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# Long-term outcomes of laparoscopic versus open D3 dissection for stage II/III colon cancer: Results of propensity score analyses

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ABSTRACT

*Background:* Non-inferiority of the laparoscopic approach for stage II/III colon cancer has not been clearly established. This study aimed to evaluate the long-term outcomes of laparoscopic versus open D3 surgery.

*Methods:* Subjects were 1230 consecutive patients with stage II/III colon cancer, who were referred to the National Cancer Center Hospital from 2004 to 2013. Open surgery was performed in 821 (67%) patients, and laparoscopic surgery was performed in 409 (33%). Propensity score analyses with overall survival as the primary endpoint were performed in three different propensity score methods.

*Results:* Regression adjustment using the propensity score as a linear predictor in the model showed similar overall survival between laparoscopic and open surgeries [hazard ratio (HR), 0.98 (95% CI [0.64−1.46]; p = 0.916)]. Stratification analysis of the entire cohort revealed that, among five strata, only the highest stratum (clinical T2/T3, clinical N0/N1, tumor size <6 cm, and body mass index (BMI) < 28) had an HR of <1 (0.37). In the other four strata, open surgery was favored as reflected by HRs of >1 (1.13 −1.26). The propensity score-matched cohort (365 matched pairs), from which patients with advanced disease and high BMI were excluded, yielded an HR of 0.93 (95% CI [0.57−1.52]; p = 0.772).

*Conclusions:* Laparoscopic surgery appeared to be a safe and reasonable option for patients with stage II/III colon cancer in general. Patients with high BMI, clinical N2 and T4 disease, and tumor size ≥6 cm might require prudent selection of surgical approach.



## Introduction

Laparoscopic surgery has been performed in an increasing number of patients worldwide as a surgical option for the treatment of colon cancer. Most randomized controlled trials in the United States and Europe [1–4] reported short-term benefits as compared with open surgery, with no significant differences in long-term outcome. However, these trials had a high proportion of patients with pathological stage 0–1 disease (21–37%), which included rectal cancer in some trials, and moreover, the extent of lymph node dissection was not specified. Furthermore, the concept of complete mesocolic excision (CME) with central vascular ligation (CVL), the current standard in Europe, had not been introduced at the time of these studies [5].

Japanese D3 lymph node dissection [6], comprising a part of the more extended CVL, is almost identical to CME with CVL, in principle as well as in technique, except that the length of colon resection is slightly shorter in the former. Previous studies showed that both techniques are superior to conventional colon surgery in terms of oncological outcomes [7,8]. JCOG0404, investigating laparoscopic D3 surgery versus open D3 surgery for clinical stage II/III colon cancer, is the first randomized controlled trial that focused on assessing long-term outcomes of Japanese D3 (or CME with CVL) [9]. The results of JCOG0404 showed that, while long-term survival outcomes were almost identical between open and laparoscopic surgeries, non-inferiority of the laparoscopic approach, in terms of overall survival of patients with stage II/III colon cancer, could not be established. Subgroup analyses of overall survival revealed that patients with clinical T4 disease, advanced clinical node metastasis (N2), and high body mass index (BMI) tended to show worse survival after laparoscopic surgery compared to open surgery [9].

*Abbreviations:* 5-FU, 5-fluorouracil; BMI, body mass index; CI, confidence interval; CME, complete mesocolic excision; CVL, central vascular ligation; HR, hazard ratio; IQR, interquartile range; OS, overall survival.

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One meta-analysis showed that oncologic outcomes of laparoscopic resection for pathological T4 colon cancer appeared to be poorer (hazard ratio [HR]: 1.28) compared to open resection, although differences were not significant [10]. Another meta-analysis showed that higher BMI is associated with worse perioperative outcomes in patients undergoing laparoscopic colorectal surgery [11]. Taken together, there appear to be specific cases or conditions that warrant non-laparoscopic treatment.

In the present study, we aimed to evaluate the long-term survival outcomes of laparoscopic D3 surgery versus open D3 surgery for stage II/III colon cancer at our hospital, and identify conditions that require prudent decision-making regarding surgical options. Given the observed heterogeneity as well as potential selection bias between the laparoscopic surgery group and open surgery group, we used propensity score analysis to minimize selection bias.

## Materials and methods

### *Patient selection and data*

Inclusion criteria of this study were the patients with stage II/III colon cancer who were referred to the National Cancer Center Hospital and underwent curative resection from 2004 to 2013. Patients with cancers involving other organs, for whom open surgery was exclusively chosen, were excluded, since our analysis specifically targeted laparoscopic surgery versus open surgery. Decisions about surgical approach were typically made by several colorectal surgeons, who took into account disease severity as well as patient condition, including comorbidities.

According to the UICC TNM classification (8th edition), clinical TNM classification is based on evidence acquired before treatment, and pathological TNM classification is based on postoperative pathological examination. When pathological stage III was confirmed, adjuvant chemotherapy, mainly with oral 5-fluorouracil (5-FU) prodrugs or the Rowell Park regimen (5-FU and *l*-leucovorin), was considered.

### *Follow-up*

Postoperative follow-up consisted of CT and serum tumor marker measurements every six months for five years. Follow-up data were documented prospectively until an event occurred, or until the study cutoff date of November 2015. Complete follow-up was conducted for the entire cohort of patients, with a median follow-up time for survivors of 62 months (range, 1–134 months).

### *Statistical analysis*

Pearson's chi-square test for categorical variables, and the Wilcoxon rank sum test for continuous variables, were used to examine various factors in both groups. The primary study endpoint was overall survival (OS), or all-cause mortality, defined as the interval between the date of operation and the date of either death or the end of the observation period. Patients alive at the end of follow-up were censored. The Kaplan-Meier method was used to estimate OS. Differences in survival outcomes were assessed with the log-rank test. Multivariate Cox proportional hazards regression models were subsequently fitted to evaluate the relationship between laparoscopic surgery and OS while controlling for potential confounding covariates. Results are presented as HR and 95% confidence interval (CI).

In order to adjust for heterogeneity between the treatment groups (laparoscopic surgery and open surgery), propensity score analyses were conducted [12,13]. Multivariable logistic regression was used to generate propensity scores predicting treatment (laparoscopic surgery versus open surgery) based on confounding covariates, including gender, age, year, BMI, clinical T stage, clinical N stage, and tumor size. Each patient was then assigned an estimated propensity score, which is the probability that the patient is in the 'laparoscopic surgery' group given their measurable characteristics.

By applying propensity scores to adjust for group differences in the following three manners, cox models were created [12,14]. First, propensity scores were used for regression adjustment, which include the score as a linear predictor in the model [12,13]. By adjusting for the impact of background covariates the treatment effect is estimated in a regression model. Second, propensity scores were used for stratification. Defined by quintiles of the estimated propensity score, the entire cohort was divided into five strata. It has been shown that stratification based on the propensity score yields strata, within which the average treatment effect is an unbiased estimate of the true treatment effect [12]. Third, propensity score were used for matching, which pairs open surgery patients and laparoscopic surgery patients according to similarities in his/her observed baseline characteristics. Each patient who underwent laparoscopic surgery was matched 1:1 with an open surgery patient with the closest estimated propensity score on the logit scale within a specified range (smaller than 0.05 of estimated logits as the caliper width) to reduce differences between treatment groups, and a comparison of outcomes in matched patients is analyzed. All statistical analyses were performed using the JMP12 software program (SAS Institute Japan Ltd., Tokyo, Japan). $P < 0.05$ was considered statistically significant.

This study was approved by the Institutional Review Board (IRB) of the National Cancer Center Hospital (IRB code: 2014-414).

## Results

### *Characteristics of the study cohort*

Details of our study cohort are shown in Fig. 1. Between January 2004 and December 2013, 1400 patients with stage II/III colon cancer were referred to the National Cancer Center and underwent curative resection. Of these, 1230 patients excluding those with cancers involving other organs (n = 170) met the aforementioned inclusion criteria for stage II/III colon cancer, and underwent open surgery (open group; n = 821, 67%) or laparoscopic surgery (laparoscopic group; n = 409, 33%). Proportion of open surgery was 84% at the beginning of the one-third of the study (January 2004–April 2007), 62% at the next one-third (May 2007–August 2010), and 49% at the last one-third (September 2010–December 2013). In the laparoscopic group, 11 (2.7%) patients converted to open surgery. Patient characteristics by group are shown in Table 1. Significant group-dependent differences were observed in operation year ($p < 0.001$), BMI ($p = 0.011$), preoperative T stage ($p < 0.001$), preoperative N stage ($p = 0.030$), and tumor size ($p < 0.001$), suggesting that more patients who were obese or had locally advanced cancer (i.e., clinical T4, clinical N2/N3, and large tumor size) tended to undergo open surgery. Gender ratios and age did not differ between the two groups ($p = 0.527$ and $p = 0.455$, respectively). These results indicate that a clear treatment selection bias existed between laparoscopic and open surgeries, with laparoscopic surgery being more preferentially performed in less advanced cases of colon cancer.

Table 2 shows pathological characteristics by group. The median number of harvested lymph nodes was similar between the two groups (28 [IQR 20–37] in the open group vs 26 [IQR 19–34] in the laparoscopic group), although the difference was statistically significant ($p = 0.003$). Tumor size was significantly larger in the open group compared to the laparoscopic group ($p < 0.001$). The proportion of pathological T4a was similar in the open group and in the laparoscopic group (13% in the open group vs 10% in the laparoscopic

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