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Comparison of oncologic outcomes in laparoscopic versus open surgery for non-metastatic colorectal cancer: personal experience in a single institution

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Abstract:

The oncologic merits of laparoscopic technique for colorectal cancer surgery remain debatable. Eligible patients with non-metastatic colorectal cancer who were scheduled for an elective resection by only one surgeon in a medical institution were randomized to either laparoscopic or open treatment. During this period, total 188 patients received laparoscopic surgery and other 163 patients to open approach. The primary endpoint was cancer-free 5-year survival after operative treatment and secondary endpoint was the tumor recurrence incidence. We found there was no statistically significant difference between open and laparoscopic groups regarding average number of lymph nodes dissected, overall mortality rate, cancer recurrence rate or cancer-free 5-year survival. Nevertheless, laparoscopic approach was more effective for colorectal cancer treatment with shorter hospital stay and less blood loss despite operation time was significantly longer. Meanwhile fewer patients receiving laparoscopic approach developed postoperative urinary tract infection, wound infection, pneumonia or anastomosis leakage, which reached statistical significance. For non-metastatic colorectal cancer patients, laparoscopic surgery resulted in better short-term outcomes whether in total complications and intra-operative blood loss. Though there was no significant statistical difference in terms of cancer-free 5-year survival and tumor recurrence, we favor patients receiving laparoscopic surgery if not

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contraindicated.

Keywords: laparoscopic; open surgery; non-metastatic colorectal cancer; single surgeon experience

1. Introduction

Since the first laparoscopic assisted colon resection introduced in 1991 by Jacobs et al., it has become gradually popular [1]. More and more colorectal surgeons admit that laparoscopic technique leads quicker functional recovery [2-5] and improved short-term results when compared to open approach [6-12]. However, laparoscopic technique has not previously been proved to gain major benefits in colorectal surgeries [13-17]. Recently, oncologic outcomes of colorectal cancer resection, in terms of lymph node harvest number and excision safety margin lengths, achieved under laparoscopy could be comparable to those obtained using conventional open technique. However, curability of colorectal cancer under laparoscopic technique remains controversial because of the uncertainty about overall recurrence rate [18]. Besides, three major, randomized clinical trials have proven that laparoscopic technique can lead to same oncological outcomes related to open approach but did not distinguish a survival benefit favoring laparoscopy [2,4,6].

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We believe that the role of laparoscopic technique for advanced non-metastatic colorectal cancer management will be clarified through this study. The aim of our research was comparison of 5-year oncologic results of non-metastatic colorectal cancer patients receiving laparoscopic resection (LR) or open resection (OR) by one surgeon in a medical institution.

2. Materials and Methods

2.1. Ethics Statement

This study was permitted by the institutional Ethics of Research Committee of Chi Mei Medical Center, Taiwan. The protocol conformed to ethical standards according to the Declaration of Helsinki published in 1964. Moreover, the written or verbal patients' consent for this study was acquired.

2.2. Study Population

From January 2008 to December 2013, total 375 consecutive colorectal cancer patients scheduled for resection by Dr. Chiu with LR or OR were assessed (Figure 1). The treatment protocol was based on the National Comprehensive Cancer Network (NCCN) Guidelines®. The exclusion criteria included patients with cancer distant metastasis, synchronous tumors, adjacent organ invasion, intestinal obstruction,

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combined operations for other disease, previous colorectal surgery, history of inflammatory bowel disease, polyposis, past episode of ileus related to intra-abdominal adhesions, severe medical disease, pregnancy, emergent surgeries, patient unwilling to participate in the study or conversion to open approach. Conversion to open approach was defined as an abdominal incision larger than necessary for specimen retrieval. After written informed consent was obtained, the patients were randomized into two treatment groups, either LR or OR, according to a predetermined randomization scheme per tumor site and surgeon, using random numbers. In LR group, all patients needed to pay for the extra fee of the Harmonic scapel and wound retractor. Thus, the final decision as to whether LR should be performed was at the surgeon's discretion after discussion with patient. Data were collected in a prospectively maintained database that was supplemented by a retrospective chart review.

2.3. Pre-operative Staging Work-up

Evaluation included physical examination, colonoscopy with biopsy, abdominal and pelvic computed tomography (CT) scan. Pelvic magnetic resonance imaging was routinely performed for rectal cancer patients. Serum level of carcinoembryonic antigen (CEA) was sampled before operation. Pre-operative clinical oncologic staging

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was classified by tumor node metastasis (TNM) system of the International Union Against Cancer (not listed in Table 1).

2.4. Surgical Techniques

All LR and OR procedures were proceeded with a standardized medial-to-lateral approach and non-touch technique. During LR surgery, the surgeon and camera operator stood on the opposite side of the colorectal lesion, while the first assistant positioned to the same side of the lesion. Briefly, right hemicolectomy including range extended to mid-transverse colon with lymphadenectomy about ileocolic, right colic, and middle colic vessel origin was selected for proximal lesions (those sited proximal to flexure of spleen). Left hemicolectomy with lymphadenectomy at the level of left colic and the left branch of the middle colic vessel origins was selected for lesions at descending colon. The omentum was transected to allow entry into the omental bursa and mobilization of the liver flexure (right hemicolectomy) or splenic flexure (left hemicolectomy). As lesions of sigmoid colon or rectosigmoid junction, sigmoid colectomy with upper rectum resection and lymphadenectomy extended to inferior mesenteric vessel origin were selected. At least 5 cm safety surgical clearance margin were mandatory for all patients. As for rectal cancer, the technique was standardized as follows: (1) for upper third rectal lesions, a 5-cm mesorectal resection

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with end-to-end colorectal anastomosis was done, (2) for mid and low rectal lesions, total mesorectal excision with pouch supra-anal or anal anastomosis was performed, and (3) abdominoperineal excision was indicated once the levator muscle was involved by tumor. According to the principle of non-touch technique, high ligation of the inferior mesenteric artery and mobilization of the splenic flexure were systematically performed first, whether the procedures were performed in LR or OR group. Dissected tissue was pulled out via a wound retractor at extended umbilical wound for abdominal wall protection. For proximal lesions, anastomosis was routinely performed extra-corporeally. We routinely performed trans-anally intra-corporeal circular stapled anastomosis after descending colon, sigmoid colon or rectum lesion resection. In OR group, the procedures were finished through a midline laparotomy with the same rules and the wound was protected by gauze covering. However, we generally used Harmonic scalpel for soft tissue dissection in LR group but not in OR group.

2.5. Post-operative Management

Post-operative treatment was the same for both groups. Patients were discharged when they had sufficient oral intake, well-controlled complications or no complications. Complications designated as more severe than grade I according to the

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Clavien–Dindo classification system were categorized as ileus, urinary tract infection, wound infection, pneumonia, anastomotic leakage, etc.

2.6. Post-operative Follow-up

One specialized pathologist assessed all specimens. All patients were followed up with clinical examination, serum CEA assay, chest X-ray exam every 3 months, and liver ultrasound every 6 months for the first 2 years, and then annually. An abdominal computed tomography was examined annually. A colonoscopy was performed at 1 year after operation, then every 3 years.

2.7. Statistical Analysis

The main endpoint of this study was cancer-free 5-year survival. Secondary endpoint was incidence of tumor recurrence. Predefined baseline variables were listed in Tables 1 and 2. For the univariate analysis were gender, age, American Society of Anesthesiologists (ASA) class, tumor location, TNM stage, histopathology, pre-surgery serum CEA level, type of intervention, postoperative complications and tumor recurrence. Categorical variables were compared by means of the x^2 test. Continuous variables (e.g. number of lymph nodes removed, hospitalization period, intra-operative blood loss and operation time) were compared by means of the Student

t test. Survival period was evaluated from day of surgery to the last visit or death. For cancer-free survival, patients dying by other reasons were censored at the time of death. Probability curves were constructed according to the Kaplan-Meier method and compared with the log-rank test (Table 3)(Figure 2). *P* value of less than 0.05 was regarded as statistically significant. All calculations were performed by using the SPSS software package version 20 (SPSS Inc., Chicago, IL).

3. Results

3.1. Baseline Characteristics of Patients

Basic profile of this study was shown in Figure 1. Initially, 375 colorectal cancer patients under Dr. Chiu's service were sorted. Of these, 11 were excluded from the study. Total 364 patients receiving curative resection were assessed in this study: 195 were managed by LR and 169 by OR. Carcinomatosis were detected intra-operatively in 7 patients of LR and 6 patients of OR, which were also excluded. The remaining patients were compliant with the follow-up protocol. Median surveillance period was about 60 months.

In Table 1, we found that both groups of patients were well matched in terms of demographic and clinicopathologic parameters. During this study period, we analyzed 188 patients of LR group compared with the data obtained from other 163 patients of

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OR group. In LR group, the mean age was 68.6 ±12.7 years and 102 (54.3%) were male. Three patients were classified in stage 0, 68 in stage I, 30 in stage II, 87 in stage III. In OR group, the mean age was 71.5 ±12.1 years and 87 (53.4%) were male, none was affected by tumors in stage 0, 53 in stage I, 29 in stage II, 81 in stage III. Other characteristics of tumors and patients were summarized and there was no statistical difference between these two groups.

3.2. Surgical Outcomes

In Table 2, the rate of tumor recurrence was 9.0% (17/188) in the LR and 13.5% (22/163) in the OR. Although the difference was not statistically significant, tumor recurrence seemed to be lower in the LR group (p=0.186). Average number of lymph nodes removed in LR was 16.0 ± 9.2 and 19.2 ± 13.7 in OR (p=0.07). Tumor margins were clear in all patients of both groups. However, this study demonstrated LR was more effective for treatment of colorectal cancer in terms of hospital stay (p<0.001) and blood loss (p<0.001). Conversely, operation time was significantly longer in the LR than OR (191.4 ± 71.1 minutes vs. 150.8 ± 46.3 minutes, p<0.001). Compared with the LR group, more patients in the OR group encountered postoperative urinary tract infection, wound infection, pneumonia and anastomosis leakage rate, which reached statistical significance. About these two leakage patients, only mild leakage

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was found and no further surgical intervention was needed.

3.3. Cancer-free Survival Rates and Tumor Recurrence Incidence

In Table 3, twenty-one patients (11.2%) of the LR group and 32 patients (19.6%) of the OR group expired. There was a trend of higher overall mortality in the OR group, whereas 4 in stage I, 5 in stage II, and 23 in stage III, but it was not statistically different. In stage 0, there were only three patients in the LR group and none in the other. All three patients survived more than five years after surgery. In stage I, all four deaths of the OR group were non-cancer related. All patients survived for at least 30 months after surgery. In stage II with two patients in the OR group died within second year after surgery, but they were non-cancer related. Others died later in both groups were all cancer-related. In stage III patients, all eighteen deaths in the LR group and twenty-three deaths in the OR group were cancer related. Two cancer recurrent OR patients died fewer than 6 months after a second oncologic surgery, about three years after previous surgery.

There was a phenomenon of a higher cancer-free 5-year survival in stage I (p=0.206, Figure 2 (A)), stage II (p=0.713, Figure 2 (B)), stage III (p=0.426, Figure 2 (C)) and all stages (p=0.328, Figure 2 (D)) in the LR group when compared with the OR group, although the difference was not statistically significant.

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At the conclusion of follow-up, we noted the median time for tumor recurrence was 57.0 months (range 25–68 months) in LR and 53.5 months (range 25–63 months) in OR. Importantly, no difference was observed in the cumulative incidence of recurrence between two groups (p=0.186)(Figure 3). Besides, there was no incidence of port-site recurrence in the LR group, or wound recurrence in the OR group.

4. Discussion

Previously randomized controlled studies demonstrated that LR benefits favorable operative outcomes with less pain, quick recovery of the gastrointestinal tract, a shorter hospital stay and better cosmetics when compared with OR [19,20]. Moreover, a meta-analysis [21] and two large retrospective studies [22,23], which included a large number of patients, also showed a significant reduction in mortality rate and lower morbidity after LR.

However, survival is the most important concern for assessing success for malignant disease treatment. In our study with a 60-month follow-up comparing LR and OR for non-metastatic colorectal cancer, we noted cancer-related survival and incidence of tumor recurrence favored the LR group, despite there was no statistically significant difference regarding the oncological results. Clinical Outcome of Surgical Therapy study, which was the largest randomized controlled trial so far, also showed

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the same results like ours and even overall survival between the two groups after a median 4-year follow-up [2]. However, in a single institution randomized study, Lacy et al. advocated that there was a cancer-related survival advantage after LR for stage III colon cancer patients [24]. Capussotti et al. also demonstrated that LR was related to significantly better disease-free and cancer-related survival stage III colon cancer patients [25]. Other studies have reported better survival for patients undergoing LR, even for those with stage II colorectal cancer [26].

One of the assumptions about better survival might be the number difference in dissected lymph nodes between the LR and OR groups. Laparoscopy provides a better visualization of intra-abdominal conditions [27], including a wider, clearer and brighter image to allow surgeons to perform a more radical and precise resection of the mesocolon and mesorectum, while facilitating an accurate and complete lymphadenectomy [28,29]. Complete lymphadenectomy for colorectal cancer is essential for the patient's oncological prognosis due to reduced risk of residual nodal disease, and accurate nodal staging (achieving a better stratification of tumor staging) [19]. We noted no statistical difference in lymph node retrieval number between our two groups. Besides, the retrieved and assessed lymph node number was higher than the threshold of 12 lymph nodes recommended by the American Joint Committee on Cancer (AJCC) in our study.

Other proved benefits in oncologic results about LR includes its effect on cellular immunity, intra-operative tumor manipulation, related stress response and subsequent cytokine release, surgical complication rate, and blood transfusion amount [24]. Conclusively, one of the most essentially beneficial theories of LR is regarded as preservation of patient's immunological response against cancer from the first postoperative days [30]. There has been significant evidence of that surgical stress interferes with immunity and this phenomenon is more apparent in OR than in LR [31]. The role of immunosuppression has been advocated because immunologic response mediators (*e.g.* C-reactive protein, interleukin 1–6, and tumor necrosis factor alpha) are apparently decreased after LR in colorectal surgery than in OR approach. On the other hand, immunosuppression deteriorates both sepsis and cancer cell proliferation [32]. Lacy et al. have also pointed out that stress response of post- LR of colorectal cancer is less pronounced and finally leads to better preservation of cellular immune function and attenuated inflammatory mediator interference [33,34]. Correlation of the stress response degree after the trauma of surgery with the host resistance to cancer has been clearly proved in an animal model [24]. Immunity is a critical barrier against tumor progression and metastatic spread [31]. LR could therefore theoretically increase either overall or cancer-free survival.

Tumor manipulation has been proved to contribute cancer cell spread. In fact,

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there is some evidence that tumor mobilization is related to cancer cells exfoliation into the peritoneal cavity and portal vein bloodstream migration, which might be alleviated by non-touch surgical techniques or avoidance of tumor manipulation. Preliminary reports have shown that cancer cell spread is not made worse [35], and dissemination of cancer cells is reduced by LR [31]. However, in our study we are unable to assess these phenomenons. Under laparoscopic vision, limited access inside abdominal cavity leads to minimal tumor handling and compliance of non-touch technique, both favoring the important oncology principle to avoid tumor cell spread during surgery. Our patients received non-touch isolation techniques in both LR and OR groups. So we think there is no difference of manipulation effect in our two groups.

There is evident statistical difference in fewer complication rates, and amount of blood loss in our LR than OR group. These factors theoretically contribute to better prognosis of tumor recurrence and cancer-free survival in LR patients. Despite the differences regarding the oncological results did not reach statistical significance of our both groups, other better short-term outcomes, including smaller incisions, lesser postoperative pain, quicker functional recovery, shorter hospital stays, and earlier return to normal activity, suggested colorectal cancer patients receiving LR if not contraindicated.

Several experienced colorectal surgeons pointed out that most colectomies could be performed with an abdominal wound of less than 7 cm and thus opposed the wound benefits of LR [36]. However, the advantages of LR for colorectal cancer not only include comparatively smaller wound size, but also relate to the properties of laparoscopy, especially the operation field magnification, more precise tumor resection and its minimal invasiveness [5].

In fact, application of LR for colorectal cancer encountered much criticism in the early 1990s due to several case reports about port site recurrence and suspicion of adverse effect of oncologic outcome [23]. However, many surgeons advocated that LR did not aggravate cancer cell spillage intra-corporeally when surgeons followed the oncologic principles strictly [5]. However, routine practice of laparoscopic technique in colorectal cancer treatment is still performed in a few experienced centers in Taiwan. The phenomenon of slow popularity of this minimally invasive technique reflects its complexity, especially at the initial stage of learning curve; the lack of three-dimensional visualization, the absence of safe laparoscopic instruments, and the paucity of tactile feedback are still usually the causes of barrier of popularity and the causes of conversion during surgery [37]. Moreover, practicing a new or pioneer surgical technique on patients with malignant disease is not permitted in the ethical aspect. Many experts pointed out that the learning curve for laparoscopic

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colorectal surgery is about greater than twenty cases [38]. However, safety control, quality monitor and technique standardization applied to the surgical aspects of the study would make a solution to learning curve issues by collaboration of interested experts to set up safe and reproducible experiment steps even in the setting of new technology [39].

Compared with previously published randomized studies in the literature, there were some weak points of our present study that needed to be further addressed. Admittedly the patient number included in this study was too small (only 351 patients) for comparison of the oncological outcomes; we should increase the sample size to make a reliable comparison between these two groups and wound avoid the related bias.

Meanwhile, our study included all colorectal cancers at different sites for analysis of oncologic outcomes and functional results. This study design was debatable because the lymphatic drainage route, range of dissection during tumor resection, operation technique, and even the biologic behavior were not the same in various colorectal locations [5]. However, all patients of LR and OR groups were performed by a single surgeon and there was no related bias of this aspect.

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5. Conclusions

Within the limitations of our study, our results showed better short-term outcomes in terms of complications and blood loss in LR versus OR for non-metastatic colorectal cancer. Despite the differences regarding cancer-free 5-year survival and tumor recurrence did not reach statistical significance of our both groups, we recommended patients receiving LR as possible if not contraindicated.

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Author Contributions

Chong-Chi Chiu performed the operations, cared the patients, designed the study, obtained IRB approval, wrote the first and final draft; **Wen-Li Lin** collected clinical records and analyzed the statistical data; **Hon-Yi Shi** assisted the statistical data analysis; **Chien–Cheng Huang** managed patients in emergency room; **Jyh-Jou Chen** performed pre-operative colonoscopy exams; **Shih-Bin Su** performed stool occult blood screening; **Chih-Cheng Lai** and **Chien-Ming Chao** cared patients after

operation; **Chao-Jung Tsao** and **Shang-Hung Chen** performed chemotherapy or concurrent chemoradiotherapy for patients; **Jhi-Joung Wang** provided critical feedback, supervision and opinion of this study**.**

Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

Figure and Table Legends

Figure 1 The flowchart of the study design

Table 1 Comparison of baseline characteristics between laparoscopic resection (LR) versus open resection (OR)

Table 2 Comparison of surgical outcomes between laparoscopic resection (LR) versus open resection (OR)

Table 3 Cancer-free survival rates between laparoscopic resection (LR) versus open resection (OR)

Figure 2(A) Kaplan-Meier curve of cancer-free 5-year survival in stage I patients (p=0.206)

Figure 2(B) Kaplan-Meier curve of cancer-free 5-year survival in stage II patients (p=0.713)

Figure 2(C) Kaplan-Meier curve of cancer-free 5-year survival in stage III patients (p=0.426)

Figure 2(D) Kaplan-Meier curve of cancer-free 5-year survival in all stage patients (p=0.328)

Figure 3 Cumulative incidence curve of tumor recurrence in all stage patients (p=0.186)

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