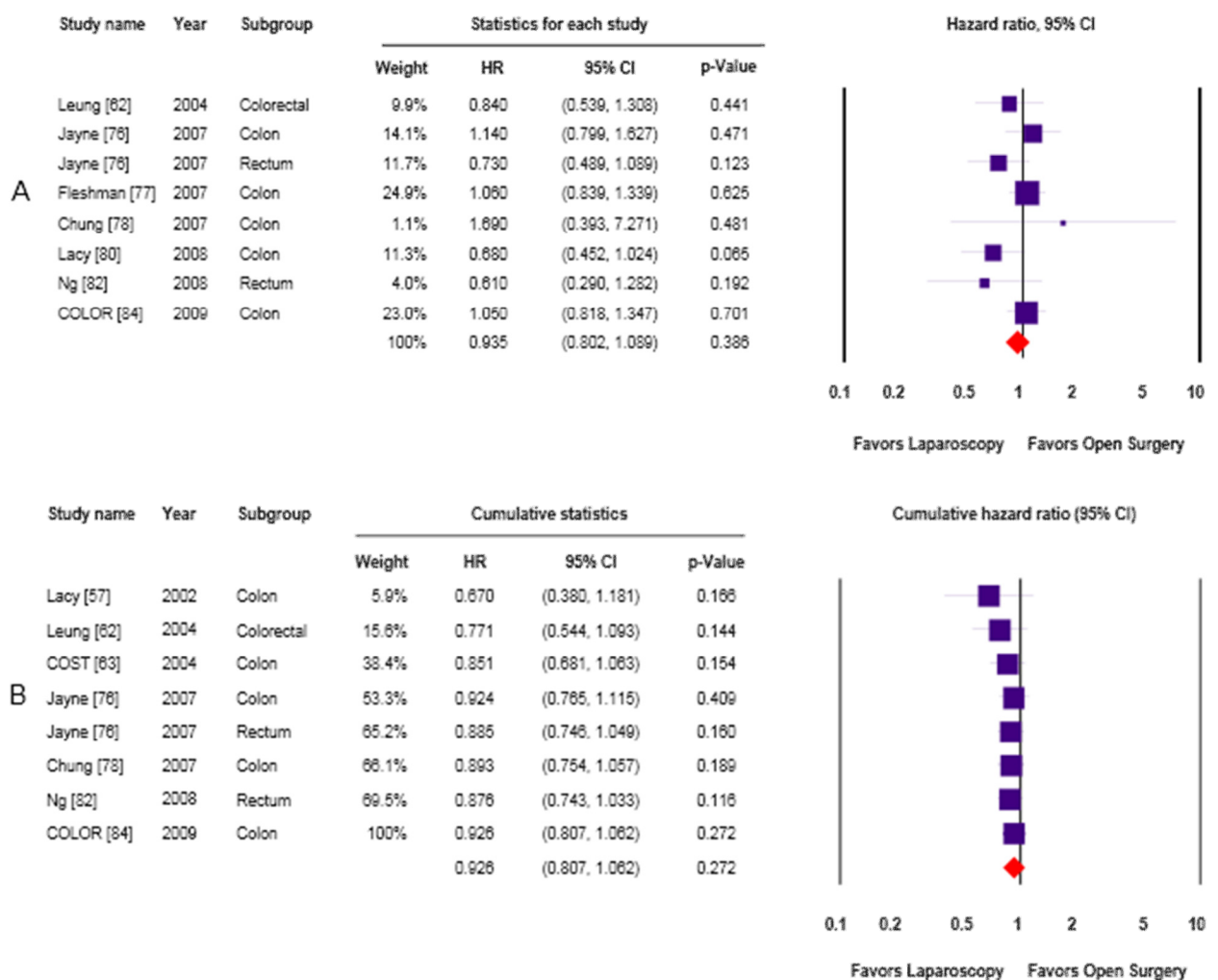
**Figure 10.** Risk of bias assessment divided by individual trials.



### Analysis of short- and long-term oncologic data from included trials

Data pertaining to overall survival following laparoscopic and open resection for colorectal cancer were presented in 16 (41%) publications, originating from 13 (56%) individual trials. Median follow-up time among these trials ranged from 12-95 months. One trial did not report a median follow-up time period for either intervention group [32]. For all trials reporting on overall survival (or overall mortality), data was provided on the number of patients alive and dead at maximal follow-up.

**Figure 11. a)** Random-effect meta-analysis of overall survival; **b)** Random-effect cumulative meta-analysis of overall survival



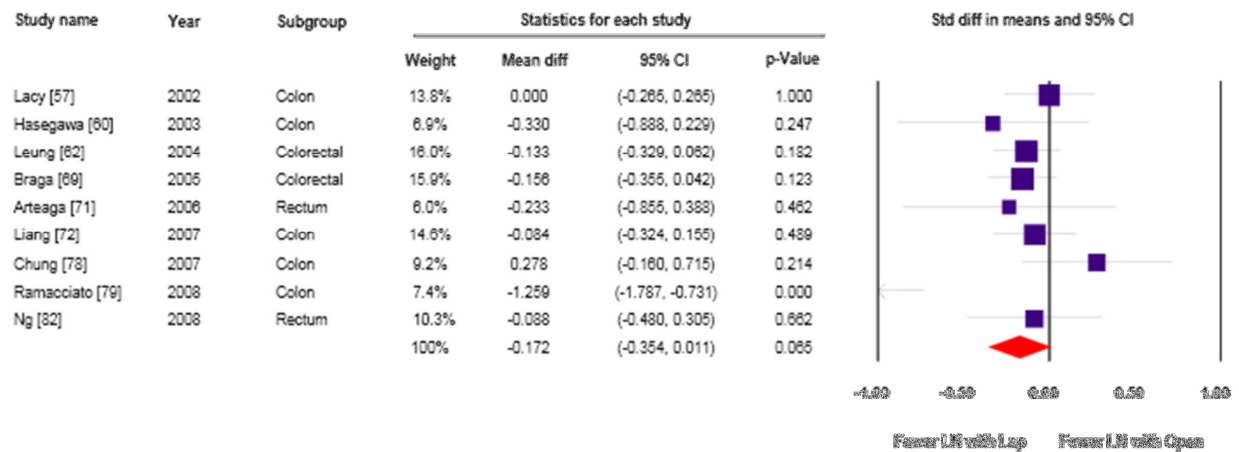
Among trials providing data on overall survival, 7 presented sufficient data in text, table, for survival curve format to allow for the calculation of hazard ratios. No significant difference in overall survival between laparoscopic and open surgery for colorectal cancer was identified, after pooling using the most mature trial data available (HR=0.94, 95% CI 0.80, 1.09) (figure 11a). This meta-analysis demonstrated no evidence of statistical heterogeneity ( $Q=8.996$ ,  $p=0.255$ ;  $I^2=22\%$ ). A cumulative meta-analysis using overall survival data as they became available in time for each trial, rather than using the most mature data, yielded a comparable hazard ratio of 0.93 (95% CI 0.81, 1.06) (figure 11b).

Pooling of studies including only colon cancer patients ( $n=5$ ) yielded a HR of 1.01 (95% CI 0.86, 1.19), with no significant statistical heterogeneity ( $Q=4.762$ ,  $p=0.313$ ;  $I^2=16\%$ ). The addition of a sixth trial, which included both sigmoid colon and high rectal cancers, did not alter these data significantly. In contrast, the pooling of trials including only rectal cancer patients ( $n=2$ ) yielded a HR of 0.70 (95% CI 0.49, 1.00), with no statistical heterogeneity ( $Q=0.174$ ,  $p=0.676$ ;  $I^2=0\%$ ). The addition of the third trial including only rectosigmoid cancer patients to the rectal cancer group further emphasized the distinct results obtained for this subgroup (HR=0.75, 95% CI 0.57, 0.99,  $I^2=0\%$ ). Pooling of the two trials with the lowest risk of bias did not significantly alter the results (HR=1.06, 95% CI 0.89, 1.25,  $I^2=0\%$ ). Similarly, pooling all trials except one with the greatest risk of bias did not alter the outcomes, but it did increase the degree of statistical heterogeneity (HR=0.93, 95% CI 0.79, 1.09,  $I^2=28\%$ ).

Data on the number of lymph nodes harvested with the surgical specimen was reported by 19/23 trials (83%). Among these, nine trials presented sufficient data to allow for meta-analysis (figure 12). All other groups presented means or medians, but omitted measures of dispersion around the mean, hence preventing pooling. The range of reported lymph nodes harvested for those undergoing laparoscopic resection was 5.5-23.0. Similarly, the range among open procedures was 7.8-26.0. The pooled weighted mean difference

between laparoscopic and open resection was -0.17 lymph nodes (95% CI -0.35, 0.011). While this result trended towards significance, it was also highly statistically heterogeneous ( $Q=22.64$ ,  $p=0.004$ ;  $I^2=65\%$ ).

**Figure 12.** Random-effect meta-analysis of the number of lymph nodes harvested at the time of surgery.



A sensitivity analysis of colon resections independently from rectal cancer patients yielded a similar mean difference (-0.241, 95% CI -0.632, 0.150), but with increased heterogeneity ( $Q=22.44$ ,  $p<0.001$ ;  $I^2=82\%$ ), indicating that much of the statistical variation originates with trials addressing colon cancer rather than colorectal or rectal cancer. In contrast, analysis of rectal cancer trials alone ( $n=2$ ) eliminated all traces of statistical heterogeneity (mean difference -0.129, 95% CI -0.461, 0.203,  $I^2=0\%$ ). Adding trials addressing colorectal cancer to those limited to rectal cancer yielded a statistically significant mean difference of -0.142 (95% CI -0.271, -0.014), with no statistical heterogeneity ( $Q=0.185$ ,  $p<0.001$ ;  $I^2=0\%$ ). Finally, excluding high-risk of bias trials from the pooling yielded a mean difference of -0.106 (95% CI -0.211, 0.000,  $p=0.05$ ), with no evidence of statistical heterogeneity ( $Q=0.974$ ,  $p=0.914$ ,  $I^2=0\%$ ).

### ***Description of included reviews***

A total of 421 review citations were included after the final screen (figure 2). This total comprised 336 narrative reviews, 30 textbook chapters, 28 guidelines/position statements, and 27 systematic reviews. Among the 27 systematic reviews, 7 were ultimately excluded from the current work, as they did not specifically address the primary outcomes, but were included in a separate umbrella review of systematic reviews (see chapter two). The final count of review papers was thus 414. The full reference list is available upon request.

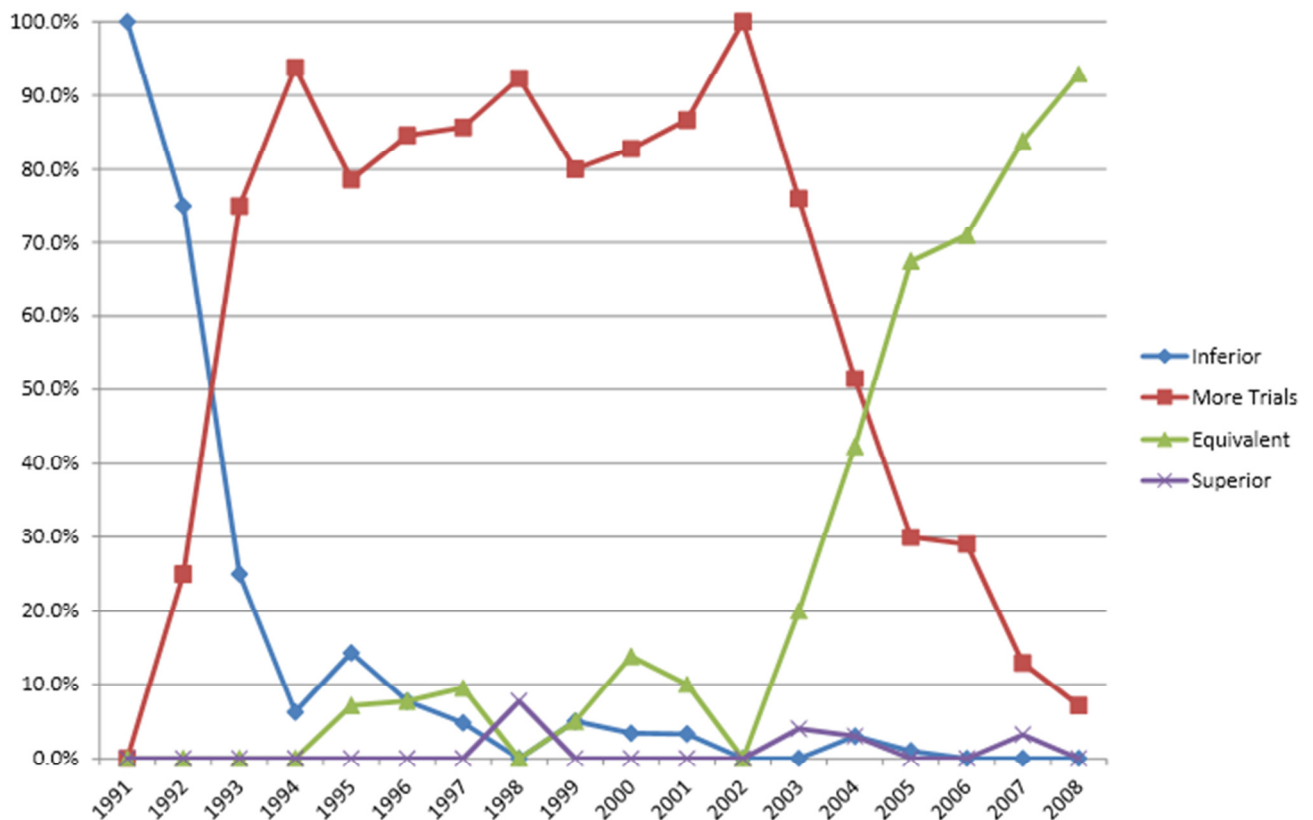
Included review papers were published between 1991 and 2008. The number of retained reviews per year appeared to increase in time, with 2005 being the most prolific publication year (n=51). Over half included reviews were published between 2003 and 2008 (51%, n=212), while only 11% (n=45) of citations originated in 1991-1995.

Review papers included in this work originated in 28 different countries. The United States, Germany, the United Kingdom, and France accounted for 77% of reviews (n=319), or 43% (n=179), 14% (n=60), 11% (n=46), and 8% (n=34), respectively. On the whole, most reviews were from Europe (47%, n=193) and North America (45%, n=188), while Latin America (2%, n=8), Australia/New Zealand (2%, n=9), and Asia/Middle East (4%, n=16) accounted for smaller proportions. Reflecting the origin of most reviews, 95% were published in English (75%, n=311), German (13%, 52), and French (7%, n=29). Six other languages of publication were identified (Spanish, Italian, Danish, Dutch, Portuguese, Norwegian), each accounting for fewer than 3% of reviews. All textbook chapters retrieved for this work were published in the United States and in English. All systematic reviews except one were published in countries other than the United States, with 65% (13/20) originating in Europe.

### Analysis of expert opinion

Among the 414 review papers included in this work, 362 (87%) and 332 (80%) provided data pertaining to colon and rectal cancer, respectively. Most reviews (67%, n=280) addressed both cancer types concurrently. The summary of expert opinions extracted from all review papers are presented as temporal plots in figures 13 and 14.

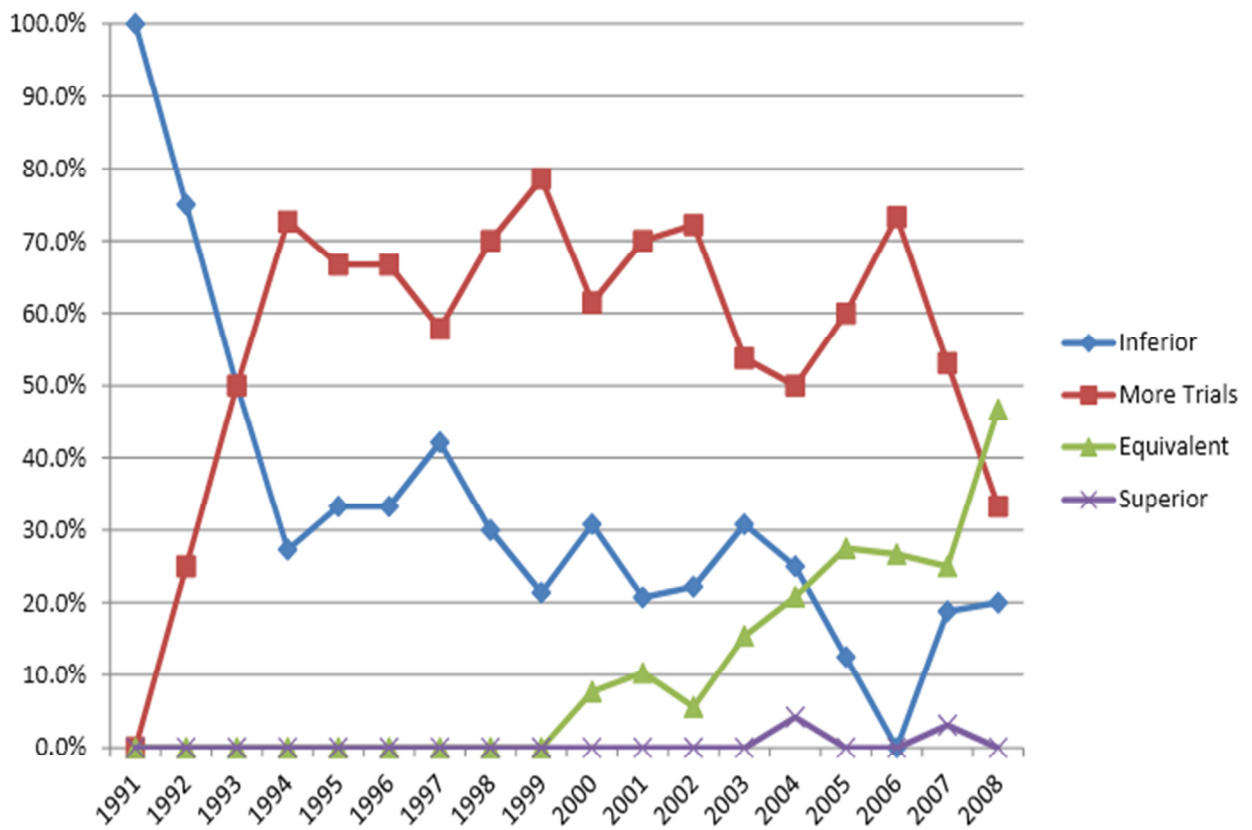
**Figure 13.** Temporal summary of expert opinion in the literature pertaining to laparoscopic surgery for colon cancer



For colon cancer (figure 13), laparoscopy was initially considered inferior to open surgery, with 100% and 75% of expert opinions scoring “inferior” in 1991 and 1992, respectively. As of 1993, expert opinions curves were found to shift towards equipoise, with well over 75% of reviews opinionating that laparoscopic surgery could be considered for

colon cancer in the context of prospective trials. This trend was maintained until 2003. Starting in 2003, a second major shift in opinions can be identified, as experts were found to consider laparoscopic surgery equivalent to open surgery in growing proportions. As of 2005, opinion curves were found to have crossed over, with a majority of surgeons favoring equivalency between the two technologies. After 1993, almost no surgeons considered laparoscopy inferior to laparotomy. Similarly, only four reviewers considered laparoscopy superior to open surgery at any given time point.

**Figure 14.** Temporal summary of expert opinion in the literature pertaining to laparoscopic surgery for rectal cancer



Temporal expert opinion trends for rectal cancer were found to be distinct from colon cancer (figure 14). Experts initially considered laparoscopy inferior to open surgery in 1991-

1992. A shift towards equipoise was again noted – albeit not as strongly – from 1993-2006 with 50-78.6% of expert considering laparoscopy appropriate within clinical trials. In contrast to colon cancer, experts continued to consider laparoscopy inferior to open surgery in variable proportions (20.7-50%) from 1993-2004. A much smaller proportion of experts began to regard laparoscopy as equivalent to laparotomy for rectal cancer in 2003 onwards, although this rise was much more gradual than for colon cancer.

## **DISCUSSION**

We have conducted a systematic review and meta-analysis of trials comparing laparoscopic and open surgery for colorectal cancer, addressing the primary outcome of overall survival and the oncologic quality indicator of total lymph node harvest. In addition, we have synthesized expert opinion on this topic by utilizing the entire body of relevant review literature as a surrogate for the state of the field as a whole, and have attempted to correlate these findings with that of our meta-analysis.

In summary, this work identified 23 RCTs presented in 39 distinct published reports comparing laparoscopic and open surgery for patients suffering from colorectal cancer. A meta-analysis of time-to-event data on overall survival demonstrated no significant difference between the two interventions. This finding is not surprising as no large trial in this area of research has yielded a significant survival advantage favoring either type of surgery. As illustrated in chapter two of this thesis, other groups have also previously conducted systematic reviews and meta-analyses pertaining to oncologic outcomes and found no significant difference. That being said, most existing meta-analyses have opted to pool survival data using the proportion of patients alive or dead at maximal follow-up. This approach has the potential to introduce bias in a meta-analysis, as the pooling of such a dichotomous outcome involves the combination of trials at different stages of maturity and completely omits information pertaining to the timing of death following cancer surgery. In

order to circumvent these issues, we have pooled hazard ratios, which are more appropriate measures of time-to-event data. Unfortunately, these data are not always reported in clinical trials. As such, we have utilized a combination of published data on hazard ratios where possible, together with estimations of HR obtained from published survival curves. This statistical approach allowed us to generate the most comprehensive and rigorous meta-analysis of survival data pertaining to laparoscopic and open surgery for colorectal cancer available to date, as well as to confirm existing findings of non-inferiority of laparoscopy when compared to open surgery. Two other groups have also partially incorporated this technique in systematic reviews, but theirs lacked more mature survival data [53, 54].

For a novel technology to be adopted by practitioners, it must be demonstrated to be as safe and effective as the gold standard. If one accepts the short-term and cosmetic benefits of laparoscopy over open surgery, then one must only demonstrate non-inferiority compared to the gold standard. Taking the pooled mortality finding into account, determining the size of a hypothetical trial that could overturn the observed results was thought to be useful. Using a minimal clinically important difference of 10% in overall survival between laparoscopy and open surgery, one can calculate the minimal size of a hypothetical missing clinical trial that would significantly change the result of our meta-analysis. For laparoscopy to be demonstrated inferior to open surgery, one would need to obtain a pooled HR whose lower 95% confidence interval boundary is  $\geq 1.10$ . As such, it can be demonstrated that for inferiority to be achieved, a missing hypothetical trial of at least 5,000 patients would be required to meet the inferiority boundary (table 4). Using random-effects meta-analytic models, inferiority is not achieved with the addition of over 10,000 patients, which is double the number included in the current meta-analysis. Given that the largest multi-center study examining laparoscopy surgery for colorectal cancer enrolled just over 1,000 patients, it is highly improbable that 5,000-10,000 patients would ever be recruited in a missing hypothetical trial. This reasoning further strengthens our findings of non-inferiority and

supports the claim that additional trials addressing colon and high rectal cancer are unnecessary.

**Table 4.** Hypothetical trial size required to demonstrate inferiority.

Simulated n	Simulated HR*	Pooled n	Pooled HR (random effects)	Pooled HR (fixed effects)
-	-	3,525	0.935 (0.802, 1.089)	
500	1.46 (1.03, 2.08)	4,025	0.976 (0.823, 1.159)	1.002 (0.889, 1.129)
1,000	1.46 (1.14, 1.88)	4,525	0.985 (0.818, 1.186)	1.041 (0.929, 1.166)
2,000	1.46 (1.23, 1.75)	5,525	0.985 (0.804, 1.207)	1.103 (0.995, 1.223)
3,000	1.46 (1.27, 1.69)	6,525	0.983 (0.795, 1.217)	1.151 (1.047, 1.266)
5,000	1.46 (1.31, 1.64)	8,525	0.981 (0.786, 1.225)	1.211 (1.114, 1.318)
10,000	1.46 (1.35, 1.58)	13,525	0.979 (0.776, 1.234)	1.298 (1.214, 1.387)

\*Simulated hazard ratios assumed a minimum and maximum follow-up of 12 and 72 months, respectively, a 1:1 randomization, and a 5-year overall survival rate of **65%** and **75%** for laparoscopy and open surgery, respectively. As well, 50% of deaths occurred within the first two years of follow-up, with the remaining 50% occurring over the last 3 years.

In the second portion of this work, we have demonstrated in a semi-quantitative manner that expert opinion in the literature pertaining to laparoscopic and open surgery for colorectal cancer shifted dramatically in 2003-2006. This finding was observed specifically and quite clearly among publications from 2003-2004 for colon cancer. For rectal cancer, a similar – albeit weaker – trend was noted in 2006. In both instances, the majority expert opinion deemed that laparoscopic surgery was equivalent to open surgery after a long period of time during which this technique had reached clinical equipoise and was considered only acceptable in clinical trials. We argue that the abrupt shift in opinion in 2003 was a direct result of the publication of the first moderate-size RCT by Lacy and colleagues that presented medium-term survival data [25]. This single-center trial from Barcelona randomized 219 patients to laparoscopic and open surgery for colon cancer and argued that

laparoscopy was superior to open surgery in terms of postoperative morbidity, length of hospital stay, tumor recurrence, and cancer-related survival. Overall survival was also found to be superior in an adjusted Cox model, but only trended towards significance in unadjusted data. Despite subsequent criticisms in the literature, and more modest long-term results [48], it remains that this paper was undoubtedly seminal in shifting expert opinion regarding laparoscopy colon cancer surgery. Finally, we also argue that this transition was further promoted by the publication in 2004 of the COST trial, for which the influence was probably greatest in North America where this trial was funded and conducted [31].

Regarding rectal cancer surgery, it is not surprising that a notably weaker transition in expert opinion did not occur before 2006, as neither the Lacy [25] nor COST [31] trials included any rectal cancer patients. Although some rectal cancer surgeons may have extrapolated from the data on colon cancer, it is unlikely to have affected the prevailing expert opinion in the literature. In 2005, however, the CLASICC trial from the UK included 381 (48%) patients with rectal cancer [34], and it likely that this paper may have had a slight encouraging influence on expert opinion. Although survival data from this trial were not published until 2007 [44], we argue that this paper's publication, together with mounting evidence of equivalency for laparoscopic colon cancer surgery, began the transition for rectal cancer. That being said, since 2005, only a fraction of patients enrolled in trials of laparoscopic and open surgery have done so for rectal cancer, and it likely that many experts in the field have continued to wait for the publication of further large scale trials addressing this topic specifically. It should also be noted that, from a clinical standpoint, many surgeons argue that rectal cancer patients included in trials thus far have been carefully selected and have not included challenging mid- to low-rectal lesions [50]. For this reason, it is likely that a full shift from equipoise to equivalency will await results from the ongoing COLOR II [59], ACOSOG Z6051 [56] rectal cancer trials.

In addition to the above qualitative rationalization for the observed patterns in expert opinion, we have also attempted to do so quantitatively by generating a cumulative meta-analysis of overall survival. As shown in figure 11b, the accumulation of survival data has yielded an increasingly precise point estimate of the hazard ratio for overall survival following laparoscopic and open surgery for colorectal cancer. Although the direction of the point estimate and its lack of statistical significance have not changed in time, it is clear that the inclusion of patients from the COST trial [31] to that of Lacy [25] and Leung [30] in 2004 has narrowed the confidence interval significantly. On the whole, we thus argue that this analysis lends further support to our interpretation of the expert opinion patterns provided above.

There are several limitations to this study. First, our meta-analysis of survival outcomes and lymph node harvest is limited on the basis of incomplete reporting of data within primary publications. Although we have utilized statistical methods to generate estimates of hazard ratios in order to complete published data, it remains that there were relatively few trials with sufficient long-term data to pool. While convenient and more robust than odds ratios or relative risks in pooling survival outcomes, estimates of HR are imperfect. We have nevertheless attempted to minimize any limitations associated with their use by respecting the statistical “hierarchy” of techniques used to generate them, as advocated by Tierney and colleagues [12]. In essence, this approach prescribed using incomplete published data on HR before generating HR estimates from Kaplan Meier curves. When Kaplan Meier curves did have to be used to obtain HR, we have attempted to lessen measurement errors by using large-scale printouts of each curve and duplicating all results. In the absence of individual patient data which is impractical for 23 distinct surgical trials, the methods used in the current review represent the most robust option for pooling time-to-event data.

Limitations pertaining to our analysis of expert opinion in the literature include a certain degree of subjectivity in grading included review citations, as well as a lack of formal validation of our grading scale. We have attempted to minimize these limitations by piloting our scale prior to implementation. As well, we have constructed a scale that holds great face validity from a clinical standpoint and that reflects terminology and issues that are commonly raised in the literature on this topic. Finally, it should be mentioned that this type of analysis and semi-quantitative correlation with our meta-analysis cannot determine with certainty the precise reason for shifts in expert opinion, as our evaluation of individual reviews did not seek to capture the reasoning behind opinions. As well, this work has sought to capture only indirect evidence of the adoption of laparoscopic surgery for colorectal cancer, as proof of adoption would require data on actual uptake by surgeons rather than the utilization of a surrogate in the literature. Nevertheless, we argue that the analysis carried out in the current work is highly valuable as it provides a global evaluation of the state of the literature on this topic, which is presumably used by many – if not most – practitioners in evaluating novel technologies. At the very least, this analysis provides important insight into one of the critical knowledge translation links between the introduction of a technology and uptake into practice.

## **CONCLUSION**

A large number of trials comparing laparoscopic and open surgery for colorectal cancer can be identified in the literature. Laparoscopic surgery for colon cancer appears to be non-inferior to open surgery in terms of overall survival and in terms of lymph node harvest. Since 2003, the majority expert opinion in the literature has considered these two techniques to be equivalent in terms of oncologic outcomes. This shift in expert opinion appears to be temporally associated with the publication of landmark clinical trials in 2002 and 2004. Although increasingly accepted since 2006, laparoscopic surgery for rectal

cancer remains controversial, likely owing to the current lack of dedicated large-scale randomized controlled trials.

## REFERENCES

1. Fowler DL, White A. Laparoscopy-assisted sigmoid resection. *Surg Laparosc Endosc* 1991;1:183-8
2. Jacobs M, Verdeja JC, Goldstein HS. Minimally invasive colon resection (laparoscopic colectomy). *Surg Laparosc Endosc* 1991;1:144-50
3. Martel G, Boushey RP. Laparoscopic colon surgery: past, present and future. *Surg Clin N Am* 2006;86:867-97
4. Milsom JW. Laparoscopic surgery in the treatment of Crohn's disease. *Surg Clin N Am* 2005;85:25-34
5. Senagore AJ. Laparoscopic sigmoid colectomy for diverticular disease. *Surg Clin N Am* 2005;85:19-24
6. Barkun JS, Aronson JK, Feldman LS, Maddern GJ, Strasberg SM. Surgical innovation 1: evaluation and stages of surgical innovation. *Lancet* 2009;374:1089-96
7. Murray A, Lourenco T, de Verteuil R, Hernandez R, Fraser C, McKinley A, Krukowski Z, Vale L, Grant A. Clinical effectiveness and cost-effectiveness of laparoscopic surgery for colorectal cancer: systematic reviews and economic evaluation. *Health Technol Assess* 2006;10:1-141

8. Higgins JPT, Altman DG. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester (UK): John Wiley & Sons, 2008, pp. 187-241
9. Ramsay CR, Grant AM, Wallace SA, Garthwaite PH, Monk AF, Russell IT. Statistical assessment of the learning curves of health technologies. *Health Technol Assess* 2001;5:1-79
10. Williamson PR, Smith CT, Hutton JL, Marson AG. Aggregate data meta-analysis with time-to-event outcomes. *Statist Med* 2002;21:3337-3351
11. Parmar MKB, Torri V, Stewart L. Extracting summary statistics to perform meta-analysis of the published literature for survival endpoints. *Statist Med* 1998;17:2815-2834
12. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007;8:16
13. Sydes M, Tierney J. HR calculation spreadsheet, MRC Clinical Trials Unit, London, UK, 2004. [<http://www.biomedcentral.com/content/supplementary/1745-6215-8-16-S1.xls%5D>]. Accessed November 2010
14. Lacy AM, Garcia-Valdecasas JC, Pique JM, Delgado S, Campo E, Bordas JM, Taura P, Grande L, Fuster J, Pacheco JL, Visa J. Short-term outcome analysis of a randomized study comparing laparoscopic vs open colectomy for colon cancer. *Surg Endosc* 1995;9:1101-1105

15. Stage JG, Schulze S, Moller P, Overgaard H, Andersen M, Rebsdorf-Pedersen VB, Nielsen HJ. Prospective randomized study of laparoscopic versus open colonic resection for adenocarcinoma. *Br J Surg* 1997;84:391-39
16. Schwenk W, Böhm B, Haase O, Junghans T, Müller JM. Laparoscopic versus conventional colorectal resection: a prospective randomized study of postoperative ileus and early postoperative feeding. *Langenbecks Arch Surg* 1998;383:49-55
17. Schwenk W, Bohm B, Muller JM. Influence of laparoscopic or conventional colorectal resection on postoperative quality of life. *Zentralbl Chir* 1998;123:483-490
18. Milsom JW, Böhm B, Hammerhofer KA, Fazio V, Steiger E, Elson P. A prospective, randomized trial comparing laparoscopic versus conventional techniques in colorectal cancer surgery: a preliminary report. *J Am Coll Surg* 1998;187:46-54
19. Lacy AM, Delgado S, Garcia-Valdecasas JC, Castells A, Pique JM, Grande L, Fuster J, Targarona EM, Pera M, Visa J. Port site metastases and recurrence after laparoscopic colectomy: a randomized trial. *Surg Endosc* 1998;12:1039-1042
20. Schwenk W, Bohm B, Muller JM. Postoperative pain and fatigue after laparoscopic or conventional colorectal resections. *Surg Endosc* 1998;12:1131-1136
21. Schwenk W, Bohm B, Witt C, Junghans T, Grundel K, Muller JM. Pulmonary function following laparoscopic or conventional colorectal resection: a randomized controlled evaluation. *Arch Surg* 1999;134:6-12

22. Delgado S, Lacy AM, Garcia-Valdecasas JC, Balague C, Pera M, Salvador L, Momblan D, Visa J. Could age be an indicator for laparoscopic colectomy in colorectal cancer. *Surg Endosc* 2000;14:22-26
23. Curet MJ, Putrakul K, Pitcher DE, Josloff RK, Zucker KA. Laparoscopically assisted colon resection for colon carcinoma: prospective results and long-term outcome. *Surg Endosc* 2000;14:1062-1066
24. Weeks JC, Nelson H, Gelber S, Sargent D, Schroeder G. Short-term quality-of-life outcomes following laparoscopic-assisted colectomy vs open colectomy for colon cancer: a randomized trial. *JAMA* 2002;287:321-328
25. Lacy AM, Garcia-Valdecasas JC, Delgado S, Castells A, Taura P, Pique JM, Visa J. Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomized trial. *Lancet* 2002;359:2224-2229
26. Winslow ER, Fleshman JW, Birnbaum EH, Brunt LM. Wound complications of laparoscopic vs open colectomy. *Surg Endosc* 2002;16:1420-1425
27. Quah HM, Jayne DG, Eu KW, Seow-Choen F. Bladder and sexual dysfunction following laparoscopically assisted and conventional open mesorectal resection for cancer. *Br J Surg* 2002;89:1551-1556

28. Hasegawa H, Kabeshima Y, Watanabe M, Yamamoto S, Kitajima M. Randomized controlled trial of laparoscopic versus open colectomy for advanced colorectal cancer. *Surg Endosc* 2003;17:636-640
29. Araujo SE, da Silva e Sousa AH Jr, de Campos FG, Habr-Gama A, Dumarco RB, Caravatto PP, Nahas SC, da Silva J, Kiss DR, Gama-Rodrigues JJ. Conventional approach x laparoscopic abdominoperineal resection for rectal cancer treatment after neoadjuvant chemoradiation: results of a prospective randomized trial. *Rev Hosp Clin Fac Med Sao Paulo* 2003;58:133-140
30. Leung KL, Kwok SP, Lam SC, Lee JF, Yiu RY, Ng SS, Lai PB, Lau WY. Laparoscopic resection of rectosigmoid carcinoma: prospective randomized trial. *Lancet* 2004;363:1187-1192
31. Clinical Outcomes of Surgical Therapy Study Group. A comparison of laparoscopically assisted and open colectomy for colon cancer. *N Engl J Med* 2004;350:2050-2059
32. Zhou ZG, Hu M, Li Y, Lei WZ, Yu YY, Cheng Z, Li L, Shu Y, Wang TC. Laparoscopic vs open total mesorectal excision with anal sphincter preservation for low rectal cancer. *Surg Endosc* 2004;18:1211-1215
33. Kaiser AM, Kang JC, Chan LS, Vukasin P, Beart RW Jr. Laparoscopic-assisted vs. open colectomy for colon cancer: a prospective randomized trial. *J Laparoendosc Adv Surg Tech A* 2004;14:329-334

34. Guillou PJ, Quirke P, Thorpe H, Walker J, Jayne DG, Smith AM, Heath RM, Brown JM. Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. *Lancet* 2005;365:1718-1726
35. Colon Cancer Laparoscopic or Open Resection Study Group. Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. *Lancet Oncol* 2005;6:477-484
36. Jayne DG, Brown JM, Thorpe H, Walker J, Quirke P, Guillou PJ. Bladder and sexual function following resection for rectal cancer in a randomized clinical trial of laparoscopic versus open technique. *Br J Surg* 2005;92:1124-1132
37. Braga M, Frasson M, Vignali A, Zuliani W, Civelli V, Di Carlo V. Laparoscopic vs. open colectomy in cancer patients: long-term complications, quality of life, and survival. *Dis Colon Rectum* 2005;48:2217-2223
38. King PM, Blazeby JM, Ewings P, Franks PJ, Longman RJ, Kendrick AH, Kipling RM, Kennedy RH. Randomized clinical trial comparing laparoscopic and open surgery for colorectal cancer within an enhanced recovery programme. *Br J Surg* 2006;93:300-308
39. Arteaga Gonzalez I, Diaz Luis H, Martin Malagon A, Lopez-Tomassetti Fernandez EM, Arranz Duran J, Carrillo Pallares A. A comparative clinical study of short-term results of laparoscopic surgery for rectal cancer during the learning curve. *Int J Colorectal Dis* 2006;21:590-595

40. Liang JT, Huang KC, Lai HS, Lee PH, Jeng YM. Oncologic results of laparoscopic versus conventional open surgery for stage II and III left-sided colon cancers: a randomized controlled trial. *Ann Surg Oncol* 2007;14:109-117
41. Pechlivanides G, Gouvas N, Tsiaoussis J, Tzortzinis A, Tzardi M, Moutafidis M, Dervenis C, Xynos E. Lymph node clearance after total mesorectal excision for rectal cancer: laparoscopic versus open approach. *Dig Dis* 2007;25:94-99
42. Braga M, Frasson M, Vignali A, Zuliani W, Capretti G, Di Carlo V. Laparoscopic resection in rectal cancer patients: outcomes and cost-benefit analysis. *Dis Colon Rectum* 2007;50:464-471
43. Janson M, Lindholm E, Anderberg B, Haglind E. Randomized trial of health-related quality of life after open and laparoscopic surgery for colon cancer. *Surg Endosc* 2007;21:747-753
44. Jayne DG, Guillou PJ, Thorpe H, Quirke P, Copeland J, Smith AMH, Heath RM, Brown JM. Randomized trial of laparoscopic-assisted resection of colorectal carcinoma: 3-year results of the UK MRC CLASICC trial group. *J Clin Oncol* 2007;25:3061-3068
45. Fleshman J, Sargent DJ, Green E, Anvari M, Stryker SJ, Beart RW Jr, Hellinger M, Flanagan R Jr, Peters W, Nelson H. Laparoscopic colectomy for cancer is not inferior to open surgery based on 5-year data from the COST Study Group Trial. *Ann Surg* 2007;246:655-664

46. Chung CC, Ng DCK, Tsang WWC, Tang WL, Yau KKK, Cheung HYS, Wong JCH, Li MKW. Hand-assisted laparoscopic versus open right hemicolectomy: a randomized controlled trial. *Ann Surg* 2007;246:728-733
47. Ramacciato G, D'Angelo F, Aurello P, Nigri G, Valabrega S, Pezzoli F, Ravaioli M, Cescon M, Cucchetti A, Lauro A, Del Gaudio M, Ercolani G. Right hemicolectomy for colon cancer: a prospective randomised study comparing laparoscopic vs open technique. *Chir Ital* 2008;60:1-7
48. Lacy AM, Delgado S, Castells A, Prins HA, Arroyo V, Ibarzabal A, Pique JM. The long-term results of a randomized clinical trial of laparoscopy-assisted versus open surgery for colon cancer. *Ann Surg* 2008;248:1-7
49. King PM, Blazeby JM, Ewings P, Kennedy RH. Detailed evaluation of functional recovery following laparoscopic or open surgery for colorectal cancer with an enhanced recovery programme. *Int J Colorectal Dis* 2008;23:795-800
50. Ng SSM, Leung KL, Lee JFY, Yiu RYC, Li JCM, Teoh AYB, Leung WW. Laparoscopic-assisted versus open abdominoperineal resection for low rectal cancer: a prospective randomized trial. *Ann Surg Oncol* 2008;15:2418-2425
51. Hewett PJ, Allardyce RA, Bagshaw PF, Frampton CM, Frizelle FA, Rieger NA, Smith JS, Solomon MJ, Stephens JH, Stevenson ARL. Short-term outcomes of the Australasian randomized clinical study comparing laparoscopic and conventional open surgical treatments for colon cancer: the ALCCaS trial. *Ann Surg* 2008;248:728-738

52. The Colon Cancer Laparoscopic or Open Resection Study Group. Survival after laparoscopic surgery versus open surgery for colon cancer: long-term outcome of a randomised clinical trial. *Lancet Oncol* 2009;10:44-52
53. Jackson TD, Kaplan GG, Arena G, Page JH, Rogers SO Jr. Laparoscopic versus open resection for colorectal cancer: a metaanalysis of oncologic outcomes. *J Am Coll Surg* 2007;204:439-446
54. Kuhry E, Schwenk W, Gaupset R, Romild U, Bonjer HJ. Long-term results of laparoscopic colorectal cancer resection. *Cochrane Database Syst Rev* 2008;CD003432
55. COLOR II Study Group, Buunen M, Bonjer HJ, Hop WC, et al. COLOR II. A randomized clinical trial comparing laparoscopic and open surgery for rectal cancer. *Dan Med Bull* 2009; 56: 89-91
56. American College of Surgeons Oncology Group. Laparoscopic-assisted resection or open resection in treating patients with stage IIA, stage IIIA, or stage IIIB rectal cancer. 2011. Available at [www.clinicaltrials.gov](http://www.clinicaltrials.gov), identifier NCT00726622. [Accessed 12 February 2011]

## **BRIDGE**

In the previous chapters of this work, we have provided an overview of existing systematic reviews addressing oncologic outcomes from laparoscopic and open surgery for colorectal cancer. As well, we have carried out a systematic review and meta-analysis of evidence on this topic derived from randomized controlled trials and have reviewed patterns of expert acceptance in the literature.

In the next chapter of this work, we provide a systematic review and meta-analysis of observational studies of laparoscopic surgery for colorectal cancer. As well, we provide a comparison of outcomes generated from our meta-analyses of randomized controlled trials, observational studies, and other existing systematic reviews. This thesis chapter is particularly important given the high reliance upon observational study designs in surgical research.

## **CHAPTER FOUR: OBSERVATIONAL STUDIES**

### **ONCOLOGIC OUTCOMES OF LAPAROSCOPIC AND OPEN COLORECTAL CANCER SURGERY: SYSTEMATIC REVIEW OF OBSERVATIONAL STUDIES**

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## **INTRODUCTION**

Randomized controlled trials (RCTs) and well-conducted systematic reviews of trials are widely considered to provide the highest standard of evidence in evaluating healthcare interventions. In contrast, observational studies are generally considered to be of lesser value in the hierarchy of healthcare research evidence.

Empirical work in support of this well-established evidence hierarchy has traditionally indicated that, when compared to RCTs, observational studies tend to overestimate the magnitude of effect of therapies [1-5]. More recent work has demonstrated that outcomes from trials and observational studies can differ, but not always, and that the direction and magnitude of these differences is unpredictable [6, 7].

Unfortunately, little empirical work comparing randomized and observational study designs has included data from the surgical disciplines. Because few trials are being conducted in surgical research [8], it is particularly important to define the relative value of observational studies in this context, as this study design remains highly prevalent today and many novel surgical technologies are often never evaluated in trials. Laparoscopic surgery for colorectal cancer presents an excellent opportunity for empiric work in this area, as there has been a large volume of trial and observational literature published on this topic.

The objective of this study was to synthesize the oncologic outcomes from observational studies comparing laparoscopic and open surgery for colorectal cancer, and to assess the congruence of these outcomes with that obtained from RCTs.

## **MATERIALS AND METHODS**

The global methodological approach to this work was that of a comprehensive systematic review of the literature pertaining to laparoscopic and open surgery for colorectal cancer. The details of the methodology used to carry out this review have been described in Chapter 4 of this thesis. The eligibility criteria, comprehensive search strategy, and citation

selection were unchanged, except where noted below. The current chapter focused solely on observational studies, and excluded RCTs and review articles.

Allowable primary study designs were observational studies, both controlled and uncontrolled. Studies providing data on fewer than 10 patients undergoing laparoscopic resection were excluded from consideration. Inclusion and exclusion criteria are otherwise unchanged from Chapter 4.

### ***Risk of bias assessment***

The risk of bias of included observational studies was assessed using the Methodological Index for Non-Randomized Studies (MINORS) instrument (appendix 5) [9]. The utilization of this scale represents an amendment to the review protocol, which originally called for the utilization of the Newcastle-Ottawa scale [10]. The later scale was found to be best suited for use in systematic reviews of causation [6], which rendered it challenging to use in pilot analyses for the current review of effectiveness of an intervention. The MINORS instrument was thus selected, as it has been specifically designed and validated for use with studies of surgical interventions [9]. This was considered to be an acceptable amendment to the review protocol, as almost all items within the Newcastle-Ottawa scale are also found within MINORS, and other groups have utilized this instrument within systematic reviews of effectiveness of surgical interventions [11-13].

Included observational studies were graded using the 12 items of the MINORS instrument. Among these, 8 items were applicable to all study types, while the last 4 were only applicable to controlled studies. Each item was scored as 2 ('reported and adequate'), 1 ('reported but inadequate'), or 0 ('not reported'). The maximal MINORS score available for controlled studies was 24, while uncontrolled studies could score up to 16. Although the authors of the MINORS instrument do not provide a cutoff score denoting high-quality studies, other groups have utilized  $\geq 17$  within sensitivity analyses as an arbitrary definition

of high-quality studies [11]. This is likely to be an appropriate cutoff point, as it presupposes that only controlled studies can be considered of high value.

In determining the appropriateness of follow-up times within individual studies (item 6), we considered that the minimal meaningful mean/median time required to accrue data on oncologic outcomes such as survival or disease recurrence was 36 months. The baseline equivalence of two study groups within controlled studies (item 11), was determined on the basis of adequately reported data on age, comorbidities, tumor location/resection type, and pathological staging. All other items were scored according to the instructions provided by the scale authors.

### ***Data abstraction and management***

Given the large number of observational studies available in the literature pertaining to laparoscopic and open surgery for colorectal cancer, a convenient sample of 30 randomly-selected controlled observational studies and 30 uncontrolled observational studies were chosen among all included observational studies, in order to mirror the number of trials identified in Chapter 4. Studies were assigned computerized random numbers and the first 30 controlled and 30 uncontrolled studies in the sequence were chosen for further data abstraction and analysis. The selection process was completely random, and no selection preference was applied on the basis of publication language, year of publication, or availability of outcome data. All studies were considered to be of equal value, with the exception of controlled and uncontrolled designs.

Data abstraction forms and methods were as described in Chapter 4. Although each citation was abstracted separately, studies with multiple publications were identified and labeled so as to avoid duplication of patients within this systematic review. Individual study authors were contacted selectively whenever questions arose during data abstraction about outcomes, or to check whether individual citations overlapped. When study authors did not

answer our queries, citations from common institutions with overlapping dates and procedures were assumed to have included the same patients and were treated as duplicates.

### ***Data synthesis***

Methods pertaining to data synthesis were as described in Chapter 4. For controlled observational studies, overall survival was evaluated by pooling estimates of hazard ratios, whereas lymph node harvest was evaluated using weighted mean differences. For uncontrolled observational studies, comparative outcomes could not be generated due to the lack of a control group. Instead, the available data were summarized and attempts were made to generate a pooled point estimate based on data quality and availability.

Outcomes from meta-analyses of RCTs (Chapter 4), observational studies, and other existing published meta-analyses (Chapter 2) were compared and contrasted using Forest plots. As well, the congruence between HRs derived from different study designs was assessed statistically by determining whether differences in HRs were larger than that expected from chance alone. The following formula was utilized to compute a Z score [14]:

$$Z = \frac{\ln(HR_{RCT}) - \ln(HR_{OBS})}{\sqrt{\text{var}[\ln(HR_{RCT})] + \text{var}[\ln(HR_{OBS})]}}$$

Using this approach, a Z score >1.96 or <-1.96 would suggest a significant difference between study designs at a 0.05 level of significance.

## **RESULTS**

### ***Description of included studies***

A total of 5,800 single citations were screened for inclusion (figure 2). After applying a two-step screening process, a total of 215 observational studies were included in the final review, comprising 91 controlled (laparoscopy vs. open surgery) and 124 uncontrolled case

series (laparoscopy only). From these two sets of citations, 30 controlled [15-44] and 30 uncontrolled [45-74] series were selected randomly for further analysis, comprising 33% and 24% of included citations, respectively. In total, 16,804 patients were included between the two subsets of observational studies. In the controlled papers, there were 1,849 patients undergoing laparoscopy and 8,943 patients undergoing open surgery, or 4.8 open patients for each laparoscopic patient. This large discrepancy between the two groups of patients is driven primarily by a German multicenter study by Ptok et al. that included 6,952 open control patients for 237 laparoscopic patients [39]. Excluding for this study yielded 1,612 and 1,991 laparoscopic and open patients, respectively. In the uncontrolled case series, there were 6,012 patients undergoing laparoscopy. In this case, one multicenter study from Japan was particularly large, accounting for 34% (n=2,036) of the sample [56].

A summary of included studies is provided in table 4. The majority of included papers were from Western Europe (50%, 30/60) and Asia (28%, 17/60). For both sets of studies, English was the predominant language of publication (87% and 77%). Following random selection, there was a fairly even distribution of citations per five-year publication block, with the exception of 1991-1995, which was underrepresented with uncontrolled series. For both samples, few authors reported solely on colon cancer (23% and 10%), whereas a larger proportions of papers addressed rectal cancer specifically (37% and 40%). Intraoperative (87% and 97%) and short-term (90% and 93%) outcomes were reported by a large majority of papers. Similarly, both oncologic surrogates and long-term oncologic outcomes were reported in over three-quarters of publications. Other types of outcomes such as quality of life or long-term rates of bowel obstruction or incisional hernia were infrequently reported in both study samples.

**Table 5.** Summary of included observational studies

<b>Characteristics</b>		<b>Controlled studies (n=30)</b>	<b>Uncontrolled studies (n=30)</b>
<i>Origin</i>	Western Europe Asia North America South America Australia/New Zealand	14 (47%) 9 (30%) 4 (10%) 2 (6.7%) 1 (3.3%)	16 (53%) 8 (27%) 4 (10%) 2 (6.7%) 0
<i>Publication years</i>	1991-1995 1996-2000 2001-2005 2006-2008	5 (17%) 8 (27%) 9 (30%) 8 (27%)	1 (3.3%) 6 (20%) 10 (33%) 13 (43%)
<i>Study size</i>	≤50 patients 51-100 patients 101-200 patients 201-1000 patients >1000 patients	5 (17%) 12 (40%) 7 (23%) 5 (17%) 1 (3.3%)	9 (30%) 4 (10%) 7 (23%) 9 (30%) >1 (3.3%)
<i>Population</i>	Colon Colorectal Rectum	7 (23%) 12 (40%) 11 (37%)	3 (10%) 15 (50%) 12 (40%)
<i>Outcomes</i>	Operative Short-term postoperative Oncologic surrogate Long-term oncologic Other long-term Quality of life	26 (87%) 27 (90%) 25 (83%) 23 (77%) 4 (13%) 2 (6.7%)	29 (97%) 28 (93%) 24 (80%) 25 (83%) 1 (3.3%) 0
<i>Follow-up</i>	≤12 months 13-24 months 25-36 months 37-60 months >60 months Missing	1 (3.3%) 5 (17%) 9 (30%) 7 (23%) 1 (3.3%) 7 (23%)	3 (10%) 8 (27%) 5 (17%) 4 (13%) 5 (17%) 5 (17%)

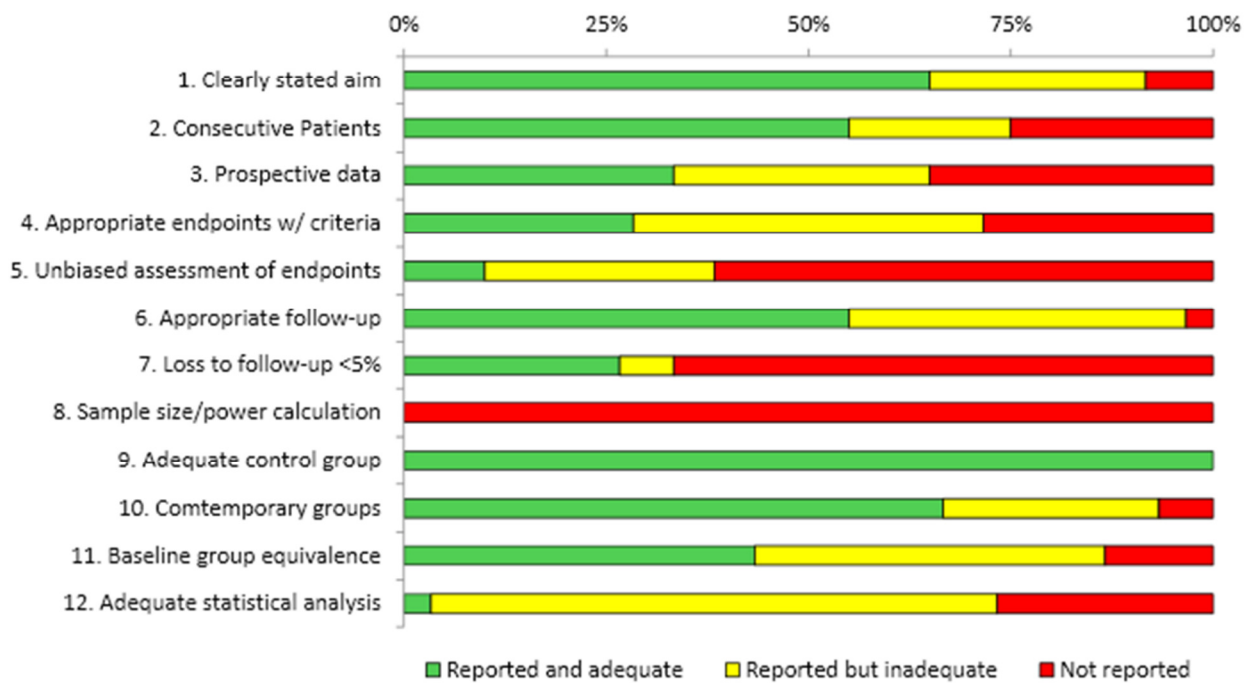
***Risk of bias assessment***

A total of 12 and 8 MINORS items were evaluated among controlled and uncontrolled observational studies, respectively. The median MINORS score was 13 (range 6-20) for controlled studies, and 7 (range 1-14) for uncontrolled studies. Using a cutoff value

≥17, 8 controlled studies were found to demonstrate a lower overall risk of bias [21, 24, 26, 27, 31, 33, 34, 41].

The risk of bias associated with individual MINORS items is presented in figure 15. Most studies provided a clearly stated aim (item 1, 65%), presented consecutive patients (item 2, 55%), reported an appropriate length of follow-up (item 6, 55%), had an appropriate control group (item 9, 100%), and utilized contemporary study groups (item 10, 67%). In contrast, a majority of studies did not provide an unbiased assessment method of study endpoints (item 5, 62%), did not report on losses to follow-up (item 7, 67%), and did not provide a sample or study power calculation (item 8, 100%).

**Figure 15.** Global risk of bias among observational studies divided by individual items



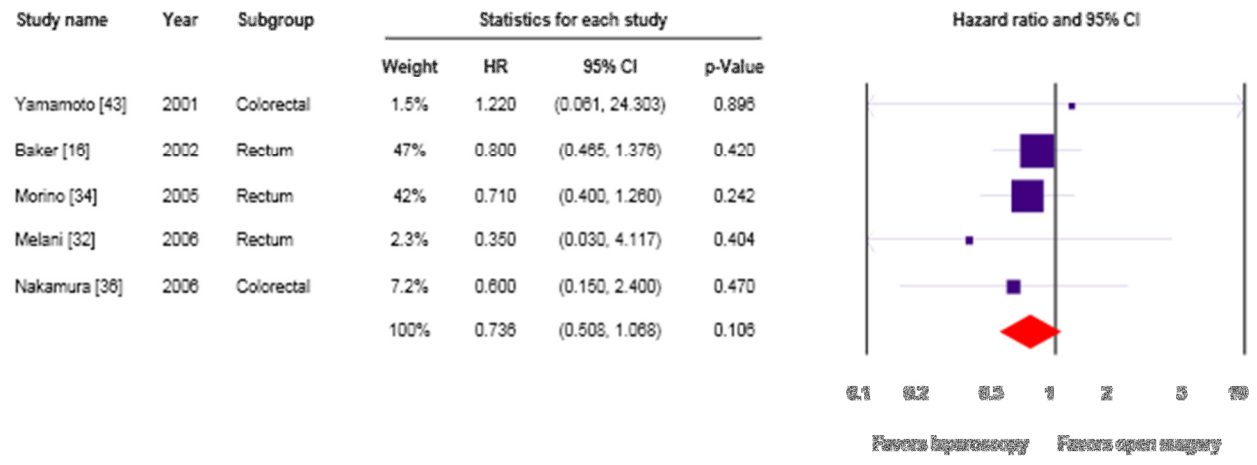
### ***Analysis of long-term oncologic data from included studies***

Data pertaining to long-term follow-up after surgery was presented in 23 (77%) controlled studies. The format in which this information was presented was variable. The

combined mean/median follow-up for both laparoscopic and open patients ranged from 28-49 months (n=4). Individual mean/median follow-up data for laparoscopic patients ranged from 17-56 months (n=18), whereas that of open patients ranged from 11-68 (n=15).

Overall survival following laparoscopic and open surgery for colorectal cancer was reported by 12 (40%) controlled observational studies. Of these, 10 studies presented data as a proportion of patients alive/dead at follow-up. The time point at which the proportion of alive patient was reported varied between studies, and included maximal follow-up, median follow-up, and actuarial calculations at 3- and 5-year follow-up, hence making meta-analysis impossible. A total of 84-100% of laparoscopic patients (n=10 studies) and 56-93% of open patients (n=8 studies) were alive at follow-up.

**Figure 16.** Random-effect meta-analysis of overall survival among controlled observational studies



In addition to the proportion of patients alive at follow-up, five studies presented sufficient data within Kaplan-Meier curves to estimate hazard ratios for overall survival [16, 32, 34, 36, 43]. No significant difference in overall survival was identified in a random-effect meta-analysis (figure 16). There was no evidence of statistical heterogeneity within this

analysis ( $Q=0.648$ ,  $p=0.958$ ;  $I^2=0\%$ ). Separate sensitivity analyses based on patients labeled as having colorectal or rectal cancer did not affect the magnitude, direction, or significance of the pooled estimate. Similarly, these analyses did not increase the degree of heterogeneity. Sensitivity analysis of studies at low risk of bias was not possible as only one such study was included [34]. Excluding this study at low risk of bias from the meta-analysis did not affect the magnitude, direction, or heterogeneity of the pooled point estimate.

Follow-up data was presented in variable formats among 25 (83%) uncontrolled observational studies. The mean/median duration of follow-up ranged from 10-84 months. Overall survival data was reported in 16 (53%) uncontrolled observational studies. All such papers presented data as a proportion of patients alive at maximum follow-up or at a fixed time point (1, 3, or 5 years). The reported overall survival rate at follow-up ranged from 50-94.5%. Due to significant variability as well as differences in durations in follow-up, no attempt was made to pool overall survival rates among uncontrolled observational studies.

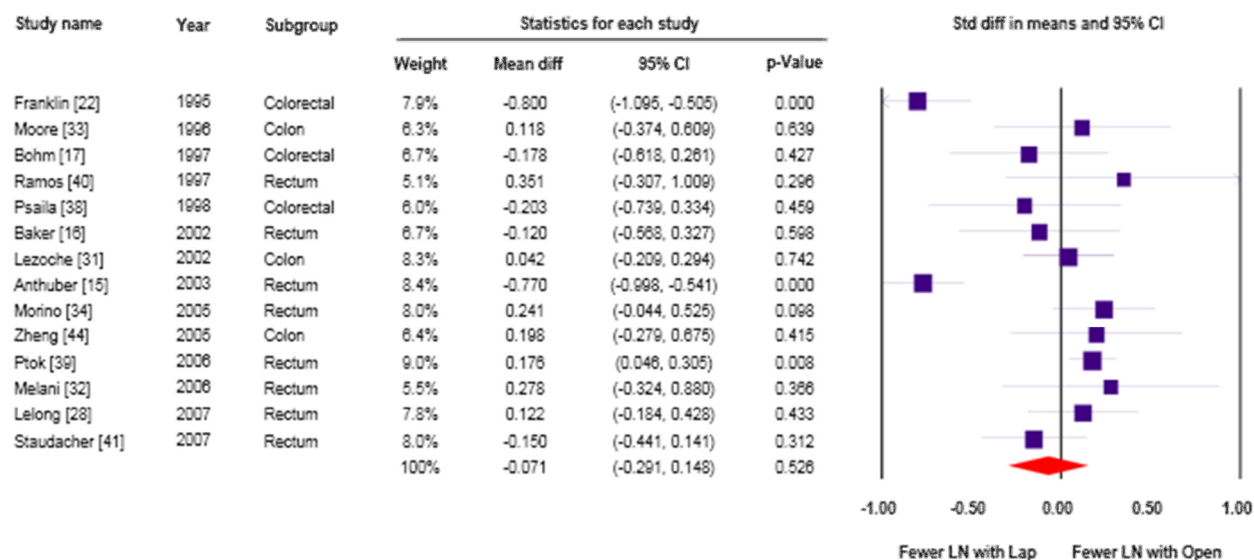
### ***Analysis of short-term oncologic surrogate data from included studies***

Data pertaining to total lymph node harvest was reported in 80% ( $n=24$ ) of controlled studies. Among these, 14 studies presented sufficient data to allow for meta-analysis [15-17, 22, 28, 31-34, 38-41, 44] (figure 17). All other studies ( $n=10$ ) presented point estimates of lymph node harvest as means or medians, but did not present adequate measures of dispersion around the mean. The range of means/medians for these studies was 9.5-16.5 for laparoscopy and 6.0-31.5 for open surgery. The pooled weighted mean difference between laparoscopic and open surgery was  $-0.071$  (95% CI  $-0.29, 0.15$ ). This meta-analysis demonstrated highly significant statistical heterogeneity ( $Q=85.6$ ,  $p<0.001$ ;  $I^2=85\%$ ).

A sensitivity analysis of pooled total lymph node limited to colon cancer yielded a non-significant weighted mean difference of the reciprocal direction ( $0.083$ , 95% CI  $(-0.12,$

0.29)), with no evidence of statistical heterogeneity ( $Q=0.343$ ,  $p=0.842$ ;  $I^2=0\%$ ). A pooled analysis of studies limited to rectal cancer (-0.011, 95% CI (-0.31, 0.29)) accounted for much of the statistical heterogeneity identified in the main meta-analysis ( $Q=57.3$ ,  $p<0.001$ ;  $I^2=88\%$ ). Further exploratory analysis revealed that much of the statistical heterogeneity within the main meta-analysis could be accounted for on the basis of three studies with statistically significant findings [15, 22, 39], and that removal of these studies eliminated this heterogeneity ( $Q=8.00$ ,  $p=0.623$ ;  $I^2=0\%$ ). Finally, meta-analysis limited to four studies with a low risk of bias [31, 33, 34, 41] yielded a weighted mean difference of 0.053 (95% CI -0.097, 0.204), with minimal statistical heterogeneity ( $Q=3.614$ ,  $p=0.306$ ;  $I^2=17\%$ ).

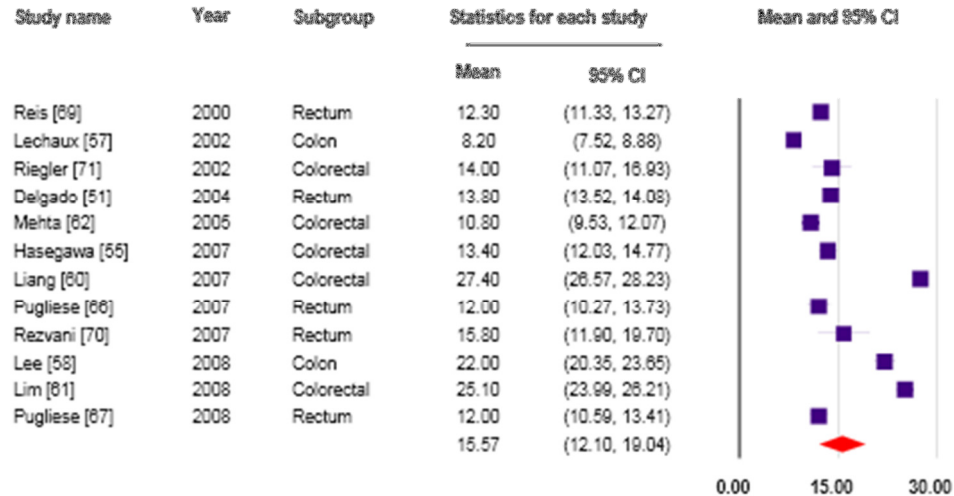
**Figure 17.** Random-effect meta-analysis of harvested lymph nodes among controlled observational studies



Uncontrolled observational studies presented data on lymph node harvest in 21 studies (70%). Among these, 12 studies presented sufficient data to generate a pooled random-effects mean number of harvested lymph node of 15.6 (95% CI 12.1, 19.0) [51, 55,

57, 58, 60-62, 66, 67, 69-71] (figure 18). All other 9 studies presented means/medians with insufficient measures of variability to allow inclusion in the pooled estimate.

**Figure 18.** Random-effects meta-analysis of mean lymph node harvest among uncontrolled observational studies

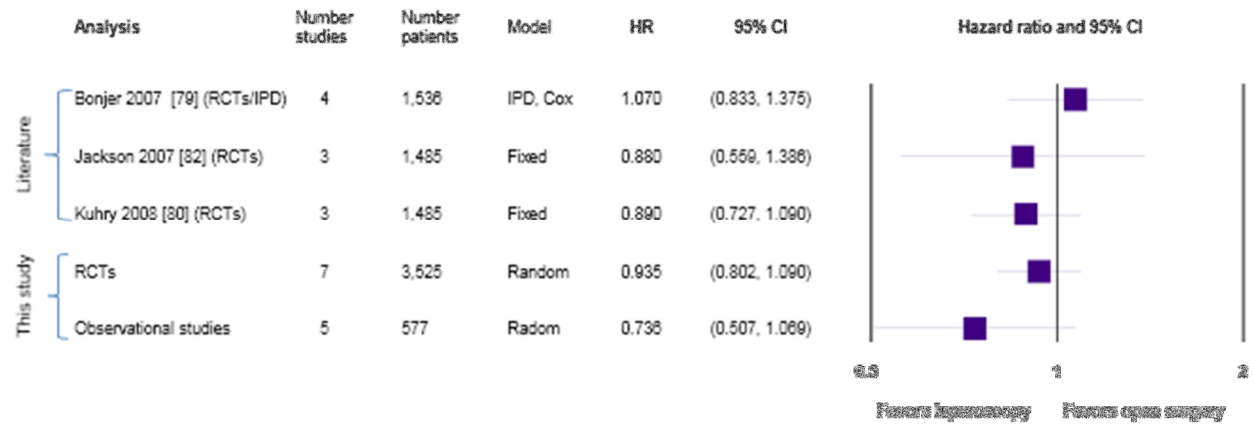


**Comparison of oncologic data from different study types**

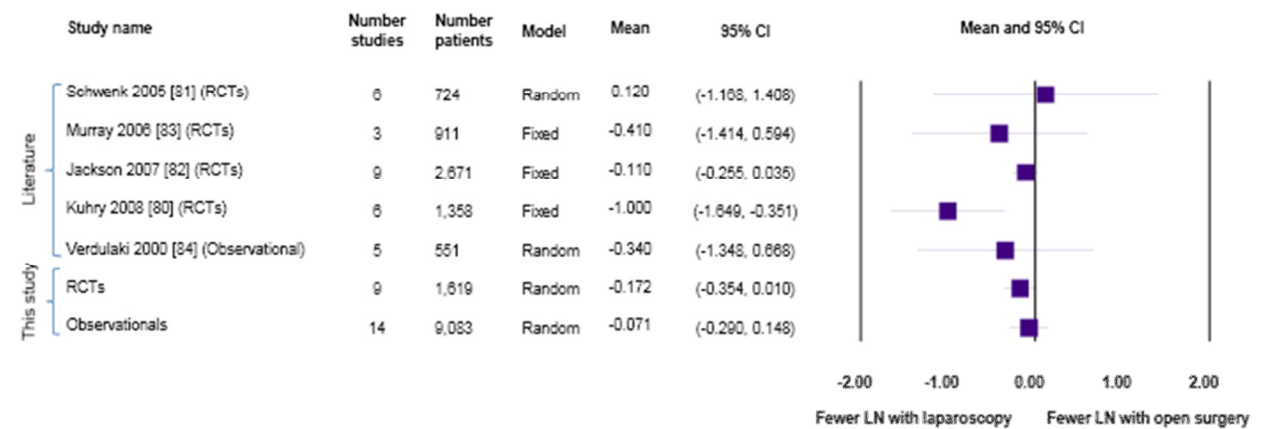
Pooled hazard ratios for overall survival and weighted mean differences of lymph node harvest were obtained from RCTs (chapter 4), observational studies, and other existing systematic reviews (chapter 2). These data are presented in figures figure 19 and 20, respectively.

The statistical comparison of HRs from RCTs ( $\ln HR = -0.068$ ,  $\text{var}(\ln HR) = 0.078$ ) and observational studies ( $\ln HR = -0.306$ ,  $\text{var}(\ln HR) = 0.036$ ) yielded a Z score of 0.70. The statistical difference between both pooled HRs was thus not more than that expected by chance alone.

**Figure 19.** Comparison of pooled estimates of overall survival across different study types



**Figure 20.** Comparison of pooled estimated of total harvested lymph nodes across different study types



## DISCUSSION

This systematic review has identified 215 relevant observational studies pertaining to laparoscopic surgery for colorectal cancer. Among these papers, a convenient random sample of 30 controlled and 30 uncontrolled series was selected for further analysis, comprising 16,804 patients with colorectal cancer.

A meta-analysis of time-to-event data on overall survival among controlled series found no significant difference between patients undergoing laparoscopy or open surgery. Although these data would support that laparoscopy for colorectal cancer provides comparable oncologic outcomes to open surgery, one must interpret these findings cautiously. Indeed, among 30 sampled controlled case series, 23 reported long-term oncologic data, with only 12 of these addressing overall survival outcomes. In this group, only 5 papers (577 patients) provided sufficient data to allow for the estimation of hazard ratios and meta-analysis. Unfortunately, most other papers and all uncontrolled series presented incomplete survival data that did not permit meta-analysis, due to variable lengths of follow-up and inconsistent inclusion/exclusion of stage 4 patients within survival statistics.

Similarly to overall survival, no significant difference in total lymph node harvest was identified between laparoscopy and open surgery. While these data demonstrated significant heterogeneity, we argue that this analysis was supportive of laparoscopy as an equivalent technology to open surgery for colorectal cancer. Indeed, controlled studies found no difference upon pooling, and also demonstrated that the difference in harvested lymph nodes among most studies invariably fell within  $\pm 1$  lymph node, which is unlikely to be of clinical significance. In addition, pooling of uncontrolled case series documented a mean harvest of 15.6 nodes (95% CI 12.1, 19.0). This mean and its confidence interval are well above the 12 lymph nodes routinely prescribed by expert panels and professional societies as an oncologic surrogate marker of good colorectal cancer surgery [75]. The significant heterogeneity identified within these analyses is likely related to the degree of radicality associated with lymph node harvest by individual surgeons, to inherent differences in available lymph nodes between different segments of colon and/or rectum, to differences in utilization of neoadjuvant chemo-radiotherapy between rectal cancer studies, and to differences in pathological processing of surgical specimens [76-78].

In comparing overall survival data across study types, the pooled HRs were found to be congruent, in that no significant statistical difference in any point estimate could be identified. The direction of the HRs was also congruent in all meta-analyses except for that by Bonjer et al [79]. The magnitude of the pooled estimates was similarly conservative for all analyses of RCTs, but was moderately larger for observational studies. In our analysis, pooled HRs from RCTs and observational studies yielded comparable estimates of overall survival, albeit somewhat more exaggerated for observational studies. Unfortunately, we were unable to distinguish high- vs low-risk of bias studies in this analysis, as there were too few studies with sufficient data to allow for pooling. In the case of Bonjer et al, the authors utilized individual patient data from 4 trials to generate true HRs, and then corrected their data for age, gender, and stage using a stratified Cox regression model. All other pooled estimates of HR utilized meta-analytic techniques to pool estimates of HRs.

Pooled estimates of the weighted mean difference in total lymph node harvest were congruent across study designs. All existing meta-analyses except one [80], as well as our own analyses of RCTs and observational studies yielded non-significant weighted mean differences between the two study groups. In all meta-analyses except that by Schwenk et al [81], the direction of the point estimate favored open surgery (ie. fewer harvested lymph nodes with laparoscopy). For all analyses, the magnitude of the point estimates was small, such that at most one fewer lymph node could be expected to be removed with laparoscopy. In our own meta-analyses, the pooled estimates for RCTs and observational studies were highly congruent.

Other groups have also conducted empiric evaluations of observational studies in gastrointestinal surgery. In 2006, Shakita and colleagues examined 52 outcomes from 18 different topics in digestive surgery, and determined that observational studies and RCTs yielded significantly different outcomes in 25% of topics [14]. In addition, observational studies were found to be more likely to have between-study heterogeneity than RCTs did

(42% vs. 11%). In another study, Abraham et al compared data obtained from two meta-analyses of RCTs and observational studies of short-term outcomes of laparoscopic and open surgery for colorectal cancer conducted before the end of 2003 [11]. This group reported that meta-analytic results from RCTs and observational studies were “remarkably” similar, and that study conduct and quality issues accounted for much of the statistical homogeneity among well-designed observational studies. While this group did not address survival outcomes, they did report on lymph node harvest and documented identical cumulative weighted ratios of 0.98 for pooled data from RCTs and observational studies. These data appear supportive of our findings, particularly as they evaluated the same clinical problem but with a focus on short-term outcomes.

Limitations of the current study included our using a random sample of 33% and 24% of included controlled and uncontrolled observational studies, respectively. This pragmatic decision was driven by the large volume of observational literature published on this topic. Although we cannot rule out that inclusion of all studies would have significantly altered our pooled point estimates, we argue that this is unlikely. Indeed, point estimates for both overall survival and difference in lymph node harvest were generally comparable to that of other pooled estimates of RCTs and observational studies. An alternative methodological option would have been to limit the analysis to studies including a larger number of patients, but this approach was felt to be inferior as it would have introduced additional bias by eliminating smaller series.

The restriction of included outcomes to overall survival and lymph node harvest represents another limitation of this study. Indeed, many studies presented oncologic data using other formats (eg. disease-free survival, stage-specific survival, local or distant recurrence) that were not directly captured by the current analysis. While this decision may have limited the availability of data for meta-analysis, we argue that overall survival represents the most objective type of data available to evaluate an intervention in oncology,

and as such should be reported by all studies presenting oncologic outcomes. As a corollary to this limitation, the current study was also constrained by the incomplete reporting of survival and lymph node data by individual study authors. For instance, out of 12 papers reporting on overall survival, only 5 presented complete time-to-event data that permitted meta-analysis. All other papers chose to present survival as a dichotomous outcome, which greatly limited its utility for research and for practicing clinicians.

## **CONCLUSION**

A large number of published observational studies pertaining to laparoscopic and open surgery for colorectal cancer can be identified in the literature. The methodological quality of these studies is highly variable. Survival and lymph node harvest data can be identified in a majority of observational studies, but most report insufficient data to allow for meta-analysis. Among those papers presenting adequate data for meta-analysis, no difference in overall survival and total lymph node harvest can be identified between patients undergoing laparoscopic and open surgery for colorectal cancer. Pooled estimates of overall survival and total lymph node harvest appear to be congruent between observational studies and randomized controlled trials.

## **REFERENCES**

1. Chalmers TC, Matta RJ, Smith H, Kunzler AM. Evidence favoring the use of anticoagulants in the hospital phase of acute myocardial infarction. *New Engl J Med* 1977;297:1091-1096
2. Chalmers TC, Celano P, Sacks HS, Smith H. Bias in treatment assignment in controlled clinical trials. *N Engl J Med* 1983;309:1358-1361

3. Sacks H, Chalmers TC, Smith H. Randomized versus historical controls for clinical trials. *Am J Med* 1982;72:233-240
4. Colditz GA, Miller JN, Mosteller F. How study design affects outcomes in comparisons of therapy. I: medical. *Stat Med* 1989;8:441-454
5. Miller JN, Colditz GA, Mosteller F. How study design affects outcomes in comparisons of therapy. II: surgical. *Stat Med* 1989;8:455-466
6. Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, et al. Evaluating non-randomised intervention studies. *Health Technol Assess* 2003;7(27)
7. Kunz R, Vist GE, Oxman AD. Randomisation to protect against selection bias in healthcare trials. *Cochrane Database Syst Rev* 2007;(2):MR000012
8. Solomon MJ, McLeod RS. Surgery and the randomised controlled trial: past, present and future. *Med J Aust* 1998;169:380-383
9. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (MINORS): development and validation of a new instrument. *ANZ J Surg* 2003;73:712-716
10. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. *Clinical Epidemiology Program, Ottawa Hospital Research Institute*. [[http://www.ohri.ca/programs/clinical\\_epidemiology/oxford.asp](http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp)]. Accessed August 2011

11. Abraham NS, Byrne CJ, Young JM, Solomon MJ. Meta-analysis of well-designed nonrandomized comparative studies of surgical procedures is as good as randomized controlled trials. *J Clin Epidemiol* 2010;63:238-245
12. Slater NJ, Hansson BM, Buyne OR, Hendriks T, Bleichrodt RP. Repair of parastomal hernias with biologic grafts: a systematic review. *J Gastrointest Surg* 2011;15:1252-1258
13. Van Raaij TM, Reijman M, Furlan AD, Verhaar JA. Total knee arthroplasty after high tibial osteotomy: a systematic review. *BMC Musculoskelet Disord* 2009;10:88
14. Shikata S, Nakayama T, Noguchi Y, Taji Y, Yamagishi H. Comparison of effects in randomized controlled trials with observational studies in digestive surgery. *Ann Surg* 2006;244:668-676

***Controlled observational studies***

15. Anthuber M, Fuerst A, Elser F, Berger R, Jauch KW. Outcome of laparoscopic surgery for rectal cancer in 101 patients. *Dis Colon Rectum* 2003;46:1047-1053
16. Baker RP, White EE, Titu L, Duthie GS, Lee PWR, Monson JRT. Does laparoscopic abdominoperineal resection of the rectum compromise long-term survival? *Dis Colon Rectum* 2002;45:1481-1485
17. Bohm B, Schwenk W, Grundel K, Junghans T, Muller JM. [The importance of laparoscopic techniques in cases of primary colorectal carcinoma]. *Chirurg* 1997;68:231-236

18. Buchmann P, Christen D. Pro laparoscopic surgery for colorectal cancer. *Dig Surg* 1995;12:296-301
19. Buchmann P, Christen D, Flury R, Luthy A, Bischofberger U. [Is laparoscopic assisted colorectal surgery for cancer equal to open operation regarding radicality of resection?] *Schweiz Med Wochenschr* 1995;125:1825-1829
20. Darzi A, Lewis C, Menzies-Gow N, Guillou PJ, Monson JRT. Laparoscopic abdominoperineal excision of the rectum. *Surg Endosc* 1995;9:414-417
21. Feliciotti F, Paganini AM, Guerrieri M, De Sanctis A, Campagnacci R, Lezoche E. Results of laparoscopic vs open resections for colon cancer in patients with minimum follow-up of 3 years. *Surg Endosc* 2002;16:1158-1161
22. Franklin Jr ME, Rosenthal D, Norem RF. Prospective evaluation of laparoscopic colon resection versus open colon resection for adenocarcinoma. *Surg Endosc* 1995;9:811-816
23. Franklin Jr ME, Rosenthal D, Abrego-Medina D, Dorman JP, Glass JL, Norem R, Diaz A. Prospective comparison of open vs. laparoscopic colon surgery for carcinoma: five-year results. *Dis Colon Rectum* 1996;39:s35-s46
24. Inoue Y, Kimura T, Noro H, Yoshikawa M, Nomura M, Yumiba T, Taniguchi E, Ohashi S, Souda S, Matsuda H. Is laparoscopic colorectal surgery less invasive than classical open surgery? Quantitation of physical activity using an accelerometer to assess postoperative convalescence. *Surg Endosc* 2003;17:1269-1273

25. Kakisako K, Sato K, Adachi Y, Shiraishi N, Miyahara M, Kitano S. Laparoscopic colectomy for Dukes A colon cancer. *Surg Laparosc Endosc Percutan Tech* 2000;10:66-70
26. Kojima M, Konishi F, Okada M, Nagai H. Laparoscopic colectomy versus open colectomy for colorectal carcinoma: a retrospective analysis of patient followed up for at least 4 years. *Surg Today* 2004;34:1020-1024
27. Laurent C, Leblanc F, Bretagnol F, Capdepon M, Rullier E. Long-term wound advantages of the laparoscopic approach in rectal cancer. *Br J Surg* 2008;95:903-908
28. Lelong B, Bege T, Esterni B, Guiramand J, Turrini O, Moutardier V, Magnin V, Monges G, Pernoud N, Blache JL, Giovanni M, Delpero JR. Short-term outcome after laparoscopic or open restorative mesorectal excision for rectal cancer: a comparative cohort study. *Dis Colon Rectum* 2007;50:176-183
29. Leung KL, Meng WCS, Lee JFY, Thung KH, Lai PBS, Lau WYL. Laparoscopic-assisted resection of right-sided colonic carcinoma: a case-control study. *J Surg Oncol* 1999;71:97-100
30. Leung KL, Kwok SPY, Lau WY, Meng WCS, Chung CC, Lai PBS, Kwong KH. Laparoscopic-assisted abdominoperineal resection for low rectal adenocarcinoma. *Surg Endosc* 2000;14:67-70
31. Lezoche E, Feliciotti F, Paganini AM, Guerrieri M, De Sanctis A, Minervini S, Campagnacci R. Laparoscopic vs open hemicolectomy for colon cancer: long-term outcome. *Surg Endosc* 2002;16:596-602

32. Melani AGF, De Campos FGCM. [Laparoscopic resection after neoadjuvant therapy in the treatment of middle and low rectal cancer]. *Rev Bras Coloproct* 2006;26:89-96
33. Moore JWE, Bokey EL, Newland RC, Chapuis PH. Lymphovascular clearance in laparoscopically assisted right hemicolectomy is similar to open surgery. *ANZ J Surg* 1996;66:605-607
34. Morino M, Allaix ME, Giraud G, Corno F, Garrone C. Laparoscopic versus open surgery for extraperitoneal rectal cancer: a prospective comparative study. *Surg Endosc* 2005;19:1460-1467
35. Nakamura T, Kokuba Y, Mitomi H, Onozato W, Hatate K, Satoh T, Ozawa H, Ihara A, Watanabe M. Comparison between the oncologic outcome of laparoscopic surgery and open surgery for T1 and T2 rectosigmoidal and rectal carcinoma: matched case-control study. *Hepato-Gastroenterology* 2007;54:1094-1097
36. Nakamura T, Mitomi H, Ohtani Y, Kukoba Y, Sato T, Ozawa H, Ihara A, Watanabe M. Comparison of long-term outcome of laparoscopic and conventional surgery for advanced colon and rectosigmoid cancer. *Hepato-Gastroenterology* 2006;53:351-353
37. Osarogiagbon RU, Ogbeide O, Ogbeide E, George RK. Hand-assisted laparoscopic colectomy compared with open colectomy in a nontertiary care setting. *Clin Colorectal Cancer* 2007;6:588-592
38. Psaila J, Bulley SH, Ewings P, Sheffield JP, Kennedy RH. Outcome following laparoscopic resection for colorectal cancer. *Br J Surg* 1998;85:662-664

39. Ptok H, Steinert R, Meyer F, Kroll KP, Scheele C, Kockerling F, Gastinger I, Lippert H. [Long-term oncological results after laparoscopic, converted and primary open procedures for rectal carcinoma: results of a multicenter observational study]. *Chirurg* 2006;77:709-717
40. Ramos JR, Petrosimolo RH, Valory EA, Polania FC, Pecanha R. Abdominoperineal resection: laparoscopic versus conventional. *Surg Laparosc Endosc* 1997;7:148-152
41. Staudacher C, Vignali A, Saverio DP, Elena O, Andrea T. Laparoscopic vs. open total mesorectal excision in unselected patients with rectal cancer: impact on early outcome. *Dis Colon Rectum* 2007;50:1324-1331
42. Van Ye TM, Cattet RP, Henry LG. Laparoscopically assisted colon resections compare favorably with open technique. *Surg Laparosc Endosc* 1994;4:25-31
43. Yamamoto S, Watanabe M, Hasegawa H, Kitajima M. Oncologic outcome of laparoscopic versus open surgery for advanced colorectal cancer. *Hepato-Gastroenterology* 2001;48:1248-1251
44. Zhen MH, Feng B, Lu AG, Li JW, Wang ML, Mao ZH, Hu YY, Dong F, Hu WG, Li DH, Zang L, Peng YF, Yu BM. Laparoscopic versus open right hemicolectomy with curative intent for colon carcinoma. *World J Gastroenterol* 2005;11:323-326

### ***Controlled observational studies***

45. Agha A, Furst A, Ilesalnieks I, Fichtner-Feigl S, Ghali N, Krenz D, Anthuber M, Jauch KW, Piso P, Schlitt HJ. Conversion rate in 300 laparoscopic rectal resections and its influence on morbidity and oncological outcome. *Int J Colorectal Dis* 2008;23:409-417
46. Antropoli M, Di Palma D, Tufo P, Lanni R, Petrillo P, Berruti G, Frattolillo FM. Laparoscopic procedures for colorectal cancer: analysis of 134 cases. *Chir Ital* 2006;58:77-82
47. Barlehner E, Heukrodt B, Anders S. [Laparoscopic rectum surgery in carcinoma]. *Zentralbl Chir* 1998;123:1164-1168
48. Bretagnol F, Rullier E, Couderc P, Rullier A, Saric J. Technical and oncological feasibility of laparoscopic total mesorectal excision with pouch coloanal anastomosis for rectal cancer. *Colorectal Dis* 2003;5:451-453
49. Buchmann P, Christen D, Rentsch RU. [Rectal cancer: minimally invasive procedure]. *Chir Gastroenterol* 1995;11:380-384
50. Cheung HYS, Chung CC, Yau KKK, Siu WT, Wong SKH, Chiu E, Li MKW. Risk of deep vein thrombosis following laparoscopic rectosigmoid cancer resection in Chinese patients. *Asian J Surg* 2008;31:63-68
51. Delgado S, Momblan D, Salvador L, Bravo R, Castells A, Ibarzabal A, Pique JM, Lacy AM. Laparoscopic-assisted approach in rectal cancer patients: lessons learned from >200 patients. *Surg Endosc* 2004;18:1457-1462

52. Dell'abate P, Del Rio P, Giannino G, Arcuri MF, Soliani P, Sianesi M. [Laparoscopic colectomy in the treatment of colon cancer: prospective study]. *G Chir* 2004;25:121-124
53. Fleshman JW, Nelson H, Peters WR, Kim HC, Larach S, Boorse RR, Ambroze W, Leggett P, Bleday R, Stryker S, Christenson B, Wexner S, Senagore A, Rattner D, Sutton J, Fine AP. Early results of laparoscopic surgery for colorectal cancer: retrospective analysis of 372 patients treated by Clinical Outcomes of Surgical Therapy (COST) study group. *Dis Colon Rectum* 1996;39:s53-s58
54. Glatti A, Birrer S, Buchmann P, Christen D, Frei E, Klaiber C, Krahenbuhl, Lange J, Metzger U. [Technique and results of laparoscopic abdominoperineal resection of the rectum]. *Schweiz Med Wochenschr* 1996;126(suppl. 79):85S-88S
55. Hasegawa H, Ishii Y, Nishibori H, Endo T, Watanabe M, Kitajima M. Short- and midterm outcomes of laparoscopic surgery compared for 131 patients with rectal and rectosigmoid cancer. *Surg Endosc* 2007;21:920-924
56. Kitano S, Kitajima M, Konishi F, Kondo H, Satomi S, Shimizu N, Japanese Laparoscopic Surgery Study Group. A multicenter study on laparoscopic surgery for colorectal cancer in Japan. *Surg Endosc* 2006;20:1348-1352
57. Lechaux D, Trebuchet G, Le Calve JL. Five-year results of 206 laparoscopic left colectomies for cancer. *Surg Endosc* 2002;16:1409-1412

58. Lee YS, Lee IK, Kang WK, Cho HM, Park JK, Oh ST, Kim JG, Kim YH. Surgical and pathological outcomes of laparoscopic surgery for transverse colon cancer. *Int J Colorectal Dis* 2008;23:669-673
59. Leroy J, Jamali F, Forbes L, Smith M, Rubino F, Mutter D, Marescaux J. Laparoscopic total mesorectal excision (TME) for rectal cancer surgery. *Surg Endosc* 2004;18:281-289
60. Liang JT, Huang KC, Lai HS, Lee PH, Sun CT. Oncologic results of laparoscopic D3 lymphadenectomy for male sigmoid and upper rectal cancer with clinically positive lymph nodes. *Ann Surg Oncol* 2007;14:1980-1990
61. Lim SB, Choi HS, Jeong SY, Park JG. Feasibility of laparoscopic techniques as the surgical approach of choice for primary colorectal cancer: an analysis of 570 consecutive cases. *Surg Endosc* 2008;22:2588-2595
62. Mehta PP, Griffin J, Ganta S, Rangraj M, Steichen F. Laparoscopic-assisted colon resections: long-term results and survival. *JLS* 2005;9:184-188
63. Moloo H, Mamazza J, Poulin EC, Burpee SE, Bendavid Y, Klein L, Greoire R, Schlachta CM. Laparoscopic resection for colorectal cancer: does conversion affect survival? *Surg Endosc* 2004;18:732-735
64. Noceti A, Perata O, Rota F, Arzillo GP, Calvi G, Terlizzi C, Piccardo A. [Videolaparoscopic oncologic surgery of the left and right colon: our experience]. *Tumori* 2003;89(4 suppl):118-120

65. Nozaki I, Kubo Y, Kurita A, Ohta K, Aogi K, Tanada M, Takashima S. Laparoscopic colectomy for colorectal cancer patients with previous abdominal surgery. *Hepato-Gastroenterology* 2008;55:943-946
66. Pugliese R, Di Lernia S, Sansonna F, Ferrari GC, Maggioni D, Scandroglio I, Costanzi A, Magistro C, De Carli S. Outcomes of laparoscopic Miles' operation in very low rectal adenocarcinoma: analysis of 32 cases. *EJSO* 2007;33:49-54
67. Pugliese R, Di Lernia S, Sansonna F, Scandroglio I, Maggioni D, Ferrari GC, Costanzi A, Magistro C, De Carli S. Results of laparoscopic anterior resection for rectal adenocarcinoma: retrospective analysis of 157 cases. *Am J Surg* 2008;195:233-238
68. Reis Neto JA, Quilici FA, Cordeiro F, Reis Junior JA, Kagohara O. [Low rectal cancer: neoadjuvant radiotherapy, total mesorectal excision and videolaparoscopic access – a combination of factors that diminishes local recurrences]. *Rev Bras Coloproct* 1999;19:214-218
69. Reis Neto JA, Marin Marmolejo JC, Quilici FA, Cordeiro F, Reis Junior JA, Kagohara OH, Simoes Neto J. [Laparoscopic surgery for low rectal cancer]. *Rev Colomb Cir* 2000;15:13-17.
70. Rezvani M, Franko J, Fassler SA, Harper SG, Nejman JH, Zebley DM. Outcomes in the patients treated by laparoscopic resection of rectal carcinoma after neoadjuvant therapy for rectal cancer. *JSL* 2007;11:204-207

71. Riegler M, Muller W, Beller S, Sznicz G. Survival following oncological minimally invasive colorectal procedures. *Eur Surg* 2002;34:354-358

72. Scheidbach H, Schneider C, Konradt J, Barlehner E, Kohler L, Wittekind C, Kockerling F. Laparoscopic abdominoperineal resection and anterior resection with curative intent for carcinoma of the rectum. *Surg Endosc* 2002;16:7-13

73. Schiedeck THK, Schwandner O, Baca I, Baehrehner E, Konradt J, Kockerling F, Kuthe A, Buerk C, Herold A, Bruch HP. Laparoscopic surgery for the cure of colorectal cancer: results of a German five-center study. *Dis Colon Rectum* 2000;43:1-8

74. Yamamoto S, Fujita S, Akasu T, Uehara K, Moriya Y. Reduction of prolonged postoperative hospital stay after laparoscopic surgery for colorectal carcinoma. *Surg Endosc* 2006;20:1467-1472

### ***Other references***

75. Smith AJ, Driman DK, Spithoff K, Hunter A, McLeod RS, Simunovic M, Langer B, Expert Panel on Colon and Rectal Cancer Surgery and Pathology. Guideline for optimization of colorectal cancer surgery and pathology. *J Surg Oncol* 2010;101:5-12

76. Lemmens VE, Van Lijnschoten I, Janssen-Heijnen ML, Rutten HJ, Verheij CD, Coebergh JWW. Pathology practice patterns affect lymph node evaluation and outcome of colon cancer: a population-based study. *Ann Oncol* 2006;17:1803-1809

77. Evans MD, Barton K, Rees A, Stamatakis JD, Karandikar SS. The impact of surgeon and pathologist on lymph node retrieval in colorectal cancer and its impact on survival for patients with Dukes' stage B disease. *Colorectal Dis* 2008;10:157-164
78. Wong SL, Ji H, Hollenbeck BK, Morris AM, Baser O, Birkmeyer JD. Hospital lymph node examination rates and survival after resection for colon cancer. *JAMA* 2007;298:2149-2154
79. Bonjer HC, Hop WC, Nelson H, Sargent DJ, Lacy AM, Castells A, Guillou PJ, Thorpe H, Brown J, Delgado S, Kuhri E, Haglund E, Pahlman L; Transatlantic Laparoscopically Assisted vs Open Colectomy Trials Study Group. Laparoscopically assisted vs open colectomy for colon cancer: meta-analysis. *Arch Surg* 2007;142:298-303
80. Kuhry E, Schwenk W, Gaupset R, Romild U, Bonjer HJ. Long-term results of laparoscopic colorectal cancer resection. *Cochrane Database Syst Rev* 2008;CD003432
81. Schwenk W, Haase O, Neudecker JJ, Müller JM. Short term benefits for laparoscopic colorectal resection. *Cochrane Database Syst Rev* 2005;CD003145
82. Jackson TD, Kaplan GG, Arena G, Page JH, Rogers SO Jr. Laparoscopic versus open resection for colorectal cancer: a metaanalysis of oncologic outcomes. *J Am Coll Surg* 2007;204:439-446
83. Murray A, Lourenco T, de Verteuil R, Hernandez R, Fraser C, McKinley A, Krukowski Z, Vale L, Grant A. Clinical effectiveness and cost-effectiveness of laparoscopic

surgery for colorectal cancer: systematic reviews and economic evaluation. Health Technol Assess 2006;10(45)

84. Vardulaki KA, Bennett-Lloyd BD, Parfitt J, Normond C, Paisley S, Darzi A, Reeves BC. A systematic review of the effectiveness and cost-effectiveness of laparoscopic surgery for colorectal cancer. National Institute for Health and Clinical Excellence, 2000. Report no longer available on NICE website, full-text obtained from [<http://www.bristolsurgery.com/Documents/HTAreportonlapsurgcoloreccanc.pdf>] on 5 February 2011

## **CHAPTER FIVE: CONCLUSIONS AND FUTURE DIRECTIONS**

The current thesis has provided a critical appraisal of the processes of evaluation and adoption of laparoscopic and open surgery for colorectal cancer, as an example of a novel surgical technology. Specifically, a synthesis of short-term surrogate and long-term oncologic outcomes pertaining to this technology has been derived from randomized controlled trials, observational studies, and other existing systematic reviews. In doing so, a methodological evaluation of the risks of bias of each study type has been carried out, and used to qualify the primary data synthesis. Finally, the acceptance of this novel technology has been evaluated in the literature and correlated with outcomes from randomized controlled trials, as surrogate for adoption of this novel technology by surgeons.

In summary, this thesis has identified a significant pre-existing body of research literature pertaining to laparoscopic and open surgery for colorectal cancer. A large number of systematic reviews were found in the literature, the total of which was superior to the number of existing trials. The quality of existing systematic reviews was low to moderate, with higher quality being found in Cochrane Reviews and one Health Technology Assessment report. Similarly, a large number of randomized controlled trials was identified. Meta-analysis of these studies demonstrated non-inferiority of laparoscopic surgery when compared to open surgery in terms of overall survival. For this finding to be reversed in favour of inferiority, a prohibitively large number of patients would have to be randomized in a hypothetical missing clinical trial. In contrast to randomized trials, observational studies on this topic included almost three times more patients. A meta-analysis of survival data based on a random sample of observational studies also demonstrated non-inferiority, although with less power than randomized trials. Statistical testing demonstrated that the observed difference in overall survival between the study designs was not significant, and within the range that can be expected from chance alone.

The current inclusion and assessment of observational data is highly important. Indeed, observational data of varied quality remains a cornerstone of surgical decision-making. Although randomized data are widely considered to be preferable, many common clinical questions can be very difficult to answer using trials, both for practical and methodological reasons [1-5]. Practical reasons include limited funding for surgical research, pre-existing patient preferences and perceptions of novel technologies, the generalizability of surgical trial results, the rarity of many surgical pathologies and consequent lack of potential trial patients, and attitudinal biases in favour of large institutional case series. Methodological reasons include difficulty with blinding of patients, surgeons, and outcome assessors, difficulty with differential procedural expertise among surgeons, centers, and geographic regions, and difficulty with defining and standardizing interventions. While none of these challenges are insurmountable for dedicated clinician-scientists, they do nevertheless greatly complicate the conduct of surgical trials, over and above that encountered in drug trials. In this context, it is thus highly important to investigate the relative value of observational research in surgery, and to differentiate between high- and low-quality observational research evidence. The current work adds to an evolving body of empirical research comparing experimental and observational study designs in surgery, and highlights the potential for overestimation of effect sizes with this type of work. Although a focus on high-quality observational studies may minimize this finding, the current thesis was unable to measure this effect due to the overly small number of such high-quality studies.

On the whole this work represents an important examination of the process of surgical innovation, from technology evaluation, to knowledge translation, to adoption. In global terms, this large-scale case study has demonstrated that the technological innovation of laparoscopic surgery for colorectal cancer has been appropriately followed by widespread and significant research and evaluative efforts. While the quantity of research carried out

was noteworthy, its quality was at times noticeably lacking. Nevertheless, this work has also demonstrated that the process of adoption of laparoscopic surgery for colorectal cancer, at least as it pertains to expert opinions in the literature, has generally been driven by evidence from high-quality randomized controlled trials.

As with all scientific efforts, the current work has generated additional research questions. Notably, the role, quality, and labeling of systematic reviews in surgery will require further evaluation, in the context of ongoing efforts to promote registration and updating. From a methodological standpoint, high-quality observational studies in surgery will require a better definition, and will need to be further studied in delineating their value in surgical technology evaluation. From a clinical standpoint, oncologic outcomes of laparoscopic and open surgery for rectal cancer will require further evaluation from large-scale randomized clinical trials. Finally, patterns of adoption observed in the expert literature will require further confirmation from actual surgical practice patterns at the national and international levels.

## **REFERENCES**

1. Solomon MJ, McLeod RS. Surgery and the randomised controlled trial: past, present and future. *Med J Aust* 1998;169:380-383.
2. Desvereaux PJ, Bhandari M, Clarke M, Montori VM, Cook DJ, Yusuf S, Sackett DJ, Cina CS, Walter SD, Haynes B, Schunemann HJ, Norman GR, Guyatt GH. Need for expertise based randomised controlled trials. *BMJ* 2005;330:88
3. McCulloch P, Taylor I, Sasako M, Lovett B, Griffin D. Randomised trials in surgery: problems and possible solutions. *BMJ* 2002;324:1448-51.

4. Cook JA. The challenges faced in the design, conduct and analysis of surgical randomised controlled trials. *Trials* 2009;10:9.

5. Somolon MJ, McLeod RS. Should we be performing more randomized controlled trials evaluating surgical operations? *Surgery* 1995;118:459-467.

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## **APPENDIX 1: SEARCH STRATEGY**

### ***Ovid MEDLINE (1950 to July Week 4 2008)***

### ***Ovid MEDLINE In-Process & Other Non-Indexed Citations (4 August 2008)***

1. exp colorectal neoplasms/su
2. exp colectomy/
3. (colectom\$ or hemicolect\$ or colotom\$).tw.
4. ((mesorect\$ adj3 excision\$) or (anterior adj3 resection) or abdominoperineal or proctectomy or proctocolectomy).tw.
5. or/1-4
6. exp colorectal neoplasms/
7. ((cancer or neoplas\$ or adenocarcinoma\$ or carcinoma\$ or malignan\$) adj3 (colorectal or colon\$ or rectal or rectum or recto\$ or sigmoid\$ or instest\$ or bowel)).tw.
8. or/6-7
9. adenocarcinoma/
10. carcinoma/
11. neoplasms/
12. or/9-11
13. exp colon/
14. rectum/
15. or/13-14
16. 12 and 15
17. colorectal surgery/
18. Surgical procedures,operative/
19. su.fs.
20. (surgery or surgical or surgeon\$).tw.

21. resect\$.tw.
22. operat\$.tw.
23. or/17-22
24. (8 or 16) and 23
25. 5 or 24
26. laparoscopy/
27. Surgical procedures,minimally invasive/
28. (minimal\$ adj3 (invasiv\$ or access\$)).tw.
29. laparoscop\$.tw.
30. (key hole or keyhole).tw.
31. (hand assist\$ or hand-assist\$ or HALS or hand-port).tw.
32. or/26-31
33. 25 and 32
34. limit 33 to yr=1991-2008
35. animal/ not human/
36. 34 not 35
37. remove duplicates from 36

***Ovid EMBASE (1980 to 2008 Week 31)***

1. exp colon cancer/su
2. exp rectum cancer/su
3. exp colon resection/
4. exp rectum resection/
5. (colectom\$ or hemicolect\$ or colotom\$).tw.
6. ((mesorect\$ adj3 excision\$) or (anterior adj3 resection) or abdominoperineal or proctectomy or proctocolectomy).tw.

7. or/1-6
8. exp colon cancer/
9. exp rectum cancer/
10. ((cancer or neoplas\$ or adenocarcinoma\$ or carcinoma\$ or malignan\$) adj3 (colorectal or colon\$ or rectal or rectum or recto\$ or sigmoid\$ or instest\$ or bowel)).tw.
11. or/8-10
12. adenocarcinoma/
13. carcinoma/
14. neoplasms/
15. or/12-14
16. exp colon/
17. exp rectum/
18. or/16-17
19. 15 and 18
20. colorectal surgery/
21. surgery/
22. su.fs.
23. (surgery or surgical or surgeon\$).tw.
24. resect\$.tw.
25. operat\$.tw.
26. or/20-25
27. (11 or 19) and 26
28. 7 or 27
29. laparoscopy/
30. laparoscopic surgery/
31. Minimally invasive surgery/

32. (minimal\$ adj3 (invasiv\$ or access\$)).tw.
33. laparoscop\$.tw.
34. (key hole or keyhole).tw.
35. (hand assist\$ or hand-assist\$ or HALS or hand-port).tw.
36. or/29-35
37. 28 and 36
38. limit 37 to yr=1991-2008
39. (animal/ or nonhuman/) not human/
40. 38 not 39
41. remove duplicates from 40

***Cochrane Library (Issue 3, 2008)***

- #1 MeSH descriptor Colorectal Neoplasms explode all trees with qualifier: SU
- #2 MeSH descriptor Colectomy explode all trees
- #3 colectom\* in All Fields or hemicolect\* in All Fields or colotom\* in All Fields
- #4 ((mesorect\* NEAR/3 excision\*) OR (anterior NEAR/3 resection) OR abdominoperineal OR proctectomy OR proctocolectomy) in All Fields
- #5 (#1 OR #2 OR #3 OR #4)
- #6 MeSH descriptor Colorectal Neoplasms explode all trees
- #7 ((cancer OR neoplas\* OR adenocarcinoma\* OR carcinoma\* OR malignan\*) NEAR/3 (colorectal OR colon\* OR rectal OR rectum OR recto\* OR sigmoid\* OR instest\* OR bowel)) in All Fields
- #8 (#6 OR #7)
- #9 MeSH descriptor Adenocarcinoma, this term only
- #10 MeSH descriptor Carcinoma, this term only
- #11 MeSH descriptor Neoplasms, this term only

- #12 (#9 OR #10 OR #11)
- #13 MeSH descriptor Colon explode all trees
- #14 MeSH descriptor Rectum, this term only
- #15 (#13 OR #14)
- #16 (#12 AND #15)
- #17 MeSH descriptor Colorectal Surgery, this term only
- #18 MeSH descriptor Surgical Procedures, Operative, this term only
- #19 su.fs in All Fields
- #20 (surgery OR surgical OR surgeon\*) in All Fields
- #21 (resect\* OR operation\*) in All Fields
- #22 (#17 OR #18 OR #19 OR #20 OR #21)
- #23 ((#8 OR #16) AND #22)
- #24 (#5 OR #23)
- #25 MeSH descriptor Laparoscopy, this term only
- #26 MeSH descriptor Surgical Procedures, Minimally Invasive, this term only
- #27 (minimal\* NEAR/3 (invasiv\* or access\*)) in All Fields
- #28 laparoscop\* OR key hole OR keyhole OR hand assist\* OR hand-assist\* OR HALS  
OR hand-port in All Fields
- #29 (#25 OR #26 OR #27 OR #28)
- #30 (#24 AND #29)

***Science Citation Index Expanded (Web of Knowledge, 1991 to 14 August 2008)***

***BIOSIS Previews (Web of Knowledge, 1991 to 14 August 2008)***

- #1 TS=(colectom\* OR hemicolect\* OR colotom\*)
- #2 TS=(mesorect\* SAME excision\*)
- #3 TS=((colon or colorectal) SAME resect\*)

- #4 #1 OR #2 OR #3
- #5 TS=(cancer SAME (colorectal or colon\* OR rectal OR rectum OR rectosigmoid OR cecal OR caecal OR intestin\* OR bowel))
- #6 TS=(carcinoma SAME (colorectal OR colon\* OR rectal OR rectum OR intestin\* OR rectosigmoid OR cecal OR caecal OR bowel))
- #7 TS=(neoplas\* SAME (colorectal OR colon\* OR rectal OR rectum OR intestin\* OR rectosigmoid OR cecal OR caecal OR bowel))
- #8 TS=(adenocarcinoma\* SAME (colorectal OR colon\* OR rectal OR rectum OR intestin\* OR rectosigmoid OR cecal OR caecal OR bowel))
- #9 TS=(malignan\* SAME (colorectal OR colon\* OR rectal OR rectum OR intestin\* OR rectosigmoid OR cecal OR caecal OR bowel))
- #10 #5 OR #6 OR #7 OR #8 OR #9
- #11 TS=laparoscop\*
- #12 TS=(minimal\* SAME (invasiv\* OR access\*))
- #13 TS=(key hole or keyhole)
- #14 TS=(hand assist\* OR hand-assist\* OR HALS)
- #15 #11 OR #12 OR #13 OR #14
- #16 (#4 OR #10) AND #15

***BIREME LILACS (16 September 2008)***

(Colorectal or colon\$ or rectal or rectum or recto\$ sigmoid\$) and (cancer or neoplas\$ or adenocarcinoma\$ or carcinoma\$ or malignan\$) and laparoscop\$

***Database of Abstracts and Reviews of Effectiveness (crd.york.ac.uk, 16 September 2008)***

Colorectal AND laparoscop\*

***Health Technology Assessment Database (crd.york.ac.uk, 16 September 2008)***

Colorectal AND laparoscop\*

***NHS Economic Evaluation Database (crd.york.ac.uk, 16 September 2008)***

Colorectal AND laparoscop\*

***NIHR Health Technology Assessment Programme (ncchta.org, 9 September 2008)***

“Cancers” ICD Chapter Heading, by “Surgery”

***TRIP Database (tripdatabase.com, 15 September 2008)***

Colorectal cancer AND laparoscopy

***Clinical Trials (clinicaltrials.gov, 15 September 2008)***

Colorectal AND laparoscopy

***Current Controlled Trials (controlled-trials.com, 15 September 2008)***

Colorectal AND laparoscop%

***National Guideline Clearinghouse (guideline.gov, 16 September 2008)***

Gastrointestinal Neoplasms MeSH Category

***CMA Infobase (www.mdm.ca/cpgsnew/cpgs/, 16 September 2008)***

Laparoscopy OR laparoscopic

***NICE England (nice.org.uk, 16 September 2008)***

(Colorectal OR colon OR rectal OR rectum) AND Surgical procedures

***SIGN Scotland (sign.ac.uk, 16 September 2008)***

Cancer topic

***NHMRC Australia (nhmrc.gov.au, 16 September 2008)***

Health guidelines

***New Zealand Guidelines Group (www.nzgg.org.nz, 16 September 2008)***

Cancer category, surgery category

***Surgical Textbooks (all editions since 1991)***

Schwartz's Principles of Surgery

Sabiston Textbook of Surgery

Greenfield's Surgery: Scientific Principles and Practice

Current Surgical Therapy (Cameron)

Shackelford's Surgery of the Alimentary Tract

Mastery of Surgery (Fischer)

Principles and Practices of Surgery of the Colon, Rectum and Anus (Gordon)

Colon and Rectal Surgery (Corman)

Current Therapy in Colon & Rectal Surgery (Fazio)

## APPENDIX 2: SUMMARY OF OUTCOMES FROM SYSTEMATIC REVIEWS

Review	Comparative Risk (%)		Relative Effect* (95% CI)	P-value	No. patients Lap/Open or total (studies)	Notes
	OPEN	LAP				
<b>Overall Survival</b>						
Vardulaki 2000 [18]			OR 0.74 (0.47, 1.16)	p=0.19	(8)	All observational studies
Reza 2004 [23]	545/718 (76%)	577/733 (79%)	OR 1.23 (0.90, 1.72)	p=0.19	718/733 (4)	
Murray 2006 [10]	655/827 (79%)	684/843 (81%)	RR 1.03 (0.98, 1.09)	p=0.28	827/843 (6)	
Reza 2006 [29]	545/718 (76%)	577/733 (79%)	OR 1.23 (0.90, 1.72)	p=0.19	718/733 (4)	
Kahnamoui 2007 [32]	448/586 (76%)	485/608 (80%)	OR 1.32 (0.90, 1.94)	p=0.15	586/608 (4)	
Bonjer 2007 [34]	83.5%	82.2%	HR 1.07 (0.83, 1.37)	p=0.61	1536(4)	IPD meta-analysis, Cox model for age, sex, stage
Jackson 2007 [35]			HR 0.88 (0.56, 1.39)	p=0.59	1494 (3)	Time-to-event data
Kuhry 2008 [38]	975/1309 (74.5%)	1199/1572 (76.3%)	OR 1.19 (1, 1.43) HR 0.89 (0.72, 1.08)	p=0.05 for OR	2881 (9) for OR	Time-to-event data
Lourenco 2008 [39]	655/827 (79%)	684/843 (81%)	RR 1.03 (0.98, 1.09)	p=0.28	827/843 (6)	
Anderson 2008 [40]	65%	72%	Zc= -0.03, cohen's d=0.1	p=0.5	1995 (11)	
<b>Disease-Free Survival</b>						
Vardulaki 2000 [18]			OR 0.60 (0.36, 0.98)	<b>p=0.043</b>	(5)	All observational studies
Murray 2006 [10]	496/666 (74%)	513/683 (75%)	RR 1.01 (0.95, 1.07)	p=0.83	666/683(4)	
Bonjer 2007 [34]	75.3%	75.8%	HR 0.99 (0.80, 1.22)	p=0.92	1536(4)	IPD meta-analysis, Cox model for age, sex, stage

Lourenco 2008 [39]	496/666 (74%)	513/683 (75%)	RR 1.01 (0.95, 1.07)	p=0.83	666/683(4)	Heterogeneity (I <sup>2</sup> =59%)
<b>Cancer-Related Mortality</b>						
Vardulaki 2000 [18]			OR 1.29 (0.86, 1.92)	p=0.219	(8)	All Observational studies
Reza 2004 [23]	47/290 (16%)	41/298 (14%)	OR 0.70 (0.28, 1.72)	p=ns	290/298(3)	Significant heterogeneity
Reza 2006 [29]	47/290 (16%)	41/298 (14%)	OR 0.70 (0.28, 1.72)	p=0.44	290/298(3)	Significant heterogeneity
Kahnamoui 2007 [32]	91/586 (16%)	67/608 (11%)	OR 0.67 (0.48, 0.94)	<b>p&lt;0.05</b>	586/608(5)	
Jackson 2007 [35]			RR 0.80 (0.62, 1.04)	p=ns	1577(6)	
Kuhry 2008 [38]	159/1108 (14.4%)	185/1382(13.4%)	OR 0.84 (0.67, 1.06)	p=0.15	1108/1382(8)	
<b>Port-Site and/or Wound Metastases</b>						
Chapman 2000 [17]		1.28% (0.64, 2.27)				
Chapman 2001 [19]		1.28% (0.64, 2.27)				
Yong 2001 [20]		0.8%				
Reza 2004 [23]	0-0.2%	0-0.9%			(3)	
Manterola 2005 [25]		0.4% (0-0.9%)				
Murray 2006 [10]	1/637 (0.16%)	2/649 (0.31%)	RR 1.97 (0.18, 21.62)	p=0.58	637/649(4)	
Kahnamoui 2007 [32]	0/149 (0%)	1/159 (0.63%)	OR 1.36 (0.21, 8.80)	p=ns	149/159(4)	
Jackson 2007 [35]	1/801 (0.12%)	3/826 (0.36%)			801/826(7)	
Kuhry 2008 [38]	5/1463 (0.34%)	15/1724 (0.87%)	OR 1.97 (0.77, 5.02)	p=0.16	1463/1724(10)	
Lourenco 2008 [39]	1/485 (0.21%)	5/997 (0.50%)			485(3)/997(11)	
Liang 2008 [41]	2/356 (0.25%)	2/342 (0.26%)	OR 1.04 (0.18, 6.03)	p=0.97	356/342(3)	

<b>Number of Harvested Lymph Nodes</b>						
Vardulaki 2000 [18]			WMD -0.34 (-1.34, 0.68)	p=0.516	(6)	All observational studies
Korolija 2003 [21]	10.7	11.8	WMD 0.31	p=0.558		
Abraham 2004 [22]			WR 0.98	p=ns	412(5)	
Schwenk 2005 [26]			WMD 0.12 (-1.17, 1.41)	p=0.86	688 (7)	Colorectal cancer only
Aziz 2006 [27]			WMD -0.87 (-2.24,0.49)	<b>p&lt;0.001</b>	925/ 550(17)	Rectal cancer only
Tjandra 2006 [28]	12	12	WMD 0.36	p=0.48	(9)	
Murray 2006 [10]			WMD -0.41 (-1.42, 0.59)	p=0.42	453/458(3)	
Bonjer 2007 [34]	12.2 ± 7.8	11.8 ± 7.4		p=0.40	1536(4)	Individual patient data
Jackson 2007 [35]			SMD -0.11 (-0.25, 0.04)	p=ns	2671(9)	
Abraham 2007 [36]			WR 0.98	p=ns	3063/ 1988(37)	
Kuhry 2008 [38]			WMD -1.00 (-1.65, -0.35)	<b>p=0.0026</b>	678/680(6)	Significant heterogeneity (I <sup>2</sup> =71%)
Lourenco 2008 [39]			WMD -0.41 (-1.42, 0.59)	p=0.42	911(3)	
Anderson 2008 [40]	11	10	Zc= 3.0	<b>p=0.001</b>	2442(17)	Rectal cancer only
<b>Local Disease Recurrence</b>						
Vardulaki 2000 [18]			OR 0.70 (0.38, 1.31)	p=0.262	(9)	RCT and observational
Kahnamoui 2007 [32]	19/187(10%)	7/201 (3.5%)	OR 0.39 (0.17, 0.89)	<b>p=0.02</b>	187/201(5)	
Bonjer 2007 [34]	40/740 (5.4%)	29/796 (3.6%)		p=ns	740/796(4)	Individual patient data
Kuhry 2008 [38]	46/865 (5.3%)	58/1122 (5.2%)	OR 0.81 (0.54, 1.22)	p=0.31	865/1122(8)	
Anderson 2008 [40]	8%	7%	Zc= -0.2, Cohen's d=0.1	p=ns	2277(16)	

Liang 2008 [41]	43/679 (6.3%)	34/680 (5%)	OR 0.8 (0.5, 1.29)	p=0.36	679/680(7)	
<b>Distant Disease Recurrence</b>						
Vardulaki 2000 [18]			OR 1.05 (0.68, 1.61)	p=0.834	(9)	RCT and observational
Bonjer 2007 [34]	73/740 (9.9%)	74/796 (9.3%)		p=ns	740/796(4)	Individual patient data
Kuhry 2008 [38]	100/796 (12.6%)	140/1057 (13.2%)	OR 1.01 (0.76, 1.34)	p=0.93	796/1057(7)	
Anderson 2008 [40]	14%	12%	Zc= -1, Cohen's d=0.1	p=0.54	1408(10)	
Liang 2008 [41]	71/584 (12.2%)	65/579 (11.2%)	OR 0.90 (0.62, 1.29)	p=0.56	584/579(6)	
<b>Overall Disease Recurrence</b>						
Reza 2004 [23]	143/718 (20%)	132/733 (18%)	OR 0.89 (0.68, 1.16)	p=0.39	718/733(4)	
Manterola 2005 [25]	6.5% (0-10%)	13.1% (0-21%)				
Reza 2006 [29]	143/718 (20%)	132/733 (18%)	OR 0.88 (0.61, 1.27)	p=0.51	718/733(4)	I <sup>2</sup> =30%
Jackson 2007 [35]			RR 0.9 (0.73, 1.10) HR 0.85 (0.53, 1.36)	p=ns p=0.50	1494 (3) for HR	Time-to-event data for HR
Lourenco 2008 [39]	144/765 (19%)	135/789 (17%)	RR 0.92 (0.74, 1.14)	p=0.44	789/765 (7)	
Liang 2008 [41]	190/1242 (15.3%)	183/1232 (14.8%)	OR 0.93 (0.71, 1.21)	p=0.58	584/579(6)	

\*All comparisons pertain to laparoscopic vs. open surgery; ratios compare laparoscopy/open surgery.

Abbreviations – HR: hazard ratio; OR: odds ratio; RR: risk ratio; SMD: standardized mean difference; WMD: weighted mean difference; WR: weighted ratio; Zc: Stouffer's composite Zc

## APPENDIX 3: DATA ABSTRACTION FORM (DATA PAPERS)

**Study ID:** 10000

**Author:** abcdefghijkl

**Year:** 1900

1. Paper Data			
<b>Journal</b>			
<b>Country</b>		<b>Language</b>	
<b>Funding</b>			
<b>Notes</b>			

2. Study Design	
<input type="checkbox"/> Randomized controlled trial	<input type="checkbox"/> Controlled observational study
<input type="checkbox"/> Uncontrolled case series	<input type="checkbox"/> Unclear
<b>Notes</b>	

3. Patients			
<b>Recruitment Dates</b>			
<b>No. Eligible Patients</b>		<b>No. Randomized/Recruited Patients</b>	
<b>Inclusion Criteria</b>		<b>Exclusion Criteria</b>	
<b>Notes</b>			

4. Providers					
<b>Centers</b>	<input type="checkbox"/> Single	<input type="checkbox"/> Multiple	<b>Specify No.</b>		
<b>Origin of Centers</b>	<input type="checkbox"/> North America	<input type="checkbox"/> Latin America	<input type="checkbox"/> Western Europe		
<input type="checkbox"/> Eastern Europe	<input type="checkbox"/> Asia	<input type="checkbox"/> Africa	<input type="checkbox"/> Australasia		
<b>Type of Centers</b>	<input type="checkbox"/> University/Academic	<input type="checkbox"/> Community	<input type="checkbox"/> Mixed		
<b>No. of Surgeons</b>		<b>Inclusion of Trainees</b>	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unclear
<b>Criteria for Inclusion</b>					
<b>Provider Expertise Level</b>					
<b>Evidence of Learning</b>					
<b>Notes</b>					

5. Interventions		
	<b>Description</b> (technique, instruments, pre-/postop care, anesthesia, standardization, adherence)	<b>No. Patients</b>
<b>Intervention 1</b>		
<b>Intervention 2</b>		
<b>Intervention 3</b>		
<b>Notes</b>		

### 6. Patient Characteristics

	Intervention 1	Intervention 2	Intervention 3
No. patients			
Age (years)			
Gender (M/F)			
BMI (kg/m <sup>2</sup> )			
ASA (1/2, 3, 4)			
Previous abdo surgery			
<b>Notes</b>			

### 7. Tumor Characteristics

	Intervention 1	Intervention 2	Intervention 3
<i>Colon</i>			
Cecum			
Ascending colon			
Hepatic flexure			
Transverse colon			
Splenic flexure			
Descending colon			
Sigmoid colon			
Rectosigmoid junction			
<i>Rectum</i>			
Upper 1/3			
Middle 1/3			
Lower 1/3			
Staging Specify type: <input type="checkbox"/> TNM <input type="checkbox"/> Duke <input type="checkbox"/> Other ( )			
<b>Notes</b>			

<b>8. Tumor Resection</b>			
	<b>Intervention 1</b>	<b>Intervention 2</b>	<b>Intervention 3</b>
<i>Resection Type</i>			
Right segmental			
Transverse colectomy			
Left hemicolectomy			
Sigmoid resection			
Anterior resection			
Low anterior resection			
Abdominoperineal			
Other			
Curative resections			
Neoadjuvant therapy			
Adjuvant therapy			
Lymph nodes			
Specimen length			
Proximal margin			
Distal margin			
Radial margin			
Completeness of resection			
<b>Notes</b>			

<b>9. Intraoperative Outcomes</b>			
	<b>Intervention 1</b>	<b>Intervention 2</b>	<b>Intervention 3</b>
Operating time (min.)			
Incision length (cm)			
Blood loss (mL)			
Transfusions			
Conversions			
Reasons:			

Intraop complications Descriptions:			
<b>Notes</b>			

### 10. Short-Term Postoperative Outcomes

	Intervention 1	Intervention 2	Intervention 3
Mortality at 30 days			
Reoperation			
Overall complications			
Surgical complications			
Anastomotic leak			
Bleeding			
Ileus			
Obstruction			
Wound infection			
Other			
Medical complication			
Cardiac			
DVT/PE			
Pneumonia			
UTI			
Other			
Length of hospital stay			
Recovery of bowel function (specify):			
Postoperative pain (specify):			

Return to normal activities (specify):			
<b>Notes</b>			

### 11. Long-Term Postoperative Outcomes

	Intervention 1	Intervention 2	Intervention 3
Follow-up period			
Survival			
Stage-specific survival			
Disease-free survival			
Recurrence			
Port-site/wound			
Local			
Distant			
Time to recurrence			
Incisional hernia			
Bowel obstruction			
Quality of life			
<b>Notes</b>			

**12. Others****Other comments/  
contact with author**

## APPENDIX 4: DATA ABSTRACTION FORM (REVIEW PAPERS)

**Study ID:** 10000

**Author:** abcdefghij

**Year:** 1900

1. Paper Data			
<b>Journal</b>			
<b>Country</b>		<b>Language</b>	
<b>Funding</b>			
<b>Review type</b>	<input type="checkbox"/> Systematic Review/Meta-Analysis		<input type="checkbox"/> Narrative Review
<input type="checkbox"/> Guideline	<input type="checkbox"/> Position Paper	<input type="checkbox"/> Textbook Chapter	<input type="checkbox"/> Other
<b>Notes</b>			
2. Conclusions on Primary Outcome			
Laparoscopic surgery for curable <b>colon</b> cancer is:			
<input type="checkbox"/> Not mentioned	<b>Notes</b>		
<input type="checkbox"/> Inferior to open surgery			
<input type="checkbox"/> Experimental or only acceptable in clinical trials			
<input type="checkbox"/> Equivalent to open surgery with anatomical restrictions			
<input type="checkbox"/> Equivalent to open surgery for "expert" surgeons			
<input type="checkbox"/> Equivalent to open surgery in general practice			
<input type="checkbox"/> Standard of care or superior to open surgery			
Laparoscopic surgery for curable <b>rectal</b> cancer is:			
<input type="checkbox"/> Not mentioned	<b>Notes</b>		
<input type="checkbox"/> Inferior to open surgery			
<input type="checkbox"/> Experimental or only acceptable in clinical trials			
<input type="checkbox"/> Equivalent to open surgery with anatomical restrictions			
<input type="checkbox"/> Equivalent to open surgery for "expert" surgeons			
<input type="checkbox"/> Equivalent to open surgery in general practice			
<input type="checkbox"/> Standard of care or superior to open surgery			

## APPENDIX 5: MINORS INSTRUMENT

Methodological items for non-randomized studies	Score <sup>f</sup>
<ol style="list-style-type: none"> <li>1. <b>A clearly stated aim:</b> the question addressed should be precise and relevant in the light of available literature</li> <li>2. <b>Inclusion of consecutive patients:</b> all patients potentially fit for inclusion (satisfying the criteria for inclusion) have been included in the study during the study period (no exclusion or details about the reasons for exclusion)</li> <li>3. <b>Prospective collection of data:</b> data were collected according to a protocol established before the beginning of the study</li> <li>4. <b>Endpoints appropriate to the aim of the study:</b> unambiguous explanation of the criteria used to evaluate the main outcome which should be in accordance with the question addressed by the study. Also, the endpoints should be assessed on an intention-to-treat basis.</li> <li>5. <b>Unbiased assessment of the study endpoint:</b> blind evaluation of objective endpoints and double-blind evaluation of subjective endpoints. Otherwise the reasons for not blinding should be stated</li> <li>6. <b>Follow-up period appropriate to the aim of the study:</b> the follow-up should be sufficiently long to allow the assessment of the main endpoint and possible adverse events</li> <li>7. <b>Loss to follow up less than 5%:</b> all patients should be included in the follow up. Otherwise, the proportion lost to follow up should not exceed the proportion experiencing the major endpoint</li> <li>8. <b>Prospective calculation of the study size:</b> information of the size of detectable difference of interest with a calculation of 95% confidence interval, according to the expected incidence of the outcome event, and information about the level for statistical significance and estimates of power when comparing the outcomes</li> </ol> <p><i>Additional criteria in the case of comparative study</i></p> <ol style="list-style-type: none"> <li>9. <b>An adequate control group:</b> having a gold standard diagnostic test or therapeutic intervention recognized as the optimal intervention according to the available published data</li> <li>10. <b>Contemporary groups:</b> control and studied group should be managed during the same time period (no historical comparison)</li> <li>11. <b>Baseline equivalence of groups:</b> the groups should be similar regarding the criteria other than the studied endpoints. Absence of confounding factors that could bias the interpretation of the results</li> <li>12. <b>Adequate statistical analyses:</b> whether the statistics were in accordance with the type of study with calculation of confidence intervals or relative risk</li> </ol>	

<sup>f</sup>The items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). The global ideal score being 16 for non-comparative studies and 24 for comparative studies.

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