Current Status of Laparoscopic Therapy of Colorectal Cancer

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Key Words

Colon cancer · Rectal cancer · Laparoscopy · Laparoscopic-endoscopic 'rendezvous' procedures · Curative resection

Abstract

Laparoscopic colorectal resections offer several benefits postoperatively, including minimal impairment of gastrointestinal and pulmonary function, less immunosuppression, shorter hospital stay and improved reconvalescence. Since the introduction of laparoscopic surgery for the therapy of curable colorectal cancer, some concern was voiced in terms of oncologic radicality, the issue of port-site metastases and tumor cell distribution. However, the clinical reality has demonstrated that oncologic radicality is equivalent to open surgery, and the incidence of port-site metastases is not increased when compared to wound recurrence at the laparotomy site. Focusing on colon and rectum, various indications of laparoscopic-endoscopic 'rendezvous' procedures exist including laparoscopic-assisted endoscopic transluminal resection, endoscopic-assisted wedge or anatomical resections, and, finally, intraoperative tumor location by colonoscopy to achieve oncologic resection margins in laparoscopic curative resections. In terms of colorectal curative resections, long-term results provide level I evidence that laparoscopic surgery for colon cancer is oncologically adequate and can be performed with equivalent

morbidities and mortality rates when compared to conventional surgery. In terms of rectal cancer, no level I evidence is available. However, short-term data from experienced centers do not report inferior oncologic outcome particularly related to laparoscopic total mesorectal excision.

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Introduction

The theoretical advantages of laparoscopic surgery include reduction of pain, early return of bowel function, less impaired respiratory function, decreased disability with shorter hospitalization and early return of normal activities, fewer adhesions and incisional hernia formation, finally, better cosmesis. These benefits have been well established for the surgical treatment of benign colorectal disease. However, these advantages are all secondary in malignancy. There is the issue whether laparoscopic surgery maintains adequate oncologic radicality. Additionally, the role of potential tumor cell distribution during laparoscopic surgery for cancer has been a focus of concern. Finally, the incidence of port-site metastases in the late 1990s has raised major controversy. In fact, postoperative immune and metabolic response seems to be favorably influenced by laparoscopic surgery. However, if less immunosuppression after laparoscopic resection has a definite clinical impact on prognosis is still

unknown to date. In this context, it was the aim of this review to assess the actual role of laparoscopic therapy of colorectal cancer.

Are Principles of Oncologic Radicality Maintained?

Oncologic standards of curative surgery for colorectal cancer include en-bloc resection, no-touch isolation technique with primary ligation of the corresponding vessels, and systematic lymph node dissection – these principles are mandatory for both open and laparoscopic surgery [1–3]. With the introduction of laparoscopic curative surgery in colorectal cancer, some concern was voiced regarding the ability to maintain the oncologic principles of open cancer surgery. Standard procedures were right hemicolectomy, left hemicolectomy, anterior resection and abdominoperineal resection with central ligation of the inferior mesenteric vein and artery. In the meantime, laparoscopy has been introduced into total mesorectal excision (TME) for rectal cancer without compromising radicality in experienced centers [3–14].

It has been argued in the last decade that the extent of adequate radical surgery may be a major problem of laparoscopic surgery, but all series including retrospective and prospective registries as well as comparative studies have clearly demonstrated that oncologic principles are not compromised by laparoscopic techniques, and the yield of lymph nodes, surgical margins (proximal, distal, and radial), and length of bowel resected were comparable to open cancer surgery [1, 2, 8].

Is There an Increased Risk of Tumor Cell Distribution?

A second major problem which has been discussed controversially is the issue whether laparoscopic surgery is associated with an increased hematogenous and intraperitoneal tumor cell distribution. Therefore, the no-touch isolation technique including the ligation of the blood supply prior to attempted mobilization is advocated by the majority of surgeons. These principles are not compromised by the laparoscopic procedure. However, laparoscopic cancer surgery requires, therefore, specific skills and expertise of the surgeon, including experience on both open and laparoscopic oncologic surgery.

Several experimental studies have focused on the potential tumor cell distribution during laparoscopic sur-

gery either related to pneumoperitoneum or associated with tissue handling [15–17]. Although the dissection in laparoscopic resection is similar to that in open surgery, some concern was voiced regarding tissue handling and manipulation by instruments during laparoscopic bowel palpation. However, all these animal and in vitro models, e.g. using chambers with carbon dioxide insufflation, have few drawbacks that may limit the application of their results to the understanding of the potential mechanisms of tumor cell distribution in humans. Firstly, these models have used an inoculum of various cancer cell lines, installed into different sites in the peritoneal cavity. Secondly, all investigational models have been performed in artificial conditions in which the rates of port-site metastases derived from tumor cell distribution were intentionally higher. Therefore, the application of these experimental studies to humans was not acceptable, and did not show ‘real life’. Consequently, the best prevention strategy of potential tumor cell distribution during laparoscopic surgery is maintained by the surgeon strictly using the principles of the no-touch technique, the use of atraumatic instruments, and not to use cautery close to the tumor. Additionally, the instruments and the abdominal cavity have to be irrigated regularly. Finally, the correct oncologic operation must not be compromised by the laparoscopic technique: manipulation of the tumor-bearing segment is not standard of oncologic surgery – independent of laparoscopic or open procedures.

Are Port-Site Metastases Still a Problem?

The incidence of port-site metastases after laparoscopic resection in the beginning era has caused a major concern [1, 15–17]. Although port-site metastases have not been restricted to laparoscopic colorectal surgery for cancer, the major impact of this phenomenon has been in this field. The rapid accumulation of reports of port-site recurrence in the first years of laparoscopic colectomy, compared to the total number of laparoscopic resections for colorectal cancer performed at that time, suggested that there was an extraordinarily high incidence of port-site metastases following laparoscopic surgery for cancer. This fear turned the primary enthusiasm from the laparoscopic benefits into a more prudent and careful attitude.

The fact that most experienced surgeons have never observed a case of wound recurrence at the laparotomy site after curative resection for colorectal cancer intimates its rarity. In 1993, the first sporadic cases of port-

site recurrence after laparoscopy were reported. This report was followed by several publications of port-site metastases which were not restricted to advanced tumor stages, but have also been reported in patients with Dukes A or B tumors. Reviewing the reports of port-site metastases, Wexner and Cohen [15] reported an incidence of port-site metastases ranging from 0 to 4% in 1995.

In the late 1990s, various hypotheses were investigated and proposed to explain port-site metastases including evidence from clinical cases and experimental studies. Many research studies have provided evidence for direct implantation of the port site by exfoliated cancer cells, hematogenous seeding, tissue manipulation, aerosolization by pneumoperitoneum, patients' positioning and immune dysfunction as potentially etiologic factors. However, a generally accepted explanation could not be derived. Although the pathophysiology leading to port-site recurrence in laparoscopic surgery for colorectal cancer was poorly understood, several preventive measures derived from animal models were suggested including peritoneal irrigation with various solutions (e.g. povidone-iodine, heparin, methotrexate, and cyclophosphamide). These agents, however, were potentially hazardous, and the application of these results to humans does not seem to be currently acceptable. According to the investigational evidence that the pneumoperitoneum itself has been shown to increase the occurrence of port-site metastases, the application of gasless laparoscopy has been suggested. Furthermore, the hypothesis that carbon dioxide may contribute to port-site recurrence led Neuhaus et al. [16] to compare different types of insufflation gas for pneumoperitoneum in an animal model. They reported that only helium was found to reduce the rate of port-site metastases significantly [16]. However, the clinical implication of the use of helium in humans is not sufficiently investigated. The assumption that the withdrawal of the specimen through a small wound at the port site may cause wound recurrence, led to the application of plastic wound protectors and cell-impermeable specimen bags. At present, the use of wound protection combined with the strict surgical principles of the no-touch technique, and closing of fascia and peritoneum at the port-site seem to be the most common preventive methods currently in use.

Despite extensive research efforts, neither the incidence of port-site recurrence nor its causes were definitely elucidated. However, the clinical results of large prospective trials of laparoscopic surgery for colorectal cancer published within the last 10 years clearly demonstrated an incidence of less than 1%, which is not in-

creased when compared to wound recurrence at the laparotomy site. Therefore, obviously, insufficient technical skills and experience at the beginning of the laparoscopic era have potentially created a problem which has been overestimated initially, and, in 2005, the issue of port-site metastases is not a problem anymore.

Better Immunofunction, Better Oncologic Results?

A specific issue of laparoscopic curative surgery for colorectal cancer is related to the fact that postoperative stress is reduced and immunologic response is better preserved after laparoscopy when compared to open colorectal resections. Particularly in colorectal malignancy, a positive influence of the minimally invasive access on immune function seems to be of high priority, as immune malfunction plays a potential role in malignancy. Therefore, the hypothesis 'the less immunosuppression by laparoscopic therapy, the better impact on prognosis' would be desirable. To date, many randomized studies have clearly demonstrated that postoperative stress and immune function is positively influenced after laparoscopic resection for colorectal cancer when compared to open colectomy (table 1, [18–27]). However, whether these results really have an impact on prognosis can only be answered if long-term recurrence and survival data of the randomized multicenter trials are available. In the meantime, an influence on immune function remains speculative, since the reduced postoperative stress after laparoscopy is more related to a reduction of the access.

Laparoscopy Meets Endoscopy

Since the widespread use of the laparoscope, the combination of laparoscopic surgery and intraoperative colonoscopy improve the feasibility of both laparoscopic procedure and therapeutic endoscopy, and, finally increase patients' safety and postoperative convalescence [28]. Focusing on colon and rectum, various indications of laparoscopic-endoscopic 'rendezvous' procedures exist including laparoscopic-assisted endoscopic transluminal resection, endoscopic-assisted wedge or anatomical resections, and, finally, intraoperative tumor location by colonoscopy to achieve oncologic resection margins in laparoscopic curative resections. However, combined laparoscopic-endoscopic procedures are not seldom challenging, and require technical and personal skills in particular.

Table 1. Comparison of immunofunction and postoperative stress after laparoscopic vs. conventional resection for colorectal cancer (only randomized studies included)

Author	Year	Patients	Results	Reduction of postoperative stress by lap.
Hewitt [18]	1998	16 (8 lap. vs. 8 open)	IL-6↓, T-cell activity→, CD4/CD8 ratio→, HLA-DR→	No
Leung [19]	2000	34 (17 lap. vs. 17 open)	IL-1β↓, IL-6↓, CRP↓, TNF-α→	Yes
Schwenk [20]	2000	60 (30 lap. vs. 30 open)	IL-6↓, CRP↓, IL-1RA→, IL-10→	Yes
Delgado [21]	2001	97 (39 lap. vs. 58 open)	IL-6↓, CRP↓, cortisol→, prolactin→	Yes
Ordemann [22]	2001	40 (20 lap. vs. 20 open)	Leukocytes↓, lymphocytes→, CD4/CD8 ratio→, HLA-DR↑, TNF-α↓	Yes
Tang [23]	2001	236 (118 lap. vs. 118 open)	T- and B-cell activity→, CD4/CD8 ratio→, NK cells→, leukocyte-phagocytose activity→, immunoglobulin (IgG, IgM, IgA), C3, C4→	Yes
Braga [24]	2002	79 (40 lap. vs. 39 open)	Lymphocytes→, CD4/CD8 ratio↑, CRP↓, cortisol→, lactate→	Yes
Targarona [25]	2002	54 (27 lap. vs. 27 HA-lap.)	IL-6↓, CRP↓	Yes
Hasegawa [26]	2003	59 (29 lap. vs. 30 open)	CRP↓	Yes
Wu [27]	2003	26 (12 lap. vs. 14 open)	IL-6↓, IL-8↓	No

↓ = Reduced after laparoscopic surgery; → = no difference; ↑ = increased after laparoscopic surgery; lap. = laparoscopy; HA-lap. = hand-assisted laparoscopy.

Following our own experiences with ‘rendezvous’ procedures and derived from published results, the combination of laparoscopy and colonoscopy is safe and effective, particularly in benign or premalignant polyps (potentially bearing early colon cancer) with a certain size not removable by endoscopic polypectomy or in locations difficult or high-risk for flexible endoscopic polypectomy (e.g. hepatic and splenic flexure). However, in awareness of published case reports from the beginning era of laparoscopy, the intraoperative location of a tumor by colonoscopy is mandatory to overcome the ‘dark side’ of cases in which a wrong colonic segment was resected by the laparoscopic approach. Figure 1a and b show the possibilities of combined laparoscopic-endoscopic procedures.

Laparoscopy for Colorectal Cancer: Where Are We Now?

As the introduction of laparoscopic surgery representing an innovative approach to the treatment of colorectal diseases has a tremendous impact on general outcomes, the question whether laparoscopic surgery should be performed for cancer is still under debate. Surgical innovation as maintained by laparoscopy takes place in ‘real time’, with the understanding that novel clinical decisions and conclusions will be made as necessary. More-

over, the introduction of new surgical techniques is integral to the advancement of surgical knowledge.

Early non-randomized publications of laparoscopic therapy of colorectal cancer showed comparable results to those of the standard conventional approach for the treatment of colorectal cancer, and numerous studies have determined that short-term benefits in terms of oncologic principles and prognosis after laparoscopy do exist. The principal unanswered question, however, has been whether long-term outcomes are as good in laparoscopic as in conventional surgery. Therefore, the general application of laparoscopic curative resection for colorectal cancer has been examined by three randomized multicenter trials (COST, COLOR, CLASICC), and the first results have been published recently [29–31].

Fig. 1. Combination of laparoscopic resection and endoscopic intraluminal tumor location prior to laparoscopic resection: **a** view from the laparoscope and **b** view from the colonoscopy.
Fig. 2. Central ligation of inferior mesenteric vein by laparoscopy.
Fig. 3. Central ligation of inferior mesenteric artery by laparoscopy.
Fig. 4. Laparoscopically removed complete TME specimen.
Fig. 5. Preservation of plexus hypogastricus after laparoscopic rectal resection.

1a

1b

2

3

4

5

Table 2. Own experiences of laparoscopic colorectal surgery for curable colorectal cancer

	Laparoscopic-completed procedures	Converted procedures
Patients	166	30
UICC I	93	13
UICC II	29	6
UICC III	40	11
UICC IV	4	0
Follow-up	48 months (n = 163)	42 months (n = 29)
Local recurrence without metastases	1 (0.6%)	0
Local recurrence with metastases	2 (1.2%)	0
Metachronous metastases	10 (6.0%)	3 (10.3%)

Both the short-term results of the European COLOR trial and the short-term data of the UK CLASICC trial showed no differences in oncologic radicality, morbidity, or mortality. However, conversion rates were considerably high in both studies (COLOR: 17%; CLASICC: 29%), and patients with converted treatment had higher complication rates as reported by the CLASICC trial [29, 30].

The COST Study Group published the first large, prospective randomized trial comparing the long-term results of laparoscopic-assisted and open colectomy for colon cancer (rectal cancer was not included in this study). Median follow-up was 4.4 years. This study showed similar rates of recurrence, postoperative mortality, and intraoperative complications between the two groups as well as a shorter hospital stays and less use of analgesics for the laparoscopic group [31]. These new results from the COST Study Group providing long-term data closely resemble those in the initial short-term studies. Moreover, a meta-analysis conducted by Abraham et al. [32] published in 2004 included 12 randomized studies (2,512 patients with colorectal cancer), and clearly showed adequate radicality and less morbidity (wound infection) after laparoscopic surgery (among other advantages in the postoperative period). The results of the consensus development conference published by the EAES (European Association of Endoscopic Surgery) in 2004 also concluded that the results of laparoscopic surgery for colon cancer are safe and feasible which improves short-term outcome [33].

In summary, derived from the long-term results of the COST Study Group [31], there is now a level of evidence IA that laparoscopic surgery is applicable to curative resection for colon cancer; however, there is no level of evidence I with grade A recommendation in terms of rec-

tal cancer, as the COST Study Group did not include rectal cancer. For rectal cancer, only limited randomized single-center studies exist [34–36]; however, long-term data on prognosis are not available to date.

Own Experiences

Reflecting our own experience of laparoscopic colorectal surgery (January 1993 to April 2005), laparoscopic curative resections for colon and rectal cancer were introduced in 1996. In the meantime, our institution has joined randomized multicenter trials (COLOR, LAP-KON II).

From the technical aspect, oncologic principles could be maintained by the laparoscope, e.g. central ligation of the inferior mesenteric vein (fig. 2), artery (fig. 3), resection of a complete TME specimen (fig. 4) and preservation of the autonomic hypogastric plexus (fig. 5).

To date, 1,349 laparoscopic colorectal resections have been performed at our institution. Out of these, 196 procedures (colon cancer: n = 111; rectal cancer: n = 86) were curative laparoscopic resections for colorectal cancer (table 2). The conversion rate was 15.3% (n = 30), so that 166 procedures were completed laparoscopically. Providing a prospective computerized PC database which is regularly updated by the follow-up data, local recurrence rate is 1.8% (mean follow-up 48 months) after laparoscopic-completed procedures (only pT3 tumors, no local recurrence after pT1/T2). No local recurrence had to be documented in converted patients. Short-term data also show a potentially low incidence of metachronous metastases after curative laparoscopic operation (6.0% after laparoscopic and 10.3% after converted procedures).

Conclusion

More than a decade of laparoscopic curative surgery for colorectal cancer has passed. Derived from our own experience, published by other experts and clearly demonstrated by the long-term results of the COST Study Group, there is level of evidence I with grade A recommendation that laparoscopic resection of curable colon cancer results in equivalent oncologic radicality and

cancer-related survival when compared to open surgery and if a surgical expertise is maintained. However, for rectal cancer no level of evidence I (with grade A recommendation) exists, as long-term results of randomized multicenter trials are not available. However, as developed in colon cancer, there is no question that laparoscopic surgery for rectal cancer (including TME) can be performed safe and effective by experienced surgeons.

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