

Laparoscopic surgery is feasible for the treatment of rectal cancer after neoadjuvant chemoradiotherapy

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Abstract: This case-control study aimed to clarify the short- and long-term outcomes of laparoscopic surgery for rectal cancer after neoadjuvant chemo radiotherapy compared with conventional open resection. Between January 2008 and December 2014, a series of 227 patients with rectal cancer underwent radical surgery after neoadjuvant chemo radiotherapy. Age, gender, American Society of Anesthesiologists score, clinical stage, and type of resection were matched by propensity scoring and 106 patients (53 patients with laparoscopic total mesorectal excision and 53 patients with open resection) were selected for analysis. There were no significant differences in the clinicopathological features between the two groups. With regard to short-term outcomes, blood loss, postoperative analgesia and hospital stay were significantly shorter in the laparoscopy group than in the open group, whereas operative time was significantly longer in the laparoscopy group than in the open group. The overall morbidity was similar in the two groups. There were no significant differences in the 5-year overall and disease-free survival rates between the two groups. In summary, laparoscopic surgery may be both feasible and efficient compared with open resection for rectal cancer after neoadjuvant chemo radiotherapy.

Keywords: laparoscopy; minimally invasive surgery; neoadjuvant chemo radiotherapy; rectal cancer; long-term outcomes

INTRODUCTION

Laparoscopic surgery is revolutionizing surgery worldwide (Ghoneum *et al.*, 2015; Liu *et al.*, 2016; Mellotte *et al.*, 2015; Morise *et al.*, 2016), particularly in areas with high rectal cancer incidence. In literature, reports regarding laparoscopic techniques for treating patients with clinical stage I (cT1-2N0M0) rectal cancer have shown equivalent oncological outcomes to the open technique, with known benefits of a minimally invasive approach, including less pain, earlier recovery, shorter hospital stay, and better quality of life. However, applying laparoscopic techniques for locally advanced rectal cancer after neoadjuvant chemo radiotherapy is controversial because of the technical difficulty, possibility of port site seeding of malignant cells, and insufficient data regarding the procedure's oncological adequacy. Here we described our experience with laparoscopic surgery for treating locally advanced rectal cancer after neoadjuvant chemo radiotherapy and evaluated the short- and long-term outcomes of this approach through a case-control study.

MATERIAL AND METHODS

From January 2008 to December 2014, 83 patients with rectal cancer underwent laparoscopic surgery following neoadjuvant chemo radiotherapy, whereas 144 cases underwent open surgery, which was performed by an

exclusive surgical team. The patients selected their surgical procedures (laparoscopic surgery or open resection) after obtaining informed consent following detailed explanations of the advantages, disadvantages, and any possible outcomes of each procedure. Inclusion criteria were as follows: histologically confirmed rectal cancer, ECOG 0-1 performance status, no evidence of distant metastasis or invasion to adjacent organs, cT3N1-2M0 clinical stage, and following neoadjuvant chemo radiotherapy. All patients underwent radical resection. The exclusion criteria included procedures that were performed under emergency conditions such as bleeding or perforation and patients who were referred for palliative surgery. Based on the inclusion and exclusion criteria, those meeting the requirements were included in the propensity score matching. The propensity score for an individual was calculated based on the covariates of age, gender, American Society of Anesthesiologists (ASA) score, clinical stage, and type of resection using a multivariable logistic regression model. Using these propensity scores, we finally compared the 53 patients undergoing laparoscopic surgery with the 53 matched patients undergoing open surgery with respect to short- and long-term outcomes.

All patients underwent endoscopy; endoscopic ultrasonography; magnetic resonance imaging of pelvis; computed tomographic scans of the brain, chest, pelvis and abdomen; and ultrasonography of the abdomen to determine the clinical stage and exclude the presence of

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clinical metastases (Liu *et al.*, 2016; Wu 2016; Yung *et al.*, 2015; Zheng *et al.*, 2015). Positron emission tomography-computerized tomography (PET-CT) was performed in selected cases when required.

Clinical staging of rectal cancer was performed according to the 7th edition of the TNM classification of colorectal cancer, which was proposed by the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) (Aldea *et al.*, 2016; August *et al.*, 2016; Brenner *et al.*, 2014). For patients who were operated before 2010, staging was recalculated to match the latest TNM classification by UICC and AJCC.

Patients with clinical T3, T4, or N+ disease were considered for neoadjuvant chemo radiotherapy. Radiotherapy was administered to the entire pelvis at a dose of 45 Gy in 25 fractions, followed by a boost of 5.4 Gy to the primary tumor in three fractions over 5.5 weeks. 5-Fluorouracil or Xeloda-based chemotherapy was administered (Phang and Wang 2014; Weiser *et al.*, 2014). Surgery was performed 6–8 weeks after administration of the neoadjuvant therapy (Laurent *et al.*, 2009). Laparoscopic surgery was performed using five trocars. The rectum was mobilized and dissection was performed between the visceral and parietal pelvic fascia without injuring the hypogastric nerves. Details of the laparoscopic or open resection procedures have been described elsewhere (Laurent *et al.*, 2009).

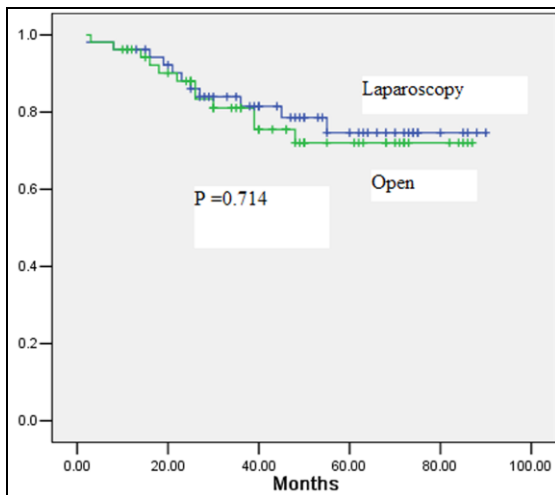


Fig. 1: Comparison of overall survival rate between laparoscopy group and open group. There was no significant difference between the 2 groups ($P=0.714$).

Postoperative complications, including morbidity occurring within 30 postoperative days or during the hospital stay, were graded according to the Clavien–Dindo classification (Othman *et al.*, 2015). Major complications were defined according to grades 3b, 4a, 4b, and 5. Minor complications were classified as 1, 2, and 3a. Operative death was defined as mortality within 30 days or hospital stay after surgery (Chen *et al.*, 2016;

Guo *et al.*, 2015; Imada *et al.*, 2016; Jin *et al.*, 2016; Qian *et al.*, 2016; Sheng *et al.*, 2015; Spiliotis *et al.*, 2016; Tsiaras *et al.*, 2016; Yamada *et al.*, 2016; Zaharie *et al.*, 2015).

During the first year after treatment completion, patients were observed every 3 months at the outpatient department. In the second year, follow-up occurred every 6 months, after which follow-up was performed at the end of each year after treatment. During follow-up, diagnostic investigations were performed. Disease recurrence was defined as the presence of locoregional or distant metastases as evidenced by radiological or pathological findings (Cahill *et al.*, 2015; Dobson *et al.*, 2015; Lee *et al.*, 2015; Sterling *et al.*, 2015; Toyozumi *et al.*, 2016). The last follow-up occurred in September 2015.

Analysis was performed using the SPSS 13.0 software (SPSS Inc., Chicago, IL, USA). Variables were presented as mean and standard deviations for variables following normal distribution and were analyzed using *t* test. For variables following non-normal distribution, data were expressed as median and range and were compared using nonparametric tests. Differences in the semiquantitative results were analyzed using the Mann–Whitney *U*-test, whereas differences in qualitative results were analyzed using the chi-square or Fisher exact tests. Survival rates were analyzed using the Kaplan–Meier method and differences between the two groups were analyzed using the log-rank test. The overall survival was assessed from the date of surgery until the last follow-up or death from any cause. The disease-free survival was calculated from the date of surgery until the date of cancer recurrence or death from any cause. Prognostic factors for overall and disease-free survival were analyzed using the Cox regression model. All statistical tests were two-sided, with the threshold of significance set at $P<0.05$ level.

RESULTS

As shown in table 1, there were no significant differences in the clinical features between the laparoscopic and open surgery groups, including age, sex ratio, ASA score, body mass index, clinical stage, comorbidity disease, and type of resection (table 1). The surgical outcomes of both cohorts were summarized in table 2. The operative time for laparoscopic surgery was longer compared with that for open resection ($P=0.013$). The blood loss ($P=0.000$), use of analgesia ($P=0.000$), and hospital stay ($P=0.009$) after laparoscopic surgery were lesser than those after open surgery, which were among the advantages of laparoscopic surgery. No hospital stay or death after 30 days occurred in this study. Although postoperative morbidity was less frequently noted in the laparoscopy group, the difference was not statistically significant ($P=0.278$).

A pathologist who specialized in colorectal disease performed the pathological analysis. The pathological

Table 1: Demographic data

	Laparoscopy (n=53)	Open (n=53)	P value
Age (y)	56.0 (43-72)	56.0 (42-75)	0.653
Gender (Male: Female)	39: 14	37: 16	0.666
Comorbidity			
Hypertension	3	2	0.648
Diabetes Mellitus	5	4	
Liver cirrhosis	1	3	
Chronic cholecystitis	2	1	
BMI (kg/m ²)	22.0 (18-26)	24.0 (20-30)	
Clinical stage (cTNM)			
II	34	32	0.690
III	19	21	
ASA score			
I	35	37	0.641
II	16	15	
III	2	1	
Surgical procedure			
Anterior resection	5	6	0.750
Abdominoperineal resection	48	47	

BMI: body mass index

Table 2: Surgical data

	Laparoscopy (n=53)	Open (n=53)	P value
Operative time (min)	200.0 (160-240)	190.0 (150-230)	0.013
Blood loss (ml)	180.0 (100-240)	220.0 (160-390)	0.000
Post-operative analgesia needed	2.0 (1.0-3.0)	4.0 (2.0-5.0)	0.000
Post-operative hospital stay (d)	11.0 (10-23)	14.0 (11-24)	0.009
Post-operative complications	6	10	0.278
Severity of complications			
Major (3b, 4a, 4b and 5)	1	3	0.713
Minor (1, 2 and 3a)	5	7	

data did not differ between the two groups with respect to histologic differentiation, circumferential resection margin, excised lymph nodes, surgical margins, and pathological TNM stage (7th AJCC–UICC).

After a median follow-up of 40 months, the 5-year overall survival rate in the laparoscopy group was 75%, compared with 73% in the open group. The overall survival analysis shown in fig. 1 indicated no significant differences in the overall survival rate between both groups ($P=0.714$). The disease-free survival rate was 70% and 67% in the laparoscopy and open groups, respectively, with no significant differences between both groups (fig. 2, $P=0.750$). Recurrent tumors developed in 7.5% and 11.3% of patients in the laparoscopy and open groups, respectively. There were no significant differences between the two groups with respect to the sites of recurrence. With regard to prognostic factors for overall survival, age, adjuvant therapy, and pathological T and N stages were identified as prognostic factors during univariate analysis. In the multivariate analysis, the pathological T and N stages were independent prognostic factors.

DISCUSSION

Recently, there have been several reports on the safety and feasibility and short-term outcomes of laparoscopic surgery after neoadjuvant chemo radiotherapy for patients with rectal cancer (Akiyoshi *et al.*, 2009; Hu *et al.*, 2014; Kang *et al.*, 2010; Liu *et al.*, 2016). However, few studies have been reported, most of which did not have large sample sizes and long-term follow-up results (Jeong *et al.*, 2014).

In China, rectal cancer is one of the most common neoplasms and the fourth most frequent cause of cancer-related deaths. This study was designed to compare the outcomes of laparoscopic and open surgeries for locally advanced rectal cancer after neoadjuvant chemo radiotherapy with regard to short-term outcomes and survival rates. In the present study, laparoscopic surgery was associated with significantly less blood loss and analgesia and shorter hospital stay, but longer operative time compared with open surgery. Consequently, we observed that laparoscopic and open surgeries had similar morbidity and mortality rates, with comparable oncological outcomes between both groups.

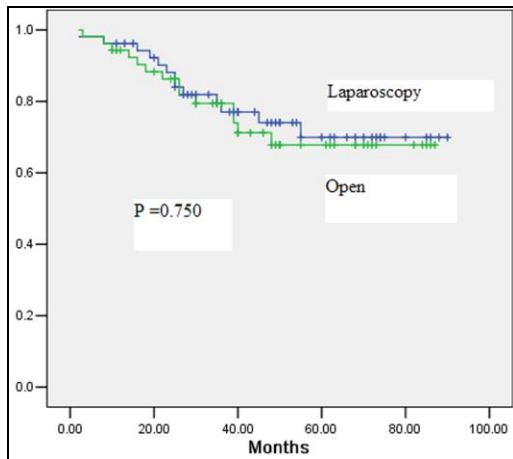


Fig. 2: Kaplan-Meier disease-free survival curves of the laparoscopy group and the open group. No significant difference was observed ($P=0.750$).

Operative time was longer in our series of laparoscopic surgeries for locally advanced rectal cancer after neoadjuvant chemo radiotherapy, whereas median blood loss was remarkably lower than that of open resection. We expect that this issue will be resolved in the near future by improvements in laparoscopic devices and techniques. However, reduction of tissue trauma is clearly one of the benefits of laparoscopic surgery. Patients undergoing laparoscopic surgery experienced fast recovery. The median hospital stay after laparoscopic surgery was shorter than that after open surgery, but relatively longer than that with regard to other series from Eastern and Western centers (Akiyoshi *et al.*, 2009; Hu *et al.*, 2014; Kang *et al.*, 2010; Liu *et al.*, 2016). This longer hospital stay may be explained by differences in healthcare structures. In China, where rehabilitation centers are not well developed, most patients are discharged from the hospital when their condition recovers. Nevertheless, there are clear benefits with regard to postoperative hospital stay after laparoscopic surgery.

To date, there have been few studies comparing the oncological outcomes of patients undergoing laparoscopic and open surgeries for treating locally advanced rectal cancer after neoadjuvant chemo radiotherapy. Although oncological safety appeared identical between the groups, these studies only involved small samples sizes and shorter follow-ups. Our study reported the results of a series of 106 consecutive patients who underwent laparoscopic surgery and open resection for locally advanced rectal cancer following neoadjuvant chemo radiotherapy. All patients were treated with curative intent. Direct comparison of other results with our series is difficult; however, the rate of 5-year overall survival from our series appeared to be comparable to those of previous studies from specialized Eastern and Western centers. Although our study was limited by the nature of our consecutive but retrospective study design and

potential bias in the patient selection criteria, the current data support the concept that laparoscopic surgery is an oncologically safe treatment for locally advanced rectal cancer following neoadjuvant chemo radiotherapy.

We realize the limitations of our study. Furthermore, because this is a retrospective study from a single center, our findings may be limited by the retrospective nature of the analysis. Therefore, we included all consecutive patients who met the inclusion and exclusion criteria between January 2008 and December 2014 to avoid any selection bias. Furthermore, although characteristics (age, gender, ASA score, clinical stage, and type of resection) were well-balanced between both groups, we did not consider several potential confounding factors such as histological type and tumor location (upper, middle, or lower rectum), which are not expected to have significant clinical roles in influencing the results of this study. Moreover, although this case-control study presented with acceptable outcomes of laparoscopic surgery for treating rectal cancer after neoadjuvant chemo radiotherapy, our results only indicated the correlation between surgical procedures and survival rate, but not the actual influence of laparoscopic surgery on long-time outcomes. A randomized controlled trial with longer follow-up and a large sample size is required to further confirm the results reported in this study.

CONCLUSION

In conclusion, this preliminary retrospective study was informative and suggests that laparoscopic surgery for locally advanced rectal cancer after neoadjuvant chemo radiotherapy produces acceptable short-term outcomes, is safe, and produces good long-term oncological outcomes. Further randomized trials will provide valuable evidence for the oncological safety of laparoscopic surgery for treating locally advanced rectal cancer after neoadjuvant chemo radiotherapy.

REFERENCES

- Akiyoshi T, Kuroyanagi H, Oya M, Konishi T, Fukuda M, Fujimoto Y, Ueno M, Yamaguchi T and Muto T (2009). Safety of laparoscopic total mesorectal excision for low rectal cancer with preoperative chemo radiation therapy. *J. Gastrointest. Surg.*, **13**(3): 521-525.
- Aldea M, Worni M and Dedivitis RA (2016). Medical comorbidities in surgical oncology. *Asian Pac. J. Surg. Oncol.*, **2**(3): 163-172.
- August DA, Kallogjeri D, Lewison G and Chen X (2016). Nutrition support in surgical oncology. *Asian Pac. J. Surg. Oncol.*, **2**(3): 153-162.
- Brenner H, Kloor M and Pox CP (2014). Colorectal cancer. *Lancet*, **383**(9927):1490-1502.
- Cahill G, Tran L, Baker RA, Brown A, Huang YC and Ou CW (2015). Principles of radiation oncology. *Asian Pac. J. Surg. Oncol.*, **1**(1): 27-38.

- Chen XL, Wang P and Lai EC (2016). Current advances in minimally invasive surgery for esophageal carcinoma. *Asian Pac. J. Surg. Oncol.*, **2**(4): 237-250.
- Dobson PR, Brown BL, Beck D, Yang H, Zhou J and Voon YL (2015). Management of surgical oncologic emergencies. *Asian Pac. J. Surg. Oncol.*, **1**(2): 59-72.
- Ghoneum M, Felo N, Nwaogu OM, Fayanju IY, Jeffe JA and Margenthaler DB (2015). Clinical trials in surgical oncology. *Asian Pac. J. Surg. Oncol.*, **1**(2): 73-82.
- Guo C, Zhang Z, Ren B and Men X (2015). Comparison of the long-term outcomes of patients who underwent laparoscopic versus open surgery for rectal cancer. *J. BUON.*, **20**(6): 1440-1446.
- Hu JJ, Liang JW, Wang Z, Zhang XM, Zhou HT, Hou HR and Zhou ZX (2014). Short-term outcomes of laparoscopic ally assisted surgery for rectal cancer following neoadjuvant chemo radiotherapy: A single-center experience. *J. Surg. Res.*, **187**(2): 438-444.
- Imada T, Yukawa N, Nakatsuji M, Tan B, Tan JY and Fock KM (2016). Lymph node dissection for gastric cancer. *Asian Pac. J. Surg. Oncol.*, **2**(2):101-120.
- Jeong SY, Park JW, Nam BH, Kim S, Kang SB, Lim SB, Choi HS, Kim DW, Chang HJ, Kim DY, Jung KH, Kim TY, Kang GH, Chie EK, Kim SY, Sohn DK, Kim DH, Kim JS, Lee HS, Kim JH and Oh JH (2014). Open versus laparoscopic surgery for mid-rectal or low-rectal cancer after neoadjuvant chemo radiotherapy (COREAN trial): Survival outcomes of an open-label, non-inferiority, randomised controlled trial. *Lancet Oncol.*, **15**(7): 767-774.
- Jin XL, Guo Y, Ye M, Shibasaki H and Davidson LE (2016). Outcomes of gastric cancer Resection in elderly. *Asian Pac. J. Surg. Oncol.*, **2**(2): 143-152.
- Kang SB, Park JW, Jeong SY, Nam BH, Choi HS, Kim DW, Lim SB, Lee TG, Kim DY, Kim JS, Chang HJ, Lee HS, Kim SY, Jung KH, Hong YS, Kim JH, Sohn DK, Kim DH and Oh JH (2010). Open versus laparoscopic surgery for mid or low rectal cancer after neoadjuvant chemo radiotherapy (COREAN trial): short-term outcomes of an open-label randomised controlled trial. *Lancet Oncol.*, **11**(7): 637-645.
- Laurent C, Leblanc F, Wütrich P, Scheffler M and Rullier E (2009). Laparoscopic versus open surgery for rectal cancer: long-term oncologic results. *Ann. Surg.*, **250**(1): 54-61.
- Lee R, Yeung AW, Hong SE, Brose MS and Michels DL (2015). Principles of medical oncology. *Asian Pac. J. Surg. Oncol.*, **1**(1): 39-46.
- Liu HP, Ichikawa Y, Nagano Y and Shiono S (2016). Surgery for colorectal cancer lung metastases. *Asian Pac. J. Surg. Oncol.*, **2**(3): 183-192.
- Liu K, Chen XZ, Nakamura I, Ohki S and Eslick GD (2016). Laparoscopic surgery for gastric cancer: Survival outcome and prognostic factor. *Asian Pac. J. Surg. Oncol.*, **2**(2): 135-142.
- Mellotte G, Maher V, Devitt PG, Shin VY and Leung CP (2015). Minimally invasive surgical oncology: State of the art. *Asian Pac. J. Surg. Oncol.*, **1**(2): 101-112.
- Morise Z, Kayaalp C and Nakatsuji M (2016). Laparoscopic surgery for operable colon cancer: State of the art. *Asian Pac. J. Surg. Oncol.*, **2**(1): 25-36.
- Othman N, Nagoor NH, Pongrakhananon V, Chang JY, Peterson DR and Siddik ZH (2015). Mediastinal lymph node dissection in non-small cell lung cancer. *Asian Pac. J. Surg. Oncol.*, **1**(3): 141-156.
- Phang PT and Wang X (2014). Current controversies in neoadjuvant chemo radiation of rectal cancer. *Surg. Oncol. Clin. N. Am.*, **23**(1): 79-92.
- Qian YN, Tang QF, Lee JH and Han S (2016). Outcomes of radical esophagectomy for esophageal squamous cell carcinoma. *Asian Pac. J. Surg. Oncol.*, **2**(4): 251-260.
- Sheng W, Zhang B, Chen W, Gu D and Gao W (2015). Laparoscopic colectomy for transverse colon cancer: comparative analysis of short- and long-term outcomes. *Int. J. Clin. Exp. Med.*, **8**(9): 16029-16035.
- Spiliotis J, Efstathiou E, Matsubara A, Osman MM and Choo SP (2016). Molecular biology of gastric cancer. *Asian Pac. J. Surg. Oncol.*, **2**(2): 86-100.
- Sterling B, Cole R, Jen KK and Shieh JS (2015). Surgical oncology in the elderly. *Asian Pac. J. Surg. Oncol.*, **1**(2): 83-100.
- Tsiaras N, Nishi T and Takahashi T (2016). Radical surgery for esophageal carcinoma. *Asian Pac. J. Surg. Oncol.*, **2**(4): 225-236.
- Toyozumi T, Suito H, Chen L and Ando K (2016). Outcomes after radical esophagectomy for esophageal carcinoma in elderly patients. *Asian Pac. J. Surg. Oncol.*, **2**(4): 261-270.
- Weiser MR, Beets-Tan R and Beets G (2014). Management of complete response after chemo radiation in rectal cancer. *Surg. Oncol. Clin. N. Am.*, **23**(1): 113-125.
- Wu X (2016). Surgical management of colorectal cancer liver metastases. *Asian Pac. J. Surg. Oncol.*, **2**(3): 173-182.
- Yamada N, Maeda K, Sawada T, Jeong ID, Noh SH and Zhao Y (2016). Surgical management of gastric cancer. *Asian Pac. J. Surg. Oncol.*, **2**(2): 121-134.
- Yung KW, Yung TT, Chung CY, Tong GT, Liu Y, Henderson J, Welbeck D and Oseni S (2015). Principles of cancer staging. *Asian Pac. J. Surg. Oncol.*, **1**(1): 1-16.
- Zaharie F, Ciorogar G, Zaharie R, Mocan T, Zdrehus C, Mocan L, Berindan-Neagoe I, Achimas P, Iancu C and Tomus C (2015). Laparoscopic rectal resection versus conventional open approach for rectal cancer - a 4-year experience of a single center. *J. BUON.*, **20**(6): 1447-1455.
- Zheng YF, Tan LK, Tan BH, Sterling H and Kane R (2015). Principles of surgical oncology. *Asian Pac. J. Surg. Oncol.*, **1**(1): 17-26.

