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META-ANALYSIS

Evidence based medicine and surgical approaches for colon cancer: Evidences, benefits and limitations of the laparoscopic *vs* open resection

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Abstract

AIM: To report a meta-analysis of the studies that compared the laparoscopic with the open approach for colon cancer resection.

METHODS: Forty-seven manuscripts were reviewed, 33 of which employed for meta-analysis according to the PRISMA guidelines. The results were differentiated according to the study design (prospective randomized trials *vs* case-control series) and according to the tumor's location. Outcome measures included: (1) short-term results (operating times, blood losses, bowel function recovery, post-operative pain, return to the oral intake, complications and hospital stay); (2) oncological adequateness (number of nodes harvested in the surgical specimens); and (3) long-term results (including the survivals' rates and incidence of incisional hernias) and (4) costs.

RESULTS: Meta-analysis of trials provided evidences in support of the laparoscopic procedures for a several short-term outcomes including: a lower blood loss, an earlier recovery of the bowel function, an earlier return to the oral intake, a shorter hospital stay and a lower morbidity rate. Opposite the operating time has been confirmed shorter in open surgery. The same trend has been reported investigating case-control series and cancer by sites, even though there are some concerns regarding the power of the studies in this latter field due to the small number of trials and the small sample of patients enrolled. The two approaches were comparable regarding the mean number of nodes harvested and long-term results, even though these variables were documented reviewing the literature but were not computable for meta-analysis. The analysis of the costs documented lower costs for the open surgery, however just few studies investigated the incidence of post-operative hernias.

CONCLUSION: Laparoscopy is superior for the majority of short-term results. Future studies should better differentiate these approaches on the basis of tumors' location and the post-operative hernias.

Key words: Laparoscopy; Colon resection; Colon can-

cer; Meta-analysis; Evidence-based medicine

Core tip: This is a comprehensive meta-analysis of studies investigating laparoscopic resection in comparison with the open surgery for colon cancer, with the aim of evidencing short term and long term results of the surgical approaches. Results were provided according to the study designs (randomized trials, case control series) and according to the tumor's location.

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INTRODUCTION

Colon cancer remains a major health and social issue affecting in the US more than 100000 new patients/year[1]; the surgical resection remains the standard of care for treating and staging non-metastatic colon cancer. During the last twenty years several progresses were made for improving the treatments, the survivals and the quality of life of cancer patients; the main innovation in the surgical technique was that outbreak of the laparoscopy. The use of laparoscopy for colon resection has been introduced in 1991[2,3]. Initial concerns (including *e.g.*, a long training/learning curve, the possible development of port-site metastasis and an inadequate oncologic resection[4-7]) were subsequently surmounted; indeed in recent years a number of studies recognized the adequateness of the laparoscopic approach along with a number of short-term functional benefits and equivalent long-term results. Nevertheless, the scientific literature in this field is quite heterogeneous regarding the study design adopted (randomized/non-randomized studies), objectives and outcome measures (short-term and log-term results, costs analysis), population enrolled (colon and/or rectal cancer patients), thus it might be difficult for clinicians and surgeons to summarize results and "take at home" univocal messages.

The aim of this manuscript is to review the studies comparing the laparoscopic and the open approach for colon cancer differentiating results by: (1) prospective randomized trials; (2) case-control series (including prospective and retrospective studies); and (3) the comparison of these techniques according to the tumor's location. This type of differentiation is seldom conducted and might implement the analysis and help the readers in understanding the results. Moreover we focused our investigation on the costs' analyses provided in the series and trials that were herein reviewed. Indeed, the goal of this paper is to divulgate a comprehensible meta-analysis of the evidences by each category of investigation and to provide a message of clinical use for clinicians and surgeons committed in the care of colon cancer patients.

MATERIALS AND METHODS

Data source and search strategies

This investigation has been conducted adhering at the PRISMA Statements for review and meta-analysis (Figure 1, Table 1). We conducted a systematic review of the literature by searching PubMed database for all the published series and trials comparing the laparoscopic and open surgical approach for colon cancer from 1995 to December 2012. Keywords: "laparoscopic *vs* open colectomy" AND "colon cancer", languages: "English", limit to "human" including clinical trials and comparative studies. We also included references from the retrieved publications. Duplicate references were removed by manual search.

Authors of this study were blinded to authors' and journals' name while reviewing the series, and did not have any contacts with the authors of the included papers. We did not consider any journal's scores (*e.g.*, journal's Impact Factors) of the published series as exclusion criteria for this review.

Study design and selection of papers

Each paper retrieved was assessed for inclusion or exclusion for this manuscript, by revision of the titles and the abstracts. Published series with the aim to investigate exclusively rectal carcinomas and/or non cancer-diseases (*i.e.*, laparoscopic proctocolectomies for ulcerative colitis or diverticulitis) were excluded (Figure 1). Conversely manuscripts including few rectal cancers (or few non-malignant diseases) into the series, along with the other colon cancer localizations were included into this review.

Hand-assisted and totally laparoscopy procedures were considered altogether into the laparoscopic group, whereas all the open procedures (midline or transverse incisions) were considered as open resections.

All selected papers were categorized into the following sub-groups: (1) randomized studies; and (2) non-randomized studies (including prospective and retrospective case-control series).

Furthermore we identified those researches that investigated the comparison of these two approaches according to the tumor's location (*i.e.*, right side colectomies, left side colectomies and transverse resections) and highlighted within these groups the comparison of the costs derived by these two approaches.

Outcome measures

Whenever possible we collected data regarding: study design, population and power of the study, types of surgical procedure. We considered as short-term outcome measures: operating times (measured in minutes), blood

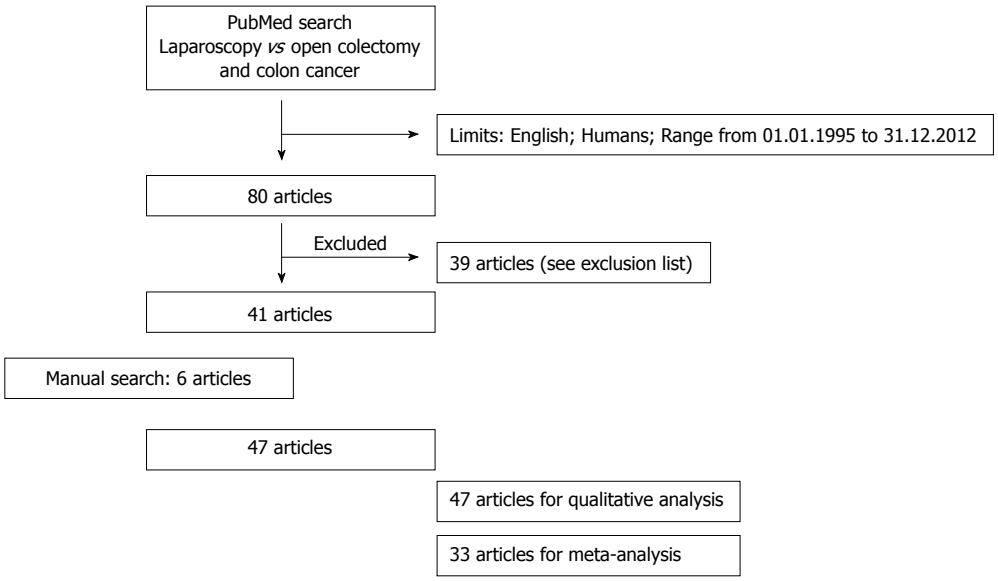

Figure 1 Study design. Study design according to the PRISMA statement for systematic reviews and meta-analysis.

Table 1 Exclusion list of the manuscripts

No.	Author	Ref.	Cause of exclusion
1	Sasaki J	*J Nippon Med Sch* 2012; **79**:259-66	Different outcome measure
2	Turagava J	*N Z Med J* 2012; **125**: 17-26	Only laparoscopy group
3	Poulsen M	*J Gastrointest Surg* 2012; **16**: 1554-1558	Only laparoscopy group
4	Roscio F	*Int J Surg* 2012; **10**: 290-295	Only laparoscopy group
5	Wang G	*Hepatogastroenterology* 2012; **59**: 2158-2163	Only laparoscopy group
6	Rottoli M	*Surg Endosc* 2012; **26**: 1971-1976	Different outcome measure
7	Campos FG	*Surg Laparosc Endosc Percutan Tech* 2011; **21**: 327-333	Exclusively familial polyposis patients
8	Panait L	*Chirurgia* (Bocur) 2011; **106**: 475-478	Only laparoscopy group
9	Hendren S	*Dis Colon Rectum* 2011; **54**: 1362-1367	Different outcome measure
10	Issa N	*J Gastrointest Surg* 2011; **15**: 2011-2015	Only laparoscopy group
11	McNicol FJ	*Colorect Dis* 2012; **14**: 458-462	Rectal cancers
12	Fujii S	*Hepatogastroenterology* 2011; **58**: 406-410	Only laparoscopy group
13	Akmal Y	*Surg Endosc* 2011; **25**: 2967-2971	Only laparoscopy group
14	Senthil M	*Arch Surg* 2010; **145**: 840-843	Different outcome measure
15	Han SA	*Int J Colorect Dis* 2010; **25**: 631-638	Different outcome measure
16	Park IJ	*J Gastrointest Surg* 2009; **13**: 960-965	Emergency resections
17	Heise CP	*Dis Colon Rectum* 2008; **51**: 1790-1794	Rectal cancers
18	Strhölein MA	*Dis Colon Rectum* 2008; **51**: 385-391	Rectal cancers
19	Moloo H	*Dis Colon Rectum* 2008; **51**: 173-180	Only laparoscopy group
20	Zhang H	*Minim Invasiv Ther allied Technol* 2007; **16**: 187-191	Rectal cancers
21	Polle SW	*Surg Endosc* 2007; **21**:1301-1307	Rectal cancers
22	Hasegawa H	*Surg Endosc* 2007; **21**: 920-924	Rectal cancers
23	Del Rio P	*Minerva Chir* 2006; **61**: 923-927	Only laparoscopy group
24	Schlachta CM	*Surg Endosc* 2007; **21**: 396-369	Only laparoscopy group
25	Wong DC	*Tech Coloproctol* 2006; **10**: 37-42	Rectal cancers
26	Moloo H	*Dis Colon Rectum* 2006; **49**: 213-218	Only laparoscopy group
27	Larson DW	*Dis Colon Rectum* 2005; **48**: 1845-1850	Rectal cancers
28	Kuhry E	*Surg Endosc* 2005; **19**: 687-692	Different outcome measure
29	Adaki Y	*Hepatogastroenterology* 2003; **50**: 1348-1351	Different outcome measure
30	Dunker MS	*Dis Colon Rectum* 2003; **46**: 1238-1244	Different outcome measure
31	Pasupathy S	*Tech Coloproctol* 2001; **5**: 19-22	Rectal cancers
32	Weeks JC	*JAMA* 2002; **287**: 321-328	Different outcome measure
33	Nelson H	*Swiss Surg* 2001; **7**: 248-251	Different outcome measure
34	Delgrado S	*Dis Colon Rectum* 2001; **44**: 638-646	Different outcome measure
35	Brown SR	*Dis Colon Rectum* 2001; **44**: 397-400	Rectal cancers
36	Marcello PW	*Dis Colon Rectum* 2000; **43**: 604-608	Rectal cancers
37	Hewitt PM	*Dis Colon Rectum* 1998; **41**: 901-909	Different outcome measure
38	Fukushima R	*Dis Colon Rectum* 1996; **39** (Suppl): S29-34	Different outcome measure
39	Bokey EL	*Dis Colon Rectum* 1996; **39** (Suppl): S29-34	Only laparoscopy group

loss (measured in milliliter), bowel function recovery (defined by the passage of the first flatus/stool; measured in days), post-operative pain (defined as the usage of analgesic -measured in days- and/or the score obtained by the visual analogue scale), return to the oral intake (usually liquid diet; measured in days), morbidity defined by peri-operative complications and hospital stay (measured in days).

Of note, since complications were often reported using different modalities (*e.g.*, major *vs* minor complications, rate of adverse events *etc.*), we extrapolated the overall morbidity rate in each category (laparoscopic and open surgery) reported in all the investigated series.

The oncologic adequateness was recorded whenever considered by the authors as the mean number of lymph nodes harvested in the surgical specimen. Mean follow-up (months) was recorded and long-term outcome measures were considered as the rate of relapses, the survivals and the incidence of incisional hernias. The costs analysis has been conducted recording the overall hospital costs for both procedures, providing results in US dollars, in order to analyze a single currency.

We did not considered conversion surgery, since it might bias the results of the open surgery procedures. On the same extent we did not consider the hospital volume, since it is seldom reported, even though the learning curves and the volume of patients might vary short-term results and costs.

A first analysis has been conducted reviewing papers in each category (prospective-randomized trials; case control series; studies investigating cancer by sites) and highlighting in each article were the evidences stand for (*e.g.*, significant statistical analyses supporting laparoscopy or open surgery) for the different outcome measures (*e.g.*, considering the operating time, blood losses etc.). Moreover and whenever computable we provided a meta-analysis of the results.

Statistical analysis

Continuous variables were analysed using means, medians and standard deviations, whereas categorical variables were analysed using frequencies and percents. Statistical analyses and Meta-analysis were performed using MedCalc for Windows, version 10.2.0.0 (MedCalc Software, MariaKerke, Belgium). In order to provide significant results, a meta-analysis has been conducted for all variables in different categories (prospective-randomized trials; case control series; studies investigating cancer by sites) whenever at least 3 studies provided data computable.

The Mantel-Haenszel method was used for calculating the weighted summary Odds ratio under the fixed effects model. Next the heterogeneity statistic is incorporated to calculate the summary odds ratio under the random effects model. The total odds ratio with 95%CI is given both for the Fixed effects model and the Random effects model. If the value 1 is not within the 95%CI, then the Odds ratio is statistically significant at the 5% level ($P < 0.05$).

For meta-analysis of studies with a continuous measure (comparison of means between treated cases and controls), the Hedges g statistic was used as a formulation for the standardized mean difference (SMD) under the fixed effects model. Next the heterogeneity statistic is incorporated to calculate the summary standardized mean difference under the random effects model. If the value 0 is not within the 95%CI, then the SMD is statistically significant at the 5% level ($P < 0.05$).

Statistical heterogeneity of the results of the trials was assessed on the basis of a test of heterogeneity (standard chi-squared test on N degrees of freedom where N equals the number of trials contributing data minus one). Three possible causes for heterogeneity were pre-specified: (1) differing response according to difference in the quality of the trial; (2) differing response according to sample size; and (3) differing response according to clinical heterogeneity. If the test of heterogeneity is statistically significant ($P < 0.05$) then more emphasis should be placed on the random effects model.

RESULTS

Figure 1 outlines the study design. PubMed search provided 80 results, however 39 studies were excluded due to different outcome measures (*e.g.*, investigations aimed to outline the quality of life or the immunological response), due to the evaluation of the laparoscopy procedures *per se* (missing the open surgery group) or evaluating rectal cancer patients (see exclusion list). All the 47 articles retrieved were included in the systematic review, however only 33 articles provided data computable for meta-analysis.

Randomized controlled trials

Figure 2 outlines results of this analysis. 11 studies were included for review[8-18] from 1995 to 2012, including overall 2992 patients in the laparoscopy group and 2717 in the open surgery group. Of note 4 studies enrolled less than 50 patients/arm[8,10-11,13]. The systematic review of the manuscripts documented a number of benefits of the laparoscopic procedure for the vast majority of the short-term outcome measures (bowel function recovery, return to the oral intake, post-operative pain, blood loss and hospital stay), whereas it was documented a longer operating time comparing the open approach. Of note, all the studies - with the exclusion of the first trial conducted by Lacy and co-authors in 1995[8] - reported a comparable morbidity rate within the two approaches. Similarly the mean count of the nodes harvested (LNH) in the surgical specimens were similar in the 3 studies investigating this variable[8-9,15], and the survivals were reported homogeneous in the vast majority of the studies[11,12,14,17,18], with the sole exception of the trial conducted by Lacy in 2002[9]. It seems important to highlight that only two randomized trials investigated

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Author	Year	Lap arm *n*	OS arm *n*	FU (mo)	OT		BF		OI		PP		BL		HOSP		Morbidity		LNH		Survival/ relapse		Hernia	
					Lap	OS	Lap	OS	Lap	OS	Lap	OS	Lap	OS	Lap	OS	Lap	OS	Lap	OS	Lap	OS	Lap	OS
Lacy *et al*[8]	1995	25	26			X	X		X				NS		X		X		NS					
Lacy *et al*[9]	2002	111	108	43.5		X	X		X				X		X		NS		NS		X			
Winslow *et al*[10]	2002	37	46	30.1		X	X										NS						NS	
Kaiser *et al*[11]	2004	29	20	35.0			X		X		X		NS		X		NS					NS		
COST Trial	2004	437	435	52.0		X					X				X		NS					NS		
Kang *et al*[13]	2004	30	30		NS		X		X		X		X		X		NS							
Braga *et al*[14]	2005	190	201	36.0											X		NS					NS	NS	
COLOR Trial	2005	627	621			X	X		X		X		X		X		NS		NS					
CLASiCC Trial	2005	526	268		NS		NS		NS						NS		NS							
COLOR Trial	2009	627	621	36.0		X							X									NS		
Bagshaw *et al*[18]	2012	299	302	62.0																		NS		
Total		2992	2717																					

B

Variable	Laparoscopy	Open surgery	Total	SMD/OR	95%CI	*P* value
Operative time	203	210	413	0.534	0.133-0.935	0.017
Bowel function	166	164	330	-1.037	-1.702-(-0.371)	0.002
Oral intake	166	164	330	-0.693	-0.917-(-0.469)	0.07
Blood loss	166	164	330	-0.649	-0.872-(-0.425)	0.06
Hospital stay	356	365	721	-0.707	-1.061-(-0.352)	0.007
Morbidity	302/2012	330/1755		0.609	0.415-0.896	0.0018

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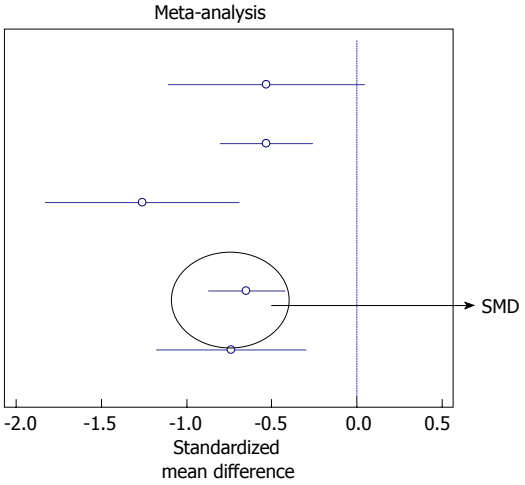

Figure 2 Randomized studies. A: Randomized trails comparing laparoscopy and open surgery. X in the table refers to a statistical association provided in the studies; B: Meta-analysis of the out-come measures; C: Forest plot graph regarding studies investigating blood loss. Lap arm: Laparoscopy arm; OS arm: Open surgery arm; FU: Mean follow-up; OT: Operative time; BF: Bowel function; OI: Oral intake; PP: Post-operative Pain; BL: Blood loss; HOSP: Hospital stay; LNH: Lymph node harvest; NS: Not significant.

the incidence of post-operative hernias[10,14], reporting a comparable rate of events (Figure 2A).

Meta-analysis conducted on 9 studies in this group[8-16] confirmed the evidences of the short-term outcome measures in favour of the laparoscopy (bowel function recovery, return to the oral intake, blood loss and hospital stay), plus it documented a better morbidity rate for the laparoscopy group (OR = 0.609; 95%CI: 0.415-0.896). Conversely the operating time has been confirmed shortly in the open procedure group (Figure 2B and C).

Case-control studies

Figure 3 reports data from this analysis. 16 case-control studies were included, counting overall 3819 patients in the laparoscopy group and 6990 in the open surgery group[19-34]. The vast majority of these studies agree in reporting shorter operating time in the open surgery group comparing with the laparoscopic procedures, with the exceptions of the studies conducted by Saba, Bilimoira and de Campos Lobato that provided homogeneous results[19,27,30]. All studies investigating the bowel function recovery recognized a benefit for the laparoscopy procedure[19,21-22,24,26]; similarly the investigation of the return to the oral intake provided homogeneous results in the 2 studies that investigated this outcome measure[19,29].

Even if Shabbir reported a similar use of analgesic in the post-operatory recovery[22], the other studies reported significant benefits associated with the laparoscopic procedure in this field[21,22,24]. A significant reduction in the blood loss for the patients undergone laparoscopy has been reported by all the authors[20,26,30,32,33], with the sole exception of Slow[24]. The hospital stay has been reported in favour of the laparoscopy group in all the studies, with the exclusion of the series investigated by

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Author	Year	Lap group	OS group	FU (mo)	OT		BF		OI		PP		BL		HOSP		Morbidity		LNH		Survival/ relapse		Hernia	
		n	*n*		Lap	OS	Lap	OS	Lap	OS	Lap	OS	Lap	OS	Lap	OS	Lap	OS	Lap	OS	Lap	OS	Lap	OS
Saba *et al*[19]	1995	25	25		NS		X		X						X				NS					
[1]Franklin *et al*[20]	1996	191	224	30[2]									X[1]		X[1]		X[1]		NS[1]		NS[1]			
Lezoche *et al*[21]	2000	150	160	35.1		X	X				X				X		NS				X			
Stocchi *et al*[22]	2000	42	42			X	X				X				X		X							
Feliciotti *et al*[23]	2002	74	75	48.9																	NS			
Sklow *et al*[24]	2003	77	77			X	X				X		NS		X		NS							
Patankar *et al*[25]	2003	172	172	55.5													NS				NS		NS	
Vignali *et al*[26]	2005	61	61			X	X						X		X		NS		NS					
Bilimoira *et al*[27]	2008	837	2222		NS										X		X							
Cermak *et al*[28]	2008	39	120												NS		NS				NS			
Shabbir *et al*[29]	2009	32	32			X			X		NS				X				NS					
de Campos-Lobato *et al*[30]	2011	289	289		NS								X		X		NS							
Gouvas *et al*[31]	2012	49	41																NS					
McKay *et al*[32]	2012	434	742			X							X		X		X		NS					
SCOAP Study	2012	1232	2336			X							X		X		X							
Cianchi *et al*[34]	2012	147	404																X					
Total		3819	6990																					

B

Variable	Laparoscopy	Open surgery	Total	SMD/OR	95%CI	*P* value
Operative time	2683	5480	8163	1.188	0.740-1.637	< 0.0001
Hospital stay	802	1224	2026	-1.505	-2.661-(-0.349)	< 0.0001
Morbidity	389/2292	1101/4109		0.641	0.477-0.862	0.0007
LNH	686	1027	1713	0.316	-0.418-1.050	< 0.0001

C

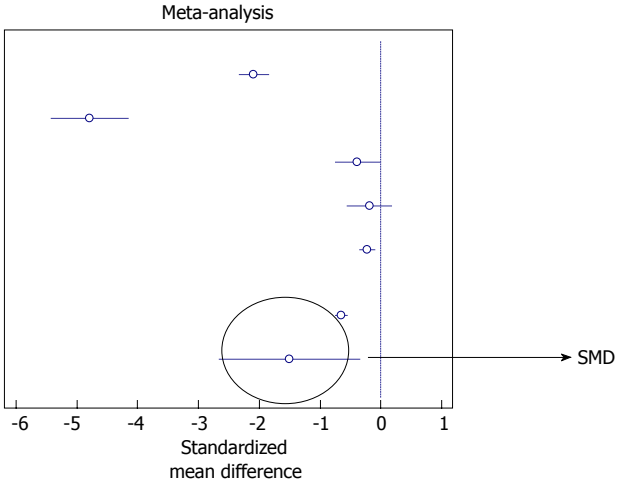

Figure 3 Non-randomized studies. A: Case-control studies comparing laparoscopy and open surgery. X in the table refers to a statistical association provided in the studies; B: Meta-analysis of the out-come measures; C: Forest plot graph regarding studies investigating hospital stay. [1]Statistic analysis not performed; [2]Significant difference of follow-up according to the stage of the disease. Lap: Laparoscopy; OS: Open surgery; FU: Mean follow-up; OT: Operative time; BF: Bowel function; OI: Oral intake; PP: Post-operative Pain; BL: Blood loss; HOSP: Hospital stay; LNH: Lymph node harvest; NS: Not significant.

Cermak *et al*[28] in 2008. The study of the morbidity rate provided dis-homogeneous results: even though some studies documented some benefits in the laparoscopy group[20,22,27,32,33], others documented comparable results between the 2 approaches[21,24-26,28,30]. Notably, Cianchi in 2012 highlighted a better LNH in the laparoscopy group[34], whereas the others reported homogeneous results.

Similarly, with the exception of Lezoche *et al*[21], the authors reported comparable survival rates within these 2 approaches. Seems important to highlight that the vast majority of the studies did not investigate the rate of post-operative hernias, with the sole exception of Pantankar in 2008[25] that reported similar results in the 2 groups.

A meta-analysis has been conducted for 11 studies in this category[20-22,24-28,30,32,33], Figure 3B. The operative time has been reported longer in the laparoscopy group, whereas this procedure showed a shorter hospital stay, Figure 3C. Interestingly the meta-analysis provided also in this category of studies some evidences regarding a lower rate of morbidity in the post-operative period following a laparoscopy operation (OR = 0.644; 95%CI: 0.447-0.862). The analysis of the LNH variable was not

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Author	Year	Lap group *n*	OS group *n*	Study design; FU (mo)	OT		BF		OI		PP		BL		HOSP		Morbidity		LNH		Survival/ relapse		Hernia	
					Lap	OS	Lap	OS	Lap	OS	Lap	OS	Lap	OS	Lap	OS	Lap	OS	Lap	OS	Lap	OS	Lap	OS
Lezoche *et al*[35]	2002	55	44	CC; 42.2		X	X								X		NS		NS		NS			
Sklow *et al*[24]	2003	40	42	CC		X[2]	X[3]				X[3]				X[3]									
Zheng *et al*[36]	2005	30	34	CC; 26.6	NS		X		NS		X		X		X		NS		NS		NS			
Lohsiriwat *et al*[37]	2007	13	20	CC		X		NS		NS		NS		NS			NS		NS					
Tong *et al*[38]	2007	77	105	CC; 21.5		X		NS	X					NS	X		NS		NS		NS			
Chung *et al*[39]	2007	41	40-M	R; 29.0		X	X		X		X		X		X		NS				NS			
Braga *et al*[40]	2007	113	113-M	R; 48.0		X			X				X		X		NS				NS[1]			
Nakamura *et al*[41]	2009	100	100	CC; 135.5	NS								X		X		X				NS			
Veenhof *et al*[42]	2010	25	28-T	CC; 19.0		X							X		X		NS		NS		NS		NS	
Tanis *et al*[43]	2012	30	22-M 23-T	CC		X	X		NS		NS				X		NS		NS					
Total		427	485																					

B

Variable	Laparoscopy	Open surgery	Total	SMD/OR	95%CI	*P* value
Operative time	83	106	189	3.431	0.613-6.249	< 0.0001
Bowel function	83	106	189	-1.689	-2.953-(-0.426)	< 0.0001
Post-operative pain	53	72	125	-2.068	-3.828-(-0.307)	< 0.0001
Blood loss	83	106	189	-0.387	-1.116-0.342	< 0.0001
Hospital stay	196	219	415	-1.589	-2.670-(-0.508)	< 0.0001
Morbidity	57/454	100/484		0.524	0.365-0.754	0.37
LNH	233	272	505	0.0567	-0.449-0.562	0.0002

C

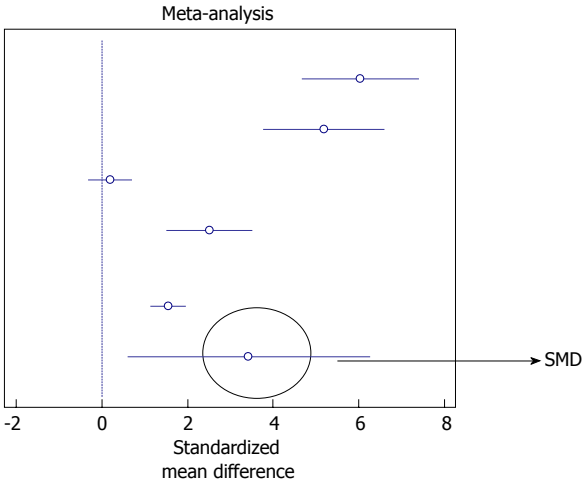

Figure 4 Right sided colectomies. A: Studies comparing right-side laparoscopy colectomy and open surgery. X in the table refers to a statistical association provided in the studies; B: Meta-analysis of the out-come measures; C: Forest plot graph regarding studies investigating operative time. [1]Statistic analysis not performed; [2]Exclusively if patients > 75 years old; [3]Exclusively if patients < 75 years old. Lap: Laparoscopy; OS: Open surgery; M: Midline incision; T: transverse incision R: Randomized, CC: Case-control; FU: Mean follow-up; OT: Operative time; BF: Bowel function; OI: Oral intake; PP: Post-operative Pain; BL: Blood loss; HOSP: Hospital stay; LNH: Lymph node harvest; NS: Not significant.

of statistical value (95%CI: -0.418-1.050).

Right-sided colectomies

We identified 10 studies in this category[24,35-43], involving 427 laparoscopy patients and 485 open colectomy patients, Figure 4. Overall we included 8 case-control series[24,35-38,41-43] and 2 randomized trials[39,40]. Of note the open surgical approach (midline *vs* transverse incisions) has been categorized exclusively in 4 studies[39,40,42,43]. All the studies analysed documented homogeneous results regarding the hospital stay (statistically better associated with the laparoscopy approach), LNH and survival rate (comparable results between the 2 procedures). Discordant data were documented for the operating time: even though the vast majority of the authors reported a shorter operation in the open group, the studies conducted by Zheng in 2005 and by Nakamura in 2009 documented comparable results[36,41]. The bowel function recovery has been reported shorter in the laparoscopy group in the studies conducted by Lezoche, Slow, Zeng, Chung and Tanis[24,35,36,39,43], whereas other 2 articles provided similar recoveries for both groups[37,38]. Three studies reported comparable results within the 2 surgical approaches regarding the return to the oral intake[36,37,43]; opposite Tong, Chung and Braga[38-40] reported results in favour of the laparoscopy group. Zeng, Chung and Slow (exclusively in patients < 75 years old)[24,36,39] reported a lower use of analgesics in the laparoscopy group,

A

Author	Year	Lap group *n*	OS group *n*	Study design; FU (mo)	OT		BF		OI		PP		BL		HOSP		Morbidity		LNH		Survival/ relapse		Hernia	
					Lap	OS	Lap	OS	Lap	OS	Lap	OS	Lap	OS	Lap	OS	Lap	OS	Lap	OS	Lap	OS	Lap	OS
Lezoche *et al*[35]	2002	86	63	CC; 42.3		X	X								X			NS		NS		NS		
Sklow *et al*[24]	2003	35	27	CC		X	X[1]				X[1]				X[1]									
Leung *et al*[44]	2004	203	200	R; 50.9		X	X		X		X			NS	X			NS		NS		NS		
Liang *et al*[45]	2007	135	134	R; 40.0		X	X				X		X		X			NS		NS		NS		
Hinojosa *et al*[46]	2007	1092	9511	CC											X		X							
Cheung *et al*[47]	2009	24	24	R		NS					X		X			NS	X		X					
Nakashima *et al*[48]	2011	33	22	CC		X	X		X				X		X		X		X					
Total		1608	9981																					

B

Variable	Laparoscopy	Open surgery	Total	SMD/OR	95%CI	*P* value
Hospital stay	1262	9672	10934	-2.244	-4.188-(-0.300)	1262
Morbidity	293/1573	2504/9954		0.849	0.473-1.525	0.0003

C

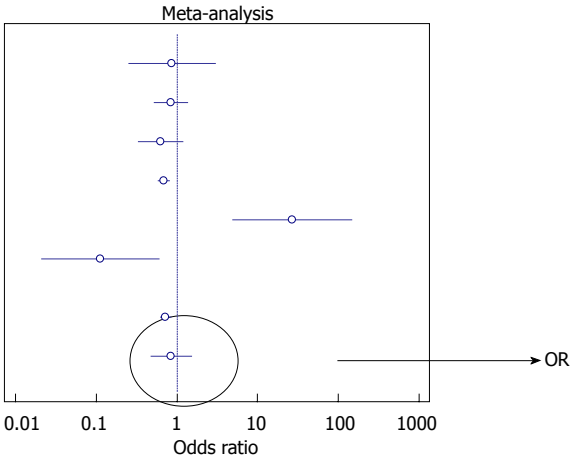

Figure 5 Left sided colectomies. A: Studies comparing left-side laparoscopy colectomy and open surgery. X in the table refers to a statistical association provided in the studies; B: Meta-analysis of the out-come measures; C: Forest plot graph regarding studies investigating morbidity rate. [1]Exclusively if patients > 75 years old. Lap: Laparoscopy; OS: Open surgery; M: Midline incision; T: transverse incision R: Randomized, CC: Case-control; FU: Mean follow-up; OT: Operative time; BF: Bowel function; OI: Oral intake; PP: Post-operative Pain; BL: Blood loss; HOSP: Hospital stay; LNH: Lymph node harvest; NS: Not significant.

whereas Lohsiriwat and Tanis failed in reporting a statistical association[37,43]. Within the laparoscopy procedures, all the authors with the exceptions of Lohsiriwat and Tong[37,38], documented lower blood losses. Also in this category, the investigation of the rate of post-operative hernias has been conducted in a single study[42].

A meta-analysis has been conducted or 9 manuscripts[24,35-42] within this category, Figure 4B. Significant evidences were highlighted for the laparoscopy procedures regarding the bowel function recovery, post-operative pain, blood losses, hospital stay and interestingly for the morbidity rate (OR = 0.524; 95%CI: 0.365-0.754). Also in this category the investigation of the LNH variable was not of statistical value (95%CI: -0.4149-0.562). Conversely the operating time has been confirmed shorter in the open surgery group, Figure 4C.

Left-sided colon cancers

Seven studies were included in this category[24,35,44-48], encompassing 1608 patients undergone laparoscopy and 9981 patients undergone open surgical resections, Figure 5. Three studies were randomized[44,45,47], the remaining were case-control studies. It seems important to highlight that 3 studies enrolled less than 50 patients/arm[24,47,48]. The analyses of the bowel function recovery, the return to the oral intake, the post-operative pain and the survival rates provided homogeneous results among studies (benefits for the laparoscopy patients for the short-term outcome measures, comparable results between the 2 approaches for long term survivals). The operating time has been reported in favour of the open approach in all the studies with the exception of Cheung *et al*[47]. Conversely the analysis of the blood losses was in favour of the laparoscopy procedures in all the researches, excluding the article by Leung *et al*[44]. A shorter hospital stay has been reported statistically associated to the laparoscopy procedure in all the studies with the sole exclusion of the report by Cheung *et al*[47].

Interestingly the analysis of the morbidity rate provided discordant data: 3 studies reported benefits for the laparoscopy procedure[46-48], whereas other 3 studies reported comparable results[35,44,45]. Notably the analysis of the LNH reported homogeneous results among different studies, with the exceptions of Cheung and Nakashima[47,48].

A meta-analysis has been provided including all the

Author	Year	Lap group *n*	OS group *n*	Study design	OT		BF		OI		PP		BL		HOSP		Morbidity		LNH		Survival/ relapse		Hernia	
					Lap	OS	Lap	OS	Lap	OS	Lap	OS	Lap	OS	Lap	OS	Lap	OS	Lap	OS	Lap	OS	Lap	OS
Kim *et al*[49]	2009	37	50	CC	NS		X		X				X		NS		NS		NS					
Akiyoshi *et al*[50]	2010	53	39	CC		X	X		X				X		X		NS			X				
Fernández-Cebrián *et al*[51]	2012	34	52	CC	NS		X			NS			X		NS		NS		NS					
Total		124	141																					

Figure 6 Transverse colectomies. Studies comparing transverse laparoscopy colectomy and open surgery. X in the table refers to a statistical association provided in the studies. Lap: Laparoscopy; OS: Open surgery; M: Midline incision; T: transverse incision; R: Randomized; CC: Case-control; OT: Operative time; BF: Bowel function; OI: Oral intake; PP: Post-operative Pain; BL: Blood loss; HOSP: Hospital stay; LNH: Lymph node harvest; NS: Not significant.

7 studies, but it was computable for only two variables (Figure 5B) and interestingly both the hospital stay and the morbidity rate were confirmed in favour of the laparoscopy group, Figure 5C.

Transverse colon cancers

Three studies were included in this category of investigation[49-51], including 124 patients in the laparoscopy group and 141 in the open surgery group, Figure 6. All the studies were case-controls series with some concerns regarding the power of the analyses due to the small samples enrolled. These studies reported homogeneous results in favour of the laparoscopy procedures for the bowel function recovery and the intra-operative blood loss. Notably all the studies documented similar morbidity rates for both surgical approaches. The studies conducted by Kim *et al*[49] and by Fernández-Cebrián *et al*[51] documented comparable operating times, whereas Akiyoshi *et al*[50] reported benefits in this field in the open surgery group. Fernández-Cebrián *et al*[51] documented comparable results within the 2 procedures regarding the return to the oral intake, whereas the others documented a statistical correlation with the laparoscopy procedure[49,50]. The hospital stay has been reported comparable by Kim and by Fernández-Cebrián[49,51], whereas Akiyoshi *et al*[50] reported a shorter hospitalization in the laparoscopy group. The analysis of the LNH reported similar results between the surgical procedures in the studies conducted by Kim *et al*[49] and by Fernández-Cebrián *et al*[51], whereas Akiyoshi *et al*[50] documented a higher mean number of nodes harvested in the open surgery group. None of these studies investigated the survivals or the incidence of post-operative hernias.

It was not possible to computable data for meta-analysis within this category of investigation.

Costs analysis

Nine studies were included in this investigation[19,29,36,44-46,52-54], including 3 randomized trials[44,45,52], Figure 7. The overall number of patients pooled in the laparoscopy group has been of 102763; otherwise 72264 patients were included in the open surgery group. Costs were expressed or converted whenever necessary in United States dollars. Overall laparoscopy procedures provided costs ranging from $4000 to $41000; conversely the open surgery expenses were ranging from $1800 to $43000. 4 studies were meta-analysed[36,44-46]. Results of the meta-analysis confirmed a significant reduction of the costs in the open surgery group comparing with laparoscopy (SMD = 4.843; 95%CI: 3.031-6.656), Figure 7B and C.

DISCUSSION

The primary goal of this manuscript was to divulgate the evidences obtained reviewing 47 manuscripts in this field, 33 of which provided data computable for meta-analysis; the results were categorized on the basis of the study design (randomized trials, case-control series) and on the basis of the tumor locations. Moreover we conducted an analysis of the costs derived by the two surgical procedures. Our results are in agreement with that of other meta-analyses in this field documenting better short-term results in the laparoscopy groups comparing with the open surgery procedures[55,56], even though it is associated with a significant longer operative time.

We considered any complications provided by different studies in the "morbidity rate" outcome measure, since it was very difficult to provide homogeneous results reviewing studies in this field; indeed authors considered different complications in the analyzed studies (infections, bleeding *etc.*). The interpretation of results, however, might be implemented if future studies could stratify the severity of adverse events using standard classifications (*e.g.*, the Clavien's classification)[57].

Nevertheless, the laparoscopy procedure for colon cancer resection has been reported oncologically safe[58,59]. The same results were reporting analysing exclusively right-sided colectomies[60]. In the field of the evaluation of resections by cancers' site, we noted that still to-date few studies compared the right-side colectomy by transverse incisions with the laparoscopy procedures; indeed as highlighted by Tanis *et al*[43] the short-term results obtained by the transverse incisions are often between laparoscopy and the midline approach. It is our opinion that this field of studies should be implemented. Moreover in the field of left-side colectomies the some series pool left-sided and recto-sigmoid cancers[45,46], thus it is often difficult to differentiate "pure" colectomies from the recto-sigmoid resections. Of note just 4 studies out of the 47 reviewed, investigated the rate of post-operative hernias, providing homogeneous

A

Author	Year	Lap group	OS group	Study design	Cost		*P* value
		n	*n*		Laparoscopy (mean ± SD)	Open surgery (mean ± SD)	
Saba *et al*[19]	1995	25	25	CC	4338	1839	< 0.05
Leung *et al*[44]	2004	203	200	R	9297 ± 2091	7148 ± 2164	< 0.001
Zheng *et al*[36]	2005	30	34	CC	11498.54 ± 2618.86	10228.34 ± 2372.57	NS
Liang *et al*[45]	2007	135	134	R	6076.3 ± 82.68	4263.12 ± 86.0	<0.001
Hinojosa *et al*[46]	2007	1092	9511	CC	13507 ± 8238	15248 ± 17373	
Franks *et al*[52]	2006	452	230	R	11092.21	10661.32	
Steele *et al*[53]	2008	95627	3296	CC	34685	34178	NS
Shabbir *et al*[29]	2009	32	32	CC	7943	7253	NS
Vaid *et al*[54]	2012	5147	58802	CC	41971	43459	< 0.001
Total		102763	72264				

B

Variable	Laparoscopy	Open surgery	Total	SMD/OR	95%CI	*P* value
Costs	1460	9879	11339	4.843	3.031-6.656	< 0.0001

C

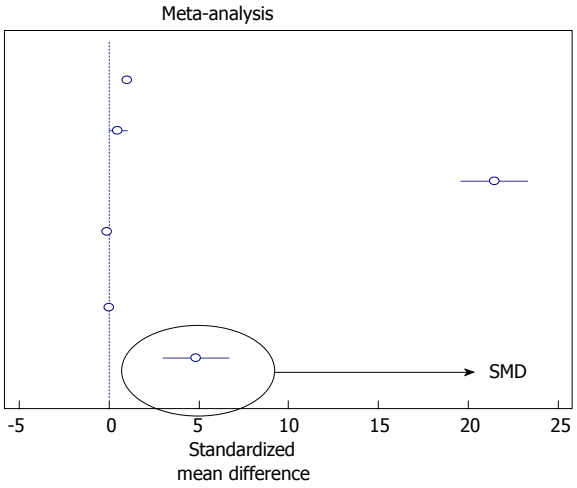

Figure 7 Costs analysis. A: Studies comparing laparoscopy and open surgery: analysis of the costs; B: Meta-analysis; C: Forest plot graph. Lap: Laparoscopy; OS: Open surgery; NS: Not significant; R: Randomized; CC: Case-control.

results comparing the 2 methodologies[11,14,25,42], thus also this field of investigation should be implemented by incoming studies.

Take at home messages

Short term outcome measures including: a lower blood loss, an earlier recovery of the bowel function, an earlier return to the oral intake, a shorter hospital stay and a lower morbidity rate were statistically associated to the laparoscopic procedures in randomized trials. Opposite the operating time has been confirmed shorter in the open surgery group.

Even though the majority of the trials reported a statistical association with less post-operative pain in the laparoscopic group, this data was not computable on meta-analysis, similarly the comparable results of the LNH within the 2 procedures was documented at the review but not computable at the meta-analysis.

This trend has been confirmed analyzing case-control series and cancer by sites, even though there are some concerns regarding the power of the studies in this latter field due to the small number of trials and the small sample of patients often enrolled.

The analysis of the costs documented lower costs for the open surgery procedures, however seems important to highlight that just few studies investigated the incidence of post-operative hernia. The analysis of the post-operative hernia could add important information; indeed a re-intervention might substantially implement the costs and might put into question the cost-effectiveness of the procedure.

COMMENTS

Background

Colon cancer is a major health issue. Over the last twenty years several progresses were made for improving the treatment and the quality of life of cancer patients, and the main innovation in the field of colon cancer surgical technique was that outbreak of the laparoscopy procedures (minimally-invasive treatments).

Research frontiers

Several studies recognized the adequateness of the laparoscopic approach along with a number of short-term functional benefits and equivalent long-term results comparing to "open" approach. Nevertheless, the scientific literature in this field is quite heterogeneous, thus it might be difficult for clinicians and surgeons to summarize results and "take at home" univocal messages.

Innovations and breakthroughs

The goal of this paper is to divulgate a comprehensible meta-analysis of the evidences and to provide a message of clinical use for clinicians and surgeons committed in the care of colon cancer patients.

Applications

The results are in agreement with that of other meta-analyses in this field documenting better short-term results in the laparoscopy groups comparing with the open surgery procedures, even though it is associated with a significant longer operative time.

Peer review

This is a comprehensive review and meta-analysis of laparoscopic *vs* open colectomy for colon cancer. It's well-written with a solid analysis.

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