Randomized Controlled Trial to Evaluate Laparoscopic Surgery for Colorectal Cancer: Japan Clinical Oncology Group Study JCOG 0404

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A randomized controlled trial was started in Japan to evaluate whether laparoscopic surgery is the optimal treatment for colorectal cancer. Patients with T3 or deeper carcinoma in the colon or rectum without transverse and descending colons are pre-operatively randomized to either open or laparoscopic colorectal resection. Surgeons in 24 specialized institutions will recruit 818 patients. The primary end-point is overall survival. Secondary end-points are relapse-free survival, short-term clinical outcome, adverse events, the proportion of conversion from laparoscopic surgery to open surgery, and the proportion of completion of laparoscopic surgery.

Key words: colorectal cancer – laparoscopic surgery – randomized controlled trial

INTRODUCTION

The benefits of laparoscopic surgery (LAP) in comparison with open surgery (OPEN) have been suggested with respect to decreased morbidity, decreased pain, faster recovery and shorter hospital stay (1–4). However, the long-term survival of LAP for colorectal cancer is still unclear, especially for advanced colorectal cancer requiring extended lymphadenectomy. Thus, we designed a study which investigates whether LAP is suitable for advanced colorectal cancer with respect to survival and post-operative morbidity. The Clinical Trial Review Committee of the Japan Clinical Oncology Group (JCOG) approved the protocol in September 2004, and the study was activated in October 2004.

PROTOCOL DIGEST OF THE JCOG 0404

PURPOSE

To evaluate LAP in comparison with OPEN for T3 and T4 colorectal cancer.
ELIGIBILITY CRITERIA

Tumors are staged according to the TNM classification system.

Inclusion criteria. For inclusion in the study, patients must fulfill the following requirements pre-operatively: (i) histologically proven colorectal carcinoma; (ii) tumor located in the cecum, ascending colon, sigmoid colon or rectosigmoid colon; (iii) T3 or deeper lesion without involvement of other organs; (iv) without multiple lesions other than carcinoma in situ; (v) cancer classified as N0–2 and M0, according to the TNM classification system; (vi) tumor size \(<8\) cm; (vii) no bowel obstruction; (viii) age \(\geq 20\) and \(<75\) years; (ix) sufficient organ function; (x) no history of gastrointestinal surgery; (xi) no history of chemotherapy or radiotherapy; and (xii) provide written informed consent.

Exclusion criteria. Exclusion criteria are as follows: (i) synchronous or metachronous (within 5 years) malignancy other than carcinoma in situ; (ii) severe pulmonary emphysema, interstitial pneumonitis or ischemic heart disease; (iii) pregnant or lactating women; (iv) severe mental disease; and (v) continuous systemic steroid therapy.

RANDOMIZATION

By telephone or fax to the JCOG Data Center after confirmation of the inclusion/exclusion criteria, the patients are randomized by the minimization method of balancing the arm according to the location of tumor and institution.

QUALITY CONTROL OF SURGERY

To control the quality of the operation, we limit the operator to accredited surgeons and perform central review of the surgical procedure by photograph in all patients and by videotape in arbitrarily selected patients in both the LAP and OPEN arms. All operations are done or directly supervised by certified surgeons. Surgeons who have experience of at least 30 cases of open surgery in the OPEN arm, and experience of at least 30 case of both open and laparoscopic surgeries in the LAP arm are certified by the study chair.

TREATMENT METHOD

In both arms, resection of the colon or rectum with D3 lymphadenectomy is performed according to the Japanese Classification of Colorectal Carcinoma (5). In the LAP arm, pneumoperitoneal and intracorporeal approaches are used to explore the abdomen, mobilize the colon, identify critical structures and ligate the vascular pedicle. Mobilization of the colon and identification of critical structures are performed by the pneumoperitoneal approach only. Resection of the colon, ligation of the vascular pedicle and reconstruction are performed by the pneumoperitoneal approach or the intracorporeal approach via a small incision (\(\approx 8\) cm). Hand-assisted laparoscopic surgery is permitted, but sliding window and moving window methods are not permitted.

ADDITIONAL TREATMENT

In the case of pathological stage III colorectal carcinoma, three cycles of adjuvant chemotherapy with fluorouracil (500 mg/m² by bolus infusion on days 1, 8, 15, 22, 39 and 36) and l-leucovorin (250 mg/m² by 2 h drip infusion on days 1, 8, 15, 22, 39 and 36) are administered.

FOLLOW-UP

Patients are observed by their surgeon every 4 months for the first 2 years and then every 6 months for 3 years after operation. Blood tests, abdominal computed tomography and plain chest X-ray are carried out at each visit.

STUDY DESIGN AND STATISTICAL METHOD

This trial is designed to evaluate the non-inferiority of LAP to standard OPEN in terms of overall survival. If the overall survival is equivalent, LAP will be the preferred treatment. The null hypothesis to be tested is that the hazard ratio for the primary end-point with the LAP technique, as compared with the OPEN technique, was 1.366. The planned sample size is 818, 409 cases per arm, with 5 years of follow-up after 3 years of accrual. This provides 80% power to reject the null hypothesis when the survival is equivalent. This calculation assumed that there was a 5-year survival of 75% among patients treated with the OPEN technique.

INTERIM ANALYSIS AND MONITORING

Interim analysis is planned to take place twice, taking multiplicity into account by the Lan-Demets method with O’Brien and Fleming type boundaries. The Data and Safety Monitoring Committee (DSMC) of the JCOG will independently review the interim analysis report and consider stopping the trial early. In-house interim monitoring will be performed by the Data Center to ensure data submission and study progress. The monitoring reports will be submitted to and reviewed by the CCSG every 6 months.

PARTICIPATING INSTITUTIONS (FROM NORTH TO SOUTH)

Jichi Medical School Omiya Medical Center, National Cancer Center Hospital East, Juntendo University Urayasu Hospital, Toho University School of Medicine Sakurakike Hospital, National Cancer Center Hospital, Kyorin University School of Medicine, Keio University Hospital, Tokyo Medical and Dental University, Toranomon Hospital, Toho University School of Medicine Ohashi Hospital, Kitasato University East Hospital, Teikyo University school of Medicine Misonokuchi Hospital, Ishikawa Prefectural Central Hospital, Showa University Northern Yokohama Hospital, Nagano Municipal Hospital, Shizuoka Cancer Center, Fujita Health University, Osaka University Graduate School of Medicine Faculty of Medicine, Osaka City General Hospital, Osaka Medical College, Hiroshima University...
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References


