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(Citation)

International Journal of Colorectal Disease, 34:1259-1265

(Issue Date)

2019-05-30

(Resource Type)

journal article

(Version)

Accepted Manuscript

(Rights)

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(URL)

<https://hdl.handle.net/20.500.14094/90008130>



Title

Outcomes of laparoscopic surgery for pathological T4 colon cancer

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Key words: Pathological T4, Colon Cancer, Laparoscopic Surgery, Colectomy

Abstract

Purpose: The surgical indication of laparoscopic surgery for pT4 colon cancer remains to be established because only a few studies have investigated the short- and long-term outcomes of laparoscopic surgery for them to date. Therefore, we aimed to elucidate the validity of laparoscopic surgery for them.

Methods: We retrospectively analyzed 81 patients with pT4 colon cancer who underwent surgical resection with a curative intent at Kobe University Hospital from January 2007 to December 2015. The short- and long-term outcomes were compared between the propensity score-matched patients who underwent laparoscopic colectomy (LAP group, n = 25) and those who underwent open colectomy (OP group, n = 25).

Results: Intraoperative blood loss was significantly less in the LAP group than in the OP group ($p = 0.029$). Operative time, R0 resection rate, and morbidity did not significantly differ between the two groups. The 5-year overall survival (OS) and the 5-year recurrence-free survival (RFS) did not significantly differ between the propensity score-matched groups. Univariate and multivariate analysis of entire cohort showed the surgical approach (LAP vs OP) selected was not a significant prognostic factor for OS or RFS.

Conclusions: The short and the long-term outcomes were similar between the LAP and OP groups. Laparoscopic surgery might be safe and feasible option for pT4 colon cancer patients.

Introduction

Colorectal cancer is a malignant tumor with a high prevalence worldwide. In fact, it is the third most diagnosed cancer in the world [1]. Although several treatment options for colorectal cancer, including chemotherapy, molecular targeted therapy, and radiotherapy, have emerged, surgical resection remains the only approach to achieve complete cure. Since the 1990s, when Jacobs for the first time reported the use of laparoscopic colectomy for colon cancer, laparoscopic surgery has become widespread [2]. Numerous studies had reported the safety and validity of laparoscopic surgery for colorectal cancer, with the same outcomes as those of open surgery. Additionally, in the majority of randomized trials, the short-term outcomes of laparoscopic surgery were better than those of open surgery [3, 4]. However, only a limited number of studies have reported the short- and long-term outcomes of laparoscopic surgery for pathological T4 (pT4) colorectal cancer. Therefore, no consensus exists regarding the surgical indication of laparoscopic surgery for pT4a/pT4b colorectal cancer [5–15]. In the present study, we aimed to elucidate the validity of laparoscopic surgery for pT4a/pT4b colon cancer by comparing the short- and long-term outcomes of patients with pT4 colon cancer who underwent laparoscopic or open surgery.

Materials and Methods

Patients

Patients with pT4a/pT4b colon cancer who underwent surgery at Kobe University Hospital from January 2007 to December 2015 were enrolled in this study. The study patients were staged according to the American Joint Committee on Cancer (AJCC) TNM classification system [16].

Between January 2007 and December 2015, 114 patients with pT4 colorectal cancer underwent colorectal resection. Of these, 5 patients who underwent recurrent tumor resection, 6 patients who presented with other concomitant cancers, 9 patients who underwent palliative surgery, and 13 patients who underwent proctectomy were excluded from the study. Then, 81 patients, including 46 patients who underwent laparoscopy surgery (LAP group) and 35 patients who underwent open surgery (OP group), remained. For adjusting heterogeneity between the treatment groups, propensity analyses were conducted. Propensity scores (i.e., predicted probability of receiving laparoscopic surgery) were generated based on confounding covariates including sex, age, BMI, tumor size, cStage. After propensity score matching, 25 matched pairs of patients were selected and analyzed by retrospective chart review.

Written informed consent for this publication was obtained from all patients. All procedures and subsequent analyses were performed with the approval of the Clinical & Translational Research Center of Kobe University

Hospital in Japan. The study was conducted in accordance with the guidelines of the 1975 Declaration of Helsinki, as revised in 2000 (5), concerning Human and Animal Rights.

Surgical procedure

All patients underwent surgical resection in conformity with the Japanese Society for Cancer of the Colon and Rectum guidelines [17]. Depending on the tumor site, the following methods of resection were adopted as required: ileocecal resection, right colectomy, transverse colectomy, left colectomy, descending colectomy, sigmoid colectomy, anterior resection, Hartmann's operation, and multivisceral resection. Ileocecal resection, right colectomy, and transverse colectomy were considered as right hemicolectomy (RHC), whereas left colectomy, descending colectomy, and sigmoid colectomy were considered as left hemicolectomy (LHC). Surgical approach whether laparoscopy or open was selected according to surgeon's preference. Open approach tended to be selected at the beginning of the cohort, whereas laparoscopic approach gradually increased later in the cohort. Conversion cases were analyzed as the LAP group.

Follow-up

All patients with high-risk stage II, III, or IV disease were recommended to receive adjuvant chemotherapy. If the patients agreed with chemotherapy, medical oncologists managed their chemotherapeutic regimen. The patients were followed up every 3 months for the first 2 years and at every 6 months thereafter. The follow-up program comprised physical examinations and blood tests, including tests for tumor markers, carcinoembryonic antigen, and carbohydrate antigen 19-9 (CA19-9), at each visit; thoracic and abdominal computed tomography at every 6 months; and total colonoscopy at every 2 years.

Statistical analysis

The data on clinicopathological characteristics were obtained by retrospective chart review. OS and RFS were derived from the Kaplan–Meier estimates. Additionally, univariate and multivariate analyses of the clinical factors were performed to predict the long-term outcomes, OS, and RFS.

Statistical analyses were performed using JMP 11.2.0 (SAS Institute Inc., Cary, NC, USA). Quantitative data were expressed as the median and range. Categorical data were compared by χ^2 test or Fisher's exact test. The OS and RFS rates were compared by log-rank test. Multivariate Cox proportional hazards regression analyses for predicting prognostic factors were reported as hazard ratio with 95% confidence interval. $P < 0.05$ was considered statistically significant.

Results

Table 1 summarizes demographic and tumor characteristics of the entire cohort patients and propensity score-matched patients. The mean tumor size was significantly larger ($p < 0.001$) and cStage tended to be advanced ($p = 0.068$) in the OP group before propensity score-matching. After propensity score-matching, these heterogeneity were balanced.

<Table 1 about here>

Table 2 presents the clinical data and the operative outcomes of propensity score-matched patients. Although the operative time did not differ between the groups, the estimated blood loss was significantly higher in the OP group. The number of patients who underwent multivisceral resection was greater in the OP group. In the LAP group, only 2 patients (8.0%) required conversion to open surgery. R0 resection was achieved in 68.0% and 48.0% of the patients in the LAP and OP groups, respectively.

<Table 2 about here>

The 5-year OS rate was 53.4% in the LAP group and 53.7% in the OP group ($p = 0.658$). The 5-year RFS rate was 62.3% in the LAP group and 48.6% in the OP group ($p = 0.434$) (Figure 1).

<Figure 1 about here>

Table 3 indicates the patterns of recurrence. The recurrence rates of propensity score-matched patients in the LAP and OP groups were 36.8% (7/19) and 50.0% (9/18), respectively, albeit with no significant difference ($p = 0.419$). The recurrence of liver, lung, or lymph node tended to develop more often in the OP group, while the local or peritoneal recurrence was more frequent in the LAP group, although these difference did not reach significance.

<Table 3 about here>

In univariate and multivariate analyses of entire cohort, the factors of age, CA 19-9, tumor location, and R0 resection were significant predictors of OS and the factors of age, CA19-9, tumor location, and pT were significant predictors of RFS. pT4a was a significant independent predictor of poorer RFS compared with pT4b. The surgical approach (LAP vs OP) selected was not a significant prognostic factor for OS or RFS (Table 4).

<Table 4 about here>

Discussion

Since several large clinical trials have reported the safety and favorable long-term outcomes of laparoscopic surgery for colorectal cancer compared with those of open surgery, laparoscopic surgery has become the standard procedure for colorectal cancer [18–20]. However, reports regarding the outcomes of laparoscopic surgery for pT4 colon cancer remain scarce [10, 11, 15]. As with previous reports, in terms of the short-term outcomes, laparoscopic surgery was not inferior to open surgery in this study. Intraoperative blood loss in the LAP group

was significantly less than that in the OP group, with no difference in the operative time. Because major blood loss has been demonstrated to be an independent prognostic factor for survival, less intraoperative blood loss in the LAP group should be a favorable result in terms of the long-term outcomes [21]. The conversion rate of surgery in this study was 8.0% (2 of the 25 patients in the LAP group), which was comparable with the conversion rate of 3.8% to 23% reported in previous studies [5–15]. The requirement of multivisceral resection (ileum or peritoneum) is the reason for the conversion.

Notably, no significant differences were noted between the groups in terms of postoperative complications.

Although the 5-year OS and 5-year RFS did not significantly differ between the propensity score-matched groups, entire cohort showed the local recurrence rate was significantly higher in the LAP group (10/36, 27.8%) than in the OP group (2/25, 8.0%) ($p = 0.045$). Multivariate analysis of clinical factors predicting local recurrence detected no independent prognostic factors including surgical approach, however, all 10 patients who had local/peritoneal recurrence in the LAP group showed pT4a. Fujii et al. compared laparoscopic colectomy group and open colectomy group of pStage II/III colon cancer, and revealed that the peritoneal recurrences of pT4 were higher in the laparoscopic colectomy group than the open colectomy group, which was presented at the annual meeting of the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) in 2016. Similarly, a large-scale phase 3 randomized controlled trial JCOG0404, in which survival outcomes following laparoscopic versus open colectomy for stage II or III colon cancer were investigated, revealed that patients with clinical T4 disease in the laparoscopic surgery group tended to show worse survival compared with those in the open surgery group [22]. Importantly, it is presumed that most of T4 patients were likely to be with T4a staging, because only patients with T4 disease without involvement of other organs were eligible in JCOG0404. Therefore, surgeons might be better to have caution for the indication of laparoscopic surgery for pT4a colon cancer. Large-scale analysis is warranted to investigate this in the future.

To date, only three studies have examined the prognostic factors for the outcomes of curative resection for pT4 colorectal cancer [11, 13, 15]. On the basis of the findings of these studies, we identified CA19-9 and tumor location as significant independent predictors for both OS and RFS, pN for RFS, and R0 resection for OS. Right-sided tumor was a significant independent predictor related to poor prognosis compared with left-sided tumor, which is consistent with the reports of previous studies on whole or metastatic colorectal cancers [23, 24]. Ishihara et al. [25] have reported that stage IV right-sided colon cancer showed a worse prognosis than left-sided colon cancer, suggesting that stage IV right-sided colon cancer is biologically more aggressive than left-sided colon cancer. Right-sided colon cancer is characterized by a high frequency of BRAF mutation, which is correlated with

worse prognosis [26–28]. Such biological characteristics may have resulted in the worse prognosis of the right-sided pT4 colon cancer in this study.

Interestingly, we identified pT4a as a significant independent predictor of poorer RFS compared with pT4b. Similarly, Kyang et al. [29] have reported that T4a tumors were prognostically worse in terms of peritoneal metastasis than T4b tumors. Thus, we ascertained that tumor cell spillage might develop more frequently in T4a tumor than in T4b tumor. However, further studies are warranted to arrive at a definitive conclusion.

In conclusion, this study revealed favorable short-term and long-term outcomes of laparoscopic surgery for patients with pT4 colon cancer. However, recurrence pattern might differ between the open and laparoscopic approaches for pT4 colon cancer, and further analysis was essential for more definitive conclusions.

Compliance with Ethical Standards

Conflict of Interest: The authors declare that they have no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Acknowledgements

The authors would like to thank Enago (www.enago.jp) for the English language review.

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Figure Captions

Fig. 1 Kaplan–Meier curves for the overall survival (OS) rates and the recurrence-free survival (RFS) rates of laparoscopic (LAP) and open colectomy (OP) groups

No apparent difference was noted between the two groups. The 5-year OS rate was 53.4% in the LAP group and 53.7% in the OP group ($p = 0.658$). The 5-year RFS rate was 62.3% the LAP group and 48.6% in the OP group ($p = 0.434$).