



Review

What should we intend for minimally invasive treatment of colorectal cancer?



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ARTICLE INFO

Article history:
Accepted 1 June 2014

Keywords:
Colon cancer
Rectal cancer
Laparoscopy
Minimally invasive treatment
ERAS

ABSTRACT

Non-inferiority of laparoscopic treatment of colorectal cancer (CRC) has been demonstrated in randomized controlled trials although operative and perioperative management varies widely among centers. Literature data in English language published up to April 15, 2014 were analyzed in order to give an up to date analysis that would highlight the key aspects of a modern and factual minimally invasive treatment of CRC. Laparoscopic resection is the first choice treatment of colon cancer. Laparoscopic resection of rectal cancer should be considered an investigational procedure to be performed in high volume centers with special interest in laparoscopy and colorectal surgery. Less invasive approaches should be taken into account with the aim of reducing surgical stress. The adoption of ERAS programs has demonstrated to optimize short-term results. Future research should be directed to prove possible long-term advantages, in terms of overall and disease-free survival, of minimally invasive treatment of CRC.

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Introduction

Colorectal cancer (CRC) is the second leading cause of cancer-related death in Western countries. The end of the eighties and the beginning of the nineties entailed two crucial innovations which revolutionized the treatment of CRC namely, total mesorectal excision (TME) and laparoscopic surgery [1,2].

Whereas TME shortly gained wide acceptance and application, the extensive use of laparoscopy in the treatment of CRC is still debated. Randomized controlled trials (RCTs) and **meta-analyses published over the last two decades demonstrate that laparoscopy** is not inferior to open **surgery** in terms of long-term survival and recurrence rate [3–11]. Beside statistical analysis, **several** potential benefits may have been missed due to the multicenter nature of most of these studies and the consequent heterogeneity in surgical technique and perioperative management. **Better results were actually** reported by single center experiences both in the setting of randomized [12–15] and prospective cohort studies [16,17].

Firstly introduced by Kehlet [18] in the mid 1990s, fast-track surgery, now preferably called Enhanced Recovery After Surgery (ERAS), took more than a decade to become popular and widespread. At present, ERAS programs are becoming **increasingly** popular although they are not yet adopted as the standard.

The purpose of this review was to analyze the literature data on laparoscopic treatment of CRC with special reference to technical novelties and perioperative management in order to give an up to date analysis that would highlight the key aspects that should be the basis of a modern and factual minimally invasive treatment.

Clinical evidence of laparoscopic versus open resection for colon cancer

RCTs provide level I evidence supporting a better and shorter postoperative recovery and **rebutting** any disadvantage in overall and disease-free survival of laparoscopic resection with respect to open surgery for treatment of colon cancer (CC) (Table 1).

Regarding short-term **results**, besides the study by Lacy et al. [13], that solely reported significantly less complications (10.8% vs. 28.7%, $P = 0.001$), the benefits of laparoscopic **colonic** resection related to 70–100 mL less blood loss, one day shorter duration of post-operative ileus, one day shorter and lesser use of parenteral analgesics and one day shorter hospital stay (Fig. 1).

Regarding long-term outcomes, laparoscopic resection was superior to open resection in the study by Lacy et al. [14] in which a

statistically significant difference in the probability of cancer-related survival was evidenced. This difference was due to the superiority of laparoscopy in the treatment of stage III CCs. In this subset of tumors a significant improvement in overall survival ($P = 0.048$), cancer-related survival ($P = 0.02$) and disease-free survival ($P = 0.048$) was demonstrated. In other randomized trials the equivalence of laparoscopic with respect to open resection in the treatment of CC was **demonstrated**.

However, when translating these results in actual clinical practice some considerations should be stressed: i) to avoid inclusion of confounders, rigorous study design including stringent exclusion criteria are often adopted in RCTs, as a consequence, the internal validity of these studies is very high although the external validity may show several limitations; ii) the multicenter nature of most of these studies may lead to the underestimation of potential benefits due to the differences among centers in surgical expertise and quality of treatment. As a matter of fact, the number of patients treated in each center per year was quite low (Table 1); iii) none of these studies proposed a standardization of perioperative management and, **at that time, the adoption of ERAS programs was not consider**; iv) accrual period mainly belonged to the first decade of experience of laparoscopic colon resection. Actually several improvements have been achieved both in surgical technique and available instrumentations; v) the results mainly refer to tumors of the right and sigmoid colon. Tumors of the transverse colon and left angle were excluded, whilst tumors of the left colon were infrequently treated (7–10% of the cases).

To be really effective, minimally invasive treatment of CC requires adequate surgical skills in laparoscopic as well as CC surgery together with focalized and standardized perioperative management. The combination of these elements allows reaching high standard of **care** as demonstrated by several experiences from highly specialized centers (Fig. 1).

Actually, non-inferiority of laparoscopic surgery in the treatment of CC has been demonstrated by RCTs **and meta-analyses whilst** the possibility to achieve excellent short-term results in terms of postoperative morbidity and early resumption of normal functions has been proved just by selected experiences [15,16,27].

Clinical evidence of laparoscopic versus open resection for rectal cancer

TME, as proposed by Heald in 1988 [1], is the accepted treatment for adenocarcinoma of the middle and lower rectum.

Table 1

Main characteristics and results of randomized controlled trials comparing laparoscopic and open surgery for the treatment of colorectal cancer.

Author (Country)	Accrual period (No. of centers)	Tumor type	No. of pts	No. of pts/centre/yr	No. of yielded nds ^e	Positive margins ^h	Mortality ^h	Morbidity ^h	Local ^h recurrence	5-yr survival ^h
Lacy et al. (Spain) [13,14]	'93-98 (1)	CC ^a	111 (108)	48.7	11.1 (11.1)	0 (0) ^f	0.9 (2.8)	10.8 (28.7)	7.5 (13.7)	76 (64)
Leung et al. (Hong Kong) [12]	'93-02 (1)	CRC ^b	203 (200)	44.8	11.1 (12.1)	NA	0.5 (2.4)	19.7 (22.5)	2.5 (2)	76.1 (72.9)
COST (US, Canada) [3,4]	'94-01 (48)	CC ^a	435 (428)	2.6	12 (12)	NA	0.5 (0.9)	21.1 (19.9)	2.3 (2.6)	76.4 (74.6)
CLASICC (UK) [5,6,19,20]	'97-02 (27)	CRC ^a	526 (268)	4.9	12 (13.5)	10.7 (8.8) ^g	4 (4.9)	32.7 (31.7)	10.8 (8.7)	57.9 (57.9)
COLOR (Europe) [7,8]	'97-03 (29)	CC ^a	536 (546)	6.2	10 (10)	1.9 (1.7) ^g	1.1 (1.8)	20.7 (20.2)	4.8 (4.8)	74 (74)
LAPKON II (Germany) [21]	'98-04 (20)	CRC ^{a,c}	250 (222) ^d	3.9	16 (17)	0 (0) ^f	1.2 (0.9)	25.2 (23.9)	NA	NA
ALCaS (Aus, NZD) [22-24]	'98-05 (31)	CC	294 (298)	2.5	13 (13)	0.3 (0) ^f	1.4 (0.7)	37.8 (45.3)	NA	78 (77)
Lujan et al. (Spain) [25]	'02-07 (1)	RC	101 (103)	39.8	13.6 (11.6)	4 (2.9) ^g	1.9 (2.9)	33.7 (33)	4.8 (5.3)	72.1 (75.3)
COREAN (S. Korea) [26]	'06-09 (3)	RC	170 (170)	34.3	17 (18)	2.9 (4.1) ^g	0 (0)	21.2 (23.5)	NA	NA
COLOR II (Europe) [9]	'04-10 (30)	RC	699 (345)	5.4	13 (14)	9.5 (10) ^g	1.1 (1.7)	39.9 (37.1)	NA	NA

^a Tumors of the transverse colon and left angle were excluded.

^b Tumors other than sigmoid colon and upper rectum cancer were excluded.

^c Tumors of the middle and lower rectum were excluded.

^d 207 patients were excluded after explorative laparoscopy and before randomization.

^e Numbers with decimals are means whilst whole numbers represent medians.

^f Positive longitudinal margins were reported.

^g Positive longitudinal and circumferential margins were reported.

^h Numbers are percentages.

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